OSTEOPOROSIS AND FRACTURE PREVENTION: COSTS AND EFFECTS MODELED ON THE ROTTERDAM STUDY

CHRIS DE LAET

Acknowledgements

The author gratefully acknowledges the collaboration with the Department of Internal Medicine III, the Institute for Medical Technology Assessment, the Department of Epidemiology & Biostatistics and the principal investigators of the Rotterdam Study (principal investigator A. Hofman, for cardiovascular studies: J.C.M. Witteman, formerly D.E. Grobbee, for neurologic studies: M.M.B. Breteler; for ophtalmologic studies: P.T.V.M. de Jong; for loco-motor studies: H.A.P. Pols and for pharmaco-epidemiology : B. Stricker).

This study was financed by the Erasmus Center for Research on Aging.

The financial support of MSD BV for the publication of this thesis is gratefully acknowledged.

ISBN: 90-9012477-2

OSTEOPOROSIS AND FRACTURE PREVENTION: COSTS AND EFFECTS MODELED ON THE ROTTERDAM STUDY

Preventie van osteoporose en fracturen: kosten en effecten gemodeleerd met gegevens uit het ERGO-onderzoek

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de Rector Magnificus

Prof. Dr. P.W.C. Akkermans M.A.

en volgens het besluit van het college voor promoties

De openbare verdediging zal plaatsvinden op

woensdag 17 maart 1999 om 11.45 uur

door

Christiaan Emmanuel Daniël Henri De Laet

Geboren te Antwerpen

Promotiecommissie

Promotores:	Prof. dr. H.A.P. Pols
	Prof. dr. A. Hofman
Co-promotor:	Dr. B.A. van Hout
Overige leden:	Prof. dr. R. Huijsman
	Prof. dr. J.A. Kanis
	Prof. dr. F.F.H. Rutten

CONTENTS

Manuscripts based on studies described in this thesis

Part 1

De Laet CEDH, Van Hout BA, Pols HAP 1996 Osteoporosis in the Netherlands; A burden of Illness study. Institute for Medical Technology Assessment, Rotterdam.

De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Kosten wegens osteoporotische fracturen in Nederland; mogelijkheden voor kostenbeheersing. Ned Tijdschr Geneeskd 1996;140:1684-8.

De Laet CEDH, Van Hout BA, Burger H, Weel AEAM, Hofman A, Pols HAP. Incremental cost of medical care after hip fracture and first vertebral fracture: the Rotterdam Study. Osteoporosis Int 1999 (in press)

Part 2

De Laet CEDH, Van Hout BA, Burger H, Hofman A, Pols HAP. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997; 315:221-5.

De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998; 13:1587-1593

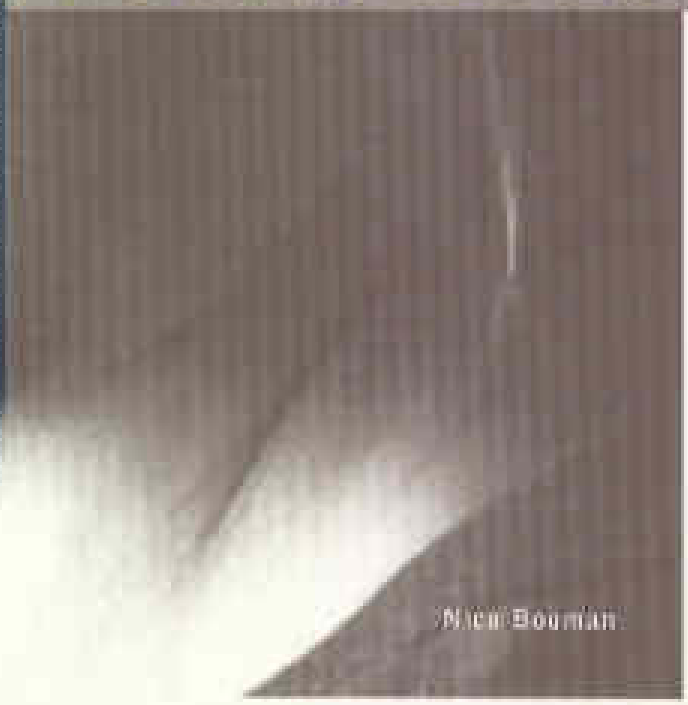
De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Hip fracture prediction in the individual. (submitted)

Part 3

De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Lifetime risk of hip fracture in women (submitted)

De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. The modeling of the effects of therapeutic interventions on osteoporosis. (submitted)

THE PSYCHOSOCIAL ADJUSTMENT OF CHILDREN WITH MAJOR CONGENITAL ABDOMINAL ANOMALIES



Nicu Bouman

INTRODUCTION

Osteoporosis is defined, by consensus, as a systemic skeletal disease, characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.[1] It is well known that there is an important age-related decrease in bone mass and bone strength as witnessed by the exponential increase of hip fractures with age.[2] Osteoporosis is primarily described in post-menopausal women but men are not free from it, and a quarter of the hip fractures occurs in men.[3]

Osteoporosis and its direct consequences, fractures, are major concerns for public health since they are associated with increased death rates and with substantial disability. Moreover, they represent an important cost for the public health budget. The European Commission estimated in a recent report the cost of osteoporosis in the countries of the European Union at € 3.5 billion annually for hospital health care alone,[4] and an American study estimated the total health care expenditure attributable to osteoporotic fractures in the United States at US$ 13.8 billion (€ 12.4 billion) in 1995.[5] Without intervention, the improved life expectancy and the demographic evolution will cause the number of hip fractures worldwide to increase from around 1.7 million in 1990 to over 6 million in 2050.[6] Therefore, it can be expected that medical expenditure will also increase in the coming decades.

Osteoporosis, defined as a reduction in bone mass below a specified threshold, has been shown to be a major determinant of fracture risk.[7] Bone mass can be measured with sufficient accuracy and precision and it is currently the best available indicator of fracture risk, other than age and gender. There is, however, a considerable overlap of bone density values between people who develop fractures and people who do not.[2]

The central goal of this thesis is to study the cost of osteoporosis and fractures in the Netherlands and to develop mathematical models for estimating fracture risk based on Dutch epidemiological data. These models are then used in simulations to analyze the effects of potential preventive measures against osteoporotic fractures. The most disabling of these is the hip fracture, but also wrist fractures and fractures of the vertebrae are considered as osteoporotic fractures.[8] Also from a cost perspective the importance of hip fractures appears to be overwhelming, and therefore the models focus is on hip fractures.

Several treatments are currently available,[2] but to design effective and cost-effective intervention strategies it is important to know who needs to be treated and when this should be done. Ideally, we would like to have long-term data from intervention studies to assess the effectiveness of different intervention strategies, but those studies would be unacceptably long especially when considering hip fractures. Moreover, when the results would finally be available they would most likely not be of interest anymore, since by then new prevention techniques would be more appropriate.

For the development of clinical guidelines, decisions need to be taken now. To handle the existing uncertainties we choose a modeling approach. Modeling allows for the

simulation of reality but should be used with caution. It is important that the assumptions used are reasonable and supported by the best available evidence.

Most of the data used in the models described in this thesis were derived from the Rotterdam study, a large population based prospective cohort study of the occurrence and determinants of disease and disability in the elderly.[9] The study is conducted in Ommoord, a suburb of Rotterdam. It began in 1990, and 7983 men and women aged 55 years and over underwent baseline assessments and are followed-up longitudinally for several disease outcomes including fractures. In the domain of osteoporosis it is one of largest studies in the world, and one of the few that also include men. Additionally, we have used information from other sources, including Dutch registration data, and data from literature.

Part 1 of this thesis focuses on the basic epidemiological information and on information about the cost of osteoporosis and fractures. Chapter 1.1 is mainly a review of the information on the epidemiology and cost of osteoporosis and fractures that was available at the start of this research project in 1995.

Chapter 1.2 takes a closer look at the impact of different fractures on the cost, and it gives some indications on how a more adequate discharge strategy might be a direct way for cost-containment. Additionally it discusses the potential impact of different intervention strategies.

Chapter 1.3 describes a cost study that was performed within the Rotterdam Study population. The aim of this study was to estimate incremental cost of medical care after hip fracture and first vertebral fracture. This was done in a nested case cohort design comparing the health expenditure in fracture patients to the costs generated in a control group that was comparable at baseline.

Part 2 is devoted to the development and validation of risk estimation models for hip fractures. The conventional method of evaluating fracture risk is by bone densitometry, and the World Health Organization has even defined osteoporosis as a bone mineral density that is more than 2.5 standard deviations below the average for young adults.[10] Therefore, the models will be based on bone mineral density, age and gender.

In chapter 2.1 a risk model is theoretically derived, mainly based on Dutch data. Such a model needs validation, and this is done in chapter 2.2. Here, the risk model is validated for its use as a general risk stratification tool, using the fracture follow-up data from the Rotterdam Study.

Finally, in chapter 2.3 the performance of this risk model is evaluated as a prognostic test for the prediction of hip fractures in the individual. The performance of the risk function is compared to the mere prediction by age and gender, and to the use of the conventional T-score and Z-score BMD thresholds.

In Part 3, the previously developed short-term risk estimates for hip fracture are extrapolated to model the long-term hip fracture risk and the potential effects of interventions to reduce this risk. For the purpose of this thesis, this was done for women, but obviously the models could also be applied to men.

In chapter 3.1, the short-term risk estimates are extrapolated to long-term and lifetime risks at different ages. In this chapter the design of the models and the input assumptions are discussed, and special emphasis is given to the uncertainties surrounding future bone mineral density in the individual.

Finally, in chapter 3.2 theoretical intervention scenarios that aim at reducing the long-term risk are modeled. Screening strategies are compared to a population approach considering effectiveness, but also with a focus on cost-effectiveness and the burden related to screening. By comparing different interventions, changing the age of intervention and taking into account the uncertainties about long-term bone mineral density evolution, the expected dynamics of the interventions are analyzed. This finally leads to a series of conclusions that define the context in which prevention strategies can become both effective and cost-effective.

Part 4 concludes this thesis with a general discussion of the results, including suggestions for further research.

REFERENCES

1 Anonymous. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-50.

2 Eddy DM, Johnston CC, Cummings SR, Dawson-Hughers B, Lindsay R, Melto LJ. Et al. Osteoporosis: Review of the Evidence for Prevention, Diagnosis and Treatment and Cost-Effectiveness Analysis. Osteoporos Int 1998;8 Suppl 4.

3 Seeman E. The dilemma of osteoporosis in men. Am J Med 1995;98(2A):76S-88S.

4 European Commission. Report on Osteoporosis in the European Community – Action for prevention.., Brussels 1998

5 Ray NF, Chan JK, Thamer M, Melton LJ. Medical Expenditures for the Treatment of Osteoporotic Fractures in the United States in 1995: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12(1):24-35.

6 Melton LJ3. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14(1):S1-8.

7 Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993;341:72-5.

8 Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. Ann Intern Med 1991;115(11):837-42.

9 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA 1991 Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 7:403-422.

10 Kanis JA 1994 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 4:368-381.

PART 1

BURDEN OF ILLNESS OF OSTEOPOROSIS

1.1 OSTEOPOROSIS IN THE NETHERLANDS: BURDEN OF ILLNESS

This chapter is an abbreviated version of a report that was published as: De Laet CEDH, Van Hout BA, Pols HAP Osteoporosis in the Netherlands; A burden of Illness study. 1996 Institute for Medical Technology Assessment, Rotterdam. It was re-edited for this thesis and redundant details were omitted. The full results can be found in the original report.

1.1.1 INTRODUCTION

In this chapter, we an overview is given of the publicly available quantitative information about osteoporosis in the Netherlands, and of the costs associated with it. It is based on information that was available at the start of our research in 1995. Although the main subject is osteoporosis, the focus is on fractures, as these are clinically the most relevant outcome events. The data were collected from publicly available data sources and from international literature. Information is mostly about the year 1993 (the *reference year*), but on a few occasions information from other years had to be used. When this is so, it is clearly indicated. No primary data collection was carried out for this chapter, except for the section on bone mineral density where recent data from the Rotterdam Study were used. Conversion of cost from Dutch guilders to Euro was done using the official conversion coefficient (2.20371 guilders for € 1).

The information in this chapter was collected from the following data sources:

Central Bureau for Statistics (CBS)

The CBS[1,2] (Centraal Bureau voor de Statistiek) is the official Dutch organization that covers the national registration of a wide variety of statistics, including demography, registration of causes of death, etc. Some of this information is published in yearly and monthly publications. Other information, such as causes of death related to osteoporosis was specifically obtained from CBS for this study.

Foundation for Health Care Information (SIG)

The SIG[3] (Stichting Informatiecentrum voor de Gezondheidszorg) is a national registry collecting various health care related data. All of the hospital admissions in academic and general hospitals within the Netherlands are included in this registration as is most of the nursing home information. Both published information and files specifically obtained from SIG for the purpose of this study were used.

Institute for Medical Statistics (IMS)

IMS[4] is a company that collects data on health care use by sampling General Practitioners and Medical Specialists and asking them about the patient contacts they had within a given week. The reason for encounter, diagnosis, patient demographics, and therapy was recorded. Furthermore, data from pharmacies were sampled to estimate the actual sales of drugs. It is clear that, due to this sampling technique, this information can be expected to be less precise than the information from the previous data sources.

Home Health Care Service Rotterdam

The Home Health Care Service Rotterdam[5] (Thuiszorg Rotterdam) collects information on all home health care activities in the city of Rotterdam. This registration was used to estimate the use of home health care in the Netherlands, assuming that data from Rotterdam could be extrapolated to the whole of the Netherlands.

Literature

Whenever specific data for the Netherlands were lacking, data from the international literature were used for formulating assumptions. Whenever this is done, it will be clearly indicated in the text.

In section 1.1.2 the epidemiology of osteoporosis and fractures will be described. In the subsequent sections, the use of health care, the mortality and the medical cost of the treatment of osteoporosis and fractures will be covered. To take into account the uncertainties surrounding the cost estimates, we will present a minimal and a maximal estimate. When, due to the unavailability of data, assumptions were made in the original report that could be compared to data that became available afterwards, this will also be mentioned.

1.1.2 THE EPIDEMIOLOGY OF OSTEOPOROSIS AND FRACTURES

Demography

As in most Western countries, the population of the Netherlands is aging. The size of the population increased from 10 million to 15 million in the period 1950-1990 mainly due to the post-war baby boom. At the same time there was a gradual increase in the proportion of elderly people. Over the next decades this latter trend will continue. The Dutch population is primarily white Caucasian, and the incidence of osteoporosis is known to be different in other races. No ethnic specific information about osteoporosis is available for the Netherlands.

The Netherlands Central Bureau of Statistics (CBS) produces, on a regular basis, forecasts to predict the future composition of the population. Those forecasts are known as the high, medium and low variant, but their basic assumption is that there will be no drastic changes in neither behavior, policy, (medical) technology and that there will be no major catastrophes. It is what is called a *surprise-free forecast.* The forecasts are based on the trends from the near past. The CBS forecasts are updated each year, on the basis of the latest developments. For this chapter, we used the 1994-2050 forecast.[6]

Different variants of these forecasts are published. The medium variant is the most likely development. In the low variant birth rates as well as immigration and divorce rates are lower, while mortality, emigration and marriage rates are higher. Opposite assumptions are used in the high variant. In the elderly population of interest in this chapter, however, the difference between the several variants is very small. These persons are born, and only changes in mortality rates and migration effects their numbers.

Bone mineral density and the definition of osteoporosis

The bone mineral density (BMD) reference data in this chapter come from the first phase of the Rotterdam Study that was conducted between 1990 and 1993. Baseline BMD measurements (Lunar DPX-L densitometer) were performed in 5814 ambulatory subjects (2446 men) aged 55 years and more.[7,8]

Osteoporosis was defined by the World Health Organization as a bone mineral density (BMD) of 2.5 SD below the mean for young adults,[9] while a BMD between –2.5 SD and –1 SD was defined as osteopenia. This number of standard deviations under the mean for young adults is referred to as the *T-score*. To determine the reference BMD for young adult women, we used a study on BMD and age in Dutch women by Erdtsieck et al..[10] In this relatively small study, the average BMD was 1.01 g/cm^2 for women aged 20-40 years of age. With a SD =0.134 g/cm^2 that is the same at all ages,[8] threshold values are 0.675 g/cm^2 for osteoporosis, and 0.876 g/cm^2 for osteopenia.

Table 1 lists the prevalence of osteoporosis and osteopenia at different ages when these threshold values are applied to the Rotterdam Study. For men, no corresponding Dutch reference values were available. Therefore, the same threshold values were used, since it was felt that the absolute BMD level is more important for fracture risk than the relative level.

Table 1: *Prevalence of osteoporosis and osteopenia at different ages in the Rotterdam Study*

Women	55-59	60-64	65-69	70-74	75-79	80-84	≥85
Osteopenia	42%	47%	50%	53%	53%	53%	50%
Osteoporosis	7%	10%	13%	18%	23%	29%	37%
Men							
Osteopenia	32%	35%	38%	41%	43%	46%	48%
Osteoporosis	3%	4%	5%	6%	7%	9%	11%

It should be remembered that these threshold values are arbitrary. Moreover, the bone densitometers are shipped with manufacturer specific reference values. In the Lunar DPX-L densitometer, the default reference values are those for the USA Femur Reference Population, ages 20-45. Here, a T-score of –2.5 corresponds to 0.681 g/cm^2 for women, which is very similar to our estimate, but to a threshold of 0.769 g/cm^2 for men, which is much higher. Using those values, similar results are obtained for women but for men the prevalence rates are much higher (table 2).

Table 2: *Prevalence of osteoporosis and osteopenia in men at different ages using the thresholds from the Lunar DPX-L, USA Reference population in the Rotterdam Study*

Men	55-59	60-64	65-69	70-74	75-79	80-84	≥85
Osteopenia	47%	48%	49%	50%	50%	49%	48%
Osteoporosis	15%	18%	21%	24%	28%	32%	36%

Hip fractures

In the Netherlands, virtually all persons with hip fractures are treated clinically. Therefore, hospital data give an accurate view of the incidence of hip fractures. Data for

hip fractures in 1993 were collected from SIG hospital registration data. A specific file of all hospital admissions for hip fracture was obtained and analyzed.

