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ORIGINAL ARTICLE

At what hip fracture risk is it cost-effective to treat?

International intervention thresholds for the treatment of osteoporosis

F. Borgström · O. Johnell · J. A. Kanis · B. Jönsson · C. Rehnberg

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Abstract *Introduction:* Intervention thresholds (ITs), the 10-year hip fracture risk at which treatment can be considered to be cost-effective, have previously been estimated for Sweden and the UK. *Objective:* The aim of this study was to provide a Markov cohort model platform for a multinational estimation of thresholds at which intervention becomes cost-effective and to investigate and determine the main factors behind differences in these thresholds between countries. *Results and discussion:* Intervention thresholds were estimated for Australia, Germany, Japan, Sweden, Spain, the UK and USA using a societal perspective. The model was populated with as much relevant country-specific data as possible. Intervention was assumed to be given for 5 years and to decrease the risk of all osteoporotic fractures by 35%. The societal willingness to pay (WTP) for a quality-adjusted life-year (QALY) gained was set to the gross domestic product (GDP) per capita multiplied by two. In the base case analysis, the 10-year hip fracture probability at which intervention became cost-effective varied across ages and countries. For women starting therapy at an age of 70 years, the IT varied from a hip fracture probability of 5.6% in Japan to 14.7% in Spain. The main factors explaining differences in the IT between countries were the WTP for a QALY gained, fracture-related costs and intervention costs. *Conclusion:* The ITs presented in this paper are appropriate for use in treatment guidelines that consider health economic aspects, and they can be used in combination with fracture risk prediction algorithms to improve the selection of patients who are suitable for osteoporotic intervention.

Keywords Cost-effectiveness · Hip fracture · Intervention threshold · Osteoporosis

F. Borgström · C. Rehnberg
Medical Management Centre, Karolinska Institutet,
Stockholm, Sweden

F. Borgström (✉)
Stockholm Health Economics,
Vasagatan 38 2tr,
111 20 Stockholm, Sweden
e-mail: fredrik.b@healthecomonics.se
Tel.: +46-8-54528544
Fax: +46-8-54528549

O. Johnell
Department of Orthopaedics, Malmö General Hospital,
Malmö, Sweden

J. A. Kanis
Centre for Metabolic Bone Diseases (WHO Collaborating Centre),
University of Sheffield Medical School,
Sheffield, UK

B. Jönsson
Stockholm School of Economics,
Stockholm, Sweden

Introduction

Intervention thresholds (ITs) can be defined as the absolute disease risk at which an intervention becomes acceptable. Assessing the risk of disease for which it is acceptable or cost-effective to treat with an intervention can serve as a helpful tool for the synthesis of treatment guidelines. In the derivation of ITs, several components related to the disease and the intervention have to be considered. One component is clinical, which relates to the effects of the intervention: for example, fracture risk reduction and potential side effects of the treatment. A second component is epidemiological, which relates to incidence, mortality and morbidity. The third component is economic, which includes disease-related costs, the cost of intervention and, potentially, the costs associated with a longer life. The economic component always has to be considered since health care budgets are restricted.

Health economic evaluation has been shown to be a useful tool for the estimation of ITs because it facilitates the integration of these components into the same analytical framework. In recent years cost-effectiveness analyses have been used to estimate ITs in areas such as cardiovascular disease and osteoporosis [1–4]. With respect to

osteoporosis, the IT that is most relevant for use in clinical practice has been defined as the probability of fracture at which intervention becomes cost-effective. The clinical manifestation of osteoporosis is variable due to the different fracture types that may arise, each with different consequences for health and costs. For this reason, the IT has been expressed as the 10-year probability of hip fracture at which intervention is cost-effective. However, when only hip fracture is considered in the IT assessment, the probability at which intervention is considered to be cost-effective will be too high since the burden of osteoporosis will be underestimated. The relative importance of hip fracture compared to all osteoporotic fractures differs over age groups. In younger populations (50–60 years), hip fracture represents only about 10% of all osteoporotic fractures, while in elderly populations (80 years and above), about 50% of all fractures occur at the hip. For the purpose of taking all osteoporotic fractures into account when assessing ITs, Kanis et al. estimated age- and gender-differentiated morbidity of other osteoporotic fractures relative to hip fractures, which they denoted hip fracture equivalents [3, 5]. By adjusting the risk of hip fracture using HFEs, the multiple outcomes of osteoporosis are reduced to a common currency which facilitates the estimation of ITs. To date, ITs, using hip fracture equivalents, have been estimated for Sweden and the UK [2–4].

Ideally, data for all components (epidemiological, clinical and costs) should be derived from the country on which the study is based. Fracture risks, morbidity, mortality, costs and the willingness to pay (WTP) for a quality-adjusted life-year (QALY) gained vary between countries, leading to different ITs for similar patient groups in different countries. Therefore, it is extremely relevant to the field of health economic evaluation to estimate ITs for each country separately to be able to reflect these differences. The use of inappropriate ITs when assessing the appropriateness of an intervention might lead to the inconsistent allocation of available resources. That is, patients for whom an intervention is not cost-effective could receive treatment, and vice versa. However, a full set of relevant data is available only for a few countries. The main objective of this study was to estimate and investigate the potential differences in ITs for osteoporosis for women in different countries.

In this study ITs were estimated for women in seven countries representative of different regions around the developed world: Australia, Germany, Japan, Sweden, Spain, UK and USA. These countries were chosen because local estimates of age-differentiated hip fracture risk and cost of hip fractures were available. Local data were used to the greatest possible extent, and where data were missing, a uniform procedure was used to convert Swedish data to other countries for the missing variables. Intervention thresholds were estimated both by using hip fracture equivalents, thereby incorporating the multiple outcomes of fractures, and more conservatively by using the hip fracture risk only. The cost-effectiveness analysis was estimated in a societal perspective with the intention to include morbidity costs, indirect costs and costs of increased survival, where available.

Materials and methods

The model

A Markov cohort model was used to estimate the probability at which intervention is cost-effective. The cohort model is a simplified version of a bone-specific model that has been used to estimate the cost-effectiveness of osteoporotic treatments in various countries [6–12]. The model consists of four health states: *Well*, *Fracture*, *Postfracture* and *Dead*. A cohort of patients starts the simulation at a given age in the *Well* state and passes through the various transition stages of the model at yearly risks of fracture or dying. If a fracture occurs, the patient moves to the fracture state for 1 year. The following year the patient is at risk of dying or sustaining another fracture. If neither occurs, the patient moves to the *Postfracture* state, which captures the long-term consequences of fracture. From the *Postfracture* state it is possible to remain in the same state, the *Fracture* state or die (*Death*). The simulation ends when patients die or reach 100 years of age.

