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843

ASSESSMENT OF FRACTURE RISK AND ITS APPLICATION TO SCREENING FOR POSTMENOPAUSAL OSTEOPOROSIS

Report of a
WHO Study Group

World Health Organization

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Contents

WHO Study Group on Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis

Rome, 22–25 June 1992

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1. Introduction

A WHO Study Group on Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis met in Rome from 22 to 25 June 1992. The meeting was opened by Dr N.Khaltaev who welcomed participants on behalf of the Director-General of the World Health Organization.

1.1 Background

In the past decade, osteoporosis has been widely recognized as a major health issue by both the medical profession and the general public in many Member States. Public awareness has increased the demands on health care agencies, particularly in the areas of hormone replacement and women's health. The response of the medical profession, however, has been variable (*1, 2*). On the one hand, medical interest among experts in bone disease is very high, and the number of papers, congresses and journals devoted to the subject is rapidly growing. On the other hand, many general practitioners remain unaware of the problem; in one survey in the United Kingdom, 20% of general practitioners had "never seen a case" (*3*). Others are reluctant either to assess patients or to prescribe interventions. None the less, attitudes seem to be changing, as indicated by the growing number of general practitioners' consultations for osteoporosis and by the prescription of bone-specific agents, which is continuing to rise in many countries.

The views of bone experts on the assessment and treatment of osteoporosis are not, however, consistent. In the past few years several consensus development conferences have reviewed these problems (*4-6*). Although partly a reflection of the increasing awareness of the problem, such conferences also indicate the difficulties that experts have on matters of substantial importance. The areas of disagreement apply less to the efficacy of interventions available for the prevention or treatment of osteoporosis than to the question of whom to treat (*7-10*). In the case of hormone replacement therapy (HRT), for example, some experts advocate universal screening of postmenopausal women to identify those who would benefit from HRT (*10*).[1] Indeed, several centres in Australia, Europe and the USA have developed screening programmes and many others offer facilities for bone density measurements. Others advocate the universal use of HRT in postmenopausal women, while a minority hold the view that the risks of HRT outweigh any benefits and believe that few, if any, women should receive HRT. Yet others argue that screening for fracture risk is either uneconomic or impractical (*7, 8, 11*). Inevitably, these widely differing attitudes are having a significant impact on the use of health care resources for screening or interventions or both (*12*).

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[1] HRT refers to the use of estrogens and/or progestogens.

1.2 Scope and aims of the Study Group

Awareness of osteoporosis has coincided with the realization that the disorder can be to some extent prevented, by means not only of hormone replacement therapy but also of other interventions that prevent or delay bone loss. Since the prospects for treatment of the established disorder are significantly less than those for prevention (13), much attention has focused on the latter approach and, therefore, on the use of clinical, physical and biochemical techniques to assess the future risk of osteoporotic fracture.

The major aims of the Study Group were to evaluate the available methods for assessment of fracture risk and their suitability for use in screening for osteoporosis. There have been no randomized controlled trials of screening using bone density measurements to direct intervention, and no evaluation of its efficacy in reducing fracture frequency. Indeed, such studies may not be feasible given the long interval between the onset of bone loss and the occurrence of fractures. Thus, any evaluation is dependent upon inferential evidence.

The suitability of any screening test in the context of osteoporosis is determined by various factors, which must include a consideration of risks that are unacceptable or acceptable to the community. Moreover, the application of a screening test is relevant only if subsequent intervention will prevent the development of fractures. For these reasons the Study Group also considered the health risks, benefits and likely use of interventions. The specific aims of the report are therefore:

- to define the value and limitations of possible screening tests for osteoporosis
- to identify the population at risk for whom screening is appropriate
- to determine the likely costs and benefits of interventions in osteoporosis
- to determine the likely costs and benefits of screening for low bone mineral density.

2. Osteoporosis

The value and application of screening tests depend in part upon the magnitude of the public health problem posed by osteoporosis, and this varies from country to country. This section of the report therefore reviews the impact of osteoporosis in various WHO Member States, after first providing a practical definition of the disorder.

2.1 Definitions

The term "osteoporosis" is commonly used without a clear indication of its meaning. For example, it may describe both the clinical end result

(fracture) and the process that gives rise to fracture (*14*). As a disease process, it causes a decrease in bone density that is a major contributing factor to the increased risk of fracture.

Osteoporosis is a disorder in which there is a diminution of bone mass without detectable changes in the ratio of mineralized to non-mineralized matrix. These terms of reference are appropriate if osteoporosis is not complicated by osteomalacia or subclinical osteomalacia (*15, 16*). Where the bone is fully mineralized, measurements of bone mineral content or bone mineral density provide estimates of skeletal mass. Many techniques (reviewed in section 3) have been developed to measure indices of bone mass or loss. Since mass is one of the major determinants of the compressive and torsional strength of bone, fracture will occur more easily if there is substantial bone loss. Osteoporosis is therefore commonly considered simply in terms of the amount of bone present. It is recommended, however, that the definition used by a consensus development conference in 1991 (*6*) be retained since it embraces the concept of a heterogeneity of skeletal and extraskeletal factors in the causation of fractures:

"A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."

Within this general framework, several approaches can be used to define osteoporosis on the basis of bone mineral measurements. One approach has been to consider as osteoporotic those patients in whom measurements fall below the range for the young healthy adult population (*17-19*) or lie within the lowest quartile, quintile or decile of the reference range for the young healthy female. The implication is that such women should be offered intervention. Osteoporosis has also been defined as a bone mineral density that is below the age-adjusted reference range or more than 1 standard deviation below the mean for a particular age. The precision of these definitions permits the calculation of the prevalence and incidence of osteoporosis. Estimates of the prevalence of low bone mineral density based on these various criteria differ markedly (Table 1), yielding a 32-fold range in the numbers of women affected.

A second approach has been to characterize the osteoporotic population to derive a "fracture threshold" based on the range of bone mineral density measurements in the population with vertebral or hip fractures. This can be arbitrarily set, for example, at 2 standard deviations above the mean value of patients with osteoporotic fracture (*20*). The consequences of applying this threshold on the apparent prevalence of low bone mineral density are reflected in the values given in column A of Table 1.

Table 1

Vertebral bone mineral density in healthy women, and number of cases and apparent prevalence of osteoporosis in women aged 50–70 years in England and Wales according to various criteria for defining osteoporosis

Age range (years)	Bone mineral density (g/cm²)[b]		Number of cases, n (prevalence, %)[a]							
	mean	SD	A		B		C		D	
			n	(%)	n	(%)	n	(%)	n	(%)
40–49	1.063	0.112	—	—	—	—	—	—	—	—
50–59	0.929	0.127	60 624	(24)	169 242	(67)	6 315	(2.5)	40 416	(16)
60–69	0.792	0.108	153 450	(62)	235 125	(95)	6 188	(2.5)	39 600	(16)
50–69	—	—	214 074	(43)	404 367	(81)	12 503	(2.5)	80 016	(16)

Estimates from Office of Population Censuses and Surveys, 1985.

A = values more than 1 standard deviation below the mean for young healthy adult women
B = values in the lowest quintile of young healthy adult women
C = values below age-adjusted reference range
D = values more than 1 standard deviation below age-adjusted mean

[a] From Hall ML et al. The range of bone density in normal British women. *British journal of radiology*, 1990, **63**:266–269. Reproduced with the permission of the publisher.

A third approach is to use the results of densitometric measurements to derive a lifetime fracture risk (*21, 22*). Computed in this way, risk will depend on the site of measurement, the technique used, and the age, sex and life expectancy of the individual. Ross et al. (*23*) have suggested that a doubling of risk compared with average young healthy individuals might constitute an intervention threshold, and by implication be used to define osteoporosis. Such a definition would include 10% or more of young healthy women.

The most straightforward approach to the diagnosis of osteoporosis by bone mass measurements (loosely termed bone mineral density or BMD) is to define a "fracture threshold" – namely a cut-off for BMD that captures most patients with osteoporotic fractures. However, age (or more likely co-variates with age, such as likelihood of falling) significantly affects fracture risk and thus also the fracture threshold, so that the risk of fracture for a given BMD is higher in the elderly (*24-26*). This approach, like those outlined above, fails to overcome the problem of the overlap in BMD between populations with and without fragility fractures. Thus, an osteoporotic patient will not invariably fracture, and a patient assigned a low risk from measurements of BMD may sustain a fragility fracture.

The risk of osteoporotic fracture is stochastic and increases progressively as bone density decreases (*25, 27-30*), but factors other than the amount of bone also contribute to fracture risk. Thus, while bone mineral measurements may provide an index of the risk, the index does not reflect all elements of risk, which vary with the techniques used, age, cause of bone loss and site of interest.

In the consideration of these issues, it is important to distinguish assessments of (fracture) risk from the diagnosis of disease (osteoporosis). Depending on factors such as rates of bone loss, falls and life expectancy, the disease may or may not give rise to symptoms. All cut-off values are somewhat arbitrary, but a measured value of bone mineral more than 2.5 standard deviations below the mean for young healthy adult women at any site (spine, hip or mid-radius) identifies 30% of all postmenopausal women as having osteoporosis (Table 2), more than half of whom will have sustained a prior fracture of the proximal femur, spine, distal forearm, proximal humerus or pelvis. For reasons discussed subsequently, a less substantial deficit of bone mass is termed osteopenia.

The following four general diagnostic categories can thus be established in women (Fig. 1):

- *Normal.* A value for BMD or bone mineral content (BMC) within 1 SD of the young adult reference mean.
- *Low bone mass (osteopenia).* A value for BMD or BMC more than 1 SD below the young adult mean but less than 2.5 SD below this value.
- *Osteoporosis.* A value for BMD or BMC 2.5 SD or more below the young adult mean.

Table 2
Percentage of white women with osteoporosis[a] (adjusted to 1990 US white women)

Age range years	Osteoporosis of	
	any site %	hip alone %
30–39	0	0
40–49	0	0
50–59	14.8	3.9
60–69	21.6	8.0
70–79	38.5	24.5
80+	70.0	47.5
≧50	30.3	16.2

[a] Osteoporosis is defined as a bone mass more than 2.5 SD below the young adult reference mean at the spine, hip or mid-radius.

Figure 1
Bone mineral content at the distal forearm in women (mean ± 2 SD)

Notes: The hatched area denotes women with osteopenia, the shaded area women with osteoporosis.
The z-score is units of standard deviation: a score of 0 is the mean value for women at the age of menopause.
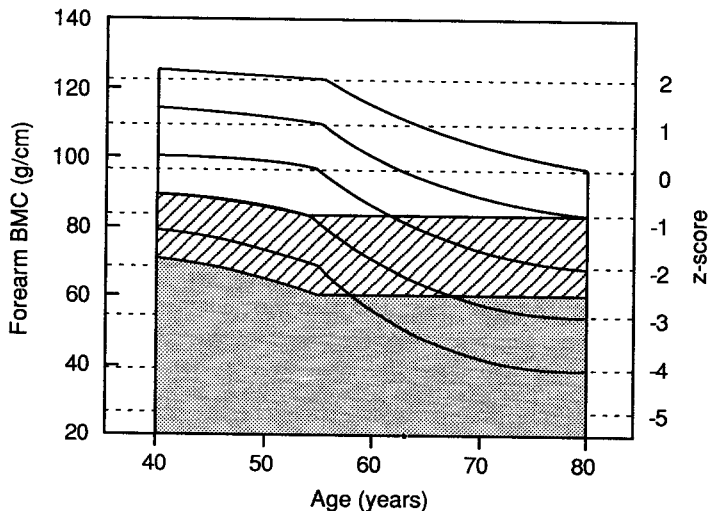
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- *Severe osteoporosis (established osteoporosis).* A value for BMD or BMC more than 2.5 SD below the young adult mean in the presence of one or more fragility fractures.

These categories for diagnosis do not overcome all the problems. In particular, individuals will be categorized differently according to the site and technique of measurement, and the equipment and the reference

Table 3
Examples of the distinction between risk factors and disease

Disease	Risk factor	Clinical expression
Coronary heart disease	Hypercholesterolaemia	Myocardial infarction
Hypertension	High blood pressure	Stroke
Osteoporosis	Low bone mineral density	Fracture
Gout	Hyperuricaemia	Arthritis

population used. For example, in one recent study of white women aged 50 years and over, 32% had a lumbar spine BMD more than 2 SD below the young normal mean, while 29% had a low BMD at either the cervical or the intertrochanteric regions of the proximal femur, 26% had a low BMC at the mid-radius and 31% had a low BMC in the distal radius (*31*). Altogether, 45% of postmenopausal women had low bone mass at the spine, hip or mid-radius using this cut-off value.

It is important to distinguish between the diagnostic and prognostic use of bone mineral density measurement. As a diagnostic tool, it gives information concerning the presence or absence of the disease with the cut-off values chosen. Its potential as a prognostic tool is to determine the future probability of osteoporosis or, better, the probability of fragility fractures where different cut-off values may be used (section 3.3). In this sense bone density values are used as a risk factor. Useful analogies may be drawn with other diseases for which major risk factors have been identified (see Table 3).

2.2 Osteoporotic fractures

There is no evidence that postmenopausal bone loss itself causes any symptoms, and progressive bone loss has therefore been called "the silent epidemic" or "silent thief". The morbidity arises from the type of fracture sustained. A detailed account of the epidemiology of osteoporotic fracture is beyond the scope of this review (but may be found elsewhere in the literature (*32-36*)). None the less, a summary of the important fractures and their epidemiology is relevant since it helps to define the size of the problem, appropriate target populations for screening, and intervention thresholds, and to identify areas where knowledge is lacking.

In many developed countries, the prevalence of all fractures is similar in men and women but only the minority are associated with osteoporosis. In both sexes, the age-specific incidence of fractures is bimodal (*37, 38*): fracture rates in childhood are higher than in young adult life, where the rate is low – particularly in women – but rise again after the age of 45 years. The vast majority of osteoporotic fractures occur in elderly women and the incidence increases markedly with age. Most occur at the spine, wrist and hip, but many fractures at other sites are also associated with low bone

Table 4

Estimated lifetime fracture risk (%) in women (95% confidence intervals) from Rochester, MN, USA, at age 50 years[a]

Fracture site	Women	Men
Proximal femur	17.5 (16.8–18.2)	6.0 (5.6–6.5)
Vertebra[b]	15.6 (14.8–16.3)	5.0 (4.6–5.4)
Distal forearm	16.0 (15.7–16.7)	2.5 (2.2–3.1)
Any of the above	39.7 (38.7–40.6)	13.1 (12.4–13.7)

[a] Source: reference 31.
[b] Clinically diagnosed fractures.

mass, independently of age, and should be considered osteoporotic (*39*). Women are at particular risk from fracture and the incidence in women is twice that in men in many places including Hong Kong, the USA, and the countries of northern Europe (*10, 35, 36*). The reason for this relates to the lower bone mass of women at the time of maturity (peak bone mass), the accelerated bone loss that occurs after the menopause and the greater likelihood of falling among women over the age of 70 years (*40*). Women also live significantly longer than men so that the frequency of osteoporotic fracture among elderly women is six times that among elderly men in these countries. The lifetime risks from osteoporotic fracture in women are at least 30% and probably closer to 40% (*31, 32, 41*) (Table 4).

In men the incidence of fractures increases substantially after the age of 75 years whereas in women an increase is seen after the age of 45 years. In women, increases up to the age of 65 years are due largely to an increase in forearm fractures. After this age, hip fractures assume greater importance in both men and women, with the hip becoming the most common site of fractures after the age of 85 years (Fig. 2).

2.2.1 *Vertebral fracture*

There are particular problems in identifying the frequency of vertebral fracture and its attendant morbidity (*42*); many such fractures are asymptomatic, or at least cause too few symptoms to prompt investigation of the cause of back pain. However, available data indicate that the incidence of vertebral fractures, like that of other osteoporotic fractures, is greater in women than in men and rises with age (*43*). Between the ages of 60 and 90 years the incidence rises 20-fold in women but only 10-fold in men (*42*). The age-related increase in incidence is less pronounced than in the case of hip fracture.

The direct costs of vertebral fracture are low compared with those of hip fracture, since most cases do not come to medical attention. However, the exact proportion of vertebral fractures that cause invalidity is unknown. Estimates from USA indicate that about one-third of all cases of vertebral

Figure 2
Patterns of hospital admission for fracture for women in the Trent Region of England, 1989/90[a]

Note: After the menopause, fractures of the femoral neck become increasingly important and are the reason for the majority of admissions of women aged 75 years and over.
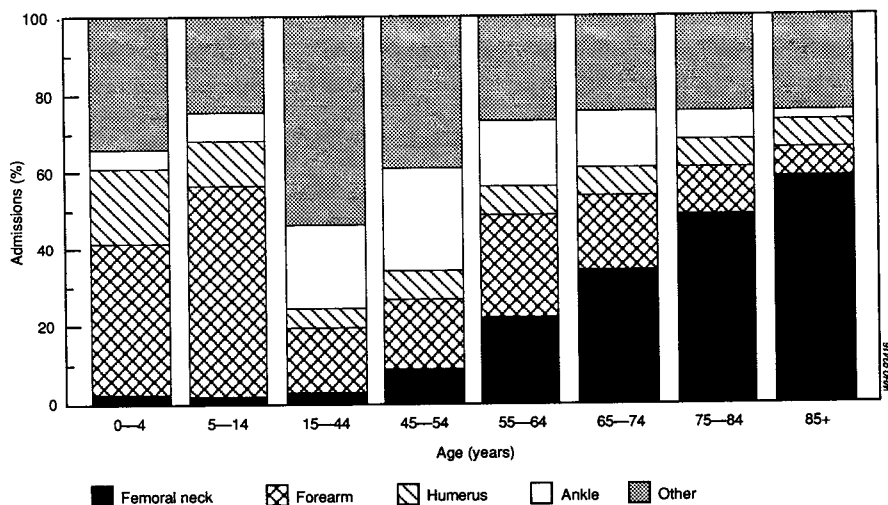
[a] Based on data from reference 36 used with kind permission from Elsevier Science Ltd.

fracture are clinically attended and one-tenth are hospitalized (44). This estimate depends on the criteria for diagnosis of vertebral fracture, on which there is no general agreement. Most investigators assess the presence or absence of fracture on the basis of the height of vertebral bodies on lateral radiographs of the spine, taking a given reduction of height (e.g. 15-20% of anterior, posterior or central) to denote vertebral deformity. The absolute prevalence and incidence of vertebral fracture depends critically upon the diagnostic criteria used and will in turn influence the apparent proportional morbidity. For example, estimates of the annual incidence of osteoporotic vertebral fracture in England and Wales range from 70 000 to 140 000 (42).

2.2.2 *Hip fracture*

The most severe osteoporotic fracture is that of the hip. Typically, hip fracture results from a fall but some fractures occur spontaneously. Women are more often affected than men and, as noted above, rates rise exponentially with aging (32, 35). The lifetime risk of hip fracture is 15.6-17.5% in white women and 5.2-6.0% in white men (31, 32), and has been estimated at 5.6% for black women and 2.8% for black men from age 50 years onward (32).

A hip fracture is usually painful, nearly always necessitates hospitalization, and is associated with significant morbidity (45, 46). The importance of hip

fractures in the United Kingdom has been recently reviewed by the Royal College of Physicians (*10*). In 1985, the average length of hospital stay was 30 days and the overall bed use was 3500 beds/day. Mortality is high, both perioperatively and subsequently, and only a minority of elderly patients regain their former mobility (*47*). Chrischilles et al. (*48*) have estimated that 10% of women who sustain a hip fracture become functionally dependent in the activities of daily living (taking functional status before fracture into account) and that 19% require long-term care in a nursing home as a direct result of the fracture. Similar figures are available from many other countries (*46, 49*).

The number of deaths attributable to hip fracture increases with age (*32, 35*). It is possible that the increased mortality is a result of patients who are destined to suffer hip fracture being in poorer health than the general community; certainly, some evidence for this view is provided by the greater coexisting morbidity in patients with hip fracture than in those without. The implications of this comorbidity for the costs and benefits of interventions or screening have not been considered.

2.2.3 *Forearm fractures*

Fractures of the distal forearm are common among the middle-aged and elderly, and are caused by a fall on the outstretched hand (*32, 35*). The incidence in women increases rapidly from the first five years of the menopause, reaching a peak between the ages of 60 and 70 years. For European women, the lifetime risk of a wrist fracture is approximately 15% (Table 4), and about 20% of 70-year-old women have had at least one wrist fracture. Forearm fractures are much less common in men.

Although fracture of the wrist causes less morbidity than hip fracture, is very rarely fatal and seldom requires hospitalization, the consequences are often underestimated (*50*). Fractures are painful, usually require one or more reductions and need 4-6 weeks in plaster to establish union. A proportion of patients do not recover function without physiotherapy (*51*). There is a high incidence of algodystrophy after Colles fracture (30%), which gives rise to pain and tenderness, stiffness, swelling and vasomotor disturbances of the hand and, more rarely, to frozen shoulder syndrome (*52*).

2.2.4 *Costs*

The total costs of osteoporosis are difficult to assess because they include acute hospital care, loss of working days, long-term care in the home or nursing homes, medication, etc. Cost estimates are based on many assumptions that are difficult to test. Moreover, there is little information that is helpful in translating costs from one Member State to another. The costs of osteoporotic fractures in the USA are estimated at US$7-10 billion annually for a population of 250 million (*53*). In England and Wales, the total cost of osteoporosis is estimated to be £614 million

annually for a population of 50 million (*36*). In France, the annual number of vertebral fractures is estimated at 40 000–65 000, hip fractures 56 000 and fractures of the distal forearm 35 000. When vertebral fractures are excluded, the costs are estimated at 3.7 billion French francs each year (*54*).

The vast majority of these costs are attributable to hip fracture because of the inpatient and subsequent nursing-home needs of patients. Among women aged 45 years and over, hip fractures account for more than half of all osteoporosis-related hospital admissions in the USA (*47*), where hip fracture costs exceeded US$8 billion in 1988 (*55*). In England and Wales, hip fracture patients occupy one-fifth of all orthopaedic beds, at a direct cost of £160 million per year in 1988 (*10*). The costs of vertebral fracture are estimated to be 2% of total costs for osteoporosis in the United Kingdom (*42*) and somewhat higher in the USA (*47*).

2.3 Magnitude of osteoporosis today and future predictions

Of the limited available data on the prevalence of osteoporosis in different regions of the world, most relate to hip fractures since hospitalized patients are easier to identify and study.

It is estimated that about 1.7 million hip fractures occurred worldwide in 1990 (*56*). These were not distributed uniformly in that incidence rates are higher in women than men and higher in Caucasian populations than others (Fig. 3). Even among white populations, however, rates vary by geographic region. Age-adjusted hip fracture incidence rates by sex are higher in Scandinavia, for example, than in North America or Oceania and lower in the countries of southern Europe (*57, 58*). However, the absolute number of hip fractures in each region is determined not only by ethnic composition but also by the size and age distribution of the population. Consequently, about one-third of hip fractures in 1990 occurred in Asia, despite lower incidence rates among Asians (*35, 56*). Almost half of the fractures occurred in Europe, North America and Oceania, even though the population was smaller (380 million of 35 years of age compared with 920 million in Asia in 1990), because the population was older on average and composed largely of whites.

The explanation for these regional differences is unclear. The race and sex differences are partly explained by the heritability of skeletal size. Bone mass is greatest in those of African heritage, who have the lowest fracture rate, and is least in Caucasian women of northern European extraction, who have the highest fracture rate (*57*); within each ethnic group, men have greater bone mass and lower fracture rates than women. Differences in bone mass might also relate to regional patterns of diet and exercise. A positive effect of calcium supplementation on bone mass was recently demonstrated in elderly women with low calcium intake (*59, 60*), but population studies have not demonstrated a strong relationship between calcium intake and peak bone mass, bone loss or fracture rates (*61*).

Figure 3

Hip fracture incidence around the world as a ratio of the rates observed in various populations to those expected for white women in USA[a]

Legend:
● North America
◆ Northern Europe
○ Southern Europe/Africa
■ Asia
◇ Oceania

Y-axis: Ratio to US white women, %

X-axis categories: White, Black, Asian (Women); White, Black, Asian (Men)

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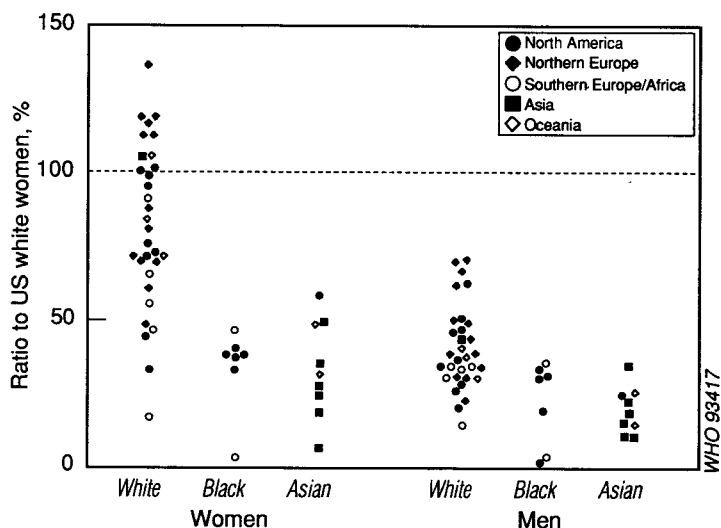
[a] Based on data from reference *57* used with the permission of the author and publisher.

Similarly, a protective effect of exercise has been proposed to explain the lower prevalence of osteoporosis among women of Asian or African heritage (*57*). Clinical trials do suggest that exercise programmes can preserve bone mass, but it is not certain whether gains can be maintained or the risk of fractures reduced (*62*). Recent studies fail to confirm associations between hip fractures and northern climates (*63*), although regional differences in exposure to trauma may account in part for variable risks (*64*). Moreover, black women are less likely to fall than white women (*33*), possibly as a result of greater fitness from a lifetime of more physical work. Greater balance and strength or smaller stature might also account for the lower risk of hip fracture among Japanese women (*65*).

2.3.1 *Effect of demographic changes on future fractures*

Because life expectancy is increasing around the world, the number of elderly individuals is rising in every geographic region. The 323 million individuals aged 65 years or over now will increase to an estimated 1555 million by the year 2050 (*56*). Growth will be especially marked in Africa, Asia, South America and the eastern Mediterranean region (from 190 million in 1990 to 1271 million in 2050). The influence of such changes on the number and regional distribution of hip fractures will be dramatic (Fig. 4). In the USA, demographic changes alone could cause the annual number of hip fractures to more than double from 238 000 in 1986 to 512 000 in 2040 (*29*). However, the elderly population in the USA has

Figure 4
Estimated number of fractures for men and women in different regions of the world in 1990, 2025 and 2050[a]
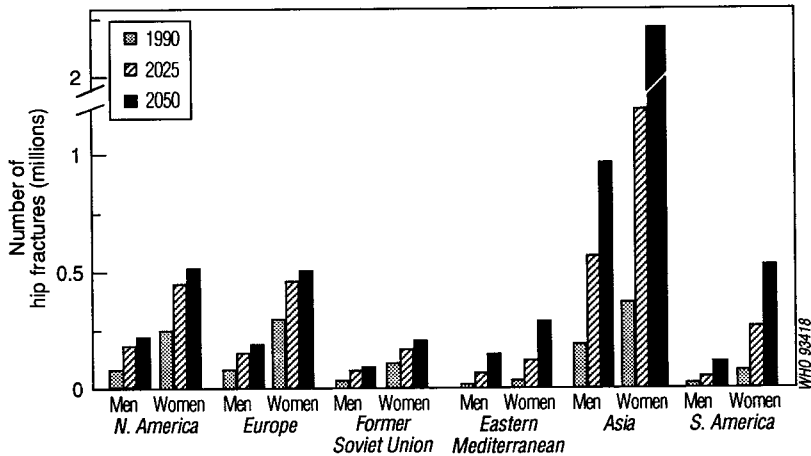
ª Modified from reference 56.

been growing even faster than predicted by the most optimistic assumptions about improving life expectancy (66). If these trends continue, the number of people aged 65 years and over in the USA in the year 2040 could be 22% higher than currently expected and the resulting hip fractures could total 840 000 (66). Worldwide, the number of hip fractures could rise to 6.26 million by 2050. While 56% of fractures (930 000) occurred in Europe, North America and Oceania in 1990, 71% (4 430 000) are likely to be in Africa, Asia, South America or the eastern Mediterranean region by the year 2050 (56).