In 1993 there were 15.107 hospital admission for hip fracture in the Netherlands (3882 in men). In figure 1, these absolute numbers of fractures were combined with the age and gender distribution of the 1993 Dutch population to calculate the hip fracture incidence in men and women.[2]

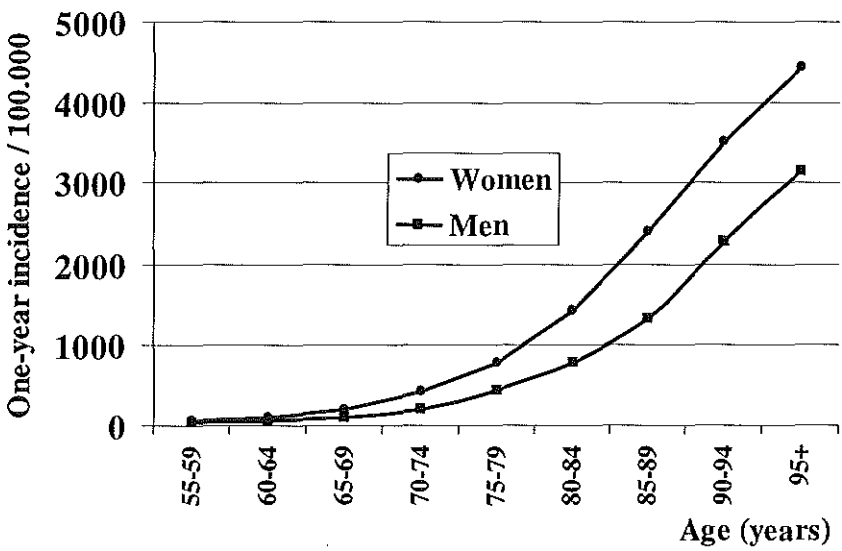


Figure 1: *Hip fracture incidence in the Netherlands in 1993 per 100.000*

Hip fracture incidence data from 1972 till 1987 for the Netherlands were published for men and women aged 50 years and older.[11] Those data were based on the same (SIG) hospital registration source. Hip fracture incidence was age-adjusted by direct standardization. To compare the 1993 data with the published data, we obtained the standard population for the standardization in the same way as in this study by Boereboom et al. (summation of the Dutch population for the calendar years 1972-1987).

When we added the 1993 data to the previous analysis the significant upward trend that was described previously was confirmed. In women, the age standardized hip fracture incidence, that increased from 249/100.000 in 1972 to 345/100.000 in 1987, reached 371/100.000 in 1993. For men, the increase was from 105/100.000 in 1972 over 150/100.000 in 1978 to 168/100.000 in 1993. This trend was highly significant in both men and women ($p<0.001$). Trends in age-adjusted hip fracture incidence in the Netherlands in men and women aged 50 years and older are given in figure 2. The strange peak in the 1979 data remains unexplained, and may be due to a data artifact in that year.

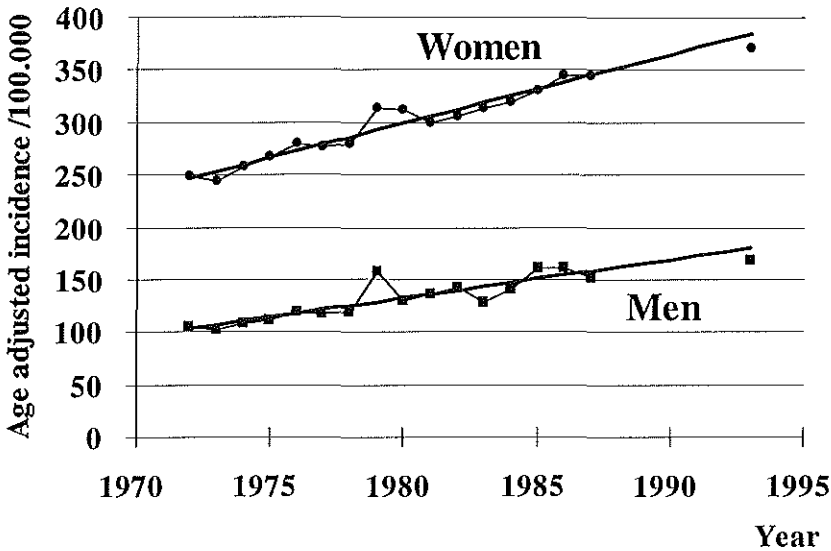


Figure 2: Trend in age adjusted hip fracture incidence in the Netherlands per 100.000

Apart from this important age-adjusted upward trend, it is expected that the total number of hip fractures in the Netherlands will also increase due to the demographic changes with the aging of the population. In figure 3 the current age specific hip fracture rates were applied to the population forecast figures, showing that the total number of hip fractures will double by the year 2050 due to demography alone.

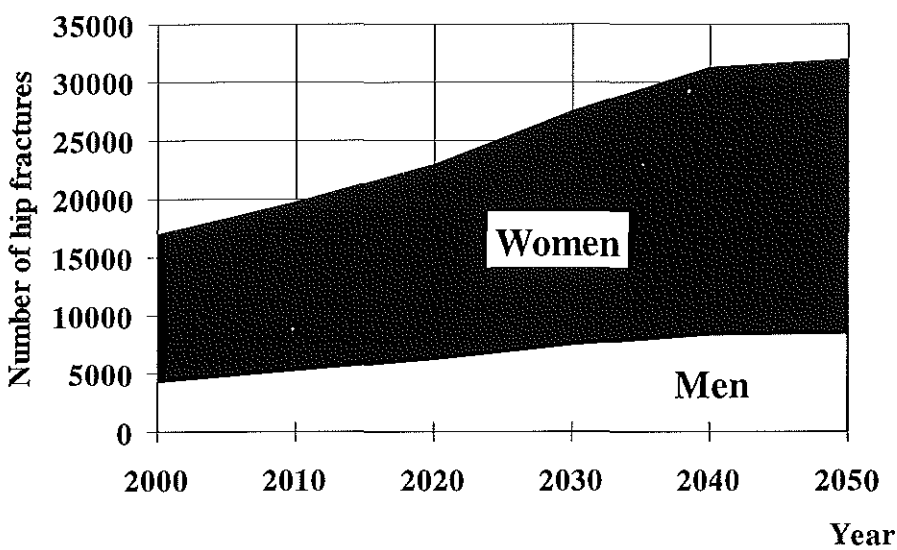


Figure 3: Expected yearly number of hip fractures in the Netherlands due to demographic changes

Other fractures

Dutch data for other fractures

Although hip fractures are the most serious consequences of osteoporosis, other fractures also occur. Those are mainly fractures of the vertebrae and the forearm.[12] Most frequently, those fractures do not require a hospital admission and are treated either in an outpatient setting or, in the case of vertebral fractures, are often not treated at all. When looking at the hospital admissions for fractures other than the hip, we observed smaller numbers and we miss the typically high percentage of persons over 65 years of age. Furthermore, we did not observe the typically high female/male ratio of fractures. Therefore, it seems that those hospital admission data are not reflecting the osteoporosis related fractures, and that they cannot be used to estimate the incidence of osteoporosis related non-hip fractures.

Since, at the moment of writing this report in 1995, no reliable data for osteoporosis related non-hip fractures in the Netherlands were available, we were forced to use data from the international literature. In 1998, however, incidence data for wrist fractures became available from the Rotterdam Study.[13] Those data largely confirmed the assumptions that were made here based on American incidence data.

International data for other fractures

Melton et al., in an 1992 overview article,[14] presented incidence figures for hip, wrist, and vertebral fractures in men and women in Rochester, Minnesota. Although those data should be used with caution, since the incidences refer to different time periods and the vertebral fractures only refer to clinically diagnosed fractures, they appeared to be the best available estimates. We choose to use clinically diagnosed vertebral fractures, since there is some debate about how to define radiographic vertebral deformities. Different techniques of measurement and different criteria can produce varying results and varying fracture rates.[15,16] Additionally, clinically diagnosed vertebral fractures can be expected to be more relevant to cost.

When we compared the Rochester incidence data for hip fractures with the registration data for the Netherlands in 1993, they appeared to be remarkably similar. Therefore, we assumed that we could also use these Rochester data to estimate the number of non-hip fractures in the Netherlands, although we are aware that time trend, and incidence might be different. The upward time trend in the hip fracture incidence for example appears to have stopped in several countries, including the US.[17]

Based on this information we estimated for the Netherlands an annual number of 14.500 wrist fractures, and 15.000 vertebral fractures that came to clinical attention.

1.1.3 HEALTH CARE UTILISATION ASSOCIATED WITH OSTEOPOROSIS AND FRACTURES

Pharmacotherapy

The use of drugs for the treatment and prevention of osteoporosis was estimated based on IMS data. The total figures were adjusted for the estimated proportion of the drug that was used for osteoporosis. Since presentation and dosage can differ from one prescription to another, data were recalculated to estimate patient-years of treatment. The cost of pharmacotherapy is included in the bottom-up cost assessment given in section 1.1.5.

Hospital admissions for hip fractures

Hospital admission data were collected from the SIG hospital registration data. We used the same file of hospital admissions as used for estimating the hip fracture incidence.

The mean length of stay (LOS) was 26.03 days, with a standard deviation of 29 days. The distribution of the LOS was highly skewed and an association with age and gender was observed. Mean LOS in men was 23.7 days; mean LOS in women was 26.8 days ($p<0.001$). Median LOS was 16 days for men and 19 days for women.

After the acute episode, women were discharged more often to a home for the elderly or to a nursing home than men. Some of these patients were probably already a nursing home resident at the moment they suffered a hip fracture, but no information is available about this. In men the crude in-hospital mortality was almost twice that of women. The trends in discharge status are also strongly age dependent as can be seen in figures 4 and 5.

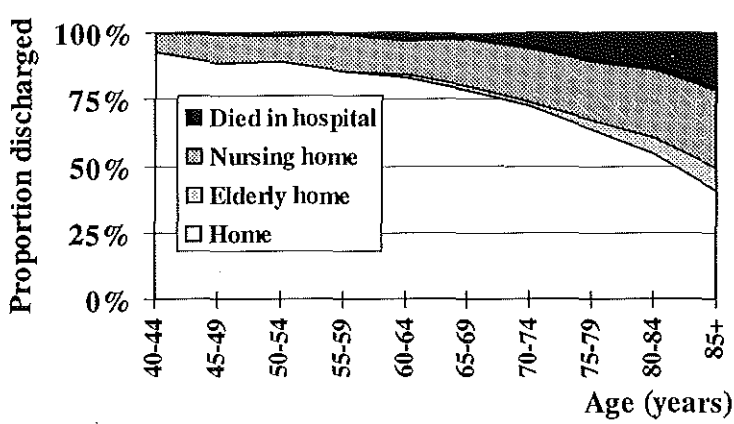


Figure 4: Discharge status by age for men

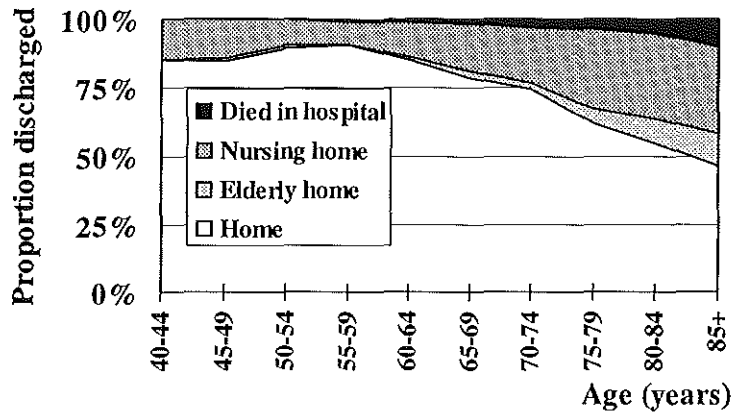


Figure 5: *Discharge status by age for women*

Hospital admissions for other fractures

For other fractures, only data for 1992 were readily available.[18] As mentioned before, we need to be cautious while interpreting those data. These hospital admissions do not seem to reflect the typical osteoporosis related fracture pattern such as a high female/male ratio, and might be more related with high energy trauma. Most people with those fractures were indeed treated as out-patients. Therefore, the cost associated with those hospital admission will only be included in the maximum cost estimate in section 1.1.5

Nursing home care (full care and day care)

Data for nursing home care were obtained from the SIG data source. Data were collected for both full care as for day care in nursing homes. Data collection was relatively complete but less so than for the hospital admission data. Information was available for 89.9 % of nursing homes, corresponding to 92.8 % of the *'somatic' beds* and 91.2 % of the *'psycho-geriatric'* beds. Overall information was available from 92 % of the nursing home beds,[19] and patients with fractures were mainly (98%) treated in the somatic nursing home wards. To obtain a more accurate estimate of the absolute numbers for the Netherlands, we adjusted for this. In addition to the published data, files of all 1993 discharges (full care and day care) with admission diagnosis of hip- or other fractures were obtained and analyzed.

Full care

When analyzing the total population of people in nursing homes, the proportion of people with admission diagnose of fracture seems to be relatively stable. Two cross-sectional views at specific days were compared; one from our data analysis, the other from the published data. Admissions due to fractures accounted for 8.7 % of the population of nursing homes. Over 80 % of these were admitted for hip fractures and its sequels.

We estimated that in 1993, 4588 persons were treated every day in nursing homes for all-fractures. Of those, 3702 were treated for hip-fractures and its sequels.

It was important however to consider that some of the patients might also have been admitted without a hip fracture because of co-morbidity, while the hip fracture event was only the precipitating factor. Therefore, we analyzed the length of stay and the discharge status.

The average length of stay was approximately the same for both genders: 238 days (SD=553) for men and 241 days (SD=553) for women (p=0.85). Median LOS was 67 days for men and 70 days for women. The high mean LOS and its high standard deviation were explained by the relatively large group of people that stayed extremely long (up to 21 years). It was hypothesized that those long stays in nursing homes cannot solely be attributed to the hip-fracture but must largely be due to co-morbidity leading to a more dependent state.

The majority of patients were discharged within 3 months. When those people that stayed up to 3 months in the nursing home were considered separately, the average LOS were 41.6 days (SD=23.6) for men, and 44.0 days (SD=22.4) for women (p=0.02).

When looking at discharge status, we again analyzed those people that stayed for a shorter period separately from those that stayed longer. The majority of people that stayed more than one year in a nursing home, stayed there until they died (over 80 % in both men and women and for all diagnosis groups).

Those persons who stayed for less than one year had a completely different discharge pattern. In general, about 60 % of the people admitted to a nursing home stayed there for a maximum of 3 months. Over 70 % of those returned home afterwards, 8.6 % died in the nursing home. The rest went primarily to homes for the elderly, or to a lesser degree to day care.

For longer stays, the discharge status changed: gradually more people were dying and less people were going home. At 4 months LOS the percentage going home dropped to 54.8 %, after 5 months to 34.6 %. These persons with longer stays clearly represented a more dependent group of people, with more concomitant illnesses. Based of the length of stay and discharge patterns, we hypothesized that only the first few months of stay in a nursing home represented the direct effect of osteoporosis and fractures. Therefore, we included only the cost of the first three months of stay in the nursing home in the calculation of costs in section 1.1.5.

Day care

When analyzing the total population of people in day care, the proportion of people with admission diagnosis of fracture again seemed relatively stable. Two cross-sectional views were compared, one from our data analysis, the other from published data.[19] Admissions due to fractures accounted for 3.1 % of the population in day care. About 85 % of these admissions were for hip fractures and its sequels.

Applying the same adjustment as before, we estimated that in 1993, 239 persons per day were treated in day care for fractures, and 201 for hip-fractures and its sequels.

The average length of stay was 201 days (SD=416) for men and 151 days (SD=215) for women (p=0.27). Median LOS was 86 days for men and 97 days for women. The high averages combined with a high standard deviation (especially in men), were explained by the relatively large group of people that stayed long in day care.

Again, we estimated the total number of day care days on the basis of the registered nursing home days and by applying the same adjustment as before.

Outpatient care

Outpatient care was not systematically registered in the Netherlands. For General Practitioners, there are series of surveys, but those deal primarily with the typical GP pathology and they do not allow to estimate the fracture- or osteoporosis-related number of contacts. For the assessment of the direct cost of outpatient care, we used published cost estimates.[21]

Home health care

The number of clients of home health care and the number of contacts was estimated on the basis of data available for the Rotterdam district. No specific information was available on clinical indication for home health care. To estimate the maximum possible home health care consumption for hip fractures in the Netherlands, we used the number of patients that went home after discharge from hospital. Next we assumed that they all needed home health care. We concluded that at the maximum about 5 % of the total home health care cost could be allocated to hip fractures.

1.1.4 MORTALITY ASSOCIATED WITH OSTEOPOROSIS AND FRACTURES

Osteoporosis related mortality is due to fractures, mainly hip fractures, and mortality following hip fractures is indeed high and age dependent.[21] Attributing death to fractures, however, is not easy. Hip fractures may be associated with death in various ways and official death certification does not necessarily reflect the underlying cause. Therefore, official death certification is not sufficient to indicate the real death toll of osteoporosis. In fact, the numbers from official death certification, combined with the number of hip fractures in the Netherlands, even show a lower mortality rate after hip fracture than in the population at large. Therefore, we also used our data about in-hospital mortality and published mortality data from a follow-up study in the Netherlands.[22]

We observed an overall in-hospital mortality of 10.1 % for men and 5.9 % for women. This in-hospital mortality was strongly age dependent, rising from almost non-existent at younger ages to 22% for men and 10 % for women in the highest age group. Mortality in men was twice as high as in women for all age groups.

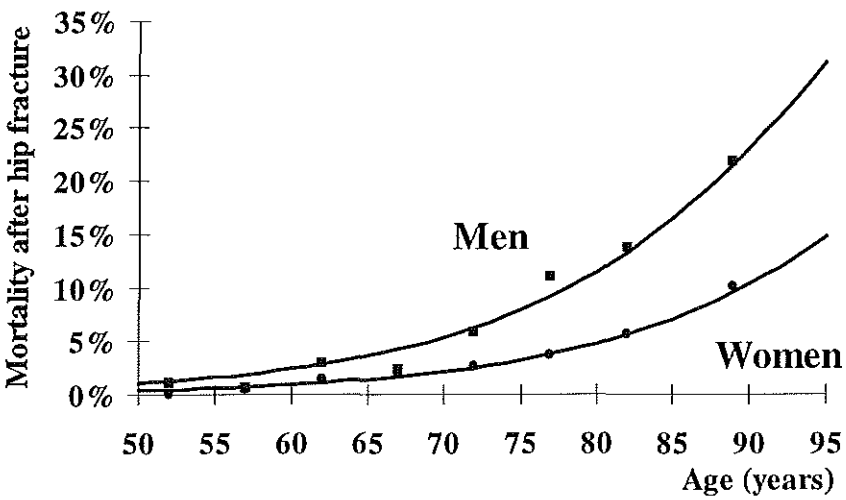


Figure 6: In-hospital mortality after hip fracture (observed values in 5 year age classes, and calculated regression curves)

We cannot correctly assess mortality after the hospital stay from our data, although we do present some information on mortality in nursing homes. For a better idea of the mortality after hip fracture, we need follow-up data. Boereboom et al. studied 493 patients with a hip fracture during the period 1982-1984 in three hospitals in Utrecht.[22] In-hospital mortality was similar to our findings with 9.1 % of the patients dying during hospital admission. One year after the hip fracture, 23.6 % of the women and 33 % of the men had died.

This study also showed that mortality was highest during the first 8 weeks after the hip fracture and strongly age and gender dependent. The relative risk of dying for men was 1.9 (95% CI 1.4-2.5) compared to women. Concomitant illness and hospital complications were also related to mortality. When looking at the official cause of death mentioned on the death certificate, it was found that in only 19 % of the women and 25 % of the men, hip fracture was mentioned as cause of death. Although mortality after hip fracture was strongly increased in the months following the event, especially in men, one should be careful not to attribute all of this excess mortality exclusively to the hip fractures. Patients with a hip fracture often had concomitant illnesses and a poor general condition. This condition in itself can increase the risk of falling and the perioperative risk.