Hip fracture equivalents

The pattern and burden of osteoporotic fractures by age and gender were characterised by Kanis et al. [5]. The site of fractures considered to be osteoporotic (i.e. fractures at the hip, vertebrae, wrist, ribs, pelvis, humerus, clavicle, scapula, sternum, other femoral fractures, tibia and fibula) were weighed according to their morbidity. Morbidity was assessed as utility values – i.e. the reduction in quality of life of having a fracture measured on a scale from 0 to 1. The cumulative disutility over time was calculated for each fracture and each age interval over the remaining lifetime. The total morbidity was then estimated from the age-differentiated incidence for each fracture. The total morbidity for all fractures divided by the hip fracture morbidity resulted in an index of excess morbidity from all fractures in hip fracture morbidity equivalents (HFMQ).

In the latest version, the HFMQ index varies from 6.1 in women between 50 and 55 years of age to 1.5 in women from ages of 80 years and above [3]. In order to take all osteoporotic fractures into account when estimating ITs, the HFMQ indices were multiplied by the population hip fracture risk.

In previous analyses that have estimated ITs for osteoporosis, proportionality was assumed between fracture-related costs and disutility. There is some support for this assumption in the literature [13], but a recent analysis has found that hip fracture-related costs account for a larger proportion of all fracture costs than does disutility [14]. Failure to take this into account will overestimate the overall fracture-related costs and, consequently, give too low fracture probabilities at which intervention becomes cost-effective. Adjusting the fracture cost downwards using a hip fracture cost equivalent index (HFCQ) (varying from 2.3 at ages of 50–55 years to 1.4 at ages of 85 years

and above) in a Markov cohort model gave a markedly better fit compared to a model that included all fractures explicitly as health states [15]. For this reason both the HFMQ and the HFCQ indices were applied when estimating ITs in this study (Table 1).

The data used to derive the HFEs are derived mainly from Swedish sources. Thus, when applying the equivalent indices internationally, an assumption is made that the pattern of relative morbidity and costs between fractures is similar to those in Sweden. This assumption appears to hold true for the developed world [5].

Costing and discounting

All costs are given in the year 2004 values. Costs were, when necessary, inflated using country-specific consumer price indices and converted to the US dollar ($) at the average annual exchange rates for 2004. Both costs and effects were discounted at an annual rate of 3% in the base analysis. In addition, discount rates for costs and effects were based on current recommendations and guidelines for health economic evaluation in the respective countries (a discount rate of 3% in Sweden, Japan and USA, 5% in Germany and Australia, 6% in Spain and 3.5% in the UK [16]) tested.

Intervention

An intervention of 5 years was assumed, which was chosen to approximate the time period where there are direct or indirect clinical data on intervention effects. However, durations of 3 and 10 years were also tested in the sensitivity analyses. After treatment was stopped, the risk reduction was assumed to reverse in a linear manner (also called the offset time of treatment effect) over a 5-year period [17–19] in the base case. No offset time of the treatment effect was assumed in the sensitivity analysis. A recent meta-analysis of the effects of bisphosphonates in postmenopausal osteoporosis [20] indicate an efficacy (relative risk reduction; RRR) on vertebral, hip and other nonvertebral fractures of 43, 39 and 19%, respectively. When ITs were estimated using HFEs, an RRR of 35% was assumed. This was computed from the expected distribution of osteoporotic fractures at each age, the associated utility losses [21] and the efficacy estimates given above. For example, at the age of 60 years the proportion of spine, hip and other fractures is 21, 11 and 68%, respectively, but accounts for 40, 33 and 27%, respectively, of the utility loss. Risk reduction, weighed by the latter figures, gives an overall RRR of 35%. This figure was stable with age, increasing to 36.1% at the age of 80 years. In the sensitivity analysis, an effectiveness of 20% and 50% was also tested.

The intervention cost was assumed to include drug costs and monitoring [one visit to the physician yearly and a bone mineral density (BMD) test every second year]. The yearly drug costs were approximated by the lowest average cost of a bisphosphonate (risedronate or alendronate) (daily regimens) treatment in each country. The total annual intervention costs were estimated at $602, $470, $584, $810, $785, $800 and $500 for Sweden, UK, Germany, USA, Spain, Australia and Japan, respectively. In the sensitivity analysis, ITs were also estimated using a same yearly intervention cost ($600) for all countries.

Table 1 Hip fracture equivalents (HFEs) used for the accounting of all osteoporotic fractures[a]

Age group	HFMQ index[b]	HFCQ index[b]
50–54	6.07	2.33
55–59	4.00	1.83
60–64	3.03	1.70
65–69	2.46	1.55
70–74	2.00	1.49
75–79	1.74	1.41
80–84	1.55	1.33
85+	1.60	1.36

[a]Sources: [3, 14]
[b]HFMQ index, Hip fracture morbidity equivalent index; HFCQ index, hip fracture cost equivalent index

Willingness to pay for QALY gained

Intervention thresholds cannot be determined without a set value for the WTP for a QALY gained. However, no health care system has a set explicit cost-effectiveness threshold value [22]. One way to infer threshold values is to base these on past reimbursement decisions and guidelines made by national government agencies, such as in the UK ($32,000–$48,000/QALY), Australia ($28,200–$51,000/life-year gained) and New Zealand ($10,900/QALY) [22]. Other threshold values that can be derived from the literature vary quite substantially (from $18,000–$650,000), depending on country, perspective, outcome measure (e.g. life-year or a QALY) and methodology [22].

The WHO Commission on Macroeconomics and Health have suggested that interventions with a cost-effectiveness ratio lower than threefold the gross domestic product (GDP) per capita for each averted disability-adjusted life-year (DALY) can be considered good value for money [23] in undeveloped countries. This criterion has been used in health economics studies by, for example, Murray et al. [24] who categorised interventions that gained a year of healthy life at a cost lower than the GDP per capita as very cost-effective and interventions with a cost-effectiveness ratio below threefold the GDP per capita as cost-effective. Accepting this method of setting threshold values would facilitate a differentiation between countries of affordability for one unit of outcome. However, although the DALY and the QALY are measured on the same scale (0 to 1), they are based on different methodologies and are, therefore, not directly comparable. A comparison of available estimates for different disease areas for the two outcome measures fails to suggest any differences of a magnitude that would lead to any major alteration of the

GDP per capita threshold assumption if the QALY were used instead of the DALY [22, 25, 26] . Based on this, we assumed, for the calculation of ITs, a WTP per QALY gained equal to the GDP per capita multiplied by two in each country in the base case analysis (Table 2). The impact of using GDP per capita and GDP per capita multiplied by three as a threshold value was also analysed. Also, ITs were estimated using the same WTP for a QALY ($60,000) for all countries.

Fracture risk

Age-differentiated hip fracture risk for women are available for each country [27–33] and are shown in Fig. 1. The hip fracture risk was given within age intervals for all countries. Simple interpolation was used to obtain age-specific risks. In higher age groups for which no fracture risk data were available, extrapolation was used, based on the trend in the last age interval. In the sensitivity analysis, the same hip fracture incidence (Swedish data) for all countries was tested.

