ASSESSMENT OF OSTEOPOROSIS AT THE PRIMARY HEALTH CARE LEVEL

Report of a WHO Scientific Group

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WHO Scientific Group Technical Report

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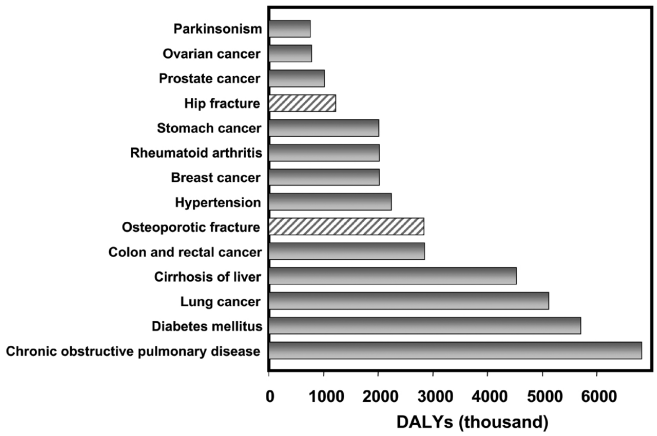
1. Introduction

A WHO Scientific Group on the Assessment of Osteoporosis at the Primary Health Care Level met in Brussels from 5 to 7 May 2004. The meeting was opened by Dr N. Khaltaev, Responsible Officer for Chronic Respiratory Diseases and Arthritis, who welcomed the participants on behalf of the Director-General of the World Health Organization (WHO).

1.1 Background

Following the publication of the report of a WHO Study Group meeting on *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis,* osteoporosis has been recognized as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan *(1)*. Osteoporosis causes more than 8.9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe (Table 1.1). The lifetime risk for a wrist, hip or vertebral fracture has been estimated to be in the order of 30% to 40% in developed countries – in other words, very close to that for coronary heart disease. Osteoporosis is not only a major cause of fractures, it also ranks high among diseases that cause people to become bedridden with serious complications. These complications may be life-threatening in elderly people. In the Americas and Europe osteoporotic fractures account for 2.8 million disability-adjusted life years (DALYs) annually, somewhat more than accounted for by hypertension and rheumatoid arthritis *(2)*, but less than diabetes mellitus or chronic obstructive pulmonary diseases (Fig. 1.1). Collectively, osteoporotic fractures account for approximately 1% of the DALYs attributable to noncommunicable diseases.

Fig. 1.1
Burden of diseases estimated as disability-adjusted life years (DALYs) in 2002 in the Americas and Europe combined



Source: reference 2 (data extracted from Annex Table 3, pp. 126-131) and WHO unpublished data.

Table 1.1
Estimated number of osteoporotic fractures by site, in men and women aged 50 years or more in 2000, by WHO region

	Expected number of fractures by site (thousands)				All osteoporotic fractures	
WHO region	Hip	Spine	Proximal humerus	Forearm	No.	%
Africa	8	12	6	16	75	0.8
Americas	311	214	111	248	1 406	15.7
South-East Asia	221	253	121	306	1 562	17.4
Europe	620	490	250	574	3 119	34.8
Eastern Mediterranean	35	43	21	52	261	2.9
Western Pacific[a]	432	405	197	464	2 536	28.6
Total	1 672	1 416	706	1 660	8 959	100

Source: O Johnell & J A Kanis, unpublished data, 2006.
[a]Includes Australia, China, Japan, New Zealand and the Republic of Korea.

Because of the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population. In May 1998, the Fifty-first *World Health Assembly, having considered The world health report 1997: conquering suffering, enriching humanity (3)*, which described the high rates of mortality, morbidity and disability from major noncommunicable diseases – including osteoporosis, adopted a resolution requesting the Director-General to formulate a global strategy for the prevention and control of noncommunicable diseases *(4)*. A scientific group meeting subsequently reported on the prevention and management of osteoporosis *(5)*. The report of the present Scientific Group on Assessment of Osteoporosis at the Primary Health Care Level is a further step in the development of cohesive strategies for tackling osteoporosis in response to the World Health Assembly resolution *(4)*. It is expected that the report of this meeting will lead to improvements in the assessment of osteoporosis patients throughout the world, and make a valuable contribution to the development of effective global strategies for the control of this important disease.

Osteoporosis has been operationally defined on the basis of bone mineral density (BMD) assessment. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD) *(1,6)*. This criterion has been widely accepted and, in many Member States, provides both a diagnostic and intervention threshold. The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DXA), and diagnostic criteria based on the T-score for BMD are a recommended entry criterion for the development of pharmaceutical interventions in osteoporosis *(7–9)*. Since therapeutic trials in osteoporosis usually require a low BMD value as an entry criterion, drugs are licensed for use in patients

below a given BMD threshold. The implication is that BMD should be assessed before treatment is considered.

There are, however, several problems with the use of BMD tests alone. In many Member States, BMD tests using DXA are not widely available, or are used predominantly for research, in part because of the high capital costs of DXA. In other Member States, BMD tests are not reimbursed despite the availability and approval of effective drug treatments. For this reason, many other techniques for measuring bone mineral have been developed, which have lower costs and are more portable. The experience with several of these is limited, however, and there is no clear guidance as to how these should be used with or without DXA, either for the diagnosis of osteoporosis or for the assessment of fracture risk. This report updates criteria for the diagnosis of osteoporosis in the light of these developments.

A second major problem with bone mineral measurement is that these tests alone are not optimal for the detection of individuals at high risk of fracture. Over most reasonable assumptions, the tests have high specificity but low sensitivity *(1)*. In other words, the risk of fracture is very high when osteoporosis is present, but by no means negligible when BMD is normal. Indeed, the majority of osteoporotic fractures will occur in individuals with a negative test. Thus, the potential impact of widespread testing of BMD on the burden of fractures is less than optimal, and this is one of the reasons why many agencies do not recommend population screening of BMD *(1,10,11)*. Current recommendations for the assessment of patients also have several difficulties. None is suitable for international use. Those produced by nongovernmental organizations are either conservative, e.g. the European Foundation for Osteoporosis guidelines *(12)*, or border on a population screening strategy, e.g. National Osteoporosis Foundation of the USA *(13–15)*. Both approaches rely critically on testing of BMD, and there is little guidance for Member States without such facilities.

In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk. Examples include age, sex, the degree of bone turnover, a prior fracture, a family history of fracture, and lifestyle risk factors such as physical inactivity and smoking. Some of these risk factors are partially or wholly independent of BMD. Independent risk factors used with BMD could, therefore, enhance the information provided by BMD alone. Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. For this reason, the consideration of well-validated risk factors, with or without BMD, is likely to improve fracture prognostication and the selection of individuals at high risk for treatment.

Against this background, WHO approved a programme of work within the terms of reference of the WHO Collaborating Centre at Sheffield. The project also had the support of the International Osteoporosis Foundation,

the National Osteoporosis Foundation (USA), the International Society for Clinical Densitometry and the American Society for Bone and Mineral Research. A position paper on the general approach was endorsed by the International Osteoporosis Foundation and the United States National Osteoporosis Foundation *(16)*. The aims of the programme were to identify and validate clinical risk factors for use in fracture risk assessment on an international basis, either alone, or in combination with bone mineral tests. A further aim was to develop algorithms for risk assessment that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available.

1.2 Risk factors

Risk factors for any osteoporotic fracture and for hip fracture were identified from 12 prospectively studied population-based cohorts in many geographic territories using the primary databases. The cohorts included the European Vertebral Osteoporosis Study (Pan-European), the Dubbo Osteoporosis study (Australia), the Canadian Multicentre Osteoporosis study (Canada), Rochester (USA), Sheffield (UK), Rotterdam (Netherlands), Kuopio (Finland), Hiroshima (Japan), the OFELY *(L'os des femmes de Lyon)* cohort from Lyon and the multicentre EPIDOS *(Epidémiologie de l'osteoporose)* cohort from France, and two cohorts from Gothenburg (Sweden). The cohort participants had a baseline assessment documenting clinical risk factors for fracture. Approximately 75% also had BMD measured at the hip. The follow-up was approximately 250 000 patient–years in 60 000 men and women during which more than 5000 fractures were recorded.

1.3 Model synthesis

Work over the past few years has clarified many of the features necessary for improved patient assessment. A central component is that the diagnostic criterion for osteoporosis using the WHO definition is not always an appropriate threshold to identify patients at high fracture risk for treatment. The use of the T-score alone is inappropriate since age is as great a risk factor as BMD. Rather, thresholds should be based on a more global evaluation of risk, and in particular on that risk which is amenable to an intervention (i.e. modifiable risk). There are problems with the use of relative risks, and these have contributed to the view, now increasingly accepted, that the risk of patients for fracture should be determined according to absolute probability of fracture. A 10-year probability of fracture is preferred to lifetime risks because:

- Assumptions on future mortality introduce increasing uncertainties for risk assessment beyond 10 years.
- Treatments are not generally given feasibly over a lifetime.
- The long-term prognostic value of some risk factors may decrease with time.
- The 10-year interval accommodates clinical trial experience of

interventions (generally 3–5 years) and the reversal phase (offset time) when treatment is stopped.

Models have been created that are based on the hazard functions for fractures and for death in Sweden, which are used to compute the long-term probability of different fracture types. The models accommodate risk factors such as age, sex, BMD at the hip (femoral neck) and clinical risk factors that have proven international validity.

The first operational model was based on Sweden because of the robustness and extent of the epidemiological data available in that country. Fracture rates, however, differ markedly in different regions of the world. Even within Europe, the risk of hip fracture varies more than 10-fold between countries *(17,18)*, and there is comparable variation in the rate of hospitalization for vertebral fracture *(19)*. The lowest absolute risk of hip fracture is found in the developing world, in part because of the lower fracture risk, but also because of lower life expectancy.

Notwithstanding, the general pattern of osteoporotic fracture is broadly similar across nations. Since extensive epidemiological data exist worldwide for hip fracture, the methodology has been extended to quantify osteoporotic fracture probabilities where hip fracture rates alone are available. This permits probabilities of fracture to be quantified in many regions of the world. Separate models have been constructed for countries with very high risk (e.g. Scandinavia), high risk (e.g. western Europe), moderate risk (e.g. southern Europe) and low risk (e.g. the developing countries). The models have been validated in independent cohorts that did not participate in the model construct.

The choice of risk factors examined was governed by availability of data, and the ease with which the risk factors might be used in primary care. Potential risk factors were examined by a series of meta-analyses using Poisson models for each risk factor in each of the study cohorts and for each sex. Covariates examined included age, sex, BMD, time since assessment and the covariate itself, e.g. to determine whether BMD or body mass index (BMI) are equally predictive for fracture at different levels of BMD or BMI. Results from the different studies were merged using the weighted β-coefficients.

Candidate risk factors included age, sex, glucocorticoid use, secondary osteoporosis, family history, prior fragility fracture, low BMI, smoking, excess alcohol consumption, contraceptive pills, age at menopause, age at menarche, hysterectomy, diabetes, consumption of milk and femoral neck BMD. Risk factors for falling were not considered, since there is some doubt whether the risk identified would be modified by a pharmaceutical intervention. Risk factors recommended for use were selected on the basis of their international validity and evidence that the identified risk was likely to be modified by subsequent intervention (modifiable risk). Modifiable risk

was validated from clinical trials (BMD, prior fracture, glucocorticoid use, secondary osteoporosis), or partially validated by excluding interactions of risk factors on therapeutic efficacy in large randomized intervention studies (e.g. smoking, family history, BMI).

A further step was then to merge these meta-analyses of each risk factor so that account could be taken of the interdependence of the risk factors chosen, and therefore the risk provided by any combination of risk factors, with and without the additional use of BMD.

Assessment algorithms (FRAX™) have been developed for the prediction of hip fracture and other osteoporotic fractures, based on clinical risk factors alone, or the combination of clinical risk factors plus BMD, available at www.shef.ac.uk/FRAX The FRAX algorithms are suitable for men and women. Guidance is given on the economic use of BMD where resources for BMD exist but must be used sparingly.

Given that the probability of fracture can be quantified, information is required on the level of risk that is sufficiently high to merit intervention. This is a complex issue that depends on the wealth of Member States, the place of osteoporosis in the health-care agenda and the proportion of gross domestic product spent on health care, as well as on fracture risk. Against this background, intervention thresholds will vary markedly around the world. Examples of intervention thresholds are provided, based on cost-effectiveness analyses which can be tailored to national requirements. There will be some Member States where supportive programmes only are appropriate, such as attention to adequate physical activity, nutrition and the avoidance of smoking. In other Member States, case-finding can be based on the use of clinical risk factors alone. In many developed countries, the clinical risk factors can be used with the selective use of BMD. There will be segments of society or countries where BMD will always be used. The guidance in this report accommodates these very different approaches to case-finding.

1.4 Possibilities for the future

Until recently, osteoporosis was an under-recognized disease and considered to be an inevitable consequence of ageing. Perceptions have changed since epidemiological studies have highlighted the high burden of the disease and its costs to society and health care agencies, as well as the adverse effects on millions of patients worldwide. The past 15 years have seen major improvements in diagnostic technology and assessment facilities; it is now possible to detect the disease before fractures occur. This has been associated with the development of treatments of proven efficacy (4).

The scope of this report is to direct attention away from the sole use of BMD to determine who will receive treatment and to shift towards the assessment of absolute fracture risk, whether this be determined by BMD testing or

other validated instruments. The use of clinical risk factors together with BMD provides a mechanism for the effective and efficient delivery of health care to individuals at high risk and the avoidance of unnecessary treatment to others. The application of this approach may be expected to reduce, though not eliminate, the burden of osteoporotic fractures.

Against this background, WHO has considered osteoporosis to be of increasing importance. The Director-General of WHO has stated that "WHO sees the need for a global strategy for prevention and control of osteoporosis focusing on three major functions; prevention, management and surveillance" *(20)*. In order to amplify the existing and past activities of WHO in osteoporosis, the object of this Scientific Group meeting was to review the scientific basis for the identification of patients at high or low risk of osteoporotic fracture with or without the use of BMD. The aim was to optimize the detection of high risk patients so that therapy can be better directed. The meeting did not consider specific pharmacological interventions. Rather, the approach to be developed was a case-finding strategy where risk factors are identified to quantify absolute risks.

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2. Consequences of osteoporosis

Age-related bone loss appears to be asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that occur.

2.1 Osteoporotic fractures

The definition of an osteoporotic fracture is not straightforward. Irrespective of the methods used, opinions differ concerning the inclusion or exclusion of different sites of fracture. A widely adopted approach is to consider fractures from low energy trauma as being osteoporotic. "Low energy" may variously be defined as a fall from a standing height or less, or trauma that in a healthy individual would not give rise to fracture. The attribution can either be done by coding fractures or by expert opinion, an approach that has been used in Switzerland *(1)* and the United States of America *(2,3)*. This characterization of low trauma indicates that the vast majority of hip and forearm fractures are low energy injuries. At the age of 50 years, approximately 75% of people hospitalized for vertebral fractures have fractures that are attributable to low energy injuries, increasing to 100% by

the age of 90 years *(4)*. The consideration of low energy has the merit of recognizing the multifactorial causation of fracture, but osteoporotic individuals are more likely to fracture than their normal counterparts following high energy injuries *(5)*. As might be expected, there is also an imperfect concordance between low energy fractures and those associated with reductions in BMD *(6,7)*.

The rising incidence of fractures with age does not provide direct evidence for osteoporosis, since a rising incidence of falls could also be a cause. By contrast, a lack of increasing incidence with age is reasonable presumptive evidence that a fracture type is unlikely to be osteoporosis-related. An indirect arbiter of an osteoporotic fracture is the finding of a strong association between the fracture and the risk of classical osteoporotic fractures at other sites. Vertebral fractures, for example, are a very strong risk factor for subsequent hip and vertebral fracture *(8–10)*, whereas forearm fractures predict future spine and hip fractures *(11)*.

The approach used here was to characterize fracture sites as osteoporotic when they are associated with low bone mass and their incidence rises with age after the age of 50 years *(12)*. The most common fractures defined in this way are those at the hip, spine and forearm, but many other fractures after the age of 50 years are related at least in part to low BMD and should be regarded as osteoporotic *(6,13,14)*. These include fractures of the humerus, ribs, tibia (in women, but not including ankle fractures), pelvis and other femoral fractures. Their neglect underestimates the burden of osteoporosis, particularly in younger individuals. Under this schema, the fracture sites that would be excluded include those at the ankle, hands and feet, including the digits, skull and face, and kneecap.

2.1.1 Hip fracture

Hip fracture is the most serious osteoporotic fracture. Most hip fractures follow a fall from the standing position, although they sometimes occur spontaneously *(13)*. The risk of falling increases with age and is somewhat higher in elderly women than in elderly men. About one third of elderly individuals fall annually, and 5% will sustain a fracture and 1% will suffer a hip fracture *(15)*. Hip fracture is painful and nearly always necessitates hospitalization.

A hip fracture is a fracture of the proximal femur, either through the femoral cervix (sub-capital or trans-cervical: intra-capsular fracture) or through the trochanteric region (intra-trochanteric: extra-capsular fracture). The two hip fracture types, cervical or trochanteric, have a somewhat different natural history and treatment. Trochanteric fractures are more characteristically osteoporotic, and the increase in age-specific and sex-specific risks for hip fracture is greater for trochanteric than for cervical fractures *(16)*. Trochanteric fractures are also more commonly associated with a prior

fragility fracture. In many countries both fracture types occur with equal frequency, though the average age of patients with trochanteric fractures is approximately 5 years older than for cervical fractures.

Displaced cervical fractures have a high incidence of malunion and osteonecrosis following internal fixation, and the prognosis is improved with hip replacement. Trochanteric hip fractures appear to heal normally after adequate surgical management. For both fracture types, there is a high degree of morbidity and appreciable mortality that depends in part on age, the treatment given and the associated morbidity *(17)*. Both morbidity and mortality are greater with trochanteric than with cervical fractures *(18)*. Complications may arise because of immobility. The outcome is much poorer where surgery is delayed for more than 3 days. Up to 20% of patients die in the first year following hip fracture, mostly as a result of serious underlying medical conditions (19), and less than half of survivors regain the level of function that they had prior to the hip fracture *(20)*.

2.1.2 Vertebral fracture

Vertebral fracture has been the most difficult osteoporosis-related fracture to define. The problem arises in part because the diagnosis is made on a change in the shape of the vertebral body. The deformities that result from osteoporotic fracture are usually classified as a crush fracture (involving compression of the entire vertebral body), a wedge fracture (in which there is anterior height loss), and biconcavity (where there is relative maintenance of the anterior and posterior heights with central compression of the end-plate regions). A number of morphometric approaches have been developed to quantify the shape of the vertebral body, and this has helped in defining the prevalence and incidence of vertebral fracture. A widely used clinical system is to classify vertebral fractures as mild (20%–25% height loss), moderate (>25%–40% height loss), or severe (>40% height loss).

A further problem in describing the epidemiology of vertebral fracture is that not all fractures come to clinical attention *(21–23)*. In the United States, about one in three vertebral deformities reaches immediate clinical attention through either back pain, height loss or other functional impairment *(24)*. Estimates for the proportion of vertebral deformities that reach primary care attention vary, however, in different countries *(21,24,25)*. In Sweden, approximately 23% of vertebral deformities come to clinical attention in women, and a somewhat higher proportion in men *(26)* (Table 2.1). A similar proportion has been observed in the placebo wing of multinational intervention studies *(27)*.

Table 2.1
Incidence of all morphometric and clinically evident vertebral fractures and the first morphometric and clinical fracture (per 100 000 per year) by age and site in men and women

	Any fracture				First fracture				Ratio (%)	
	Morphometric		Clinical		Morphometric		Clinical		Clinical/ morphometric	
Age range (years)	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
50–54	365	874	153	190	244	577	81	104	33	19
55–59	462	1164	193	253	311	762	111	148	36	20
60–64	592	1562	248	339	392	1021	155	215	39	21
65–69	767	2115	322	459	511	1376	215	303	42	22
70–74	1011	2891	424	628	666	1880	296	422	44	23
75–79	1348	3986	566	865	888	2583	407	599	46	23
80–84	1820	5544	744	1204	1191	3574	562	844	47	24
85–89	2485	7776	1043	1688	1613	4995	777	1184	48	24

Source: reference 26 (Table 2).

Falls account for only about one third of new clinical vertebral fractures, and most are associated instead with other activities such as lifting or changing position. The vast majority of vertebral fractures are a result of moderate or minimal trauma.

2.1.3 Distal forearm fracture

The most common distal forearm fracture is Colles fracture. This fracture lies within 2.5 cm of the wrist joint margin and is associated with dorsal angulation and displacement of the distal fragment of the radius. It may be accompanied by a fracture of the ulna styloid process. A Smith fracture resulting in ventral angulation usually follows a forcible flexion injury to the wrist and is relatively uncommon in the elderly.

The cause of fracture is usually a fall on the outstretched hand *(28)*. Although fractures of the wrist cause less morbidity than hip fractures, are rarely fatal, and seldom require hospitalization, the consequences are often underestimated. Fractures are painful, usually require one or more reductions and need 4–6 weeks in plaster. Approximately 1% of patients with a forearm fracture become dependent as a result of the fracture *(29)*, but nearly half report only fair or poor functional outcome at 6 months (30). There is a high incidence of algodystrophy which gives rise to pain, tenderness, stiffness and swelling of the hand, and more rarely to frozen shoulder syndrome *(31)*. Moreover, the risk of other osteoporotic fractures in later life is much increased after Colles fracture *(32)*.

2.2 Incidence of osteoporotic fractures

Despite a large number of studies that have examined the incidence of fractures by age and sex, our knowledge of the incidence and the pattern of fractures worldwide is incomplete.

2.2.1 Hip fracture

The incidence of hip fracture has been characterized in just over 30 countries worldwide *(33)*. In general, incidence rates for hip fracture increase exponentially with age in both men and women. In Scandinavia and the United States, the annual incidence rises from about 0.4 per 1000 in women at the age of 50 years, reaching about 68 per 1000 at the age of 85 years and over. Rates for white men at any age are about half this figure *(13)*. Overall, approximately 90% of all hip fractures occur among people aged 50 years and over, and 80% occur in women. The reason for the very high frequency in women is attributable to their longevity compared to men. The average age at which hip fractures occur is about 80 years in industrialized countries, but is less in countries with lower life expectancies. Age-adjusted and sex-adjusted hip fracture incidence rates are generally higher in white than in black or Asian populations *(34)*, although urbanization has led to higher hip fracture rates in Asia and certain parts of Africa. Furthermore, the pronounced female preponderance observed in white populations is not seen in countries with low fracture rates, e.g. among blacks or Asians, in whom the male and female rates are broadly similar.

Hip fractures also show a seasonal variation in incidence, being more frequent in the winter months in temperate climates. This is not, however, a result of slipping on snow or ice since hip fractures most commonly occur indoors, suggesting a contribution of vitamin D nutrition in their pathophysiology.

There is a remarkable heterogeneity in the age-adjusted and sex-adjusted incidence for hip fracture in various regions of the world *(13,34–37)*. The highest incidence rates have been observed in northern Europe and the United States. Even within Europe, there is considerable variation in hip fracture incidence. Thus, rates vary approximately 10-fold between Sweden and Turkey *(36,37)*. In the United States, the higher hip fracture rates among Caucasians than among people of African descent may be in part explicable on the basis of differences in BMD, but differences in BMD do not explain the lower rates in Hispanics and Asians *(38,39)*. Differences in BMD may explain differences in fracture risk between men and women within a country. They may also explain regional differences between urban and rural areas *(40,41)*. Differences in BMD worldwide are too small, however, to account for the very large variations in age-specific and sex-specific incidence (see section 3). Indeed in Asia, hip fracture rates are lower than in developed countries, despite lower values for BMD *(42)*. These variations imply an important role of environmental factors in the incidence of hip fractures. Ecological studies do not suggest important roles for body weight, cigarette smoking, alcohol, or calcium nutrition *(36,43)*. Nonetheless, the observation that differences in incidence between countries are much larger than those observed between men and women suggests that factors other than oestrogen deficiency play a crucial role. A plausible hypothesis is differences in the risk

of falls *(44)* and the force of impact. Asians, for example, appear to fall less than Caucasian populations *(45)* and their shorter stature provides a lower fall energy. The identification of these factors is an important area for further research.

2.2.2 Spine fracture

Epidemiological information on vertebral fractures is limited by the lack of a universally accepted definition of what constitutes a vertebral deformity, and because a substantial proportion of vertebral deformities are clinically silent or not attributable to osteoporosis. Scheuermann disease (osteochondritis) and vertebral osteoarthritis are common disorders that give rise to deformities not attributable to osteoporosis. The problem is compounded in that radiologically evident fractures are commonly not reported *(46)*.

Until recently, most information on spine fracture was from studies of prevalence. Radiographic surveys indicate that 19%–26% of postmenopausal white women have a morphometric vertebral fracture *(13,47–49)*. Most such fractures involve the mid-thoracic vertebra or the thoracolumbar junction. They are as frequent in Asians and native Mexicans as in white women *(50–52)*, but are less common in African American and Hispanic populations *(53,54)*.

It is of interest that the prevalence of morphometric vertebral deformities in men is as great as it is in women up to the age of 60 years *(49)*, possibly because some deformities in men are not related to fractures. In addition, severe trauma may account for over a third of clinically detected vertebral fractures in men, but only about 10% of those in women. It is also notable that the international variation in the prevalence of morphometric vertebral fractures is much less than that for hip fracture. Rates appear to vary 2-fold to 3-fold in different countries *(42)* (Table 2.2).

Table 2.2
Prevalence by age of vertebral fracture assessed by vertebral morphometry among women from different regions

Age range (years)	Beijing	Europe	Hawaii	Hiroshima	Minnesota	Taiwan
50–54	4.9	11.5	0	5.4	4.7	4.5
55–59	-	14.6	0	4.1	5.8	4.8
60–64	16.2	16.8	10	4.9	6.3	6.7
65–69	-	23.5	6.1	8.2	13.2	13.9
70–74	19.0	27.2	14.8	24.8	15.0	20.7
75–79	-	34.8	25.0	36.8	22.2	24.3
80–84	36.6	-	26.3	42.9	50.8	29.7
>85	-	-	-	25.0	50.8	-

Source: reference 42 (Table 3).

Incidence rates can be expressed as the incidence of vertebral deformity (morphometric fractures) or the incidence of clinically overt fractures (clinical vertebral fractures). Incidence rates for morphometric vertebral fractures have been obtained through the European Prospective Osteoporosis Study, representing many European countries. The available data indicate that the incidence of vertebral morphometric deformities, like that of other osteoporotic fractures, is greater in women than in men, and rises with age. The age-related increase is less steep than that of hip fractures and the variation between countries is less marked *(55)*. In the European Prospective Osteoporosis Study, men and women aged 50–79 years were enrolled from population registers in 19 European countries, and the incidence of new vertebral deformities was estimated from radiographs at baseline and at follow-up 4 years later. Overall, age-adjusted and sex-adjusted incidence rates for vertebral morphometric fractures were 1% per year among women and 0.6% per year among men *(55)*. Similar incidence estimates have been reported from the Study of Osteoporotic Fractures in the USA *(55)*, where spinal radiographs have been obtained in some 5000 women. Other sources of data for vertebral fracture incidence have included the Rotterdam study, and studies from Sweden (see Table 2.1), Japan and Mexico *(26,52,56–58)*.

The age-adjusted incidence of clinically diagnosed vertebral fractures has been estimated in Sweden. (see Table 2.3), the northern United States, and from the placebo arm of multinational studies of intervention *(21,26,27)*. Between the ages of 50 and 80 years, the incidence rises approximately 10-fold in women but only 5-fold in men *(26)*. The incidence of clinically evident vertebral fractures is 20%–40% that of morphometric fractures. For white women aged 50 years and over this has been estimated at 5.3 per 1000 person–years with comparable male rates being about half this figure.

The incidence of vertebral fractures can also be studied from hospital discharge rates. As calculated from register-based studies, the incidence of hospitalized vertebral fracture is substantially smaller than estimates of clinical vertebral fracture *(22)*. There is, however, a marked variation in the estimated number of people with vertebral fractures who are hospitalized between different countries, with a range from 2% to 10% *(17,22,25,59)*. In a study of hospitalization discharge rates in Europe, there was a striking geographic correlation among countries between the incidence of hospitalization for vertebral fractures and for those of the hip *(22)*.

2.2.3 Forearm fracture

Forearm fractures display a different pattern of incidence from that of hip or spine fractures. In many countries, rates increase linearly in white women between the ages of 40 and 65 years and then stabilize *(13)*. In other countries, Sweden for example, incidence rises progressively with age. Forearm fractures are much less frequent in men; the incidence is commonly constant between the ages of 20 and 80 years, and where this rises, it does so

at a much slower rate than in women *(13)*. The reason for the plateau in female incidence in some countries is not known, but may relate to a change in the pattern of falling with advancing age *(60)*. As in the case of hip fractures, the majority of wrist fractures occur in women and around half occur in women aged 65 years and over. Forearm fractures are less frequent in African American *(61,62)* and Japanese populations *(63)*, but there is still a substantial excess female risk. In Africa and South-East Asia, however, distal forearm fractures are even less common and rates for women are little more than those for men *(64)*.

2.2.4 All fractures

A majority of fractures in patients aged 50 years or more is attributable to osteoporosis. As mentioned, attempts to classify fractures as being a result of osteoporosis are imperfect. Fractures considered in this report to be osteoporotic are shown in Table 2.3 *(12)*. The incidence rates of proximal humeral, pelvic and proximal tibial fractures rise steeply with age and are greater among women than among men. At the age of 50 years, rib, vertebral and forearm fractures are the most commonly found fractures in men, whereas in women the most common fractures comprise distal forearm, vertebral, rib and proximal humeral fractures. Over the age of 85 years, hip fracture is the most frequent fracture among men and women, but still accounts for only approximately one third of all osteoporotic fractures (Table 2.4).

Table 2.3
Incidence of osteoporotic fractures (per 100 000 population per year) by age and site in men and women from Sweden

Site of fracture	Age range (years)							
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89
Men								
Vertebra	195	119	226	242	499	619	933	1 194
Ribs	324	750	399	790	855	805	3 072	3 007
Pelvis	12	16	21	31	51	80	179	288
Humeral shaft	22	10	20	31	69	60	78	168
Proximal humerus	65	31	60	92	207	179	235	505
Clavicle, scapula, sternum	116	139	89	216	198	81	659	859
Hip	42	68	134	274	495	940	1 923	3 241
Other femoral fractures	15	18	24	41	43	51	88	128
Tibia and fibula[a]	-	-	-	-	-	-	-	-
Distal forearm	101	151	140	282	89	175	259	323
Total	892	1 302	1 113	1 999	2 506	2 990	7 430	9 713
Women								
Vertebra	161	158	303	439	778	1 111	1 163	1 641
Ribs	126	162	167	340	433	903	1 400	3 194
Pelvis	9	16	29	47	125	203	436	698
Humeral shaft	41	42	42	117	128	210	195	373
Proximal humerus	124	127	126	352	384	629	585	1 120
Clavicle, scapula, sternum	77	97	42	145	121	362	415	356
Hip	41	91	181	387	817	1 689	3 364	5 183
Other femoral fractures	11	17	36	52	89	150	239	404
Tibia and fibula	60	79	88	98	106	145	146	207
Distal forearm	417	456	568	691	904	1 032	1 208	1 387
Total	1 067	1 245	1 582	2 668	3 885	6 434	9 151	14 563

Source: reference *12* (Table 2).
[a]Excluded in men.

Table 2.4
Proportion (%) of osteoporotic fractures at different sites in men and women from Sweden by age

Site of fracture	Age range (years)							
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89
Men								
Vertebra	21.9	9.1	20.3	12.1	19.9	20.7	12.6	12.3
Ribs	36.3	57.6	35.8	39.5	34.1	26.9	41.3	31.0
Pelvis	1.3	1.2	1.9	1.6	2.0	2.7	2.4	3.0
Humeral shaft	2.5	0.8	1.8	1.6	2.8	2.0	1.0	1.7
Proximal humerus	7.3	2.4	5.4	4.6	8.2	6.0	3.2	5.1
Clavicle, scapula, sternum	13.0	10.7	8.0	10.8	7.9	8.7	8.9	8.8
Hip	4.7	5.2	12.0	13.7	19.8	31.4	25.9	33.3
Other femoral	1.7	1.4	2.1	2.1	1.7	1.7	1.2	1.3
Tibia and fibula[a]	-	-	-	-	-	-	-	-
Distal forearm	11.3	11.6	12.6	14.1	3.6	5.9	3.5	3.3
Women								
Vertebra	15.1	12.7	19.2	16.4	20.0	17.3	12.7	11.3
Ribs	11.8	13.0	10.6	12.7	11.1	14.0	15.3	21.9
Pelvis	0.8	1.3	1.8	1.8	3.2	3.2	4.8	4.8
Humeral shaft	3.8	3.4	2.7	4.4	3.3	3.3	2.1	2.6
Proximal humerus	11.6	10.2	8.0	13.2	9.9	9.8	6.4	7.7
Clavicle, scapula, sternum	7.2	7.8	2.7	5.4	3.1	5.6	4.5	2.4
Hip	3.8	7.3	11.4	14.5	21.0	26.3	36.8	35.6
Other femoral	1.0	1.4	2.3	1.9	2.3	2.3	2.6	2.8
Tibia and fibula	5.6	6.3	5.6	3.7	2.7	2.3	1.6	1.4
Distal forearm	39.1	36.6	35.9	25.9	23.2	16.0	13.2	9.5

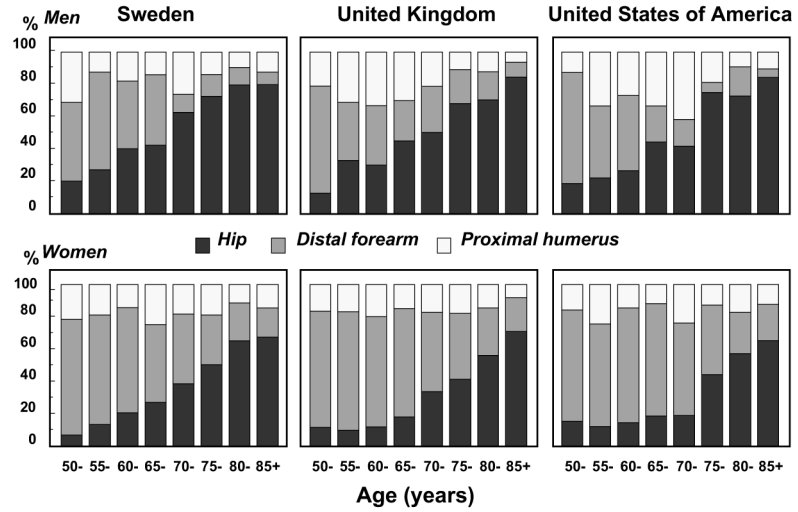
Source: reference *12* (Table 3).

[a]Excluded in men.

2.3 Pattern of fractures

The available information suggests that the pattern of fractures is similar in Australia, Sweden, the United Kingdom and the United States, despite differences in the absolute incidence *(1,38,65,66)*. For example, the annual incidence of forearm, proximal humeral and hip fracture in women aged 80–84 years is 5157 per 100 000, 2558 per 100 000, and 3206 per 100 000 in Sweden, the United Kingdom and the United States, respectively *(12,38,65)*, but the pattern of these fractures with age is remarkably similar (Fig. 2.1). The relationship between the incidence of hip, vertebral and forearm fracture is also similar between these series and in Australia *(66)*. Within the USA, the pattern appears to be similar among blacks and whites. For example, among white women aged 65–79 years, the relative frequency of hip, distal forearm and proximal humerus fractures is 43%, 38% and 19%, respectively. For black women, the distribution is 45%, 36% and 18% *(61)*.

Fig. 2.1
Pattern of common osteoporotic fractures expressed as a proportion (%) of the total in Sweden, the United Kingdom and the United States



Source: reference 12 (Fig. 3).

This commonality of pattern is supported by register studies which indicate that in those regions where hip fracture rates are high, so too is the risk of Colles' fracture and vertebral fractures that require hospital admission *(13,22)*. Studies of the incidence of morphometric vertebral fractures, however, indicate less commonality.

Since the pattern of osteoporotic fractures appears to be broadly similar in the developed countries, this permits the size of the problem of osteoporosis to be determined in those countries where the epidemiological information is not complete. For example, between the ages of 50 and 54 years, fractures of the hip account for 4.7% of all osteoporotic fractures in men and for 3.8% in women. Thus, osteoporotic fractures account in this age range for 21 times or 26 times the number of hip fractures in men and women, respectively. Such calculations have been used to estimate the burden of osteoporotic fractures (see later in this section).

The societal burden of osteoporosis is highest in North America and in European countries, particularly in Scandinavia *(22,35,37)*. The risk of osteoporotic fractures is lower in other regions such as Africa and Asia *(67,68)*. Osteoporotic fractures are also less common in men. The reasons relate to the higher skeletal mass in men than in women at the time of skeletal maturity *(69)* and the slower rates of bone loss in men compared to women. In addition, men live several years less than women, so that they are exposed to lower BMD for a shorter period of their lifetime.

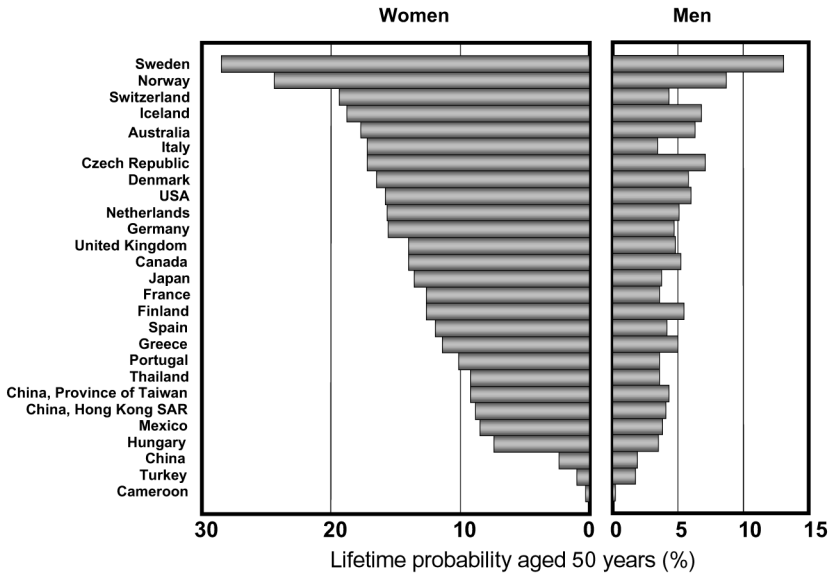
Lifetime risk depends both on fracture incidence and life expectancy. At the age of 50 years, the lifetime risk of hip fracture in women in Scandinavia exceeds 20% and is nearly as high in North America *(70)* (Table 2.5). In the USA, the lifetime risk of a hip, spine or forearm fracture has been estimated at 40% in white women from the age of 50 years onwards, and 13% in white men *(13)*. These figures are conservative, since they take into account only vertebral fractures that have come to clinical attention, and do not include osteoporotic fractures at other sites. Estimates of the variation in lifetime risk are more complete for hip fracture than other fractures. Such data suggest that lifetime risks vary markedly around the world *(33,71,72)* (Fig. 2.2). The variation is related more to variations in hip fracture incidence than to variations in mortality risk.

Table 2.5
Remaining lifetime probability (%) of common osteoporotic fractures in Swedish men and women aged 50 years

Site of fracture	Women aged 50 years	Men aged 50 years
Hip	22.9	10.7
Distal forearm	20.8	4.6
Spine (clinical)	15.1	8.3
Proximal humerus	12.9	4.9
Any of the above	46.4	22.4

Source: reference 70 (Table 3).

Fig 2.2
International variations in remaining lifetime probability of hip fracture at the age of 50 years in men and women



Source: references 33, and new data from references 71, 72.

Calculations of lifetime risk based on current life expectancy assume that life expectancy will no longer continue to improve, which given past trends is an unreasonable assumption. Factoring in improvements in life expectancy increases estimates of lifetime risk. Based on current mortality in Swedish men and women, the lifetime risk of hip fracture is 8.1% and 19.5%, respectively, but these figures rise to 11.1% and 22.7%, respectively, when based on predicted mortality trends *(73)*.

2.4 Mortality from osteoporotic fractures

It is widely recognized that osteoporosis is associated with increased mortality *(74–77)*. For each standard deviation decrease in bone mineral density, the mortality risk is increased approximately 1.5-fold. Excess mortality is also well described in patients who develop fractures at sites characteristic for osteoporosis, including the spine (radiographic and clinical fractures) and hip *(17,75,78–86)*. For morphometric vertebral deformities, the increase in risk is lower than that for clinical vertebral fractures but increases with the number of prevalent fractures *(82,83)*. For clinically apparent vertebral fractures the risk of death appears to be much higher, and the presence of multiple fractures further increases this risk *(79, 83,87)*. Some studies suggest that the mortality risk appears to be higher after vertebral fracture in men than in women, even accounting for the higher mortality rates for men in the general population. In the larger studies, the differences in mortality between men and women after vertebral fracture were not marked when account was taken of age *(88)*.

In contrast, no excess mortality has been shown following fractures of the distal forearm *(79,80,89)*.

In the case of hip fracture, most deaths occur in the first 3–6 months following the event *(81,84,86,90)*, and excess mortality decreases thereafter, though the mortality does not reach that of the general population *(91)*. Comparisons of death rates by age suggest that the relative mortality risk is higher at lower ages, and figures for Sweden are supplied in Table 2.6 *(92)*. The reason for the difference in mortality by age is unclear. This might be a result of greater comorbidity among those who have a hip fracture at the age of 60 years than at the age of 80 years. Some investigators have reported increased mortality in men compared with women, but others show that when standardized to the higher mortality of men, the excess mortality in men and women is approximately the same.

Table 2.6
Relative risk of death after fracture at the sites shown in men and women from Sweden compared with that of the Swedish general population, by age (years)

Year after fracture	Spine		Hip		Shoulder		Forearm	
	Age 60	Age 80	Age 60	Age 80	Age 60	Age 80	Age 60	Age 80
Men								
0	13.4	3.9	11.6	3.1	4.7	3.7	1.1[a]	0.9[a]
1	10.7	3.2	10.2	3.7	4.0	3.2	1.1[a]	0.9[a]
2	8.5	2.5	8.8	3.3	3.4	2.8	1.1[a]	0.9[a]
3	6.8	2.0	7.7	2.9	2.9	2.4	1.2[a]	1.0[a]
4	5.4	1.6	6.7	2.5	2.5	2.0	1.2[a]	1.0[a]
5	4.3	1.3	5.8	2.2	2.1[a]	1.8[a]	1.2[a]	1.0[a]
Women								
0	12.9	3.4	10.4	3.4	3.1	2.2	1.8	1.3[a]
1	10.3	2.7	9.1	3.0	2.7	1.9	1.8	1.3
2	8.3	2.1	8.0	2.5	2.3	1.6	1.8	1.3
3	6.6	1.7	7.0	2.2	2.0	1.3[a]	1.8	1.3
4	5.3	1.3	6.2	1.9	1.7[a]	1.1[a]	1.9	1.3[a]
5	4.3	1.0[a]	5.4	1.6	1.4[a]	0.9[a]	1.9	1.2[a]

Source: reference 92 (Table 5).

[a]Not significantly different from the general population.

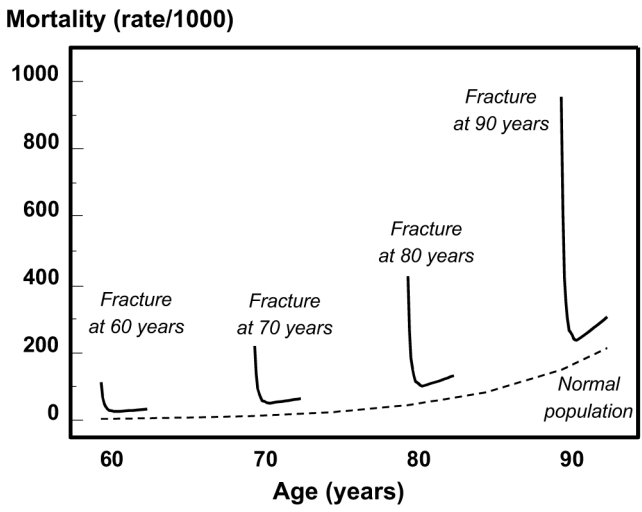
In large series it has been possible to characterize the pattern of mortality with time after hip fracture *(91)* (Fig. 2.3). Note the steep decrease in mortality following the fracture. After a nadir value, mortality increases at a rate greater than that of the general population. This type of analysis suggests that 24% (17%–32% depending on age) of all deaths associated with hip fracture might be causally related to the fracture itself. Other approaches to quantify the components of hip fracture mortality *(19,93,94)* come to broadly similar conclusions. The estimates of deaths in Sweden that are causally related to hip fracture are appreciable, suggesting that more than 1% of all deaths are attributable to hip fracture, a somewhat higher proportion than that of deaths attributed to pancreatic cancer and somewhat lower than that of deaths attributed to breast cancer (Table 2.7).

Table 2.7
Principal causes of death from selected diseases in Swedish men and women in 1998

	Men	Women	Total	%
Acute myocardial infarction	7 113	5 335	12 448	13.3
Cardiovascular accident	4 411	6 069	10 480	11.2
Lung cancer	1 761	1 112	2 873	3.1
Prostate cancer	2 480	0	2 480	2.6
Chronic obstructive airways disease	944	723	1 667	1.8
Diabetes	744	819	1 563	1.7
Breast cancer	11	1 549	1 560	1.7
Hip fracture	566	854	1 420	1.5
Pancreatic cancer	603	736	1 339	1.4
Suicide	880	349	1 229	1.3
Atrial fibrillation	413	687	1 091	1.2
Stomach cancer	489	334	823	0.9
Transport accidents	422	142	564	0.6
Smoke inhalation and fire	85	53	138	0.2
All deaths	46 840	46 788	93 628	100

Source: reference 91 (Table 4).

Fig. 2.3
Pattern of mortality in the general population following hip fracture at the ages shown



Source: reference 91 (Fig. 2, p. 471).

By contrast to hip fracture, where most excess deaths occur early after the event, the pattern of mortality following morphometric vertebral fractures shows that survival decreases progressively with time *(80)*. For clinical vertebral fracture there appears, however, to be a high mortality risk that decreases with time, though does not reach that of the general population (see Table 2.6). In a large series of 16 000 hospitalized patients, approximately 28% of deaths were considered to be causally related to the fracture event

(88). It should be noted that the causal attribution of deaths following a vertebral fracture relates only to patients admitted to hospital who may have higher comorbidity than those with asymptomatic fractures or those treated at home. In Sweden, approximately 10% of women with vertebral fractures (15% of men) are admitted to hospital. The low admission rate may result in large selection biases that may affect estimates of both the causally-related and the associated deaths.

More recently, it has become apparent that similar patterns of mortality are found after other osteoporotic fractures. In one series, excess mortality, shown for spine, hip and shoulder fractures, was higher at younger ages and declined significantly with time after the fracture event (see Table 2.6) *(89)*. In common with the findings of other investigators, no excess mortality was observed for forearm fractures. The declining death risk with time after humeral fractures suggests that there may also be causally-related deaths, but much larger numbers of fractures would be needed to quantify this.

If some deaths are causally related to vertebral, hip and other osteoporotic fractures, then it might be expected that interventions that decreased the risk of these fractures would also increase survival. This has important implications for health economic modelling, and increased survival (at least for a short period after fracture) would be an important dividend of treatment. Previous studies have shown lower morbidity in patients treated with bisphosphonates because of the decrease in subsequent fracture risk *(95,96)*. There are, however, no data to suggest that there is a survival advantage associated with the prevention of fracture. This question is unlikely to be resolved from empirical observation. Assume, for example, that a random sample of women at the age of 80 years are recruited from the normal population and enrolled into a placebo controlled trial for 3 years. On the assumption that the intervention decreased vertebral fracture frequency by 50%, the probability of dying as a consequence of vertebral fracture would be 14.104% for the placebo group and 14.099% for the actively treated group. In order to achieve power of 80% at a significance level of 0.05 with a two tailed test, the sample size in each group would need to be 533 million, exceeding the world population at this age. For this reason, knowledge in this field is likely to remain based on indirect calculations of the type presented above.

2.5 Disability attributable to osteoporotic fracture

The common osteoporotic fractures are a major cause of morbidity in the population. Hip fractures cause acute pain and loss of function, and nearly always lead to hospitalization. Recovery is slow and rehabilitation is often incomplete, with many patients permanently institutionalized in nursing homes. Vertebral fractures may cause acute pain and loss of function but may also occur without serious symptoms *(97–99)*. Vertebral fractures often recur, however, and the consequent disability increases with the number of

fractures. In Sweden, approximately 10% of women with a vertebral fracture (15% of men) are admitted to hospital *(26)*. Distal radial fractures also lead to acute pain and loss of function, but functional recovery is usually good or excellent. In addition to pain and disturbance of physical function, a fracture may decrease mobility and social interaction and cause emotional problems (100). All these characteristics determine quality of life.

There are two approaches to the estimation of quality of life. The first is a generic approach which poses general questions on health status that could be used to compare various diseases. Whereas the strength of this approach lies in the ability to compare different diseases, it is not specific for any disease or age group. Examples of generic questionnaires are the Nottingham Health Profile *(101)*, the Sickness Impact Profile *(102)*, the Short Form 36 of the Medical Outcomes Study *(103,104)*, and the EuroQOL (EQ-5D) *(105)*.

In contrast, disease-specific or disease-targeted questionnaires are designed for patients with a specific disease or specific outcome, such as osteoporosis in general or a type of fracture. These questionnaires contain more specific questions and thus discriminate between individuals with and without the disease, but a disadvantage is that different diseases cannot be compared *(106,107)*. Both generic and disease-specific questionnaires usually comprise several domains, such as pain, physical function, mobility, general health, emotional impact and fears. Some of the characteristics of disease-specific instruments for osteoporosis are shown in Table 2.8 *(100,108-115)*.

Table 2.8
Characteristics of quality of life questionnaires specific for osteoporosis

Instrument	Acronym	Number of questions	Domains	References
Osteoporosis quality of life questionnaire[a]	OQLQ	30	Physical function, activities of daily living, emotional function	Cook et al., 1993 (109) Osteoporosis Quality of Life Study Group, 1997 (110)
Osteoporosis functional disability questionnaire[a]	OFDQ	69	General health and back pain, activities of daily living, socialization, depression, confidence	Helmes et al., 1995 (111)
Osteoporosis targeted quality of life questionnaire[a]	OPTQOL	33	Physical activity, adaptation, fears	Lydick et al., 1997 (112) Chandler et al., 1998 (113)
Osteoporosis assessment Questionnaire[b]	OPAQ	67	Physical function, emotional status, symptoms, social interactions	Randell et al., 1998 (114)
Quality of life questionnaire of the European Osteoporosis Foundation (now the International Osteoporosis Foundation)[b]	QUALEFFO-41	41	Pain, physical function, social function, general health perception, mental function	Lips et al., 1997, 1999 (100,108)
Questionnaire quality of life in osteoporosis[b]	QUALIOST	23	Physical function, emotional status	Marquis, Cialdella & De La Loge, 2001 (115)

[a] Interviewer-based.
[b] Can be self-administered.

2.5.1 Quality of life following osteoporotic fractures

Impairments of quality of life following fracture are ill-documented for many fracture outcomes, but a considerable body of information exists for hip fracture, somewhat less for vertebral fracture and even less for forearm fractures *(116)*. This relates to the paucity of disease-specific instruments.

Hip fracture

Collection of data on quality of life is impaired by the advanced age of the patients. Many patients have impaired cognition before the fracture and, in addition, the hospital admission and operation may cause disorientation. Notwithstanding, it is clear that morbidity is considerable. Only half of the

hip fracture patients who survive will walk again, but often not to the same degree as before the hip fracture event *(117)*. The best predictor of recovery is pre-fracture health status *(118)*. In a prospective study of individuals with hip fracture *(119)*, only 8% were able to climb stairs compared with 63% before the fracture; and only 6% could walk half a mile compared with 41% before the fracture. In a case-control study, hip fracture patients were 4.2 times more likely to be unable to function in a wider community two years after the fracture and 2.6 times more likely to be functionally dependent than controls *(120)*.

Vertebral fracture

A number of studies have shown impairment of health status in patients with vertebral fractures *(95,121–126)*. Osteoporosis-specific questionnaires have documented significant decrements in patients with prevalent vertebral fractures compared to non-fracture controls in the context of a clinical trial in osteoporosis *(24,123,127)*. Quality of life decreased significantly with increasing number of prevalent vertebral fractures and the impact of lumbar fractures appeared to be greater than that of thoracic fractures. For example, with the QUALEFFO instrument, patients without vertebral fractures had a mean total score of 25.6 ± 14.3 and those with more than three thoracic fractures a score of 35.8 ± 19.7, whereas patients with more than three lumbar fractures had a score of 53.2 ± 15.8.

Approximately 4% of women with a clinical vertebral fracture become dependent in the activities of daily living *(28)*. Quality of life becomes progressively impaired as the number and severity of vertebral fractures increases *(24)*. Most of these difficulties are confined to those with severe or multiple vertebral deformities *(23)*, but the adverse influence of vertebral fractures on many of the activities of daily living is almost as great as that seen for hip fracture *(128)*, and is reviewed later.

Changes in quality of life following incident vertebral fractures have also been assessed in the context of clinical trials *(123,127)*. Quality of life was significantly worse in those with a new vertebral fracture. This was also true for patients who had vertebral fractures that were only diagnosed on a scheduled radiograph and did not, therefore, come to clinical attention at the time of fracture *(96)*. This confirms the view that sub-clinical vertebral fractures, even when not immediately diagnosed, cause a decrease in quality of life *(127)*.

Forearm fractures

There are no disease-specific instruments available for forearm fractures, though these are being developed by the International Osteoporosis Foundation.

2.5.2 Utility and disutility following osteoporotic fractures

Utility is a value attached to a specific health state and is derived from generic rather than disease-specific instruments. Utility takes the preferences of individuals into account *(129)* using a standard gamble or time trade-off method. Utility assessment results in one single value for the patient's health status, ranging from zero (death) to one (perfect health). These values can be used to calculate loss or gain of quality-adjusted life years (QALYs). Thus, when a certain disease causes a utility change from 1.0 to 0.6 for one year, the utility loss is 0.4 and the QALY loss is 0.4. When the same disease causes a utility loss of 0.4 for 6 months or 2 years, the QALY loss is 0.2 or 0.8, respectively. The QALY loss (or disutility) is equivalent to utility loss with time. Instruments used for the calculation of utility and QALYs include the EQ-5D or EuroQOL (105), and the health utility instrument (130). The most widely used for economic modelling in osteoporosis is the EQ-5D. Valuations can be done by expert panels and by the time trade-off method among healthy controls to obtain the utility values *(105,131,132)* or utility values can be obtained from patients. The utility values obtained by experts or from healthy controls may differ substantially from data obtained in patients *(133)*.

Utility data for patients with different fractures have recently been reviewed (134). Most data have been obtained with the time trade-off method. These indicate that utility is lower in patients after hip and vertebral fracture. Other methods such as the standard gamble and health utility index yield somewhat different results (130,133,135,136). Two studies in older women who were asked to value different outcomes for hip or vertebral fractures showed that older women without osteoporotic fractures judged a worse quality of life after fracture than the patients themselves *(133,136)*.

The utility loss after fracture has also been estimated by expert panels *(137,138)*. Although fracture outcomes may be given different weights from those obtained from patients or the general population, they have the merit of being able to consider all osteoporotic fractures and form the basis for computing the burden of osteoporosis in society. The health state values of the National Osteoporosis Foundation have recently been modified in the light of empirical prospective information available for vertebral fracture which indicates that disutility may have been markedly underestimated. In a prospective study, 40 patients attending the Accident and Emergency Department at Malmo Hospital were studied by administering the EQ-5D at 14 days, and 6, 9 and 12 months after the fracture event (26). From a clinical vertebral fracture, the utility loss was 0.260 in the first year, which was greater than that for hip fracture *(0.149)*, or fracture of the proximal humerus *(0.153)* and forearm fracture *(0.017)*. The utility loss after a clinical vertebral fracture is much greater than previously recognized, but accords with independent observations that the effect of vertebral fracture on many of the activities of daily living is almost as great as that for hip fracture *(128)*. Utility values of health state, according to the site of fracture, are

shown in Table 2.9 *(26)*. These are shown as multipliers. This means that the average health state value for the age-matched and sex-matched population needs to be multiplied by the given value to estimate the health state value in the first or second year after a fracture.

Table 2.9
Utility values of health state, by site of fracture

	Multiplier for utility		Multiplier for utility loss	
Fracture site	1st year	2nd year	1st year	2nd year
Spine (clinical)	0.626	0.909	0.374	0.091
Spine (morphometric)				
Men	0.777	0.912	0.223	0.088
Women	0.820	0.913	0.180	0.087
Ribs	0.977	0.999	0.003	0.001
Pelvis	0.794	0.815	0.206	0.185
Humerus	0.794	0.973	0.206	0.027
Clavicle, scapula, sternum	0.977	0.999	0.003	0.001
Hip	0.792	0.813	0.208	0.187
Other femoral	0.792	0.813	0.208	0.187
Tibia	0.794	0.926	0.206	0.074
Forearm	0.977	0.999	0.003	0.001

Source: reference 26 (Table 1).

The utility loss after a morphometric deformity not coming to clinical attention is not known. Patients with sub-clinical fractures are reported to have impaired activities of daily living (ADLs) that are about one third to one half of the ADL impairment seen in patients with clinical fracture*s (95,96)*. They also have impaired scores on the QALEFFO scale *(24)*. On this basis, it has been assumed that the utility loss of subclinical fracture is about one third that of a clinically overt fracture, since a proportion of the decrement observed may have resulted from comorbidity. From the ratio of clinical to non-clinical fractures (42% in men and 23% in women), the utility loss from all vertebral fractures can be computed (see Table 2.9).

When utility loss cumulated over a lifetime is computed (disutility), the burden of different types of fracture can be compared *(26)*. As expected, average disutility is greatest in the case of hip fractures over all ages, intermediate for vertebral fractures and lower for humeral and Colles fracture (Table 2.10). Disutility values are higher for the younger age groups because of their higher life expectancy and higher population tariff value. Considering all vertebral fractures, rather than clinical spine fractures alone, decreases the average disutility of vertebral fractures by 15%–30% depending on age. In men and women aged 50 years, a clinical spine fracture incurred a disutility of 62% of that for a hip fracture, and was substantially higher than the loss incurred from humeral fractures (23% of the loss incurred by a hip fracture). The comparative disability from each fracture type can be computed, which varies somewhat by age (see Table 2.10). For example, in women between the ages of 85 and 89 years, a hip fracture would incur a

disutility of 0.57, whereas a morphometric spine fracture would incur a disutility of 0.32. Thus approximately two spine fractures incur the same disability as one hip fracture. Similarly, three humeral fractures are approximately equivalent to the disutility incurred by one hip fracture.

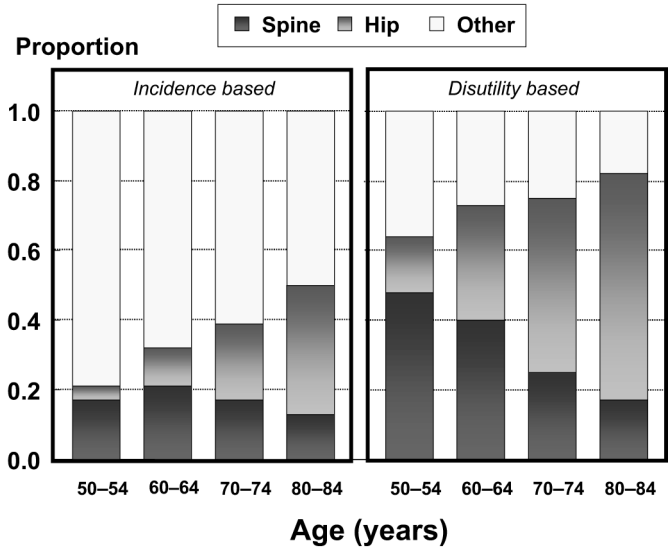
Table 2.10
Disutility for different fracture types by age, adjusted for the population tariffs

Site of fracture	Age range (years)							
	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Men								
Morphometric spine	0.887	0.800	0.757	0.713	0.714	0.557	0.420	0.350
Clinical spine	1.026	0.938	0.895	0.850	0.768	0.687	0.538	0.472
Humerus	0.383	0.353	0.339	0.327	0.301	0.277	0.228	0.212
Hip	1.643	1.491	1.402	1.304	1.148	0.980	0.701	0.943
Forearm	0.010	0.009	0.009	0.009	0.008	0.007	0.005	0.005
Women								
Morphometric spine	0.857	0.640	0.621	0.733	0.622	0.545	0.444	0.321
Clinical spine	1.053	0.751	0.734	0.917	0.790	0.706	0.594	0.460
Humerus	0.392	0.282	0.278	0.349	0.305	0.279	0.243	0.200
Hip	1.692	1.193	1.149	1.430	1.202	1.041	0.829	0.570
Forearm	0.011	0.007	0.007	0.009	0.008	0.007	0.006	0.004

Source: reference 26 (Table 6).

Such data permit the quantification of the morbidity of different fracture types in the population. For example, in women between the ages of 50 and 54 years, clinical spine fractures account for 17% of all osteoporotic fractures. When this incidence is adjusted for disutility, then clinical spine fractures account for 48% of the morbidity at that age. In women aged 80–84 years, hip fractures account for 37% of all fractures but, when adjusted for disutility, account for 65% of the morbidity in that age group. Further examples are provided in Fig. 2.4 *(26)*. An appreciation of the disutility in populations permits the computation of the burden of disease in society.

Fig. 2.4
The proportion of osteoporotic fractures by age at different sites (left-hand panel) and their proportional morbidity (right-hand panel) in men and women from Sweden



Source: reference 26 (Table 7, p. 24).

2.6 Global burden of disease

Osteoporosis is increasingly recognized as an important public health concern because of the fractures that arise *(139)*. Of the fractures associated with osteoporosis, most attention has been given to hip fracture, in part because of the more complete epidemiological information available compared with other fractures, and particularly because hip fracture accounts for the majority of direct medical costs and morbidity in the community *(17,140–145)*. Despite its significance worldwide, there are few estimates of the global burden of osteoporosis. Three studies have provided calculations of the current number of hip fractures and those expected in the future, based on the expected changes in the population demography with or without assumptions concerning secular trends in fracture incidence *(67,68,89)*. These studies arrive at broadly similar conclusions and indicate that the number of hip fractures is now greatest in the developed world, but is set to increase markedly in developing countries, particularly in Asia. In the absence of information on health-care costs worldwide, it has been difficult to assess the global burden of disease in monetary units *(142)*.

A general approach to quantifying the burden of disease, favoured by WHO and the World Bank, is to assess the disability incurred by disease, including deaths attributable to the disorder as well as the disability that arises in survivors *(146)*. The approach, based on disability and life years lost, permits a comparison across diseases *(147)*.

The number of hip fractures worldwide estimated for 1990 amounted to 1.3 million in men and women *(92)* (Table 2.11). Of these, 69% occurred in women. The female to male ratio (2.2 in the world overall) varied between regions, being highest in Eastern Europe and the established market economies (4.0 and 3.2, respectively). In India and China, more hip fractures occurred in men than in women (female to male ratios of 0.8 and 0.9, respectively). In other regions, the female to male ratio varied from 1.2 to 2.2. Slightly more than half of all hip fractures occurred in the established market economies (north America, Australasia, western Europe and Japan).

Table 2.11
Estimated burden of hip fracture worldwide in 1990

	Men	Women	Total
Number of hip fractures	404 912	908 613	1 313 525
Patients suffering consequences of hip fracture	1 206 051	3 275 490	4 481 541
Deaths after hip fracture	246 289	491 818	738 107
Deaths attributable to hip fracture	61 572	122 954	184 526
Years of life disabled	332 370	880 812	1 213 182
Years of life lost	355 038	595 846	950 884
Disability-adjusted life years	924 000	1 998 000	2 922 000

Source: reference 92 (Tables 1–6).

By estimating the time course of disutility, the number of patients suffering the consequences of hip fracture can be computed. In 1990, these amounted to 4.5 million worldwide, estimated from an average duration of disability following hip fracture of 3.0 and 3.6 years in men and women, respectively. The annual number of deaths in 1990 was estimated at 738 000, of which 67% were in women. Approximately half were in the established market economies (49%). From previous calculations, it can be inferred that approximately 25% of associated deaths resulted from the hip fracture event itself. Thus, deaths causally related to hip fracture amounted to 185 000 in 1990. The estimated number of life years disabled is also shown in Table 2.11. A total of 1.2 million years of life disabled occurred in 1990, the majority of which (55%) were in the established market economies. The life-years lost from hip fracture amounted to 951 000 years in 1990 alone. Note that the life years lost are weighted by age, and the weighting attributes a greater value to a year during young adult life than to a year in the life of a child or an elderly person *(146)*. For example, a life year valued at 1.0 at the age of 55 years is valued at 0.8 at the age of 60 years and 0.7 at the age of 70 years. The weighting is used to assess disability-adjusted life years and, in 1990, these were estimated to be 2.9 million.

In the present analysis, hip fractures were identified as a major cause of premature death. In the established market economies, the global burden in terms of disability was somewhat less than that for rheumatoid arthritis, but greater than that of cancer of the stomach, ovaries or cervix (Table 2.12). In these regions, hip fracture accounted for 1.4% of the burden of disease, though much less (0.1%) worldwide *(92)*. The burden of disease is, however, greater when account is taken of all osteoporotic fractures, rather than hip fracture alone (see section1).

Table 2.12
Disability-adjusted life years (DALYs) lost among women from established market economies, by cause

Cause	DALYs (thousand)	%
All causes	437 714	100
Ischaemic heart disease	3 407	7.8
Cardiovascular disease	2 510	5.7
Breast cancer	1 436	2.8
Diabetes mellitus	1 203	2.8
Lung cancer	970	2.2
Chronic obstructive pulmonary disease	953	2.2
Colon and rectal cancer	786	1.8
Rheumatoid arthritis	762	1.7
Hip fracture	591	1.4
Cirrhosis of the liver	500	1.1
Stomach cancer	403	0.9
Ovarian cancer	377	0.9
Iron deficiency anaemia	364	0.8
Parkinson disease	285	0.7
Cervical cancer	191	0.4

Source: reference 92 (Table 8).

It should be recognized that epidemiological information on hip fracture rates is scanty in several regions of the world. Indeed, there are no reliable data for India, where it has been assumed that hip fracture rates are similar to those of China. India, however, contributed only 8% to the global burden of osteoporosis. The greatest confidence can be placed on incidence rates in the established market economies, a region that accounted for the greatest morbidity. There are also scanty data on the mortality attributable to hip fracture worldwide. In the analysis above, it has been assumed that the proportional excess mortality is similar to that of Sweden and the causal mortality is also consistent with that derived from Sweden. The data on outcomes in Sweden may not be applicable elsewhere, where surgical management and post-fracture care may be less than optimal. If so, the assumptions made here would underestimate the mortality after hip fracture. The same holds true for morbidity. Estimates of morbidity are critically dependent on the adequacy of estimates of the QALYs lost, which are also derived from the established market economies. Thus, the assumptions made are conservative, but nevertheless indicate that hip fracture is an important cause of death and disability, particularly in the developed regions of the world. In view of the high morbidity occasioned by other osteoporotic

fractures, particularly in young people, it will be important to document the global burden of disease taking these additional fractures into account.

2.7 Future predictions

The financial and health-related costs of osteoporosis can only rise in future generations *(148)*. Life expectancy is increasing around the globe, and the number of elderly individuals is rising in every geographic region. There are an estimated 323 million individuals aged 65 years or more at present, and this number is expected to reach 1555 million by the year 2050 *(149)*. These demographic changes alone can be expected to cause the number of hip fractures to increase from about 1.5 million in 1990 to between 4.5 and 6.3 million in 2050 *(67,68)*. Using current hip fracture incidence in various parts of the world, it can be estimated that about half of all hip fractures among elderly people in 1990 occurred in north America and Europe. By 2050, however, the rapid ageing of the Asian and Latin American populations will result in the north American and European contribution falling to only 25%, with over half of all hip fractures then occurring in Asia.

In Europe, the size of the population is expected to increase by 26% in women and by 35% in men between the years 2000 and 2050. The increase will be most marked in elderly people at the age when hip fractures are most common *(150)*. Between 2000 and 2050, the population aged 80 years or more will increase by 160% in women and by 239% in men (Table 2.13).

Table 2.13
Percentage increase expected in the male and female population of Europe, by age category in years (the population in thousands in 2000 is shown in parentheses)

Calendar year	Men 50+ (99 433)	Women 50+ (130 786)	Men 65+ (41 032)	Women 65+ (66 146)	Men 80+ (6 205)	Women 80+ (15 042)
2000	0	0	0	0	0	0
2010	15	12	12	8	49	38
2020	29	22	34	23	85	61
2030	37	28	60	42	122	81
2040	42	31	75	52	187	130
2050	36	26	81	55	239	160

Source: reference 150 (Table 6).

Even more marked increases are projected in different regions of the world, particularly in Asia. In Asia, a 7.6-fold increase in elderly people is predicted between the years 2000 and 2050 (Table 2.14). In 2000, approximately 46% of men aged 80 years and older were from Asia; this proportion is expected to rise to 60% in 2050. For women the figures are 41% and 59%, respectively.

Table 2.14
Demographic projections for different regions of the world

		Population (thousand)		Increase (multiplier)	
Region	Year	Men	Women	Men	Women
Africa	2000	1 168	1 696		
	2050	7 882	11 798	6.75	6.96
Asia	2000	11 190	18 212		
	2050	85 212	138 505	7.62	7.61
Europe	2000	6 205	15 042		
	2050	21 006	39 090	3.39	2.60
Latin America and Caribbean	2000	1 914	2 986		
	2050	13 737	24 156	7.18	8.09
North America	2000	3 472	6 527		
	2050	12 622	20 459	3.64	3.13
Oceania	2000	245	439		
	2050	1 048	1 760	4.28	4.01
World	2000	24 193	44 905		
	2050	141 506	235 767	5.84	5.25

Source: *World population prospects: the 2002 revision and world urban prospects.* New York, United Nations Population Division, Department of Economic and Social Affairs, 2003 (http://esa.un.org/unpp/, accessed 12 February 2005).

Such projections are worsened by increases in fracture incidence seen in some countries, even after adjustment for growth of the elderly population *(151)*. Although age-adjusted hip fracture rates appear to have levelled off in the northern area of the USA, in parts of Sweden and in the United Kingdom (84,152–154), rates in other parts of the world have risen substantially. If the secular trend continues in regions other than north America and Europe, hip fracture totals may double again to over 8 million by 2050 *(68)*.

There are three broad explanations for the secular trends. First, they might reflect the influence of some increasingly prevalent risk factor for bone loss or falling. Secular changes in BMD are unlikely. In Sweden, for example, the age-specific incidence of hip fractures rose by 100% between 1970 and 2001, but without measurable changes in BMD, at least at the forearm (155). Time trends for a number of other risk factors, including oophorectomy, oestrogen replacement therapy, cigarette smoking, alcohol consumption and low dietary calcium intake do not match those observed for hip fractures.

Physical activity, however, appears to be a likely candidate. There is ample epidemiological evidence linking inactivity to the risk in hip fracture incidence *(36,156,157)*, whether this effect is mediated through bone density, the risk of falls, or both. There may also be important secular trends in environmental factors and the surfaces on which individuals fall. Thus, urbanization has resulted in a progressive increase in harder surfaces. A second possible explanation for these secular changes is that the elderly population is becoming increasingly frail. The prevalence of disability is known to rise with age, and to be greater among women than men at any age. Since many of the disorders contributing to frailty are independently associated with osteoporosis and the likelihood of falling, this tendency might have contributed to the secular increases in fracture risk in developed countries during earlier decades. Finally, the trends could arise from a cohort phenomenon: some adverse influence on bone mass or falling risk which acted at an earlier time but is now being manifested as rising fracture incidence in successive generations of elderly people *(158)*. Generational effects do explain some of the secular trends in adult height during this century. Similar effects on the skeleton are likely, and might be mediated through intrauterine or early postnatal programming, as well as childhood nutrition and physical activity.

2.8 Costs

The burden of osteoporosis in terms of the number of fractures has been evaluated in several national studies. There has, however, been no cohesive attempt to translate this into estimates of the global economic burden. Doing so is not without difficulty because the costs of health care differ as widely as the patterns of treatment. For example, in the United Kingdom the average duration of hospital stay after hip fracture is close to 30 days *(17)*, whereas in Sweden it is closer to 15 days *(4)*. In a large southern European study (the Mediterranean Osteoporosis Study) a substantial minority of hip fractures were treated conservatively in Portugal, whereas in many other countries the overwhelming majority are treated surgically *(159)*. Even characterizing the burden of disease in a single country is problematic in the sense that there are multiple fracture types, each with different consequences, which also differ by age.

All estimates that have been made indicate very substantial costs attributable to osteoporotic fractures. In England and Wales, for example, the cost was recently estimated at £1.7 billion each year *(160)*, and this figure will increase as the proportion of elderly people in society rises. In Europe, direct medical expenditures for osteoporotic fractures were estimated at €36 billion annually *(150)*, of which two thirds were accounted for by hip fracture (Table 2.15). These costs are expected to double by the year 2050. In the USA, direct medical expenditures for osteoporotic fractures were estimated at US$ 20 billion in 2000 *(42)*.

Table 2.15
Estimated costs of osteoporotic fractures in Europe (in thousands of Euros) by fracture site, age and sex, in 2000

Age range (years)	Fracture site			
	Hip	Spine	Other	Total
Men				
50–64	544	69	473	1 086
65–74	1 111	63	389	1 563
75–84	1 637	45	360	2 042
85+	1 264	21	2 781	4 067
50+	4 556	198	4 003	8 757
Women				
50–64	813	101	1 253	2 168
65–74	2 751	165	1 376	4 293
75–84	9 120	152	2 553	11 824
85+	7 112	102	1 992	9 206
50+	19 796	521	7 173	27 491
Total				
50–64	1 358	171	1 725	3 254
65–74	3 863	230	1 764	5 856
75–84	10 757	197	2 915	13 868
85+	8 376	123	4 773	13 272
50+	24 353	719	11 177	36 248

Source: reference 150 (Table 5).

Financial analyses of the costs of osteoporosis have considered principally, though not exclusively, the most common osteoporotic fractures *(142)*. In the case of hip fracture, cost estimates differ for patients discharged home (45% of cases in the United Kingdom), for those discharged to long-term residential care (25%), and for patients dying within the first year of hip fracture (30%) (161). Age is also an important determinant of cost, so that costs rise progressively with age *(162)*. Aggregate costs of hip fracture (1999–2000 prices) in the United Kingdom were £13 519 in the first year, and £5291 in the second year, giving a total cost of £18 810 per hip fracture. Costs of vertebral fractures were estimated at £771 but age-weighted. In the USA, the average direct cost of hip fracture was estimated at US$ 21 000 in the first year; that for vertebral fracture was US$ 1200 per patient and that of a Colles fracture US$ 800 (137).

Hip fractures account for the greatest costs because of the long duration of hospitalization and the frequent need for after-hospital care. In Australia, hip fractures account for 63% of the total health-care expenditure for osteoporosis *(163)*. For Europe, the figure is 67% *(150)*. In Holland, hip fractures account for about 85% of the hospital costs of osteoporosis, of which 80% results from hospital admissions *(140,163)*. In the United Kingdom, hip fractures account for more than 90% of all hospital bed–days

attributable to osteoporosis *(17)* because of the lengthy hospital admission for hip fracture. Indeed, hospitalization for hip fracture accounts for direct in-patient medical costs that are comparable with many other chronic diseases in the Netherlands *(140)*, Sweden *(4)* (Table 2.16; Fig. 2.5) and the United Kingdom *(17)*.

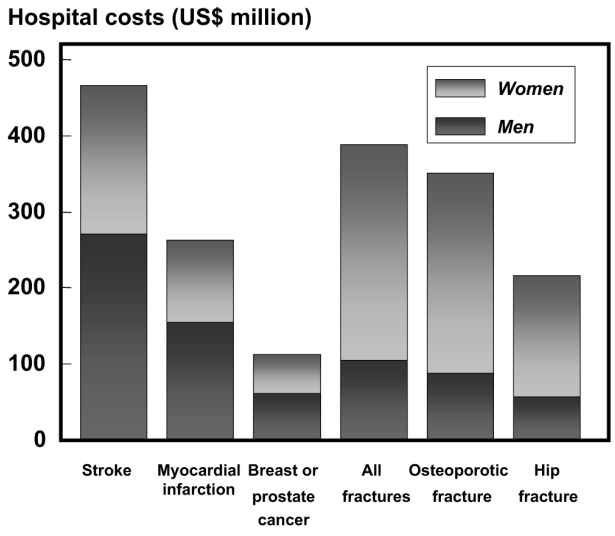
Table 2.16
Hospital burden of different disorders in Sweden, 1996

	Men			Women			
Disease	Number of cases	Hospital stay (days)	Bed days	Number of cases	Hospital stay	Bed days	Cost (US$ million)[a]
Myocardial infarction	47 171	5.05	238 214	29 358	5.67	166 460	263
Stroke	26 668	15.70	418 688	20 548	12.98	266 713	446
Prostate cancer	12 285	7.77	95 454				62
Breast cancer				11 078	7.06	78 211	51
Hip fracture	7 151	12.22	87 385	18 684	13.11	244 475	216
Osteoporotic fracture	12 357	11.00	135 916	34 380	11.81	406 192	351
All fractures	15 825	10.24	162 050	38 278	11.25	437 283	388

Source: reference 4 (Table 7).

[a]Daily cost of hospital bed estimated at US$ 648.

Fig. 2.5
Inpatient hospital costs of fractures (US$ million) in Sweden
Source: reference 4.



Vertebral fracture rarely leads to hospitalization. In Europe, approximately 8% of people with vertebral fractures are admitted to hospital *(59)*. In the United Kingdom, as few as 2% of patients may be admitted, although clinical coding inaccuracies may underestimate this figure (164). In Sweden, the admission rate is higher at 10% for women and 15% for men. The cost of each hospital stay has been estimated at €3900 for men and women in the European Union *(59)* (Table 2.17). This represents about 48% of the cost of a hip fracture.

Table 2.17
Hospital costs of vertebral fracture in the European Union

Country	Discharge rate (per 100 000)[a]	Hospitalization rate (%)[b]	Length of stay	Hospital cost per day (€)	Cost per hip fracture (€ thousand)	Cost per vertebral fracture (€ thousand)[c]
Austria	140	11	8	370	13.4	2.7
Belgium	69	7	16	255	9.1	4.3
Denmark	49	5	14	220	7.4	3.0
Finland	100	10	13	210	7.1	2.8
France	49	5	20	310	12.2	6.1
Germany	112	14	17	240	13.8	4.4
Greece	39	4	5	85	3.8	0.4
Ireland	55	9	8	395	3.7	3.6
Italy	95	12	7	300	4.7	2.1
Luxembourg	83	8	12	255	11.5	3.0
Netherlands	27	4	14	255	12.1	3.9
Portugal	39	5	12	120	5.8	1.4
Spain	38	6	10	260	5.8	2.6
Sweden	144	18	9	440	5.6	4.0
United Kingdom	24	3	15	230	8.9	3.5
European Union	69	8	13		8.1	3.9

Source: reference 59 (Tables 1–3, 5).
[a]Aged 50+ years; 45+ years for Germany and Spain.
[b]Estimated from the European Prospective Osteoporosis Study (2002).
[c]Fractures in women without neurological involvement.

The economic burden results, therefore, mainly from outpatient care, provision of nursing care and lost working days, particularly in patients with severe or multiple vertebral fractures *(23,128)*. Few studies have, however, examined the additional costs of re-fracture following a vertebral fracture. Estimates from Sweden and the United States suggest that the incremental costs of further fractures in the subsequent year are €2712 and US$ 4361, respectively *(165)*.

In the USA, the medical expenditure for osteoporotic fracture has been assessed by sex and ethnicity (145). Of US$ 13.8 billion spent on the treatment of osteoporotic fractures in 1995 for individuals aged 45 years and older, 75% was accounted for by treating white women, 18% for treating white men, 5% for treating non-white women, and 2% for treating non-white men. Of the total cost, 62.4% was for inpatient care, 28.2% for nursing home care and 9.4% for outpatient care, consistent with estimates from other

industrialized countries. These relative costs cannot be universally applied because the risk of fracture varies widely. So too does the sex ratio. Thus, as noted previously, osteoporotic fractures are as prevalent in men as in women in developing countries.

As mentioned, the estimated cost of osteoporotic fractures in Europe was €36.3 billion in 2000. Based on the expected changes in demography this figure is set to rise to €76.9 billion in 2050 *(150)*. These estimates may be conservative since they do not take into account any changes in the secular trend for fracture incidence that may occur.

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3. Measurement of bone mineral and definition of osteoporosis

The internationally agreed description of osteoporosis is: "A systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" *(1,2)*. This description captures the notion that low bone mass is an important component of the risk of fracture, but that other abnormalities occur in the skeleton that contribute to skeletal fragility. Thus, ideally, clinical assessment of the skeleton should capture all these aspects of fracture risk. At present, the assessment of bone mineral is the only aspect that can be readily measured in clinical practice, and it forms the cornerstone for the general management of osteoporosis. The objectives of bone mineral measurements are to provide diagnostic criteria, prognostic information on the probability of future fractures, and a baseline on which to monitor the natural history of the treated or untreated patient.

A wide variety of techniques is available to assess bone mineral. These are reviewed briefly below.