1.1.5 MEDICAL COSTS ASSOCIATED WITH THE TREATEMENT OF OSTEOPOROSIS AND FRACTURES

To assess the medical cost of osteoporosis and fractures, we used two separate approaches. In the first (top-down approach) we used published Dutch cost estimates for hip, forearm and vertebral fractures. Those estimates were combined with our incidence

figures. In a second approach (bottom-up), the detailed costs of medical consumption related to osteoporosis and fractures were calculated, based on the medical consumption described in this chapter.

Top-down approach

In a 1993 iMTA report, Al et al. estimated the cost of hip, vertebral and forearm fractures.[21] Costs for hospital treatment, complications, home care, physiotherapy and GP visits were estimated, and these cost estimates are listed in table 3. Nursing home care, however, was not included in this estimate, since it was argued that the fracture very often was the trigger, rather than the cause of the admission to a nursing home. The demand for home health care was used as a proxy for the additional help needed. For vertebral fractures, we used the cost for clinically diagnosed fractures, since the incidence figures only reflected this category of vertebral fractures.

Table 3: *Estimated costs of fractures in the Netherlands*[21]

Hip fracture	€ 10.400
Vertebral fracture	€ 1.041
Forearm fracture	€ 844

These costs were applied to the estimated 1993 incidence figures for the Netherlands. For this part of the analysis, only fractures at the age of 50 and older were considered, the age of 50 being an arbitrary cut-off point for osteoporotic fractures. The resulting global estimates are given in table 4.

Table 4: *Global estimated yearly costs for hip, vertebral and forearm fractures in the Netherlands (million €)*

Hip fracture	149.52
Vertebral fracture	15.81
Forearm fracture	12.23
Total	177.56

Bottom-up approach

In this bottom-up approach, the analysis was again limited to individuals aged 50 years and older. The choice of the costs corresponding to one day of hospital stay, one contact, etc. was based on the Dutch guidelines for cost calculations in health care.[23]

Pharmacotherapy

The cost per person-year was calculated based on cost information in the *Pharmacotherapeutisch kompas*,[24] and on the recommended dosage.

Hospital admissions for hip fractures

To assess the direct cost of hip fracture hospital admission, the number of hospitalization days for persons over age 50, were combined with an average daily price for hospitalization of € 351.

Hospital admissions for other fractures

Hospital admission for other fractures can only be estimated from 1992 data.[18] We only had the proportion of people aged 65 and older. Thereby, we disregarded the patients aged between 50 and 64 leading to an underestimation. On the other hand, these data also included fractures that where not osteoporosis-related, leading to an overestimation.

For the reasons mentioned in the corresponding section, it is unclear whether or not those figures should be included in an estimate of the cost of osteoporosis. We included them here for reasons of completeness in the maximum cost estimate.

Average length of stay in 1992 for those fractures that led to a hospital admission was 5.7 days for forearm fractures and 17.2 days for vertebral fractures.[20]

Nursing home care (full care)

Including all nursing home patient days after a fracture would lead to an overestimation of costs. A fracture can be the trigger that changes a borderline independent state into a dependent state of life, for people who would anyhow be admitted into nursing home care. As argued in the chapter on nursing homes, we only considered the first three months of stay in a nursing home in the calculation of the cost. It should be clear that using the cut-off point of 3 months was an arbitrary choice based upon the arguments developed in the discussion on length of stay and discharge status.

An average daily price for nursing home care of € 95 was used.

Nursing home care (day care)

For the same reason as with the nursing homes, only the first 3 months of day care were included in the calculation of the cost. An average daily price for day care of € 55 was used.

Outpatient care

No hard data on the outpatient care for osteoporosis related fractures were available for the Netherlands. In the absence of those data we used the assumptions for outpatient care from Al et al.[20] that were also used in the top-down approach.

For *hip fractures*, it was assumed that patients had on the average 2 GP visits after the discharge from hospital and that 50 % of the patients had an average of 12 treatment sessions by a physiotherapist. This leads to a global outpatient care price of € 145 per hip fracture.

For *vertebral fractures*, it was assumed that 5 out of 6 of the total number of clinically diagnosed patients were treated by the GP. 5 GP visits, one specialist visit (including an X ray) and 12 treatment sessions by a physiotherapist were assumed with a total cost of € 546, leading to an outpatient cost of € 455 per vertebral fracture.

For *forearm fractures*, it was assumed that 95 % of patients were treated in the outpatient clinic with a total cost of € 752. This leads to a cost per forearm fracture of € 715.

Home health care

Based on the assumptions made in the chapter on Home health care, we calculated the *maximum* possible cost for home health care related to hip fractures. In order to do so, we used a price of € 25 per contact.

Overview of the bottom-up approach

In table 5, we present an overview of the estimated yearly cost, with and without the maximum estimates, using this bottom-up approach.

Table 5: *Detailed overview of the estimated cost of osteoporosis and the treatment of fractures in the Netherlands in 1993 (million €)*

	Estimated yearly cost
Pharmacotherapy	7.09
Hospitalisations hip fractures	133.77
Non-hospital inpatient care (full care)	36.80
Day care	1.66
Outpatient care	19.36
Total (excluding maximum estimates)	198.68
Hospitalisations other fractures (maximum estimate)	*7.70*
Home health care (maximum estimate)	*5.77*
Total (including maximum estimates)	*212.15*

1.1.6 CONCLUSIONS

Epidemiology

Osteoporosis and fractures are a major source of illness and health care costs in the elderly, both today as in the foreseeable future. Especially the most serious consequence, hip fracture, is frequent and the incidence is increasing. Both in men and women, the incidence increases exponentially with age. Men reach the same hip fracture incidence at an age 5-6 year older than women, and for instance a 80-year-old male has the same hip fracture risk as a 75-year-old female.

The total number of hip fractures will inevitably rise if no serious preventive strategies are developed. An upward time trend in age-adjusted hip fracture rates, as well as the aging of the population are responsible for this. Several possible explanations for the upward trend have been suggested, such as the decreasing physical activity and sedentary lifestyle, nutrition, or even the fact that people are growing taller than before. In the US, Sweden, and the UK, this upward trend of age-adjusted hip fractures seems to have leveled off.[17] In other regions such as Hong Kong and, as we showed, also in the Netherlands, the rates are still increasing. While it is difficult to predict the further

evolution of this trend, the aging of the population is certain. Even when current incidence rates remain stable in the future, the total number of hip fractures in the Netherlands will double by the year 2050 to over 30.000 per year. When the current upward trend continues, this number will be even higher.

We did not have Dutch incidence data of other fractures, and we derived incidence rates from international data. The accuracy of these estimates is likely to be poorer, but, since we focus on cost and personal illness burden, these fractures appear to be less relevant in this context. Recent incidence data from the Rotterdam Study, however, are similar to the estimates used in this chapter.

Health care utilization

Osteoporosis and fractures are an important cause of health care consumption. Hip fractures lead to long hospital stays with a mean length of stay of 26 days. Forearm and vertebral fractures are most frequently treated in an outpatient setting. People over age 85, representing less than 2 % of the population nevertheless are responsible for over one third of the hospitalization days for hip fractures. This is due both to the exponential increase of hip fracture with age, and to the longer length of stay. With an aging population this proportion is highly likely to increase.

After the acute phase and the hospital stay, nursing home care is often needed. Using *hospital data*, we see that 21 % of men and 27 % of women are discharged directly into nursing home care. This difference can partly be explained by the higher in-hospital mortality of men. In the *nursing home data* we see a similar number of men being admitted, meaning that they are mainly discharged from the hospital into nursing home care directly. For women, however, more were ultimately admitted to nursing home care (about 33 % of the hip fractures). Apparently, some of the women return to their homes first, but are afterwards transferred to a nursing home. Nursing home stays can be very long, but the majority of patients leave the nursing home within 3 months. In our cost estimates, we assumed that stays longer than 3 months were not only related to the hip fracture, and that pre-existing co-morbidity was important. We used the same approach dealing with day care cost.

Other health care consumption is home healthcare and outpatient care. Hard data about those activities were scarce and we made an attempt to estimate them using indirect information. Their contribution to the total cost of osteoporosis is substantial but secondary to hospital and nursing home cost. In 1993, drug use for osteoporosis prevention and treatment was also relatively unimportant for the total cost.

Mortality

Although hip fractures occur less frequently in men, their mortality after a hip fracture is more important. We found an in-hospital mortality that is twice that of women. Mortality was also strongly age dependent and related to concomitant illnesses and in-hospital complications. Published follow-up data showed that mortality after hip fracture is strongly elevated in the first few months following the event,[21-22] but the available data for the Netherlands did not allow a more precise estimate of the duration of this excess mortality.

One should be careful not to attribute exclusively all of this excess mortality to hip fractures. Patients with a hip fracture more often had concomitant illnesses and a poor general condition. This condition in itself can increase the risk of falling and the perioperative risk. This situation can also impair the rehabilitation after treatment and hamper mobilization.

Medical costs

In this study we estimated the direct cost associated with fractures at older age. The majority of these fractures were osteoporosis related, but not all. A clear indication of the fact that most of these fractures are osteoporosis related is found in the observation that incidence increases exponentially with age. It is not possible to differentiate between osteoporotic fractures and non-osteoporotic fractures but we believe that the impact of the latter category is small.

The cost of osteoporosis is mainly the cost of hip fractures. It is this cost we could determine most accurately. In comparison, the cost of other fractures and the current cost of pharmacotherapy for the treatment and prevention of osteoporosis is low. We used two approaches to estimate the global yearly cost of osteoporosis and fractures in the population aged 50 and over. The results of both the top-down and the bottom-up approach are comparable, and indicate a yearly cost between € 175 million and € 210 million. The main difference between both approaches lies in the cost of nursing home care (non-hospital inpatient care). Nursing home care was not included in the top-down approach. In the bottom-up approach, we assumed that only the first three months of nursing home care should be attributed to the fracture, the remainder being due to co-morbidity and frailty.

The medication cost of osteoporosis was difficult to ascertain, and the validity of the IMS data is unclear. It was however the only currently available source. It appears that the cost of medication was minor, compared to the cost of clinical treatment of the fractures.

We did not include indirect costs as osteoporosis mainly affects the elderly and their production losses can be neglected.

When comparing these costs with international figures, we found both higher and lower estimates.[17] Several studies indicate a cost of US$ 7 - 10 billion for the United States,[17] resulting in a yearly cost per capita of € 20 - 30 for osteoporosis and hip fractures. Our maximum global cost estimate is equivalent to about € 15 per head of the population. The US estimates however did include the indirect costs that we choose not to include. Estimates for France,[17] for example, were much lower with a global cost of FF 3.5 billion (€ 500 million) and a per capita cost of € 9.

REFERENCES

1 Centraal Bureau voor de Statistiek (CBS). Postbus 4000, 2270 JM Voorburg.

2 Statistisch Jaarboek 1994. Voorburg: CBS, 1994.

3 Stichting Informatiecentrum voor de gezondheidszorg, Maliebaan 50, 3508 SC Utrecht.

4 Institute for Medical Statistics.

5 Thuiszorg Rotterdam. Coolsingel 75, 3012 AD Rotterdam.

6 CBS, CBS-Publikaties: Maandstatistiek van de bevolking, January 1995. Results Population and Household Forecasts 1994.

7 Burger H, van Daele PL, Algra D, et al. The association between age and bone mineral density in men and women aged 55 years and over: the Rotterdam Study. Bone Miner 1994;25:1-13.

8 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Pols HAP Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ1997;315:221-225.

9 Kanis JA Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 4 1994;4:368-381.

10 Erdtsieck RJ, Pols HA, Algra D, Kooy PP, Birkenhager JC. Bone mineral density in healthy Dutch women: spine and hip measurements using dual-energy X-ray absorptiometry. Neth J Med 1994;45:198-205.

11 Boereboom FT, de Groot RR, Raymakers JA, Duursma SA. The incidence of hip fractures in The Netherlands. Neth J Med 1991;38:51-8.

12 Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. Ann Intern Med 1991;115:837-42.

13 Weel AEAM, Burger H, De Laet CEDH, Hofman A, Van Leeuwen JPTM, Pols HAP. Fractures in Elderly Men and Women: Incidence and Association with Bone Mineral Density (submitted)

14 Melton L3, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis?. J Bone Miner Res 1992;7:1005-10.

15 Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. Bone 1992;13:S1-10.

16 Black DM, Palermo L, Nevitt MC, et al. Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res 1995;10:890-902.

17 Melton L3. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14:S1-8.

18 SIG Zorginformatie, Jaarboek Ziekenhuizen 1995, ISBN 90-70755-36-X

19 SIG Zorginformatie, Jaarboek Verpleeghuizen 1992, ISBN 90-70755-37-8.

20 instituut voor Medische Technology Assessment, Al MJ, van Hout BA, Duursma SA. Kosten en effecten van Didronel profylaxe, iMTA 93.25.

21 Schroder HM, Erlandsen M. Age and sex as determinants of mortality after hip fracture: 3,895 patients followed for 2.5-18.5 years. J Orthop Trauma 1993;7:525-31.

22 Boereboom FT, Raymakers JA, Duursma SA. Mortality and causes of death after hip fractures in The Netherlands. Neth J Med 1992;41:4-10.

23 Stuurgroep Toekomstscenario's Gezondheidszorg, Kostenberekening bij Gezondheidsonderzoek, Richtlijnen voor de praktijk, ISBN 90-6224-320-7.

24 Centrale Medische Pharmaceutische Commissie van de ZiekenfondsRaad, Pharmacotherapeutisch kompas 1994, ISBN 90-70918-10-2.

1.2 COSTS OF OSTEOPOROSIS RELATED FRACTURES IN THE NETHERLANDS: POSSIBILITIES FOR COST CONTROL

This chapter is a translation of an article published as: De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Kosten wegens osteoporotische fracturen in Nederland; mogelijkheden voor kostenbeheersing. Ned Tijdschr Geneesk 1996;140:1684-8

INTRODUCTION

Osteoporosis-related fractures are a major problem for public health, both because of the health consequences for the individual patient as for the high costs related to the treatment of these fractures. The most serious fracture is the hip fracture. Besides this, also wrist fractures and fractures of the vertebrae are considered as osteoporotic fractures. Moreover, most other fractures in elderly people are also, at least partially, associated with a low bone mineral density (BMD).[1]

The direct medical cost attributed to osteoporosis was estimated at more than 10 billion US$ (€ 9 billion) in the USA.[2] The further aging of the population will cause a strong increase of these costs if current policy is maintained. Moreover, in several countries, including the Netherlands,[3] an age-adjusted increase is observed in the incidence of hip fractures.

The aim of this study was to evaluate the direct medical costs of osteoporosis-related fractures in the Netherlands. Additionally, based on the cost distribution, the potential effect of different intervention strategies was evaluated.

DATA AND METHODS

As a rule, data from 1993 were used in this analysis. The analysis was restricted to fractures of the hip, the forearm and the vertebrae in men and women age 50 years and older. The validity of the assumptions was examined and their influence on the costs was evaluated by sensitivity analyses.

Demographic data from the Central Bureau for Statistics were used.[4] The incidence of hip fractures was estimated based on detailed registration data of hospitalizations (Landelijke Medische Registratie, LMR) registered by the SIG Zorginformatie.[5] Dutch incidence data for fractures of the forearm and of the vertebrae were not available. To estimate these, incidence data from the USA,[6] were projected on the Dutch age distribution.

Information on the length of stay in the hospital, on the place of residence after discharge and on admissions in a nursing home because of fractures was retrieved from registration data and published data of SIG Zorginformatie.[7-9]. Using linear regression, it was investigated how the length of stay in a hospital after a hip fracture was related to age, gender and hospitalization in a nursing home afterwards.

Outpatient care for the treatment of fractures is not systematically recorded in the Netherlands. To estimate these costs, we used previously published assumptions.[10] To translate the use of health care in costs, Dutch cost accounting guidelines for healthcare were used.[11]

RESULTS

Incidence of fractures.

In 1993, 15.107 (3882 in men) hospital admissions because of hip fractures were recorded, 96% of which were in persons of 50 year of age and older. These figures showed an exponential increase of the number of hip fractures with age, for women as well as for men. In men, the incidence of hip fractures lagged behind that of women by approximately 5 years of age. Based on the comparison with international data we estimated the annual amount of fractures of the vertebrae and wrist fractures at 15,000 and 14,500, respectively (see also section 1.1.2).

Length of stay in a hospital after a hip fracture.

The median length of stay was 17 days for men and 19 days for women. The average length of stay (24,9 and 27,1 days, respectively) was influenced strongly by a relatively small group that stayed hospitalized for a long period. The longer length of stay of women was explained mainly by age. The average length of stay increased with age: 0,32 days/year (95% confidence interval (CI): 0,26-0,37). Patients who went to a nursing home after discharge from the hospital, stayed on average 7,9 days longer in the hospital (CI: 6,7-9,0) than patients of the same age and gender who went to their own home after discharge. After adjusting for age and admission in a nursing home after hospitalization, the length of stay of men approximately equaled that of women: women stayed +0,28 days (-0,96-+1,52) longer in the hospital than men.

Admission in a nursing home after a hip fracture.

Nearly 60% of the patients with a hip fracture returned home after discharge from the hospital. 7% went to an elderly people's home and another 7% died in hospital. The remaining 26% of the patients were admitted to a nursing home after hospitalization. The proportion of patients that went to a nursing home increased with age: from less than 10% of 50-54 year old patients to more than 30% of patients older than 85. We also included nursing home admissions due to other fractures in the analysis of the costs.

The median length of stay in the nursing home was 67 days for men and 70 days for women. The average length of stay (238 and 241 days respectively) was, once again, strongly influenced by a relatively small group that stayed in the nursing home for a long period. More than 60% left the nursing home within three months; more than 70% of those returned to their own homes. After 4 months of stay in the nursing home, only 55% of the patients returned to their own home and after 5 months this number was reduced to 35%. When length of stay was more than one year, more than 80% stayed in the nursing home until they died.

Because of this, we only used the first 3 months in the nursing home in the calculation of the costs. This was an arbitrary choice, assuming that those long lengths of stay of some patients were connected with a greater need of care and with comorbidity , rather than with the fracture itself. The cost of day care in a nursing home was calculated in the same way.

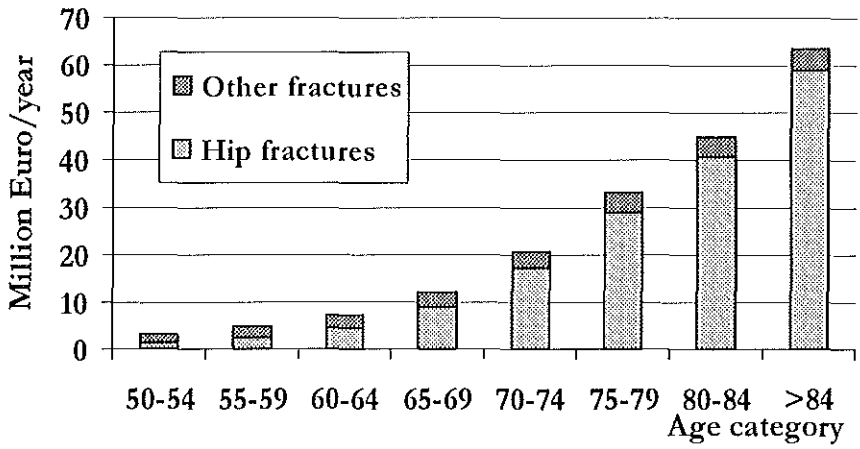


Figure 1: Annual cost of fractures per age category in the Netherlands, 1993.