Mortality

Age-differentiated mortality for the general female population was derived from various country-specific sources [34–37]. While hip fracture is associated with an increase in mortality [38], appropriate data on the hip fracture-related mortality are relatively scarce. Therefore, data on age-differentiated excess mortality after hip fracture were derived from a Swedish study [39]. These estimates were adjusted for each country by assuming that the relative risk of mortality during the years after a hip fracture was the same as in Sweden.

Not all excess mortality following a fracture can be related to the fracture event [38, 40]. Therefore, in line with findings in the literature [38, 40], it was assumed that only 30% of the total excess mortality could be related to the fracture event.

Table 2 Purchasing power parity-adjusted GDP per capita (2003)[a]

Country	GDP per capita (US$)
Australia	30,297
Germany	27,094
Japan	28,935
Spain	23,889
Sweden	28,881
UK	29,826
USA	37,658

[a]Source: [49]

Quality of life

Based on the results in a recent Swedish study estimating cost and the quality of life related to osteoporotic fractures, it was assumed that a hip fracture reduced the quality of life by 21% the first year after hip fracture [41]. For the second and following years after the hip fracture, a 10% reduction in quality of life relative to a healthy individual was used [18, 42].

Hip fracture cost

Hip fracture-related costs the first year after fracture were available from the literature for all countries [31, 43–48]. However, the quality of the cost estimates varied quite considerably. None of the estimates were directly comparable for the following reasons, among others: they were based on different methods of collecting data (e.g. prospective/retrospective); they were estimated at different points in time; they did not include all relevant resource items. Sweden is the only country having data on fracture costs that include both direct and indirect costs. The lack of indirect costs does not have any major impact on the results in elderly patient groups since a very low proportion of them will have an active working status. In younger patient groups (below 65 years of age) the exclusion of indirect costs may lead to somewhat underestimated fracture probabilities at which intervention is cost-effective.

In the base case analysis, country-specific hip fracture cost estimates were used. Because of the relatively high variation in the reliability of the country fracture cost estimates, an alternative approach was also tested. Local first-year hip fracture costs were derived from the most recent and comprehensive fracture cost study which had been performed in Sweden [41]. The Swedish hip fracture costs were converted to other country settings by using purchasing power parity (PPP) health care relative price indices where available and general PPP-based relative prices where not [49]. This cost transformation does not incorporate potential differences in the resource use for hip fracture treatment. However, no comparative resource use data appropriate for the use of cost conversion could be found, and this factor was therefore not included.

The long-term cost of a hip fracture (from the second year and on) was based on the proportion (varying from 7% between the ages of 50–54 years to 23% for ages above 85 years) of patients that had to move to a nursing home due to the hip fracture (data on file). All hip fracture cost data are summarised in Table 3.

Costs of increased survival

It has been argued that the difference in consumption and production in added life-years due to an intervention should be added as a cost component in analyses having a societal perspective [50]. Age-differentiated estimates of the costs in added life-years are only available for Sweden

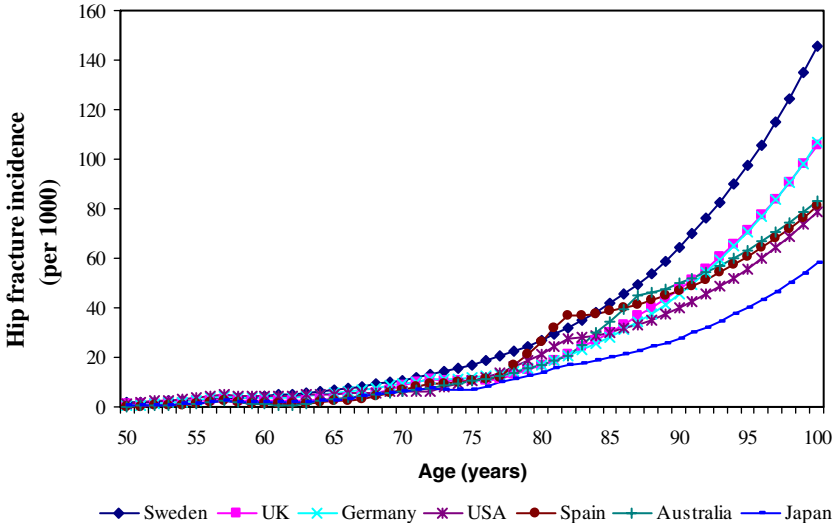

Fig. 1 Hip fracture risk among women in the general population

and the USA [51, 52]. Therefore, ITs were estimated with and without these future costs. The Swedish costs were applied and then converted using the above-mentioned PPP approach for those countries without any available estimates of costs in added life-years. The obvious caveat is that the structure of consumption and production will differ between countries.

Results

Base case analysis

The estimated cost per QALY gained from an intervention compared to no intervention for Swedish patients at the population level of risk of fracture is shown in Fig. 2. The cost-effectiveness improved with increasing starting age of treatment, which is a result of the rising risk of fracture with increasing age. The difference in cost per QALY gained between the HFE approach (i.e. accounting for all osteoporotic fractures) and when looking at hip fracture alone diminishes with increasing starting age because of the higher relative importance of hip fractures, both in terms of costs and morbidity, with advancing age. The exclusion of costs of increased survival did not have any major impact on the results. However, the impact on the cost-effectiveness of this cost item increased with an increase in the fracture risk because of the improved savings of treatment during life. At starting ages of intervention of older than 75 years, intervention was cost saving for all scenarios.

The cost per QALY gained for all seven countries, accounting for all osteoporotic fractures, is shown in Fig. 3. The costs of increased survival are excluded, but as shown in Fig. 2, this did not have any major impact on the results of analyses in women at the population level risk of fracture. A consistent finding for all countries was that the cost per QALY gained decreased (i.e. the cost-effectiveness improved) with increasing starting age of intervention. Overall, cost-effectiveness ratios were similar between countries, with the exception of Australia and Spain, which stood out as having markedly higher cost-effectiveness ratios than the other countries investigated. This is mainly explained by a combination of lower fracture risk, lower estimated hip fracture-related costs and relatively high intervention costs. The cost per QALY gained based on hip fracture risk alone is not shown, but it follows the same pattern as seen for Sweden in Fig. 2.

