IOF
International
Osteoporosis
Foundation

IOF COMPENDIUM
OF OSTEOPOROSIS




Our vision is a world without fragility fractures, in which healthy mobility is a reality for all.

IOF Compendium of Osteoporosis

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About IOF

The International Osteoporosis Foundation (IOF) is the world's largest nongovernmental organization dedicated to the prevention, diagnosis and treatment of osteoporosis and related musculoskeletal diseases. IOF members, including committees of scientific researchers as well as 240 patient, medical and research societies in 99 locations, work together to make fracture prevention and healthy mobility a worldwide heath care priority. www.iofbonehealth.org www.facebook.com/iofbonehealth @iofbonehealth

World Osteoporosis Day October 20 LOVE YOUR BONES

Early diagnosis, a bone-healthy lifestyle, and medication have helped Jane remain fracture free ever since her diagnosis of severe osteoporosis at age 50.

FOREWORD

The 21st Century will bear witness to the most profound change in the age structure of the human population in history. In 2015, of the 7.3 billion individuals living in our global society, about 12 per cent were aged 60 years or over. By 2050, the United Nations projects that there will be more than 9.7 billion of us, which will include 2.1 billion people who have enjoyed their 60th birthday.

While this longevity miracle should be celebrated, we are obligated to undertake due diligence with respect to the impact that a demographic shift on this unprecedented scale will have upon our civilisation. The prevalence of chronic conditions which afflict older people is poised to rise considerably, and this will include osteoporosis and the fragility fractures it causes.

Osteoporosis is a very common condition. Among the population aged over 50 years, one in three women and one in five men will suffer a fragility fracture. At the turn of the century, 9 million fragility fractures occurred annually. This included 1.6 million hip fractures which impose a devastating burden on sufferers and their families, and all too often result in premature death. The 1.4 million individuals who sustained vertebral fractures endure back pain, loss of height and many other adverse effects on the quality of their lives. And the cost that osteoporosis imposes on healthcare budgets is staggering. In 2010, European Union countries spent Euro 37 billion (US$40 billion), while in 2015 the United States spent US$20 billion.

However, there is reason for optimism. Osteoporosis can be readily diagnosed and fracture risk is easily accessed. A broad range of effective treatments are available throughout the world that have been shown to reduce the risk of hip, vertebral and other fragility fractures. Effective models of care have been developed in many countries to ensure that the right patient receives the right treatment at the right time. In recent years, national alliances – comprised of national osteoporosis societies and other relevant non-governmental organisations, policymakers and healthcare professional organisations (and some include private sector companies) - have been formed in a growing number of countries to combine expertise, resources and the desire to improve outcomes for those who have sustained fragility fractures.

There is still much to be done. Access and reimbursement for diagnosis and treatment remains highly variable across the world. Public awareness of osteoporosis is persistently low. Some of the world's most populous countries lack robust epidemiological data to inform policy development.

The IOF Compendium of Osteoporosis marks a new era in IOF's commitment to improve the bone health of humankind. The IOF Compendium will be updated on a regular basis to serve as the definitive reference point for all organisations who share IOF's vision of a world without fragility fractures, in which healthy mobility is a reality for all.

Fifty-eight year-old Maria Filomena, has suffered many fractures due to osteoporosis. She is very fearful of falling as this could result in more fractures which could be devastating to her independence.

CONTENTS

EXECUTIVE SUMMARY

- The IOF Compendium of Osteoporosis serves as a reference point for all key stakeholders in the field of musculoskeletal health globally.
- To be updated periodically, the IOF Compendium provides:
  - A summary of current knowledge of bone biology and risk factors which pre-dispose individuals to suffer fragility fractures, the clinically significant consequence of osteoporosis.
  - Updates on:
    - Costs and burden of osteoporosis and fragility fractures worldwide.
    - Prevention of osteoporosis and the role of nutrition in maintaining bone health.
    - Osteoporosis treatments and public awareness of the benefits versus risks of treatment.
    - Models of care which efficiently target treatments to individuals at high fracture risk.
  - Clear recommendations for achieving optimal bone health for all.
- Overarching objectives for good bone health at the various stages of life are:
  - **Children and adolescents:** Achieve genetic potential for peak bone mass.
  - **Adults:** Avoid premature bone loss and maintain a healthy skeleton.
  - **Seniors:** Prevent and treat osteoporosis.
- Osteoporosis is the most common bone disease. One in three women aged 50 years and over will sustain a fragility fracture, as will one in five men.
- Fragility fractures impose a tremendous burden on our older people, their families and carers, and national economies:
  - In 2010, the number of individuals aged 50 years and over at high risk of osteoporotic fracture worldwide was estimated at 158 million and is set to double by 2040.
- A broad range of osteoporosis treatments, available in an array of dosing regiments, have been shown to significantly reduce the risk of hip fractures, vertebral fractures and other clinically apparent fractures.
- All individuals who are at high fracture risk according to national osteoporosis clinical guidelines should be prioritised for osteoporosis assessment and receive guidelines-based treatment.
- The Orthogeriatric Service and Fracture Liaison Service models of care have been shown to deliver secondary preventive care for fracture patients in a highly cost-effective manner.
- The incidence of fragility fractures is currently very high and set to increase dramatically as the world's population ages:
  - **Asia-Pacific:** By 2050, 1.3 billion people in Asia will be aged 60 years or older and more than a quarter of a billion will be aged 80 years or older. Consequently, the annual incidence of hip fracture in China is set to rise from 411,000 cases in 2015 to 1 million cases in 2050.
  - **Europe:** In 2010, the 3.5 million fragility fractures which occurred in the European Union contributed to the total cost of osteoporosis reaching Euro 37 billion (US$40 billion).
  - **Latin America:** The most rapidly ageing region of the world between 2015 and 2030. In Brazil, the number of hip fractures will more than double, from 80,640 cases in 2015 to 198,000 cases by 2040.
  - **North America:** By 2025, the annual incidence of fragility fractures in the United States is projected to exceed 3 million cases, at a cost of US$25 billion.

The IOF Compendium proposes 8 key priorities for the period 2017-20:

Priority 1: Secondary fracture prevention

Policymakers, healthcare professional organisations and national osteoporosis societies must collaborate to provide Orthogeriatric Services and Fracture Liaison Services to all older people who suffer fragility fractures in their jurisdictions.

Priority 2: Osteoporosis induced by medicines

Where treatments are licensed to prevent osteoporosis induced by medicines, and guidelines have been published to inform best clinical practice, osteoporosis management must become a standard consideration for clinicians when prescribing medicines with bone-wasting side effects.

Priority 3: Primary fracture prevention

National osteoporosis societies to incorporate messaging regarding self-assessment of fracture risk with FRAX® into public awareness and education initiatives, as advocated in Priority 6. National osteoporosis societies to collaborate with healthcare professional organisations for primary care providers (PCPs) to jointly advocate for PCPs to routinely undertake fracture risk assessment when interacting with patients aged 50 years and over.

Priority 4: Nutrition and exercise

Specific initiatives encompassing nutrition and exercise are required for particular age groups:

Expectant mothers: National osteoporosis societies to collaborate with national obstetrics organisations to advise government on optimising bone health of mothers and infants.

Children and adolescents: National osteoporosis societies to collaborate with government Ministries of Education, national teachers' organisations, national nutrition foundations/councils, national dietician/nutritionist organisations, government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to educate children and adolescents on achieving their genetic potential for peak bone mass.

Adults and seniors: National osteoporosis societies to collaborate with government Ministries for Seniors, national nutrition foundations/councils, national dietician/nutritionist organisations, non-governmental organisations concerned with seniors' welfare and government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to inform adults on their nutritional and exercise needs to maintain a healthy skeleton, avoid premature bone loss and avoid malnutrition in the elderly.

Priority 5: Healthcare professional education

National osteoporosis societies and healthcare professional organisations to collaborate to develop and encourage widespread participation in national professional education programmes designed for 3 distinct audiences: Lead Clinicians in Osteoporosis, orthopaedic surgeons and primary care providers.

Priority 6: Public awareness and education

National osteoporosis societies, healthcare professional organisations, policymakers and regulators to collaborate to develop impactful public awareness campaigns which empower consumers to take ownership of their bone health.

Priority 7: Improving access and reimbursement for diagnosis and treatment

Osteoporosis must be designated a national health priority in all countries, with commensurate human and financial resources to ensure that best practice is delivered for all individuals living with this condition. In countries where the current disease burden is not known, epidemiological studies must be commissioned as a matter of urgency.

Priority 8: Formation of national falls and fracture prevention alliances

In countries without an existing national alliance, national osteoporosis societies to initiate dialogue with other relevant non-governmental organisations, policymakers, healthcare professional organisations and private sector companies to propose formation of a national falls and fracture prevention alliance modelled on successful examples from elsewhere. Formation of a national alliance has the potential to facilitate delivery of Priorities 1-7.

For years, Peter suffered severe, unexplained back pain without being investigated for osteoporosis. He was finally referred for bone mineral density testing after receiving advice from the Irish Osteoporosis Society.

INTRODUCTION

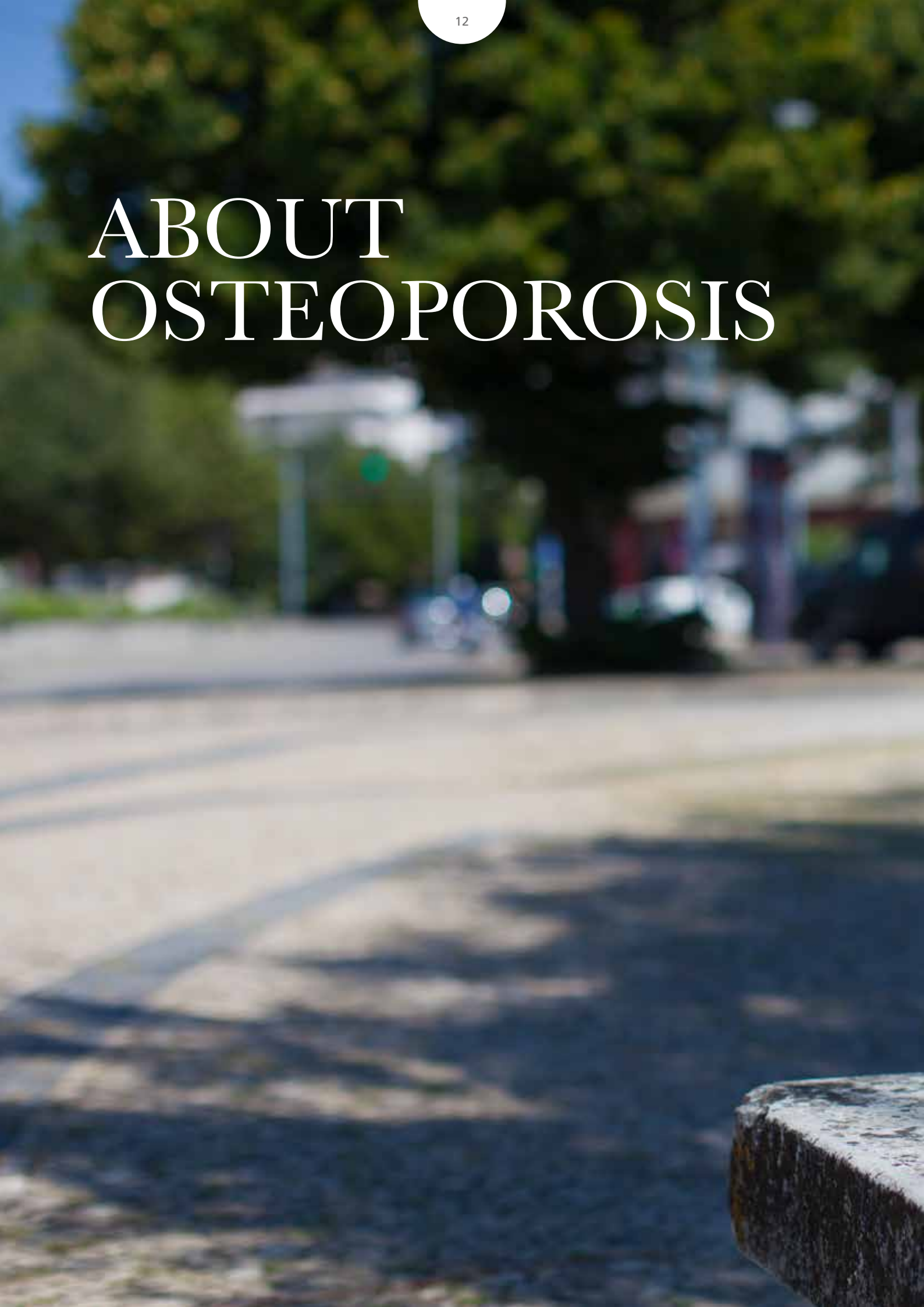
The IOF Compendium of Osteoporosis provides a summary of current knowledge of bone biology and risk factors which pre-dispose individuals to suffer fragility fractures, the clinically significant consequence of osteoporosis. The burden imposed by osteoporosis – from epidemiological, quality of life and socio-economic perspectives – are documented at the global and regional level. Preventive strategies, including the role of nutrition and exercise in maintaining bone health throughout life is considered. Evidence for the effectiveness of treatments is reviewed and will be expanded as new research is published and new therapies become available. Public awareness of benefits versus risks of treatment are analysed. Considerable activity is ongoing worldwide to establish models of care which ensure that the right patient receives the right treatment at the right time. The Compendium describes how these services are organised and the outcomes that they achieve. Finally, and perhaps most importantly, a Blueprint for Action provides all stakeholders with clear recommendations for achieving optimal bone health for all. The Blueprint will lead to widespread implementation of proven models of care, better education for healthcare professionals, greater public awareness, improved access to diagnosis and treatment and formation of new national alliances.

The IOF Compendium is intended to serve as a reference point for all key stakeholders within the field of musculoskeletal health, including:

- National level policymakers
- Government representatives
- Healthcare professionals and their organizations
- National osteoporosis societies
- The healthcare industry
- The media

We hope that you enjoy reading this first edition of the IOF Compendium, act upon the recommendations made and share this inaugural publication with your colleagues so that they can do similar. As the population of the world continues to age, left unchecked, the burden imposed by osteoporosis will be enormous, both in terms of human suffering and financial costs to our societies. The IOF Compendium of Osteoporosis provides you with the knowledge required to prevent this from happening in your community. We would welcome any feedback you may have for consideration in subsequent editions of the Compendium.

ABOUT OSTEOPOROSIS



ABOUT OSTEOPOROSIS

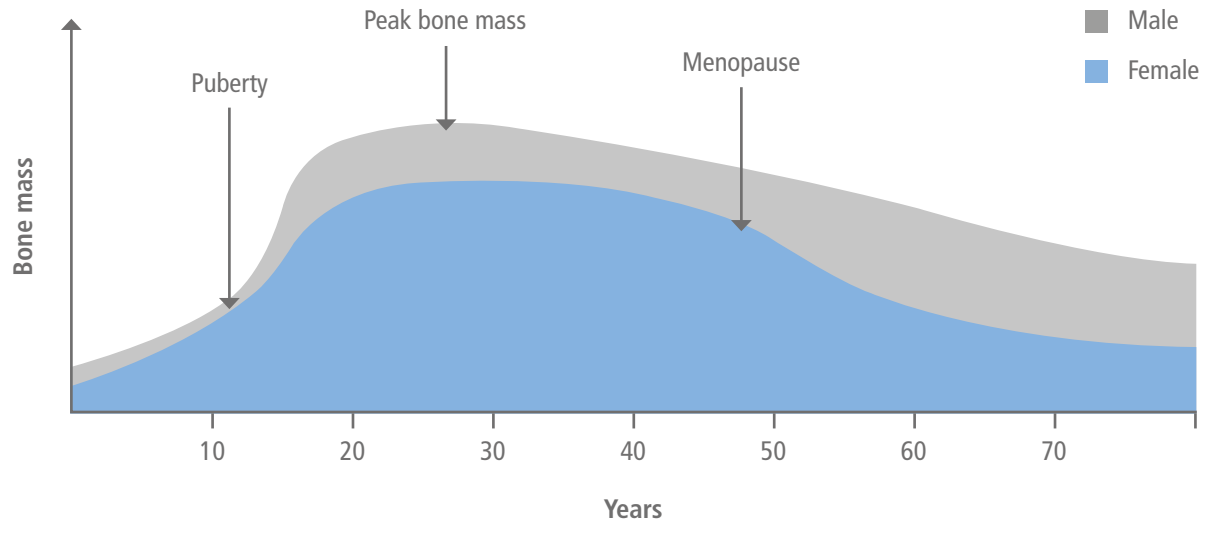
> **"Our skeleton is formed before we are born, supports us throughout our lives, and can remain long after we die. Regardless of age, gender, race, nationality, or belief set, we all have one. Yet this essential organ is so often taken for granted."**
>
> World Osteoporosis Day Report 2015 [1]

Bone biology

Our skeleton is a remarkably active living tissue comprised of a myriad of cells, blood vessels, proteins and minerals. At birth, we have 300 soft bones which are transformed during childhood and adolescence into hard bones. As some bones fuse during the developmental process, the adult skeleton has 206 bones. The size of our skeleton, and the amount of bone contained in it, changes significantly throughout life. As illustrated in figure 1, peak bone mass is achieved for both males and females by the mid-twenties. Thereafter, a gradual decline into old age occurs in men, while a plateau followed by an accelerated period of bone loss for several years after the menopause occurs in women. Overarching objectives for good bone health at the various stages of life are [1]:

- **Children and adolescents:** Achieve genetic potential for peak bone mass.
- **Adults:** Avoid premature bone loss and maintain a healthy skeleton.
- **Seniors:** Prevent and treat osteoporosis.

Figure 1. Bone mass throughout the life cycle



Our bones are comprised of two types of tissue:

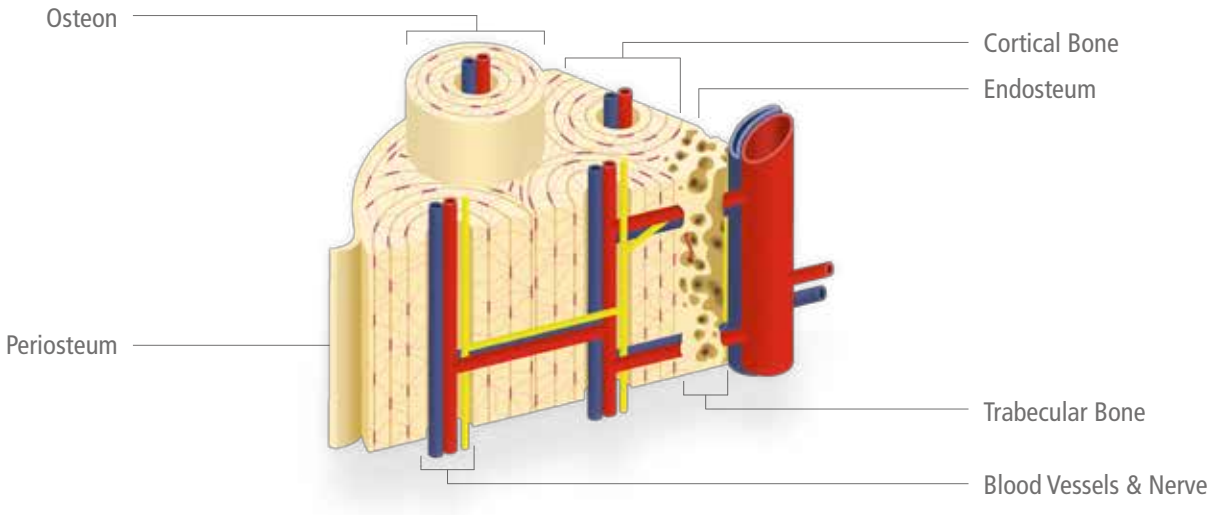
- **Cortical bone:** Also known as compact bone, this hard outer layer is strong and dense.
- **Cancellous bone:** Also known as trabecular bone, this spongy inner network of trabeculae is lighter and more flexible than cortical bone.