2.3.2 *Influence of changing rates of fracture incidence*

The projections in section 2.3.1 assume that race-specific hip fracture incidence rates will not change. However, rates in Hong Kong rose substantially between 1966 and 1985 (67), possibly as a result of declining physical labour and increased use of motor transportation. Indeed, marked increases in incidence have been seen in all areas of the world (Fig. 5), although age-adjusted rates appear to have levelled off somewhat in Sweden, the United Kingdom and the USA (68-71). Additionally, there is evidence that the incidence of fractures of the distal forearm (72), ankle (73), proximal humerus (74) and distal tibia (73) and possibly vertebral fractures (42) has increased over time. No convincing explanation for these secular trends has been offered. However, it is clear that any increase in fracture incidence, over and above that resulting from population aging, will cause the number of fractures in the future to be substantially greater than current estimates indicate.

Figure 5
Incidence of hip fractures over time as reported from various centres[a]

Time period

1 Rochester, MN	4 USA	7 Oxford, England
2 Gothenburg, Sweden	5 Funen, Denmark	8 Netherlands
3 Uppsala, Sweden	6 New Zealand	9 Dundee, Scotland
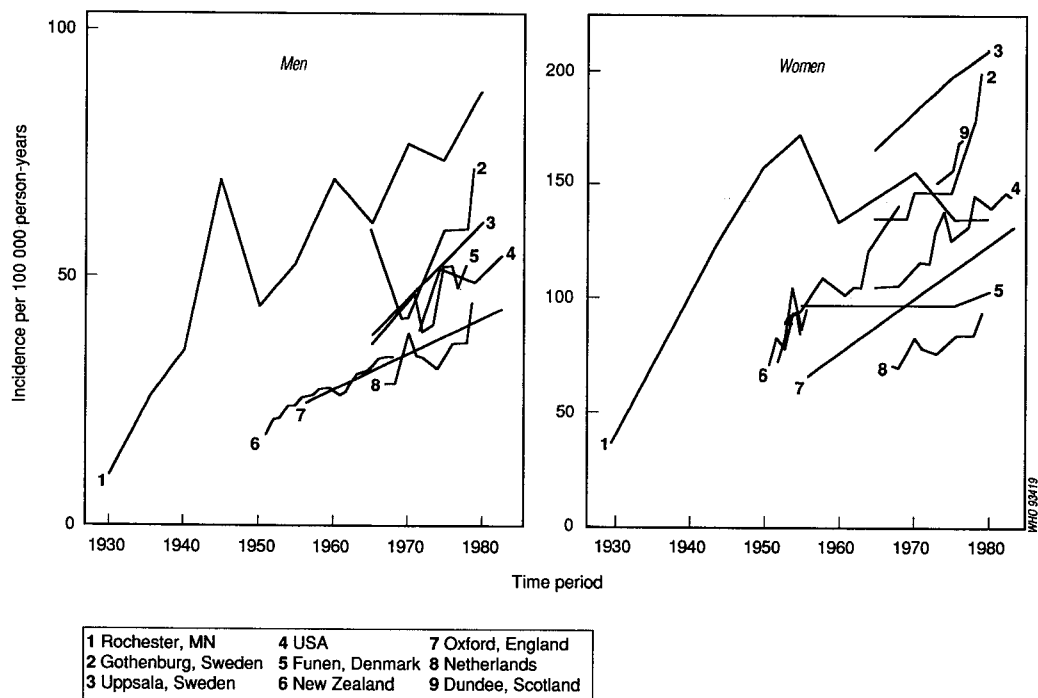
[a] Based on data from reference 68 used with the permission of the authors and Springer-Verlag.

2.4 Determinants of bone mass

The distribution of bone mass or bone mineral density is Gaussian, and there is therefore no evidence for an abnormal subset of the community having osteoporosis. This characteristic limits the value of a single measurement of bone density for the unequivocal identification of individuals at risk, and implies a multifactorial etiology for the condition. In addition to age-related bone loss in men and women and specific diseases that cause osteoporosis in some individuals (Table 5), the most important cause of osteoporosis is the bone loss that occurs after the menopause. A great deal of evidence indicates that postmenopausal bone loss is causally related to the menopause. Moreover, the process of bone loss can be slowed by the administration of female sex hormones. The amount of bone present, however, is not solely a function of bone loss in late adult life but is in part dependent upon bone mass at maturity. Indeed, bone mass at age 70 years is about equally dependent upon these two influences (75).

Table 5
Causes of generalized secondary osteoporosis in adults

Endocrine disease/metabolic causes

   Hypogonadism
   Hyperadrenocorticism
   Thyrotoxicosis
   Anorexia nervosa
   Hyperprolactinaemia
   Systemic mastocytosis
   Porphyria
   Adult hypophosphatasia
   Diabetes mellitus
   Thalassaemia
   Pregnancy

Nutritional causes

   Malabsorption syndromes/malnutrition
   Chronic liver disease
   Scurvy
   Vitamin D deficiency
? Calcium deficiency
   Alcoholism
   Gastric surgery

Drugs

   Chronic heparin administration
   Vitamin D toxicity
   Anticonvulsants

Inherited disorders of collagen metabolism

   Osteogenesis imperfecta
   Homocystinuria due to cystathionine deficiency
   Ehlers–Danlos syndrome
   Marfan syndrome

Other

   Rheumatoid arthritis
   Myeloma and some cancers
   Immobilization/space flight

Skeletal mass increases progressively during growth. In absolute terms, this represents a rise in calcium content from about 25 g at birth to 900–1300 g at maturity. In the first 7 years of life, the daily calcium increment in the skeleton is about 100 mg, rising to about 350 mg in puberty. After longitudinal skeletal growth ceases, calcium retention is about 15 mg per day (*61*). For some years after the cessation of growth, bone mass increases to consolidate the skeleton; this increase varies in extent and rate with sex and site (*76–78*). At skeletal maturity men have 10–50% greater bone mass than women (Fig. 6), depending on the skeletal site (*77, 79*).

Figure 6
Forearm bone mineral content (% of average values for premenopausal women ± SD) as a function of age in men and women[a]

Note: The differences between the sexes disappear when mass is adjusted for lean body mass (LBM) except after the age of 50 years.
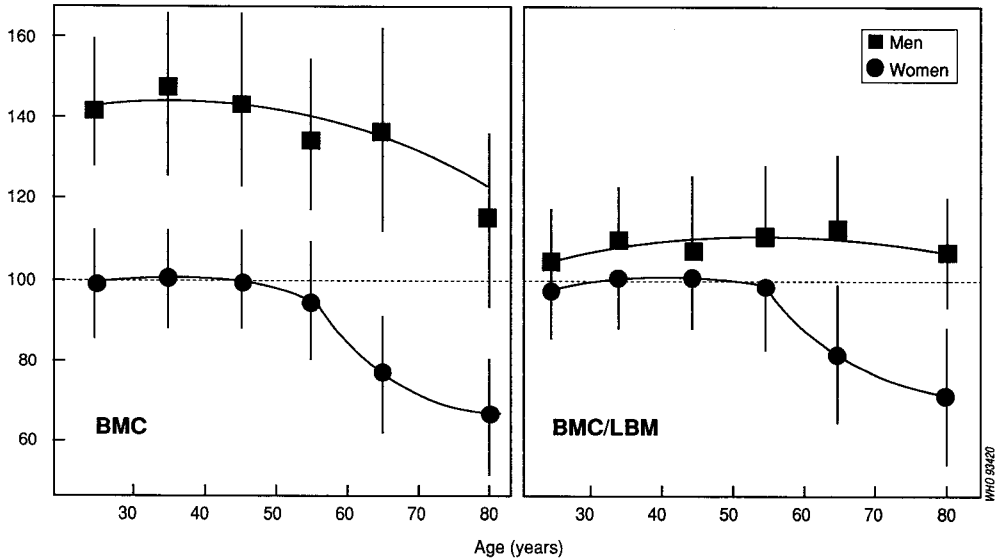
[a] Modified from reference 83 with the permission of the authors and Springer-Verlag.

The age at which bone loss starts is uncertain but, on the basis of cross-sectional studies, it is generally believed to be during the thirties in both sexes (80-82). It is also widely believed that, after reaching peak bone mass (i.e. the maximal bone mass obtained at skeletal maturity), men are exposed to a small annual loss of bone mass with a corresponding negative calcium balance. This age-related loss of bone has been compared to the loss of other functions with age, e.g. loss of muscle mass. Indeed, when bone mineral density of the distal forearm is adjusted for lean body mass, the age-related decreases in bone mineral disappear (83) (Fig. 6). The rate of bone loss in men is low, probably about 3-5% per decade, which partly explains the comparatively low incidence of osteoporotic fractures in men. However, low peak bone mass, higher than average bone loss, and long life may result in osteoporotic fracture.

In women the process is more complicated. Bone loss before the menopause is small and probably parallels that in men. The belief that substantial losses of bone occur in women well before the age of the menopause (80-82) is derived from population studies or inadequate methodology; other studies, including a well controlled prospective study, do not substantiate the view (84, 85). Irrespective of premenopausal losses, bone loss accelerates around the menopause and averages 2% per year over the next 5-10 years (86). During this period the bone loss follows an

exponential decline: loss is greatest in the early postmenopausal years, levels off thereafter and finally reaches the premenopausal level (Fig. 6). This pattern of bone loss has been derived largely from population studies, which are difficult to interpret accurately and may in fact underestimate the degree of age-related loss. However, the accelerated postmenopausal bone loss and relatively lower peak bone mass at least partly explain why osteoporosis is much more common in women than in men.

Losses occur at all sites including the head, arms, hands, chest, spine, pelvis and legs (87, 88). During the early postmenopausal years, the proportion of bone lost from the peripheral skeleton (largely cortical bone) differs from that lost from the axial skeleton (cortical and cancellous bone); the rate of bone loss is more rapid in the spine than in the forearm for example. By the age of 75 years, however, women have lost about the same amount of bone from the peripheral and the axial skeleton, which suggests that the relatively higher rate of spinal bone loss in the early postmenopausal years has slowed by this time. The more rapid losses from the axial skeleton may account in part for the earlier presentation of vertebral fracture compared with hip fracture, which characteristically occurs in later life (89). There is additionally some evidence that specific fractures are related to regional differences in bone mass (in losses or in peak bone mass) (88, 90).

The rate of postmenopausal bone loss varies widely, not only from site to site, but also from one woman to another, ranging from less than 1% to more than 5% per year. On this basis postmenopausal women have been stratified into two populations, with 25-30% belonging to a group of particularly "fast bone losers" who may be especially vulnerable to osteoporotic fractures in later life (91). Such observations provide the rationale for including assessments of bone loss in screening programmes (see section 4). There is, however, no compelling evidence to suggest that the distribution of bone loss or peak bone mass is bimodal; studies that have examined this directly indicate a continuous unimodal distribution (84, 92, 93).

The factors that determine the rate of bone loss after the menopause are incompletely understood: few studies have examined prospectively the rates of loss and their determinants before and during the climacteric (84). Moreover, the errors of measurement in assessing loss are greater than those of a single estimation and the risk factors themselves are imperfectly quantifiable. The degree of estrogen deficiency is an important factor and oophorectomized women lose bone more rapidly than women who undergo a natural menopause. The ultimate effect on bone density is unknown, however, since rates of loss decrease over time. Some but not all studies suggest that women who undergo a premature menopause for any reason are at high risk of osteoporosis (94). Postmenopausal bone loss is probably modulated by a variety of nutritional and environmental factors, but it cannot be prevented merely by eliminating the known environmental factors. Whether the presence of these factors can be utilized for screening is considered in section 5.

Little or no relationship has been found between bone mass at maturity and the rate of bone loss (75, 84, 92, 95). In a large number of patients studied prospectively, no relationship has been found between gonadal hormone levels and the rate of loss (C.Christiansen, 1992 – personal communication). In contrast, others have found a higher incidence of osteoporosis in women with menopausal symptoms, suggesting a relationship between residual gonadal status and bone loss (96). These uncertainties underline the importance of measuring bone loss if rates are of clinical importance.

2.4.1 *Organization and turnover of bone tissue*

The maintenance of bone mass depends upon the metabolic activity and turnover of the skeleton, which in turn may affect the strength of bone by altering its architecture. The general architecture of most bones is similar, being composed of cancellous (trabecular) and cortical (compact) bone. In cancellous bone, the trabeculae form an interconnecting lattice designed to resist mechanical loads; the cortical component forms a compact shell that surrounds cancellous bone and contributes to its structural integrity. The adult skeleton is composed largely of cortical bone (75%), but cancellous bone contributes to skeletal strength particularly at the spine, hip and distal radius, which are the common sites for osteoporotic fracture.

In the healthy adult bone *mass* at skeletal maturity is neither increasing nor decreasing. There is considerable *turnover* of bone, however, of which the majority (95%) in the adult is accounted for by remodelling (97, 98). The remodelling process comprises a discrete series of cellular events on bone surfaces, which have been well characterized morphologically. The surface area of cancellous bone is greater than that of cortical bone, even though cancellous bone may occupy only 25% of total skeletal mass in health and as little as 10% in an osteoporotic patient. Because of the high surface-to-volume ratio of cancellous bone tissue, disorders of bone remodelling such as osteoporosis more commonly affect trabecular sites earlier and more floridly in the disease process.

At the start of the remodelling sequence, bone-resorbing cells (osteoclasts) migrate to or differentiate at a specific location on the bone surface to excavate a resorption activity. At the completion of this phase, osteoclasts disappear; several days later, bone-forming cells (osteoblasts) are attracted principally to sites of previous resorption and infill the resorption cavity with new bone (Fig. 7). This sequence of events permits the self-repair of bone and is one of the mechanisms for preserving both skeletal mass and architecture.

The term "coupling" describes the attraction of osteoblasts to sites of previous resorption, but the basis of this process is ill-understood. The osteoporotic process may involve uncoupling of bone formation from previous resorption (e.g. in neoplastic bone disease); more commonly, however, a decrease in bone mass is caused by an imbalance between the

Figure 7
Steps in the remodelling sequence of trabecular bone

Resting trabecular bone surfaces are covered by lining cells or resting osteoblasts (A). Early in the sequence, osteoclasts are attracted to a quiescent bone surface and excavate a resorption cavity (B, C). Mononuclear cells smooth off the resorption cavity (D), which is a subsequent site for the attraction of osteoblasts, which synthesize an osteoid matrix (E). Continuous new matrix synthesis (F) is followed by calcification (G) of newly formed bone. When complete, lining cells once more overlie the trabecular surface (H).
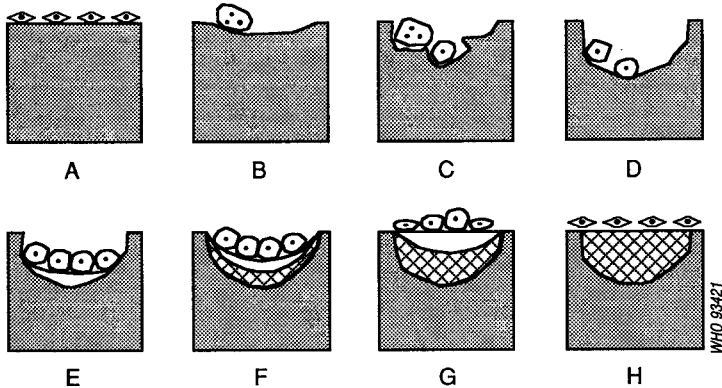
amount of mineral and matrix removed and subsequently incorporated into each resorption cavity, so that skeletal mass decreases progressively. In postmenopausal and many other types of osteoporosis, the imbalance between the amount resorbed and that formed at each remodelling site is caused by a decrease in the functional capacity of osteoblasts or a decrease in the number of osteoblasts recruited to resorption sites. There is also evidence for an increase in the depth of erosion shortly after the menopause.

Irrespective of the mechanism, a finite deficit of bone is the end result of each remodelling sequence in osteoporosis. If bone turnover is increased, the number of bone remodelling units in existence at any one time increases. If the imbalance at each site remains constant, the result of increasing bone turnover will be an increased rate of bone loss (Fig. 8). There is now good evidence that estrogen deficiency not only induces a focal imbalance at remodelling sites, but also increases the remodelling rate of bone (99), thus accelerating bone loss.

The significance of this for the measurement of bone loss is that the rate of loss depends upon the site measured and is greater at cancellous sites than at cortical sites. Even within trabecular bone tissue, there is marked heterogeneity in rates of bone remodelling, so that rates of cancellous bone loss differ at different sites. Thus, correlations between bone density at one site and another become progressively weaker during the process of bone

Figure 8

Schematic representation of trabecular bone surface to illustrate the effect of balance and remodelling on bone loss

The top panel shows the infilling of a resorption cavity with an equal volume of new bone. The centre panel shows less bone deposited at a site of previous resorption. If bone turnover is increased without altering this balance (lower panel), the rate of trabecular bone loss will increase in proportion to the increment in bone turnover.
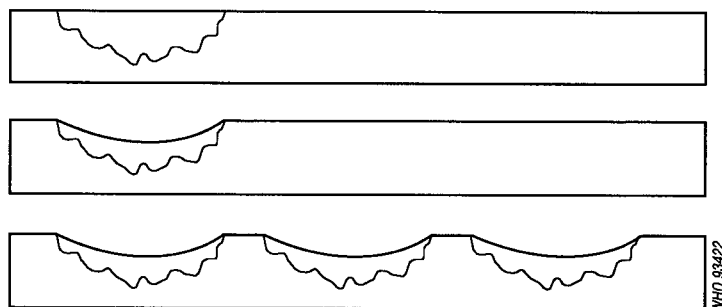
loss. This has implications for the timing of screening tests in the osteoporotic process and the selection of the type and site of test (section 3). Moreover, the action of bone agents on the remodelling sequence has indirect implications for screening. Agents such as calcium, calcitonins and the bisphosphonates decrease the rate of bone remodelling but may not correct the imbalance at each remodelling site (*100*). This contrast with the more complete activity of gonadal hormones so that the efficacy of these non-HRT interventions is likely to be less (section 6).

2.5 Determinants of fracture

The age-related increase in the frequency of fractures, which usually occur with mild or moderate trauma, may be the result either of increased skeletal fragility or of the increased occurrence of non-skeletal factors, for example the loss of protective soft tissue over the bone.

Bone mass decreases at most skeletal sites with age, and there is a high correlation between bone mass and bone strength tested *in vitro* (*101*). In addition, measurement of bone mass allows the assessment of fracture risk (*29, 75, 102-105*). Risk of fracture increases continuously as bone mass declines, and recent data suggest that measurements of bone mass at the site of fracture (the hip, for example) yield better fracture risk estimates (*106-108*). However, when individuals with fracture are compared with those of similar age without fracture, an overlap in bone mass measurements is apparent. It has therefore been suggested that factors other than low bone mass may also play a role in the pathogenesis of fractures; these factors may be entirely extraskeletal, such as the level of trauma that occurs in the population, but other skeletal factors may also contribute.

2.5.1 *Spatial organization of bone tissue*

The continuous imbalance between formation and resorption that is found in osteoporosis would be expected to result in an increase in cortical porosity, a decrease in cortical width and a progressive decrease in the width of trabecular bone elements. A decrease in the width of trabecular bars occurs in many forms of osteoporosis, but in postmenopausal osteoporosis there is a marked *loss* of the trabecular elements themselves (*109–111*). Indeed, there is little evidence for trabecular thinning in postmenopausal osteoporosis, so that the loss of trabecular elements must be, in part, a result of the generation of resorption cavities that transect or perforate trabecular structures.

These architectural abnormalities in cancellous bone may have important implications for skeletal strength. The selective destruction of cross-bracing elements leads to mechanical incompetence that is disproportional to the amount of material removed (Fig. 9). Remaining trabeculae in postmenopausal osteoporosis can thicken – and this is evident even radiographically – but compensation may be inadequate (*112*). Similarly, therapeutic manipulation of the remodelling process might be expected to thicken trabecular structures without necessarily restoring trabecular connectivity (Fig. 9). However, the majority of techniques used to measure bone density do not yield information on trabecular connectivity, which suggests that changes in bone mass, particularly as a

Figure 9
Schematic representation of trabecular bone loss

The diagrams show normal trabecular architecture and the discontinuity of trabecular elements (upper panels) or thinning of trabecular elements. The disruption of continuity weakens the structure out of proportion to the amount of bone lost. Conversely, the deposition of new bone by influencing bone remodelling (right-hand panels) may thicken remnant structures without necessarily restoring trabecular connectivity where this is disrupted.

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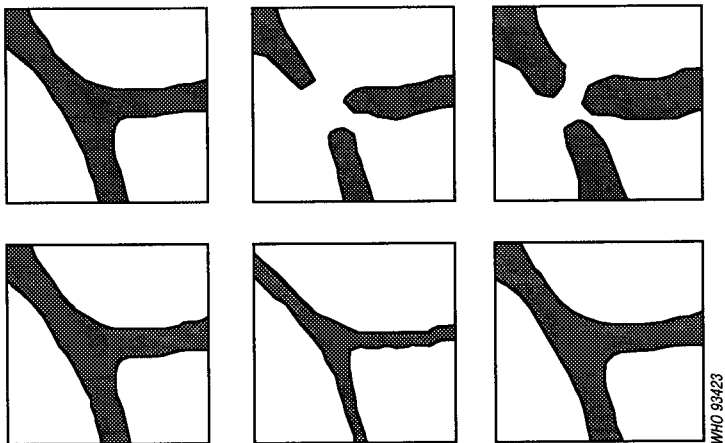
result of therapeutic intervention late in the natural history of bone loss, cannot be reliably interpreted as having a proportional effect on fracture susceptibility (*13*).

At present, the connectivity of cancellous bone can be measured reliably only by invasive techniques (*109, 113*). Hip X-rays provide a semi-quantitative index in the form of Singh scores, which have been of value in population studies (*24, 114*), and it has been suggested that broad-band ultrasound attenuation of bone provides an index of skeletal competence (*115*). Notwithstanding, loss of trabeculae associated with loss of bone mass would be expected to correlate with bone mass measurements. Thus, measurement of bone mass alone may capture a component of the contribution made by architectural abnormalities to bone fragility.

The importance of structural abnormalities to overall risk is difficult to assess. In one study, osteoporotic patients with vertebral fractures were compared with individuals without fractures who were matched for age, sex, race, menopausal status and several indices of bone mass. Mean trabecular plate density was significantly lower in those with fracture (*116*). It has also been shown that the presence of several vertebral fractures raises the risk of subsequent fractures appreciably above that associated with reduced bone mass alone (*65*). This finding may also be related to changes in mechanical loading of the vertebrae after fracture.

Remodelling activity is important for skeletal strength (*117*). Clinical and experimental studies both suggest that, if the rate of remodelling is substantially reduced, the risk of spontaneous fractures will increase, not because of a reduction in skeletal mass, but because of the inability of the skeleton to undergo self-repair (*13, 118*). The femoral bone becomes more brittle in the elderly, and thus breaks rather than bends.

Micro-damage or fatigue fractures occur in bone (*119*) and may contribute to increased skeletal fragility, but the clinical significance of this in osteoporosis is unknown.

2.5.2 *Extraskeletal factors*

The skeletal determinants of bone strength summarized in Table 6 do not reflect all the factors relating to fracture risk. Density-independent components of fracture risk are clearly important for hip fracture but have also been shown to have significance for other fractures. Women with vertebral fracture have lower spinal bone mass than controls (*17, 120, 121*) but, as in the case of hip fracture, there is a large overlap between the two groups. Also, as for hip fracture, bone mineral density does not entirely account for the age-related increase in vertebral fracture prevalence (*102, 103*). In a recent study, a 10-year increase in age was associated with a 94% increase in vertebral fracture risk (*43*); a reduction in BMD of 0.1 g/cm^2 (the loss in 10 years) was associated with a 44% increase in risk. Thus, for any given bone density, the risk of fracture is greater in the elderly (*24-26*).

Table 6
Determinants of osteoporotic fracture

Skeletal
    Bone mass
    Spatial organization of bone
    Turnover of bone
    Quality of bone (plasticity)

Extraskeletal
    Falls – frequency, type and severity
    Response to trauma – neuromuscular coordination
    Soft tissue cushion

The increased frequency of falling, the type of fall that occurs among the elderly and the loss of protective soft tissue covering may all account for the larger contribution of "age" and lesser contribution of bone mass in later life (*25*).

Many ordinary activities create forces in the spine and elsewhere that are of similar magnitude to the forces necessary to produce fracture (*122*). However, the majority of fractures, e.g. of hip and distal forearm, are associated with falls, generally from standing height, and the frequency of falls increases with aging. Among postmenopausal women in the USA, for example, the likelihood of experiencing at least one fall annually rises from about one in five women aged 60-64 years to one in three aged 80-84 years (*33*). A survey in Oxford, England, produced comparable data: about one in three women aged 80-84 years had a fall in the previous year, and this rose to nearly half of women aged 85 years and over; a third of the men in the oldest age-group experienced a fall in the preceding year (*40*).

The increase in falling is not sufficient to explain the increasing incidence of fracture, however, since only 5-6% of falls lead to fracture (*123*). This is because the extent of the trauma delivered to the proximal femur depends on various protective responses (*124*) and upon the orientation of the fall. For example, Hayes and colleagues (*122*) have shown that the risk of a hip fracture is 13 times greater when the point of impact is directly over the hip. In addition, the likelihood of fracture is influenced by the thickness of soft tissues over the bone, which are able to dissipate a surprising amount of force. Thus, there may be reason to consider the importance of soft tissue covering, which may be of lesser thickness in those who sustain fractures. Indeed, preliminary data suggest that an external protective device can substantially reduce the risk of hip fracture, even among individuals who fall frequently (*41*).

2.5.3 *Implications for screening*

These important non-skeletal determinants of fracture risk assume greater importance with advancing age (*24, 25*). It has been suggested that they account for the poorer discrimination between the bone mass of fracture

and non-fracture cases in later life (e.g. hip fracture) compared with vertebral fracture (*7, 43*). However, the many factors that are subject to age-related change make it difficult to quantify the precise contribution of bone density as a separate factor. On the one hand, the importance of density alone is overestimated if these are ignored. On the other, the contribution of density will be underestimated if an attempt is made to adjust for age, since bone loss will have occurred in both fracture patients and non-fracture controls of similar age.