3.1 Methods of assessment

Bone mineral density (BMD) is the amount of bone mass per unit volume (volumetric density), or per unit area (areal density), and both can be measured in vivo by densitometric techniques. The most widely used techniques are based on X-ray absorptiometry in bone, since the absorption of X-rays is particularly sensitive to the calcium content of the tissue, of which bone is the most important source. Techniques using quantitative ultrasound (QUS) provide information on the attenuation of ultrasound or the speed of sound in skeletal tissue. Thus, the determinants of QUS are quite different from X-ray attenuation. Ultrasound variables depend not only on bone mineral, but also the microstructure, anisotropy, or elasticity of the mineralized matrix. It can be expected, therefore, that results derived from QUS or BMD – even from the same site – do not correlate perfectly, partly because of the different aspects of skeletal status that are captured and the different sources of error.

Techniques for the measurement of bone mineral can be divided into central techniques that give information on the spine or hip, and peripheral techniques applied to the forearm and bones of the hand, leg and foot.

3.1.1 Central techniques

Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DXA) is the most widely used bone densitometric technique. It is versatile in the sense that it can be used to assess bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fracture *(3–5)*. The term "bone mineral content" describes the amount of mineral in the specific bone site scanned. Bone mineral content can then be used to derive a value for BMD by dividing the amount of mineral by the area measured. BMD is, therefore, an areal density (g/cm^2) rather than a true volumetric density (g/cm^3) since the scan is two-dimensional.

The widespread clinical use of DXA, particularly at the proximal femur and lumbar spine, arises from many prospective studies that have documented a strong gradient of risk for fracture prediction. For example, a widely cited meta-analysis *(6)* indicated that the risk of hip fracture increased 2.6-fold for each standard deviation decrease in BMD. This gradient of risk is better than many other techniques, and the use of central DXA predicts other types of fracture with as high a gradient of risk as other competing techniques.

DXA measurements at the hip have particular utility in the diagnosis of osteoporosis (see later), but measurements at the lumbar spine are also widely used. In early postmenopausal women in whom vertebral fractures are common, vertebral fractures may be predicted with greater effect by measurements at the lumbar spine than with measurements made at the hip. With advancing years, however, osteoarthritis progressively confounds measurements in the spine. Notwithstanding, spinal measurements are sensitive to treatment-induced changes, and the spine represents the most widely used site for monitoring the response to treatment. The use of DXA techniques on the lateral spine rather than in the customary postero-anterior projection further improves the responsiveness of the measurement to treatment-induced changes, but at the expense of precision. Lateral DXA may, however, have advantages in subjects with marked degenerative changes.

There are a number of limitations to the general application of DXA which should be recognized in its use *(7)* (Table 3.1). The presence of osteomalacia, a complication of poor nutrition in elderly people, will underestimate total bone mass because of decreased mineralization of bone. Osteoarthrosis at the spine or osteoarthritis at the hip are common in elderly people, and contribute to the density measurement, but not necessarily to skeletal strength. Heterogeneity of density attributable to osteoarthrosis, previous fracture or scoliosis can often be detected on the scan and in some cases excluded from the analysis. Some of these problems can be overcome with

adequately trained staff and rigorous quality control. As mentioned, the image is two-dimensional and therefore provides an areal BMD rather than a volumetric BMD. The computation of BMD is sensitive to changes in bone size. For example, areal bone density will overestimate volumetric bone density in individuals with large bones. In adults, this error is fortuitously beneficial since larger bones in general have higher strength. Thus, this "error" may improve fracture prediction in adults.

Table 3.1
Sources of error in the diagnosis of osteoporosis by dual energy X-ray absorptiometry (DXA)

Osteomalacia
Osteoarthritis (particularly spine but also the hip)
Soft tissue calcification (especially aortic calcification for spine measurements)
Overlying metal objects
Contrast media and recent technecium-99m bone scan
Previous fracture (spine, hip and wrist)
Severe scoliosis
Extreme obesity or ascites
Vertebral deformities attributable to osteoarthritis, Scheuermann disease
Inadequate reference ranges
Inadequate operating procedures (e.g. calibration, region selection, acquisition mode, positioning)

Source: reference 7 (Table 3).

The vast amount of information available for central DXA has meant that it has now become the reference standard. The adoption of DXA as a reference standard provides a platform on which the performance characteristics of less well established methods can be compared.

Quantitative computed tomography

Quantitative computed tomography (QCT) has been applied both to the appendicular skeleton and to the spine (8,9). Conventional whole-body CT scanners, which typically generate density information in terms of Houndsfield units, need calibration to convert their results into units relevant to bone mineral density. QCT allows the assessment of skeletal status of cancellous bone of the vertebral bodies from the twelfth thoracic to the fourth lumbar vertebra. The patient is usually scanned simultaneously with a calibration phantom which can be used to standardize the machine automatically. The major advantage of QCT is that, in the assessment of cancellous bone, the result provides a measure of true volumetric density (mg/mm^3) rather than an area-adjusted result as is the case with DXA. The technique is thus one of the most sensitive techniques for the assessment of early postmenopausal skeletal losses. Indeed, case-control studies have shown better discrimination of fractures cases and unfractured controls using QCT compared to DXA. Cancellous bone is more responsive to many interventions than cortical bone, so the technique is also suitable for

monitoring treatment *(3)*. The technique avoids the influence of degenerative disease, which is a particular problem with DXA at the spine. It is also free from the artefact of bone size, but is not accurate with metallic objects in the scan field of view.

QCT radiation levels are somewhat higher than for DXA. In adults, radiation exposure is smaller than the radiation dose required for antero-posterior and lateral spine X-rays (typically 500–1500 mSv). Newer approaches available on spiral CT scanners permit the measurement of volumetric BMD at higher levels of spatial resolution and are capable of generating three-dimensional images of the disposition of trabecular elements in cancellous bone, but at the expense of a higher radiation dose. The technique has been successfully applied on a research basis at the proximal femur, and may be available in the future for clinical use.

The major disadvantage with QCT is the relatively high radiation exposure compared to DXA, difficulties with quality control and the high costs compared with DXA.

3.1.2 Peripheral techniques

Peripheral DXA

The application of DXA to peripheral sites has supplanted the use of single energy absorptiometry either based on X-rays or single photon absorptiometry. The sites most widely measured include the radius and the calcaneus. Both sites have been shown to predict future fractures, but the predictive value for hip fracture is somewhat less than that provided by central DXA measurements.

Dual X-ray laser is a variant of peripheral DXA. A laser is used to measure the thickness of the calcaneus and thereby reduces accuracy errors attributable to variable soft tissue thickness. Early validation studies have been published *(10,11)*.

Peripheral QCT

Peripheral QCT measurements are typically obtained at the radius or the tibia *(12)*. As in the case for spinal QCT, cancellous bone can be evaluated selectively. Recently high resolution QCT has permitted quantitation of trabecular numbers and disposition in cancellous bone. There is, however, a lack of prospective studies on which to judge the performance characteristics of peripheral QCT for fracture risk assessment. In addition, biomechanically relevant properties of bone can be computed, such as the areal moment of inertia and other indices of bone strength. It is, however, uncertain whether these additional measurements provide greater clinical value in the prediction of fracture risk.

Digital X-ray radiogrammetry

Standardized radiographs of the hand and forearm, including the radius and metacarpals, provide the basis for digital X-ray radiogrammetry. The most widely applied technique is the estimation of cortical width, most commonly applied to the 2nd, 3rd and 4th metacarpals *(13)*. The size of tubular bones increases with age, and thinning of the cortex represents an increase in net endocortical bone resorption. The cortical width divided by the total width or the cortical area divided by the total cross-sectional area are commonly used indices. Evaluation can be improved by magnification and the use of fine grain films, and can be semi-automated *(14)*.

Automated image processing techniques have been developed to measure a variety of structure-related features *(15)*. Mathematical modelling allows estimation of areal BMD and in some instances some aspects of bone structure *(16,17)*. Direct comparisons with central DXA suggest that the technique has predictive ability for fracture risk, but perhaps with a lower predictive value. Nonetheless, these low cost techniques have the potential for widespread application where access to more sophisticated technology is limited.

Radiographic absorptiometry

Radiographic absorptiometry has been established for a long time. The technique allows the measurement of BMD either by digitizing conventional radiographs, or by directly measuring X-ray absorption using coupled devices as detectors. An index of mineral density is derived by comparing the absorption with appropriate standards. Measurement sites include peripheral bones like the phalanges or metacarpals (14). Central processing of radiographs has been used to improve quality control.

3.1.3 Other radiographic techniques

The diagnosis of osteoporosis can often be made from visual inspection of plain radiographs, albeit with low sensitivity. There are also a number of characteristic features of osteoporosis which help in diagnosis, or in differential diagnosis *(18)*.

In many regions of the world, X-rays will be the sole assessment tool available. A decrease in the apparent density of bone is not specific for osteoporosis and is more appropriately termed osteopenia. In addition to osteopenia, osteoporosis is associated with abnormalities in the trabecular architecture of bone, a decrease in cortical width and visible evidence of past fractures. Fractures are particularly prominent in the spine, and of the vertebral deformities seen on X-ray approximately one third will come to clinical attention (see section 2).

In postmenopausal osteoporosis, trabecular number decreases. The remaining trabeculae hypertrophy, particularly the vertebral trabeculae. The preferential loss of horizontal trabeculae relative to vertical trabeculae gives rise to a striated appearance. These changes in trabecular markings differ

from those observed in glucocorticoid-induced osteoporosis or in osteomalacia, where trabecular markings usually become indistinct, giving rise to a fuzzy or ground glass appearance. In glucocorticoid induced osteoporosis, pseudo-callus may also be found in the absence of overt vertebral deformities. It is important to recognize that abnormalities in vertebral shape are not invariably a result of osteoporosis. Common other causes include osteoarthrosis and Scheuermann disease.

The proximal femur has a distinctive pattern of trabecular architecture, which is disturbed in the course of osteoporosis. The pattern of loss provides a semi-quantitative estimate of trabecular losses *(19)* that can be used to predict hip fracture.

3.1.4 Quantitative ultrasound techniques

Many quantitative ultrasound (QUS) methods have been introduced for the assessment of skeletal status in osteoporosis. The most widely evaluated assessments are broadband ultrasound attenuation and speed of sound (or ultrasound velocity) at the heel. There is interest in their use because they do not involve ionizing radiation and may provide some information concerning the structural organization of bone as well as bone mass. In addition, the techniques are easily portable and may be cheaper than DXA. This makes QUS an attractive technology for assessing risk of fracture in larger populations, where use of DXA may be unsuitable or unfeasible.

Transverse transmission QUS of the calcaneus

The calcaneus is the most commonly measured site and comprises largely cancellous bone. In experimental settings, the technique captures some structural aspects, as shown from scans undertaken in different axes of cubes of bone *(20)*. In the clinical setting, however, both speed of sound and broadband ultrasound attenuation largely reflect calcaneal BMD. The performance of these QUS techniques has been evaluated in a large number of studies *(21,22)*. The technique cannot currently provide diagnostic criteria for osteoporosis, but current evidence supports its use for the assessment of fracture risk in elderly women where the prognostic value of future hip fracture is as good as several other peripheral measurements *(23,24)*. Indeed, in elderly people, QUS may perform as well as central DXA *(25–28)*. It also appears to predict hip fracture and non-spine fracture in men *(29)*. Since calcaneal QUS has not been used as an entry criterion in large randomized control studies of treatment, it is not proven that patients selected on the basis of low QUS results would benefit from treatment.

Transverse transmission of QUS of the phalanges

A substantial body of evidence has accumulated for the utility of this site. In the phalanges, amplitude dependent speed of sound is typically assessed, which integrates both attenuation and speed of sound. Cross-sectional studies have, with few exceptions, shown that fracture cases can be discriminated from controls, though not as well as by central DXA

techniques *(30,31)*. A small prospective study has also shown the predictive value of the technique for incident appendicular fractures *(32)*. Some, but not all, studies show that the technique can detect treatment-induced changes, but further studies are required. The use of the technique for diagnostic criteria is problematic since there is a relatively weak correlation of measured values with those obtained by DXA at the femoral neck.

Axial transmission of QUS

Axial transmission techniques rely on the placing of transducers on the same surface of a long bone such as the radius, the phalanges or the metacarpals. The ultrasound wave travels along the cortex and thus the technique is dependent upon the cortical properties of bone. Confounding effects of soft tissues can be minimized by arrays of multiple pairs of transducers in the same probe. The technique has shown some validity in cross-sectional studies *(33–35)*.

3.2 Performance characteristics of bone mineral measurements

The performance characteristics of many measurement techniques have been well documented *(6,21,36)*. For the purpose of risk assessment and for diagnosis, the characteristic of major importance is the ability of a technique to predict fractures. This is traditionally expressed as the increase in relative risk per standard deviation (SD) unit decrease in bone mineral measurements. This is termed the gradient of risk.

There are significant differences in the performance of different techniques at different skeletal sites. In addition, the performance depends on the type of fracture that is to be predicted *(6)*. For example, BMD assessments by DXA to predict hip fracture are better when measurements are made at the hip rather than at the spine or forearm (Table 3.2). For the prediction of hip fracture, the gradient of risk provided by hip BMD is 2.6. In other words, the fracture risk increases 2.6-fold for each SD decrease in hip BMD. Thus, an individual with a Z-score of –3 at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual of the same age with a Z-score of 0 SD. Where the intention is to predict any osteoporotic fracture, the commonly used techniques are comparable: the risk of fracture increases approximately 1.5-fold for each standard deviation decrement in the measurement. Thus, an individual with a measurement of 3 SD below the average value for age would have a 1.5^3 or greater than 3-fold higher risk than an individual with an average BMD. Note that the risk of fracture in individuals with an average BMD is lower than the average fracture risk, since BMD is normally distributed whereas the risk of fracture increases exponentially with decreasing BMD.

These considerations indicate the importance of gradient of risk. Consider, for example, two techniques which at the same site give a gradient for hip fracture risk of 1.5 and 2.6, as illustrated above. Assume that it might be considered desirable to intervene in individuals with a risk of hip fracture

that was four times that of individuals with an average BMD. In the former scenario with a gradient of risk of 1.5/SD, almost no patients at the age of 60 years would exceed this risk and be selected for treatment, but a substantial minority would be detected using a test with the higher gradient of risk. The formalization of the relationship between gradient of risk and the population selected is considered in section 6.

Table 3.2
Age-adjusted increase in risk of fracture (with 95% confidence interval) in women for every 1 SD decrease in bone mineral density (by absorptiometry) below the mean value for age

Site of measurement	Forearm	Hip fracture	Vertebral fracture	All fractures fracture
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

Source: reference 6 (adapted from Table 2).

A further point of relevance is the level of evidence on which information about performance characteristics has been obtained. The most secure level of evidence comes from population-based prospective studies. Less reliance can be placed on retrospective cohort studies and cross-sectional or case-control studies. The grading of levels of evidence for prognostic risk factors, including BMD, is reviewed in section 6.

The gradient of risk depends on the technique used, the site measured and the fracture of interest. In general, site-specific measurements show higher gradients of risk for fractures at their respective sites. For example, measurements at the hip predict hip fracture with greater power than do measurements at the heel, lumbar spine or forearm *(6,37)*. For other combinations of measurement sites and fractures, gradients of risk range from 1.5 to 3.0 for each standard deviation decrease in bone mineral measurement (see Table 3.2). The performance characteristics of ultrasound are similar. Most studies suggest that measurements of broadband ultrasound attenuation or speed of sound at the heel are associated with a 1.5-fold to 2-fold increase in risk for each standard deviation decrease in bone mineral density *(21)*. Comparative studies indicate that these gradients of risk are very similar to those provided by peripheral assessment of bone mineral density at appendicular sites by absorptiometric techniques to predict any osteoporotic fracture *(6,38)*.

3.3 Definition of osteoporosis

Skeletal mass and density remain relatively constant once growth has ceased, until the age of 50 years or so *(39)*. The distribution of bone mineral content or density in young healthy adults ("peak bone mass") is approximately normal (in a statistical sense), irrespective of the measurement technique used. Because of this normal distribution, bone density values in individuals

may be expressed in relation to a reference population in standard deviation units. This reduces the problems associated with differences in calibration between instruments. When standard deviations are calculated in relation to the young healthy population, this is referred to as the T-score.

3.3.1 Diagnostic thresholds

The following four general descriptive categories are proposed for men and women using measurements of DXA.

- Normal. A value for BMD that is higher than 1 SD below the young adult female reference mean (T-score greater than or equal to –1 SD).
- Low bone mass (osteopenia). A value for BMD more than 1 SD below the young female adult mean, but less than 2.5 SD below this value (T-score less than -1 and greater than -2.5 SD).
- Osteoporosis. A value for BMD that is 2.5 SD or more below the young female adult mean (T-score less than or equal to –2.5 SD).
- Severe osteoporosis (established osteoporosis). A value for BMD that is 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures.

The recommended reference range is the NHANES III reference database for femoral neck measurements in women aged 20–29 years *(40,41)*, as previously recommended by the International Osteoporosis Foundation *(42)*.

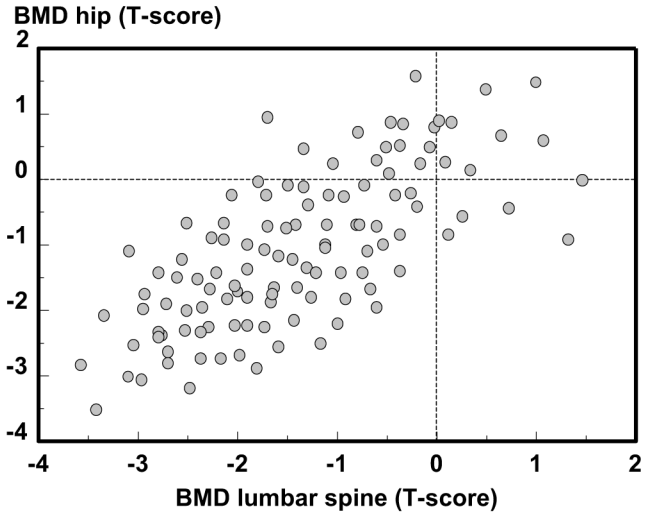
These diagnostic criteria for osteoporosis are similar to those previously proposed by the World Health Organization in 1994 *(36,43)*, but differ by specifying a reference site (the femoral neck), providing a young normal reference range, and by accommodating diagnostic criteria for men. The reasons for these clarifications are reviewed briefly below.

3.3.2 Choice of reference site and technology

The original 1994 WHO criteria provided for diagnosis of osteoporosis at the hip, lumbar spine or forearm. With the techniques available for measuring bone mineral at that time, the prevalence of osteoporosis was roughly equal at any one of these sites. Since introduction of the operational definition of osteoporosis, much attention has focused on its application to epidemiology, clinical trials and patient care. Several problems have emerged. The first is that there has been a plethora of new measurement techniques applied to many different skeletal sites. It is now clear that the same T-score derived from different sites and techniques yields different information on fracture risk. Reasons relate to differences in the gradient of risk for techniques to predict fracture *(42,44)*, discrepancies in the population standard deviation at different sites and with different equipment *(22,45)*, and differences in the apparent rate of bone loss with age *(46)*. A second problem that arises is that the inter-site correlations, though of statistical significance, are inadequate

for predictive purposes *(38,47,48)*. For example (Fig. 3.1), with a T-score of 0 SD at the spine, the T-score at the hip varied from –1 to +1. The problem arises because of biological variations that occur in the composition of bone between sites, as well as technical errors of accuracy in the various measurements *(42)*.

Fig. 3.1
Bone mineral density (BMD) T-scores measured at the total hip and lumbar spine in a sequential series of post-menopausal women referred for BMD tests



Source: J.A. Kanis, unpublished data.

For these reasons, it is evident that the T-score cannot be used interchangeably with different techniques and at different sites. For example, in Caucasian women at the age of 60 years, the T-score may vary from –0.7 to –2.5 SD, depending on the technique used *(42)* (Table 3.3). These considerations indicate that a reference standard should be adopted in terms of skeletal site and measurement technology for descriptive purposes. DXA is the most widely available and validated technique. Measurements at the femoral neck have the highest predictive value for hip fracture, and this has been well established in many prospective studies *(6,49)*. Moreover, the hip is the site of highest biological relevance, since hip fracture is the dominant complication of osteoporosis in terms of morbidity and cost. The choice of a reference site holds true in principle for many other multifactorial diseases. For example, in essential hypertension, measurements made at the leg may differ substantially from measurements made at the arm. In the field of osteoporosis, as for hypertension, it is appropriate to select a standardized site for descriptive purposes. This does not preclude the use of other validated technologies for diagnostic use in clinical medicine, though account should be taken of any difference in performance characteristics.

Table 3.3
Estimate of the average T-score at the age of 65 years in women

Measurement site	Technique	T-score at age 60 years
Spine	QCT	–2.5
Spine	Lateral DXA	–2.2
Heel	Achilles	–1.5
Spine	DXA	–1.3
Forearm	DXA	–1.4
Femoral neck	DXA	–1.2
Total hip	DXA	–0.9
Heel	Sahara	–0.7

Source: reference 42 (adapted from Table 3).
QCT, quantitative computed tomography; DXA, dual energy X-ray absorptiometry.

There is, however, an argument to be made for using the total hip measurement, since this site has a better reproducibility than measurements made at the femoral neck because a larger area of bone is involved. Reference data are also available for the total hip *(41)*. A similar argument can be made for the diagnostic use of measurements at the lumbar spine, which are widely used in clinical practice. The principal reason why these sites are not currently favoured as the reference standard is that their ability to predict fracture has not been as adequately validated as BMD measurements derived from the femoral neck (see section 5 for further details). As mentioned, these considerations should not be taken to infer that the use of other techniques or other sites do not have clinical utility for diagnosis or prognosis where they have been shown to provide information on fracture risk.

In order to avoid confusion, it may be preferable to reserve the T-score for the diagnostic use of BMD measured by DXA at the femoral neck. In the case of other sites and techniques it may be preferable that deviations of measurement from normal values are expressed in the units of measurement or in units of risk *(42)*.

3.3.3 Descriptive criteria for men

Suitable diagnostic cut-off values for osteoporosis in men are less well defined than for women. Many studies that have examined fracture risk in men and women have come to disparate conclusions concerning the relationship between fracture risk and BMD or the gradient of risk *(50–54)*. There are several reasons for these discrepancies. First, the relation between BMD and fracture risk changes with age *(55,56)*, so that age-adjustment is required. Second, a difference between sexes in the gradient of risk (relative risk per SD increase in BMD) could be the result of differences in the SD of measurements. Third, data derived from referral populations of osteoporotic men and women are likely to be biased. These difficulties are overcome by population-based sampling and expressing fracture risk as a function of

BMD or standardized T-scores, with age adjustment. The few studies available show that the risk of hip fracture is similar in men and women for any given absolute value for BMD *(49,57–59)*. Likewise, the risk of vertebral fracture is also similar in men and women for any given BMD *(52,60)*. These studies indicate that a cut-off value for hip BMD similar to that used in women can be used in the description of osteoporosis in men – namely, a value for BMD 2.5 SD or more below the average for young adult women.

3.3.4 Normative reference ranges

The prevalence of osteoporosis, as defined by the T-score, depends critically upon the reference range adopted. Normal ranges for DXA are available for many countries including France *(47)*, Germany *(61)*, the Netherlands *(58,62)*, the United Kingdom *(63–65)*, and several other European countries *(66)*, where the differences in mean BMD and standard deviations are relatively small. For the proximal femur it is suggested that the United States reference data generated from the NHANES III study *(41)* serve as a reference standard. The NHANES III data come from a large population-based study of a representative sample of the United States population. The adoption of this reference population implies that different countries or different races should not use their own reference ranges. The use of reference ranges in whites in the USA accommodates, however, the higher bone mass and lower fracture risk in blacks *(40)*.

There are differences in BMD in different regions of the world. Nevertheless, although the differences between the centres listed in Table 3.4 are highly significant ($p<0.001$ for all), they vary only by approximately one standard deviation *(67)*. Variations in BMD between populations appear to be substantially less, therefore, than variations in fracture risk (see section 2.3). Age-specific and sex-specific risks of hip fracture differ more than 10-fold, even within Europe *(68)*. These differences are very much larger than can be accounted for by any differences in BMD between communities. Indeed, in Asia, hip fracture risk is lower than in northern Europe or the USA, but BMD is also lower *(67,69,70)*. In view of the disparity between population fracture risks and BMD, it is uncertain whether reference ranges drawn from local populations would be of any added value. It would seem appropriate to use the large and adequately sampled NHANES reference values until further research tempers this view *(42)*. A caveat, however, is that the same BMD in different geographic locations does not necessarily carry the same risk of fracture.

Table 3.4
Mean and SD of spine and femoral neck BMD (g/cm²) adjusted using linear regression to age 35 years, height 170cm and weight 70 kg in men, and age 35 years, height 160 cm and weight 60 kg for women

	Men				Women			
	Spine (g/cm²)		Femoral neck (g/cm²)		Spine (g/cm²)		Femoral neck (g/cm²)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ankara	1.060	0.147	0.946	0.139	1.037	0.130	0.872	0.109
Beijing	1.082	0.128	0.908	0.121	1.115	0.105	0.857	0.102
Cape Town	1.077	0.172	0.898	0.131	1.109	0.150	0.864	0.115
Debrecen	0.967	0.124	0.874	0.137	1.033	0.104	0.818	0.087
Manila	1.054	0.144	0.920	0.134	1.055	0.143	0.817	0.111
Moscow	1.067	0.152	0.969	0.144	1.058	0.136	0.868	0.131
Obninsk	1.132	0.139	0.950	0.115	1.085	0.129	0.849	0.111
Santiago	1.080	0.137	0.935	0.128	1.103	0.126	0.874	0.110
Sao Paulo	0.957	0.166	0.852	0.147	0.998	0.151	0.840	0.142
Shanghai	0.992	0.103	0.832	0.094	1.000	0.117	0.793	0.105
Singapore	1.058	0.148	0.920	0.133	1.083	0.135	0.842	0.119
Toronto	1.062	0.159	0.882	0.183	1.139	0.148	0.860	0.123
Zagreb	0.998	0.144	0.854	0.110	1.042	0.099	0.850	0.114

Source: reference 67 (Table 6).

3.3.5 Prevalence of osteoporosis

The threshold for diagnosing osteoporosis using DXA at the femoral neck is 0.577g/cm² derived from the young white female population aged 20–29 years using the Hologic device. Approximately 10 million men and women over the age of 50 years have osteoporosis in the United States. The prevalence of osteoporosis in Sweden using these criteria is shown for Swedish men and women in Table 3.5 *(71)* and for various other places in Table 3.6. Approximately 6% of men and 21% of women aged 50–84 years are classified as having osteoporosis. The prevalence of osteoporosis in men over the age of 50 years is three times less frequent than in women – comparable to the difference in lifetime risk of an osteoporotic fracture in men and women *(71)*. In the United States, the prevalence of osteoporosis in postmenopausal white women is 17% compared with 21% in the United Kingdom. Within the USA the prevalences are 6% for black women and 14% for Mexican Americans *(40)*. Prevalence is approximately 8% in Canada *(72)*. These differences may explain in part the differences in fracture rates (see section 2), and support the need for a standardized normative reference range.

Table 3.5
Prevalence of osteoporosis at the age intervals shown in Sweden using female-derived reference ranges at the femoral neck

	Men		Women	
Age range (years)	% of population	Number affected (thousand)	% of population	Number affected (thousand)
50–54	2.5	7.0	6.3	17.0
55–59	3.5	7.6	9.6	21.1
60–64	5.8	11.4	14.3	30.0
65–69	7.4	14.2	20.2	43.7
70–74	7.8	14.6	27.9	63.0
75–79	10.3	13.7	37.5	68.3
80–84	16.6	14.7	47.2	67.8
50–80	6.3	83.2	21.2	310.9

Source: reference 71 (Table 3).

Table 3.6
Prevalence (%) of osteoporosis in different regions of the world

	Age (years)				
Study population[a]	50	60	70	80	90
Men					
EVOS, Europe	0.6	1.4	3.7	9.2	21.0
CaMos, Canada	0.5	1.5	4.3	11.6	27.9
Rotterdam, Netherlands	1.0	2.2	4.8	10.4	20.8
Dubbo, Australia	0.5	1.4	4.1	11.4	28.2
Rochester, USA	1.0	2.0	4.1	8.2	15.7
Hiroshima, Japan	0.9	2.2	5.1	11.4	23.5
All cohorts	0.6	1.7	4.3	10.4	22.6
Women					
EVOS, Europe	3.8	8.5	17.9	33.9	54.6
CaMos, Canada	2.9	7.8	19.1	39.8	64.9
Rotterdam, Netherlands	4.0	9.2	19.8	37.6	59.4
Dubbo, Australia	3.6	8.8	20.0	39.1	62.2
Rochester, USA	1.9	6.2	18.8	44.8	73.9
Hiroshima, Japan	5.6	10.7	19.5	32.8	49.7
All cohorts	3.4	8.5	19.2	37.7	61.3

[a] See Section 5.2.
EVOS, European Vertebral Osteoporosis Study.

The use of a male reference range to denote osteoporosis would increase the apparent prevalence of osteoporosis in that group. For example, the prevalence of osteoporosis in Swedish men aged 70 years is 7.6%, but increases to 8.6% using male values to derive the diagnostic threshold *(71)*.

The prevalence of osteoporosis obtained using either the total hip or the femoral neck is similar, suggesting that the total hip could eventually supplant the femoral neck when adequate meta-analyses have delineated the performance of total hip BMD to estimate fracture risk. This is discussed further in section 5.

3.3.6 Measurement of multiple skeletal sites

A number of investigators favour the concurrent use of BMD at the proximal femur and at the lumbar spine for patient assessment. Patients are defined as having osteoporosis on the basis of the lower of two T-scores. For example, the International Society for Clinical Densitometry recommends that patients who have a BMD test receive scans of both the lumbar spine and hip *(72)*. Patients are characterized as having osteoporosis where the T-score is –2.5 SD or less at the spine, femoral neck, total hip or trochanter. The reasons for this are not entirely clear, but may relate to the assumption that the combined use of two or more sites may improve prognostic ability. The basis for this belief is, however, erroneous as shown on theoretical grounds *(4)*. A recent meta-analysis undertaken on seven population-based cohorts showed that for the prediction of any osteoporotic fracture, the gradient of risk provided by femoral neck BMD was 1.51/SD. That provided by BMD at the lumbar spine was 1.47/SD, and that provided by the minimum value at either site was 1.55/SD *(73)*. Thus, the choice of the minimum value does not improve the gradient of risk. The same pertains to the prediction of hip fracture *(73)* (Table 3.7). This suggests that there is no diagnostic advantage for combining sites in this way. The view is supported by an independent study of the predictive value of hip, spine or the combination for vertebral fracture risk in the placebo arm of a large multicentre intervention study of vertebral fracture. In this instance, the combined measurement gave lower risk ratios than for measurements either at the lumbar spine or the femoral neck *(74)*. In a further cross-sectional study the sensitivity for vertebral fracture was increased using the lowest T-score of each of the lumbar vertebral bodies, rather than the average value of the lumbar spine, but at the expense of reduced specificity *(75)*.

Table 3.7
Gradient of risk (GR) for each SD decrease in bone mineral density at the femoral neck, lumbar spine or the minimum of the two sites in men and women combined

	Femoral neck		Lumbar spine		Minimum value	
Outcome fracture	GR	95% CI	GR	95% CI	GR	95% CI
Any fracture	1.43	1.37–1.51	1.42	1.35–1.49	1.45	1.38–1.52
Any osteoporotic fracture	1.51	1.42–1.61	1.47	1.38–1.56	1.55	1.45–1.64
Hip fracture	2.45	2.10–2.87	1.57	1.36–1.82	2.11	1.81–2.45
Vertebral fracture[a]	2.47	1.79–3.42	1.84	1.19–2.85	1.75	1.23–2.49

Source: reference 73 (Table 2).
[a]Risk ratio comparing women with and without osteoporosis (74).

Selection of patients on the basis of a minimum value from two or more tests will, however, increase the number of patients selected. For example, the correlation coefficient between BMD at the lumbar spine and femoral neck was 0.638 in the 19 000 patients assessed in the meta-analysis described in Table 3.6. From the correlation coefficient, if 10% of individuals in a population were characterized as having osteoporosis on the basis of BMD at the femoral neck, the prevalence of osteoporosis would increase to 15.3%

with the addition of lumbar spine measurements and taking the minimum value to dichotomize an osteoporotic population. Where 50% of the population are characterized by a single technique to have osteoporosis, the apparent prevalence increases to 64.1% with the additional measurement. Thus, the sole effect of using this approach is to increase the apparent prevalence of osteoporosis, but not to improve fracture prediction. The apparent prevalence would increase still further with the minimum value from multiple sites. The same result can be achieved by less stringent criteria for the definition of osteoporosis, by defining osteoporosis, for example, as a T-score of <–2.0 SD rather than <–2.5 SD. This would undermine, however, the value of a single descriptive threshold.

3.3.7 Osteopenia

Provision is still made for the description of osteopenia, but osteopenia should not be considered to be a disease category. This is intended more for descriptive purposes for the epidemiology of osteoporosis rather than as a diagnostic criterion. Also, the identification of osteopenia will capture the majority of individuals who will develop osteoporosis in the next 10 years. The original intention of WHO was to choose a threshold that would make osteopenia and osteoporosis uncommon at the time of the menopause, on the assumption that bone loss began at that time. Thus, the diagnostic category of a T-score between –1 SD and –2.5 SD was anticipated to capture approximately 50% of the population. It is now evident that bone loss occurs from the proximal femur at a much earlier age *(76)*. If peak bone mass were constant up to the average age of menopause, then the expected frequency of osteopenia would be 16% at the age of 50 years, whereas it is actually much higher. By the age of 50 years, the prevalence of osteopenia is 35.5% in women and 21.8% in men (Table 3.8) *(71)*. The high prevalence poses some problems in risk assessment. For example, in women at the age of 50 years, a T-score of –1 SD would carry a relative risk of 0.79 compared to the general population of the same age. This is because the general population on average has a T-score that is <–1 SD.

Table 3.8
The prevalence of osteopenia and the population relative risk (RR) of hip fracture at the bone mineral density threshold for osteopenia (T-score = –1 SD) at the ages shown in Swedish men and women

	Men		Women	
Age (years)	Prevalence (%)	RR	Prevalence (%)	RR
50	21.8	1.2	35.5	0.8
55	24.7	1.1	44.8	0.6
60	27.6	1.0	49.2	0.5
65	29.4	0.9	51.8	0.4
70	33.8	0.8	55.6	0.3
75	39.1	0.7	64.3	0.2
80	45.9	0.6	49.5	0.2

Source: reference 71(Table 4).

3.4 Assessment of osteoporosis

3.4.1 Diagnostic approach

The same diagnostic approach should be undertaken in all patients with osteoporosis irrespective of the presence or absence of fragility fractures. However, the range of clinical and biological tests will depend on the severity of the disease, the age at presentation and the presence or absence of vertebral fractures. The aims of the clinical history, physical examination and clinical tests are:

- to exclude a disease which can mimic osteoporosis (e.g. osteomalacia, myelomatosis);
- to elucidate causes of osteoporosis and contributory factors;
- to assess the severity of osteoporosis to determine the prognosis of the disease, i.e. the risk of subsequent fractures;
- to select the most appropriate form of treatment;
- to perform baseline measurements for subsequent monitoring of treatment.

The procedures that may be relevant to the investigation of osteoporosis are shown in Table 3.9. These investigations may be used to:

- establish the diagnosis of osteoporosis (e.g. DXA or X-rays);
- establish the cause (e.g. thyroid function tests for hyperthyroidism, and urinary free cortisol for Cushing syndrome);
- establish differential diagnosis (e.g. protein electrophoresis for myeloma, and serum calcium and alkaline phosphatase for osteomalacia).

Table 3.9
Routine procedures that have been proposed in the investigation of osteoporosis

* History and physical examination
* Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
* Lateral radiograph of lumbar and thoracic spinal column
* Bone densitometry (dual energy X-ray absorptiometry, single energy X-ray absorptiometry, quantitative ultrasound, quantitative computed tomography)
* Sex hormones (particularly in men)

Investigations commonly reserved for specialist centres include measurement of the biochemical indices of bone turnover, serum parathyroid hormone, serum 25-hydroxyvitamin D, serum or urine protein electrophoresis, fasting and 24-hour urinary calcium, urinary free cortisol, thyroid function tests and transiliac bone biopsy. Free testosterone, gonadotrophin and prolactin measurements may be of value in men. Assessment is guided by the clinical findings, and some patients who apparently have primary osteoporosis, are subsequently found to have mild hyperparathyroidism or hyperthyroidism, systemic mastocytosis, the late appearance of osteogenesis imperfecta or osteomalacia.

3.4.2 Differential diagnosis of osteoporosis

Specific underlying causes of bone loss are more commonly found in men than in women. A high proportion of men presenting with symptomatic vertebral crush fractures have an underlying cause of osteoporosis identified, such as hypogonadism, oral steroid therapy or alcoholism *(77,78)*. A case-control study from the Mayo Clinic showed a significantly increased risk of vertebral fractures with smoking, alcohol consumption and underlying causes of osteoporosis *(79)*. A recent case-control study of men from Newcastle shows an increased risk of vertebral fractures with oral glucocorticoid therapy, anticonvulsant treatment, smoking, alcoholism and hypogonadism *(80)*. For hip fractures, the risk factors in men are similar to those found in women *(81–83)*.

Osteomalacia and malignancy commonly induce bone loss and fractures. Osteomalacia is characterized by a defect of mineralization of bone matrix most commonly attributable to impaired intake, production or metabolism of vitamin D. Other causes include impaired phosphate transport or the chronic use of some drugs such as aluminium salts (and other phosphate binding antacids), high doses of fluoride or etidronate, and the chronic use of anticonvulsants. In most cases, the diagnosis of osteomalacia is suspected by the clinical history and by abnormalities in biochemical tests such as low values of serum and urinary calcium, serum phosphate and 25-hydroxyvitamin D, and high values for alkaline phosphatase and parathyroid hormone. A transiliac bone biopsy after tetracycline labelling may be necessary to demonstrate unequivocally a defect in mineralization.

Diffuse osteoporosis with or without pathological fracture is common in patients with multiple myeloma, a condition suspected by the severity of bone pain, increased sedimentation rate and Bence Jones proteinuria, and identified by marrow aspirate, and serum and urine (immuno) electrophoresis of proteins. Similarly, pathological fractures resulting from metastatic malignancies can mimic osteoporosis and can be excluded by clinical and radiological examination, biological tests such as tumour markers, and scintigraphy or other imaging techniques. Vertebral fractures in osteoporosis should be differentiated from vertebral deformities attributable to other disorders such as scoliosis, osteoarthrosis and Scheuermann disease.

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4. Overview of clinical risk factors for fractures

The skeleton is designed to accommodate the stresses encountered in everyday activities. The structure of limb bones, for example, is optimized to resist bending and twisting forces by concentrating a dense layer of cortical bone on the outer surface where such forces are greatest. These bones are therefore quite strong, and any fractures result from severe trauma, such as road traffic accidents. Patients with osteoporosis are not immune to severe trauma such as this, but they are uniquely at risk of fractures from so-called "low energy" trauma, e.g. falling from a standing height or less. These fractures mainly occur at the ends of long bones or sites in the axial skeleton, such as the vertebrae, where cancellous (trabecular) bone predominates. In these patients, osteoporosis may compromise the ability of bones to withstand even normal skeletal loads.

Conceptually, then, clinical risk factors for osteoporotic fractures can be separated into those that impair bone strength and those that lead to excessive loads on weakened bone from falls or, in some cases, ordinary activities of daily living. Many risk factors have been identified, although it is not always possible to confidently place them in one of these two categories. Moreover, the relative influence of specific risk factors may vary from one type of fracture to another. These issues are reviewed in the following sections. Even though our understanding of the pathogenetic mechanisms that underlie these various risk factors remains somewhat limited, it is still possible to exploit them empirically to refine the assessment of fracture risk for individual patients.

4.1 Risk factors related to impaired bone strength

4.1.1 Bone density

There are many determinants of bone strength, including the size of bone, its shape, microarchitectural arrangement, mineralization and microdamage. These cannot be directly measured for clinical use. It is estimated that the strength of cortical bone decreases by about 2% per decade in postmenopausal women and cancellous bone by 12% per decade. Thus, the strength of cortical and cancellous bone decreases by about 11% and 68%, respectively, throughout life *(1)*. From a clinical perspective, most of our current knowledge of fracture risk factors relates to those that are determinants of BMD, which is a surrogate measure of bone strength and a strong predictor of future fracture risk (see section 3). A large number of clinical risk factors may exert their effects partly through BMD as shown in Table 4.1 *(2,3)*. It is possible, however, to reduce this long list to a smaller group of more general categories.

Table 4.1
Risk factors for fracture related to bone mineral density (BMD)

High fracture risk	Moderate fracture risk
Ageing (> 70 years)	Female sex
Low body weight	Current smoking
Weight loss	Low sunlight exposure
Physical inactivity	Family history of osteoporotic fracture
Corticosteroids	Surgical menopause
Anticonvulsant drugs	Short fertile period (< 30 years)
Primary hyperparathyroidism	No lactation
Diabetes mellitus (type I)	Low calcium intake (< 500–850 mg/day)
Anorexia nervosa	Hyperparathyroidism
Gastrectomy	Hyperthyroidism
Pernicious anaemia	Diabetes mellitus (type II)
Prior osteoporotic fracture	Rheumatoid arthritis

Source: adapted from reference 3 (Table 5).

Age

Almost all studies indicate that increasing age is a strong determinant of fracture risk *(4)*. Greater age is associated with lower BMD in both sexes and all races, but age also predicts fracture risk independently of BMD. At present, it is still not clear to what extent age is independent of unmeasured risk factors such as calcium or vitamin D deficiency, the onset of gait and balance disorders that increase the risk of falling, or reductions in physical activity that may induce a form of disuse osteoporosis *(5)*.

Hormonal abnormalities

Excessive hormone production may be associated with increased fracture risk in patients with hyperthyroidism (including overdoses of thyroid hormone replacement), primary or secondary (e.g. chronic renal disease)

hyperparathyroidism, hyperprolactinemia and Cushing syndrome *(6)*. However, insufficient hormone production poses a greater problem. In particular, estrogen deficiency has long been blamed for rapid bone loss seen at the menopause, but it also appears to be responsible in part for later age-related bone loss in both men and women *(7)*. A number of fracture risk factors probably act through estrogen deficiency, including female sex, premature ovarian failure, surgical menopause and a short fertile period (menarche to menopause) *(8,9)*. Since testosterone is converted to estrogen, hypogonadism in men may also be related to low estrogen levels. Further, hypogonadism may account for the association of bone loss and fracture risk with some specific diseases such as acromegaly, haemochromatosis and other chronic liver diseases *(10)*. While many of these diseases are uncommon, iatrogenic hypogonadism from the use of gonadotropin-releasing hormone agonists and aromatase inhibitors in breast and prostate cancer, for example, is becoming more widespread *(11)*. The endocrine abnormalities seen in Turner or Klinefelter syndromes, athletic amenorrhoea, anorexia nervosa and insulin-dependent diabetes mellitus may also enhance future fracture risk by impeding growth and compromising the peak bone mass (and bone size) attained during adolescence *(12)*.

Nutritional deficiencies

Nutritional deficits can also impair the development of optimal peak bone mass *(13)*. If the supply from the diet is insufficient, calcium is withdrawn from the skeleton. Low calcium intake per se is obviously a problem, especially when combined with general nutritional deficits as seen in younger patients with anorexia nervosa and in frail elderly people. Even if dietary intake were adequate, absorption of calcium and other nutrients from the gastrointestinal tract may be directly impaired by gastrectomy, pernicious anaemia and various malabsorption syndromes, all of which have been associated with increased fracture risk *(14)*. Calcium intake may be indirectly impaired by a deficiency of vitamin D, which enhances calcium absorption and conservation, and that may lead to rickets or osteomalacia. Insufficient vitamin D levels may result from low sun exposure, especially in housebound elderly individuals, certain liver diseases such as cirrhosis and chronic hepatitis, or the use of drugs that interfere with vitamin D metabolism, e.g. some anticonvulsants *(15)*. Vitamin D deficiency also accelerates the catabolism of active forms of vitamin D *(16)*.

Specific pathological processes

In addition to hormonal and nutritional disturbances, some patients are affected by specific diseases, surgical procedures or drug exposures that occur sporadically in the population and exacerbate bone loss (so-called "secondary" osteoporosis). For instance, bone loss may be increased in patients with serious inflammatory diseases such as systemic lupus erythematosis, rheumatoid arthritis and Crohn disease *(6,17)*, although this may be partly attributable to the need for glucocorticoid therapy, an important risk factor reviewed in section 5. Whether the increase in fracture

risk is independent of corticosteroid use remains equivocal in inflammatory bowel disease, asthma and chronic obstructive pulmonary disease. Other diseases may increase fracture risk by distorting or destroying bone tissue. Thus, Paget disease produces foci of disorganized bone structure susceptible to pathological fractures *(18)*. Such fractures may also occur through regions where bone has been destroyed by multiple myeloma or other marrow proliferative disorders, by primary bone tumors such as osteosarcoma or by malignant lesions that have metastasized to the skeleton from other areas *(19)*.

Toxins

Adverse effects on bone of these malignant conditions may be exacerbated by treatment, especially chemotherapy and radiation, although effects can be difficult to distinguish from the underlying disease or from hypogonadism induced by toxic therapies. Much more common, obviously, are potential toxic effects on bone from cigarette smoking and excessive alcohol consumption, as reviewed in section 5.

4.1.2 Bone quality

It is important to keep in mind that fractures are related to the biomechanical characteristics of the skeleton, not to abnormal bone metabolism itself. Thus, bone strength may also be compromised by elevated bone turnover, a feature of estrogen deficiency and some other conditions such as hyperthyroidism. In addition, some measures of bone strength, e.g. the section modulus, are related more to bone diameter than to BMD *(1)*. The fact that bigger bones are more resistant to breaking may account for the lower fracture risk among men compared to women, as well as the protective effect of height found in some studies. Conversely, smaller bone size may partly account for the negative influence on future fracture risk of a personal history of osteoporotic fracture (see section 5) or a family history of such fractures (see section 5). A positive family history is often presumed to reflect an underlying genetic predisposition. Certainly, bone size is heritable, and there is a bewildering array of mostly rare genetic disorders (e.g. cystic fibrosis, osteogenesis imperfecta and osteopetrosis) that increase fracture risk *(20)*. Nevertheless, family history reflects similar behaviours and shared environments, as well as the effects of multiple genes, and the specific mechanisms responsible for the familial increase in fracture risk remain somewhat uncertain.

4.2 Risk factors related to excessive bone loads

4.2.1 Fall predisposition

Some fractures occur "spontaneously" in the course of everyday activities. Vertebral fractures, in particular, frequently result from seemingly innocuous behaviours such as opening a stuck window, although it has been shown that such activities can result in surprisingly large compression forces on the spine *(1)*. However, most osteoporotic fractures are precipitated by a "simple" fall, and these are very common: the likelihood of falling in a given year rises from

about one in five women 45–49 years old to nearly half of women aged 85 years and over, along with a third of elderly men *(21)*. Essentially all distal forearm fractures result from a fall to the ground, along with at least 90% of hip fractures and about a third of vertebral fractures. However, the pathogenesis of falls is anything but simple. Thus, many falls are caused primarily by so-called "extrinsic" factors such as slippery surfaces or obstacles such as steps, curbs or electric cords *(2)*. Although clinicians can advise patients about environmental hazards such as these, the clinically-evident risk factors for falling relate more to intrinsic characteristics of the patient and, again, a large number have been identified (Table 4.2). Most fallers have more than one deficit, and the risk of falling increases with the number of them that are present. These diverse factors can also be combined into a number of more general groupings.

Table 4.2
Intrinsic risk factors for falls among elderly people

Strong evidence	Moderate evidence
Older age	Arthritis
Female sex	Acute illness
Reduced functional level	Anti-Parkinson drugs
Cane or walker use	Cardiac and antihypertension drugs
History of falls	Alcohol use
Low walking speed	
Reduced lower extremity strength	
Increased postural sway	
Impaired reflexes	
Impaired vision	
Reduced lower extremity sensory perception	
Neuromuscular diseases (e.g. stroke)	
Urinary incontinence	
Hypnotic and sedative drugs	
Antipsychotic drugs	
Cognitive impairment	
Depression, antidepressant drugs	

Source: adapted from reference 2 (Table 1).

Reduced sensory input

Visual problems that have been linked to an increased risk of falling include blindness, cataracts, diabetic retinopathy, etc. More generally, decreased visual acuity, depth perception and contrast sensitivity impair the ability to identify and navigate environmental hazards. Poor vision and auditory problems may also exacerbate balance disturbances *(22)*.

Balance and gait problems

Any number of gait and balance disorders increase the risk of falling *(2)*. Such difficulties are obviously enhanced by a variety of neuromuscular

diseases such as polio, cerebral palsy, multiple sclerosis, paraplegia, Parkinson disease and stroke. However, risk assessment is not necessarily straightforward. Thus, fractures are not much increased in patients with mild strokes who recover completely nor in patients with severe strokes who are unable to ambulate without assistance *(23)*. Instead, fracture risk is concentrated among the patients who attempt to ambulate independently but have residual hemiplegia or hemiparesis.

Impaired strength and reflexes

Intact reflexes and adequate strength are essential to remaining upright. Impaired physical performance assessed by a variety of objective methods is an important risk factor for fractures *(24,25)*. Differences in neuromuscular competence may also explain regional differences in fracture risk. For example, the lower risk of falling, and of hip fracture, among Asian compared to white women has been attributed to their greater musculoskeletal competence; the risk of vertebral fractures, which derive less from falling, is comparable in the two groups *(26)*.

Drug side-effects

Some drugs, particularly psychotropic medication and sedatives, increase the likelihood of falls and fractures *(2)*. Such agents may also help explain the fracture risk associated with Alzheimer disease and depression. Likewise, postural hypotension from aggressive antihypertensive therapy may precipitate falls and fractures, as does syncope from other causes.

4.2.2 Fall mechanics

Unfortunately, it has proven difficult to prevent falls. A recent Cochran review concluded that a comprehensive intervention to reduce multiple risk factors for falling lowered the likelihood of falling by only 14%–27% and had little influence on reducing actual fracture risk *(27)*. Moreover, even among elderly fallers, fewer than 5% experience a fracture. Therefore, it is important to also consider risk factors that relate to the actual mechanics of falling. These include the energy generated by the fall, protective responses which mitigate that potential energy and any factors that help absorb the energy before it is delivered to the skeleton *(28)*. Some clinically evident risk factors for fracture relate to these aspects of the problem. Thus, hip fractures are more likely upon falling backwards and forearm fractures more likely when falling forwards. Falling backwards, in turn, is a consequence of slow gait speed and impaired neuromuscular coordination. The limited muscle strength and impaired reflexes that characterize a large number of neuromuscular disorders also reduce the effectiveness of automatic protective responses that are initiated by falling. Finally, the protective effects of fat (e.g. body mass index) on bone density, brought about by enhanced endogenous estrogen production by fat tissue, extend to energy-absorbing properties of fat that help decrease fracture risk. The importance of soft tissue loss over the hip in elderly individuals is shown by the substantial reduction in hip fractures achieved with the use of energy-absorbing hip pads in some settings *(29)*.

4.3 Use of clinical risk factors for fracture prediction

In the absence of other risk predictors, such as BMD, clinical risk factors can be used to assess fracture risk. Interestingly, most such risk factors have effects of similar magnitude, generally increasing the likelihood of fracture by 1.5 to 3 times more than that seen among unaffected individuals *(8,30–38)*. This suggests that different clinical risk factors may be substituted one for another in a fracture prediction algorithm. Although there is good evidence that these clinical risk factors exacerbate fracture risk, it is less clear that this is separate from their adverse effects on BMD. Few studies have quantified the independent influence of these conditions on fracture risk, but this information is needed if clinical risk factors are to be combined with BMD in predicting fractures (see section 5). Thus, hyperthyroidism is associated with fracture risk *(39)*, and data from the Study of Osteoporotic Fractures show that the 1.8-fold excess of hip fractures in women with hyperthyroidism is reduced only to 1.7 by adjusting for bone density and a personal history of fractures *(30)*. Likewise, after adjustment for BMD, significant associations with fractures have been shown for type I diabetes *(40)*, ankylosing spondylitis (41) and menopause *(42)*, as well as rheumatoid arthritis (see section 5). Risk factors for falling may also be independent of BMD. In the Study of Osteoporotic Fractures, for example, the relative risk of hip fracture associated with poor visual depth perception fell only from 1.5 to 1.4, and that associated with the use of long-acting benzodiazepine drugs was unchanged (1.6 versus 1.6), before and after adjustment for low bone density and fracture history *(30)*. However, risk factors for falling may not be responsive to pharmacologic treatments for osteoporosis *(43)*. If so, including them in a fracture prediction algorithm designed to identify high risk individuals for such therapy would be inappropriate.

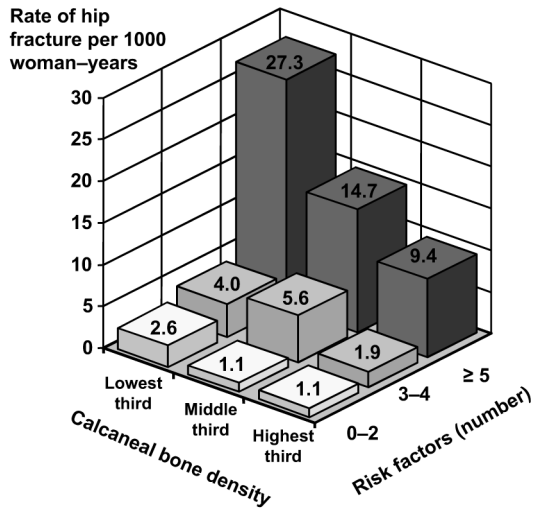
Based on the evidence available, the Osteoporosis Society of Canada *(44)* has recommended that physicians focus on a limited number of clinical risk factors (Table 4.3), the more important of which (e.g. personal and family history of fracture, glucocorticoid use and rheumatoid arthritis) are reviewed in detail in other chapters of this report. The potential value of focusing on these clinical risk factors is illustrated in Fig. 4.1, where it can be seen that hip fracture incidence is 17 times greater among older women with five or more clinical risk factors, exclusive of bone density, than women with two risk factors or fewer *(30)*. However, even women with five or more risk factors are at greater risk of fracture if their BMD is in the lowest third *(30)*. It is therefore apparent that clinical risk factors could help refine fracture risk prediction, but the choice of which ones to use for this purpose is less obvious. Data concerning many clinical risk factors are equivocal, and various risk factors themselves may be correlated. Adding to the confusion is the fact that different sets of potential risk factors have been assessed in the investigations completed to date. In addition, conditions that can have a devastating effect on the individual patient, but which are uncommon (e.g. Cushing syndrome), rarely appear among the independent risk factors identified in population-based studies.

Table 4.3
Factors that identify people who should be assessed for osteoporosis

Major risk factors	Minor risk factors
Age > 65 years	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40 years	Chronic anticonvulsant therapy
Family history of osteoporotic fracture (especially maternal hip fracture)	Low dietary calcium intake
	Smoker
Systemic glucocorticoid therapy of > 3 months duration	Excessive alcohol intake
	Excessive caffeine intake
Malabsorption syndrome	Weight < 57 kg
Primary hyperparathyroidism	Weight loss > 10% of weight at age 25
Propensity to fall	Chronic heparin therapy
Osteopenia on X-ray	
Hypogonadism	
Early menopause (before age 45 years)	

Source: reference 44 (Table 3).

Fig 4.1
Annual risk of hip fractures according to bone mineral density (BMD) at the calcaneus and the number of clinical risk factors



Source: reference 30 (Fig. 2).

There are then many clinically evident risk factors for fracture that might be used to identify high-risk patients for further evaluation and treatment. Although some of these conditions are rare, they are common in aggregate. Indeed, a third of affected women have at least one of them *(45)*, as do most men with osteoporosis *(46)*, and these are often the patients who present for care. Moreover, specific disorders associated with bone loss or falling have

been shown to account for 72% of the hip fractures in men *(31)*. What has been missing is a coordinated effort to identify a robust set of clinical predictors of fracture risk that are consistent across countries and easily ascertainable by the attending physicians *(47)*. This has now been accomplished as described in more detail in section 5. Thus, it is now possible to combine standard BMD measurements with clinical risk factors, such as those mentioned above, to improve the prediction of fracture risk for individual patients.

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5. Identification of risk factors for use in case-finding

Although osteoporosis is defined by measurement of BMD, its clinical significance rests with the fractures that arise as a consequence of the condition. Low bone mass is an important component of fracture risk, but other abnormalities arise in the skeleton that contribute to skeletal fragility. Moreover, various non-skeletal factors, such as the liability to falls, contribute to fracture risk. Thus, ideally, assessment of fracture risk should encompass all these aspects, and there is a distinction to be made, therefore, between the diagnosis of osteoporosis and the assessment of risk. From this perspective, BMD provides but one index of risk, albeit of considerable importance.

Interest in the use of clinical risk factors to assess fracture risk arises for several reasons. Measurements of bone mineral are not available in all Member States and several clinical risk factors act as surrogates for low BMD. Thus, clinical risk factors alone might be useful to identify a level of fracture risk sufficiently high that interventions could be directed on this basis alone. In the context of limited resources, the use of clinical risk factors might also be used to direct sub-populations at high risk for further testing, and economize thereby on the use of BMD. Finally, some risk factors provide information over and above that provided by BMD and can, therefore, be used to enhance risk prediction with BMD.

There are a number of factors to be considered in the selection of risk factors for case-finding. Of particular importance, in the setting of primary care, is the ease with which they might be used. For example, calcium intake has been shown in many studies to be an important determinant of fracture risk in the elderly. There are many sources of dietary calcium, and although intakes can be accurately acquired by food frequency questionnaires, such questionnaires are cumbersome to administer. A possible surrogate is intake of milk. In several countries milk provides approximately 50% of the total dietary intake of calcium. In large case-control studies, a low dietary intake of milk (less than 1 glass/day) was associated with a significant increase in hip fracture risk in men and women *(1,2)*.

The proportion of dietary calcium provided by milk, however, varies around the world and a simple question such as "do you take less than one glass of milk per day" does not reliably identify patients at risk of hip or other osteoporotic fractures *(3)*.

A second consideration is the intuitive value of the risk factors. For example, dementia is a strong risk factor for hip fracture *(4)*. In the context of case-finding, it would be difficult to persuade physicians or relatives that osteoporosis and fracture risk was high on the health-care agenda for these patients. By contrast, a prior fragility fracture or a family history of fracture has high intuitive appeal to physicians and patients, and its use may aid in motivating compliance with subsequent intervention.

A further factor to be considered is the international validity of the risk factors to be used. For example, is the gradient of fracture risk per unit change in BMD similar in different geographic settings? The same general question must also be asked of dichotomous variables such as the presence or absence of a family history of (hip) fracture. A final consideration is the reversibility of risk, i.e. is there evidence that the risk identified by a risk factor is amenable to therapeutic intervention. An example ad absurdum is the high risk of fracture when jumping from a 10th floor window. Although the fracture risk is high, there is little reason to believe that a pharmacological intervention would in any way affect the risk. It would be inappropriate, therefore, to identify such populations in a case-finding strategy. In a more realistic context, there is some evidence that the efficacy of bisphosphonates is questionable when elderly patients are selected for treatment because of strong risk factors for falling *(5)*. It is notable that in this latter study, the precise criteria for inclusion were not documented, and further work is required to determine whether risk factors for falls or a history of falls would identify a risk that was modifiable by pharmacological intervention.

5.1 Levels of evidence

The international validity of candidate risk factors and the extent to which they identify a reversible risk is amenable to an evidence-based approach.

There are well-established methods for evaluating the quality of evidence of the effectiveness of interventions *(6)*. The gold standard is meta-analysis of high quality randomized controlled studies that show consistent effects of an intervention. Though widely accepted, this criterion is inappropriate for studies that evaluate diagnostic tests or risk factors *(7)*. The evaluation of risk factors can, however, be based on similar principles. Ideally, the predictive value of such tests should be subject to meta-analyses, and be shown to have a high degree of consistency in populations similar to those in whom the test would apply (level I). Thus, the demonstration of a significant risk in postmenopausal women would not provide adequate information for use in men. The inclusion of an internal control is appropriate for the highest level of evidence. Take, for example, a study showing that smoking was a significant risk factor for fracture. The demonstration in the same study that BMD provides the expected gradient of risk for fracture, provides an internal control. Where appropriate, the demonstration of a dose-dependent effect or reversibility of effect may also be helpful in assigning high validity.

A lower level of evidence (level II studies and below) is provided by studies with any of the following deficits: a narrow population or a sample frame that does not capture the population in whom the test would be applied; the lack of a reference standard and case-control studies, or the use of a poor internal control. The lowest level of evidence is provided by expert committees or clinical experience. This provides a framework for grading levels of evidence (Table 5.1).

Table 5.1
Levels of evidence for studies of the use of risk factors

Levels of evidence	Type of evidence
Ia	Systematic reviews or meta-analysis of level I studies with a high degree of homogeneity
Ib	Systematic reviews or meta-analysis with moderate or poor homogeneity
Ic	Level I studies (with appropriate populations and internal controls)
IIa	Systematic reviews or meta-analysis of level II studies
IIb	Level II studies (inappropriate population or lacking an internal control)
IIIa	Systematic reviews or meta-analysis of level III studies
IIIb	Case-control studies
IV	Evidence from expert committees without explicit critical scientific analysis or that based on physiology, basic research or first principles.

As mentioned, the use of risk factors for case-finding presupposes that the risk so identified is responsive to a therapeutic intervention. To test this hypothesis, it would be necessary to recruit patients selected on the basis of the risk factor to a randomized controlled trial. The risk factor that is best evaluated in this way is BMD, and indeed the vast majority of therapeutic studies have recruited patients on the basis of low BMD, as recommended by regulatory agencies in the United States and Europe *(8,9)*. In recent years, other trials have recruited patients on the basis of age, sex, a prior vertebral fracture, and current exposure to glucocorticoids irrespective of BMD, and have shown therapeutic effects similar to those noted in randomized controlled trials based on BMD selection *(10–13)*.

For other risk factors, comparable data are lacking. In the absence of empirical data, an alternative approach is to demonstrate that the presence (or absence) of a risk factor does not adversely influence therapeutic efficacy against fractures. Several studies have shown no significant interaction between response to treatment and the presence or absence of other risk factors, including age, height, family history of fracture, low body weight or BMI, smoking, alcohol intake, biochemical markers of bone turnover, ultrasound attenuation or prior non-vertebral fracture *(13–17)*. In contrast, some risk factors may be associated with less therapeutic efficacy. For example, patients selected on the basis of risk factors for falling may respond less completely to agents that preserve bone mass than those selected on the basis of low BMD *(5)*.

These considerations provide four categories of risk factors, based on levels of evidence (Table 5.2):

A. those validated by use as inclusion criteria in randomized controlled trials;

B. those shown not to affect fracture outcomes adversely in randomized controlled trials;

C. those untested;

D. those shown to affect intervention outcomes adversely.

Note that A and B are not mutually exclusive.

Table 5.2
Categorization of risk factors for fracture according to evidence for reversible risk

Grade	Description	Risk factor
A	Validated by use as inclusion criteria in randomized controlled trials	Low BMD (DXA spine or hip) Prior vertebral fracture Long-term glucocorticoid treatment Age Postmenopausal status
B	Do not adversely affect fracture outcomes in randomized controlled trials	Low BMD (DXA spine or hip) Family history of fracture Prior non-vertebral fracture Prior vertebral fracture Biochemical markers of bone turnover QUS (at the heel) Smoking Body weight or BMI Age Alcohol intake
C	Untested	Other risk factors
D	Adversely affect intervention outcomes	Risk factors for falling

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; QUS, quantitative ultrasound; BMI, body mass index.

5.2 Meta-analyses of risk factors

Very many risk factors for fracture have been proposed which arise from observations in cross-sectional and case-control studies or prospective cohorts. Of those listed in Table 5.2, the general validity of candidate risk factors on an international basis is less secure. Meta-analyses are, however, available for the dependence of fracture risk on smoking *(18)*, and BMD *(19)*, use of oral glucocorticoids *(20)*, as well as the influence of a prior fragility fracture on the risk of a future fracture *(21)*. Even with these risk factors, uncertainties remain concerning differences between men and women, dependence upon age, and attenuation of the predictive value of the risk factors with time.

The WHO Collaborating Centre at Sheffield has examined a series of candidate risk factors from 12 prospectively studied cohorts drawn from the general population, using the primary data from each study (Table 5.3). Individual participant data were available for almost 60 000 men and women from 12 prospective population-based cohorts comprising: the Rotterdam study in the Netherlands; the European Vertebral Osteoporosis Study (EVOS) – later the European Prospective Osteoporosis Study (EPOS) – from 13 centres in Europe; the Canadian Multicentre Osteoporosis Study (CaMos); and cohorts from Rochester (USA), Sheffield (England), the Dubbo Osteoporosis Epidemiology Study (DOES, Australia), the EPIDOS and OFELY studies (France), as well as from Kuopio (Finland), Hiroshima (Japan), and two from Gothenburg (Sweden) *(22–38)*. The total follow-up was somewhat over 250 000 person–years (Table 5.3).

Table 5.3
Details of cohorts studied by meta-analysis of risk factors

Cohort	Number	% female	Person–years	Any fracture	Hip fracture	Osteoporotic fracture	Mean age (years)
CaMos	9 101	69	25 834	571	40	307	62
DOES	2 089	61	15 994	519	103	407	70
EPIDOS	1 183	100	3 947	NR	291	NR	82
EVOS/EPOS	13 490	52	40 681	719	50	719	64
Gothenburg I	7 065	100	29 603	440	29	312	59
Gothenburg II	1 970	59	15 201	350	271	350	78
Hiroshima	2 603	70	9 825	187	32	90	64
Kuopio	11 691	100	56 091	1043	NR	NR	52
OFELY	430	100	2 144	50	NR	NR	64
Rochester	1 001	65	6 227	289	42	244	56
Rotterdam	6 851	59	39 593	861	220	646	69
Sheffield	2 170	100	6 894	292	63	243	80
TOTAL	59 644	75	252 034	5321	1141	3318	63

NR, not recorded; EVOS, European Vertebral Osteoporosis Study; EPOS, European Prospective Osteoporosis Study; CaMos, Canadian Multicentre Osteoporosis Study; DOES, Dubbo Osteoporosis Epidemiology Study; OFELY, *L'os des femmes de Lyon,* EPIDOS, *Epidémiologie de l'osteoporose.*

Risk factors were selected on the basis of their availability and reasonable uniformity in the construct of the questionnaire used in each study. Neuromuscular disorders such as Parkinsonism and liability to falls were not assessed, since there is some doubt as to whether the risk identified on the basis of such factors would be amenable to pharmacological intervention. Additional risk factors were assessed, but were excluded because of marked heterogeneity in the acquisition of data between cohorts or because of their low prevalence in the general population. These included low intakes of calcium (3), a premature menopause, osteoarthrosis, bilateral oophorectomy and endocrine disorders affecting the skeleton.

The following risk factors were selected on the basis of the likelihood that the risk identified would be amenable to pharmaceutical manipulation and the ease with which the risk factor could be used in clinical practice as a baseline or outcome variable:

- age
- bone mineral density
- body mass index
- prior fragility fracture
- ever use of oral glucocorticoids
- parental history of fracture
- current smoking
- alcohol intake
- rheumatoid arthritis.

The cohorts with risk factors contributing to each analysis are shown in Table 5.4.

Table 5.4
Risk factors for osteoporosis, examined by cohort

Cohort	Body mass index	Family history	Bone mineral density	Glucocorticoids	Prior fracture	Smoking	Alcohol	Rheumatoid arthritis
CaMos	+	+	+	+	+	+	+	+
DOES	+	+	+	+	+	+	+	+
EPIDOS	+	-	+	-	-	-	-	-
EVOS/EPOS	+	+	+	+	+	+	-	-
Gothenburg I	+	-	+		+	+	-	-
Gothenburg II	+	+	+	+	+	+	-	-
Hiroshima	+	-	+	+	+	+	-	-
Kuopio	+	-	+	-	+	+	-	-
OFELY	+	-	+	-	+	-	-	-
Rochester	+	+	+	+	+	+	-	-
Rotterdam	+	+	+	+	+	+	+	-
Sheffield	+	+	+	+	+	+	-	+

+, contributing; –, missing; EVOS, European Vertebral Osteoporosis Study; EPOS, European Prospective Osteoporosis Study; CaMos, Canadian Multicentre Osteoporosis Study; DOES, Dubbo Osteoporosis Epidemiology Study; EPIDOS, Epidémiologie de l'osteoporose; OFELY, L'os des femmes de Lyon.

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in metres. BMD tests were available in 70% of individuals. BMD was measured at the femoral neck by DXA, except in the two Gothenburg cohorts where BMD was assessed by DXA at the distal forearm or by Dual photon absorptiometry at the right heel. The BMD data were also analysed excluding these two cohorts. BMD was expressed as sex-specific and cohort-specific Z-scores.

A history of current or past smoking was obtained by self-report. There was inadequate information to assess possible dose-response effects. The assessment of alcohol intake differed between cohorts, and was converted into a daily intake expressed as units/day. A unit of alcohol is equivalent to 8 g in the United Kingdom, though varies somewhat in different countries. A family history was collected of any fracture in first-degree relatives. In addition, a family history of hip fracture was noted but was available only in three of the cohorts *(39)*. Prior fracture history of each individual was documented, though the construct of the question varied, particularly the age from which a fracture had occurred *(40)*. Use of oral glucocorticoids ever during a person's lifetime (ever use) was used to characterize steroid exposure, because all but three cohorts did not distinguish between ever use and current use. Neither the dose nor the duration of use was analysed. The presence or absence of rheumatoid arthritis was by self-report.

Fracture ascertainment was undertaken by self-report (Sheffield, EVOS/EPOS, Hiroshima, Kuopio, EPIDOS, OFELY) or verified from hospital or central databases (Gothenburg, CaMos, DOES, Kuopio, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS, OFELY, Hiroshima and the Rotterdam studies also included sequential systematic radiography to define incident vertebral deformities, but these were not used in the analyses presented here. In the analyses, information was used on any clinical fracture considered to be osteoporotic. In the EVOS/EPOS and CaMos studies, an osteoporotic fracture was one considered to be attributable to osteoporosis by the investigators. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted *(41)*. In addition, hip fracture alone was considered separately in the analysis.

The effect of the candidate risk factor, age and sex on the risk of any fracture, any osteoporotic fracture and hip fracture alone was examined using Poisson regression models in each cohort separately. A Poisson model was chosen since it has greater power than logistic regression and can accommodate all information with variable durations of follow-up. In addition, time can be accommodated as an interaction term, and for some risk factors, relative risk may decrease with longer durations of observation. For each risk factor

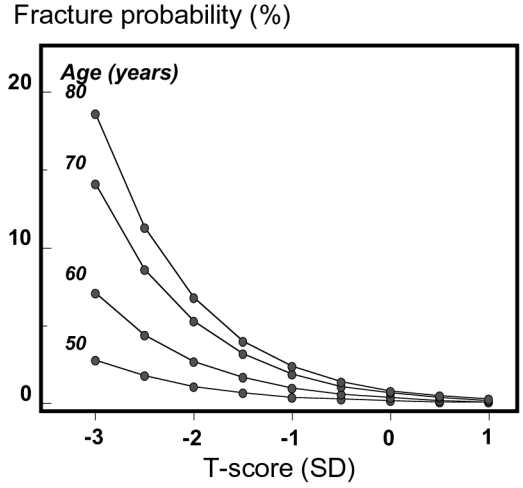
studied, covariates included current age and time since follow-up, with and without BMD. Where appropriate, interaction terms were included. Outcome variables comprised any fracture, any osteoporotic fracture and hip fracture alone. The results of different cohorts (men separate from women) were then merged using weighted coefficients.

A fixed-effects model, rather than a random-effects model was used since the latter weights the smaller cohorts disproportionately. In addition, the fixed-effects model generally gives a more conservative point estimate for the risk ratio, albeit with wider confidence estimates. Heterogeneity between cohorts was tested by means of the I^2 statistic *(42)*. Where more than moderate heterogeneity was found (>50%), risk ratios were computed using the random-effects model to determine whether the significance of estimates had changed. The following section summarizes the information derived from the meta-analyses.

5.2.1 Age

Age is a particularly strong risk factor for fracture, especially for hip fracture. From the known relationship of BMD and fracture risk, it might be expected that hip fracture risk would increase approximately 4-fold between the age of 55 and 85 years in women because of the age-related decrease in bone mass. In practice, hip fracture risk in many countries increases 40-fold *(43)*. Thus, over this age range, the impact of increasing age is 11-fold greater than the impact of decreasing BMD. The interaction of age and BMD has been formalized in several studies *(43,44)*. In the case of DXA at the femoral neck, the risk of fracture by age varies markedly at the threshold of osteoporosis, i.e. with a T-score of exactly –2.5 SD. Thus, at the age of 50 years the 10-year hip fracture probability is approximately 2% in women but at the age of 80 years it is 12% for the same T-score. For any osteoporotic fracture (hip, forearm, shoulder or clinical spine fracture), the 10-year probability in women with a T-score of –2.5 SD varies from 11% at the age of 50 years to 26% at the age of 80 years (Fig. 5.1) *(43)*. Since age is such a strong determinant of fracture risk, each risk factor was examined by age.

Fig. 5.1
The relationship between bone mineral density at the femoral neck expressed as a T-score and 10-year hip fracture probability in women from Sweden according to age



Source: reference 43 (Fig. 3).
BMD, bone mineral density; SD, standard deviation.

5.2.2 Bone mineral density

A large number of studies have examined the relationship between BMD measured at various sites and fracture risk, and the available data were summarized by meta-analysis in 1996 and 2002 *(19,45)*. With DXA measured at the hip, hip fracture risk increased 2.6-fold per SD decrease in BMD, and the risk of any fracture increased 1.6-fold per SD. Since then, many additional studies with longer follow-up times have shown broadly similar findings *(23,46–53)*.

Although the general relationship between BMD and fracture risk measured at different sites has been well characterized (19), there are still gaps in our knowledge even when using the reference of DXA at the hip. These gaps include whether the predictive value varies by age and sex, the stability of predictive value with time and whether its performance is similar at different levels of BMD.

Sex

The meta-analysis derives values similar to those found in the previous studies and is summarized in Table 5.5 *(54)*. BMD measurement at the femoral neck with DXA was a strong predictor of hip fractures. For any fracture and for any osteoporotic fracture, the gradient of risk was lower than for hip fractures. For hip fracture risk, the gradient of risk was somewhat higher in men than in women since the sex-specific standard deviation differs between men and women. The difference in gradient of risk became less apparent when a common SD was applied to both men and women.

Table 5.5
Gradient of risk (RR/SD) per SD decrease in Z-score of bone mineral density at the femoral neck in men and women

Outcome fracture		RR/SD[a]	95% confidence interval	RR/SD[b]	95% confidence interval
Any	Men	1.47	1.34–1.60	1.44	1.32–1.58
	Women	1.45	1.39–1.51	1.46	1.39–1.53
	Combined	1.45	1.39–1.51	1.46	1.40–1.52
Osteoporotic	Men	1.60	1.43–1.79	1.55	1.40–1.73
	Women	1.53	1.46–1.62	1.56	1.47–1.64
	Combined	1.55	1.47–1.62	1.56	1.49–1.64
Hip	Men	2.42	1.90–3.09	2.28	1.81–2.87
	Women	2.03	1.87–2.21	2.18	1.99–2.39
	Combined	2.07	1.91–2.24	2.21	2.03–2.41

Source: reference 54 (Table 2).
RR, relative risk; SD, standard deviation.
[a]SD is age-specific and sex-specific for each cohort.
[b]SD used is that of the young female reference range of NHANES III.

There has been some debate as to whether the gradient of risk of BMD for fracture is the same or differs between men and women *(55)*. Differences are described in selected cohorts, or when sex-specific standard deviations are used *(56,57)*. In the present analysis, no significant difference between men and women was found, as in other population-based samples *(23,58)*. Indeed, the age-specific risk of hip fracture at a given femoral neck BMD in men appears to be the same in women with the same BMD and age.

Age

Age at assessment was an important factor that affected the predictive value of femoral neck BMD. For the prediction of osteoporotic fracture, there was a modest and not significant increase in gradient of risk with age (Table 5.6). This might be expected since osteoporotic fractures include hip fractures, which increase with age and are predicted more accurately by BMD at the hip than is the case for other fractures. The exclusion, however, of hip fractures in the analysis did not markedly alter the relationship of osteoporotic fracture risk with age. A much more marked and significant relationship was found between the gradient of risk for hip fracture and age. Gradients of risk (RR/SD) were higher at younger ages than in the elderly, and decreased significantly with age (Table 5.7). For example, the gradient of risk was 3.68/SD at the age of 50 years and decreased progressively with age so that at the age of 85 years it was 1.93/SD. Similar findings have been reported in the EPIDOS study, with a lower predictive ability of DXA for hip fractures in women at the higher ages *(46,59)*. In the EPIDOS study the gradient of risk for hip fractures with a T-score of –2.5 SD or less was 4.4 at ages less than 80 years and 2.5 at ages of 80 years or more. In the Study of Osteoporotic Fractures (SOF), differences with age were less marked. For hip fractures in women assessed by DXA at the hip, the gradient of risk between the ages of 65 and 79 years was 2.9, and in women aged 80 years or more was 2.1 *(60)*.

Table 5.6
Gradient of risk (RR/SD) provided by bone mineral density of the femoral neck for osteoporotic fracture in men and women by age

Age (years)	Men		Women		Men and women	
	Risk ratio	95 % CI	Risk ratio	95 % CI	Risk ratio	95 % CI
50	1.27	1.13–1.42	1.22	1.07–1.39	1.37	1.23–1.52
55	1.31	1.19–1.45	1.27	1.14–1.41	1.40	1.29–1.52
60	1.36	1.26–1.47	1.32	1.21–1.44	1.43	1.34–1.53
65	1.41	1.33–1.51	1.38	1.28–1.48	1.45	1.37–1.53
70	1.49	1.41–1.58	1.46	1.37–1.56	1.49	1.42–1.57
75	1.59	1.50–1.68	1.57	1.48–1.67	1.57	1.50–1.66
80	1.66	1.57–1.76	1.66	1.56–1.76	1.62	1.54–1.71
85	1.66	1.54–1.78	1.65	1.53–1.79	1.54	1.44–1.63
All ages	1.60	1.43–1.79	1.53	1.46–1.62	1.55	1.47–1.62

Source: reference 54 (Table 3).
RR, relative risk; SD, standard deviation.

Table 5.7
Gradient of risk (RR/SD) with bone mineral density at the femoral neck for hip fracture in men and women combined by age

Age (years)	Relative risk	95% confidence interval
50	3.68	2.61–5.19
55	3.35	2.51–4.47
60	3.07	2.42–3.89
65	2.89	2.39–3.50
70	2.78	2.39–3.23
75	2.58	2.30–2.90
80	2.28	2.09–2.50
85	1.93	1.76–2.10

Source: reference 54 (Table 4).
RR, risk ratio; SD, standard deviation.

The clinical significance of variations in the gradients of risk with age is noteworthy. For example, an individual with a Z-score of –2 SD at the age of 50 years would have a hip fracture risk that was 13-times that of an individual with an average BMD (Z-score = 0) at that age (see Table 5.7), whereas the risk would be increased only 5-fold at the age of 80 years. This may be fortuitously advantageous in the assessment of risk. In younger patients, greater reliance can be placed on BMD, whereas in the elderly, risk can be additionally assessed by clinical risk factors, many of which increase in frequency with age.

Time since assessment

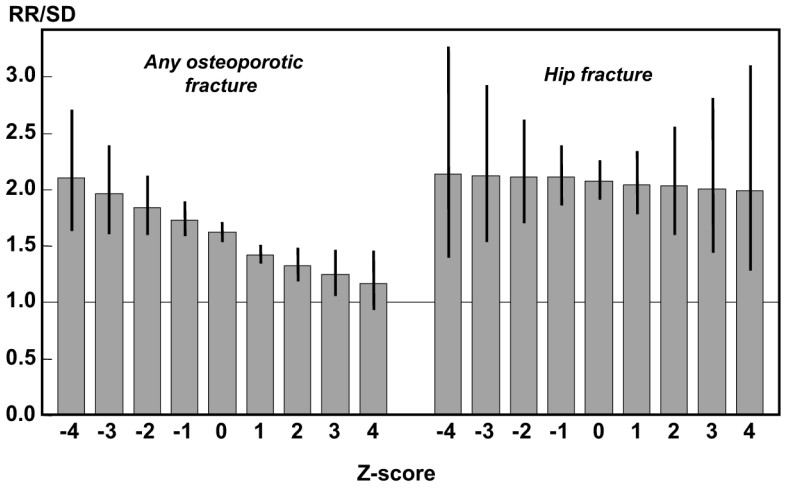
A concern with long-term prediction is that the predictive value of risk factors may decrease with time as a result of variable rates of bone loss with time. A previous study *(61)* modelled the decrease in the predictive ability of BMD with time after measurement, a phenomenon that has been supported by some but not all empirical studies *(29,62,63)*. Huang, Ross & Wasnich *(62)* showed a non-significant reduction in predicting vertebral fractures by time after measurement. After 2.7 years of follow-up, the relative risk per SD

decrease in BMD was 1.7 at the forearm and 1.8 at the lumbar spine. After 8 years, the gradients of risk were 1.5 and 1.7, respectively. A reduction with time after measurement was also observed by Düppe et al. *(63)*. In the present analysis, there was a slight but non-significant attenuation in the predictive ability of BMD for hip fractures the longer the follow-up. The immediate risk of hip fracture was 2.18/SD and the risk was 1.91/SD at 10 years. There was no effect of time since assessment for any fracture or any osteoporotic fracture. A similar result was found by Melton et al. *(29)* where femoral neck BMD predicted the risk of osteoporotic fracture as well in the first 10 years of follow-up (HR = 1.38) as in the subsequent 10 years (HR = 1.39). Since the decrease in predictive ability was rather small, it will not markedly affect the computation of 10-year fracture probability that is proposed as an index of risk assessment.