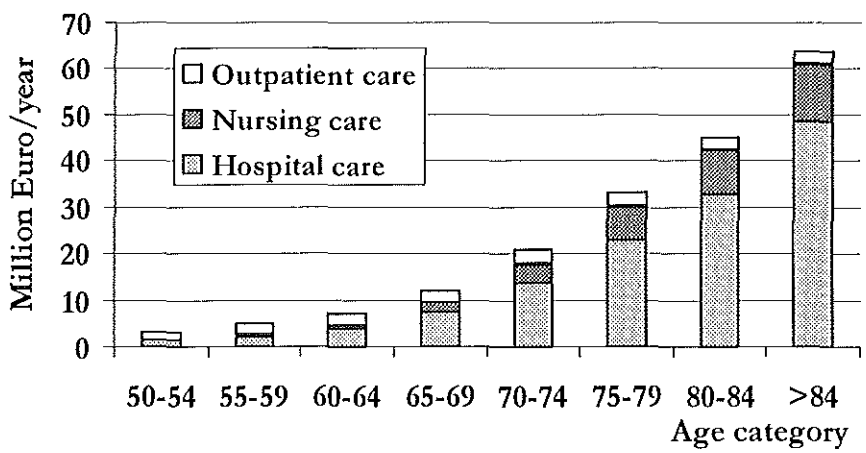


Figure 2: The contribution of different care providers in the total cost of osteoporotic fractures in the Netherlands per age category, 1993.

Total cost

Total costs of fracture-treatment in the Netherlands were estimated at about € 190 million per year. Figure 1 shows the costs of hip fractures and other fractures per age group. The contribution of hip fractures in the costs totaled 86,1%. Figure 2 shows the contribution of different care providers in the total cost of osteoporotic fractures.

SENSITIVITY ANALYSES

Other fractures than osteoporotic fractures.

To estimate the costs of hip fractures, all hospital admissions because of hip fractures were included in the analysis. It is clear that this also included some hospital admissions due to pathological hip fractures or fractures due to major trauma, besides those due to osteoporosis. This may have leaded to overestimating the number of osteoporosis related fractures. But, this was probably only a low number of cases, because of the strong relation that was observed between the incidence of the fractures with age. We did not include in the analysis the hip fractures that, occasionally, did not lead to hospitalization and that were treated conservatively. This on the contrary might have leaded to a minor underestimation of the number of osteoporotic fractures.

Relevance of other than Dutch incidence data.

Costs of vertebral fractures that came to clinical attention and forearm fractures were estimated on the basis of incidence data from the US, and this may have caused a bias. However, the recorded incidence of hip fractures in the Netherlands was very similar to the American estimates. The difference in the total estimated number of hip fractures was 4% for men and 17% for women (more hip fractures in the USA). Because of this, it seems legitimate to use the American incidence data for fractures of the vertebrae and of the wrist. Moreover, the cost of these fractures was much lower than that of the hip fractures, so the effect of these more uncertain incidence data was less relevant to the bottom line than the incidence of hip fractures, that was estimated accurately. If, for example, we would use the considerably higher Swedish incidence figures for the fractures of the forearm,[12] the annually estimated Dutch fractures of the forearm would indeed go up from 14.501 to 22.919, with an estimated additional costs of € 6 million, but the contribution of hip fractures in the total of the costs would only drop from 86,1 % to 83,5%.

Admission to the nursing home.

The estimated cost of nursing home admissions represented almost 20% of the total cost; day care on the contrary represented less than 1%. Here, all costs of fractures where included and not only those of fractures attributed to osteoporosis. This could lead to an overestimation of the cost in the nursing home. In addition, some patients already stayed in a nursing home when the fracture occurred. These patients mostly came back to the nursing home after their stay in the hospital and again this could have lead to an overestimation of the costs.

The assumption that only the first 3 months of stay in the nursing home was connected to the fracture was arbitrary, but it was based on the observation that a longer stay was associated with comorbidity and a greater need for care. In order to value the effect of this assumption on the total costs, we varied this arbitrary length of stay in our calculations. When we set this limit at 2 months, the cost of admission for full care in a nursing home dropped, for all fractures, from € 36 to € 28 million. When using a limit of 6 months they increased to € 52 million. The contribution of these nursing home admissions in the total costs varied thereby from 15,5 to 25,4%. This hardly had any

effect on the contribution of hip fractures on the total costs that varied from 86,7 to 85,2%.

Outpatient care.

Cost of outpatient care was based on expert opinion.[11] This estimated cost represented 10% of the total costs. Even when the error in estimated cost for all fractures was greater than 50% in the same direction, the final contribution changed only from 5,3 to 14,4% of the total costs. The contribution of hip fractures changed only from 90,2 to 82,5%.

Conclusions from the sensitivity analyses.

The results of these sensitivity analyses shows that, although there was some uncertainty about some data, osteoporotic fractures in the Netherlands cause annually a cost of about € 190 million of direct medical costs. Some 85% of this cost could be attributed to hip fractures. Ábout 80% of the cost of hip fractures was caused by hospitalization.

DISCUSSION

Incidence.

The number of hip fractures in the Netherlands is still increasing. There is an increase in age specific incidence, and our data for 1993 showed that this increase still continued in the Netherlands, although in some countries such as US, the incidence appears to be stabilizing.[13] At this moment, it is hard to predict whether this trend will continue in the future. Additionally, the population is aging. This will, because of the strong relation of fracture risk with age, lead to a strong increase in the total number of fractures, even with constant disease specific incidence rates. When we combined the current incidence rates with the population predictions by the CBS,[14] we predict a doubling of the number of hip fractures by the year 2050 (see also chapter 1.1).

Treatment and cost control.

The contribution of the oldest patients in the total cost was very striking. Although people from 85 years and older constituted only 1,3% of the population (1993), this group contributed to more than one third of the cost of osteoporotic fractures. The most important cause was, besides the higher incidence of hip fractures, the longer length of stay in the hospital and the higher incidence of admissions to a nursing home. This group of elderly people will increase from less than 200.000 now to 300.000 in 2020 and over 500.000 in 2050. At that moment, more than 3% of the Dutch population will be 85 years of age or older. This increment in the number of individuals aged 85 years or older will have a disproportionate impact on cost.

More than 85% of the total cost of osteoporotic fractures was caused by hip fractures and the contribution of hospital admissions was considerable. Therefore, besides prevention, a more efficient hospital stay seems to be the most obvious way to control costs in the near future. Previously it was argued that, in the Netherlands, many patients with hip fractures stay in the hospital too long because the discharge to either somatic or psychiatric nursing homes is not organized efficiently.[15] These patients stay in a "wrong"

and particularly too expensive bed for too long. The optimal length of hospital stay due to hip fracture without complications as stated in the mentioned article was 9 days.[15] It is clear that the median length of stay in hospital due to hip fractures in the Netherlands is much longer.

Our analysis supports this argument of hospital discharge problems. Patients, who were admitted to a nursing home afterwards, stayed on average almost 8 days longer in the hospital than patients who went home, even after adjusting for age and gender. Therefore, it appears that those patients stayed in the hospital waiting for a suitable place in a nursing home. An average reduction of the length of stay after hip fracture with 1 day, would in theory produce an annual cost reduction of € 5 million.

It must be noticed, however, that costs at the end of hospitalization are lower than at the beginning, when the patient is being operated upon and when care is more intensive. The use of per diem costs could therefore lead to overestimation of the potential gains of a shorter length of stay. In a British study, two groups of patients with a hip fracture were compared, where one group of patients received "hospital at home"-facilities.[16] These facilities included home care, physiotherapy at home and ergotherapy under GP supervision. Previous studies had shown that this scheme yielded a similar mortality and functional rehabilitation as conventional long-term admission in hospital. Almost 40 % of the patients in the intervention group were sent home early. For the complete group, this lead to a mean reduction of the length of stay by 9,2 days and to an average reduction of costs of £ 1015 (€ 1140) per patient for the admission in the hospital only. After deduction of the cost of the hospital-at-home facilities this lead to a reduction of £ 722 (€ 865).

Prevention and cost control.

The most obvious way to control costs is to avoid fractures. There is, however, no ideal intervention available,[17] but the structure of the cost of osteoporotic fractures can give some indications for an a-priori judgement of the cost-effectiveness of preventive measures.

The effect of measures to prevent falling has not been demonstrated convincingly until now. From some intervention studies in which it was attempted to reduce the tendency to fall through a multifactorial approach, it turned out that, although the frequency of falling diminished, there was no confirmed effect on the incidence of hip fractures.[18-20]

External hip protectors can protect against the direct impact of a trauma on the hip. A randomized trial in Denmark with patients in a nursing home showed a 50% reduction of the number of hip fractures in the intervention group.[21]

Non-pharmaceutical approaches to influence bone strength include lifestyle interventions such as physical exercise, diet counseling, and the avoidance of smoking and alcohol abuse but there is no consensus about the final effect of these schemes on osteoporotic fractures.[22-24]

Pharmaceutical prevention often needs to be taken during many years, and it is unclear, what happens to the effect after stopping the therapy.[25] Moreover, most studies on the

pharmaceutical prevention of osteoporosis have been done on relatively young, early post-menopausal women and often only the effect on vertebral deformities was studied. More recently, however, clinical trials that also looked at effects on peripheral fractures became available.[26,27]

Furthermore, the timing of the prevention is very important for the cost-effectiveness. The incidence of hip fractures surpasses 1% per year only after the age of 80 years. When intervention is started around the menopause there is a very long period between the costs and the subsequent effects. Furthermore, only half of the individuals that are 55 today will ever reach the age of 80 according to present prognoses. It might therefore be more realistic to start prevention at a moment that is closer to the age at which hip fractures occur frequently.

Strategies that have other desired effect beside an effect on osteoporotic fractures, such as hormone replacement therapy, should therefore be evaluated on their global cost effectiveness and not only on their effect on the prevention of fractures.[28]

REFERENCES

1 Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. Ann Intern Med 1991;115:837-42.

2 Lindsay R. The burden of osteoporosis: cost. Am J Med 1995;98:9S-11S.

3 Boereboom FT, Raymakers JA, de Groot RR, Duursma SA. Epidemiology of hip fractures in The Netherlands: women compared with men. Osteoporos Int 1992;2:279-84.

4 CBS, Statistisch jaarboek 1994.

5 Stichting Informatiecentrum voor de gezondheidszorg, Maliebaan 50, 3508 SC Utrecht.

6 Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis?. J Bone Miner Res 1992;7:1005-10.

7 SIG Zorginformatie, Jaarboek Ziekenhuizen 1992, ISBN 90-70755-36-X.

8 SIG Zorginformatie, Zorg in Zicht, ISBN 90-70755-41-6.

9 SIG Zorginformatie, Jaarboek Verpleeghuizen 1992, ISBN 90-70755-37-8.

10 instituut voor Medische Technology Assessment, Al MJ, van Hout BA, Duursma SA. Kosten en effecten van Didronel profylaxe, iMTA 93.25.

11 Stuurgroep Toekomstscenario's Gezondheidszorg, Kostenberekening bij Gezondheidsonderzoek, Richtlijnen voor de praktijk, ISBN 90-6224-320-7.

12 Mallmin H, Ljunghall S. Incidence of Colles' fracture in Uppsala. A prospective study of a quarter-million population. Acta Orthop Scand 1992;63:213-5.

13 Melton LJ. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14:S1-8.

14 CBS, CBS-Publikaties: Maandstatistiek van de bevolking, January 1995. Results Population and Household Forecasts 1994.

15 van Vugt AB, Touw CR.Kwantificering van te langdurige ziekenhuisopname ('verkeerde-beddenproblematiek'); heupfracturen bij bejaarden. Ned Tijdschr Geneeskd 1994;138:1806-10.

16 Hollingworth W, Todd C, Parker M, Roberts JA, Williams R. Cost analysis of early discharge after hip fracture Bmj 1993;307:903-6.

17 Eisman JA. Efficacy of treatment of osteoporotic fractures. Am J Med 1995;98:17S-23S.

18 Cummings SR, Nevitt MC. Falls. N Engl J Med 1994;331:872-3.

19 Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821-7.

20 Province MA, Hadley EC, Hornbrook MC, et al. The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT Trials. Frailty and Injuries: Cooperative Studies of Intervention Techniques. Jama 1995;273:1341-7.

21 Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. Lancet 1993;341:11-3.

22 Greendale GA, Barrett-Connor E, Edelstein S, Ingles S, Haile R. Lifetime leisure exercise and osteoporosis. The Rancho Bernardo study. Am J Epidemiol 1995;141:951-9.

23 McKnight A, Steele K, Mills K, Gilchrist C, Taggart H. Bone mineral density in relation to medical and lifestyle risk factors for osteoporosis in premenopausal, menopausal and postmenopausal women in general practice. Br J Gen Pract 1995;45:317-20.

24 Heaney RP. Bone mass, nutrition, and other lifestyle factors. Am J Med 1993;95:29S-33S.

25 Kanis JA. Treatment of osteoporosis in elderly women. Am J Med 1995;98:60S-66S.

26 Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston C, Jr., Adami S, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. Jama 1997;277(14):1159-64.

27 Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-41.

28 Cheung AP, Wren BG. A cost-effectiveness analysis of hormone replacement therapy in the menopause. Med J Aust 1992;156:312-6.

1.3 INCREMENTAL COST OF MEDICAL CARE AFTER HIP FRACTURE AND FIRST VERTEBRAL FRACTURE: THE ROTTERDAM STUDY.

This chapter is a reprint of: De Laet CEDH, Van Hout BA, Burger H, Weel AEAM Hofman A, Pols HAP. Incremental cost of medical care after hip fracture and first vertebral fracture: the Rotterdam Study. Osteoporosis Int 1999 (in press)

INTRODUCTION

In Western countries, osteoporotic fractures and especially hip fractures cause major morbidity and mortality in the elderly,[1] and are associated with substantial public health costs due to acute hospital treatment and subsequent rehabilitation.[2] Improved life expectancy and the demographic evolution will cause the number of hip fractures worldwide to increase from around 1.7 million in 1990 to over 6 million in 2050,[1] and therefore, medical expenditure will increase in the decades to come. In the Netherlands, we estimated the cost of osteoporotic fractures at € 190 million (US$ 210 million) in 1993,[3] while hip fractures accounted for 85 % of this cost.

In some studies it is argued, however, that the importance of non-hip fractures in the cost of osteoporotic fractures is underestimated: a US study estimated the health care expenditure attributable to osteoporotic fractures in the United States at US$ 13.8 billion (€ 12.4 billion) in 1995.[4] Moreover, this study concluded that only 60 % of the cost was caused by hip fractures, while the remainder was due to fractures at all other skeletal sites, including vertebral fractures that came to medical attention. The difference between both studies was probably caused by the fact that while our study included only hip-, vertebral-, and wrist fractures as osteoporosis related fractures, the US study included, based on expert opinion, a large proportion of all non-hip fractures as osteoporosis related.

To assess the cost-of fractures, it is however not sufficient to know the global health care expenditure. Some costs, such as for nursing home admissions, may also occur without a fracture, and it is therefore necessary to estimate the difference in health care expenditure between fracture patients, and similar individuals in which a fracture did not occur.

Even while a hip fracture is easy to define, and case finding relatively easy, the estimated cost for a single hip fracture varies widely from under € 5.500 to over € 36.000,[5-13] depending upon country and timeframe of interest. The cost estimate also depends on whether medical cost after fracture was simply added-up, or whether incremental cost was calculated by comparing the cost to previous health care expenditure. A further source of variation is the choice whether to include only medical cost or to take into account indirect costs as well.

Cost estimates of incident vertebral fractures are even less reliable. Vertebral fractures often remain asymptomatic, and it was estimated that only a third of vertebral fractures spontaneously come to clinical attention.[14-16] The real incidence of vertebral fractures is therefore poorly known, but there is evidence that it increases with age in much the same way as hip fractures.[14] Prevalence studies indeed show an increase of both prevalence of all vertebral deformities, and an increase in severe deformities with age.[16-19] Therefore, estimates of the total cost depend heavily upon the definition of a vertebral fracture and upon the case finding procedures. There are, however, a few estimates that range from €

240 up to € 2.200.[6,20-22] In a recent review, cost of vertebral fractures was estimated at around € 1.100.[12]

In this study, we estimate the incremental cost for medical care after hip and radiologically defined incident first vertebral fracture in a Dutch elderly population, by comparing the health expenditure in fracture patients to the costs generated in a comparable control group. We excluded indirect cost.

PATIENTS AND METHODS

Setting

We estimated the cost of incident hip fractures and incident first vertebral fractures in a matched cohort design within the Rotterdam Study. The Rotterdam Study is a prospective cohort study of the occurrence and determinants of disease and disability in the elderly. The design of this study has been described previously.[23] The Rotterdam Study focuses on neurogeriatric, cardiovascular, locomotor and ophthalmologic diseases. The study started in 1990 and all 10.275 men and women aged 55 and over, living in Ommoord, a district of Rotterdam, were invited to participate. The study was approved by the Medical Ethics Committee of Erasmus University Medical School, and participants provided written informed consent. By mid 1993, the cohort was completely assembled, and from those eligible for participation, 7.983 did participate, bringing the overall response rate of this study to 78 %.

The baseline survey included a home interview for all participants. The independently living participants were subsequently invited for two visits to the research center for an extensive series of clinical examinations and laboratory assessments. Baseline assessments in the home interview included self-perceived health and the assessment of the impairment of activities of daily living (ADL) using a questionnaire modified from the Stanford Health Assessment Questionnaire.[18,24] During the visit to the research center we performed a lateral radiograph of the spine from the fourth thoracic to the fifth lumbar vertebra, as described previously.[18] Between mid 1993 and 1995, all independently living participants were again invited for a follow-up visit to the research center, and at this time we performed a second lateral radiograph of the spine using the same protocol.

Incident hip fractures

Follow-up of hip fractures was achieved through a link with the computer systems of the general practitioners of the district and through hospital admission data, covering about 80 % of the study population. For all participants not covered by this system, annual checks were performed on the complete medical records of their general practitioners. Reported fractures were verified by retrieval and review of the appropriate discharge reports from the patient record. Participants with an incident hip fracture between the beginning of 1991 and the end of 1994 were included as cases.

Incident vertebral fractures

Vertebral deformities were diagnosed by morphometry on the second radiograph according to the Eastell method,[25] and as modified by Black et al.[26] As described

previously,[18] deformities were categorized as moderate or severe. Moderate deformities (grade I) were defined as a deviation of any ratio of the heights between the -3 and the -4 SD cutoff value. Severe deformities (grade II) were defined as a ratio below the –4 SD cutoff value. These thresholds were obtained in the same study population and were published.[18] For all participants with a prevalent vertebral deformity on the second radiograph, the first radiograph was also digitized and vertebral deformities were diagnosed using the same method. We defined a first vertebral fracture as at least one severe deformity on the second radiograph, without any vertebral deformity on the first.

Matched control group

For every participant with an incident fracture, we randomly choose a participant matched at baseline on age (within the same 5 year age group), gender, self-perceived health, composite ADL activity score,[18] living situation (alone or with partner, and independently living or in residential care), and general practitioner. This matching was an attempt to make medical consumption at baseline as similar as possible. For the same reason, it was a prerequisite for the matched control to be alive at the moment of the hip fracture, or at the moment of the second radiograph in case of vertebral fractures.

