



# What evidence is there for the prevention and screening of osteoporosis?

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## ABSTRACT

This is a Health Evidence Network (HEN) synthesis report seeking to determine the effectiveness of the prevention and screening of osteoporosis. The review of evidence shows that several measures, such as moderate physical activity, an appropriate intake of calcium and vitamin D, cessation of smoking, and pharmaceutical intervention in high-risk groups for preventing osteoporosis are effective. The review found no direct evidence that screening for osteoporosis reduces fractures, but it shows that there is good indirect evidence that screening is effective in identifying postmenopausal women with low bone mineral density and that treating osteoporosis can reduce the risk of fractures (wrist and spine) in this population.

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## **Summary**

### **The issue**

Osteoporosis – an excessive decrease in bone mass – is more common in women than in men. It is a particularly common condition among elderly women in affluent countries. Osteoporosis is a risk factor for fractures, which occur most commonly at the wrist, spine and hip. Other important risk factors for fractures include those both related and unrelated to an excessive decrease in bone mass. Those related to an excessive decrease in bone mass include such causes as physical inactivity, smoking, low body weight, a history of fractures and the use of corticosteroids; those unrelated to bone mass loss include such causes as falls, high alcohol intake and visual impairment.

Osteoporosis and the fractures associated with it are a major public health concern, because of related morbidity and disability, diminished quality of life, and mortality. The condition is responsible for about 1700 fractures a day (about 650 000 a year) in the European Union alone. Measures to prevent osteoporosis usually focus on a healthy lifestyle, which includes being physically active, no smoking, and taking adequate amounts of calcium and vitamin D. Pharmaceutical treatment in high-risk groups (such as people with an elevated risk of fracture) and measures to prevent falls are also proposed as important interventions for preventing fractures. Screening for osteoporosis, by measuring bone density or other measures, is suggested to identify and treat people at risk for fracture.

### **Findings**

Essentially all studies on osteoporosis focus on women. Virtually no study has addressed it in men.

Some of the most prominent preventable risk factors for fractures are age, previous fractures, low bone density, inadequate physical activity, impaired vision, tendency to fall, smoking, and the use of corticosteroids. Several randomized controlled trials have demonstrated that the physical activity of walking increases the bone density of both the spine and the hip in postmenopausal women. Also, other physical activities, such as aerobics and weight-bearing exercises, increase the bone density of the spine. Moreover, several epidemiological studies have demonstrated that smoking decreases bone density and increases the risk of fractures in both men and women and that quitting smoking decreases the risk of fractures. An increased tendency to fall, due to many factors (such as impaired vision and poor body balance), may be effectively prevented – for example by doing T'ai Chi exercises, doing muscle and balance training, and reducing psychopharmacological treatments.

Strong evidence shows that many different pharmaceuticals are effective in both preventing (by increasing bone density) and treating (by decreasing fractures) osteoporosis in women with an increased risk of fractures after menopause. When taking the most prominent risk factors into account, a modeled cost-effectiveness analysis based on clinical trials suggests that pharmaceuticals can be cost effective also. For women without documented osteoporosis after menopause, there is no evidence that vitamin D alone prevents fractures related to osteoporosis. However, a combination of vitamin D and calcium may reduce the rate of fracture by about 30% – in particular, for people more than 60 years old and for those who show adherence to treatment. Also, the evidence base for the efficacy of preventing fractures in women more than 80 years of age needs to be strengthened.

Although there is no direct evidence that screening for osteoporosis reduces fractures, there is good indirect evidence that screening is effective in identifying postmenopausal women with low bone mineral density and that treating osteoporosis can reduce the risk of fractures (wrist and spine) in this population.

### **Policy considerations**

Several measures for preventing osteoporosis show evidence of being effective. Such measures include moderate physical activity, an appropriate intake of calcium and vitamin D, a cessation of

smoking, and pharmaceutical intervention in high-risk groups. Also, effective dissemination of findings from research should be used to increase the awareness of osteoporosis, both among the general population and in the health services, to increase early detection of risk factors and to motivate preventive measures.

Although there is some evidence for the indirect effectiveness of selective screening in reducing the risk of fractures (mainly in women over 65 years of age), by identifying and treating those at high risk, there are several questions that remain to be answered before such programmes can be recommended at the population level. Also, the total cost of a general screening programme for women more than 65 years of age may not be affordable or cost effective for many countries. Moreover, there is insufficient evidence of the effectiveness of treating low-risk populations. Furthermore, currently available findings from trials of pharmacological treatments are only relevant under controlled circumstances and to certain risk groups.

## **Contributors**

### *Authors*

Professor Olof Johnell  
Department of Orthopaedics  
Malmö University Hospital  
SE-205 02 Malmö  
Sweden

Peter Hertzman, PhLic.  
Karolinska Institute  
SE-171 77 Stockholm  
Sweden  
and  
European Director, Health Economics  
Amgen GmbH  
Alpenquai 30  
Box 2065  
CH-6002 Lucerne  
Tel: +41 41 369 2549  
Fax: +41 41 369 0403  
E-mail: [peter.hertzman@amgen.com](mailto:peter.hertzman@amgen.com)

### *Technical editor*

Professor Egon Jonsson, Health Evidence Network, WHO Regional Office for Europe.

### *Peer reviewers*

Dr Laura Sampietro-Colom, Ministry of Health of Catalonia, Spain; Professor Lars Werkö, Consultant for the Swedish Council on Technology Assessment in Health Care (SBU), Sweden; and Dr Deborah Marshall, Innovus, Canada.

## **Introduction**

Osteoporosis, from the Greek words *osteon* for bone and *poros* for pore, is a condition characterized by an excessive decrease in bone mass. It is a common condition, especially among elderly women, and is a major risk factor for fractures, which occur most commonly at the wrist, spine and hip. However, other important risk factors for fractures include those both related and unrelated to an excessive decrease in bone mass. Those related to an excessive decrease in bone mass include such causes as physical inactivity, smoking, low body weight, a history of fractures and the use of corticosteroids; those unrelated to bone mass loss include causes such as falls, high alcohol intake and visual impairment.

Because of related morbidity and disability, diminished quality of life, and mortality, osteoporosis and the fractures associated with it are major public health concerns. As a result of osteoporosis, the European Union alone has about 1700 fractures a day, or about 650 000 a year (1, 2). The worldwide prevalence of disability from hip fractures only (although the definition of osteoporosis related fractures is much broader) has been projected to be about 2.6 million people by 2025, and deaths following hip fracture have been projected to be about 700 000 deaths a year by the year 2025 (3, 4).

Recommendations to prevent osteoporosis usually focus on a healthy lifestyle, which includes no smoking, moderate alcohol consumption, an intake of adequate amounts of calcium and vitamin D, and sufficient physical activity. Pharmaceuticals and measures to prevent falls are also important interventions for preventing fractures.

Screening for osteoporosis is often suggested for identifying and treating people at risk for fractures (5). There are a number of screening procedures available, including so called prescreening questionnaires, to identify people at risk for bone fracture, and there are several technologies for measuring bone density.