Baseline bone mineral density

A more important interaction was the effect of the baseline BMD value itself on predictive value. Gradients of risk were lower the higher the Z-score (Fig. 5.2). The effect was marked for the prediction of osteoporotic fracture or any fracture, and was also evident for hip fracture prediction, though not statistically significant. Reasons for this are conjectural but might be related to the lower body mass index which is associated with lower values of BMD, and also perhaps to co-morbidity, muscle weakness or less padding with fat to protect against injury *(32,64,65)*. In addition, lower BMD values may be associated with structural changes in bone (e.g. increased bone area but thinner cortices or higher rates of bone remodelling) that reduce resistance to fracture *(66)*. Irrespective of the mechanism, the effect is large in the case of osteoporotic fracture risk, so that account should be taken of this for the optimal assessment of patients.

Fig. 5.2
Risk ratio for 1 SD change in Z-score for bone mineral density in men and women combined (Z-score range from –5.1 to +5.8)



Source: reference 54 (adapted from Table 6).
RR, risk ratio; SD, standard deviation.

These analyses indicate that assessment of femoral neck BMD provides a strong indicator for fracture risk that is largely independent of sex. Its predictive value is not significantly attenuated with time after assessment over a 10-year interval, suggesting that it can be used to compute long-term fracture probabilities. The significance of BMD as a risk factor depends upon the absolute level of BMD when used to predict any fracture or any osteoporotic fracture. In addition, the gradient of risk for hip fracture is higher in younger individuals. These characteristics need to be accounted for to make best use of BMD in a clinical setting.

5.2.3 Body mass index

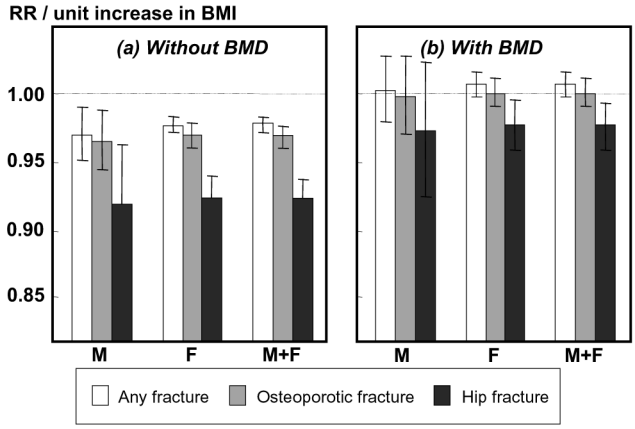
Low weight, or low BMI, is a well-documented risk factor for future fracture, whereas a high BMI appears to be protective *(67–76)*. The increasing prevalence of overweight and obesity in high-income societies *(77,78)* might at first seem a promising development from the point of view of osteoporosis and fracture prevention. From a public health point of view, however, being overweight or obese is associated with increased morbidity from diabetes, hypertension and cardiovascular diseases, as well as increased mortality *(79)*. Recently it was estimated that overweight (BMI>25 kg/m^2) 40-year-old female non-smokers lost on average 3.3 years of life, whereas obese (BMI>30 kg/m^2) female non-smokers lost 7.1 life years (80). It is important, therefore, to quantify the association between BMI and fracture risk, and to explore its relationship to age, sex and BMD, with the aim of being able to give balanced advice on lifestyle. These relationships are also important when using BMI to assess fracture risk in case-finding *(68,81–84)*.

The present meta-analysis explored the relationship of BMI with fracture risk (any fracture, any osteoporotic fracture and hip fracture alone) in men and women. BMI was chosen rather than weight to explore this association because of the wide variation in average weight and height between different countries, which is reduced by adjusting weight for height. Moreover, BMI is as good a predictor of fractures as weight in most studies of hip fracture outcomes *(2,85)*.

Sex and age

The principal finding of this analysis was the confirmation that low BMI is associated with a substantial increase in fracture risk, of similar magnitude in men and women, whereas a high BMI is protective *(86)*. This risk associated with a low BMI was present at most ages and for all types of fracture studied, but was strongest for hip fracture. Without information on BMD, the risk ratio per unit increase in BMI for any fracture was 0.98, for osteoporotic fracture 0.97 and for hip fracture 0.93 (Fig. 5.3). As this figure shows, the RRs per unit change of BMI in men and women were very similar and not significantly different (p>0.30).

Fig. 5.3
Risk ratio for fracture per unit increase in body mass index: (a) adjusted for current age and time in study; (b) additionally adjusted for bone mineral density

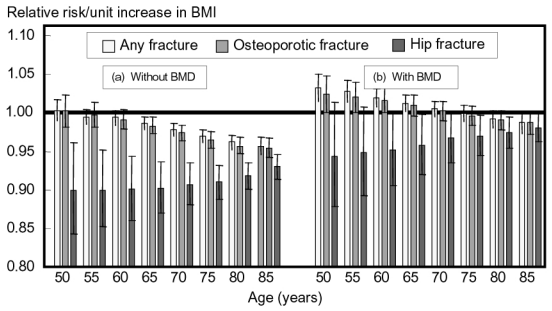


Source: reference 86 (Fig. 1).
RR, risk ratio; BMI, body mass index; BMD, bone mineral density; M, male; F, female.

Although there were no significant differences in the gradients of fracture risk between men and women, there was a significant increase in risk associated with low BMI with age, for any fracture and for osteoporotic fractures, but an opposite trend for hip fractures (Fig. 5.4). For any fracture and for any osteoporotic fracture, the gradient of risk per unit of BMI increased with advancing age (without adjustment for BMD). In contrast, for hip fractures the gradient of risk decreased with age, although this trend was not significant. When hip fractures were excluded from the osteoporotic

fractures, a similar trend with age was observed as seen for all osteoporotic fractures. After correction for BMD, the risk gradients showed similar, but non-significant trends with age, but at most ages were not significantly different from 1.

Fig. 5.4
Relative fracture risk per unit increase in body mass index by age for men and women combined: (a) adjusted for current age and time in study; (b) additionally adjusted for bone mineral density



Source: reference 86 (Fig. 2).
BMI, body mass index; BMD, bone mineral density.

In the case of any fracture or osteoporotic fracture, the higher risk with age may be the result of longer exposure to gonadal deficiency *(87)*. A further possible explanation is that in young individuals, low BMI may be associated with physical fitness and a lower risk of fracture. In contrast, in elderly people, where hip fractures are more common, low BMI may more likely be related to frailty.

Baseline body mass index

Although the risk of fracture increased with decreasing BMI, the risk ratio with BMI was non-linear (Table 5.8). The risk ratio was markedly higher at the lower values of BMI, particularly with a BMI of 20 kg/m^2 or less. By contrast, between a BMI of 25 and 35 kg/m^2, the differences in risk ratio were small. For example, when compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with a nearly 2-fold increase in risk ratio (RR = 1.95) for hip fracture. In contrast, a BMI of 30kg/m^2 when compared with a BMI of 25 kg/m^2 was associated with only a 17% reduction in hip fracture risk (RR = 0.83).

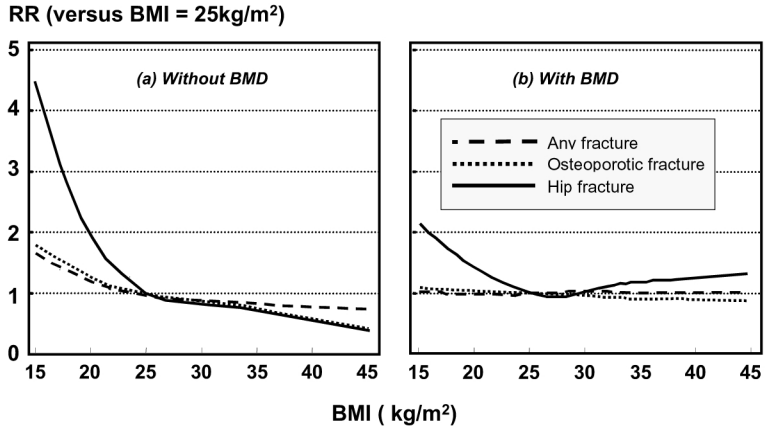
Table 5.8
Risk ratio for fracture at various levels of body mass index (kg/m²) for men and women combined, adjusted for current age and time in study, without and with adjustment for bone mineral density (the reference is a body mass index of 25 kg/m²)

	Any fracture		Osteoporotic fracture		Hip fracture	
BMI	RR	95 % CI	RR	95 % CI	RR	95 % CI
Not adjusted for BMD						
15	1.66	1.31–2.09	1.79	1.35–2.37	4.48	3.11–6.45
20	1.21	1.12–1.30	1.27	1.16–1.38	1.95	1.71 –2.22
25	1.00	Reference	1.00	Reference	1.00	Reference
30	0.92	0.85–1.00	0.89	0.81–0.98	0.83	0.69–0.99
35	0.85	0.74–0.98	0.74	0.62–0.90	0.75	0.50–1.11
40	0.80	0.62–1.03	0.57	0.39–0.85	0.53	0.18–1.56
Adjusted for BMD						
15	1.00	0.75–1.33	1.07	0.78–1.48	2.16	1.42–3.28
20	0.98	0.9–1.08	1.02	0.92–1.13	1.42	1.23–1.65
25	1.00	Reference	1.00	Reference	1.00	Reference
30	1.01	0.91–1.11	0.96	0.86–1.08	1.00	0.82–1.21
35	0.99	0.82–1.19	0.91	0.73–1.13	1.18	0.78–1.80
40	0.99	0.68–1.43	0.89	0.56–1.4	1.25	0.44–3.57

Source: reference 86 (Table 3).
RR, risk ratio; BMI, body mass index; BMD, bone mineral density; CI, confidence interval.

There appears to be, therefore, an inflection point such that increased BMI over 22 kg/m² is associated with modest decreases in fracture risk, whereas below this threshold the risk is markedly increased (Fig. 5.5).

Fig. 5.5
Relative fracture risk at various levels of body mass index (BMI) for men and women combined (reference level: BMI=25 kg/m²): (a) adjusted for current age and time in study; (b) additionally adjusted for bone mineral density



Source: reference 86 (Fig. 3).
RR, risk ratio; BMI, body mass index; BMD, bone mineral density.

The threshold of 22 kg/m^2 and lower corresponded overall in these cohorts to about 10% of men and 17% of women. A non-linear relationship of BMI with fracture risk, with thresholds of BMI of approximately 22 kg/m^2 and 26 kg/m^2, has been described previously in case-control studies of men and women, respectively *(2,85)*. These studies all indicate that obesity should not be regarded as an important protective factor for fracture risk *(88,89)*. Rather, leanness should be regarded as a significant risk factor. The finding that leanness is much more important as a risk factor, than obesity is as a protective factor, means that advice concerning body weight and osteoporosis need not be inconsistent with the weight control advocated for the prevention of cardiovascular disease or diabetes.

Bone mineral density

The analysis additionally demonstrates that this gradient of risk with BMI is markedly reduced when adjusted for BMD (see Fig. 5.3), suggesting that BMD is an important intermediary or confounder. In contrast, the use of low BMI as a risk factor in the absence of BMD, will identify populations with a low BMD and hence a high risk of fracture.

After adjustment for BMD, a low BMI was not predictive of fracture risk except for hip fracture at a BMI of 20 kg/m^2 or less. Since low BMI remained a significant risk factor for hip fracture, it can still contribute to enhance the predictive value of BMD in case-finding. The mechanisms for this effect are conjectural but might include muscle weakness *(90)*, perhaps associated with nutritional deficiencies of protein or vitamin D (90,91), decreased padding over the greater trochanter *(92)*, or a greater liability to fall *(76)*.

For BMD, it is customary to express the relation with fracture risk as a gradient of risk per SD change. For hip fracture, for example, the most commonly cited number is that of a relative risk of 2.6/SD decrease in BMD *(19)*. In the populations that we studied, the average SD for BMI was around 4 kg/m^2, corresponding to a RR for hip fracture of 1.4/SD decrease in BMI, much lower than the estimate for BMD. The analogy is, however, not wholly appropriate in view of the non-linearity of risk with BMI.

Overall, the analysis indicates that low BMI confers a risk of fracture of substantial importance that is largely independent of sex. The significance of BMI as a risk factor varies according to the level of BMI and to a lesser extent with age. Its validation on an international basis permits the use of this risk factor, at least in the absence of a BMD measurement, in case-finding strategies. Even with BMD included in the assessment, a low BMI remains an independent risk factor for hip fracture.

5.2.4 Previous fracture

It is well established from many cohort, case-control and cross-sectional studies that a prior osteoporotic fracture increases the risk of future fractures *(93–100)*. A prior forearm fracture is associated with about a 2-fold increase

in the subsequent risk of fracture *(101–105)*. More recently, significant increases in risk have been described for prior fractures at other sites characteristic of osteoporosis *(99,106–114)*. The risk of another vertebral fracture is particularly high after a spine fracture *(106,115–117)*. Similar observations are found in the setting of randomized clinical trials. In the placebo arm, the risk of vertebral deformities is approximately 5-fold higher in patients with a prior vertebral deformity than in those without *(96,118,119)*. The interrelationships between the site of prior fracture and site of subsequent fracture have been summarized by meta-analysis *(21)*, and a large case-control study, published more recently, found broadly similar relationships *(100)*. The increase in fracture risk appears to be highest immediately after a fracture event, particularly in the first year. The risk decreases over subsequent years, but remains higher than that of the general population *(96–98)*.

Increased fracture risk may be in part attributable to the fact that patients with fracture have low BMD. Studies that have adjusted for BMD suggest that the relative risk is only modestly downwardly adjusted *(64,67,95,117,120–122)*.

The consistent association between a prior fracture and subsequent fracture risk has led to the inclusion of prior fracture as a risk factor to be used in assessment guidelines *(81–83,123)*. There are still some unresolved questions that concern the effect of age, sex and BMD on this risk.
In the present analysis (40), the probability of a positive fracture history rose almost linearly with age from about 24% at the age of 30 years to 45% at the age of 90 years. The probability of a prior fracture was significantly higher in men than in women (odds ratio = 1.19; 95% CI = 1.14 – 1.25).

Sex and fracture outcome

The present study confirms that a history of prior fracture is a significant risk factor for future fractures. Previous fracture was associated with a significantly increased risk of any subsequent fracture (Table 5.9). There was no difference in the risk ratio between men and women. Previous fracture was also associated with a significantly increased risk of an osteoporotic fracture at all ages, with and without adjustment for BMD. The unadjusted risk ratios for an osteoporotic fracture were almost identical with the risks of a prior fracture for any fracture. For example, at the age of 80 years the risk of any fracture was 1.88 in men and women combined, and for an osteoporotic fracture was 1.89. A prior fracture history was a significant risk factor for hip fracture at all ages.

Table 5.9
Risk ratio and 95% confidence interval of fracture associated with a history of prior fracture in men and women, without and with adjustment for bone mineral density

	Men		Women		Men and women	
Outcome fracture	RR	95% CI	RR	95% CI	RR	95% CI
Without BMD						
Any	2.02	1.73–2.38	1.84	1.72–1.96	1.86	1.75–1.98
Osteoporotic	1.93	1.61–2.33	1.85	1.70–2.01	1.86	1.72–2.01
Hip	2.30	1.56–3.41	1.77	1.49–2.11	1.85	1.58–2.17
With BMD						
Any	2.04	1.67–2.48	1.73	1.59–1.88	1.77	1.64–1.91
Osteoporotic	1.91	1.50–2.43	1.74	1.57–1.92	1.76	1.60–1.93
Hip	1.97	1.12–3.48	1.56	1.23–1.98	1.62	1.30–2.01

Source: reference 40 (Table 4).
RR, risk ratio; CI, confidence interval; BMD, bone mineral density.

The risk of subsequent fractures is not as great as that identified in some studies *(100)* but, as expected, falls within the confidence intervals of most estimates *(21)*. Discrepancies may be related to the duration of follow-up, since the risk of subsequent fracture may not be linear over time *(96–98)*. Other possible reasons may relate to differences in the populations studied and the questionnaire used to identify prior fractures.

Age

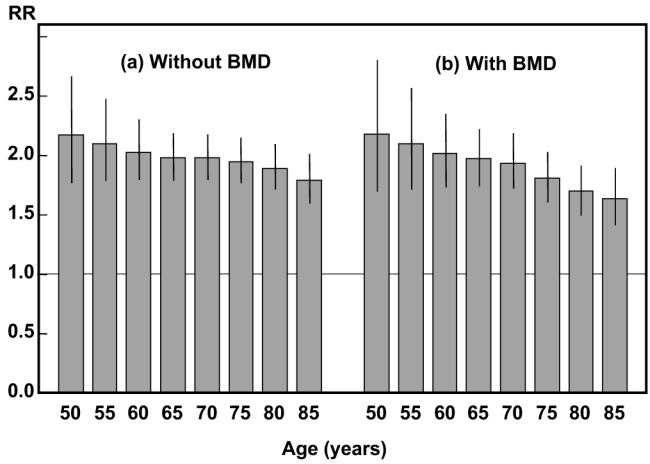
The large sample size permitted the quantification of risk by age. For all fractures and for osteoporotic fractures, the risk ratios were relatively constant with age. In the case of hip fracture, risk ratios decreased (Table 5.10) by about 10% per decade of age (Fig. 5.6) but the trend was short of conventional significance ($p=0.089$). The risk ratio was highest at younger ages and decreased progressively with age ($p<0.002$ for the interaction term). The risk ratio was significantly increased at all ages, but at ages less than 60 years, the confidence estimates were wide (because of the small number of hip fractures). There was no difference in the risk ratio between men and women.

Table 5.10
Risk ratio for any fracture and 95% confidence interval and for hip fracture comparing with and without adjustment for bone mineral density when combining men and women as well as with and without a previous fracture by age

Age (years)	Any fracture				Hip fracture			
	RR without BMD[a]		RR with BMD[a]		RR without BMD		RR with BMD	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
50	1.92	1.63–2.20	1.91	1.59–2.29	5.04	2.66–9.56	3.88	1.79–8.43
55	1.90	1.73–2.09	1.83	1.60–2.10	4.20	2.46–7.15	3.98	2.08–7.62
60	1.98	1.80–2.18	1.94	1.73–2.17	3.40	2.21–5.24	3.16	1.88–5.32
65	2.02	1.86–2.20	1.99	1.81–2.20	2.60	1.85–3.64	2.28	1.52–3.41
70	2.03	1.87–2.21	1.98	1.79–2.18	2.31	1.76–3.02	1.90	1.37–2.65
75	1.96	1.80–2.13	1.82	1.65–2.02	2.14	1.71–2.68	1.64	1.24–2.17
80	1.88	1.72–2.06	1.72	1.54–1.91	1.90	1.58–2.28	1.41	1.12–1.78
85	1.83	1.65–2.04	1.72	1.51–1.96	1.66	1.39–1.98	1.32	1.04–1.68
All ages	1.86	1.75–1.98	1.77	1.64–1.91	1.85	1.58–2.17	1.62	1.30–2.01

Source: reference 40 (Tables 5 and 6).
RR, risk ratio; CI, confidence interval; BMD, bone mineral density.
[a]Prior fracture versus no fracture.

Fig. 5.6
Risk ratio for an osteoporotic fracture in men and women combined, with a prior history of fracture, with and without adjustment for bone mineral density



Source: reference 40 (Fig. 1).
RR, risk ratio; BMD, bone mineral density

Bone mineral density

In addition, the effect of fracture history is over and above that which can be explained by variations in BMD. The risk ratio was marginally lower, by approximately 10%, when account was taken of BMD. If it is assumed that the risk of any fracture increases 1.60-fold for each SD deviation decrease in

femoral neck BMD, then the difference in risk between those with and without a prior fracture is equal to an expected difference in BMD of 1.32 SD. In reality the overall difference in BMD at all ages in men and women combined was approximately 0.11 SD. Thus, low BMD accounts for only about 8% of the difference in risk between those with or without a prior fracture.

Adjustment for BMD had an effect on the risk estimate for hip fracture that was quantitatively greater than for all fractures. The risk ratio adjusted for BMD fell by approximately 30%. As in the case of all fractures, differences in BMD explained a minority of the increased risk ratio for hip fracture. In men and women combined, low BMD explained 22% of the increase in risk ratio attributable to a prior fracture and was constant by age (assuming a gradient of risk for hip fracture of 2.6/SD decrease in BMD).

The mechanism for the BMD-independent increase in risk could not be determined from this analysis but is likely to be attributable, in part, to co-existing morbidity that might increase the risk of falls or impair the protective responses to injury *(99,114,121,124)*. In addition, changes in the micro-architecture of cancellous and cortical bone with rapid bone loss after fracture or immobilization *(125–127)* may weaken the resistance to mechanical force out of proportion to any effect on BMD. Irrespective of the underlying mechanism, these data indicate that the risk of fractures is substantially greater in individuals with a prior fragility fracture than in individuals of the same age, sex and BMD without such a fracture.

5.2.5 Glucocorticoids

The adverse effects of glucocorticoids on bone fragility have been appreciated for many years. A major mechanism relates to the progressive loss of bone that occurs once glucocorticoids are started, but the underlying condition for which they are used may also be a factor. Irrespective of the mechanism, epidemiological data suggest that the risk of hip, forearm and shoulder fractures is increased approximately 2-fold in patients taking glucocorticoids *(128–130)*. The risk for vertebral fracture may be somewhat higher *(130)*. The largest and most recent study examined fracture risk in the general practice research data base of the United Kingdom *(130)*, where approximately 250 000 glucocorticoid users were compared with age-matched and sex-matched controls. A dose-dependent effect on fracture risk was noted, and at a dose of prednisolone or its equivalent greater than 7.5 mg daily, the relative risk of vertebral fracture was 5.2, whereas between 5 mg and 7.5 mg daily the risk was lower (relative risk = 2.6). The dependence of this risk on BMD is not known. Of particular interest was the observation that the increase in fracture risk had a rapid onset when starting glucocorticoids, and waned rapidly when they were stopped *(130)*. This rapid onset and offset of effect suggests that risk may in part be independent of BMD, since BMD does not change so quickly.

Glucocorticoid use has been recognized as a significant risk factor in current clinical guidelines for the assessment of osteoporosis *(81–83, 131–134)*. Under most of these guidelines, patients taking glucocorticoids should be considered for treatment if BMD falls below the threshold for osteoporosis. If, however, the use of glucocorticoids is not wholly dependent on BMD, then fracture risk assessment should take into account the independent risk associated with glucocorticoids. This is not well established, nor is the possible variation of risk with age and sex well understood. These uncertainties motivated the present analysis.

The principal finding was that prior glucocorticoid use confers a substantial increase in fracture risk *(135)*, as was shown in the large United Kingdom general practice study *(130)*. The present analysis additionally demonstrated that this risk is largely independent of BMD or a prior fragility fracture.

The ever use of glucocorticoids was associated with a significantly increased risk of any fracture at all ages, compared to the risk faced by people with no history of the use of glucocorticoids (Table 5.11). This increase in relative risk was not explained by differences in BMD. For example, for individuals aged 50 years, the relative risk for any fracture for a person ever treated with glucocorticoids was 1.98 compared to an individual never treated with glucocorticoids when adjusted for BMD; and the relative risk was also 1.98 when the model did not take account of BMD. The relative risk ranged from 1.98 at the age of 50 years to 1.66 at the age of 85 years. Although the increase in relative risk was most marked at ages younger than 65 years, as previously observed *(46)*, there was no statistical difference in relative risk by age, or between men and women.

Table 5.11
Risk ratio of any fracture, osteoporotic fracture and hip fracture, and 95% confidence interval, associated with ever use of glucocorticoids in men and women combined, according to age and adjusted for bone mineral density

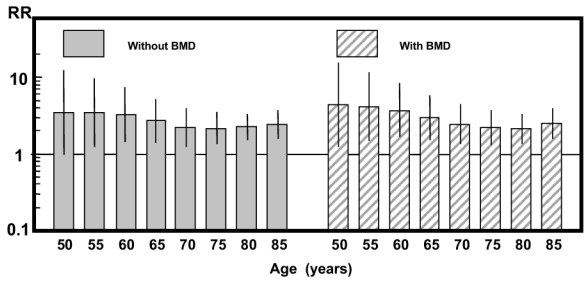
Age (years)	Any fracture		Osteoporotic fracture		Hip fracture	
	Risk ratio[a]	95% CI	Risk ratio	95% CI	Risk ratio	95% CI
50	1.98	1.35–2.92	2.63	1.68–4.13	4.42	1.26–15.49
55	1.83	1.35–2.47	2.32	1.63–3.30	4.15	1.50–11.49
60	1.67	1.33–2.09	2.00	1.52–2.62	3.71	1.67–8.23
65	1.56	1.29–1.88	1.81	1.43–2.27	2.98	1.55–5.74
70	1.55	1.30–1.86	1.76	1.42–2.19	2.44	1.37–4.36
75	1.64	1.37–1.97	1.70	1.36–2.11	2.22	1.35–3.63
80	1.62	1.31–2.00	1.59	1.26–2.02	2.13	1.39–3.27
85	1.66	1.26–2.17	1.71	1.29–2.28	2.48	1.58–3.89
All ages	1.57	1.37–1.80	1.66	1.42–1.92	2.25	1.60–3.15
All ages[b]	1.53		1.61		2.13	

Source: reference 135 (Table 3).
CI, confidence interval.
[a]Ever use versus no use.
[b]Ever use versus population risk.

For osteoporotic fractures, risk ratios were higher than those for all fractures combined (see Table 5.11). As in the case for all fractures, relative risk was higher at younger ages, but not significantly so. Nor was there a significant difference in relative risk between men and women. There was a small increase in relative risk when BMD was excluded from the model, but the quantitative effect was small: relative risk at 50 years with and without BMD in the model was 2.54 and 2.63, respectively.

The highest gradients of risk were observed for hip fracture (see Table 5.11). The risk ratios ranged between 2.13 and 4.42, depending on age. As in the case of osteoporotic fractures, the relative risk was higher at younger ages, but not significantly so. Also, there was no significant difference between men and women. When BMD was excluded from the model, the risk ratio was lower up to the age of 75 years (Fig. 5.7).

Fig. 5.7
Relative risk of hip fracture associated with ever use of glucocorticoids according to age, with and without adjustment for bone mineral density, in men and women combined



Source: reference 135 (Fig. 1).
RR, risk ratio; BMD, bone mineral density.

Current use of glucocorticoids was documented in cohorts from Rotterdam, Dubbo and Sheffield. BMD at the femoral neck was lower in current users of glucocorticoids, but the effect was small (Table 5.12).

Table 5.12
Bone mineral density at the femoral neck according to use of glucocorticoids

	Use of glucocorticoids			
	Never	Past	Ever	Current
(a) Rotterdam study				
Sample size		5665		116
Age (years)[a]		70.3 ± 9.6		69.7 ± 9.6
BMD (g/cm^2)		0.84 ± 0.14		0.80 ± 0.12[b]
(b) Sheffield cohort				
Sample size	1942		137	64
Age (years)[a]	80.0 ± 3.9		79.5 ± 3.7	79.6 ± 3.3
BMD (g/cm^2)	0.65 ± 0.12		0.64 ± 0.13	0.62 ± 0.10[c]
(c) DOES				
Sample size	1980		24	56
Age (years)[a]	70.7 ± 7.2		71.1 ± 7.4	70.0 ± 5.5
BMD (g/cm^2)	0.83 ± 0.15		0.78 ± 0.13	0.77 ± 0.15[d]

Source: reference 135 (Table 4).
BMD, bone mineral density; DOES, Dubbo Osteoporosis Epidemiology Study.
[a]Age in individuals where use is documented.
[b]$P<0.01$ compared with past use.
[c]$P<0.05$ compared with never use.
[d]$P<0.01$ compared with never use.

The mechanism for the BMD-independent increase in risk could not be determined from this analysis, but could be attributable, at least in part, to the nature of the underlying diseases for which glucocorticoids were prescribed. In the cohorts in which this could be examined, rheumatoid arthritis was associated with an independent risk of fracture which persisted when adjusted for glucocorticoid use (see below). There was, however, a significant effect of glucocorticoid treatment on fracture risk even when adjusted for rheumatoid arthritis. Adverse effects of glucocorticoids on muscle strength and metabolism may also have increased the liability of falling or impaired protective responses to falling, thereby increasing fracture risk. A further possibility is the effects of these agents on skeletal architecture, which appear to differ from the effects of gonadal deficiency at sites of cancellous bone *(136,137)*. It is also suggested that glucocorticoids affect osteocyte viability *(138)* resulting in alterations in the material properties of bone.

Irrespective of the mechanism, these data indicate that the risk of all fractures is substantially greater in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis for the same level of BMD.

5.2.6 Family history

There is a great deal of evidence for the importance of genetic factors in the determination of BMD *(139–143)*. Studies in twins have shown less difference in bone mass between monozygotic than dizygotic twins *(144–147)*. With few exceptions *(148)*, however, studies that have measured

BMD have used absorptiometric techniques, so that it is difficult to distinguish the component of skeletal size from true differences in bone density. Indeed, the hereditability of height is probably as great as that reported for apparent bone density *(149)*. The genetic component of peak bone mass appears to vary between skeletal sites, and is more marked at the lumbar spine than at the forearm, hip or calcaneus *(150)*. With advancing age, differences in BMD between monozygotic and dizygotic twins are less apparent, suggesting that environmental factors assume greater importance than earlier in life *(144–145)*.

A family history of fracture appears also to be a risk factor for fracture *(47,73)*. Hip fracture risk is increased among daughters whose mothers had a prior history of fragility fractures after the age of 50 years *(151–153)*. In the Study of Osteoporotic Fractures in the United States, the risk of hip or wrist fracture was increased in those women with a family history of wrist or hip fracture and was not wholly dependent on BMD *(67,154)*. This is not well established in other communities, nor has the possible variation of risk with age and sex been well studied. Nonetheless, a family history of fracture has been recognized as a significant risk factor in current clinical guidelines for the assessment of osteoporosis *(81–83, 123,133,134,155)*.

In the present meta-analysis, 16% of individuals reported a maternal history of any fracture *(39)*. A paternal and sibling history of fractures was reported by 13% and 15% of individuals, respectively. Maternal, paternal or sibling histories of hip fracture were reported by 6%, 4% and 2% of individuals, respectively.

Family history of fracture

There was no significant difference in fracture risk ratios between men and women, even though the point estimates were generally higher in men than in women. The risk ratios of men and women combined are shown in Table 5.13. A parental history of fracture was associated with a significantly increased risk of any fracture, any osteoporotic fracture or hip fracture. Risk ratios were slightly higher for hip fracture (RR = 1.63) than for any fracture (RR = 1.18) or for any osteoporotic fracture (RR = 1.22).

Table 5.13
Risk ratio and 95% confidence interval associated with (a) a parental history of fracture in men and women combined, with and without adjustment for bone mineral density and (b) a parental history of hip fracture in men and women combined

	Without BMD		With BMD	
Outcome fracture	RR	95% CI	RR	95% CI
Parental history of fracture[a]				
Any	1.18	1.06–1.31	1.18	1.07–1.31
Osteoporotic	1.22	1.08–1.37	1.22	1.08–1.38
Hip	1.63	1.25–2.12	1.63	1.24–2.13
Parental history of hip fracture[a]				
Any	1.42	1.19–1.71	1.41	1.17–1.71
Osteoporotic	1.54	1.25–1.88	1.54	1.25–1.88
Hip	2.27	1.47–3.49	2.28	1.48–3.51

Source: reference 39 (Table 7).
BMD, bone mineral density; RR, risk ratio; CI, confidence interval.
[a] The analysis only includes individuals for whom a BMD test was available.

The association of maternal or paternal history was stronger for hip fracture risk than for the risk of osteoporotic or any fracture. When maternal, paternal and sibling history was combined, risk ratios were marginally higher, but the findings were similar to the combination of maternal and paternal history.

Thus, the present analysis confirms that a family history of fracture confers a small increase in fracture risk, as has been shown in several observational studies *(47,67,73,154)*.

Family history of hip fracture

A parental history of hip (rather than any) fracture gave a risk ratio for any fracture of 1.42, similar to that for any osteoporotic fracture (RR = 1.54). The highest risk was for hip fracture (RR = 2.27; see Table 5.13).

Family history and age

Analyses were undertaken for a parental history of osteoporotic fracture and of hip fracture. There were no differences between men and women ($p>0.3$), and the data were combined. For a family history of any fracture, risk ratios remained stable up to the age of 70 years and thereafter appeared to decrease, and the risk ratio was no longer significantly increased at the age of 80 years or more (Table 5.14). The changes with age were not significant. For hip fracture outcomes, the risk ratios were higher than for osteoporotic fracture, but the confidence intervals were wide and the association not significant at ages 50 or 55 because of the small number of fractures (Table 5.15). Risk ratios appeared to decrease with age but the trend was not significant for hip fracture ($p>0.30$), for any osteoporotic fracture ($p>0.2$) or for osteoporotic fracture ($p = 0.08$).

Table 5.14
Risk ratio with 95% confidence interval for osteoporotic fracture and for hip fracture, with a parental history of fracture, in men and women combined, by age

Age (years)	Osteoporotic fracture		Hip fracture	
	RR	95% CI	RR	95% CI
50	1.31	1.02–1.69	1.63	0.69–3.86
55	1.29	1.05–1.59	1.73	0.84–3.58
60	1.28	1.08–1.51	1.82	1.01–3.27
65	1.27	1.11–1.46	1.86	1.17–2.96
70	1.25	1.10–1.42	1.79	1.24–2.57
75	1.20	1.06–1.35	1.53	1.14–2.07
80	1.12	0.98–1.28	1.35	1.04–1.75
85	1.08	0.91–1.27	1.31	0.99–1.73

Source: reference 39 (Table 5).
RR, risk ratio; CI, confidence interval.

Table 5.15
Risk ratio with 95% confidence interval for osteoporotic fracture and for hip fracture with a parental history of hip fracture, by age, in men and women combined

Age (years)	Osteoporotic fracture		Hip fracture	
	RR	95% CI	RR	95% CI
50	1.80	1.19–2.72	2.34	0.64–8.52
55	1.66	1.21–2.30	2.36	0.81–6.90
60	1.56	1.22–1.98	2.41	1.03–5.64
65	1.50	1.23–1.82	2.44	1.27–4.68
70	1.47	1.21–1.77	2.57	1.53–4.30
75	1.31	1.07–1.61	1.75	1.08–2.82
80	1.14	0.91–1.44	1.26	0.82–1.94
85	1.14	0.86–1.51	1.33	0.87–2.02

Source: reference 39 (Table 6).
RR, risk ratio; CI, confidence interval.

Family history and bone mineral density

The influence of a maternal or paternal history of fracture on osteoporotic fracture or hip fracture was not affected by the inclusion of BMD in the models (see Table 5.13). For a family history of hip fracture, the risk ratios were also unaffected by the inclusion of BMD.

The total independence of this risk factor from BMD is consistent with some reports *(122,156)*, but several studies suggest that a family history is associated with modest reductions in BMD *(153,157–160)*. Genetic influences on BMD, however, appear to wane with time (144,145), and this view is consistent with the trend that we observed with parental history and age on the risk of fracture.

The mechanism for the BMD-independent increase in risk could not be determined from this analysis, but it may not be entirely attributable to skeletal factors, at least as captured by the measurement of BMD. A family

history may act, for example, as a surrogate for falls. The frequency of falling is less in black people than among whites *(161)*, as is the risk of fracture, which might indicate an important genetic factor related to falls. It was not possible to investigate other important skeletally-related factors such as the size and shape of bone or the micro-architecture of trabecular elements in cancellous bone. It was possible, however, to determine that height did not affect the relationship between family history and fracture outcome. Increasing height was associated with an increased risk of osteoporotic fracture independently of a parental history of fracture. For osteoporotic fracture, the risk ratio increased by 1.02 for each centimetre increase in height. A similar effect was noted for hip fracture (RR = 1.03). There was, however, little or no effect of the adjustment on the RR associated with a parental history.

Although the separate effects of maternal, paternal or sibling history, either alone or in combination, have been assessed *(39)*, attention is focused on the combination of a maternal or paternal history of fracture. This may be preferred to a combination of maternal, paternal and sibling history, even though the risk ratio of the latter may be somewhat higher, since the probability of a positive sibling fracture history varies markedly around the world.

5.2.7 Smoking

It is well established that smoking is associated with a reduction in BMD in postmenopausal women and in men *(139)*. A meta-analysis has suggested that the risk of hip fracture may also be markedly increased (18). In current smokers compared with non-smokers, the risk of hip fracture was similar in women up to the age of 50 years, but increased thereafter with age, with a risk ratio of 1.17, 1.41 and 1.71 at the ages of 60, 70 and 80 years, respectively. In women at the age of 90 years, the risk ratio was 2.08 *(18)*. In population-based samples, the risk of other osteoporotic fractures appears also to be increased *(162)*, but this is not an invariant finding *(163)*. The risk of forearm fractures does not appear to be increased among smokers *(162,164–166)*.

Increased fracture risk may in part be attributable to the fact that patients who smoke have low BMD. Studies that have adjusted for BMD suggest that the relative risk is only modestly downwardly adjusted *(67)*. In the meta-analysis of Law and Hackshaw *(18)*, the difference in bone density between smokers and non-smokers was not apparent at the age of 50 years, but increased with increasing age, so that at the age of 80 years BMD at the hip was 0.45 SD lower in smokers compared to non-smokers. From the relationship between hip BMD and hip fracture risk, the risk ratio in smokers was estimated at 1.56, compared with a direct estimate of 1.71 for hip fractures, leading the authors to suppose that the majority of any risk was attributable to decreased bone density. The aim of the present analysis was to examine the relationship between fracture risk and smoking, and the

interactions with age and BMD (167).

The prevalence of smoking among the cohorts decreased almost linearly with age in men and women. At all ages, current smoking was higher in men than in women. At the age of 50 years a smoking history was obtained in 41% of men and 27% of women and, by the age of 85 years, was 17% and 6%, respectively.

Current smoking and sex

Current smoking was associated with a significantly increased risk of any fracture, any osteoporotic fracture or a hip fracture in both men and women (Table 5.16). For any fracture and for osteoporotic fracture, the risk in smokers was significantly higher in men than in women. For hip fracture, there was no difference in the risk ratio between men and women. For hip fracture risk in women, the increase in risk ratio (RR = 1.85) was comparable to that described in the meta-analysis by Law and Hackshaw (18). In men and women combined, the risk of fracture with current smoking was highest for hip fracture (RR = 1.84), lowest for any fracture (RR = 1.25) and intermediate for osteoporotic fracture (RR = 1.29).

Table 5.16
Risk ratio of fracture and 95% confidence interval associated with current smoking, by fracture outcome in men and women

Outcome	Sex	RR	95% CI	RR[a]	95% CI
Any fracture	M	1.50[b]	1.26–1.77	1.49[b]	1.20–1.84
	F	1.18	1.07–1.30	1.02	0.90–1.16
	M+F	1.25	1.15–1.36	1.13	1.01–1.25
Osteoporotic fracture	M	1.53[b]	1.27–1.83	1.54[b]	1.21–1.95
	F	1.20	1.06–1.35	1.01	0.87–1.17
	M+F	1.29	1.17–1.43	1.13	1.00–1.28
Hip fracture	M	1.82	1.34–2.49	1.69	1.16–2.48
	F	1.85	1.46–2.34	1.55	1.16–2.07
	M+F	1.84	1.52–2.22	1.60	1.27–2.02

Source: reference 167 (Table 3).
RR, risk ratio; CI, confidence interval.
[a]Adjusted for bone mineral density.
[b]Significantly higher RR compared with women.

Age

The large sample size studied permitted the examination of risk by age. Risk ratios attributable to smoking increased with age for any fracture and for osteoporotic fracture (Table 5.17) and were significantly higher than unity at all ages. In contrast, for hip fracture risk, the risk ratio decreased with age but was significantly higher than unity at all ages. This contrasts with the findings of Law and Hackshaw *(18)*, where risk ratios increased with age. The decrease with age was, however, not significant and, if real, much larger samples would be needed to verify such an effect.

Table 5.17
Risk ratio and 95% confidence interval for osteoporotic fracture and hip fracture in current smokers, for men and women combined

Age (years)	Without BMD		Adjusted for BMD	
	RR	95% CI	RR	95% CI
Osteoporotic fracture				
50	1.05	0.80–1.37	0.82	0.57–1.18
55	1.06	0.86–1.30	0.85	0.65–1.12
60	1.08	0.92–1.26	0.88	0.72–1.08
65	1.14	1.00–1.30	0.91	0.76–1.09
70	1.27	1.12–1.45	1.01	0.85–1.20
75	1.45	1.28–1.65	1.20	1.01–1.43
80	1.54	1.34–1.77	1.30	1.08–1.57
85	1.52	1.28–1.80	1.28	1.00–1.63
Hip fracture				
50	2.52	1.24–5.10	2.28	0.94–5.51
55	2.35	1.32–4.19	2.09	1.03–4.24
60	2.17	1.38–3.44	1.87	1.07–3.25
65	1.98	1.38–2.86	1.68	1.07–2.65
70	1.92	1.42–2.60	1.69	1.15–2.48
75	1.94	1.52–2.49	1.76	1.30–2.37
80	1.91	1.55–2.35	1.69	1.31–2.19
85	1.80	1.43–2.26	1.57	1.16–2.13

Source: reference 167 (Table 5).
BMD, bone mineral density; RR, risk ratio; CI, confidence interval.

Bone mineral density and body mass index

The present analysis also quantified the independent contributions of low BMD or BMI to the risks associated with smoking. Risk ratios were adjusted downwards somewhat when account was taken of BMD (see Tables 5.16 and 5.17). In women, the associations between smoking and osteoporotic fracture were no longer significant. In men, the effect was less marked or not apparent. In men and women together, after adjustment for BMD, current smoking was a significant risk for fractures only from the age of 70 years. For any osteoporotic fracture, 40% of the risk was explained by BMD. For hip fracture, the risk of smoking was adjusted downwards but the effect was less marked and remained significantly higher than unity at all ages. For hip fracture, only 23% was explained by BMD. Low BMD explained a minority of the total risk, a result which is in contrast with the findings of Law and Hackshaw *(18)* but in agreement with others *(67)*.

The risk ratios for smokers were also adjusted downwards with adjustment for BMI, though all ratios remained significantly increased compared with non-smokers (Table 5.18). The downward adjustment was less than with the adjustment for BMD. When smoking, BMI and BMD were entered into the model, a further decrease in risk ratio was observed, although the risk ratios remained above unity, and significantly so for the risk of any fracture and for hip fracture.

Table 5.18
Risk ratio for fracture and 95% confidence interval in current smokers (men and women combined) adjusted for age, BMD, BMI, and both BMD and BMI

	Outcome fracture					
	Any		Osteoporotic		Hip	
Adjustment	RR	95% CI	RR	95% CI	RR	95% CI
Age	1.25	1.15–1.36	1.29	1.17–1.43	1.84	1.52–2.22
Age, BMD	1.13	1.01–1.25	1.13	1.00–1.28	1.60	1.27–2.02
Age, BMI	1.19	1.09–1.30	1.21	1.08–1.34	1.65	1.34–2.03
Age, BMI, BMD	1.12	1.01–1.25	1.11	0.98–1.26	1.55	1.23–1.96

Source: reference 167 (Table 4).
BMD, bone mineral density; BMI, body mass index; RR, risk ratio; CI, confidence interval.

With regard to BMD, there are several mechanisms whereby smoking might adversely affect fracture risk. Female smokers may have increased rates of bone loss after the menopause (168), but this is not consistently found *(120,169)*. Women smokers also have a younger age at menopause *(169–171)*. It has been suggested that smoking may enhance estrogen catabolism *(172)*, and the effects of hormone replacement therapy have in some, but not all, studies been attenuated among smokers *(173–175)*. Smokers are also thinner and hence have lower body mass index *(1,170)*, so that the protective effects of adipose tissue and peripheral estrogen metabolism are impaired. Bone loss is reported to be higher in men than women who smoke *(170)*, perhaps because of the higher exposure to cigarette smoking of men than women. In the present analysis, higher risk ratios were found for men than for women for any fracture and for osteoporotic fracture. Such effects may explain the component of fracture risk attributable to low BMD or BMI, but as shown in the present analysis, this represents a minority of the risk.

The mechanism for the BMD-independent increase in risk could not be determined from this analysis, but might be attributable in part to lower levels of physical activity or to co-existing morbidity that might in turn increase the risk of falls or impair the protective responses to injury *(99,121,124)*. It is also possible that changes in the micro-architecture of cancellous bone, if induced by smoking, would weaken the resistance to mechanical force out of proportion to any effect on BMD. Finally, accuracy errors inherent in the measurement of BMD *(176)* will result in the underestimation of the contribution of bone to fracture risk.

A limitation of this study was that we were unable to examine the dose dependency of the association because of the differences in the manner that a smoking history was ascertained. In this regard, men tend to smoke more heavily than women and this may account for the slightly higher risk ratios observed in men. Indirect evidence for exposure dependency is that the risk ratios for ever smoking were lower than for current smoking (data not shown), consistent with the view that the effect of smoking appears to wane

slowly after stopping smoking *(177)*. As in the case for current smoking, risk ratios were highest for hip fracture. There was no significant difference in risk ratio between men and women, no difference when adjusted for BMD, and no significant effect of age on the risk ratio.

These findings indicate that a history of smoking confers a substantial risk for future fractures and that this risk is largely independent of BMD.

5.2.8 Alcohol intake

Excessive alcohol intake is a well-recognized cause of secondary osteoporosis, particularly in men *(178–180)*. The effects of more moderate intakes are not thought to be deleterious to skeletal health. Indeed, intakes of 210 g (26 units) per week may be associated with a higher BMD than in individuals who abstain from alcohol *(179,181–183)* and a lower risk of hip fracture *(174)* and other atraumatic fractures *(64)*.

By contrast, higher intakes appear to be associated with an increased fracture risk *(110)* and hip fracture risk (38,175,181). The threshold intake for high risk appears to be approximately 100g per week in women (110) but is higher in men *(174,181)*. In one study, hip fracture risk was not increased in women who had less than 14 units per week or in men who took less than 28 units per week *(174)*.

The standard alcoholic measure (= 1 unit) used in the present analysis contains 10 g ethanol. This is equivalent to a standard glass of beer (285 ml), a single measure of spirits (30 ml), a medium-sized glass of wine (120 ml) or one measure of aperitif (60 ml). There are, however, some differences in the definition of a unit in different countries (e.g. 8 g ethanol in the United Kingdom).

Current assessment guidelines for osteoporosis do not include a high intake of alcohol as a risk factor for use in case-finding strategies. The question arises whether a high alcohol intake might be used as a risk factor in the stratification of fracture risk. The aim of the present analysis was to quantify the fracture risk associated with alcohol consumption and to identify the threshold risk.

Intake of alcohol was higher in men than in women: 77% of women abstained from alcohol, whereas 49% of men took no alcohol. At the other extreme, 8% of men took 5 or more units per day compared with 1% of women. Overall, 19% of men and 4% of women drank more than 2 units daily.

Age, sex and dose–response

The present analysis confirms that a high intake of alcohol confers a significant risk of future fracture. When alcohol intake was assessed as a continuous variable, high intakes of alcohol were associated with an

increased risk of osteoporotic fracture or of hip fracture (184).

As found in previously published studies, there was a threshold effect, and no increased risk of osteoporotic or hip fracture was found in individuals who took 2 units or less per day of alcohol. When the risk ratio was assessed according to units of alcohol consumed (using 1 unit as the reference) risk ratio increased with more than 2 units per day in both men and women in a dose-dependent manner (Table 5.19), but was not increased below this level. When the data for alcohol intake were dichotomized by intake of more than 2, more than 3 or more than 4 units daily (versus those who took less), the risk of any osteoporotic fracture or of hip fracture was somewhat, but not significantly, higher in men than in women (Fig. 5.8 and Table 5.20).

Table 5.19
Risk ratio for fracture of the type indicated and 95% confidence interval, according to intake of alcohol, in men and women

	Men				Women			
	Osteoporotic fracture		Hip fracture		Osteoporotic fracture		Hip fracture	
Alcohol intake (units/day)	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
0	1.06	0.83–1.34	0.94	0.58–1.54	0.96	0.85–1.08	0.98	0.75–1.27
1	1.00	NA	1.00	NA	1.00	NA	1.00	NA
2	1.05	0.92–1.20	1.21	0.92–1.59	1.07	0.99–1.16	1.09	0.91–1.29
3	1.38	0.87–2.18	1.91	1.21–3.03	1.20	0.91–1.58	1.33	1.01–1.75
4	1.81	1.24–2.64	2.84	1.21–6.64	1.38	1.12–1.69	1.72	1.08–2.73

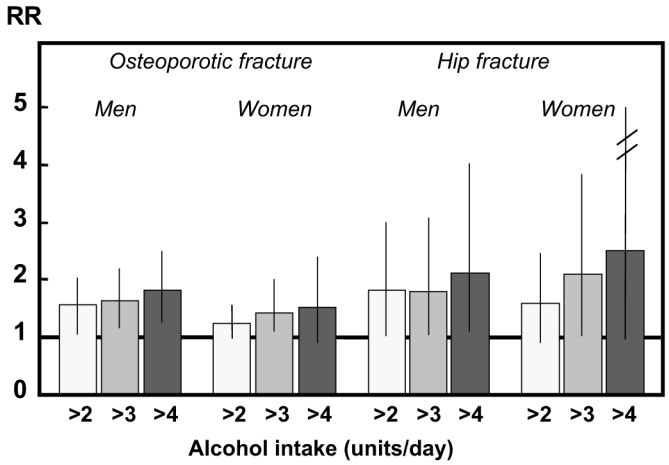
Source: reference 184 (Table 4).
RR, risk ratio; CI, confidence interval; NA, not applicable.

Table 5.20
Risk ratio for fracture and 95% confidence interval according to intake of alcohol in men and women combined, with and without bone mineral density

	Without BMD		Adjusted for BMD	
Categorization (units/day)	RR	95% CI	RR	95% CI
Any fracture				
>2	1.23	1.06–1.43	1.24	1.06–1.45
>3	1.33	1.10–1.60	1.34	1.11–1.62
>4	1.51	1.20–1.91	1.51	1.19–1.93
Any osteoporotic fracture				
>2	1.38	1.16–1.65	1.36	1.13–1.63
>3	1.55	1.26–-1.92	1.53	1.23–1.91
>4	1.70	1.30–2.22	1.64	1.24–2.17
Hip fracture				
>2	1.68	1.19–2.36	1.70	1.20–2.42
>3	1.92	1.28–2.88	2.05	1.35–3.11
>4	2.26	1.35–3.79	2.39	1.39–4.09

Source: reference 184 (Table 5).
BMD, bone mineral density; RR, risk ratio; CI, confidence interval.

Fig. 5.8
Relative risk of an osteoporotic fracture or hip fracture in men and women according to the intake of alcohol without adjustment for bone mineral density



Source: reference 184 (Fig. 1).
RR, risk ratio

This threshold is comparable to that advocated for cardiovascular health and is similar to that noted in other studies *(110,174)*. Using the level of >2 units daily as an indication of high intake of alcohol, the data showed that 19% of men and 4% of women exceeded this intake. Assuming a causal relationship, the data suggest that 7% and 2% of hip fractures in men and women, respectively, might be attributable to a high intake of alcohol. Causality, however, is conjectural and these results should not form the basis for any recommendations on the intake of alcohol.

In contrast with some studies, there was no evidence for a different threshold in men compared with women in the present analysis *(174,181)*. Some studies have shown that the relationship between alcohol intake and hip fracture risk or BMD is J-shaped *(1,64,174,176,182,183)* in that abstainers from alcohol have a higher risk than that of individuals consuming 1 or 2 units daily. In the present analysis, no difference in the risk between these categories or any systematic difference in femoral neck BMD was found. There were no differences in femoral neck BMD between individuals who abstained from alcohol (Z-score = -0.03 ± SD 1.02), those taking 1–2 units daily (Z-score = 0.02 ± 0.99) and those taking >2 units daily (Z-score = 0.01 ± 1.00).

Not all studies show an association between alcohol and fracture risk *(1,2,185–188)*. A weakness of cross-sectional studies may be that individuals who have suffered fracture have higher co-morbidity and their intake of alcohol may be less. However, not all prospective studies show an increased fracture risk with intake of alcohol either *(67,75,162,189–192)*. The

discrepancy in results may be related to the low proportion of heavy drinkers, and the lack of power to examine threshold effects.

Bone mineral density

The effect of high alcohol consumption is over and above that which can be explained by variations in BMD. Indeed, low BMD explained a minority of the total risk attributable to alcohol (see Table 5.20). With regard to BMD, there are several mechanisms whereby alcohol might adversely affect fracture risk. Alcohol is shown to have direct adverse effects on osteoblasts *(193)*, and also increases the endogenous secretion of calcitonin *(194)*. In addition, heavy drinkers may have poor nutrition with respect to calcium, vitamin D or protein *(195)*. The mechanism for the BMD-independent increase in risk could not be determined from this analysis, but it was not accounted for by current smoking or low BMI (Table 5.21). It might be attributable in part to coexisting morbidity that in turn increases the risk of falls *(89)* or interferes with the protective response to injury *(99,121,124)*.

Table 5.21
Risk ratio for fracture and 95% confidence interval associated with a consumption of >2 units daily of alcohol, with and without adjustment for smoking, body mass index and bone mineral density

	Any fracture		Any osteoporotic fracture		Hip fracture	
Model	RR	95% CI	RR	95% CI	RR	95% CI
Base case	1.23	1.06–1.43	1.38	1.16–1.65	1.68	1.19–2.36
+ smoking	1.22	1.03–1.43	1.36	1.13–1.63	1.50	1.05–2.15
+ smoking + BMD	1.24	1.05–1.46	1.38	1.14–1.66	1.54	1.07–2.22
+ BMI	1.21	1.04–1.41	1.35	1.13–1.61	1.64	1.16–2.32
+ BMI + BMD	1.22	1.04–1.43	1.34	1.11–1.61	1.67	1.16–2.38

Source: reference 184 (Table 6).
RR, risk ratio; CI, confidence interval; BMD, bone mineral density; BMI, body mass index.

5.2.9 Secondary osteoporosis

There is some evidence that several secondary causes of osteoporosis may provide a risk of fracture over and above that provided by BMD. These disorders include rheumatoid arthritis, hyperthyroidism, type I diabetes and ankylosing spondylitis (see section 4). However, there were insufficient cases of classic causes of secondary osteoporosis such as hyperparathyroidism and untreated thyroid disease to provide a general category of secondary osteoporosis for use in this analysis. Instead, a surrogate for secondary osteoporosis was provided by rheumatoid arthritis.

Previous studies have documented an association between rheumatoid arthritis and fractures of the hip *(128,129,196)*, spine *(197–199)* and pelvis *(128)*. The excess risk has usually been attributed to glucocorticoid-induced bone loss in these patients *(200)*, although functional limitations related to rheumatoid arthritis could be as important *(129)*. Some inconsistency in results stems from the limited sample size in many studies.

With the additional data available, it was possible to show that rheumatoid arthritis is a significant risk factor for any fracture (RR = 1.45; 95% CI = 1.16–1.80), osteoporotic fracture (RR = 1.56) and hip fracture (RR = 1.95). The risk persisted after adjustment for glucocorticoid use, BMD and prior fracture (Table 5.22). The results are consistent with the finding that vertebral fracture risk is approximately 2-fold higher in patients with rheumatoid arthritis than in population-based controls, independently of BMD and prior use of glucocorticoids *(199)*.

Table 5.22
Risk ratio for fracture and 95% confidence interval associated with rheumatoid arthritis, with and without adjustment for glucocorticoids, prior fracture and bone mineral density

	Any fracture		Any osteoporotic fracture		Hip fracture	
Model	RR	95% CI	RR	95% CI	RR	95% CI
Base case	1.45	1.16–1.80	1.56	1.20–2.02	1.95	1.11–3.42
+ BMD	1.38	1.10–1.73	1.47	1.12–1.92	1.73	0.94–3.20
Glucocorticoids	1.38	1.11–1.72	1.46	1.12–1.90	1.76	0.97–3.19
+ BMD	1.30	1.03–1.64	1.35	1.02–1.77	1.46	0.75–2.83
Prior fracture	1.40	1.12–1.73	1.49	1.15–1.94	1.85	1.05–3.26
+ BMD	1.36	1.08–1.71	1.45	1.11–1.91	1.71	0.93–3.17

Source: reference 135 (table constructed from results in text).
RR, risk ratio; CI, confidence interval; BMD, bone mineral density.

5.3 Summary of effects

This series of meta-analyses has characterized several important aspects of the assessment of risk for fracture that need to be taken into account. In the case of BMD, account needs to be taken of age and the prevailing BMD value, since the risk of osteoporotic fracture is dependent on both variables. Several other risk factors have been identified which add to risk independently of BMD (Tables 5.23 and 5.24) and represent the variables to be used in the synthesis of assessment algorithms (see section 7).

Table 5.23
Risk ratio for osteoporotic fracture and 95% confidence interval associated with risk factors adjusted for age, with and without adjustment for bone mineral density

	Without BMD		With BMD	
Risk indicator	RR	95% CI	RR	95% CI
Body mass index (20 versus 25 kg/m2)	1.27	1.16–1.38	1.02	0.92–1.13
(30 versus 25 kg/m2)	0.89	0.81–0.98	0.96	0.86–1.08
Prior fracture after 50 years	1.86	1.72–2.01	1.76	1.60–1.93
Parental history of hip fracture	1.54	1.25–1.88	1.54	1.25–1.88
Current smoking	1.29	1.17–1.43	1.13	1.00–1.28
Ever use of systemic corticosteroids	1.65	1.42–1.90	1.66	1.42–1.92
Alcohol intake 3+ units daily	1.38	1.16–1.65	1.36	1.13–1.63
Rheumatoid arthritis	1.56	1.20–2.02	1.47	1.12–1.92

BMD, bone mineral density; RR risk ratio; CI, confidence interval.

Table 5.24
Risk ratio for hip fracture and 95% confidence interval associated with risk factors adjusted for age, with and without adjustment for bone mineral density

	Without BMD		With BMD	
Risk indicator	RR	95% CI	RR	95% CI
Body mass index (20 versus 25 kg/m2)	1.95	1.71–2.22	1.42	1.23–1.65
(30 versus 25 kg/m2)	0.83	0.69–0.99	1.00	0.82–1.21
Prior fracture after 50 years	1.85	1.58–2.17	1.62	1.30–2.01
Parental history of hip fracture	2.27	1.47–3.49	2.28	1.48–3.51
Current smoking	1.84	1.52–2.22	1.60	1.27–2.02
Ever use of systemic corticosteroids	2.31	1.67–3.20	2.25	1.60–3.15
Alcohol intake 3+ units daily	1.68	1.19–2.36	1.70	1.20–2.42
Rheumatoid arthritis	1.95	1.11–3.42	1.73	0.94–3.20

BMD, bone mineral density; RR, risk ratio; CI, confidence interval.

Several important interactions were noted. The interactions tested for each risk factor were: the attenuation of the risk with time; the dependency on age, sex and BMD; and, for continuous variables, the interaction with the risk factor itself. An example of the latter is for BMI where an increase of 1 unit from a low value (e.g. from 20 kg/m^2 to 21 kg/m^2) is more protective than from a high value (e.g. 30 kg/m^2 to 31 kg/m^2). The interactions found are summarized in Table 5.25.

Table 5.25
Significant interactions determined from meta-analyses of risk factors for hip fracture or any osteoporotic fracture

	BMD		Age		Variable[a]		Sex		Time	
Risk factor	HF	OPF	HF	OPF	HF	OPF	HF	OPF	HF	OPF
BMI	–	–	–	++	++	–	–	–	++	+
Prior fracture	–	–	++	+			–	–	–	+
Corticosteroids	–	+	–	+			–	–	–	–
Family history	_	_	–	+			–	–	–	+
Smoking	–	–	–	–			–	–	–	–
Rheumatoid arthritis	–	–	–	–			–	–	–	–
BMD			++	++	–	++	–	–	–	–
Alcohol	–	–	–	–			–	–	–	+

BMD, bone mineral density; HF, hip fracture; OPF, any osteoporotic fracture; BMI, body mass index; –, no effect ($p>0.1$); +, a trend ($0.05 <p<0.10$); ++, a significant interaction.
[a] Denotes an interaction of the variable with the variable, e.g. BMI·BMI.

Although many interactions were found for each risk factor, it is necessary to determine the interactions between each of the risk factors, e.g. to what extent does the risk of glucocorticoid treatment depend upon smoking and how does this affect the interaction of smoking with age. This requires a meta-analysis of the meta-analyses (referred to as a mega-analysis), which is considered further in section 7.

It is important to recognize that the strength of the risk factors varies according to fracture outcome. In general, risk factors were more strongly associated with hip fracture risk than with the risk of any osteoporotic fracture. This consideration indicates that integrated models to assess overall fracture risk should use risk ratios separately determined for hip fracture and for other osteoporotic fracture (without hip fracture). These risk ratios are summarized in Table 5.26.

Table 5.26
Risk ratio for osteoporotic fracture other than hip fracture and 95% confidence interval associated with risk factors adjusted for age, with and without adjustment for bone mineral density

	Without BMD		With BMD	
Risk indicator	RR	95% CI	RR	95% CI
Body mass index (20 versus 25 kg/m^2)	1.07	0.96–1.20	1.07	0.95–1.22
(30 versus 25 kg/m^2)	0.98	0.89–1.09	0.90	0.80–1.02
Prior fracture after 50 years	1.92	1.75–2.10	1.78	1.59–1.99
Parental history of hip fracture	1.52	1.21–1.91	1.51	1.20–1.91
Current smoking	1.16	1.03–1.31	1.03	0.89–1.20
Ever use of systemic corticosteroids	1.55	1.30–1.84	1.56	1.27–1.90
Alcohol intake 3+ units daily	1.24	1.01–1.53	1.19	0.96–1.49
Rheumatoid arthritis	1.48	1.09–2.02	1.42	1.03–1.95

BMD, bone mineral density; RR, risk ratio; CI, confidence interval.

5.3.1 Heterogeneity

The generalizability of these data to all countries is uncertain, though the studies reported included many European countries, and cohorts from North America, Japan and Australia. Within the cohorts examined, an index of applicability is provided by tests for heterogeneity. Where there is no evidence for heterogeneity, the case is stronger for the generalizability of combined data. For each of the risk factors examined, heterogeneity was tested for by means of the I^2 statistic *(42)*. No or little heterogeneity is denoted by a value of <25%, and moderate heterogeneity by a value of <50%. For the risk factors examined, most showed little or moderate heterogeneity (Table 5.27). For several risk factors there was evidence for heterogeneity (attributable to the difference in age between cohorts), but when age was used as an interaction term there was very low heterogeneity between cohorts, suggesting the general applicability of the use of these factors for fracture prediction, at least in high-income countries. For a prior fracture, there was some evidence for greater heterogeneity between cohorts for osteoporotic and hip fracture outcome.

Table 5.27
Tests for heterogeneity (I^2) between cohorts according to risk factors for hip fracture and all osteoporotic fractures

	Hip fracture			Osteoporotic fracture		
Risk factor	I^2	95% CI	p	I^2	95% CI	p
BMI	8	0–44	NS	0[a]	0–51	NS
Family history	43	0–79	NS	0	0–69	NS
BMD	27[b]	0–62	NS	0[b]	0–49	NS
Smoking	0[c]	0–99	NS	0[c]	0–26	NS
Alcohol	0	0–92	NS	0	0–72	NS
Prior fracture	44	0–69	0.04	64[d]	38–79	<0.001
Rheumatoid arthritis	0	0–97	NS	0	0–53	NS
Glucocorticoids	0[e]	0–95	NS	14[e]	0–54	NS

CI, confidence interval; p, probability; BMI, body mass index; BMD, bone mineral density; NS, not significant.

[a]When used with the interaction with age (age·BMI).

[b]When used with the interaction with age (age·BMD).

[c]When used with the interaction with age (age·smoking).

[d]When used with the interaction with age (age·prior fractures).

[e]When used with the interaction with age (age·glucocorticoids).

5.3.2 Strengths and weaknesses

The strength of this analysis is that estimates of risk are derived from several studies from a wide international setting using population-based cohorts and the individual participant data. The large sample permitted the examination of the general relationship of each risk factor by age, sex, duration of follow-up and, for continuous variables (BMD, BMI, alcohol), the relationship of risk with the variable itself in a manner hitherto not possible. The use of primary data also eliminates the risk of publication biases. The validity of the clinical risk factors identified is supported by the expected relationships between BMD and fracture risk. Thus, these analyses fulfil the criteria for the highest level of evidence outlined in section 5.1.

There are several limitations that should be mentioned. As with nearly all randomly drawn populations, non-response biases may have occurred which were not completely documented in all cohorts. The effect is likely to exclude sicker members of society, and may underestimate the absolute risk of fracture. Thus, the probability of fracture associated with a given risk factor may be underestimated from a societal perspective, but this is unlikely to affect risk ratios.

The analyses also have significant limitations that relate to the outcome variables and the characterization of risk factors. The definition of what was considered to be an osteoporotic fracture was not the same in all cohorts, but the effect of this inconsistency is likely to underestimate rather than overestimate the associations that were found. For the hip fracture outcome, the definition was similar in all cohorts, and may explain in part the higher

risk ratios associated for this fracture rather than for osteoporotic fracture. Also, the analyses were confined to clinical fractures, and the results might differ from those for vertebral fractures diagnosed by morphometry or as an incidental radiographic finding. This possibility is addressed further in section 5.4.

There are also limitations with regard to the risk factors themselves. We chose BMI, rather than weight, as the measure for body composition. This has the advantage that there is less variability across countries and between sexes. A potential drawback, however, is that BMI can be influenced by height loss associated with vertebral deformities. Therefore, in individuals with important loss of height, the risk conferred through BMI could be underestimated *(201)*. The use of maximal attained height, rather than current height, might be a solution in the future, if it were shown that risk prediction could be improved.

Further problems relate to the construct of the questions, which varied between cohorts. These included questions on family history, prior fracture, smoking and glucocorticoid use. The effect of this heterogeneity is likely to weaken rather than strengthen the associations found. Recall is also subject to errors and was not validated in any of these cohorts. This is particularly problematic in elderly people. In addition, the validity of self-reported alcohol intake is notoriously unreliable *(202)*. Indeed, alcohol consumption was significantly less in both men and women than that assessed in the United Kingdom *(203)*. Given that these studies were prospective, however, much of this error should be random, giving rise to non-directional misclassification. Thus, the associations may actually be stronger than reported here. It is, however, possible that recall is more accurate in individuals with other risk factors for fracture. If true, this would overestimate a true effect. Any overestimate would have limited consequences for case-finding since the populations to be tested are similar to the populations interrogated. Biases that arise have more significance where causality is inferred.

A further limitation is that several of the clinical risk factors identified take no account of dose-response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risk associated with excess alcohol consumption and the use of glucocorticoids is dose-responsive *(204)*. In addition, the risk of fracture increases progressively with the number of prior fractures *(205)*.

These limitations are nearly all conservative. In addition, a fixed effects model was used, justified by the low heterogeneity between cohorts. The use of a fixed effects rather than random effects model is also conservative where point estimates are used for model building.

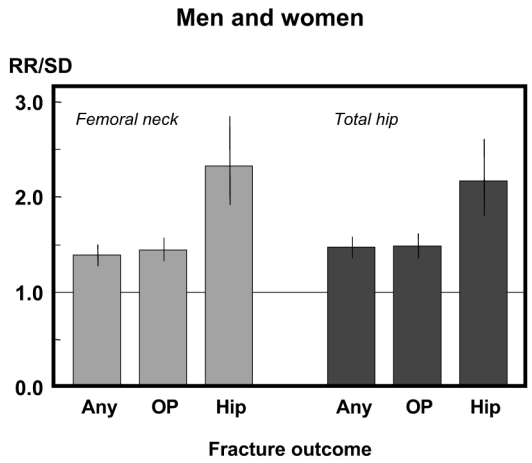
5.4 Other risk factors

The updated diagnostic criteria for osteoporosis, outlined in section 3, use BMD measurements at the femoral neck as the reference standard, and the question arises whether the total hip measurement is to be preferred because of the lower errors of precision. In addition, there are several other risk factors (Grade B in Table 5.2) that are of potential interest in risk assessment but which are not covered by this series of meta-analyses. These include peripheral bone mineral measurements including quantitative ultrasound and biochemical indices of bone turnover. The available cohorts that incorporated these variables were too few to provide a meta-analytic framework of high international validity. Moreover, for ultrasonography and indices of bone turnover, there are a large number of techniques available, all of which have variable degrees of biological validity and may also differ in the gradients of risk. The following analyses of limited material and a review of the evidence suggest, however, that these indices of risk should be incorporated into risk assessment algorithms when they are more adequately characterized on an international basis.

5.4.1 Total hip bone mineral density

Few cohorts examined BMD at both the femoral neck and total hip in men and women. Data for men were confined to the cohorts from Rochester and Hiroshima. For women, additional information was available from the cohorts at Sheffield. Because of the limited material, the data were enriched by adding data from the Osteoporosis Ultrasound Study (OPUS), a validation cohort – discussed further in section 7. When the data were combined, there was no difference between men and women and no significant differences between femoral neck and total hip BMD in the gradients of fracture risk *(206)* (Fig. 5.9). For osteoporotic fractures, the femoral neck gave slightly lower gradients of risk compared with the total hip (RR = 1.44/SD and 1.48/SD, respectively). The gradients of risk for hip fracture outcome were marginally better with the femoral neck site (RR = 2.33/SD and 2.17/SD, respectively). These data suggest that the two regions can be used interchangeably, consistent with previous reports (207), but do not indicate a clear superiority of one measurement site over the other.

Fig. 5.9
Prediction of any fracture, any osteoporotic fracture and hip fracture (risk ratio/SD) in men and women combined, with bone mineral density measurements at the femoral neck and total hip



Source: O. Johnell and J.A. Kanis (unpublished data).
RR, risk ratio; SD, standard deviation; OP, osteoporotic fracture.

5.4.2 Quantitative ultrasound

From the cohorts used for the meta-analysis, ultrasound measurements (broadband ultrasound attenuation and speed of sound) were made at the heel in women only from the EPIDOS and the Sheffield cohorts. Because of the limited material, the data were enriched by adding data from the OPUS cohort. The OPUS cohort was used to validate the assessment tool and is described in section 7. The cohort comprised random population-based samples of 2374 women aged 55–80 years from five European towns (Paris, France; Berlin and Kiel, Germany; Aberdeen, Scotland, and Sheffield, England). Ultrasound measurements were taken at the heel using the Achilles and at baseline, and fracture outcomes recorded prospectively.

Broadband ultrasound attenuation significantly predicted any fracture and any osteoporotic fracture (Table 5.28). For speed of sound, the gradient of risk was not significantly greater than unity for these fracture outcomes (RR/SD = 0.91 and 1.05, respectively). Gradients of risk for hip fracture outcomes were higher, significantly so as measured with both broadband ultrasound attenuation and speed of sound.

With adjustment for BMD, gradients of risk decreased but remained significantly increased in the case of broadband ultrasound attenuation and speed of sound measurements for hip fracture risk. The gradient of risk for hip fracture decreased significantly with age in much the same way as that seen for hip fracture risk prediction with BMD using DXA. For broadband ultrasound attenuation, the gradient of risk was 3.79 at the age of 50 years

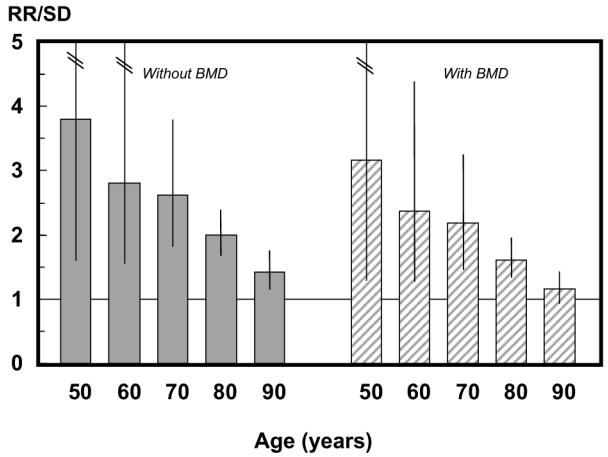
and fell to 2.00 at the age of 80 years (Fig. 5.10). For speed of sound, the gradient of risk fell from 3.14 at the age of 50 years to 1.77 at the age of 80 years.

Table 5.28
Gradients of risk (RR/SD) for broadband ultrasound attenuation and speed of sound using quantitative ultrasound in women, with and without adjustment for bone mineral density at the hip

		Without BMD		With BMD	
Variable	Outcome fracture	RR/SD	95% CI	RR/SD	95% CI
BUA[a]	Any	1.40	1.25–1.58	1.22	1.06–1.41
BUA[a]	Osteoporotic	1.40	1.26–1.56	1.20	1.06–1.36
BUA[a]	Hip	1.72	1.52–1.95	1.40	1.22–1.61
SoS[a]	Hip	1.51	1.33–1.71	1.24	1.09–1.40
Peripheral BMD	Any	1.30	1.22–1.39		
	Osteoporotic	1.35	1.25–1.45		
	Hip	1.30	1.15–1.48		

Source: O. Johnell and J.A. Kanis, unpublished data, 2005.
BMD, bone mineral density; RR, risk ratio; SD, standard deviation; CI, confidence interval; BUA, broadband ultrasound attenuation; SoS, speed of sound.
[a]Women only.

Fig. 5.10 Hip fracture prediction (risk ratio/SD) with broadband ultrasound attenuation in men and women, by age, with and without adjustment for bone mineral density



Source: J.A. Kanis and O. Johnell (unpublished data).
RR, risk ratio; SD, standard deviation; BMD, bone mineral density.

These data, though limited, confirm the potential utility of quantitative ultrasound in the evaluation of fracture risk. It should be noted that greatest experience of the technique is available for women *(19,208)*, though it has been shown recently that quantitative ultrasound predicts hip and all non-spine fractures in men *(209)*.

5.4.3 Peripheral bone mineral density

Peripheral BMD measurements were obtained in three cohorts: Rochester (1/3 radius); Gothenburg I (dual photon absorptiometry at the heel); and Gothenburg II (DXA at the forearm). Gradients of fracture risk were significant for all fracture outcomes but, as expected, were lower than those observed for BMD at the femoral neck by DXA (see Table 5.28).

5.4.4 Biochemical indices of bone turnover

A second risk factor of high potential importance is high bone turnover. Recent reviews *(210,211)* have considered the use of biochemical indices of bone turnover as a predictor of fracture risk in postmenopausal osteoporosis. A review of prospective and cross-sectional studies concluded that increased resorption markers were associated with an increase in fracture risk in women *(212)*. For example, in the EPIDOS study in elderly women, the risk of hip fracture increased by 1.4 for each SD increase in urinary free deoxypyridinoline (D-Pyr) and by 1.3 for urinary type I C-telopeptide of collagen (CTX) *(213)*. If instead the highest quartile was examined, the odds ratio for hip fracture was 2.1 with CTX and 1.5 with free D- Pyr. The predictive value of indices of skeletal turnover appears to be independent of bone mass in that the risk persists even after adjustment for BMD. Thus, the combination of high CTX and low BMD had an odds ratio of 4.8 for hip fracture in elderly women. In the OFELY study, the same combination in women aged 65 years gave a relative risk of 4.2 for all fractures *(34)*. Similar findings were reported for undercarboxylated osteocalcin, an index of impaired bone formation *(214)*. The analyte predicted hip fracture risk in the highest quartile with an odds ratio of 1.9, a risk that persisted (with an odds ratio of 1.8) after adjustment for BMD. A combination of the lowest quartile of BMD and the highest quartile of undercarboxylated osteocalcin was associated with an odds ratio of 5.5 *(214)*. Associations have also been found between later spine and non-spine fracture and high serum bone alkaline phosphatase, with an odds ratio of 1.5–1.88 per SD increase, which persisted after adjustment for BMD *(49)*. In the same study, urinary CTX predicted fracture with an odds ratio of 1.43–1.84 per SD change, which also remained after adjustment for BMD (1.33/SD–1.70/SD). These various studies indicate that indices of skeletal turnover give information on fracture risk independently of BMD and might therefore complement and augment fracture risk assessment by BMD.

The biochemical markers have not been evaluated in this series of meta-analyses because of the lack of availability of internationally representative material. Moreover, many potential analytes have been examined and there is insufficient information available to select a reference standard, both in terms of the analyte and the technique for measurement. Notwithstanding, the markers clearly hold promise as risk prediction tools and should be considered for inclusion in assessment algorithms as the body of information increases. Although no intervention trials have selected patients for treatment

on the basis of bone resorption measurements, the responses to treatment appear to be greater in patients with increased resorption rates *(215)*.

5.4.5 Morphometric vertebral fracture

One of the limitations of the meta-analyses is that vertebral fractures are not included as an outcome variable nor have they been assessed as a specific risk factor. The reason is that fewer cohorts were available that documented prevalent and incident fractures assessed clinically (480 fractures in 7 cohorts) or by morphometry (819 fractures in 3 cohorts). The available data are summarized briefly below.

Risk factors for clinical vertebral fractures (Table 5.29) were similar to those reported for any osteoporotic fracture (see Table 5.23). The risk associated with a parental history was somewhat lower than for osteoporotic fracture (RR = 1.29 versus 1.54) and was not significant. For alcohol intake, the risk ratio was comparable (RR = 1.49 versus 1.38) but was also not significant. Femoral neck BMD predicted clinical fractures as strongly as BMD at the lumbar spine. The risk ratios for morphometric fractures were qualitatively similar, though the mid-point estimates were generally lower than for clinical fractures. Note that some caution is required in the comparison since, for morphometric fractures, only three cohorts could be examined (Hiroshima, EVOS and Rotterdam; 819 fractures in 13 344 individuals).

Table 5.29
Risk factors, risk ratio and 95% confidence interval for clinical vertebral fracture and morphometric vertebral fractures

	Clinical fracture[a]		Morphometric fracture[b]	
Risk factor	RR	95% CI	RR	95% CI
BMI (per unit)	0.96	0.93–0.98	0.96	0.94–0.98
Prior fracture	1.80	1.45–2.23	1.36	1.16–1.59
Parental history of hip fracture	1.29	0.63–2.64	1.05	0.68–1.62
Current smoking	1.67	1.19–2.35	1.47	1.21–1.79
Systemic corticosteroids	2.17	1.55–3.04	1.20	0.82–1.76
Rheumatoid arthritis	2.24	1.34–3.77	NA	NA
Alcohol (> 2 units daily)	1.49	0.96–2.31	1.04	0.69–1.56
BMD femoral neck (per SD)	1.58	1.43–1.76	1.66	1.50–1.84
BMD lumbar spine (per SD)	1.63	1.44–1.85		

RR, risk ratio; CI, confidence interval; NA, not available; BMI, body mass index; BMD, bone mineral density.

[a]Data from Australia (the Dubbo Osteoporosis Epidemiology Study), Canada (the Canadian Multicentre Osteoporosis Study), Japan (Hiroshima), the Netherlands (Rotterdam), Sweden (Gothenburg), the United Kingdom (Sheffield), and the United States (Rochester).

[b]Data from Japan (Hiroshima), the Netherlands (Rotterdam), and the European Vertebral Osteoporosis Study.

The available data suggest that the risk factors for morphometric fractures are, if anything, weaker than for other fractures. These data accord with previously published results that have examined risk factors for morphometric fractures (216 –219), and suggest that the meta-analyses do not suffer from their omission.

With respect to vertebral fracture as a risk factor, a prior morphometric fracture was documented in three cohorts (EVOS, Japan and Rotterdam). The risk of a subsequent osteoporotic fracture (RR = 2.27), hip fracture (RR = 2.68) or clinical vertebral fracture (RR = 3.66) was somewhat greater than the risk associated with a prior fracture of any type to predict osteoporotic fracture (RR = 1.86) or hip fracture (RR = 1.86). The DOES also reported that a prevalent vertebral deformity was a very strong risk factor for a clinical vertebral fracture (RR = 7.4) *(64)*, a much higher risk than the findings above and elsewhere *(220)*.

These variable risk ratios may arise because of a dependence on age. For example, in the cohorts examined in this report, the risk of hip fracture was markedly increased in individuals with a morphometric fracture at the age of 60 years (RR = 9.6; 95% CI = 3.1–3.0) and fell progressively with age so that at the age of 80 years the hip fracture RR was 3.3 (95% CI = 2.3–4.8).

In the present analysis, a prior clinical spine fracture (data available only for women from CaMoS, DOES, Rochester, Gothenburg and Sheffield) was associated with a very high risk of hip fracture (RR = 3.06; 95% CI = 2.11–4.42) and vertebral fracture (RR = 5.40; 95% CI = 3.18–9.18), suggesting that a previous clinical spine fracture provided a stronger risk indicator than a prior morphometric vertebral fracture and a prior fracture of any other type. A similarly high risk has been shown in the EPOS cohort *(221)*, where a self-reported spine fracture was associated with a RR = 7.52 for a subsequent morphometric vertebral fracture. These findings need to be examined in men and, if confirmed, incorporated into tools to assess fracture risk.

All these findings indicate that a prior morphometric fracture is a strong risk factor. For this reason, the term prior fragility fracture in assessment algorithms should take account not only of clinical vertebral fractures but also of morphometric vertebral fractures. Indeed, clinicians should be aware that fracture risk is likely to be underestimated by the algorithms in the case of a prior vertebral fracture, irrespective of its clinical expression.