Intervention thresholds, i.e. the 10-year probability of hip fracture at which intervention becomes cost-effective, based on all osteoporotic fractures and hip fractures only, for different ages and countries are shown in Tables 4 and 5. The IT, as with fracture risk, rises for all countries with increased starting age of treatment. This trend is more marked when all fractures taken into account than when only hip fracture is accounted for. The reason for this relates to the higher share of the total fracture morbidity that is related to nonhip fractures at younger ages. The

Table 3 Hip fracture-related costs

	Australia	Germany	Japan	Spain	Sweden	UK	USA
Hip fracture related cost first year after fracture	11,784 [71]	17,400 [43]	23,227 [31]	8,393 [44]	50–64: 12,523, 65–74: 12,822, 75–84: 13,383, 85+: 18,388 [45]	50–59: 9,226, 60–69: 11,222, 70–79: 13,678,80–89: 20,470, 90–22,906 [46, 47]	13,173 [48]
Yearly cost of nursing stay	29,636 [72]	51,692[a]	37,045 [31]	34,351 [44]	67,355 [73]	30,344 [74]	67,592 [75]

[a]Based on an average cost of three long-term care facilities in Germany

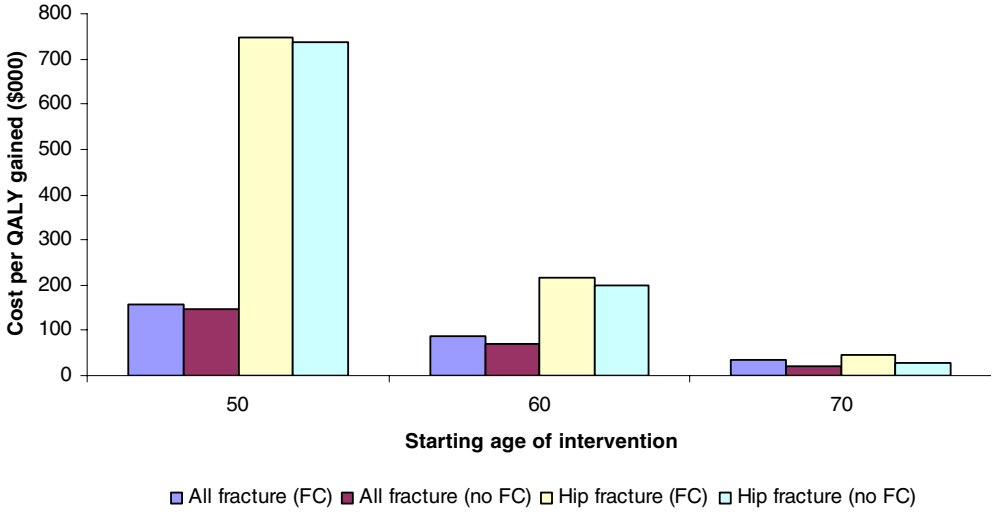

Fig. 2 Cost per QALY gained for Swedish patients according to age based on hip fracture equivalents (HFEs) and on hip fractures only. *FC* Future mortality costs/cost in added life-years/costs of increased survival

inclusion of cost in added life-years (i.e. future cost) gave somewhat higher ITs because of the pattern of higher consumption than production among the elderly. Intervention thresholds were found to be the lowest for the UK and Japan and the highest for Spain. The reason for differences in ITs between countries is due to a combination of a number of different factors which are given in the sensitivity analysis section below.

The relative risk of hip fracture (IT related to the fracture risk of the general population) at which treatment became cost-effective varied between countries and decreased with increasing age (Table 6). There were differences between countries in relative risk at which it was cost-effective. For example, it was cost-effective to treat women at an average risk of hip fracture from the age of 60 years in Sweden but from the age of 78 years in Spain. This difference is due to the higher population fracture risk in Sweden.

Sensitivity analysis

To estimate the impact of parameters that are sensitive to the results and to analyse which parameters are the main contributors to differences between countries, ITs were estimated for 70-year-old women without including costs in added years of life. The estimated ITs based on all osteoporotic fractures for each country is given in Table 7. The impact of a change in a parameter on the IT compared to the base case was quantified as the mean relative country change in the estimated IT compared to the base case. The impact of parameter changes on the estimated IT difference between countries was analysed by calculating the standard deviation (SD) of the estimated thresholds over all countries. For example, if an estimated SD after a parameter change was lower than the SD in the base case, then the difference in the IT had diminished.

Impact of discounting

When costs and effects were not discounted, the threshold decreased by about 30% for all countries, and the difference between the estimated thresholds for different countries diminished somewhat. The application of discount rates in line with national health economic guidelines enhanced the differences in the estimated thresholds between countries.

Impact of costs

The use of converted Swedish fracture costs as PPPs for each country neither altered the base case estimate nor markedly affected the differences in thresholds between countries. When Swedish fracture costs were directly applied without any conversion, the difference between

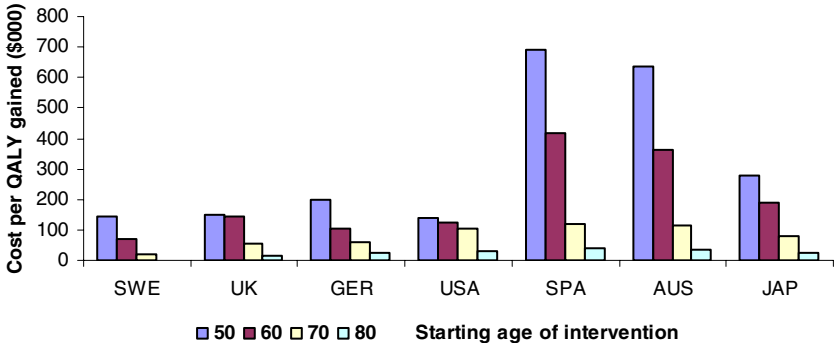

Fig. 3 Cost-effectiveness of intervention for patients at the population fracture risk based on the HFE approach

Table 4 Ten-year hip fracture probability at which intervention becomes cost-effective when accounting for all osteoporotic fractures

Age	Australia		Germany		Japan		Spain		Sweden		UK		USA	
	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)
50	1.93	1.63	1.48	1.23	1.14	0.97	3.05	2.49	1.38	1.16	1.02	0.84	1.09	0.99
55	3.41	2.76	2.65	2.10	2.17	1.78	5.32	4.11	2.59	2.08	2.03	1.58	2.07	1.81
60	5.64	4.47	3.65	2.87	3.11	2.55	8.73	6.42	3.55	2.84	3.18	2.42	2.76	2.40
65	6.04	4.92	4.80	3.78	3.94	3.25	10.83	7.93	4.58	3.72	4.35	3.32	3.95	3.45
70	8.73	7.17	6.88	5.44	5.61	4.67	14.66	10.88	6.56	5.35	5.70	4.37	6.61	5.83
75	10.82	9.20	8.83	7.22	6.95	5.97	18.04	14.20	8.25	6.94	7.43	5.99	7.97	7.20
80	13.11	11.66	10.52	9.04	8.05	7.18	18.91	15.57	9.33	8.18	8.44	7.23	9.27	8.60
85	11.57	10.59	9.49	8.49	7.74	7.14	17.49	15.16	8.35	7.60	7.46	6.70	9.15	8.68
90	10.76	9.99	8.19	7.46	7.30	6.84	15.79	14.06	7.39	6.83	6.48	5.95	8.87	8.50