## **Sources for this review**

The main sources for this review have been the databases of PubMed/MEDLINE, The Cochrane Library, the Centre of Reviews and Dissemination (CRD), and the International Network of Agencies for Health Technology Assessment (INAHTA). The latter includes about 40 databases from its member agencies. The terms used in the searches included “osteoporosis and prevention”, “screening and osteoporosis”, and “prevention and screening and osteoporosis”. Reference lists in systematic reviews were used to obtain more specific information. Also, systematic searches were made up to the year 2003, and selected studies published in 2004 and 2005 were added later. For studies on economic evaluations of the condition, searches were done on MEDLINE and the National Health Service Economic Evaluation Database (NHS EED) through the OVID database for the years 1990–2005, using the following key words: “osteoporosis (or osteopenia) and economics (or costs or cost-effectiveness or cost-benefit) and English”. In addition, a comprehensive systematic review by the Swedish Council on Technology Assessment in Health Care (SBU) was used as an important source (6).

## **Findings on prevention**

The risk factors for fractures related to osteoporosis are both preventable and unpreventable. Unpreventable risk factors include age, heredity, ethnicity, tall stature, being female and having early menopause. Preventable risk factors include smoking, excessive alcohol consumption, impaired vision, inadequate physical activity, low weight, use of corticosteroids, secondary osteoporosis, the tendency to fall, low exposure to sunlight and low bone density.

## **Preventable/treatable risk factors**

### Bone-mass-related risk factors for fracture

#### *Physical activity/inactivity*

One case-control study, two prospective cohort studies and a meta-analysis of observational studies show good evidence that, among both women and men, physical inactivity is a risk factor for osteoporosis as well as for fractures (7–10).

A Cochrane review of 18 randomized controlled trials concluded that walking is effective in increasing the density of the bone mass in the spine and the hip in postmenopausal women (11). Aerobics and weight-bearing and weight-resistance exercises were also found to be effective in increasing the bone density of the spine and the wrist in postmenopausal women. The review, however, contained no specific information about the amount of walking or exercise needed.

#### *Previous fractures*

A previous fracture is a major risk factor for new fractures. A meta-analysis based on individual data showed that the risk of new fractures among people having experienced an earlier fracture doubled (12), which is also the conclusion of another meta-analysis (11). Since these individuals are already identified in the health care system, this finding is important.

#### *Low weight*

Five prospective cohort studies and two cross-sectional studies showed that women with low body weight and low body mass index are at higher risk for both osteoporosis and fractures (13–18). The risk, however, appears to be lower for men.

#### *Smoking*

Several studies, mainly prospective cohort studies, have demonstrated that smoking decreases bone density and increases the risk of fractures for both men and women; they also demonstrated that quitting smoking decreases the risk of fractures (9, 19–24).

#### *Low exposure to sunlight*

A few studies (prospective multicentre and cross-sectional studies) have demonstrated an association between low levels of exposure to sunlight and the prevalence of hip fractures in all people more than 50 years of age (25, 26). A meta-analysis showed the same results (11). A potential explanation of this finding may be that a low level of exposure leads to poor uptake of vitamin D.

#### *Treatments with cortisone*

Some pharmacological treatments with corticosteroids reduce bone density and increase the risk of fractures (10, 27). However, inhalation steroids taken in low to moderate doses for long-term treatment of asthma do not seem to increase the risk of osteoporosis and fractures (28).

### Other risk factors for fracture

#### *Tendency to fall*

An increased tendency to fall may be due to weak muscles, impaired mobility, medications that cause dizziness or reduced awareness, urinary incontinence, impaired vision, high alcohol consumption, and poor balance. Several cross-sectional and prospective cohort studies have demonstrated that falling is a



major risk factor for fractures among the elderly, whether related to osteoporosis or not. It has also been shown that about 25% of people over 65 years of age have fallen at least once in the recent year and that 40% of people 80–84 years of age have fallen at least once in the recent year (6).

A Cochrane review on the prevention of falls concluded that several measures have shown to be effective, although the dose and intensity needed for sustainable prevention are yet unknown (11). Effective measures for preventing falls are:

- T'ai Chi exercises
- muscle and balance training
- multidisciplinary/multifactor interventions
- reduction of psychopharmacological treatments.

#### *Alcohol consumption*

A meta-analysis showed that alcohol is not a risk factor for fractures related to a decrease in bone mass (10). However, two large prospective cohort studies showed that the risk of fractures, particularly hip fractures, increases for both men and women with an increased and very high weekly consumption of alcohol – from 28 to 41 drinks a week, including 4 cl of hard liquor per drink – due probably to reduced stability (29, 30).

#### *Impaired vision*

Three case-control studies demonstrated a significant increase in falls and hip fractures (40% higher risk) among both men and women with impaired vision (31–33).

#### *Low bone density*

The risk of fractures of the hip, wrist, upper arm and vertebrae increases for both men and women with decreased bone density (7, 34–38). Lifestyle changes, calcium and vitamin D supplementation, and pharmacological treatments for low bone density decrease the risk of fractures (see the following section on “Prevention by calcium supplementation and vitamins”).

#### *Environmental factors*

The skeleton is able to store certain toxins, such as lead, cadmium and aluminum. Though the effects on the skeleton are unknown, a few studies point to an association between exposure to cadmium and an increased risk of fracture (39, 40).

#### *Combined risk factors*

Some studies have assessed the effect of several risk factors present at the same time (7, 25, 41). These studies show that the greater the number of risk factors present, the greater the risk of fracture. However, the information about which risk factors add to others is unavailable.

## **Prevention by calcium supplementation and vitamins**

### Calcium supplementation

Calcium supplementation would be a simple and inexpensive strategy to prevent osteoporotic fractures. In a consensus statement, the United States National Institutes of Health claimed that the intake of high levels of calcium – for example, from milk and cheese – reduces the risk of osteoporosis (42).

A recent Cochrane systematic review of 38 randomized controlled trials compared both vitamin D alone and combinations of it with calcium (43–45). A meta-analysis showed no evidence of reduced fracturing with vitamin D alone. The combination of calcium and vitamin D, however, reduced the fracture rate by 19%, with people living in institutions receiving the greatest benefit.

A recent cohort study of 36 282 women showed that women older than 60 years who receive calcium plus vitamin D supplements have a significantly reduced risk of hip fractures (about 30% less risk) if they adhere to treatment (46).

### Vitamin A

Several epidemiological studies show an association between increased intake of vitamin A and an increased risk of hip fractures, for both men and women (47–49). These findings, however, are inconsistent.

### Vitamin C

The results of studies on the effect of vitamin C on bone density and the risk of fractures are contradictory (50–52).

### Vitamin D or vitamin D analogues

A systematic review of all available randomized or quasi-randomized trials on the use of vitamin D or vitamin D analogues to reduce fractures found that vitamin D3 alone (without calcium supplementation) was not associated with any reduction in the incidence of hip fracture or other non-vertebral fractures (43–46). However, in combination with calcium supplements, vitamin D3 was associated with a reduced incidence of hip fractures among frail elderly people. In healthy younger participants, the effect on hip fractures is unknown.

### Vitamin K

Dark green vegetables are rich in vitamin K, which is also produced by the body. Some epidemiological studies have found that low intake of vitamin K is associated with low bone density and increased prevalence of fractures (53, 54). This association is difficult to verify, since vitamin K also is a marker of poor dietary intake.

### Prevention by hip protectors

A hip protector usually consists of specially designed underwear with a built-in plastic shield for the hip. Several trials of hip protectors found both positive and no effects. A recent systematic review of 15 trials pooled data from 11 of these and showed evidence of a marginally significant reduction in the incidence of hip fracture (55). The authors of the review point to the great heterogeneity of the patients studied in the different trials, which were included in this meta-analysis. In reviewing data from three individually randomized trials, involving 5135 community-dwelling participants provided with hip protectors, no reduction in the incidence of hip fractures was demonstrated (55).