In addition to osteoid (the unmineralized, organic portion of the bone matrix which forms prior to the maturation of bone tissue) and inorganic mineral salts deposited within the matrix, cells are present which are responsible for bone formation (osteoblasts and osteocytes) and resorption (osteoclasts) [2]:

- **Osteoblasts:** These cells are derived from mesenchymal stem cells and are responsible for bone matrix synthesis and its subsequent mineralization. In the adult skeleton, the majority of bone surfaces that are not undergoing formation or resorption (i.e. not being remodelled) are lined by bone lining cells.
- **Osteocytes:** These cells are osteoblasts that become incorporated within the newly formed osteoid, which eventually becomes calcified bone. Osteocytes situated deep in bone matrix maintain contact with newly incorporated osteocytes in osteoid, and with osteoblasts and bone lining cells on the bone surfaces, through an extensive network of cell processes (canaliculi). They are thought to be ideally situated to respond to changes in physical forces upon bone and to transduce messages to cells on the bone surface, directing them to initiate resorption or formation responses.
- **Osteoclasts:** These cells are large multinucleated cells, like macrophages, derived from the hematopoietic lineage. Osteoclasts function in the resorption of mineralized tissue and are found attached to the bone surface at sites of active bone resorption. Their characteristic feature is a ruffled edge where active resorption takes place with the secretion of bone-resorbing enzymes, which digest bone matrix.

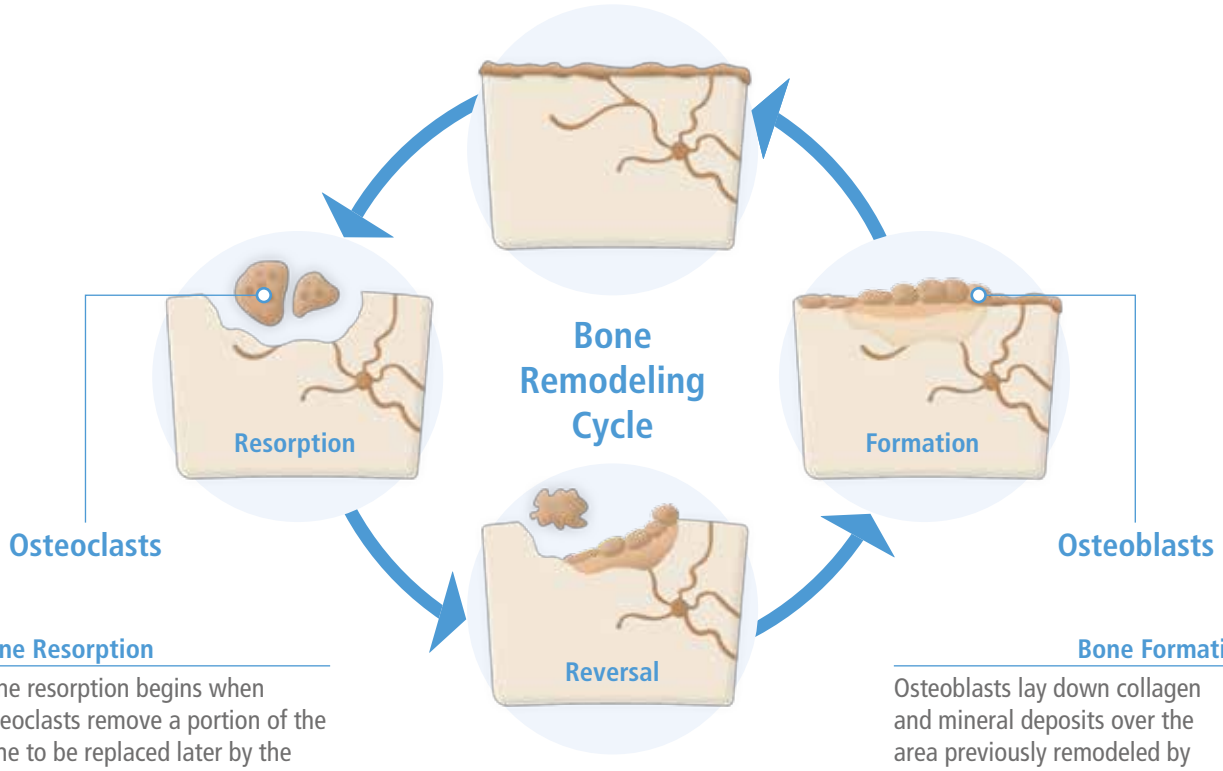
Once peak bone mass has been achieved, the structural integrity of bone is maintained by a process called remodelling, illustrated in figure 3 on the following page. Remodelling continues throughout life so that most of the adult skeleton is replaced about every 10 years.

Figure 2. The structure of bone



(adapted from the Servier Medical Art Slide Kit)

Figure 3. Bone renewal through the bone remodelling cycle



Bone Resorption

Bone resorption begins when osteoclasts remove a portion of the bone to be replaced later by the action of osteoblasts. This is a vital step for signalling bone formation.

Bone Formation

Osteoblasts lay down collagen and mineral deposits over the area previously remodeled by osteoclasts. Osteoblast activity is vital for maintaining bone mineral density and bone strength.

A multifactorial disease

Many factors influence an individual's propensity to develop osteoporosis and suffer the fragility fractures it causes. Some of these factors are non-modifiable, such as family history, while others can be avoided or ameliorated. From the perspective of the patient or their physician, as in all things, knowledge is power.

Risk factors for osteoporosis and fracture

Osteoporosis has been characterized as a paediatric disease with geriatric consequences [3]. Achieving peak bone mass during youth is paramount, as was clearly demonstrated by an analysis of relative influences on peak bone mineral density (BMD), age-related bone loss and menopause on the development of osteoporosis [4]:

> "A 10% increase in peak BMD was predicted to delay the development of osteoporosis by 13 years, while a 10% change in the age at menopause or the rate of non-menopausal bone loss was predicted to delay osteoporosis by approximately 2 years, suggesting that peak BMD may be the single most important factor in the development of osteoporosis."

In 1994, the World Health Organization (WHO) established four general operational categories relating to BMD in postmenopausal women, principally for epidemiological classification, but which have become regarded as clinical diagnostic categories for osteoporosis [5]:

- **Normal:** A value for BMD within 1 standard deviation (SD) of the young adult reference mean, subsequently referred to as a T-score < -1.
- **Low bone mass (osteopenia):** A value for BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value, subsequently referred to as a T-score in the range -1 to -2.5.
- **Osteoporosis:** A value for BMD 2.5 SD or more below the young adult mean, subsequently referred to as a T-score < -2.5.
- **Severe osteoporosis (established osteoporosis):** A value for BMD more than 2.5 SD below the young adult mean in the presence of one or more fragility fractures.

In 2014, investigators in the United States determined the prevalence of osteoporosis and low bone mass at the femoral neck and the lumbar spine in adults aged 50 years and older in the 2010 US Census population [6]. The key findings from this study shown in table 1 highlight two risk factors for osteoporosis: gender and age. Among the 10.2 million adults estimated to have osteoporosis in the United States, more than 80% were women. Further, a clear correlation exists between the prevalence of osteoporosis and increasing age.

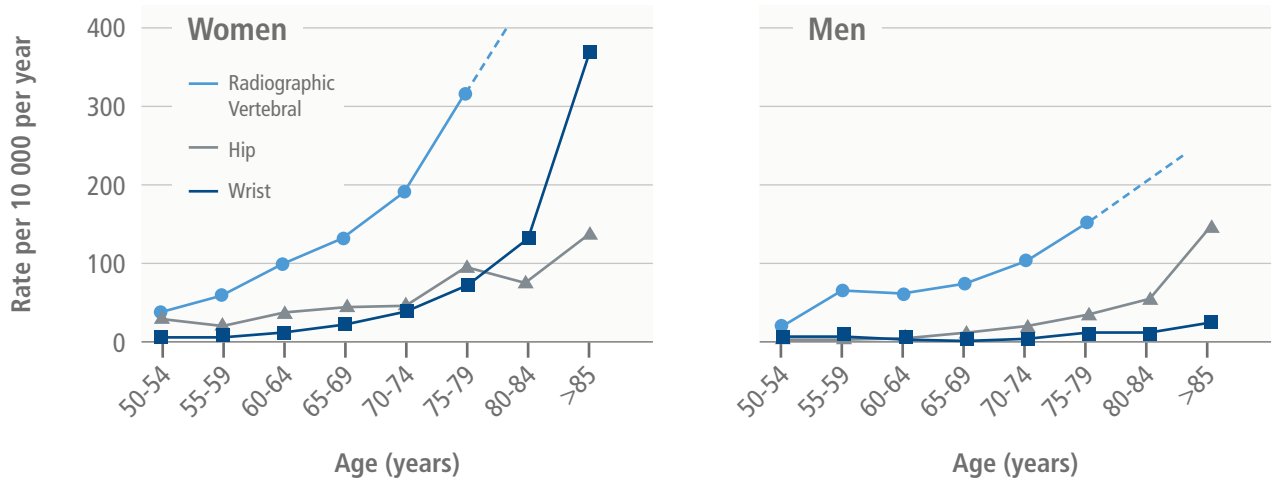
Table 1. Prevalence of osteoporosis and low bone mass in the United States in 2010 [6]

	Total population (millions)	Osteoporosis prevalence (%)	Low bone mass prevalence (%)
Women	53.2	15.4	51.4
50-59 years	21.5	6.8	49.3
60-69 years	15.3	12.3	53.4
70-79 years	9.2	25.7	51.8
80+	7.2	34.9	52.7
Men	45.9	4.3	35.2
50-59 years	20.5	3.4	30.7
60-69 years	13.9	3.3	32.9
70-79 years	7.4	5.0	41.8
80+	4.1	10.9	53.1

(Adapted with permission of the authors, P. Sambrook and C. Cooper)

Just as the prevalence of osteoporosis increases with age, the incidence of fragility fractures increases dramatically among older people, as illustrated in figure 4. Furthermore, individuals who have sustained a fragility fracture are at approximately twice the risk of suffering future fractures, as compared to their fracture-free peers [7, 8]. From the obverse perspective, approximately half of patients who present to hospital with a hip fracture have sustained prior fractures in the months or years before breaking their hip [9]. As such, fragility fracture patients are an obvious group to target for secondary preventive care. This theme will be explored in more detail later in the Compendium.

Figure 4. Age- and gender-specific incidence of hip, vertebral and distal forearm fractures [10]



(Adapted with permission of the authors, P. Sambrook and C. Cooper)

In addition to age, gender and a history of fragility fracture, the following risk factors identify individuals likely to be at increased fracture risk:

- **Underweight:** In 2005, a meta-analysis evaluated body mass index (BMI) as a predictor of fracture risk [11]. When compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with almost a two-fold increase in the risk ratio for hip fracture.

- **Parental history of fracture:** Meta-analysis has also shown parental history of fracture to be associated with increased risk of any fracture, osteoporotic fracture and hip fracture in men and women combined [12]. The increases in the risk ratios were 17%, 18% and 49% for any fracture, any osteoporotic fracture and hip fracture, respectively.

- **Frequent falls:** Falls are very common among older people, with one third of people aged 65 years and over falling each year and half of those aged 85 years and over [13]. Notably, half of those who fall do so repeatedly and approximately 5% of falls result in a fracture.

- **Early menopause:** Women who experience menopause before age 40 years have a higher risk of any fracture than women reporting menopause at an older age [14]. This effect is not altered for women treated with osteoporosis therapies, suggesting that early age of menopause is an independent contributor to postmenopausal fracture risk. Investigators have also evaluated the impact of hysterectomy on long-term fracture risk [15]. About a 20% increase in overall fracture risk is observed, but no significant effect on the typical osteoporotic fractures, defined as hip, wrist or spine fractures, collectively.

- **Lifestyle considerations:**

  - **Alcohol:** The relationship between alcohol intake and fracture risk is non-linear [16]. No significant increase in risk is observed for intakes of 2 units or less daily (e.g. 2 glasses of 120 ml of wine). Above this threshold, alcohol intake is associated with an increased risk of 23%, 38% and 68% for any fracture, any osteoporotic fracture, and hip fracture, respectively.

  - **Smoking**: The impact of smoking on fracture risk has been evaluated in a meta-analysis [17]. Current smoking was associated with an increased risk of 25% for any fracture compared to non-smokers and 60% for hip fracture, after adjustment for BMD.

Osteoporosis induced by medicines

Adverse effects on BMD and/or fracture risk have been reported for many classes of drugs [18-29]. Associations for commonly used drug classes and bone loss and/or fragility fracture incidence are summarised in table 2.

Table 2. Commonly used drug classes associated with bone loss and/or fragility fractures [18]

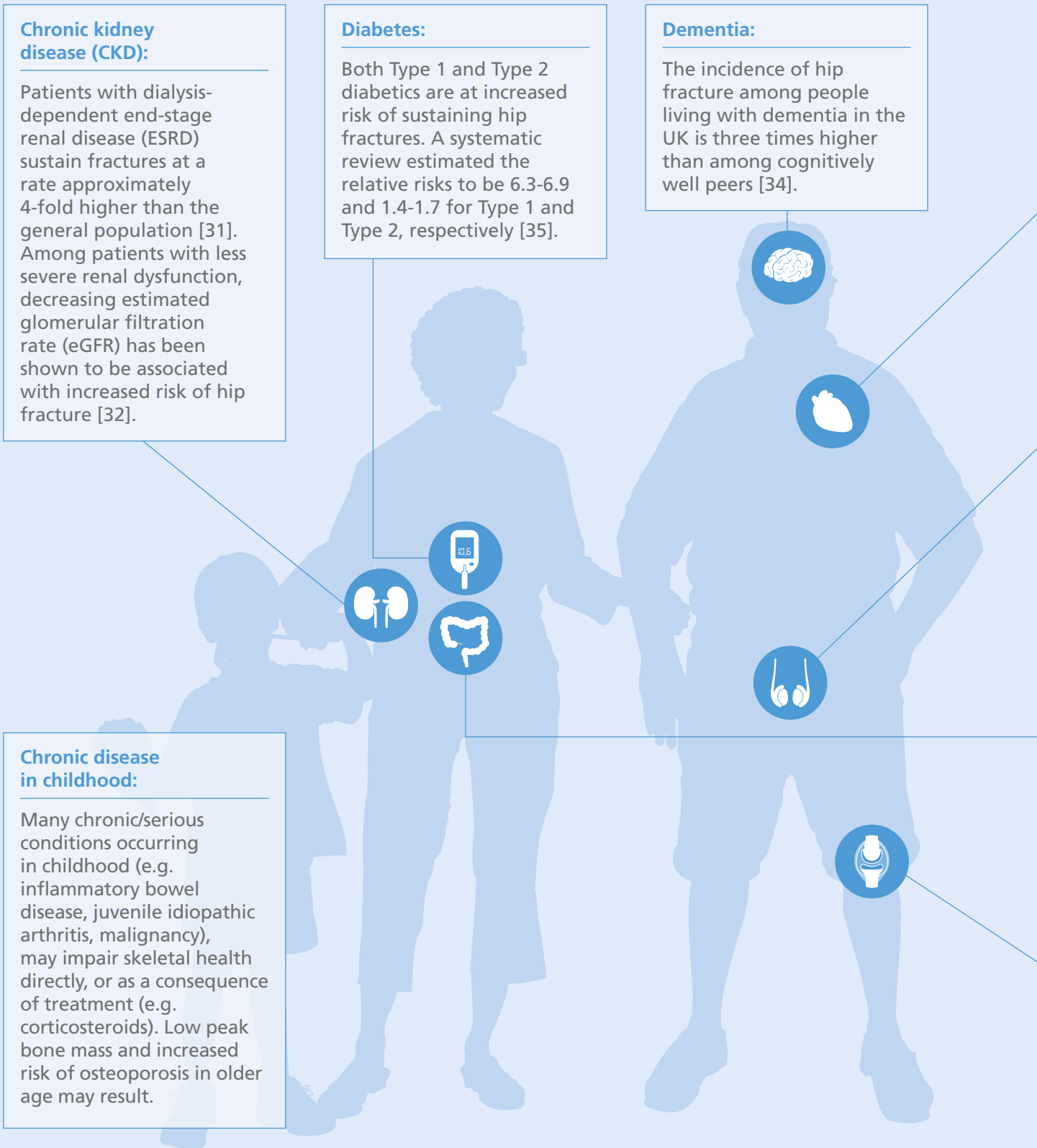
Drug class	Loss of BMD [19]	Increased fracture risk [19]	Literature review
Androgen deprivation therapy	Gonadotropin-releasing hormone agonists (GnRHs) are the most commonly used ADT. BMD declines by 2-5% during the first year of ADT.	The risk of hip and vertebral fractures increases to 20-50% after 5 years of ADT. Fracture risk correlates with age, rate of BMD loss and ADT exposure.	Bienz and Saad [20]
Aromatase inhibitors	The annual rate of bone loss in women taking AIs is approx. 2.5% as compared to 1-2% for healthy postmenopausal women [23].	Women treated with AIs have a 30% higher fracture risk than age-matched healthy women. AI users sustain more peripheral fractures than hip or vertebral fractures [23].	Rizzoli et al [23]
Glucocorticoids	While all recipients of GCs are at increased risk of bone loss, older men and postmenopausal women are at highest risk with GC doses of >20 mg daily.	30-50% of patients receiving GCs develop fractures. GC-induced osteocyte apoptosis leads to early increase in fracture risk prior to loss of BMD.	Whittier and Saag [25]
Selective serotonin reuptake inhibitors	Small studies have found an association between SSRI use and bone loss. However, meta-analysis has reported SSRI-related fractures in the absence of bone loss.	Two meta-analyses have reported the adjusted odds ratio for fracture among SSRI users to be approx. 1.7. Fracture risk is dependent on dose and duration of SSRI treatment.	Rizzoli et al [28]
Thiazolidinediones	TZDs reduce bone formation through impairing differentiation of osteoblast precursors, and increase resorption through several mechanisms, resulting in bone loss.	Two meta-analyses have reported that TZDs significantly increase fracture incidence in women with Type 2 diabetes, but not in men. Notably, fracture risk is increased in young women without risk factors.	Napoli et al [29]

(Adapted from *Osteoporos Int. 2017 May;28(5):1507-1529* with kind permission of Springer)

Other related comorbidities

Individuals who are living with a broad array of diseases are pre-disposed to develop osteoporosis or sustain fragility fractures. Common examples are illustrated in figure 5, several of which were described in more detail in a recent review article [18].