Table 5 Ten-year hip fracture probability at which intervention becomes cost-effective when accounting for hip fracture only

Age	Australia		Germany		Japan		Spain		Sweden		UK		USA	
	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)	Future costs included (%)	Future costs excluded (%)
50	10.98	9.61	8.18	6.98	6.62	5.75	12.87	12.70	7.75	6.71	6.18	5.17	6.29	5.74
55	13.08	10.96	9.36	7.69	8.11	6.77	21.26	17.73	9.37	7.74	8.14	6.42	7.79	6.91
60	15.11	12.34	9.18	7.55	8.31	7.00	27.46	21.00	8.95	7.47	9.15	7.12	7.41	6.58
65	11.35	9.74	9.21	7.67	7.90	6.78	24.51	18.44	8.58	7.34	9.31	7.38	8.24	7.37
70	12.70	11.04	10.43	8.74	8.99	7.79	25.48	19.74	9.66	8.34	9.62	7.71	10.73	9.72
75	13.12	11.73	11.28	9.73	9.37	8.34	26.19	21.43	10.14	8.98	10.52	8.84	10.67	9.88
80	13.77	12.69	11.66	10.43	9.39	8.61	23.95	20.32	9.94	9.06	10.35	9.14	10.59	10.01
85	12.52	11.78	10.96	10.10	9.32	8.77	23.05	20.40	9.33	8.72	9.45	8.66	10.70	10.29
90	11.62	11.04	9.50	8.86	8.85	8.41	20.82	18.84	8.27	7.82	8.22	7.68	10.31	10.00

Table 6 Relative risk and 10-year hip fracture probability (%) at which treatment becomes cost-effective

	Age (years)	50	60	70	80	90
Australia	Intervention threshold (%)	1.63	4.47	7.17	11.66	9.99
	General population (%)[a]	0.24	1.05	5.14	15.26	16.48
	RR	6.79	4.27	1.39	0.76	0.61
Germany	Intervention threshold (%)	1.23	2.87	5.44	9.04	7.46
	General population (%)[a]	0.53	2.01	5.81	12.55	14.67
	RR	2.32	1.42	0.94	0.72	0.51
Japan	Intervention threshold (%)	0.88	2.30	4.10	6.16	5.89
	General population (%)[a]	0.30	1.09	4.22	10.39	11.53
	RR	2.90	2.12	0.97	0.59	0.51
Spain	Intervention threshold (%)	2.49	6.42	10.88	15.57	14.06
	General population (%)[a]	0.23	0.91	5.83	17.79	14.67
	RR	10.61	7.05	1.87	0.88	0.96
Sweden	Intervention threshold (%)	1.16	2.84	5.35	8.18	6.83
	General population (%)[a]	0.70	2.88	11.17	25.02	24.43
	RR	1.66	0.99	0.48	0.33	0.28
UK	Intervention threshold (%)	0.84	2.42	4.37	7.23	5.95
	General populatio (%)[a]	0.46	1.30	5.29	13.08	15.77
	RR	1.83	1.86	0.83	0.55	0.38
USA	Intervention threshold (%)	0.99	2.40	5.83	8.60	8.50
	General population (%)[a]	0.75	1.80	5.18	13.92	13.99
	RR	1.31	1.34	1.12	0.62	0.61

[a]General population (RR=1)

countries decreased somewhat. When the same annual intervention cost was used, the country threshold difference was reduced – for example, at an intervention cost of $600, the SD of the IT between countries was reduced from 0.023 in the base case to 0.013. The IT also seemed to be quite sensitive to changes in the intervention cost – for example, the threshold decreased, on average, by 60% when the cost was set to $400.

Impact of WTP for a QALY

When using GDP per capita as the WTP for a gained QALY, the threshold value increased by about 36% compared to the base case. When the GDP per capita multiplied by three was used as the WTP, the threshold decreased by 35%. When the WTP for a QALY was set to $60,000 for all countries, the difference in the estimated thresholds was slightly reduced.

Impact of mortality and fracture risk

Alterations in the population mortality did not seem to have any major impact on the estimated ITs. Both the SD of an IT between countries and the relative change of the IT compared to the base case were only slightly changed when the same population mortality rate was used for all countries. As for the mortality rate, the population fracture risk did not appear to have a major impact on the threshold estimates. The small changes that were seen were due to different patterns in the gradient of increased risk and mortality with increasing age.

Impact of treatment effect

The IT was found to be relatively sensitive to changes in the treatment effect. At fracture risk reductions of 20 and 50%, the threshold decreased by 41% and increased by 41%, respectively. When no residual effect of treatment after the intervention period was assumed, the IT increased on average by 38%.

Changes in the treatment duration (3 and 10 years) did not appear to have any major impact on the ITs compared to the 5-year treatment duration used in the base case.

The variables that appeared to have the largest impact on the ITs were treatment effect, WTP per QALY gained and the intervention cost. The major contributors to the difference in estimated thresholds between countries seemed to be the fracture-related costs, intervention costs and the WTP per a QALY gained. Indeed, when these variables were assumed to be the same, the ITs were more or less equal for all countries.

Discussion

The absolute risk of a disease at which it is cost-effective to treat (i.e., an IT) has been estimated previously for a cholesterol-lowering intervention aimed at preventing cardiovascular disease in Sweden [1]. In the study by

Table 7 Sensitivity analysis: 10-year hip fracture probability at which intervention become cost-effective for women starting treatment at age 70

	Australia	Germany	Japan	Spain	Sweden	UK	USA		
	HFE - all fractures (%)	HFE - all fractures (%)	HFE - all fractures (%)	HFE - all fractures (%)	HFE - all fractures (%)	HFE - all fractures (%)	HFE - all fractures (%)	Standard deviation of IT between countries	Mean relative change compared to base case
Base analysis	7.17	5.44	4.10	10.88	5.35	4.37	5.83	0.023	1.00
Discounting									
No discounting	5.44	4.24	3.11	8.39	4.10	3.37	4.40	0.018	1.31
Guidelines recommendations	8.46	6.31	4.10	13.60	5.35	4.54	5.83	0.033	0.92
Costs									
Swedish fracture costs	7.15	5.35	4.52	8.67	5.35	3.93	5.83	0.016	1.04
Swedish PPP converted fracture costs	7.60	5.31	4.27	9.61	5.35	4.05	6.11	0.020	1.01
Annual intervention cost=$600	5.42	5.58	4.90	8.41	5.34	5.54	4.35	0.013	1.15
Annual intervention cost=$400	3.65	3.77	3.30	5.69	3.60	3.73	2.93	0.009	1.60
Annual intervention cost=$800	7.17	7.35	6.46	11.08	7.04	7.31	5.76	0.017	0.82
WTP for a QALY									
1*GDP/capita	10.93	8.21	5.85	18.10	8.15	7.17	9.36	0.040	0.64
3*GDP/capita	5.36	4.07	3.16	7.83	3.99	3.15	4.24	0.016	1.35
$60 000	7.22	5.07	4.01	9.07	5.22	4.35	6.88	0.018	1.02
Mortality									
Same absolute normal mortality	7.28	5.43	4.19	10.68	5.35	4.51	6.11	0.022	0.99
Fracture risks									
Same absolute hip fracture risk	6.98	5.72	4.11	10.25	5.35	4.63	5.41	0.021	1.01
Effect of intervention									
20 risk reduction of treatment	12.30	9.27	7.05	18.49	9.16	7.51	9.97	0.039	0.59
50 risk reduction of treatment	5.07	3.85	2.89	7.73	3.79	3.08	4.12	0.016	1.41
3-year treatment duration	6.28	4.51	3.51	9.43	4.59	3.57	5.25	0.021	1.17
10-year treatment duration	7.46	6.17	4.19	10.34	5.64	4.86	5.68	0.020	0.96
No offset time	12.07	8.28	6.61	17.32	8.63	6.48	10.17	0.038	0.62
Same costs and WTP for a QALY	5.44	5.12	5.26	5.75	5.20	4.97	5.15	0.003	1.16