### Prevention by pharmaceuticals

There are a number of well-performed randomized controlled trials of pharmaceutical interventions for the prevention and treatment of osteoporosis – mainly in high-risk groups. Many of these trials have demonstrated beneficial effects in women at high risk of fracture after the onset of menopause, including increased bone density, decreased loss of bone density and decreased risk of different types of fractures. There are few studies, however, on women more than 80 years of age.

Most studies were performed in relatively wealthy regions of the world, such as Australia, Europe and the United States. Therefore, the findings reported in the following subsections may not be relevant to less affluent countries. Because of space limitations in this synthesis, the side-effects of different pharmaceutical treatments are not reported here.

### Bisphosphonates

The ability of these pharmaceuticals, which include etidronate, alendronate and risedronate, to reduce the incidence of osteoporotic fractures among populations at high risk is well documented.

*Etidronate* increases bone density and reduces the risk of hip and spinal fractures among postmenopausal women with osteoporosis. It also appears to reduce the risk of spinal fractures among men. Moreover, etidronate reduces the loss of bone mass that results from treatments with cortisone (56–58).

*Alendronate* reduces the risk of osteoporotic fractures among postmenopausal women with the condition and also reduces the loss of bone mass in patients being treated with cortisone (59, 60).

*Risedronate* reduces the risk of spinal and peripheral fractures among postmenopausal women with osteoporosis, and it decreases the loss of bone mass in patients treated with cortisone. Evidence from randomized trials shows that risedronate is able to achieve this without increasing the overall risk of withdrawal due to adverse effects. In one study, it was also shown to reduce the risk of hip fracture among women 70–79 years of age (60). This particular bisphosphonate is preferred over previously mentioned bisphosphonates due to its lower risk of adverse effects.

### Hormone replacement therapy

For a long time, hormone replacement therapy (HRT) was considered the primary treatment for osteoporosis in postmenopausal women. Among other things, it helps prevent the loss of bone mass. Also, HRT in combination treatment with gestagen helps reduce the risk of non-vertebral fractures (61–63), especially in women younger than 60 years old. When treatment starts after the age of 60 years, no beneficial effect has been shown (61).

However, HRT in combination with gestagen increases the risk of breast cancer, venous thromboembolism, stroke and possibly other heart diseases, and is therefore no longer the first choice of treatment (64).

Estrogen analogues, such as Raloxifene (a selective estrogen receptor modulator or SERM), reduce the prevalence of spinal fractures among postmenopausal women with osteoporosis and also increase bone density (65, 66).

Although the estrogen analogue Tibolone has shown a positive effect on bone density, its effect on fractures remains to be demonstrated (67).

### Other pharmaceuticals

Other pharmaceuticals have been considered in the treatment of osteoporosis in postmenopausal women. These include parathyroid hormone, fluoride, growth hormones, androgens, calcitonin, strontium, statins, tiazides, magnesium, bicarbonates and Ipriflavon.

*Parathyroid hormone* seems to increase bone density in the back and the hip in elderly women with postmenopausal osteoporosis, and it reduces the risk of spinal fractures (68).

*Fluoride* appears to increase bone density in the back; however, it does not reduce the occurrence of vertebral fractures. In increasing the dose of fluoride, the risk of non-vertebral fractures and gastrointestinal side-effects increases without any effect on the vertebral fracture rate (69).

*Growth hormones*, after long-term treatment with them, increase bone density among men and women with osteoporosis; however, data on the effect on fractures are missing (70–72).

*Androgens* include anabolic steroids, corticosteroids and testosterone. There is limited data on their effect on bone density, and there are no data on their effect on fractures.

*Calcitonin* studies show limited evidence of a reduced risk of spinal fracture among women with postmenopausal osteoporosis (73, 74).

*Strontium*, in one randomized study, reduced vertebral and clinical fractures in women with postmenopausal osteoporosis; however, more studies are needed to confirm these findings (75).

*Statins, thiazides, magnesium, bicarbonates and Ipriflavon* have either limited or no data from studies on their impact on fractures.

### Prevention by screening

Screening for osteoporosis, by measuring bone density, can be done with a number of technologies: dual-energy x-ray absorptiometry (DXA), which can measure bone density in the whole body; ultrasound, for measurement in the heel, finger, wrist and knee; CTXA [a software application] for measurement on the hip; and quantitative computed tomography (QCT) for measurement of the vertebrae and wrist.

Very few studies address the use of these technologies in a mass-screening scenario. Though there are studies of the relative detection rate and of the cost of different technologies, these studies do not mention whether population-based screening is effective or cost effective. One study, however, has calculated that the use of ultrasound examinations, in screening at the population level before an actual measurement is done by DXA, is not a cost-effective strategy (76).

Validated questionnaires may also be used to identify high-risk patients who might benefit from treatment or to prescreen those who may need to have their bone density measured. Such questionnaires include the Osteoporosis Self-assessment Tool (OST), the Osteoporosis Index of Risk (OSIRIS), the Simple Calculated Osteoporosis Risk Estimation (SCORE), the Osteoporosis Risk Assessment Instrument (ORAI), and the Age, Body Size, No Estrogen (ABONE) decision rules (41, 77, 78).

Findings from studies of the use of different prescreening tests demonstrate that these tests may be cost effective in mass-screening strategies. One study calculated that prescreening at the population level would cost about €300 per patient. Again, this calculation does not provide any information on whether mass screening is effective or cost effective (79).

A prospective study on the effect of bone mineral density measurements for screening was performed in the United Kingdom on a population of 6282 women 50–54 years of age, with a 5-year follow-up. Of the women screened, 36% were found to have a bone density that required intervention. These patients were sent to a general practitioner (GP) for treatment and follow-up. A total of 1462 women were followed up and, of these, 12% were already being treated (with HRT, which was the treatment of choice at that time) at the start of screening, 57% were found to be suitable for HRT after consultation with a GP, and 60% of these rejected treatment. The authors concluded that screening all postmenopausal women by measuring bone mineral density was not acceptable for several reasons, of

which the potentially low adherence to treatment following screening was a prominent reason (80). Also, the sensitivity and specificity of population-based screening for osteoporosis is rather low (81).

Screening for osteoporosis has been discussed in WHO technical reports, in which the arguments for general screening of all women were found to be weak (2, 82). Many other studies, reviews, and agencies have concluded that the evidence is insufficient to recommend general screening for osteoporosis, although they acknowledge the evidence that bone density measurements may be used to diagnose patients in need of treatment (6, 83–88).

However, this conclusion, that the evidence is insufficient to recommend general screening for osteoporosis, is not shared universally. Based on a systematic review of the literature, the United States Preventive Services Task Force found good evidence that the risk of osteoporosis and fracture increases with age and other factors, that bone density measurements accurately predict the risk of fractures in the short term, and that treating asymptomatic women with osteoporosis reduces their risk of fracture. On the basis of this indirect evidence, the Task Force concluded that the benefits of screening and treatment are, at least, of moderate magnitude for women at increased risk by virtue of age or presence of other risk factors, and it recommended that routine screening begin at 65 years of age for women at increased risk for osteoporotic fractures (5, 89).

## **Findings from economic analysis of prevention and screening for osteoporosis**

The costs and other economic implications of treatment and rehabilitation of osteoporosis related fractures are high. For example, in some western countries, the cost of treating one hip fracture alone during the first year is estimated to be about US\$ 20 000 (90).