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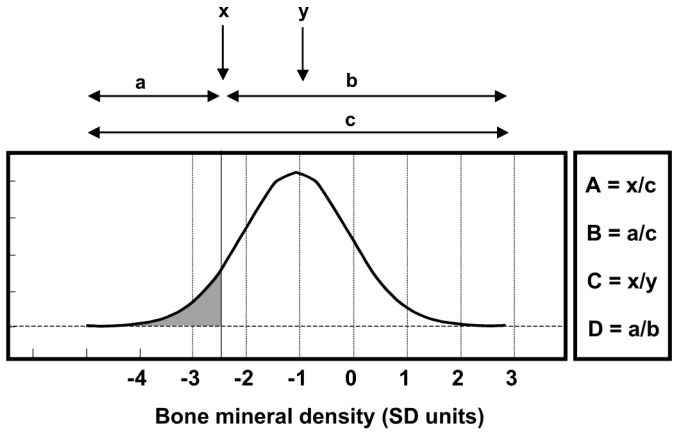
6. Combining risk factors for risk assessment

Several factors should be considered when integrating risk factors for fracture risk assessment. One of these is that risk is variably expressed. For dichotomous variables like the clinical risk factors, epidemiological studies commonly report the risk ratio (RR) (or relative risk) of fracture in individuals compared to those without the exposure variable. However, the risk of fracture can also be compared with an average risk, for example, the risk of hip fracture at a given BMD compared to an individual with an average fracture risk (which differs from the risk compared with average BMD). Whereas risk ratios or relative risks are commonly used for dichotomous variables, in the case of BMD, the performance characteristics are commonly expressed as a gradient of fracture risk, e.g. the change in fracture risk per standard deviation change in BMD. Other examples are given in Fig. 6.1 *(1)*. All these approaches give differing risk ratios. The heterogeneity of these risk indicators necessitates an awareness of the different methods and, if they are to be combined, they need to be reduced to a uniform metric. The most attractive candidates for use in the assessment of patients are:

- population relative risk, i.e. the risk of an individual compared with the population of the same age and sex;
- gradient of risk, i.e. the increased likelihood of fracture risk per standard deviation change in risk score;
- absolute fracture probability, i.e. the risk that an individual will sustain a fracture within a given time interval.

Fig. 6.1
Different methods of expressing risk ratio (e.g. for hip fracture) in individuals or populations:[a] A, risk ratio of an individual at the threshold value for osteoporosis compared with that of the general population; B, risk ratio of all women with osteoporosis compared with that of the general population; C, risk ratio of a woman at the threshold value for osteoporosis compared with a woman with an average BMD for that age; D, risk ratio of osteoporotic women compared with those without osteoporosis



Source: reference 1 (Fig. 1).
BMD, bone mineral density.

[a] The diagram shows the normal distribution of hip BMD in women aged approximately 65 years. The average BMD is 1 SD below the mean value for young healthy women and approximately 16% have osteoporosis (T score < –2.5 SD).

Each of these approaches is discussed in the sections that follow.

6.1 Population relative risks

The meta-analyses reviewed in section 5 provide risk ratios for dichotomous variables and gradients of risk for continuous variables. For dichotomous variables, the risk ratios given are the risk of individuals with the risk factor compared with the risk of individuals without the risk factor but who are otherwise similar. In order to convert these risk ratios to the risk of an individual compared to that of the general population, i.e. the population relative risk (PRR), it is necessary to take account of the prevalence of the risk factors. An example is the risk associated with the use of glucocorticoids where ever use was associated with a relative risk of hip fracture of 3.71 at the age of 60 years (see section 5, Table 5.11) compared with individuals of the same age without the exposure. Ever-use of glucocorticoids was found in 4.9% of the population at that age. Since the general population comprises those with and without the risk factor, the adjusted PRR is given by

$$RR/(p \cdot RR+(1-p)), \quad [1]$$

where p is the prevalence of the risk factor and RR the relative risk of ever use versus never use. In the example above the PRR is

$$3.71/(0.049 \times 3.71 + (1 - 0.049)) = 3.28.$$

The higher the prevalence of the risk factor, the greater the downward adjustment. Further examples of this formula are given in Table 6.1.

Table 6.1
Estimates of population relative risks derived from relative risks in epidemiological studies (RR cases versus controls) according to the prevalence of risk factors in the population

Prevalence of risk factor (%)	RR			
	1.5	2.0	2.5	3.0
5	1.46	1.90	2.33	2.73
10	1.43	1.82	2.17	2.50
20	1.37	1.67	1.92	2.14
30	1.30	1.54	1.72	1.88
50	1.20	1.33	1.43	1.50

Where two dichotomous risk factors are to be combined, the risk ratios must first be adjusted to take account of the contribution of one to the other. An example is provided from the EPIDOS study *(2,3)*. In this study of 80 year old women, low BMD, high urinary excretion of a bone resorption marker and a history of prior fractures were all significant risk factors for hip fracture (Table 6.2). The combination of these risk factors improved the assessment of risk in that any two of these risk factors predicted fracture more strongly than any one factor alone.

Table 6.2
The effect of risk factors alone or in combination on the relative risk of hip fracture in women at the age of 80 years

Risk factor	Threshold values	Prevalence (%)	Odds ratio	RR[a]
Average	-	100	-	1.0
Low BMD	T-score <-2.5	56	2.8	1.40
Prior fracture	yes	39	3.5	1.77
High CTX[b]	above premenopausal values	23	2.4	1.82
Low BMD + prior fracture	as above	23	4.1	2.39
Low BMD + high CTX	as above	16	4.1	2.74
Prior fracture + high CTX	as above	12	5.3	3.50
All of the above	as above	7	5.8	4.43

Source: reference 3 (Table 1).
RR, risk ratio; BMD, bone mineral density; CTX, urinary type I C-telopeptide of collagen.
[a]Adjusted to the population.
[b]C-telopeptide of type I collagen.

In the example above, BMD was dichotomized by categorizing individuals with and without osteoporosis. It is, however, also possible to determine population relative risk from gradient of risk (GR). The population relative risk is equal to the incidence of fracture at a given BMD (Ix) divided by the average incidence of fractures in the population (Ia). Thus, the incidence Ix = PRR/Ia. Ia is given by

$$Ia = \exp(-\ln(GR)(x - \mu)/\sigma - (\ln(GR))^2/2), \quad [2]$$

where m is the mean BMD, s is the SD, and I is the yearly incidence of fracture in the age group (4). Note that the part $(x - \mu)/\sigma$ in formula [2] is the Z-score.

If the mean (μ) of BMD at a certain age and sex, and the standard deviation (σ) are known, the risk ratios versus the normal population (i.e. the PRR) can be derived for: those below a threshold g of BMD or those with a specified Z-score for BMD; and those at a value x of BMD.

Consider the calculation of population relative risk (PRR) from the relationship between BMD at the femoral neck and hip fracture. For the purposes of illustration, the hip fracture risk is assumed to increase by 2.6 per standard deviation decrease in BMD, as described in the meta-analysis of Marshall, Johnell and Wedel *(5)*, rather than to vary by age as described in section 5. Using this assumption, the PRR of hip fracture in an individual with a Z-score of BMD of exactly –1 (1 SD below the mean for that age) would be

$$\exp((-\ln(2.6)\cdot -1)-(1\mathrm{n}(2.6))^2/2) = 2.6\ \exp(-1\mathrm{n}(2.6)^2/2) = 1.65,$$

given a normal distribution of BMD *(6)*. Thus, the risk of hip fracture in an individual with a Z-score of –1 SD is 1.65-fold higher than the average risk of the general population. It is important to note, however, that this is not the risk of an individual compared with an individual with a Z-score of 0 (which would be 2.6). The reason is that hip fracture rates increase exponentially with decreasing BMD, but BMD is normally distributed. Thus, individuals with an average BMD have a risk of hip fracture that is lower than the average fracture risk in the population (Jensen's inequality).

The risk of fracture in the short perspective (i.e. not accounting for deaths) of those with BMD below a threshold for BMD (x) at a certain age is:

$$I \cdot \Phi((x - \mu)/\sigma + \ln(GR))/\ \Phi((x - \mu)/\sigma), \qquad [3]$$

where I is the yearly incidence for the same age and sex, m is the mean and s is the SD of BMD at the current age, ln(GR) is the e-log of the risk ratio for each SD decrease in BMD (as in formula [2]) and Φ is the standard normal distribution function with a mean = 0 and SD = 1 *(6)*.

Examples of the different risk estimates for hip fracture are provided for men and women with osteoporosis in Table 6.3 based on femoral neck measurements of BMD using the NHANES reference ranges *(1)*. For an individual at the threshold of osteoporosis, relative risk (although not absolute risk) decreases with age. It is notable that the risk ratio decreases below unity in women at the age of 75 years. The reason for this is that the average BMD is below a T-score of –2.5 SD at this age, so that a bone density of exactly –2.5 SD carries a risk lower than that of the general female population of the same age.

Table 6.3
Proportion of the male and female population of Sweden, at the ages shown, identified as having osteoporosis and the risk of hip fracture

Age (years)	Men				Women			
	% population	PRR[a]	PRR[b]	RR[c]	% population	PRR[a]	PRR[b]	RR[c]
50	2.4	4.2	6.4	6.6	5.4	2.9	4.8	4.6
55	2.8	3.9	6.1	6.2	8.1	2.4	4.1	3.8
60	4.8	3.1	5.0	4.9	12.3	1.9	3.4	3.0
65	7.3	2.5	4.2	4.0	17.7	1.5	2.9	2.4
70	7.6	2.5	4.2	3.9	24.5	1.2	2.5	1.9
75	8.0	2.4	4.1	3.8	33.8	0.95	2.1	1.5
80	14.0	1.8	3.2	2.8	43.3	0.74	1.8	1.2
84	19.4	1.4	2.8	2.3	51.0	0.62	1.6	0.98

Source: reference 1 (Table 5).
PRR, population relative risk; RR, risk ratio.

[a]For an individual at the threshold value for osteoporosis (T-score = –2.5 SD) compared with the whole population of the same age and sex.

[b]For all individuals with a T-score value exceeding the threshold for osteoporosis (T-score = < –2.5 SD).

[c]Risk ratio of individuals at the threshold of osteoporosis compared with an individual with a mean value for bone mineral density for that age and sex.

Table 6.3 also shows the need to choose appropriate relative risks. For example, the risk of an individual at the threshold of osteoporosis compared to an individual with a mean value for BMD in women at the age of 60 years is 3.0, but the risk of that individual compared to the population of the same age and sex is only 1.9, for the reasons given above.

Few individuals have, however, a BMD value that lies exactly at the threshold for osteoporosis. It is, therefore, sometimes appropriate to express risk as the risk of individuals that lie within the diagnostic criterion relative to the risk of fracture of the whole population. Risk ratios for populations with osteoporosis (i.e. below the T-score threshold for BMD) are also given in Table 6.3. For example, a randomly drawn population of women aged 50 years with a BMD value of less than -2.5 SD would have a risk ratio of 4.8, and women of the same age at exactly the threshold of osteoporosis a risk ratio of 2.9. It should be noted that the estimates of risk provided are modelled for hip fractures from measurements made at the hip with BMD using dual energy X-ray absorptiometry (DXA). The risks computed would differ for other fracture outcomes, and from those derived from measurements made with other densitometry techniques or the use of DXA at other sites.

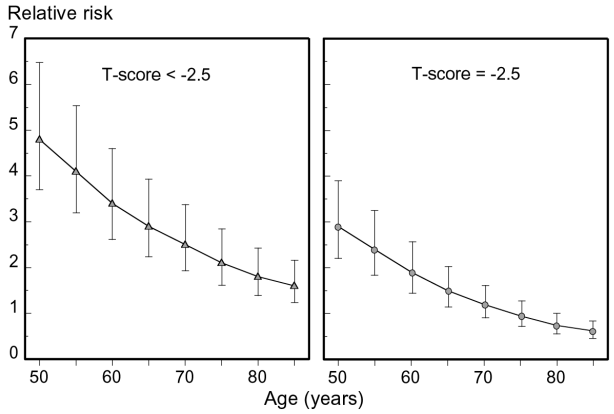
Where population relative risks from clinical risk factors are combined with BMD, they must be first adjusted for BMD, because many risk factors exert their effects partly through reduced BMD. In the example mentioned at the beginning of this section, the use of glucocorticoids was associated with a relative risk of hip fracture of 3.71 in men and women aged 60 years

compared with individuals not exposed to these agents. The population relative risk was 3.28. In this example, the relative risk did not change with adjustment for BMD, indicating that the adverse influence of glucocorticoid use on fracture risk was largely independent of BMD. In women at the age of 60 years at the threshold for osteoporosis, the population relative risk is 1.90. In women exposed to glucocorticoids the relative risk at the threshold for osteoporosis is, therefore, the product of the two estimates, because of their independence:

3.28 x1.90 = 6.23.

The relative risk of hip fracture with glucocorticoid exposure decreases with age (although absolute risk increases). The same is true for BMD. The decrease in risk ratios with age poses some problems with the use of age-specific risks. In the case of BMD, the risk ratio at the diagnostic threshold for osteoporosis decreases with age (Fig. 6.2 and Table 6.3), although the absolute risk (probability) of hip fracture increases *(1)*. This apparent paradox is confusing for clinicians. This is one of the reasons to prefer the use of absolute (e.g. 10 year) fracture risks in patient care (see section 6.3, below).

Fig. 6.2
Population relative risks for hip fracture over 10 years in Swedish women with osteoporosis according to age[a]



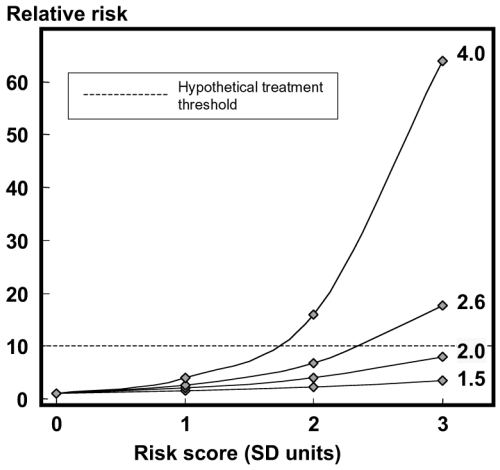
Source: reference 1 (Fig. 2).
[a]Risk is shown for women at the threshold value for osteoporosis (T = –2.5 SD) or those below the threshold (T < –2.5 SD). Hip fracture risk is assumed to increase 2.6-fold per 1 SD change in BMD ± the 95% confidence estimate of the gradient.

6.2 Gradients of risk

The dichotomous categorization of continuous variables such as BMD or BMI is inefficient for individual patient assessment, and is the principal argument for preserving the actual measurement when integrating risks. In population studies, BMD is normally distributed, as are many other continuous variables. When fracture risk is additionally assessed with a dichotomous variable (e.g. past fragility fracture) or with another continuous

variable (e.g. BMI), the combined distribution is continuous but, when the risk indicators are totally or partially independent, there is a higher gradient of risk *(7)*. The relationship between a measured variable and a combination of variables with gradients of risk of 1.5, 2.0, 2.6 and 4.0 per standard deviation in risk score is shown in Fig. 6.3. The steeper the gradient of risk, the greater the potential for identifying individuals at higher risk. For example, when the dotted line in Fig. 6.3 is taken as a treatment threshold, fewer individuals with a risk score of +3 SD would be identified above the threshold with a test whose gradient of risk was 1.5 compared with tests that had higher gradients of risk.

Fig. 6.3
Relative risk (RR) of fracture in the population at a given age for different assumptions for the gradient of risk (RR/SD)[a]



Source: J. A. Kanis (unpublished data).
[a]The risk at the average risk score of 1 is the referent.

If it is assumed that the combination of risk factors is also distributed normally, the risk of individuals compared to the average risk in the population (stratified by age and sex) can be determined.

The proportion of individuals (p) above a given risk threshold can be calculated from the combination of distributions *(7)*. This proportion is dependent on the chosen risk threshold (x) and the gradient of risk (GR), i.e. the relative risk per SD increase in risk score. It can be shown that this proportion is given by:

$$p = \Phi\left[\frac{-\left[\ln(x) + (\ln(GR))^2/2\right]}{\ln(GR)}\right] \quad [4]$$

where F is the standard normal distribution function as before.

The average risk (AR) in the group above the chosen risk threshold can also be calculated. This is given by:

$$AR = e^{(a+b^2/2)} \cdot \Phi(z-b)/\Phi(z) \quad [5]$$

where $a = -(\ln(GR)^2/2)$, $b = -\ln(GR)$ and $z = (\ln(x)-a)/b$.

The important assumption that combinations of several variables of both continuous and dichotomous risk factors lead to a normal distribution of the risk score in the population is based on the central limit theorem. The adequacy of this assumption has been validated empirically using baseline data on BMD and risk indicators from the Rotterdam Study *(7)*.

The proportion of individuals above a given risk threshold is shown in Table 6.4, with a range of assumptions. When, for example, the assumed gradient of risk is 2.0 per SD change in risk score, the proportion of individuals at average, double or triple risk is 36%, 9% and 3% respectively. When a much steeper gradient of risk is assumed, such as 4 per SD, 24%, 12% and 7% of individuals were identified above these risk thresholds, respectively. Thus, with increasing gradients of risk, the proportion of the population identified decreased when the risk threshold was near the average risk in the population. By contrast, at higher risk thresholds, the population identified increased with increasing gradients of risk. For example, when the risk threshold was set at 2 (twice the average risk in the whole population), the proportion of the population detected to be at risk increased from 9% with a gradient of risk of 2/SD up to 12% with a gradient of risk of 4/SD (see Table 6.4).

Table 6.4
Proportion (%) of individuals detected above a given risk threshold according to gradient of risk

Gradient of risk (score/SD)	Risk threshold (individual risk versus population risk)						
	1	1.5	2.0	2.5	3.0	3.5	4.0
2.0	36.4	17.6	8.9	4.8	2.7	1.6	0.9
2.5	32.3	18.4	11.2	7.2	4.9	3.4	2.4
3.0	29.1	17.9	11.9	8.3	6.1	4.6	3.5
4.0	24.4	16.2	11.6	8.8	6.9	5.5	4.5
5.0	21.1	14.5	10.8	8.5	6.8	5.7	4.8

Source: reference 7 (Table 1).

The performance of a test is much better when the risk ratio per SD is greater (Table 6.5). When the average population risk is used as a threshold, the average risk in the test-positive category is 1.7 times the average population risk when the gradient of risk is 2/SD. At a risk gradient of 4/SD, the average risk becomes 3.1 times the average population risk at the same threshold. When the threshold was a risk twice the population risk, the average relative risks in those identified increased to 2.9 and 5.0 with gradients of risk of 2.0 or 4.0/SD, respectively. Thus, tests with a progressively higher gradient of risk identify progressively higher-risk patients, and lead, therefore, to a greater effectiveness of subsequent intervention.

Table 6.5
Average risk in individuals above a given risk threshold for different gradients of risk

Gradient of risk (score/SD)	Risk threshold (individual risk versus population risk)						
	1	1.5	2.0	2.5	3.0	3.5	4.0
2.0	1.74	2.31	2.88	3.46	4.03	4.61	5.18
2.5	2.09	2.75	3.41	4.06	4.71	5.35	5.98
3.0	2.43	3.19	3.93	4.66	5.38	6.09	6.79
4.0	3.10	4.04	4.95	5.84	6.70	7.55	8.39
5.0	3.75	4.88	5.96	7.00	8.01	9.00	9.98

Source: reference 7 (Table 2).

The gradients of risk are a useful description of the performance characteristics of assessment tools. When logistic regression models are used, performance is commonly expressed as an area under the receiver operator characteristic (ROC) curve. There is a mathematical relationship between gradient of risk and area under the ROC curve; examples are given in Table 6.6.

Table 6.6
The relationship between gradient of risk (relative risk per SD change in risk score) and area under the receiver operator characteristic (ROC) curve

Gradient of risk/SD	Area under ROC curve
1.0	0.50
1.1	0.53
1.5	0.61
2.0	0.69
2.5	0.74
3.0	0.78
4.0	0.84
5.0	0.87
6.0	0.90

To achieve high performance characteristics, a combination of risk factors that give totally or partially independent contributions to the risk is required. The risk factors identified in section 5 that are partly independent of both age and BMD include previous fragility fractures, a family history of hip fracture, exposure to oral glucocorticoids, rheumatoid arthritis, smoking, high intakes of alcohol and biochemical estimates of bone resorption. These various risk factors, used in combination with BMI or BMD, have the potential to enhance the gradient of risk and thus the efficiency of case-finding. The extent to which this is achieved is reviewed in section 7.

6.3 Absolute probability of fracture

Although multiple clinical risk factors can be used to assess risk, the use of Z-scores, T-scores, gradients of risk and areas under the ROC curve raise practical problems for patient assessment, particularly at the primary health

care level, since they are not readily understood or used by physicians and other health-care professionals. As mentioned, the use of risk ratios is also problematic since, for example, the relative risk of fracture for a given BMD decreases with age *(1)*, whereas the absolute incidence of fracture rises.

These considerations have led to the view that risk assessment should be based on absolute risk, i.e. the probability of fracture *(4,8,9)*. This probability should ideally take account not only of age and sex, but also of validated independent risk assessment tools, including but not limited to bone mass measurements. The use of absolute fracture risk has the potential to be applicable to both sexes, all ages, all races and all countries even though the incidence of osteoporotic fractures varies widely by age, sex, ethnicity and geography. Similar approaches are now used in the management of cardiovascular disease *(10–16)*. In cardiovascular disease, the simultaneous consideration of smoking, blood pressure, diabetes and serum cholesterol permits the identification of patients at high risk, whereas the use of serum cholesterol alone has a low gradient of risk, significantly poorer than the assessment of BMD alone to predict hip fracture *(5,17,18)*.

6.3.1 Estimating fracture probability

The term "risk" is used to describe several well-defined notions of mathematical statistics, one of which is the probability of an event and the other is the hazard function. In contrast, a risk ratio is a characterization of risk but not an expression of absolute risk. Gradient of risk per 1 SD is a measure of the goodness of a single variable or a risk score (combination of variables) to serve as a predictor.

If a type of event is considered where the follow-up period is not important, e.g. the presence of a certain malformation among newborn children, the actual probability is the only figure of interest. In most instances, however, clinical events evolve over time. Where individuals are followed to determine whether and when certain events occur (e.g. fracture, stroke, death), the hazard function is of interest. The hazard function is a function of at least one type of time parameter (e.g. time since start of follow-up, age, calendar time) and there may also be several other components of the function, such as sex, BMI and BMD, as described in section 5. The hazard function describes the risk at a certain moment and is defined as the limit value of the quotient between the expected number of events in a small interval of time divided by the length of that interval when the interval becomes infinitely small and shrinks to zero. A survival function, which can be calculated from the hazard function, gives the probability that an event has not occurred before any given time. The survival function is the natural number e to the power of minus the area under the hazard function curve from 0 to t over a given time interval.

There is no single method to determine and present hazard functions; and it is appropriate to compare Cox regression, logistic modelling and Poisson regression models.

From Cox regression analysis, the ratios between hazard functions (i.e. hazard ratios) can be determined. Sometimes survival functions determined by Cox regression analyses are also presented, but not hazard functions.

A logistic model means that the probability of an event is $1/(1+ \exp(-S))$, where $S = \beta_0 + \beta_1 \cdot x_1 + \ldots + \beta_k \cdot x_k$ and $x_1, \ldots, x_k$ are the values of k variables. From a logistic regression analysis, odds ratios are calculated. If p_1 is the probability of an event, $p_1/(1-p_1)$ is the odds of the event. It can be shown that the odds ratio of an event (e.g. a malformation), depending on whether the age of the mother is x+1 or x years, is $\exp(\beta)$ where β is the coefficient of age. When p_1 is a small number, the probability and the odds are almost the same and thus an odds ratio, $(p_1/(1-p_1))/(p_2/(1-p_2))$, will be close to the quotient between two probabilities, p_1/p_2 . Thus, odds ratios may be good surrogates for risk ratios, which are quotients between probabilities (risks).

The most common information on risks (probabilities or hazard functions) given in the literature is presented as odds ratios (close to risk ratios) or hazard ratios. The probabilities or the hazard functions themselves are seldom presented. There are situations when it is crucial to determine hazard functions (not only hazard ratios) in order to generate new knowledge. A study on excess mortality attributable to hip fracture events is an example *(19)*. The hazard functions are also important in order to determine 10-year probability of fracture taking competing risks such as death into account (see Annex 5).

It is important to note that when the risk of fracture is studied by Cox regression analysis (or by Poisson regression), death is usually censored. But the simple application of the results to determine a survival function giving the probability of being free from fracture neglects the possibility of dying before fracture.

The Poisson regression model used in the present analyses allows the interaction between a variable x and the time parameter to be introduced. Thus the linear combination can contain expressions like $\beta_1 \cdot x1 + \beta_2 \cdot x1 \cdot t = (\beta_1 + \beta_2 \cdot t) \cdot x_1$. We can consider $(\beta_1 + \beta_2 \cdot t)$ as a time-dependent beta coefficient of x_1 . Hence, the beta coefficient can be decreasing (or increasing) with time. If the predictive power of a variable is decreasing with time, such models are needed in order to reflect the decrease. An example is provided in the case of BMD, where the gradient of risk for hip fracture prediction decreases significantly with age (see section 5, Table 5.7). Note that a time-dependent beta coefficient is not the same as a time-dependent covariate x. The latter means that the variable x is allowed to change its value with time, and that can also be handled by Cox regression. By introducing interactions, i.e. products between variables, the model can be made more realistic (with a better fit to the data). Another way of improving a model is to exchange a simple expression of the form $\beta_1 \cdot x$ with $b_1 \cdot \min(x, g) + \beta_2 \cdot \max(x-g, 0)$, where

min(x, g) is the minimum of the numbers x and g and max(x-g, 0) is the maximum of the numbers x-g and 0. The number g (for example, a specific value for BMI) is a limit chosen somewhere in the range of the risk variable X. Below g the change of risk is characterized by β_1 and above g by β_2. The new function is also a continuous function of x. An example is the interrelationship between BMI and fracture risk, where a change in BMI has a different significance at different levels of BMI (section 5).

When several variables are considered simultaneously, the beta coefficients will differ from the coefficients obtained when each variable is studied alone. However, the change in a beta coefficient may be small if the corresponding risk variable is of great importance. In order to estimate the beta coefficients for a model that includes several variables, we generally need sufficient data for all the variables.

In the types of models mentioned (logistic regression model, Cox and Poisson regression models), the importance of different variables is reflected by beta coefficients. The linear combination $\beta_1 \cdot x_1 + \ldots + \beta_k \cdot x_k$ of the variables gives a risk score, which can be considered as a new variable. When the goodness of the combination as a predictor is studied, the same type of description (gradient of risk per standard deviation, area under the ROC curve, etc.) can be applied as for a single variable x_i.

6.3.2 Fracture probability

In individuals who have not yet sustained a fracture, estimates of long-term risk of fracture require documentation of the incidence of the first fracture at a particular site. Second or subsequent fractures are common, particularly at the spine, but also at other sites. The overestimate of the first fracture rates from unadjusted data on incidence varies from 0% to 58% in studies for the major osteoporotic fractures, depending on site and age *(20)* (Table 6.7).

Table 6.7
Overestimation (%) of first fracture at the sites shown from incidence estimates in Sweden

Age	Spine		Forearm		Shoulder		Hip	
(years)	Men	Women	Men	Women	Men	Women	Men	Women
50-59	29	31	7	10	3	2	0	9
60-69	58	38	16	13	16	55	29	9
70-79	50	40	33	26	0	4	8	14
80-89	38	40	25	29	0	2	19	22

Source: reference 20 (Tables 1 and 2).

Probability also depends upon the risk of death. Where the risk of death is high, the probability of fracture will decrease for the same fracture hazard. A commonly used method for estimating lifetime risk of fracture assumes that all deaths occur at a given age *(21–24)*. Lifetime risks of hip fracture are underestimated using this method *(25)*. In Sweden, for example, the average lifetime risk of hip fracture from the age of 50 years onwards was estimated at 4.6% and 13.9% in men and women, respectively, assuming that all

individuals die at the time of average life expectancy *(25)*. However, these estimates increased to 8.1% and 19.5%, respectively, using the death hazard functions based on current mortality. On the reasonable assumption that life expectancy will continue to improve, as it has done over the past several centuries *(26)*, the future burden of fractures will be underestimated even more. When the expected future mortality rates were taken into account, the lifetime risk for hip fracture at the age of 50 years in Sweden rose to 11.1% and 22.7% in men and women, respectively *(25)*.

In addition to secular trends in mortality, there is evidence that a secular trend in hip fracture rates is occurring in many Member States *(17)*. In most countries, the age-specific and sex-specific fracture incidence is increasing, though it appears to have levelled off in Sweden, the United Kingdom and the United States *(27–29)*. Incorporating assumptions concerning the secular trend in fracture rates has a marked impact on lifetime risks and, hence, on the future burden of fractures in the community. For example, the estimated number of hip fractures in 2050 is expected to be 4.6 million worldwide assuming no change in the age-specific and sex-specific incidence, but could range between 7.3 and 21.3 million with modest assumptions concerning the secular trend *(30)*.

6.3.3 Lifetime risks

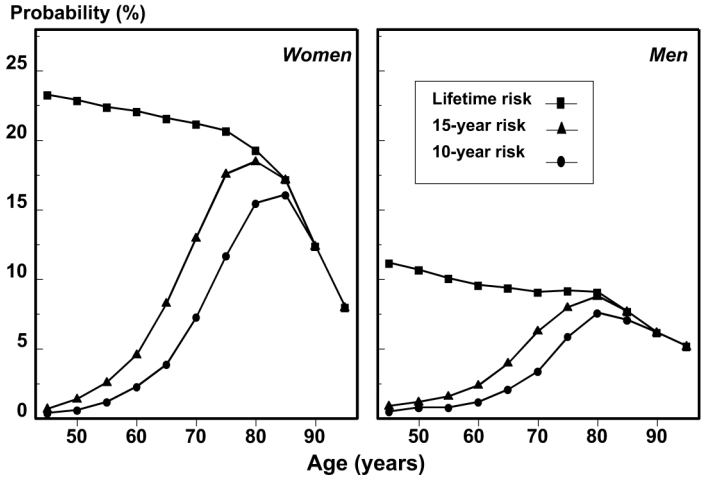
The variability in lifetime risks of hip fracture in different Member States is reviewed in section 2. The pattern of risk also varies according to age and the type of fracture. In general, remaining lifetime risks decrease progressively with age, since the death hazard exceeds the fracture hazard (see Table 6.8 and Fig. 6.4) *(20)*.

Table 6.8
Remaining lifetime probability of fracture (%) in men and women at the ages shown

Type of fracture	At 50 years			At 80 years		
	Men	Women	Risk ratio	Men	Women	Risk ratio
Forearm	4.6	20.8	4.5	1.6	8.9	5.6
Hip	10.7	22.9	2.1	9.1	19.3	2.1
Spine[a]	8.3	15.1	1.8	4.7	8.7	1.9
Proximal humerus	4.1	12.9	3.1	2.5	7.7	3.1
Any of these	22.4	46.4	2.1	15.3	31.7	2.1

Source: reference 20 (Table 3).
[a]Clinical spine fracture.

Fig. 6.4
Probability of a first hip fracture in men and women by age



Source: reference 1 (Fig.1).

For hip fracture, for example, lifetime risk remains relatively constant with age up to the age of 80 years. Thereafter, lifetime risk decreases, since the risk of death reaches a much higher level compared to the risk of hip fracture above this age.

It is important to recognize, however, that the lifetime probability of fracture at a given age may differ in other communities where there are differences in current mortality, mortality trends, or the slope of hip fracture incidence with age. Mortality varies widely between countries, as does the slope of the risk of hip fracture with age *(31,32)*.

As would be expected, lifetime probabilities increase with increasing relative risk of fracture (Tables 6.9) *(6)*.

Table 6.9
Lifetime probability of hip fracture in men and women from Sweden according to relative risk (RR) at the ages shown

	Age (years)							
RR	50	55	60	65	70	75	80	85
Women								
1.0	22.7	22.3	21.9	21.5	21.2	20.9	20.0	18.9
1.5	30.9	30.3	29.9	29.4	29.1	28.7	27.6	26.3
2.0	37.6	37.0	36.5	36.0	35.6	35.3	34.0	32.6
2.5	43.2	42.5	42.0	41.5	41.1	40.8	39.5	38.1
3.0	47.9	47.2	46.6	46.1	45.8	45.5	44.2	42.8
3.5	51.8	51.1	50.6	50.1	49.8	49.6	48.3	47.0
4.0	55.2	54.5	54.0	53.5	53.3	53.1	51.9	50.6
5.0	60.7	60.0	59.6	59.1	59.0	58.9	57.7	56.7
6.0	64.9	64.3	63.9	63.5	63.5	63.5	62.4	61.5
Men								
1.0	11.1	10.6	10.1	9.8	9.6	9.6	10.1	10.7
1.5	15.7	14.9	14.4	13.9	13.6	13.7	14.4	15.3
2.0	19.8	18.9	18.2	17.7	17.3	17.4	18.2	19.4
2.5	23.4	22.4	21.6	21.0	20.6	20.7	21.8	23.1
3.0	26.7	25.6	24.7	24.1	23.6	23.8	25.0	26.5
3.5	29.7	28.5	27.6	26.9	26.4	26.6	27.9	29.6
4.0	32.4	31.1	30.2	29.5	29.0	29.2	30.6	32.5
5.0	37.2	35.8	34.8	34.0	33.5	33.8	35.4	37.6
6.0	41.3	39.8	38.7	38.0	37.4	37.8	39.6	42.0

Source: reference 6 (adapted from Tables 1 and 2).
Lifetime risk at any age is determined from the competing probabilities of death or hip fracture.

6.3.4 Ten-year fracture probability

Estimates of lifetime probability of fracture are of value in considering the burden of disease in the community and the likely effects of intervention strategies on the population. They are less relevant for assessing risk in individuals in whom treatment might be envisaged. This is because treatments today are not given for a lifetime, because of side-effects, low adherence and cost. In addition, the feasibility of lifelong interventions has never been tested using either high-risk or global public health strategies *(33,34)*. Moreover, as noted above, the remaining lifetime risk for many fractures decreases progressively with age (see Fig. 6.4) but the absolute risk during the period of treatment (i.e. the short-term risk) increases with age.

Thus, timeframes in excess of 10 years may be misleading for patients considering treatment when the period of greatest fracture risk will occur far in the future after treatment has ceased. Long timeframes also pose problems when incorporating risk factors, the predictive value of which may change over time. For example, theoretical calculations indicate that the long-term predictive value of BMD for fractures wanes with time because of variations in rates of bone loss, and this is substantiated by some but not all empirical observation *(35,36)*, but the effect is not marked over a 10-year interval (see section 5). The same may be true for other risk factors for fracture, for example, the ratio of carboxylated to total serum osteocalcin, the predictive value of which decreases progressively with time *(37)*.

For these reasons, a shorter timeframe is appropriate for clinical risk assessment. The optimal duration of specific treatments is not well evaluated, but interventions of 3–5 years or so correspond to information available from randomized clinical trials and models of the cost–effectiveness of treatment. For a number of treatments, positive effects on BMD appear to persist when treatment is stopped, and there is some evidence that this may be true also for fracture risk *(38–40)*. A 10-year timeframe accommodates, for example, a treatment for 5 years with an offset of effect over the subsequent 5 years. It should be recognized, however, that the risk of a second fracture is much higher immediately after the first event, particularly during the first year after a first fracture *(41,42)*. The risks thereafter decrease though they do not reach that of the general population. Ten-year probabilities will underestimate, therefore, immediate fracture risk after a first fracture, since the risk is integrated over the entire 10-year interval. Against this background, 10-year fracture probabilities have been considered appropriate for clinical use by the NOF and IOF *(4,43)*.

As in the case of lifetime probabilities, 10-year fracture probabilities demand knowledge of the incidence of a first fracture as well as mortality risks. These have been well characterized for Sweden. In contrast with lifetime probability, 10-year probability commonly increases with age in both men and women up to the age of approximately 80 years (Table 6.10) (see Fig. 6.4). Thereafter, probabilities decline and approach the lifetime risk at that age, since in the elderly, the 10-year or 15-year risk is more or less equivalent to the remaining lifetime risk.

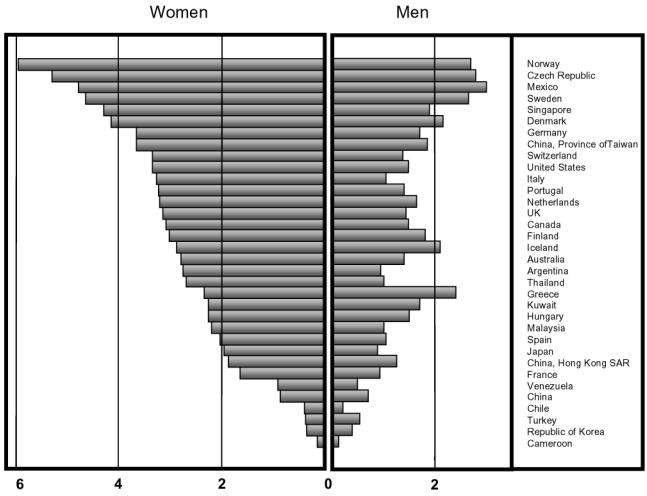
Table 6.10
Ten-year risk (%) of an osteoporotic fracture at the sites shown or of the first fracture of these sites in the population of Malmo at the ages shown

Age (years)	Forearm		Hip		Spine		Proximal humerus		Any of these	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
45	1.2	2.5	0.5	0.4	0.8	0.6	0.5	0.8	2.6	3.8
50	1.2	3.9	0.8	0.6	1.1	1.2	0.5	1.2	3.3	6.0
55	1.3	4.7	0.8	1.2	1.4	1.7	0.4	1.4	3.9	7.8
60	1.7	5.6	1.2	2.3	1.7	2.7	0.7	2.3	4.9	10.6
65	1.5	6.5	2.1	3.9	2.1	4.3	1.3	3.4	5.9	14.3
70	0.9	7.2	3.4	7.3	3.1	5.9	1.5	4.4	7.6	18.9
75	1.2	7.6	5.9	11.7	3.8	6.5	1.5	5.0	10.4	22.9
80	1.4	7.3	7.6	15.5	4.4	6.9	1.9	5.6	13.1	26.5
85	1.1	6.0	7.1	16.1	4.0	6.8	2.3	6.3	13.1	27.0
90	0.8	4.3	6.2	12.4	1.4	5.0	2.1	5.8	10.3	21.4
95	1.3	2.8	5.2	8.0	0.1	2.6	1.3	3.9	8.3	13.9

Source: reference 20 (Table 4).

The heterogeneity in lifetime probabilities between countries is also reflected in 10-year probabilities. Fig. 6.5 shows 10-year probabilities of hip fracture averaged for men and women in different areas of the world *(44)*. Probabilities are highest in the Nordic countries and vary by more than 10-fold worldwide. This is also true of lifetime probabilities.

Fig. 6.5
Ten-year probability of hip fracture averaged for age (ages 60 and 70 years)

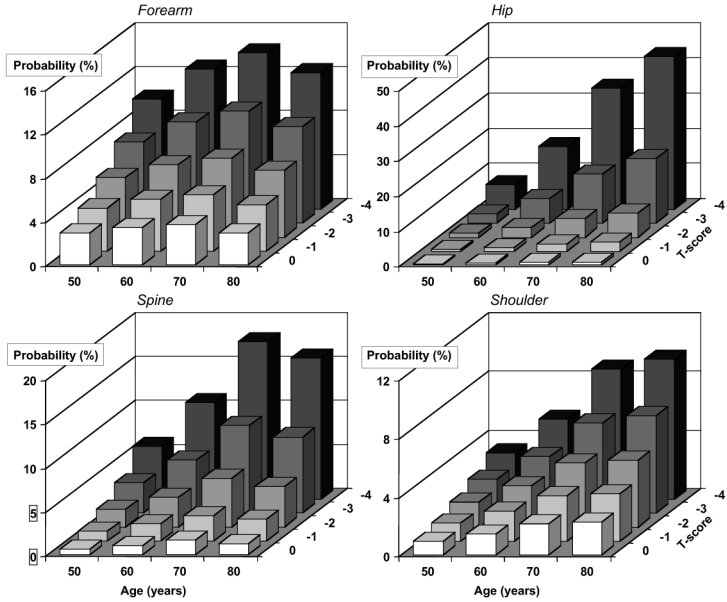


Source: reference 44 (Fig. 1 with updated data).

6.3.5 Integration of 10-year probability with BMD

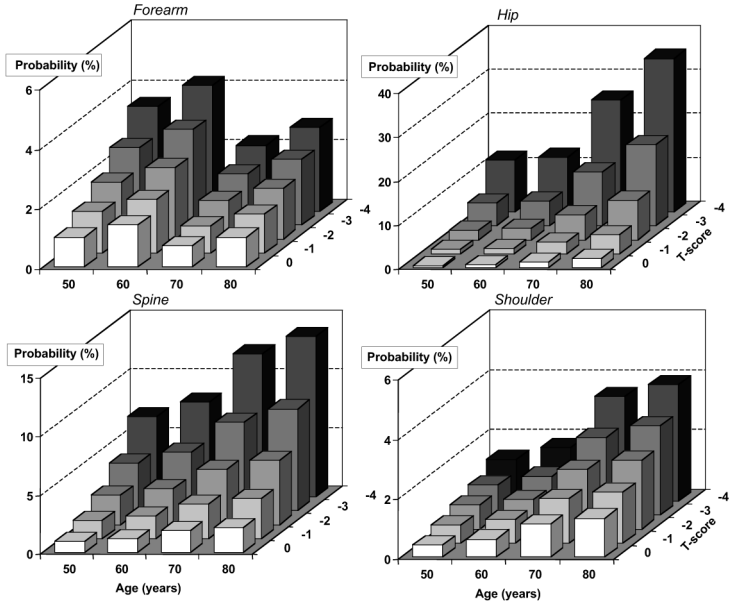
The 10-year probability of different fractures by age, sex and T-score is shown in Figs 6.6 and 6.7 *(45)*. The hazard function of fracture at the hip and proximal humerus is assumed to increase 2.6-fold for each 1 SD decrease in BMD at the hip. The gradient of risk for forearm fracture is set at 1.4, for vertebral fracture at 1.8, and for any fracture at 1.6. These estimates accord with the meta-analysis of Marshall et al. *(5)* rather than the age-specific gradients of risk given in section 5.

Fig. 6.6
Ten-year probability (%) of fracture at the sites[a] shown in women by T -score and age



Source: reference 45 (Fig. 2).
[a] "Forearm" describes the distal forearm and "shoulder" the proximal humerus.

Fig. 6.7
Ten-year probability (%) of fracture at the sites[a] shown in men by T -score and age



Source: reference 45 (Fig. 1).
[a]"Forearm" describes the distal forearm and "shoulder" the proximal humerus.

Fracture probabilities increase with decreasing T-score and increasing age, with the exception of forearm fractures in men. Thus, as reviewed in section 5, age provides an important independent element of risk not captured by BMD. The effect is particularly marked for hip fracture, because of the steep gradient of risk for hip fractures with decreasing BMD, but a similar phenomenon is observed in both sexes for all fracture types (Table 6.11) *(45)*.

Table 6.11
Ten-year probability of sustaining any osteoporotic fracture (i.e. a hip, forearm, shoulder or clinical vertebral fracture) in men and women, by age and T-score

Age	T-score									
(years)	+1	+0.5	0	–0.5	–1.0	–1.5	–2.0	–2.5	–3.0	–4.0
Men										
45	1.5	1.9	2.3	2.8	3.4	4.2	5.1	6.3	7.7	11.4
50	1.8	2.2	2.7	3.4	4.2	5.1	6.3	7.7	9.4	14.0
55	1.9	2.4	3.0	3.7	4.6	5.7	7.0	8.6	10.6	16.0
60	2.5	3.0	3.6	4.4	5.4	6.5	7.9	9.5	11.5	16.7
65	3.0	3.6	4.3	5.1	6.2	7.4	8.8	10.4	12.4	17.4
70	3.4	4.2	5.1	6.1	7.4	9.0	10.9	13.1	15.7	22.4
75	4.1	5.1	6.3	7.8	9.6	11.8	14.4	17.5	21.2	30.4
80	5.3	6.4	7.7	9.2	11.1	13.3	15.8	18.7	22.2	30.3
85	5.3	6.3	7.5	8.8	10.4	12.2	14.3	16.7	19.5	26.1
Women										
45	1.8	2.3	2.8	3.5	4.3	5.4	6.6	8.1	10.0	15.0
50	2.4	3.0	3.8	4.7	5.9	7.4	9.2	11.3	14.1	21.3
55	2.6	3.3	4.1	5.3	6.7	8.5	10.7	13.4	16.8	26.0
60	3.2	4.1	5.1	6.5	8.2	10.4	13.0	16.2	20.2	30.6
65	4.0	5.0	6.3	8.0	10.0	12.6	15.6	19.3	23.9	35.5
70	4.3	5.5	7.1	9.0	11.5	14.6	18.3	22.8	28.4	42.3
75	4.2	5.4	7.0	9.1	11.8	15.2	19.4	24.5	30.8	46.2
80	4.6	6.0	7.7	9.9	12.7	16.2	20.5	25.6	31.8	46.4
85	4.5	5.8	7.4	9.4	12.0	15.3	19.1	23.8	29.4	42.7

Source: reference 45 (Table 2).

At each threshold of BMD, probabilities are higher in women than in men for forearm fracture and humeral fractures, but the female to male ratio is lower than the sex ratio using average probabilities (see Table 6.10). This effect of reducing the female to male ratio is more marked in the case of hip and spine fracture. For hip fracture, for example, the female to male ratio at the age of 70 years is 2.1 using average probabilities, but is close to unity (1.02) in 70-year-old men and women at the threshold of osteoporosis (T-score = -2.5) and 0.73 at the threshold of osteopenia (see Figs 6.6 and 6.7). For all fractures, the effect is intermediate, with a sex ratio of 1.7 (women aged 70 years; T -score = -2.5; see Table 6.11) compared with 2.5 using average probabilities. The lower sex ratios when BMD-specific criteria are used are expected, since the incidence of fracture, particularly hip fracture, at any given BMD is similar in men and women. There are, however, also changes in the female to male ratio of probabilities as a function of age because of the higher mortality hazard in men.

Fracture probabilities in populations below threshold values for osteoporosis and low bone mass are shown in Table 6.12 *(45)*. Probabilities exceeded those observed in men and women at the threshold values for osteoporosis or low bone mass, since the sample includes individuals not only at, but also below the threshold for low bone mass or osteoporosis.

Table 6.12
Ten-year probability of fracture at the sites shown (%) in men and women, by age and diagnostic category, according to the T-score[a]

Age (years)	Forearm fracture		Hip fracture		Spine fracture		Shoulder fracture		Any fractures of these	
	Men <–1	Women <–2.5	Men <–1	Women <–2.5	Men <–1	Women <–2.5	Men <–1	Women <–2.5	Men <–1	Women <–2.5
Men										
45	1.9	2.7	1.2	3.3	1.6	3.0	0.8	1.1	4.7	7.6
50	1.8	2.5	2.0	5.2	2.2	4.0	0.7	1.0	5.7	9.2
55	1.9	2.8	1.9	5.2	2.6	4.9	0.6	0.9	6.4	10.4
60	2.3	3.2	2.6	6.2	3.0	5.1	1.0	1.3	7.6	11.6
65	2.0	2.7	4.1	8.8	3.5	5.7	1.7	2.3	8.8	13.0
70	1.2	1.7	6.2	13.7	4.8	8.0	2.0	2.7	10.8	16.2
75	1.5	2.1	9.5	21.4	5.6	9.7	1.9	2.6	14.1	21.5
80	1.7	2.3	11.0	21.2	6.0	9.7	2.4	3.1	16.6	23.2
85	1.3	1.6	9.6	16.9	5.2	7.7	2.8	3.5	16.0	21.4
Women										
45	3.6	5.2	0.8	2.2	1.1	2.1	1.2	1.7	6.1	9.9
50	5.1	7.3	1.1	2.9	1.9	3.5	1.6	2.3	8.6	13.9
55	5.8	8.4	2.0	5.1	2.5	4.6	1.7	2.5	10.3	16.8
60	6.7	9.3	3.3	7.8	3.6	6.4	2.8	4.0	13.2	20.5
65	7.5	10.2	5.0	10.9	5.3	9.0	4.0	5.4	16.8	24.9
70	7.9	10.6	8.3	16.7	6.7	10.9	4.8	6.5	20.7	29.8
75	8.0	10.4	11.8	21.5	6.9	10.7	5.3	7.0	23.6	32.6
80	7.6	9.5	14.6	23.8	7.1	10.2	5.7	7.2	26.6	34.4
85	6.1	7.4	14.7	21.9	6.9	9.4	6.4	7.8	26.7	33.1

Source: reference 45 (Table 3).
[a]Probabilities are shown for each age for all individuals below the thresholds for osteopenia and osteoporosis.

6.3.6 Ten-year probabilities and relative risk

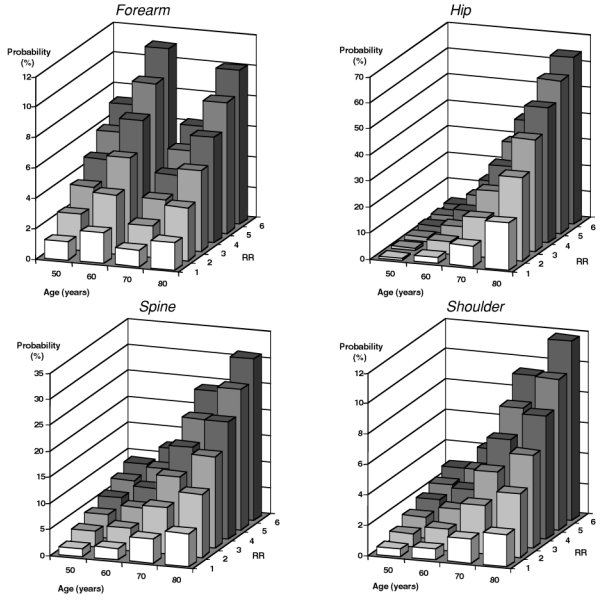
With progressive increases in relative risk in individuals because of the presence of risk factors, the absolute fracture risk increases at any given age. For most fractures, however, the probability decreases in the very elderly as a result of the dominating effect of mortality over the fracture risk. With the caveat that data are computed for Sweden, 10-year probabilities can be computed for hip, clinical spine, forearm or shoulder fractures (Figs 6.8 and 6.9) or for any one of those fractures (Table 6.13) *(46)*.

Table 6.13
Ten-year probability (%) of osteoporotic fracture (clinical spine, forearm, hip or proximal humerus) in men and women from Sweden according to relative risk (RR) at the ages shown

	Age (years)							
RR	50	55	60	65	70	75	80	85
Men								
1	3.3	3.6	4.7	5.5	7.0	9.9	12.6	11.4
2	6.5	7.2	9.1	10.7	13.5	18.7	23.1	21.1
3	9.6	10.5	13.3	15.5	19.4	26.4	31.9	29.4
4	12.6	13.8	17.3	20.1	24.9	33.2	39.3	36.5
5	15.5	16.9	21.1	24.4	30.0	39.2	45.5	42.6
6	18.3	19.9	24.8	28.5	34.6	44.5	50.8	47.8
Women								
1	5.8	7.2	9.6	12.4	16.1	18.7	21.5	20.7
2	11.3	13.8	18.2	23.3	29.4	33.5	37.4	36.1
3	16.5	20.0	26.0	32.6	40.4	45.2	49.2	47.6
4	21.4	25.7	33.1	40.8	49.5	54.6	58.1	56.4
5	26.0	31.0	39.4	47.9	57.2	62.1	64.8	63.1
6	30.3	35.9	45.2	54.2	63.5	68.1	70.0	68.3

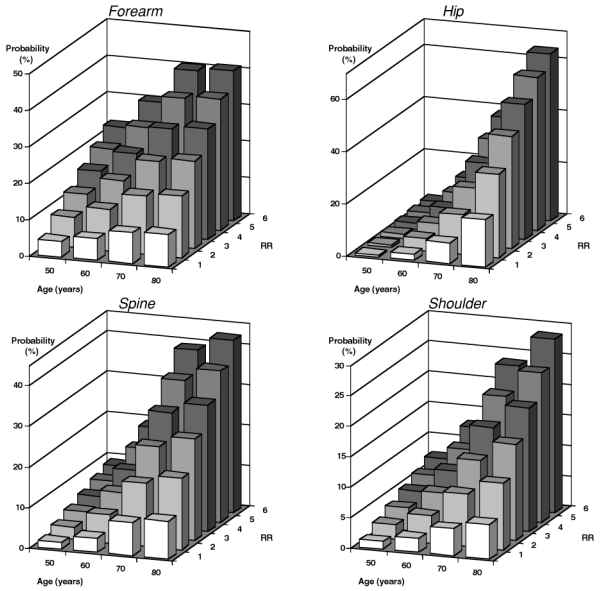
Source: reference 46 (Table 1).

Fig. 6.8
Ten-year probability (%) of a first fracture at the sites shown in men according to population risk ratio (RR), by age



Source: reference 46 (Fig. 1).

Fig. 6.9
Ten-year probability (%) of a first fracture at the sites shown in women according to population risk ratio (RR), by age



Source: reference 46 (Fig. 1).

From the distribution of 10-year hip fracture probabilities, index countries can be chosen to examine the effects of variations in relative risk in that setting (Table 6.14). The large variation in hip fracture incidence in different populations means that 10-year probability of hip fracture in the general female population of Sweden (RR = 1.0) is substantially higher than that for women from Venezuela, who have a relative risk of 4.0.

Table 6.14
Ten-year probability of hip fracture in women according to age and relative risk (RR), in four index countries with different absolute risks

	Age (years)				Age (years)			
RR	50	60	70	80	50	60	70	80
	Very high risk (Malmo, Sweden)				High risk (Edinburgh, Scotland)			
1.0	0.6	2.7	10.2	24.6	0.4	1.1	4.9	13.0
2.0	1.3	5.2	19.3	41.8	0.9	2.2	9.5	23.8
3.0	1.9	7.8	27.4	53.9	1.3	3.3	13.8	32.6
4.0	2.6	10.2	34.5	62.5	1.8	4.4	4.4	39.9
	Moderate risk (Spain)				Low risk (Venezuela)			
1.0	0.2	0.9	3.1	7.0	0.1	0.4	1.4	3.2
2.0	0.4	1.9	5.9	12.5	0.2	0.9	2.7	5.8
3.0	0.7	2.7	8.5	16.7	0.3	1.3	3.9	7.7
4.0	0.9	3.6	10.8	20.1	0.4	1.7	5.0	9.3

Source: unpublished data and reference 44 (Table 3).

If treatments were given solely on the basis of 10-year probabilities, then fewer patients would qualify for treatment in countries where the background fracture probability was lower. In practice, there are many factors to consider in determining intervention thresholds, and these are reviewed in section 8.

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7. Assessment tools for case-finding

The aims of clinical risk assessment are to identify patients at particular risk of fracture so that intervention can be considered. Examples include the identification of women with low BMD and a previous fragility fracture, and the identification of individuals with certain diseases in whom the risk of osteoporosis or fracture is high. Conversely, a parallel aim is to avoid unnecessary treatment in individuals at low risk. Since fracture risk prediction will always be imperfect because of the multifactorial causation of fracture, the fulfilment of these aims is one of the greatest challenges facing practitioners.

The approaches most widely considered are population-based screening and opportunistic case-finding. To date, case-finding strategies have focused on the identification of individuals with low BMD. The integration of risk factors for fracture permits the development of both screening and case-finding strategies based on the fracture probability of an individual, and these various options are reviewed in this section.

7.1 Population screening

Population screening is the means whereby apparently healthy individuals are selected for intervention according to a "high risk" strategy, i.e. to identify and treat that part of the population at greatest risk of fracture. It should be

distinguished from opportunistic case-finding that is sometimes also termed "screening". The advantage of population screening is that it is an extension of the physician–patient relationship in the sense that the intervention is considered appropriate by the individuals concerned, and motivation on the part of patients and physicians is high. Disadvantages, however, include the difficulties in organization and the expense of screening, as well as the limited contribution of treating the high risk subset to disease prevention in the community as a whole. Various criteria for the evaluation of screening programmes have been proposed which differ in their emphasis *(1)*. One criterion to justify a screening programme for the population is that the disease must have been demonstrated to be an important public health problem, and this criterion has been met by osteoporosis in Caucasian populations (see section 2). The natural history of osteoporosis in the context of screening should also be delineated. The pattern of change in BMD with age is reasonably understood, and the independent contribution of BMD to fracture risk has also been unequivocally demonstrated. A critical component is the performance characteristics of the screening test in different clinical settings, which is reviewed below.

7.1.1 Screening at the menopause

Because bone loss in women accelerates at menopause, a readily diagnosable event, it has been intuitively reasoned that screening should be considered in women at the time of menopause. The most obvious candidate is testing by BMD.

There have been several analyses of the potential utility of screening with BMD at the time of the menopause *(1–8)*. These analyses acknowledge that the cost of screening itself is not the dominant factor since most treatments are relatively more expensive. Opinions vary over the use of BMD as a screening tool, but most do not recommend widespread or mass screening at the time of the menopause on the basis of bone density alone *(1,2,9–11)*. The reasons relate to sensitivity and specificity of the measurement when applied to the population aged 50 years. The aim of screening is obviously to direct interventions to those most in need, and to avoid treatment of healthy individuals who will never fracture. Thus, the test should have high specificity, in the order of 90% or more. It can be calculated that, in order to achieve this kind of specificity, approximately 10% of the postmenopausal population might be selected as a high risk category *(12)* (Table 7.1). Under this assumption, however, the sensitivity of the test is low, even with relatively high gradients of risk. Thus, assuming that fracture risk increases 1.5-fold for each standard deviation decrease in BMD, the sensitivity (or detection rate) is only 18%. In other words, 82% of all fractures would occur in individuals designated by the test to be at low risk. Taking a gradient of risk of 2.5 per standard deviation decrease in BMD (i.e. the prediction of hip fracture from hip BMD), sensitivity still remains low at approximately 32% *(12)*. Under the former scenario (gradient of risk = 1.5/SD), 1000 patients would need to

be screened to detect 100 for treatment, and the maximal impact on the community after menopause (percentage of fractures saved) would be approximately 8% *(12)* (Table 7.2). With a risk gradient of 3.0/SD, approximately 15% of fractures would be averted, assuming 100% compliance and 50% effectiveness over 10 years.

Table 7.1

Estimates of positive predictive value (PPV), sensitivity and specificity of measurements to predict any osteoporotic fracture over 10 years or to death in men and women aged 50 years, according to different population cut-offs to define a high risk category

	High risk category (% of population)														
	0.5			5			10			15			25		
Gradient of risk	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity
(RR/SD)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Men aged 50 years															
1.5	10.0	1.5	99.5	7.2	10.9	95.2	6.1	18.2	90.3	5.8	26.3	85.4	5.0	37.8	75.4
2.0	18.7	2.8	99.6	11.1	16.7	95.4	8.7	26.1	90.6	7.9	35.7	85.7	6.4	48.2	75.8
2.5	28.2	4.2	99.6	14.7	22.1	95.6	10.9	32.9	90.8	9.6	43.3	86.0	7.5	55.9	76.1
3.0	37.4	5.6	99.7	17.8	26.7	95.7	12.8	38.3	91.0	10.9	49.1	86.2	8.2	61.3	76.3
4.0	52.3	7.9	99.8	22.5	33.7	96.0	15.3	46.0	91.2	12.6	56.7	86.4	9.0	67.6	76.5
5.0	62.7	9.4	99.8	25.4	38.1	96.1	16.8	50.3	91.4	13.4	60.3	86.6	9.3	69.7	76.5
6.0	69.7	10.5	99.8	27.2	40.8	96.2	17.5	52.4	91.5	13.7	61.6	86.6	9.3	69.6	76.5
Women aged 50 years															
1.5	17.3	1.5	99.6	12.7	10.7	95.4	10.7	18.0	90.5	10.3	26.1	85.7	8.9	37.6	75.8
2.0	31.3	2.6	99.6	19.2	16.2	95.7	15.1	25.5	91.0	13.8	35.1	86.3	11.3	47.5	76.4
2.5	45.0	3.8	99.7	24.8	21.0	96.0	18.7	31.6	91.4	16.5	41.9	86.7	12.9	54.5	76.9
3.0	56.7	4.8	99.8	29.4	24.9	96.3	21.5	36.3	91.7	18.5	47.0	87.0	14.0	59.2	77.1
4.0	73.0	6.2	99.9	35.8	30.3	96.6	25.1	42.3	92.0	20.9	52.9	87.4	15.1	63.8	77.4
5.0	82.3	7.0	99.9	39.5	33.4	96.8	26.8	45.3	92.2	21.8	55.2	87.5	15.3	64.7	77.5
6.0	87.8	7.4	99.9	41.5	35.0	96.9	27.5	46.5	92.3	21.9	55.6	87.6	15.1	63.7	77.4

Source: reference 12 (Tables 2 and 3).

RR, relative risk.

Table 7.2

Impact of screening women at the age of 65 years according to the target group selected and the gradient of risk of the test used

		Percentage of population targeted			
		5	10	15	25
Number screened to detect 100 for treatment		2000	1000	667	400
Number of fractures prevented[a]					
RR/SD =	1.5	14	12	12	10
	2.0	20	16	15	13
	3.0	28	22	19	15
	4.0	32	24	21	15
	5.0	34	25	21	15
	6.0	34	25	21	15
Number screened to prevent 1 fracture					
RR/SD =	1.5	143	83	56	40
	2.0	100	63	44	31
	3.0	71	45	35	27
	4.0	63	42	32	27
	5.0	59	40	32	27
	6.0	59	40	32	27
Expected number of fractures in the screened community in 10 years[b]		286	143	95	57
Impact on community (% fractures saved)[c]					
RR/SD =	1.5	4.9	8.4	12.6	17.5
	2.0	7.0	11.2	15.8	22.8
	3.0	9.8	15.4	20.0	26.3
	4.0	11.2	16.8	22.1	26.3
	5.0	11.9	17.5	22.1	26.3
	6.0	11.9	17.5	22.1	26.3

Source: reference 12 (Table 6).

RR, relative risk; PPV, positive predictive value.

[a]Assumes 50% effectiveness of treatment over 10 years (PPV/2).

[b]Ten-year fracture probability times the number of women screened.

[c]Calculated from the number of fractures saved and the total expected.

There are also specific problems with the intervention in the context of screening at the menopause. Whereas there is good evidence for the efficacy of treatments from randomized controlled studies *(13)*, the continuance with treatment is low. In the case of hormone replacement treatment, only about 10% of women in the United States continue treatment for more than 1 year *(14)*, though it is likely that uptake and continuance can be improved by screening *(15)*. Thus, the return on investment is correspondingly low.

7.1.2 Screening in later life

Screening may, however, yield a higher dividend if higher risk individuals can be selected. There are approaches to this problem that are not mutually exclusive. The first is to select individuals much older than the age of 50

years, because the risk of fractures rises exponentially with age *(16)* and older individuals may be more amenable to treatment. Theoretical analyses suggest that treatments would be given cost-effectively to very elderly people without a need for screening *(17)*. A potential example is the use of vitamin D in elderly people; it has been estimated that if such a regimen could be shown to prevent 10% of hip fractures, there would be savings to the health-care system in the United Kingdom *(18)*. The second option is to improve the gradient of risk of the test used for assessment, for example to combine the information provided by BMD and independent risk factors.

The effect of screening men or women at the age of 65 years is compared with screening at the age of 50 years in Tables 7.1 and 7.3. The major advantage of screening in later life is to increase the proportion of individuals identified who will sustain fractures and be targeted for treatment. For example, where 10% of the female population is designated to be at high risk, the specificity remains high over all ranges of risk assumption (over 90%). The sensitivity, however, varies between 17% and 35%. Sensitivity increases the larger the targeted population and the higher the gradient of risk assumed. The major effect of screening women at the age of 65 years rather than 50 years is in the positive predictive value (PPV; the proportion of detected individuals who sustain a hip fracture). Assuming a gradient of risk of 1.5/SD and when 10% of the population is to be targeted, the PPV increases from 11% at the age of 50 years to 24% at the age of 65 years *(12)*.

Table 7.3

Estimates of positive predictive value (PPV), sensitivity and specificity of measurements to predict any osteoporotic fracture over 10 years or to death in men and women aged 65 years, according to different population cut-offs to define a high risk category

	High-risk category (% of population)														
	0.5			5			10			15			25		
Gradient of risk	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity
(RR/SD)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Men aged 65 years															
1.5	17.0	1.5	99.6	12.5	10.7	95.4	10.5	18.0	90.5	10.2	26.0	85.7	8.8	37.5	75.8
2.0	30.6	2.6	99.6	18.9	16.1	95.7	14.9	25.4	91.0	13.6	34.9	86.2	11.1	47.4	76.4
2.5	43.8	3.7	99.7	24.4	20.8	96.0	18.4	31.4	91.3	16.3	41.7	86.7	12.7	54.3	76.8
3.0	55.0	4.7	99.8	28.8	24.6	96.2	21.1	36.0	91.6	18.2	46.6	87.0	13.8	58.8	77.1
4.0	70.5	6.0	99.8	35.0	29.9	96.5	24.5	41.9	92.0	20.5	52.4	87.3	14.8	63.3	77.4
5.0	79.4	6.8	99.9	38.5	32.9	96.7	26.2	44.8	92.2	21.3	54.6	87.5	15.0	64.1	77.4
6.0	84.6	7.2	99.9	40.4	34.5	96.8	26.9	45.9	92.2	21.5	55.0	87.5	14.8	63.1	77.4
Women aged 65 years															
1.5	37.8	1.3	99.6	28.8	10.2	95.9	24.4	17.3	91.2	23.7	25.3	86.7	20.7	36.7	76.9
2.0	60.2	2.1	99.8	40.8	14.5	96.6	32.9	23.4	92.2	30.7	32.7	87.9	25.3	45.0	78.3
2.5	76.3	2.7	99.9	49.8	17.7	97.1	39.0	27.7	92.9	35.4	37.7	88.7	28.2	50.1	79.1
3.0	86.1	3.1	99.9	56.2	19.9	97.4	43.1	30.6	93.4	38.3	40.8	89.2	29.8	52.9	79.6
4.0	95.3	3.4	100.0	63.5	22.6	97.9	47.5	33.8	93.9	41.2	43.8	89.7	30.9	54.8	79.9
5.0	98.7	3.5	100.0	67.0	23.8	98.1	49.2	34.9	94.1	41.7	44.4	89.8	30.4	54.0	79.8
6.0	100.2	3.6	100.0	68.5	24.3	98.2	49.4	35.1	94.1	41.2	43.8	89.7	29.4	52.1	79.4

Source: reference 12 (Tables 2 and 3).

RR, relative risk.

Population screening in women aged 65 years or more is advocated in North America *(19–24)*, but is not recommended in many other parts of the world *(3,4,8,9,11,25,26)*. The conflicting positions arise in part from differing clinical practices and attitudes to prevention *(27)*, the availability of DXA machines, and willingness to pay for health care *(28)*. In the United States, the gross domestic product (GDP) per capita is US$ 37 000, whereas that of the United Kingdom is lower at US$ 25 300. The proportion of GDP spent on health care is 13.9% in the United States and 7.6% in the United Kingdom *(29)*. Willingness to pay is even lower in many other countries (see section 8). Thus, health-care policies need to take account of the local health-care priorities, which will differ in different regions of the world, not only for reasons of affordability *(30)*, but also because of the large regional differences in fracture risk (see section 2).

As mentioned above, another approach is to select individuals at higher risk than is possible on the basis of age or BMD alone. The manner in which BMD can be combined with other risk factors, such as clinical risk factors or biochemical markers of bone turnover, is reviewed later in this section. The effect of using a test with a higher gradient of risk improves PPV and

sensitivity without sacrificing specificity (see Tables 7.1 and 7.3). There may, therefore, be a stronger case for screening in later life, depending on the extent to which risk factors add to the value of BMD tests.

7.2 Case-finding

Because of the problems with population screening at the menopause, and because screening at later ages has not yet been widely adopted, attention has turned towards a case-finding strategy (opportunistic screening). In this scenario, patients who present with clinical risk factors are identified for further assessment, most commonly by the measurement of BMD.

A large number of treatment guidelines have been published that follow a case-finding strategy wherein treatment is offered to patients in whom BMD lies below a specific threshold value. This strategy has been widely adopted in many European countries *(11)* and other regions of the world. Those guidelines that are derived from an evidence base are reviewed below.

7.2.1 Evidence-based guidelines

The importance of an evidence-based approach to the management of disease has become widely accepted in the past decade *(31)*. Application of such guidelines provides a means by which a high standard of clinical care can be uniformly practised, and enables the sharing of best practice within and between countries. Evidence-based guidelines should be rigorous with respect to their evidence base, objectivity, stakeholder involvement and editorial independence. Clarity of presentation is also important, with unambiguous, easily identified key recommendations. Implementation tools, such as an executive summary, management algorithms and patient information sheet, should be provided. Guidelines should be appropriately disseminated to relevant health professionals, and their use audited to define resulting changes in management. Finally, a mechanism should be in place for regular updating *(32)*.

In recent years, national evidence-based guidelines for the prevention and treatment of osteoporosis have been produced by a number of countries, mainly but not exclusively in Europe and North America *(4,9,10,19,24,33–50)* (Table 7.4). The majority have been produced by expert groups. Most of these guidelines address the management of postmenopausal osteoporosis, although some also include men with osteoporosis; two are devoted to glucocorticoid-induced osteoporosis, and one is restricted to the management of patients with hip fracture. The majority of guidelines are directed primarily towards pharmacological interventions, for which a substantial evidence base now exists, with less emphasis on the case-finding strategy itself or the development of intervention thresholds.

Table 7.4

Currently available evidence-based guidelines for the management of osteoporosis

Country	Title of guidelines	Date
Austria	Treatment of postmenopausal osteoporosis (33)	2003
Canada	Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (35)	2002
Denmark	Consensus report on osteoporosis (34)	2000
France	Indications for the measurement of bone mineral (49)	2000
Germany	Prevention, clinical assessment and therapy of osteoporosis for women after menopause, and for men after age 60 years (36)	2006
Greece	Guidelines for diagnosis and management of osteoporosis (37)	2004
Italy	Guidelines for the diagnosis, prevention and treatment of osteoporosis (38)	2006
Lebanon	Lebanese guidelines on osteoporosis assessment and treatment (39)	2004
Netherlands	Osteoporosis (24)	2002
Saudi Arabia	Guidelines for prevention and management of osteoporosis in adults	2003
Spain	Practice guidelines in postmenopausal osteoporosis (40)	2001
Sweden	Diagnosis, prevention and treatment of osteoporosis (4)	2003
	Treatment of osteoporosis to prevent fractures (50)	2004
United Kingdom	Guidelines on prevention and treatment of osteoporosis (9)	1999/2000
	Prevention and treatment of glucocorticoid-induced osteoporosis (41)	2002
Scotland	Prevention and management of hip fracture in older people (42)	2002
	Management of osteoporosis (43)	2003
United States	Physician's guide to prevention and treatment of osteoporosis (19)	2003
	Medical guidelines for the prevention and treatment of osteoporosis (44)	2003
	Screening for osteoporosis in postmenopausal women (46)	2002
	Position statements of the International Society for Clinical Densitometry (47)	2004
	Management of postmenopausal osteoporosis (48)	2002/6
	Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (45)	2001

7.2.2 Approaches to fracture risk assessment

Most guidelines advocate a case-finding approach by which individuals are selected for bone densitometry on the basis of risk factors for osteoporosis. An exception to this is the guidelines from North America, which recommend bone density measurement in all women aged 65 years and over (*19,35*). All the guidelines recommend the use of dual energy X-ray absorptiometry as the method of choice for measurement of BMD for the diagnosis of osteoporosis.

Choice of risk factors

There is broad similarity in the risk factors that are identified as indications for further investigation. The risk factors fall into major and additional categories. Major risk factors include a personal history of fracture as an adult, history of fragility fracture in a first degree relative, low body weight (e.g. less than 127 lbs, less than 60kg, less than 57kg, or a BMI of less than 19 kg/m^2), current smoking and the use of oral glucocorticoid therapy for more than 3 months.

The Osteoporosis Society of Canada identifies four key factors – age, low BMD, prior fragility fracture, and family history of osteoporosis – that stand out as predictors of fractures related to osteoporosis *(35)*. They also recognize the risk of glucocorticoid therapy. The Canadian group suggests BMD testing for all women over the age of 65 years, and for women and men over 50 who have at least one major or two minor risk factors. Their list consists of 11 major factors (including age greater than 65 years), and 10 minor ones (see section 4, Table 4.3). Overlap with the National Osteoporosis Foundation list is evident, as are differences. Among major risk factors, for example, are medical conditions such as hypogonadism, malabsorption syndrome, and primary hyperparathyroidism. Listed with the minor risks are smoking and weight less than 57 kg, factors that are independent predictors of fracture in a variety of multi-variable models.

The Royal College of Physicians in the United Kingdom recommend a case-finding strategy in which patients are identified because of a fragility fracture or by the presence of strong risk factors (9,10). Included in their risk factor list are ten items, most, but not all, of which overlap with the North American items (Table 7.5). The guidance in the United Kingdom, however, stops short of recommending BMD testing for any group of women on the basis of age alone. Criteria for bone densitometry in these and other guidelines are shown in Table 7.6.

Table 7.5

Indications provided by the Royal College of Physicians, United Kingdom, for testing bone mineral density

Radiographic evidence of osteopenia or vertebral deformity
Loss of height, thoracic kyphosis (after radiographic conformation of vertebral deformity)
Previous fragility fracture
Prolonged corticosteroid therapy (prednisolone >7.5mg for 6 months or more)[a]
Premature menopause (age <45 years)
Prolonged secondary amenorrhoea (> 1 year)
Primary hypogonadism
Chronic disorders associated with osteopenia
Maternal history of hip fracture
Low body mass index (< 19kg/m^2)

Source: reference 9.

[a] Indication subsequently modified to: any dose of prednisolone by mouth for more than 3 months (40).

Table 7.6

Criteria for bone densitometry in national guidelines[a]

Country	Reference	Criteria for bone densitometry
Austria	33	No specific recommendations
Canada	35	Men and women aged 50 years or more, with 1 major or 2 minor risk factors. Men and women aged over 65 years
Denmark	34	Presence of at least one risk factor
France	49	Presence of risk factors
Germany	36	Women aged 50 years or more (men aged 60 years or more) with a previous vertebral fracture
		Women aged 60 years or more (men aged 70 years or more) with risk factors:
		- peripheral low trauma fracture
		- family history
		- BMI<20
		- smoking
		- falls or immobility
		Women aged 70 years or more (men aged 80 years or more) regardless of risk factors
Greece	37	Presence of risk factors
Italy	38	Postmenopausal women above the age of 65 years
		Women below 65 years of age or men with risk factors:
		- family history of severe osteoporosis
		- smoking
		- low body weight (BMI<20)
		- postmenopausal women with X-ray evidence of osteopenia
		- fraglity fracture
		- menopause before 47 years of age
		- diseases or treatment known to cause osteoporosis

Lebanon	39	Postmenopausal women with one or more risk factors
		Women aged 65 years or more
		Premenopausal women with medical conditions known to be associated with bone loss
		Men with one or more strong risk factors
Netherlands	24	Women aged 50 years or more with a previous non-vertebral fracture
		Women aged 60 years or more with three risk factors
		Women aged 70 years or more with two risk factors
		Women with a vertebral fracture, regardless of age
Saudi Arabia		Postmenopausal women, particularly those over 60 years of age, or males over 65 years with risk factors or with a fracture index ≥4[b] (without BMD)
		Other disorders associated with osteoporosis
		X-ray evidence of osteopenia or vertebral deformity or both, height loss, or thoracic kyphosis
		Fragility fracture after age 40 years
		Monitoring of treatment
Spain	40	Presence of risk factors
Sweden	4, 50	Presence of risk factors :
		Strong risk factors:
		- men and women with low-energy trauma
		- men and women taking oral glucocorticoids for 3 months or more
		- five minor risk factors also listed
United Kingdom	9	Men and women aged over 45 years with risk factors
		Men and women aged over 45 years with previous fragility fracture
	41	Men and women taking oral glucocorticoids for 3 months or more in whom primary prevention has not been initiated
	42	No specific recommendations
Scotland	43	Men and women with risk factors
United States	19	Postmenopausal women aged under 65 years if at least one risk factor
		Postmenopausal women aged 65 years or more
	44	Perimenopausal or postmenopausal women with risk factors
		Women aged 40 years or more who have sustained a fracture
		Women aged over 65 years
	46	Postmenopausal women aged 60 years or more with risk factors
		Postmenopausal women aged over 65 years
	47	Postmenopausal women aged under 65 years with risk factors
		Postmenopausal women aged over 65 years
		Men aged 70 years
		Adults with a fragility fracture

	48	Postmenopausal women aged under 65 years with at least one risk factor (including fracture)
		Postmenopausal women aged over 65 years
	45	All patients initiating long-term (>6 months) oral glucocorticoid therapy (equivalent 5 mg/d prednisone)

[a] See Table 7.4 for list of guidelines by country.

[b] The fracture index is a score based on age, previous fracture, history of maternal hip fracture, weight < 57 kg, current smoker, uses arms to stand from chair and hip BMD T-score (if done).

Criteria for intervention

The majority of guidelines use BMD T-scores determined by DXA as a guide to intervention thresholds (Table 7.7). None of the currently available guidelines use assessment of fracture probability, although the Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of osteoporosis recommend that 10-year hip fracture probability is documented on BMD measurement reports, based on age and Z-scores for BMD *(42)*. The guidelines of the National Osteoporosis Foundation use BMD thresholds, but these were based on the assessment of 5-year probabilities in the resource documentation *(51)*. Some guidelines use selected risk factors in addition to BMD T-scores, particularly age and previous fragility fracture. Most do not distinguish between BMD-dependent and BMD-independent risk factors, and few consider potential interactions between risk factors in determining intervention thresholds. None of the guidelines explicitly advocate initiation of therapy after hospitalization for a fragility fracture.

Table 7.7
Criteria for intervention in evidence-based guidelines[a]

Country	Reference	Criteria for intervention
Austria	33	No specific recommendations
Canada	35	Long-term glucocorticoid therapy
		Men and women with fragility fracture after age 40 years and T-score <-1.5
		Men and women with non-traumatic vertebral compression deformity and T-score <-1.5
		Men and women with at least one major or two minor risk factors and T-score <-1.5
		Men and women with T-score < -2.5
Denmark	34	T-score ≤-2.5 and at least one risk factor
		Fragility fracture (hip or spine).
France	49	No specific recommendations
Germany	36	T-score ≤-2.0 and 10-year fracture probability >30%
Greece	37	Postmenopausal women with multiple vertebral fractures
		Postmenopausal women with T-score ≤ -2.5 ± fracture
		Elderly men and women with low-energy fracture of the peripheral skeleton
		Men with T-score ≤ -2.5 ± fracture
		Patients receiving glucocorticoids for more than 3 months

Italy	38	Postmenopausal women and men with previous fracture at the hip or spine
		Postmenopausal women and men on treatment with prednisone/equivalent > 5 mg daily
		Postmenopausal women with T-score < -3.5
		Postmenopausal women with T-score < -3 associated with other risk factors:
		- early menopause, previous Colles fracture, smoking, rheumatoid arthritis
Lebanon	39	Postmenopausal women with T-score < -2.5
		Postmenopausal women with vertebral fractures and low BMD
		Postmenopausal women on long-term glucocorticoid therapy + T-score < -1.5
		Men with fragility fractures and low BMD
		Men aged over 70 years + T-score < -2.5
		Men treated with glucocorticoids for 3 months or more with T-score < -1.5
Netherlands	24	Osteoporotic vertebral fracture
		T-score < -2.5
		Men with vertebral fracture and T-score < -2.5
		Patients treated with ≥15 mg/d prednisolone for 3 months or more
		Postmenopausal women or men aged over 70 years treated with ≥7.5 mg/d prednisolone (or equivalent) for 3 months or more
		Patients treated with <7.5 mg/d prednisolone (or equivalent) for 3 months or more if Z-score < -1 or T-score < -2.5
Saudi Arabia		Postmenopausal women with T-score –1 to –2.5 + fracture or > 1 risk factor for fracture or fracture index ≤6
		Postmenopausal women with T-score ≤-2.5 + fracture or > 1 strong risk factor for fracture or fracture index[b] ≥6
Spain	40	Postmenopausal women with vertebral fracture
		Postmenopausal women with T-score < -2.5
		Postmenopausal women with non-vertebral fracture and T-score ≤ -2.5
Sweden	4,50	Postmenopausal women with T-score < -2.5
		Women with oral glucocorticoid therapy with T-score ≤ -1.0
		Postmenopausal women with a previous fracture with T- score ≤ -2.0
United Kingdom	9,41	Postmenopausal women with T-score ≤ -2.5
		Postmenopausal women with fragility fracture
		Women and men on oral glucocorticoid therapy for 3 months or more with T-score ≤ -1.5
		Men and women aged over 65 years
		Men and women with previous fragility facture
	42	Not relevant
Scotland	43	Postmenopausal women with more than one vertebral fracture
		Postmenopausal women with one vertebral fracture and T-score < -2.5 at femoral neck or < -2 at lumbar spine

		Postmenopausal women with non-vertebral fracture and T-score <-2.5 at femoral neck or <-2 at lumbar spine
		Postmenopausal women with T-score ≤-2.5
		Frail elderly women with T-score <-2.5 ± fracture
		Men with T-score ≤-2.5 ± fracture
United States	19	Postmenopausal women with vertebral or hip fractures
		Postmenopausal women with T-score <–2 or <–1.5 + one or more risk factors
	44	Postmenopausal women with low trauma fracture + low BMD
		Postmenopausal women with T-score ≤-2.5
		Postmenopausal women with T-score ≤-1.5>-2.5 + risk factors
		Women in whom non-pharmacological preventive methods are ineffective (bone loss continues or low trauma fractures occur)
	46	No specific recommendations
	47	No specific recommendations
	48	Postmenopausal women with T-score –2 to –2.5 + one risk factor
		Postmenopausal women with T-score ≤ -2.5
		Women with previous vertebral fracture
	45	All individuals starting oral glucocorticoids (equivalent prednisolone 5 mg/d or more) for 3 months or more
		All individuals on long-term glucocorticoid therapy (equivalent prednisolone 5 mg/d or more) with T-score <-1

[a] See Table 7.4 for list of guidelines by country.