All fractures included and cost in added life years excluded

Johannesson et al. [1], the IT was estimated on the basis of cardiovascular disease being defined as a single event. The consequences of osteoporosis (i.e. fractures) are difficult to define as a single event because of the different impacts of different fracture types. This has posed a problem for the estimation of ITs for osteoporosis. It has been resolved by the use of hip fracture equivalents (HFEs) that enable all osteoporotic fractures to be accounted for on a single scale [5]. Previous studies have estimated ITs for Sweden and the UK using hip fracture morbidity equivalents, i.e., total fracture morbidity related to hip fracture morbidity, assuming that the fracture-related costs are proportional to the fracture-related morbidity [2–4]. A recent study has found, however, that this assumption is not entirely valid and suggests that the hip fracture costs should be converted using hip fracture cost equivalents when estimating ITs for

osteoporosis [14]. For this reason, hip fracture cost equivalents were used for the estimation of ITs in this study.

From a health economic viewpoint, it is relevant to base treatment guidelines on the absolute fracture risk rather than on other risk factors such as BMD or prevalent fracture. BMD does not predict fracture risk to an degree of satisfaction; for example, it cannot explain the tenfold difference in hip fracture risk between northern and southern Europe [53]. A hurdle to be overcome with ITs (i.e. the 10-year hip fracture probability at which intervention is cost-effective) is to identify the relevant patients at risk of fracture to be treated. In an ongoing project, an individual fracture prediction model is being developed by a WHO working group [54–59]; this model will be able to be used in combination with the IT cost-effectiveness model presented in this study. It is important, however, that the estimated thresholds are relevant for the region in question when making decisions whether to treat or not to treat based on cost-effectiveness thresholds. This is illustrated in the present study in which ITs were estimated for seven countries representative of different regions of the developed world. The ITs were found to vary between countries; for example, the threshold was on average 2.5-fold higher in Spain than in the UK. The analyses show that the most important variables for explaining these country differences are fracture-related costs, intervention costs and the WTP for a QALY gained. These are variables that are likely to continue to differ internationally, consequently making it relevant to estimate country-specific ITs. Variations in fracture risk and mortality were not found to have a major impact on the thresholds and are, therefore, a less important consideration when estimating country-specific thresholds. Of the three important variables, information on treatment costs and the WTP for a QALY (if based on the GDP per capita approach as in this study) is available for most countries. However, data on fracture-related costs are scarce and only available for a few countries. Even the fracture cost data used in this study differ quite markedly in quality, which is a contribution factor to some of the uncertainty in the results. The only fracture cost estimates that included all of the relevant information needed for the societal perspective (i.e. direct and indirect costs) were the Swedish costs [41]. However, it is not appropriate to apply Swedish costs directly to other countries due to differences in both resource use and price levels of health care. It is possible, however, to estimate the costs to other countries indirectly by, for example, converting Swedish costs using PPPs (i.e. only considering price levels), as was done in the sensitivity analysis.

The choice of countries included in this study was based on data availability and an attempt to obtain a reasonable geographic distribution. The countries selected are all high-income countries; no low-income countries were included due to a lack of data and because of other major health priorities in these countries which make osteoporosis a less important disease than in their high-income counterparts. It would be more relevant to define ITs in middle-income countries (e.g. in Eastern Europe and East Asia), but the data on which to base this are lacking. A lower economic performance combined with similar costs of medication for these latter countries will lead to higher fracture risks at which intervention becomes cost-effective compared with high-income countries. For example, assuming an intervention cost of $600 and using PPP-converted Swedish fracture costs, the ITs for 70-year-old women can be estimated to be 25% for the average low-income country, 19% for the average middle-income country and 7% for the average high-income country using the World Bank country income categorisation [60]. An alternative could be to estimate ITs for country categories based on economic performance, such as the low-/middle-/high-income classification. However, while such an approach would group countries with similar WTP for a QALY gained, it would ignore different treatment and fracture costs, which are not uncommon.

There are some limitations in the calculation of ITs that need to be considered. The HFEs that are used to take all fractures into account are mainly derived from Swedish data. Thus, using the equivalents in another country assumes that the fracture pattern in that country, in terms of risk, morbidity and costs, are similar to the pattern in Sweden. While there is some evidence that the fracture pattern is similar throughout the Western world [13, 29, 53, 61, 62], this use of HFEs based on Swedish data does contribute some uncertainty to the results when applied in non-Swedish settings. For this reason we also estimated ITs based on hip fracture only. The latter, of course, gives higher probabilities at which intervention becomes cost-effective, since only hip fracture is accounted for, but it can be considered to be a conservative option.

We adopted a societal perspective in this report, which is to say that all costs were included no matter who incurs them. However, country-specific costs in added life-years were only available for Sweden and the USA. Therefore, the Swedish PPP converted values were used for countries for which these data were missing, a factor which may to some extent limit the interpretability of the results when future costs are included.

The societal willingness to pay for a QALY gained, which is needed for the estimation of ITs, is generally not known. In this article we derived country-specific values for a QALY based on the economic performance measured by the GDP per capita, which is a method that has been suggested by the WHO [23, 24].

For the purposes of this paper, we assumed an average effectiveness of 35% on all osteoporotic fractures and a cost of intervention that would include that of the second-generation bisphosphonates. Teriparatide is more expensive but may have comparable efficacy. Calcium and vitamin D are less expensive, but their efficacy may be also less.

The impact of interventions that have generalised extraskeletal benefits and risks would markedly alter cost-effective ITs [6, 10, 63, 64]. The obvious examples are hormone replacement treatment and the selective oestrogen receptor modulators, both of which appear to have an effect on the risk of breast cancer, though perhaps

in different directions [65, 66], and both decrease markers of cardiovascular morbidity [65–67], though no favourable effects of hormone replacement on cardiovascular events have been shown [66, 68].