For the present synthesis, the literature search on the economic analysis in the field of osteoporosis produced 255 references, of which 44 studies (Annex 1) compared at least two options and included both costs and effects.

Published economic analyses of osteoporosis have moved from the early 1990's preoccupation with appropriate methodology to the rather sophisticated modeling studies of the last five years, which are based on data from randomized controlled trials. Leading health economists (91) have stated that:

*The preferred approach [in economic analysis] is cost utility analysis involving the calculation of cost per quality-adjusted life year [QALY] gained from intervention, since such analyses provide an established mechanism for comparing cost effectiveness across diseases – an important component of investment strategies.*

The preferred approach to modeling uses a Markov model, in which the probability of being in different states of a disease is the basis for the calculations (92). In addition to providing improved epidemiological data, the modeling approach has been central to modern economic analysis of osteoporosis. Further methodological developments, however, are needed to strengthen aspects related to patient preferences, as well as quality of care.

In a meta-analysis of 90 randomized controlled trials – including 5 pharmaceutical interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) in comparison with 5 comparators (calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy, and exercise), as well as with placebo or no treatment – it was shown that all proposed interventions provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the age of the patient – that is, the ratio of cost per QALY fell dramatically with greater age (93).

Many of the other economic studies on prevention of osteoporosis indicate that some pharmaceutical interventions are cost effective. Also, most studies of secondary prevention through pharmaceutical interventions (after an earlier fracture) have shown these interventions to be cost effective – in particular, for HRT and bisphosphonates. However, only two studies on bisphosphonates are based on actual fracture data from clinical trials (94, 95). All other studies model fracture reductions with data from the literature.

Most economic analyses referred to in Annex 1 vary in patient selection and in the assumptions made about duration and effectiveness of interventions, assessment of quality of life, and mortality following hip fracture. Also, they rely on limited empirical data on costs and adverse effects and are based on simulations of the long-term cost-effectiveness of a specific intervention. This has also been observed in another review (96).

The outcome of different preventive approaches on other fractures, besides hip fractures, is usually not included in published economic analyses, although this may have a substantial impact on the cost-effectiveness ratios. The relative adherence of patients to different pharmaceuticals (as a consequence of side-effects) and other patient preferences (such as feelings of being less vulnerable when treated) are also absent from current economic studies. Their inclusion would be expected in future economic evaluations of options for primary or secondary prevention of osteoporosis.

The true cost-effectiveness of different strategies for preventing osteoporosis and related fractures – particularly, in routine clinical care – has not been established.

## **Conclusions**

There is some evidence showing that physical exercise (to reduce falls) can prevent fractures in the elderly. Also, a combination therapy of calcium and vitamin D can reduce the risk of fractures (except vertebral fractures) in elderly women with osteoporosis. Moreover, several pharmaceutical interventions show evidence of effectiveness and cost-effectiveness in increasing bone density and in preventing fractures in selected high-risk groups. However, data are still lacking from studies on patients in clinical routine practice. Furthermore, no direct scientific evidence supports mass screening by the use of bone density measurement. Still remaining to be answered is the important question about the effectiveness of interventions in asymptomatic populations.

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## Annex 1. Table of studies on economic evaluation and outcome of prevention of osteoporosis

Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jonsson B. Intervention thresholds for osteoporosis in the UK. <i>Bone</i> , 2005, 36(1):22–32.	Unspecified	Postmenopausal osteoporotic women	Unspecified, identifies key variables	United Kingdom	Modelling based on risk of fracture	Literature	Quality-adjusted life years	Cost-effective scenarios were found for women at the threshold for osteoporosis, from the age of 60 years. Treatment of established osteoporosis was cost effective, regardless of age. Inclusion of all osteoporotic fractures had a marked effect on intervention thresholds, which varied with age. Available treatments can be targeted cost effectively to individuals from the United Kingdom at moderately increased risk of fracture.
Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, Jonsson B. Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. <i>Osteoporosis International</i> , 2005, 16(1):6–14.	Unspecified	Postmenopausal osteoporotic women	Unspecified, identifies key variables	Sweden	Modelling based on risk of fracture	Literature	Quality-adjusted life years	Intervention thresholds were sensitive to the effectiveness assumed and to the cost of the intervention. The exclusion of osteoporotic fractures other than hip fracture significantly increased the cost-effectiveness ratio because of the substantial morbidity from other such fractures, particularly at younger ages. The inclusion of all osteoporotic fractures had a marked effect on intervention thresholds, which varied with age. Available treatments can be targeted cost effectively to individuals at moderately increased risk of fracture.

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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Schousboe JT, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. <i>Annals of Internal Medicine</i> , 2005, 142(9):734-741.	Medicine	Postmenopausal osteoporotic women with osteopenia but no fractures	Alendronate vs no treatment	United States	Modelling from fractures	Literature	Number of cases detected	For women with no additional risk factors for fracture, the cost per quality-adjusted life year gained ranged from US\$ 70 000 to US\$ 332 000, depending on age and femoral neck bone density. <i>Results of sensitivity analyses:</i> Results were sensitive to changes in the reduced risk of fracture attributable to alendronate and the cost of alendronate.
Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D. Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. <i>Osteoporosis International</i> , 2005, 16(1):15-25.	Medicine	Postmenopausal osteoporotic women 60 years of age and older with a relative risk of vertebral fracture of 2	Raloxifene vs no treatment	United Kingdom	Markov model using Multiple Outcomes of Raloxifene (MORE) study data on vertebral fractures	Multiple Outcomes of Raloxifene (MORE) study	Quality-adjusted life years and life years gained	The cost per quality-adjusted life year gained from treating postmenopausal women without prior vertebral fractures was £18 000, £23,000, £18 000 and £21 000 at the ages of 50, 60, 70 and 80 years, respectively. Corresponding estimates for women with prior vertebral fractures were £10 000, £24 000, £18 000 and £20 000. In relation to threshold values that are recommended in the United Kingdom, the analysis suggests that raloxifene is cost effective in the treatment of postmenopausal women at an increased risk of vertebral fractures.

Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Richy F, Ethgen O, Bruyere O, Mawet A, Reginster JY. Primary prevention of osteoporosis: mass screening scenario or prescreening with questionnaires? An economic perspective. <i>Journal of Bone and Mineral Research</i> , 2004, 19(12):1955–1960.	Screening	Postmenopausal osteoporotic women	Seven different screening scenarios	Belgium	Modelling based on patient cohort data	Cohort, n = 4016	--	In the systematic dual-energy x-ray absorptiometry strategies, the cost per patient detected ranged from €123 (when measuring all women more than 45 years of age) to €91 (when focusing on women more than 65 years of age). The corresponding percentage of cases detected ranged from 100% (age more than 45 years) to 50% (age more than 65 years). The cost-effectiveness analysis showed that mass screening strategies were best for people more than 50 and 65 years of age and when using the Osteoporosis Risk Assessment Instrument.
Brecht JG, Kruse HP, Mohrke W, Oestreich A, Huppertz E. Health-economic comparison of three recommended drugs for the treatment of osteoporosis. <i>International Journal of Clinical Pharmacology Research</i> , 2004, 24(1):1–10.	Medicine	Women 70 years of age with osteoporosis and at least one vertebral fracture	Risedronate vs alendronate vs raloxifene vs no treatment	Germany	Markov model based on risk of fracture	Literature	Fractures avoided and quality-adjusted life years	From the perspective of statutory health insurance, the cost per averted hip fracture was €37 348 for risedronate and €48 349 for alendronate (costs for raloxifene were not calculated due to a non-significant effect on prevention of hip fractures); and the cost per quality-adjusted life year gained was €32 092 for risedronate, in comparison with patients in Germany with no therapy (for alendronate, the cost per quality-adjusted life year gained was €41 302; for raloxifene, it was €1 247 119). This cost-effectiveness analysis shows evidence that bisphosphonates are cost effective.