Figure 5. Common diseases associated with bone loss and/or fragility fractures [18]



Chronic obstructive pulmonary disease (COPD):

In Taiwan, a nationwide population-based cohort study reported that COPD sufferers were 24% more likely to sustain an osteoporotic fracture compared to a matched comparator group [33].

Hypogonadism:

The Massachusetts Male Aging Study estimated the prevalence of testosterone deficiency in men to be 12.3% among US men aged 40 to 69 years, representing a common contributor to osteoporosis in men [36].

Inflammatory bowel disease (IBD):

A large study from Canada reported that the incidence of fracture among individuals with IBD was 40% greater than that of the general population [37].

Coeliac disease (CD):

Analysis of data from the US National Health and Nutrition Examination Survey (NHANES) demonstrated that CD is associated with reduced BMD in children and adults aged 18 years and over, and is a risk factor of osteoporotic fractures in men aged 40 years and over [30].

Rheumatoid arthritis (RA):

A large study from the UK found RA patients' risk of hip fracture and vertebral fracture to be increased 2-fold and 2.4-fold as compared to a control group [38].

The role of nutrition in bone health

In 2015, the World Osteoporosis Day Report and an associated comprehensive review described how nutritional factors affect musculoskeletal health throughout life [1, 39]. The evidence was appraised from a life-course perspective:

- Maternal nutrition.
- Building bone in childhood and adolescence.
- Maintaining bone mass in adulthood.
- The special nutritional needs of seniors.

Expectant mothers should be well nourished to support an infant's development in utero. In this regard, it is of concern that surveys conducted throughout the world report both low levels of calcium intake and vitamin D insufficiency to be common in pregnancy. In 2016, results were published from the UK Maternal Vitamin D Osteoporosis Study (MAVIDOS) [40]. This large-scale randomised-controlled trial was designed to test whether offspring of mothers supplemented with vitamin D during pregnancy have higher bone mass at birth than those of mothers who were not supplemented. Although there was no difference in whole body bone mineral content (BMC) between offspring of mothers supplemented with 1,000 International Units (IU) per day of cholecalciferol (vitamin D3) compared with offspring of mothers randomised to placebo, in a pre-specified secondary analysis, there was a large (0.5 SD) increase in neonatal BMC amongst offspring of supplemented mothers versus offspring of placebo mothers, for births occurring during winter months. The supplement appeared safe, and these findings suggest potential season-dependent benefits for antenatal vitamin D supplementation. Further results will follow from the ongoing MAVIDOS childhood follow-up study.

An individual's peak bone mass is determined to a great extent during the first two decades of life. While genetics plays a significant role, decisions regarding nutrition and exercise impact on a child's likelihood, or not, of achieving their genetic potential for peak bone mass. In this regard, osteoporosis has been characterised as a paediatric disease with geriatric consequences, and for good reason. In 2003, Hernandez and

colleagues undertook a theoretical analysis to determine the relative influences of peak BMD, age-related bone loss and age at menopause on the development of osteoporosis in women [4]. Osteoporosis would occur 13 years later if peak BMD was increased by 10%. By comparison, a 10% change in the age at menopause or the rate of postmenopausal bone loss would delay the onset of osteoporosis by just 2 years. Findings from the MAVIDOS study and similar work suggest that environmental contributions to bone mass begin even as early as in the womb.

In adulthood, the combination of a well-balanced diet and regular weight-bearing exercise play an important part in ensuring good adult bone health. The key components of a "bone healthy" diet include:

- **Calcium:** Consensus is evident among leading organisations regarding recommended dietary intake of calcium for adults. The National Health and Medical Research Council in Australia [41], the Institute of Medicine in the United States (now known as the National Academy of Medicine) [42] and the World Health Organization/Agriculture Organization of the United Nations [43] all recommend intake of 1,000 mg per day of calcium.

- **Vitamin D:** While sun exposure provides the primary source of vitamin D by triggering synthesis in the skin, increasingly indoor lifestyles are contributing to vitamin D insufficiency becoming a global problem. In 2009, an IOF Working Group published a review of global vitamin D status and determinants of insufficiency [44]. Low levels of vitamin D were highly prevalent among adults, as subsequently illustrated on the IOF vitamin D status map [45].

- **Protein:** Protein provides a source of amino acids which are needed to maintain bone structure, and stimulates release of IGF-I which may increase osteoblast activity resulting in increased production of bone matrix. In 2009, a systematic review and meta-analysis reported a small positive association between protein intake and BMD and BMC, and a reduction in markers of bone resorption [46].

Further studies are required to determine the impact of several other vitamins on bone health (A, B and K). With regards to minerals, magnesium and zinc play a role in bone metabolism. Accordingly, ensuring adequate dietary intake of these minerals is important.

Malnutrition is highly prevalent in the elderly, and as such, ensuring adequate dietary intake of calcium, vitamin D and protein in this age group is paramount. A summary of recommendations on this subject by expert groups was provided in the 2015 World Osteoporosis Day Report [1]. The key recommendations made in a consensus statement published in 2014 by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) are illustrative of themes common to all such recommendations [47]:

- Optimal dietary protein intake of 1.0–1.2 g/kg body weight/day with at least 20-25g of high-quality protein at each main meal.

- Vitamin D intake of 800 IU per day to maintain serum 25(OH)D levels greater than 50 nmol/L (20 ng/mL).

- Calcium intake of 1,000 mg per day.

- Regular physical activity/exercise 3–5 times per week combined with protein intake in close proximity to exercise.

Supplementation with calcium and vitamin D

The role of calcium supplementation, with or without concomitant vitamin D supplementation, has been the subject of considerable scientific debate in the literature in recent years. Many clinical trials, and meta-analyses of these trials have explored the benefits of supplementation, in terms of fracture reduction, and adverse events. In 2017, an expert consensus meeting of ESCEO and IOF was convened to review the evidence for the value of calcium supplementation, with or without vitamin D supplementation, for healthy musculoskeletal ageing. The report which documented the meeting reached the following conclusions [48]:

1. Calcium and vitamin D supplementation leads to a modest reduction in fractures, but use of calcium supplementation alone is not robustly supported.

2. The evidence for calcium and vitamin D supplementation for fracture reduction is most robust in those who are likely to be at greatest risk of calcium and/or vitamin D insufficiency; population-based interventions have not convincingly demonstrated benefit.

3. Although calcium is intimately involved in muscle physiology, the best clinical evidence suggests that vitamin D optimisation, rather than supplementation with calcium, leads to reduced risk of falls.

4. Calcium supplements are associated with gastrointestinal side effects and a small increased risk of renal stones.

5. The assertion that calcium with vitamin D supplementation increases cardiovascular risk is based on inadequate evidence; several studies demonstrate the converse or no cardiovascular effect.

6. A large randomised control trial of calcium supplementation powered to detect validated fractures and cardiovascular events is required to ultimately clarify this issue.

7. On the basis of the current evidence, we recommend that calcium and vitamin D supplements are generally appropriate for those with a high risk of calcium and vitamin D insufficiency and in those who are receiving treatment for osteoporosis.

Dietary sources of calcium

Calcium is contained in several food groups and is most readily accessible in dairy foods such as milk, yoghurt and cheeses. Common non-dairy foods containing calcium include certain vegetables (e.g. kale); whole canned fish with soft edible bones such as sardines; some nuts; calcium-set soy products (tofu, soy milk); and some mineral waters, among others.

Recent publications from France and Belgium have demonstrated the efficacy and cost-effectiveness of dairy products as a source of calcium, proteins and, where supplemented, vitamin D to relieve the burden of osteoporosis [48-52]. Public beliefs regarding benefits versus perceived detrimental effects of dairy products need to be considered by clinicians to enable their patients to make informed decisions. In 2016, a commentary from the Belgian Bone Club and ESCEO sought to bring some clarity to this issue [53]. Key conclusions included:

- Lactose intolerant individuals may not need to completely eliminate dairy products from their diet, as both yogurt and hard cheese are well tolerated.

- Dairy products do not increase the risk of cardiovascular disease, particularly if low fat.

- Intake of up to three servings of dairy products per day appears to be safe and may confer a favourable benefit with regard to bone health.

Prevention of osteoporosis

Childhood to adolescence

Building strong bones starts in the womb, and thus a healthy diet and lifestyle during pregnancy can help the next generation. Bones are living tissue, and after birth, the skeleton continues to grow to the end of the teenage years, reaching a maximum strength and size (peak bone mass) in early adulthood, around the mid-20s. It's therefore never too early to invest in bone health. The prevention of osteoporosis begins with optimal bone growth and development in youth.

Children and adolescents should:

- Ensure a nutritious diet with adequate calcium intake.
- Avoid protein malnutrition and under-nutrition.
- Maintain an adequate supply of vitamin D.
- Participate in regular physical activity.
- Avoid the effects of second-hand smoking.

It has been estimated that a 10% increase of peak bone mass in children reduces the risk of an osteoporotic fracture during adult life by 50% [54].

Adulthood

Bone mass acquired during youth is an important determinant of the risk of osteoporotic fracture during later life. The higher the peak bone mass, the lower the risk of osteoporosis. Once peak bone mass has been reached, it is maintained by a process called remodelling. This is a continuous process in which old bone is removed (resorption) and new bone is created (formation). The renewal of bone is responsible for bone strength throughout life.

During childhood and the beginning of adulthood, bone formation is more important than bone resorption. Later in life, however, the rate of bone resorption is greater than the rate of bone formation and results in net bone loss –a thinning of your bones. Any factor which causes a higher rate of bone remodelling will ultimately lead to a more rapid loss of bone mass and more fragile bones. The nutritional and lifestyle advice for building strong bones in youth is just as applicable to adults to.

Adults should:

- Ensure a nutritious diet and adequate calcium intake.
- Avoid under-nutrition, particularly the effects of severe weight-loss diets and eating disorders.
- Maintain an adequate supply of vitamin D.
- Participate in regular weight-bearing activity.
- Avoid smoking and second-hand smoking.
- Avoid heavy drinking.

Clinical assessment and treatment of osteoporosis

The previous section of the Compendium has identified a substantial number of risk factors for osteoporosis and fragility fractures. In the broadest sense, the population can be sub-divided into two distinct groups with respect to future fracture risk:

- Individuals with a history of fragility fracture: the secondary prevention population.
- Individuals without a history of fragility fracture: the primary prevention population.

The secondary prevention population is by definition a high fracture risk group. Individuals with a fragility fracture history should undergo clinical assessment and be offered osteoporosis treatment, where warranted. Disease models developed for several European countries have estimated the proportion of women aged 50 years and over who have sustained at least one fragility fracture [18]. This ranges from 10% in France to almost 23% in Sweden. This highlights the fact that at any point in time, the majority of older people lack a fracture history. As such, tools to stratify fracture risk across the highly heterogeneous primary prevention population are required. In this regard, the advent of absolute fracture risk calculators such as FRAX® provide a platform to readily identify individuals who should undergo further clinical assessment [55]. FRAX® can be accessed online at https://www.sheffield.ac.uk/FRAX/.

Clinical assessment

Clinicians use the following techniques to make a diagnosis of osteoporosis:

- BMD testing by dual-energy X-ray absorptiometry (DXA).
- X-Rays or Vertebral Fracture Assessment (VFA) to identify vertebral fractures.
- Measurement of Bone Turnover Markers (BTM) in the serum or urine.

The information obtained, in combination with clinical risk factors ascertained from the patient's medical history, will inform the inputs to the FRAX® fracture risk calculation. FRAX® estimates the patient's probability of sustaining a hip fracture or a major osteoporotic fracture over a 10-year period.

Bone density testing by DXA is a non-invasive, comparatively inexpensive, convenient diagnostic procedure which enables clinicians to stratify fracture risk of individuals. However, the advent of DXA technology has resulted in some unintended consequences. Importantly, the majority of individuals who sustain fragility fractures do not have a BMD T-score below -2.5 standard deviations, the WHO category for osteoporosis [5]. The majority of fracture patients have osteopenia rather than osteoporosis as defined by BMD [56], which has resulted in confusion among patients and generalists in the healthcare profession. In 2017, a perspective paper from leading clinicians in the field highlighted this issue:

> "Particularly harmful may be the term "osteoporotic fracture", which has been interpreted by some as requiring both an osteoporotic bone mineral density (BMD) value, i.e., a T-score ≤ -2.5, and fracture [57]."

The authors proposed that all fractures in older people should trigger secondary preventive assessment, including lifestyle, non-pharmacological and pharmacological interventions to reduce future fracture risk. Indeed, the limitations of DXA for identifying individuals who will experience a fragility fracture led to the development of the FRAX® calculator, which integrates BMD with other, at least partly BMD-independent risk factors.

Bone density testing has an additional limitation in that it provides a measure of the quantity of bone, but does not provide information on the quality of bone [58]. Moving forwards, new diagnostic modalities are required which can readily provide clinically meaningful information relating to the determinants of bone quality, which is likely to include measures of bone microarchitecture, turnover, mineralisation and accrual of damage.

Treatment of osteoporosis

During the last 25 years, a broad range of therapeutic options have become available to reduce an individual's risk of sustaining a fragility fracture. These medicines are available in a uniquely flexible array of dosing regimens, which includes daily, weekly or monthly oral tablets, daily, three-monthly and six-monthly injections, or annual infusions. The anti-fracture efficacy of the most commonly used agents for postmenopausal osteoporosis is summarised in table 3 [59].

Numerous national clinical guidelines are available to inform best practice. While the detail of these recommendations varies between countries, practically all guidelines advocate pro-active case-finding of fragility fracture patients and individuals at high risk of sustaining a first major fragility fracture. A recent systematic review noted that FRAX® has been incorporated into a substantial number of guidelines worldwide [60].

Table 3. Anti-fracture efficacy of the most commonly used treatments for postmenopausal osteoporosis [59, 61-63]

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	osteoporosis	established osteoporosis[a]	osteoporosis	established osteoporosis[a]
Alendronate	+	+	n/a	+ (including hip)
Risedronate	+	+	n/a	+ (including hip)
Ibandronate	n/a	+	n/a	+[b]
Zoledronic acid	+	+	n/a	+[c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	n/a	n/a
Abaloparatide	+	+	n/a	+[c]
Teriparatide and PTH	n/a	+	n/a	+
Denosumab	+	+[c]	+ (including hip)	+[b]

n/a 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 fracture

As illustrated previously in figure 4 of this Compendium, the incidence of fragility fractures increases dramatically with increasing age [10]. In 2014, an ESCEO expert working group evaluated management of osteoporosis in the "oldest old" segment of the population (i.e. individuals over 80 years of age) [64]. The authors noted that undertreatment of osteoporosis in this age group was potentially attributable to the perception that osteoporosis treatments must be used in the long-term to demonstrate a fracture reduction benefit. Given that studies of many of the agents described above reported statistically significant benefits by 12 months of treatment, this concern is without foundation. Further, the authors highlighted several precautionary measures that can be taken to ensure patient safety in this population.

Recently, ESCEO and IOF working groups have considered currently unmet needs in the management of individuals who are at high risk of sustaining fragility fractures [65, 66]. These groups concluded that the future research agenda should focus on the following areas:

- Identification of risk factors for imminent fractures.
- Periods in the life-cycle of high fracture risk.
- The most appropriate treatments for individuals at high fracture risk.
- The role of preventive surgical intervention for individuals at imminent and/or very high risk of hip fracture.
- Optimal implementation strategies in primary, secondary and tertiary care.

Models of care

Secondary fracture prevention

Case finding individuals who have sustained fragility fractures represents the obvious first step in implementation of a systematic approach to fragility fracture prevention [9]. However, numerous audits conducted throughout the world have identified a persistent and pervasive secondary prevention care gap [18]. In 2017, an ESCEO expert consensus meeting highlighted that approximately one-fifth of eligible fracture patients receive osteoporosis treatment after a fracture, and that considerable variation is evident between countries [66]. Despite effective treatments having been available since the mid-1990s and publication of many national clinical guidelines which advocate assessment and treatment of fracture patients, osteoporosis is neither assessed nor treated in the majority of cases.

In response to this missed opportunity for intervention, models of care have been developed to ensure that fracture patients reliably receive osteoporosis management and interventions to prevent future falls. Two complementary models of care have been established in a growing number of countries [18, 67-69]:

- **Orthogeriatric Services (OGS):** Also known as Orthopaedic-Geriatric Co-Care Services or Geriatric Fracture Centres, OGS focus on delivering best practice for hip fracture patients. This includes expedited surgery, optimal management of the acute phase through adherence to clinical standards overseen by senior orthopaedic and geriatrician/internal medicine clinicians, and delivery of secondary fracture prevention addressing both bone health and falls risk.
- **Fracture Liaison Services (FLS):** A FLS is a coordinated model of care for secondary fracture prevention. A FLS ensures that all patients aged 50 years or over, who present to urgent care services with a fragility fracture, undergo fracture risk assessment and receive treatment in accordance with prevailing national clinical guidelines for osteoporosis. The

FLS also ensures that falls risk is addressed among older patients through referral to appropriate local falls prevention services.

Detailed analysis of the clinical effectiveness and cost-effectiveness of OGS and FLS was the subject of a recent review article [67]. In summary, OGS in combination with national hip fracture registries have been demonstrated to transform care of hip fracture patients. The UK National Hip Fracture Database (NHFD) is currently the largest continuous audit of hip fracture care in the world, with more than 500,000 cases entered since launch in 2007. The NHFD, in combination with national clinical standards [70] and a major workforce development program has resulted in widespread implementation of OGS in UK hospitals during the last decade. In 2015, 97% of patients underwent bone health and falls prevention assessments [71].

In hospitals without an OGS, the FLS provides secondary preventive care for all fragility fracture patients. In hospitals with an OGS, the FLS provides care specifically for non-hip fragility fracture patients, which usually represents 80% of the entire fracture case load. FLS have been shown to dramatically improve osteoporosis treatment rates for fragility fracture patients and reduce secondary fracture incidence [67]. Further, FLS may have potential beneficial effects on mortality outcomes. Patients followed up in a FLS in the Netherlands had a significant reduction in mortality of 35% over 2 years of follow-up when compared with those who underwent standard non-FLS care [72].