This does not imply that the prevention of early bone loss would have less impact on the elderly (though it may), since increased bone capital is likely to delay the development of other skeletal abnormalities (of turnover, architecture, etc.) and to improve the resistance of bone to trauma. This consideration has enormous importance for screening on the basis of bone mass measurements. The argument is offered that screening (say, at the menopause) is unlikely to predict hip fractures in later life because of the greater overlap of bone density measurements in old age compared with middle life and the dominant role of factors not revealed by measurement of BMD (*7*). The extent to which this modulates views on screening is reviewed in section 3. However, it is clear that trauma, low bone mass and architectural abnormalities of bone are together responsible for the increased incidence of fracture that occurs with aging. Of these contributing factors, only bone mass can currently be measured as a predictor of future fracture risk, and only bone mass can be manipulated in mid-life in the hope of preventing fractures decades later.

2.6 Recommendations for research

1. Few data exist on the worldwide frequency of osteoporotic fractures, which are essential to assessing the current size of the problem as well as for predicting future trends. Such studies should, wherever possible, use standardized methods of data capture.

2. The risk of fracture worldwide may be only partly explained by differences in bone mineral density between communities. Data describing the relationship between fracture risk at specific sites and the distribution of bone mineral density are required to clarify this. Studies should also address the effect on risk prediction of different normalization procedures to compute apparent density, since this may help to explain cross-national differences in risk.

3. Information on the prevalence and incidence of vertebral fractures in the community is particularly scanty, for both men and women. Moreover, the morbidity arising from these fractures is not well documented. Studies to document these aspects are required in the majority of Member States. Comparative studies are particularly useful, but should utilize comparable techniques to assess vertebral deformities.

4. There is a need to develop and validate instruments to assess morbidity, such as quality-of-life assessments in osteoporotic patients with fractures (particularly of the spine and distal forearm).

5. It is important to determine the causes of the secular trends in hip and other fractures, since they have a major potential impact on the future size of the problem in many Member States. Research on the relationship between the causes of interregional differences and the secular trends should also be given high priority.

6. The costs of osteoporotic fractures are not well documented, even in Europe and the USA. Algorithms that are applicable on a multinational basis should be developed for assessing costs.

7. It is recommended that an expert group be convened by WHO to consider the methods most appropriate to explore these areas of future research and make recommendations concerning their implementation.

3. Assessment of bone mass

A large number of techniques may be used to assess the risk of fracture. In general, they fall into two major categories: clinical assessment of risk factors and physical measurement of skeletal mass. The clinical assessment of risk is reviewed in section 5; both this section and section 4 consider non-invasive physical techniques, which variously assess mineral content of the whole skeleton and of particular appendicular and axial sites.

The rationale for the use of any of these techniques is dependent on the well established relationship between bone mineral density and the ability of bone to withstand compressive, torsional and bending forces. In excised bone, the correlation between bone density and the load necessary to induce skeletal failure is very high (125–129). In women, the correlation coefficient (r) between density and the load causing skeletal failure in the radius is 0.83. One study reports the correlation in 61 femoral necks as 0.89 (128). Thus, 70–80% of the variability in bone strength *in vitro* is determined by its mass or apparent density. The compressive strength in trabecular bone is proportional to the square of the apparent density, while the modulus of elasticity of bone is proportional to the cube of density. Comparatively small changes in density are thus associated with large changes in strength.

Techniques to measure bone mineral at appendicular sites such as the wrist and heel have been available for several decades. More recently, techniques have become available for measuring total body calcium or mineral content at axial sites of high biological relevance (e.g. hip and spine). They are safe and widely available in some Member States, particularly Australia and Japan and the countries of North America and western Europe. The development and application of these methods have contributed significantly to the rapidly increasing knowledge of the epidemiology, pathogenesis, prevention and treatment of osteoporosis,

and there is a growing body of opinion that these techniques should be applied to screening.

3.1 Techniques for measuring bone mass or density

3.1.1 Conventional skeletal radiography

Conventional X-ray is relatively insensitive and bone loss is apparent only when mass has decreased by about 30–50%. For purposes of intervention in women at the time of the menopause, the use of simple radiography is inappropriate for a screening test. Several semiquantitative techniques exist for assessing trabecular morphology. The most commonly used is the Singh index, which evaluates trabecular markings at the hip; the technique has proved useful in epidemiological studies of hip fracture (24), but it has less value in young, healthy women.

3.1.2 Radiographic photodensitometry

The technique of radiographic photodensitometry, which has been largely superseded by photon absorptiometry, depends on measuring the optical density of X-ray films of the bones. The exposure of a reference wedge alongside the area of interest is necessary to minimize errors. The radiation dose is the same as for radiogrammetry, and results are usually expressed as an equivalent thickness of the wedge material. In assessing the accuracy of the technique, Shimmins et al. (130) found a close correlation between measured values and bone ash ($r = 0.88$). Use of the technique is likely to increase once more because of the recent development of computer-assisted methods.

3.1.3 Radiogrammetry

Radiogrammetry has been used for many years and is simple and inexpensive to perform. It relies on linear measurements on X-ray films of cortical bone taken under standardized conditions (131, 132). Bones measured have included the radius, humerus, femur, clavicle and tibia, but the site most commonly used is the mid-shaft of the second metacarpal. The technique gives values for the cortical width of bone, from which cortical area can be derived (133, 134). The density of tubular bones is largely a function of the cortical component, and for this reason the technique has a relatively high accuracy in predicting ash weight. However, it is less sensitive and specific than absorptiometric measurements, probably because it takes no account of trabecular density or cortical porosity.

The absorbed radiation dose to the hand is small: ~ 100 µGy/exposure with an effective dose equivalent below 10 µSv.

3.1.4 Single-energy absorptiometry

Single-photon absorptiometry (SPA) has been available for several decades and is widely used (135). It most commonly uses a gamma-ray

source coupled with a scintillation detector, which together scan across the area of interest.

The amount of bone mineral in the tissue traversed by a well collimated gamma-ray beam is derived from its attenuation through bone plus soft tissue relative to that through soft tissue alone (136). The overall thickness of the "soft tissue" is standardized, usually by immersing the limb in water or cuffing with a fluid-filled bag. The value obtained is proportional to the bone mineral content of the segment scanned. The value may be divided by the bone width (yielding a result in g/cm) or by an estimate of the cross-sectional area to give a value for bone mineral density in g/cm^2. The technique has been applied to the femur, humerus, metacarpal, os calcis, hand and foot, but the most commonly used site is the forearm. The most frequently used source is [125]I (27 keV), but has the major drawback of a relatively short half-life (60 days).

The bones of the forearm are not regular and the relative composition of cortical and trabecular bone also varies along their length. For this reason, difficulties in repositioning have been a major limitation in achieving accurate reproducibility. These problems are lessened when the mid-shaft site is used, since this is largely cortical and the mineral content does not change markedly with position. More distal sites contain a higher proportion of trabecular bone. Precision of repositioning and standardization of the measuring site are now commonly achieved by automatic site selection based on the separation of the radius and ulna. A separation of 6–8 mm is often used. Distal to this point, the trabecular/cortical ratio is approximately 50:50 (137, 138); scans proximal to this site measure predominantly cortical bone (87%).

Accuracy may be compromised by a non-uniform thickness of fat, which has attenuation characteristics different from those of water or lean soft tissue. In some equipment, the programme assumes the fat to be a uniform shell around the bone and makes a correction, but the correction requires a number of assumptions that influence the accuracy of the method. The heterogeneity of surrounding tissues is nevertheless considerably less than that of tissue surrounding axial sites such as the spine. Although true *in vivo* estimates of accuracy have not been made, errors in cadaveric studies of excised bone (coefficient of determination, $r^2 = 88$–96%) (139) have been sufficiently low to make the technique attractive for screening.

The radiation dose of SPA is very low and applied to a small volume of tissue, giving an effective dose equivalent of $< 1 \mu Sv$. Typical scanning times are 10–15 minutes.

Single-energy X-ray absorptiometry (SXA) is a newly developed technique suitable for scanning appendicular sites. It avoids the need for isotopes and is likely to replace SPA.

3.1.5 *Dual-energy absorptiometry*

The proximal femur and the vertebral bodies, with their associated processes, are very irregular bones that are difficult to delineate. Furthermore, they are surrounded by a widely varying amount of fat, muscle mass and, in the case of the spine, gut (with or without gas) and aorta (with or without atherosclerosis). The ratio of bone mass to soft tissue is thus lower in the spine or hip than in the forearm, and standardization of soft tissue by immersion in water is not feasible for these sites. These and other factors limit the use of SPA or SXA to the appendicular skeleton. The development of dual-photon absorptiometry (DPA) and, more recently, dual-energy X-ray absorptiometry (DXA) have resolved at least some of these problems. The different thicknesses of soft tissue can be accommodated by simultaneous measurement of the transmission of gamma-rays of two different energies, which makes the techniques applicable to any part of the body, but particularly the lumbar spine (usually L1–L4) and hip.

Measurements at the lumbar spine are taken in the antero–posterior position with the legs elevated to reduce lumbar lordosis. Although it is the vertebral body that fractures, measurements include the vertebral body, arches and spinous processes. The bone mass of the posterior processes and arch is similar in amount to that in the region of interest, the vertebral body. Aortic calcification or the presence of osteophytes adversely influences the result. Similarly, measurement of the femoral neck, trochanter and Ward's triangle, the region that may be most sensitive to loss of trabecular bone (*140*), is done by scanning the whole region of the proximal femur. The femoral anteversion is corrected by internally rotating the foot during scanning. DPA is also used for measuring total body bone mineral; the procedure involves rectilinear scanning of the whole body. Precision errors for DPA are 2–3% for repeat measurements at the spine, 3–5% at the hip and < 2% for total body calcium determinations. The radiation dose equivalent is 1–3 µSv.

Theoretical studies of optimal photon energies (*141, 142*) have shown that, for the trunk, ^{153}Gd provides in a single radionuclide a combination of energies (44 and 100 keV) that is close to ideal. This is the source most commonly used in commercially available DPA equipment; its cost and relatively short half-life (240 days) are the main drawbacks. A combination of ^{241}Am and ^{137}Cs is cheaper and longer-lived, but results suffer from greater statistical variance and poorer geometrical resolution (*142*). The combination of ^{125}I and ^{241}Am has been used for the forearm (*84*).

As is the case for SPA, the source is mechanically linked to a collimating detector. All modern DPA equipment includes computing facilities that make necessary corrections and calculations and produce a bone mineral image. Areas of interest over the bone and background are selected by the operator, assisted by the computer, and bone mineral content in a number

of vertebrae can be assessed. Division of mass by the length (g/cm) or area (g/cm^2) considered provides some normalization for size and reduces the variation that results from difficulties in defining intervertebral spaces.

The theory underlying DPA and DXA requires that there are only two components present – bone and soft tissue of uniform composition. In practice, fat forms a further component with attenuation characteristics that differ from those of water, muscle and most organs. A uniform layer of fat is unimportant, but fat is distributed non-uniformly in the region of the lumbar spine (143, 144) and may cause errors of up to 10% in spinal bone mineral. Errors can also be introduced by fat within the vertebral bone marrow.

Total body bone mineral can be measured by DPA (145), but instrumental problems are greater because of the wide range of count rates and the non-uniform distribution of fat, which introduces errors. However, total body bone mineral measured by absorptiometry correlates closely with total body calcium measured by neutron activation analysis (146). As with SPA, the radiation dose for DPA is low, the effective dose equivalent for part-body examinations being only a few microsieverts.

3.1.6 *Dual-energy X-ray absorptiometry*

Within the past few years, sources of gamma radiation have been replaced by X-ray generators (136, 147). The necessary pairs of effective energies can be obtained either by K-edge filtering, using cerium or samarium (148, 149), or by rapidly switching the generator potential (150, 151). The advantages of these approaches are a higher beam intensity and therefore faster scan (less than 5 minutes instead of 20 minutes for the lumbar spine), improved spatial resolution with easier identification of vertebrae, and better precision. The absence of source decay also eliminates problems associated with decreasing count rates over the lifetime of the source.

Like DPA, this technique determines bone mineral density from an anterior–posterior image, i.e. in two dimensions. The sites most commonly measured are the lumbar spine, generally L2–L4 or L1–L4, including the intervertebral discs. Other sites include the hip, forearm, whole body and skeletal segments. The error in reproducibility *in vitro* is 0.4%. DXA has been reported to have a high short-term and long-term precision *in vivo* (151–155), which is about twice that of DPA. This has led to its widespread use in studies of osteoporosis.

A recent development has been scanning of the lumbar spine in the lateral position (121, 156, 157), which has the advantage of eliminating the posterior arch and the spines of the vertebrae as well as aortic calcification from the measurement. Its limitations are the increased soft tissue mass and overlap of the projected image by the ribs and pelvis, so that only one or two vertebrae are measured. Lateral scanning provides a measurement of vertebral depth which, together with the antero-posterior area, can provide a volumetric measurement for calculating bone mineral mass per unit volume. Whether this "volumetric density" measure is a better

predictor of fracture is unknown. The technique may be useful in assessment of bone density in children, allowing accurate assessment of vertebral size. Uebelhart et al. (158) have shown that the precision error of measurement of the vertebral body and mid-slice *in vivo* is of the order of 2%. The potential of lateral DXA for screening has not been adequately investigated.

DXA has now largely replaced DPA for screening because of its greater precision, ease of use and freedom from several technical artefacts. There is no evidence to suggest that DXA has any disadvantages compared with DPA.

3.1.7 *Quantitative computed tomography*

In quantitative computed tomography (QCT) a thin transverse slice through the body is imaged. Under appropriate conditions the image can be quantified to give a measure of volumetric bone mineral density (g/cm^3 or g/ml), and cancellous bone can be measured independently of surrounding cortical bone and aortic calcification. Developments have been concentrated in two directions: the construction of special equipment using a radionuclide source for measurements of the forearm, and the adaptation of X-ray CT machines installed for general radiology to measure vertebral bone mineral density.

The attraction of the technique is that cancellous bone can be examined separately from cortical bone. It also gives a *true* value for mineral density (g/cm^3 or g/ml) unlike other techniques, but its value as a screening tool has not been well investigated.

Forearm CT
A dedicated forearm scanner was first described by Rüegsegger et al. (159). The photon source is ^{125}I and is mounted in a gantry with a sodium iodide scintillation detector. A linear scan is performed at each of 48 angular positions. Computer reconstruction generates an image in which a region of interest in the cancellous bone of the distal ulna is selected. Hosie and Smith (160) made further developments to give higher precision (errors less than 1% instead of 2%) and a 2-minute, rather than 5-minute, scan. The local absorbed dose is well below 1 mGy.

CT of the spine
Capital and running costs of an X-ray CT system are so high that an installation solely for bone mineral measurement would not be feasible. Nevertheless, the possibility of measuring cancellous bone density in the vertebrae rather than the integral of compact and cancellous bone (as with DXA and DPA) has attracted considerable attention (161, 162).

A lateral plane projection scan is necessary for precise slice positioning through the centres of the vertebrae. Comparison between the CT Hounsfield numbers and a calibration standard scanned simultaneously

allows bone mineral density to be expressed in terms of the equivalent concentration of the material of the standard. Regions of interest within the vertebral bodies are selected: circular, elliptical, rectangular or other chosen areas are selected to include all the cancellous bone just inside the cortex. Automatic choice of region to minimize subjectivity and to enhance precision has been introduced (*163*). Precision errors *in vivo* are relatively low (2–5%).

The relationship between the observed CT number and the true attenuation coefficient is subject to short- and long-term variation, so that it is necessary to scan the patient and a calibration standard simultaneously. The standard placed under the patient by Cann and Genant (*164*) is crescent-shaped and contains tubes filled with solutions of different concentrations of dipotassium hydrogen phosphate. More recently, simpler standards with fewer components, based on suspensions of calcium hydroxyapatite in plastic, have been adopted and are commercially available (*163*). Comparison between the standard and the Hounsfield numbers of the trabecular region of the vertebral bodies allows bone mineral density to be expressed in terms of the equivalent concentration of the material of the standard.

The biggest source of error in single X-ray CT systems is fat within the bone marrow: accuracy errors of up to 30% may be introduced (*165*). The accuracy can be improved by carrying out scans at two different potentials; typically, 80 and 120 kVp are used. Kalender et al. (*163*) claim an accuracy error of 1–2% *in vitro*, but errors *in vivo* are likely to be larger. A drawback of dual-energy CT, however, is that the precision is poorer, with errors of about 10%, much higher than the 2% obtainable with single-energy CT.

A wide range of radiation doses has been quoted for CT, with values as high as 40 mGy for a dual-energy measurement (*163, 166*). This comparatively high dose limits the number of repeated measurements that can be done. Measurements are possible at lower doses, reportedly as low as 1 mGy (*166*). The effective dose equivalent may be only 0.2 mSv for females and less for men (the gonads receive a lower dose).

3.1.8 *Photon-scattering methods*

Photon-scattering methods also allow measurements of trabecular bone to be made without interference from the surrounding cortex, although only at peripheral sites such as the heel (*167–169*). Only a small proportion of photons interact by coherent scattering, and most attention has been paid to Compton scattering. Neither of these techniques has been adequately assessed for screening.

3.1.9 *Neutron activation analysis*

The application of neutron activation analysis (NAA) to bone mineral measurement relies on the fact that 99% of the calcium in the body is in the skeleton. When the area under examination is irradiated with neutrons,

many of its constituent elements become radioactive and can be identified and quantified by examining the characteristic gamma-ray emission. The most widely exploited reaction is the transient conversion of ^{48}Ca to ^{49}Ca. ^{48}Ca is only 0.18% abundant and the half-life of ^{49}Ca is only 8.8 minutes. Irradiation is achieved with a fast neutron beam, with thermalization in the body and possibly a pre-moderator to obtain sufficient uniformity of thermal neutron flux. There have been reviews of part-body (170, 171) and whole-body (172) NAA for bone mineral determination.

Part-body NAA
Radionuclide neutron sources such as californium are normally used to irradiate the area of investigation. Large sodium iodide scintillation crystals are required to maximize sensitivity, particularly as the main gamma-ray emission has a high energy of 3.1 MeV. Sites examined include the hand, forearm and spine. The dose equivalent received in part-body NAA is of the order of 50 mSv; while this has been considered acceptable (the effective dose equivalent is probably below 10 mSv), it is much higher than in any of the other techniques considered. Although useful clinical results have been obtained (173), part-body NAA is now obsolete and has been replaced largely by absorptiometric techniques except in the case of systems that examine the whole trunk (174), which are more analogous to whole-body measurements.

Whole-body NAA
Whole-body NAA can measure several chemical elements simultaneously and until quite recently was the only way to assess total bone mineral. Cyclotrons or neutron generators have been used as neutron sources (175–178); radionuclide neutron sources such as ^{238}Pu/Be have also been used (174, 179). The patient is positioned in a special enclosure at a distance of several metres from the source, with rotation to give bilateral irradiation. Mean incident neutron energy is typically between 4 and 8 MeV.

Accuracy errors based on phantom measurements are about 5%. Assessment of precision is most commonly based on repeated measurements of phantoms; for most systems the precision error is about 2%, and as expected, errors assessed from repeated measurements on patients give higher estimates (approx 3–4%) (180).

The dose equivalent associated with NAA has ranged from about 3 to 20 mSv, mostly using a quality factor of 10. However, it has recently been proposed that the quality factor for neutrons should be doubled, so that the dose equivalent may be higher.

An interesting recent development has been the introduction of a prompt-gamma NAA method of measuring calcium (181). A ^{252}Cf source is used and hyperpure germanium detectors count the high-energy gamma-rays during the irradiation while the patient passes through the sensitive volume. The precision and dose equivalent compare favourably with the performance of the delayed gamma technique.

3.1.10 *Ultrasound evaluation of bone*

Several methods have been developed that variously examine the velocity, attenuation or reflection of ultrasound in bone. Interest in their use lies in the fact that they do not involve ionizing radiation and may provide some information concerning the structural organization of bone in addition to bone mass or density. Equipment is generally portable.

Ultrasound attenuation

Ultrasound attenuation has not yet been validated for use as a screening tool, but the results are sufficiently encouraging to warrant consideration in the future (*182, 183*). So far only the os calcis has been examined. The system consists of a water tank containing two broad-band ultrasonic transducers, one acting as a transmitter, the other as a receiver, at a fixed separation, together with a computer-interfaced electronic generation and detection unit. A short burst of ultrasound is passed through the heel, the frequency varying from 200 to 1000 kHz. The amplitude spectrum is compared with that from water alone to give a plot of attenuation in the os calcis against frequency, and the slope of the linear portion of this graph is taken to characterize the bone. Attenuation is related both to the amount of bone in the path of the ultrasound and to the trabecular structure. A reproducibility error of 2.5–3.5% is achieved (*184, 185*).

The technique has been partially validated (*185–191*). Despite a large population variance (coefficient of variation, CV, 43%), age-related bone loss has been demonstrated and attenuation values are significantly lower in patients with hip fracture than in controls. The technique discriminates patients with and without osteoporosis at least as well as measurements of bone mineral density (*188*). Moreover, it may capture some aspects of true bone density that are not dependent on mineral density (*189*), suggesting the partial dependence of ultrasound attenuation on the intrinsic trabecular architecture of cancellous bone.

Ultrasound velocity and reflection

Ultrasound reflection may also provide some index of the material properties of bone (*192*) but has not been widely studied. Several techniques have been developed to measure the velocity of ultrasound in bone. Sites include the tibia, radius (*193*) and patella (*194*), all of which are reasonably accessible. The speed of sound is proportional to the square root of the product of the stiffness or modulus of elasticity and the bone density (*195*). Although the speed of sound in bone is a function of both the mass and the modulus of elasticity of the bone, there have been no studies examining whether or not the speed of sound provides a measure of bone "quality" and a better assessment of bone fragility than bone densitometry alone.

3.2 Choice of techniques

The techniques that merit consideration as potential screening tools are listed in Tables 7 and 8, together with some of their advantages, disadvantages and performance characteristics. They are selected largely because they have been extensively evaluated both *in vitro* and *in vivo*.

The methods by which these techniques have been evaluated differ widely, however, and not all types of evaluation are relevant to screening. It is therefore necessary to consider carefully the evaluation methods and the results they produce in order to identify the most appropriate.

QCT is the only technique that measures volumetric bone mineral density (g/cm^3). Both SPA and DPA provide information on bone mineral content (g) which can be adjusted, for example, to the area of the vertebral bodies seen in the antero–posterior projection to give an estimate of bone mineral density (g/cm^2). Other adjustments can be made for muscle mass and the width of bone. It is important to recognize that none of these adjustments provides a measurement of true density. The adjustments do, however, have effects on the variance of measurements observed in the population and differences between the sexes, and may affect ability to discriminate individuals with fracture from those without (*196*).

The arguments in favour of the measurement of skeletal mass or mineral content all depend upon various aspects of accuracy. Accuracy represents the extent of agreement between a test result and the true value of the parameter being measured. In this context, "true value" has been variously defined as the amount of skeletal calcium at the site measured or at another site, the presence or absence of fracture at other sites, the future bone mineral density at the site measured or elsewhere, the future risk of fracture, and the lifetime risk of fracture. Each of these aspects of accuracy is reviewed in turn.

3.2.1 *Correlation between sites*

Invasive techniques such as ash weight or histomorphometry have shown variable relationships of bone density between sites. For example, the correlation coefficient (*r*) between cancellous bone volume at the ilium and at the lumbar spine is reported as 0.83 despite a twofold difference in mean value (*197*). Similarly, the ash weight of the metacarpals correlates closely with that of the midradius (*r* = 0.96) and the femur (*r* = 0.85) (*198*); in contrast, the correlation between metacarpal ash weight and vertebral ash weight is poor (*r* = 0.47). Thus, measurement of ash weight at a cortical site will probably predict accurately that at another cortical site but not at cancellous sites.

Many studies have examined the correlation between *in vivo* measurements made at one site and those made at another, or between measurements made at the same site with different techniques. Some examples of correlations between sites are given in Table 9, for

Table 7

Advantages and disadvantages of various techniques to assess fracture risk

Technique[a]	Advantages	Disadvantages
QCT	Gives true density values Discriminates completely trabecular from cortical bone High resolution Low precision error (radius)	Comparatively high radiation dose High cost High accuracy error (single energy) Precision errors (spine)

DXA	No isotopes
	High precision
	Low radiation dose
	Multiple sites of assessment,
	    including spine and hip
		Uncertain accuracy errors *in vivo*
		Relatively high cost
		Influenced by osteoarthrosis and aortic
		    calcification at lumbar sites

SPA and SXA	Low radiation High accuracy High reproducibility Low cost Portability	Restricted to appendicular sites Isotope half-life short for SPA

[a] QCT = quantitative computed tomography
DXA = dual-energy X-ray absorptiometry
SPA = single-photon absorptiometry
SXA = single-energy X-ray absorptiometry

35

Table 8

Performance characteristics of various techniques of bone mass measurement at various sites

Technique[a]	Site	Type of bone (% cancellous)	Precision error in vivo (%)	Accuracy error in vivo (%)	Scan time (minutes)	Effective dose equivalent (μSv)
SPA	Forearm[b]	5	1–2	2–5	10	<1
	Forearm[c]	40	1–2	2–5	10	<1
	Heel	95	1–2	2–5	10	<1
DXA	Lumbar	50	1	5–8	10	1
	Lumbar[d]	90	3	5–10	20	5
	Femur[e]	40	1–2	5–8	10	1
	Total body	20	1	1–2	20	3
QCT	Spine (SE)[f]	100	2–4	5–10	15	60
	Spine (DE)[g]	100	4–6	3–6	20	90

[a] SPA = single-photon absorptiometry   DXA = dual-energy X-ray absorptiometry   QCT = quantitative computed tomography

[b] Distal   [c] Ultradistal   [d] Lateral   [e] Proximal   [f] Single-energy   [g] Dual-energy

Table 9

Examples of the correlation (r) between bone mass measurements at different sites in healthy individuals

Site 1	Technique[a]	Site 2	Technique[a]	Correlation, r	Reference
Spine	QCT	Metacarpal	CW	0.5	199
Distal forearm	SPA	Total body	DPA	0.86	200
Forearm	SPA	Lumbar spine	QCT	0.5	199
Femoral neck	DXA	Lumbar spine	DXA	0.77	201
Lumbar spine	QCT	Distal forearm	SPA	0.45	202
Proximal femur	SPA	Lumbar spine	DPA	0.56	203
Distal forearm	SPA	Lumbar spine	DPA	0.4	203
Proximal forearm	SPA	Femoral neck	DPA	0.59	203

[a] QCT = quantitative computed tomography
SPA = single-photon absorptiometry
DXA = dual-energy X-ray absorptiometry
CW = cortical width
DPA = dual-photon absorptiometry

37

measurements made in a young, healthy population. Highly significant correlations are commonly reported. For example, a correlation coefficient of 0.86 is reported between (fat-corrected) values for SPA in the distal forearm and total body calcium in normal subjects (*200, 204*). The correlation coefficient between cortical and trabecular bone is typically between 0.4 and 0.7 or more (*138, 139, 204-206*). On this basis, it has been argued that the measurement at one site, for example the forearm, can be used to predict bone mineral content at the spine (*139*).