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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Borgstrom F, Johnell O, Kanis JA, Oden A, Sykes D, Jonsson B. Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. <i>Pharmacoeconomics</i> , 2004, 22(17):1153–1165.	Medicine	Postmenopausal osteoporotic women 60 years old and older with a relative risk of vertebral fracture of 2	Raloxifene vs no treatment	Sweden	Markov model using Multiple Outcomes of Raloxifene (MORE) study data on vertebral fractures	Vertical fracture rates and breast cancer from Multiple Outcomes of Raloxifene (MORE) study	Quality-adjusted life years and life years gained	Intervention costs (in Swedish kronor (SKr) and euros, year 2001 values) in postmenopausal women with a relative risk of vertebral fracture of 2 were SKr 372 000 (€40 000), SKr 303 000 (€33 000) and SKr 263 000 (€28 000) per quality-adjusted life year for women aged 60, 70 and 80 years old, respectively, at the start of treatment, when the clinical definition of vertebral fracture was used.
Borgstrom F, Johnell O, Jonsson B, Zethraeus N, Sen SS. Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. <i>Bone</i> , 2004, 34(6):1064–1071.	Medicine	Men with osteoporosis and previous vertebral fractures	Alendronate vs no treatment	Sweden	Markov model, 10 years with 5 year treatment	Modelling from clinical trial data for women	Quality-adjusted life years	Taking a societal perspective, treating a 71-year-old man (mean age in the fracture intervention trial) with low bone mineral density and prior vertebral fracture with alendronate was found to be associated with a cost of €14 843 per quality-adjusted life year gained. <i>Conclusions:</i> The results in this study indicate that treating osteoporotic men with alendronate was projected to be cost effective, under the assumption of the same fracture-risk-reducing effect of alendronate for men as for women.



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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Singh S, Sun H, Anis AH. Cost-effectiveness of hip protectors in the prevention of osteoporosis related hip fractures in elderly nursing home residents. <i>Journal of Rheumatology</i> , 2004, 31(8):1607–1613.	Device	Elderly women in nursing homes with high risk of fracture	No treatment, and calcium and vitamin D	Canada	Modelling, probabilistic analysis	Various sources of data	Fractures	The use of hip protectors was found to be a dominant strategy, compared with no treatment and with treatment with calcium and vitamin D supplements. Dominance here implies lower cost and better effect, generating cost–effectiveness ratios less than zero. Dominance with respect to cost and effectiveness of hip protectors in preventing hip fractures persisted when the model was subjected to probabilistic sensitivity analysis.
Ohsfeldt RL, Gavin NI, Thorp JM. Medical care costs associated with postmenopausal estrogen plus progestogen therapy. <i>Value in Health</i> , 2004, 7(5):544–553.	Medicine	Women more than 55 years of age	Hormone replacement therapy vs no hormone replacement therapy in matched controls	Canada	Retrospective utilization with matched pairs	Utilized database in Saskatchewan	Only costs included	Excluding drug acquisition costs for hormone replacement therapy and costs of care for osteoporosis, women in their first year of postmenopausal hormone replacement therapy had total medical care costs of about Can\$ 400 greater than women who had never used hormone replacement therapy (1997 Canadian dollars). This total medical care cost differential falls between Can\$ 90 and Can\$ 120 per annum after the first year of therapy. If osteoporosis-related medical care costs are not excluded, the cost differential is about Can\$ 390 during the first year of therapy and between Can\$ 80 and Can\$ 110 per annum after the first year of therapy. These excess costs are primarily the result of excess rates of resource utilization for uterine- and breast-related diagnostic and treatment procedures.

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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Fleurence RL. Cost-effectiveness of fracture prevention treatments in the elderly. <i>International Journal of Technology Assessment in Health Care</i> , 2004, 20(2):184–191.	Device and medicine	Male and female population more than 70 years of age with high risk and with general risk	Hip protector vs vitamin D/calcium vs no treatment	United Kingdom	Markov model based on risk of fracture	Literature	Quality-adjusted life years	In the general-risk female (male) population, the incremental cost per quality-adjusted life year was US\$ 11 722 (US\$ 47 426) for hip protectors. In the high-risk male population, the incremental cost per quality-adjusted life year was US\$ 17 017 for hip protectors. In the high-risk female population, hip protectors were cost saving. Hip protectors dominated Vitamin D and calcium alone in all four subgroups.
Marin F, Lopez-Bastida J, Diez-Perez A, Sacristan JA, ECOSAP DXA Substudy Group. Bone mineral density referral for dual-energy X-ray absorptiometry using quantitative ultrasound as a prescreening tool in postmenopausal women from the general population: a cost-effectiveness analysis. <i>Calcified Tissue International</i> , 2004, 74(3):277–283.	Screening and device	Women more than 65 years of age	Dual-energy X-ray absorptiometry using quantitative ultrasound vs dual-energy X-ray absorptiometry	Spain	Modelling from patient data	Cohort study, n = 267	Cost per true positive	The average cost per osteoporotic case detected based on dual-energy X-ray absorptiometry measurement alone was €23.85. The average cost per osteoporotic case detected using quantitative ultrasound as a prescreen was €22.00. The incremental cost-effectiveness of dual-energy X-ray absorptiometry versus quantitative ultrasound was €114.00 per true positive case detected. Our results suggest that screening for osteoporosis with quantitative ultrasound while applying strict cut-off values in postmenopausal women of the general population is not substantially more cost effective than dual-energy X-ray absorptiometry measurement alone for the diagnosis of osteoporosis.

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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Mullins CD, Ohsfeldt RL. Modeling the annual costs of postmenopausal prevention therapy: raloxifene, alendronate, or estrogen-progestin therapy. <i>Journal of Managed Care Pharmacy</i> , 2003, 9(2):150–158.	Medicine	Postmenopausal osteoporotic women	Raloxifene vs alendronate vs estrogen–progestin vs no treatment	United States	Budget impact modelling	Literature	Fracture events avoided	The annual cost of long-term postmenopausal prevention therapy is highest during the first few years of therapy. Long-term prevention does not provide a return on investment in fewer than three years, but savings in medical costs partially offset intervention costs after two years. For postmenopausal women, pharmacologic interventions with multiple prevention benefits tend to be more cost effective than interventions with a single source of health benefit.
Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. <i>Maturitas</i> , 2003, 44(4):299–305.	Medicine	Institutionalized elderly women	Vitamin D vs no treatment	Seven European countries	Retrospective analysis from clinical trial	Clinical trial	Number of hip and vertebral fractures and non-vertebral fractures	Adjusted to 1000 women, 46 hip fractures were avoided by supplementation with calcium and vitamin D <sub>3</sub> . For all countries, the total costs in the placebo group were higher than in the group receiving supplementation, resulting in a net benefit of between €79 000 and €711 000 per 1000 women.
Johnell O, Jonsson B, Jonsson L, Black D. Cost effectiveness of alendronate (fosamax) for the treatment of osteoporosis and prevention of fractures. <i>Pharmacoeconomics</i> , 2003, 21(5):305–314.	Medicine	Women 71 years of age with previous fractures	Alendronate vs no treatment	Sweden	Modelling based on risk of fracture from the Fracture Intervention Trial	Data from the Fracture Intervention Trial	Quality-adjusted life years	Using alendronate to treat 71-year-old osteoporotic women with a prior spine fracture resulted in a cost per quality-adjusted life-year gained of SKr 76 000, which is well below the threshold for cost-effectiveness of SKr 300 000. For women aged 65 years, the cost-effectiveness ratio increased to SKr 173 000; for women aged 77 years, the cost-effectiveness ratio decreased to SKr 52 000.