Widespread implementation of FLS is the objective of IOF's flagship initiative, the Capture the Fracture® Programme [68]. The Capture the Fracture® Programme, hosted on http://www.capturethefracture.org/, provides resources, best practice guidance, and global recognition to help support the implementation of new FLS or improve existing FLS worldwide.

Primary fracture prevention

> "Secondary prevention is the single most important, immediate mechanism to directly improve patient care and reduce spiraling fracture related healthcare costs. The ultimate goal in the longer term would be the prevention of the first fracture, and advances in fracture risk assessment during the last decade provide a platform for development of clinically effective and, crucially, cost-effective approaches."
>
> World Osteoporosis Day Report 2016 [73]

Once a health system has implemented a systematic approach to secondary fracture prevention, attention must be focused on primary prevention of major fragility fractures. Such a strategy will likely be achieved through pursuit of several "tracks":

- Consistent bone health assessment and treatment for individuals taking medicines which induce osteoporosis.
- Incorporation of routine bone health assessment and treatment for individuals living with diseases related to osteoporosis and fragility fractures.
- Systematic application of tools such as FRAX® to risk stratify the older population served by a medical practice, hospital or entire health system.
- Incorporation of fracture risk assessment into routine practice by primary care providers when interacting with older individuals.

Two leading health systems in the United States have implemented systematic approaches to primary fracture prevention in parallel to secondary prevention strategies, the Kaiser Permanente Health Bones Program [74] and the Geisinger Health System Hi-ROC Program [75]. Recently, evidence from the UK SCOOP trial, has demonstrated that actively screening older women for fracture risk (using FRAX®) in the primary care setting leads to a reduction in the risk of incident hip fracture [76].

Public awareness of the importance fracture prevention

First and foremost, the bone health community globally must develop public awareness campaigns which ensure that individuals who sustain fragility fractures understand that osteoporosis was the likely underlying cause of their fracture. Award-winning campaigns such as 2Million2Many developed by the National Bone Health Alliance (NBHA) in the United States provide a successful case study which could inform efforts elsewhere [77]. The 3.6 metre by 3.6 metre "Cast Mountain" installation shown in figure 6 served as a physical representation of the 5,500 fractures which occur daily among people aged 50 years and over in the US. The key messages for 2Million2Many are very simple and compelling:

- Every year, there are two million bone breaks that are no accident (in the USA).
- They are the signs of osteoporosis in people as young as 50.
- But only 2 out of 10 get a simple follow-up assessment.
- Together, we can break osteoporosis before it breaks us. But we must speak up. Remember:
    - Break a bone, request a test.

Supplementary campaigns which put the benefits of osteoporosis treatment, as compared to the risks, into context, and highlight the importance of staying on treatment will contribute to improved long-term management of osteoporosis. In this regard, taking into account patients' preferences regarding the attributes of an optimal osteoporosis treatment may play an important role in enhancing adherence with treatment in the long-term. In 2017, a discrete choice experiment conducted in seven European countries reached the following conclusions [78]:

- Statistically significant differences existed between patients' preferences in different countries.
- In all countries, patients preferred treatment with higher effectiveness and less frequent dosing (i.e. 6-monthly subcutaneous injection was preferred to weekly oral tablets).
- In five countries, patients preferred monthly oral tablets or annual intravenous injections over weekly oral tablets.
- In three countries, where out-of-pocket cost was included as an attribute, lower costs significantly influences treatment preference.

Figure 6. US National Bone Health Alliance 2Million2Many "Cast Mountain" [77]

(Reproduced with kind permission of the National Bone Health Alliance in the United States)

THE GLOBAL BURDEN

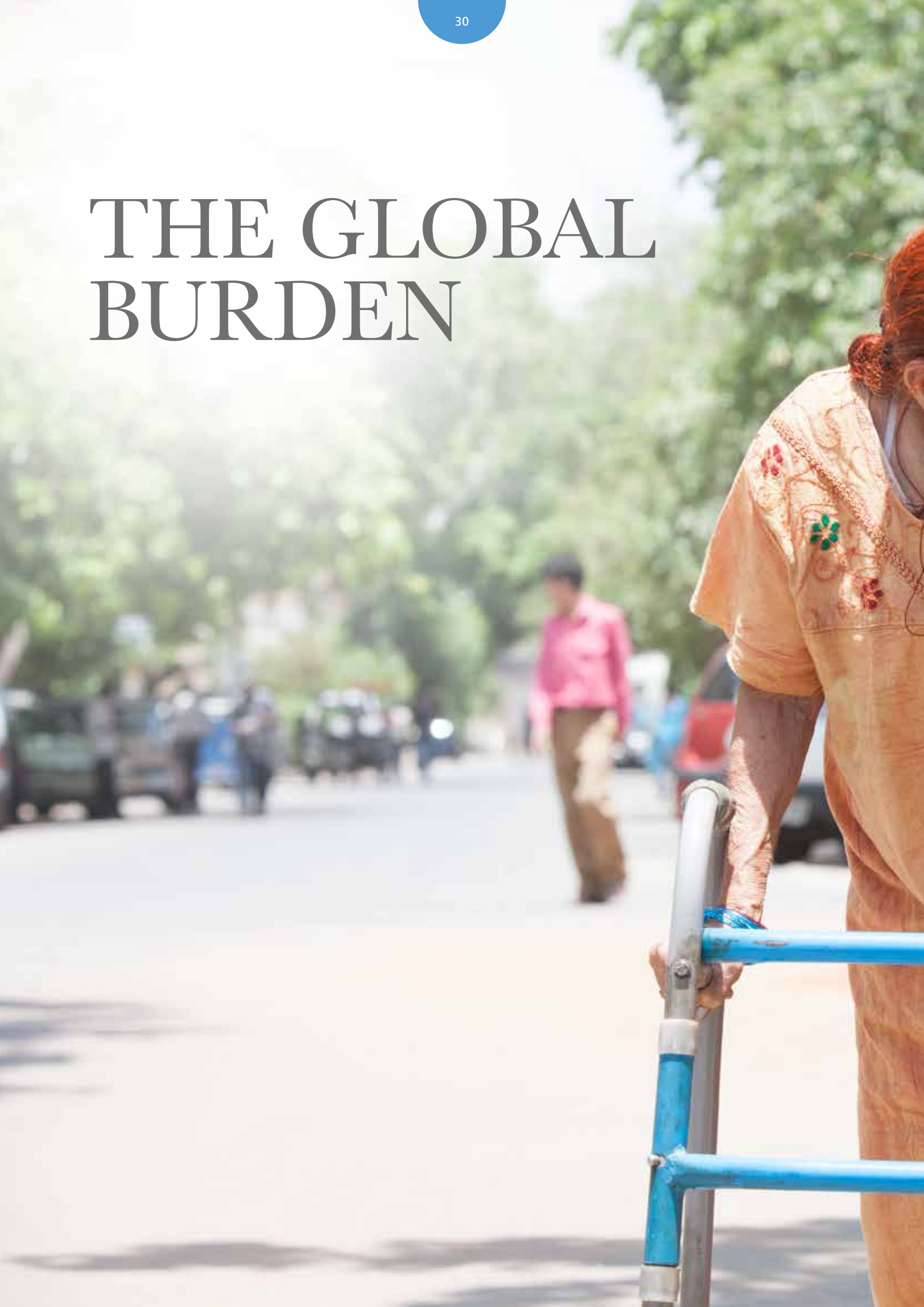


Photo: Gilberto D Lontro/IOF

THE GLOBAL BURDEN

This section of the Compendium considers the global epidemiology of fragility fractures, regional disparities, the human costs and socio-economic burden imposed by these fractures.

In the year 2000 there were an estimated 9.0 million fragility fractures, of which 1.6 million were at the hip, 1.7 million at the forearm, 1.4 million were clinical vertebral fractures, 0.7 million at the humerus and 3.6 million fractures at other sites [79]. The total disability-adjusted life-years lost was 5.8 million, of which half were accounted for by fractures that occurred in Europe and the Americas. Worldwide, fragility fractures accounted for 0.83% of the global burden of non-communicable disease.

Global incidence, prevalence and future projections

As the population of the world has aged over the last three decades, the incidence of hip fracture has increased significantly. In 1990, it was estimated that 1.3 million hip fractures occurred worldwide and the prevalence of hip fracture sufferers living with disability was almost 4.5 million [80]. By 2010, the global incidence of hip fracture was estimated to have increased to 2.7 million cases per year [81]. The most recent estimate of the prevalence of any fragility fracture, defined as the number of individuals suffering disability, was 56 million worldwide in year 2000 [79].

In 1997, worldwide projections for hip fracture incidence were made for the period 1990 to 2050 [82]. Assuming no change to the age- and sex-specific incidence, it was projected that almost 4.5 million hip fractures would occur in 2050. However, making modest changes to the assumptions concerning secular trends suggested that this estimate could be much higher, in the range 7 million to 21 million cases. Notably, this analysis estimated that almost 1.9 million hip fractures would occur in 2010, which is considerably lower than the more recent estimate of 2.7 million cases cited above for same year [81].

In 2015, Kanis and colleagues sought to quantify the number of individuals worldwide aged 50 years or more at high risk of fracture in the years 2010 and 2040 [83]. High fracture probability was defined as the age-specific 10-year probability of suffering a major osteoporotic fracture (i.e. hip, humeral, wrist or clinically apparent vertebral fracture) which was equivalent to that of a woman with a body mass index (BMI) of 24 kg/m^2 and a prior fragility fracture, but with no other clinical risk factors for fracture. In 2010, 21 million men (3.1%) and 137 million women (18.2%) had a fracture probability at or above the threshold. By 2040, the number of men and women combined who will be above the threshold is expected to almost double, from 158 million in 2010 to 319 million in 2040.

Regional disparity

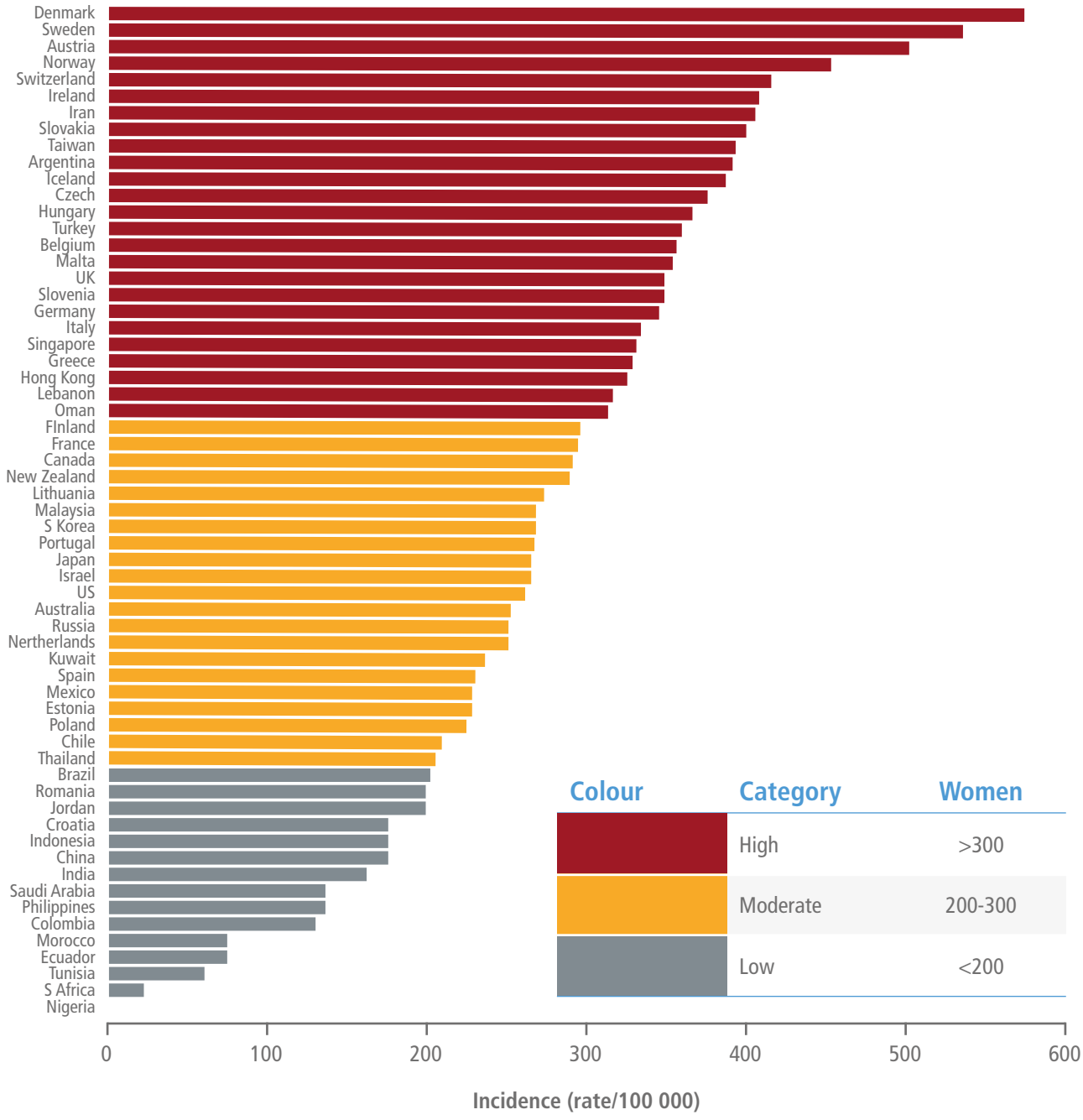
Marked variations in the incidence of hip fractures, the prevalence of vertebral fractures and the 10-year probability of major osteoporotic fractures have been reported for different regions of the world.

The findings of a systematic literature review of hip fracture incidence studies are shown in figure 7 for women [84]. Age-standardised rates varied approximately 10-fold for both men and women. Why hip fracture risk varies so much between countries is not currently known. The authors suggest that environmental factors may play a greater role than genetic factors. Epidemiological studies of immigrant populations lend support to this hypothesis. While African Americans living in the United States have lower fracture probabilities than their Caucasian countrymen and women, their hip fracture risk is higher than native Africans [85]. Similar patterns are observed for the Japanese population of Hawaii [86] and Chinese living in Hong Kong or Singapore [84].

During the next 3 decades, the demographic shift

in Asia, Africa and Latin America will result in these regions bearing the brunt of the increase in hip fracture incidence worldwide. In absolute terms, Asia faces the most marked increases, with projections suggesting 1 million cases annually in 2030 and 2 million annually in 2050, estimates which assume no increase in age- and sex-specific rates which were modelled in 1997 [82].

Figure 7. Age-standardised annual incidence of hip fractures in women (per 100,000) according to country, colour-coded as high, moderate or low incidence [84]



(Reproduced from *Osteoporos Int* 2012 Sep;23(9):2239-56 with kind permission of Springer)

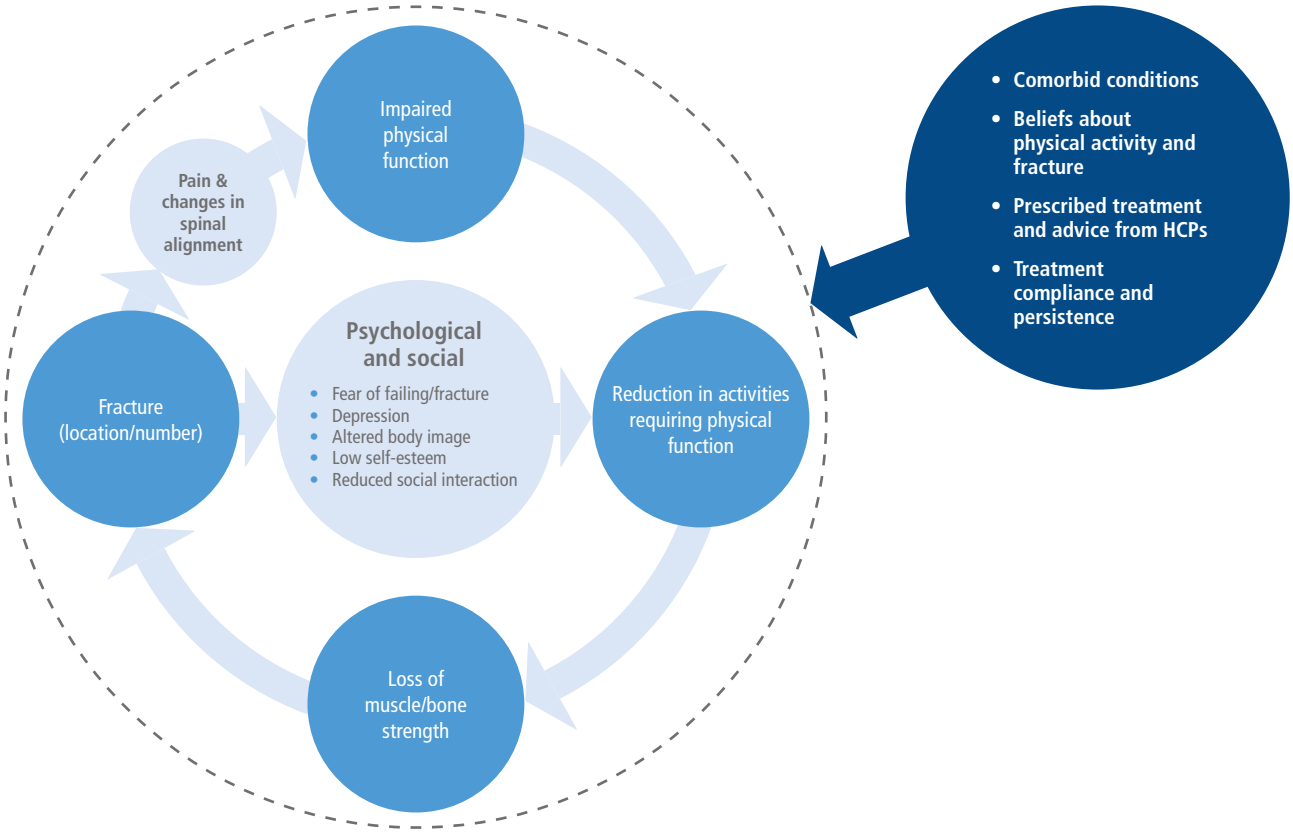
In 2017, El-Hajj Fuleihan and colleagues investigated the prevalence and incidence of vertebral fractures worldwide [87]. In terms of prevalence, the highest rates were reported for Scandinavia (26%), intermediate rates for Western Europe, USA and Mexico (20%), and low rates for Latin America (15%). Studies concerned with the incidence of vertebral fractures were comparatively sparse. Studies which combined individuals with vertebral fractures who were either hospitalised or ambulatory indicated that the highest age-standardised rates were evident in South Korea, the United States and Kong Kong, while the lowest rate was in the UK.

In terms of the regional disparity of the 10-year probability of major osteoporotic fractures, the majority (55%) of individuals deemed to be at or above the high fracture probability in 2010, as described above, lived in Asia [83].