A key assumption used in the model concerns the duration that an effect persists after treatment has stopped [18]. There is a great deal of uncertainty over the offset time of many treatments. Relatively rapid offset times of a few years have been observed with calcium, calcitonins and vitamin D metabolites. Longer offset times are described for the bisphosphonates, oestrogens, tamoxifen and, more recently, parathyroid hormone [69, 70]. Our assumption of a 5-year offset time is therefore conservative, and longer offset times have been shown to markedly improve cost-effectiveness [18]. A further consideration is that we modelled a fixed treatment time of 5 years; however, altering the duration of intervention has been shown to have only modest effects on the ITs [2].

The ITs are estimated by comparing intervention to no intervention. The comparison of different osteoporotic treatments is not relevant for the estimation of ITs. The primary purpose of ITs is not to select the most appropriate treatment, but to decide whether to treat at all. In clinical practice the first step is to assess the patient, thereafter comes the decision whether to treat and, finally, which agent to use. Thus, the choice of intervention comes later in the decision-making process and can then be tempered by information about the cost-effectiveness of specific treatment options.

In this paper, ITs were estimated only for women. However, about one third of all fractures occur in men, which makes it relevant to estimate thresholds for both sexes. Men were not included in this paper due to a lack of space. A previous study that estimated thresholds for both men and women in Sweden found the ITs to be broadly similar [3].

Intervention thresholds have been estimated for Sweden and the UK in earlier studies [2–4]; the ITs found for Sweden were slightly lower [3] and those for the UK slightly higher [4] than the estimates in this paper. The introduction of hip fracture cost equivalents, i.e. a down adjustment of fracture costs, reduces the benefit of avoiding fractures and thus leads to the higher probabilities at which intervention becomes cost-effective. This is the main underlying clarification of the slightly higher Swedish ITs estimated in this study. This effect also applies to the UK, but since a higher willingness to pay for a QALY gained [about €60,000 (present study) compared to €48,000 (previous study)] and different discount rates [3% for both costs and effects (present study) compared to 6% for costs and 1.5% for effects (previous study)] were used in this study, the ITs derived were a little lower than those calculated in the previous UK study.

This paper presents results based on the best currently available information. However, when new information becomes available (e.g. fracture-related costs, treatment costs, fracture risk reduction or the WTP for a QALY), it will be important to make reassessments of the ITs. For the purpose of facilitating the use of ITs in treatment decisions, an interface version of the model presented in this paper will be made available on the internet (http://www.osteofound.org and http://www.healtheconomics.se). The model will be presented in a user friendly format making it possible for anyone to reassess ITs over a given range of important variables (e.g. treatment effect and costs, treatment duration, discount rates and WTP for a QALY). In addition, more countries than those presented in this paper will be added to the model.

One of the most common uses of cost-effectiveness evaluations is and has been on a health care macro- and mesolevel; for example, giving guidance about reimbursement for the decision makers and in national and regional treatment guidelines. The use of health economic tools has not been all that common at the health care microlevel, i.e. in the decision by the physician of whether to treat the individual patient or not. Through the introduction and use of ITs for osteoporosis in combination with fracture risk score algorithms, cost-effectiveness analysis can also become an important and practical tool in clinical practice.

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References

1. Johannesson M (2001) At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? Eur Heart J 22:919–925
2. Kanis JA, Johnell O, Oden A, De Laet C, Oglesby A, Jonsson B (2002) Intervention thresholds for osteoporosis. Bone 31: 26–31
3. Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, Jonsson B (2005) Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. Osteoporos Int 16:6–14
4. Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jonsson B (2005) Intervention thresholds for osteoporosis in the UK. Bone 36:22–32
5. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
6. Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B (2005) Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. Osteoporos Int 16:15–25
7. Kanis JA, Borgstrom F, Johnell O, Jonsson B (2004) Cost-effectiveness of risedronate for the treatment of osteoporosis and prevention of fractures in postmenopausal women. Osteoporos Int 15:862–871
8. Jonsson L, Borgstrom F, Zethraeus N (2003) Cost-effectiveness of alendronate treatment of osteoporosis in Denmark. An economic evaluation based on the Fracture Intervention Trial. Ugeskr Laeger 165:4112–4116
9. Borgstrom F, Zethraeus N (2003) Economic assessment based on a clinical study of risedronate. Fracture prevention in elderly women with osteoporosis is cost-effective. Lakartidningen 100:36–40
10. Borgstrom F, Johnell O, Kanis JA, Oden A, Sykes D, Jonsson B (2004) Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. Pharmacoeconomics 22:1153–1165
11. Borgstrom F, Johnell O, Jonsson B, Zethraeus N, Sen SS (2004) Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. Bone 34:1064–1071