Medical consumption

In the Dutch health care system, the general practitioner (GP) is the gatekeeper of the healthcare system. This means that referrals need to be done by the GP, and that the GP record is the central repository of medical information about a patient. Medical consumption was assessed by retrieval of the medical records in the general practice. All hospital admissions and their duration from 1990 until the end of 1996 were recorded. Admission to nursing homes was recorded similarly. We also recorded all general practice, and out-patient visits. Pharmaceutical consumption was assessed by retrieval of the computerized records of the central pharmacy of the district, covering all participants.

Analysis

Unit prices for cost of medical consumption were based on the Dutch guidelines for cost calculations in health research for 1993.[27] Those guidelines use comprehensive per diem prices including medical care and hotel costs: for hospital admissions these were € 351 per day and € 95 for nursing homes. The price for a GP visit was € 13, the price for a medical specialist contact € 90. For pharmaceutical consumption, the net cost to society was used. For hip fracture we calculated the cost during the year preceding the hip fracture, and compared it to the cost in the 2 years following the hip fracture. For the control group we did the same, using as reference the date of hip fracture of the matching case. Survival was described with Kaplan Meier survival analysis.

Since we did not know the exact date of incident vertebral fractures, we compared the average yearly cost in the years preceding the first radiograph with the average yearly cost in the years following the second radiograph (until the end of 1996 or until death). To account for the period in between the two radiographs, where important acute care costs might be incurred, we also calculated the average yearly cost for this period.

Because the distribution of the cost data was extremely skewed, we did not use conventional parametric tests for assessing the precision of the estimates. As an alternative we used a bootstrap method to calculate the averages and the 95 % confidence intervals.[28] Cases and controls were sampled as pairs, and for every parameter 100.000 Monte Carlo bootstraps were calculated.

RESULTS

During the follow-up period, 48 hip fractures occurred, and an equal number of matched controls were selected. In two cases of hip fracture and in two controls we were not able to obtain all the necessary information to calculate medical cost. Therefore, those 4 pairs were deleted from the analysis, giving us valid information for 44 pairs (91 %).

We detected 45 severe first vertebral deformities, and again selected matched controls. Here, we did not obtain all the information on medical consumption for 3 cases, and those 3 pairs were deleted from the analysis, leading to valid information for 42 pairs (93 %). Table 1 presents the baseline characteristics for the four groups.

Table 1: *Overview of participants*

	Hip fractures		Vertebral fractures	
	Cases	Controls	Cases	Controls
Number	44	44	42	42
Women (n)	34	34	32	32
Independently living (n)	31	31	42	42
Mean age in years (SD)	81.6 (7.9)	81.3 (8.2)	73.1 (7.3)	73.0 (7.3)
Alive at end 1996	22	30	38	40

Incident hip fractures

In the year preceding the hip fracture, the total cost of medical consumption was similar in both groups. Average cost was € 1638 in the hip fracture group and € 1511 in the control group. In the first year following the hip fracture, the average cost increased to € 10139 in the hip fracture group and remained at the same level in the control group (€ 1481).

Table 2: *Average incremental cost (€) after hip fracture*

		ALL SUBJECTS IN STUDY		ONLY SURVIVING SUBJECTS	
	Year before	1st year	2nd year	1st year	2nd year
Pharmacy	71	-123	46	-42	244
Hospital admissions (Orthopedic surgery)	32	6832*	38	6891*	101
Other hospital admissions	-152	-327	-64	-316	91
Nursing home	191	2298*	934	2682*	1326
Physician visits	-15	-23	-32	3	2
Total	127	8658*	923	9218*	1.763
(95 % CI)	(-850 – 1107)	(6402 – 11202)	(-651 – 2953)	(6688 – 12141)	(-379 – 4604)

* significant within 95 % confidence limits

Table 2 presents the estimated incremental cost between the hip fracture and control groups broken down by area of health care expenditure. The increased costs were mainly incurred during the first 3 months after the hip fracture, the main component being the initial hospital stay at the orthopedic ward. The cost difference in those first 3 months was € 7280 (5884 – 8740). During the remainder of the first year there was an additional cost of € 1378 (25 – 3042) mainly associated with nursing home stays. In the second year the average cost in cases was € 2342 compared to € 1419 in controls. Again, this additional cost was associated with nursing home admissions.

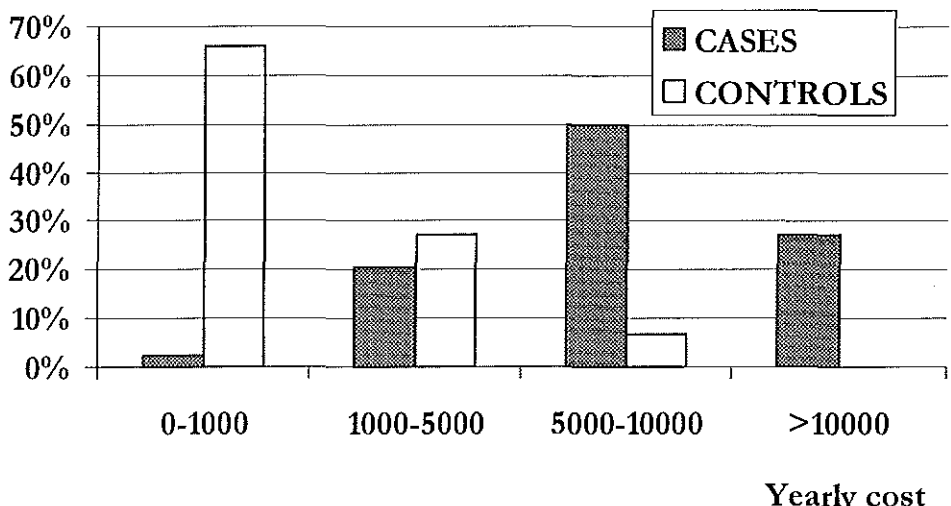


Figure 1: *Distribution of the cost (€) of medical care in the year after hip fracture*

Figure 1 indicates the distribution of yearly direct medical costs in cases and controls during the first year following the event. It shows that in controls over 65 % of the controls had a yearly cost below € 1.000 and that cost exceeded € 5.000 in only 10 %. In cases, however, cost exceeded € 5.000 in almost 80 % of the cases.

In this cost calculation, we disregarded the important extra mortality after a hip fracture. There was indeed an obvious increase in the death rates in the hip fracture patients in the 6 months following the event. Figure 2 gives the Kaplan-Meier survival curves comparing the survival of hip fracture cases with controls. When we excluded participants after the moment they died, the average incremental cost during the first year rose only slightly to € 9218. The main raison for this modest increase was that the majority of costs were incurred immediately after the hip fracture, also in people dying subsequently. In the second year, however, the cost difference almost doubled, from € 923 to € 1763, mainly caused by nursing home and pharmacy costs.

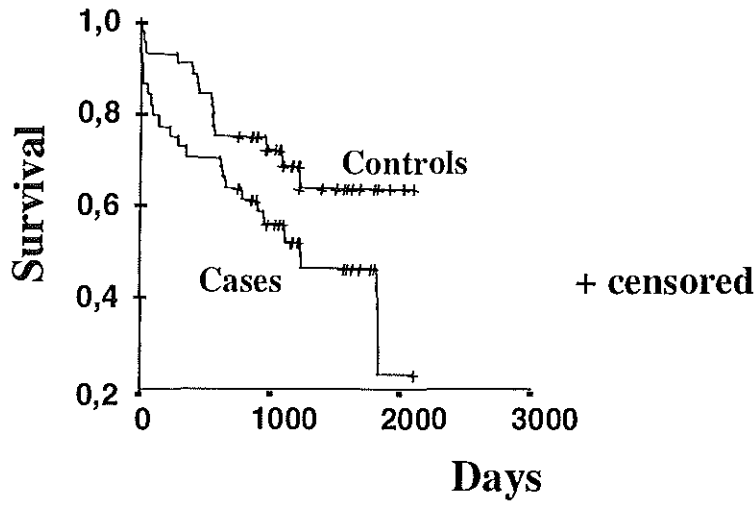


Figure 2: Survival after hip fractures (cases vs controls)

Incident vertebral fractures

For vertebral fractures the cost differences were less pronounced. In this population, the average cost of medical consumption before the first radiograph was € 1069 for cases and € 608 for controls. During the period in between the two radiographs the average yearly cost was € 1478 for cases and € 1087 for controls. The second radiograph was taken on average 2.2 years after the first, and the yearly cost afterwards was on average € 2836 for cases versus € 1877 for control subjects. In the GP records we could find a trace of vertebral deformities in only 14 of the cases (33%). Moreover, 4 of those were only detected after the second radiograph in our study, indicating that these vertebral deformities were not detected at the moment of their occurrence.

Table 3: Average incremental cost (€) after first vertebral fracture

	Years before first radiograph	Years in between radiographs	Years after second radiograph
Pharmacy	25	162	320*
Hospital admissions (Orthopedic surgery)	-37	-44	136
Other hospital admissions	432*	209	452
Nursing home	-13	0	11
Physician visits	54	66*	40
Total	461	391	959
(95 % CI)	(-167 – 1213)	(-208 – 1065)	(-646 – 2650)

significant within 95 % confidence limits

Table 3 presents the estimated incremental cost between cases and controls broken down by area of health care expenditure. The cost difference before the vertebral fracture was almost entirely due to hospital admissions. After the second radiograph this difference in hospital costs persisted, while the remainder of the increase was mainly associated with pharmacy costs and also to a lesser extend with admissions in orthopedic surgery wards.

The € 320 incremental pharmacy cost was not attributable to specific medication, and the cost difference was present in almost every drug category. The most marked increase in yearly cost (€ 136) was in the category of the anti-ulcer drugs, and the use of Omeprazol and Ranitidine was responsible for most of this difference, although this was not due to volume but to the price levels of those products. Incremental cost was also recorded in several other drug categories such as the cardiovascular, hormonal, and respiratory drugs and also in the non-steroidal anti-inflammatory drugs, but without presenting a clear pattern. For the period in between the two radiographs we see no indication of any acute phase costs, apart from a significantly increased cost of physician visits, but these represent low costs. But, since we do not know the exact moment of the vertebral deformity these costs are more difficult to interpret.

Figure 3 shows the distribution of average yearly cost in cases and controls after the second radiograph. For controls this distribution is similar to that in the hip fracture control patients. In cases, however, a large majority had a yearly cost of over € 1.000.

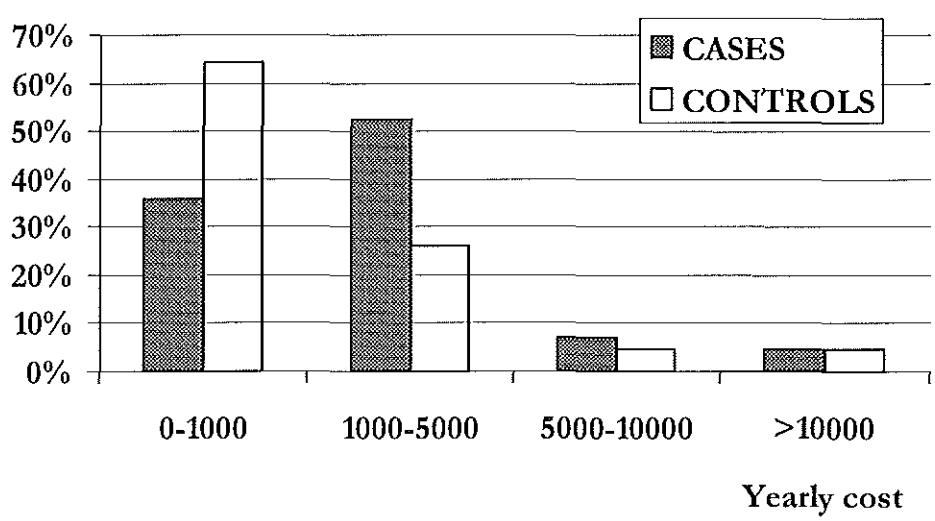


Figure 3: *Distribution of the yearly cost (€) of medical care after first vertebral fracture.*

DISCUSSION

Main findings

We estimated that, in this population, a hip fracture caused an extra cost of about € 8600 during the first year and € 920 in the subsequent year. There was an important extra mortality in the 6 months after the hip fracture as other studies reported before.[29,30] Taking this excess mortality into account and calculating average cost for surviving patients and controls, did not dramatically change our estimate during the first year, since most cost was incurred directly after the fracture. But, assessing surviving participants only, incremental cost in the second year almost doubles, mainly due to nursing home admissions and pharmacy cost. In two other studies that also compared cost before and after the event, incremental cost during the first year was estimated at between € 14.350 to € 17.000 for the US,[13] and € 19.700 for Sweden.[11] This is substantially higher than what we found in this Dutch population. The main reason for this difference appears to be the cost per day for hospital admissions, which is substantially lower in the Netherlands. Estimates from UK studies are generally lower,[8-10] but these studies only focussed on the acute phase costs. Their estimates, however, correspond to our results for the first 3 months after the event.

Costs of vertebral fractures are largely unknown, and cost estimates based on prevalent fractures are bound to be biased, since, in practice, those fractures often remain undiagnosed. Therefore, estimates vary widely. In our study we determined vertebral fractures by comparing radiographs made in a population based cohort, and we found that, even before the occurrence of the fracture, the average yearly cost was € 460 higher in cases compared to their matched controls. This incremental cost was largely caused by hospital admissions and seems to point to preexisting co-morbidity that was not avoided by the matching procedure used.

Most of the vertebral deformities in our study remained undiagnosed. Therefore, it is no surprise that the observed incremental cost is only modest. While the higher cost for admissions to orthopedic surgery wards after the occurrence of a vertebral fracture is not surprising, the higher pharmacy cost is, especially the observation that there was no specific drug category causing this. The single category causing most of this cost difference was the category of the anti-ulcer drugs although this was not due to volume but to the price levels of those products. Other extra consumption was recorded in the groups of cardiovascular, hormonal, and respiratory drugs and in the non-steroidal anti-inflammatory drugs. The importance of this cost for vertebral fractures becomes, however, important since it appear to be a yearly recurrent cost, at least during the first few years following the vertebral fracture.

The finding of this pre-existing incremental hospital cost and the unspecific drug usage in patients with incident vertebral fractures may have important implications. When confirmed by additional research, this would mean that the cost-effectiveness of strategies to prevent vertebral fractures might be overestimated, since at least part of the cost was pre-existing and will probably not be avoidable.

Strengths and limitations

International comparisons of cost are difficult, because health care is organized differently in different countries. The average initial stay at the orthopedic ward for instance, is only 11 days in Sweden[11] while it is 26 days in the Netherlands.[3] However, in Sweden it is followed by a longer stay at a geriatric ward. Moreover, the definition of what is included in health care cost and what is not differs from one country to another. While the severity of hip fractures is probably comparable between studies, the severity of vertebral deformities heavily depends upon the definition. Here we choose to include all severe incident deformities whether or not they caused complaints.

In this study, we studied incremental cost caused by fractures by comparing health care cost directly between individuals with and without a fracture, matching for potential determinants of health care consumption, while previous studies on incremental costs utilized health care use by the patient in the months before the hip fracture rather than using control patients.[11-13] This method allowed us to compare costs directly, but also to take into account the excess mortality in the hip fracture group, compared to the control group. For hip fractures, the matching appears to have achieved its purpose, since average cost before fracture was roughly equal between cases and controls. For vertebral fractures however, there was, even before any fracture, a cost difference of € 460. This was possibly caused by underlying co-morbidity that was not avoided by the matching, and it clearly underlines the need for a control group when assessing the cost of vertebral fractures. Since the exact date of the vertebral deformity was impossible to determine, we accounted for those costs by analyzing the complete period in between the two radiographs, and we did not find indications of any substantial acute phase cost.

In this study we only included direct medical costs, and the average cost was small, compared to overall average health care costs for individuals of the same age in the Netherlands.[31] This is because we included only relatively healthy and mostly independently living individuals. We also investigated only incremental cost after a first vertebral fracture, and this study gives no information on the cost consequences of multiple vertebral fractures. Moreover, we included a large proportion of vertebral deformities that never came to clinical attention, and this has to be considered when extrapolating these results to other populations. In calculating the medical consumption we did not include health care costs such as home care and home help, paramedical care, ambulatory physiotherapy, equipment costs and transportation cost. From Dutch health expenditure data,[31] we estimated that these costs only account for about 15 % of all health care costs in this age group. Indirect cost due to lost production was not included as we felt this was irrelevant in this elderly population, but this is an important reason why our estimates are low.

The most important limitation, however, is that this study for assessing the cost of incident fractures by direct comparison of patients with a control group was relatively small, and although the approach appears feasible, the results should be interpreted with caution, as is obvious from the relatively wide confidence intervals. Further investigation is needed, especially to validate our finding that co-morbidity might be an important determinant in the cost of vertebral fractures. The observation of the increased and unspecific drug consumption is intriguing, and to our knowledge no other study has included this individual pharmaceutical consumption in a cost analysis of fractures.

Conclusions

In this study, we used a novel approach for assessing the cost of incident fractures by direct comparison of medical expenditure in fractures patients with that in a matched control group. While, for hip fractures, our results largely confirm previous cost estimates both in the Netherlands as in other countries, the results for vertebral fractures are surprising. Hip fractures cause an important cost and excess mortality, and prevention of hip fractures would probably avoid those. For vertebral fractures we could not detect important acute care costs, but we did observe a higher medical expenditure even before the occurrence of the fracture, while an important part of the additional incremental cost after fracture was caused by unspecific use of pharmaceutical drugs. This appears to point to co-morbidity, and it is therefore unlikely that prevention of vertebral fractures will eliminate all the incremental cost. When confirmed, this finding would have important implications for the evaluation of the cost effectiveness of preventive strategies.

REFERENCES

1 Melton LJ3. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14(1):S1-8.

2 Lindsay R. The burden of osteoporosis: cost. Am J Med 1995;98(2A):9S-11S.

3 De Laet CE, van Hout BA, Hofman A, Pols HA. [Costs due to osteoporosis-induced fractures in The Netherlands; possibilities for cost control]. [Dutch]. Ned Tijdschr Geneeskd 1996;140:1684-8.

4 Ray NF, Chan JK, Thamer M, Melton LJ. Medical Expenditures for the Treatment of Osteoporotic Fractures in the United States in 1995: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24-35.

5 Tosteson AN, Rosenthal DI, Melton LJ3, Weinstein MC. Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. Ann Intern Med 1990;113:594-603.

6 Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. Bone 1994;15:377-86.

7 Clark AP, Schuttinga JA. Targeted estrogen/progesterone replacement therapy for osteoporosis: calculation of health care cost savings. Osteoporos Int 1992;2:195-200.

8 French FH, Torgerson DJ, Porter RW. Cost analysis of fracture of the neck of femur. Age Ageing 1995;24:185-9.

9 Hollingworth W, Todd CJ, Parker MJ. The cost of treating hip fractures in the twenty-first century. J Public Health Med 1995;17:269-76.

10 Hollingworth W, Todd C, Parker M, Roberts JA, Williams R. Cost analysis of early discharge after hip fracture. Bmj 1993;307:903-6.