Human costs

Fragility fractures impose a substantial burden on individuals who suffer them, their carers and family members. When a fracture occurs, a cycle of impairment follows, as illustrated in figure 8. A correlation exists between the number of fractures an individual suffers and decline in physical function and health-related quality of life (HRQL) [88, 89].

Figure 8. The cycle of impairment and fracture in osteoporosis [90]



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Hip fractures are particularly devastating:

- Less than half of individuals who survive a hip fracture will walk unaided again [91] and a significant proportion will never regain their former degree of mobility [92].
- A year after hip fracture, 60% of sufferers require assistance with activities such as feeding, dressing or toileting, and 80% need help with activities such as shopping or driving [93].
- Between 10-20% of sufferers will become residents of care homes in the year following a hip fracture [94-96].

Vertebral fractures adversely affect sufferers in many ways:

- Back pain, loss of height, deformity and immobility [97, 98].
- Loss of self-esteem, distorted body image and depression [99-101].
- A significant negative impact on routine activities of daily living [102].

Survival is also impacted by hip and vertebral fractures. Mortality during the 5 years after a hip or vertebral fracture is approximately 20% higher than would be expected, with most premature deaths occurring within the first 6 months after hip fracture [93].

Non-hip, non-vertebral (NHNV) fractures account for approximately two-thirds of all fragility fractures. The Global Longitudinal Study of Osteoporosis in Women (GLOW) has reported that NHNV fractures have a detrimental effect on HRQL [103]. Further, analysis of data from the Canadian Multicentre Osteoporosis Study (CaMOS) has demonstrated that NHNV fractures also are associated with increased mortality [104].

Improving the quality of life of individuals who are living with osteoporosis should be a focus for interventions to prevent and treat the disease. Consequently, there has been considerable research activity to develop effective measures of HRQL, which can be classified as generic or specific tools [105]. Six specific tools have been developed for use in the context of osteoporosis:

- Quality of life questionnaire of the European foundation for osteoporosis (QUALEFFO) [98].
- Quality of life questionnaire in osteoporosis (QUALIOST) [106].
- Osteoporosis assessment questionnaire (OPAQ) [107].
- Osteoporosis quality of life questionnaire (OQLQ) [108].
- Osteoporosis functional disability questionnaire (OFDQ) [109].
- Osteoporosis-targeted quality of life questionnaire (OPTQoL) [110].

Whilst the direct benefits of anti-osteoporosis therapies on HRQL remain to be elucidated, recent findings from the UK SCOOP trial suggest that treatment on the basis of population screening is likely to improve HRQL compared with usual care [76]. One recent cohort study incorporated HRQL measurement using the EuroQol- 5 Dimension (EQ-5D) standardised instrument into follow-up and demonstrated modest increases in values with treatment, albeit in a non-intervention design [111].

Socio-economic burden

Global health expenditure attributable to osteoporosis is currently not known, on account of a lack of data on fracture rates for many developing countries [18]. The most obvious example is India, which is set to become the world's most populous country within the next few decades. However, information is available for many countries/regions, including the 4 largest economies in the world (USA, European Union [EU], China and Japan), which provide an indication of the immense financial burden osteoporosis imposes on our global society.

United States of America

In 2007, Burge and colleagues modelled the incidence and economic burden of fragility fractures in the United States for period 2005 to 2025 [112]. Inpatient, outpatient and long-term care costs were included in the model. In the base year (2005), hip fractures accounted for 72% of all costs but just 14% of fractures. The projected costs for years 2015, 2020 and 2025 were US$20 billion, US$22 billion and US$25 billion, respectively.

European Union

In 2013, IOF in collaboration with the European Federation of Pharmaceutical Industry Associations (EFPIA) published a comprehensive report on osteoporosis in the EU which included the economic burden [113]. For year 2010, the total cost of osteoporosis in the EU, including pharmaceutical intervention, was estimated to be Euro 37 billion (US$40 billion). Two-thirds of this cost was attributed to treating incident fractures, long-term care accounted for 29% and pharmacological prevention just 5%. Excluding the cost of pharmacological prevention, hip fractures represented 54% of the costs.

China

In 2015, Chen and colleagues modelled the incidence and economic burden of fragility fractures in China for period 2010 to 2050 [114]. The projected costs to the Chinese healthcare system for all osteoporosis-related fractures for the years 2015, 2035 and 2050 were US$11 billion, US$20 billion and US$25 billion, respectively.

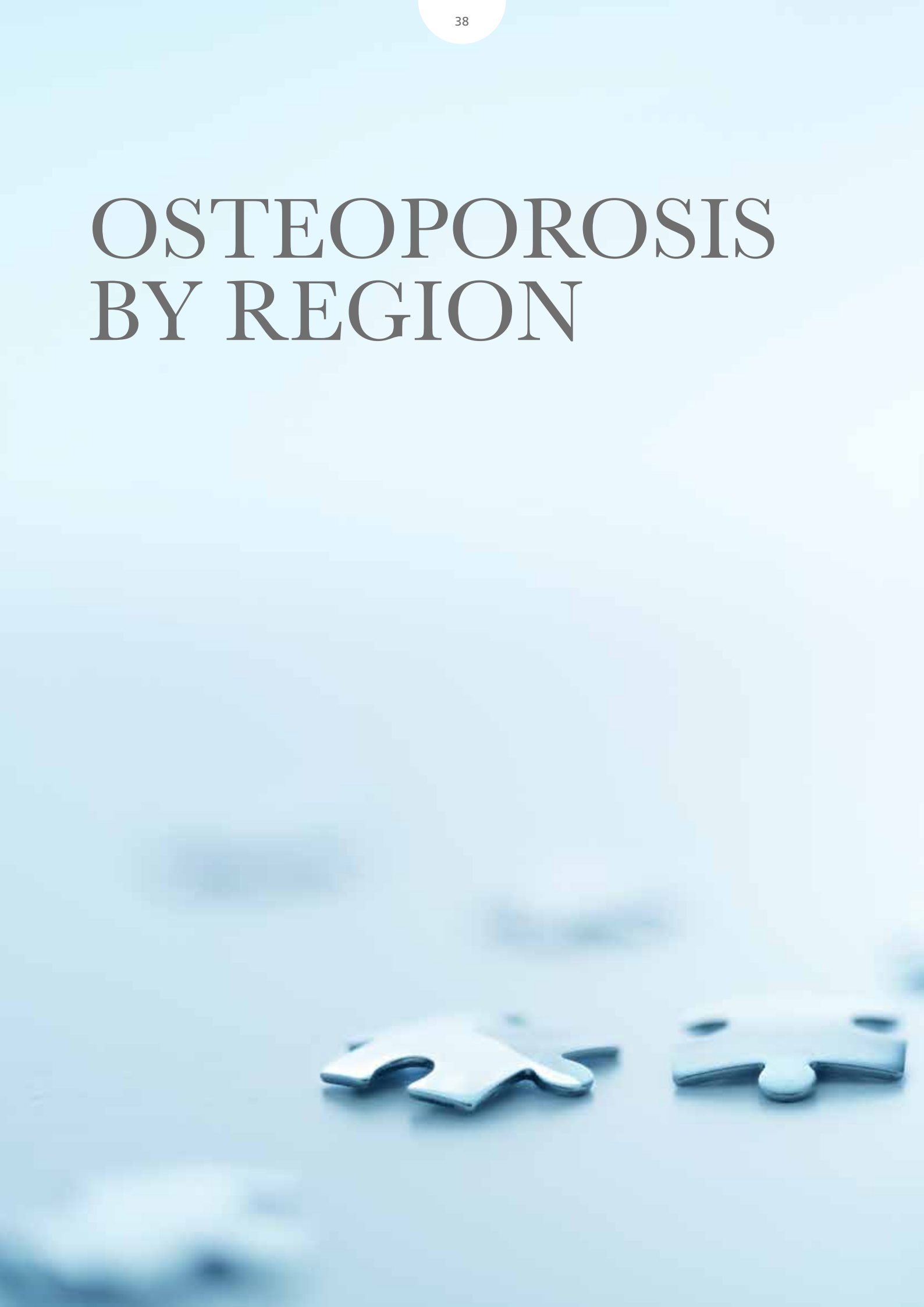
Japan

In 2016, the Japanese Ministry of Health, Labour and Welfare undertook a survey to quantify the costs related to deficiencies of bone density and bone structure, as well as fracture-related expenditure in the population aged 65 and over [115]. In 2013, total costs were estimated to be almost JPY 944 billion (US$8 billion).

The impact of fracture in the workplace

The proportion of older people remaining active in the workforce is growing as the world's population ages. As such, health conditions associated with ageing have the potential to adversely affect work place productivity. In 2014, investigators from The Netherlands evaluated total costs of clinical fractures in osteoporotic patients aged 50 years and older [116]. Indirect costs accounted for half of total costs and sick leave for employed patients accounted for more than 80% of the mean indirect costs for a fracture.

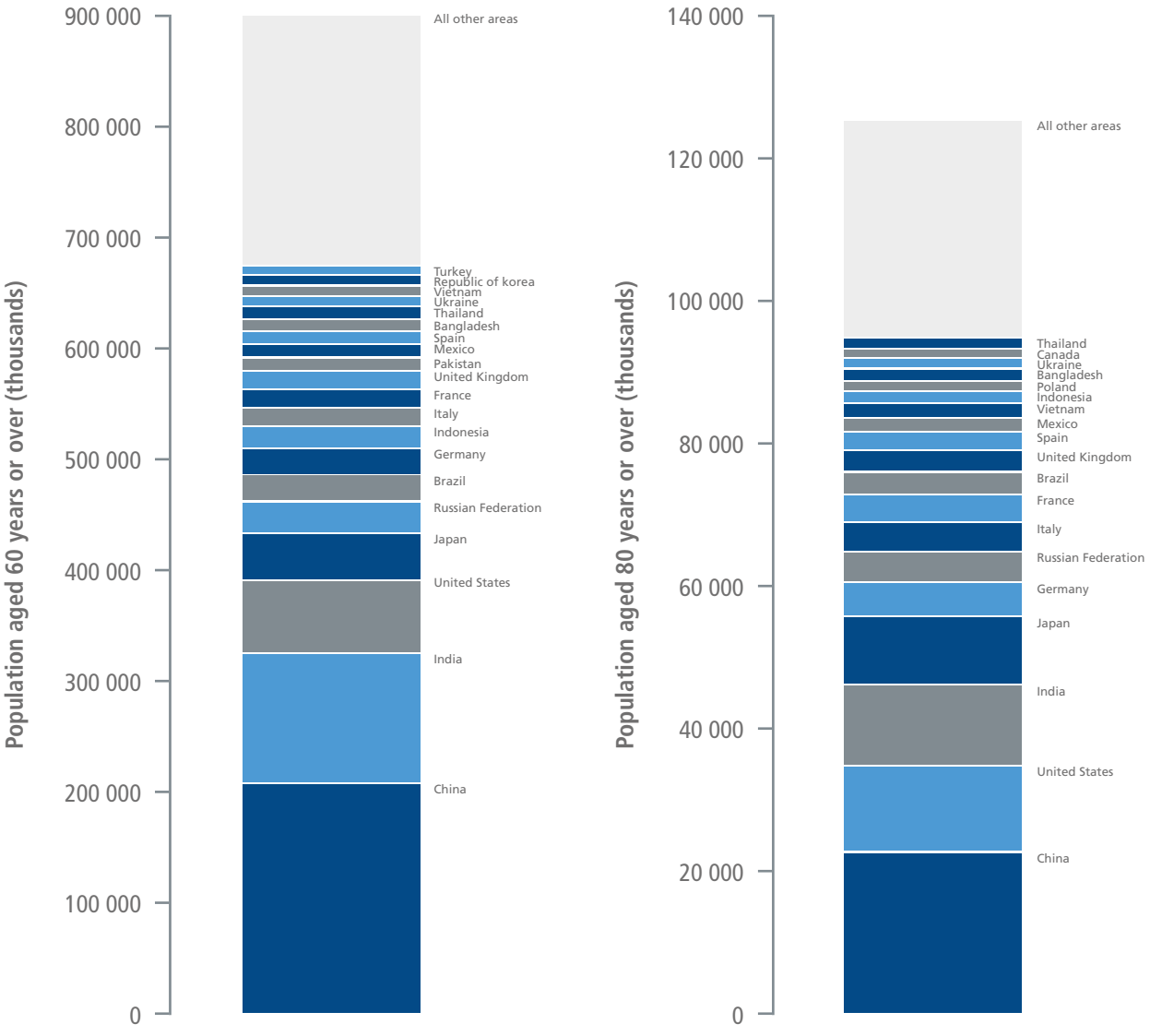
OSTEOPOROSIS BY REGION



OSTEOPOROSIS BY REGION

The world's population is ageing, and ageing fast. In 2015, the United Nations report on World Population Ageing described the demographic shift for the various regions of the world [117]. The relative distribution of the world's older population in 2015, as illustrated in figure 9, is set to change dramatically. Consequently, during the first half of this century, absolute hip fracture incidence will remain high and costly in the West and will increase enormously in the East. This section of the Compendium considers the current and future impact of osteoporosis on the regional populations of the world.

Figure 9. Population aged 60 years or over and aged 80 years or over by country, 2015 [117]



(Reproduced from *World Population Ageing Report 2015* with kind permission of the United Nations Department of Economic and Social Affairs Population Division)

Following a vertebral fracture, a bone mineral density test revealed that Ms. Tang (66) had osteoporosis. She is strict about taking her medication, eating bone-healthy foods, and taking regular exercise. She says: "Luckily I never suffered another fracture, otherwise my life would be very different now."

Asia-Pacific

The Asia-Pacific region is currently home to more than 4.4 billion people. In 2016, the United Nations Economic and Social Commission for Asia and the Pacific (ESCAP) Social Development Division estimated that 12.4% of this population was aged 60 years or older, a figure which is set to rise to 25.1% by 2050 [118]. Further, the proportion of the population classified as the "oldest-old" (i.e. 80 years or older) will increase from 12.3% in 2016 to 19.9% in 2050. Accordingly, by the middle of this century, 1.3 billion people in Asia will have celebrated their 60th birthday, and more than a quarter of a billion will have celebrated their 80th birthday.

In 2013, IOF published the second Asia-Pacific Regional Audit which provided an overview of the epidemiology, costs and burden of osteoporosis for 16 jurisdictions: Australia, China, Chinese Taipei, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Pakistan, Philippines, Republic of Korea, Singapore, Sri Lanka, Thailand and Vietnam [119]. Key findings from the IOF Audit, and more recent studies where available, relating to epidemiology, mortality, health expenditure, and access and reimbursement follow.

Epidemiology

On account of the mass ageing of the population of this region, it has been projected that half of all hip fractures will occur in Asia by 2050 [120]. Estimates of the annual incidence of hip fracture in the most populous countries in the region are as follows:

- **China:** The incidence of 411,000 cases of hip fracture in 2015 is projected to exceed 1 million cases by 2050 [114].
- **India:** Currently, there is a paucity of hip fracture epidemiology available for India. Application of hip fracture rates reported for the Rohtak district of North India in 2013 [121] to the most recent United Nations Population Projection for India [122] suggests that 306,000 hip fractures occurred in 2015 [73].
- **Indonesia:** The IOF Audit reported that 43,000 hip fractures occurred in men and women aged over 40 years in 2010 [119].
- **Japan:** In 2012, the annual incidence of hip fracture was estimated to be almost 176,000 cases [123].

Mortality

According to the 2013 IOF Audit, in Pakistan, Philippines, Sri Lanka and Vietnam only half of hip fracture patients receive surgery [119]. While published studies are currently not available, post-fracture mortality is likely to be very high for these individuals.

In China, one year mortality among hip fracture patients in Beijing is 23%, representing an approximately two-fold excess compared to controls [124]. A small-scale study in India reported that at least a quarter of hip fracture patients died within a year of surgery [125]. In 2007, Tsuboi and colleagues described post-hip fracture mortality for a cohort from Nagoya in Japan [126]. The overall survival rates at one, two, five and ten years after fracture were 81%, 67%, 49% and 26%, respectively. Mortality rates were approximately double that of the general population throughout the entire period of observation.

Health expenditure

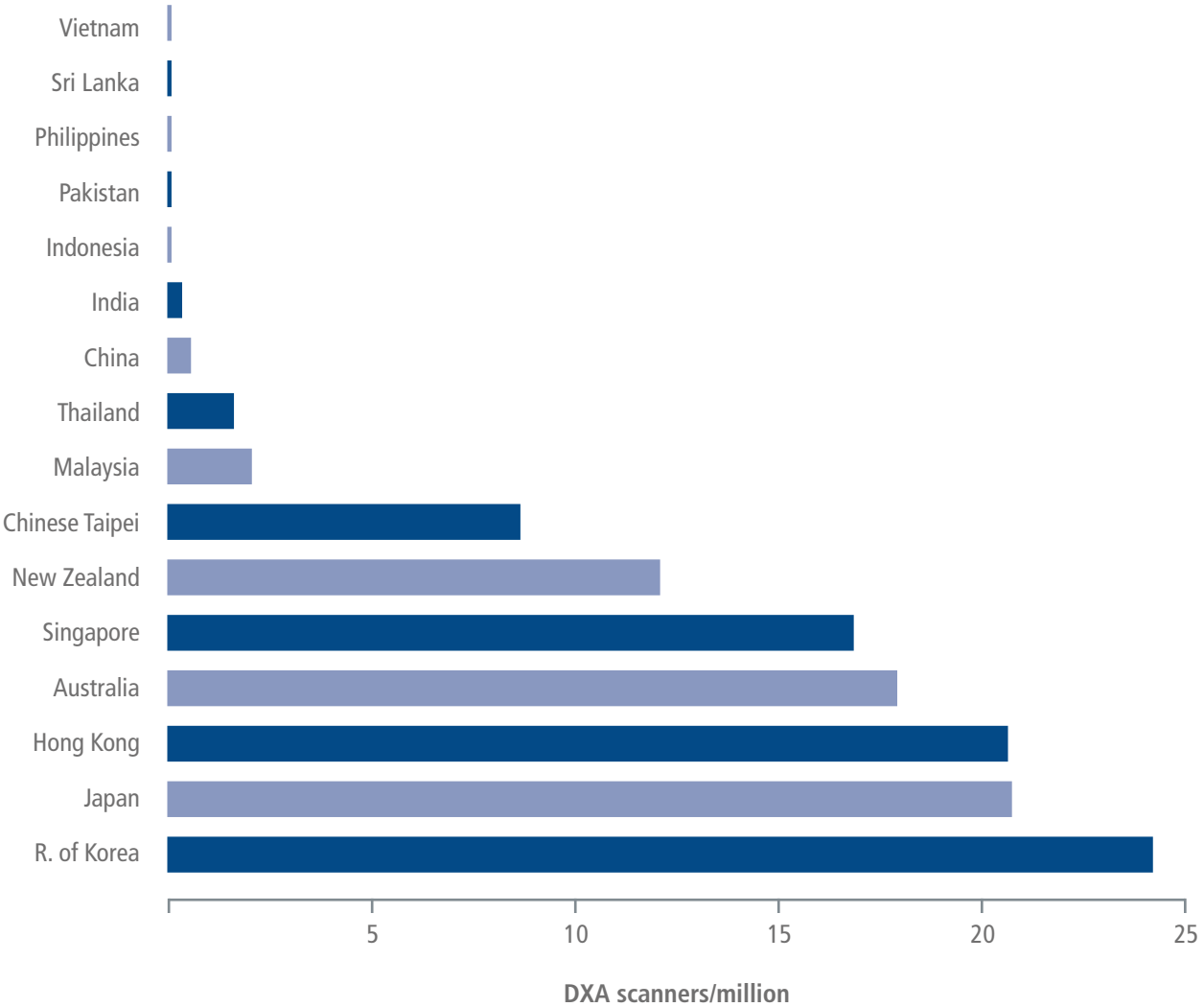
The costs of fragility fractures in this region are currently enormous, and set to rise substantially in the coming decades:

- **Australia:** Osteoporosis Australia estimates the total costs of fragility fractures to be AU$2.2 billion (US$1.7 billion) in 2017, increasing to AU$2.6 billion (US$2 billion) by 2022 [127].
- **China:** The projected costs to the Chinese healthcare system for all osteoporosis-related fractures for the years 2015 and 2050 are US$11 billion and US$25 billion, respectively [114].
- **Japan:** In 2013, total costs related to fragility fractures in the population aged 65 and over were estimated to be almost JPY 944 billion (US$8 billion) [115].
- **Republic of Korea:** In 2011, the total societal cost of osteoporotic fractures was estimated to be US$149 million [128].