[b] The fracture index is a score based on age, previous fracture, history of maternal hip fracture, weight < 57 kg, current smoker, uses arms to stand from chair, and hip BMD T-score (if done).

The BMD threshold at which intervention is recommended varies between guidelines. The National Osteoporosis Foundation recommends intervention in postmenopausal women with central DXA T-scores below –2.0 SD in the absence of risk factors and in women with T-scores below –1.5 SD if one or more risk factors are present *(19)*. They also suggest considering postmenopausal women with prior vertebral or hip fractures as candidates for treatment without measurement of BMD. The intervention threshold for BMD recommended by the National Osteoporosis Foundation is less stringent than that given by other expert groups. For example, the Royal College of Physicians, London *(41)* recommends treatment where individuals have osteoporosis (T-score of less than –2.5 SD).

7.2.3 Economic evaluation

The guidelines of the International Osteoporosis Foundation (then the European Foundation), the National Osteoporosis Foundation, the Osteoporosis Society of Canada and the Royal College of Physicians in the United Kingdom all provide economic evaluations *(24,41,51,52)*.

Health economic analyses of the United Kingdom and European guidelines indicate that treatment can be developed with favourable cost–effectiveness.

Typical costs are US$ 2100 per fracture averted for a treatment that costs US$ 300 per year. Costs compare favourably with the costs of management of other chronic disorders *(41,52)*. Moreover, the use of BMD assessment after pre-selection of patients by the presence of clinical risk factors improves the cost benefit, depending on the cost of treatment. For a treatment that costs US$ 75 per year and reduces fracture by 50%, skeletal assessment is of uncertain benefit; whereas BMD assessment saves resources compared with assessment based on risk factors alone, although the amount is small. The cost–effectiveness becomes more favourable, however, as the cost of treatment increases. For a treatment that costs US$ 300 per patient per year and reduces fracture risk by 50% over a 5-year period, the cost per fracture averted would be US$ 550 by using densitometry as compared to US$ 1800 without BMD assessment. Thus, the cost–effectiveness of the case-finding strategy becomes greater as the costs of the treatment rise *(41,52)*. A major problem with the European guidelines is their conservative position. Patients identified for treatment require both the presence of a major clinical risk factor to be eligible for BMD testing, and to be subsequently shown to have osteoporosis.

The National Osteoporosis Foundation (NOF) has published a detailed health economic assessment set within a target of intervening at costs below US$ 30 000 per quality of life year saved *(51)*. Unlike the European guidelines *(52)*, the assessment recognized that individuals with combinations of risk factors might be profitably treated with a less severe BMD threshold than in the absence of clinical risk factors. The NOF subsequently published a practical guide for physicians based on the published resource document *(53)*.

The differences in recommendations between countries *(54)* indicate the need to develop cohesive strategies that can be applied worldwide but that take into account local factors, for example the very different risks that are found in different countries and the variable ability to pay for assessment and treatment.

7.2.4 Limitations

Several limitations are evident in the approaches used to identify and manage patients with increased fracture risk. The first is the reliance on BMD as the chief arbiter of risk. Current guidelines lean heavily on BMD to guide pharmacological treatment, although thresholds for intervention vary. The problem is that BMD thresholds of -2.5 SD or even -2.0 SD fail to identify the majority of individuals who will experience fractures *(54–57)*.

A second limitation in current guidelines lies in the lack of integration of all the risk factors available to formulate strategy. Each of the guidelines proposes a list of clinical risk factors that are linked to fractures. Almost 30 individual characteristics (e.g. increasing age, body weight, personal or family history of fracture, assorted medical conditions and attendant treatments, and personal behaviours) are identified. The lists overlap to some extent but also exhibit many differences. The guidelines suggest that various clinical risk factors carry different weights of importance by designating some major and others secondary or minor, but they largely fail to specify how these implied weights can be used to determine fracture risk.

Because risks identified as singly important interact with one another and co-exist in differing combinations, there is a need for methods to determine their combined effects. A number of investigators have employed multi-variable statistical techniques to build scoring systems that assess the influence of each risk factor while controlling or adjusting for the presence of the others. Factors that are found to contribute independently to risk are weighted by importance (as determined in the modelling) and allocated points. Individuals are then evaluated and receive a score, based on accumulated points, that predicts their risk. These approaches have been used either for the prediction of osteoporosis or the prediction of fracture.

7.3 Prediction of osteoporosis

Several studies have integrated the combined effects of risk factors for the prediction of osteoporosis where scores are derived from adjusted odds ratios *(53,58–65)*. The majority combine age and weight, and are summarized in Table 7.8. The most widely tested and the most simple is the osteoporosis self-assessment tool (OST), originally developed for Asians but tested in several different settings *(58,61,66–68)*. The score is derived from the integer (INT) of age (in years) and the integer of weight (in kg):

OST score = INT ((2 x weight)/10)-INT((2 x age)/10).

A score of –1 or less is indicative of osteoporosis.

Several studies have compared the various osteoporosis risk tools *(60,69–78)*. The tools offer comparable performance characteristics in that they have high sensitivity (detection rate) but poor specificity, as shown in Table 7.8. The high sensitivity provides opportunities for cost savings by excluding patients who do not need a BMD assessment. In one study, it was estimated that approximately 55% of BMD tests would be saved, compared with 100% BMD testing with mass screening *(73)*. The low specificity indicates that BMD tests should be undertaken in people who are categorized a priori as being at high risk.

Table 7.8

Risk assessment tools for the prediction of osteoporosis

Acronym	Age	Weight	Prior fracture	Estrogen status	Other	Sensitivity (%)	Specificity (%)	AUC (%)
ABONE	+	+		+		83	48	72
DOEScore	+	+	+		RA	82	52	
HAQ	+	+			Glucorticoids	84	44	
NOF	+		+		Family history	96	18	70
ORAI	+	+		+		90	42	64–79
OSIRIS	+	+	+	+		78	58	69–82
OST(A)	+	+				92	39	69–84
POST	+	+	+		Family history, years since menopause	100	29	75–87
SCORE	+	+	+	+	RA	91	31	65–79
SOFSURF	+	+	+		Smoking	86	36	54–79

AUC, area under the receiver operating characteristics curve; ABONE, age, bone size, no estrogen (62); +, risk factor included; DOEScore, Dubbo osteoporosis epidemiology study score (64); RA, rheumatoid arthritis; HAQ, health assessment questionnaire (specific for patients with rheumatoid arthritis) (63); NOF, National Osteoporosis Foundation (United States) (53); ORAI, osteoporosis risk assessment instrument (60); OSIRIS, osteoporosis risk index (61); OST(A), osteoporosis self-assessment tool (for Asians) (59); POST, postmenopausal osteoporosis screening tool (65); SCORE, simple calculated osteoporosis risk estimation (58); SOFSURF, Study of Osteoporotic Fractures simple, useful risk factors system (78).

Few studies are reported in men *(61,66,74)*. The performance characteristics of OST for the prediction of osteoporosis have been examined in the cohorts used for meta-analyses of risk factors, as described in section 5. Sensitivity was higher in women, at 83% (95% CI = 81%–84%), than in men, at 58% (53%–64%). Conversely, specificity was higher in men, at 85% (95% CI 84%–86%), than in women, at 63% (95% CI = 62%–64%), because of the higher BMD in men.

There is, however, marked heterogeneity in both sensitivity and specificity. Sensitivity varied in women from 66% to 96%, and in men from 50% to 91% (Table 7.9). Where sensitivity was higher, specificity was lower, reinforcing a view that these instruments require calibration for different geographic settings *(77)*.

Table 7.9

Sensitivity and specificity of osteoporosis self-assessment tool in the prediction of osteoporosis in population-based cohorts

	Sensitivity (%)		Specificity (%)	
Cohort[a]	Men	Women	Men	Women
EVOS/EPOS	51	66	89	76
CaMos	58	77	91	75
Rotterdam	50	74	85	72
DOES	70	87	81	52
Rochester	55	90	88	78
Hiroshima	91	96	53	27
Sheffield	-	96	-	21

[a]For cohort descriptions see section 5.

-, no data.

The question arises whether OST might be used for the prediction of fracture rather than the prediction of osteoporosis, and this is discussed below.

7.4 Prediction of fracture

Other researchers have targeted fractures as the outcome of importance. In these schemes, BMD becomes just one of the predictor variables *(55,79)*. This approach has the dual virtues of using easily obtained clinical risk factors (e.g. age, sex and weight, and personal fracture history) to estimate risk before resorting to the added expense of a bone density determination, as well as using all of this information to predict the outcome (fracture) of clinical importance.

The performance characteristics of OST have been tested in the population-based cohorts reviewed in section 5 that include men as well as women. A score for OST <-1 was associated with a significant increase in fracture risk. Risk ratios were higher for hip fracture than for osteoporotic or any fracture, and there were no significant differences between men and women (Table 7.10). When OST was considered as a continuous variable, the risk of any fracture decreased by 3% for each unit increase in OST (95% CI = 2%–4%). For osteoporotic fracture, the decrease was by 4% (95% CI = 3%–6%); for hip fracture, the decrease was by 13% (95% CI = 10%–16%).

Table 7.10

Risk ratios for fracture in men and women with a positive or negative test result from the osteoporosis self-assessment tool

Outcome fracture	Sex	Risk ratio	95% confidence interval
Any fracture	Males	1.40	1.15_1.69
	Females	1.17	1.08_1.28
	Combined	1.21	1.12_1.31
Osteoporotic fractures	Males	1.41	1.14_1.75
	Females	1.23	1.11_1.36
	Combined	1.26	1.15_1.38
Hip fractures	Males	1.54	1.06_2.21
	Females	1.61	1.27_2.06
	Combined	1.59	1.30_1.94

Two large population-based studies, one in Europe and one in North America, provide useful illustrations of how variables can be combined to estimate fracture risk. A cohort of over 5000 women and men aged 55 years and above from a community in the Netherlands *(79)* was evaluated from 1990 to 1993, and then followed over a four-year period for the occurrence of hip fracture. Ten factors assessed at entry were associated with subsequent hip fracture. Significant independent contributors to fracture risk included age, sex, height, use of an aid for walking, and current cigarette smoking. In addition, nine categories of BMD were included. A score was devised from the estimates of the beta coefficients for these variables. Within the Dutch population on which the scoring system was devised, subjects' scores ranged from 6 to 103, with a median value of 43. Those with a score of less than 50 had only a one in 1000 chance of sustaining a hip fracture over a four-year interval. This risk increased 100-fold for those with scores of 75 or higher, in whom the risk of hip fracture was 10%.

In developing their prediction scheme, the investigators also created a set of scores that excluded bone mineral density. When BMD was excluded, model variables remained the same with the addition of weight as an independent contributor. Performance of the two models (with and without BMD) was similar, with an area under the ROC curve of 88%. The model has not been tested prospectively.

Data from the Study of Osteoporotic Fractures, based in the United States, included a subset in which hip DXA measurements were available. This subset was used to produce a multi-variable derived prediction model *(55)*. Twenty potential risk factors were included in the modelling, both including and excluding BMD determinations of the total hip. Like the Dutch models, age, weight and cigarette smoking appeared as independent risk factors, as did an indicator of physical condition, in this instance "using arms to stand from a chair" instead of "using a walking aid". Significant additions to the SOF model were a history of maternal hip fracture after the age of 50 years

and a history of a prior fracture in adult life.

Scores derived from the model showed good discrimination for fracture risk. Subjects with scores in the lowest quintile had a five-year risk of hip fracture of 0.6% compared with about a 14-fold increased risk of 8.2% for those with scores in the highest quintile without BMD. The gradient of risk can be computed at 2.52/SD change in risk score, assuming a normal distribution of risk score (Table 7.11). Good separation for those at high and low risk of vertebral fracture was also demonstrated (Table 7.11). Gradients of risk were lower for non-vertebral fractures, there being about a 3-fold difference in risk between the highest and lowest quartile for risk score (gradient of risk = 1.39 and 1.51 without or with BMD, respectively). As with the Dutch models, adding BMD values to the models derived from clinical variables alone improved performance, although not markedly.

Table 7.11

Five-year fracture risk by quintiles of risk in 9704 women from the United States, according to risk score

Fracture outcome	I	II	III	IV	V	Gradient of risk[a]
Without BMD						
Hip	0.6	1.4	2.1	3.2	8.2	2.52
Non-vertebral	10.5	12.5	16.4	18.7	26.1	1.39
Vertebral	1.4	2.9	5.1	7.0	9.9	2.00
With BMD						
Hip	0.4	0.9	1.9	3.9	8.7	2.95
Non-vertebral	8.6	13.1	16.5	19.8	27.5	1.51
Vertebral	1.2	2.5	5.3	7.1	11.2	2.21

Source: reference 55 (data taken from Figures 1 and 2).

[a]Gradients of fracture risk per SD change in risk score assuming a normal distribution of risk score.

A particular strength of the SOF study is the partial validation of the instrument in a different population. The scoring system was applied to 6600 women aged 75 years and older from five regions in France who were participants in a hip fracture follow-up study (the EPIDOS study). Although this group was on average 10 years older than SOF participants, the models, both with and without BMD, showed good discrimination with 23-fold and 6-fold increases in estimated hip fracture risk, respectively, between lowest and highest quintiles, though the absolute risk differed between cohorts (55).

Other studies that have combined risk factors have identified more than 20 characteristics that predict increased fracture risk in multivariate models *(79–92)* (Table 7.12). These include activities of daily living (ADLs), impaired cognition, propensity to fall, poor overall health status, history of stroke, seizure disorder, and several different medications; BMD has not been included. In four of five of these studies, the risk of fracture has been shown to increase progressively with the number of risk factors. Data from the Duke

Established Population for Epidemiologic Studies of the Elderly in the United States *(88)* showed an approximate doubling in relative risk as each of nine factors was summed, so that the presence of one factor carries a risk of 1.8 and four factors a risk of almost 10. Findings from the General Practice Research Database in the United Kingdom *(89)* indicated that the presence of three or more of 11 medical risk factors (diagnoses and medications) was associated with an 8-fold increase in risk of vertebral fracture and 4.6-fold increase in hip fracture risk when compared to women with none of the attributes.

Table 7.12

Studies of risk assessment for the prediction of fractures

			Risk factors						
Cohort	Site	Author	Age	BMD	Family history	Prior fracture	Weight	Smoking	Other
OFELY	France	Albrand et al. (80)	+	+	+[a]	+			Physical exercise, grip strength
SOF	USA	Black et al. (55)	+	+	+[a]	+	+	+	Ability to stand from chair,
	USA	Carrol et al. (81)	+	+			+		years since menopause
EPESE	USA	Colon-Emeric, Pieper & Artz (88)	+				+[b]		Stroke, cognitive impairment
									Rosow-Breslau, impairment
EPIDOS	France	Dargent-Molina et al. (82)	+						Tandem walk, gait speed,
									visual acuity, history of falls
	USA	Girman et al. (83)	+				+		Height, locomotor status, falls, ADLs, incontinence
OSPRE	Finland	Honkanen et al. (84)				+[c]	+[b]		Dietary calcium, HRT
SOF	USA	Leslie et al. (85)			+	+		+	Health status, hyperparathyroidism, mobility, falls, maximum height, height loss, ability to stand from chair
MOF	UK	McGrother et al. (91)	+				+		Kyphosis, poor circulation, corticosteroids, health status, epilepsy
NORA	USA	Miller et al. (86)	+		+				Health status, mobility
GPRD	UK	van Staa, Leufkens & Cooper (89)	+						Disease history, drug history
	USA	Westfall et al. (87)							Glucocorticoids, medical history
Rotterdam	Holland	Burger et al. (79)	+	+	-	-	+[d]	+	Height, walking aid
GPRD[e]	UK	van Staa et al. (90)	+	-	-	+	+[b]	+	Sex, falls, drug and disease history

OFELY, L'os des femmes de Lyon; SOF, Study of Osteoporotic Fractures; EPESE Epidemiology study of the elderly; EPIDOS, Epidémiologie de l'osteoporose; OSPRE, Osteoporosis Risk Factor and Prevention Study; MOF, Melton osteoporosis fracture index; NORA, National Osteoporosis Risk Assessment (United States); GPRD, General Practice Research Database (United Kingdom); ADL, activity of daily living; HRT, hormone replacement therapy.

[a]Maternal history. [b]Body mass index. [c]Forearm fracture. [d]Weight excluded with bone mineral density in the model. [e]For patients on glucocorticoids.

A recent study examined the likelihood of fracture in a cohort of more than 57 000 women using a regression tree analysis based on peripheral densitometry, self-rated health status and mobility *(86)*. The test had moderate specificity (46%) and sensitivity (77%) but, as expected, the positive predictive value (the probability that a woman with a positive test would develop a fracture) was low (2.9%) as was the likelihood ratio *(1.42)*, i.e. how much more likely was a positive test to be found in a woman with the disease, than in a woman without the disease.

A limitation of many of these studies is that, with the exception of the Study of Osteoporotic Fractures *(55)* and one of the general practice research database studies *(90)*, they have not been tested in other cohorts. Moreover, several are case-control studies, and many of the risk factors used may not identify a risk amenable to pharmacological intervention. For example, risk factors for falling may identify a risk that is not responsive to treatment with bone-specific agents *(93)*. This concern is greatest in models that omit BMD (see Table 7.11) because anti-resorptive agents may not be equally effective across the entire range of BMD (94).

7.5 WHO fracture assessment tool (FRAX)

The series of meta-analyses reviewed in section 5 identified several clinical risk factors that might be used for assessing fracture risk. These included body mass index as a continuous variable, as well as dichotomous variables comprising a parental history of hip fracture, a prior fragility fracture, current smoking, exposure to oral glucocorticoids, rheumatoid arthritis and the consumption of more than two units of alcohol daily. The risk factors in general had low to moderate heterogeneity between cohorts and fulfilled, in so far as possible, levels of evidence for validity and for identifying "reversible risk", as described in section 5. Each of the risk factors was examined for interactions with sex, age, BMD and the variable itself. An example of the latter interaction was the different significance of a unit change in BMI at high or low values. Before such risk factors can be used for fracture prediction, their independent contribution requires to be assessed. But with the exception of BMI, all risk factors were associated with fracture risk independently of BMD.

7.5.1 Approach to model building

Four models were constructed from the risk factor analysis to compute fracture probabilities. These comprised the probability of hip fracture, with and without BMD, and the probability of other osteoporotic fractures, with and without BMD. The two cohorts from Gothenburg were not used in the models with BMD, since BMD was not measured at the femoral neck in those studies. For each model, fracture and death as continuous hazard functions were computed using a Poisson regression, as described in section 6 *(95,96)*. For each risk factor, all significant interactions that were identified

by meta-analysis were entered in the model (with age, time, sex and the risk factor), with and without BMD. Interactions that were significant for hip fracture risk were also entered in the model for other osteoporotic fractures, and also included in the model for death. Where interactions noted in the "mega-analyses" were no longer significant for hip fracture and other osteoporotic fractures, these were omitted in a stepwise manner by dropping the interaction with the largest p value. Take, for example, the interaction of BMD and age for hip fracture risk: hip fracture risk prediction was significantly higher with BMD at younger ages and the higher predictive values persisted when entered in the model. The respective b functions for the interaction (BMD · current age) were retained in both the model for hip fracture and other osteoporotic fracture, though this fell short of significance in the model for other osteoporotic fractures (p=0.074). Conversely, for BMI, a significant interaction was noted with age in the meta-analysis (an increase in risk ratio of BMI for osteoporotic fracture with age), but this was no longer significant in any model, and the interaction term was dropped from the hazard functions for fracture. The other interactions shown in Table 7.13 that were retained were: (age · sex), (BMD · age); (BMD · BMD); (prior fracture · age); (BMI · BMI); and (age · age). For the death hazard, all significant interactions for fracture risk were included and thereafter omitted if appropriate in a stepwise manner, as described for the fracture hazard.

Table 7.13

Significance of interactions with risk factors for hip fracture, any osteoporotic fracture, and osteoporotic fracture excluding hip fracture

	BMD	Age	Variable	Sex	Time
Hip fracture					
BMI	-	-	++	-	++
Prior fracture	-	++	na	-	-
Age	++	++	++	-	++
Corticosteroids	-	-	na	-	-
Family history	-	-	na	-	-
Smoking	-	-	na	-	-
Rheumatoid arthritis	-	-	na	-	-
BMD	-	++	-	-	-
Alcohol	-	-	na	-	-
Osteoporotic fracture					
BMI	-	++	-	-	+
Prior fracture	-	+	na	-	+
Age	++	-	-	++	-
Corticosteroids	+	+	na	-	-
Family history	-	+	na	-	+
Smoking	-	-	na	-	-
Rheumatoid arthritis	-	-	na	-	-
BMD	++	++	++	-	-
Alcohol	-	-	na	-	+
Osteoporotic fracture without hip fracture					
BMI	-	++	-	-	-
Prior fracture	-	-	na	-	-
Age	++	na	-	++	-
Corticosteroids	-	-	na	-	+
Family history	-	++	na	-	-
Smoking	-	-	na	-	-
Rheumatoid arthritis	++	-	na	-	-
BMD	++	++	++	-	-
Alcohol	-	-	na	-	-

BMD, bone mineral density; BMI, body mass index; -, no effect ($p>0.1$); +, denotes a trend ($p>0.05$; $p<0.1$); ++, a significant interaction ($p<0.05$); na, not applicable.

Complete information from all cohorts used in the model was available for the continuous variables (BMI and BMD). Not all cohorts had complete information on all the dichotomous risk factors (see section 5). For example, a history of smoking was not available from CaMos and Rochester. When one dichotomous variable (e.g. smoking) was deleted from the model, this had a very minor effect on the b coefficients for the other variables. Since these deletions had little or no effect, the original b coefficients were used.

The risk factors used comprise:

- age
- sex
- body mass index
- a prior fragility fracture (including a morphometric vertebral fracture)

- parental history of hip fracture
- current tobacco smoking
- ever long-term use of oral glucocorticoids
- daily consumption of alcohol of >2 units
- rheumatoid arthritis.

In addition to rheumatoid arthritis, provision was made for the inclusion of other secondary causes of osteoporosis. Of the secondary causes of osteoporosis reviewed in section 4, the following have been consistently documented to be associated with a significant increase in fracture risk:

- untreated hypogonadism in men and women, e.g. bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism *(97–104)*;
- inflammatory bowel disease, e.g. Crohn disease and ulcerative colitis *(105–107)*; the risk is in part dependent on the use of glucocorticoids, but an independent risk remains after adjustment for glucocorticoid exposure *(108)*;
- prolonged immobility, e.g. spinal cord injury, Parkinson disease, stroke, muscular dystrophy, ankylosing spondylitis *(109–115)*;
- organ transplantation *(41,116–118)*;
- type I diabetes *(119–122)*;
- thyroid disorders, e.g. untreated hyperthyroidism, over-treated hypothyroidism *(123–125)*.

Whereas there is strong evidence for the association of these disorders with fracture risk, the independence of these risk factors from BMD is uncertain. It was conservatively assumed, therefore, that the fracture risk was mediated via low BMD but, in the absence of data on BMD, the risk ratio assumed for these other secondary causes was similar to that noted in rheumatoid arthritis.

7.5.2 Performance characteristics

The performance characteristics of the models, given the name of the FRAX™ tool, are shown in Table 7.14 expressed as gradients of risk per SD change in risk indicator. Note that the category of other osteoporotic fracture excludes hip fracture, whereas hip fracture was included in the meta-analyses in section 5 under the term "any osteoporotic fracture".

Table 7.14

Gradients of risk per SD change in risk score with the use of bone mineral density (BMD), clinical risk factors or BMD and clinical risk factors combined

	Gradient of risk		
Age	BMD only	Clinical risk factors alone	Clinical risk factors + BMD
Hip fracture			
50	3.68 (2.61-5.19)	2.05 (1.58-2.65)	4.23 (3.12-5.73)
60	3.07 (2.42-3.89)	1.95 (1.63-2.33)	3.51 (2.85-4.33)
70	2.78 (2.39-3.23)	1.84 (1.65-2.05)	2.91 (2.56-3.31)
80	2.28 (2.09-2.50)	1.75 (1.62-1.90)	2.42 (2.18-2.69)
90	1.70 (1.50-1.93)	1.66 (1.47-1.87)	2.02 (1.71-2.38)
Other osteoporotic fractures			
50	1.19(1.05-1.34)	1.41 (1.28-1.56)	1.44 (1.30-1.59)
60	1.28 (1.18-1.39)	1.48 (1.39-1.58)	1.52 (1.42-1.62)
70	1.39 (1.30-1.48)	1.55 1.48-1.62)	1.61 (1.54-1.68)
80	1.54 (1.44-1.65)	1.63 (1.54-1.72)	1.71 (1.62-1.80)
90	1.56 (1.40-1.75)	1.72 (1.58-1.88)	1.81 (1.67-1.97)

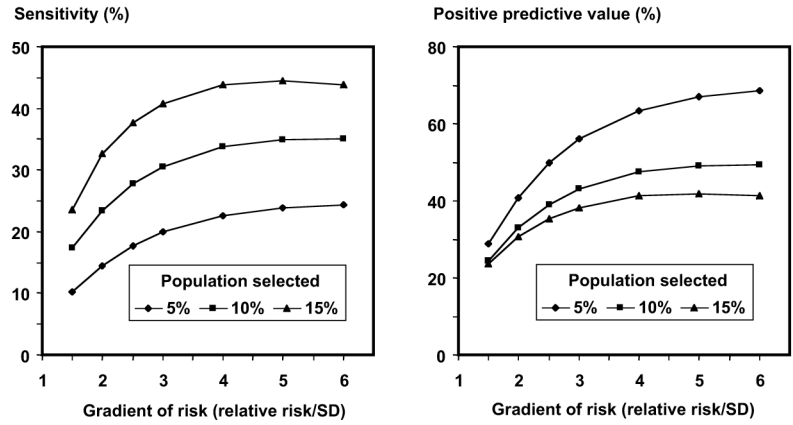
For hip fracture prediction, BMD outperformed the clinical risk factors alone, but in combination there was an increment in the gradient of risk. For example, hip fracture risk increased by 3.68 per SD decrease in femoral neck BMD at the age of 50 years, and by 2.05 with the use of clinical risk factors, but their combined use gave a gradient of risk of 4.23. For the prediction of other osteoporotic fractures, gradients of risk with BMD were, as expected, lower than for the prediction of hip fracture. Gradients of risk varied from 1.26 to 1.52 depending on age and tended to increase with age, in contrast to the prediction of hip fracture. When clinical risk factors alone were used, the gradient of risk also increased with age and, unlike for hip fracture prediction, the use of clinical risk factors out-performed BMD. As in the case of hip fracture prediction, however, there was an increment in gradient of risk when the clinical risk factors were used in combination with BMD.

The increment in gradient of risk using BMD alone and in conjunction with clinical risk factors is more substantial in the case of hip fracture prediction than for the prediction of other osteoporotic fractures. It should be recognized, however, that gradients of risk are not multiplicative. For example, at the age of 50 years (see Table 7.14) BMD alone gave a gradient of risk of 1.19 for osteoporotic fractures excluding hip fracture. For the clinical risk factors the gradient of risk was 1.41. If these two tests were totally independent the combined gradient of risk would be $\surd (1.192 + 1.412) = 1.85$. The observed gradient of risk (1.44) falls short of the theoretical upper limit since there was a significant correlation between the clinical risk factor score and BMD ($r = 0.10$). The increment in gradient of risk for hip fracture prediction was larger, but there was also a significant correlation between risk factor score using the clinical risk factors and BMD alone ($r = 0.25$).

As discussed in section 7.1, increasing gradients of risk improve sensitivity and positive predictive value without markedly affecting specificity. The relationship between sensitivity and positive predictive value and gradient of risk is shown in Fig. 7.1. It is of interest that modest increases in the gradient of risk have a marked impact on both sensitivity and positive predictive value, but that the gains are proportionately less above gradients of risk of 3 SD or 4/SD. As mentioned in section 6, there is a mathematical relationship between gradient of risk and area under the ROC curve. From Table 7.14, for example, the gradient of risk of 4.23 is equivalent to an area under the ROC curve of 84%. At the other extreme, a gradient of risk of 1.44 is equivalent to an area under the ROC curve of 60%. An area equivalent to 50% indicates a predictive value no better than chance.

Fig. 7.1

The effects of different gradients of risk on sensitivity (%) and positive predictive value (%) in women aged 65 years, by the proportion of the population selected



Source: reference 12 (data drawn from Table 3).

7.5.3 Calibration

The hazard functions of fracture and death are applied to specific populations where fracture risks and mortality can be established. This assumes that the relative importance of the risk factors and their interactions are the same as in the original material. Algorithms were developed for regions of the world using epidemiological information for index countries, based on average 10-year hip fracture probability. Regions were categorized as follows:

(a) very high risk (e.g. Denmark, Iceland, Norway, *Sweden, United States*);

(b) high risk (e.g. Australia, Canada, China (Province of Taiwan), Finland, Germany, Greece, Hungary, Italy, Kuwait, Netherlands, Portugal, Singapore, Switzerland, *United Kingdom*);

(c) moderate risk (e.g. Argentina, *China, France*, Hungary, China (Hong Kong Special Administrative Region), *Japan, Spain*);

(d) low risk (e.g. Cameroon, Chile, Republic of Korea, *Turkey*, Venezuela).

The italics indicate the index countries used in the calculations. For all countries, the risk of death was taken from United Nations estimates for 1999, except for the United States where the National Vital Statistics reports were used for 2001 *(126)*. The United Kingdom model used fracture data from Singer et al. *(127)*, except for clinical vertebral fracture where incidence was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture would be similar to that in Sweden *(128)*. For Sweden and Caucasians in the United States, complete information on fracture incidence was available *(129,130)*.

For Japan, the incidence of forearm and proximal humerus fracture was taken from Hagino et al. *(131)*. For hip fracture, a nationwide survey for 2002 was used (H. Orimo, personal communication, 2005). In the case of vertebral fractures, the data in the Hiroshima cohort were analysed to provide the incidence of morphometric vertebral deformities. This gave comparable estimates with an earlier survey *(132)*. It was assumed that the ratio of clinically evident to clinically silent fractures was the same in Japan as in Sweden.

For China, Spain, Turkey and ethnic minorities in the United States, it was assumed that the ratio of hip fracture to other fracture types was similar to that observed in Australia, Sweden, the United Kingdom and the United States. The adequacy of this assumption is discussed in section 2. For Spain, the average incidence of hip fracture from Barcelona (1984), the Canary Islands (1996), Seville (1989), Madrid (1989) and Zamora (1991) was used as reported by Kanis et al. *(133)*. For China, mean incidence was taken from two surveys in Beijing (1988–1992) and surveys in Sanyang (1994) and Tangshan (1994) from the same source *(133)*. For Turkey, the survey in Istanbul was used (1988–1989). For ethnic minorities (black, Asian and Hispanic), ratios of hip fracture rates to those of the Caucasian population were computed for men and women separately and a mean value used (L.J. Melton, personal communication, 2005). For blacks, the ratios in men and women were 0.53 and 0.43, respectively *(134–140)*; for Asians, the respective rates were 0.64 and 0.50 *(135,140,141)*; and for Hispanics, 0.58 and 0.53 *(134,135,139,140)*.

7.5.4 Input and output variables

The index country is selected from the FRAX tool and individual subject details are input. These comprise age (41 to 87 years), sex, weight (in kg) and height (in cm). BMI is automatically computed from height and weight

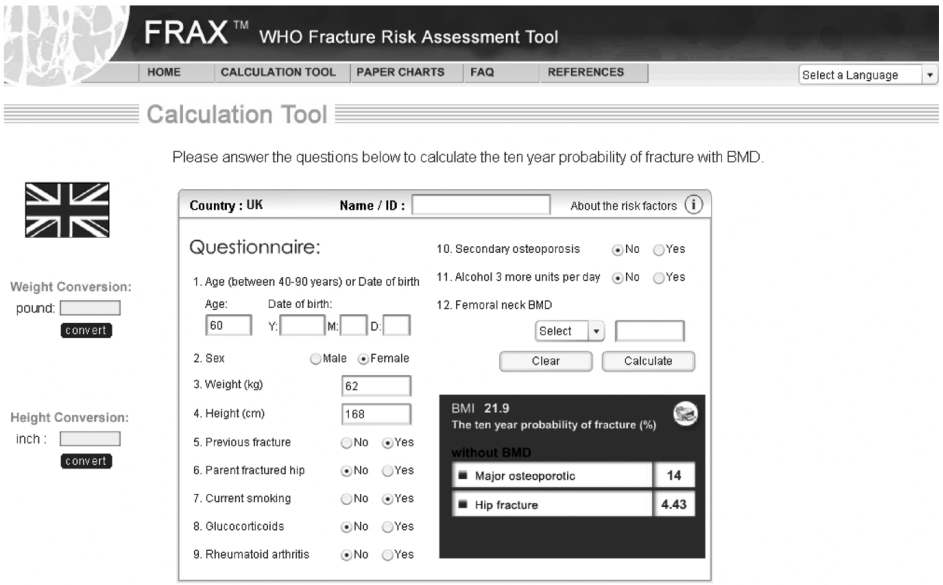
(kg/m^2). Dichotomized risk variables are then entered:

- a prior fragility fracture including morphometric vertebral fractures (yes/no)
- parental history of hip fracture (yes/no)
- current tobacco smoking (yes/no)
- ever long-term use of oral glucocorticoids (yes/no)
- rheumatoid arthritis (yes/no)
- other causes of secondary osteoporosis (yes/no)
- daily alcohol consumption of >2 units daily (yes/no).

If any of the fields for dichotomous variables is not completed, a negative response is assumed. Fracture probability can then be calculated. The output (without BMD) comprises the 10-year probability of hip, clinical spine, shoulder or wrist fracture and the 10-year probability of hip fracture (Fig. 7.2). It should be noted that the probability of all osteoporotic fractures is not given, but is limited to the major sites of fracture. Inclusion of other sites such as the ribs, pelvis and other femoral fractures would increase the probabilities computed. The omission can be rectified when adequate epidemiological data become available for the index countries.

Fig. 7.2

Screen showing the input and output of the fracture risk assessment model for the United Kingdom



Femoral neck BMD can additionally be entered either as a Z-score or a T-score. The method of transforming Z-score to T-score is based on the NHANES III reference values as described in section 2. It should be noted that computation of the T-score (T) from the Z- score (Z) does not assume a linear relationship between the two variables. The relationship derived from NHANES III is given as

$T = c^0 + c^1 \cdot Z + c^2 \cdot age + c^3 \cdot Z \cdot age$

The constants (c^0–c^3) in women below the age of 55 years are 0.892, 0.984, -0.034 and 0.0007 and in women aged 55 years or more are 1.6617, 1.2658, -0.0480 and -0.0044, respectively.

When entered, calculations give the 10-year probabilities as defined above, with or without the inclusion of BMD.

A special situation pertains to rheumatoid arthritis and other secondary causes of osteoporosis. As reviewed in section 5, there is good evidence that rheumatoid arthritis carries a fracture risk over and above that provided by BMD. Whereas this may hold true for other secondary causes of osteoporosis, the evidence base is weak. From an operational point of view, where the field for rheumatoid arthritis is entered as "yes", a risk is computed with and without BMD. If the field for other secondary osteoporosis is also filled as "yes", this does not contribute to the calculation of fracture probability. Conversely, where the field for rheumatoid arthritis is entered as "no", and the field for secondary osteoporosis as "yes", the same b functions as used for rheumatoid arthritis contribute to the computation of probability where BMD is not entered. In the presence of BMD, however, no additional risk is assumed in the presence of secondary osteoporosis, since its independence of BMD is uncertain.

7.5.5 Clinical performance characteristics

Clinical risk factors

The effect of a single risk factor is shown by age in Table 7.15, based on the FRAX tool for Sweden. The BMI is held constant at 24 kg/m^2. As expected, the 10-year probability of fracture increased with age in the absence of any clinical risk factors. Between the age of 50 and 80 years, the probability of a hip, spine, shoulder or forearm fracture increased 6-fold. For hip fracture probability, there was a 33-fold increase between these ages. It should be recognized that the probabilities shown for women without risk factors are lower than the population average, since risk factors are widely prevalent in the general population. The presence of any single risk factor increased fracture probabilities. The effect was moderate for smoking and alcohol, and most marked for glucocorticoid use. Prior fracture was an important risk factor at younger ages.

Table 7.15

Ten-year probability of fracture at the sites shown for a Swedish woman with a body mass index of 24 kg/m2 according to age and the absence or presence of single clinical risk factors[a]

Age (years)	None	Smoking	Alcohol	RA	Gluco-corticoids	FH	Prior fracture
Hip, spine, shoulder or forearm							
50	4.2	4.5	5.1	5.7	6.9	8.2	9.1
60	7.7	8.4	9.4	10.6	12.7	14.4	15.6
70	14.4	16.4	18.1	20.3	23.5	23.0	26.2
80	25.9	29.1	32.8	36.3	38.2	46.8	39.1
Hip							
50	0.4	0.6	0.6	0.7	0.9	0.5	1.6
60	1.3	2.0	2.0	2.3	2.8	1.7	3.8
70	4.7	6.9	7.1	8.2	9.6	9.9	9.8
80	13.1	17.8	19.2	21.8	23.4	37.8	19.6

RA, rheumatoid arthritis; FH, parental family history of hip fracture.

[a]Bone mineral density is not included in the model.

The inclusion of more than one risk factor increased fracture probability in an incremental manner. For example, in a woman from Sweden aged 65 years with a BMI of 24 kg/m^2, the 10-year hip fracture probability in the absence of clinical risk factors was 2.3%. With one clinical risk factor, the probability ranged from 3.1% to 5.7%. With two risk factors, the range was 4.6%–12.0% and with 3, 4 and 5 risk factors the ranges were 7.0%–20.1%, 12.0%–29.0% and 23.6%–39.7%, respectively. In the presence of all six clinical risk factors, the 10-year probability of hip fracture was 48.3%. Examples of the use of the number of risk factors, rather than using the weight of each risk factor, are given later in this section.

Age and BMD

The independent contribution of age is shown in Table 7.16 in men and women from Sweden with a fixed BMI of 24 kg/m^2 at the threshold for osteoporosis (T-score = -2.5 SD). Fracture probabilities increased with decreasing T-scores more markedly in women than in men. The effect was more marked for hip fracture than for hip, shoulder, spine or forearm fractures combined. Between the ages of 50 to 80 years, 10-year fracture probability for spine, forearm and humerus increased 2-fold to 3-fold in women. The increment was greater for hip fracture.

Table 7.16

Ten-year fracture probability (%) in men and women from Sweden with a body mass index of 24kg/m², no clinical risk factors and a T-score of -2.5 SD at the femoral neck

Age	Men		Women	
(years)	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip
50	9.1	4.3	8.2	2.8
55	10.2	4.8	9.8	3.2
60	11.9	5.5	12.5	4.0
65	13.0	6.0	14.9	4.9
70	14.5	7.2	18.2	6.9
75	15.5	8.8	21.3	9.4
80	15.1	8.8	24.1	10.9
85	13.5	7.3	23.6	10.0

[a]Hip, shoulder, spine or forearm fracture.

BMI

Increases in BMI were associated with decreasing fracture risks. As expected, low BMI was no longer an important risk factor when BMD was introduced (Table 7.17).

Table 7.17

Effect of variations in body mass index on 10-year fracture probability in women from Sweden aged 65 years

	Probability of fracture (%)			
BMI	Major osteoporotic fracture[a]		Hip fracture	
(kg/m²)	Without BMD	With BMD[b]	Without BMD	With BMD[b]
16	13.4	13.5	6.1	5.4
18	12.4	14.2	4.8	5.5
20	11.5	15.0	3.8	5.7
22	10.9	15.7	3.0	5.8
24	10.3	16.4	2.3	6.0
26	9.8	16.7	2.0	6.0
28	9.3	16.4	1.8	5.8
30	8.8	16.0	1.6	5.6
32	8.3	15.7	1.5	5.5

BMD, bone mineral density.

[a]Clinical spine, hip, forearm or humerus.

[b]Probabilities with BMD are computed at a T-score of –2.7 SD.

There are several interesting comparisons to be made with the use of BMI and BMD for risk assessment. For example, in Swedish women without clinical risk factors and a BMI of 20 kg/m², the 10-year hip fracture probability ranged from 0.4% at the age of 50 years to 13.3% at the age of 80 years (a 33-fold range). The range was nearly as high with a BMI of 40 kg/m²

(a 29-fold range). At a T-score of –1 SD, the range was 9-fold (0.4% and 3.6% at the ages of 50 and 80 years, respectively). At lower T-scores the range was less. With a T-score of –4 SD, the probabilities of hip fracture ranged from 19.1% to 31.6% at the ages of 50 and 80 years, respectively. Thus, BMD captures age-dependent aspects of risk more completely than BMI. In contrast, the dynamic range of probabilities is greater with the use of BMD than with BMI. For example, with no clinical risk factors, hip fracture probabilities more than doubled for each SD decrease in BMD (Table 7.18). In contrast, for BMI the gradient of risk was much lower (given that the SD of BMI is less than 5 kg/m^2; see Table 7.17).

Table 7.18

Ten-year fracture probability (%) in men and women from Sweden with a body mass index of 24 kg/m^2 and no clinical risk factors, by age and T-score at the femoral neck

	Age (years)							
	50		60		70		80	
T-score (SD)	Males	Females	Males	Females	Males	Females	Males	Females
Spine, forearm or shoulder fracture								
+1	2.9	3.4	3.7	4.9	4.3	6.2	4.8	7.7
0	3.2	3.8	4.3	5.7	5.3	7.7	6.2	10.2
-1	4.3	4.4	5.7	6.8	7.2	9.9	8.3	13.7
-2	6.6	6.4	9.0	9.8	11.3	14.2	12.3	19.4
-3	13.1	11.2	16.2	16.4	18.7	23.7	18.5	30.5
-4	31.2	25.3	32.1	31.1	31.5	41.1	27.5	47.1
Hip fracture								
+1	0.1	<0.1	0.1	0.1	0.4	0.3	1.2	0.8
0	0.2	0.1	0.4	0.2	0.9	0.7	2.1	1.8
-1	0.6	0.4	1.1	0.7	2.1	1.6	3.6	3.7
-2	2.3	1.4	3.2	2.3	4.9	4.2	6.5	7.5
-3	8.0	5.4	9.3	7.1	11.0	11.2	11.7	15.9
-4	26.3	19.1	25.0	21.1	23.5	27.5	20.1	31.7

Sex

Probabilities were comparable in men and women for any given T-score except at the extremes of age and T-score (see Table 7.18). At low T-scores, probabilities were somewhat higher in men than in women at the younger ages. In elderly people, fracture probabilities were higher in women than in men (because of the longer survival in elderly women).

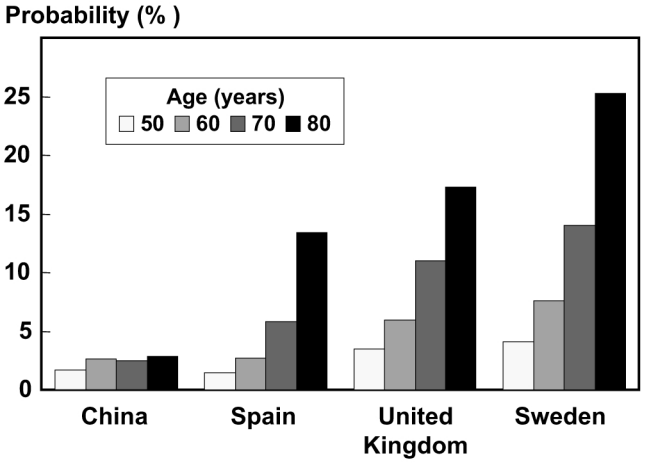
Geographic region

The 10-year probabilities of hip, spine, forearm and clinical vertebral fracture are shown for several index countries by age in Fig. 7.3. As expected, probabilities were lowest for China and increased progressively for Spain, the United Kingdom and Sweden. For any given T-score, probabilities varied by

region in a similar fashion. As expected, regional variations were marked. For example, women aged 65 years with a T-score of –4 SD from China had a lower probability of osteoporotic fracture than women of the same age from Sweden but with a T-score of –2.5 SD (10.9% versus 12.0%, respectively; Fig. 7.4).

Fig. 7.3

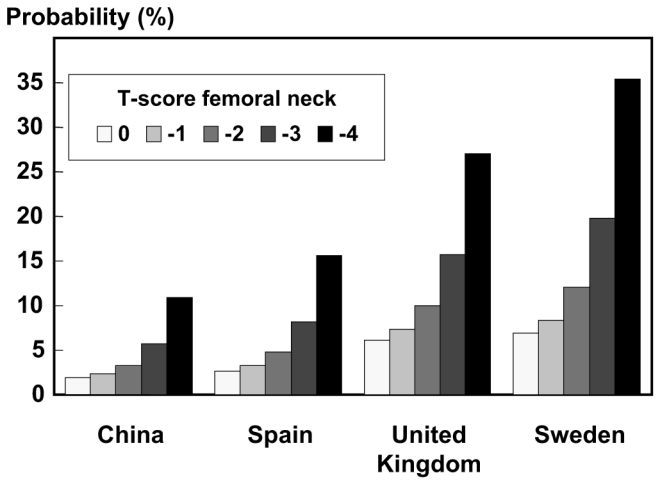
Ten-year probability (%) of hip, forearm, humeral or clinical spine fracture in women according to age and index country[a]



[a]Data shown for a BMI of 25 kg/m^2, in the absence of clinical risk factors or a measurement of BMD.

Fig. 7.4

Ten-year probability (%) of hip, forearm, proximal humeral or clinical spine fracture in women aged 65 years, according to index country and femoral neck T-score[a]



[a]Data shown for women without clinical risk factors and a BMI of 25 kg/m^2.

Other risk factors

For reasons discussed in section 5, it has not been possible to integrate all potentially important risk factors into the FRAX algorithms. Candidates include the biochemical markers of bone turnover, genetic phenotypes, and a wide range of measurements of bone mineral at various sites and using different techniques. The performance characteristics of the latter are commonly given as gradients of fracture risk/SD change in BMD, whereas the others are usually reported as risk ratios. Using tables given as annexes, gradients of risk (Annex 1) or risk ratios (Annex 2) can be converted to fracture probabilities based on the epidemiology of the United Kingdom. An example is provided with BMD at the lumbar spine. Meta-analysis indicates that the risk of osteoporotic fracture is increased 1.5-fold for each SD decrease in BMD (2). Reference to Annex 1, Table A1.1 gives 10-year fracture probabilities for the United Kingdom according to Z-score and gradient of risk. For a man aged 65 years and a Z-score of -2 SD, the 10-year hip fracture probability is 3.9% (see Table A1.1); for a woman it is 7.4% (see Table A1.2).

7.5.6 Simplification of the model

The most sophisticated model (the FRAX tool) has the feasibility to incorporate up to six clinical risk factors, any variation in BMI and to include or exclude BMD at the femoral neck, input either as a T-score or a Z-score. This, however, demands access to computer facilities to carry out the calculations, available at www.shef.ac.uk/FRAX . But there is scope for simplified "paper versions" of the model, also available at the web site above.

Use of all risk factors

As shown in Table 7.19, stratification can be approached using all clinical risk factors by computing the risk for all combinations (26 combinations). In the example provided, any single risk factor gave a 10-year hip fracture probability that ranged from 3.1% to 5.7%. For any two risk factors, the range of probabilities was from 4.6% to 12.0%, and the range of probabilities increases progressively with the number of clinical risk factors. A simplified tool, therefore, will integrate these probabilities, but it also needs to take account of BMD or (in the absence of BMD) of BMI. Annex tables show the relationship between BMD (Annex 3) or BMI (Annex 4) and the number of clinical risk factors, for men and women from the United Kingdom.

Table 7.19

Ten-year fracture probability according to the number of clinical risk factors (CRFs) present in women from Sweden aged 65 years with a body mass index of 24 kg/m² in the absence of a bone mineral density test

Number of CRFs	10-year fracture probability (%)			
	Hip fracture		Osteoporotic fracture[a]	
	Average	Range	Average	Range
0	2.3	-	10.3	-
1	4.2	3.1_5.7	15.8	11.5_20.1
2	7.3	4.6_12.0	23.4	14.5_34.0
3	12.4	7.0_20.1	33.7	20.7_50.2
4	20.4	12.0_29.0	46.6	33.3_62.7
5	32.2	23.6_39.7	61.5	50.5_71.3
6	48.3	-	76.2	-

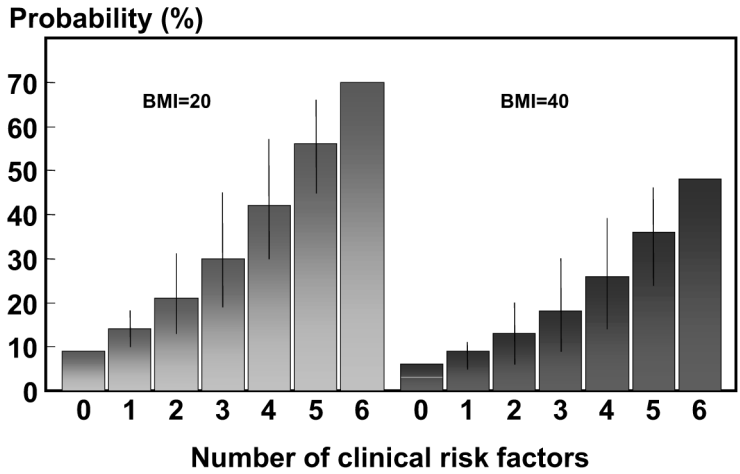
[a]Hip, forearm, shoulder or clinical spine fracture.

-, no range.

Fig. 7.5 shows the mean probabilities for any osteoporotic fracture together with the range according to the number of clinical risk factors at two levels of BMI for women aged 65 years from the United Kingdom. The range of probabilities is, as expected, higher with lower values of BMI. The dispersion around the mean is not an error bar in the traditional sense. Rather, it reflects the range of probabilities arising because the weight of each of the risk factors varies. The computed probabilities for hip fracture or any major osteoporotic fracture for men and for women at different levels of BMI is given in section 9 for men and women from the United Kingdom.

Fig. 7.5

Ten-year fracture probability of spine, hip, forearm and proximal humerus (%),by the number of clinical risk factors present in women from the United Kingdom aged 65 years: mean and range of probabilities are given at two levels of body mass index (BMI)



Selective use of risk factors

More limited numbers of risk factors can readily be used in a paper version of the prediction algorithm. An example is given in Fig. 7.6 for women from the United Kingdom according to age, T-score and selected risk factors. The clinical scenarios are: no risk factors; a prior fragility fracture; the use of oral glucocorticoids; and the combination of glucocorticoids and fracture. Such charts may be of value to rheumatologists. In many regions of the world, orthopaedic surgeons have little access to BMD, and a paper version combining BMI, fracture history and glucocorticoid use may be appropriate. An example based on the United Kingdom is shown in Table 7.20.

Table 7.20

Ten-year probability of a major osteoporotic fracture (hip, spine, forearm or humeral fracture) in men and women from the United Kingdom, by age, body mass index (BMI) and clinical risk factors in the absence of a bone mineral density test

	Men BMI					Women BMI				
Age (years)	15	20	25	30	35	15	20	25	30	35
No risk factors										
50	2.8	2.8	2.7	2.4	2.1	3.9	3.6	3.4	3.0	2.6
60	4.2	4.0	3.9	3.4	2.9	7.4	6.5	6.0	5.2	4.6
70	6.0	5.8	5.6	4.8	4.1	14	12	11	9.5	8.2
80	7.8	7.4	7.2	5.9	4.8	22	19	17	15	12
Prior fracture										
50	6.5	6.0	5.8	5.1	4.4	9.1	7.9	7.3	6.4	5.6
60	9.2	8.4	7.9	6.8	5.9	16	14	12	11	9.2
70	12	11	11	9.1	7.7	26	22	20	18	15
80	12	12	12	9.8	8.1	32	30	28	24	20
Prior fracture and glucocorticoid use										
50	11	9.8	9.3	8.1	7.1	15	13	12	10	9.1
60	14	13	12	11	9.2	26	22	20	17	15
70	16	16	16	13	11	39	34	31	27	24
80	16	16	16	13	11	42	40	39	34	29

Fig. 7.6

Stratification of hip fracture risk by age and T-score in men and women from the United Kingdom[a]

No clinical risk factors

Age	T-score						
	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.1	0.2	0.4	0.8	1.6	3.1	12
60	0.1	0.4	0.8	1.4	2.4	4.3	13
70	0.4	0.9	1.4	2.3	3.8	6.1	16
80	1.0	2.1	3.0	4.2	6.2	9.1	19

Prior fracture

Age	T-score						
	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.1	0.5	0.9	1.7	3.4	6.5	22
60	0.3	0.8	1.4	2.5	4.4	7.7	23
70	0.5	1.4	2.2	3.5	5.8	9.3	23
80	1.3	2.7	3.9	5.6	8.1	12	24

Steroids

Age	T-score						
	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.1	0.4	0.8	1.5	3.0	5.8	21
60	0.3	0.8	1.4	2.5	4.5	7.9	23
70	0.6	1.6	2.5	4.1	6.7	11	26
80	1.7	3.5	5.0	7.1	10	15	29

Steroids and fracture

Age	T-score						
	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.2	0.9	1.7	3.2	6.3	12	39
60	0.5	1.5	2.6	4.5	7.8	14	38
70	1.0	2.5	3.9	6.3	10	16	37
80	2.3	4.6	6.5	9.2	13	19	35

[a]BMI is set at 24 kg/m^2.

When more clinical risk factors are used, paper versions become more cumbersome because of the large number of possible combinations, but up to four clinical risk factors can easily be used when intervention thresholds (i.e. the fracture probability above which intervention should be undertaken) are determined. Intervention thresholds are discussed in section 8.

7.6 External validation

The performance characteristics of the assessment tool were evaluated in eleven independent cohorts that did not participate in the model synthesis. These comprised the Epidémiologie de l'osteoporose (EPIDOS) study in France *(142)*, the Study of Osteoporotic Fractures (SOF) in the United States *(143)*, two cohorts from the Geelong study in Australia *(144,145)*, the Osteoporosis Ultrasound Study (OPUS) study drawn from five European countries *(146)*, the Prospective Epidemiological Risk Factors Study (PERF) from Denmark *(147)*, the York cohort in the United Kingdom (148), the Health Improvement Network (THIN) research database from the United Kingdom *(149)*, the Swiss Evaluation of Measurement of Osteoporotic Fracture Risk (SEMOF) study in Switzerland *(150)*, the Women's Health Initiative (WHI) from the United States *(151,152)* and the Miyama cohort from Japan *(153)*. The characteristics of the cohorts are described in Table 7.21.

Table 7.21

Characteristics of the cohorts used for validation of the risk assessment model

								Other risk factors assessed					
Cohort	Source	Sample size	Follow-up (p years)	Percentage female	Mean age (years)	Hip fractures	osteoporotic fractures	Prior fracture	Glucocorticoids	Parental history	Smoking	Alcohol	RA
THIN	United Kingdom	135 695	606 822	100	60	1 336	4 802	+	+	-	+[a]	+	+
SOF	USA	5 251	57 388	100	71	523	1 313	+	+	+	+	+	+
York	United Kingdom	3 409	5 927	100	77	35	195	+	+	+[b]	+	-	-
Geelong I	Australia	1 173	7 315	100	62	32	143	+	+	+	+	+	+
Geelong II	Australia	1 865	-[c]	100	63	73	443	+	+	+	+	+	+
OPUS	Europe	2 155	4 161	100	67	6	100	+	+	+	+	+	+
PERF	Denmark	5 415	39 096	100	64	58	511	+	-	-	-	-	-
EPIDOS	France	7 435	19 820	100	81	228	642	+	+	+	+	+	-
Miyama	Japan	353	3 173	53	59	7	44	+	+	-	+	+	+
SEMOF	Switzerland	6 721	18 712	100	75	73	581	+	+	+	+	+	-
WHI[d]	USA	61014	439 296	100	66	915	6 250	+	+	+	+	+	+
TOTALS		230 486	1 201 683	100	63	3 286	15 024						

+, data available; -, no data available; RA, rheumatoid arthritis; THIN, The Health Improvement Network (United Kingdom); SOF, Study of Osteoporotic Fractures; OPUS, Osteoporosis Ultrasound Study; PERF, Prospective Epidemiological Risk Factors Study; EPIDOS, Epidémiologie de l'osteoporose; SEMOF, Swiss Evaluation of Measurement of Osteoporotic Fracture Risk; WHI, Women's Health Initiative.

[a]Ever smoking.

[b]Maternal family history.

[c]Case control study.

[d]Excludes women on bone-active treatment.

In all, 230 486 individuals were followed for 1.2 million person–years. As seen in Table 7.21, some of the cohorts had incomplete information on the risk factors assessed in the mega-analysis. Where one or more risk factor was unavailable, the gradient of risk was still computed from the original model but with a b value of zero.

The performance characteristics of the validation cohorts are shown in Table 7.22. Since gradients of risk were age-dependent, these were standardized to the age of 70 years.

Table 7.22

Gradient of risk of original and validation cohorts standardized to the age of 70 years (areas under the receiver operating characteristics curve are shown in parentheses)

	Hip fractures		Other osteoporotic fractures	
Cohort	Without BMD	With BMD	Without BMD	With BMD
Geelong I	1.88 (0.67)	1.71 (0.65)	1.34 (0.58)	1.57 (0.63)
Geelong II	1.50 (0.61)	3.40 (0.81)	1.30 (0.57)	1.54 (0.62)
OPUS	2.48 (0.74)	2.09 (0.70)	1.32 (0.58)	1.38 (0.59)
York	2.05 (0.69)	- (-)	1.74 (0.65)	- (-)
PERF	1.28 (0.57)	2.72 (0.76)	1.14 (0.54)	1.19 (0.55)
SOF	1.58 (0.63)	2.21 (0.71)	1.24 (0.56)	1.31 (0.58)
THIN	1.54 (0.62)	- (-)	1.29 (0.57)	- (-)
EPIDOS	1.70 (0.65)	2.89 (0.77)	1.41 (0.60)	1.47 (0.61)
Miyama	2.87 (0.77)	3.07 (0.79)	3.50 (0.81)	2.80 (0.77)
SEMOF	1.76 (0.65)	2.18 (0.71)	1.32 (0.58)	1.44 (0.60)
WHI	1.54 (0.62)	1.44 (0.74)	1.26 (0.56)	1.46 (0.60)
Original cohorts	1.84 (0.67)	2.91 (0.78)	1.55 (0.62)	1.61 (0.63)

BMD, bone mineral density; OPUS, Osteoporosis Ultrasound Study; PERF, Prospective Epidemiological Risk Factors Study; SOF, Study of Osteoporotic Fractures; THIN, The Health Improvement Network (United Kingdom); EPIDOS, Epidémiologie de l'osteoporose; SEMOF, Swiss Evaluation of Measurement of Osteoporotic Fracture Risk; WHI, Women's Health Initiative.

In all the validation cohorts, the use of clinical risk factors alone or in combination with BMD gave gradients of fracture risk that differed significantly from unity. Thus, the use of clinical risk factors alone provided some discriminative value in the categorization of fracture risk. With one exception (the small cohort from Miyama), the addition of BMD improved the performance characteristics as judged by the gradient of risk or area under the receiver operating characteristics curve.

As found in the source cohorts, the improvement in performance characteristics with the addition of BMD to the clinical risk factors was more marked for hip fracture prediction than for the prediction of other osteoporotic fractures.

Gradients of risk and area under the ROC curve (AUC) were in general comparable to the original cohorts used for model building. For example, for hip fracture prediction without BMD, the mean AUC was 0.66 in the validation cohorts compared with 0.67 in the original cohorts. With the addition of BMD, the mean AUC was 0.74 and 0.78 in the validation and original cohorts, respectively.

In the case of other osteoporotic fractures, the mean AUC was 0.60 in the validation cohorts and 0.62 in the original cohorts, excluding BMD. With the addition of BMD, the average AUC was 0.62 and 0.63, respectively. These

data give some credence to the view that the original algorithms may be widely applicable, though further validation is required in men and in ethnic groups not covered in these analyses. Despite the general applicability of the assessment tool in different population-based settings, there are several additional aspects that would add to its validation *(154)*. These include studies of the feasibility of implementing an assessment tool, and an evaluation of the risks and benefits, preferably by randomized controlled trials.

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8. Intervention thresholds

The development of assessment algorithms to categorize fracture probability is limited if guidance is not given to delineate the probability at which intervention becomes acceptable. A component of the logic in deriving an intervention threshold relates to the efficacy and side-effects of intervention. An effective treatment with no side-effects can reasonably be given to individuals with a low probability of fracture, even if efficacy is moderate. The same treatment, but with significant side-effects affecting a substantial proportion of the population exposed, would demand that patients have a much higher fracture probability so that fewer who would not fracture would be exposed to such treatment. A second consideration is the costs involved, particularly where health-care budgets are restricted. A very expensive treatment, even if effective, may not be considered worthwhile if the disorder treated is not life-threatening or occasions only minor morbidity. For this reason, intervention thresholds are usually also based on health economic assessment.

8.1 Types of evaluation

A widely used measure is the "number needed to treat" (NNT) to prevent a fracture. For example, if a treatment reduces the incidence of vertebral fracture from 10% to 5% during the conduct of a trial, then 5 fractures are saved for each 100 patients treated, which gives an NNT of 20. There are several limitations in the use of NNT. First, it takes no account of the cost of intervention. Second, its use is only relevant to one population setting. In the example above, the effectiveness of the intervention is 50%. If the same efficacy occurs in other populations at different risk, the NNT changes. Thus, if the background fracture risk is say 5% and treatment reduces this by half then the NNT = 40. A further feature of the use of NNT is that it takes no account of the offset of effect of therapeutic intervention (1).

In the context of treatments, the most straightforward pharmacoeconomic evaluation is cost-minimization analysis. This approach can be used when two strategies or interventions have identical effects, for example where both agents decrease fracture rates by a fixed percentage, and neither have adverse effects. The advantage of one over the other will then relate only to differences in cost.

In practice, the benefits and risks of different strategies are rarely equal. Cost-effectiveness analyses take this into account. In this approach, outcomes are converted into a common currency. Examples include the cost per life-year saved, and the cost per fracture averted. A limitation of this approach is that comparisons across diseases are difficult, and difficulties can also arise within the same disease area. The cost per fracture averted has, for example, a different significance where the outcome is a hip fracture rather than a forearm fracture.

These considerations have led to the use of cost_utility analysis. In the context of evaluating treatment strategies, this approach takes account, not only of fractures avoided, but also of any change in morbidity from both beneficial and unwanted effects. Quality-adjusted life years (QALYs) are the accepted unit of measurement in health economic assessment of interventions using cost_utility analysis. In order to estimate QALYs, each year of life is valued according to its utility to the patient. Values range from 0, the least desirable health state, to 1, perfect health. The decrement in utility associated with fractures is the cumulative loss of utility over time. A comparable approach favoured by WHO is the use of disability-adjusted life years (DALYs). This has been extensively used to characterize the burden of disease worldwide (2) and is reviewed in section 2.

8.2 Selection of intervention thresholds

The intervention threshold can be defined as the level of costs (including avoided costs from fracture) and effects that an intervention must achieve to be acceptable to a given health-care system. Both costs and effects depend critically upon the payer, which may variously be society as a whole (the societal perspective), managed health-care systems, hospitals, pharmacies or individuals. For this reason, several types of costs are used in socioeconomics. Direct costs describe the consumption of resources, which may also be applied from a number of perspectives. For example, the direct hospital costs will differ from the direct health-care costs, which in turn will differ from direct non-medical costs such as transport of patients to and from hospitals and the costs to the patient of buying medication. Indirect costs are those associated with the loss of income generation, for example as a result of the time off work following a fracture. These costs are not confined, however, to the patient. For some fractures, the impact on carers and the household in general is not negligible. Intangible costs are by definition those

that are difficult to quantify in monetary units. In the context of osteoporosis they cover largely the morbidity associated with osteoporotic fractures.

The majority of health economic analyses have considered direct costs to the health service. The threshold of cost–effectiveness that has been recommended by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom is £30 000 per QALY gained *(3)*. Somewhat lower thresholds have also been used *(4–6)* but are comparable to thresholds used more recently *(7–10)*. The threshold is relevant for direct costs only. When taking a societal perspective, the additional cost of added years of life as a result of treatment should be included *(6,11,12)*. The effect of adding these costs is to decrease the fracture probability at which treatment becomes cost effective at the age of 50 years, because of the earning capacity of younger individuals. In elderly people, the reverse pertains – namely that the threshold probability would be lower when costs of added years are excluded because of a lower earning capacity. Thus, the effect of not adding future costs biases cost–effectiveness in favour of interventions directed at the elderly people, and conversely discriminates against young people. For this reason, the threshold value for cost–effectiveness might be adjusted upwards for elderly patients where future costs of added years of life are included *(12)*. Their inclusion is not, however, favoured by health-care purchasers, who are more concerned about costs to the health service.

In the context of osteoporosis and fracture risk, the intervention threshold that is relevant for clinicians can be defined as the probability of fracture at which intervention becomes cost-effective. In view of the multiple outcomes (i.e. different sites of fracture) this has been expressed as the 10-year probability of hip fracture at which treatment is cost-effective, i.e. using hip fracture as a common denominator to measure the impact of all fracture outcomes.

The most serious osteoporotic fracture in terms of cost to the individual and to health-care agencies is hip fracture. However, intervention thresholds determined on hip fracture risk alone neglect the many other fractures that occur, particularly in younger age groups. Even in elderly people, hip fractures represent less than 50% of all fractures in men and women *(13–15)*. Thus, recommendations that are based on hip fracture alone underestimate considerably the value of treatment to reduce the risk of other fractures *(15,16)*. For this reason, the setting of intervention thresholds in osteoporosis should take account of the multiple outcomes of osteoporosis – namely the different fracture outcomes and their associated morbidity. Several approaches have been used to characterize intervention thresholds of fracture risk that can be justified from a cost–effectiveness perspective *(4,17–19)*. The most recent have been derived for Sweden and the United Kingdom *(19)*, and that for the United Kingdom is described briefly below, by way of an example.

8.3 Intervention thresholds in the United Kingdom

The model used for the United Kingdom was based on a Markov model, with data on fracture risk derived from the population of the United Kingdom. The model has been used in several studies to predict fracture and mortality risks and for cost–effectiveness calculations, and is well validated and calibrated *(1,10,16,18–24)*. In a review of models that assessed the cost–effectiveness of osteoporosis, the model was suggested as a reference standard for the economic evaluation of osteoporosis *(25)*.

For the purposes of illustration, fractures of the spine, rib, pelvis, humerus, forearm, hip and other femoral fractures, tibia and shoulder girdle are considered to be osteoporotic. As described in section 2, fractures at these sites in women are associated with low BMD and increase in incidence with age *(15,26)*. The incidence of hip and forearm fracture in the United Kingdom was taken from Singer et al. *(27)*. Because data on vertebral fracture risk in the United Kingdom are scarce, the incidence of clinical vertebral fracture was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture would be similar to that in Sweden *(7)*. A similar approach was used to assess the risk of other osteoporotic fractures. Clinical vertebral fracture was used rather than all morphometric vertebral fractures. There are, however, relatively small differences in cost-utility between using these two fracture types *(22)*.

8.3.1 Effect of intervention

The wide range of intervention costs and efficacy of agents available for the management of osteoporosis poses problems in setting intervention thresholds, since changes in the assumptions for both have marked effects on cost–effectiveness *(4)*. The most conservative scenario would lead to the most expensive intervention and the lowest efficacy. Conversely, the most exuberant would be to choose the level of risk at which the cheapest intervention had the greatest effectiveness. From a societal perspective, a basket of treatments would be used, with a range of efficacy and costs. Consideration might also be given to major extraskeletal effects of interventions. For example, hormone replacement therapy and raloxifene have extraskeletal risks and benefits which will affect cost–effectiveness, even assuming equal efficacy and price *(22)*.

Although all agents should be evaluated for cost–effectiveness, it becomes impractical to guide treatment on this basis alone. This was an approach used by the National Osteoporosis Foundation *(4)*, which assessed the cost–effectiveness of screening and treating with each agent available in the United States. The National Osteoporosis Foundation came to the conclusion that it was worthwhile to undertake a BMD test to assess risk at a given age when one treatment was envisaged, but at a different age with another treatment. This may be scientifically sound, but is counter-intuitive

to clinical practice, which normally demands assessment of patients first, thereafter a decision whether to treat, and finally the choice of which agent to use. Thus, the choice of intervention comes later in the decision-making process, which can then be tempered by information on cost–effectiveness. There is, however, a need to provide some general guidance on whom to treat, particularly since there are many clinical risk factors that can be used for case-finding.

For the purposes of this illustration, an average treatment effectiveness of 35% on all osteoporotic fractures was chosen, based on a meta-analysis of the effects of bisphosphonates on all fracture types *(19)*. The meta-analysis estimated the efficacy (relative risk reduction) on vertebral, hip and other non-vertebral fractures of 43%, 39% and 19%, respectively, in postmenopausal osteoporosis. When all osteoporotic fractures were considered, a relative risk reduction of 35% was computed from the expected distribution of osteoporotic fractures at each age, the associated utility losses *(28)* and the efficacy estimates given above. The cost of intervention was set at that of the second generation bisphosphonates. The relative risk reduction of 35% for all osteoporotic fractures also approximates the effect of hormone replacement treatment on all fractures *(29)* but is greater than that observed for vitamin D with calcium on hip fracture risk (20%–25%) in elderly institutionalized women *(30)*. The calcitonins and teriparatide are more expensive, but the latter has greater efficacy. Hormone replacement treatment (oral), calcium and vitamin D are less expensive in the United Kingdom (9).

An intervention of 5 years was assumed, targeted to the female population at a given 10-year hip fracture probability at any given age. The 5-year treatment was chosen to approximate the time period where there are direct or indirect clinical data on intervention effects. After stopping intervention, the risk reduction was assumed to reverse in a linear manner over a subsequent 5-year period *(1,17)*.

A key assumption concerns the duration of persisting effect after stopping treatment, termed the offset time *(1)*. There is a great deal of uncertainty over the offset time of many treatments. Relatively rapid offset times of a few years have been observed with calcium, calcitonins and vitamin D metabolites. Longer offset times are described with the bisphosphonates, estrogens, tamoxifen, and more recently with parathyroid hormone (1,31,32). The assumption of a 5-year offset time is therefore conservative, and longer offset times would markedly improve cost–effectiveness *(1)*. A further consideration is that a fixed treatment time of 5 years was modelled, but altering the duration of intervention has relatively modest effects on costs and effectiveness *(17)*.

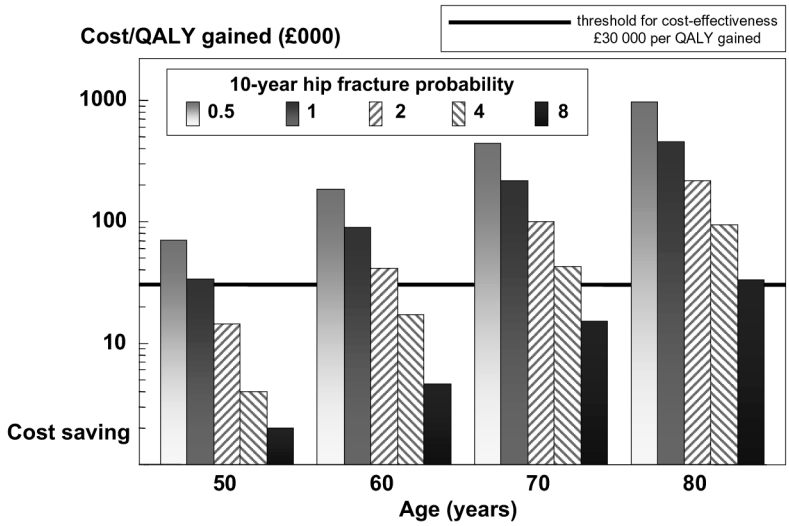
8.3.2 Cost utility

A threshold value of £30 000 per QALY gained compared to no treatment was taken as an indication of cost–effectiveness using direct costs, in line with the recommendations of the United Kingdom National Institute for Health and Clinical Excellence *(3)*.

The cost-effectiveness of the base case treatment (£350) and efficacy (35% effectiveness) is shown in Fig. 8.1 at different ages and different hip fracture probabilities *(19)*. As expected, cost–effectiveness improved at any age with increasing fracture probability, because of the higher risk of fracture and thus the greater number of fractures avoided. For any given hip fracture probability, cost–effectiveness improved with decreasing age, since more non-hip fractures were avoided at the younger ages.

Fig. 8.1

Cost–effectiveness of an intervention costing £350 per annum with an efficacy of 35%, by age and hip fracture probability[a]



Source: reference 19 (Fig. 1).

QALY, quality-adjusted life year.

[a] Logarithmic scale.

The threshold of hip fracture probability at which treatment becomes cost-effective is lower with decreasing age (Table 8.1). Indeed, for intervention at the age of 50 years, a 10-year probability that exceeds 1.1% is cost-effective in women. By contrast at the age of 80 years, treatment became cost effective with a hip fracture probability of 8.5%. This appears to be paradoxical, but arises because it is assumed that intervention decreases the risk of all osteoporotic fractures. In younger women, proportionately more fractures

occur at sites other than the hip. Thus, for a given hip fracture probability, more fractures at sites other than the hip are also averted. The effect of age to increase the hip fracture probability at which treatments become cost-effective should not be misconstrued to infer that the younger the age, the more cost-effective treatments become. Indeed, the converse is true.

Table 8.1

Relative risk (RR) and 10-year hip fracture probability (%) at which treatment becomes cost effective in a United Kingdom setting

		10-year hip fracture probability (%)		
Age (years)	RR	Threshold	General population[a]	Selected population[b]
50	3.77	1.10	0.30	2.50
55	2.63	1.81	0.70	4.2
60	1.89	2.64	1.42	5.9
65	1.42	3.70	2.64	8.8
70	1.11	5.24	4.73	12.3
75	0.91	6.87	7.59	14.8
80	0.77	8.52	10.83	18.2
85	0.65	8.99	13.0	19.2

Source: reference 19 (Table 1).

[a]General population (RR = 1.0).

[b]Selected according to clinical risk factors and the selective use of bone mineral. density (see section 9 for details).

As also shown in Table 8.1, the hip fracture probability in the selected population exceeds the threshold risk. Thus, in a population of 50 year old women, treatment of the selected population would be even more cost-effective.

The effect of averting hip fracture alone, or hip plus spine plus forearm fracture, or all osteoporotic fractures is shown in Table 8.2 for women aged 70 years. When therapy was assumed to decrease hip fracture only, it was not cost-effective to intervene unless the 10-year hip fracture probability exceeded about 10%. Where treatment had effects on hip, spine and forearm fractures, the threshold probability was approximately 7%. Where all osteoporotic fractures were assumed to decrease with intervention (i.e. the base case), it was cost-effective to intervene with a 10-year hip fracture probability of approximately 6%.

Table 8.2

Cost–effectiveness of intervention (£000) in women aged 70 years, by the type of fracture averted, assuming a relative risk reduction of 35%

10-year hip fracture probability (%)	Cost/QALY gained (£000)		
	Hip	Hip, spine and forearm	All osteoporotic fractures
5.0	78	32	32
10.0	33	15	10
15.0	18	8	2
20.0	10	5	-2
25.0	5	3	-6

Source: reference 19 (Table 2).

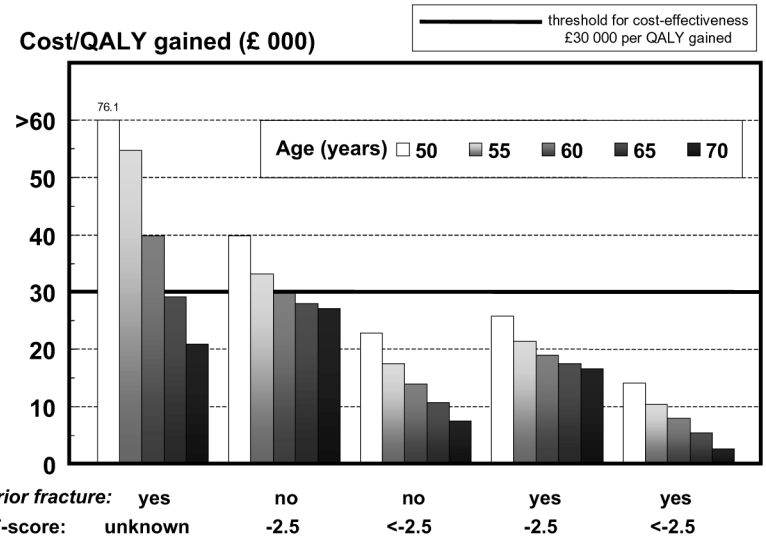
QALY, quality-adjusted life year.

For women aged 75 years or more, it is, using the base case, cost-effective to treat women at the average population risk. For example, it is cost-effective to treat women at the age of 75 years with a 10-year hip fracture probability of 6.9% whereas the population probability at this age is 7.6% (see Table 8.1). It is, however, not entirely certain whether intervention thresholds for elderly people should be set below the average hip fracture probability for age and sex. The reason is that most trials of intervention have targeted men and women with low bone density (with a T-score for BMD commonly <-2.0 or <-2.5 SD), so that the experience of treating individuals with higher values for BMD is less. Recent studies suggest that efficacy of interventions on vertebral fracture risk is not markedly affected by baseline BMD *(8,33–38)*. For non-vertebral fractures, the information base is less but would suggest that anti-fracture efficacy with bisphosphonates might be less marked in individuals with the higher values for BMD *(39,40)*. On the other hand, hormone replacement treatment has also been shown to decrease fracture risk when targeted to the general population *(29)*. Until these uncertainties are resolved, it may be unwise to recommend intervention in individuals whose risk is not increased above that of the general population of the same age and sex.

The cost-effectiveness and 10-year hip fracture probabilities of different clinical scenarios are shown in Figs 8.2 and 8.3. In women with a prior fragility fracture, and without knowledge of BMD, it was cost-effective to intervene from the age of 65 years. In women at the threshold of osteoporosis (i.e. a T-score at the femoral neck equal to –2.5 SD and no prior fracture), it was cost-effective to intervene from the age of 60 years. In women at the threshold of osteoporosis with a T-score of –2.5 SD, it was cost-effective to intervene if there was a history of a prior fracture, irrespective of age. In women with a T-score of less than –2.5 SD it was, therefore, also cost-effective to intervene, irrespective of the presence or absence of a prior fragility fracture and irrespective of age.

Fig. 8.2

Cost–effectiveness (£000/QALY gained) of treatment in women aged 50–70 years, by the presence or absence of a prior fracture and osteoporosis

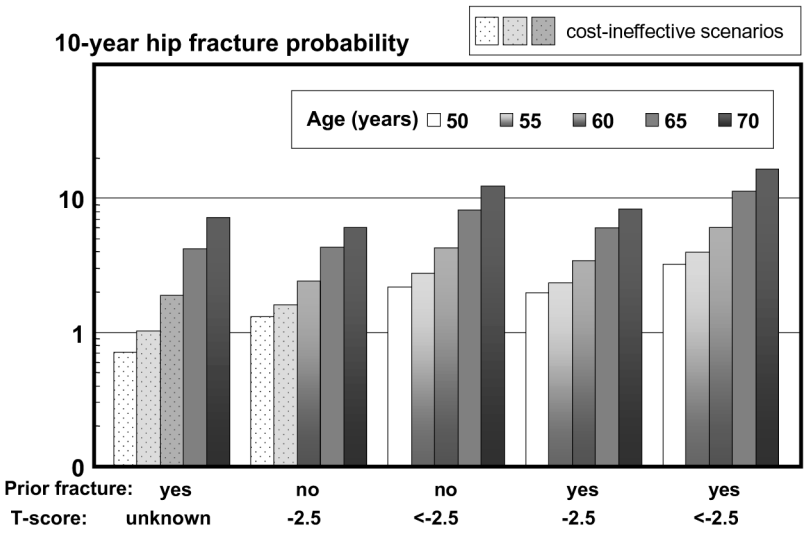


Source: reference 19 (Fig. 3).

QALY, quality-adjusted life year.

Fig. 8.3

Ten-year hip fracture probabilities (%), by age and the presence or absence of a prior fragility fracture and osteoporosis[a]



Source: reference 19 (Fig. 4).

QALY, quality-adjusted life year.

[a] Logarithmic scale.

In the present analysis, a prior fracture was assumed to increase subsequent fracture risk by 1.85 (1.74 after adjustment for BMD). With a prior vertebral fracture, subsequent fracture risk is markedly increased *(41,42)* and this would improve cost-effectiveness still further. These findings, modelled on the general population, illustrate the importance of combining independent risk indicators. Strategies based on the individual patient approach are reviewed in section 9.