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Full reference	Technology	Patient population	Comparator	Country	Method	Clinical evidence	Outcome	Results/Conclusions
Buckley LM, Hillner BE. A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. <i>Journal of Rheumatology</i> , 2003, 30(1):132–138.	Medicine	Women 30 years old with normal bone mineral density starting treatment with glucocorticosteroids as well as elderly women with additional risks	Vitamin D plus etidronate, alendronate vs no treatment	United States	Modelling	Literature	Vertebral fractures avoided	At 10 years, calcium and vitamin D supplements decreased fracture rates by 30–50% at a minimal cost (US\$ 800 or less per vertebral fracture avoided) or at a cost saving compared with no treatment for women with osteopenia (T-score of -1 to -2). Etidronate and alendronate are most cost effective in women with borderline osteoporosis (T-scores of -1.5 and -2, respectively) in the 10-year analysis. In the lifetime analysis, calcium and vitamin D treatment yielded a cost savings when compared with no treatment for all groups with osteopenia.
Willis MS. The health economics of calcium and vitamin D3 for the prevention of osteoporotic hip fractures in Sweden. <i>International Journal of Technology Assessment in Health Care</i> , 2002, 18(4):791–807.	Medicine	Elderly women and younger women with high risk of fracture	Vitamin D and calcium vs no treatment	Sweden	Modelling based on risk of fracture	Literature	Unclear	Treatment of 70-year-old women was cost saving at efficacy as low as two thirds that seen in the clinical trials. Even at modest rates of efficacy, treatment of the high-risk 50- and 60-year-old cohorts was generally cost effective and, in some cases, even cost saving. Particularly cost effective was treatment of women with identified osteoporosis or a maternal family history of hip fracture.

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Nagata-Kobayashi S, Shimbo T, Fukui T. Cost-effectiveness analysis of screening for osteoporosis in postmenopausal Japanese women. <i>Journal of Bone and Mineral Metabolism</i> , 2002, 20(6):350–357.	Screening and medicine	Subgroup of postmenopausal osteoporotic women with osteopenia included in one strategy of the four compared	No intervention vs various screening plus hormone replacement therapy vs hormone replacement therapy for all	Japan	Modelling	Literature	Quality-adjusted life years	Hormone replacement therapy for patients with osteoporosis after screening was the most cost-effective strategy, with the marginal cost-effectiveness being ¥5.36 million per quality-adjusted life year. The ratios for other strategies exceeded ¥10 million per quality-adjusted life year. Sensitivity analyses showed that the drug effect and treatment cost of hormone replacement therapy had a significant influence on the results.
Fleurence R, Torgerson DJ, Reid DM. Cost-effectiveness of hormone replacement therapy for fracture prevention in young postmenopausal women: an economic analysis based on a prospective cohort study. <i>Osteoporosis International</i> , 2002, 13(8):637–643.	Medicine	Young postmenopausal osteoporotic women with low bone mineral density	Hormone replacement therapy vs no treatment	United States	Cohort study	Cohort study, n = 3645	Number of fractures	The cost per averted fracture was about £11 000 (95% CI: £8625 to £13 872) for the whole group; for hysterectomized women, the corresponding figure was substantially less (£1784; 95% CI: £59 to £3532). Hormone replacement therapy given to women at or shortly after menopause is associated with a halving of the incidence of fractures.
Kanis JA, Johnell O, Oden A, De Laet C, Oglesby A, Jonsson B. Intervention thresholds for osteoporosis. <i>Bone</i> , 2002, 31(1):26–31.	Unspecified	Postmenopausal osteoporotic women with different risk factors	Unspecified, identifies key variables	Sweden	Modelling based on risk of fracture	Literature	Quality-adjusted life years	In the base case, intervention was cost effective when treatment was targeted at women at average risk at the age of 65 years and older. Irrespective of the efficacy modeled (10–50%) or of the cost of intervention (US\$ 200–500 per year), segments of the population at average risk could be targeted cost effectively: The lower the intervention cost and the higher the effectiveness, the lower the age at which intervention was cost effective.

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Ben Sedrine W, Broers P, Devogelaer JP, Depresseux G, Kaufman JM, Goemaere S, Reginster JY. Interest of a prescreening questionnaire to reduce the cost of bone densitometry. <i>Osteoporosis International</i> , 2002, 13(5):434-442.	Screening	Postmenopausal osteoporotic women at risk	Different screening approaches	Europe	Cohort study	Questionnaire to cohort, n = 3998	Number of cases detected	A prescreening strategy based on these indications, concomitantly with an age-selective criterion, could represent a promising way towards a more rational use of bone mineral density measurements.
Iglesias CP, Torgerson DJ, Bearne A, Bose U. The cost utility of bisphosphonate treatment in established osteoporosis. <i>QJM</i> , 2002, 95(5):305-311.	Medicine	Postmenopausal osteoporotic women with established osteoporosis	Risedronate vs no treatment	United Kingdom	Modelling from randomized controlled trial data	Literature	Quality-adjusted life years	The use of risedronate therapy in 75-year-old women at high risk of hip fracture leads to an improvement in quality of life with possible cost savings. Restricting the analysis to a time horizon of only three years leads to a quality-adjusted life year gain at a modest net cost.
Chrischilles EA, Dasbach EJ, Rubenstein LM, Cook JR, Tabor HK, Black DM, Fracture Intervention Trial Research Group. The effect of alendronate on fracture-related healthcare utilization and costs: the fracture intervention trial. <i>Osteoporosis International</i> , 2001, 12(8):654-660.	Medicine	Postmenopausal osteoporotic women with previous fractures	Alendronate vs no treatment	United States	Costing from within trial	Randomized controlled trial (Vertebral Fracture Arm of the Fracture Intervention Trial study)	Number of fractures	Alendronate significantly reduced the proportion of patients utilizing fracture-related health care (such as emergency room, hospital, rehabilitation hospital or nursing home) by 25% ( $P = 0.038$ ). Alendronate significantly reduced the costs associated with hip-fracture-related care by 58%, or US\$ 181 per patient randomized ( $P = 0.036$ ). The reduction in fracture-related total costs was 35% (US\$ 190 per patient randomized) in the alendronate group relative to the placebo group ( $P = 0.114$ ).