Access and reimbursement

The 2013 IOF Audit documented considerable variation in access and reimbursement for diagnosis of osteoporosis and treatment [119]. As illustrated in figure 10, the number of DXA scanners per million of population varied from 24 in the Republic of Korea to less than 1 in Sri Lanka and Vietnam.

Figure 10. Number of DXA scanners per million of population in Asia-Pacific [119]



Country-specific FRAX® Fracture Risk Assessment Tools are available for the following countries in the Asia-Pacific region [55]: Australia, China, India, Indonesia, Japan, New Zealand, Philippines, Singapore, Republic of Korea, Sri Lanka, Taiwan and Thailand.

Reimbursement of osteoporosis treatment varied greatly across the region, ranging from 0 to 100% reimbursement for the most commonly prescribed medications.

Central Asia

In 2010, IOF published the Eastern European and Central Asian Regional Audit which provided an overview of the epidemiology, costs and burden of osteoporosis for 21 countries, including 4 countries in Central Asia: Republic of Kazakhstan, Kyrgyz Republic, Republic of Tajikistan and Republic of Uzbekistan [129]. Key findings from the IOF Audit, and more recent studies where available, relating to epidemiology, mortality, health expenditure, and access and reimbursement follow.

Epidemiology

Epidemiological studies in this region are limited. In 2009, government statistics suggested that 2,238 hip fractures occurred in the Republic of Kazakhstan [129]. In 2016, Tlemissov and colleagues described the epidemiology of geriatric trauma in an urban Kazakhstani setting [130]. More than 80% of injuries were the result of a fall. The IOF Audit estimated the incidence of hip fracture in the Kyrgyz Republic to be 2,300 cases per year, while no data was available for the Republic of Tajikistan [129]. In 2016, Ismailov and colleagues determined the prevalence of osteoporosis among Uzbek women aged over 50 years to be 36% [131]. The Research Institute of Traumatology and Orthopaedics of the Ministry of Public Health estimate that 30,000 Uzbeks have osteoporosis and 150,000 have osteopenia [129].

Mortality

The IOF Audit highlights that a significant proportion of hip fracture patients in this region do not undergo surgery. Accordingly, post-hip fracture mortality is likely to be significantly higher than in countries where surgical intervention is standard practice.

Health expenditure

The costs of fragility fractures to health systems in this region have not been studied.

Access and reimbursement

The IOF Audit documented low levels of access to DXA scanners and reimbursement of treatment across this region. Country-specific FRAX® Fracture Risk Assessment Tools are currently not available for the countries of the Central Asia region.

Europe

In 2015, the combined population of the 28 European Union member states (EU-28) was 508.5 million [132]. Almost a fifth (18.9%) of this population was aged 65 years and over. By 2050, Eurostat projections suggest that 28.1% of the EU-28 population will be aged 65 years and over, representing 147.7 million people. More than 57 million of these will be aged 80 years and over (n.b. the departure of the United Kingdom from the EU is not reflected in these figures).

In 2013, IOF in collaboration with the European Federation of Pharmaceutical Industry Associations (EFPIA) undertook a comprehensive osteoporosis and fragility fracture audit of the 27 EU member states at the time [113, 133, 134]. Key findings from the IOF Audit, and more recent studies where available, relating to epidemiology, mortality, health expenditure, and access and reimbursement follow. Additional information relating to Switzerland [135], the Russian Federation [136] and several other Eastern European/Western Asian countries [129] is also available.

Epidemiology

In 2010, it was estimated that 22 million women and 5.5 million men in the EU had osteoporosis in accordance with the diagnostic criterion of the WHO [113]. The total number of new fractures in the same year was estimated to be 3.5 million, comprised of 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million other fractures. In addition, the number of individuals with 'prior' fracture was estimated. A prior fracture was defined as a fracture in an individual who was alive during 2010, which had occurred after the age of 50 years and before 2010. The unit was the individual so that multiple fractures at the same site in one individual were only counted as one prior fracture of that site. The prevalence of prior hip fracture was 3.3 million individuals and prior clinical vertebral fracture was 3.5 million individuals. Studies from France [137], Germany [138], Italy [139], Sweden [140] and the UK [141] suggest that prior hip and vertebral fractures combined account for approximately 30% of all prior fractures. Accordingly, it is likely that 22.7 million individuals in the EU had a prior fracture history in 2010.

A total of 74,000 fragility fractures occurred in Switzerland in 2010, including 14,000 hip fractures [135]. In the same year, it was estimated that 112,000 hip fractures occurred in the Russian Federation, a figure expected to rise to 159,000 by 2035 [136]. The IOF Eastern European and Central Asian Regional Audit published in 2010 [129] included the following Eastern European/ Western Asian countries which were not included in the subsequent EU audit described previously [113, 133, 134]: Armenia, Azerbaijan, Republic of Belarus, Georgia, Republic of Moldova, Russian Federation and Ukraine. With the exception of the Russian Federation, epidemiological studies are scarce in these countries.

Mortality

In 2010, the number of deaths causally related to fractures in the EU was estimated at 43,000 [113]. Approximately half of fracture-related deaths in women were attributable to hip fractures, 28% to clinical vertebral fractures and 22% to other fractures. The IOF Eastern European and Central Asian Regional Audit reported high rates of post-hip fracture mortality in the Russian Federation and some of the Eastern European/Western Asian countries [129]. In the Russian Federation, 33-40% of hip fracture patients were hospitalised and just 13% received surgical intervention. Consequently, mortality rates for hip fracture in some Russian cities reached 50%.

Without proper surgical treatment, hip fracture patients are invariably left bedridden and unable to walk. This Russian patient suffered a fracture of the femur (hip) several years ago. She did not receive surgical treatment, or treatment of any kind. Now, even several years later, she is unable to walk. Twice a day, everyday, her husband pushes her in a wheelbarrow all the way to town. This way she is at least able to leave the house and maintain some social contact.

Health expenditure

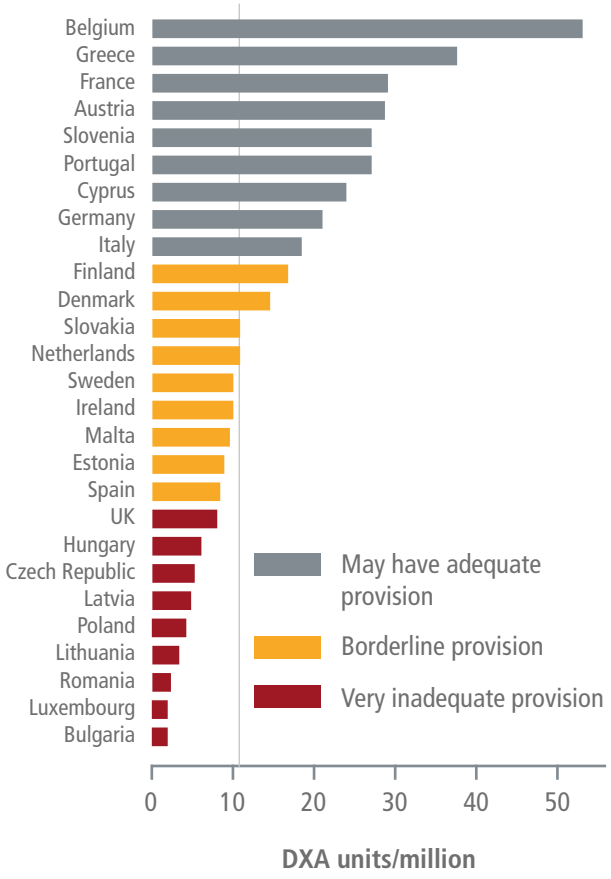
In 2010, the cost of osteoporosis in the EU, including pharmacological intervention, was estimated to be Euro 37 billion (US$40 billion) [113]. Two-thirds of this costs was attributable to treatment of new fractures, long-term care accounted for 29% and pharmacological prevention just 5%. Excluding cost of pharmacological prevention, hip fractures accounted for 54% of the costs. Assuming a Quality-Adjusted Life Year (QALY) to be valued at twice the GDP per capita, the total cost of osteoporosis in 2010 would be Euro 98 billion (US$106 billion). In 2010, the economic burden of new and prior fragility fractures in Switzerland was estimated to be CHF 2 billion (US$2 billion).

The costs of fragility fractures to the Russian Federation and health systems in the Eastern European/Western Asian countries have not been studied.

Access and reimbursement

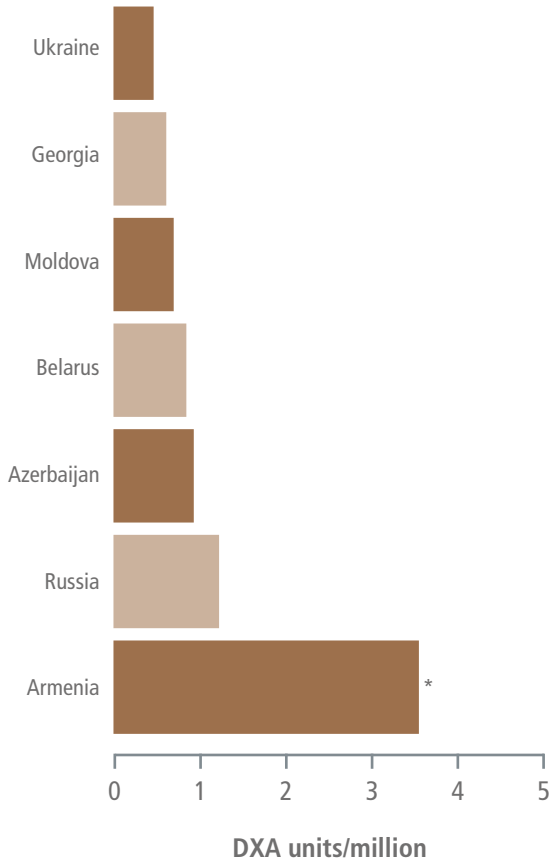
The IOF-EFPIA EU audit documented considerable variation in access and reimbursement for diagnosis of osteoporosis and treatment [113, 133, 134]. As illustrated in figure 11a, the number of DXA scanners per million of population varied from 53 in the Belgium to 1.2 in Bulgaria. Access to DXA is considerable lower in the Eastern European/Western Asian countries, as illustrated in figure 11b.

Figure 11a. Number of DXA scanners per million of population in the European Union [134]



(Reproduced from *Arch Osteoporos*. 2013;8:144 with kind permission of Springer)

Figure 11b. Number of DXA scanners per million of population in Eastern Europe/Western Asia [129]



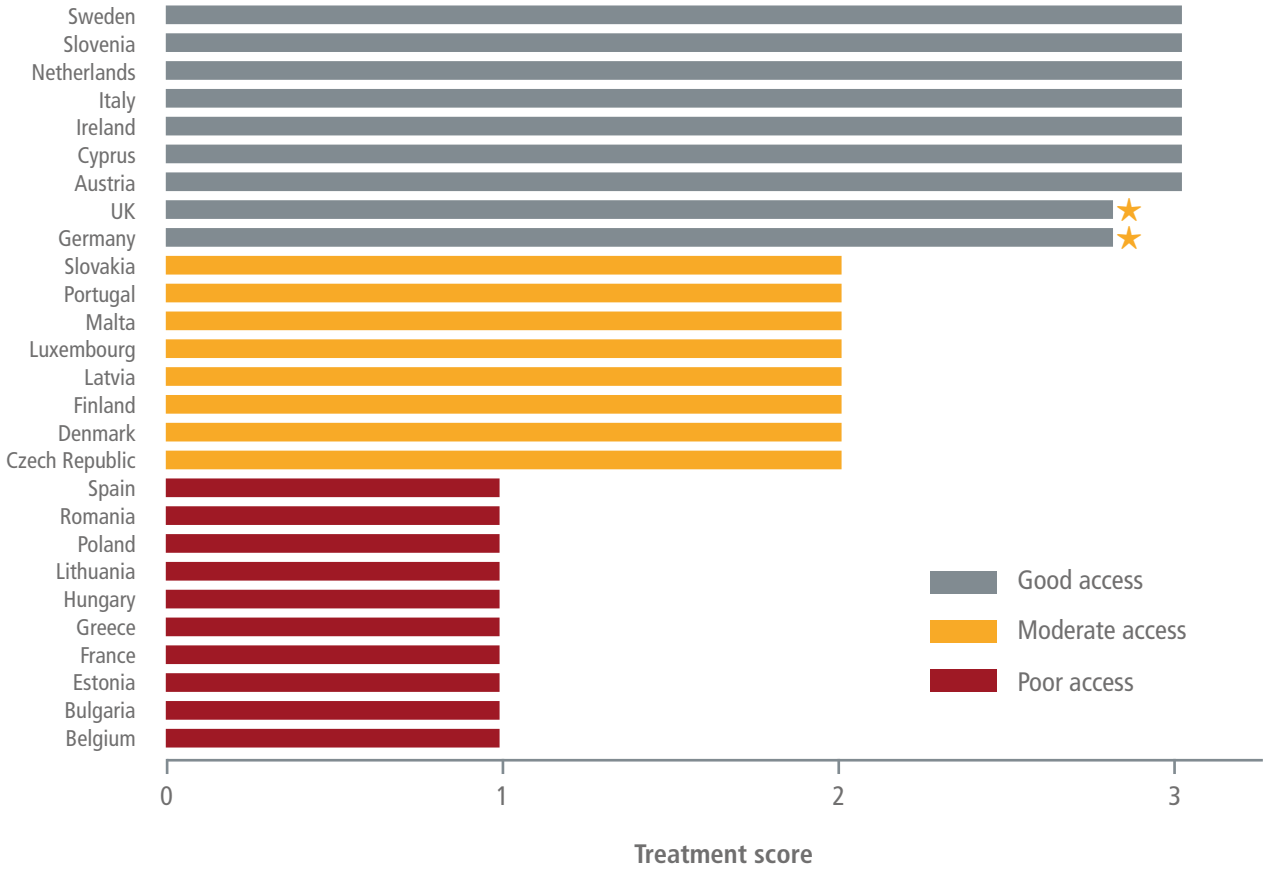
*2017

Country-specific FRAX® Fracture Risk Assessment Tools are available for the following countries in Europe [55]: Armenia, Austria, Republic of Belarus, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Lithuania, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, the Russian Federation, Slovakia, Spain, Sweden, Switzerland, UK and Ukraine.

Regarding access to treatments for osteoporosis, the IOF-EFPIA EU Audit noted that most interventions were reimbursed in most countries [134]. However, significant variation in the degree of reimbursement was evident, with only 7 member states providing full reimbursement. An overall ranking and score for access to medical intervention was provided for each country as shown in figure 12.

The IOF Eastern European and Central Asian Regional Audit noted that access to osteoporosis treatments was extremely limited throughout the region, including in the Eastern European/ Western Asian countries [129].

Figure 12. Ranking and score for access to medical intervention in the European Union [134]



(Reproduced from *Arch Osteoporos*. 2013;8:144 with kind permission of Springer)

Euripedes, from Brazil, lost 19 cm in height as a result of painful vertebral fractures caused by osteoporosis. He now finds daily activities more difficult and can't sit for long periods of time because of the pain.

Latin America

In 2015, the United Nations report on the ageing of the world's population stated [117]:

> "Over the next 15 years, the number of older persons is expected to grow fastest in Latin America and the Caribbean with a projected 71 per cent increase in the population aged 60 years or over."

The report estimated that 71 million individuals in this region were aged 60 years or older in 2015, a figure which is set to rise to 200 million by 2050. Further, the number of individuals classified as the "oldest-old" (i.e. 80 years or older) will increase from 10 million in 2015 to 45 million in 2050.

In 2012, IOF published the Latin America Regional Audit which provided an overview of the epidemiology, costs and burden of osteoporosis for 14 countries [142]: Argentina, Bolivia, Brazil, Chile, Columbia, Costa Rica, Cuba, Guatemala, Mexico, Nicaragua, Panama, Peru, Uruguay and Venezuela. Key findings from the IOF Audit, and more recent studies where available, relating to epidemiology, mortality, health expenditure, and access and reimbursement follow.

Epidemiology

The rapid ageing of the Latin American population in the coming decades is projected to result in 12.5% of all hip fractures occurring in this region by 2050 [120]. Estimates of the annual incidence of hip fracture in the most populous countries in the region are as follows:

- **Argentina:** The incidence of 34,000 cases of hip fracture in 2009 is projected to increase to 76,000 cases by 2050 [143, 144].
- **Brazil:** Zerbini and colleagues estimated that 80,640 hip fractures occurred in 2015 [145]. By 2040, the number of cases is projected to be almost 198,000 per year.
- **Colombia:** Jaller-Raad and colleagues estimated that 7,900 hip fractures occurred in 2010 [146]. By 2035, the number of cases is projected to exceed 22,700 per year.
- **Mexico:** Johansson and colleagues estimated that more than 29,700 hip fractures occurred in 2005 [147]. Assuming no change in the age- and sex-specific incidence of hip fracture, the number of hip fractures was expected to increase to almost 156,000 cases by 2050. Should the age-specific incidence continue, the number of hip fractures would increase by a further 46% to almost 227,000 by 2050.