An approach similar to that described above has been used to determine intervention thresholds for women from Sweden (18). Intervention thresholds, expressed as 10-year hip fracture probabilities for Swedish women, were 1.2, 1.8, 2.7, 4.0 and 5.1 at the ages of 50, 55, 60, 65 and 70 years, respectively. The current estimates for the United Kingdom (see Table 8.1) are rather similar, despite the different costs and fracture risks in Sweden compared with the United Kingdom.

In men, intervention thresholds are likely to be broadly similar to those found in women, at least from the age of 60 years or more. In one study, intervention thresholds were higher in Swedish men than in women below the age of 60 years *(18)*. This was partly explained by the exclusion of tibial fractures, since there is little evidence that these can be considered to be osteoporotic in men *(15)*.

In this analysis, only the effects of osteoporotic fractures have been modelled. The effect of interventions that have generalized extraskeletal benefits and risks would markedly alter cost-effective intervention thresholds *(9,10,22,24)*. The obvious examples are hormone replacement treatment and raloxifene. Both appear to affect breast cancer, though probably in different directions *(43,44)*, and both decrease markers of cardiovascular morbidity *(43–45)*, though no favourable effects of hormone replacement on cardiovascular events have been shown in prospective studies (29,46).

8.4 Other socioeconomic settings

Intervention thresholds developed for Sweden or the United Kingdom may not be applicable to many WHO Member States. The 10-year probability of fracture varies markedly in different countries. For countries with low hip fracture rates, as found in developing countries, the relative risk at which intervention is cost-effective will be higher, though the absolute risk at which intervention is cost-effective would not change assuming comparable costs. Thus, in countries with fracture rates lower than those in the United Kingdom, a lower proportion of the population would be identified for treatment. Intervention thresholds would, however, change with differences in costs, particularly fracture costs, which vary markedly between Member States.

Some countries may, however, be less able to afford interventions, particularly since the costs of pharmaceuticals for osteoporosis are more or less the same worldwide (with the exception of higher prices in the United States). This raises the issue of affordability or willingness to pay for a strategy. The gross domestic product (GDP) per capita provides an index of affordability. The GDP varies markedly in different regions of the world. In the United Kingdom, the GDP per capita is estimated at US$ 25 300 in 2002, as compared with US$ 7000 in Turkey. Thus, for the same fracture risk and the same costs, treatment will be less affordable (at least to health services) in Turkey than in the United Kingdom. Nevertheless, individuals in Turkey, rather than society as a whole, may be willing to pay "United Kingdom prices" for health care. There is also a marked heterogeneity in the proportion of GDP devoted to health care, and in the proportion of the population at risk from osteoporotic fracture (i.e. elderly people) (Table 8.3) *(47–51)*.

Table 8.3

Ten-year hip fracture probability (ratio to Sweden), life expectancy and indices of wealth and health-care expenditure

Country	% of 10-year hip fracture probability[a]	population aged 60+ years	Life expectancy at 60 years		Government spending on Health expenditure % GDP	health care (% total health expenditure)	Per capita expenditure on health US$	GDP/capita
			Males	Females				
Norway	1.24	19.6	16.2	18.9	8.0	85.5	2 981	37 263
Iceland	1.02	15.3	17.5	18.7	9.2	82.9	2 441	26 533
Sweden	1.00	22.9	17.1	19.6	8.7	85.2	2 150	24 713
Denmark	0.85	20.4	15.2	17.2	8.4	82.4	2 545	30 274
USA	0.78	16.2	15.3	17.9	13.9	44.4	4 887	35 158
China (Province of Taiwan)	0.72	-	-	-	-	-	-	-
Germany	0.72	24.0	15.9	19.0	10.8	74.9	2 412	22 333
Switzerland	0.71	22.1	17.1	20.4	11.0	57.1	3 779	34 354
Finland	0.68	20.3	15.7	18.9	7.0	75.6	1 631	23 300
Greece	0.66	23.8	16.0	18.1	9.4	56.0	1 001	10 649
Canada	0.65	17.1	16.1	19.3	9.5	70.8	2 163	22 768
Netherlands	0.64	18.5	15.5	18.4	8.9	63.3	2 138	24 022
Hungary	0.63	20.0	12.1	16.0	6.8	75.0	345	5 073
Singapore	0.62	11.1	14.5	16.3	3.9	35.5	816	20 923
Italy	0.61	24.5	16.4	19.4	8.4	75.3	1 584	18 857
United Kingdom	0.60	20.8	15.7	18.1	7.6	82.2	1 835	24 145
Kuwait	0.59	2.7	13.8	14.2	3.9	78.8	537	13 769
Australia	0.57	16.7	16.9	19.5	9.2	67.9	1 741	18 924
Portugal	0.57	21.1	14.9	17.7	9.2	69.0	982	10 674
China (Hong Kong SAR)	0.49	-	-	-	-	-	-	-
France	0.41	20.5	16.6	20.4	9.6	76.0	2 109	21 969
Japan	0.39	24.4	17.5	21.7	8.0	77.9	2 627	32 837
Mexico[b]	0.38	7.2	14.4	16.2	6.1	44.3	370	6 066
Spain	0.36	21.6	16.4	19.9	7.5	71.4	1 088	14 507
China	0.29	10.0	13.1	14.7	5.5	37.2	49	891
Turkey	0.18	8.2	12.8	14.2	5.0	71.0	109	2 180
Republic of Korea	0.18	11.8	13.2	17.1	6.0	44.4	532	8 867
Venezuela	0.17	6.9	13.9	15.7	6.0	62.1	307	5 117
Morocco[c]	0.12	5.1	11.4	12.7	5.9	39.3	23	4 628
Chile	0.08	10.7	13.9	16.8	7.0	44.0	303	4 329
Iran (Islamic Republic of)	0.03	6.4	10.4	11.9	6.3	43.5	350	5 556
Cameroon[d]	0.02	5.6	9.7	10.4	3.3	37.1	20	606

Source: references 47, 48.

[a]Averaged for men and women. [b]Hip fracture probabilities from Clark et al. (49). [c]Computed from El Maghraoui et al. (50). [d]Computed from Zebaze and Seeman (51).

GDP, gross domestic product; -, no data from same source.

For all these reasons, it is important to define intervention thresholds on a country by country basis that takes into account the setting for service provision and willingness to pay, as well as considerations of absolute costs.

As mentioned, there is a great deal of heterogeneity in fracture risk around the world *(47,52–54)*, as well as in mortality, costs of fracture and costs of intervention. Table 8.3 shows relative 10-year probabilities of hip fracture in different countries compared to Sweden (RR=1).

The large variation means that, if individuals are identified for treatment on the basis of fracture probability alone (e.g. a 10-year hip fracture probability of, say, 7%), many more individuals would be selected from high risk countries than from countries with lower risk. Indeed, a 10-year hip fracture probability of 7% approximates the risk in the general Swedish population. In Turkey, a very small minority of 70 year olds with the same hip fracture probability would be selected, but with a very high risk relative to the general population.

It is likely that absolute fracture risk will be increasingly used as the intervention threshold. This will demand greater information on hip fracture probabilities than is available to date. Indeed, hip fracture probabilities are available from only approximately 30 countries. Mortality hazards are, however, available worldwide, so data on incidence of fractures from other countries are required to enlarge this database. Where probabilities are required for countries without data on hip fracture, a surrogate region would need to be chosen that best represented the local mortality and hip fracture risks.

There is at present little or no information as to when treatment can be considered to be cost-effective in the majority of Member States. Suggested values for each QALY gained have been €66 000 in Sweden (55), €6000–€30 000 in Spain *(56)* and, as mentioned, £30 000 in the United Kingdom.

The WHO Commission on Macroeconomics and Health *(57)* suggested that interventions with a cost–effectiveness ratio lower than 3-times the GDP per capita for each averted disability-adjusted life year (DALY) should be considered cost effective *(57)*. Assuming that the values for a DALY and a QALY are reasonably comparable, then a cost-effective threshold for the United Kingdom would be US$ 75 900. It is not specified in the report of the WHO Commission what costs are included, but if all costs are included, such as cost of added years, then the threshold value should be set at a lower level when a health-care perspective is taken. Using the same ratio (0.6) for adjustment as suggested by Kanis and Jönsson *(12)*, the threshold values would be about US$ 45 000 in the United Kingdom, close to the recommendation of the National Institute for Health and Clinical Excellence, and about US$ 12 500 in Turkey.

In developed countries, an approach to cost–effectiveness might be approximated by a multiple of GDP per capita. For example, the GDP per capita in the United Kingdom is US$ 24 145, which is approximately £15 000. Interventions are considered to be cost-effective at a threshold of £30 000/QALY gained, suggesting a multiple of two. From knowledge of costs, mortality and fracture risk, possible intervention thresholds can be approximated (Table 8.4) indexed to Sweden *(58)*. For example, in the Netherlands, GDP per capita is lower than that of Sweden, but so too are costs of fracture and risk of fracture, so that the intervention threshold in terms of 10-year hip fracture risk is comparable to that of Sweden. The lowest intervention thresholds are found for Switzerland where, compared with Sweden, the GDP per capita is somewhat higher but the costs of fractures are markedly increased and greater savings are incurred by intervention. Broadly similar intervention thresholds are found for Denmark, Finland, France, Japan, the Netherlands, Norway, Sweden, the United Kingdom and the United States.

Table 8.4
Determinants of intervention thresholds in different countries, indexed to Sweden

Country	GDP/capita US$ (000)	Cost index[a]	Hip fracture index[b]	Mortality index[c]	RR[d]	Probability index[e]
Australia	18.9	0.47	0.75	1.29	1.2	1.3
Canada	22.8	0.49	0.74	1.13	1.1	1.3
Denmark	30.3	1.01	0.88	1.19	0.7	0.9
Finland	23.3	0.76	0.64	1.09	1.1	1.1
France	22.0	0.74	0.46	1.29	1.6	1.2
Germany	22.3	1.80	0.76	0.89	2.2	1.8
Italy	18.9	0.57	0.77	0.95	1.1	1.3
Japan	32.8	1.46	0.50	0.99	1.0	0.8
Netherlands	24.0	0.96	0.70	1.16	0.9	1.0
Norway	37.3	1.11	1.12	1.25	0.4	0.8
Portugal	10.7	0.81	0.49	1.18	1.8	1.4
Singapore	20.9	0.76	0.40	1.31	2.0	1.3
Spain	14.5	0.62	0.51	1.04	1.8	1.5
Switzerland	34.3	2.76	0.81	0.99	0.4	0.5
Sweden	30.3	1.00	1.00	1.00	0.6	1.0
UK	24.1	0.99	0.71	1.13	0.9	1.0
USA	35.2	0.56	0.79	1.46	0.9	1.0

Source: reference 58.

[a]Cost index computed from mean bed-days for musculoskeletal diseases and differences in health-care prices as a ratio to those of Sweden.

[b]Index related to 10-year probabilities in Sweden at the age of 70 years.

[c]Index related to the population of Sweden.

[d]Risk relative to population risk at which intervention becomes cost effective.

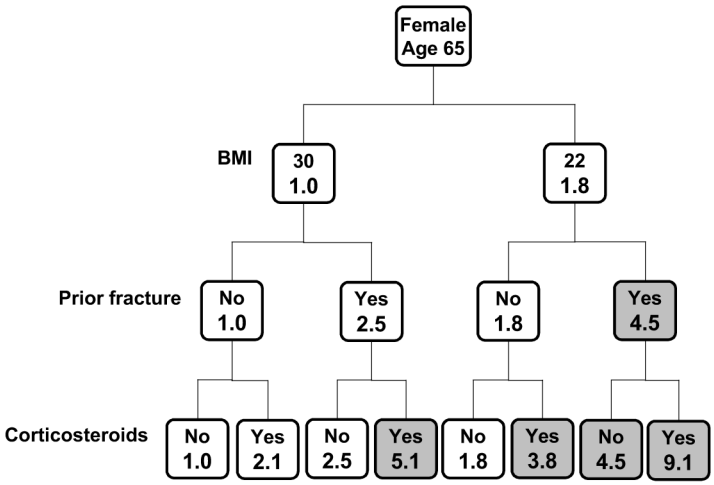
[e]Hip fracture probability at threshold of cost–effectiveness index related to Sweden.

This approach is probably not robust in the developing countries where different health-care priorities pertain *(59)*. Also, the approach is particularly sensitive to differences in fracture costs, an estimate that is poorly investigated. It is also important to recognize that fracture risks vary within countries, being higher in urban compared to rural communities. In urban communities, the fracture risks may not differ substantially from those in the more developed economies, and individuals living in urban areas may have higher socioeconomic prosperity than the average for the country as a whole. Finally, treatment decisions in this context are not always governed by policy-makers, but are also taken by individuals, particularly in that segment of society with the highest socioeconomic prosperity (i.e. "privatization of risk").

8.5 Individual patient-based scenarios

The stratification of risk can be illustrated by the consideration of prior fractures and use of glucocorticoids, both of which are strong risk factors for fracture. The example in Fig. 8.4 considers a female aged 65 years. At the extreme of BMI, there is a 1.8-fold difference in the 10-year probability of hip fracture. In the presence of a prior fracture, the range of probabilities increases and, in the case of low BMI and prior fracture, the United Kingdom intervention threshold is exceeded. With chronic use of glucocorticoids, a prior fracture and low BMI, there is a 9-fold range in probabilities. In the presence of any two risk factors (low BMI, prior fracture, glucocorticoids), the intervention threshold is exceeded.

Fig. 8.4
Stratification of fracture risk based on body mass index (BMI), prior fracture and exposure to glucocorticoids in a woman aged 65 years from the United Kingdom



It is important to recognize that these thresholds are based on the example provided for the United Kingdom and will not necessarily apply elsewhere. In addition, clinical judgement should also influence decision-making, since, for example, a prior vertebral fracture confers a somewhat higher risk than the model provides and no account is taken of the dose of glucocorticoids.

With BMD taken into account, BMI has a very modest independent impact on fracture probability. Table 8.5 shows the relationship between clinical risk factors according to BMD T-score at an average BMI (24 kg/m2). In women without risk factors, probabilities of hip fracture exceed the United Kingdom intervention threshold with a T-score of –3.0 SD or less and, in the case of 50 year old women, a T-score of –2.5 SD. In the presence of a prior fragility fracture or exposure to glucocorticoids, the intervention threshold is exceeded between a T-score of –2.0 SD and –3.0 SD, depending on age. In women with both risk factors, treatment is cost-effective between a T-score of –1.5 and –2.0 SD. In the clinical scenario above, intervention becomes cost-effective in the absence of risk factors at T-scores of –2.3, –2.6, –2.9 and –2.9 SD at the ages of 50, 60, 70 and 80 years, respectively. In the presence of a prior fragility fracture and exposure to glucocorticoids, the respective T-scores are –1.2, -1.5, -1.9 and –1.9 SD.

Table 8.5

Ten-year probability of hip fracture (%) in women from the United Kingdom (BMI = 24.1 kg/m^2), by age, femoral neck BMD T-score and clinical risk factors: probabilities that exceed the intervention threshold are shown in bold typeface

	No clinical risk factors T-score							Prior fragility fracture T-score						
Age (years)	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.1	0.2	0.4	0.8	**1.6**	**3.1**	**12**	0.1	0.5	0.9	**1.7**	**3.4**	**6.5**	**23**
60	0.1	0.4	0.8	1.4	2.4	**4.3**	**13**	0.3	0.8	1.4	2.5	**4.4**	**7.7**	**23**
70	0.4	0.9	1.4	2.3	3.8	**6.1**	**16**	0.5	1.4	2.2	3.5	**5.8**	**9.3**	**23**
80	1.0	2.1	3.0	4.2	6.2	**9.1**	**19**	1.3	2.7	3.9	5.6	8.1	**11.8**	**24**

	Ever-use of glucocorticoids T-score							Glucocorticoids and prior fracture T-score						
Age (years)	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0	0	-1.0	-1.5	-2.0	-2.5	-3.0	-4.0
50	0.1	0.4	0.8	**1.5**	**3.0**	**5.8**	**21**	0.1	0.9	**1.7**	**3.2**	**6.3**	**12**	**39**
60	0.3	0.8	1.4	2.5	**4.5**	**7.9**	**23**	0.5	1.5	**2.6**	**4.5**	**7.8**	**14**	**38**
70	0.6	1.6	2.5	4.1	**6.7**	**11**	**26**	1.0	2.5	3.9	**6.3**	**10**	**16**	**37**
80	1.7	3.5	5.0	7.1	**10.0**	**15**	**29**	2.3	4.6	6.5	**9.2**	**13**	**19**	**35**

BMI, body mass index; BMD, bone mineral density.

8.6 Implications for case-finding

The effect of adopting intervention thresholds depends upon the accuracy with which individuals at or above a threshold level of risk can be identified. The relationship between gradient of risk and risk threshold has been reviewed in section 6. Assuming that the gradient of risk of fracture assessment lies between 2.0 and 3.0/SD change in risk score, less than 4% of women from the United Kingdom would be identified to be at high risk at the age of 50 years, a proportion that increases with age, but decreases with higher gradients of risk *(19)* (Table 8.6). The higher the gradient of risk, the higher the risk of the population selected (Table 8.7). For example, at the age of 65 years, 20% of the population would be selected to be above an intervention threshold. The relative risk of fracture compared with the population risk would be 2.2 with a test with a gradient of risk of 2.0, but would rise to 3.1 where the gradient of risk was 3.0 *(19)*.

Table 8.6

The proportion (%) of women at the ages shown that would be identified to have a risk that exceeds the intervention threshold, by gradient of fracture risk/SD of an assessment algorithm

	Proportion of population identified (%) when the gradient of risk is:		
Age (years)	2.0	2.5	3.0
50	1.2	2.8	3.9
55	4.1	6.5	7.7
60	10.3	12.5	13.0
65	19.7	20.0	19.3
70	30.8	28.2	25.9
75	42.0	36.3	32.3
80	51.4	43.3	37.9
85	61.2	50.7	44.0
90	71.3	59.0	50.9

Source: reference 19 (Table 5).

Table 8.7

Risk ratio of those above the threshold versus average risk of the general population, by gradient of risk

Age (years)	Risk ratio of those above the threshold[a] versus average risk of the general population when the gradient of risk is: 2.0	2.5	3.0
50	4.9	5.7	6.5
55	3.6	4.2	4.8
60	2.8	3.3	3.8
65	2.2	2.7	3.1
70	1.9	2.2	2.6
75	1.6	2.0	2.3
80	1.5	1.8	2.1
85	1.4	1.6	1.9
90	1.3	1.5	1.7

Source: reference 19 (Table 6).

[a]The risk ratios of those at the threshold risk are shown in Table 8.1.

The application of threshold risks to case-finding is discussed in section 9.

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9. Assessment and the formulation of a therapeutic strategy

It is appropriate to consider the development of assessment tools in the context of therapeutic strategies for osteoporosis. Strategies will vary in different Member States and the requirements for assessment will also differ.

Two distinct, but not mutually exclusive, preventive strategies can be envisaged *(1)*. The first is to identify patients at particular risk and to offer an intervention termed the "high risk" strategy. Examples include identification of women with low bone density, those most likely to fall, or

individuals with certain diseases. A second approach, the "public health" strategy, is population-based and the aim is to modify a risk factor within the entire community. For example, if BMD were to be increased by 10% in the entire female population, this would be expected to decrease the risk of fragility fracture by around 50% *(2)*. Such approaches might be directed at any stage or at all stages of life.

9.1 Population-based prevention

Bone mass and rates of bone loss are continuously distributed throughout the population, so it is not possible to distinguish precisely an individual with disease from the normal population *(3)*. Nonetheless, a number of risk factors have been identified which, if causally related and correctable, might have a significant impact on the burden attributable to osteoporosis *(4)*. The more obvious remedial factors that have been proposed include a higher level of exercise, stopping smoking, the prevention of falls and the optimization of nutrition, particularly the ingestion of a diet high in calcium and vitamin D *(5–8)*. There are, however, several problems with these approaches. The first is that not all these risk factors are necessarily causally related to osteoporosis; in particular, uncertainties exist with respect to smoking and moderate alcohol consumption. A second problem relates to the ability to change a lifestyle habit, as illustrated by the limited success of risk factor intervention in coronary heart disease *(9)*. This raises a third problem, namely that the value and feasibility of population programmes in osteoporosis prevention have not been coherently evaluated. This consideration even applies to falls, where intuition indicates that attempts to prevent falls in elderly people might be of benefit in reducing fractures. There is, however, currently no controlled trial evidence showing that strategies which prevent falls serve to decrease the risk of fracture in individuals *(10)*.

A further problem relates to the effect of remedial factors on the frequency of fractures within a community. Despite the high prevalence of many of these factors, the increase in risk associated with each is relatively small, as is the attributable risk. Where the attributable risk is small, the same overall reduction in hip fracture incidence might be achieved by targeting that segment of the population with the risk factor itself rather than the whole population. If all the risk factors identified for hip fracture were causal and could be reversed, the impact on fracture incidence might be as high as 50% *(11)*. In practice, it is not feasible to modify the majority of these risk factors, so the potential effect of risk factor modification at the population level is substantially smaller.

9.1.1 Behavioural risks

Five factors that are related to behaviour or lifestyle have been evaluated for their relationship to fragility fractures: nutrition, cigarette smoking, alcohol consumption, physical activity and falls.

Nutrition

The role of nutrition, particularly with respect to dietary calcium, has been investigated extensively. A 1997 meta-analysis reviewed 23 observational studies that related dietary calcium intake to fracture outcomes (18 studies were of hip fracture and five of other fracture sites) *(12)*. The five population-based cohort studies of hip fracture, as well as the overall pooled risk estimate, showed declining fracture risk with increasing dietary calcium. The pooled odds ratio indicated a 4% reduction in hip fracture risk for each 300 mg increase in daily dietary calcium intake, equivalent to one glass of milk per day. The likely benefit from calcium is reinforced by results of several small clinical trials with calcium supplements, which show reduced fractures among those receiving supplements *(12)*. However, the effect of changing calcium nutrition alone is likely to be small. For example, in a large survey of European women, calcium was shown to be a significant protective factor against the risk of hip fracture *(11)*, but the risk was confined to the 10% with the lowest intake. Even if the relationship between calcium intake and risk were causal, increasing the calcium intake above about 500 mg daily would prevent just 4% of hip fractures *(13)*.

Vitamin D deficiency occurs in many regions of the world and gives rise to rickets in childhood and to osteomalacia in adults. There has been an increasing recognition that vitamin D insufficiency is common in elderly people, particularly those who are not fully independent and therefore less exposed to sunlight. Case-control studies of hip fracture risk indicate that lack of sunlight exposure is significantly associated with an increase in fracture risk *(11)*. In addition, ecological studies suggest that hip fracture risk increases progressively with latitude, an effect that is independent of socioeconomic prosperity (which is also associated with high fracture risk). For each 10 degrees increase in latitude, the prosperity-adjusted 10-year hip fracture probability increases by 0.6% in Sweden *(14)*.

Intervention studies with vitamin D alone, or in combination with calcium, have shown inconsistent effects on fracture rates. In one large study from Holland *(15)*, no difference in fracture incidence was observed in 2578 men and women over the age of 70 years randomized to calciferol 400 IU daily or to placebo. Likewise, two large studies in the United Kingdom have recently reported no effect of vitamin D on fracture rates (16,17). In contrast, a study in Finland *(18)* showed that 150 000–300 000 IU of vitamin D annually reduced symptomatic fracture rates by 25% in a cohort of 800 elderly subjects. In the United Kingdom, the use of 100 000 IU vitamin D given 4-monthly decreased non-vertebral fracture rates by 22% in elderly people (19). These discrepant results may relate to the underlying adequacy of calcium and vitamin D nutrition in the various populations studied.

Two further studies have examined the effects of calciferol with a calcium supplement on fracture outcomes. One study in France examined non-

vertebral and hip fracture rates in a cohort of 3000 elderly women in sheltered accommodation given 800 IU vitamin D and 1200 mg calcium daily *(20)*. Over a 3-year interval, fracture rates decreased by approximately 25%. In a study based in the United States, non-vertebral fracture rates were decreased by more than half in 400 elderly men and women randomized to calcium 500 mg plus 700 IU vitamin D daily, or to placebo *(21)*.

More consistent effects of vitamin D have been observed on the risk of falling. Vitamin D deficiency is associated with muscle weakness and an increased risk of falls. Several randomized controlled trials have shown that vitamin D supplements decrease the risk of falls, even though benefits in terms of fracture outcomes are less consistent *(22)*.

These considerations indicate that a diet adequate in calcium and vitamin D may be of benefit for fracture outcomes in later life. The provision of a daily intake of 400–800 IU vitamin D is a straightforward, safe and inexpensive means of prevention. The dietary intake of calcium that is considered to be adequate varies markedly around the world and reflects some of the scientific uncertainties *(23)*. Of the principal food sources of calcium, dietary products have a higher fractional absorption of calcium than vegetables, and cheese may be marginally superior to milk *(24)*. The effects of calcium and vitamin D intake in childhood or in young adult life on later fracture risk are less well studied. Nevertheless, dietary habits acquired in early life correlate with dietary habits in later life, so that there is an argument to be forwarded for adequate nutrition in calcium and vitamin D for the entire population, irrespective of age.

Cigarette smoking

A meta-analysis in 1997 reviewed 29 cross-sectional studies that related smoking to bone density and 19 cohort and case-control studies that reported risks of hip fracture in smokers and non-smokers *(25)*. Lower BMD was found in postmenopausal women who smoked, and the relative risk of hip fracture rose progressively with age. In the current meta-analysis described in section 5, the risk of all fractures was increased in smokers, though more so in the case of hip fracture (RR = 1.84). Unlike the earlier meta-analysis, risks did not increase with age. An increased fracture risk was also found in men. In general, risk ratios were higher in men than in women, though not significantly so, perhaps because of higher exposure to tobacco. Although cigarette smoking is less prevalent at older ages, it is estimated to be responsible for 13% (or 1 in 8) of fractures in women. The mechanism by which smoking influences risk are uncertain, but findings of the meta-analyses persist when possible confounding factors known to be related to smoking (e.g. lower weight, high intakes of alcohol, anti-estrogen effects and physical activity) are considered.

Alcohol use

The heavy use of alcohol has been associated with increased fracture risk *(26,27)*. As alcohol intake is closely associated with smoking, poor diet, and propensity to fall, it has been difficult to identify its independent influence on fracture. Inconsistent findings from several studies have shown no effect, a slightly increased fracture risk, and a protective effect from low and moderate alcohol consumption (section 5) *(27,28)*. Evidence of higher risk among heavy drinkers is more consistent but difficult to evaluate because of the complex interrelationship between the factors mentioned above, particularly the increased propensity to fall. The meta-analysis given in section 5 suggests a threshold effect where the risk is increased when intake exceeds 2 units daily, but the causal association of alcohol with fracture risk cannot be proven, nor can the effects of decreasing alcohol consumption be predicted with certainty.

Exercise

Very many studies have shown the dependence of BMD on the level of physical activity. In particular, immobilization induces marked loss of skeletal tissue, for example in an immobilized limb or during prolonged bed-rest *(29)*. The relationship between everyday variations in physical activity and fracture outcomes is less secure. A number of case-control studies have shown a relationship between customary exercise levels and fracture risk *(11,30–33)*. The data are, however, inconsistent for different osteoporotic fractures and by sex *(31,33)*, and these observational studies may be misleading to the extent that individuals may have chosen a particular activity because of their physical attributes, rather than the activity levels themselves determining their physical attributes. Moreover, it is likely that benefits are lost if individuals cease an exercise programme, and long-term compliance is likely to be low *(34,35)*. The value of exercise for five years around the age of 40 years is therefore questionable later, at the age of 75 years, especially where age is accompanied by other disorders (e.g. stroke). In the case of exercise, the optimal type and duration are also not known.

These considerations suggest that there is as yet no compelling evidence for the efficacy of exercise programmes in fracture prevention. Notwithstanding, there is good evidence that the avoidance of immobilization wherever possible is a valuable adjunct to a global programme for osteoporosis. In addition, regular physical activity is associated with improved health and reduced mortality generally *(36)*. Thus, exercise can be encouraged but cannot be depended upon to reduce the fracture burden in the community.

Falls

Some stress upon a fragile bone is generally required to precipitate a fracture. Although fragility fractures may be defined as resulting from minimal trauma, this is merely a convention to make the distinction from severe

trauma (e.g. road traffic accidents) capable of breaking any bone, including an osteoporotic bone. In many cases, particularly with hip and wrist fractures, a fall from a standing height is involved and the forces involved may be substantial *(37)*. Such falls become more common as people age. By one estimate as many as 50% of women aged 85 years and older experience a fall in any year *(38)*. The likelihood of falling (and fractures) increases as individuals age, experience declining health and impaired vision, and lose muscle strength and balance. Side-effects from medications, such as orthostatic hypotension, sedation or disequilibrium, also contribute to falls *(39)*. There may be an interrelationship between physical activity and liability to falls *(40)*. A meta-analysis of seven trials which included an exercise intervention in elderly people indicated a 10% reduction in fall frequency *(41)*. No study to date, however, has shown a significant reduction in fracture rates *(42)*. A component of the beneficial effects of vitamin D may be mediated by a decrease in falls and, in a recent meta-analysis, the use of vitamin D decreased the risk of falls by 22% (95% CI = 8%–36%) compared with patients taking placebo or calcium alone *(43)*. The minimization of skeletal trauma following falls has been inconsistently achieved by the use of hip protectors *(44,45)*, though adequate compliance with these devices has been a problem *(46)*.

Recommendations

Although evidence that modifying lifestyle-related factors reduces fracture risk is not considered compelling by some expert groups, there is general agreement that data are of sufficient quality to suggest courses of action. Global programmes should include adequate attention to nutritional factors, particularly related to calcium and vitamin D. Cigarette smoking should be avoided, not solely because of its possible effects on skeletal metabolism, but for the many other adverse effects associated with smoking. The avoidance of excessive intakes of alcohol is also recommended. It has been suggested that intakes of greater than 14 units weekly in women and 21 units weekly in men are associated with adverse effects, and these thresholds are more or less in line with meta-analyses of the effects of alcohol consumption on fracture risk in this report. Note that a unit of alcohol is commonly defined as 10 grams of alcohol, but this varies slightly by country. Another area of agreement is that immobilization is an important cause of bone loss and fracture. The detrimental effect of immobility on bone mass is far greater than the beneficial effect of additional exercise in an already ambulatory subject *(47)*. Motor deficits attributable to neurological disorders such as hemiplegia or paraplegia are important risk factors for fracture *(29)*, and support the view that the avoidance of immobilization is an important aspect of a global strategy.

Most of the world's ageing population resides in developing countries where neither bone densitometry nor drugs for osteoporosis are available. Population-based strategies are, therefore, the only practicable preventive measure. They can also be advocated as a component of the adequate care of osteoporosis, even where high risk strategies are applied.

9.2 Case-finding without measurement of bone mineral density

In those countries where the utility of population screening is found wanting, case-finding strategies are widely accepted as a method of identifying individuals suitable for the treatment of osteoporosis *(6,23,48–50)*. The general principles are that individuals are identified by the presence of risk factors and subsequently undergo a BMD examination. When BMD is below a given threshold, intervention for osteoporosis is recommended. As reviewed in section 7, the threshold for BMD that is used varies in different guidelines. Thus, both assessment and treatment focus critically on the estimation of BMD. A major aim of this report has been to evaluate the utility of clinical risk factors for assessment, and the question arises of whether clinical risk factors alone could be used for patient assessment in those Member States with limited or no access to DXA.

The general characteristics of the combined use of clinical risk factors suggest that this might be so. The gradient of risk per SD change in risk score depends upon age and the fracture outcome predicted (see section 7). For osteoporotic fractures, excluding hip fractures, the gradient of risk with the use of clinical risk factors is 1.4, 1.5, 1.6 and 1.6/SD at the ages of 50, 60, 70 and 80 years, respectively. This is comparable with the use of central DXA at the femoral neck for predicting these fracture outcomes (1.4, 1.5, 1.6 and 1.7/SD, respectively). In the case of hip fracture prediction, gradients of risk with clinical risk factors are higher than those to predict other osteoporotic fractures, but less than the gradients of risk provided by femoral neck BMD. For people aged 50 years, the gradient of risk with clinical risk factors is 2.1/SD (compared with 3.7/SD for DXA) and decreases with age, so that at the age of 80 years the gradient of risk is 1.8/SD (2.3/SD with DXA at the femoral neck). Despite the poorer relative performance of the clinical risk factors alone for hip fracture prediction, the gradient of risk is as good, if not better than that provided by many peripheral devices for the prediction of hip fracture. In a 10-year time frame, a technique with a gradient of risk of 2.0/SD would have a sensitivity of 35% and a positive predictive value of 13.6% when applied to men aged 65 years where 15% of the population is considered to be at high risk. The corresponding figures for women are 33% for sensitivity and 31% for positive predictive value (see section 7, Table 7.3).

A critical question in proposing the use of clinical risk factors alone for patient assessment relates to the reversibility by pharmacological intervention of the risk so identified. The efficacy of inhibitors of bone resorption has been well characterized in individuals with low bone mass. Their efficacy in individuals with normal bone density is less secure and it has been suggested that efficacy is less likely *(51)*. Many recent studies indicate, however, that pharmacological interventions have efficacy in patients with osteopenia or in whom BMD was not assessed *(19,52–57)*, although perhaps not those selected on the basis of a high risk of falling *(58)*.

A particular concern is whether treatment would be offered to individuals with normal BMD in whom the effects of treatment might be less than adequate. This question is not entirely resolved, but it should be noted that there are several precedents provided by interventions with estrogens and bisphosphonates *(52,59,60)*, and more variably with vitamin D with or without calcium *(19,20)*, that show anti-fracture efficacy when given to populations unselected on the basis of BMD. In addition, for patients selected only on the basis of a prior fragility fracture or glucocorticoid use, there is strong evidence for the reversibility of risk (see section 5).

A further argument for the use of clinical risk factors in the absence of BMD measurement is that their use generally selects individuals with low BMD. A good example is weight (or BMI) which can with age be used to predict low BMD. Tests, such as the osteoporosis self-assessment tool (see section 7), have high sensitivity for the detection of osteoporosis. The question arises as to what extent patients selected by additional clinical risk factors alone have low BMD independently of age.

This question has been addressed in one of the cohorts studied in section 5 (Sheffield). The cohort was a randomly drawn sample of elderly women (aged 75 years or more) from Sheffield *(61)*. Approximately 2000 women were assessed at baseline for risk factors for fracture, had a baseline BMD test performed at the femoral neck and were followed up 6-monthly to record fractures and deaths for 6700 patient–years.

In women characterized by significant risk factors without reference to BMD, mean BMD values decreased with increasing 10-year probability of fracture (Table 9.1). In women above an arbitrary risk threshold, 10-year probability was approximately 1 SD lower than in women below the threshold.

Table 9.1

Distribution of 10-year fracture probabilities in women assessed with and without BMD measurements

Fracture probability (% in 10 years)		BMD (g/cm^2)			
With BMD	Without BMD	Mean	95% CI	T-score (SD units)	Age (years)
<10					
10–15	15	0.93	0.86–1.00	-0.13	77.8
15–20	302	0.85	0.84–0.86	-0.75	78.5
20–25	621	0.76	0.75–0.77	-1.50	80.3
25–30	312	0.78	0.76–0.80	-1.33	79.5
30–35	509	0.74	0.73–0.75	-1.67	79.6
35–40	245	0.66	0.64–0.68	-2.33	82.1
40–45	55	0.69	0.64–0.74	-2.08	80.6
45–50	45	0.67	0.64–0.70	-2.25	80.6
50–55	9	0.57	0.45–0.69	-3.08	82.1

Source: reference 61 (modified from Table 3).

In the cohorts used for the meta-analyses it was possible to assess the effect of clinical risk factors on BMD. For this example, BMI was dichotomized (<19 kg/m2), thus providing seven clinical risk factors. In the absence of risk factors (53% of 31 385 men and women) the average Z-score for BMD was +0.08. With 1, 2, 3 or 4 clinical risk factors the average Z-score was -0.08, -0.24, -0.44 and -1.37, respectively. Thus individuals with, say, 3 clinical risk factors have on average a BMD that is 0.52 SD below those without risk factors. Similar findings have been reported in clinic-based studies where patient referrals follow the guidelines of the Royal College of Physicians, United Kingdom *(62)*.

9.2.1 Performance characteristics of the use of clinical risk factors

From knowledge of the gradient of risk, the impact of case-finding on the basis of the clinical risk factors can be computed where intervention thresholds are established. An example of intervention thresholds can be provided for the United Kingdom, as discussed in section 8. For 10-year hip fracture probability, these vary from 1.10 at the age of 50 years and rise with age (Table 9.2). The proportion of the population selected with the use of clinical risk factors alone, varies from 0.3% to 50% depending on age, and the average 10-year probability in those so identified to be at high risk, varies from 1.6% to 11.7% for hip fracture and from 8.6% to 22.9% for a major osteoporotic fracture.

Table 9.2

Performance characteristics of the use of clinical risk factors alone, bone mineral density (BMD) testing alone or in concert with the use of clinical risk factors to identify high risk women in a United Kingdom setting

Age (years)	Gradient of risk	Threshold probability[a]	% with BMD test	Proportion of population selected (%)	Average 10-year fracture probability in population selected		NNT[c]
					Hip	Osteoporotic[b]	
Risk factors alone							
50	2.05	1.10	0	3.1	1.6	8.6	33
60	1.95	2.64	0	2.6	3.3	13.6	21
70	1.84	5.24	0	20.5	6.6	18.9	15
80	1.75	8.52	0	46.9	11.7	22.9	13
BMD alone							
50	3.7	1.10	100	7.5	2.2	8.4	34
60	3.1	2.64	100	6.8	5.1	14.1	20
70	2.8	5.24	100	18.6	10.8	22.0	13
80	2.3	8.52	100	41.7	17.6	27.3	10
BMD ± clinical risk factors							
50	4.2	1.10	6.5	2.3	2.5	11.5	25
60	3.5	2.64	5.3	2.0	5.9	19.2	15
70	2.9	5.24	26.9	10.4	12.3	26.2	11
80	2.4	8.52	77.1	32.0	18.2	29.3	10

[a]Ten-year hip fracture probability.

[b]Clinical spine, distal forearm, hip or proximal humerus.

[c]Number needed to treat to prevent one osteoporotic fracture (defined as clinical spine, distal forearm, hip or proximal humerus), assuming an efficacy of 35%.

9.2.2 Application to clinical practice

The number of risk factors

An example of the use of clinical risk factors alone is given in Table 9.3 based on women from the United Kingdom with a BMI arbitrarily fixed at 24 kg/m2. Hip fracture probabilities are given according to the number of clinical risk factors present at different ages. The greater the number of risk factors, the higher the probability. The range reflects the differing importance of different clinical risk factors. These hip fracture probabilities can be categorized according to any chosen intervention threshold, for example that derived for the United Kingdom in section 8. Four categories of risk can thus be identified:

- Probabilities always below a threshold risk. Take, for example, in Table 9.3, an individual aged 50 years with two clinical risk factors. The average 10-year probability of hip fracture is 0.5% (range 0.2% – 1.1%) which lies consistently below the intervention threshold (>1.10% for 50 year olds).
- Probabilities sometimes above an intervention threshold. For example, the same clinical scenario, but in a woman aged 60 years,

gives an average 10-year hip fracture probability of 1.5%, which is below the intervention threshold (2.64% at the age of 60 years). However, the range of probabilities (0.9% – 2.7%) crosses the intervention threshold. Thus, her actual probability may exceed the threshold, depending on the nature of the two risk factors.

- Probabilities sometimes below an intervention threshold. An example is provided in women aged 50 years with four risk factors (probability = 1.8%, range 0.7% – 2.9%, compared to the age-specific intervention threshold of 1.10%).
- Probabilities consistently above a treatment threshold. For example, at the age of 80 years, the 10-year probability is 23% (range 13% – 37%) with three clinical risk factors, which exceeds the intervention threshold (8.52% at the age of 80 years), irrespective of the type of clinical risk factor.

Table 9.3

Ten-year probability (%) of hip fracture and a major osteoporotic fracture (hip, clinical spine, forearm or proximal humerus fracture) in women from the United Kingdom with a BMI of 24kg/m²

	Age[a] (years)							
	50		60		70		80	
Number of CRFs	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Hip fracture								
0	0.1	-	0.4	-	1.4	-	4.2	-
1	0.3	0.2–0.5	0.8	0.6–1.3	2.6	2.0–3.0	7.8	5.7–14
2	0.5	0.2–1.1	1.5	0.9–2.7	4.7	3.1–6.3	14	8.5–2.4
3	0.9	0.4–1.9	2.6	1.3–4.7	8.4	5.4–12	23	13–37
4	1.8	0.7–2.9	4.6	2.3–7.0	15	11–21	36	21–49
5	3.1	1.4–4.3	7.9	4.8–10	25	21–30	51	33–61
6	5.6	-	13	-	39	-	66	-
Forearm, spine, proximal humerus or hip fracture								
0	2.6	-	4.6	-	8.2	-	12	-
1	4.1	2.8–5.6	7.0	4.8–9.2	12	8.8–15	18	13–22
2	6.3	3.3–11	11	5.9–17	17	11–24	25	17–33
3	9.4	4.5–17	16	8.2–27	24	15–35	35	25–46
4	14	7.4–23	23	14–35	34	25–47	47	35–59
5	20	14–27	32	24–41	46	38–55	60	48–68
6	29	-	44	-	60	-	71	-

CRFs, clinical risk factors; -, no range.

[a]Intervention thresholds for 10-year hip fracture probability in the United Kingdom set at:age 50 years, 1.10%; age 60 years, 2.64%; age 70 years, 5.24%; age 80 years, 8.52%.

In practice, few individuals in the cohort material had four or more clinical risk factors (Table 9.4), which simplifies the tabular presentation

Table 9.4

Distribution (%) of clinical risk factors in men and women by age

Number of risk factors[a]	Age (years)				
	50–59	60–69	70–79	80–89	90+
Men					
0	39.0	43.8	51.9	61.3	43.1
1	44.4	42.3	39.0	32.9	54.9
2	15.0	13.0	8.5	5.6	2.0
3	1.6	0.9	0.6	0.2	0.0
Women					
0	66.4	56.0	56.0	60.3	64.5
1	29.1	36.6	36.6	34.6	33.2
2	4.3	6.8	6.7	4.7	2.3
3	0.2	0.6	0.6	0.3	0

[a] Excludes low BMI.

The categorization of women by age, the number of clinical risk factors and BMI is shown in Figs 9.1 and 9.2. Fig. 9.1 shows the categorization of women according to hip fracture probability, whereas Fig. 9.2 gives the corresponding probabilities for the major osteoporotic fractures. It is important to note that the categorization in each instance is based on thresholds of hip fracture probability.

Fig. 9.1

Ten-year probability of hip fracture in women from the United Kingdom, by age, body mass index (BMI) and the number of clinical risk factors (CRFs)

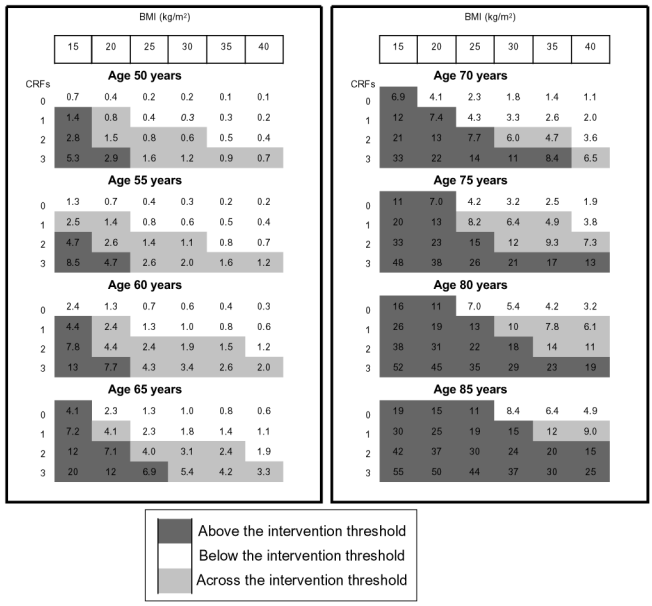
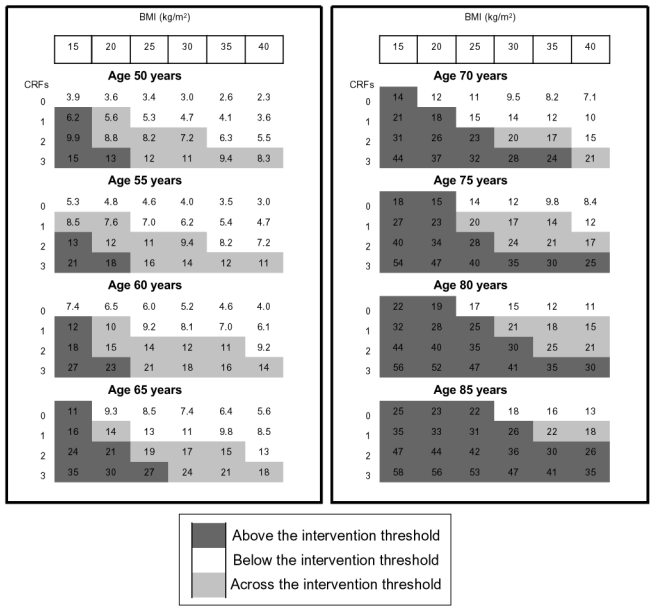


Fig. 9.2

Ten-year probability of a major osteoporotic fracture in women from the United Kingdom, by age, body mass index (BMI) and the number of clinical risk factors



Use of specific risk factors

Two or three clinical risk factors can readily be used in paper versions of the FRAX tool. Table 9.5 shows for women in the United Kingdom the way 10-year hip fracture probability is related to age, BMI and selected risk factors appropriate for the assessment of glucocorticoid-induced osteoporosis. A positive sign denotes probabilities that exceed the intervention thresholds given in section 8 for the United Kingdom. In women taking glucocorticoids but without other risk factors, probabilities do not exceed the intervention threshold except at the extremes of age and low BMI. Probabilities increase with the chronic use of glucocorticoids in the presence of a prior fragility fracture, so that more women exceed the intervention threshold. In the presence of glucocorticoid exposure and a prior fracture, the fracture probability exceeds the intervention threshold in all patients irrespective of age. Clinical judgement must, however, be exercised in the interpretation of risks, since the probabilities computed are for individuals on average doses of glucocorticoids. Patients taking higher than average doses will have higher fracture probabilities since there is a significant relationship between glucocorticoid exposure and fracture risk.

Table 9.5

Clinical scenarios where 10-year probabilities of hip fracture are characterized to be above (+) or below (-) an intervention threshold for women from the United Kingdom taking glucocorticoids, by age, BMI and the presence of a prior fragility fracture

	BMI (kg/m^2)				
Age (years)	15	20	25	30	35
Glucocorticoids					
50	+	-	-	-	-
60	+	+	-	-	-
70	+	+	-	-	-
80	+	+	+	+	-
Glucocorticoids and prior fracture					
50	+	+	+	+	+
60	+	+	+	+	+
70	+	+	+	+	+
80	+	+	+	+	+

Algorithms can also be developed for other clinical contexts. Examples include rheumatology clinics where the inclusion of rheumatoid arthritis would be of value (Table 9.6). The use of risk factors such as smoking and excessive alcohol use may be appropriate in the setting of general practice. Such algorithms can also be used either to direct patients for further tests, particularly for densitometry, or to avoid unnecessary densitometry. As described for glucocorticoid use above, clinical judgement should temper treatment decisions.

Table 9.6

Clinical scenarios where 10-year probabilities of hip fracture are characterized to be above (+) or below (-) an intervention threshold for women from the United Kingdom with rheumatoid arthritis, by age, BMI, glucocorticoids and prior fragility fracture

	BMI (kg/m^2)				
Age (years)	15	20	25	30	35
Glucocorticoids					
50	+	+	-	-	-
60	+	+	+	-	-
70	+	+	+	+	-
80	+	+	+	+	+
Prior fracture					
50	+	+	+	-	-
60	+	+	+	+	-
70	+	+	+	+	-
80	+	+	+	+	+
Glucocorticoids and prior fracture					
50	+	+	+	+	+
60	+	+	+	+	+
70	+	+	+	+	+
80	+	+	+	+	+

9.3 Case-finding with measurement of bone mineral density

In those Member States where BMD tests are widely used, any of the designated risk factors can be integrated with information on BMD. For simplified versions suitable for charts, the same general approach can be used as for case-finding without BMD, where BMD values are substituted for BMI. An example is given in Table 9.7 according to the number of risk factors in men and women at the age of 60 years. In this example, the BMI is set to 25 kg/m2 but, as shown in section 7, variations in BMI have little impact on computed probabilities in the presence of BMD.

Table 9.7

Average 10-year fracture probability (%) in men and in women from the United Kingdom (aged 60 years), by the number of clinical risk factors (range given in parentheses)

	Femoral neck BMD (T-score)			
Number of clinical risk factors	-4	-3	-2	-1
Osteoporotic fracture[a] in women				
0	23	12	7.7	5.5
1	32 (29–37)	18 (15–21)	11 (8.2–14)	8.1 (5.5–11)
2	44 (38–55)	26 (19–34)	16 (10–24)	12 (6.7–18)
3	58 (48–68)	35 (25–49)	23 (14–36)	16 (8.7–28)
Hip fracture in women				
0	13	4.3	1.4	0.4
1	20 (14–23)	6.7 (4.6–7.9)	2.1 (1.4–2.5)	0.7 (0.5–0.8)
2	29 (19–38)	10 (6.4–14)	3.3 (2.0–4.6)	1.0 (0.6–1.5)
3	41 (28–55)	15 (9.6–23)	5.0 (3.1–7.7)	1.6 (1.0–2.5)
Osteoporotic fracture[a] in men				
0	21	11	6.6	4.4
1	31 (28–35)	16 (14–19)	9.6 (7.3–12)	6.4 (4.4–8.5)
2	41 (35–51)	23 (18–29)	14 (9.5–20)	9.2 (5.5–14)
3	53 (44–62)	31 (24–42)	19 (13–29)	13 (7.3–22)
Hip fracture in men				
0	15	5.4	1.9	0.6
1	22 (16–26)	8.3 (5.7–9.7)	2.9 (2.0–3.4)	1.0 (0.7–1.1)
2	31 (22–40)	12 (8.0–17)	4.3 (2.8–5.9)	1.5 (0.9–2.0)
3	42 (31–54)	18 (12–25)	6.5 (4.2–9.4)	2.2 (1.4–3.3)

BMD, bone mineral density.

[a]Clinical spine, hip, forearm or proximal humerus.

In the United Kingdom, the intervention threshold at the age of 60 years is a hip fracture probability that exceeds 2.64%. This is exceeded in all men and women aged 60 years with a femoral neck T-score of –3 SD or less and, as expected, with a less stringent T-score in men and women with multiple risk factors. A more detailed estimate of probabilities (Table 9.8) shows that the intervention threshold is (coincidentally) rather close to that of the WHO thresholds for the diagnosis of osteoporosis. It should be noted, however, that the threshold is based on cost–utility analysis for the United Kingdom and different thresholds will pertain in different health-care settings.

Table 9.8

Ten-year probabilities of hip fracture and osteoporotica fracture in men and women from the United Kingdom without clinical risk factors according to the T-score for femoral neck bone mineral density (body mass index is set at 24 kg/m2): an intervention threshold of 2.64% for hip fracture probability is exceeded in women with a T-score of –2.6 SD or less and in men with a T-score of –2.2 SD or less

T-score (SD)	Women		Men	
	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip
-2	7.62	1.35	6.53	1.85
-2.2	8.28	1.71	7.18	2.29
-2.4	9.05	2.16	7.94	2.85
-2.6	9.94	2.72	8.83	3.53

[a]Fracture of hip, spine, forearm or proximal humerus.

In the presence of risk factors, an average together with an interval is given since the risk will vary according to the nature of the clinical risk factor, in much the same way as discussed for BMI (section 9.2). In many instances, the range is clearly above or clearly below the intervention threshold. An exception in Table 9.7 is for hip fracture in women with two risk factors and a T-score of –2 SD at the femoral neck (average 3.3%; range 2.0% – 4.6%). Thus, the average probability exceeds the nominal intervention threshold. The opposite pertains in men with a T-score of –1 and three clinical risk factors (average 2.2%; range 1.4% – 3.3%) in that the average risk lies below the threshold but the range exceeds this. As for BMI, this permits the characterization of probability estimates as:

- always below the threshold;
- always above the threshold;
- average above the threshold, but sometimes below;
- average below the threshold, but sometimes above.

The characterization of probabilities in this manner according to age and T-score is shown in Table 9.9. An interesting feature is that, although probabilities increase with age, the increase is less than when BMI, rather than BMD is used. For example, in the presence of a single clinical risk factor and with a T-score of –1 SD, the 10-year hip fracture probability ranged from 0.4% at the age of 50 years to 4.0% at the age of 80 years; a 10-fold difference (see Table 9.9). Women with a single clinical risk factor and a BMI of 24 kg/m^2 at the age of 50 years had a similar hip fracture probability (0.3%) but the probability increased more than 25-fold to 7.8% at the age of 80 years (see Table 9.3). Thus the use of BMD captures age-dependent risk more completely than the use of BMI.

Table 9.9

Average 10-year probability of hip fracture in women from the United Kingdom, by the number of clinical risk factors (body mass index is set at 24 kg/m²)

Number of clinical risk factors	Femoral neck BMD (T-score)					
	-4	-3	-2	-1	0	+1
Age 50						
0	12[a]	3.1[a]	0.8	0.2	0.1	0.0
1	18[a]	5.0[a]	1.3[a,b]	0.4	0.1	0.0
2	27[a]	8.0[a]	2.1[a]	0.6	0.2	0.0
3	39[a]	12[a]	3.4[a]	0.9[c]	0.2	0.1
Age 60						
0	13[a]	4.3[a]	1.4	0.4	0.1	0.0
1	20[a]	6.7[a]	2.1	0.7	0.2	0.1
2	29[a]	10[a]	3.3[a,b]	1.0	0.4	0.1
3	41[a]	15[a]	5.0[a]	1.6	0.5	0.2
Age 70						
0	16[a]	6.2[a]	2.3	0.9	0.4	0.1
1	25[a]	10[a]	3.9	1.5	0.6	0.2
2	38[a]	16[a]	6.4[a,b]	2.5	1.0	0.4
3	53[a]	25[a]	10[a]	4.2[c]	1.7	0.7
Age 80						
0	19[a]	9.2[a]	4.3	2.1	1.0	0.5
1	31[a]	17[a]	8.1[a,b]	4.0[c]	2.0	1.0
2	45[a]	27[a]	14[a,b]	7.3[c]	3.6	1.8
3	59[a]	40[a]	23[a]	13[a,b]	6.4[a]	3.2

[a]Average value above a treatment threshold.

[b]Some values in the range below a treatment threshold.

[c]Some values in the range above a treatment threshold.

Examples of the use of specific risk factors (rather than the number of risk factors) are given in Table 9.10 in the context of glucocorticoid-induced osteoporosis. In the United Kingdom setting, probabilities exceed an intervention threshold in women taking glucocorticoids at a T-score below –2 SD at the femoral neck (below –1 SD at the age of 50 years). In the presence of a prior fracture, intervention probabilities are exceeded with a T-score of somewhat less than –1 SD.

Table 9.10

Clinical scenarios where 10-year hip fracture probabilities are characterized to be above (+) or below (-) an intervention threshold in men and women from the United Kingdom taking glucocorticoids, by age, T-score for bone mineral density, and the presence of a prior fragility fracture

	T-score in men					T-score in women				
Age (years)	-4	-3	-2	-1	0	-4	-3	-2	-1	0
No risk factors										
50	+	+	+	-	-	+	+	-	-	-
60	+	+	-	-	-	+	+	-	-	-
70	+	+	-	-	-	+	+	-	-	-
80	+	-	-	-	-	+	+	-	-	-
Glucocorticoids										
50	+	+	+	-	-	+	+	+	-	-
60	+	+	+	-	-	+	+	-	-	-
70	+	+	-	-	-	+	+	-	-	-
80	+	-	-	-	-	+	+	-	-	-
Glucocorticoids and prior fracture										
50	+	+	+	+	-	+	+	+	-	-
60	+	+	+	-	-	+	+	+	-	-
70	+	+	+	-	-	+	+	+	-	-
80	+	+	-	-	-	+	+	+	-	-

A more detailed appraisal derives an intervention threshold for women taking glucocorticoids and with a prior fracture. Hip fracture probabilities exceed an intervention threshold with T-scores of –1.2, –1.6 and –1.9 SD, respectively, at the age of 50, 60, and 70 years and above (data not shown). In women with the same clinical scenarios but who have rheumatoid arthritis, the respective T-score thresholds are –1.0, –1.3 and –1.5 SD.

The use of T-score thresholds is a further approach by which a number of clinical risk factors can be evaluated. A similar approach has been used for targeting lipid-lowering drug therapy in coronary artery disease (63). Its adaptation to hip fracture risk is shown in Table 9.11 for up to four clinical risk factors in any combination. The relevant combinations of risk factors are found at the head of the table. The main body of the table gives T-scores according to age. For example, for a woman with a prior fracture and taking long-term glucocorticoids, a T-score value is given at –1.2 SD at the age of 50 years. If a woman has a T-score at that value or lower, then her fracture probability exceeds an intervention threshold.

Table 9.11

Table for targeting intervention[a] in women from the United Kingdom, by clinical risk factors (upper panel) and T-score for femoral neck bone mineral density (lower panel)

	Number of clinical risk factors															
	4	3				2						1				0
Prior fracture	+	-	+	+	+	+	+	+	-	-	-	+	-	-	-	-
Family history	+	+	-	+	+	+	-	-	+	+	-	-	+	-	-	-
Smoking	+	+	+	-	+	-	+	-	+	-	+	-	-	+	-	-
Glucocorticoids	+	+	+	+	-	-	-	+	-	+	+	-	-	-	+	-
Age (years)																
50	-0.8	-1.3	-0.8	-1.2	-1.3	-1.6	-1.3	-1.2	-1.8	-1.8	-1.4	-1.7	-2.2	-1.8	-1.8	-2.3
60	-1.1	-1.6	-1.1	-1.5	-1.6	-2.1	-1.6	-1.6	-2.1	-2.0	-1.6	-2.1	-2.6	-2.2	-2.1	-2.6
70	-0.5	-1.0	-1.3	-1.0	-1.1	-1.7	-1.9	-1.9	-1.6	-1.5	-1.8	-2.4	-2.1	-2.4	-2.3	-2.9
80	+0.7	+0.3	-1.4	+0.1	0	-0.6	-2.0	-1.9	-0.4	-0.3	-1.7	-2.6	-1.0	-2.4	-2.3	-3.0

[a]A patient whose value falls at or below the T-score given has a probability of fracture that exceeds an intervention threshold.

9.3.1 Performance characteristics of case-finding with measurement of bone mineral density

The impact of case-finding on the basis of BMD tests alone is shown in Table 9.2 for women in the United Kingdom. The proportion of the population selected to be above a treatment threshold varies from 7.5% at the age of 50 years to 41.7% at the age of 80 years, with a 10-year hip fracture probability that ranges from 2.2% to 17.6%, respectively. When this strategy is compared with the use of clinical risk factors alone, BMD testing in all individuals identifies a higher risk population because of the higher gradient of risk. At younger ages, a higher proportion of patients is identified above the treatment threshold, whereas at older ages fewer are selected than by using clinical risk factors alone. Overall, the proportion of the population selected varies little between strategies, but a higher risk group is selected where BMD tests are used.

9.3.2 Approaches to practice guidelines

The combination of assessments with and without BMD can be used to form a basis for the development of practice guidelines. An example is provided in Fig. 9.3, in the context of patients with rheumatoid arthritis taking glucocorticoids. In women with rheumatoid arthritis and a prior fragility fracture, hip fracture probabilities are sufficiently high that treatment might be recommended from the age of 50 years irrespective of other clinical risk factors, since probabilities consistently exceed the treatment threshold. For women without fractures, BMD measurement might therefore be reserved for women without a prior fracture. As noted above, intervention thresholds, based on cost–utility are then a T-score of –1.0, –1.3 or –1.5, respectively, at the ages of 50, 60, and 70 years or older. In practice, BMD might be measured in all patients in order to form a baseline for monitoring treatment, but the decision to treat is not predicated by the measurement.

Fig. 9.3
Assessment algorithms for women with rheumatoid arthritis taking glucocorticoids

BMI, body mass index; BMD, bone mineral density.

It is important to recognize that the example above is based on probabilities derived from individual clinical scenarios, rather than on populations. In developing practice guidelines, consideration of populations is relevant; somewhat different conclusions might be derived where decision trees are based on population-based probabilities or cost–utility. For example, in Fig. 9.3, a decision step is taken in women aged 60–69 years without a prior fracture on the basis of BMD at or below a T-score of –1.3 SD. The rationale is that a woman with a T-score of –1.3 can be cost-effectively treated, whereas at a value of –1.0 SD intervention is cost ineffective. In populations it may well be cost effective to treat all women with a BMD T-score of less than, say, –1.0 SD.

The manner in which the use of other clinical risk factors can be combined with BMD is discussed in the following section.

9.4 Selective use of bone mineral density with clinical risk factors

The scenarios given in sections 9.2 and 9.3 consider the use of BMD with clinical risk factors or the use of clinical risk factors alone, i.e. the use of BMD in all case-finding or in none. It is possible, however, to envisage scenarios between these extremes. Such strategies would be appropriate for those Member States where access to DXA is limited. A primary objective of a case-finding strategy in osteoporosis is to identify individuals above or

below a threshold fracture risk. When patients are categorized by risk factors alone, the following categories pertain:

- individuals much above a threshold risk;
- individuals close to a threshold risk in whom BMD might be measured to more accurately categorize risk;
- individuals much below a threshold risk.

It might be assumed that patients in the first or last categories above are unlikely to have their categorization of risk changed by performing a BMD test. The assumption can be tested by determining the probability that a BMD test would change an individual's categorization from high to low risk or vice versa.

This requires a consideration of the concordance of risk assessment with clinical risk factors alone and in combination with BMD. The Sheffield cohort has been used by way of illustration *(61)*, taking BMI and glucocorticoid use as risk factors. An intervention threshold for any fracture was arbitrarily set at a 10-year probability of 35% (close to an individual at the threshold for osteoporosis).

The 10-year fracture probabilities were computed in the absence of a BMD measurement and with the inclusion of BMD, and the discordance in classification of individuals (above or below the intervention threshold) was examined using the two approaches. With the use of clinical risk factors alone, the 10-year probability of fracture ranged from 11% to 55% with a mean of 28% (± SD 7%). Approximately 17% of women lay above the treatment threshold of a 35% 10-year fracture probability (Table 9.12) when based on the use of clinical risk factors alone. When BMD was undertaken, 210 women (10%) changed category from low risk to high risk and 109 women (5%) changed category from high risk to low risk. Thus, errors of classification were found in a minority (210 + 109 women, or 15%).

Reclassification was most frequent close to the threshold value chosen (see Table 9.12). Conversely, errors were less frequent the larger the difference between the calculated probability using clinical risk factors and the intervention threshold. For example, no women with a probability of fracture between 0% and 15% were re-classified and none with a probability of more than 50% needed to be reclassified with the additional use of BMD. This indicates an important principle, namely that not all patients require a BMD test to assess fracture risk.

Table 9.12

Distribution of 10-year fracture probabilities in women assessed with and without bone mineral density (BMD) measurements

Fracture probability (% in 10 years)	Number of women			Percentage reclassified with BMD
	Assessed without BMD	Assessed with BMD	Reclassified	
0–5				
5–10		9		
10–15	15	76		
15–20	302	349	1	0.04
20–25	621	502	9	0.42
25–30	312	399	36	1.70
30–35	509	323	164	7.76
Subtotals (0–35)	**1 759**	**1 658**	**210**	
35–40	245	218	99	4.68
40–45	55	126	8	0.38
45–50	45	59	2	0.09
50–55	9	35		
55–60		10		
60–65		6		
65–70		1		
70–75				
Subtotals (35+)	**354**	**455**	**109**	

Source: reference 61 (adapted from Table 3).

9.4.1 Threshold probabilities of risk for assessment of bone mineral density

Threshold probabilities can be used to determine the proportion of the population in whom BMD assessment would be required to optimize a case-finding strategy. If P_1 is the probability accepted of reclassifying a high-risk patient to low risk, then if P_1 is exceeded a BMD measurement would be required. Similarly, if P_2 is the probability accepted of reclassifying a low-risk patient as high risk, then a BMD measurement would be required if P_2 is exceeded.

The proportion of patients that require a BMD test is shown in Table 9.13 according to the probability of reclassification. If a very low probability of reclassification is accepted, say P_1 and $P_2 = 0.0$, then 354 patients judged to be at high risk without BMD would require a BMD measurement, and 1759 patients judged clinically to be at low risk would require a BMD measurement (i.e. the whole sample). At the other extreme, accepting a higher probability of reclassification of say 0.5, then 59 individuals (2.8% of total)

would require a BMD measurement. A higher probability of misclassification might be accepted for high to low risk (e.g. $P_1 = 0.8$), whereas a low probability might be accepted for low to high risk (e.g. P2 = 0.2). Under these assumptions, no individuals considered to be at high risk would require a BMD measurement since the probability of reclassification was consistently less than 0.8. In contrast, 452 women classified initially at low risk would require a BMD test, representing 21% of the population. This strategy implies that 13% (59 of 455) high-risk women were not detected and the proportion of reclassified women of the whole population was 8% (59 + 109 of 2113). The requirements for BMD testing for other permutations of P_1 and P_2 are given in Table 9.13.

Table 9.13

Percentage of 2113 women aged 75 years or more in whom bone mineral density (BMD) tests would be required to classify a fracture risk according to the probabilities of misclassification accepted[a]

	P_2					
P_1	0	0.1	0.2	0.3	0.4	>0.5
0	100	47.8	38.1	30.6	22.9	16.8
0.1	96.4	44.2	34.5	27.0	19.2	13.1
0.2	94.9	42.7	33.1	25.6	17.8	11.7
0.3	92.7	40.5	30.9	23.3	15.6	9.5
0.4	89.9	37.7	28.0	20.5	12.7	6.6
0.5	86.0	33.8	24.2	16.7	8.9	2.8
>0.6	83.2	31.0	21.4	13.9	6.1	0

Source: reference 61 (Table 4).

P_1 , the probability of reclassifying a patient at high risk to low risk with a BMD test.

P_2 , the probability of reclassifying a patient at low risk to high risk with a BMD test.

[a]The threshold between high and low risk was set at 35% ten-year fracture probability, which was found in 16.8% of the population if a BMD test was not used. Given the assumptions described in the text (P_1> 80% and P_2>20%), BMD measurements would be required in 21.4% of the population.

The clinical characteristics of women allocated to high and low risk using the example above is shown in Table 9.14. As expected, there were highly significant differences in the risk indicators, as well as in the fracture outcomes. The T-score for BMD at the hip was –2.96 SD for the high-risk group and –1.79 SD for the low-risk group.

Table 9.14

Clinical characteristics of women identified at high or low risk using clinical risk factors and the selective use of bone mineral density (BMD) tests: base case where P_1=0.8 and P_2=0.2

	Low risk	High risk	P<
Age (years)	79.6 ± 3.7	81.1 ± 4.3	0.001
Height (cm)	156 ± 6	154 ± 6	0.001
Weight (kg)	67.3 ± 11.6	56.7 ± 8.8	0.001
BMI (kg/m2)	27.6 ± 4.4	23.6 ± 3.3	0.001
Prior fracture (%)	36.6	97.2	0.001
Hip BMD (g/cm2)	0.79 ± 0.12	0.64 ± 0.13	0.001
T-score <–2.5 SD (%)	22	73	0.001
Corticosteroids (%)	4.9	24.0	0.001
Subsequent fracture (%)	10.9	21.0	0.001
Subsequent osteoporotic fracture (%)	8.6	18.8	0.001
Subsequent hip fracture (%)	2.0	5.7	0.001

Source: reference 61 (Table 5).

P_1, the probability of reclassifying a patient at high risk to low risk with a BMD test.

P_2, the probability of reclassifying a patient at low risk to high risk with a BMD test.

BMI, body mass index.

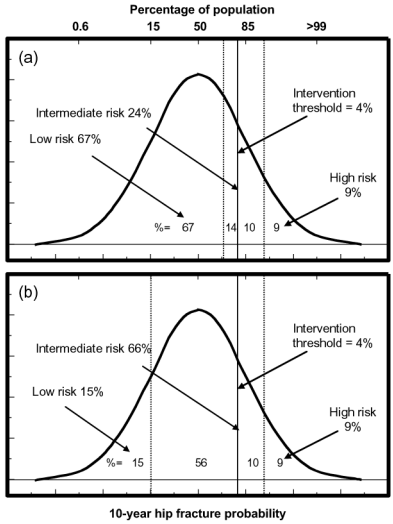
The same principles could be applied to screening *(64–67)* and thereby improve the cost–effectiveness of screening by decreasing the burden of BMD tests required.

The present example is confined to a randomly selected cohort of women aged 75 years or more from the United Kingdom. The prevalence of risk factors and their importance for fracture prediction will, however, differ by age and sex and possibly also in different regions of the world. For this reason, these data should not be applied to other settings, although the general principles still apply.

A further example is provided in Fig. 9.4, which shows the distribution of risk in women aged 65 years drawn from the European cohort material for the meta-analyses performed in section 5, comprising the Sheffield Cohort, the Rotterdam Study, OFELY, Kuopio and the two cohorts from Gothenburg. A total of 12 027 men and 33 157 women aged 50 years or more were studied. Approximately 250 000 patient years of follow-up were available, during which time there were approximately 1100 hip fractures. The clinical risk factors included age, BMI (higher or lower than 25 kg/m2), previous fragility fracture, a maternal history of any fragility fracture, smoking (ever versus never), long-term use of glucocorticoids, and secondary causes of osteoporosis *(68)*.

Fig. 9.4

Distribution of 10-year hip fracture probability in women aged 65 years from the EVOS/EPOS, Sheffield, Rotterdam, OFELY, Kuopio and Gothenburg studies, with an intervention threshold of 10-year hip fracture probability set at 4%: (a) categorization of individuals from risk assessment giving a category at low risk (67%), a category at high risk (9%), and an intermediate category of risk (14% + 10%) in whom risk stratification is improved by the additional measurement of BMD; (b) categorization with a more liberal use of BMI tests



EVOS, European Vertebral Osteoporosis Study; EPOS, European Prospective Osteoporosis Study; OFELY, L'os des femmes de Lyon; BMD, bone mineral density; BMI, body mass index.

In this example of women aged 65 years, the intervention threshold was set at a 10-year hip fracture probability of 4% and reclassification probabilities were set at P_1=0.8 and P_2=0.2. Thus BMD tests could be avoided in 67% of women because of very low risk and in 9% because of very high risk. Furthermore, BMD could aid in the risk stratification in 24% of the women (14% who lay below the threshold based on clinical risk factors alone plus 10% who lay above the threshold based on clinical risk factors alone). In practice, thresholds can be set at any limit. A further example is given in Fig. 9.3.

9.4.2 Application to the United Kingdom

When the intervention thresholds are used for the United Kingdom, the limits around the threshold can be set according to the probabilities accepted for reclassification when information from BMD is added to that derived from clinical risk factors. The upper and lower limits are given in Table 9.15, where the probabilities of reclassification are set at P_1=0.8 and P_2=0.2, as discussed above. For example, at the age of 50 years, an individual with a 10-year hip fracture probability of anywhere between 0.92% and 1.91% on the basis of clinical risk factors alone would have a BMD test to more accurately

characterize probability. Where the combination of the clinical risk factors and BMD give a probability that exceeds the intervention threshold, treatment would be recommended.

Table 9.15

Performance characteristics for the use of clinical risk factors and the selective use of bone mineral density (BMD) tests

Age (years)	Intervention threshold[a]	Upper and lower limits[b]	% tested by BMD	% selected for treatment	False negatives[c] (%)
50	1.10	0.92–1.91	6.5	2.3	5.3
55	1.81	1.48–2.87	3.8	3.1	4.0
60	2.64	2.27–4.68	5.3	4.4	4.9
65	3.70	3.21–8.70	18.9	15.9	9.1
70	5.24	3.03–13.38	26.9	10.4	8.9
75	6.87	5.30–18.72	45.0	17.5	6.7
80	8.52	2.95–25.58	77.1	32.0	1.6
85	8.99	3.48–27.24	90.9	42.5	0.5

[a]Ten-year hip fracture probability.

[b]P_1 and P_2 set at 0.8 and 0.2, respectively, where P_1 is the probability of reclassifying a patient at high risk to low risk with a BMD test, and P_2 is the probability of reclassifying a patient at low risk to high risk with a BMD test.

[c]Individuals at high risk unselected by the strategy.

Table 9.15 also shows the effect of such a strategy on the requirements for BMD testing. The proportion of the population screened with BMD varies from 4% to 90%, depending on age. The proportion selected for treatment varies from 2.3% at the age of 50 years to 42.5% at the age of 85 years. The false negative rate, i.e. those who are categorized at low risk but with a BMD measurement would have been designated at high risk, is consistently less than 10%.

9.4.3 Performance characteristics of selective use of bone mineral density

The performance characteristics of the selective use of BMD measurement in conjunction with clinical risk factors is shown in Table 9.2 and compared with use of BMD alone or the clinical risk factors alone. When compared with the use of BMD alone, the selective use of BMD with clinical risk factors identifies a slightly lower proportion of women above an intervention threshold. This, however, is not at the expense of fracture risk in the population identified. Indeed, fracture probabilities were higher, because of the higher gradients of risk. The major difference between the use of BMD alone and its use with clinical risk factors lies in the number of BMD measurements required.

A further way of assessing performance characteristics is to compare the selective use of BMD using the FRAX algorithm with the guidance currently given in Europe, whereby individuals with a clinical risk factor are recommended for a BMD test, and recommended for treatment where the T-score for BMD is <–2.5 SD. There are thus three categories of individual identified: those with clinical risk factors and osteoporosis; those with one or more clinical risk factors but without osteoporosis; those without clinical risk factors. Only the first category is treated.

The FRAX algorithm is highly specific (Table 9.16). For example, at the age of 50 years, 27 individuals are identified for treatment, of whom 25 have a 10-year hip fracture probability that lies above the intervention threshold described for the United Kingdom in section 8. By contrast, the sensitivity is low. At the age of 50 years, 68 high-risk individuals are not detected (61+7; Table 9.16), the majority of whom have a clinical risk factor. Thus, only 27% of high-risk individuals are detected at 50 years of age, a proportion that rises to 47% at the age of 80 years. Therefore, the majority of high-risk patients are not detected.

Table 9.16

Simulation of Royal College of Physicians guidelines by age, where N is the number of individuals in each triage category per 1000 of the population at that age, and n is the number of individuals per 1000 with a 10-year hip fracture probability that exceeds an intervention threshold for the United Kingdom

	Individuals with CRF and osteoporosis		Individuals with CRF but no osteoporosis		No CRF	
Age (years)	N	n	N	n	N	n
50	27	25	512	61	461	7
60	65	52	487	23	448	6
70	115	100	455	73	430	36
80	189	168	401	94	410	93

CRF, clinical risk factor.

These performance characteristics of the guidelines of the Royal College of Physicians *(6)* can be compared with the use of clinical risk factors and the selective use of BMD tests. An example is shown in Table 9.17. In this example, P_1 and P_2 are set so that the total numbers of BMD tests are similar to those required to fulfil the Royal College of Physicians guidance. At the age of 50 years, 88% of high-risk individuals are detected compared with 27% with the Royal College of Physicians algorithm. Thus, for the same number of BMD tests, many more high-risk individuals are detected by taking account of that component of risk given by the clinical risk factors.

Table 9.17

A comparison of the performance of the guidance of the Royal College of Physicians (RCP) and the use of clinical risk factors (CRFs) with the selective use of bone mineral density (BMD)

	RCP guidance			CRFs ± BMD		
Age (years)	BMD tests[a]	High-risk patients detected (%)	Efficiency of BMD tests[b]	BMD tests[a]	High-risk patients detected (%)	Efficiency of BMD tests[b]
50	539	27	4.2	538	88	15.2
60	552	64	9.4	507	90	14.3
70	570	48	17.5	552	82	31.1
80	592	47	28.4	562	85	53.5

Source: reference 6 and authors' estimates.

[a]Per thousand individuals at each age.

[b]Percentage of BMD tests where a high risk individual is selected.

An alternative view is that fewer BMD tests are required to identify the same number of high-risk individuals with the use of clinical risk factors than with the Royal College of Physicians guidance.

Savings in BMD testing have been independently found in the EPIDOS study *(69)* in women aged 75 years or more followed for an average time of 3.9 years. The treatment threshold was set at a twofold increase in hip fracture risk. When a triage system was used, 10% of women required a BMD test, compared with 50% using the current case-finding strategy recommendations in Europe *(23,49)*.

It should be acknowledged that physicians may be reluctant to give pharmacological interventions without objective evidence of a diagnosis of osteoporosis or other BMD threshold. In practice, BMD testing might be considered in individuals characterized at high risk, but in whom a test was not required for this purpose, in order to establish a baseline for monitoring treatment. In such cases it might be appropriate to measure BMD at the lumbar spine, rather than the hip, if it could be shown that the spinal site is more predictive of the effects of pharmacological interventions. In other words, a BMD test would be done in order to judge the effects of treatment rather than to decide whom to treat. This approach may be more logical than BMD testing at the hip and may still be relatively economic

9.4.4 Alternative strategies for the selective use of bone mineral density

The examples given above have used a fixed probability of reclassification of fracture risk to determine the requirements for BMD testing (e.g. $P_1 = 0.8$; $P2 = 0.2$). This results in a given proportion of the population receiving a BMD test at any given age. The proportion varies from 6.5% at the age of 50 years to 77% at the age of 80 years (see Table 9.15). These probabilities are, however, arbitrary and could be set at a number of different levels (see Fig.

9.4), depending upon clinical considerations, or health economic or public health criteria. The effect of varying the proportions of the population having a BMD test is shown in Tables 9.18 and 9.19, where the number of BMD tests at any age is varied from 10% to 50%.

Table 9.18

Number of women selected at high risk (per 1000) above the United Kingdom intervention threshold, by age and the number of bone mineral density (BMD) tests per 1000 women

Age (years)	Number of BMD tests/1000				
	100	200	300	400	500
50	17	27	37	42	49
55	21	24	31	33	36
60	31	53	55	50	60
65	144	164	185	197	210
70	283	308	325	343	355
75	443	461	482	501	511
80	679	705	721	703	636

Table 9.19

Number of high-risk women selected (per 1000) who would sustain a hip fracture over 10 years, by age and the number of bone mineral density (BMD) tests per 1000 women

Age (years)	Number of BMD tests/1000				
	100	200	300	400	500
50	<1	1	1	1	1
55	1	1	2	2	2
60	2	3	3	3	4
65	10	11	12	13	14
70	23	26	28	30	30
75	47	49	52	54	55
80	90	94	96	95	93

Increasing the number of BMD tests increases the number of women categorized at high risk using the intervention threshold for the United Kingdom (Table 9.18). The effect is more marked in the younger women. For example, increasing the number of BMD tests from 200 to 400 per 1000 women at the age of 50 years nearly doubles the number of high risk women selected (from 27 to 42). In contrast, when increasing the number of tests in the same way in women aged 75 years, the number of high risk women is increased by approximately 10% (from 461 to 501). The gain in the number of women selected who would sustain a hip fracture is modest at the age of 50 years, where the absolute risk of hip fracture is low, but more evident in elderly women (see Table 9.19). Thus, increasing the number of tests from 200 per 1000 to 400 per 1000 would identify an additional 5 hip fracture cases per

1000 at the age of 75 years, whereas at the age of 50 years the additional number would be less than 1 (0.3 per 1000).

9.5 Resource implications for dual energy X-ray absorptiometry

Estimates have been made of the potential requirements for DXA in Europe using several possible strategies for osteoporosis management *(68)*. The first strategy to be considered was screening with the use of BMD, targeted to women at the age of 65 years, assuming 100% compliance. This age was chosen since screening of women at 65 years of age with BMD tests is advocated in some Member States *(50,66)*, and health economic analyses in Europe and the United States suggest that a meaningful proportion of women at this age have a fracture risk above a threshold at which intervention becomes cost effective. In addition to screening women at the age of 65 years, account was taken of the requirements for those aged 66 years or more, amortized over a 10-year interval.

The second strategy to be considered was a screening policy based on the elicitation of clinical risk factors every 10 years in women from the age of 65 years. BMD tests would be offered in those close to a threshold risk, as outlined above *(61)*. It was assumed that all patients identified above the risk threshold would have a BMD test (femoral neck or lumbar spine), which would be repeated in 2 years.

The third scenario was a case-finding strategy that is currently applied in several European countries and supported by the European Union *(6,23,48,49)*. This envisages the referral of women with strong risk factors for fracture for densitometry. The risk factors examined were low body mass index (<19kg/m^2), prior fragility fracture, current or ever long-term use of glucocorticoids, parental history of hip fracture, secondary causes of osteoporosis (e.g. rheumatoid arthritis), excessive alcohol use (>2 units daily) and current smoking. It was additionally assumed that individuals over the age of 65 years would be tested over the ensuing 10 years.

9.5.1 Current use of dual energy X-ray absorptiometry

A survey was undertaken of the Committee of Scientific Advisors of the International Osteoporosis Foundation to determine the service use of DXA (68). Details of service throughput were provided by the 23 centres that responded. On average, 3000 patients were screened annually per centre, with a staffing requirement of 2.39 full-time equivalents to service this workload. On average 1256 patients were scanned by each DXA unit per year, usually (91%) at both the lumbar spine and proximal femur. This information provided the basis for the assumptions used in the analysis below.