Although the correlations are statistically significant, they do not permit the value of one parameter to be predicted from that of the other (*207*). Moreover, the correlation of bone mineral density at one site with that at another is greater in premenopausal women than in patients who have already lost bone. Indeed, it is expected that, as bone loss occurs, rates of loss will differ at different sites because of the type of bone (cortical/cancellous) and even within cancellous bone because of different rates of turnover, which vary 10-fold throughout the skeleton. It therefore appears that site selection is of critical importance to improving the accuracy of assessment. Several studies have reported that BMC of the forearm is not a reliable predictor of either mineral content or mineral density of the spine (*138, 205, 207*). It is argued that, if the desired value is bone mineral density of the spine, measurement techniques should be applied at that site and not elsewhere; since osteoporosis commonly presents with vertebral crush fracture, a vertebral site should be selected for risk assessment (*89, 207-209*).

At any one site, measurements made by the different techniques are highly correlated. For example, both SPA and DXA perform similarly *in vivo* in assessing the calcium content. There are close correlations, of the order of 0.8-0.9, between vertebral densities assessed by QCT, DXA or DPA (*199, 210-212*) and even better correlation between DXA and QCT in cadaveric studies ($r = 0.96$) (*156*) and DPA and DXA *in vivo* (*213*). However, correlation analysis cannot quantify the strength of the relationship between BMD and fracture risk (*214*).

3.2.2 *Comparative accuracy*

Concerns have been expressed about the accuracy of various techniques, particularly of DPA and QCT. Systematic inaccuracies are a particular problem in the spine: the vertebrae are irregular in shape, and apparent density and mineral content depend in part upon the algorithm used for edge detection. For example, in a comparison of DXA with DPA, a highly significant correlation was observed for bone mineral density of the lumbar spine ($r = 0.94$; SEE 6%), but the slope of the regression differed from unity and the intercept was significantly different from zero. Using bone mineral content, rather than density, produced a slope closer to unity with the intercept at zero (*155*), which indicates a systematic difference between techniques in the assessment of area. The effect of systematic inaccuracies is shown in Fig.10. Their relevance to screening is three-fold:

- Systematic errors alter the apparent normal range for bone density in the population; at the spine, the mean value of populations measured by DXA may differ by as much as 20% (*152*).
- Alterations in slope (see Fig. 10) alter the variance of the population. An increase in slope will decrease the apparent population variance, which may, depending upon precision characteristics, decrease the ability to locate a patient accurately within a population range.
- Non-linear systematic errors skew the distribution of normal values and the accuracy will vary according to the density value.

These factors have some impact on screening but the greatest concern is the presence of non-systematic errors of accuracy, the effects of which are illustrated in Fig.11. An estimate of the accuracy error is given by the coefficient of determination (r^2). The lower the value of r^2, the less

Figure 10

Hypothetical relationships between measured bone mineral density (BMD) and ash weight of the skeleton

The top left-hand panel describes the relationship with no accuracy errors (SEE=0%; slope=1; intercept=0). The top right-hand panel shows the effect of a consistent overestimate of BMD (intercept – 0.05). In the second example of an error in accuracy (bottom left), the mean value of BMD is higher than the ash weight due to a proportional error of accuracy (slope >1). The final example shows a non-linear but systematic error.
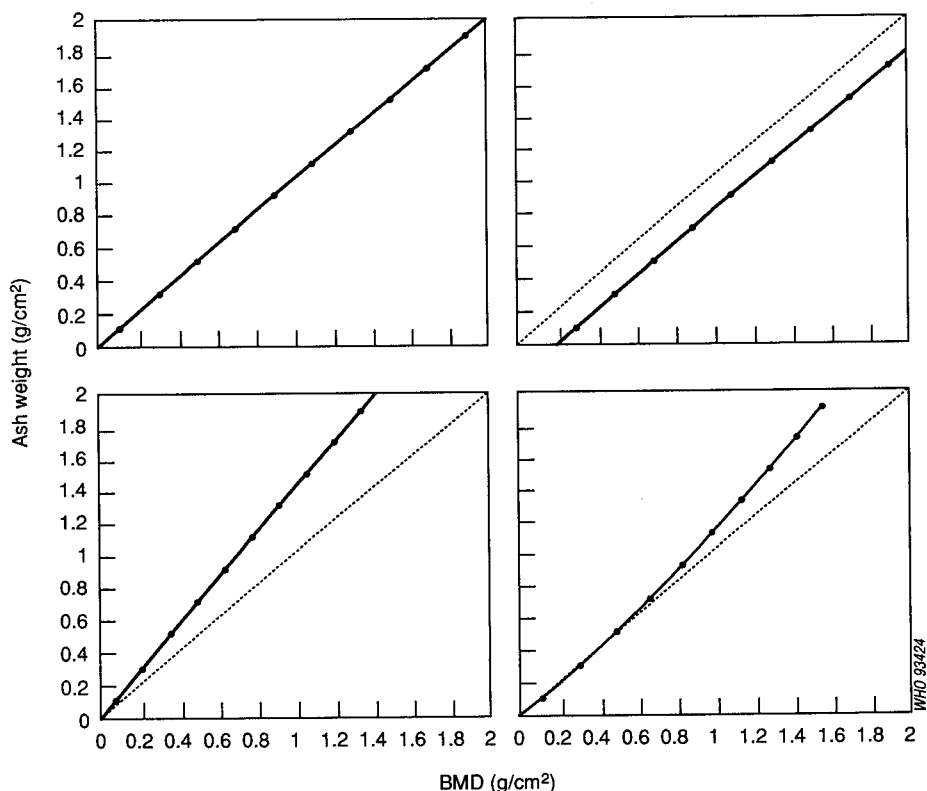
confidently can ash weight be predicted from bone mineral density. There is a great deal of evidence to suggest that many of the techniques advocated for screening incur this type of error.

In the case of DPA, values may change significantly as a function of source life and source replacement (215, 216). In addition, both DPA and DXA traditionally measure bone mineral content from an antero–posterior projection of the spine. Both include intervertebral discs, which may also give rise to non-systematic errors. Osteophytes and soft tissue (especially aortic) calcification may also make a significant contribution to apparent density (217). Some of these factors are of less concern in younger women but the prevalence of spinal osteoarthrosis is high at the age of the menopause.

Use of DXA in the lateral projection may overcome some of the difficulties. The major problem, however, arises from the variable densities of soft tissues, which in the spine include lean body mass and fat mass, plus air. The vertebrae are surrounded by a thick layer of these tissues, the

Figure 11

The effect of non-systematic errors on prediction of ash weight from measurements of bone mineral density (BMD)

Note: The coefficient of determination (r^2) is proportional to the accuracy.
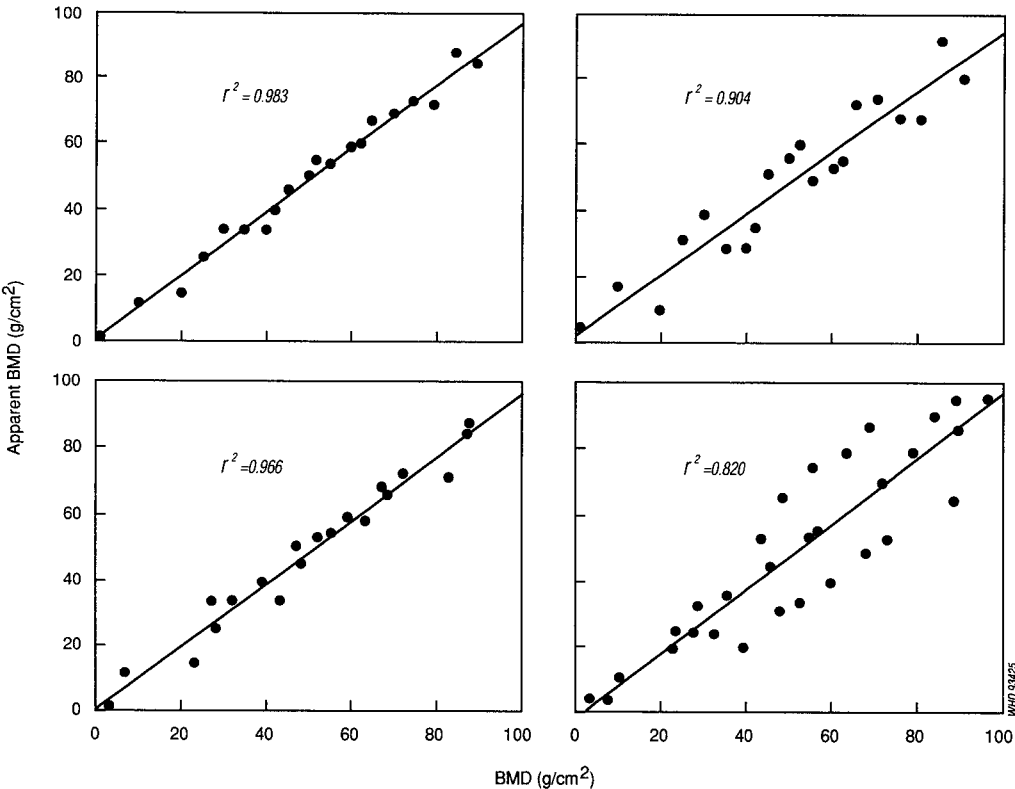
composition of which varies widely from one person to another. Bone mineral content may be underestimated in obese subjects unless adequate fat correction is applied (155, 204, 218). The correction for fat makes a number of assumptions (204) that are difficult to assess, the most important being the heterogeneous disposition of fat in the body. For example, a non-systematic inaccuracy arises from the variable fat content of the kidney capsule (219). Fat content also varies within individuals; menopause, for example, is associated with an increase in fat content of surrounding tissue as well as that within cancellous bone (220, 221). Conversely, treatment with estrogens reduces the proportion of fat in soft tissues. The presence of soft tissues also affects edge detection and therefore the calculated bone mineral density. In the case of lumbar vertebrae, the area measured reportedly varied by more than 7% with an error (SEE) of 8.1-11.1% for the same equipment used under different conditions (218).

The effects of variations in body and marrow fat have been partially investigated. In general, changes occurring concurrently in soft tissues and marrow have relatively little impact on the density value measured, but changes in fat content of either compartment have profound effects. In the case of DPA and DXA, a change in fat content of 10% affects bone mineral density by about 0.7-1% (155, 222). The marrow fat-induced inaccuracy of QCT is at least 5 times greater than that with DXA or DPA, i.e. a change in fat content of 10% affects bone mineral density by 5% (221, 223). Homogeneously distributed fat affects DXA to a greater extent than DPA, whereas non-homogeneously distributed lean tissue affects both techniques (144, 155). In contrast, the forearm consists mainly of cortical bone and is more regular in shape than the spine. It is covered by only a thin layer of soft tissue, less complex than in the area of the spine. For this reason, a change in marrow fat of 10% will affect mineral content of the wrist by only 0.2-0.3% in normal individuals and by up to 0.8% in osteoporotic patients.

Many investigations have reported on the accuracy of various techniques, usually *in vitro* on phantoms, or on excised skeletal tissue. As might be expected, higher estimates of accuracy are generally derived in such circumstances than from studies on cadavers. In standards *in vitro*, the accuracy error of DPA ranges from 1.2% (224) to 1.3% (225); estimates from skeletal material *in vitro* range from 3% (226) to 5.3% (222) or 3-10% (211, 218). The estimate of accuracy most relevant to screening is that derived as closely as possible from the situation *in vivo*, particularly for sites with a large soft tissue component. Estimates of accuracy errors *in vivo* are significantly higher than those reported from *in vitro* studies (Table 10).

The accuracy error of SPA in cadaveric studies is in the range 2-5% (228, 229) and of DPA 6-12% (88). There have been no formal estimates of accuracy in cadaveric studies with DXA, but where comparative data are available for DPA and DXA *in vivo*, there is close correlation between the

Table 10

Estimates of accuracy of dual-photon absorptiometry of the spine *in vitro* (phantom studies), *ex vivo* (on skeletal material) and *"in vivo"* (cadaveric studies)

Note: Accuracy errors are given as standard error of the estimate (SEE, %) or as $1-r^2$ (%) where r^2 is the coefficient of determination.

Type of study	Accuracy	error	Reference
	SEE	$1-r^2$	
In vitro	1.2		224
	1.3		225
Ex vivo	5.2[a]	2.0[a]	88
	8.4	7.8	88
		4.0[b]	227
		2.0	151
	10		222
In vivo	8.1[a]	5.9[a]	88
	10.3	11.6	88

[a] Bone mineral content rather than bone mineral density.
[b] Source ^{241}Am/^{137}Cs.

techniques for measurements at the lumbar spine ($r = 0.94$, SEE 6%) (*155*). This degree of correlation is closer than the accuracy estimate for DPA, which suggests that DPA and DXA are subject to similar non-systematic accuracy errors. Moreover, the SEE for the regression of forearm bone mineral content against DXA is 12% and for DPA 14% (*155*) in a series of pre- and postmenopausal women. This additionally suggests little difference in accuracy between DXA and DPA, in marked contrast to the precision of the two techniques (discussed later) which is significantly better with DXA (*152, 155*).

The accuracy errors of the various techniques commonly used for screening varies from 1–10% (Table 8). These figures must be considered in parallel with the variance in measurements in the population to be examined, which ranges from 10% to 50%, depending upon the techniques used and any normalization procedures applied (*196*). Typical estimates are given in Table 11, but small variations occur in different healthy female populations and at different sites. In general, the variance (CV) is no greater than 22% (*43, 82–84, 230–233*). It is therefore evident that techniques with an accuracy error of more than 10% cannot be used to define fracture risk where the population variance is of the order of 20% or less (Table 11; Fig. 12). Of the candidates for screening, the accuracy performance in relation to the population variance is highest in the case of SPA by a factor of about 2 (Table 11). This would suggest that SPA should

Table 11
Characteristics of the healthy female population and the accuracy of bone density measured by different techniques[a]

Note: The ratio *A/B* provides an index of the relative power of each technique to position correctly a single estimate of bone density within a population reference range.

	Technique[b]			
	SPA	DPA	DXA	QCT
A = population coefficient of variation (%)	13.3	12.1	14.0	17.9
B = accuracy error (%)	2–5	8–10	?5–8	5–10
A/B	2.6–6.7	1.2–1.5	1.8–2.8	1.8–3.6

[a] Source: reference *100*.
[b] SPA = single-photon absorptiometry
DPA = dual-photon absorptiometry
DXA = dual-energy X-ray absorptiometry
QCT = quantitative computed tomography

Figure 12
The importance of accuracy in bone mineral density (BMD) measurements in relation to the variance of a normal population

The curve describes the normal range for bone mineral density expressed as percentage positive or negative deviation from the mean, or in units of standard deviation (SDU). The solid horizontal lines indicate the confidence estimate for a given bone mineral density measurement with different degrees of accuracy.
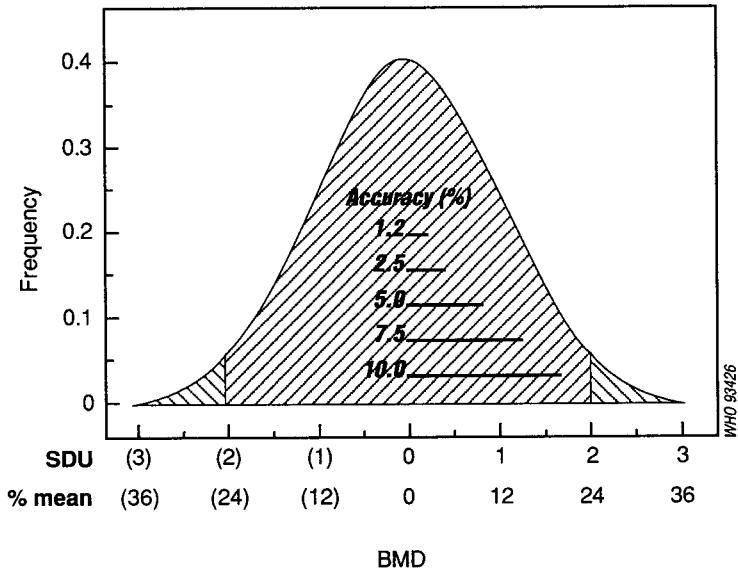
be the technique of choice for a screening test utilizing a single estimate of bone density, unless it could be shown that an appendicular measurement (at the wrist) was more than twice as weak as axial DXA in predicting osteoporotic events.

3.2.3 *Predictive value*

In the context of screening, the ultimate gauge of accuracy is the ability to predict from bone assessment at one site, say at the time of the menopause, the probability of a future osteoporotic fracture. This contrasts with the use of bone mineral measurements to diagnose osteoporosis, where accuracy is the concordance between actual and measured bone mineral density at that site. A number of studies have examined the sensitivity and specificity of bone mass measurements to discriminate osteoporotic patients with fracture from populations without fracture (*19, 20, 234*). Generally, but not invariably, both sensitivity and specificity are improved by measuring at sites of biological relevance such as spine, hip and distal forearm (*90*). For example, ultrasound attenuation at the heel is as good as DPA of the spine in distinguishing patients with and without thoracic vertebral osteoporosis (*188*). Similarly, when comparing patients with hip fracture with young, healthy, female controls, the discriminating ability provided by bone mineral content measured at the distal forearm (particularly the proximal site) with SPA is greater than that provided by measurements made at the spine by DPA (*235*). Similar observations have been made using SPA of the heel, which in some prospective studies gave a more powerful index of risk than DPA at the hip or spine (*28, 236*).

The relatively small difference in bone density between fracture patients and apparently healthy individuals is offered as evidence that screening would not be efficient (*7, 11*). Ultimately, however, assessments based on differences in bone density between fracture patients and controls (*19, 90, 237*) are flawed (*238*).

The most relevant type of investigation assesses the future risk of fracture in women, preferably at the time of the menopause, and studies the incidence of fracture prospectively. The studies that come closest to these ideals have been undertaken in Hawaii (*23, 102, 104*). They used various absorptiometric techniques to measure bone mineral content or density at the os calcis, distal and proximal radius and lumbar spine in a cohort of 1098 women, mainly premenopausal. Over 6 years, 39 new fractures occurred and it was found that fracture incidence increased with diminishing bone at all sites. Many other studies have examined future fracture risk in cohorts of women of varying ages for up to 20 years (*25, 29, 65, 102, 104, 105, 107, 108, 239-242*). Estimates consistently show a risk gradient of between 1.5 and 8.1 for each standard deviation decrease in bone mineral density with all the absorptiometric techniques (Fig.13; Table 12). Similar estimates have been obtained from measurements of cortical width at the radius or metacarpal (*243*).

Figure 13
The gradient of risk (change in relative risk) for each standard deviation (± 95% confidence intervals) decrease in BMD derived from prospective cohort studies
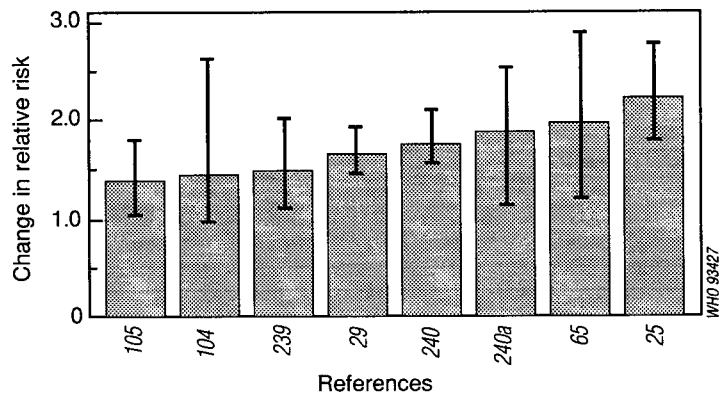
Table 12
Unadjusted relative risk of fracture for each standard deviation decrease in bone mineral according to site of measurement and fracture[a]

Site	Technique[b]	Measurement	Fracture site (number of cases)			
			Any (93)	Hip (14)	Forearm (21)	Spine (37)
Spine	DPA	BMD	1.9	3.2	2.3	2.7
Trochanter	DPA	BMD	1.6	3.3	2.0	2.4
Femoral neck	DPA	BMD	1.8	3.8	2.0	2.6
Distal radius	SPA	BMC	1.5	3.9	2.8	2.0
Mid-radius	SPA	BMC	1.6	2.7	2.0	2.6

[a] Source: reference *106*.
[b] DPA = dual-photon absorptiometry
SPA = single-photon absorptiometry

There are, nevertheless, several potential limitations in the interpretation of these data, particularly where older women have been studied. The most important is whether the fracture threshold of bone mineral density is the same in women with the denser bone at menopause as in women with less dense bones. It might be supposed that structural arrangement of trabecular bone architecture would be equally favourable in both groups of women, and that the risk of future fracture would then depend largely on the amount of bone *lost* by the individual rather than on bone capital. However, this is unlikely to be true for two reasons. First, the prospective studies of Wasnich et al. (*102*) were carried out in predominantly

premenopausal women. Second, women with Colles fracture before the menopause have lower forearm bone mineral density than age-matched premenopausal women without fracture (*230*). These data indicate that premenopausal bone status is clearly an important component of future risk.

Another argument that is offered is that the predictive value of density measurements is likely to be less in the very elderly than is suggested by studies with a limited follow-up, because extraskeletal factors such as falls assume greater importance with age (*11*). However, the difference in bone density values between those with and without fracture does not appear to vary markedly with age (*244*).

The gradients of risk of fracture with low mineral measurements are somewhat steeper than those reported for the risk of coronary artery disease in men with elevated serum cholesterol or hypertension. In a large study of risk factor intervention, more than 300 000 men were followed for 12 years. There was approximately a 1.5-fold increase in the risk of death from coronary artery disease with each standard deviation increase in serum cholesterol or diastolic pressure after adjusting for potential confounding factors (*245*) (Fig.14). This gradient of risk is also similar to that reported in women for systolic pressure and the risk of stroke-associated mortality (*246*).

Figure 14
Relative risk (RR) of hip fracture estimated from forearm bone mineral content (BMC) in a cohort of 399 women aged 40–70 years, followed up for 10 years[a]

The relative risks in the population are shown by quartiles of BMC. The lower panel shows the change in relative risk for coronary artery disease (CAD) according to quartiles of serum cholesterol in men.
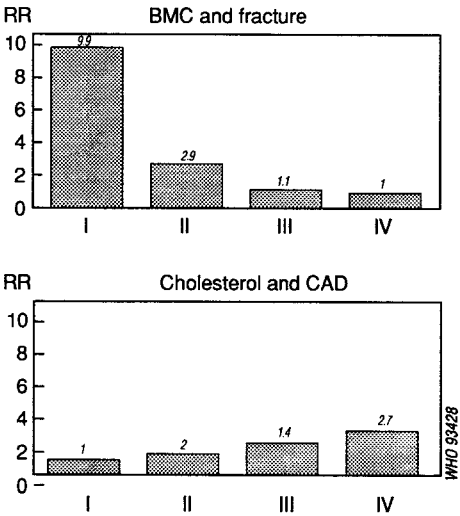
[a] Based on data from reference *245* (copyright 1992, American Medical Association).

Table 13
Lifetime risk of hip fracture according to bone mineral density measured at the hip in women aged 50 years

Bone mineral density (g/cm^2)[a]	Percentage of population[b]	Lifetime risk (%)[c]
>1.2	18.1	2
1.10–1.19	20.7	8
1.00–1.09	24.6	16
0.90–0.99	20.0	27
0.80–0.89	11.1	40
0.70–0.79	4.2	47
0.60–0.69	1.1	50
<0.60	0.2	51

[a] By dual-photon absorptiometry
[b] Women aged 50 years at Rochester, MN, USA (250)
[c] Derived using the model described by Tosteson (251)

Prospective studies of this type provide a more rational basis for assessment of sensitivity and specificity, but they should not be based on fracture risk over a short period of observation (3–15 years) as is sometimes the case (247). A woman with low bone mineral density who has not suffered a fracture during a 5-year period but will do so 10 years later cannot be considered as a false positive. As argued by others (21, 26, 238), probabilistic rather than deterministic approaches are more appropriate, since the number of high-risk individuals who will fracture will increase over the lifetime of the cohort. Lifetime risk should be computed for all ages to take account of the bone mineral content-independent effect of age on fracture risk (248, 249). The relationship between bone mineral density and the risk of hip fracture is shown in Table 13 for age 50 years and subsequently (see also section 7).

3.3 Sensitivity and specificity of assessments

As recognized many years ago, the traditional concepts of sensitivity and specificity collapse when continuous variables are considered (252). A useful analogy to illustrate this point is provided by the relationship between smoking and lung cancer. At any point in time most smokers do not have lung cancer, which means that smoking has a low specificity for the diagnosis of cancer. This should not be taken to mean that smoking does not increase the risk of lung cancer: the correct interpretation is that smoking is common in those who do not have lung cancer (i.e. the general population). In other words, the apparent specificity of risk factors such as smoking or low bone mineral density is only a measure of the prevalence of those risk factors in the community. There are similarities with other

etiological risk factors. Most strokes, for example, occur in normotensive individuals, but this does not necessarily invalidate the use of blood pressure measurements to identify individuals at risk from strokes.

In the context of a lifetime risk, rather than the presence, of a fracture, sensitivity is defined as the proportion of individuals who would in their lifetime sustain a fracture with a bone mineral density *below* a defined cut-off value (Table 13). Specificity is defined as the proportion of subjects who would not sustain a fracture in their lifetimes with bone mineral density values *above* the cut-off. It should be noted that the terms "sensitivity" and "specificity" used in this way do not denote the presence or absence of disease in individuals at the time of the test (the diagnosis of osteoporotic fracture is clinically obvious, with a predictive value much greater than can be obtained with density measurements); instead they reflect the proportion who do or do not suffer fractures in the future.

Table 14 provides some estimates of such sensitivity and specificity under a number of different conditions. The gradient of risk of future fracture for each standard deviation shift in bone mineral density is modelled at 1.5, 2.0 or 2.5, covering the range identified in prospective studies. The average lifetime risk of fracture is modelled at 15% and 30%; the former is an accurate assessment of hip fracture risk in England and Wales and the latter a very conservative assessment of the risk of any osteoporotic fracture (see section 2). Specificity and sensitivity are calculated assuming the high-risk category is 6.5% or 30% of the perimenopausal population (i.e. the range over which intervention might be contemplated). When considered in this way, the false-positive rate is close to 0, indicating that the specificity of bone mineral measurements is high since the lifetime risk of fracture is close to 100% using the 6.5% cut-off. When a 30% cut-off is used, the specificity remains high (over 75%) over all ranges of risk assumptions. In contrast, the test lacks sensitivity (29% to 80% depending on the assumptions made). The relatively low sensitivity indicates that a substantial proportion of fractures will occur in women who lie in the lower risk groups when bone mineral density is used as a single test to assess fracture risk.

Sensitivity increases with the gradient of risk assumed. This indicates that improved accuracy would increase the sensitivity of test. One recent study followed a cohort of 304 age-stratified women for 8 years after measuring bone density at multiple sites (*106*). The gradient of risk for each standard deviation difference in initial bone density was similar between fracture types and between measurement sites (see Table 12). There is a trend towards higher gradients of risk when the technique measures the site of future fracture, but these differences are not significant. However, among 8134 elderly non-black women followed for 1.2 years, Cummings and co-workers (*108*) found a statistically significant increase in the risk of hip fracture, ranging from 2.4 to 3.0 per standard deviation decline in baseline bone mineral density depending on the site in the proximal femur that was measured. Because of the large size of this population, it was possible to

Table 14

Estimates of sensitivity and specificity of a single measurement of bone mass to predict hip fracture (15% lifetime risk) or osteoporotic fracture (30% risk) in postmenopausal women according to different cut-offs to define the high-risk category

Note: Values are given where the risk of fracture is assumed to increase by 1.5, 2.0 or 2.5 for each standard deviation decrease in bone mineral density.