11 Zethraeus N, Stromberg L, Jonsson B, Svensson O, Ohlen G. The cost of a hip fracture. Estimates for 1,709 patients in Sweden. Acta Orthop Scand 1997;68:13-7.

12 Johnell O. The socioeconomic burden of fractures: today and in the 21st century. Am J Med 1997;103:25S-26S.

13 Brainsky A, Glick H, Lydick E, Epstein R, Fox KM, Hawkes W, et al. The economic cost of hip fractures in community-dwelling older adults: a prospective study. J Am Geriatr Soc 1997;45:281-7.

14 Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. Bone 1992;13:S1-10.

15 Ross PD. Clinical consequences of vertebral fractures. Am J Med 1997;103:42S-43S.

16 Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone 1993;14:S89-97.

17 Black DM, Palermo L, Nevitt MC, et al. Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res 1995;10:890-902.

18 Burger H, Van Daele PLA, Grashuis K et al. Vertebral deformities and functional impairment in men and women. Bone Miner Res 1997;12:152-7.

19 Lunt M, Felsenberg D, Reeve J, Benevolenskaya L, Cannata J, Dequeker J, et al. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study. J Bone Miner Res 1997;12:1883-94.

20 Francis RM, Anderson FH, Torgerson DJ. A comparison of the effectiveness and cost of treatment for vertebral fractures in women. Br J Rheumatol 1995;34:1167-71.

21 Jonsson B, Christiansen C, Johnell O, Hedbrandt J. Cost-effectiveness of fracture prevention in established osteoporosis. Osteoporos Int 1995;5:136-42.

22 Ankjaer-Jensen A, Johnell O. Prevention of osteoporosis: cost-effectiveness of different pharmaceutical treatments. Osteoporos Int 1996;6:265-75

23 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

24 Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum. 1983;26:1346-53.

25 Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton L3. Classification of vertebral fractures. J Bone Miner Res 1991;6:207-15.

26 Black DM, Palermo L, Nevitt MC, et al. Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res 1995;10:890-902.

27 Rutten FFH, van Ineveld BM, van Ommen R, van Hout BA, Huijsman R. Stuurgroep Toekomstscenario's Gezondheidszorg, Kostenberekening bij Gezondheidsonderzoek, Richtlijnen voor de praktijk. Utrecht: Van Arkel, 1993.

28 Efron B, Tibshirani R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science 1986;1: 54-77.

29 Schroder HM, Erlandsen M. Age and sex as determinants of mortality after hip fracture: 3,895 patients followed for 2.5-18.5 years. J Orthop Trauma 1993;7:525-31.

30 Boereboom FT, Raymakers JA, Duursma SA. Mortality and causes of death after hip fractures in The Netherlands. Neth J Med 1992;41:4-10.

31 Polder JJ, Meerding WJ, Koopmanschap MA, Bonneux L, van der Maas PJ. Kosten van ziekten in Nederland 1994. Rotterrdam: Erasmus Universiteit, instituut Maatschappelijke Gezondheidszorg/instituut voor Medische Technology Assessment, 1997.

PART 2

MODELING THE RISK OF HIP FRACTURES

2.1 BONE DENSITY AND RISK OF HIP FRACTURE IN MEN AND WOMEN: CROSS SECTIONAL ANALYSIS

This chapter was published as: De Laet CEDH, Van Hout BA, Burger H, Hofman A, Pols HAP. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997; 315:221-5.

INTRODUCTION

The number of people with fracture of the hip is increasing rapidly and by the year 2050 may exceed 6 million a year worldwide, up from 1.6 million in 1990.[1] The aging of the population is the most important reason for this increase. In addition, the age specific incidence of hip fractures has also increased in several countries, including the Netherlands.[1,2] Hip fractures are a major cause of mortality and disability in elderly people and an important burden for the health services in many countries.[3]

As most hip fractures occur in women, most attention has focused on bone loss in women, predominantly around the menopause. Less is known about the relation of hip fractures with bone loss later in life, and the high incidence of hip fracture in older men is largely neglected.[4]

Detailed quantitative knowledge about the effect of age and bone density on the absolute risk of hip fracture is necessary to evaluate the potential benefit of interventions aimed exclusively at bone density. The association of low bone mass with an increased risk of hip fracture is well documented.[5] The strong increase of risk with age and the bone loss associated with age are also evident,[6] but the effect of both determinants together is poorly understood. This information could be obtained directly from follow up studies, but the numbers and time required make those studies difficult to accomplish. Combination of data can, however, lead to indirect estimates of the absolute risk comparable with the approach used previously to estimate the lifetime risk of hip fracture.[7]

In the present study we combined cross sectional data on bone mineral density from a population based sample of elderly men and women living independently with incidence data on hip fracture from a national registry in the Netherlands. In combination with data from the literature, this allowed us to estimate the effect of age and bone density on the risk of hip fracture in men and women.

METHODS

Distribution of bone mineral density

The Rotterdam study, started in 1991, is a prospective follow up study of the occurrence and determinants of disease and disability in elderly people. The design of this study has been described.[8] The study focuses on four primary topics of research: neurogeriatric diseases, cardiovascular diseases, locomotor diseases, and ophthalmological diseases. All 10275 men and women aged 55 and over living in a district of Rotterdam were invited to participate. The study was approved by the appropriate medical ethics committee, and participants provided written informed consent. From those eligible, 7983 participated, bringing the overall response rate of this study to 78%.

The baseline survey included an initial home interview followed by two visits to the research centre for a series of clinical examinations and laboratory assessments. Those baseline assessments included dual energy x ray absorptiometry scans of the femoral neck.

Methods of measuring bone mineral density and data on bone density in a subsample of 1762 subjects have been reported.[9] The present study used the data on femoral neck bone density from the total study population. This site was chosen because of the growing consensus that prediction of fractures is best done with site specific measurements.[3] People in nursing homes (11%) did not visit the research centre and thus were not eligible for bone density measurements.

We present the results for men and women separately, using the age on the day of the bone density measurement. The bone density distribution by age and sex is presented in 5 year age classes; additionally it was analysed continuously by linear regression. This regression model was extended with quadratic and cubic terms to detect a possible non-linear association between age and bone density. As obesity is well known to affect bone density,[9,10] and as in this study body mass index seemed to be related to age, it was added to the regression model as a potential confounder. The results are presented with 95% confidence intervals.

Distribution of hip fractures

The SIG (Foundation for Health Care Information) is a national registry that collects various data related to health care.[11] All admissions to hospital in the Netherlands are included in this registration as is most of the information from nursing homes. In the Netherlands virtually all patients with a hip fracture are treated clinically. Therefore, hospital data give accurate information about the incidence of hip fractures.

Data for hip fractures in 1993 (*International Classification of Diseases*, ninth revision (ICD-9) code 820xx) were collected from the detailed SIG hospital registration data. They were combined with Dutch demographic data for 1993 from the Dutch Central Bureau for Statistics.[12] The data were aggregated in one year age classes and a best fitting function estimated with the SPSS curve fitting facility.[13]

Probability of hip fracture

The relative risk for hip fractures, expressed as relative risk per SD decrease in bone density measured at the femoral neck, was estimated by Cummings et al to be 2.6 (95% confidence interval 1.9 to 3.6) in women.[14] Combining this relative risk with data on incidence and bone density made it possible to estimate the probabilities of hip fracture by age, sex, and bone density. The mathematical details are given in the Appendix A. We used the same relative risk estimate for men. We also estimated the isolated effects of aging and decline in bone density related to age and calculated confidence intervals for these separate effects by using the 95% confidence intervals of the relative risk per SD decrease in bone density.

RESULTS

Distribution of bone mineral density

Table 1 shows the overall characteristics of the study population. From the 7086 people eligible, bone density data were obtained for 5814 (82%). This response rate remained above 70% up to the age of 85 years; in people aged over 85 the response dropped to 54%. Men were slightly younger than women (mean 67.6 (SD 7.6) years v 68.5 (8.3) years). The age at menopause was the same in all age groups (48.9 (5.2) years).
The bone density values, stratified by age and sex, were normally distributed, and the SD was almost constant over the age categories. Bone density declined linearly, and introducing quadratic and cubic terms did not improve the model. The apparent decrease in bone density at the femoral neck was 0.0046 (95% confidence interval 0.0040 to 0.0051) g/cm2/year for women and 0.0031 (0.0024 to 0.0038) g/cm2/year for men. Correction for body mass index changed those values only slightly (0.0050 g/cm2/year for women and 0.0028 g/cm2/year for men).

Table 1: *Mean (SD) height, weight, body mass index, and bone mineral density of elderly people, Rotterdam.*

	Men					Women				
Age	No	Height (cm)	Weight (kg)	BMI (kg/m^2)	BMD (g/cm^2)	No	Height (cm)	Weight (kg)	BMI (kg/m^2)	BMD (g/cm^2)
55-59	449	177.2 (6.8)	80.9 (10.7)	25.7 (2.9)	0.917 (0.133)	613	164.0 (6.2)	70.0 (11.0)	26.1 (3.9)	0.862 (0.129)
60-64	572	176.0 (6.5)	80.5 (11.3)	26.0 (3.2)	0.888 (0.121)	730	163.1 (6.1)	70.6 (11.2)	26.5 (3.9)	0.832 (0.126)
65-69	547	175.1 (6.4)	78.7 (10.4)	25.7 (2.9)	0.866 (0.131)	650	162.6 (6.1)	71.3 (10.9)	27.0 (3.9)	0.815 (0.134)
70-74	418	174.1 (6.3)	78.4 (10.5)	25.9 (3.0)	0.865 (0.138)	606	161.0 (6.2)	69.9 (10.9)	27.0 (4.0)	0.791 (0.129)
75-79	301	172.0 (6.3)	75.8 (9.8)	25.6 (2.9)	0.855 (0.145)	433	158.8 (6.2)	67.9 (11.2)	26.9 (4.2)	0.763 (0.126)
80-84	126	171.2 (6.8)	74.0 (9.7)	25.3 (3.2)	0.829 (0.139)	240	157.9 (5.9)	68.0 (10.8)	27.2 (4.1)	0.752 (0.127)
85+	33	170.1 (7.2)	71.9 (8.3)	24.9 (2.8)	0.804 (0.149)	96	157.3 (6.3)	67.1 (9.9)	27.1 (3.7)	0.729 (0.137)
Total	2446	174.9 (6.8)	78.8 (10.8)	25.7 (3.0)	0.876 (0.135)	3368	161.7 (6.5)	69.9 (11.1)	26.7 (4.0)	0.809 (0.134)

Distribution of hip fractures

In the Netherlands in 1993 there were 15 107 registered hospital admissions for hip fractures in a population of 15 million, a quarter of which occurred in men. The one year incidence of hip fracture (per 100 000) increased from around 40 at age 55-59 to about 3150 over age 95 in men and from around 40 to about 4450 in women. In each age group, the incidence of hip fracture in men was equivalent to that in women approximately five years younger. Figure 1 shows the one-year cumulative incidence of hip fractures by age and sex with the fitted curves; details of these functions are given in Appendix B.

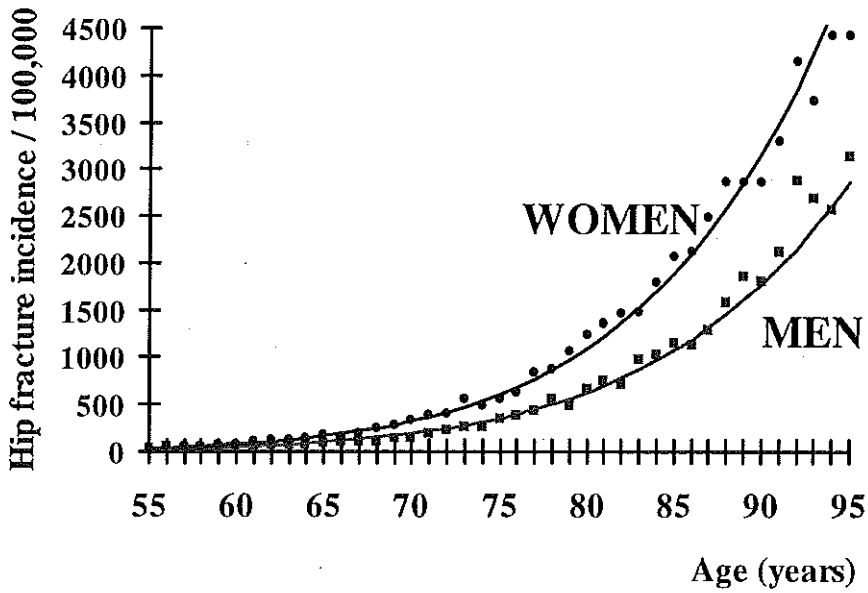


Figure 1: *One year cumulative incidence of hip fracture per 100 000 population, Netherlands, 1993.*

Probability of hip fracture

From the preceding results we estimated the probability of hip fracture by age, sex, and bone density (Appendix B). Figure 2 represents the association of the incidence of hip fracture with bone density at the femoral neck for different ages in men and women. Comparing an 80 year old woman with average bone density with a 60 year old woman, we found a relative risk for hip fracture of 13.6. When we separated the effects, age contributed 7.1 (5.7 to 8.8) to this relative risk, and age related decline in bone density contributed 1.9 (1.5 to 2.4). For men the relative risk was 12.7; the contribution of age was 8.2 (7.1 to 9.5) and of age related decline in bone density was 1.6 (1.3 to 1.8).

The magnitude of the relative risk per SD change in bone density affected the slope of the risk function (fig 3), which shows the curves for the central estimate (2.6) together with the curves at the lower and upper limits of the 95% confidence interval (1.9 to 3.6). As the incidence of hip fracture specific for age remains constant the risk of low bone density becomes higher, and the risk of high bone density becomes smaller when we assume a higher relative risk. The opposite happens at the lower confidence limit.
Fig 2 One year cumulative incidence of hip fracture by femoral neck bone density at ages 60, 70, and 80 in women and men

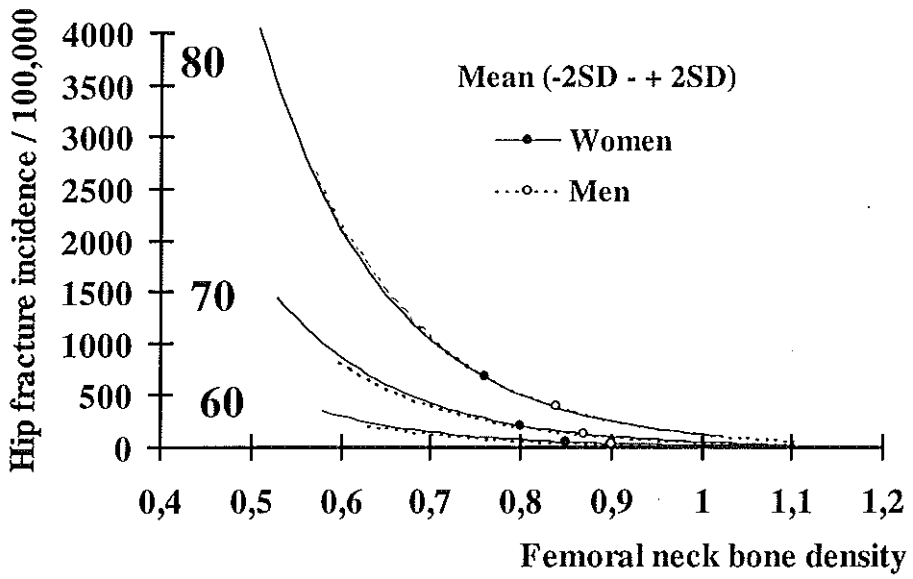


Figure 2: One-year cumulative incidence of hip fracture by femoral neck bone density at ages 60, 70 and 80.

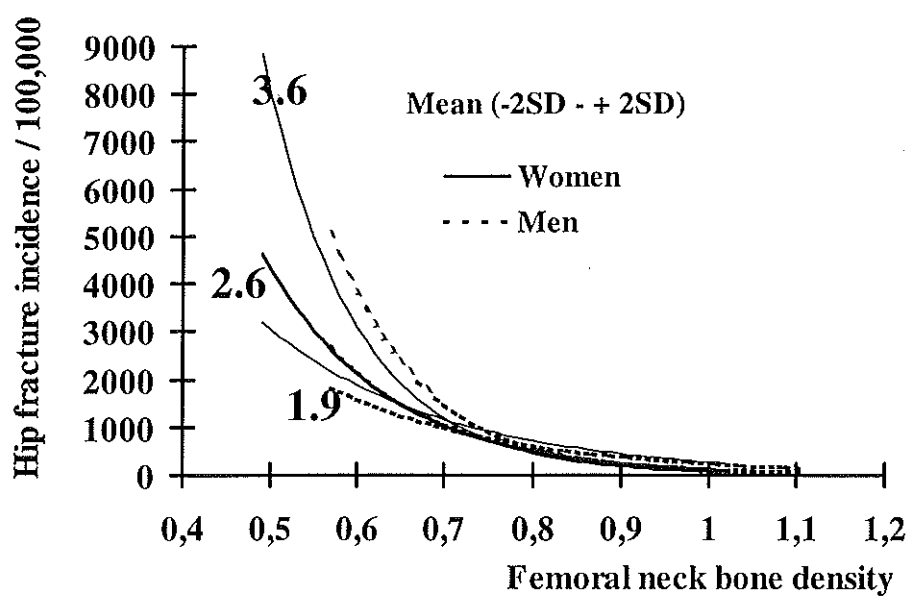


Figure 3: One year cumulative incidence of hip fracture in men and women aged 80 with a relative risk (per SD decrease of femoral neck bone density) of 2.6 and 95% confidence limits 1.9 and 3.6. For central estimate (2.6) solid and dotted lines overlap

DISCUSSION

After the age of 60 the incidence of hip fracture is consistently lower in men than in women of the same age. Men have about the same risk of hip fracture five years later than women. Though the age related decline in bone density is larger in women, the risk of hip fracture when age and bone density are considered together is remarkably similar in men and women. The five year difference in the age specific incidence of hip fracture between men and women can, in this study, be explained by the different bone density distributions at those ages.

Though the risk for hip fracture increased 13-fold from age 60 to age 80 in both men and women, the age related decline in bone density explained merely a doubling of this risk. The rest of the increased risk is explained by other determinants of risk that have been accounted for by using age as a surrogate and that are approximately equal in men and women. Previous research identified several skeletal and extraskeletal determinants.[15] Though bone density is not the main component of the increased risk of hip fracture in old age, risk would be substantially reduced if the age associated decline in bone density between the ages 60 and 80 could be excluded: a 36% reduction in men and 48% in women. Recent clinical trials indicate that part of this risk reduction might be achievable.[16,17]

Assumptions

The stronger effect of age on risk of fracture in general and of hip fracture in particular has been observed in women,[18] but previous studies were based on relatively small numbers of fractures. Our design allowed us to use the information from more than 15 000 hip fractures in the analysis. The data presented here, however, were derived from several sources, which involves some assumptions that need to be examined. We assumed that the distribution of femoral neck bone density in the Netherlands corresponds to the distribution in this study. Even though our sample was population based, it could have been influenced by selection bias: healthy people could have been overrepresented. The high response rates indicate that this effect was probably small.