Mortality

Studies from several Latin American countries have reported high rates of post-hip fracture mortality as compared to European and North American countries. In 2000, a study conducted in Luján, Argentina reported in-hospital mortality of 10% and 1-year mortality of 33% [148]. In 2010, Pereira and colleagues described mortality rates for individuals aged 60 years and over who were admitted with hip fracture to hospitals in Rio de Janeiro, Brazil [149]. Nine percent of patients died in hospital and a further 26% died within a year of discharge. In 2016, a description of outcomes for an Orthogeriatric Care Program in a Colombian Hospital was very encouraging [150]. The annual survival rate increased from 80% to 89% ($p = .039$) 4 years after implementation of the program.

Health expenditure

The costs of fragility fractures in this region are currently significant, and set to rise substantially in the coming decades:

- **Argentina**: In 2009, hospitalization costs of hip and vertebral fractures were estimated to exceed US$190 million per year [144].

- **Brazil:** In 2014, Moraes and colleagues analysed expenditure by the Ministry of Health in the Brazilian Public Health System on osteoporosis and related fractures [151]. During the period 2008-10, more than 3.2 million procedures resulted in expenditure of almost R$289 million (US$92 million).
- **Colombia:** The IOF Audit estimated that the direct hospital cost for treating a hip fracture in Colombia was US$6,457 [142]. Accordingly, this would suggest that more than US$51 million was spent on hip fracture care in 2010 [146].
- **Mexico:** In 2010, Carlos and colleagues estimated the cost of fragility fractures in Mexico to be US$256 million [152]. These costs are projected to rise to US$305 million and US$364 million in 2015 and 2020, respectively.

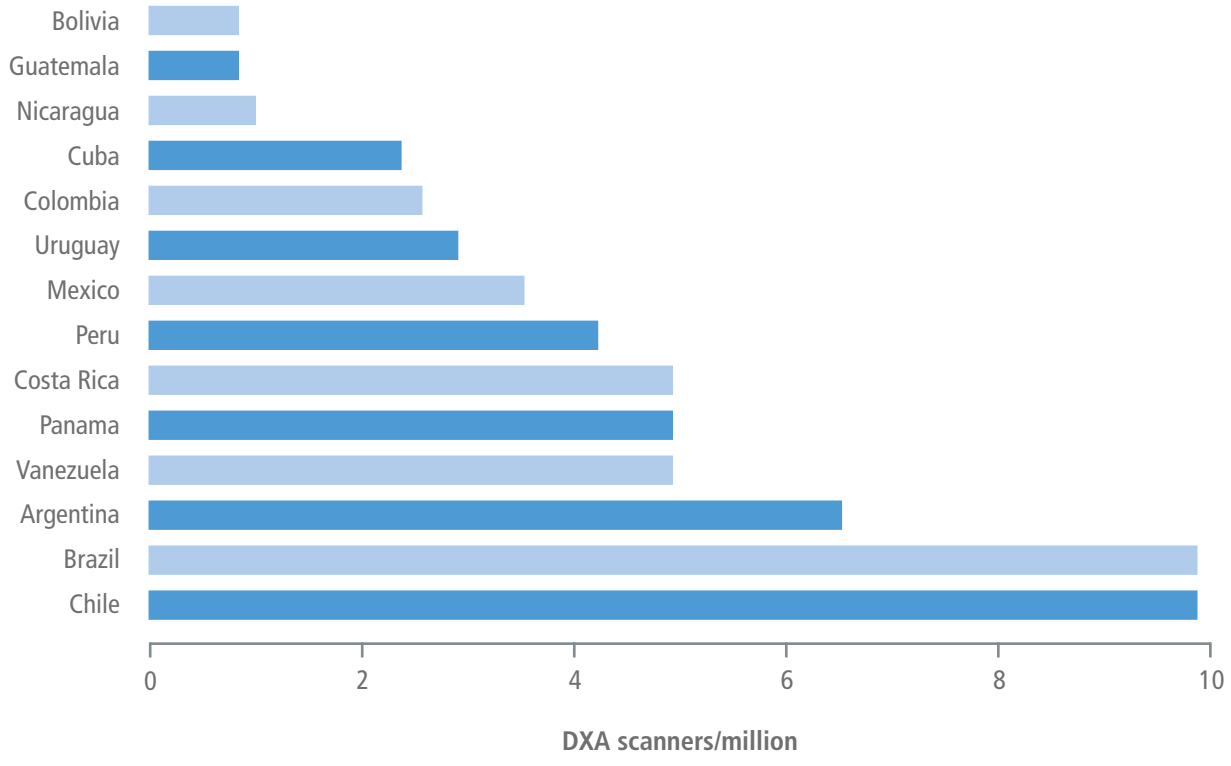
Access and reimbursement

The IOF Latin American Audit documented considerable variation in access and reimbursement for diagnosis of osteoporosis and treatment [142]. As illustrated in figure 13, the number of DXA scanners per million of population varied from 10 in Brazil and Chile to approximately 1 in Bolivia, Guatemala and Nicaragua.

Country-specific FRAX® Fracture Risk Assessment Tools are available for the following countries in Latin America [55]: Argentina, Brazil, Chile, Columbia, Ecuador, Mexico and Venezuela.

Bisphosphonate therapies were reported to be widely available throughout the region [142]. However, there was considerable variability in reimbursement policy. Other osteoporosis therapies such as selective estrogen receptor modulators (SERMs), recombinant forms of parathyroid hormone (PTH), hormone replacement therapy (HRT) were also available, but access was often restricted.

Figure 13. Number of DXA scanners per million of population in Latin America [142]



Maria-Grazia, 62 years old, developed osteoporosis after taking cortisone injections for rheumatoid arthritis over the course of 10 years. Rheumatoid arthritis and long-term glucocorticoid therapy are major risk factors for osteoporosis.

Middle East and Africa

In 2011, IOF published the Middle East and Africa Regional Audit which provided an overview of the epidemiology, costs and burden of osteoporosis for 17 countries [153]: Bahrain, Egypt, Kuwait, Iran, Iraq, Jordan, Kenya, Lebanon, Morocco, Palestine, Qatar, Saudi Arabia, South Africa, Syria, Tunisia, Turkey and United Arab Emirates. At the time of writing, 8-20% of the population of this region was aged over 50 years, which is set to increase to 25% and 40% by 2020 and 2050, respectively. Key findings from the IOF Audit, and more recent studies where available, relating to epidemiology, mortality, health expenditure, and access and reimbursement follow.

Epidemiology

Epidemiological studies in this region are limited. Estimates of the annual incidence of hip fracture in two countries in the region are as follows:

- **Saudi Arabia:** The incidence of more than 7,500 cases of hip fracture in 2013 is projected to increase to more than 9,700 by 2025 [154].

- **Turkey:** In 2009, there were approximately 24,000 cases of hip fracture in Turkey [155]. Assuming no change in the age- and sex-specific incidence, the number of hip fractures was expected to increase to nearly 64,000 by 2035.

Mortality

Mortality rates post-hip fracture may be higher in this region than those reported from western populations. In 2004, El-Hajj Fuleihan and colleagues reported 1-year mortality among Lebanese hip fracture patients to be 33% [156]. In 2006, a retrospective study from Saudi Arabia reported an average 2-year mortality rate of 27% [157]. In 2008, a case series from Turkey reported a 3-year mortality rate of 61% in females and 50% in males [158]. A more recent Turkish study reported 3-year mortality of 37% [159].

Health expenditure

In 2010, the IOF Audit noted that information on costs relating to osteoporosis and fragility fractures was practically non-existent [153]. In Iran, it was estimated that the direct costs of hip fractures would increase from US$28 million in 2010 to US$250 million by 2050. In Turkey, similar estimates suggested that direct costs for hip fracture would increase from US$72 million in 2010 to US$205 million in 2050. A more recent study from Saudi Arabia estimated the overall hospital cost due to hip fractures, including the indirect costs for the first year, to be SR2.4 billion (US$629 million) [154]. This cost was projected to increase to SR3.9 billion (US$1 billion) by 2025.

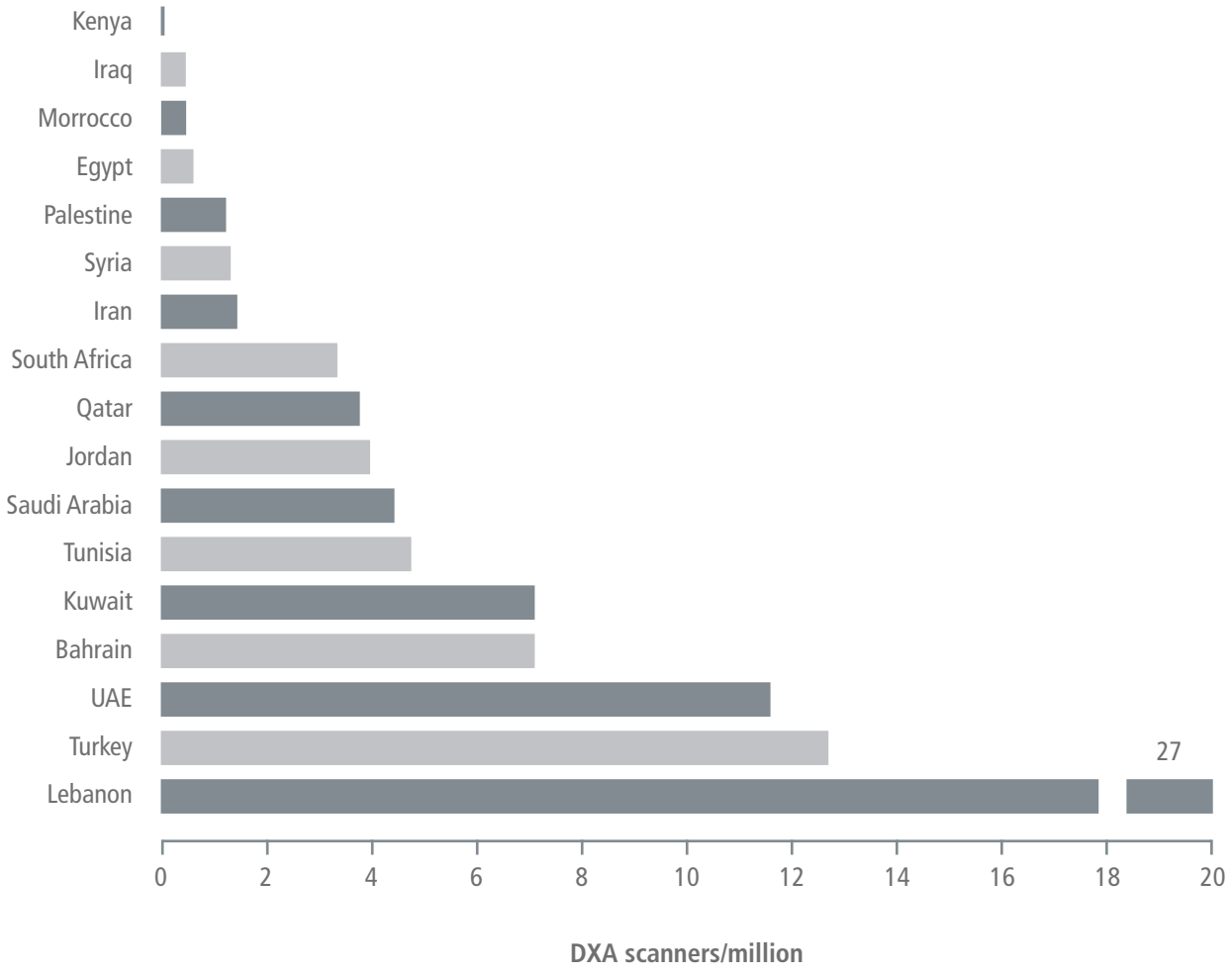
Access and reimbursement

The IOF Audit documented considerable variation in access and reimbursement for diagnosis of osteoporosis and treatment [153]. As illustrated in figure 14, the number of DXA scanners per million of population varied from 27 in Lebanon to none in Kenya.

Country-specific FRAX® Fracture Risk Assessment Tools are available for the following countries in the Middle East and Africa [55]: Abu Dhabi, Iran, Jordan, Kuwait, Lebanon, Morocco, Palestine, Tunisia and Turkey.

Bisphosphonates, SERMs, HRT and strontium ranelate were available in most countries. However, reimbursement varies from 100% to 0%.

Figure 14. Number of DXA scanners per million of population in the Middle East and Africa [153]



North America

In 2015, the United Nations report on the ageing of the world's population stated that the proportion of the North American population aged 60 years and over will increase by 41% by 2030 [117]. The report estimated that 75 million individuals in this region were aged 60 years or older in 2015, a figure which is set to rise to 123 million by 2050. Further, the number of individuals classified as the "oldest-old" (i.e. 80 years or older) will increase from 14 million in 2015 to 37 million in 2050. Key findings of studies from Canada and the United States relating to epidemiology, mortality, health expenditure, and access and reimbursement follow.

Epidemiology

In 2016, Hopkins and colleagues described the incidence of osteoporosis attributable fractures during financial year 2010-11 in Canada [160]. A total of 131,443 fractures resulted in 64,884 acute care admissions and 983,074 acute hospital days. The proportion of fractures by type was hip (18.1%), wrist (20.8%), vertebral (5.7%), humerus (6.4%), other (41.4%) and multiple (7.5%), respectively.

The 2010 US Census population suggested that there were 99 million adults aged 50 years and over living in the US in 2010. Based on this data and osteoporosis prevalence rates taken from the National Health and Nutrition Examination Survey (NHANES) 2005-2010, 10.2 million older adults were estimated to have osteoporosis [6]. A further 43.4 million older adults had low bone mass (i.e. osteopenia). The most recent estimate of the incidence of all osteoporosis-related fractures occurring in the US was published a decade ago [112]. Burge and colleagues' study suggested that more than 2 million fractures occurred among Americans aged 50 years and over in 2005. This included almost 297,000 hip fractures, 547,000 vertebral fractures, 399,000 wrist fractures, 135,000 pelvis fractures and 675,000 other fractures. By 2025, the total number of fractures was projected to exceed 3 million cases per year. A more recent study based on data from the National Hospital Discharge Survey estimated the incidence of hip fracture in the US to be 258,000 cases in 2010, which was projected to rise to 289,000 cases by 2030 [161].

Mortality

Efforts are ongoing in Canada and other countries to expedite surgery for hip fracture patients with a view to improve outcomes. In Manitoba, a coordinated, region-wide effort to improve timeliness of hip fracture surgery reported pre- and post-intervention mortality rates in-hospital and at 1 year [162]. The crude in-hospital mortality rate reduced from 9.6% to 6.8%, while the crude mortality rate at 1 year was not significant difference between groups (pre- 25.7% vs. post-24%, p=0.12). Another study evaluated excess mortality associated with second hip fracture in British Columbia, hazard of death was 55% higher for patients with second hip fracture compared to those without second hip fracture [163]. This study highlighted the need for effective post-hip fracture secondary prevention programmes.

In 2009, Brauer and colleagues examined trends in hip fracture incidence and mortality for the period 1985-2005 in the US Medicare population [164]. Thirty-day mortality in women decreased by 11.9% during the entire course of the study, from 5.9% to 5.2%. The adjusted 360-day mortality decreased by 8.8% from 24.0% in 1986 to 21.9% in 2004. A more recent study evaluated mortality among postmenopausal women who sustained hip fractures in the period 2000-2010 and were managed in an integrated healthcare delivery system [165]. The crude all-cause mortality rate was 6.3% and 22.8% at 1 month and 12 months, respectively. The adjusted odds of death in 2010, as compared to 2004, were 27% and 30% lower at 6 months and 1 year, respectively. In 2016, a study from California reported similar findings [166].

Health expenditure

The most recent estimate of the economic burden of osteoporosis in Canada provides information for financial year 2010-11 [160]. The total cost of CN$4.6 billion (US$3.5 billion) included CN$1.5 billion (US$1.1 billion) for acute care costs and CN$1 billion (US$0.8 billion) for long-term care costs.

In 2005, Burge and colleagues estimated the cost of the 2 million cases of fragility fracture annually to be US$17 billion [112]. By 2025, this was projected to increase to US$25 billion. In 2016, Singer and colleagues analysed data from the US Nationwide Inpatient Sample for the period 2000-2011 [167].

On an annual basis, the total population facility-related cost resulting from hospitalisation of osteoporotic fractures was US$5.1 billion. Another study estimated the cost burden of second fracture to the US health system [168]. On an annual basis, nationwide, this amounted to $834 million for patients with commercial insurance and $1.1 billion for Medicare patients. This study clearly highlighted the need for widespread implementation of FLS.

Access and reimbursement

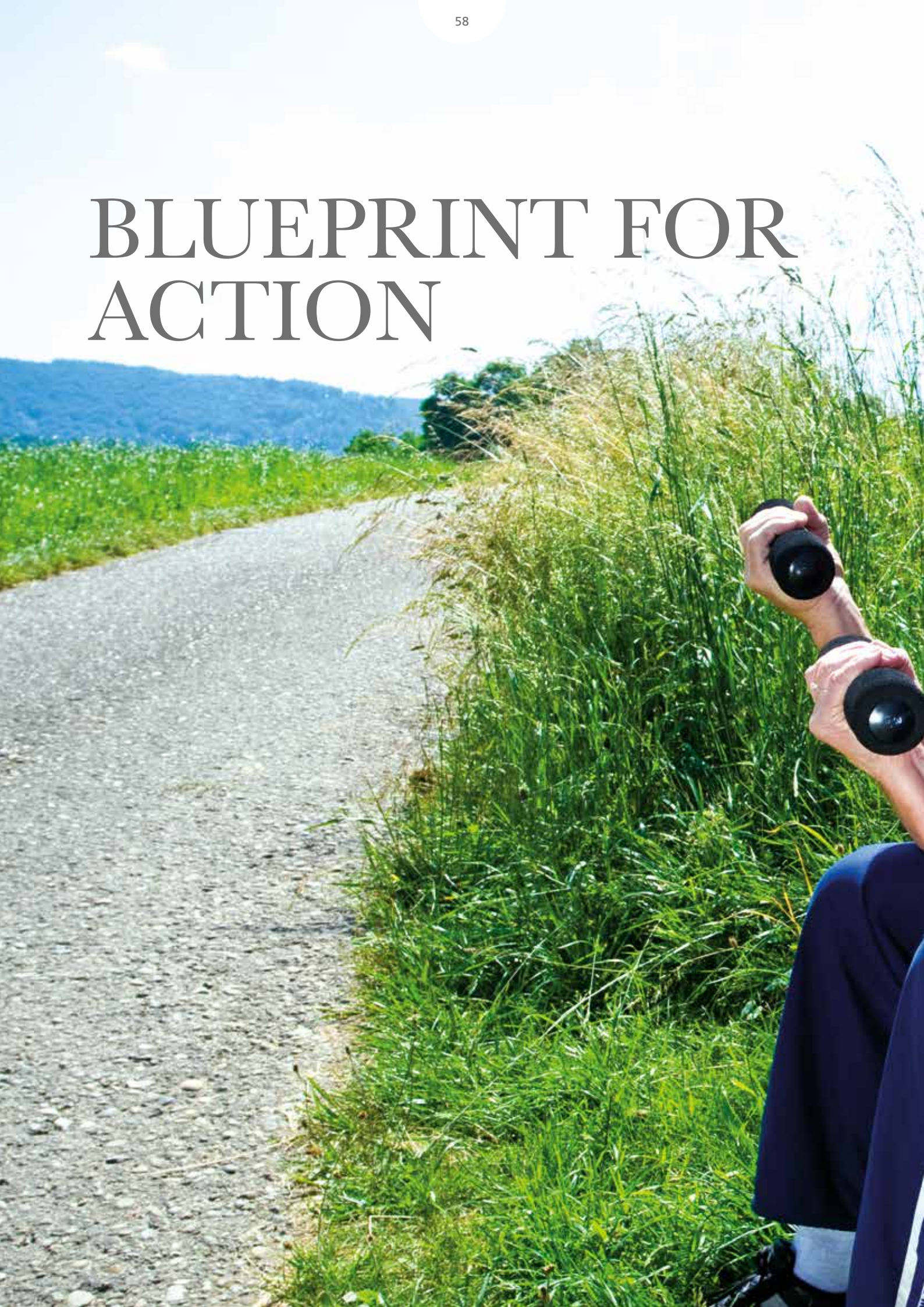
The current number of DXA scanners in Canada or the United States is not documented. In 2005 it was estimated that there were 16.3 and 35.8 DXA scanners per million of population in Canada and the United States, respectively [169]. Country-specific FRAX® Fracture Risk Assessment Tools are available for Canada and the United States.