		High-risk category (% of population)					
		6.5			30		
Gradient of risk	Lifetime risk (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
1.5	15	38	98	89	65	75	74
	30	29	100	79	58	78	72
2	15	47	100	92	75	77	77
	30	31	100	79	68	80	76
2.5	15	52	100	93	81	77	78
	30	35	100	81	74	80	78

show that proximal femur bone mineral density assessed by DXA was statistically a significantly better predictor of hip fracture risk than were measurements made in the spine, calcaneus, mid-radius or distal radius. Thus, site-specific measurements were not dramatically better in predicting fracture risk in general, but may be superior for predicting specific fractures of interest.

3.4 Recommendations for research

1. The ability of densitometric techniques to predict fracture is imperfect, owing in part to accuracy errors of the techniques. Estimates of accuracy made under appropriate conditions are relatively few and further studies would be welcome.

2. There is a continuing need to develop new techniques with good accuracy; in existing techniques, errors of accuracy are large in comparison with the population variance of bone mineral density.

3. New techniques such as ultrasound attenuation are of interest because of portability, low cost and the fact that they use no radiation, but long-term prospective studies in appropriate populations are required to provide biological validation of their relevance to screening.

4. Assessment of bone loss

In the context of postmenopausal osteoporosis, bone density at any time after the menopause will depend in part on the peak bone mass or density at maturity and the amount of bone lost thereafter (75). The rate of bone loss after the menopause varies, but present evidence suggests that the rate is unimodally distributed and that "fast losers" represent the extreme of a normal distribution. None the less, individuals who lose bone at the faster rates are more likely to reach a threshold of bone density below which the risk of fracture is unacceptably high (Table 15). Bone loss can be measured by a variety of techniques but those relevant to screening involve the repeated estimation of bone mass. In addition, there is some evidence to indicate that rates of loss can be predicted from biochemical estimates of bone formation and resorption in the early postmenopausal years.

4.1 Repeated measurements of bone density

The most direct method of assessing bone loss is by repeated measurements of bone density, but several factors determine the suitability of bone mass measurements for accurately measuring rates of bone loss. Apparent changes are liable to misinterpretation. For example, the width of many bones increases with age (133) and there is an age-related increase in extraskeletal calcification (254). Changes in the distribution of fat can lead to additional artefacts. The apparent anabolic effects of estrogens or anabolic steroids on skeletal density are due in part to a significant

Table 15
Expected age of reaching a fracture threshold in women divided according to bone density at menopause (50 years) and rate of bone loss[a]

Note: Fracture threshold is defined as a skeletal mass 60% of the average of young healthy women.

Skeletal loss (%/year)	Age of reaching fracture threshold (years)				
	Bone density at menopause				
	−2 SD	−1 SD	Mean	+1 SD	+2 SD
1.0	68	>80	>80	>80	>80
2.5	58	63	68	72	>80
5.0	54	57	58	61	64

[a] Source: reference 100.

decrease in fatty tissue surrounding bone (204, 255). Similarly, apparent increases in bone density ascribed to exercise may be due to a decrease in body fat, an increase in lean body mass or both. Conversely, a proportion, perhaps as much as 50%, of the apparent bone loss after oophorectomy is attributable to an increase in marrow fat.

The precision or reproducibility of the technique used is also a critical factor in determining whether or not a change has occurred (196). The conditions under which reproducibility is assessed are important. For example, the precision error of SPA is consistently less than 1% when bone mineral content of a standard is determined on the same day. But reproducibility error is doubled (1–2%) when the measurements are made repeatedly over long periods. In osteoporotic patients with reduced bone mineral content, the coefficient of variation exceeds 3% in most laboratories. Similar or slightly better figures for precision are obtained using DXA but errors are greater in patients than in phantoms (Table 16). The importance of determining the coefficient of variation applicable to working conditions is obvious: the probability of detecting a difference between two measurements (when a true difference exists) depends upon the confidence that can be placed on each measurement. With less precise techniques, individuals must be followed for longer periods to determine with certainty whether or not a change has occurred (Table 17). Techniques for improving the statistical power of measurements to detect changes in individuals and in populations, reviewed elsewhere (196), can considerably enhance the value of bone mass and density measurements.

At present, the performance characteristics of various techniques vary between centres, even when the same equipment is used. Typical estimates of *in vivo* reproducibility are given in Table 18.

These precision errors must be judged against the rates of bone loss expected in a population. Average postmenopausal bone loss over one

year is about 2%, i.e. of the same order as the precision of SPA and DXA. This might suggest (Table 17) that average or greater than average rates of bone loss can be detected with confidence within 2 years by a repeated measurement, but slower losses would take longer to detect.

Although the average annual rate of bone loss is 2%, rate of loss can differ by a factor of 3-5 depending on the site (*84, 91, 92, 133, 239*). It is lower at cortical than at cancellous sites (Table 19). Thus, the ratio of loss to

Table 16
In vitro and in vivo short- and long-term precision errors of dual-photon absorptiometry (DPA) and dual-energy X-ray absorptiometry (DXA) in measurements of bone mineral density[a]

	Coefficient of variation (%)			
	Short-term (within 1 day)		Long-term (6 months)	
	DPA	DXA	DPA	DXA
Phantom	0.5	0.5	1.4.	0.3
Premenopausal women	1.2	0.9	1.6	0.8
Early postmenopausal women	1.8	1.2	2.1	1.1
Late postmenopausal women	2.1	1.5	–	–

[a] Reproduced from reference *155* with the permission of the publisher.

Table 17
Duration of study necessary to determine significant bone loss ($P < 0.05$) in an individual patient[a]

Rate of bone loss (%/year)	Reproducibility (coefficient of variation, %)	Minimum duration of study (years)
1	1	2
	2	4
	5	8
	10	16
2	1	1
	2	2
	5	4
	10	8
5	1	1
	2	1
	5	2
	10	3

[a] Reproduced from reference *196* with the permission of the publisher.

Table 18
Estimates of long-term reproducibility (coefficient of variation) of various techniques applied *in vivo* to healthy individuals

Technique[a]	Site	Coefficient of variation (%)	Reference
SPA	Forearm	1.8	*256*
	Forearm[b]	1.0	*59*
	Forearm[c]	1.2	*235*
	Forearm[d]	1.6	*235*
	Forearm[d]	2.2	*257*
	Forearm[c]	1.1	*257*
	Forearm[b]	1.7	*257*
	Forearm	1.5	*258*
DPA	Heel	1.8	*259*
	Spine	2.3	*59*
	Femoral neck	3.3	*59*
	Spine	1.6	*153*
	Spine	5.5	*88*
	Total body	2.1	*260, 261*
	Spine	3.9	*262*
DXA	Spine	0.8	*155*
	Spine	0.23	*152*
	Forearm	1.3	*258*

[a] SPA = single-photon absorptiometry
  DPA = dual-photon absorptiometry
  DXA = dual-energy X-ray absorptiometry
[b] Cortical
[c] Proximal
[d] Distal

Table 19
Rate of bone loss in the immediate postmenopausal period in prospective studies of healthy women undergoing natural menopause[a]
Note the more rapid rates of loss at predominantly trabecular bone sites (*a* and *b*) compared with a predominantly cortical site (*c*) and with cortical width (*d*)

Site	Technique[b]	Bone loss (% ± SD)
a. Spine	DPA	4.4 ± 4.2
b. Forearm, distal	DPA (^{125}I ^{241}Am)	3.7 ± 1.3
	SPA	3.3 ± 2.34
c. Forearm, proximal	DPA (^{125}I ^{241}Am)	2.8 ± 1.3
	SPA	2.4 ± 1.4
d. Metacarpal	CCW	1.3 ± 1.0
e. Whole body	DPA	3.2 ± 1.6

[a] Based on data from references *84* and *263*.
[b] SPA = single-photon absorptiometry
  DPA = dual-photon absorptiometry
  CCW = combined cortical width

precision error is more favourable in the case of DXA than SPA. The paradoxical situation arises, then, that SPA possibly has greater power than DXA when used for a single measurement to place a subject accurately within a population distribution, but less power than DXA to detect a change over a given period. Indeed, the interval required to detect an average rate of bone loss with confidence by SPA is greater than 2 years depending on the radial site. In addition, rates of bone loss decline several years after the menopause (93, 95) (Fig.15), so that a longer interval between measurements is required to evaluate a given change. The relative performance of several techniques based on the data of Davis et al. (264) is given in Table 20 and is greater for SPA than DPA or QCT. An interval of 5 years is likely to be more than adequate to assess rates of loss in the majority of individuals, but this time is less than optimal for clinical purposes such as assessment of responses to treatment.

The question then arises of the relative importance of rates of loss and peak bone density. If rates of loss are important, this implies that the use of sequential measurements of bone density would improve the assessment of fracture risk. Few data are directly concerned with this issue and there is at present no evidence that the rate of loss contributes to fracture risk independently of low bone mass (30).

Several studies (30, 133, 241) indicate that the major determinant of bone density in later life is peak bone density rather than variable rates of bone loss, at least in the appendicular skeleton. In other words, fracture may be more accurately predicted from assessment of bone mass at appendicular sites than from rates of loss. However, the real question concerns the extent to which the combined assessment increases accuracy. Correlation between bone mass measurements made at the menopause and those made 12 years later is approximately 0.8 (91); thus, 64% of the variance in density measurement at 12 years is attributable to bone density at

Table 20

Relative duration of follow-up required to detect a bone density change with a given level of confidence (SE = 1%)[a]

Site	Technique[b]	Relative time
Radius, distal	SPA	1.00
Radius, proximal	SPA	1.01
Calcaneus	SPA	1.09
Spine	DPA	1.30
Trochanter	DPA	2.57
Femoral neck	DPA	2.67
Ward's triangle	DPA	3.50
Spine	QCT	4.10

[a] Reproduced from reference 264 with the permission of the authors and Springer-Verlag.
[b] SPA = single-photon absorptiometry
  DPA = dual-photon absorptiometry
  QCT = quantitative computed tomography

Figure 15

Average rates of bone loss in postmenopausal women assessed at cortical sites (mid-radius, metacarpal) or predominantly cancellous sites (spine, distal radius), calculated from a literature survey
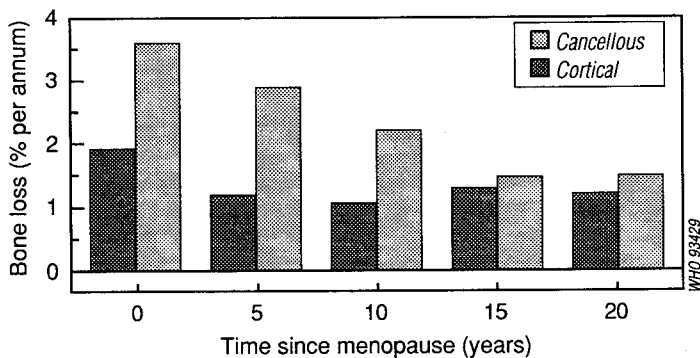
menopause. The remaining 36% may be explained on the basis of precision errors (say 6%) and differential rates of bone loss. However, it is to be expected that, if rates of bone loss vary markedly between individuals, rate of loss would assume progressively greater importance with time: the longer the interval between menopause and a second assessment, the larger the effect of bone loss. Thus, assessment of losses becomes progressively more important with advancing years, in parallel with the increasing risk of fracture. By the age of 70, the contributions of initial mass and rates of loss approach statistical equality (*75*), but the errors of repeated measurements are greater so that a minority of the variance is accounted for by bone loss. Similar conclusions are derived from studies of cortical width. In a prospective study, the correlation coefficient between cortical area of the second metacarpal in women entering the study aged 40–49 years and the value 20 years later was 0.82 (*133*). This suggests that less than 30% of the variance in the age range 60–69 years could be accounted for by differential rates of loss.

As regards the extent to which ultimate losses can be predicted from losses around the time of menopause, present evidence suggests that knowledge of losses over the first 5 years will improve the estimate of ultimate bone density by about 50%. Similar conclusions are derived from mathematical models (*265*); it has been estimated that 31% of hip fracture cases would occur in individuals in the highest quartile of bone loss, compared with 20% in those in the lowest quartile. Unfortunately, the duration of prospective studies of bone loss is relatively limited (12 to 20 years) compared with the latency of many osteoporotic fractures. There is therefore no direct information available to assess the degree to which predictive value would improve with an assessment of rates of loss measured over 5 or 10 years in addition to an assessment at the age of menopause in the very elderly. This is an important area of research to develop.

These uncertainties do not necessarily mean that a repeated measurement of bone density might not form a component of screening methodology. Prevailing bone density predicts future fracture risk at both 70 and 50 years of age, and the later determination will provide an improved estimate of risk, irrespective of the losses. The possible use of repeated measurements is considered further in section 7.

4.2 Biochemical indices of bone turnover

A number of biochemical markers of bone turnover have been identified (Table 21). Bone resorption can be indirectly assessed from the excretion of calcium and hydroxyproline in the urine. Measurements are made on a sample of urine taken in the post-absorptive state (after an overnight fast) which diminishes the effect of these dietary sources. The concentration of calcium or hydroxyproline in the fasting urine is divided by the concurrent creatinine concentration to avoid the need for timed collections. Plasma concentrations of tartrate-resistant acid phosphatase, particularly the osteoclast-derived fraction (267), and measurement of fragments of bone matrix proteins such as the deoxypyridinoline cross-links (268, 269), hydroxylysine glycosides or fragments of non-collagenous proteins, released during resorption, may provide new, more specific resorption parameters in the future (270).

The most widely used biochemical method for assessment of bone formation is determination of the plasma activity of total alkaline phosphatase, which is derived in part from bone-forming cells. This measurement is not specific, since serum activity of alkaline phosphatase includes activity from other sources. In health, the bone-related fraction constitutes about 50% of total activity; the remainder comes from a liver-

Table 21
Biochemical markers of bone turnover[a]

Formation	Resorption
Total alkaline phosphatase	Tartrate-resistant acid phosphatase
Skeletal alkaline phosphatase	Free gamma-carboxyglutamic acid
Osteocalcin (bone Gla-protein)	Fragments of non-collagenous
Procollagen type 1 extension peptides	protein (?)
α_2 HS glycoprotein	Total and dialysable hydroxyproline
Other noncollagenous bone proteins (?)	Hydroxylysine and its glycosides
	Pyridinoline and deoxypyridinoline
	(collagen cross-links)
	Proline immunopeptidase

[a] Reproduced from reference 266 with the permission of the author.

derived fraction together with a small intestinal fraction. The measurement of total alkaline phosphatase is widely available and precise and, if other conditions known to be associated with high serum concentrations of total alkaline phosphatase can be excluded, indirectly reflects the rate of bone formation. Methods to determine the osteoblast-derived fraction of alkaline phosphatase are currently being developed and will eventually increase the specificity of the measurement. Osteocalcin (or bone Gla protein), a bone-specific protein, is produced solely by osteoblasts and in osteoporosis provides an index of bone formation. It has been shown to be a more sensitive marker of bone formation than serum alkaline phosphatase in the clinical investigation of osteoporosis.

Several other markers of bone formation have been developed, such as assays for procollagen fragments. These are valuable research tools but more information is required before their value in the assessment of bone loss can be known with certainty (271). The value of residual postmenopausal estrogen or sex hormone binding globulin is poor in predicting fractures or rates of bone loss (272).

4.3 Biochemical estimation of rates of bone loss

At the menopause, biochemical estimates of both bone resorption and formation increase significantly, by about 30-100% (273, 274), and decrease after HRT (275, 276). The large changes in these parameters, together with the low precision errors of their measurement in the laboratory (5-10%), have been the basis of arguments that they can be used to assess rates of bone loss. The rapid assessment of skeletal metabolism would have particular clinical relevance in allowing treatments to be targeted at reducing bone turnover and in assessing the response to any form of treatment.

The precision error of laboratory measurement is less relevant than the long-term reproducibility of these indices in patients or normal individuals. The available evidence suggests that errors of the order of 30-40% occur *in vivo* (277). Thus, the ratio of reproducibility error to the changes seen at the menopause is no more favourable than is the case for bone density measurements. The great potential advantage of biochemical assessments therefore lies in the avoidance of repeated determinations. In the context of screening, biochemical assessment would avoid the need for repeated measurements spaced over several years and so permit more timely clinical decisions.

The sensitivity and specificity of each of the markers of bone loss is variable, but low. However, multivariate analysis of a panel of markers offers greater accuracy than a single measurement. As expected from knowledge of bone remodelling, an increase in resorption precedes the increase in formation, so that information on both these aspects improves estimates of rates of loss. The analytes shown to be of value are serum activity of alkaline phosphatase, serum osteocalcin, and the fasting

calcium/creatinine and hydroxyproline/creatinine ratios in urine. Pyridinoline cross-links provide similar information to hydroxyproline, but the assays are generally more difficult to perform; however, certain more recently developed cross-link immunoassays are simpler and are at present the subject of research and biological validation (278-280).

Clinical evidence suggests that rates of bone loss can be predicted from a panel of biochemical estimates in the early postmenopausal years (91, 92, 281, 282), because indices of resorption increase to a greater extent than those of formation with estrogen deficiency (273). The use of panels of biochemical indices has been tested prospectively over a 12-year period in postmenopausal women (91). The investigators have characterized 25–30% of these early postmenopausal women who lose more than 3% of bone mass per year as "fast" bone losers, and the remainder as "intermediate" or "slow" bone losers. Biochemical estimates of bone turnover are significantly higher in fast bone losers than in others. This indicates that the higher the level of bone turnover, the greater the increase in bone resorption compared with bone formation. By combining the biochemical estimates of bone turnover, for instance the fasting urinary calcium/creatinine ratio, the fasting urinary hydroxyproline/creatinine ratio, plasma alkaline phosphatase, and serum osteocalcin, it is possible to estimate the future rate of bone loss with reasonable sensitivity and specificity. Thus 80% of the women can be correctly characterized as fast or slow bone losers (true positives, true negatives) (see Fig.16). A number of other potential markers of bone turnover are currently being evaluated (269, 276) which may increase still further the specificity and sensitivity of this approach to the assessment of bone loss.

Figure 16
Observed (obs) bone mineral content (BMC) at baseline (1977) and 12 years later (1989) compared with the levels predicted (pred) by baseline bone mass and biochemical tests for slow, intermediate and fast losers of bone in the postmenopausal period[a]
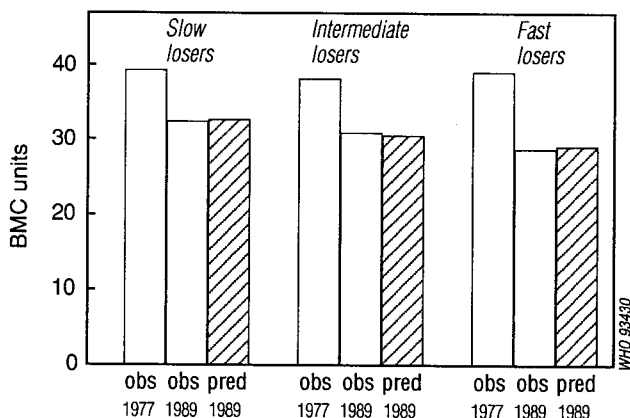
[a] Modified from reference 91 with the permission of authors and publisher.

The interpretation of biochemical markers (and bone mass) clearly depends upon the timing of the sample with respect to the interval since menopause, since rates of loss are greatest in the immediate postmenopausal period (93, 95). Indeed, the categorization of fast and slow losers has been criticized when no account is taken of the timing of the menopause (283). In the elderly, for example, in whom bone loss is slower, there are small differences in these measurements between patients with or without hip fracture (284, 285). For purposes of screening at the menopause, it has been shown that biochemical markers can predict the change in bone mineral density for up to at least 12 years after the menopause (91). The degree of correlation between bone loss measured directly at the forearm and that judged indirectly by biochemical tests is between 0.70 and 0.77. This suggests that the biochemical tests have an efficiency of about 50% compared with direct sequential measurements of bone mass and are therefore likely to improve the stratification of fracture risk. Whether biochemical measurements can aid in the prediction of fracture risk is not yet known. Data are likely to be available within the next few years (C. Christiansen, 1992 – personal communication); until then, the value of biochemical measurements as an element of screening will be difficult to quantify, but remains an important area of further research.

4.4 Recommendations for research

1. Large-scale prospective studies are needed to document rates of bone loss at different skeletal sites throughout pre- and postmenopausal life and to study the relationships of peak bone mass, bone loss and osteoporotic fracture.

2. There is a continued need to develop specific and sensitive biochemical markers of skeletal turnover. Their use in screening will demand studies of validation and applicability, in particular ease of assay and quality control.

3. There are obvious potential advantages in adding biochemical assessments of bone loss to measurements of bone density in determining fracture risk. Prospective cohort studies, over many years, are required to assess the improved accuracy that results in predicting bone loss at different skeletal sites and in predicting fracture risk.

5. Clinical assessment of risk

A number of studies have assessed risk factors for low bone density measured at various sites (286–289), while others have evaluated risk factors for fractures apart from bone density (32, 290-295). Lists of risk factors and protective factors have been drawn up (Tables 22 and 23), and the use of such factors to identify high-risk individuals (296), bone structure, formation and disease (4, 297, 298) is frequently advocated. In several instances, there is a clear relationship between these risk factors

and low bone density or other causes of osteoporotic fracture (see Table 5). It may be that historical risk factors of this sort could be usefully applied in the identification of individuals at risk.

Table 22
Factors that have been associated with reduced risk of osteoporotic fracture

Negro race
Muscular strength
Osteoarthrosis
Lactation
Multiparity
High calcium intake
Moderate exercise
Obesity
Fluoridation of drinking-water
Some drugs
– estrogen
– thiazide diuretics
– calcium supplements

Table 23
Factors that have been associated with increased risk of osteoporotic fracture in women

Age
Primary amenorrhoea (e.g. in Turner syndrome)
Secondary amenorrhoea (e.g. in athletes, anorexia nervosa, prolactinoma)
Anovulatory menstrual cycles
Premature menopause
– idiopathic
– surgical oophorectomy
– hysterectomy (with ovarian conservation)
Nulliparity
Prolonged immobilization and inactivity
Race – Caucasian or Asian
Smoking
Alcohol abuse
Lack of physical exercise
Nutritional factors (low calcium intake, high caffeine, protein, fibre or sodium intake)
Some drugs
– corticosteroids
– anticonvulsants
– prolonged heparin infusions
– thyroxine
Certain diseases[a]
Low body mass index
Positive family history
Prior fragility structure
Short stature and small bones

[a] For complete list, see Table 5.

5.1 Gonadal status

The mean age of menopause is approximately 50 years, and a premature menopause – whether natural or surgically induced – will extend the time for which a women is exposed to a hypogonadal state (*299*). There is some evidence to suggest that the menopause is accelerated in some women who undergo hysterectomy and perhaps tubal ligation, even though the ovaries are left in place. Similarly, late menarche and primary or secondary amenorrhoea will also increase the risk of osteoporosis (*300*), and more subtle abnormalities of menstrual function may also contribute to low bone mineral density (*301*). Hypogonadism also occurs in a small proportion of men and may lead to bone loss (*302*) and fractures (*303*).

Postmenopausal women are capable of producing adrenal steroids, of which androstenedione is converted to estrogens in adipose tissue. This may explain why thin women are at greater risk than their plumper counterparts, and possibly why smoking, which decreases appetite and body fat, is a risk factor (*304*). There may, however, be additional factors related to smoking, and there is some evidence that it may accelerate the peripheral metabolism of exogenously administered estrogen (*305*).

5.2 Other disorders

The term "osteoporosis" implies a decrease in the amount of bone tissue without a change in its quality. This distinguishes it from osteomalacia (defective mineralization of bone) due, for example, to vitamin D deficiency. Vitamin D deficiency may coexist with, and aggravate, osteoporosis, particularly in the elderly, because of secondary hyperparathyroidism (*306, 307*). Many other disorders may also contribute to bone loss (see Table 5); the more important of these include endocrine disorders such as hyperthyroidism, hyperparathyroidism, insulin-dependent diabetes mellitus and Cushing disease (*308*). Myelomatosis may be present with osteoporotic crush fractures. Rarer causes of osteoporosis include osteogenesis imperfecta, malabsorption, chronic renal failure and some drugs. All these disorders are comparatively rare and therefore have relatively little impact upon any general screening strategy. They do, however, provide a clinical indication for bone density assessment in affected individuals (see section 7).

5.3 Other factors

A number of other factors are associated with a decreased or increased risk of osteoporosis. Immobility (or, more correctly, the loss of gravitational stresses) is an important cause of bone loss, and of concern for prolonged space flight as well as for osteoporotic women. A woman immobilized for 1 month can lose more bone than she would normally do in 1 or 2 years of the osteoporotic process (*309, 310*). It follows that women with a sedentary lifestyle are probably at greater risk of bone loss, and it has been postulated that an increasingly sedentary lifestyle explains the

increase in the age-specific increase in fracture rates in both men and women.

The negro races have less osteoporosis and fewer fractures than Caucasians because of greater skeletal mass. A family history of osteoporosis may be important and there is some evidence for a genetic component to peak bone mass (*311-315*). Drugs such as corticosteroids and thyroid replacement treatments increase the risk of osteoporosis, as does excessive alcohol consumption. Cigarette smoking is perhaps a risk factor for a number of reasons: female cigarette smokers are thinner than non-smokers, have an earlier natural menopause, and may catabolize exogenous estrogen more rapidly. As in the case of high alcohol consumption, cigarette smoking in itself may inhibit osteoblasts.

The role of nutrition is perhaps the most controversial area in the causation of osteoporosis. It is widely believed that inadequate calcium intake throughout life is an important risk factor (*61, 316*). The recommended dietary allowance of calcium for adults is 500 mg daily in the United Kingdom (but higher in some other countries) and a substantial proportion of the at-risk population consumes less than this. Some workers, however, believe that dietary calcium has little effect, and indeed there is a lack of convincing evidence that bone mass at the menopause is affected by the amount of calcium intake in earlier life (*266*). Nevertheless, there is probably a therapeutic role for calcium as a pharmaceutical agent in delaying bone loss in the elderly (see section 6). Other nutritional factors include caffeine and alcohol consumption and diets high in protein and phosphate, but there is only circumstantial evidence linking these with osteoporosis.

Undernutrition in the elderly is commonly reported (*317-319*) and may contribute to bone loss, the risk of falling or the response to injury (*320, 321*). Nutritional intervention appears to affect favourably the prognosis of patients with hip fracture (*322-324*).

Most risk factors relate to bone density and in turn to gonadal status, but decreased bone density or skeletal mass and reduced gonadal function are not the sole causes of fracture. Additional factors affecting bone strength are the destruction of trabecular architecture, bone turnover, trauma and the neuromuscular response to falls (*321*). The clinical identification of those factors not directly related to bone mass may aid in screening to target preventive interventions.