More importantly, the sample included only people who were living independently. The more frail patients in nursing homes, presumably with lower average bone density, were excluded, resulting in an underestimation of the age associated decline of bone density. Fewer than 9% of elderly people aged under 80 were in nursing homes, but this proportion rose greatly at higher ages. This means that the validity of the data seems assured up to the age of 80, but that the effect of the age associated decline in bone density will probably be somewhat higher than estimated in the older age categories. The age associated decline in bone density that we found was of the same magnitude as in other cross sectional, population based studies, although the absolute levels are slightly higher.[19-21]

Finally, cohort effects cannot be excluded as the bone density data used in this study are cross sectional. If present, these cohort effects would affect the estimated rate of bone loss but not the risk function.

Other risk indicators

In the analysis, age was used as a surrogate marker for several risk indicators, including propensity to fall, types of fall, muscle strength, and bone quality. We used the distribution of bone density and the age related decline in bone density without correction for height, weight, or for the age at menopause as we were interested in the combined effect of these determinants. Moreover, the confounding effect of body mass index was small, and in women the age at menopause was unrelated to age at fracture.

Choice of relative risks

We assumed the relative risk of 2.6 per SD to be the same at all ages, and we also assumed this relative risk applies to the Netherlands. This relative risk estimate influences the slope of the association between incidence of hip fracture and bone density but it does not alter the level of those curves, as is clear from figure 3. It could, however, influence the contribution of the age related decline in bone density to the risk of hip fracture. But, even at the upper confidence limit, this merely doubles the risk over 20 years of aging. It was previously shown in women that bone mineral density predicted fractures equally well at different ages up to the age of 80.[22] Additionally, in a recent meta-analysis the relative risk estimate remained at 2.6 while the confidence interval narrowed slightly (2.0 to 3.5).[5] This same study also indicated that the estimates of relative risk for different measurement and fracture sites seem to be comparable in different parts of the world.

As no relative risk based on large samples was available for men we assumed the same relative risk in men and women, as others have suggested,[23,24] and as was confirmed in a recent follow up study of bone density measurements in 752 men in Australia.[25] That study estimated the relative risk for hip fractures per SD lower bone density at the femoral neck at 2.9 (1.7 to 5.0). This seems compatible with our a priori assumption of no difference. When we applied this point estimate of 2.9 the results changed only slightly; the contribution of aging (age 60 to age 80) became 7.8 (6.1 to 10) and that of bone density decline 1.6 (1.3 to 2.1), supporting our conclusions.

Conclusions

The risk of hip fracture, when expressed as a function of bone density and age, is remarkably similar in men and women, and the difference in age specific incidence of hip fracture can be explained completely by the different distribution of bone density in men and women. Our results also show that the contribution of age associated decrease in bone density to the exponential increase of the risk of hip fracture with age is limited.

REFERENCES

1 Melton LJ 3d. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14:S1-8.

2 Boereboom FT, Raymakers JA, de Groot RR, Duursma SA. Epidemiology of hip fractures in The Netherlands: women compared with men. Osteoporos Int 1992;2:279-84.

3 Kanis JA, Mc Closkey EV. Evaluation of the Risk of Hip Fracture. Bone 1996;18:127S-32S.

4 Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int 1994;4:277-82.

5 Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurence of osteoporotic fractures. BMJ 1996;312:1254-9.

6 Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-50.

7 Black DM, Cummings SR, Melton LJ 3d. Appendicular bone mineral and a woman's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639-46.

8 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

9 Burger H, van Daele PL, Algra D, van den Ouweland FA, Grobbee DE, Hofman A, et al. The association between age and bone mineral density in men and women aged 55 years and over: the Rotterdam Study. Bone Miner 1994;25:1-13.

10 Toss G. Effect of calcium intake vs. other life-style factors on bone mass. J Intern Med 1992;231:181-6.

11 Stichting Informatiecentrum voor de Gezondheidszorg, Maliebaan 50, 3508 SC Utrecht.

12 CBS, Statistisch Jaarboek 1994.

13 SPSS for windows, Release 6.1.

14 Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993;341:72-5.

15 Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995;332:767-73.

16 Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-43.

17 Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.

18 Hui SL, Slemenda CW, Johnston Jr CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988;81:1804-9.

19 Hannan MT, Felson DT, Anderson JJ. Bone mineral density in elderly men and women: results from the Framingham osteoporosis study. J Bone Miner Res 1992;7:547-53.

20 Steiger P, Cummings SR, Black DM, Spencer NE, Genant HK. Age-related decrements in bone mineral density in women over 65. J Bone Miner Res 1992;7:625-32.

21 Pearson J, Dequeker J, Henley M, Bright J, Reeve J, Kalender W, et al. European semi-anthropomorphic spine phantom for the calibration of bone densitometers: assessment of precision, stability and accuracy. The European Quantitation of Osteoporosis Study Group. Osteoporos Int 1995;5:174-84.

22 Nevitt MC, Johnell O, Black DM, Ensrud K, Genant HK, Cummings SR. Bone mineral density predicts non-spine fractures in very elderly women. Study of Osteoporotic Fractures Research Group. Osteoporos Int 1994;4:325-31.

23 Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, et al. Prediction of osteoporotic fractures by postural instability and bone density. BMJ 1993;307:1111-5.

24 Kanis JA,Devogelaer J,Gennari C. Practical Guide for the Use of Bone Mineral Measurements in the Assessment of Treatment of Osteoporosis: A Position Paper of the European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1996;6:256-61.

25 Nguyen TV,Eisman JA,Kelly PJ,Sambrook PN. Risk Factors for Osteoporotic Fractures in Elderly Men. Am J Epidemiol 1996;144:255-63.

APPENDIX A

To obtain the incidence of hip fracture specific for age, sex, and bone mineral density (BMD) we combined the BMD distribution in this population based sample, the observed incidence of hip fracture specific for age and sex in the Netherlands, and the relative risk for hip fractures per SD decrease in the femoral neck bone density as described by Cummings et al.[14] When we assume a constant relative risk per SD decrease of BMD, the age, sex and BMD specific incidence for hip fractures is given by:

$$p_{age,sex,BMD} = p_{age,sex} \cdot a^{-z} \qquad (1)$$

where page,sex denotes the incidence for people with mean BMD for that age and sex, where a is the relative risk per SD decrease in BMD, and where z is the BMD difference from the age and sex specific mean BMD expressed in SDs. The distribution of hip fractures by BMD in people of the same age and sex will then be given by the product of the risk of hip fracture specific for BMD given above and the BMD distribution in this same population, which we know is normal. The distribution of cases is therefore given by:

$$f_{age,sex}(z) = \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5z^2} \cdot p_{age,sex} \cdot a^{-z}$$

The total incidence of hip fracture can be calculated by the integration of this distribution over the whole range of z. The incidence of hip fracture specific for age and sex is thus given by:

$$i_{age,sex} = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5z^2} \cdot p_{age,sex} \cdot a^{-z} \cdot dz = p_{age,sex} \cdot \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5z^2} \cdot a^{-z} \cdot dz$$

As the age and sex specific hip fracture incidence is known from population data, we can calculate

From (1) and (2) it follows that:

$$p_{age,sex,BMD} = \frac{i_{age,sex}}{\int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5z^2} \cdot a^{-z} \cdot dz} \cdot a^{-z}$$

(3)

In practice this means that, to obtain the incidence of hip fracture for people with mean BMD, the observed incidence specific for age and sex needs to be divided by a correction factor C, given by:

$$C = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5x^2} \cdot a^{-z} \cdot dz$$

C equals 1 when a equals 1. In all other cases C is larger than 1. When a=2.6, as is the central estimate in this article, the correction factor C equals 1.578541. (At the lower confidence limit (1.9) the correction factor is 1.228739 and at the upper limit (3.6) it is 2.271399.)

APPENDIX B

The one year cumulative incidence of hip fracture (per 100 000) in this article is estimated from population data. The best fitting curves are power functions given by:

$$i_{age,men} = 9.3 \cdot 10^{-15} \cdot age^{8.8431}$$

and

$$i_{age,women} = 5.9 \cdot 10^{-15} \cdot age^{9.0731}$$

The relation of femoral neck BMD (g/cm^2) with age is best described by a linear function:

$$BMD_{age,men} = 1.08586 - 0.0031 \cdot age$$

and

$$BMD_{age,women} = 1.121284 - 0.00456 \cdot age$$

With the conditions of normality and homoscedasticity fulfilled, and by assuming a relative risk of 2.6 per SD decrease of BMD at the femoral neck, the one year incidence of hip fracture (per 100 000) is thus given by (3):

$$p_{age,men,BMD} = \left(\frac{9.3 \cdot 10^{-15} \cdot age^{8.8431}}{1.578541} \right) \cdot 2.6^{\frac{1.08586 - 0.0031 * age - BMD}{0.135}}$$

and

$$p_{age,women,BMD} = \left(\frac{5.9 \cdot 10^{-15} \cdot age^{9.0731}}{1.578541} \right) \cdot 2.6^{\frac{1.121284 - 0.0045 * age - BMD}{0.134}}$$

2.2 HIP FRACTURE RISK ESTIMATION IN ELDERLY MEN AND WOMEN: VALIDATION IN THE ROTTERDAM STUDY

This chapter was published as: De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998; 13:1587-1593.

INTRODUCTION

In Western societies, hip fractures cause major morbidity and mortality in the elderly.[1] Consequently, they generate substantial costs due to acute hospital treatment and subsequent rehabilitation.[2,3] Improved life expectancy and the demographic evolution will cause the number of hip fractures worldwide to increase from about 1.7 million in 1990 to over 6 million in 2050.[1] To target prevention at those with the highest risk, it is important to be able to predict hip fractures.

Although the immediate cause of a hip fracture is mostly a fall, their occurrence is closely associated with osteoporosis.[4] Osteoporosis is defined as a condition characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[5] The conventional method of estimating bone mass is by bone densitometry. The World Health Organization defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviation (SD) below the mean for young adults.[6]

It is, however, important to distinguish between BMD as a tool for defining osteoporosis and BMD measurement as a tool for fracture risk prediction.[7] The association of BMD with subsequent hip fracture has been demonstrated in several studies with an estimated relative risk, for women, of 2.6 per SD decrease in femoral neck BMD.[4,8] With this relative risk estimate, the registered hip fracture incidence in the Netherlands, and the BMD distribution from a Dutch population-based sample, we derived a theoretical one-year hip fracture risk function by age and femoral neck BMD for men and women.[9] In the present study we validated this tool for predicting hip fracture incidence rates in a prospective follow-up study. Additionally, we calculated the risk of hip fracture per SD decrease in femoral neck BMD for both men and women.

METHODS

Study participants

We previously estimated the one-year cumulative risk of hip fracture by age and BMD, based on Dutch hip fracture incidence data, the distribution of BMD in a sample of 5814 men and women aged 55 years and over, and on data from the literature.[9] In the present study, we validated this risk estimate in the Rotterdam Study, a population based prospective cohort study of the occurrence and determinants of disease and disability in the elderly. The Rotterdam Study focuses on neurologic, cardiovascular, locomotor and ophthalmologic diseases. The study started in 1990 and all 10275 men and women aged 55 and over, living in Ommoord, a district of Rotterdam, were invited to participate. The study was approved by the Medical Ethics Committee of Erasmus University Medical School, and participants provided written informed consent. From those eligible for participation, 7983 did participate, bringing the overall response rate of this study to 78 %. The design of this study has been described previously.[10]

The baseline survey included an initial home interview followed by two visits to the research center for a series of clinical examinations and laboratory assessments. Baseline assessments included dual energy X-ray absorptiometry scans of the femoral neck in the independently living participants, using a Lunar DPX-L densitometer. Measurement procedures have been reported previously.[11]

Risk estimation

For each participant, we calculated the one-year cumulative risk according to the risk function, as an individual risk estimate. The equations used for this purpose are given in the appendix. Participants with an incident hip fracture prior to BMD measurement were excluded from the risk classification. Based on the same risk functions, a nomogram indicating the one-year hip fracture risk by age and BMD was constructed for men and women. To avoid that these nomograms would only be useful to users of Lunar machines, we also converted those risk functions to other brands of densitometers. This conversion was done using the conversion algorithms provided by Genant et al.,[12] and the resulting equations can also be found in the appendix.

Hip fracture follow-up

Follow-up for hip fractures was achieved through a link with the computer systems of the general practitioners of the district and on hospital admission data, covering about 80 % of the study population. For all participants not covered by this system, annual checks were performed on the complete medical records of their general practitioners. Reported fractures were verified by retrieval and review of the appropriate discharge reports from the patient record. Follow-up started either at January 1, 1991 or at the time of the baseline interview when this was later. Follow-up ended either at death, at the time of the first hip fracture, or February 29, 1996.

Analysis

To assess the performance of the risk function, we divided the population with a valid BMD measurement into categories by gender and risk. The individual one-year risk estimate was categorized as either low (< 0.1 %), moderate (0.1 - < 1 %) or high (≥ 1 %). These cut-off levels were arbitrary but based on clinical common sense: a one-year risk of 0.1 % approximately corresponds to the risk for an average women at the age of 60, (9) while a 1 % risk approximately corresponds to the risk for an average 80 year old women. Incidence rates of first hip fracture were then calculated for each of these categories. To account for the events occurring in participants without a BMD measurement, hip fracture incidence was calculated separately for those living in institutions for residential care and for community dwelling persons without BMD measurement.

To assess the effect of age, we subdivided these risk-categories into ten-year age groups. To avoid categories without outcome events, we combined for this analysis by age the low and moderate risk categories into a single category. For categories where follow-up time was less than 100 pyrs, we did not to calculate incidence rates since those results were considered too unreliable.

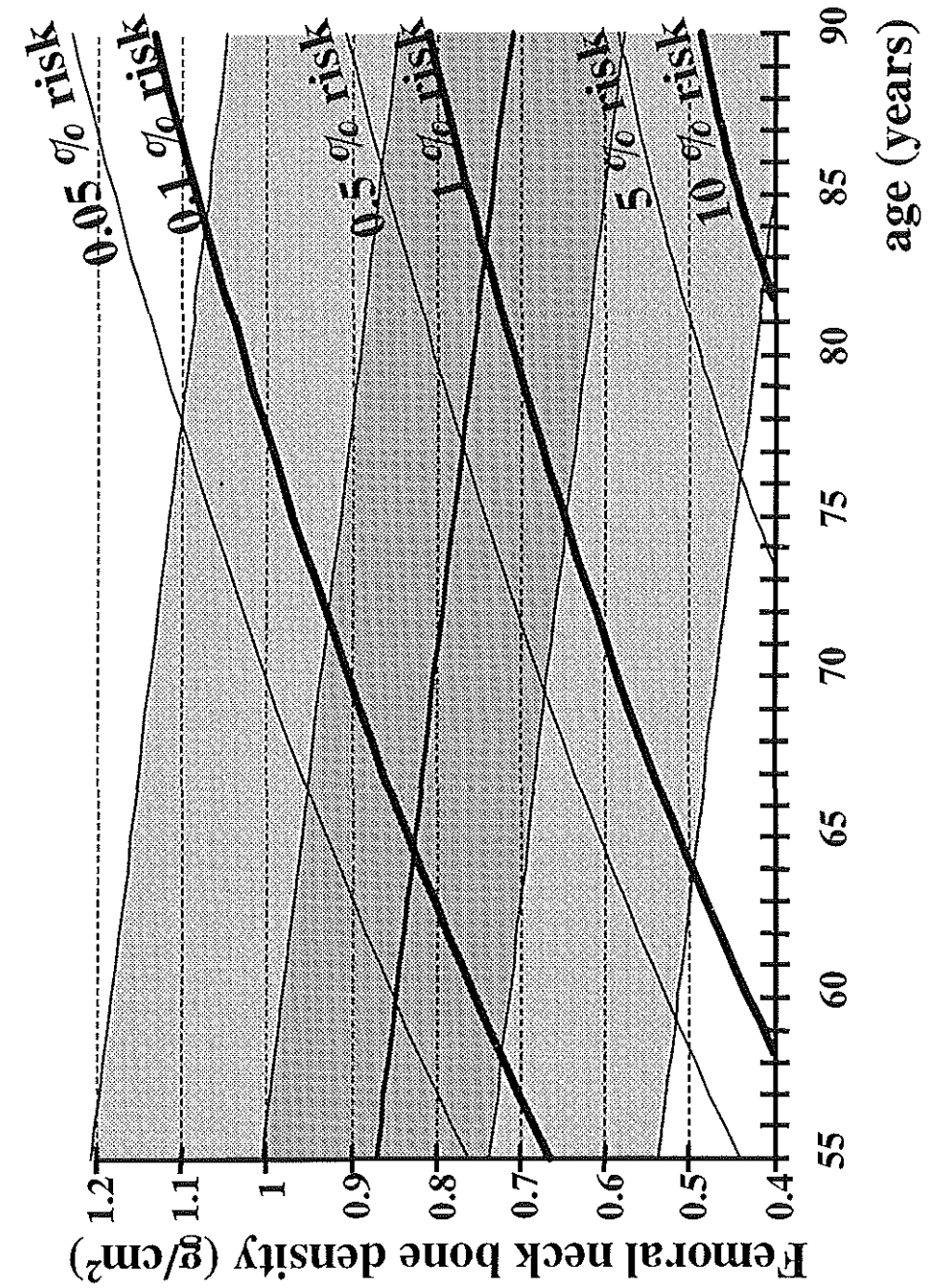


Figure 1: *One-year hip fracture risk by age and bone mineral density (g/cm2) in women. The dark gray area indicates average BMD ± 1SD, the light gray area indicates average BMD ± 2.5 SD.*

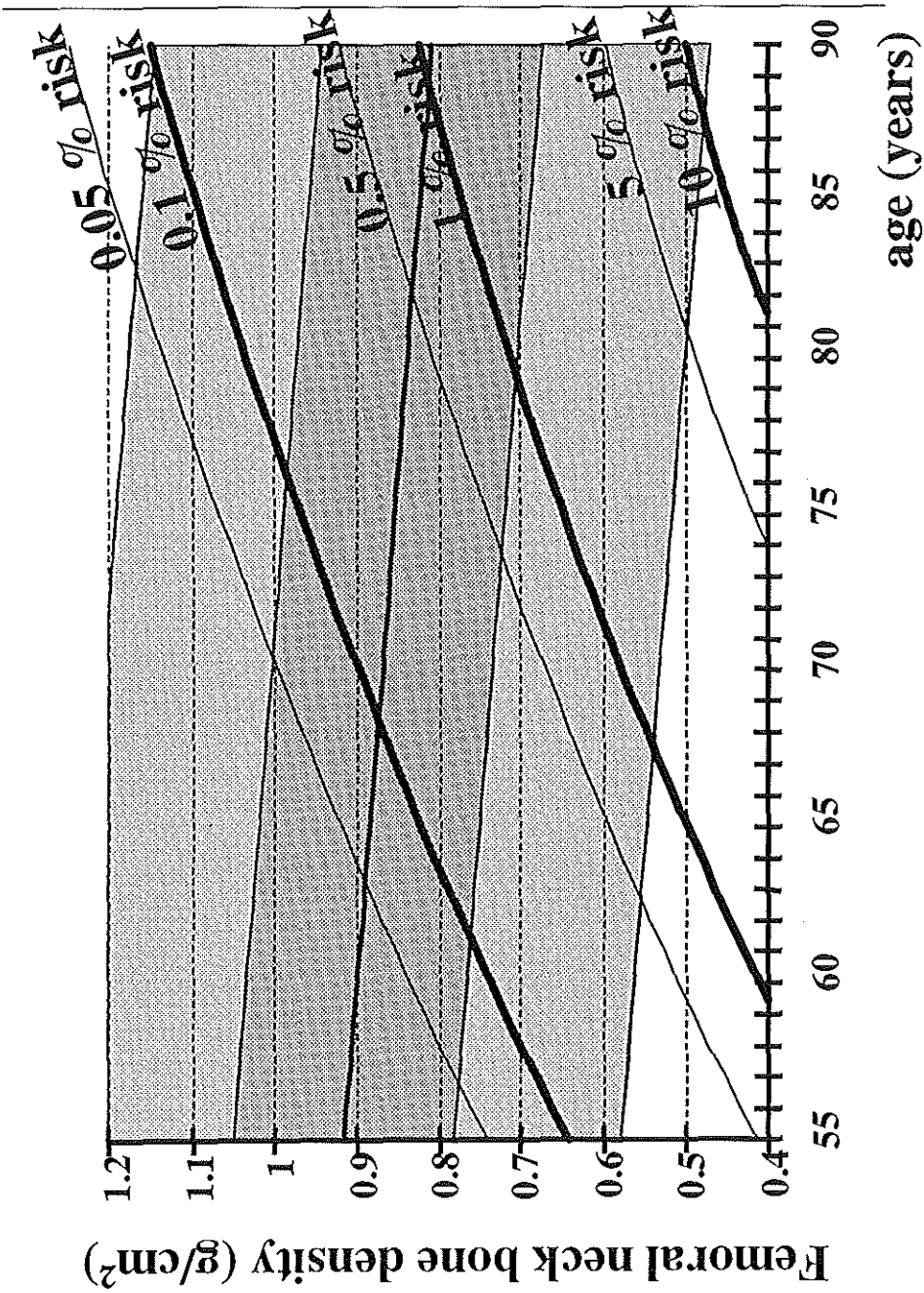


Figure 2: *One-year hip fracture risk by age and bone mineral density (g/cm2) in men. The dark gray area indicates average BMD ± 1SD, the light gray area indicates average BMD ± 2.5 SD.*

Finally, we calculated the age-adjusted relative risk per SD decrease in BMD using Cox's proportional hazards model. All point estimates are presented with their 95 % confidence intervals (CI).