In Canada, there is no single national healthcare system. Health care falls under the independent jurisdiction of each of the 10 provinces and 3 territories. There is reimbursement for many of the oral bisphosphonates in all Canadian provinces for seniors who are indicated for such treatment. However, coverage for other osteoporosis medications such as denosumab and zoledronic acid is quite variable depending on the province/territory.

In the USA, reimbursement for screening, treatment and other bone health interventions varies greatly depending on each patient's health plan. In 2007, Medicare initiated a series of cuts to reimbursement for DXA services performed in the non-facility setting. By 2010, payments for these services had been reduced by more than 60% compared with 2006 levels. Analyses showed that as compared to the 2-year period prior to the cuts in reimbursement, in the 2-year period after the cuts, both the number of DXA scans and prescriptions for FDA-approved osteoporosis drugs had declined [170].

To address these gaps, the National Bone Health Alliance (NBHA) convened a bone health 'payer summit' in May 2017 comprising the major payers to solicit their feedback on the scientific and clinical evidence needed to reconsider these coverage and reimbursement decisions. This feedback will be used to inform the development of an evidence report that will provide evidence of the cost-effectiveness of these interventions to reduce future fracture risk.

BLUEPRINT FOR ACTION




Club Med
Club Med
Club Med

BLUEPRINT FOR ACTION

At the time of writing of this Compendium, the world's population was approaching 7.4 billion individuals [171]. In 2015, the United Nations report on World Population Ageing highlighted the unprecedented change to the age structure of our civilisation that is set to unfold this century [117]:

> **"Between 2015 and 2030, the number of people in the world aged 60 years or over is projected to grow by 56 per cent, from 901 million to 1.4 billion, and by 2050, the global population of older persons is projected to more than double its size in 2015, reaching nearly 2.1 billion."**

Considering the dramatic influence this demographic shift will have upon the prevalence of osteoporosis - and the fragility fractures it causes – it is imperative that all nations develop and implement a strategy to improve the bone health of their populations.

During the last year, IOF has developed two key initiatives to support national level policymakers, government representatives, healthcare professionals and their organizations, national osteoporosis societies and the healthcare industry to improve the bone health of the populations that they serve:

- The IOF Global Patient Charter.
- The IOF Global Framework for Improvement.

Details of these potentially transformational initiatives follow.

Launched in 2017, the IOF Global Patient Charter articulates the rights and responsibilities of all key stakeholders to ensure that the right patient receives the right treatment at the right time [77]:

IOF Global Patient Charter

Through this Charter, as a patient or family member of a patient, I call for the rights to:

1

DIAGNOSIS:

Timely and accurate assessment of fracture risk, falls risk and diagnosis of osteoporosis.

2

PATIENT CARE:

Access to effective intervention options (treatment, lifestyle changes) and to regular drug treatment review by appropriate healthcare professional.

3

PATIENT VOICE:

Involvement and choice in a long-term management plan with defined goals.

4

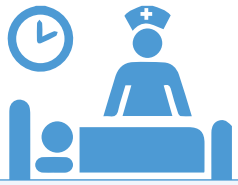
SUPPORT:

Care and support from society and healthcare providers, to ensure active and independent living.

Help drive improvement, and show your support:

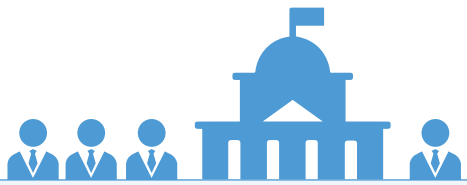
PATIENTS:

Speak to your physician to identify your risk, and take action for change.



HEALTHCARE PROFESSIONALS:

Protect communities' bone health through appropriate assessment and treatment.



POLICYMAKERS, HEALTHCARE AUTHORITIES AND NATIONAL GOVERNMENTS:

Support the establishment of coordinated models of care (Fracture Liaison Services) to help reduce the global human and socioeconomic burden of fragility fractures.

Show your commitment by signing the IOF Global Patient Charter. Your signatures will help raise the profile of this insidious disease and make fracture prevention a global health priority.

Visit https://www.iofbonehealth.org/iof-global-patient-charter now.

The IOF Global Framework for Improvement

The 2016 World Osteoporosis Day Report provided a new Global Framework for Improvement to equip national policymakers, leaders within the healthcare professions and national osteoporosis societies to deliver optimal management of bone health for all [18, 73]. The Report identified 10 key gaps pertaining to delivery of optimal care for all, and proposed evidence-based solutions to close those gaps:

Case finding and management:

- Gap 1: Secondary fracture prevention
- Gap 2: Osteoporosis induced by medicines
- Gap 3: Diseases associated with osteoporosis
- Gap 4: Primary fracture prevention for individuals at high risk of fracture

Public awareness:

- Gap 5: The importance of staying on treatment
- Gap 6: Public awareness of osteoporosis and fracture risk
- Gap 7: Public awareness of benefits versus risks of osteoporosis treatment

Government and health system issues:

- Gap 8: Access and reimbursement for osteoporosis assessment and treatment
- Gap 9: Prioritization of fragility fracture prevention in national policy

Lack of data:

- Gap 10: The burden of osteoporosis in the developing world

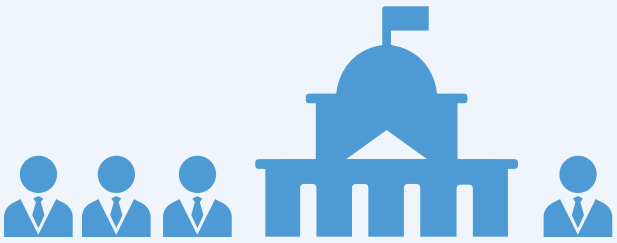
Priority Actions

The IOF Compendium of Osteoporosis, to be updated periodically, provides an opportunity for ongoing review of the components of the Global Framework and a platform to document progress in its the implementation. During the period 2017-2020, IOF would recommend that all stakeholders prioritise the following actions in their jurisdictions.

Secondary fracture prevention

The majority of individuals who suffer fragility fractures are neither assessed nor treated for osteoporosis [18]. This global care gap has persisted despite publication of numerous clinical guidelines in many countries which advocate secondary fracture prevention.

Effective models of care are required to reliably implement the recommendations made in clinical guidelines. As described previously in this Compendium, Orthogeriatric Services (OGS) and Fracture Liaison Services (FLS) have been shown repeatedly to deliver best practice in a highly cost-effective manner, and reduced mortality. These models of care have been endorsed by governments and healthcare professional organisations in a growing number of countries, including Australia, Canada, New Zealand, Singapore, Sweden, United Kingdom and the United States [67]. The IOF Capture the Fracture® Programme provides a comprehensive suite of resources to support development of new FLS and optimisation of existing FLS [68, 69, 172].



PRIORITY 1:

Policymakers, healthcare professional organisations and national osteoporosis societies must collaborate to provide Orthogeriatric Services and Fracture Liaison Services to all older people who suffer fragility fractures in their jurisdictions.

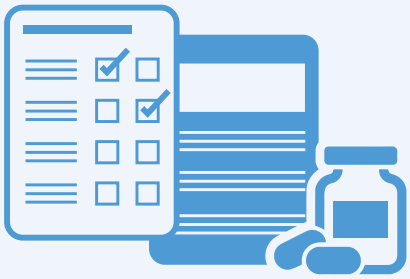
Osteoporosis induced by medicines

While a range of treatments are available to prevent osteoporosis induced by medicines, guidelines based care is frequently not delivered, as has been reported for several commonly used drug classes:

- **Glucocorticoids:** A systematic review evaluated the proportion of patients receiving chronic oral glucocorticoid (GC) therapy who received osteoporosis management for studies published between 1999 and 2013 [173]. Less than 40% of GC users underwent BMD testing or received osteoporosis treatment in more than 80% of studies. This is disappointing given that clinical guidelines for the prevention and treatment of GC-induced osteoporosis are available in many countries [174].
- **Androgen Deprivation Therapy:** Approximately one third of prostate cancer patients receive androgen deprivation therapy (ADT). Information from the Texas Cancer Registry was linked to the Medicare

database to establish what proportion of men diagnosed with prostate cancer underwent BMD testing and/or received osteoporosis treatment [175]. Less than a tenth of these men had a BMD test within 6 months of initiation of ADT, and among those enrolled in the Medicare part D scheme, only 5.6% received bone sparing drugs when they were initiated on ADT. Many guidelines have been published on the prevention and treatment of ADT-induced osteoporosis, such as those produced by the IOF Committee of Scientific Advisors (CSA) Working Group on Cancer-induced Bone Disease [176].

- **Aromatase inhibitors:** Aromatase inhibitors (AIs) are considered to be the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer. A study conducted in Seattle in the United States reported that less than half of women underwent BMD testing within 14 months of continuous AI use for at least 9 months [177]. As for GCs and ADT, many guidelines are available to inform best practice in osteoporosis management for AI users, such as those published by the European Society for Clinical and Economical Aspects of Osteoporosis (ESCEO) in 2012 [23].

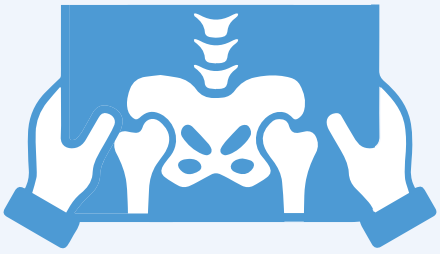


PRIORITY 2:

Where treatments are licensed to prevent osteoporosis induced by medicines, and guidelines have been published to inform best clinical practice, osteoporosis management must become a standard consideration for clinicians when prescribing medicines with bone-wasting side effects.

Primary fracture prevention

The advent of absolute fracture risk calculators such as FRAX® provide individuals and their clinicians with a readily accessible, online tool to estimate fracture risk. Individuals can visit https://www.sheffield.ac.uk/FRAX/ to access their own risk. FRAX®, in combination with access to axial DXA scanning, provides primary care providers with an opportunity to stratify fracture risk within their practice population.



PRIORITY 3:

National osteoporosis societies to incorporate messaging regarding self-assessment of fracture risk with FRAX® into public awareness and education initiatives, as advocated in Priority 6. National osteoporosis societies to collaborate with healthcare professional organisations for primary care providers (PCPs) to jointly advocate for PCPs to routinely undertake fracture risk assessment when interacting with patients aged 50 years and over.

Nutrition and exercise

Nutrition has a profound effect on bone health throughout the life course. Primary objectives for specific populations are:

- **Expectant mothers:** Must be well nourished to support an infant's development in utero.
- **Children and adolescents:** Achieve genetic potential for peak bone mass through a nutritious diet with adequate calcium intake and regular physical activity.
- **Adults:** Avoid premature bone loss through a nutritious diet with adequate calcium intake, maintaining a healthy body weight and participation in regular weight-bearing activity.
- **Seniors:** Avoid malnutrition, ensuring adequate dietary intake of calcium, vitamin D and protein, and participation in regular weight-bearing activity.

PRIORITY 4:

Specific initiatives encompassing nutrition and exercise are required for particular age groups:

Expectant mothers: National osteoporosis societies to collaborate with national obstetrics organisations to advise government on optimising bone health of mothers and infants.

Children and adolescents: National osteoporosis societies to collaborate with government Ministries of Education, national teachers' organisations, national nutrition foundations/councils, national dietician/nutritionist organisations, government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to educate children and adolescents on achieving their genetic potential for peak bone mass.

Adults and seniors: National osteoporosis societies to collaborate with government Ministries for Seniors, national nutrition foundations/councils, national dietician/nutritionist organisations, non-governmental organisations concerned with seniors' welfare and government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to inform adults on their nutritional and exercise needs to maintain a healthy skeleton, avoid premature bone loss and avoid malnutrition in the elderly.

Healthcare professional education

The pervasive and persistent care gaps relating to individuals who are at high risk of sustaining fragility fractures suggests a new approach is needed to healthcare professional education concerning osteoporosis. Osteoporosis is a very common condition and, as such, most healthcare providers need to be able to reliably identify high risk individuals and understand their own clinical role and responsibility to enable their patients to achieve optimal outcomes. The following groups of clinicians should be primary targets to be engaged in professional education activities:

- **Lead Clinicians in Osteoporosis:** Whether an endocrinologist, rheumatologist, geriatrician, orthopaedic surgeon or other specialist, the individual who takes the role of "Lead Clinician in Osteoporosis" in their institution is vital to the success of quality improvement initiatives. Where secondary fracture prevention services do not exist, these individuals should be targeted to participate in educational programmes to drive widespread adoption of OGS and FLS. Such education could be delivered through face-to-face meetings hosted by existing Centres of Excellence, virtual interactions through webinars and other internet-based programmes, or a combination of the two approaches.

- **Orthopaedic Surgeons:** Successful OGS and FLS are highly reliant on orthopaedic surgeons being supportive of both service models. Accordingly, a major global effort is required to share experience of successful OGS and FLS with all practicing orthopaedic surgeons and trainees. In countries which have implemented nationwide, systematic approaches to fragility fracture care and prevention, orthopaedic surgeons – and their professional organisations - have played leading roles in the development of clinical guidelines, care standards, fracture registries and workforce training initiatives. In this regard, best practice should be shared between national orthopaedic associations to expedite development of effective national professional education programmes for orthopaedic surgeons worldwide.

- **Primary care providers:** Osteoporosis is a long-term condition which requires development of, and adherence to a long-term care plan. Just as primary care providers (PCPs) have played a leading role in the long-term management of individuals with cardiovascular disease, PCPs are central to the delivery of efficient, long-term care for individuals who are living with osteoporosis. National osteoporosis societies and national primary care organisations should collaborate to develop educational programmes which enable PCPs to audit their practice population to identify high risk individuals, navigate local referral pathways for diagnostic assessment, and be confident in the initiation guidelines-based care. Practical, user-friendly guidance and maximum leverage of information technology should underpin these educational initiatives to minimise the time commitment required by PCPs to deliver best clinical care.

PRIORITY 5:

National osteoporosis societies and healthcare professional organisations to collaborate to develop and encourage widespread participation in national professional education programmes designed for 3 distinct audiences: Lead Clinicians in Osteoporosis, orthopaedic surgeons and primary care providers.

Public awareness and education

The 2016 World Osteoporosis Day Report identified three major gaps in public awareness relating to osteoporosis [18, 73]:

- Gap 5: The importance of staying on treatment
- Gap 6: Public awareness of osteoporosis and fracture risk
- Gap 7: Public awareness of benefits versus risks of osteoporosis treatment

PRIORITY 6:

National osteoporosis societies, healthcare professional organisations, policymakers and regulators to collaborate to develop impactful public awareness campaigns which empower consumers to take ownership of their bone health.

Improving access and reimbursement for diagnosis and treatment

This Compendium has documented considerable variation across the world in terms of access and reimbursement of BMD measurement and osteoporosis treatments. In light of the burgeoning impact of osteoporosis upon our older people, their families and carers, and national economies, the status quo in many countries is untenable. Health Technology Assessment (HTA) is an important tool to help policymakers to allocate healthcare resources efficiently. HTA is increasingly being used to inform development of policy relating to the management of osteoporosis to prevent fragility fractures [178].

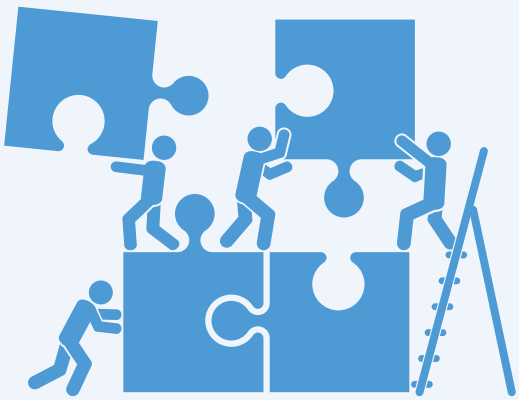
PRIORITY 7:

Osteoporosis must be designated a national health priority in all countries, with commensurate human and financial resources to ensure that best practice is delivered for all individuals living with this condition. In countries where the current disease burden is not known, epidemiological studies must be commissioned as a matter of urgency.

Formation of national falls and fracture prevention alliances

In recent years, national alliances focused on the development and implementation of systematic approaches to falls and fragility fracture prevention have formed in a growing number of countries. These alliances have been comprised of national osteoporosis societies and other relevant non-governmental organisations, policymakers and healthcare professional organisations, and some include private sector companies. Alliances combine expertise, resources and the desire to improve outcomes for those who have sustained falls and fragility fractures. Examples from several countries include:

- **Australia:** The SOS Fracture Alliance [179].
- **New Zealand:** The Live Stronger for Longer alliance [180].
- **UK:** The Falls and Fractures Alliance [181].
- **USA:** The National Bone Health Alliance [182].



PRIORITY 8:

In countries without an existing national alliance, national osteoporosis societies to initiate dialogue with other relevant non-governmental organisations, policymakers, healthcare professional organisations and private sector companies to propose formation of a national falls and fracture prevention alliance modelled on successful examples from elsewhere. Formation of a national alliance has the potential to facilitate delivery of Priorities 1-7.

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The IOF vision is a world without fragility fractures in which healthy mobility is a reality for all.

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