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Coyle D, Cranney A, Lee KM, Welch V, Tugwell P. Cost effectiveness of nasal calcitonin in postmenopausal women: use of Cochrane Collaboration methods for meta-analysis within economic evaluation. <i>Pharmacoeconomics</i> , 2001, 19(5 Pt 2):565–575.	Medicine	Postmenopausal osteoporotic women with previous fractures	Nasal calcitonin vs no therapy vs alendronate/etidronate	Canada	Modelling	Meta-analysis	Quality-adjusted life years	The meta-analysis showed evidence of the positive effect of both nasal calcitonin and alendronate in reducing the risks of hip, wrist and vertebral fractures in postmenopausal women. However, there was a lack of evidence of the effect of etidronate on hip and wrist fractures. For a 65-year-old woman, with 5 years of therapy, the incremental cost per quality-adjusted life year gained for nasal calcitonin was Can\$ 46 500 compared with no therapy and \$C 32 600 compared with etidronate (1998 values).
Kanis JA, Dawson A, Oden A, Johnell O, De Laet C, Jonsson B. Cost-effectiveness of preventing hip fracture in the general female population. <i>Osteoporosis International</i> , 2001, 12(5):356–361.	Medicine and screening	General female postmenopausal osteoporotic population	Treat all vs screen before treating	Sweden	Modelling based on risk of fracture	Literature	Quality-adjusted life years	Cost-effectiveness was critically dependent on the age and cost of intervention. Reasonable cost-effectiveness was shown even with relatively high intervention costs for women at average risk at the age of 84 years or older. For the cheapest interventions (US\$ 63 per year), cost-effectiveness could be found from the age of 53 years. Variations in effectiveness (15–50% risk reduction) had marked effects on the age that treatment was worthwhile.

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Sim MF, Stone M, Johansen A, Evans W. Cost effectiveness analysis of BMD referral for DXA using ultrasound as a selective prescreen in a group of women with low trauma Colles' fractures. <i>Technology and Health Care</i> , 2000, 8(5):277–284.	Diagnosis	Postmenopausal osteoporotic women	Quantitative ultrasound plus dual-energy X-ray absorptiometry vs dual-energy X-ray absorptiometry	United States	Modelling from small patient cohort	Cohort, n = 46	Number of cases detected	Quantitative ultrasound assessment does not appear cost effective as a prescreen for dual-energy X-ray absorptiometry, even in this high-risk group of women with low trauma Colles' fracture. A quantitative ultrasound prescreen would only be cost effective if the scan could be performed at a substantially lower cost.
Solomon DH, Kuntz KM. Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. <i>Arthritis and Rheumatism</i> , 2000, 43(9):1967–1975.	Screening	Postmenopausal osteoporotic women on corticosteroids	Screening vs watchfulness and waiting	United States	Modelling	Literature	Quality-adjusted life years	Compared with a watchful, waiting approach, the incremental cost-effectiveness ratio for a strategy of screen and treat with alendronate at a bone mineral density T-score of less than -1.0 was US\$ 92 600 per quality-adjusted life year gained. This result was sensitive to the cost and efficacy of osteoporosis therapy and, importantly, to the treatment threshold. At a treatment threshold of a bone mineral density T-score less than -2.5, the incremental cost-effectiveness ratio of screening and treating was US\$ 76 100 per quality-adjusted life year. None of these results differed substantially for women on estrogen replacement therapy.



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Bendich A, Leader S, Muhuri P. Supplemental calcium for the prevention of hip fracture: potential health-economic benefits. <i>Clinical Therapeutics</i> , 1999, 21(6):1058–1072.	Medicine	Postmenopausal osteoporotic women	Calcium vs nothing	United States	Population estimations from clinical data	Randomized controlled trials	Fractures avoided	The data support encouraging older adults to increase their intake of dietary calcium and to consider taking a daily calcium supplement. Even small increases in the usage rate of supplementation are predicted to yield significant savings and to reduce the morbidity and mortality associated with hip fracture at an advanced age.
Torgerson DJ, Reid DM. The pharmacoconomics of hormone replacement therapy. <i>Pharmacoeconomics</i> , 1999, 16(1):9-16.	Medicine	Asymptomatic postmenopausal osteoporotic women	Hormone replacement therapy vs no treatment	United Kingdom	Unclear	Literature	Unclear	As selective estrogen receptor modulators (SERMs) aggravate menopausal symptoms, they are not likely to be an alternative for most perimenopausal women. Therefore, SERMs are more likely to be competitive with existing and forthcoming bisphosphonates than with hormone replacement therapy.
Jonsson B, Kanis J, Dawson A, Oden A, Johnell O. Effect and offset of effect of treatments for hip fracture on health outcomes. <i>Osteoporosis International</i> , 1999, 10(3):193–199.	Unspecified	Postmenopausal osteoporotic women with different risk factors	Unspecified, varying different risk factors	Sweden	Modelling based on risk of fracture	Literature	Quality-adjusted life years	Cost-effectiveness depended critically on the absolute risk determined by the age and the relative risk of hip fracture at any given age. Reasonable cost-effectiveness was shown even with relatively high intervention costs for women with a risk about twice the average at the age of 70 years and older. Cost-effectiveness was critically dependent on the assumptions made about the offset of the effect of intervention after the end of treatment. Where no residual effect was assumed, it was difficult to show cost-effectiveness from any intervention, except for the most effective and least expensive.

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Abbott TA, III, Mucha L, Manfredonia D, Schwartz EN, Berger ML. Efficient patient identification strategies for women with osteoporosis. <i>Journal of Clinical Densitometry</i> , 1999, 2(3):223–230.	Diagnosis	Postmenopausal osteoporotic women 50 years of age and older	Dual-energy X-ray absorptiometry and various combinations	United States	Modelling scenarios from cohort data	Cohort n = 392	Per tested woman	In choosing among efficient strategies, decision-makers must determine the extent to which they are willing to trade off higher programme cost for greater sensitivity.
Langton CM, Langton DK, Beardsworth SA. Comparison of accuracy and cost effectiveness of clinical criteria and BUA for referral for BMD assessment by DXA in osteoporotic and osteopenic perimenopausal subjects. <i>Technology and Health Care</i> , 1999, 7(5):319–330.	Diagnosis	Postmenopausal osteoporotic women 60–69 years of age	Dual-energy X-ray absorptiometry vs various combinations of broadband ultrasound attenuation and clinical criteria	United Kingdom	Modelling scenarios from cohort data	Cohort, n = 107	Per diagnosed postmenopausal osteoporotic women	It is suggested that if both osteopenic and osteoporotic women are to be identified for clinical management that incorporates dual-energy X-ray absorptiometry, then neither broadband ultrasound attenuation nor clinical criteria are satisfactory referral methods. An unanswered question from this study, however, is whether ultrasound has an independent role in assessing the risk of fracture for perimenopausal women who do not have the benefit of referral for dual-energy X-ray absorptiometry.
Rosner AJ, Grima DT, Torrance GW, Bradley C, Adachi JD, Sebaldt RJ, Willison DJ. Cost effectiveness of multi-therapy treatment strategies in the prevention of vertebral fractures in postmenopausal women with osteoporosis. <i>Pharmacoeconomics</i> , 1998, 14(5):559–573.	Medicine	Postmenopausal osteoporotic women	Various combinations of medicine	Canada	Modelling	Literature	Vertebral fractures avoided	Four efficient multi-therapy strategies for the treatment of vertebral osteoporosis in postmenopausal women were identified, two of which were consistent with the practice guidelines of the Osteoporosis Society of Canada. Decision-makers may select from among these efficient strategies on the basis of incremental cost–effectiveness