5.4 Application of clinical assessment

Many of the factors implicated in the causation or aggravation of bone loss are derived from retrospective epidemiological studies comparing individuals with and without fracture. In observational studies of this type, the effect of confounding variables is uncertain. A good example is caffeine consumption, where causality is inferential and would need to be validated by prospective studies (*325*). Apart from age, sex and race, many of the risk

factors identified thus far, such as hyperparathyroidism and Cushing disease, are comparatively rare and their value for use in screening is correspondingly low. In a large retrospective survey of hip fracture cases, the impact of all identifiable risk factors, including height and weight, was small (The Mediterranean Osteoporosis (MEDOS) Study – unpublished results). One important predisposing factor, however, is a prior fragility fracture. In one study, individuals with a fragility fracture and high bone mass had a 10-fold greater risk of fracture than controls; the increase in those in the lowest tertile for bone mineral was 3-fold for the spine (65). Somewhat lower values (2-fold increases) are reported from the United Kingdom for other fractures (326). None the less, fracture occurrence is a late indicator of risk and might not be optimal for use in a screening programme if this risk factor were used at the time of the menopause.

More importantly, several studies have found that information on historical risk factors does not predict bone mass with sufficient precision to be useful in the assessment of fracture risk or bone mineral density of individuals (91, 327). For example, Slemenda and colleagues (328) identified predictors of bone mineral at various sites and then compared predicted values at those sites with observed results. For mineral density of the femoral neck, the best predictive model accounted for only 17% of the variability in bone mineral measurements at the hip and correctly classified only 65% of the perimenopausal women whose bone mass was in the lowest tertile (Fig.17). Comparable models correctly classified 68% of women with low bone mineral content at the mid-radius and 61% of those

Figure 17
Observed femoral neck bone mineral density (BMD) plotted against risk factor score[a]
Note: A higher score denotes a lower apparent risk.
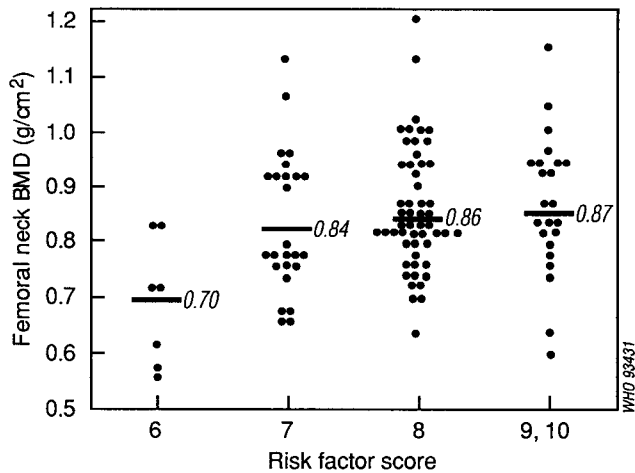
with low bone mineral density at the lumbar spine. This level of precision is inadequate for patient care and for screening, since bone mineral can be measured directly with fewer errors of classification. Similar conclusions are reached in other studies examining the power of risk factors to account for differences in bone mineral density (*133, 247, 286, 327, 329-331*).

Combinations of risk factors are also of limited value in predicting fractures in individuals. In the Netherlands, a risk factor score was able to discriminate among 1014 women aged 45-64 years who did and did not have subsequent fractures over 9 years of follow-up, but sensitivity (37-48%) was low and specificity (83-84%) modest (*332*). The lack of specificity was demonstrated further in a study by Wasnich and colleagues (*333*), in which prediction of vertebral fractures from various risk factors among a group of 704 Japanese-American women was not possible (Table 24). Similarly, the positive predictive value of a high risk factor score was only 9-17%, depending on the cut-off value used, in identifying vertebral fractures among 1012 women in the United Kingdon (*9*), and most of that modest predictive power was contributed by a history of prior vertebral fracture. Thus the specificity and sensitivity of risk factors are too low to be of great clinical value.

These conclusions, however, relate primarily to the use of clinical risk factor assessment in the perimenopause; different considerations may apply in later life. Thus, the relative risk of hip fracture is high in patients who have already sustained an osteoporotic fracture (*65, 326*). There is good evidence that interventions late in the natural history of bone loss can still significantly reduce the risk of future fracture, which would justify screening in the elderly. If this is so, clinical risk factor analysis may assume greater importance than has hitherto been recognized.

Table 24
Risk factor prevalence and relative risk of spine fracture in a group of Japanese-American women[a]

Risk factor	Prevalence (%)	Relative risk	P-value
Premature menopause (age ≤40)	4.7	1.6	NS
Family history	1.7	2.7	NS
Short stature (≤ 1.55 m)	87.2	1.6	NS
Leanness (body mass index ≤ 19.7)	14.7	1.7	NS
Calcium deficiency (intake ≤ 500 mg/day)	83.9	1.2	NS
Physical activity (index ≤ 26.9)	7.8	2.5	NS
Nulliparity	5.7	1.6	NS
Smoking	16.8	1.2	NS
Alcohol (≥2 g/day)	4.8	1.7	NS
Asian ancestry	100.0	—	—
Caffeine (≥ 300 mg/day)	29.6	2.1	NS
Chronic gastrointestinal disease	4.1	1.0	NS

[a] Modified from reference *333* with the permission of the publisher.

5.5 Recommendations for research

1. Prospective studies to test the causality of many putative risk factors are important, even though their role in screening is limited.

2. Studies of risk factors in the elderly are required particularly where the sensitivity and specificity of clinical risk factor scores may be greater than in mid-life.

3. Assessment of many risk factors is problematic; examples include lifetime dietary habits, and the type and degree of exercise. There is thus a need to develop and validate the assessment of risk factors.

6. Risks and benefits of intervention

The assessment of risk of osteoporotic fracture needs to be placed in the context of the power of therapeutic intervention. This section gives some indication of the efficacy of currently available interventions, notably HRT, and considers their side-effects in postmenopausal osteoporosis.

6.1 Primary prevention

The primary aim of intervention in osteoporosis is to prevent fractures; this may be achieved by increasing bone mass at maturity, by preventing subsequent bone loss, or by restoring the bone mineral and architecture in an otherwise osteoporotic skeleton. Theoretical calculations indicate that a relatively small increase in average bone mass would be associated with a sizeable reduction in fracture risk (Fig. 18). As reviewed previously, peak bone mass is influenced by environmental as well as genetic factors, and it is argued that bone mass at skeletal maturity might be improved by exercise, avoidance of smoking and prolonged immobilization, and the recognition of and attention to estrogen-deficiency states. More controversial is the role of dietary manipulation to increase the intake of calcium, proteins and other nutrients. Although the precise role of these factors is conjectural (266), it is important to recognize that non-hormonal (i.e. non-estrogen-dependent) factors account for the large interregional differences in the incidence of osteoporosis, since they affect both men and women. Similarly, the secular increase in the incidence of hip fracture observed in many European countries has been observed in men as well as women.

These observations suggest that lifestyle factors are of great importance in determining bone mass and consequently the risk of osteoporotic fractures (335). The most plausible lifestyle factor is exercise (336, 337): in the United Kingdom for example, food consumption has decreased over the past 20 years, whereas body weight has not changed significantly, which indicates a decrease in energy expenditure (266). Since exercise is of proven benefit in other conditions such as cardiovascular disease, attention to lifestyle factors may be a most important component of

Figure 18

Relationship between bone mineral density (BMD) of the femoral neck and the incidence of hip fracture[a]

The left-hand panel shows the change in mean BMD with age in postmenopausal women (●—●) and the increase in BMD at each age that is theoretically needed to reduce the corresponding incidence of hip fractures by half (○—○). The right-hand panel shows the age-specific incidence of fractures of the femoral neck (●—●) and the reduced incidence (○—○) that would be expected if the mean BMD were increased as shown in the left-hand panel.
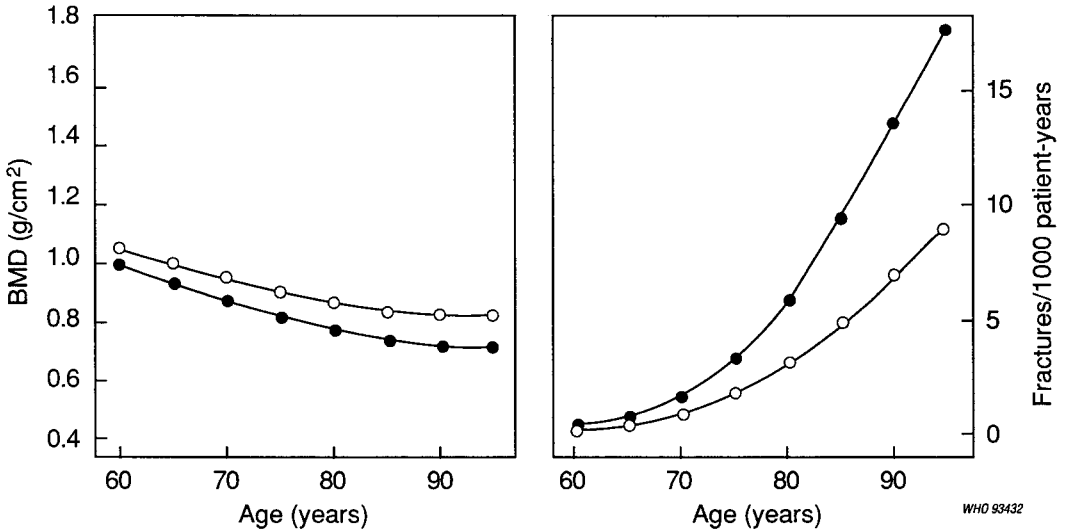
[a] Based on data from reference *334* by permission of *New England journal of medicine.*

general health measures, even though its efficacy in decreasing the incidence of fracture is unknown. Which exercise regimen would be most effective in optimizing bone mass is also unknown, and this is an important area for further research.

Whereas improved nutrition and increased exercise could be promoted in the population, there is little justification for adopting bone density measurements to assess risk in childhood or young adulthood as part of a national health care policy. This is not to say, however, that such measurements would not be useful in selected individuals; indeed, the converse is true, and bone density measurements may be a useful but minor component of case-finding among young individuals (see section 7).

6.2 Prevention of bone loss

Much work has been done on the assessment of interventions that prevent bone loss, particularly HRT at the time of the menopause. A detailed assessment of the risks and benefits of HRT is beyond the scope of this

report and is the subject of several reviews (*338–340*). However, it is inappropriate to ignore the risks and benefits of intervention, since they have critical implications for screening strategies. In addition, a number of non-HRT interventions are used in the prevention of osteoporosis, but have generally been ignored by those considering screening (*7, 11*). They are also considered, since HRT is not universally acceptable, and the arguments relating to the power of screening are fundamentally different from those concerned with HRT.

6.3 Hormone replacement therapy

The term hormone replacement therapy – or HRT – is used generically in this report to denote the use of estrogens, either alone or in combination with progestogens. Where it is necessary to distinguish between estrogen alone and estrogen combined with progestogens, this is made explicit; such distinction can be important, since much of the thinking concerning the risks and benefits of HRT is significantly modulated by the choice of regimen. These considerations are least complicated in the case of the effects of HRT on osteoporotic fractures.

6.3.1 *Effects on bone*

Much evidence from prospective studies indicates that the use of HRT will prevent bone loss at the menopause and thereafter (*341–347*). In some women, the doses required to prevent bone loss are higher than those required to treat menopausal symptoms. The dose of conjugated estrogens that prevents bone loss is 0.625 mg/day, but response to this dose is variable.

Generally, estrogens prevent bone loss completely, irrespective of when in the course of osteoporotic bone loss they are given (*345, 346, 348–350*). On the assumption that bone loss resumes at the expected rate when treatment is stopped, the effects of HRT on fracture rates would be marked. Thus, HRT taken for 10 years following the menopause would defer the risk of fracture with age by 10 years. Calculations based on this premise suggest that the risk of hip fracture would be reduced by more than 50%, and epidemiological data support this view.

Case-control and cohort studies consistently report that HRT reduces the risk of hip fracture in perimenopausal and postmenopausal women (*351, 352*). The pooled estimate of the relative risk of hip fracture comparing estrogen users with non-users is 0.7 (95% confidence interval, 0.6–0.8) (*340*). Some evidence indicates that the risk of hip fracture decreases with increasing duration of estrogen use. Progestogen therapy alone prevents bone loss and several studies have found that the combined estrogen-progestogen regimens also prevent loss (*346, 353, 354*). Limited epidemiological data suggest that progestogens do not adversely influence the effects of estrogens on hip fracture (*355*). There is thus no evidence that adding a progestogen to the estrogen regimen adversely affects the protective effect of estrogen against osteoporotic fracture.

There is a major uncertainty as to whether the effects of HRT persist or whether "catch-up" bone loss occurs (7, 8, 339). This is an important issue since HRT is commonly recommended for up to 10 years but the vast majority of fractures occur after the age of 70 years, i.e. two decades after the average age of menopause. Since hip fracture occurs mainly after this age, a relatively short-term exposure to HRT (e.g. 10 years) would have significant beneficial effects on fracture risk only if the effects were long-lasting. Most direct evidence suggests that bone that has been preserved is not rapidly lost when estrogen treatment is stopped and that bone loss that recurs after treatment is stopped takes place at the same rate as it did immediately before therapy was instituted. One early report that assessed bone density in oophorectomized women did suggest that catch-up bone loss occurred after treatment ceased (356), but this has not been observed in other studies (344) (R Lindsay, 1992 – personal communication). The absence of catch-up loss has recently been confirmed in a 7-year follow-up of women after cessation of HRT (238); the amount of bone saved during the estrogen therapy is saved for at least 7 years and probably much longer.

Indirect evidence also suggests that the estrogen effect may persist for as long as 25 years. Studies of osteoporotic fracture rates after the age of 50 years show that rates increase in women compared with men. The excess female morbidity is apparent up to the age of 75 years and then tails off (36). This is consistent with observational studies of the effects of estrogen on hip fracture risk with age (357).

Several epidemiological case-control studies have shown that, although the protective effects of estrogens on the risk of hip fracture persist into extreme old age, the effects are less than those in younger individuals more recently exposed to estrogens (7). One study has suggested that the risk of hip or forearm fracture in women who discontinue estrogen therapy returns to near basal values 6 or more years after the cessation of treatment (348). Other reports also show this decreased effect (357, 358). It is important to recognize that these studies have not shown a significant change in fracture risk as a function of time after stopping treatment.

A persistent effect of estrogens is plausible and supported by prospective evidence. However, there is an apparent discrepancy between the conclusions derived from epidemiological research and those from clinical research. Epidemiological data are retrospective case-control or observational studies in the elderly, which take no account of deaths since those who die are not available for investigation. In view of the increased co-morbidity and the higher death rate of osteoporotic individuals (359, 360), it is to be expected that the relative risk of hip fracture among estrogen users would be lower the more elderly the population. The case for a transient effect of estrogens thus appears to be weak, but is an important area for further research.

6.3.2 *Coronary heart disease*

The incidence of coronary heart disease is relatively low in premenopausal women, but increases steadily after the menopause. The relationship between cardiovascular disease and loss of ovarian function is well established (*361-364*) but the underlying mechanism is not.

Systematic reviews of the literature reveal fairly consistent evidence that estrogen therapy reduces the risk of coronary heart disease by about 30-50%, but the data are derived from observational studies that are subject to bias (*365*). Because the apparent protective effects of estrogen might lie in the fact that more healthy women take estrogen (*366-368*), it is important to confirm the degree of benefit in randomized controlled trials. The oral dose of conjugated estrogen used in most of the studies that have shown protection from coronary heart disease is 0.625-1.25 mg daily. There are insufficient data to determine the optimum duration of estrogen treatment to prevent coronary heart disease.

Serum lipoprotein concentrations are a strong risk factor for coronary heart disease in women. Estrogen therapy has been shown to reduce serum LDL-cholesterol and to increase serum HDL-cholesterol in a dose-dependent fashion (*369, 370*).[1] Several progestogens attenuate the beneficial effect of estrogen on lipoproteins, raising the concern that the addition of progestogens may negate some of the cardioprotective effects of estrogen therapy (*371, 372*). The extent to which the beneficial effect of estrogen on lipoproteins is reversed depends on the type, dose and duration of progestogen use (*373*). The C-21 progestogens such as medroxyprogesterone acetate have fewer side-effects and less unfavourable effects on lipoproteins than the C-19 progestogens (*374-376*). In addition, the intermittent use of progestogens has few long-term consequences on lipid profiles, in that the acute changes are ill sustained (*370*).

Changes in lipoproteins may not be the sole mechanism by which estrogens reduce cardiovascular risk. Several experiments on monkeys and rabbits fed atherogenic diets have shown that estrogen protects against the development of atherosclerosis. A combination of estradiol and progesterone had no effect on HDL and total cholesterol, but appeared to protect against the development of atherosclerosis as effectively as estrogen alone (*377-379*). Moreover, several clinical studies have determined the effect of estrogens on coronary heart disease risk after adjusting for changes in lipids; less than half of the reduction in risk by estrogen treatment was accounted for by changes in lipids (*371, 380, 381*).

These observations suggest that any adverse effects of progestogens on coronary heart disease risk are likely to be small, and much smaller than the beneficial effects of estrogens. Only two studies in women have directly

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[1] LDL = low-density lipoprotein; HDL = high-density lipoprotein.

assessed the effects of treatment with estrogen plus a progestogen on cardiovascular risk. One small, randomized, controlled trial demonstrated a substantial but non-significant reduction in relative risk (*382*). A larger study suggested that the degree of protection appears to be as great as that observed in women taking estrogen alone (*383*). These data suggest that the risk of coronary heart disease is reduced among women taking estrogen plus a progestogen, but there are inadequate data to determine whether this protective effect is as great as that of estrogen, alone.

The effects of HRT on ischaemic heart disease have significant implications for screening strategies. The greater are the benefits of HRT for cardiovascular risk, the poorer is the case for targeting intervention on the basis of bone mineral density. One study (*251*) showed that more quality-adjusted life-years would be saved by the universal use of HRT at the menopause (and the cost less) than with a programme of HRT use in high-risk women identified by screening for bone mineral density (17% of the population, 15-year treatment) if the risk for coronary artery disease decreased by 25% or more in treated women.

6.3.3 *Endometrial cancer*

The effects of estrogens on endometrial cancer are well established and reviewed elsewhere (*384-387*). From pooled estimates, relative risk of endometrial cancer in women who have used estrogen at some time compared with those who have never used estrogen is 2.4 (S. Cummings, 1992 – personal communication). Risk increases with increasing duration of estrogen use, but the effects on mortality are less certain (*388*). Although epidemiological evidence is limited, histological and clinical data suggest that the addition of a progestogen to the estrogen regimen prevents the increase in endometrial cancer risk provided that the dose and schedule of progestogen therapy are adequate to prevent endometrial hyperplasia (*389, 390*). Four prospective studies have examined the effects of combined estrogen/progestogen therapy on endometrial cancer risk (*382, 391-393*): none has shown an increased risk (compared with non-users), but the data are very limited.

6.3.4 *Breast cancer*

The view that estrogen therapy is associated with an increased risk of breast cancer is plausible, but the findings are inconsistent. There have been at least 24 case-control studies of estrogen therapy and breast cancer risks since 1970; three recently published analyses of these studies found no overall increased risk for breast cancer among women who had ever taken estrogen compared with women who had not (*394-396*). Studies that have evaluated the effect of long-term estrogen use have also produced conflicting results. Many show a small increase in risk among women who have taken estrogen for the longest duration, whereas others do not. A recent meta-analysis suggested that 15 years of estrogen use might increase the risk of breast cancer by as much as 30% (relative risk 1.3, 95%

confidence intervals 1.2-1.6) (*396*). No increase in mortality from breast cancer has been shown (*397, 398*). It seems plausible that predisposition to breast cancer is established in early life and that HRT might accelerate its development.

It is notable that the risk of breast cancer in healthy women increases progressively with age, but that the rate of this increase is attenuated at about the time of the menopause. Thus, any increased relative risk of breast cancer in women receiving HRT may reflect no more than their continuing estrogen status. This notion is consistent with the observed increase in risk of breast cancer in women with late menopause. Data for the effects of combined estrogen/progestogen therapy on the risk of breast cancer are too limited to yield a pooled estimate of the effects.

It is important to consider the impact on screening of various assumptions concerning breast cancer risk. The greater the extraskeletal risks of HRT, the less appropriate it is to screen the population on the basis of bone mineral density to target HRT without a concurrent evaluation of breast cancer risk. However, computer modelling suggests that an increased risk of breast cancer of 25% with a 15-year treatment does not markedly affect the incremental cost-effectiveness of screening and treating 17% of the female population (*251*) compared with the effects of universal use of HRT. Opposite conclusions are derived in the case of coronary heart disease (see above), where small changes in cardiovascular risk have more marked implications for the benefits of HRT.

6.3.5 *Cerebrovascular disease*

There is some evidence that estrogen reduces the risk of stroke in women (*399-401*), but no information on the effect of combined estrogen/progestogen regimens. Further work on this aspect of hormone therapy is crucial because stroke is a relatively common disorder among postmenopausal women.

6.3.6 *Overall risks and benefits of HRT*

Most of the information on the risks and benefits of HRT have been derived from observational studies. Women who elect to take HRT are known to differ in many important respects from those who do not (*365*), and data analysis can take account only of known or quantifiable biases. Moreover, there is likely to be a significant bias in the literature in that negative studies are less likely to be accepted for publication. This may result in an overestimate of both the apparent risks and the apparent benefits. With all these limitations, a number of studies have assessed the overall benefits and risks of HRT (*339*), but they are beyond the scope of this report. Under most assumptions, however, the perceived benefits outweigh the risks, in terms of both mortality (Table 25) and morbidity (*251, 400, 402*). Because of the many and varied effects of HRT, it is apparent that the benefits will differ according to the type of population exposed. For example, women who have had hysterectomies have no need

for combined preparations and are therefore not exposed to any potential risks of added progestogens. Moreover, women with a high risk of coronary heart disease may have more to gain in terms of morbidity and life expectancy than women at risk from hip fracture (*340, 403*) (Table 25). These considerations suggest that HRT should probably be recommended for women who have had hysterectomies and probably also for those at high risk of coronary heart disease. In women with coronary heart disease who have not had hysterectomies, treatment with estrogen alone is likely to cause a large increase in lifetime probability of endometrial cancer. Because this is unacceptable to physicians in some countries, a combined estrogen/progestogen regimen is preferred. Even if the added progestogen reduces the beneficial effects of estrogen on coronary heart disease by one-third, women with coronary heart disease will still benefit from a life expectancy increased by about 0.9 years.

These various considerations indicate that targeting the use of HRT cannot be based exclusively on screening for bone mineral density. An extreme example is provided by a consideration of white and black women. It has traditionally been thought that HRT is unnecessesary for black women because their risk of hip fracture is much less than that of white women. However, coronary heart disease is equally common in whites and blacks, and it would therefore be inappropriate to target HRT on the basis of bone mineral assessments alone.

The assessment of women for cardiovascular risk at the age of the menopause is beyond the scope of this report. There might be a case for targeting HRT to segments of the population, although no studies have

Table 25
Net change, according to the presence of risk factors, in life-expectancy for a 50-year-old woman (USA) treated with long-term (15 years) HRT[a]

Risk factors	Life-expectancy (years)	Change in life-expectancy (years)[b]		
		E	E+P[c]	E+P[d]
No risk factors	82.8	+0.8	+0.9	+0.1
With hysterectomy	82.8	+1.0	—	—
History of coronary heart disease	76.0	+1.8	+1.8	+0.9
Risk of coronary heart disease	79.6	+1.3	+1.4	+0.5
At risk of breast cancer	81.8	+0.4	+0.4	−1.0
At risk of hip fracture	82.4	+0.9	+1.0	+0.2

[a] Reproduced from reference *340* with the permission of the publisher.
[b] E = treatment with estrogen alone
 E+P = combination treatment with estrogen and progestins
[c] Assumes that P decreases all risk of endometrial cancer.
[d] Assumes that P additionally decreases cardiovascular benefit (relative risk = 0.8) by one-third, increases the relative risk of breast cancer from 1.3 to 2.0, but has no effect on fracture frequency (relative risk = 0.7).

been undertaken to determine whether women with adverse lipoprotein status at menopause benefit from treatment with estrogens. What is evident is that there is little justification for targeting HRT solely on the basis of bone density measurement. These conclusions might differ depending on a health care policy on HRT. If it were argued that HRT should be offered only to women at high risk of coronary artery disease, the case for bone mineral density screening would be stronger for also treating women at high risk of osteoporotic fracture.

6.4 Non-HRT methods of prevention

Alternative therapies for the prevention of osteoporosis have been studied in less depth than HRT. Until recently, there was relatively little information concerning the effects of intervention on osteoporotic fracture rates (13). Of the many agents known to affect bone metabolism, calcium, calcitonins and bisphosponates are worthy of further consideration; all are available in Member States and are increasingly widely used.

6.4.1 Calcium

Calcium is widely available throughout the world and is the major non-HRT intervention used in osteoporosis (Fig.19). The role of dietary calcium in the attainment of peak bone mass has been controversial, largely because of the inadequacy of experimental techniques applied to its investigation (61, 266), but there are now many studies which indicate that calcium supplements (0.5–2 g daily) can reduce the rate of bone loss at or after the menopause. The effects are less complete than those of estrogens, particularly at the time of menopause when losses are rapid, but several studies indicate that, even here, bone loss may be halved, at least in cortical bone (404–406). The evidence for this has been recently reviewed (266) and is supported by several more recent publications (59, 407, 408).

A number of epidemiological studies reinforce the view that a high dietary calcium intake decreases the risk of osteoporotic fracture. However, individuals who choose high-calcium diets differ significantly from those who do not in terms of their general health, education and other possible confounding factors (266). Epidemiological studies of dietary calcium should be distinguished from those that examine the pharmacological use of calcium. A large retrospective case-control study has shown a significant effect of calcium supplements on hip fracture risk (357). In addition, a controlled prospective study in elderly women showed that calcium and vitamin D_3 significantly reduced the risk of hip fracture (409). Over an 18-month follow up, 151 non-vertebral fractures occurred in the treated group compared with 204 fractures in the placebo group. The decrease in both femoral and other non-vertebral fractures was significant (Table 26). This adds credibility to the retrospective studies and to earlier but less well controlled studies (410) that produced similar results. The findings are of particular interest in that they suggest that the use of calcium and/or

vitamin D, even relatively late in the natural history of osteoporotic bone loss, may have significant benefits in terms of reducing the risk of hip fracture. This has obvious implications for screening on the basis of bone density and the ages at which screening might be appropriate. The risks of intervention with calcium or physiologically appropriate doses of vitamin D are negligible in the institutionalized population who are at particularly high risk (*408, 411*).

6.4.2 *Calcitonins and bisphosphonates*

Like calcium, the calcitonins and bisphosphonates also slow the rates of bone loss. They are currently used more in the treatment of established osteoporosis with fractures than for prevention, but their value for

Figure 19

The pattern of use of bone-active drugs in women aged 50 years or more from 14 centres in six European countries[a]
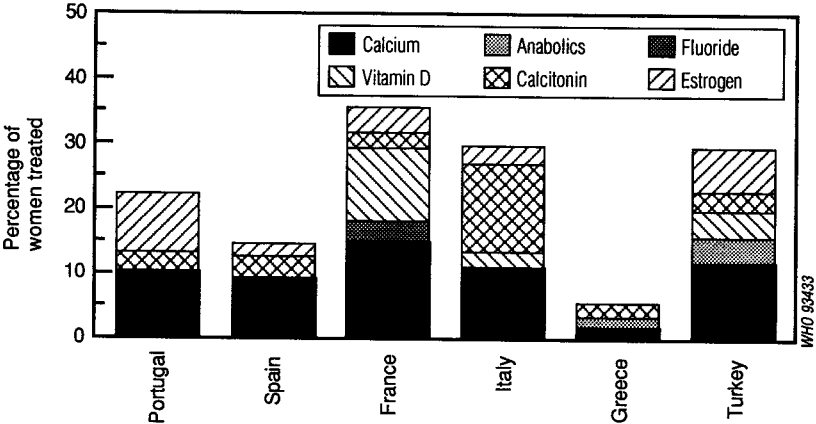
[a] Based on data from reference *357* used with the permission of the publisher.