12. Johnell O, Jonsson B, Jonsson L, Black D (2003) Cost effectiveness of alendronate (fosamax) for the treatment of osteoporosis and prevention of fractures. Pharmacoeconomics 21:305–314
13. Melton LJ 3rd, Gabriel SE, Crowson CS, Tosteson AN, Johnell O, Kanis JA (2003) Cost-equivalence of different osteoporotic fractures. Osteoporos Int 14:383–388
14. Borgström F, Kanis JA, Johnell O, Jönsson B (2006) Are costs of fracture proportional to their morbidity?. Osteoporos Int ECCEO abstract 17[Suppl 2]:47
15. Borgström F, Kanis JA, Johnell O, Jönsson B (2006) Costing fractures for use in health economics modelling. Osteoporos Int ECCEO abstract 17[Suppl 2]: 97
16. ISPOR (2005) ISPOR pharmacoeconomic guidelines. http://www.ispor.org/PEguidelines/index.asp
17. Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M (2002) Treatment of established osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 6:1–146
18. Jonsson B, Kanis J, Dawson A, Oden A, Johnell O (1999) Effect and offset of effect of treatments for hip fracture on health outcomes. Osteoporos Int 10:193–199
19. Jonsson B, Christiansen C, Johnell O, Hedbrandt J (1995) Cost-effectiveness of fracture prevention in established osteoporosis. Osteoporos Int 5:136–142
20. Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J (2005) A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 9(22):1–160
21. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, Jonsson B (2004) The risk and burden of vertebral fractures in Sweden. Osteoporos Int 15:20–26
22. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B (2004) Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 7:518–528
23. Commission on Macroeconomics and Health (2001) Report on macroeconomics and health: investing in health for economic development. WHO, Geneva
24. Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, Lawes CM, Evans DB (2003) Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet 361:717–725
25. Murray CJ, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349:1436–1442
26. Tengs TO, Wallace A (2000) One thousand health-related quality-of-life estimates. Med Care 38:583–637
27. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B (2000) Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int 11:669–674
28. Singer BR, McLauchlan GJ, Robinson CM, Christie J (1998) Epidemiology of fractures in 15,000 adults: the influence of age and gender. J Bone Joint Surg Br 80:243–248
29. Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, Dilsen G, Gennari C, Lopes Vaz AA, Lyritis G et al. (1994) The variable incidence of hip fracture in southern Europe: the MEDOS Study. Osteoporos Int 4:253–263
30. Euopean Commission – Employment and Social Affairs (1998) Report on Osteoporosis in the European Community - Action for Prevention. European Commission – Employment & Social Affairs, Brussels
31. Nagata-Kobayashi S, Shimbo T, Fukui T (2002) Cost-effectiveness analysis of screening for osteoporosis in postmenopausal Japanese women. J Bone Miner Metab 20:350–357
32. Melton LJ 3rd, Crowson CS, O'Fallon WM (1999) Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int 9:29–37
33. Sanders KM, Seeman E, Ugoni AM, Pasco JA, Martin TJ, Skoric B, Nicholson GC, Kotowicz MA (1999) Age- and gender-specific rate of fractures in Australia: a population-based study. Osteoporos Int 10:240–247
34. Government Actuary´s Department. Interim Life Tables. http://www.gad.gov.uk/policy_and_stats/life_tables.htm. Access date: 2004-10-15
35. Instituto Nacional del Estadistica (2002) Tablas de Mortalidad de la Población de España 1998–1999. Madrid
36. Statistical Yearbook of Sweden (2004). Statistics Sweden, Stockholm
37. Human Mortality Database. University of California, Berkeley (USA) and Max Planck Institute for Demographic Research (Germany)
38. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK (2003) The components of excess mortality after hip fracture. Bone 32:468–473
39. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA (1998) Lifetime risk of hip fractures is underestimated. Osteoporos Int 8:599–603
40. Parker MJ, Anand JK (1991) What is the true mortality of hip fractures? Public Health 105:443–446
41. Borgstrom F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, Abdon P, Ornstein E, Lunsjo K, Thorngren KG, Sernbo I, Rehnberg C, Jonsson B (2005) Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int 1–14
42. Jonsson B, Christiansen C, Johnell O, Hedbrandt J, Karlsson G (1996) Cost-effectiveness of fracture prevention in established osteoporosis. Scand J Rheumatol Suppl 103:30–38; discussion, pp 39–40
43. Brecht JG, Kruse HP, Felsenberg D, Mohrke W, Oestreich A, Huppertz E (2003) Pharmacoeconomic analysis of osteoporosis treatment with risedronate. Int J Clin Pharmacol Res 23:93–105
44. Hart WM, Rubio-Terres C, Burrell A, Aristegui I, Escobar-Jimenez Y (2002) Análisis farmacoeconómico del tratamiento de la osteoporosis postmenopáusica con risedronato o alendronato. Rev Esp Enferm Metab Óseas 11:97–104
45. Zethraeus N, Stromberg L, Jonsson B, Svensson O, Ohlen G (1997) The cost of a hip fracture. Estimates for 1,709 patients in Sweden. Acta Orthop Scand 68:13–17
46. Dolan P, Torgerson DJ (1998) The cost of treating osteoporotic fractures in the United Kingdom female population. Osteoporos Int 8:611–617
47. Kanis JA (2002) Epidemiology and costs of fractures in the UK: background document for male osteoporosis model. Personal communication
48. Gabriel SE, Tosteson AN, Leibson CL, Crowson CS, Pond GR, Hammond CS, Melton LJ 3rd (2002) Direct medical costs attributable to osteoporotic fractures. Osteoporos Int 13:323–330
49. OECD Health Data (2005)
50. Meltzer D (1997) Accounting for future costs in medical cost-effectiveness analysis. J Health Econ 16:33–64
51. Ekman M, Zethraeus N, Jonsson B (2001) Cost effectiveness of bisoprolol in the treatment of chronic congestive heart failure in Sweden: analysis using data from the Cardiac Insufficiency Bisoprolol Study II trial. Pharmacoeconomics 19:901–916
52. Meltzer D, Egleston B, Stoffel D, Dasbach E (2000) Effect of future costs on cost-effectiveness of medical interventions among young adults: the example of intensive therapy for type 1 diabetes mellitus. Med Care 38:679–685
53. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK (2002) International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res 17:1237–1244
54. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N (2005) Assessment of fracture risk. Osteoporos Int 16:581–589
55. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A (2005) Alcohol intake as a risk factor for fracture. Osteoporos Int 16:737–742

56. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Predictive value of BMD for hip and other fractures. J Bone Miner Res 20:1185–1194
57. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone 35:375–382
58. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, McCloskey EV, Mellstrom D, Melton LJ 3rd, Pols HA, Reeve J, Silman AJ, Tenenhouse A (2004) A family history of fracture and fracture risk: a meta-analysis. Bone 35:1029–1037
59. De Laet C, Oden A, Johansson H, Johnell O, Jonsson B, Kanis JA (2005) The impact of the use of multiple risk indicators for fracture on case-finding strategies: a mathematical approach. Osteoporos Int 16:313–318
60. World Bank (2003) World development indicators. The World Bank, Washington, D.C.
61. Bacon WE, Maggi S, Looker A, Harris T, Nair CR, Giaconi J, Honkanen R, Ho SC, Peffers KA, Torring O, Gass R, Gonzalez N (1996) International comparison of hip fracture rates in 1988–89. Osteoporos Int 6:69–75
62. Johnell O, Gullberg B, Allander E, Kanis JA (1992) The apparent incidence of hip fracture in Europe: a study of national register sources. MEDOS Study Group. Osteoporos Int 2:298–302
63. Zethraeus N, Borgstrom F, Jonsson B, Kanis J (2005) Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: results based on the Women's Health Initiative randomized controlled trial. Int J Technol Assess Health Care 21:433–441
64. Zethraeus N, Johannesson M, Jonsson B (1999) A computer model to analyze the cost-effectiveness of hormone replacement therapy. Int J Technol Assess Health Care 15:352–365
65. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC (1999) The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 281:2189–2197
66. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288:321–333
67. Hillner BE, Hollenberg JP, Pauker SG (1986) Postmenopausal estrogens in prevention of osteoporosis. Benefit virtually without risk if cardiovascular effects are considered. Am J Med 80:1115–1127
68. Beral V (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362:419–427
69. Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, Qvist P, Kanis JA, Christiansen C (2004) Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. Bone 34:728–735
70. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
71. Randell A, Sambrook PN, Nguyen TV, Lapsley H, Jones G, Kelly PJ, Eisman JA (1995) Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. Osteoporos Int 5:427–432
72. Report on Government Services 2000 (2000) Canberra, Australia
73. Stadsledningskontorets redovisningsstab. Stockholms stads budgetavräkning. http://www.stockholm.se Access date: 2004–08–22
74. Netten A, Rees T, Harrison G; Unit Costs of health and Social Care (2002) Personal Social Services Research Unit, University of Kent
75. MetLife Mature Market Institute (2003)