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Visentin P, Ciravegna R, Fabris F. Estimating the cost per avoided hip fracture by osteoporosis treatment in Italy. <i>Maturitas</i> , 1997, 26(3):185–192.	Medicine and screening	Postmenopausal osteoporotic women	Calcitonin vs calcitonin plus screening vs no treatment	Italy	Modelling	Literature	Hip fractures avoided	Given the incidence of such fractures in Italy and their cost to the health service, we calculate that to prevent one hip fracture 1285 women need to be treated with calcitonin at a cost of over US\$ 2 million.
Garton MJ, Cooper C, Reid D. Perimenopausal bone density screening – will it help prevent osteoporosis? <i>Maturitas</i> , 1997, 26(1):35–43.	Medicine and screening	Women 45 years of age	Hormone replacement therapy with screening or without screening	United Kingdom	Modelling	Literature	Fractures avoided	The proportion of future fractures averted was closely related to compliance with therapy, but for any given level of compliance universal treatment always achieved the greatest reduction in fractures. If compliance was 10%, universal hormone replacement therapy was also the most cost-effective strategy, but if compliance was higher (or if the unit cost of hormone replacement therapy increased) selective strategies were often more cost effective.
Torgerson D, Donaldson C, Reid D. Using economics to prioritize research: a case study of randomized trials for the prevention of hip fractures due to osteoporosis. <i>Journal of Health Services Research &amp; Policy</i> , 1996, 1(3):141–146.	Medicine	Postmenopausal osteoporotic women	Various clinical trials	United Kingdom	Modelling	Literature	Quality-adjusted life years	Vitamin D injection proved to be the most potentially cost-effective treatment with a cost-effectiveness ratio of £584. If averted costs are included, this leads to a saving of £9 176 496 per 100 000 women treated. In contrast, the most expensive therapy was calcitonin (marginal cost-effectiveness ratio of £433 548). This suggests that priority should be given to trials assessing the effectiveness of vitamin D injections.

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Francis RM, Anderson FH, Torgerson DJ. A comparison of the effectiveness and cost of treatment for vertebral fractures in women. <i>British Journal of Rheumatology</i> , 1995, 34(12):1167–1171.	Medicine	Postmenopausal osteoporotic women	Hormone replacement therapy vs etidronate vs calcitonin	United Kingdom	Modelling	Literature	Fractures averted	Estimation of the cost per vertebral fracture averted reflects the underlying cost of medication, with hormone replacement therapy costing £138–680 per fracture averted compared with £1880 per fracture averted for cyclical etidronate therapy and £9075–25 013 per fracture averted for salmon calcitonin therapy. Hormone replacement therapy is therefore the treatment of choice for postmenopausal women with osteoporosis, particularly as it may also decrease the risk of ischaemic heart disease.
Jonsson B, Christiansen C, Johnell O, Hedbrandt J. Cost-effectiveness of fracture prevention in established osteoporosis. <i>Osteoporosis International</i> , 1995, 5(2):136–142.	Unspecified	Postmenopausal osteoporotic women	Unspecified, varying different risk factors	Sweden	Modelling	Literature	Quality-adjusted life years	A comparison between treating the same woman for osteoporosis and mild hypertension shows a cost per life-year gained of SKr 220 000 and SKr 128 000, respectively. Cost per quality-adjusted life year gained is very similar for the two interventions: SKr 105 000 and SKr 103 000, respectively.

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Geelhoed E, Harris A, Prince R. Cost-effectiveness analysis of hormone replacement therapy and lifestyle intervention for hip fracture. <i>Australian Journal of Public Health</i> , 1994, 18(2):153–160.	Medicine	Postmenopausal osteoporotic women	Estrogen from 50 years of age and lifetime, estrogen for 15 years and lifestyle plus calcium	Australia	Modelling	Literature	Quality-adjusted life years	Lifetime estrogen therapy from age 65 years of age achieved the lowest cost per life year gained and the lowest cost per quality-adjusted life years gained. The lifestyle intervention was the most expensive intervention by all measures but was sensitive to the cost of exercise and to the effects of exercise on cardiovascular mortality. Conventionally, estrogen therapy begins at menopause, to avoid the rapid decline in bone mass that occurs with normally decreasing estrogen levels. These results indicate that there is evidence, both in terms of fracture prevention and cost, to justify the introduction of treatment at a later age.
Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. <i>Bone</i> , 1994, 15(4):377–386.	Unspecified	Postmenopausal osteoporotic women	Unspecified, varying different risk factors	United States	Modelling	Literature	Clinical descriptions	Women 65–84 years old were estimated to experience the largest number of fractures, person-years of fracture-related impaired function, and fracture care costs for the next 10 years. Also, the estimated lifetime cost was particularly sensitive to assumptions about fracture-related nursing home utilization rates.

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Daly E, Roche M, Barlow D, Gray A, McPherson K, Vessey M. HRT: an analysis of benefits, risks and costs. <i>British Medical Bulletin</i> , 1992, 48(2):368–400.	Medicine	Postmenopausal osteoporotic women with different risk factors	Hormone replacement therapy vs no treatment	United Kingdom	Modelling	Literature	Clinical descriptions	In terms of net health benefits from the use of hormone replacement therapy, the potential reduction in cardiovascular disease would have greatest effect and would overshadow any small increase in breast cancer risk possibly associated with long-term use. Net expenditure by the National Health Service will depend critically on the direct costs of treatment, rather than on any indirect costs incurred or averted as a result of side-effects.
Clark AP, Schuttinga JA. Targeted estrogen/progesterone replacement therapy for osteoporosis: calculation of health care cost savings. <i>Osteoporosis International</i> , 1992, 2(4):195–200.	Medicine and screening	Postmenopausal osteoporotic women	Hormone replacement therapy combinations with various screening approaches	United States	Modelling	Literature	Clinical descriptions	Based on calculations of the costs of screening and hormone replacement therapy and on the savings in cost of treatment and lost productivity from reduced fractures, it is estimated that the present value of savings in cost of illness for this cohort over a 40-year period is US\$ 5.1 million.

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Cheung AP, Wren BG. A cost-effectiveness analysis of hormone replacement therapy in the menopause. <i>Medical Journal of Australia</i> , 1992, 156(5):312-316.	Medicine	Postmenopausal osteoporotic women 50 years of age	Hormone replacement therapy vs no hormone replacement therapy	Australia	Modelling	Literature	Quality-adjusted life years	The analysis showed that the lifetime net increments in direct medical care costs were largely contributed by hormone drug and consultation costs. Hormone replacement was associated with increased quality-adjusted life expectancy, a large percentage of which was attributed to a relief of menopausal symptoms. Cost-effectiveness ratios ranged from under \$A 10 000 to over \$A 1 million per quality-adjusted life year. Factors associated with improved cost-effectiveness were prolonged treatment duration, the presence of menopausal symptoms, minimum progestogen side-effects (in the case of estrogen with progestogen regimens), estrogen use after hysterectomy and the inclusion of cardiac benefits, in addition to fracture prevention.

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Tosteson AN, Rosenthal DI, Melton LJ, III, Weinstein MC. Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. <i>Annals of Internal Medicine</i> , 1990, 113(8):594–603.	Medicine and screening	Postmenopausal osteoporotic women with no symptoms and with different risk profiles	Hormone replacement therapy vs no hormone replacement therapy	United States	Modelling	Literature	Life years gained	Universal treatment without screening would prevent additional fatal fractures but would expose many more women to the adverse effects of hormone replacement therapy and would cost an additional US\$ 349 000 per year of life gained, compared with the screening strategies. When quality of life was considered, screening was found to be cost effective over a wide range of assumptions. The choice between universal treatment and screening depends on the risks (such as breast cancer), perceived side-effects (such as menstrual bleeding) and benefits (such as prevention of ischaemic heart disease) of estrogen–progestin therapy.