Table 26

Effects of calcium with vitamin D or placebo on occurrence of extravertebral fractures in 3270 women[a]

There was a significant decrease in femoral and other (non-vertebral) fractures ($P<0.05$ and <0.02, respectively)

Interval & follow-up (months)	Treatment		Placebo	
	All fractures	Hip fractures	All fractures	Hip fractures
0–6	55	30	76	36
6–12	52	24	62	30
12–18	44	19	66	37
0–18	151	73	204	103

[a] Reproduced from reference *409* by permission of *New England journal of medicine*.

prevention is likely to become accepted in the foreseeable future (*412-416*). The long-term effects of calcitonins on bone mass are uncertain, but some beneficial effect probably persists throughout exposure, and serious side-effects are few (*417*). The effects of the bisphosphonates are known to persist for many months, if not years, after treatment is stopped.

The effect of these interventions on fracture frequency has been less well studied, but a decrease in vertebral fracture frequency has been demonstrated with both bisphosphonates (*412, 413*) and calcitonin (*418, 419*). In a case-control study (*357*), calcitonin has also been shown to reduce the risk of hip fractures.

The effects of calcium, calcitonins and bisphosphonates on relative risk of osteoporotic fracture are shown in Table 27, which summarizes a selection of the available data.

Table 27
Effects of non-HRT interventions on relative risk (RR) of osteoporotic fracture

Agent	Study[a]	Control	Fracture	RR[b]	Reference
Anabolics	R	Population	Hip	0.68	*357*
	P	Calcium/			
		alfacalcidol	Spine	0.35*	*420*
Thiazides	R	Population	Hip	0.31*	*421*
	P	Population	Hip	0.65*	*422*
Calcitriol	P	Placebo	Spine	0.35*	*423*
	P	Calcium	Spine	0.51*	*424*
Alfacalcidol	P	Calcium/placebo	Spine	0.46*	*425*
Vitamin D	R	Population	Hip	0.83	*327*
Calcium	P	Population	Hip	0.60*	*426*
	P	Placebo	Spine	0.50*	*410*
	P	Placebo	All	0.48*	*409*
	R	Population	Hip	0.75*	*357*
Etidronate	P	Placebo	Spine	0.41	*412*
	P	Placebo	Spine	0.47*	*413*
Calcitonin	P	Placebo	Spine	0.72	*418*
	R	Population	Hip	0.69*	*357*
	P	Calcium	Spine	0.23*	*419*
Fluoride	P	Calcium	Spine	1.23	*427*
	P	Other agents	Spine	0.75	*428*
	P	Calcium	Spine	0.73	*410*
	P	Calcium	Spine	0.85	*429*
	P	None	Spine	1.40	*430*
	R	Population	Hip	1.31	*357*

[a] P = prospective
  R = retrospective
[b] Asterisks denote significant differences (*P*<0.05).

6.4.3 *Other treatments*

Bone quality may be influenced by vitamin D deficiency, which is common in elderly people, particularly the institutionalized and patients with hip fractures (*306*). Vitamin D deficiency gives rise to secondary hyperparathyroidism, which increases bone turnover and cortical bone loss; in addition, newly formed bone may be less well mineralized, leading to accumulation of osteoid tissue and ultimately to osteomalacia. Histomorphometric data from bone biopsies of patients with hip fracture have been recently reviewed (*307*). Low-dose vitamin D supplements in elderly people improve vitamin D status, suppress parathyroid hormone function and reduce bone loss (*15, 306, 431*). The risks of osteomalacia and of hip fracture, which are, again, particularly high in institutionalized elderly patients, are an important target for preventive measures. The combined use of vitamin D_3 with calcium has been shown to decrease the risk of fragility fractures (*409*).

The risks associated with low-dose vitamin D supplementation are very small, especially in the elderly (*306*). Exceptions are cases of sarcoidosis and idiopathic hypercalciuria, in whom increased formation of 1,25-dihydroxyvitamin D may give rise to hypercalciuria and hypercalcaemia (*432*). The risks of inadvertent hypercalcaemia are much greater with the use of the 1α-hydroxylated derivatives of vitamin D such as calcitriol and alfacalcidol.

Vitamin D status may also be improved by exposure to sunshine and ultraviolet irradiation. However, the irradiation required to produce a given amount of vitamin D is at least three times as high in elderly people as in young adults because of the decreased capacity of the skin for vitamin D synthesis (*433*). Moreover, excessive sunshine exposure increases the risk of skin cancer.

Several other interventions appear to benefit patients, including the vitamin D derivatives alfacalcidol and calcitriol (*425, 434*), thiazide diuretics (*421, 422, 435*) and sodium fluoride (*429, 436, 437*). Their use is generally restricted to patients with established symptomatic osteoporosis; they are not used for primary prevention of bone loss although there is some evidence that they reduce the risks of future fractures (Table 27). Use of fluoride is reserved for vertebral osteoporosis because of concerns that it may increase the risk of appendicular fractures (*438, 439*). Some of these agents might be considered for use in screening strategies if the strategies included assessment of risk in the elderly and identification of those with severe osteoporosis.

Immobilization and lack of exercise are well documented risks for osteoporosis. However, the amount, type and duration of exercise that are optimal for preserving skeletal health are unknown. Intensive exercise is not without certain risks, including stress fracture and osteoporosis in the presence or absence of overt gonadal failure (*440–442*). Moreover, it is not

known whether the benefits of an exercise programme can be maintained in later life when various co-morbid conditions intervene.

Hip fractures in the elderly are usually the consequence of a fall and the risk of falling is greater in women than in men. Several factors are associated with falls, including co-morbidity, such as cerebrovascular disease, and concurrent medication, particularly the use of sedatives (*321*). There is no evidence, however, that changing therapeutic regimens can alter the risk of falling: this is an important subject for further research, as is the potential of cushioning falls in the elderly. In a recent randomized study, each patient in one wing of a nursing home wore a padded, external hip protector; patients in the other wing of the home wore no protection. Hip fractures occurred significantly less frequently among patients in the treatment wing (*443*).

6.4.4 *Implications for screening*

In addition to effects on fracture frequency, several other differences between HRT and alternative treatments are of interest in the context of screening. The first relates to the cost of treatment, which represents a substantial proportion of the cost of screening (*8, 339*). Currently, the costs of non-HRT interventions are substantially higher than those of endocrine therapy, even when the additional supervision required for HRT is taken into account. It should be noted that the formulations of calcitonin currently available in the United Kingdom and USA are injectable and their use is not widespread. This will probably change with the introduction of a more acceptable nasal spray, which is now available in many European countries; as use increases, the price is likely to decrease. Nevertheless, the non-HRT interventions are likely to have a significant impact on costs, both for the prevention of osteoporosis and for screening, since their use is increasing exponentially. The more expensive the intervention, the stronger the case for directing its use in a rational manner, targeting individuals at high risk and with known decrease in bone mass.

The second difference between HRT and non-HRT interventions relates to the extraskeletal risks and benefits, which are negligible in the case of calcium and calcitonins – and probably also the bisphosphonates. Thus, the indications for use of these non-HRT interventions are almost exclusively related to osteoporosis. This strengthens the argument for using bone density measurements for targeting these treatments (in contrast to the case for estrogens). The overall cost-effectiveness of non-HRT interventions and their use in organized programmes of screening are worthy of further research. In particular, the assumptions to be made concerning extraskeletal risks and benefits are more secure than is the case for HRT, and the costing of a screening programme can therefore be more accurate.

A third important difference between HRT and non-HRT interventions is that the latter are generally more acceptable later in life. Their side-effects

are fewer and their uptake by patients is known to be much greater than that of HRT (*408*). Since there is evidence for their efficacy even in patients with established bone loss, there is a case to be made for late intervention. Finally, several of the non-HRT interventions, particularly calcium and vitamin D, can be given safely for prolonged periods, which is not currently recommended for HRT. These considerations significantly affect screening strategies, particularly the ages at which screening might be offered.

6.5 Recommendations for research

1. Research to examine the causal relationship between many potentially modifiable lifestyle factors and fracture risk is needed in order to assess the potential of primary prevention strategies applied to whole populations and especially among the young.

2. There is a continuing need for long-term prospective studies to quantify the risks and benefits of HRT. In particular, further information is required on the effects of progestogens on the risks of breast cancer and cardiovascular morbidity and mortality.

3. More accurate information is needed on the effects of HRT, given from the time of the menopause for several years, on hip fracture rates in later life.

4. More information is required on the effects of progestogens on lipids and their implications for clinical end-points such as cardiovascular disease.

5. The prevention or cushioning of falls is a relatively neglected area of research and merits further investment.

6. Continued research on the effects of non-HRT interventions on fracture risk is required, particularly to generate data on long-term efficacy and compliance.

7. Screening

7.1 Principles of screening for osteoporosis

Since the risk of osteoporosis varies according to bone mineral content, which is in turn a continuously distributed variable, two different but not mutually exclusive preventive strategies can be adopted:

- a high-risk approach, whereby intervention is restricted to individuals in whom measured values of the risk factor are below a specified cut-off value; and
- a population approach, in which the aim is to shift the entire distribution of the risk factor in a favourable direction by intervening in a population.

In the context of this report, the screening test is defined as the assessment of bone mineral density of asymptomatic women in order to classify them

as likely, or unlikely, to sustain osteoporotic fractures in their remaining lifetime (*444*). Screening is the means whereby individuals are selected for intervention according to the high-risk strategy. The advantages of this approach are that it is an extension of the physician–patient relationship: 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 and costs of screening, as well as the limited contribution to disease prevention in the community as a whole.

In contrast, the population approach is radical and behaviourally appropriate, and has a substantial potential impact for the population. Unfortunately, the efficacy of population policies is unknown, mainly because the causal lifestyle factors have not been identified with any certainty, but also because specific programmes have not been developed and their feasibility and effectiveness are untested. This uncertainty is true of preventive strategies in the elderly in whom falls are frequent; there is currently no proven intervention to prevent falls (*445*). As previously reviewed, various putative risk factors (smoking, lack of exercise, inadequate nutrition, etc.) contribute to the non-skeletal morbidity of the population, and public health measures to combat these factors are appropriate. Thus, the applications of screening and general health measures are not mutually exclusive; indeed, the one can be effectively used to support the other.

Notwithstanding, the non-pharmacological interventions that might be recommended for application in the general population offer at best small skeletal benefits, and are therefore likely to be associated with poor motivation on the part of both individuals and physicians. For this reason the high-risk strategy was considered to be the most appropriate in the context of screening at present.

A number of high-risk approaches might be used to prevent osteoporotic fractures, but the application of bone density measurement to all women around the time of menopause, in order to target HRT, is the approach currently generating the greatest controversy. Other strategies include the identification of high-risk individuals in their sixties or seventies (to direct non-HRT skeletal interventions), of individuals at high risk of inadequate skeletal growth, and of individuals at the greatest risk of falling (to direct fall prevention programmes). The absence of information on these alternatives precludes their further consideration here, but it should be emphasized that all warrant further investigation before they are abandoned.

Various sets of criteria for the evaluation of screening programmes have been proposed (*252, 446, 447*). These differ in their emphasis, but the major criteria are summarized in Table 28: they include consideration of the disease, the test, the intervention and the complete programme.

Table 28
Major criteria for the evaluation of screening programmes

The disease	– an important social problem
	– natural history adequately understood
The test	– simple and safe
	– acceptable to the population
	– effective: sensitive and specific
The intervention	– accepted and effective treatment available
	– agreed policy on whom to treat
The programme	– facilities for diagnosis and treatment
	– cost-effective

7.1.1 *The disease*

In order to justify a screening programme, the disease must have been demonstrated to be an important public health problem, and its natural history must be adequately understood. Both of these criteria may be assumed to have been met by osteoporosis in Caucasian populations (see section 2.3). The cumulative incidence of osteoporotic fractures in women approaches 40%, and the medical and related costs have been shown to be substantial in several countries. An exceptionally large proportion of these costs results from hip fracture, however, and more data on the costs and outcome of other age-related fractures are urgently required. The natural history of osteoporosis, in the context of screening, is also well delineated; the patterns of change in bone density with age are reasonably clearly understood (see section 4.1), and the independent contribution of bone density to fracture risk has been unequivocally demonstrated (see sections 3.2 and 3.3). Good prospective data on hip fracture risk, over 2–3 decades, with declining bone density for women at age 50 years are not available, and probably never will be. However, the consistency of results obtained in case-control studies and shorter-term prospective studies of hip fracture strongly supports the current perception of the relationship between bone density and future fracture risk at all ages, namely a 1.6–2.5-fold increase in risk with each standard deviation reduction in bone density.

7.1.2 *The test*

There are three candidate methods for predicting future fracture risk: measurement of bone mineral density, biochemical assessment of bone turnover and profiling of historical risk factors. Risk factor profiles predict neither bone density nor fracture risk with any degree of certainty (see section 5). Biochemical markers of bone turnover appear to improve the efficiency with which future bone mass can be predicted, and may provide an adjunct to screening by bone density measurement (see section 4.3). There are as yet no data on the role of these measures in fracture prediction. In contrast, there is ample evidence that a single bone density

measurement currently provides the best measure of future fracture risk (see section 3.3). The relationship between declining bone density and fracture risk is approximately the same as that between blood pressure and the risk of stroke. The test is relatively simple and entails minimal exposure to radiation. So far, however, there have been few instances where the acceptability of bone density measurements has been assessed in the context of a screening programme in the general population.

Despite the superiority of bone density measurement over other methods as a predictor of future fracture risk, there is considerable controversy as to whether a bone density screening programme at the menopause is justified (*7, 448, 449*). One of the main reasons for this is the absence of clearly demarcated thresholds of bone density at which intervention seems appropriate. However, sufficient data have now been generated by prospective studies to allow a choice of intervention thresholds appropriate to the objectives of screening (see sections 3.3 and 7.7).

7.1.3 *The intervention*

In the context of screening, HRT at the time of the menopause is the intervention that has been widely considered. There is overwhelming evidence that HRT following the menopause retards the rate of bone loss and substantially reduces the risk of fractures. It has been argued that the effect of estrogens is reversed shortly after treatment is stopped, so that fractures in later life are not prevented, and that it is therefore inappropriate to screen the population at risk. The argument is flawed but there are other reasons why screening should not be considered in the context of HRT (see section 6.3). Non-HRT interventions are approved for use in osteoporosis in many countries and in numerous instances have been shown to have favourable effects on fracture rates (section 6.4). Their undisciplined use will be costly, and incorporation of these treatments into a screening strategy is the focus of this report.

7.1.4 *The programme*

The most appropriate method of assessing the value of a bone density screening programme would be a randomized, controlled trial, yet such a study has never been performed. It is clear that, in view of some of the uncertainties alluded to above, the necessity for such a trial will require careful consideration.

Analyses of cost-effectiveness (*251*) (see later) suggest that screening programmes might be financially more attractive than universal prescription of non-HRT interventions where compliance with treatment is higher in the screened group than in the unscreened and treated group.

Thus the principles for screening are met to a large extent in relation to osteoporosis, but several factors merit further consideration.

7.2 Facilities for diagnosis and treatment

Facilities for diagnosis and treatment are inadequate in many countries. Apart from the shortage of equipment dedicated for clinical, rather than research, use, there are few centres with expertise in bone disease. A related problem is that bone disease is not universally recognized as belonging to a particular medical speciality. In countries where this is not the case — for example France, where bone disease is a recognized component of rheumatology — expertise has been able to grow to match demand.

7.3 Limitations of the screening test

Use of bone mineral density measurements to stratify individuals at risk of osteoporotic fracture is now well established. Measurement techniques are highly accurate, yet there are still problems in using them to detect future fracture risk. Bone mineral density is continuously and not bimodally distributed, and the fractures may be in the distant future; both considerations detract from the suitability of estimating density or bone loss as a means of screening. Because of the overlap between individuals who have sustained fractures and those who, as yet, have not, the sensitivity of bone mineral density measurements for fracture prediction is low, even though specificity is high in the group at highest risk. It is thus misleading to inform individuals with normal test results that they will not sustain fractures. The expectations and the information given are therefore important aspects of selective screening.

7.4 Uptake of screening

There is little information on the uptake of bone mineral density screening. The uptake for mammography is approximately 70% (450), but varies widely from 25% to 89% (451); compliance with screening for other disorders in adults ranges from 30% to 70% (452-454). These data suggest that uptake in a national bone density screening programme would be of the same order. Information concerning screening for osteoporosis is limited, but it is thought that uptake may be reasonably high. In a study from Hull, England, an acceptance rate of 82% for osteoporosis screening was reported (D Purdie, 1992 — personal communication). In another study, 82% of 1685 men and 72% of 1594 women targeted in a study of osteoporosis screening participated in an initial examination (455). Uptake rates in Aberdeen, Scotland, varied from 54 to 75% depending on the type of approach made to individuals (456). In the Hull study of bone density screening, those who refused the procedure gave the following reasons: inconvenience, perceived risks associated with bone densitometry (especially fear of irradiation), and invitations not received.

7.5 Uptake of intervention

Approximately 10% of postmenopausal women in the United Kingdom take HRT (*457, 458*). Although some data are available concerning the numbers of individuals complying with HRT, there is relatively little reliable information available regarding the extent and causes of poor short-term and long-term compliance. Generally, uptake of HRT and compliance are low. Estimates of uptake range from 20% to 74% (*459–461*); other estimates of short-term compliance are comparable (*460, 462*), but in one study in which uptake of HRT was particularly low (36%), the 1-year compliance was high (80%) (*461*). The use of screening is likely to alter uptake of intervention. In a recent study, women with low bone mineral density were shown to be much more likely than those with normal values to take active steps to avoid fracture (*463*).

There is almost no information concerning compliance rates over 5–10 years, which is the duration of use that may be needed for prevention of fractures, particularly of the hip. In the Hull study referred to in section 7.4, 367 of the first 1000 women screened had bone density at the spine and/or proximal femur in the lower quartile. All of the "high risk" women were offered HRT and 88% accepted. Of those accepting HRT, 63.4% were compliant at 3 months and 52.8% were compliant at 12 months. Thus, only about half of the "at risk" individuals were taking HRT at the end of 12 months (D Purdie, 1992 – personal communication).

Perception of the benefits of HRT is changing rapidly and the growth in HRT prescriptions is accelerating in many countries. It is plausible that 25% or more of women will take HRT, which is the present uptake in Denmark (C Christiansen, 1992 – personal communication). These considerations significantly alter the potential impact of screening for HRT but do not provide an adequate model for the uptake of non-HRT interventions. Calcium, for example, is the major non-HRT intervention and its usage is also increasing significantly; the rarity of extraskeletal risks and side-effects suggests that uptake and compliance are likely to be very much higher. Indeed, long-term compliance with calcium therapy appears to be of the order of 80–90% over 3 years (*406*). In a large study of 2500 elderly subjects, only 30% took less than half of their tablets, which suggests that compliance is much less of a problem than with HRT. However, further studies of uptake and compliance for non-HRT interventions are required to confirm this view.

7.6 Type of intervention

The major "social" benefit of HRT lies in the area of cardiovascular morbidity and mortality. The greater are the extraskeletal benefits (or risks), the weaker is the case for screening with bone mineral density as the sole criterion for targeting HRT. Many previous studies have examined the role of mass screening in the context of HRT; whereas their conclusions may be sound within the frame of reference chosen, they are not

necessarily applicable to the wider issues raised by the use of non-HRT treatments (*8, 251, 327, 464*).

This is not to say that bone mineral density measurements might not be useful in women for whom HRT is contemplated, only that they cannot at present be justified as a general screening instrument to target HRT. The feasibility of targeting HRT on the basis of cardiovascular (and perhaps breast cancer) risk should be considered, and, in this, bone mineral density assessments might have a limited place. Indeed, screening on the basis of density might be plausible in women with a low risk of coronary heart disease (*251*) depending upon local policy for the use of HRT. This, in turn, suggests that any screening or health care programme should be optimally integrated with agreed policy on HRT and perhaps with other health care programmes.

Different considerations apply to non-HRT interventions, in which the extraskeletal risks and benefits are negligible. In these cases, measurement of bone mineral density – with or without assessment of rates of bone loss – should be seriously considered. Unfortunately, few health economic assessments have been applied to non-HRT interventions, so that firm data are not yet available to guide policy.

7.7 Intervention thresholds

Because of the continuous distribution of bone density, the relationship between fracture risk and density is stochastic. There is thus no true "fracture threshold", even though the term is widely and usefully employed to indicate a threshold for intervention. For this reason, the choice of an intervention threshold is considered to be somewhat arbitrary (*11*), and may profoundly affect the number of individuals characterized as being at high risk. The less rigorous the cut-off point that is used, the greater is the sensitivity. On the other hand, for a given accuracy, the proportion of the at-risk group that is misclassified increases with the stringency of the cut-off used. For example, assuming an accuracy error of 3% and a cut-off value one standard deviation below that in the healthy population, 10% of the population and 31% of those considered to be at risk will be misclassified. With a more stringent cut-off (−1.5 SD), only 5% of the population but 39% of those deemed to be at risk will be misclassified. A reasonable cut-off is to consider the lowest quintile of bone mineral content (the highest quintile of risk) of the healthy female population to be at significant future risk. In developing a screening strategy, it may be of value to identify a further group at intermediate risk (the fourth quintile of risk) for later re-evaluation if it can be shown that rescreening or the assessment of rates of bone loss is sufficiently accurate (see section 4).

Fracture risk approximately doubles for each standard deviation decrease in bone mineral density (section 3.2). Ross et al. (*23*) have suggested that a doubling of risk compared with the average young healthy woman might constitute an intervention threshold. This would capture 15-20% of

the population. Such estimates coincide (fortuitously) with "fracture thresholds" determined from the difference in bone density in populations with and without fracture. Set against the lifetime risks of osteoporosis (approximately 30–40% in women) and the "specificity" of bone density estimations (section 3.3), the lowest quintile of the healthy adult range is appropriate as an intervention threshold at the age of menopause. The expression of risk as a gradient per unit drift in standard deviation of bone mineral density has many attractions for modelling and ease of presentation (Fig. 20). It does, however, make the assumption that the relationship is log-linear; this may be the case, but some data suggest that the greatest increment in risk occurs at the lower density values. In the context of screening, this phenomenon, if true, would underestimate the relative risk in those with the lowest density values.

The chosen cut-off point is relevant where the aims of screening and subsequent intervention are to reduce the risk of all osteoporotic fractures. More stringent cut-offs would be appropriate if the aim were solely to prevent hip fractures. It is clear (see Table 14) that a more stringent cut-off should be used to attain maximal specificity, perhaps the lowest 5% rather than the lowest quintile. Moreover, if hip fractures were the only concern, it would be more appropriate to measure risk at the hip, where the gradient of risk is greater (section 3.3), which would identify a larger proportion of individuals at risk.

It is important to recognize that the foregoing considerations may not be applicable worldwide since there is no universally agreed definition of

Figure 20
Relative risk of hip fracture according to bone mineral density (BMD) measured at the forearm[a]
Numerical values corresponding to the diagonal lines denote the gradient of risk for each 1 SD drift in BMD. Note the higher gradient of risk with the lower values for BMD.
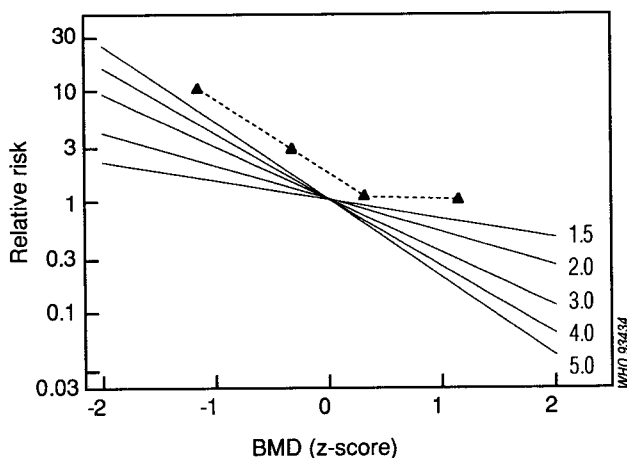
[a] Based on data from reference *245* (copyright 1992, American Medical Association).

acceptable risk in the community and since the incidence of osteoporotic fracture varies markedly (more than 10-fold in different European countries (58), for example), which also affects the appropriateness of the cut-off.

It has been argued that the predictive value of bone density measurements is likely to be less in the very elderly because extraskeletal factors such as falls assume greater importance with age (11). However, the choice of intervention thresholds in the most elderly women can be based on considerations similar to those applied to younger women. The lifetime risk of fractures of the hip and wrist are similar at all ages after the menopause (32, 41, 265). At all ages, the risk of all osteoporotic fractures increases as bone mineral density decreases; indeed, the gradient of risk with density is, if anything, higher in the elderly (25). Thus, choosing the lowest quintile for bone mineral density of an appropriate age-matched population will have a similar specificity.

An alternative approach is to set an intervention threshold more closely related to a given lifetime risk. A model has been created that links the risk of hip fracture to bone mineral density at the radius and to age (248) and this has been used to map lifetime hip fracture risk for each combination of bone mass and age (Fig. 21). This would allow the selection of patients for treatment whose lifetime risk was at a certain level irrespective of age.

Figure 21
Estimated lifetime risk of hip fracture in white women according to age and bone mineral density (BMD) at the wrist[a]

The gradient of risk is set at a 1.65 increase in risk for every SD decrement in BMD. Mean BMD at age 50 years is 0.44 g/cm^2 (z-score = 0), with SD of 0.085 g/cm^2 (equal to a z-score of 1).
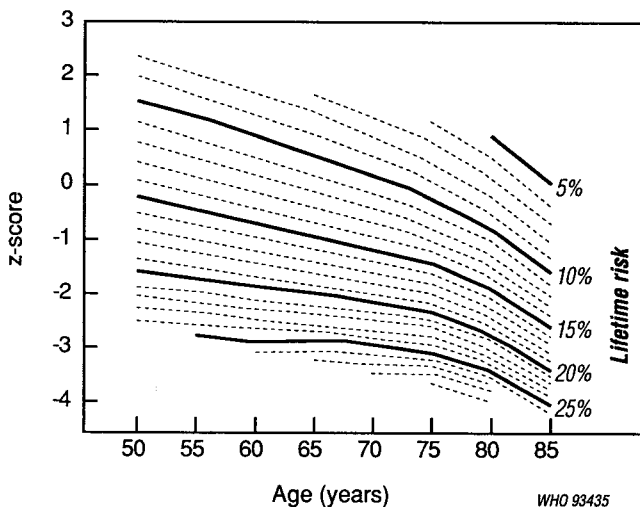
[a] Based on data from reference 249 with kind permission from Elsevier Science Ltd.

7.8 When to test

The vast majority of osteoporotic fractures occur in postmenopausal white women. Although osteoporosis occurs in men, and secondary osteoporosis is in fact much more common in men than in women, far less is known of its natural history or the effects of intervention. These considerations indicate that screening should be targeted at women, but not exclusively if segments of the male population are shown to be at high risk. There are insufficient data to permit the utility of screening in men to be evaluated, and research on this issue is an urgent need.