9.5.2 Requirements of dual energy X-ray absorptiometry for risk assessment

The first strategy envisaged screening all women with DXA at the age of 65 years. The target population comprises the 4 045 000 women in Europe at the age of 65 years (70). That target population would require 3231 DXA units, or 4.42 DXA machines per million of the total population. That calculation ignores the unscreened population aged 66 years or more. If women aged 66 years or more are included and assuming that they are screened over a 10-year period, the requirement for DXA units would be 6.79 per million of the total population, giving a total requirement of 11.2 units per million (Table 9.20).

Table 9.20

Requirements for dual energy X-ray absorptiometry (DXA) units for assessment of women using three different scenarios, and the requirements to monitor treatment in women at the age of 65 years and in women above this target age, amortized over 10 years

	Age 65 years		Age >65 years		Total	
Strategy	Units	Units/million	Units	Units/million	Units	Units/million
Screening women with BMD	3 321	4.42	4 944	6.79	8 165	11.21
Clinical case-finding with selective use of BMD	767	1.05	2 301	3.16	3 068	4.21
Classic case-finding strategy	1 481	2.03	2 423	3.33	3 904	5.36
Monitoring treatment	966	1.33	3 686	5.06	4 652	6.39

Source: reference 68 (Table 2).

BMD, bone mineral density.

The second strategy envisaged screening women at 10-yearly intervals by clinical risk factors, and referring a proportion of those women for DXA. From the distribution of hip fracture risk determined by the use of clinical risk factors at the age of 65 years, and an intervention threshold set at a 10-year hip fracture probability of 4%, screening all women at the age of 65 years would require 767 DXA units or 1.05 per million of the total population. Also testing women over the age of 65 years over 10 years would give an additional requirement of 2301 DXA units or 3.16 per million of the population, with a total requirement of 4.21 units per million (see Table 9.20).

The third strategy was to identify women with strong risk factors for fracture and refer these for densitometry. The prevalence of these risk factors (Table 9.21) varied from approximately 29% to 46%, depending on age. BMD tests at the age of 65 years would require 1481 units or 2.03 units per million of the total population. If BMD tests were also to be undertaken in women aged more than 65 years with these risk factors at a prevalence of 46%, then approximately 30 million women would require testing, or 3 million per year amortized over a 10-year interval, resulting in a requirement of 2423 scanners in Europe. This is equivalent to 3.33 units per million of the population (see Table 9.20).

Table 9.21

Prevalence (%) of risk factors for fracture in European women and men

Age range (years)	Low BMI	Current smoking	Prior fracture	Glucocorticoids	Parental history hip fracture	Rheumatoid arthritis	Alcohol 3+ units	Any risk factor
Women								
50–59	1.3	16.2	17.8	4.5	5.1	-	16.1	28.7
60–69	1.5	18.4	25.8	4.5	6.4	-	14.1	36.5
70–79	2.1	10.4	31.7	5.8	7.1	2.4	10.0	35.3
80–89	4.0	4.7	31.3	4.6	4.9	2.2	7.2	32.4
90+	0.8	3.7	22.0	2.2	6.9	7.9	0.0	26.8
Men								
50–59	0.5	35.2	37.2	3.2	7.8	-	42.3	43.9
60–69	1.2	28.5	29.7	3.2	9.6	-	38.8	42.0
70–79	1.4	22.4	25.0	3.4	8.0	-	35.0	38.4
80–89	4.6	21.3	15.8	2.2	6.0	-	32.4	31.1
90+	7.7	42.4	8.6	2.9	33.3	-	50.0	62.9

BMI, body mass index; -, no data.

9.5.3 Requirements of dual energy X-ray absorptiometry to monitor treatment

Two BMD tests could be envisaged in women committed to treatment. The requirements for DXA differ between the scenarios, since some patients would have had a BMD test for assessment and not require a further BMD test at the start of treatment.

For the selective use of BMD (the second strategy in Table 9.20), the steady state requirements would be 3068 scanners or 4.21 units per million of the population. The annual requirement for monitoring is for 4652 scanning units and a requirement of 6.39 units per million of the general population (see Table 9.20). Thus, the total for assessment plus monitoring of treatment is 10.6 scanning units per million of the total population.

The estimated requirements for DXA are relatively sound, in the sense that they are largely based on population demography. The major uncertainty relates more to the impact of the strategies modelled. For the three assessment strategies, an uptake of 100% is assumed, which is highly improbable in any country. Rather, the numbers estimated should be taken as the maximum requirements for each scenario. Uptake will vary according to the health-care setting (particularly reimbursement for DXA), and health-care priorities, since the capital costs of DXA are similar throughout Europe.

Not surprisingly, the requirement for DXA is greatest for the scenario of widespread population screening, where in excess of 8000 densitometers or 11.2 units per million of the general population would be required. This contrasts with the classic case-finding strategy that is currently practised in

many European countries and has a DXA requirement of 5.36 units per million of the population. In Sheffield, where opportunistic case-finding has been practised for more than 10 years, referrals for DXA are appropriate in the sense that they follow the guidelines of the Royal College of Physicians *(62)*. The service provision for the catchment area amounts to approximately 4.0 DXA units per million of the population (E.V. McCloskey, personal communication, 2004). Assuming that half these tests are for the monitoring of treatment rather than for the initial assessment, this might suggest an uptake rate of somewhat less than 40%.

The least requirement for DXA included the use of clinical risk factors and the subsequent selective use of BMD, since not all individuals with risk factors require an estimate of BMD.

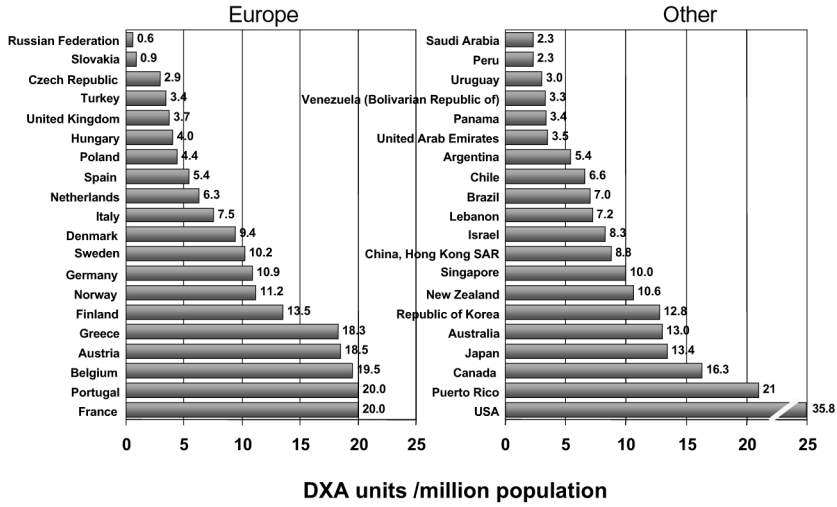
The assumptions concerning the requirements for DXA to monitor treatment are based on the assessment strategy of using clinical risk factors and selective use of BMD. There is, however, great uncertainty concerning the way in which treatments should be monitored, and the role – if any – of BMD measurements *(71)*. The problem arises because of the relatively small treatment-induced changes in BMD compared to the precision errors of the measurement, so that treatment-induced changes in BMD do not accurately predict associated reductions in fracture risk. For this reason it was conservatively assumed that the baseline BMD and only one further test two years later would be needed. Notwithstanding, the long-term requirement for the monitoring of treatment amounted to 6.39 DXA units per million of the population compared with a requirement of 4.21 scanners per million for case-finding. Thus, the monitoring consequences of treatment are greater than those for case-finding. It thus becomes important to develop internationally agreed guidance on the use of DXA for the monitoring of treatment.

The combined estimates for assessment and monitoring, based on the assessment strategy of using clinical risk factors and selective use of BMD, amount to 10.6 DXA units per million of the general population, which is similar to a previous estimate *(72)*. This requirement can be compared with the current availability of DXA in different European countries (Fig. 9.5). Of the 20 countries in Europe for which information is shown, nine have more than 10 DXA units per million of the population. It is important to note that Fig. 9.5 does not distinguish machines dedicated in part or in full to clinical research, nor machines that lie idle or are underused because of lack of funding. It is likely, therefore, that the majority of countries are under-resourced. A further consideration is the inequity of geographical location, which is known to be problematic in Italy, Spain, Switzerland and the United Kingdom. The most extreme example is found in India, where there are approximately 100 DXA units, but these are located in six cities. This inequity

results in long waiting times or long distances to travel or, in many cases, no practical access at all. Outside of Europe, only eight countries have more than 10 units per million of the general population (see Fig. 9.5).

Fig. 9.5

Density (number per million of the population) of central DXA (spine/hip) units in European and non-European countries in 2003[a]



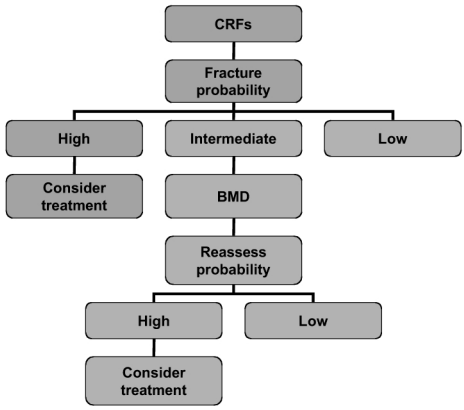
Source: reference 68 (Figs 1 and 2).

DXA, dual energy X-ray absorptiometry.

[a]Data not shown for the following countries with DXA units <2.0 per million: China, Columbia, Ecuador, Guatemala, India, Indonesia, Malaysia, Mexico, Philippines, South Africa, Thailand, Tunisia.

The guidance formulated is summarized in Fig. 9.6. The process begins with the assessment of fracture probability and the categorization of fracture risk. In those Member States with no access to bone mineral testing, treatment can be allocated on this basis alone, i.e. the intermediate risk group envisaged in Fig. 9.6 is zero (0% of the population). In those Member States where bone density testing is recommended in segments of the population, BMD testing can be done alongside the assessment by clinical risk factors. In this case, the low risk group is set to 0%. In those Member States with limited access to BMD testing, the intermediate risk group may be set anywhere between the extremes of 0% and 100%, depending upon clinical practice, availability, affordability or health economic criteria.

Fig 9.6
Algorithm for case-finding or screening for fracture risk



CRFs, clinical risk factors; BMD, bone mineral density.

9.6 Implementation of assessment guidance

The introduction of low BMD T-scores of the hip as the basis for the clinical diagnosis of osteoporosis changed the concept of the disease and required the development of clinical guidelines for the use of densitometry. In many settings, clinical practice guidelines are not well accepted by physicians and, consequently, are not broadly used. In the United States, a guideline by the National Osteoporosis Foundation outlining whom to test for low BMD and how to use the test results to determine whom to treat has had reasonably wide acceptance *(50)*. Many guidelines in Europe have been modelled on those first proposed by the European Foundation for Osteoporosis (now the International Osteoporosis Foundation) and adopted by the European Community. National guidelines modelled on these principles have been successfully adopted by the Department of Health in the United Kingdom and have been well accepted. Despite these successes, osteoporosis still suffers from under-awareness, under-diagnosis and under-treatment in many regions of the world *(72–79)*. There are lessons to be learnt from very successful initiatives in other areas, such as the public and professional awareness of serum cholesterol as an indicator of cardiovascular risk.

A recent report by the United States Surgeon General *(8)* identifies 10 lessons that can be learned from the National Cholesterol Education Programme and that could be applied to national campaigns to improve bone health:

- Establish a solid scientific base that can bring credibility and persuasion to effort.
- Create a multidisciplinary and far-reaching partnership that includes interested organizations with State and local chapters.

- Make sure that partners and target audiences have input at the concept stage, not just the dissemination stage.
- Pursue collaboration with outside interests, such as industry, as appropriate opportunities arise.
- Develop a comprehensive programme plan that includes roles for all partners.
- Research a consensus on consistent key messages that can be repeated and reaffirmed by many partners through many channels and outlets.
- To reach desired goals and objectives, make sure that the effort has the type of long-term commitment in terms of leadership and funding from sponsoring organizations that is necessary to make it sustainable over the long term.
- Both population and clinical approaches will be needed in order to change behaviour at the personal, family and community level, and choices between these two types of interventions should not be made.
- Establish or acquire baseline data pertinent to establishing goals and objectives so that progress, or lack thereof, can be measured and programme direction can be altered as needed.
- Build in a reassessment and renewal process to keep the effort vital and current.

Against this background, it is worth examining the process for implementation that allowed some general acceptability of current osteoporosis guidelines, since the use of absolute fracture risk will now require changes in the guidance provided to physicians. Lessons can be learned from the successful introduction of osteoporosis guidelines that might help to bypass barriers to modification of existing guidelines in order to accommodate this new approach to patient assessment.

9.6.1 Guideline development

The process initiated by the National Osteoporosis Foundation in the United States was to undertake a formal cost–effectiveness analysis upon which to base the development of a guide to clinical practice. The cost–effectiveness analysis was rigorous and published in full *(80)*. The philosophy behind developing a guide from this document required the determination of the efficacy and cost of each medicine then available for the prevention or treatment of osteoporosis in postmenopausal women. There was a general feeling that the best of the medicines available at the time (estrogen and bisphosphonates) were roughly similar in efficacy. Cost then became the driving force. The National Osteoporosis Foundation selected the least costly medicine (estrogen) to drive the guide, arguing that if this treatment could be justified based on efficacy and cost, it would be unethical to deny other, more costly medicines to those who were appropriate candidates for therapy, but could not or would not use estrogen.

In the United Kingdom, guideline development was undertaken through the Royal College of Physicians *(6)*. It also used an evidence-based approach to determine efficacy of interventions, but did not undertake cost–effectiveness analysis of the intervention, since approved treatments were available through the National Health Service. Rather, cost–effectiveness was determined for the assessment strategy, namely whether the additional use of BMD to direct intervention over and above case-finding by clinical risk factors was worthwhile.

9.6.2 Guideline approval

Guidelines both in the United Kingdom and the United States underwent an approval process. Before announcing their guidance, the National Osteoporosis Foundation went through an approval process, involving its Interspecialty Medical Council, which comprises representatives of major medical societies whose members might have clinical interests in osteoporosis (i.e. internists, endocrinologists, rheumatologists, radiologists, orthopaedists, etc.). In addition, the guide was presented to the Council of the American Society of Bone and Mineral Research to validate the scientific rigour. Ratification of the final document was obtained from all groups, albeit not without considerable discussion. The time required for ratification of guidance should not be underestimated. The procedure provided the National Osteoporosis Foundation with a mechanism for disseminating the guide through the national and regional meetings of these major medical societies. In addition, the Foundation worked with the American Medical Association to develop a continuing medical education course for physicians based around the principles enunciated in the guide.

In the United Kingdom, consultation on the draft guidance took place with a wide spectrum of professional bodies concerned with osteoporosis from many medical disciplines and also included nursing organizations, general practitioners and patient organizations. The guidance was then externally audited by an independent body before approval by the Department of Health.

9.6.3 Guideline implementation

In the United Kingdom, guidelines were distributed through the Department of Health and the resource document was published independently by the Royal College of Physicians (London).

The implementation process was more complex in the United States since the health-care system is more complicated and there is a need to involve specific general audiences, including government agencies (both elected officials and health agency staff), those who pay for health care (such as insurance and managed care plans), those who dispense health care (physicians, etc.), and

consumers (patients and their families). In addition, pharmaceutical and device manufacturers are interested parties; they were not considered to be fundamental to acceptance of the guide but, nonetheless, could be expected to facilitate or hinder its introduction, depending on how their products fared in the recommendations. Guideline development is viewed differently by each of these primary audiences, and each might be expected to react differently to a move that changes current approaches to disease diagnosis and management. For this reason, several strategies were developed to facilitate the acceptance of the guide, involving each audience of relevance, as follows.

Elected government officials

At the time of guideline development, the United States Congress had recently passed a law requiring Medicare to pay for prostate cancer screening for ageing men. Medicare traditionally does not pay for screening tests in asymptomatic individuals, and prostate specific antigen (PSA) became one of relatively few tests reimbursed. Active in Congress was a group known as the Congressional Women's Caucus, representing all female elected members of the United States House and Senate. The National Osteoporosis Foundation petitioned this group to support a law requiring Medicare to pay for BMD testing, using the National Osteoporosis Foundation guide as the basis, and arguing that, for women, this was as important as PSA was for men (i.e. social justice). Subsequent passage of the resulting bill mandating densitometry coverage by Medicare was pivotal in the general utility of the guide. First, Medicare is a Federal programme covering all individuals over the age of 65 years, a key group for BMD evaluation and obviously the one with the highest prevalence of osteoporosis. Second, Medicare rules are often followed by private payers, allowing availability of the test to younger women. Third, this afforded significant publicity to the test itself, as the National Osteoporosis Foundation was able to publicize the Congressional effort. Finally, the trickle-down effect regionally resulted in individual states directing more attention (and therefore resources) to osteoporosis.

Staff of government agencies

The staff of governmental agencies has responsibility for ensuring that actions mandated by elected officials are fiscally prudent, and population relevant. Medicare staff initiated a re-evaluation of BMD *(65)*, and the conclusions eventually published in a report by the United States Preventive Health Services Task Force supported the National Osteoporosis Foundation contention, as reflected in its guide, that BMD testing was "cost-effective" in all women by the age of 65 years and in selected "higher risk" women at a younger age *(67)*. At that time, Medicare did not pay for medications, and the National Osteoporosis Foundation recommendations for treatment thresholds were not addressed.

Payers

In some situations, private organizations (insurance companies, health maintenance organizations, managed care plans, etc.) have a major interest in the introduction of guidelines for disease management. These organizations often have conflicting goals, namely to provide the highest standard of health care but, at the same time, to control costs of health-care delivery. New guidelines for disease management often represent an actuarial problem, so these organizations pay close attention to "cost–effectiveness". In this area, basing the guide on a cost–effectiveness analysis was a major benefit. The combination of Government endorsement with evidence of cost–effectiveness went a long way towards acceptance (sometimes reluctantly) by individual payers that BMD was a required service. Once BMD testing was provided, it was a relatively simple step to reimbursement of the indicated medications. It should be noted, however, that the National Osteoporosis Foundation played no role in the assessment of individual medications for reimbursement. That was an issue purely decided between the insurance and pharmaceutical industries.

Health-care providers

Physicians and other health-care providers wish to provide the highest standard of care for their patients but are under considerable constraints, particularly time and money. In fact, this arm of implementation was crucial in the acceptance by providers first of the BMD test and second of the medications. The National Osteoporosis Foundation organized extensive educational programmes for physicians. More importantly, perhaps, once the public had accepted BMD (see below), physicians reacted by ordering the test. It was then an easy step to recommend treatment based on the criteria suggested in the National Osteoporosis Foundation document. Not all physicians, of course, adhered strictly to the National Osteoporosis Foundation guidance. There was a perception that prevention was critical, driven by the pharmaceutical industry, and many individuals at low risk of fracture were placed on bone-specific agents, including many premenopausal women with low T-scores who did not have osteoporosis.

Patients

Patients have the greatest vested interest in disease prevention, but they often have ambivalent views about the use of medications. Indeed, it has been a common experience for patients with a recent fracture to decline treatment for osteoporosis *(81)*. Direct-to-consumer advertising of medications in the United States has raised awareness of the preventability of fracture. Moreover, public relations efforts by the National Osteoporosis Foundation, organized in part around Osteoporosis Prevention Month but occurring throughout the year, promoted awareness of an easy test (BMD) that could predict fracture risk, driving many women to ask their physicians for referral for the test. The use of such testing has increased accordingly *(82)*.

9.6.4 Conclusions

While developing guidelines for clinical disease management requires a rigorous evaluation of the evidence, most guides are not particularly well adopted in practice situations. The key is implementation, which requires a multi-pronged approach addressing each level of health-care delivery, from government to primary care. Consideration must also be given to the patients who, by their demands, often drive changes in clinical practice. Audit is also an essential element in order to document the uptake of guidance and to track corresponding changes in fracture outcomes.

The guidance given in this report requires a change in the approach to the assessment and management of osteoporosis. The original WHO definition of osteoporosis began to move the disorder from a disease of fracture to a disease of fracture risk *(3)*. Just as high serum lipids and high blood pressure are indicators of the risk of heart disease, so BMD testing became a critical component as a predictor of fracture risk. The guidance given in this report is faithful to the concept of the disease as one of fracture risk, but enlarges the arsenal available with which to assess this risk. A concentrated educational programme at all levels of health care will be needed to ensure that fracture risk, rather than BMD alone, becomes the critical component of risk assessment in osteoporosis.

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10. Summary, conclusions and recommendations for research

The following conclusions and recommendations for research represent the unanimous views of the Scientific Group.

With the development of treatments that favourably alter the natural history of osteoporosis, there is an increasing need to develop strategies for fracture risk assessment so that treatments can be targeted more effectively to those in need and, conversely, that unnecessary treatment can be avoided in those at low risk of fracture.

10.1 Consequences of osteoporosis

Age-related bone loss is asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that occur. Common sites of fracture include the spine, hip, forearm and proximal humerus.

Fractures at the hip incur the greatest morbidity and mortality, and give rise to the highest direct costs for health services. Their incidence increases exponentially with age.

Osteoporotic fractures at other sites are generally of less economic significance, but they also give rise to significant morbidity and, in some instances, to increased mortality. They occur more commonly than hip fractures at younger ages, and their neglect in evaluating assessment strategies disadvantages the younger segment of the osteoporotic population.

The remaining lifetime probability of osteoporotic fractures in women at the age of 50 years exceeds 40% in developed countries. For hip fracture alone, the remaining lifetime probability at the age of 50 years exceeds 20% in women in these countries. In many regions of the world, the risks in men are about half those of women.

The number of osteoporotic fractures is certain to increase in both men and women (by more than 3-fold over the next 50 years) as a result of the ageing population. The major increases will occur outside of Europe and the United States, particularly in Asia and Latin America.

Over and above changes in population demography, the age- and sex-specific incidence of osteoporotic fractures appears to be increasing in developing countries. This may more than double the expected burden of osteoporotic fractures over the next 50 years.

The age- and sex-specific incidence of hip fracture varies markedly around the world, as does the incidence of other osteoporotic fractures. For hip fracture, age- and sex-specific incidence varies by more than 10-fold. More modest variations are observed for vertebral fracture risk.

Reasons for the secular changes and geographic variations in fracture risk are unknown, but cannot be explained completely on the basis of differences in bone mineral density.

In high-income countries, osteoporotic fractures account for more hospital bed days than those for myocardial infarction, breast cancer or prostate cancer. The burden of hip fracture alone accounts for 1.4% of disability-adjusted life years in the established market economies.

10.2 Bone mineral measurements and diagnosis of osteoporosis

Many techniques are available to assess bone mineral at multiple sites including those where osteoporotic fractures predominate. The most widely validated technique is dual energy X-ray absorptiometry (DXA) applied to sites of biological relevance, including the hip, spine and forearm.

The pivotal requirement for the use of bone mineral testing in diagnosis and assessment of osteoporosis is its performance characteristics for fracture prediction.

There are significant differences in the performance of different techniques to predict fractures at different skeletal sites. For the prediction of any fracture, DXA at sites of biological relevance gives measurements of bone mineral density (BMD) that predict fracture with an increase in fracture risk of approximately 1.5/SD decrease in bone mineral density (termed the gradient

of risk). The highest gradient of risk is provided by DXA at the femoral neck for hip fracture prediction, where the gradient of risk is approximately 2.6/SD.
The validation of BMD measurements and the increase in epidemiological information permit diagnostic criteria for osteoporosis to be more precisely defined than previously. The international reference standard for the description of osteoporosis in postmenopausal women and in men aged 50 years or more is a femoral neck BMD of 2.5 SD or more below the young female adult mean, using normative data from the NHANES III reference database on Caucasian women aged 20–29 years.

Although the reference standard for the description of osteoporosis is BMD at the femoral neck, other central sites (e.g. lumbar spine, total hip) can be used for diagnosis in clinical practice.

T-scores should be reserved for diagnostic use in postmenopausal women and men aged 50 years or more. With other technologies, and other populations, measurement values should be expressed as Z-scores, units of measurement or preferably in units of fracture risk.

Provision is still made for the description of osteopenia as a T-score at the femoral neck of between –1.0 SD and –2.5 SD below the young female adult mean.

10.3 Clinical risk factors for fracture

A plethora of clinical risk factors have been identified that are associated with an increase in fracture risk. In many instances their suitability for inclusion in assessment algorithms for the prediction of fracture has not been well validated. In this report, evidence-based criteria are developed for the assessment of risk factors including for BMD. These include hierarchical levels of evidence for the ability of risk factors to identify a fracture risk that is modifiable by pharmacological interventions.

Risk factors validated by their use as inclusion criteria in randomized controlled trials include low BMD (DXA at spine or hip), prior vertebral fracture, long-term glucocorticoid treatment, and age. Risk factors that do not adversely affect the efficacy of intervention in randomized controlled trials include family history of fracture, prior non-vertebral fracture, biochemical markers of bone turnover, peripheral measurements of bone mineral including quantitative ultrasound at the heel, smoking, body weight or body mass index, and alcohol intake.

In this report, the international validity of candidate risk factors was examined by meta-analyses of population-based cohorts from Asia, Australia, Europe and North America. Risk factors were assessed by age, sex, duration of follow-up, and their dependence on BMD. Those validated

comprised BMD at the femoral neck, low body mass index, a prior fragility fracture, glucocorticoid exposure, a parental history of (hip) fracture, smoking, excessive intake of alcohol, and rheumatoid arthritis.

The interdependent relationship among these risk factors was used to construct models of fracture probability.

Other risk factors of potential utility, but less extensively validated, included BMD measured at the spine or total hip, quantitative ultrasound applied to the heel, peripheral estimates of BMD, and biochemical indices of bone turnover.

10.4 Assessment tools for case-finding

Screening with BMD is recommended in some Member States, most notably in North America, but is not widely practised elsewhere. Reasons include the lack of availability of machines, variable access, expense, and poor sensitivity (detection rate for future fractures) when specificity is high.

Current evidence-based guidelines focus on the use of BMD as a criterion for intervention.

Several algorithms are available for the prediction of osteoporosis with the use of clinical risk factors alone. The most widely tested predictor of osteoporosis is the osteoporosis self-assessment tool. These tools have comparable performance characteristics with high sensitivity (detection rate) but poor specificity. The high sensitivity provides opportunities for cost savings by excluding patients who do not need a BMD assessment. Such tools require calibration in each Member State because of heterogeneity in sensitivity and specificity. They have not been well validated in men.

Sensitivity is improved by the use of multiple independent risk factors and can be used to optimize the prediction of fracture. Four FRAX™ assessment models have been constructed from the meta-analyses of risk factors for the calculation of fracture probabilities. These comprise the 10-year probability of hip fracture, with and without BMD at the femoral neck, and the 10-year probability of major osteoporotic fractures, with and without BMD at the femoral neck. Major osteoporotic fractures comprise forearm, clinical spine and proximal humerus fractures. The probability of any osteoporotic fracture is, therefore, underestimated. The FRAX™ algorithms are suitable for use in men (from the age of 40 years) and women from the age of menopause.

For hip fracture prediction, the use of BMD at each age out-performed the use of clinical risk factors alone in predictive value, but clinical risk factors in combination with BMD improved the gradient of risk still further, so that the test had improved sensitivity without loss of specificity. For the prediction of other osteoporotic fractures, gradients of risk with clinical risk factors were marginally improved with the addition of BMD, but the performance characteristics were as good as, or better than, the assessment of risk with

BMD using peripheral measurements. The performance characteristics have been validated in several independent cohorts from different regions of the world.

The FRAX models were calibrated to different Member States to reflect the high heterogeneity in fracture risk worldwide. These included countries at very high risk (Sweden, United States), at high risk (United Kingdom), at moderate risk (China, Japan and Spain), and at low risk (Turkey). The models are available at www.shef.ac.uk/FRAX.

The FRAX models can be simplified with the omission of some of the clinical risk factors, making them amenable to paper versions.

Fracture probabilities assume clinical utility once an intervention threshold is established, namely the risk above which intervention is worthwhile. Intervention thresholds should be fixed by Member States and will depend upon the priorities that osteoporosis has in a region or country, the absolute risk of fracture, and the ability to pay. An example, based on cost–utility analysis, is provided for the United Kingdom.

10.5 Assessment and the formulation of therapeutic strategy

Population-based (i.e. public health) prevention programmes are appropriate for all Member States. Global programmes should include attention to nutritional factors, particularly related to adequate intakes of calcium and vitamin D. Cigarette smoking should be avoided, not solely because of its possible effects on skeletal metabolism, but for the many other adverse effects associated with smoking. Preventing excessive alcohol consumption and the avoidance of immobility are also recommended as public health measures.

In Member States without access to densitometry, case-finding strategies can be pursued with use of clinical risk factors alone. The performance characteristics of the FRAX model are at least as good as those provided by peripheral assessment of BMD.

In Member States where BMD is universally recommended (e.g. at the age of 65 years or more in North America), the stratification of risk can be improved by consideration of clinical risk factors in conjunction with BMD. This is particularly valuable in the context of younger individuals for hip fracture prediction.

In Member States with limited access to DXA, clinical risk factors can be used to stratify target populations to those at very high risk in whom a BMD test would not alter their risk category, those with very low risk in whom a BMD would not alter the risk category, and those at intermediate risk where a BMD test would be helpful for the characterization of fracture probability.

The guidance in this report is flexible and will require that Member States make suitable accommodation to cater for regional variations in medical care. Even so, the implementation of this guidance poses many challenges for the future. There will need to be agreement on the principles of fracture risk reporting among stakeholders, including regulatory agencies, ministries of health, payers as well as the manufacturers of bone mineral measurement technologies. Ultimately, it will also become necessary to validate the responsiveness of patients so identified to the large number of interventions now available.

10.6 Recommendations for research

Health service data are required in many Member States on length of hospital stay, morbidity, mortality and institutionalization associated with osteoporotic fractures, together with the associated costs, so that osteoporosis can be placed in an adequate health-care perspective.

Hip fracture risks have been estimated for less than 40 Member States, and risks for other osteoporotic fractures in far fewer. More information is needed on the epidemiology of fracture so that FRAX algorithms can be calibrated for more communities.

The present approaches to the identification of patients at risk for fracture focus on a few clinical risk factors and on femoral neck BMD. More information is required on other risk factors and their validity to permit further refinements to the models available. Topics for study thus include:

- clinical risk factors for falls
- the use of DXA at other skeletal sites, such as the total hip and lumbar spine
- indices of bone turnover
- the use of other technologies, such as quantitative ultrasound
- secondary causes of osteoporosis other than rheumatoid arthritis.

Assessment algorithms need further validation in men and non-Caucasian populations.

Case-finding strategies require validation in clinical trials to test whether pharmacological agents reduce fracture risk in individuals identified by the use of clinical risk factors with and without the selective use of BMD.

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Annex 1 Ten-year probabilities of hip fracture (%) in the UK according to age, sex and gradient of risk
Available at www.shef.ac.uk/FRAX

Annex 2 Ten-year probabilities of hip fracture (%) in the UK population according to age, sex and risk ratio
Available at www.shef.ac.uk/FRAX

Annex 3 Ten-year probability of osteoporotic fracture (%) according to BMD, the number of clinical risk factors (CRF) and age.
Available at www.shef.ac.uk/FRAX

Annex 4 Ten-year probability of fracture (%) according to BMI, the number of clinical risk factors and age.
Available at www.shef.ac.uk/FRAX

Annex 1

Ten-year probabilities of hip fracture in the United Kingdom population, by age, sex and gradient of risk

The following tables convert Z-scores of risk factor scores into 10-year hip fracture probabilities. They can be used to approximate hip fracture probabilities from risk factors for fracture that are not incorporated in the assessment algorithms. Examples include peripheral DXA and ultrasound techniques.

The gradients of risk vary from 1.0 (i.e. the average population risk) to 3.0/SD.

The probabilities shown are derived for the United Kingdom using hip fracture hazards from Singer et al. *(1)* and the mortality hazard from the United Nations *(2)*.

Table A1.1 gives 10-year probabilities of hip fracture in men and Table A1.2 gives 10-year probabilities of hip fracture in women.

In men at the age of 80 years, the average 10-year hip fracture probability is 5.0%, from Table A1.1(a). Consider, for example, peripheral DXA measurements. Many of these techniques have a gradient of hip fracture risk of approximately 1.5/SD decrease in BMD, so Table A1.1(c) applies. With a BMD Z-score of –1 SD, the hip fracture probability in that individual would be 6.8%, and with a Z-score of –2 it would be 9.9%.

For women, the same example (i.e. aged 80 years; gradient of risk 1.5/SD) would give probabilities of 16% and 22% with Z-scores of –1 and –2, respectively, from Table A1.2(c).

References

1. Singer BR et al. Epidemiology of fracture in 1000 adults: the influence of age and gender. *Journal of Bone and Joint Surgery,* 1998, 80B:234–238.

2. *World population prospects: the 2002 revision and world urban prospects*. New York, United Nations Population Division, Department of Economic and Social Affairs, 2003.

Table A1.1

Ten-year probability (%) of hip fracture according to age and Z-score for men

(a) Gradient of risk = 1.00/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
55	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
60	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
65	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
70	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
75	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
80	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
85	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1

(b) Gradient of risk = 1.25/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	0.6	0.6	0.5	0.5	0.4	0.4	0.3	0.3	0.3
55	0.9	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4
60	1.7	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.7
65	2.9	2.6	2.3	2.1	1.8	1.7	1.5	1.3	1.2
70	3.9	3.5	3.2	2.8	2.5	2.3	2.0	1.8	1.6
75	5.7	5.1	4.6	4.1	3.7	3.3	3.0	2.7	2.4
80	7.5	6.7	6.1	5.4	4.9	4.4	3.9	3.5	3.2
85	7.6	6.9	6.2	5.6	5.0	4.5	4.0	3.6	3.3

(c) Gradient of risk = 1.50/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	0.9	0.7	0.6	0.5	0.4	0.3	0.3	0.2	0.2
55	1.2	1.0	0.8	0.7	0.5	0.4	0.4	0.3	0.2
60	2.3	1.9	1.5	1.2	1.0	0.8	0.7	0.6	0.5
65	3.9	3.2	2.6	2.1	1.7	1.4	1.2	1.0	0.8
70	5.3	4.4	3.6	2.9	2.4	2.0	1.6	1.3	1.1
75	7.6	6.3	5.2	4.3	3.5	2.9	2.3	1.9	1.6
80	9.9	8.2	6.8	5.6	4.6	3.8	3.1	2.6	2.1
85	10	8.4	6.9	5.7	4.7	3.9	3.2	2.6	2.2

(d) Gradient of risk = 1.75/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.1	0.8	0.6	0.5	0.4	0.3	0.2	0.2	0.1
55	1.5	1.2	0.9	0.7	0.5	0.4	0.3	0.2	0.2
60	2.9	2.2	1.6	1.2	0.9	0.7	0.5	0.4	0.3
65	4.9	3.7	2.8	2.1	1.6	1.2	0.9	0.7	0.5
70	6.6	5.1	3.9	2.9	2.2	1.7	1.3	1.0	0.7
75	9.5	7.3	5.6	4.3	3.2	2.5	1.9	1.4	1.1
80	12	9.5	7.3	5.6	4.3	3.3	2.5	1.9	1.4
85	13	9.7	7.5	5.8	4.4	3.4	2.6	1.9	1.5

(e) Gradient of risk = 2.00/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.3	0.9	0.7	0.5	0.3	0.2	0.2	0.1	0.1
55	1.9	1.3	0.9	0.7	0.5	0.3	0.2	0.2	0.1
60	3.4	2.4	1.7	1.2	0.9	0.6	0.4	0.3	0.2
65	5.8	4.1	3.0	2.1	1.5	1.1	0.7	0.5	0.4
70	7.9	5.7	4.1	2.9	2.1	1.5	1.0	0.7	0.5
75	11.2	8.1	5.9	4.2	3.0	2.1	1.5	1.1	0.8
80	14	11	7.7	5.5	4.0	2.8	2.0	1.4	1.0
85	15	11	7.8	5.7	4.1	2.9	2.1	1.5	1.0

(f) Gradient of risk = 2.25/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.5	1.0	0.7	0.4	0.3	0.2	0.1	0.1	0.1
55	2.1	1.4	1.0	0.6	0.4	0.3	0.2	0.1	0.1
60	4.0	2.7	1.8	1.2	0.8	0.5	0.4	0.2	0.2
65	6.7	4.5	3.0	2.0	1.4	0.9	0.6	0.4	0.3
70	9.1	6.2	4.2	2.8	1.9	1.3	0.8	0.6	0.4
75	13	8.8	6.0	4.1	2.7	1.8	1.2	0.8	0.6
80	16	12	7.9	5.4	3.7	2.5	1.7	1.1	0.7
85	17	12	8.1	5.5	3.7	2.5	1.7	1.1	0.8

(g) Gradient of risk = 2.50/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.7	1.1	0.7	0.4	0.3	0.2	0.1	0.1	0.0
55	2.4	1.5	1.0	0.6	0.4	0.2	0.2	0.1	0.1
60	4.4	2.8	1.8	1.1	0.7	0.5	0.3	0.2	0.1
65	7.5	4.8	3.1	2.0	1.2	0.8	0.5	0.3	0.2
70	10	6.6	4.2	2.7	1.7	1.1	0.7	0.4	0.3
75	14	9.4	6.1	3.9	2.5	1.6	1.0	0.6	0.4
80	18	12	8.0	5.2	3.3	2.1	1.4	0.9	0.5
85	18	12	8.2	5.3	3.4	2.2	1.4	0.9	0.6

(h) Gradient of risk = 2.75/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.9	1.1	0.7	0.4	0.2	0.2	0.1	0.1	0.0
55	2.7	1.6	1.0	0.6	0.4	0.2	0.1	0.1	0.0
60	4.9	3.0	1.8	1.1	0.7	0.4	0.2	0.1	0.1
65	8.2	5.1	3.1	1.9	1.1	0.7	0.4	0.3	0.2
70	11	6.9	4.3	2.6	1.6	1.0	0.6	0.3	0.2
75	16	9.9	6.1	3.8	2.3	1.4	0.8	0.5	0.3
80	20	13	8.0	5.0	3.1	1.9	1.1	0.7	0.4
85	20	13	8.2	5.1	3.1	1.9	1.2	0.7	0.4

(i) Gradient of risk = 3.00/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	2.0	1.2	0.7	0.4	0.2	0.1	0.1	0.0	0.0
55	2.9	1.7	1.0	0.6	0.3	0.2	0.1	0.1	0.0
60	5.3	3.1	1.8	1.0	0.6	0.3	0.2	0.1	0.1
65	8.9	5.3	3.1	1.8	1.0	0.6	0.3	0.2	0.1
70	12	7.2	4.2	2.5	1.4	0.8	0.5	0.3	0.2
75	17	10	6.1	3.6	2.1	1.2	0.7	0.4	0.2
80	21	13	8.0	4.8	2.8	1.6	0.9	0.5	0.3
85	21	13	8.2	4.9	2.9	1.7	1.0	0.6	0.3

Table A1.2

Ten-year probability (%) of hip fracture according to age and Z-score for women

(a) Gradient of risk = 1.00/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
55	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
60	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
65	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7
70	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
75	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3
80	12	12	12	12	12	12	12	12	12
85	11	11	11	11	11	11	11	11	11

(b) Gradient of risk = 1.25/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4	0.3
55	1.3	1.1	1.0	0.9	0.8	0.7	0.6	0.6	0.5
60	2.7	2.5	2.2	2.0	1.8	1.6	1.4	1.3	1.1
65	5.5	5.0	4.5	4.0	3.6	3.2	2.9	2.6	2.3
70	9.0	8.1	7.3	6.6	5.9	5.3	4.8	4.3	3.8
75	14	12	11	10	9.1	8.2	7.4	6.6	5.9
80	17	16	14	13	12	10	9.4	8.5	7.6
85	16	15	13	12	11	9.7	8.8	7.9	7.1

(c) Gradient of risk = 1.50/SD

Age (years)	Z-score (SD units)								
	-2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.1	0.9	0.7	0.6	0.5	0.4	0.3	0.3	0.2
55	1.7	1.4	1.1	0.9	0.8	0.6	0.5	0.4	0.3
60	3.7	3.0	2.5	2.0	1.7	1.4	1.1	0.9	0.7
65	7.4	6.1	5.0	4.1	3.4	2.8	2.3	1.9	1.5
70	12	10	8.2	6.8	5.6	4.6	3.8	3.1	2.5
75	18	15	13	10	8.6	7.1	5.9	4.8	4.0
80	22	19	16	13	11	9.1	7.5	6.2	5.1
85	21	17	15	12	10	8.5	7.0	5.8	4.8

(d) Gradient of risk = 1.75

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.4	1.0	0.8	0.6	0.4	0.3	0.3	0.2	0.1
55	2.2	1.6	1.2	0.9	0.7	0.5	0.4	0.3	0.2
60	4.7	3.5	2.7	2.0	1.5	1.2	0.9	0.7	0.5
65	9.3	7.1	5.4	4.1	3.1	2.4	1.8	1.4	1.0
70	15	12	8.9	6.8	5.2	4.0	3.0	2.3	1.7
75	22	17	14	10	8.0	6.1	4.7	3.6	2.7
80	27	21	17	13	10	7.9	6.0	4.6	3.5
85	25	20	16	12	9.6	7.4	5.7	4.3	3.3

(e) Gradient of risk = 2.00/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.6	1.2	0.8	0.6	0.4	0.3	0.2	0.1	0.1
55	2.6	1.8	1.3	0.9	0.7	0.5	0.3	0.2	0.2
60	5.6	4.0	2.8	2.0	1.4	1.0	0.7	0.5	0.4
65	11	8.0	5.7	4.1	2.9	2.1	1.5	1.0	0.7
70	18	13	9.3	6.7	4.8	3.4	2.4	1.7	1.2
75	26	19	14	10	7.4	5.3	3.8	2.7	1.9
80	31	24	18	13	9.5	6.8	4.9	3.5	2.5
85	29	22	17	12	8.8	6.4	4.6	3.3	2.3

(f) Gradient of risk = 2.25/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	1.9	1.3	0.8	0.6	0.4	0.3	0.2	0.1	0.1
55	3.0	2.0	1.3	0.9	0.6	0.4	0.3	0.2	0.1
60	6.4	4.3	2.9	1.9	1.3	0.9	0.6	0.4	0.3
65	13	8.7	5.9	4.0	2.7	1.8	1.2	0.8	0.5
70	20	14	9.6	6.5	4.4	3.0	2.0	1.3	0.9
75	29	21	15	10	6.8	4.6	3.1	2.1	1.4
80	34	25	18	13	8.7	5.9	4.0	2.7	1.8
85	32	24	17	12	8.2	5.6	3.8	2.5	1.7

(g) Gradient of risk = 2.50/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	2.1	1.3	0.9	0.5	0.3	0.2	0.1	0.1	0.1
55	3.4	2.1	1.4	0.9	0.5	0.3	0.2	0.1	0.1
60	7.2	4.6	2.9	1.9	1.2	0.8	0.5	0.3	0.2
65	14	9.2	6.0	3.8	2.4	1.5	1.0	0.6	0.4
70	22	15	9.7	6.3	4.0	2.6	1.6	1.0	0.7
75	32	22	15	9.6	6.2	4.0	2.6	1.6	1.0
80	37	27	18	12	8.0	5.2	3.3	2.1	1.3
85	35	25	17	11	7.5	4.8	3.1	2.0	1.3

(h) Gradient of risk = 2.75/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	2.3	1.4	0.9	0.5	0.3	0.2	0.1	0.1	0.0
55	3.7	2.3	1.4	0.8	0.5	0.3	0.2	0.1	0.1
60	7.9	4.9	3.0	1.8	1.1	0.7	0.4	0.2	0.1
65	15	9.7	6.0	3.6	2.2	1.3	0.8	0.5	0.3
70	24	15	9.7	6.0	3.7	2.2	1.4	0.8	0.5
75	34	23	15	9.2	5.7	3.5	2.1	1.3	0.8
80	40	28	18	12	7.3	4.5	2.8	1.7	1.0
85	37	26	17	11	6.9	4.2	2.6	1.6	1.0

(i) Gradient of risk = 3.00/SD

Age (years)	Z-score (SD units) -2.0	-1.5	-1.0	-0.5	0	+0.5	+1.0	+1.5	+2.0
50	2.5	1.5	0.9	0.5	0.3	0.2	0.1	0.1	0.0
55	4.0	2.3	1.4	0.8	0.5	0.3	0.2	0.1	0.1
60	8.6	5.0	2.9	1.7	1.0	0.6	0.3	0.2	0.1
65	17	10	5.9	3.5	2.0	1.2	0.7	0.4	0.2
70	26	16	9.7	5.7	3.4	2.0	1.1	0.7	0.4
75	36	24	15	8.8	5.2	3.1	1.8	1.0	0.6
80	42	29	18	11	6.7	4.0	2.3	1.3	0.8
85	39	27	17	10	6.3	3.7	2.2	1.3	0.7

Annex 2

Ten-year probabilities of hip fracture in the United Kingdom population, by age, sex and risk ratio

Tables A2.1 and A2.2 convert risk ratios into 10-year hip fracture probabilities in men and women, respectively. The risk ratio is the risk of fracture in those with a risk factor compared to the population without the risk factor. The 10-year probability depends upon the prevalence of the risk factor for any given age and sex (see section 6).

The probabilities shown are derived for the United Kingdom using hip fracture hazards from Singer et al. *(1)* and the mortality hazard from the United Nations *(2)*.

Take, for example, a high value for CTX, a marker of bone resorption. In the EPIDOS study the risk ratio for hip fracture in women aged 80 years was approximately 2.5 in women with CTX values above the normal range of premenopausal values compared to women with values below the premenopausal values. The prevalence of high CTX in women aged 80 years is approximately 25%. Inspection of Table A2.2(g) shows a 10-year hip fracture probability of 20%.

Tables A2.3 and A2.4 give 10-year probabilities in individuals without the condition. In the example above, women aged 80 years with normal values for CTX have a hip fracture probability of 8.8%, according to Table A2.4(g).

References

1. Singer BR et al. Epidemiology of fracture in 1000 adults: the influence of age and gender. *Journal of Bone and Joint Surgery,* 1998, 80B:234–238.

2. *World population prospects: the 2002 revision and world urban prospects.* New York, United Nations Population Division, Department of Economic and Social Affairs, 2003.

Table A2.1

Ten-year probability (%) of hip fracture in men, by age and the proportion of the population with the risk factor

(a) Risk ratio= 1.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
55	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
60	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
65	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
70	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
75	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
80	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
85	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1

(b) Risk ratio = 1.25

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
55	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
60	1.4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.2	1.2
65	2.3	2.3	2.3	2.2	2.2	2.2	2.2	2.1	2.1	2.1
70	3.2	3.2	3.1	3.1	3.1	3.0	3.0	3.0	2.9	2.9
75	4.6	4.6	4.5	4.5	4.4	4.4	4.3	4.3	4.2	4.2
80	6.1	6.1	6.0	5.9	5.9	5.8	5.7	5.7	5.6	5.5
85	6.2	6.2	6.1	6.0	6.0	5.9	5.8	5.8	5.7	5.7

(c) Risk ratio = 1.50

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.5	0.5
55	0.9	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.7	0.7
60	1.6	1.6	1.5	1.5	1.5	1.4	1.4	1.4	1.3	1.3
65	2.8	2.7	2.6	2.6	2.5	2.5	2.4	2.4	2.3	2.3
70	3.8	3.7	3.6	3.5	3.5	3.4	3.3	3.2	3.2	3.1
75	5.5	5.3	5.2	5.1	5.0	4.9	4.8	4.7	4.6	4.5
80	7.2	7.0	6.9	6.7	6.6	6.5	6.3	6.2	6.1	6.0
85	7.3	7.2	7.0	6.9	6.7	6.6	6.4	6.3	6.2	6.1

(d) Risk ratio = 1.75

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.6	0.5	0.5
55	1.0	1.0	0.9	0.9	0.9	0.8	0.8	0.8	0.8	0.8
60	1.9	1.8	1.7	1.7	1.6	1.6	1.5	1.5	1.4	1.4
65	3.2	3.1	3.0	2.9	2.8	2.7	2.6	2.5	2.5	2.4
70	4.3	4.2	4.1	3.9	3.8	3.7	3.6	3.5	3.4	3.3
75	6.3	6.1	5.9	5.7	5.5	5.3	5.2	5.0	4.9	4.8
80	8.2	7.9	7.7	7.5	7.2	7.0	6.8	6.6	6.5	6.3
85	8.4	8.1	7.8	7.6	7.4	7.2	7.0	6.8	6.6	6.4

(e) Risk ratio = 2.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.6
55	1.1	1.1	1.0	1.0	0.9	0.9	0.9	0.8	0.8	0.8
60	2.1	2.0	1.9	1.8	1.8	1.7	1.6	1.6	1.5	1.5
65	3.6	3.4	3.3	3.1	3.0	2.9	2.8	2.7	2.6	2.5
70	4.9	4.7	4.5	4.3	4.1	4.0	3.8	3.7	3.6	3.5
75	7.0	6.7	6.4	6.2	6.0	5.7	5.5	5.3	5.2	5.0
80	9.2	8.8	8.4	8.1	7.8	7.5	7.3	7.0	6.8	6.6
85	9.4	9.0	8.6	8.3	8.0	7.7	7.4	7.2	6.9	6.7

(f) Risk ratio = 2.25

Age (years)Proportion of population having the condition										
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.9	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6
55	1.2	1.2	1.1	1.1	1.0	1.0	0.9	0.9	0.9	0.8
60	2.3	2.2	2.1	2.0	1.9	1.8	1.7	1.6	1.6	1.5
65	4.0	3.7	3.5	3.4	3.2	3.1	2.9	2.8	2.7	2.6
70	5.4	5.1	4.9	4.6	4.4	4.2	4.0	3.9	3.7	3.6
75	7.8	7.4	7.0	6.7	6.4	6.1	5.8	5.6	5.4	5.2
80	10	9.6	9.1	8.7	8.3	8.0	7.7	7.4	7.1	6.8
85	10	9.8	9.3	8.9	8.5	8.1	7.8	7.5	7.2	7.0

(g) Risk ratio = 2.50

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.0	0.9	0.8	0.8	0.8	0.7	0.7	0.6	0.6	0.6
55	1.4	1.3	1.2	1.1	1.1	1.0	1.0	0.9	0.9	0.8
60	2.5	2.4	2.2	2.1	2.0	1.9	1.8	1.7	1.6	1.6
65	4.3	4.1	3.8	3.6	3.4	3.2	3.1	2.9	2.8	2.7
70	5.9	5.6	5.2	4.9	4.7	4.4	4.2	4.0	3.9	3.7
75	8.5	8.0	7.5	7.1	6.7	6.4	6.1	5.8	5.6	5.3
80	11	10	9.8	9.3	8.8	8.4	8.0	7.6	7.3	7.0
85	11	11	10	9.4	9.0	8.5	8.1	7.8	7.5	7.2

(h) Risk ratio = 2.75

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.0	1.0	0.9	0.8	0.8	0.7	0.7	0.7	0.6	0.6
55	1.5	1.4	1.3	1.2	1.1	1.1	1.0	1.0	0.9	0.9
60	2.8	2.6	2.4	2.2	2.1	2.0	1.9	1.8	1.7	1.6
65	4.7	4.4	4.1	3.8	3.6	3.4	3.2	3.0	2.9	2.8
70	6.4	6.0	5.6	5.2	4.9	4.6	4.4	4.2	4.0	3.8
75	9.2	8.5	8.0	7.5	7.1	6.7	6.3	6.0	5.7	5.5
80	12	11	10	9.8	9.2	8.7	8.3	7.9	7.5	7.2
85	12	11	11	9.9	9.4	8.9	8.4	8.0	7.7	7.3

(i) Risk ratio = 3.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.1	1.0	1.0	0.9	0.8	0.8	0.7	0.7	0.7	0.6
55	1.6	1.5	1.4	1.3	1.2	1.1	1.0	1.0	0.9	0.9
60	3.0	2.7	2.5	2.3	2.2	2.1	1.9	1.8	1.7	1.6
65	5.1	4.6	4.3	4.0	3.7	3.5	3.3	3.1	3.0	2.8
70	6.9	6.4	5.9	5.5	5.1	4.8	4.5	4.3	4.1	3.9
75	9.8	9.1	8.4	7.9	7.4	6.9	6.5	6.2	5.9	5.6
80	13	12	11	10	9.6	9.1	8.6	8.1	7.7	7.4
85	13	12	11	10	9.8	9.2	8.7	8.3	7.9	7.5

Table A2.2

Ten-year probability (%) of hip fracture in women, by age, risk ratio and proportion of population with the risk factor

(a) Risk ratio = 1.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
55	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
60	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
65	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7
70	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
75	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3
80	12	12	12	12	12	12	12	12	12	12
85	11	11	11	11	11	11	11	11	11	11

(b) Risk ratio = 1.25

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
55	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.9	0.9	0.9
60	2.2	2.2	2.2	2.1	2.1	2.1	2.1	2.0	2.0	2.0
65	4.5	4.5	4.4	4.4	4.3	4.3	4.2	4.2	4.1	4.1
70	7.4	7.3	7.2	7.1	7.1	7.0	6.9	6.8	6.8	6.7
75	11	11	11	11	11	11	11	11	10	10
80	14	14	14	14	14	14	13	13	13	13
85	13	13	13	13	13	13	13	12	12	12

(c) Risk ratio = 1.50

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.6
55	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.0	1.0	1.0
60	2.6	2.6	2.5	2.5	2.4	2.3	2.3	2.3	2.2	2.2
65	5.3	5.2	5.1	5.0	4.9	4.8	4.7	4.6	4.5	4.4
70	8.7	8.5	8.3	8.1	8.0	7.8	7.6	7.5	7.3	7.2
75	13	13	13	12	12	12	12	11	11	11
80	17	16	16	16	15	15	15	14	14	14
85	16	15	15	15	14	14	14	14	13	13

(d) Risk ratio = 1.75

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.9	0.8	0.8	0.8	0.8	0.7	0.7	0.7	0.7	0.7
55	1.4	1.3	1.3	1.3	1.2	1.2	1.1	1.1	1.1	1.1
60	3.0	2.9	2.8	2.7	2.6	2.6	2.5	2.4	2.4	2.3
65	6.1	5.9	5.7	5.5	5.4	5.2	5.0	4.9	4.8	4.6
70	9.9	9.6	9.3	9.0	8.8	8.5	8.3	8.0	7.8	7.6
75	15	15	14	14	13	13	13	12	12	12
80	19	18	18	17	17	16	16	15	15	15
85	18	17	17	16	16	15	15	14	14	14

(e) Risk ratio = 2.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.0	0.9	0.9	0.9	0.8	0.8	0.8	0.7	0.7	0.7
55	1.6	1.5	1.4	1.4	1.3	1.3	1.2	1.2	1.1	1.1
60	3.4	3.3	3.1	3.0	2.9	2.8	2.7	2.6	2.5	2.4
65	6.9	6.6	6.3	6.0	5.8	5.6	5.4	5.2	5.0	4.9
70	11	11	10	9.8	9.5	9.1	8.8	8.5	8.2	8.0
75	17	16	16	15	14	14	13	13	13	12
80	21	20	19	19	18	17	17	16	16	15
85	19	19	18	17	17	16	16	15	15	14

(f) Risk ratio = 2.25

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.1	1.0	1.0	0.9	0.9	0.9	0.8	0.8	0.8	0.7
55	1.8	1.7	1.6	1.5	1.4	1.4	1.3	1.2	1.2	1.1
60	3.8	3.6	3.4	3.2	3.1	2.9	2.8	2.7	2.6	2.5
65	7.6	7.2	6.8	6.5	6.2	5.9	5.7	5.4	5.2	5.0
70	12	12	11	11	10	9.7	9.3	8.9	8.6	8.3
75	18	18	17	16	15	15	14	14	13	13
80	23	22	21	20	19	18	18	17	16	16
85	21	20	19	19	18	17	16	16	15	15

(g) Risk ratio = 2.50

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.2	1.1	1.1	1.0	0.9	0.9	0.9	0.8	0.8	0.7
55	1.9	1.8	1.7	1.6	1.5	1.4	1.4	1.3	1.2	1.2
60	4.1	3.9	3.6	3.4	3.3	3.1	2.9	2.8	2.7	2.6
65	8.3	7.8	7.3	6.9	6.6	6.2	5.9	5.7	5.4	5.2
70	13	13	12	11	11	10	9.7	9.3	8.9	8.5
75	20	19	18	17	16	15	15	14	14	13
80	24	23	22	21	20	19	18	18	17	16
85	23	22	21	20	19	18	17	16	16	15

(h) Risk ratio = 2.75

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.3	1.2	1.1	1.1	1.0	0.9	0.9	0.8	0.8	0.8
55	2.1	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.3	1.2
60	4.5	4.2	3.9	3.6	3.4	3.2	3.1	2.9	2.8	2.6
65	9.0	8.4	7.8	7.3	6.9	6.5	6.2	5.9	5.6	5.3
70	15	14	13	12	11	11	10	9.6	9.1	8.7
75	21	20	19	18	17	16	15	15	14	13
80	26	25	23	22	21	20	19	18	17	17
85	24	23	22	21	19	19	18	17	16	16

(i) Risk ratio = 3.00

Age (years)	Proportion of population having the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	1.4	1.3	1.2	1.1	1.0	1.0	0.9	0.9	0.8	0.8
55	2.2	2.1	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.2
60	4.8	4.4	4.1	3.8	3.6	3.4	3.2	3.0	2.8	2.7
65	9.7	8.9	8.2	7.7	7.2	6.8	6.4	6.0	5.7	5.4
70	16	14	13	12	12	11	10	9.8	9.3	8.9
75	23	21	20	19	18	17	16	15	14	14
80	28	26	24	23	22	21	19	19	18	17
85	26	24	23	21	20	19	18	17	17	16

Table A2.3

Ten-year probability (%) of hip fractures, by age, prevalence of risk factor and risk ratio in men without the risk factor

(a) Risk ratio = 1.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
55	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
60	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
65	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
70	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
75	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
80	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
85	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1

(b) Risk ratio = 1.25

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
55	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.5
60	1.1	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0
65	1.9	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.7	1.7
70	2.6	2.5	2.5	2.5	2.5	2.4	2.4	2.4	2.3	2.3
75	3.7	3.7	3.6	3.6	3.6	3.5	3.5	3.4	3.4	3.4
80	5.0	4.9	4.8	4.8	4.7	4.7	4.6	4.6	4.5	4.5
85	5.1	5.0	4.9	4.9	4.8	4.8	4.7	4.7	4.6	4.6

(c) Risk ratio = 1.50

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3
55	0.6	0.6	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.5
60	1.1	1.1	1.0	1.0	1.0	1.0	0.9	0.9	0.9	0.9
65	1.8	1.8	1.8	1.7	1.7	1.6	1.6	1.6	1.5	1.5
70	2.5	2.5	2.4	2.4	2.3	2.3	2.2	2.2	2.1	2.1
75	3.7	3.6	3.5	3.4	3.4	3.3	3.2	3.2	3.1	3.0
80	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1	4.0
85	5.0	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1

(d) Risk ratio = 1.75

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3
55	0.6	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4
60	1.1	1.0	1.0	1.0	0.9	0.9	0.9	0.8	0.8	0.8
65	1.8	1.8	1.7	1.6	1.6	1.5	1.5	1.5	1.4	1.4
70	2.5	2.4	2.3	2.3	2.2	2.1	2.1	2.0	2.0	1.9
75	3.6	3.5	3.4	3.3	3.2	3.1	3.0	2.9	2.8	2.8
80	4.8	4.7	4.5	4.4	4.2	4.1	4.0	3.9	3.8	3.7
85	4.9	4.8	4.6	4.5	4.3	4.2	4.1	4.0	3.9	3.8

(e) Risk ratio = 2.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3
55	0.6	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4
60	1.1	1.0	1.0	0.9	0.9	0.8	0.8	0.8	0.8	0.7
65	1.8	1.7	1.6	1.6	1.5	1.5	1.4	1.4	1.3	1.3
70	2.5	2.4	2.3	2.2	2.1	2.0	1.9	1.9	1.8	1.7
75	3.6	3.4	3.3	3.2	3.0	2.9	2.8	2.7	2.6	2.5
80	4.8	4.6	4.4	4.2	4.0	3.9	3.8	3.6	3.5	3.4
85	4.9	4.7	4.5	4.3	4.1	4.0	3.8	3.7	3.6	3.5

(f) Risk ratio = 2.25

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3
55	0.6	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4
60	1.0	1.0	0.9	0.9	0.8	0.8	0.8	0.7	0.7	0.7
65	1.8	1.7	1.6	1.5	1.4	1.4	1.3	1.3	1.2	1.2
70	2.5	2.3	2.2	2.1	2.0	1.9	1.8	1.7	1.7	1.6
75	3.6	3.4	3.2	3.0	2.9	2.8	2.7	2.5	2.4	2.4
80	4.7	4.5	4.2	4.0	3.9	3.7	3.5	3.4	3.3	3.1
85	4.8	4.6	4.3	4.1	3.9	3.8	3.6	3.5	3.3	3.2

(g) Risk ratio = 2.50

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2
55	0.6	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.3
60	1.0	1.0	0.9	0.8	0.8	0.8	0.7	0.7	0.7	0.6
65	1.8	1.6	1.5	1.5	1.4	1.3	1.2	1.2	1.1	1.1
70	2.4	2.3	2.1	2.0	1.9	1.8	1.7	1.6	1.6	1.5
75	3.5	3.3	3.1	2.9	2.8	2.6	2.5	2.4	2.3	2.2
80	4.7	4.4	4.1	3.9	3.7	3.5	3.3	3.2	3.0	2.9
85	4.8	4.5	4.2	4.0	3.8	3.6	3.4	3.3	3.1	3.0

(h) Risk ratio = 2.75

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2
55	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.3	0.3	0.3
60	1.0	0.9	0.9	0.8	0.8	0.7	0.7	0.7	0.6	0.6
65	1.7	1.6	1.5	1.4	1.3	1.2	1.2	1.1	1.1	1.0
70	2.4	2.2	2.1	1.9	1.8	1.7	1.6	1.5	1.5	1.4
75	3.5	3.2	3.0	2.8	2.7	2.5	2.4	2.3	2.1	2.0
80	4.6	4.3	4.0	3.8	3.5	3.3	3.2	3.0	2.9	2.7
85	4.7	4.4	4.1	3.8	3.6	3.4	3.2	3.1	2.9	2.8

(i) Risk ratio = 3.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2
55	0.5	0.5	0.5	0.4	0.4	0.4	0.3	0.3	0.3	0.3
60	1.0	0.9	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.6
65	1.7	1.6	1.5	1.4	1.3	1.2	1.1	1.1	1.0	1.0
70	2.4	2.2	2.0	1.9	1.7	1.6	1.5	1.5	1.4	1.3
75	3.4	3.2	2.9	2.7	2.5	2.4	2.3	2.1	2.0	1.9
80	4.6	4.2	3.9	3.6	3.4	3.2	3.0	2.8	2.7	2.6
85	4.7	4.3	4.0	3.7	3.5	3.3	3.1	2.9	2.8	2.6

Table A2.4

Ten-year probability (%) of hip fracture, by age, prevalence of risk factor and risk ratio in women without the risk factor

(a) Risk ratio = 1.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
55	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
60	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
65	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7
70	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
75	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3
80	12	12	12	12	12	12	12	12	12	12
85	11	11	11	11	11	11	11	11	11	11

(b) Risk ratio = 1.25

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
55	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.7
60	1.8	1.8	1.7	1.7	1.7	1.7	1.7	1.6	1.6	1.6
65	3.6	3.6	3.5	3.5	3.5	3.4	3.4	3.3	3.3	3.3
70	6.0	5.9	5.8	5.8	5.7	5.6	5.6	5.5	5.5	5.4
75	9.2	9.1	9.0	8.9	8.8	8.7	8.6	8.5	8.4	8.3
80	12	12	11	11	11	11	11	11	11	11
85	11	11	11	11	10	10	10	10	10	9.9

(c) Risk ratio = 1.50

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4
55	0.8	0.8	0.8	0.8	0.7	0.7	0.7	0.7	0.7	0.7
60	1.8	1.7	1.7	1.6	1.6	1.6	1.5	1.5	1.5	1.4
65	3.6	3.5	3.4	3.3	3.3	3.2	3.1	3.1	3.0	2.9
70	5.9	5.8	5.6	5.5	5.4	5.3	5.2	5.1	5.0	4.9
75	9.1	8.9	8.7	8.5	8.3	8.2	8.0	7.8	7.7	7.5
80	12	11	11	11	11	10	10	10	9.8	9.6
85	11	11	10	10	9.9	9.7	9.5	9.3	9.2	9.0

(d) Risk ratio = 1.75

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4
55	0.8	0.8	0.7	0.7	0.7	0.7	0.7	0.6	0.6	0.6
60	1.7	1.7	1.6	1.6	1.5	1.5	1.4	1.4	1.4	1.3
65	3.5	3.4	3.3	3.2	3.1	3.0	2.9	2.8	2.8	2.7
70	5.8	5.6	5.5	5.3	5.1	5.0	4.8	4.7	4.6	4.4
75	9.0	8.7	8.4	8.2	7.9	7.7	7.5	7.3	7.1	6.9
80	11	11	11	10	10	9.8	9.5	9.3	9.0	8.8
85	11	10	10	9.7	9.4	9.2	8.9	8.7	8.4	8.2

(e) Risk ratio = 2.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.3
55	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.6
60	1.7	1.6	1.6	1.5	1.4	1.4	1.3	1.3	1.2	1.2
65	3.5	3.3	3.2	3.1	2.9	2.8	2.7	2.6	2.5	2.5
70	5.8	5.5	5.3	5.1	4.9	4.7	4.5	4.4	4.2	4.1
75	8.9	8.5	8.2	7.8	7.5	7.3	7.0	6.8	6.5	6.3
80	11	11	10	10	9.6	9.3	8.9	8.6	8.4	8.1
85	11	10	9.7	9.3	9.0	8.7	8.4	8.1	7.8	7.6

(f) Risk ratio = 2.25

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3
55	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.5	0.5
60	1.7	1.6	1.5	1.4	1.4	1.3	1.3	1.2	1.2	1.1
65	3.5	3.3	3.1	2.9	2.8	2.7	2.6	2.5	2.4	2.3
70	5.7	5.4	5.1	4.9	4.6	4.4	4.3	4.1	3.9	3.8
75	8.8	8.3	7.9	7.5	7.2	6.9	6.6	6.3	6.1	5.9
80	11	11	10	9.6	9.2	8.8	8.4	8.1	7.8	7.5
85	10	9.9	9.4	9.0	8.6	8.2	7.9	7.6	7.3	7.0

(g) Risk ratio = 2.50

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.5	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3
55	0.8	0.7	0.7	0.6	0.6	0.6	0.5	0.5	0.5	0.5
60	1.7	1.6	1.5	1.4	1.3	1.2	1.2	1.1	1.1	1.0
65	3.4	3.2	3.0	2.8	2.7	2.5	2.4	2.3	2.2	2.1
70	5.6	5.3	5.0	4.7	4.4	4.2	4.0	3.8	3.7	3.5
75	8.7	8.2	7.7	7.3	6.9	6.5	6.2	6.0	5.7	5.5
80	11	10	9.8	9.3	8.8	8.4	8.0	7.6	7.3	7.0
85	11	9.7	9.2	8.7	8.2	7.8	7.5	7.1	6.8	6.6

(h) Risk ratio = 2.75

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3
55	0.8	0.7	0.7	0.6	0.6	0.5	0.5	0.5	0.5	0.4
60	1.7	1.5	1.4	1.3	1.3	1.2	1.1	1.1	1.0	1.0
65	3.4	3.1	2.9	2.7	2.6	2.4	2.3	2.2	2.1	2.0
70	5.6	5.2	4.8	4.5	4.3	4.0	3.8	3.6	3.4	3.3
75	8.6	8.0	7.5	7.0	6.6	6.2	5.9	5.6	5.3	5.1
80	11	10	9.5	8.9	8.4	8.0	7.6	7.2	6.9	6.6
85	10	9.5	8.9	8.4	7.9	7.5	7.1	6.7	6.4	6.1

(i) Risk ratio = 3.00

Age (years)	Proportion of population without the condition									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	0.5	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3
55	0.8	0.7	0.6	0.6	0.6	0.5	0.5	0.5	0.4	0.4
60	1.6	1.5	1.4	1.3	1.2	1.1	1.1	1.0	1.0	0.9
65	3.3	3.1	2.8	2.6	2.5	2.3	2.2	2.1	2.0	1.9
70	5.5	5.1	4.7	4.4	4.1	3.8	3.6	3.4	3.2	3.1
75	8.5	7.8	7.3	6.8	6.3	6.0	5.6	5.3	5.0	4.8
80	11	10.0	9.3	8.6	8.1	7.6	7.2	6.8	6.5	6.2
85	10	9.3	8.7	8.1	7.6	7.1	6.7	6.4	6.1	5.8

Annex 3

Ten-year probabilities of fracture in the United Kingdom population, by bone mineral density, the number of clinical risk factors, age and sex

The following tables give the 10–year probability of fracture (%) according to BMD, the number of clinical risk factors (CRF) and age. These estimates are based on the epidemiology of the United Kingdom *(1,2)*. Each table provides a mean estimate and a range. The range is not a confidence interval but, because the weight of different risk factors varies, it is a true range.

Table A3.1 gives the probabilities for clinical spine, hip, forearm and humerus fracture (osteoporotic fracture) in men.

Table A3.2 gives the probabilities for hip fracture in men.

Table A3.3 gives the probabilities for clinical spine, hip, forearm and humerus fracture (osteoporotic fracture) in women.

Table A3.4 gives the probabilities of hip fracture in women.

References

1. Singer BR et al. Epidemiology of fracture in 1000 adults: the influence of age and gender. *Journal of Bone and Joint Surgery,* 1998, 80B:234–238.

2. *World population prospects: the 2002 revision and world urban prospects.* New York, United Nations Population Division, Department of Economic and Social Affairs, 2003.