In theory, the optimal time for intervention in women is at the menopause, before substantial bone loss and disruption of skeletal architecture have occurred. It would thus seem that screening might be appropriate at that time. However, since HRT is one of the major interventions currently used, two considerations temper this view. Firstly, HRT uptake and compliance with the long-term exposure required for osteoporotic (and probably cardiovascular) protection is low, although a greater proportion of women may elect to take short-term HRT for menopausal symptoms. Many such women might benefit from subsequent non-HRT interventions but would be missed by a single test undertaken at the time of the menopause. Secondly, because of the evidence that bone-active drugs decrease the frequency of osteoporotic fractures even late in the natural history of bone loss, it may be cost-effective to screen in later life. These considerations reinforce the view that the assessment of skeletal status is complex and that screening strategies need to take account of differing treatment strategies.

7.9 Who to test

Suggested criteria for selection of women for screening are that they:
- are of perimenopausal or postmenopausal status
- are not receiving long-term HRT for other reasons
- are willing to accept HRT or a non-HRT intervention, depending on the test result.

A principal target might be white women within 5 years of the menopause. After counselling on HRT, those who declined HRT would be offered a bone density examination. Some women might thereafter elect to reconsider long-term HRT. For an individual who might be uncertain of whether to take HRT or another intervention, the assessment of skeletal status by bone mineral density measurement would be appropriate if the result would influence her decision. Provision should be made for the subsequent review and assessment of women who elected to take HRT for short intervals, predominantly for perimenopausal symptoms.

For women who had density assessments, subsequent follow-up and intervention strategy would depend upon the result of the measurements. It is suggested that perimenopausal women in the three highest quintiles of bone mineral density would require no further action. In view of the

appreciable number of false-negative results, it is important that individuals be correctly informed that the lifetime risk of fracture is not negligible; for those with the lowest bone mineral density, in the highest quintile of risk, an HRT or non-HRT intervention would be recommended. Assuming compliance with an effective treatment, no further action would be envisaged beyond supervision of the treatment.

The greatest difficulties relate to individuals in the fourth quintile of fracture risk, for whom it is suggested that an additional assessment of the rate of bone loss might be appropriate. This could be done either by a second bone mineral assessment at a later date, or by assessment of bone loss by biochemical markers of skeletal turnover. The expediency of the latter approach needs to be weighed against the greater accuracy but inconvenience of the former.

Other populations targeted for reassessment at a later date might include those who have not complied with HRT and those who have declined screening or a non-HRT intervention within 5 years of the menopause.

Early reassessment is required to exploit the maximum effectiveness of HRT. If other interventions are emphasized, reassessment could be undertaken at a later date. Reassessment after 10–15 years is a somewhat arbitrary choice, but attractive for the following reasons:

- The time interval is sufficient for rates of bone loss to be quantifiable after an initial assessment in nearly all individuals.

- It provides the opportunity to assess risks in those not captured by screening at the menopause.

- It provides the opportunity to re-evaluate risk in those categorized as being at intermediate risk at the menopause. The degree of improvement in accuracy achieved with a repeated measurement has been partially quantified (*465*).

- The contribution of bone loss to bone mass becomes progressively greater with time. At the time suggested, bone loss will have contributed 40–50% to the value of the second density measurement.

- The average age at this time is 65 years, before the peak incidence of hip fracture.

- Intervention at this age is still reasonably cost-effective (see below).

- Overall, the number of repeated tests would be low.

7.10 The aims of screening

The aims of screening have been variously formulated, but include the following:

- reducing the hospital costs of hip fracture (*8*)
- reducing the incidence of all osteoporotic fractures (*26*)

- rationing or targeting the use of HRT (*251, 464*)
- allowing individuals to reach informed judgements about the prevention of osteoporosis (*463*)
- reducing financial burdens on the health services (*464*)
- benefiting the health of the community.

The principal aims are thus concerned with improving the health of individuals and thereby reducing the incidence of fractures in the vulnerable segment of the community.

7.11 Setting of a screening programme

The integration of a service within the framework of the primary care practitioner has several advantages:

- The menopause, osteoporosis, HRT and non-HRT interventions are inexorably linked. It is inappropriate and not easily feasible to isolate a single component such as the screening of non-HRT users.

- The optimal time for screening depends on the optimal time for intervention, which will vary according to the age at menopause, the use of short-term HRT, and the presence or absence of risk factors (e.g. prior fragility fractures, corticosteroid use). This argues for the integration of a screening service within the framework of general health care.

- A number of disorders in both men and in women which are associated with a high risk of osteoporosis (see Table 5) can be feasibly identified within a general practice framework. Suggested indications for bone mineral density measurement and intervention are given in Table 29. General practitioners should be provided with guidelines for the use of density measurements for case-finding (outside the framework of screening).

- The costs of such an integrated service are considerably less than those of a centrally organized service.

- An individual's decision to select one of several options or to decline options can be considered and taken within a wider context of health. There is therefore less risk of producing anxiety or awareness of illness in a general practice framework than in the context of a specialist service.

- It is considered advisable for doctors or other trained health care professionals to counsel all perimenopausal women about osteoporosis and the risk and benefits of HRT. Assessment of the appropriateness of intervention, particularly HRT, should depend upon an assessment of cardiovascular, breast cancer and other risks. An informed decision on the part of the patient is a prerequisite for screening.

- The various types of intervention require various degrees of medical supervision. Good medical supervision is most likely where the

individual's own doctor has participated in the decision to treat and in the choice of treatment.

7.12 Costs of selective screening

Costs can be considered in many ways — as absolute costs to health services or as savings per fracture avoided or per additional year of life or quality-adjusted year of life.

The effectiveness and the costs of the strategies outlined above are for the moment conjectural, but are amenable to estimates together with sensitivity analyses.

Within the framework of general practice, the cost of the screening test is likely to be relatively low. Bone mineral density assessments, either at central locations or at practice level with mobile machinery, plus essential supporting facilities, account for a substantial proportion of the costs. Costs in the United Kingdom have been estimated at UK £20 million, comprising the total capital cost of machines and accommodation for screening according to a policy of screening all perimenopausal women (8). These figures are based on dual-energy X-ray absorptiometry rather than single-energy absorptiometry capital costs, for the latter are about one-third of the former. The administrative costs in a general practice

Table 29
Conditions in which bone mineral density measurements and intervention may be indicated

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Women
Prolonged amenorrhoea (in):
– anorexia nervosa
– exercise-induced
– prolactinoma
Premature menopause (<45 years) (resulting from):
– idiopathic
– cancer chemotherapy
– pelvic irradiation
Late menses (>15 years)
Prolonged heparin infusion

Women and men
Primary hypogonadism
History of low-energy-induced fracture
Incidental finding of osteopenia or vertebral fracture
History of prolonged immobilization
Certain diseases, e.g. long-standing thyrotoxicosis, chronic liver disease, Cushing disease, hyperparathyroidism, chronic renal failure, haemochromatosis, mastocytosis, Marfan syndrome
Certain drugs, e.g. long-term corticosteroid use, anticonvulsants

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framework are also likely to be lower. In addition, the number of density measurements required per thousand perimenopausal women is likely to be substantially lower using the selective approach outlined previously, although this will be offset to some extent by any requirement for repeated measurements.

Evidence suggests, however, that the costs of any screening programme will depend more on the costs of intervention than on the costs of screening (8, 251, 339). The price of non-HRT intervention is currently higher than that of HRT; with increasing use of non-HRT interventions, and as evidence of their efficacy accumulates, targeting of this expenditure will become more important. Thus, the total costs of screening amount to the costs of the test, the costs of redirecting interventions to those most at risk, and the additional costs of any increase in the use of interventions.

Costs clearly depend upon a number of additional factors, including the cut-off point used to target treatment, the age of the individual, and the efficacy and duration of treatment. Some estimates are provided in Table 30 for treatment with calcium where it is assumed that the annual cost of treatment is UK £100 (e.g. 1 g of calcium daily in the United Kingdom), that the treatment is given for life, and that it reduces the rate of bone loss by 50%. This permits the costs to be computed according to age and cut-off point. Irrespective of the cut-off point, the cost per fracture prevented increases with age. When a more stringent cut-off is used, the cost is lower (but more fractures would be missed).

There have been relatively few detailed assessments of cost-effectiveness and these have principally been concerned with the use of HRT (8, 251, 466). The weakness of the approaches used lies in the assumptions made. For example, Tosteson et al. (251) argue that screening to target HRT is cost-effective, assuming that compliance is 100%, that the cost of HRT is

Table 30
The effect of age, cut-off point and treatment on the costs of preventing fractures

Age (years)	Cut-off (%)[a]	Lifetime probability of fracture[b]	Number of fractures prevented[c]	Cost per fracture prevented (UK £)[d]
50	38	2.5	1.43	2080
	8	5	2.58	776
60	38	1.5	0.73	3000
	8	3.15	1.38	1600
70	38	0.86	0.32	4700
	8	1.9	0.63	2380

[a] Perimenopausal reference range.
[b] All fractures.
[c] 50% reduction in bone loss.
[d] Assumes an annual cost of UK £100.

low, and that there is no effect on cardiovascular morbidity, etc. The authors recognized the shortcomings of this approach and performed sensitivity analyses, but such analyses allow only a few assumptions to be changed at a time. However, the methodology *does* permit the relative costs of different strategies to be assessed, even if the absolute values are open to doubt. It is also of particular value for non-HRT interventions, where extraskeletal factors (gains and losses) are negligible, and can also be used to evaluate cost-benefit at different ages of intervention.

The size of the at-risk population eligible for treatment (US-based) depends on the age and treatment threshold chosen (Table 31). When several screening and treatment strategies are considered for women of various ages, assuming that treatment stops bone loss at a cost comparable to that of HRT (US$ 255 per year), the cost per additional year of life saved increases as less rigid cut-offs for treatment are used (Table 32). It is particularly interesting that targeting interventions appears to be more cost-effective at the age of 65 years than at the age of 50 years. However, it is less cost-effective to target interventions at the age of 70 years than at 60. This is largely because of the high cost of long-term nursing-home care in the USA and the differential timing of events relative to the intervention in each age group. When long-term nursing-home costs are omitted from the analysis, the costs per additional year of life saved are much more comparable across age groups (Table 33). This suggests that selective screening strategies for the elderly are worthy of consideration.

Table 31
Proportion of women eligible for treatment according to age and bone mineral density (BMD) at the hip[a]

	Proportion of women eligible (%) Age of cohort (years)		
Treat[b]	50	65	70
None	0	0	0
If BMD <0.8	5.5	28.9	40.9
If BMD <0.9	16.6	51.5	65.8
If BMD <1.0	36.6	73.6	85.2
If BMD <1.1	61.2	89.0	95.4
All women	100	100	100

[a] Reproduced from reference *250* with the permission of the publisher.
[b] BMD (g/cm²) determined by dual-energy X-ray absorptiometry from a population-based sample of women at Rochester.

Table 32
Costs (in 1992) per additional year of life saved for each treatment strategy relative to the next less costly strategy (incremental cost-effectiveness ratio)[a]

The assumptions used include 100% compliance with prescribed treatment, no loss in bone mineral during treatment, and no additional risks or benefits from treatment. Annual costs assumed are US $255 for treatment, US $32 610 for nursing-home care, US $190 for screening, and US $13 082–15 400 for acute hospital care of hip fracture, plus a 5% discount rate per year for both economic and health endpoints.

Treat[b]	Cost (thousands of US $) Age of cohort (years)		
	50	65	70
If BMD <0.8	_c	1.5	28.4
If BMD <0.9	14.9	10.2	56.0
If BMD <1.0	28.2	70.7	171.7
If BMD <1.1	120.9	_c	_c
All women	445.4	223.5	253.9

[a] Reproduced from reference *251* with the permission of the publisher.
[b] BMD = bone mineral density (g/cm^2).
[c] Dominated; i.e. more costly and less effective than universal treatment.

Table 33
Costs (in 1992) per additional year of life saved (YOLS) and per quality-adjusted life-year (QALY) saved for each treatment strategy relative to the next less costly strategy (incremental cost-effectiveness ratio)

Treat[a]	Cost (thousands of US $) Age of cohort (years)			
	50		70	
	YOLS	QALY	YOLS	QALY
If BMD <0.8	_b	_b	61.7	31.6
If BMD <0.9	83.5	30.0	89.8	45.1
If BMD <1.0	86.7	33.7	206.2	102.0
If BMD <1.1	176.1	70.3	_b	_b
All women	496.9	204.8	289.2	141.8

[a] BMD = bone mineral density (g/cm^2).
[b] Dominated; i.e. more costly and less effective than universal treatment.

Recommendations for research

1. Screening to target non-HRT interventions has received relatively little attention, and further research is essential to generate estimates of cost-benefit.

2. The assumptions on which cost-effectiveness analyses are based require further investigation. Of particular importance is information on the uptake of non-HRT interventions, long-term compliance with treatment and the cut-off point used to identify individuals at high risk.

3. Greater consideration should be given in future to the assessment of cost-effectiveness in elderly individuals.

4. Much additional information is needed if the potential for screening both women of non-Caucasian origin and men is to be assessed.

8. **Summary and conclusions**

The following conclusions represent the unanimous views of the Study Group.

Awareness of osteoporosis and its complications is growing, as is the use of treatments that favourably alter the natural history of the disorder. There is thus increasing reason to develop strategies for screening in order to target treatments more effectively and to reduce the number of fractures, particularly in postmenopausal women.

8.1 **Osteoporotic fracture**

1. Postmenopausal osteoporosis is a major public health problem affecting all countries and giving rise to fractures, notably of the spine, forearm and hip.

2. Fractures of the hip incur the largest direct costs for health services. They occur in the elderly, particularly women, and give rise to substantial morbidity and death.

3. Osteoporotic fractures of the vertebrae and forearm are of less economic significance but also give rise to significant morbidity. The extent of vertebral osteoporosis is not well quantified.

4. In developed countries, the lifetime risk of osteoporotic fractures in women aged from 50 years upwards is 30–40%; for hip fracture alone the figure is 13–19%. The incidence of osteoporotic fractures is certain to increase in both men and women as a result of the aging of populations, probably by 50% over the next 20 years. The major increase will occur in countries outside Europe and the USA.

5. Elderly women represent the major problem in terms of numbers of fractures, which suggests that screening and prevention would be most effective if aimed at this group of the population. Although the problem is also significant in men and likely to increase in the future, the effects of intervention are less certain.

6. The incidence of osteoporotic fracture is high in Europe and the USA compared with many other countries. From a health care viewpoint, what constitutes an acceptable or unacceptable risk of fracture in these other countries is somewhat arbitrary and is likely to be determined largely by the priorities that must compete for health care resources.

8.2 Bone mass and bone loss

1. Bone mineral density in the postmenopausal years is a function of peak bone mass and postmenopausal losses. Bone mass and bone loss in women are continuously distributed in the general population and appear to vary from site to site in the skeleton.

2. Postmenopausal bone loss is also associated with disruption of skeletal architecture, which appears to be irreversible. At present there is no widely applicable method of restoring skeletal strength once it has been lost. This argues for assessment and intervention early in the natural history of the disorder.

3. The major skeletal determinants of fracture risk in postmenopausal women are bone mass, postmenopausal bone loss and the destruction of trabecular bone architecture, plus extraskeletal factors such as the frequency of falls, the type of fall and the adequacy of neuromuscular protective mechanisms. Extraskeletal factors assume increasing importance with advancing age.

8.3 Assessment of bone mass

1. Many methods of assessing bone mineral density are available. These include single-photon and single-energy X-ray absorptiometry (SPA and SXA) of the forearm and the heel, dual-energy X-ray absorptiometry (DXA) and dual-photon absorptiometry (DPA) of the lumbar spine, proximal femur, whole body or particular regions, and quantitative computed tomography (QCT) of the spine or appendicular sites. All of these techniques have high specificity and sensitivity for the diagnosis of low bone mass.

2. The requirements for a single screening test of bone mineral density are the ability to predict fractures, rapidity, reliability, low radiation dose and low error of accuracy. These requirements are largely met by SPA, SXA and DXA, less adequately by DPA and QCT.

3. SPA has the greatest accuracy *in vivo*, which is important in the correct stratification of individuals in the population reference range of bone density. It is also inexpensive and easy to use, even within the framework of general practice. The radiation dose used is lower than

that required for an X-ray of the hand. A potential disadvantage is that the sites assessed are of lesser biological relevance than those assessed by other techniques. However, the ability of SPA to predict future fracture is generally as good as that of dual-energy absorptiometric techniques in prospective studies.

4. The technique and site of measurement used depend upon the objectives of screening. If the goal is to predict any type of osteoporotic fracture, SPA and DXA perform comparably well at many sites. However, measurement of bone mineral at the site of fracture increases the sensitivity and specificity of the test for that site. Thus, if the goal is to predict hip fractures, DXA at the hip currently provides the best assessment.

5. The view that measurements of bone mineral density cannot be used for screening because of the continuous distribution of values and the large overlap in values between individuals with or without fracture is flawed, since it does not take account of the gradient of future risk. There are several situations in clinical medicine, for example the relationship between blood pressure and stroke, where measurements of a continuously distributed risk factor are used as indicators of future outcome.

6. Many prospective studies have shown that a single measurement of bone mineral density can correctly identify a proportion of women who will sustain fractures. The risk increases exponentially with decreasing values of density.

7. The accuracy of a single determination of bone mineral density is adequate to stratify individuals according to the risk of future fracture and can identify at least 20% of postmenopausal women whose lifetime risk of osteoporotic fractures is very high compared with a low-risk group. In predicting fracture it is at least comparable to blood pressure measurements in predicting mortality from stroke or to cholesterol measurement in predicting myocardial infarction, and has been validated by long-term prospective studies.

8. Probabilistic models based on prospective studies are appropriate for evaluating the usefulness of these techniques. A single measurement will capture a segment of the population in which the fracture risk is very high (low false-positive rate, high lifetime specificity) depending on the cut-off used. However, many fractures will also occur in those individuals identified as being at lower risk (i.e. high false-negative rate, low or moderate lifetime sensitivity).

9. The inability of a single test to identify all individuals at risk reduces the impact of screening on the total incidence of osteoporotic fracture. The effectiveness of a screening programme in the general community has to be balanced against its effectiveness in a subgroup at very high risk.

10. In a screening programme for women it is suggested that risk should be quantified as a lifetime risk of all fractures or hip fractures, depending on the goals of screening. If the goal is to identify those at risk from any fracture, a high-risk group comprises the highest fifth of the distribution of risk (i.e. the lowest quintile of bone mineral density). An intermediate risk group comprises the next fifth if subsequent screening or biochemical testing is contemplated.

11. The accuracy of the test depends on the cut-off value chosen, which in turn depends on the goals of screening. If the goal is solely to prevent hip fracture, more rigid cut-off values should be selected than if the goal is to prevent all types of osteoporotic fracture.

8.4 Assessment of bone loss

1. The additional requirements of bone density techniques for the assessment of bone loss are low errors of reproducibility and evidence that such measurements improve the prediction of fracture risk.

2. Of the techniques available, DXA has the highest reproducibility, followed by SPA and SXA. All techniques are suitable for assessing rates of bone loss provided that the interval between assessments is sufficiently long. An interval of 5 years will detect bone loss in the majority of women after the menopause. Shorter intervals would be appropriate to detect rapid rates of loss.

3. The contribution of bone loss to fracture risk (compared with bone mass at the menopause) increases with time. The influence of initial bone mass on current bone mass is generally greater than that of bone loss in women up to the age of 70 years, but the effects equalize between the ages of 70 and 75 years in untreated postmenopausal women.

4. The measurement of rates of bone loss by sequential estimations of bone mineral density improves the prediction of subsequent bone mass and hence the assessment of risk.

5. Biochemical tests of bone turnover at the menopause can predict rates of bone loss. They have 50% efficiency or more compared with direct methods of assessment by repeated measurement of bone mass. The convenience, but lower accuracy, of these tests must be balanced against the inconvenience of repeated measurements in any screening strategy.

6. The likelihood that the power of tests to predict fracture risk can be improved still further is a valuable area for further research. This includes the validation of other techniques for measuring skeletal status and the evaluation of rates of bone loss measured directly or by biochemical assessments.

8.5 Clinical assessment of risk

1. Surveys of risk factors for osteoporosis have focused largely on patients with fractures. The historical risk factors identified in this way are not sufficiently powerful to identify the individuals who should be selected for bone mineral density screening at the time of the menopause. Prospective studies would be needed to establish the value, if any, of clinical assessment as a screening instrument.

2. Risk factor assessment to target bone mass measurements or interventions in the elderly merits further research and may improve the value of screening in this population group.

8.6 Interventions

1. It is likely that peak bone mass in early adult life can be maximized by factors such as adequate nutrition, exercise and avoidance of smoking. However, the extent to which lifestyle changes in childhood or early adult life will alter peak bone mass and the subsequent risk of fracture is unknown. Regular exercise appears to have the greatest effect, but the elements required (extent, type, duration) are not well quantified. For this reason, a population-based approach to shifting the distribution of bone mass by means of a public health campaign is of uncertain value. Nevertheless, since lifestyle factors are known to be important for general health, avoidance of smoking, regular exercise and good nutrition can be justifiably promoted as part of an overall health strategy.

2. Knowledge of the ability to modify peak bone mass is limited and the causal impact of putative factors on fracture frequency is uncertain. Thus, assessment of bone mineral density before or at the time of skeletal maturity is not worthwhile at present, but is an important area for research.

3. Hormone replacement treatment is an effective method of reducing bone loss, and much epidemiological evidence suggests that the incidence of all osteoporotic fractures is substantially reduced (by 30-50%) with an exposure to HRT of 3-10 years.

4. Evidence that the protective effects of HRT on bone are reversed when treatment is stopped is weak and on balance it is thought that effects on fracture risk are long-lasting. There is thus good reason to believe that fractures are preventable in both the perimenopausal population and the elderly.

5. Estrogen replacement therapy is probably safe but there are concerns that it may increase the risk of some forms of cancer. In women with intact uteri, added progestogen avoids the increased risk of endometrial cancer. There is a plausible association between estrogen exposure and breast cancer but no evidence of a significant increase in risk, particularly in terms of mortality above that expected in fertile women

of the same age. The effect of added progestogens on the risk of breast cancer is unknown.

6. The greatest single potential benefit of HRT is on cardiovascular morbidity and mortality which, largely on the basis of epidemiological studies, appear to be substantially reduced by estrogens. The effects of added progestogens are less certain: the evidence to date suggests that progestogens have little influence on the protective effects of estrogens. The cardioprotective effects of HRT may become the predominant reason for its use in the general population.

7. Non-HRT interventions are widely used in the prevention of osteoporosis and fracture. Approved treatments include calcium, calcitonins and bisphosphonates. In older women there is some evidence for the efficacy of anabolic steroids and various forms of vitamin D. In some countries, particularly in north-western Europe, vitamin D deficiency is common in the elderly and there is evidence for the preventive efficacy of vitamin D supplements in such patients.

8.7 Screening

1. There is little evidence that osteoporosis can be usefully tackled by a public health policy to influence risk factors such as smoking, exercise and nutrition. Although exercise at all ages, and nutritional factors after the menopause are particularly important, the effectiveness of population-based strategies to reduce fracture incidence by altering these lifestyle characteristics on a large scale is not known. The evidence that peak bone mass can be improved is also weak. Thus, the most feasible method of preventing fractures due to osteoporosis is to prevent bone loss in those identified as being at high risk.

2. The argument for treating or screening *all* women is poor.

3. Several treatments in addition to HRT are available for the treatment of osteoporosis. They variously decrease the rate of bone loss and in some cases the risk of subsequent fracture. Their use is increasing markedly and strengthens the case for targeting them appropriately to those at need, so that unnecessary treatment is avoided.

4. The cost of preventive measures may possibly outstrip the savings made by preventing fractures. However, if preventive measures are to be used, effective screening will improve the cost/benefit ratio of intervention.

5. Bone mass measurements, with or without assessment of bone loss, meet many of the essential criteria of a screening test. The test correctly identifies individuals at high risk, and the number of individuals identified as high risk who do not sustain fracture is very low. However, many individuals who subsequently sustain fracture will not have been correctly identified. Thus, the value of screening is

greater for those individuals identified as being at higher risk, but less for those identified as low risk.

6. Since the major benefit of HRT is likely to lie elsewhere than in its effect on bone, measurement of density as part of a screening policy involving treatment with HRT is inappropriate. Bone mineral density measurements do have a role, however, in the assessment of individuals who would accept HRT if results showed them to be in the high-risk category.

7. The consideration in 6 above does not apply to the use of non-HRT interventions, which are increasingly used and available in many countries.

8. Non-HRT interventions are probably less effective than estrogen but carry fewer extraskeletal risks and benefits and, in some cases, can be given for life. The more widespread their acceptance and use, the greater the justification for targeting intervention by screening.

9. In women, the optimal time for using many interventions is at the menopause. The menopause is a clearly definable event and coincides with progressive skeletal losses. This does not necessarily suggest that this is the optimal time for a screening test, since many women who elect to take HRT are likely to do so for relatively short periods. Notwithstanding, the earlier an intervention is started, the greater will be its impact (though not its cost-effectiveness).

10. Screening strategies can be optimized only where there is a clear policy on the use of HRT. Such policies have not been formulated in many countries. It is recommended that perimenopausal women should receive professional advice on the risks of osteoporosis and the risks and benefits of HRT.

11. Selected screening is worthwhile for women within 5 years of the menopause to stratify risk and offer intervention. There is, however, no requirement for testing women who elect to take long-term HRT, nor is there a requirement where the results of the test will not change the decision to accept an intervention. A further test may be of value several years later in those women previously identified as being at intermediate risk.

12. There is a good case for screening women in older age groups. An optimal age is 65 years, at which time bone loss has had a substantial influence on bone mass, the risk of hip fracture is still low, the effects of intervention have been proved and the cost-effectiveness is favourable.

13. The increased use of HRT is likely to alter the requirements for screening tests and the design of a screening strategy. A clearly defined policy on the use of HRT would therefore be advantageous to complement a screening strategy.

14. The cost of screening is low compared with the costs of the interventions used. Ultimately, selective screening is likely to increase the number of individuals receiving drug treatment, but in many countries that treat osteoporosis, the proportion of the population treated would still be comparable to the current situation in the USA and most European countries.

15. Uptake of screening is likely to be high (70%). The long-term compliance with non-HRT interventions is unknown but, depending on the type of agent, the side-effects and the perceived advantages, is likely to be higher than for HRT. Variations in uptake and compliance rates markedly affect the impact of screening, though not the costs, and may be amenable to change by education.

16. The strategies for screening outlined above are based largely on clinical considerations but have many logistic and economic consequences that should be addressed. These include the following:

    (a) A formal assessment of the costs of any proposed strategy is appropriate, as are sensitivity analyses to determine the effect of possible differences in the assumptions used.

    (b) A policy on the use of HRT would be advantageous in all countries that envisage the use of screening tests.

    (c) There are other indications for bone density assessments aside from general population screening, and the widespread availability of access to bone assessment is justified. Where such facilities are contemplated, appropriate guidelines on their use should be provided.

    (d) Facilities and trained personnel for the assessment of bone disease are currently inadequate. It is essential to provide sufficient equipment and a clinical environment that favours the development of a specialist interest in metabolic bone disease.

Acknowledgements

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