Table A3.1

Ten-year probability of osteoporotic fracture (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in men from the United Kingdom

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	20	13	9.0	6.5	5.0	4.0	3.4	2.9	2.7	2.5	2.4
1	30 (26-38)	20 (18-25)	14 (12-17)	9.8 (7.9-12)	7.5 (5.6-9.4)	6.1 (4.3-7.8)	5.1 (3.5-6.8)	4.4 (2.9-6.0)	4.0 (2.6-5.5)	3.8 (2.4-5.3)	3.6 (2.3-5.1)
2	43 (34-56)	29 (23-40)	20 (16-28)	15 (10-20)	11 (7.3-17)	9.0 (5.4-14)	7.5 (4.3-12)	6.5 (3.5-11)	5.9 (3.1-10)	5.6 (2.9-9.7)	5.4 (2.8-9.4)
3	57 (44-70)	41 (30-51)	29 (21-39)	21 (14-31)	16 (9.7-26)	13 (7.2-22)	11 (5.6-19)	9.3 (4.6-17)	8.4 (4.0-16)	8.0 (3.7-15)	7.7 (3.5-15)
4	71 (56-81)	54 (39-64)	40 (28-48)	30 (20-39)	23 (15-32)	18 (12-28)	15 (9.1-24)	13 (7.4-22)	12 (6.4-20)	11 (6.0-19)	11 (5.7-19)
5	82 (74-88)	68 (57-75)	52 (42-57)	40 (31-46)	31 (24-38)	25 (19-33)	21 (16-28)	18 (14-25)	17 (12-23)	16 (11-22)	15 (10-22)
6	90	80	66	52	41	34	29	25	22	21	20

Age = 55 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	22	15	10	7.6	5.9	4.7	3.9	3.3	3.1	2.9	2.7
1	32 (29-38)	22 (20-26)	15 (13-19)	11 (9.1-14)	8.7 (6.6-11)	7.0 (5.0-9.0)	5.8 (4.0-7.7)	5.0 (3.3-6.8)	4.5 (3.0-6.3)	4.3 (2.7-6.0)	4.0 (2.6-5.7)
2	44 (36-55)	31 (25-41)	22 (18-30)	16 (12-22)	13 (8.6-19)	10 (6.4-16)	8.5 (5.0-14)	7.2 (4.0-12)	6.6 (3.6-11)	6.2 (3.3-11)	5.9 (3.1-10)
3	57 (46-67)	42 (33-52)	31 (24-41)	23 (16-34)	18 (11-28)	15 (8.4-24)	12 (6.5-21)	10 (5.3-18)	9.4 (4.6-17)	8.8 (4.2-16)	8.4 (3.9-16)
4	70 (57-78)	55 (42-63)	42 (31-51)	32 (23-42)	25 (18-35)	20 (14-30)	17 (10-26)	14 (8.4-23)	13 (7.3-22)	12 (6.7-21)	12 (6.2-20)
5	80 (74-85)	68 (59-73)	54 (46-60)	43 (35-50)	34 (27-42)	28 (22-36)	23 (18-31)	20 (15-27)	18 (13-25)	17 (12-24)	16 (11-23)
6	87	79	67	54	44	36	31	26	24	23	22

Age = 60 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	22	15	11	8.4	6.6	5.3	4.4	3.7	3.4	3.1	2.9
1	31 (28-35)	22 (20-26)	16 (14-19)	12 (9.8-14)	9.6 (7.3-12)	7.7 (5.6-9.9)	6.4 (4.4-8.5)	5.4 (3.6-7.3)	5.0 (3.3-6.9)	4.6 (3.0-6.5)	4.3 (2.8-6.1)
2	41 (35-51)	31 (26-39)	23 (18-29)	18 (13-24)	14 (9.5-20)	11 (7.1-17)	9.2 (5.5-14)	7.8 (4.5-13)	7.1 (4.0-12)	6.6 (3.6-11)	6.2 (3.3-10)
3	53 (44-62)	41 (33-50)	31 (24-41)	24 (17-35)	19 (13-29)	16 (9.4-25)	13 (7.3-22)	11 (5.9-19)	10 (5.1-18)	9.3 (4.6-17)	8.8 (4.3-16)
4	65 (54-71)	52 (42-60)	42 (32-50)	33 (24-43)	26 (19-36)	21 (15-31)	18 (11-27)	15 (9.2-24)	14 (8.0-23)	13 (7.2-21)	12 (6.6-20)
5	74 (69-78)	64 (57-69)	52 (45-59)	43 (36-50)	35 (29-43)	29 (23-37)	24 (19-32)	20 (16-28)	19 (14-26)	17 (12-25)	16 (11-23)
6	82	73	63	53	44	37	31	27	25	23	22

Age = 65 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	21	16	12	9.4	7.5	6.1	5.1	4.3	4.0	3.6	3.4
1	29 (26–33)	22 (19–25)	17 (14–20)	13 (11–16)	11 (8.1–13)	8.8 (6.3–11)	7.3 (5.1–9.7)	6.3 (4.2–8.5)	5.7 (3.8–7.9)	5.2 (3.4–7.4)	4.9 (3.1–6.9)
2	39 (33–46)	30 (25–36)	24 (19–30)	19 (14–25)	15 (10–21)	12 (8.0–18)	10 (6.3–16)	8.8 (5.2–14)	8.1 (4.6–13)	7.4 (4.1–12)	6.9 (3.7–11)
3	49 (41–57)	39 (33–49)	32 (25–41)	25 (18–36)	21 (14–31)	17 (11–27)	14 (8.3–23)	12 (6.8–21)	11 (6.0–19)	10 (5.3–18)	9.6 (4.8–17)
4	59 (51–65)	49 (41–57)	41 (32–50)	33 (26–43)	27 (21–38)	23 (16–33)	19 (13–29)	17 (10–26)	15 (9.0–24)	14 (8.0–23)	13 (7.3–21)
5	68 (63–73)	59 (53–65)	50 (44–58)	42 (36–50)	35 (30–44)	30 (25–38)	25 (20–34)	22 (17–30)	20 (15–28)	19 (13–26)	17 (12–25)
6	75	67	59	51	44	37	32	28	26	24	23

Age = 70 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	20	16	12	9.7	7.8	6.4	5.3	4.6	4.1	3.7	3.4
1	28 (23–34)	22 (18–26)	17 (14–21)	14 (11–16)	11 (8.2–13)	8.8 (6.5–11)	7.2 (5.2–8.6)	6.2 (4.4–7.4)	5.6 (3.9–6.6)	5.0 (3.5–6.1)	4.6 (3.1–5.6)
2	37 (30–46)	30 (23–38)	24 (18–31)	19 (14–25)	15 (11–20)	12 (8.3–16)	9.9 (6.6–14)	8.5 (5.5–12)	7.5 (4.8–11)	6.8 (4.2–9.5)	6.2 (3.8–8.7)
3	48 (39–57)	39 (31–49)	32 (24–41)	26 (18–34)	20 (14–28)	17 (11–24)	13 (8.7–20)	11 (7.2–17)	10 (6.3–15)	9.1 (5.5–14)	8.2 (4.9–13)
4	58 (49–66)	50 (41–58)	41 (33–50)	34 (26–42)	27 (20–36)	22 (16–30)	18 (13–25)	15 (11–22)	13 (9.2–20)	12 (8.1–18)	11 (7.2–16)
5	68 (61–73)	60 (52–66)	52 (44–59)	43 (36–51)	36 (30–43)	29 (24–36)	24 (19–30)	20 (16–26)	18 (14–23)	16 (13–21)	14 (12–19)
6	75	69	61	53	45	38	31	26	23	20	18

Age = 75 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	18	14	11	9.1	7.4	6.0	4.9	4.3	3.8	3.4	3.1
1	26 (20–41)	21 (16–34)	17 (12–27)	13 (9.7–21)	11 (7.6–16)	8.6 (6.1–12)	7.0 (4.9–9.7)	6.0 (4.1–7.9)	5.2 (3.6–6.5)	4.6 (3.2–5.4)	4.1 (2.8–4.8)
2	36 (26–51)	30 (21–43)	24 (16–36)	19 (13–29)	16 (10–23)	12 (8.0–18)	9.9 (6.3–14)	8.3 (5.3–12)	7.1 (4.6–9.7)	6.2 (3.9–8.2)	5.4 (3.5–7.1)
3	48 (34–61)	40 (27–53)	34 (22–45)	27 (17–38)	22 (13–31)	18 (11–25)	14 (8.4–20)	12 (7.1–17)	9.9 (6.0–14)	8.4 (5.2–12)	7.3 (4.5–10)
4	59 (42–69)	52 (35–62)	44 (29–54)	37 (23–47)	31 (19–39)	25 (15–32)	20 (12–26)	16 (10–22)	14 (8.5–18)	11 (7.4–16)	9.8 (6.5–13)
5	69 (52–75)	62 (44–69)	55 (37–62)	48 (31–55)	41 (26–47)	34 (21–40)	27 (17–33)	23 (15–28)	19 (13–23)	16 (11–20)	13 (9.8–17)
6	77	72	66	59	52	44	37	31	26	21	18

Age = 80 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	16	13	11	8.7	7.2	5.9	4.9	4.3	3.8	3.4	3.0
1	23 (17–37)	19 (14–31)	16 (11–25)	13 (9.0–21)	10 (7.3–17)	8.5 (5.9–13)	7.0 (4.8–11)	6.1 (4.1–8.8)	5.3 (3.6–7.3)	4.6 (3.1–6.2)	4.0 (2.7–5.2)
2	32 (22–47)	27 (18–40)	22 (15–33)	18 (12–28)	15 (9.7–23)	12 (7.9–18)	10 (6.4–15)	8.5 (5.4–12)	7.3 (4.6–10)	6.3 (4.0–8.8)	5.5 (3.5–7.4)
3	42 (29–55)	36 (24–49)	31 (20–42)	26 (16–36)	21 (13–30)	17 (11–24)	14 (8.6–20)	12 (7.3–17)	10 (6.2–14)	8.7 (5.3–12)	7.5 (4.6–10)
4	52 (36–63)	46 (30–57)	40 (26–50)	34 (21–44)	29 (17–37)	24 (14–31)	20 (12–26)	17 (9.9–22)	14 (8.5–19)	12 (7.3–16)	10 (6.3–14)
5	63 (44–69)	57 (38–63)	51 (32–57)	44 (27–51)	38 (23–45)	32 (19–38)	27 (16–32)	23 (14–28)	19 (12–24)	16 (10–21)	14 (9.0–18)
6	71	67	61	55	48	42	36	31	26	22	19

Age = 85 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	14	12	10	8.4	7.0	5.8	5.0	4.4	3.9	3.4	3.1
1	21 (15–34)	17 (13–29)	15 (10–24)	12 (8.6–20)	10 (7.1–17)	8.5 (5.8–14)	7.3 (4.9–12)	6.3 (4.3–9.9)	5.5 (3.7–8.5)	4.8 (3.2–7.2)	4.3 (2.8–6.2)
2	29 (20–43)	25 (17–37)	21 (14–32)	18 (11–27)	15 (9.5–23)	12 (7.8–19)	10 (6.6–16)	9.1 (5.7–14)	7.9 (4.9–12)	6.8 (4.3–9.9)	5.9 (3.7–8.5)
3	38 (25–51)	33 (22–45)	29 (18–40)	25 (15–34)	21 (13–29)	17 (11–25)	15 (8.9–21)	13 (7.6–18)	11 (6.6–16)	9.6 (5.7–13)	8.3 (4.9–12)
4	48 (32–59)	43 (28–53)	38 (24–48)	33 (20–42)	28 (17–37)	24 (14–32)	21 (12–27)	18 (10–24)	16 (8.9–21)	13 (7.7–18)	12 (6.7–15)
5	58 (40–65)	54 (35–60)	48 (30–55)	43 (26–50)	38 (22–44)	33 (19–39)	28 (16–34)	25 (14–30)	21 (12–26)	19 (11–23)	16 (9.3–20)
6	67	63	59	54	48	43	37	33	29	25	22

Age = 90 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	13	11	9.1	7.7	6.5	5.5	4.8	4.2	3.7	3.3	2.9
1	19 (14–31)	16 (12–27)	14 (9.8–23)	12 (8.2–20)	9.8 (6.9–17)	8.3 (5.8–14)	7.2 (5.0–12)	6.3 (4.4–11)	5.5 (3.8–9.1)	4.9 (3.3–7.9)	4.3 (2.9–6.8)
2	26 (18–40)	23 (15–35)	20 (13–31)	17 (11–27)	15 (9.3–23)	12 (7.8–19)	11 (6.8–17)	9.4 (5.9–15)	8.2 (5.2–13)	7.2 (4.5–11)	6.3 (3.9–9.8)
3	36 (23–48)	32 (20–44)	28 (17–39)	24 (15–35)	21 (13–30)	18 (11–26)	16 (9.2–23)	14 (8.1–20)	12 (7.0–18)	11 (6.1–16)	9.2 (5.4–14)
4	45 (30–56)	41 (26–52)	37 (23–47)	33 (20–42)	29 (17–38)	25 (14–33)	22 (12–30)	20 (11–26)	17 (9.6–23)	15 (8.4–21)	13 (7.4–18)
5	55 (37–61)	51 (33–58)	47 (29–54)	43 (26–49)	39 (22–45)	34 (19–40)	31 (17–36)	28 (15–33)	25 (13–29)	22 (12–26)	19 (10–23)
6	63	60	57	53	49	45	41	37	33	30	27

TableA3.2

Ten-year probability of hip fracture (%), by BMD, the number of clinical risk factors (CRFs) and age in men from the United Kingdom

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	16	8.6	4.6	2.4	1.3	0.7	0.4	0.2	0.1	0.1	0.0
1	24 (17–31)	13 (9.0–18)	7.3 (4.8–9.6)	3.9 (2.6–5.1)	2.1 (1.4–2.7)	1.1 (0.7–1.4)	0.6 (0.4–0.8)	0.3 (0.2–0.4)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.0 (0.0–0.1)
2	35 (23–48)	21 (13–30)	11 (6.8–17)	6.2 (3.6–9.3)	3.3 (1.9–5.0)	1.7 (1.0–2.6)	0.9 (0.5–1.4)	0.5 (0.3–0.7)	0.3 (0.2–0.4)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
3	48 (32–66)	30 (19–44)	17 (10–27)	9.6 (5.5–15)	5.1 (2.9–8.3)	2.7 (1.5–4.4)	1.4 (0.8–2.4)	0.8 (0.4–1.2)	0.4 (0.2–0.7)	0.2 (0.1–0.4)	0.1 (0.1–0.2)
4	63 (48–78)	42 (29–58)	26 (17–38)	15 (9.2–22)	7.9 (4.9–12)	4.2 (2.6–6.7)	2.2 (1.4–3.6)	1.2 (0.7–1.9)	0.6 (0.4–1.0)	0.3 (0.2–0.6)	0.2 (0.1–0.3)
5	77 (68–86)	57 (46–70)	37 (28–48)	22 (16–30)	12 (8.8–17)	6.5 (4.7–9.4)	3.5 (2.5–5.0)	1.8 (1.3–2.7)	1.0 (0.7–1.4)	0.5 (0.4–0.8)	0.3 (0.2–0.4)
6	87	71	50	31	18	9.8	5.3	2.8	1.5	0.8	0.4

Age = 55 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	16	9.3	5.2	2.9	1.6	0.9	0.5	0.3	0.1	0.1	0.0
1	24 (17–30)	14 (9.8–18)	8.1 (5.5–10)	4.5 (3.0–5.6)	2.5 (1.7–3.1)	1.4 (0.9–1.7)	0.7 (0.5–0.9)	0.4 (0.3–0.5)	0.2 (0.2–0.3)	0.1 (0.1–0.2)	0.1 (0.1–0.1)
2	35 (23–46)	21 (14–29)	12 (7.7–17)	6.9 (4.3–10)	3.8 (2.3–5.6)	2.1 (1.3–3.1)	1.2 (0.7–1.7)	0.6 (0.4–0.9)	0.4 (0.2–0.5)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
3	47 (33–62)	31 (20–43)	18 (11–27)	11 (6.4–16)	5.9 (3.6–9.1)	3.3 (2.0–5.1)	1.8 (1.1–2.8)	1.0 (0.6–1.5)	0.6 (0.3–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
4	61 (48–75)	42 (31–56)	27 (18–38)	16 (11–23)	9.0 (5.9–13)	5.0 (3.3–7.6)	2.8 (1.8–4.3)	1.5 (1.0–2.3)	0.9 (0.6–1.3)	0.5 (0.3–0.8)	0.3 (0.2–0.4)
5	74 (67–83)	55 (47–68)	37 (30–48)	23 (18–31)	13 (10–19)	7.5 (5.9–11)	4.2 (3.2–6.0)	2.3 (1.8–3.3)	1.3 (1.0–1.9)	0.7 (0.6–1.1)	0.4 (0.3–0.6)
6	84	69	50	32	19	11	6.3	3.5	2.0	1.1	0.6

Age = 60 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	15	9.2	5.5	3.2	1.9	1.1	0.6	0.4	0.2	0.1	0.1
1	22 (16–26)	14 (9.6–16)	8.2 (5.7–9.7)	4.9 (3.4–5.7)	2.9 (2.0–3.4)	1.7 (1.1–2.0)	1.0 (0.7–1.1)	0.6 (0.4–0.7)	0.3 (0.2–0.4)	0.2 (0.1–0.2)	0.1 (0.1–0.1)
2	31 (22–40)	20 (13–26)	12 (8.0–16)	7.4 (4.7–10)	4.3 (2.8–6.0)	2.5 (1.6–3.5)	1.5 (0.9–2.0)	0.9 (0.5–1.2)	0.5 (0.3–0.7)	0.3 (0.2–0.4)	0.2 (0.1–0.3)
3	42 (31–53)	28 (20–38)	18 (12–25)	11 (7.1–16)	6.5 (4.2–9.4)	3.8 (2.5–5.6)	2.3 (1.4–3.3)	1.3 (0.8–1.9)	0.8 (0.5–1.2)	0.5 (0.3–0.7)	0.3 (0.2–0.4)
4	54 (44–66)	38 (30–50)	25 (19–35)	16 (11–22)	9.6 (6.8–14)	5.7 (4.0–8.4)	3.4 (2.4–5.0)	2.0 (1.4–3.0)	1.2 (0.8–1.8)	0.7 (0.5–1.1)	0.4 (0.3–0.7)
5	66 (60–75)	50 (44–61)	35 (30–45)	23 (19–30)	14 (12–19)	8.5 (7.0–12)	5.0 (4.1–7.0)	3.0 (2.4–4.2)	1.8 (1.5–2.5)	1.1 (0.9–1.5)	0.6 (0.5–0.9)
6	76	62	46	31	20	12	7.4	4.4	2.7	1.6	1.0

Age = 65 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	14	8.8	5.6	3.5	2.1	1.3	0.8	0.5	0.3	0.2	0.1
1	20 (14–22)	13 (9.3–15)	8.2 (5.8–9.4)	5.1 (3.6–5.9)	3.2 (2.3–3.7)	2.0 (1.4–2.3)	1.2 (0.9–1.4)	0.8 (0.5–0.9)	0.5 (0.3–0.6)	0.3 (0.2–0.4)	0.2 (0.1–0.2)
2	27 (20–34)	18 (13–23)	12 (8.2–15)	7.5 (5.1–9.7)	4.7 (3.2–6.1)	3.0 (2.0–3.8)	1.8 (1.2–2.4)	1.1 (0.8–1.5)	0.7 (0.5–1.0)	0.5 (0.3–0.6)	0.3 (0.2–0.4)
3	36 (28–45)	25 (19–32)	17 (12–22)	11 (7.7–14)	6.9 (4.8–9.3)	4.3 (3.0–5.9)	2.7 (1.9–3.7)	1.7 (1.2–2.3)	1.1 (0.7–1.5)	0.7 (0.5–1.0)	0.4 (0.3–0.6)
4	46 (39–56)	34 (27–43)	23 (18–31)	15 (12–21)	10 (7.6–14)	6.3 (4.7–8.8)	4.0 (3.0–5.6)	2.5 (1.9–3.6)	1.6 (1.2–2.3)	1.0 (0.8–1.5)	0.7 (0.5–0.9)
5	57 (53–65)	44 (40–53)	31 (28–40)	21 (19–28)	14 (12–19)	9.1 (7.8–12)	5.7 (4.9–7.9)	3.6 (3.1–5.0)	2.3 (2.0–3.2)	1.5 (1.3–2.1)	1.0 (0.8–1.3)
6	66	54	41	29	20	13	8.2	5.3	3.4	2.2	1.4

Age = 70 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	12	8.4	5.6	3.7	2.5	1.6	1.1	0.7	0.5	0.3	0.2
1	19 (17–24)	13 (12–17)	9.0 (7.9–12)	6.0 (5.3–7.8)	4.0 (3.5–5.2)	2.6 (2.3–3.4)	1.7 (1.5–2.3)	1.2 (1.0–1.5)	0.8 (0.7–1.0)	0.5 (0.5–0.7)	0.4 (0.3–0.5)
2	28 (24–35)	20 (17–25)	14 (11–18)	9.5 (7.8–12)	6.4 (5.2–8.5)	4.3 (3.5–5.7)	2.8 (2.3–3.8)	1.9 (1.5–2.5)	1.3 (1.0–1.7)	0.9 (0.7–1.2)	0.6 (0.5–0.8)
3	39 (33–46)	29 (24–35)	21 (17–26)	15 (12–18)	10 (7.8–13)	6.8 (5.2–8.6)	4.5 (3.5–5.8)	3.1 (2.4–3.9)	2.1 (1.6–2.7)	1.4 (1.1–1.8)	1.0 (0.7–1.2)
4	51 (43–57)	40 (33–46)	30 (24–35)	22 (17–26)	15 (12–18)	11 (8.0–13)	7.1 (5.3–8.6)	4.9 (3.6–5.9)	3.3 (2.5–4.0)	2.3 (1.7–2.8)	1.6 (1.1–1.9)
5	62 (54–66)	52 (44–56)	41 (34–45)	31 (25–34)	23 (18–25)	16 (12–18)	11 (8.5–12)	7.7 (5.8–8.6)	5.3 (4.0–6.0)	3.7 (2.8–4.1)	2.5 (1.9–2.8)
6	71	63	53	43	33	24	17	12	8.3	5.8	4.0

Age = 75 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	11	8.1	5.8	4.1	2.9	2.0	1.4	1.0	0.7	0.5	0.4
1	19 (15–37)	14 (11–29)	11 (8.0–22)	7.6 (5.7–16)	5.4 (4.0–12)	3.8 (2.8–8.3)	2.7 (2.0–5.9)	1.9 (1.4–4.3)	1.4 (1.0–3.1)	1.0 (0.7–2.2)	0.7 (0.5–1.6)
2	30 (20–48)	23 (15–39)	18 (11–30)	13 (8.0–23)	9.5 (5.7–17)	6.8 (4.0–13)	4.9 (2.8–9.1)	3.5 (2.0–6.7)	2.6 (1.4–4.9)	1.8 (1.0–3.6)	1.3 (0.7–2.6)
3	42 (27–58)	34 (20–49)	27 (15–40)	21 (11–32)	16 (8.0–25)	11 (5.7–18)	8.3 (4.0–13)	6.1 (2.9–10)	4.5 (2.1–7.3)	3.2 (1.5–5.4)	2.4 (1.1–3.9)
4	55 (35–66)	47 (28–58)	39 (21–49)	31 (16–40)	24 (12–32)	18 (8.5–25)	14 (6.0–18)	10 (4.4–14)	7.5 (3.2–10)	5.5 (2.3–7.5)	4.0 (1.7–5.5)
5	66 (45–72)	59 (37–66)	51 (29–58)	43 (23–49)	35 (17–40)	27 (12–32)	21 (9.0–24)	16 (6.7–19)	12 (4.9–14)	9.0 (3.6–10)	6.6 (2.6–7.7)
6	76	71	64	56	47	39	31	24	19	14	11

Age = 80 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	10	7.7	5.8	4.3	3.2	2.4	1.8	1.3	1.0	0.8	0.6
1	17 (13–33)	13 (9.9–27)	10 (7.5–21)	7.8 (5.6–17)	5.9 (4.2–13)	4.4 (3.1–9.7)	3.3 (2.3–7.4)	2.5 (1.8–5.7)	1.9 (1.3–4.3)	1.5 (1.0–3.3)	1.1 (0.8–2.5)
2	26 (17–43)	21 (13–36)	17 (9.8–30)	13 (7.5–24)	10 (5.6–18)	7.6 (4.2–14)	5.8 (3.2–11)	4.5 (2.4–8.4)	3.4 (1.9–6.5)	2.6 (1.4–5.0)	2.0 (1.1–3.9)
3	37 (22–52)	31 (17–45)	25 (13–38)	20 (10–31)	16 (7.8–25)	12 (5.9–20)	9.5 (4.4–16)	7.4 (3.4–12)	5.8 (2.6–9.7)	4.5 (2.0–7.5)	3.4 (1.5–5.8)
4	49 (29–61)	42 (23–54)	35 (18–47)	29 (14–39)	24 (11–33)	19 (8.5–26)	15 (6.4–21)	12 (5.0–17)	9.3 (3.9–13)	7.3 (3.0–10)	5.6 (2.3–8.1)
5	60 (38–66)	54 (32–60)	47 (26–53)	40 (20–46)	34 (16–39)	28 (12–32)	22 (9.5–26)	18 (7.5–21)	14 (5.8–17)	11 (4.5–14)	8.9 (3.5–11)
6	70	65	59	52	45	38	32	26	21	17	14

Age = 85 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	8.9	7.1	5.6	4.4	3.5	2.7	2.2	1.7	1.4	1.1	0.9
1	15 (11–30)	12 (9.0–25)	9.9 (7.2–21)	7.9 (5.7–17)	6.3 (4.5–14)	5.0 (3.5–11)	4.0 (2.8–8.8)	3.2 (2.3–7.2)	2.6 (1.8–5.8)	2.1 (1.5–4.7)	1.7 (1.2–3.8)
2	23 (14–39)	19 (12–34)	16 (9.3–28)	13 (7.4–24)	10 (5.8–19)	8.4 (4.6–16)	6.8 (3.7–13)	5.5 (3.0–11)	4.5 (2.4–8.7)	3.7 (1.9–7.1)	3.0 (1.6–5.7)
3	33 (19–48)	28 (16–42)	24 (13–36)	20 (10–31)	16 (8.1–26)	13 (6.4–21)	11 (5.2–18)	9.0 (4.2–15)	7.4 (3.4–12)	6.0 (2.7–10)	4.9 (2.2–8.2)
4	45 (26–56)	39 (21–51)	34 (17–45)	29 (14–39)	24 (11–33)	20 (9.0–28)	17 (7.3–23)	14 (6.0–20)	12 (4.8–17)	9.6 (3.9–14)	7.9 (3.2–11)
5	56 (34–62)	51 (29–57)	45 (24–51)	39 (20–45)	34 (16–39)	29 (13–34)	24 (11–29)	21 (8.8–25)	17 (7.2–21)	15 (5.9–17)	12 (4.8–14)
6	66	62	57	51	45	40	34	30	25	21	18

Age = 90 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	7.9	6.5	5.3	4.3	3.5	2.9	2.4	2.0	1.7	1.4	1.2
1	14 (10–28)	11 (8.4–24)	9.5 (6.9–20)	7.9 (5.7–17)	6.5 (4.6–14)	5.3 (3.8–12)	4.5 (3.2–9.9)	3.8 (2.6–8.3)	3.2 (2.2–7.0)	2.7 (1.9–5.9)	2.2 (1.5–5.0)
2	21 (13–37)	18 (11–32)	16 (9.1–28)	13 (7.5–24)	11 (6.2–20)	9.1 (5.1–17)	7.7 (4.3–14)	6.5 (3.6–12)	5.5 (3.0–10)	4.7 (2.5–8.8)	3.9 (2.1–7.5)
3	31 (18–46)	27 (15–41)	24 (12–36)	20 (10–32)	17 (8.6–27)	15 (7.1–23)	12 (6.0–20)	11 (5.0–18)	9.1 (4.2–15)	7.8 (3.6–13)	6.6 (3.0–11)
4	42 (24–54)	38 (20–49)	34 (17–44)	29 (15–40)	26 (12–35)	22 (10–30)	19 (8.6–27)	17 (7.3–23)	14 (6.2–20)	12 (5.3–17)	11 (4.4–15)
5	53 (32–59)	49 (28–55)	45 (24–51)	40 (21–46)	36 (18–41)	32 (15–36)	28 (13–32)	25 (11–29)	22 (9.2–25)	19 (7.8–22)	16 (6.6–19)
6	62	59	56	52	47	43	38	35	31	27	24

TableA3.3

Ten-year probability of osteoporotic fractures (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	17	12	8.3	6.3	5.1	4.2	3.6	3.3	3.2	3.1	2.9
1	26 (23–32)	18 (15–22)	13 (10–16)	9.5 (7.2–12)	7.6 (5.4–9.7)	6.4 (4.4–8.4)	5.5 (3.6–7.4)	5.0 (3.3–6.9)	4.8 (3.1–6.6)	4.6 (2.9–6.4)	4.4 (2.8–6.2)
2	37 (30–50)	26 (20–35)	19 (14–25)	14 (9.3–21)	11 (6.8–18)	9.4 (5.4–15)	8.1 (4.4–14)	7.4 (3.9–13)	7.0 (3.7–12)	6.7 (3.5–12)	6.5 (3.3–11)
3	51 (39–64)	37 (27–48)	27 (18–39)	20 (12–32)	16 (9.0–27)	14 (7.0–24)	12 (5.7–21)	11 (5.1–20)	10 (4.7–19)	9.7 (4.5–18)	9.3 (4.3–18)
4	66 (50–77)	50 (35–58)	37 (26–48)	28 (19–40)	23 (15–34)	19 (12–30)	16 (9.3–27)	15 (8.2–25)	14 (7.6–24)	14 (7.2–23)	13 (6.9–22)
5	80 (71–87)	64 (53–69)	50 (40–56)	39 (31–47)	31 (25–40)	26 (20–35)	23 (17–31)	21 (15–29)	20 (14–27)	19 (13–27)	18 (13–26)
6	90	78	63	51	42	35	31	28	27	26	25

Age = 55 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	20	14	10	7.9	6.3	5.3	4.5	4.2	3.9	3.7	3.5
1	29 (26–34)	20 (18–24)	15 (12–18)	12 (8.9–14)	9.4 (6.8–12)	7.8 (5.4–10)	6.7 (4.5–9.1)	6.2 (4.1–8.5)	5.8 (3.8–8.1)	5.5 (3.6–7.7)	5.2 (3.4–7.3)
2	40 (34–52)	29 (23–39)	22 (16–29)	17 (11–25)	14 (8.6–21)	11 (6.7–18)	9.7 (5.5–16)	9.0 (4.9–15)	8.5 (4.5–14)	8.0 (4.2–14)	7.6 (4.0–13)
3	54 (43–65)	41 (31–53)	31 (21–44)	24 (15–37)	20 (11–32)	16 (8.8–28)	14 (7.1–25)	13 (6.3–23)	12 (5.8–22)	11 (5.4–21)	11 (5.1–20)
4	68 (54–77)	54 (40–63)	42 (30–54)	33 (24–46)	27 (18–40)	23 (14–35)	19 (12–31)	18 (10–29)	17 (9.4–28)	16 (8.7–26)	15 (8.2–25)
5	81 (74–86)	68 (59–73)	55 (46–62)	44 (37–53)	36 (30–46)	31 (25–40)	26 (20–35)	24 (18–33)	23 (16–32)	22 (15–30)	21 (14–29)
6	90	80	68	57	48	41	35	33	31	29	28

Age = 60 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	23	16	12	9.5	7.7	6.3	5.5	5.0	4.6	4.3	4.1
1	32 (29–37)	24 (20–27)	18 (15–21)	14 (11–17)	11 (8.2–14)	9.3 (6.5–12)	8.0 (5.5–11)	7.4 (4.9–10)	6.8 (4.5–9.5)	6.4 (4.2–8.9)	6.0 (3.9–8.4)
2	44 (38–54)	33 (27–42)	25 (19–34)	20 (14–28)	16 (10–24)	13 (8.1–21)	12 (6.7–18)	11 (5.9–17)	9.8 (5.4–16)	9.2 (4.9–15)	8.6 (4.6–14)
3	58 (48–68)	45 (35–58)	35 (25–49)	28 (18–42)	23 (14–36)	19 (11–31)	16 (8.7–28)	15 (7.7–26)	14 (6.9–25)	13 (6.4–23)	12 (5.9–22)
4	71 (59–78)	58 (45–68)	46 (35–59)	38 (28–51)	31 (22–44)	26 (17–39)	22 (14–35)	21 (12–33)	19 (11–31)	18 (10–29)	17 (9.4–28)
5	82 (77–85)	71 (64–76)	59 (52–67)	49 (42–58)	41 (34–51)	34 (28–44)	30 (23–40)	28 (21–38)	26 (19–35)	24 (17–33)	23 (16–32)
6	90	82	72	61	52	45	40	37	34	32	30

Age = 65 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	27	20	15	12	9.7	8.0	7.1	6.4	5.9	5.4	5.0
1	37 (33–41)	28 (24–31)	22 (18–26)	17 (13–22)	14 (10–18)	12 (8.2–15)	10 (7.1–14)	9.3 (6.3–13)	8.5 (5.7–12)	7.9 (5.2–11)	7.3 (4.8–10)
2	49 (42–58)	38 (31–47)	30 (23–40)	24 (17–34)	20 (13–29)	16 (10–25)	15 (8.6–23)	13 (7.6–21)	12 (6.8–19)	11 (6.1–18)	10 (5.6–17)
3	62 (53–72)	50 (40–64)	41 (30–55)	33 (22–48)	27 (17–42)	23 (13–37)	20 (11–34)	18 (9.8–31)	17 (8.7–29)	16 (7.9–27)	15 (7.2–26)
4	73 (63–81)	62 (52–73)	52 (42–65)	43 (34–57)	36 (26–51)	30 (21–44)	27 (18–41)	25 (15–39)	23 (14–36)	21 (12–34)	20 (11–32)
5	83 (79–87)	74 (69–80)	64 (58–72)	55 (49–65)	47 (40–57)	40 (32–51)	36 (28–47)	33 (25–44)	31 (22–41)	28 (20–39)	27 (19–36)
6	89	83	75	66	58	50	46	42	40	37	35

Age = 70 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	30	23	18	14	11	9.3	8.2	7.3	6.6	5.9	5.4
1	41 (36–47)	32 (27–37)	25 (20–29)	19 (15–23)	15 (12–18)	13 (9.5–15)	11 (8.2–13)	10 (7.2–12)	8.9 (6.3–11)	8.1 (5.7–9.6)	7.3 (5.1–8.8)
2	54 (45–64)	43 (34–53)	34 (26–42)	27 (20–34)	21 (15–27)	18 (12–23)	15 (10–20)	13 (8.6–18)	12 (7.6–16)	11 (6.8–15)	9.9 (6.1–14)
3	67 (56–77)	55 (43–68)	45 (33–58)	36 (25–48)	29 (19–40)	24 (15–34)	20 (13–30)	18 (11–27)	16 (9.8–25)	14 (8.7–23)	13 (7.8–21)
4	78 (70–84)	68 (58–77)	57 (47–67)	47 (37–58)	38 (29–49)	31 (24–42)	27 (20–38)	24 (17–34)	21 (15–31)	19 (14–28)	17 (12–26)
5	86 (81–89)	79 (73–83)	70 (63–76)	59 (52–67)	49 (43–57)	41 (35–49)	35 (30–44)	31 (27–39)	28 (24–36)	25 (21–33)	22 (19–30)
6	89	86	80	71	61	52	45	40	35	32	29

Age = 75 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	31	24	19	15	12	10	8.6	7.5	6.6	5.9	5.3
1	44 (37–62)	35 (28–49)	27 (22–38)	21 (16–29)	17 (13–22)	14 (10–17)	12 (8.7–14)	10 (7.4–12)	8.8 (6.5–10)	7.8 (5.7–9.3)	6.9 (5.0–8.3)
2	58 (46–75)	48 (36–65)	38 (28–53)	30 (21–42)	23 (16–33)	19 (13–26)	16 (11–21)	14 (9.2–18)	12 (7.9–16)	10 (6.8–14)	9.0 (6.0–13)
3	71 (56–82)	61 (45–75)	51 (35–65)	41 (27–55)	33 (21–44)	27 (17–36)	22 (14–30)	18 (12–25)	16 (10–22)	13 (8.8–19)	12 (7.7–16)
4	80 (68–86)	73 (57–82)	65 (47–75)	54 (38–65)	44 (30–54)	36 (25–45)	30 (21–38)	25 (18–32)	21 (15–27)	18 (13–24)	15 (11–21)
5	86 (77–89)	82 (70–86)	76 (61–81)	67 (51–74)	57 (42–64)	48 (36–55)	40 (31–46)	33 (26–39)	28 (23–33)	23 (20–29)	20 (17–25)
6	89	87	84	78	70	61	52	44	37	31	26

Age = 80 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	33	26	21	16	13	11	9.6	8.3	7.2	6.3	5.5
1	45 (37–62)	37 (29–52)	29 (23–42)	23 (18–33)	19 (14–26)	16 (12–21)	13 (9.7–17)	11 (8.2–13)	9.6 (7.0–11)	8.3 (6.0–9.5)	7.2 (5.2–8.4)
2	57 (45–72)	48 (37–64)	40 (29–55)	32 (23–45)	26 (18–37)	22 (15–30)	18 (12–25)	15 (10–20)	13 (8.7–17)	11 (7.4–14)	9.5 (6.4–13)
3	67 (55–79)	60 (46–73)	51 (37–65)	43 (30–55)	35 (24–46)	30 (19–39)	25 (16–33)	21 (13–28)	17 (11–24)	15 (9.6–20)	12 (8.3–17)
4	76 (64–83)	70 (55–79)	63 (47–72)	55 (38–64)	46 (31–56)	39 (26–48)	33 (22–41)	28 (19–35)	23 (16–30)	19 (14–25)	16 (12–22)
5	82 (72–86)	78 (65–83)	73 (58–78)	66 (50–72)	58 (42–65)	51 (36–57)	43 (31–50)	37 (27–43)	31 (23–37)	26 (20–31)	22 (18–27)
6	86	84	80	75	69	62	55	47	40	34	28

Age = 85 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	34	28	22	18	15	13	11	9.3	8.0	6.9	6.0
1	44 (36–60)	37 (29–52)	31 (24–44)	25 (19–36)	21 (16–30)	18 (13–25)	15 (11–20)	13 (9.2–17)	11 (7.8–14)	9.3 (6.6–11)	7.9 (5.7–9.4)
2	55 (44–69)	48 (37–62)	41 (30–54)	34 (24–47)	29 (20–40)	24 (17–34)	21 (14–29)	17 (12–24)	15 (9.9–20)	13 (8.3–17)	11 (7.0–14)
3	64 (52–75)	58 (45–70)	51 (38–63)	44 (31–56)	38 (26–49)	33 (22–43)	28 (18–37)	24 (15–32)	20 (13–27)	17 (11–23)	14 (9.2–20)
4	73 (60–80)	67 (54–76)	61 (46–70)	54 (39–64)	48 (34–58)	43 (29–52)	37 (25–46)	32 (21–40)	27 (18–34)	23 (16–29)	19 (13–25)
5	79 (68–83)	75 (62–80)	70 (55–76)	64 (48–71)	59 (43–66)	53 (38–60)	47 (33–54)	41 (29–48)	35 (25–42)	30 (22–36)	26 (19–31)
6	82	81	78	73	69	63	58	51	45	39	34

Age = 90 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	29	24	19	16	13	11	9.4	8.0	6.8	5.7	4.9
1	39 (31–55)	33 (26–48)	27 (21–40)	22 (17–33)	19 (14–28)	16 (12–24)	14 (9.9–20)	11 (8.3–16)	9.6 (7.0–13)	8.1 (5.8–11)	6.8 (4.9–9.0)
2	50 (39–65)	43 (33–58)	37 (27–51)	31 (22–45)	27 (19–39)	23 (16–33)	19 (13–28)	16 (11–24)	14 (9.1–20)	11 (7.6–17)	9.6 (6.3–14)
3	61 (48–72)	54 (41–67)	48 (34–61)	42 (28–55)	36 (24–49)	31 (20–42)	27 (17–37)	23 (14–31)	19 (12–26)	16 (10–22)	14 (8.4–19)
4	69 (56–77)	64 (50–73)	59 (43–69)	53 (36–63)	47 (32–58)	42 (27–52)	37 (23–45)	31 (20–39)	27 (17–34)	23 (14–29)	19 (12–24)
5	75 (64–80)	73 (59–78)	68 (52–74)	64 (46–70)	59 (41–65)	53 (36–60)	48 (32–54)	42 (27–48)	36 (23–42)	31 (20–36)	26 (17–31)
6	78	78	76	73	69	64	59	54	48	42	36

Table A3.4

Ten-year probability of hip fracture (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	12	6.1	3.1	1.6	0.8	0.4	0.2	0.1	0.1	0.0	0.0
1	18 (12–23)	9.7 (6.4–13)	5.1 (3.3–6.6)	2.6 (1.7–3.4)	1.3 (0.9–1.8)	0.7 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.1 (0.0–0.1)	0.0 (0.0–0.0)
2	27 (17–39)	15 (9.0–22)	8.0 (4.7–12)	4.2 (2.4–6.3)	2.1 (1.2–3.3)	1.1 (0.6–1.7)	0.6 (0.3–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.0 (0.0–0.1)
3	39 (25–57)	23 (13–35)	12 (7.0–20)	6.5 (3.6–11)	3.4 (1.9–5.6)	1.7 (1.0–2.9)	0.9 (0.5–1.5)	0.5 (0.3–0.8)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
4	54 (38–72)	33 (22–48)	19 (12–29)	10 (6.3–16)	5.3 (3.2–8.4)	2.7 (1.7–4.4)	1.4 (0.9–2.3)	0.7 (0.4–1.2)	0.4 (0.2–0.6)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
5	70 (59–83)	47 (37–61)	28 (21–38)	15 (11–22)	8.2 (6.0–12)	4.3 (3.1–6.2)	2.2 (1.6–3.2)	1.1 (0.8–1.7)	0.6 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
6	84	62	40	23	12	6.5	3.4	1.8	0.9	0.5	0.3

Age = 55 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	12	6.8	3.7	2.0	1.1	0.6	0.3	0.2	0.1	0.1	0.0
1	19 (13–23)	11 (7.1–13)	5.8 (3.9–7.1)	3.2 (2.1–3.9)	1.7 (1.1–2.1)	0.9 (0.6–1.1)	0.5 (0.3–0.6)	0.3 (0.2–0.3)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.0 (0.0–0.1)
2	28 (18–38)	16 (9.9–23)	9.0 (5.5–13)	4.9 (3.0–7.2)	2.7 (1.6–3.9)	1.4 (0.9–2.1)	0.8 (0.5–1.1)	0.4 (0.3–0.6)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
3	39 (26–56)	24 (15–36)	14 (8.2–21)	7.6 (4.5–12)	4.2 (2.4–6.6)	2.3 (1.3–3.6)	1.2 (0.7–2.0)	0.7 (0.4–1.1)	0.4 (0.2–0.6)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
4	54 (40–70)	34 (24–49)	20 (14–30)	12 (7.6–18)	6.4 (4.2–10)	3.5 (2.3–5.5)	1.9 (1.2–3.0)	1.1 (0.7–1.7)	0.6 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
5	69 (61–81)	48 (40–61)	30 (24–40)	17 (14–24)	9.7 (7.7–14)	5.4 (4.2–7.7)	2.9 (2.3–4.2)	1.6 (1.3–2.4)	0.9 (0.7–1.3)	0.5 (0.4–0.7)	0.3 (0.2–0.4)
6	82	63	42	25	15	8.1	4.4	2.5	1.4	0.8	0.4

Age = 60 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	13	7.7	4.4	2.4	1.4	0.8	0.4	0.3	0.1	0.1	0.1
1	20 (14–23)	12 (8.1–14)	6.7 (4.6–7.9)	3.8 (2.6–4.5)	2.1 (1.4–2.5)	1.2 (0.8–1.4)	0.7 (0.5–0.8)	0.4 (0.3–0.5)	0.2 (0.2–0.3)	0.1 (0.1–0.2)	0.1 (0.1–0.1)
2	29 (19–38)	18 (11–24)	10 (6.4–14)	5.8 (3.6–8.0)	3.3 (2.0–4.6)	1.9 (1.1–2.6)	1.1 (0.7–1.5)	0.6 (0.4–0.9)	0.4 (0.2–0.5)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
3	41 (28–55)	26 (17–36)	15 (9.6–23)	8.9 (5.5–13)	5.1 (3.1–7.7)	2.8 (1.7–4.4)	1.6 (1.0–2.5)	0.9 (0.6–1.5)	0.5 (0.3–0.8)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
4	54 (42–69)	36 (27–49)	22 (16–32)	13 (9.2–20)	7.6 (5.3–11)	4.3 (3.0–6.6)	2.5 (1.7–3.8)	1.4 (1.0–2.2)	0.8 (0.6–1.3)	0.5 (0.3–0.7)	0.3 (0.2–0.4)
5	68 (63–80)	49 (43–62)	32 (27–42)	19 (16–27)	11 (9.4–16)	6.5 (5.3–9.2)	3.7 (3.1–5.3)	2.2 (1.8–3.1)	1.3 (1.0–1.8)	0.7 (0.6–1.1)	0.4 (0.3–0.6)
6	81	63	44	28	17	9.7	5.6	3.3	1.9	1.1	0.6

Age = 65 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	14	8.6	5.1	3.0	1.7	1.0	0.6	0.4	0.2	0.1	0.1
1	21 (15–25)	13 (9.1–15)	7.7 (5.4–9.2)	4.5 (3.1–5.4)	2.7 (1.8–3.2)	1.5 (1.1–1.9)	0.9 (0.6–1.1)	0.6 (0.4–0.7)	0.3 (0.2–0.4)	0.2 (0.1–0.2)	0.1 (0.1–0.2)
2	30 (21–37)	19 (13–24)	11 (7.5–15)	6.8 (4.4–9.0)	4.0 (2.6–5.3)	2.4 (1.5–3.1)	1.4 (0.9–1.9)	0.9 (0.6–1.1)	0.5 (0.3–0.7)	0.3 (0.2–0.4)	0.2 (0.1–0.3)
3	41 (30–53)	27 (19–37)	17 (11–24)	10 (6.7–15)	6.1 (3.9–8.7)	3.6 (2.3–5.2)	2.2 (1.4–3.2)	1.3 (0.8–1.9)	0.8 (0.5–1.2)	0.5 (0.3–0.7)	0.3 (0.2–0.4)
4	54 (44–67)	37 (29–49)	24 (18–33)	15 (11–21)	9.0 (6.5–13)	5.3 (3.8–7.8)	3.2 (2.3–4.8)	2.0 (1.4–2.9)	1.2 (0.8–1.8)	0.7 (0.5–1.1)	0.4 (0.3–0.6)
5	67 (61–77)	49 (43–61)	33 (29–43)	21 (18–29)	13 (11–18)	7.8 (6.4–11)	4.8 (3.9–6.7)	2.9 (2.4–4.1)	1.8 (1.4–2.5)	1.1 (0.9–1.5)	0.6 (0.5–0.9)
6	79	63	45	30	19	11	7.0	4.3	2.6	1.6	1.0

Age = 70 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	16	10	6.2	3.8	2.3	1.4	0.9	0.6	0.4	0.2	0.1
1	25 (22–31)	16 (14–20)	10 (8.7–13)	6.3 (5.3–7.9)	3.9 (3.3–4.9)	2.4 (2.0–3.0)	1.5 (1.3–1.9)	0.9 (0.8–1.2)	0.6 (0.5–0.8)	0.4 (0.3–0.5)	0.2 (0.2–0.3)
2	37 (31–47)	25 (20–33)	16 (13–22)	10 (8.0–14)	6.4 (4.9–8.6)	4.0 (3.1–5.4)	2.5 (1.9–3.5)	1.6 (1.2–2.2)	1.0 (0.8–1.4)	0.6 (0.5–0.9)	0.4 (0.3–0.5)
3	53 (43–61)	38 (29–46)	25 (19–32)	16 (12–21)	10 (7.5–14)	6.5 (4.7–8.8)	4.2 (3.0–5.6)	2.6 (1.9–3.6)	1.7 (1.2–2.3)	1.1 (0.7–1.4)	0.7 (0.5–0.9)
4	68 (59–74)	53 (43–60)	38 (29–44)	26 (19–31)	17 (12–20)	11 (7.7–13)	6.9 (4.9–8.6)	4.4 (3.1–5.5)	2.8 (2.0–3.5)	1.8 (1.3–2.2)	1.1 (0.8–1.4)
5	80 (74–82)	68 (60–72)	53 (45–58)	38 (31–42)	26 (21–29)	17 (13–19)	11 (8.7–13)	7.1 (5.6–8.3)	4.6 (3.6–5.3)	2.9 (2.3–3.4)	1.8 (1.4–2.1)
6	87	80	68	53	38	26	18	12	7.4	4.8	3.0

Age = 75 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	18	12	7.6	4.9	3.1	2.1	1.4	0.9	0.6	0.4	0.3
1	30 (24–54)	21 (16–41)	14 (11–29)	9.5 (6.9–20)	6.2 (4.4–13)	4.1 (2.9–8.7)	2.7 (1.9–5.9)	1.8 (1.3–3.9)	1.2 (0.8–2.6)	0.8 (0.6–1.7)	0.5 (0.4–1.1)
2	46 (32–69)	35 (22–57)	25 (15–43)	17 (9.7–31)	11 (6.3–21)	7.7 (4.2–15)	5.2 (2.8–10)	3.4 (1.8–6.8)	2.3 (1.2–4.6)	1.5 (0.8–3.0)	1.0 (0.5–2.0)
3	62 (44–79)	50 (31–69)	39 (22–56)	28 (14–43)	19 (9.4–31)	13 (6.3–22)	9.2 (4.2–16)	6.2 (2.8–11)	4.2 (1.8–7.2)	2.8 (1.2–4.8)	1.8 (0.8–3.2)
4	75 (57–84)	66 (44–77)	55 (32–67)	42 (22–55)	31 (15–42)	22 (10–31)	16 (6.7–22)	11 (4.5–16)	7.3 (3.0–11)	4.9 (2.0–7.3)	3.3 (1.3–4.9)
5	84 (70–88)	78 (58–83)	70 (46–76)	59 (34–65)	46 (24–53)	35 (16–41)	26 (11–30)	18 (7.7–21)	12 (5.2–15)	8.5 (3.5–10)	5.7 (2.3–6.9)
6	88	86	81	74	63	51	39	29	20	14	9.6

Age = 80 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	19	13	9.2	6.2	4.3	3.0	2.1	1.4	1.0	0.7	0.5
1	31 (24–55)	23 (17–44)	17 (12–33)	12 (8.1–24)	8.1 (5.6–17)	5.8 (3.9–12)	4.0 (2.7–8.7)	2.8 (1.9–6.1)	2.0 (1.3–4.3)	1.4 (0.9–3.0)	0.9 (0.6–2.1)
2	45 (32–67)	36 (23–57)	27 (16–46)	20 (11–36)	14 (7.8–27)	10 (5.5–20)	7.3 (3.9–14)	5.2 (2.7–10)	3.6 (1.9–7.3)	2.5 (1.3–5.1)	1.8 (0.9–3.6)
3	59 (42–76)	50 (32–68)	40 (23–58)	31 (17–47)	23 (12–37)	17 (8.3–28)	13 (5.8–21)	9.0 (4.1–15)	6.4 (2.8–11)	4.5 (2.0–7.8)	3.2 (1.4–5.5)
4	71 (54–81)	63 (43–75)	54 (33–67)	45 (24–57)	35 (17–47)	27 (12–38)	20 (8.9–29)	15 (6.3–22)	11 (4.4–16)	7.7 (3.1–12)	5.5 (2.2–8.3)
5	80 (64–84)	75 (55–80)	68 (45–73)	59 (35–66)	49 (26–56)	40 (19–47)	31 (14–38)	24 (10–29)	18 (7.3–22)	13 (5.2–16)	9.1 (3.7–11)
6	85	83	78	72	64	55	45	36	27	20	15

Age = 85 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	20	15	11	7.8	5.7	4.3	3.1	2.3	1.7	1.2	0.9
1	31 (25–54)	24 (19–45)	19 (14–36)	14 (10–28)	11 (7.5–22)	8.0 (5.6–17)	6.0 (4.1–13)	4.4 (3.0–9.6)	3.3 (2.2–7.1)	2.4 (1.6–5.3)	1.8 (1.2–3.9)
2	44 (32–65)	36 (25–56)	29 (19–47)	23 (14–39)	18 (10–32)	14 (7.8–25)	10 (5.8–20)	7.9 (4.3–15)	5.9 (3.1–11)	4.4 (2.3–8.6)	3.2 (1.7–6.4)
3	56 (40–72)	49 (32–66)	41 (25–58)	34 (19–50)	27 (15–42)	22 (11–34)	17 (8.4–28)	13 (6.3–22)	10 (4.7–17)	7.5 (3.5–13)	5.6 (2.6–9.5)
4	68 (50–78)	61 (42–73)	54 (34–66)	46 (27–59)	39 (21–51)	33 (16–43)	26 (12–36)	21 (9.4–29)	16 (7.0–23)	12 (5.2–18)	9.4 (3.9–14)
5	76 (60–81)	72 (52–77)	66 (44–72)	59 (36–65)	52 (29–58)	45 (23–51)	38 (18–44)	31 (14–37)	25 (11–30)	20 (8.2–24)	15 (6.2–18)
6	82	80	76	70	65	58	51	43	36	29	23

Age = 90 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	16	12	9.4	7.2	5.6	4.3	3.3	2.6	2.0	1.5	1.2
1	27 (21–49)	21 (16–41)	17 (12–33)	13 (9.3–27)	10 (7.3–22)	8.1 (5.7–17)	6.4 (4.4–14)	4.9 (3.4–11)	3.8 (2.6–8.3)	3.0 (2.0–6.4)	2.3 (1.5–5.0)
2	40 (27–60)	33 (22–53)	27 (17–45)	22 (13–38)	18 (10–32)	14 (7.9–26)	11 (6.1–21)	8.8 (4.8–17)	6.9 (3.7–13)	5.4 (2.8–10)	4.2 (2.2–8.2)
3	53 (36–69)	46 (29–63)	39 (23–56)	33 (18–49)	27 (15–42)	23 (12–36)	18 (9.1–30)	15 (7.1–24)	12 (5.5–19)	9.2 (4.3–15)	7.2 (3.3–12)
4	65 (46–75)	59 (39–71)	52 (32–65)	46 (26–58)	40 (21–52)	34 (17–45)	28 (13–38)	23 (11–32)	19 (8.3–27)	15 (6.4–22)	12 (5.0–17)
5	73 (57–78)	70 (50–75)	65 (42–71)	59 (36–65)	53 (30–60)	47 (25–54)	41 (20–47)	35 (16–41)	29 (13–35)	24 (10–29)	19 (8.0–23)
6	78	77	74	70	66	61	55	48	42	35	29

Annex 4

Ten-year probabilities of fracture in the United Kingdom population, by body mass index, the number of clinical risk factors, age and sex

The following tables give the 10-year probability of fracture (%) according to BMI, the number of clinical risk factors (CRFs) and age. Estimates are based on the epidemiology of the United Kingdom. Each table provides a mean estimate and a range. The range is not a confidence interval but, because the weight of different risk factors varies, it is a true range.

Table A4.1 gives the probabilities for clinical spine, hip, forearm and humerus fracture (osteoporotic fracture) in men.

Table A4.2 gives the probabilities for hip fracture in men.

Table A4.3 gives the probabilities for clinical spine, hip, forearm and humerus fractures (osteoporotic fracture) in women.

Table A4.4 gives the probabilities of hip fracture in women.

Table A4.1

Ten-year probability of osteoporotic fractures (%), by body mass index (BMI), the number of clinical risk factors (CRFs) and age in men from the United Kingdom

Age = 50 years

Number of	BMI (kg/m^2)						
CRFs	15	20	25	30	35	40	45
0	2.9	2.8	2.8	2.4	2.1	1.8	1.6
1	4.5 (3.0–6.6)	4.3 (2.9–6.1)	4.3 (2.8–5.8)	3.7 (2.5–5.1)	3.3 (2.2–4.4)	2.8 (1.9–3.9)	2.5 (1.7–3.4)
2	7.1 (3.8–12)	6.7 (3.5–11)	6.5 (3.4–11)	5.7 (3.0–9.9)	4.9 (2.6–8.7)	4.3 (2.3–7.7)	3.8 (2.0–6.7)
3	11 (5.4–19)	10 (4.9–18)	9.7 (4.7–18)	8.5 (4.0–15)	7.4 (3.5–14)	6.5 (3.1–12)	5.7 (2.7–11)
4	16 (8.9–25)	15 (8.0–24)	14 (7.5–23)	12 (6.5–20)	11 (5.6–18)	9.5 (4.9–16)	8.3 (4.2–14)
5	24 (15–31)	22 (14–29)	20 (14–27)	18 (12–24)	16 (11–21)	14 (9.5–19)	12 (8.3–17)
6	34	31	29	25	22	19	17

Age = 55 years

Number of	BMI (kg/m^2)						
CRFs	15	20	25	30	35	40	45
0	3.5	3.4	3.3	2.9	2.5	2.2	1.9
1	5.5 (3.8–7.9)	5.2 (3.5–7.2)	5.1 (3.4–6.9)	4.4 (3.0–6.0)	3.9 (2.6–5.2)	3.4 (2.3–4.5)	2.9 (2.0–3.9)
2	8.6 (4.8–14)	8.0 (4.4–13)	7.7 (4.2–13)	6.7 (3.6–11)	5.8 (3.1–10)	5.1 (2.7–8.8)	4.4 (2.4–7.7)
3	13 (7.0–21)	12 (6.2–21)	11 (5.7–20)	10 (4.9–18)	8.7 (4.3–16)	7.6 (3.7–14)	6.6 (3.2–12)
4	19 (11–29)	18 (10–27)	17 (9.2–27)	15 (7.9–23)	13 (6.8–21)	11 (5.9–18)	9.6 (5.1–16)
5	28 (18–36)	25 (17–33)	24 (17–31)	21 (15–28)	18 (13–24)	16 (11–21)	14 (9.7–19)
6	39	35	33	29	25	22	19

Age = 60 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	4.2	4.0	3.9	3.4	2.9	2.5	2.2
1	6.5 (4.5–9.2)	6.1 (4.2–8.4)	6.0 (4.1–7.9)	5.2 (3.5–6.8)	4.5 (3.0–5.9)	3.9 (2.6–5.1)	3.4 (2.2–4.4)
2	10 (5.9–16)	9.3 (5.3–15)	8.9 (5.0–15)	7.7 (4.3–13)	6.7 (3.7–11)	5.8 (3.2–9.9)	5.0 (2.7–8.6)
3	15 (8.9–23)	14 (7.7–22)	13 (7.0–22)	11 (6.0–20)	9.9 (5.1–17)	8.5 (4.4–15)	7.4 (3.8–13)
4	22 (14–32)	20 (12–30)	19 (11–29)	16 (9.4–26)	14 (8.0–23)	12 (6.8–20)	11 (5.8–17)
5	31 (21–39)	28 (20–36)	27 (19–35)	23 (17–31)	20 (14–27)	18 (12–24)	15 (11–21)
6	42	39	37	32	28	24	21

Age = 65 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	5.2	5.0	4.9	4.2	3.6	3.1	2.7
1	7.9 (5.6–11)	7.5 (5.2–10)	7.4 (5.1–9.6)	6.3 (4.3–8.3)	5.5 (3.7–7.1)	4.7 (3.2–6.1)	4.0 (2.7–5.3)
2	12 (7.4–18)	11 (6.7–17)	11 (6.3–18)	9.4 (5.4–15)	8.1 (4.6–13)	6.9 (3.9–12)	6.0 (3.3–10)
3	17 (11–25)	16 (9.9–25)	16 (9.0–25)	14 (7.6–22)	12 (6.4–19)	10 (5.5–17)	8.6 (4.6–15)
4	24 (17–34)	23 (15–33)	22 (14–33)	19 (12–29)	17 (9.8–26)	14 (8.2–22)	12 (7.0–19)
5	33 (24–41)	31 (23–40)	31 (23–39)	27 (20–35)	23 (17–30)	20 (15–27)	17 (12–23)
6	43	41	41	36	31	27	23

Age = 70 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	6.0	5.8	5.7	4.8	4.1	3.5	3.0
1	9.0 (6.4–12)	8.5 (6.1–11)	8.2 (5.9–11)	6.9 (4.9–9.1)	5.9 (4.2–7.7)	5.0 (3.5–6.6)	4.2 (3.0–5.6)
2	13 (8.6–20)	12 (8.0–18)	12 (7.5–17)	9.9 (6.3–14)	8.4 (5.2–12)	7.1 (4.4–10)	6.0 (3.7–8.8)
3	20 (12–29)	18 (12–26)	17 (11–25)	14 (9.0–21)	12 (7.5–18)	10 (6.3–15)	8.5 (5.3–13)
4	28 (19–38)	26 (17–36)	24 (16–34)	20 (13–29)	17 (11–25)	14 (9.3–21)	12 (7.7–18)
5	38 (32–47)	35 (29–44)	33 (27–41)	28 (22–36)	24 (18–31)	20 (15–26)	17 (13–22)
6	49	47	44	38	32	27	23

Age = 75 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	6.6	6.3	6.1	5.1	4.3	3.6	3.0
1	10 (7.1–16)	9.7 (6.7–13)	9.1 (6.4–11)	7.5 (5.3–9.2)	6.2 (4.4–7.7)	5.1 (3.6–6.5)	4.3 (3.0–5.5)
2	16 (9.8–26)	15 (9.0–22)	13 (8.4–19)	11 (6.9–16)	9.1 (5.7–13)	7.5 (4.6–11)	6.1 (3.8–8.7)
3	24 (14–37)	22 (13–33)	20 (12–28)	16 (9.9–24)	13 (8.1–19)	11 (6.6–16)	8.9 (5.4–13)
4	35 (21–47)	32 (19–43)	29 (18–40)	24 (15–33)	20 (12–28)	16 (9.8–23)	13 (7.9–19)
5	47 (33–56)	43 (31–53)	40 (29–49)	34 (24–42)	28 (20–36)	23 (17–30)	19 (14–25)
6	59	56	52	45	39	33	27

Age = 80 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	7.8	7.4	7.2	5.9	4.8	4.0	3.3
1	12 (8.3–19)	11 (7.8–17)	11 (7.5–15)	8.7 (6.1–12)	7.1 (4.9–9.4)	5.8 (4.0–7.5)	4.7 (3.2–6.0)
2	19 (12–29)	17 (11–26)	16 (10–22)	13 (8.1–18)	10 (6.5–15)	8.4 (5.3–12)	6.8 (4.3–9.7)
3	27 (16–39)	25 (15–36)	23 (14–32)	19 (11–27)	15 (9.0–22)	12 (7.2–18)	9.9 (5.8–15)
4	38 (23–49)	34 (22–45)	32 (21–42)	26 (17–36)	22 (14–30)	18 (11–25)	14 (8.8–20)
5	49 (34–58)	46 (32–55)	43 (30–52)	36 (25–45)	30 (21–38)	25 (17–32)	20 (14–27)
6	60	57	54	47	41	34	28

Age = 85 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	9.3	8.8	8.6	7.0	5.7	4.6	3.7
1	15 (10–24)	14 (9.4–21)	13 (9.0–19)	10 (7.2–15)	8.4 (5.7–12)	6.8 (4.6–9.5)	5.4 (3.7–7.5)
2	22 (14–35)	20 (13–31)	19 (12–28)	15 (9.7–23)	12 (7.7–19)	10 (6.1–15)	8.0 (4.9–12)
3	32 (20–45)	29 (18–42)	27 (16–39)	22 (13–33)	18 (10–27)	15 (8.3–22)	12 (6.6–18)
4	43 (28–55)	40 (25–51)	37 (24–48)	31 (20–41)	26 (16–35)	21 (13–29)	17 (10–24)
5	54 (39–62)	51 (36–60)	48 (34–57)	41 (29–50)	35 (24–44)	29 (19–37)	24 (16–31)
6	63	62	59	53	46	40	33

Age = 90 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	12	10	9.3	7.5	6.0	4.8	3.9
1	18 (13–29)	16 (11–25)	14 (10–22)	12 (8.1–17)	9.3 (6.4–14)	7.4 (5.1–11)	5.9 (4.0–8.6)
2	27 (18–42)	24 (16–37)	22 (14–32)	18 (11–27)	14 (8.8–21)	11 (7.0–17)	9.0 (5.5–14)
3	38 (25–52)	35 (22–48)	31 (20–44)	26 (16–37)	21 (12–31)	17 (9.9–25)	14 (7.8–20)
4	49 (33–60)	46 (31–58)	42 (28–54)	36 (23–47)	30 (19–40)	25 (15–34)	20 (12–28)
5	57 (45–64)	57 (42–64)	54 (40–63)	48 (33–56)	41 (28–50)	35 (23–43)	29 (18–36)
6	62	65	64	59	53	46	39

Table A4.2

Ten-year probability of hip fracture (%), by body mass index (BMI), the number of clinical risk factors (CRFs) and age in men from the United Kingdom

Age = 50 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	0.4	0.2	0.1	0.1	0.1	0.1	0.1
1	0.9 (0.6–1.7)	0.5 (0.3–1.0)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.1 (0.1–0.3)	0.1 (0.1–0.2)
2	1.7 (0.8–3.5)	0.9 (0.5–2.0)	0.5 (0.3–1.1)	0.4 (0.2–0.9)	0.3 (0.2–0.7)	0.2 (0.1–0.5)	0.2 (0.1–0.4)
3	3.1 (1.3–6.1)	1.8 (0.7–3.5)	1.0 (0.4–2.0)	0.8 (0.3–1.5)	0.6 (0.2–1.2)	0.5 (0.2–0.9)	0.4 (0.1–0.7)
4	5.6 (2.2–9.1)	3.2 (1.3–5.3)	1.8 (0.7–3.0)	1.4 (0.5–2.3)	1.1 (0.4–1.8)	0.8 (0.3–1.4)	0.7 (0.3–1.1)
5	9.7 (4.5–13)	5.7 (2.6–7.7)	3.3 (1.5–4.4)	2.5 (1.1–3.4)	2.0 (0.9–2.7)	1.5 (0.7–2.1)	1.2 (0.5–1.6)
6	16	9.9	5.7	4.5	3.5	2.7	2.1

Age = 55 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	0.8	0.4	0.2	0.2	0.2	0.1	0.1
1	1.5 (1.0–2.6)	0.8 (0.6–1.5)	0.5 (0.3–0.8)	0.4 (0.3–0.6)	0.3 (0.2–0.5)	0.2 (0.2–0.4)	0.2 (0.1–0.3)
2	2.7 (1.4–5.1)	1.6 (0.8–3.0)	0.9 (0.5–1.7)	0.7 (0.4–1.3)	0.5 (0.3–1.0)	0.4 (0.2–0.8)	0.3 (0.2–0.6)
3	4.8 (2.2–8.8)	2.8 (1.3–5.3)	1.6 (0.7–3.0)	1.2 (0.6–2.4)	1.0 (0.4–1.8)	0.7 (0.3–1.4)	0.6 (0.3–1.1)
4	8.2 (3.8–13)	5.0 (2.3–7.9)	2.9 (1.3–4.6)	2.2 (1.0–3.6)	1.7 (0.8–2.8)	1.3 (0.6–2.2)	1.0 (0.5–1.7)
5	14 (7.3–18)	8.6 (4.5–11)	5.0 (2.6–6.6)	3.9 (2.0–5.2)	3.0 (1.6–4.0)	2.4 (1.2–3.1)	1.8 (0.9–2.4)
6	22	14	8.6	6.7	5.2	4.1	3.1

Age = 60 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	1.3	0.8	0.4	0.3	0.3	0.2	0.2
1	2.3 (1.7–3.8)	1.4 (1.0–2.2)	0.8 (0.6–1.3)	0.6 (0.5–1.0)	0.5 (0.4–0.8)	0.4 (0.3–0.6)	0.3 (0.2–0.5)
2	4.1 (2.4–7.0)	2.5 (1.5–4.4)	1.5 (0.9–2.6)	1.1 (0.7–2.0)	0.9 (0.5–1.6)	0.7 (0.4–1.2)	0.5 (0.3–0.9)
3	6.9 (3.6–12)	4.3 (2.2–7.6)	2.6 (1.3–4.6)	2.0 (1.0–3.6)	1.5 (0.8–2.7)	1.2 (0.6–2.1)	0.9 (0.5–1.6)
4	11 (6.2–17)	7.4 (3.9–11)	4.5 (2.3–6.9)	3.5 (1.8–5.4)	2.7 (1.4–4.2)	2.1 (1.1–3.2)	1.6 (0.8–2.5)
5	18 (11–22)	12 (7.3–15)	7.6 (4.5–9.7)	5.9 (3.5–7.6)	4.6 (2.7–5.9)	3.5 (2.1–4.5)	2.7 (1.6–3.5)
6	28	20	13	9.8	7.6	5.9	4.6

Age = 65 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	2.0	1.3	0.8	0.6	0.5	0.4	0.3
1	3.4 (2.7–5.0)	2.2 (1.7–3.2)	1.3 (1.0–1.9)	1.0 (0.8–1.5)	0.8 (0.6–1.1)	0.6 (0.5–0.9)	0.5 (0.4–0.7)
2	5.7 (3.5–8.7)	3.7 (2.3–5.9)	2.3 (1.4–3.7)	1.8 (1.1–2.9)	1.4 (0.8–2.2)	1.0 (0.7–1.7)	0.8 (0.5–1.3)
3	9.2 (5.3–15)	6.2 (3.5–10)	3.9 (2.2–6.5)	3.0 (1.7–5.0)	2.3 (1.3–3.9)	1.8 (1.0–3.0)	1.4 (0.8–2.3)
4	14 (9.0–21)	10 (6.1–15)	6.5 (3.8–9.7)	5.0 (2.9–7.5)	3.9 (2.3–5.8)	3.0 (1.7–4.5)	2.3 (1.3–3.5)
5	22 (15–26)	16 (11–19)	11 (7.2–13)	8.2 (5.5–10)	6.3 (4.3–7.9)	4.9 (3.3–6.1)	3.8 (2.5–4.7)
6	31	24	17	13	10	7.9	6.1

Age = 70 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	3.0	2.0	1.3	1.0	0.8	0.6	0.4
1	5.1 (3.8–6.3)	3.6 (2.7–4.3)	2.3 (1.8–2.8)	1.8 (1.4–2.1)	1.4 (1.0–1.6)	1.0 (0.8–1.2)	0.8 (0.6–1.0)
2	8.6 (5.7–13)	6.2 (4.1–8.9)	4.1 (2.7–5.8)	3.2 (2.1–4.5)	2.4 (1.6–3.4)	1.8 (1.2–2.6)	1.4 (0.9–2.0)
3	14 (8.8–21)	10 (6.7–15)	7.1 (4.7–10)	5.5 (3.6–8.1)	4.2 (2.8–6.2)	3.2 (2.1–4.8)	2.5 (1.6–3.7)
4	22 (15–30)	17 (11–24)	12 (8.3–17)	9.4 (6.4–14)	7.3 (4.9–11)	5.6 (3.7–8.2)	4.3 (2.8–6.3)
5	32 (27–40)	26 (22–33)	20 (16–25)	16 (13–20)	12 (10–16)	9.4 (7.7–12)	7.3 (5.9–9.5)
6	44	38	31	25	20	15	12

Age = 75 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	4.3	3.1	2.2	1.6	1.3	1.0	0.7
1	7.7 (5.1–14)	5.9 (3.9–10)	4.1 (2.8–7.3)	3.1 (2.1–5.6)	2.4 (1.6–4.3)	1.8 (1.2–3.3)	1.4 (0.9–2.5)
2	13 (7.6–22)	10 (5.9–18)	7.6 (4.3–13)	5.8 (3.3–9.9)	4.5 (2.5–7.6)	3.4 (1.9–5.9)	2.6 (1.4–4.5)
3	21 (11–34)	17 (9.1–28)	13 (7.0–21)	10 (5.4–17)	8.0 (4.1–13)	6.1 (3.1–10)	4.7 (2.3–7.8)
4	32 (18–44)	27 (15–39)	22 (12–32)	17 (9.2–26)	14 (7.0–21)	11 (5.4–16)	8.1 (4.1–13)
5	44 (29–54)	39 (25–49)	34 (20–43)	27 (16–35)	22 (12–29)	17 (9.4–23)	14 (7.2–18)
6	58	53	48	40	33	27	22

Age = 80 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	5.8	4.6	3.4	2.6	1.9	1.5	1.1
1	10 (6.8–18)	8.1 (5.5–14)	6.1 (4.2–11)	4.7 (3.2–8.5)	3.6 (2.4–6.5)	2.7 (1.8–5.0)	2.0 (1.4–3.8)
2	16 (9.9–28)	14 (8.1–23)	11 (6.3–18)	8.2 (4.8–14)	6.3 (3.6–11)	4.8 (2.8–8.6)	3.6 (2.1–6.6)
3	25 (14–37)	21 (12–32)	17 (9.6–27)	14 (7.3–22)	11 (5.6–17)	8.1 (4.2–13)	6.2 (3.2–10)
4	36 (21–47)	31 (17–42)	27 (14–37)	21 (11–30)	17 (8.6–24)	13 (6.5–19)	10 (4.9–15)
5	48 (31–57)	43 (27–52)	38 (23–47)	32 (18–40)	26 (14–33)	21 (11–27)	16 (8.4–21)
6	60	56	51	44	37	30	24

Age = 85 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	7.6	6.2	4.9	3.7	2.8	2.1	1.6
1	13 (8.8–22)	11 (7.3–19)	8.7 (5.9–16)	6.7 (4.5–12)	5.1 (3.4–9.3)	3.8 (2.5–7.1)	2.9 (1.9–5.4)
2	20 (13–34)	17 (11–29)	14 (8.7–25)	11 (6.6–20)	8.7 (5.0–15)	6.6 (3.8–12)	5.0 (2.8–9.2)
3	30 (18–44)	26 (15–39)	22 (13–34)	18 (9.8–28)	14 (7.5–22)	11 (5.7–18)	8.4 (4.3–14)
4	42 (26–54)	37 (22–49)	33 (19–44)	27 (14–37)	22 (11–30)	17 (8.6–25)	13 (6.5–20)
5	53 (38–62)	49 (33–58)	45 (29–54)	38 (23–47)	32 (18–40)	26 (14–33)	21 (11–27)
6	63	61	57	51	43	37	30

Age = 90 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	10	8.0	6.0	4.6	3.5	2.7	2.0
1	17 (12–28)	14 (9.6–24)	11 (7.5–19)	8.3 (5.7–15)	6.3 (4.3–11)	4.8 (3.3–8.8)	3.7 (2.5–6.8)
2	26 (17–41)	22 (14–36)	18 (11–30)	14 (8.5–24)	11 (6.5–19)	8.4 (4.9–15)	6.4 (3.7–11)
3	37 (23–51)	32 (20–46)	28 (16–40)	22 (13–33)	18 (9.8–27)	14 (7.5–22)	11 (5.7–17)
4	48 (32–60)	44 (28–56)	39 (24–51)	33 (19–44)	27 (15–37)	22 (11–30)	17 (8.7–25)
5	57 (44–63)	56 (40–64)	52 (35–61)	45 (29–54)	38 (23–47)	32 (19–40)	26 (14–33)
6	61	64	63	58	51	44	37

Table A4.3

Ten-year probability of osteoporotic fractures (%), by body mass index (BMI), the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	3.9	3.6	3.5	3.0	2.6	2.3	2.0
1	6.3 (4.3–9.1)	5.7 (3.9–8.0)	5.4 (3.6–7.4)	4.7 (3.2–6.4)	4.1 (2.8–5.6)	3.6 (2.4–4.9)	3.2 (2.1–4.3)
2	9.9 (5.4–16)	8.8 (4.7–15)	8.2 (4.4–14)	7.2 (3.8–12)	6.3 (3.3–11)	5.5 (2.9–9.6)	4.8 (2.5–8.4)
3	15 (7.8–26)	13 (6.6–24)	12 (6.0–22)	11 (5.2–20)	9.5 (4.5–17)	8.3 (4.0–15)	7.3 (3.4–13)
4	23 (14–35)	20 (11–31)	18 (9.9–29)	16 (8.6–26)	14 (7.5–23)	12 (6.5–20)	11 (5.7–18)
5	34 (22–43)	29 (20–37)	26 (18–34)	23 (16–30)	20 (14–27)	18 (12–24)	16 (11–21)
6	49	41	37	33	29	25	22

Age = 55 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	5.3	4.8	4.6	4.0	3.5	3.1	2.7
1	8.5 (6.0–12)	7.6 (5.3–10)	7.1 (4.9–9.5)	6.2 (4.2–8.3)	5.4 (3.7–7.2)	4.7 (3.2–6.3)	4.1 (2.8–5.5)
2	13 (7.7–21)	12 (6.5–19)	11 (5.9–18)	9.4 (5.1–16)	8.2 (4.5–14)	7.2 (3.9–12)	6.3 (3.4–11)
3	21 (11–33)	18 (9.3–30)	16 (8.1–28)	14 (7.0–25)	12 (6.1–22)	11 (5.3–19)	9.4 (4.6–17)
4	31 (19–44)	26 (16–39)	23 (13–36)	20 (12–32)	18 (10–28)	16 (8.7–25)	14 (7.6–22)
5	44 (30–53)	37 (26–46)	33 (24–42)	29 (21–38)	26 (18–34)	23 (16–30)	20 (14–26)
6	60	51	46	41	36	32	28

Age = 60 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	7.4	6.5	6.0	5.2	4.6	4.0	3.5
1	12 (8.4–16)	10 (7.2–13)	9.3 (6.5–12)	8.1 (5.6–11)	7.0 (4.9–9.2)	6.1 (4.2–8.0)	5.3 (3.7–7.0)
2	18 (11–26)	15 (9.0–24)	14 (7.9–22)	12 (6.9–20)	11 (5.9–17)	9.2 (5.1–15)	8.1 (4.4–13)
3	27 (16–40)	23 (13–36)	20 (11–34)	18 (9.5–30)	16 (8.2–27)	14 (7.1–24)	12 (6.1–21)
4	39 (26–53)	33 (22–47)	29 (18–44)	26 (16–39)	23 (14–35)	20 (12–31)	17 (10–27)
5	54 (40–63)	46 (34–56)	41 (31–51)	36 (27–46)	32 (24–41)	28 (21–36)	25 (18–32)
6	69	61	55	49	44	39	34

Age = 65 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	11	9.3	8.6	7.4	6.5	5.6	4.9
1	16 (12–21)	14 (10–18)	13 (9.2–16)	11 (7.9–14)	9.8 (6.9–12)	8.5 (5.9–11)	7.4 (5.1–9.5)
2	24 (16–34)	21 (13–31)	19 (11–29)	17 (9.8–26)	14 (8.4–23)	13 (7.3–20)	11 (6.3–18)
3	35 (24–49)	30 (19–45)	27 (16–43)	24 (14–38)	21 (12–34)	18 (10–30)	16 (8.7–27)
4	48 (35–62)	42 (30–57)	38 (26–54)	34 (22–49)	30 (19–44)	26 (16–39)	23 (14–35)
5	62 (51–71)	56 (45–66)	51 (41–62)	46 (36–56)	41 (32–51)	36 (28–46)	32 (24–41)
6	75	70	65	59	54	48	43

Age = 70 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	14	12	11	9.5	8.2	7.1	6.2
1	21 (16–26)	18 (14–22)	16 (12–20)	14 (10–18)	12 (8.8–15)	10 (7.6–13)	8.9 (6.5–11)
2	31 (22–41)	26 (18–35)	23 (15–31)	20 (13–27)	17 (11–24)	15 (9.4–21)	13 (8.0–18)
3	44 (32–58)	37 (26–51)	32 (21–46)	28 (18–40)	24 (15–35)	21 (13–31)	18 (11–27)
4	58 (46–71)	51 (39–65)	44 (33–59)	39 (29–53)	34 (24–47)	29 (21–41)	25 (18–36)
5	72 (66–79)	66 (59–74)	59 (51–68)	52 (44–62)	46 (38–55)	40 (33–49)	35 (28–43)
6	81	78	73	67	60	54	47

Age = 75 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	18	15	13	12	9.8	8.4	7.2
1	27 (20–37)	23 (17–29)	20 (15–23)	17 (13–20)	14 (11–17)	12 (9.0–15)	10 (7.6–13)
2	40 (27–54)	34 (22–46)	28 (19–37)	24 (16–32)	21 (13–27)	17 (11–23)	15 (9.6–19)
3	54 (38–69)	47 (33–62)	40 (27–54)	35 (23–47)	29 (19–41)	25 (16–35)	21 (14–30)
4	67 (51–77)	62 (46–75)	55 (41–69)	48 (35–62)	41 (30–55)	36 (25–48)	30 (21–41)
5	77 (66–83)	74 (63–81)	69 (59–78)	63 (52–72)	56 (46–65)	49 (40–58)	42 (34–51)
6	83	83	81	76	70	63	56

Age = 80 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	22	19	17	15	12	11	8.9
1	32 (24–45)	28 (21–38)	25 (19–31)	21 (16–26)	18 (13–21)	15 (11–18)	13 (9.3–15)
2	44 (32–59)	40 (28–52)	35 (24–45)	30 (20–38)	25 (17–32)	21 (14–27)	18 (12–23)
3	56 (41–69)	52 (38–65)	47 (35–59)	41 (29–52)	35 (25–46)	30 (21–39)	25 (17–34)
4	67 (53–77)	64 (51–74)	60 (47–72)	54 (41–66)	47 (35–59)	41 (30–52)	35 (25–46)
5	76 (65–81)	74 (63–80)	72 (61–79)	66 (55–74)	60 (48–68)	53 (42–62)	46 (37–55)
6	81	81	80	76	71	65	59

Age = 85 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	25	23	22	18	15	13	11
1	35 (27–49)	33 (25–45)	31 (23–39)	26 (19–33)	22 (16–28)	18 (13–23)	15 (11–19)
2	47 (34–62)	44 (32–58)	42 (30–53)	36 (25–46)	30 (21–40)	26 (17–34)	21 (14–29)
3	58 (43–71)	55 (41–69)	53 (39–66)	47 (33–60)	41 (28–53)	35 (23–46)	30 (19–40)
4	68 (55–77)	66 (53–76)	64 (51–74)	58 (45–69)	52 (39–63)	45 (33–57)	39 (28–50)
5	75 (66–79)	75 (64–80)	73 (63–80)	68 (57–76)	63 (51–71)	57 (45–65)	50 (39–59)
6	77	80	80	77	72	67	61

Age = 90 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	26	23	21	18	15	12	10
1	37 (29–52)	34 (26–46)	30 (23–40)	26 (19–34)	21 (16–28)	18 (13–23)	15 (11–19)
2	49 (37–64)	46 (33–60)	42 (30–54)	36 (25–47)	30 (21–40)	25 (17–34)	21 (14–29)
3	60 (46–72)	57 (43–71)	54 (40–67)	48 (34–61)	41 (28–54)	35 (24–47)	30 (19–40)
4	68 (57–77)	67 (55–77)	65 (53–75)	60 (46–70)	53 (40–64)	47 (34–58)	40 (28–52)
5	71 (66–75)	74 (66–78)	74 (64–80)	70 (58–76)	64 (52–72)	58 (46–67)	52 (40–61)
6	69	76	79	77	73	69	63

Table A4.4

Ten-year probability of hip fracture (%), by body mass index (BMI), the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	0.7	0.4	0.2	0.2	0.1	0.1	0.1
1	1.5 (0.9–2.8)	0.8 (0.5–1.5)	0.4 (0.3–0.8)	0.3 (0.2–0.6)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)
2	2.8 (1.4–6.0)	1.5 (0.8–3.3)	0.8 (0.4–1.8)	0.6 (0.3–1.4)	0.5 (0.3–1.1)	0.4 (0.2–0.8)	0.3 (0.2–0.7)
3	5.3 (2.2–10)	2.9 (1.2–5.7)	1.6 (0.6–3.1)	1.2 (0.5–2.4)	1.0 (0.4–1.9)	0.7 (0.3–1.5)	0.6 (0.2–1.1)
4	9.6 (3.8–15)	5.3 (2.1–8.6)	2.9 (1.1–4.7)	2.3 (0.9–3.7)	1.8 (0.7–2.9)	1.4 (0.5–2.2)	1.1 (0.4–1.7)
5	17 (7.9–22)	9.5 (4.4–13)	5.2 (2.4–7.1)	4.1 (1.9–5.5)	3.2 (1.4–4.3)	2.5 (1.1–3.4)	1.9 (0.9–2.6)
6	28	16	9.2	7.2	5.6	4.4	3.4

Age = 55 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	1.3	0.7	0.4	0.3	0.2	0.2	0.1
1	2.5 (1.7–4.4)	1.4 (0.9–2.4)	0.8 (0.5–1.3)	0.6 (0.4–1.0)	0.5 (0.3–0.8)	0.4 (0.2–0.6)	0.3 (0.2–0.5)
2	4.7 (2.6–9.1)	2.6 (1.4–5.1)	1.4 (0.8–2.8)	1.1 (0.6–2.2)	0.9 (0.5–1.7)	0.7 (0.4–1.3)	0.5 (0.3–1.0)
3	8.5 (3.9–16)	4. (2.1–8.9)	2.6 (1.2–4.9)	2.0 (0.9–3.8)	1.6 (0.7–3.0)	1.2 (0.5–2.3)	1.0 (0.4–1.8)
4	15 (6.8–23)	8.4 (3.8–13)	4.7 (2.1–7.4)	3.6 (1.6–5.8)	2.8 (1.2–4.5)	2.2 (1.0–3.5)	1.7 (0.8–2.7)
5	25 (14–32)	15 (7.8–19)	8.2 (4.3–11)	6.4 (3.4–8.5)	5.0 (2.6–6.7)	3.9 (2.1–5.2)	3.1 (1.6–4.1)
6	39	24	14	11	8.7	6.8	5.3

Age = 60 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	2.4	1.3	0.7	0.6	0.4	0.3	0.3
1	4.4 (3.1–6.8)	2.4 (1.7–3.8)	1.3 (0.9–2.1)	1.0 (0.7–1.6)	0.8 (0.6–1.3)	0.6 (0.4–1.0)	0.5 (0.3–0.8)
2	7.8 (4.6–14)	4.4 (2.6–7.9)	2.4 (1.4–4.4)	1.9 (1.1–3.4)	1.5 (0.9–2.7)	1.1 (0.7–2.1)	0.9 (0.5–1.6)
3	13 (6.9–23)	7.7 (3.9–14)	4.3 (2.2–7.7)	3.4 (1.7–6.0)	2.6 (1.3–4.7)	2.0 (1.0–3.6)	1.6 (0.8–2.8)
4	22 (12–33)	13 (6.8–20)	7.5 (3.8–11)	5.9 (2.9–9.0)	4.6 (2.3–7.1)	3.6 (1.8–5.5)	2.8 (1.4–4.3)
5	35 (23–43)	22 (14–28)	13 (7.9–17)	10 (6.1–13)	7.9 (4.8–10)	6.2 (3.7–8.1)	4.8 (2.9–6.3)
6	52	35	21	17	13	10	8.2

Age = 65 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	4.1	2.3	1.3	1.0	0.8	0.6	0.5
1	7.2 (5.4–10)	4.1 (3.1–5.7)	2.3 (1.7–3.2)	1.8 (1.3–2.5)	1.4 (1.0–1.9)	1.1 (0.8–1.5)	0.8 (0.6–1.2)
2	12 (7.7–19)	7.1 (4.5–12)	4.0 (2.5–6.6)	3.1 (2.0–5.2)	2.4 (1.5–4.0)	1.9 (1.2–3.1)	1.5 (0.9–2.4)
3	20 (12–31)	12 (6.8–19)	6.9 (3.8–11)	5.4 (3.0–9.0)	4.2 (2.3–7.0)	3.3 (1.8–5.5)	2.5 (1.4–4.3)
4	31 (19–43)	19 (12–28)	12 (6.7–17)	9.1 (5.2–13)	7.1 (4.1–10)	5.5 (3.1–8.2)	4.3 (2.4–6.4)
5	45 (34–53)	31 (22–37)	19 (13–24)	15 (11–19)	12 (8.2–15)	9.3 (6.4–12)	7.3 (5.0–9.3)
6	62	46	30	24	19	15	12

Age = 70 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	6.9	4.1	2.3	1.8	1.4	1.1	0.8
1	12 (9.6–14)	7.4 (5.9–8.6)	4.3 (3.4–5.0)	3.3 (2.6–3.9)	2.6 (2.1–3.0)	2.0 (1.6–2.3)	1.5 (1.2–1.8)
2	21 (14–27)	13 (8.8–17)	7.7 (5.2–10)	6.0 (4.0–8.0)	4.7 (3.1–6.3)	3.6 (2.4–4.9)	2.8 (1.9–3.8)
3	33 (23–44)	22 (15–31)	14 (9.0–20)	11 (7.0–16)	8.4 (5.4–12)	6.5 (4.2–9.7)	5.1 (3.3–7.6)
4	49 (38–61)	35 (27–47)	23 (17–32)	18 (14–26)	15 (11–21)	12 (8.3–16)	9.0 (6.5–13)
5	65 (59–73)	52 (47–61)	37 (33–44)	30 (26–36)	25 (21–30)	20 (17–24)	16 (13–19)
6	77	70	55	47	39	32	26

Age = 75 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	11	7.0	4.2	3.2	2.5	1.9	1.5
1	20 (14–32)	13 (9.6–22)	8.2 (5.9–14)	6.4 (4.6–11)	4.9 (3.6–8.5)	3.8 (2.7–6.6)	3.0 (2.1–5.1)
2	32 (21–49)	23 (14–36)	15 (8.9–25)	12 (6.9–20)	9.3 (5.4–16)	7.3 (4.2–13)	5.7 (3.2–9.8)
3	48 (32–65)	38 (23–54)	26 (15–40)	21 (12–33)	17 (9.3–27)	13 (7.2–21)	10 (5.6–17)
4	63 (46–75)	54 (37–69)	42 (26–58)	35 (20–49)	29 (16–41)	23 (13–34)	18 (9.9–28)
5	75 (61–81)	70 (54–78)	61 (42–70)	53 (35–62)	45 (28–54)	37 (23–46)	30 (18–38)
6	83	81	77	70	63	55	47

Age = 80 years

Number of CRFs	BMI (kg/m²) 15	20	25	30	35	40	45
0	16	11	7.0	5.4	4.2	3.2	2.5
1	26 (19–41)	19 (14–32)	13 (9.5–22)	10 (7.3–17)	7.8 (5.7–14)	6.1 (4.4–11)	4.7 (3.3–8.3)
2	38 (27–56)	31 (20–47)	22 (14–36)	18 (11–29)	14 (8.5–23)	11 (6.6–19)	8.5 (5.1–15)
3	52 (37–67)	45 (29–61)	35 (21–52)	29 (16–44)	23 (13–36)	19 (10–30)	15 (7.7–24)
4	64 (47–75)	59 (41–71)	51 (33–64)	43 (27–57)	36 (21–49)	30 (17–41)	24 (13–34)
5	74 (61–80)	71 (56–78)	66 (48–74)	59 (40–68)	51 (33–61)	44 (27–53)	37 (22–45)
6	81	80	77	72	66	59	51

Age = 85 years

Number of CRFs	BMI (kg/m^2) 15	20	25	30	35	40	45
0	19	15	11	8.4	6.4	4.9	3.8
1	30 (22–46)	25 (18–40)	19 (14–31)	15 (11–25)	12 (8.3–20)	9.0 (6.3–16)	6.9 (4.8–12)
2	42 (30–60)	37 (26–54)	30 (20–46)	24 (16–39)	19 (12–32)	15 (9.4–26)	12 (7.3–20)
3	55 (40–69)	50 (35–65)	44 (28–59)	37 (23–52)	30 (18–44)	25 (14–37)	20 (11–30)
4	66 (50–76)	62 (45–73)	57 (40–69)	50 (33–63)	43 (27–56)	36 (21–48)	30 (17–41)
5	74 (63–79)	73 (59–79)	69 (54–77)	63 (47–72)	57 (39–66)	50 (33–59)	43 (27–52)
6	77	79	79	74	69	63	56

Age = 90 years

Number of CRFs	BMI (kg/m^2) 15	20	25	30	35	40	45
0	21	16	11	8.9	6.9	5.3	4.0
1	33 (25–50)	27 (20–42)	20 (15–33)	16 (11–27)	12 (8.9–21)	9.6 (6.8–17)	7.4 (5.2–13)
2	46 (34–63)	40 (28–57)	32 (21–48)	26 (17–41)	21 (13–34)	16 (10–27)	13 (7.8–22)
3	58 (44–71)	53 (38–68)	46 (30–62)	39 (24–55)	32 (19–47)	26 (15–40)	21 (12–33)
4	67 (54–76)	65 (49–75)	60 (43–72)	53 (36–66)	46 (29–59)	39 (23–51)	32 (18–44)
5	71 (65–75)	73 (62–78)	72 (57–78)	66 (50–74)	60 (43–69)	53 (36–62)	46 (29–55)
6	69	76	78	75	71	66	59