RESULTS

Baseline risk classification

Figures 1 and 2 represent, as a nomogram, the one-year hip fracture risk by age and BMD calculated from the risk functions, for men and women respectively. The shaded areas depict our Dutch reference BMD distribution (g/cm2), while the curves connect points of equal risk at all ages. The curves are very similar in men and women, as we described before,[9] while the average BMD is higher in men than in women at every given age, and the decrease of BMD with age is slower in men.

Complete follow-up was achieved for 7046 persons (2778 men) with an average follow-up time of 3.8 years. In 5305 of those (2227 men), we also had a valid BMD measurement at baseline, and the BMD distribution by age is shown in Table 1. Based on bone density, age and gender, we classified everybody at baseline in risk categories according to the risk functions: 2360 individuals were categorized as low risk, 2567 as moderate risk and 378 as high risk. For 1741 individuals no baseline BMD measurement was available: 614 lived in residential care, and 1127 lived independently. From the independently living, 487 did not come to the study center, the others had no BMD measurement because of technical reasons, mostly caused by machine downtime.

Table 1: *Average BMD at baseline (SD) by age and gender.*

Age	Women	Men
< 60	0.862 (0.130)	0.916 (0.133)
60-69	0.825 (0.132)	0.878 (0.128)
70-79	0.778 (0.128)	0.861 (0.141)
≥ 80	0.747 (0.130)	0.827 (0.143)

Observed hip fracture incidence

Follow-up totaled 26771 person-years (10333 for men), and 110 first hip fractures were observed, 23 of them in men. The observed hip fracture incidence rate for the whole population was 4.1/1000 pyrs (3.4-5.0). Observed incidence in the low risk group (2 fractures) was 0.22/1000 pyrs (0.05-0.87). In the moderate risk group (27 fractures) the incidence was 2.7/1000 pyrs (1.8-3.9) and in the high risk group (25 fractures) the observed incidence was 18.4/1000 pyrs (12.4 - 27.2). In the group without BMD measurement incidence in residential care (36 fractures) was 19.7/1000 pyrs (14.2-27.4). In the independently living participants without BMD measurement (20 fractures) the overall incidence was 4.5/1000 PYRS (2.9-7.0). Figure 3 presents these observed hip fracture incidences for men and women separately.

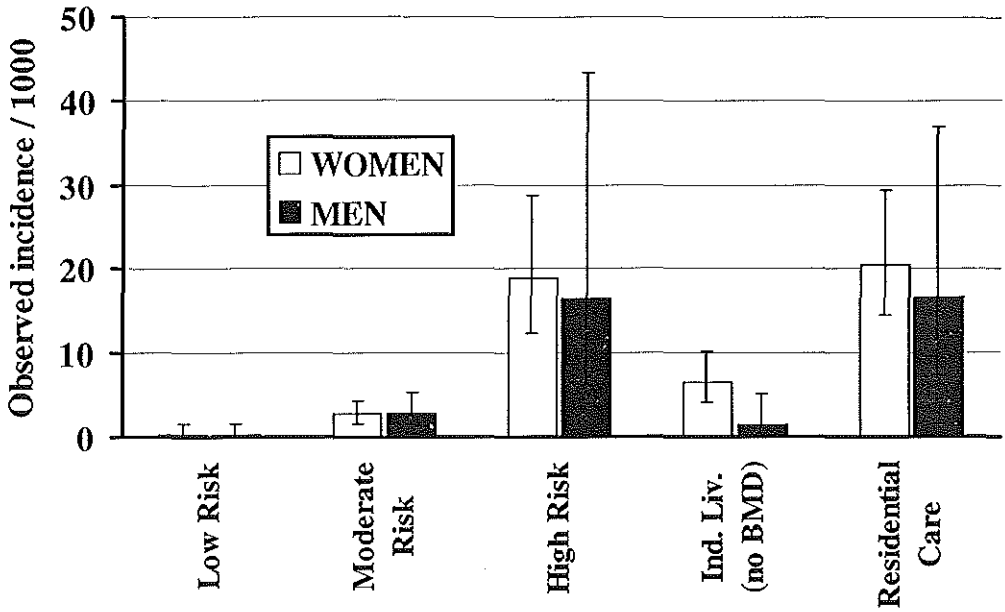


Figure 3: Observed hip fracture incidence by risk category and gender.

Table 2 gives an overview of the baseline classification according to the risk function, by gender and ten-year age groups, and the number of hip fractures that occurred during follow-up. As expected from the nomograms, the high risk group is more prominent at older ages and more important in women than in men. At ages over 80 almost nobody is still in the low risk group, but an important proportion of the independently living population can be considered, a priori, at only moderate risk, especially in men. Table 3 lists the observed incidence rates for all categories, and the point estimates confirm the a priori risk classification. However, in this analysis by age, the confidence intervals are much wider, reflecting the smaller number of events and follow-up time per category.

The observed age-adjusted relative risk for hip fractures was similar in men and women. The relative risk was 2.5 for each SD decrease in femoral neck BMD (1.8 - 3.6) in women. In men this relative risk was 3.0 (1.7 – 5.4). These relative risks were not statistically different (p=0.65).

***Table 2:** Risk classification at baseline by age and gender (number of observed hip fractures).*

	Women						Men					
Age	Low	Moderate	High	Ind. Liv.	Res. Care	Total	Low risk	Moderate	High	Ind. Liv.	Res. Care	Total
< 60	472 (0)	74 (1)		75 (1)	1 (0)	622 (2)	371 (0)	15 (1)		46 (0)		432 (1)
60-69	591 (1)	661 (1)	9 (0)	207 (2)	8 (0)	1476 (4)	667 (1)	365 (2)	1 (0)	155 (1)	5 (0)	1193 (4)
70-79	85 (0)	736 (11)	141 (9)	264 (4)	58 (3)	1284 (27)	161 (0)	478 (6)	29 (0)	147 (1)	26 (1)	841 (8)
≥ 80	7 (0)	148 (4)	154 (12)	161 (11)	416 (27)	886 (54)	6 (0)	90 (1)	44 (4)	72 (0)	100 (5)	312 (10)
Total	1155 (1)	1619 (17)	304 (21)	707 (18)	483 (30)	4268 (87)	1205 (1)	948 (10)	74 (4)	420 (2)	131 (6)	2778 (23)

Ind. Liv: Independently living, but no BMD measured
Res. Care: Residential care, no BMD measured

Table 3: Observed incidence rates / 1000 pyrs by age and gender (95 % CI).

	Women					Men				
Age	Low and moderate	High	Ind. Liv.	Res. Care	Overall	Low and moderate	High	Ind. Liv.	Res. Care	Overall
< 60	0.5		3.5	*	0.8	0.7		0		0.6
	(0.07-3.4)		(0.5-25.0)		(0.2-3.4)	(0.1-4.9)				(0.1-4.4)
60-69	0.4	*	2.3	*	0.7	0.8		1.6		0.9
	(0.1-1.6)		(0.6-9.2)		(0.3-1.8)	(0.3-2.4)	*	(0.2-11.6)	*	(0.3-2.4)
70-79	3.3	16.6	3.6	17.1	5.2	2.4		1.8		2.5
	(1.8-6.0)	(8.6-31.8)	(1.4-9.6)	(5.5-53.0)	(3.6-7.6)	(1.1-5.4)	*	(0.3-12.6)	*	(1.3-5.0)
≥ 80	6.5	22.5	19.1	21.5	18.1	2.9	27.7	0	18.6	10.2
	(2.4-17.3)	(12.8-39.6)	(10.6-34.6)	(14.7-31.3)	(13.9-23.7)	(0.4-20.6)	(10.4-73.7)		(7.7-44.6)	(5.5-19.0)
Total	1.6	18.8	6.4	20.5	5.3	1.3	16.3	1.3	16.6	2.2
	(1.0-2.6)	(12.3-28.9)	(4.0-10.1)	(14.3-29.3)	(4.3-6.5)	(0.8-2.4)	(6.1-43.4)	(0.3-5.1)	(7.5-37.0)	(1.5-3.4)

* incidence rates not calculated when observation time is < 100 pyrs
Ind. Liv: Independently living, but no BMD measured
Res. Care: Residential care, no BMD measured

DISCUSSION

Main findings

In the community dwelling individuals, the high risk group consisted mainly of individuals aged 70 years and older, predominantly women. The observed incidence rates and their precision demonstrate that the risk function accurately predicted hip fracture incidence in the various risk subgroups in men and women. The low and moderate risk groups taken together, identified a large proportion of the study group with low hip fracture incidence, even at ages over 80. However, a smaller group of individuals with high hip fracture incidence starting at age 70, could be identified.

Participants living in residential care institutions had a hip fracture risk similar to the highest risk category. This is in agreement with previous findings of high hip fracture incidence rates in nursing homes and institutions for residential care.[13,14] Both in residential care and in the high risk category, the observed incidence was slightly lower in men. This was probably due to the different age distribution, with men being, on average, younger within each group.

The relative risk for hip fracture per SD decrease in BMD observed in this study confirms previous estimates. While for women this estimate was based on large studies,[4,8] the estimate for men was only based on a small sample.[15]. For the derivation of the one-year cumulative risk function, we assumed that the relative risk was equal in men and women. Our present findings confirm the validity of this assumption.

The risk evaluation in this study was based on a one-year risk estimate and, although follow-up amounted to almost 4 years, prediction on a longer term is important for therapeutic decisions. Prediction over a longer time period is, however, dependent on assumptions about the BMD evolution. If we assume linear decline, as we found in our cross-sectional study, we can estimate long term risk by extrapolation of the current BMD level on the nomogram. There are, however, indications for a more rapid BMD decline at older ages,[16,17] and, if so, future risk would be underestimated. Additionally, it is unclear how well an individual BMD measurement correlates with bone density in the

future, and long-term risk prediction is dependent on assuming a high correlation.[18] Follow-up studies over a longer period are needed to answer this question more precisely.

Generalizability

The risk function was developed based on Dutch data, and its applicability in other populations might be limited if either the hip fracture incidence or the bone density distribution were different. But, comparing Dutch hip fracture incidence data with recent international data,[19,20] they appeared remarkably similar to incidences in Sweden, Scotland and Switzerland and slightly lower than in US Caucasians. There have also been indications that BMD distributions might be different in several European countries, but those estimates were based on small samples.[21,22] In this large sample, however, the bone density distribution was almost identical to that in US women,[23] after correction for scanner type.[12] This suggests that the application of the risk function is not limited to a Dutch population, although additional validation in other populations remains desirable.

Even while the number of hip fractures in men was small (23 fractures), we believe this is an important first attempt to validate risk estimates in a male population. We are not aware of any comparable study where an a priori risk was validated in a follow-up design in males, but especially here, additional validation remains necessary.

To facilitate the usability by users of other brands of densitometers, we have provided converted equations in the appendix, while the converted nomograms are available from the authors. These conversions, obviously, do not change the risk classification itself, but only affect the absolute levels of BMD, and the associated risk curves.

Potential limitations

Although population based, there was self-selection in the participation to the study. Even with the high response rates, this might cause selection bias towards more healthy individuals. There might also be concern about potential misclassification. Since the cases that were reported were well documented, this misclassification would most likely result in an underreporting of fractures. Both phenomena would lead to a lower hip fracture incidence than expected from Dutch overall hip fracture incidence rates. However, a comparison of our results with national incidence rates, only indicates a slightly lower incidence than expected: 110 hip fractures versus 132 expected. This is equivalent to 83 % (69 % - 100 %) of expected hip fractures, suggesting that those effects were probably small. It is, moreover, unlikely that this selection would influence the validity of the risk function.

BMD was not measured in some independently living participants because they did not come to the study center, and this could, in theory, again lead to selection bias towards more healthy individuals. When BMD was not measured for technical reasons, selection bias seems unlikely, and this applied to the majority of participants. In any case, the observed hip fracture rate in this group was very similar to the overall incidence for the same gender.

The validation was done in broad risk and age categories, which was necessary to acquire enough follow-up time to obtain stable results. In figures 1 and 2 we have indicated one-year risk levels up to 10 %, corresponding to the clinically relevant observations. In this study, there where only 3 women exceeding this 10 % risk and 2 of them suffered a hip fracture during follow-up. Although this would correspond to an incidence rate of 203/1000 pyrs (51-813), we believe this result should not be over-interpreted. We analyzed the effect of age by 10-year age categories, and although we are aware that the baseline risk is very different within those categories, taking smaller age-categories would have frustrated any validation effort.

For the original derivation of the risk functions we used the baseline BMD data from the same reference group as where the risk function was validated afterwards. Since the hip fractures in this studies were observed afterwards and prospectively, we do not perceive this as a problem. An alternative would have been to use reference data from the manufacturer, but since those data were not based on Dutch data we preferred to use our own.

Finally, the risk function generated a one-year cumulative risk, while the outcome measure of this study was incidence rates. With the expected and observed incidence rates, the difference between those two measures is negligible.

CONCLUSION

We conclude that hip fracture rates can be predicted accurately, from age and BMD, in both men and women. In prevention programs, we need a tool for risk stratification of the population. This follow-up study showed that our risk function is a valid instrument for that purpose. The majority of hip fractures (61 out of 110) occurred either in the high risk group or in the residential care group, even though these groups accounted for barely 14 % of the study population. In addition, we found a similar relation of femoral neck BMD with hip fracture in men and women.

REFERENCES

1 Melton LJ Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14:S1-8.

2 Lindsay R The burden of osteoporosis: cost. Am J Med 1995;98:9S-11S.

3 De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Kosten wegens osteoporotische fracturen in Nederland; mogelijkheden voor kostenbeheersing. Ned Tijdschr Geneeskd 1996;140:1684-1688.

4 Cummings SR, Black DM, Nevitt MC, et al Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993;341:72-75.

5 Anonymous Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-650.

6 Kanis JA Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 1994;4:368-381.

7 Kanis JA, McCloskey EV Evaluation of the risk of hip fracture. Bone 1996;18:127S-132S.

8 Marshall D, Johnell O, Wedel H Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254-1259.

9 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Pols HAP Bone density and risk of hip fracture in men and women: cross sectional analysis. 1997; BMJ 315:221-225.

10 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-422.

11 Burger H, Van Daele PL, Algra D, et al. The association between age and bone mineral density in men and women aged 55 years and over: the Rotterdam Study. Bone Miner 1994;25:1-13.

12 Genant HK, Grampp S, Gluer CC, et al. Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 1994;9:1503-1514.

13 Cumming RG Nursing home residence and risk of hip fracture. Am J Epidemiol 1996;143:1191-1194.

14 Butler M, Norton R, Lee-Joe T, Cheng A, Campbell AJ The risks of hip fracture in older people from private homes and institutions. Age Ageing 1996;25:381-385.

15 Nguyen TV,Eisman JA,Kelly PJ,Sambrook PN Risk Factors for Osteoporotic Fractures in Elderly Men. Am J Epidemiol 1996;144:255-263.

16 Burger H, De Laet CEDH, van Daele PL et al. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. Am J Epidemiol 1998;147:871-879.

17 Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ 1994;309:691-695.

18 Black DM, Cummings SR, Melton LJ. Appendicular bone mineral and a woman's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639-46.

19 De Laet CEDH,Van Hout BA, Pols HAP Osteoporosis in the Netherlands; A burden of Illness study. Institute for Medical Technology Assessment, Rotterdam 1996.

20 Bacon WE, Maggi S, Looker A, et al. International comparison of hip fracture rates in 1988-89. Osteoporos Int 1996;6:69-75.

21 Pearson J, Dequeker J, Reeve J, et al. Dual X-ray absorptiometry of the proximal femur: normal European values standardized with the European Spine Phantom. J Bone Miner Res 1995;10:315-324.

22 Lunt M, Felsenberg Dm Adams J et al. Population-based geographic variations in DXA bone density in Europe: The EVOS Study. Osteroporosis Int 1997;7:175-189.

23 Looker AC, Johnston CC Jr, Wahner HW et al. Prevalence of low femoral bone density in older US women from NHANES III. J Bone Miner Res 1995;10:796-802.

APPENDIX

Although both the derivation of the risk function by age and femoral neck bone density, and the reference data were described previously,[9] and are included in the previous chapter we felt it necessary to include them here. Additionally, this opportunity was used to expand the usability, by converting the risk functions developed from measurements on a Lunar DPX-L machine to other brands of bone density equipment.

In the Rotterdam Study, we observed a linear decline of bone density with age in men and women. The average bone density at all ages, measured with a Lunar DPX-L densitometer, was given by:

$$BMD_{age,women} = 1.121284 - 0.00456 \cdot age$$

and

$$BMD_{age,men} = 1.08586 - 0.0031 \cdot age$$

BMD was normally distributed at all ages with an overall standard deviation (SD) of 0.134 in women and 0.135 in men.

Using the conversion algorithms of Genant et al[12] we converted these regression formulas to:

$$BMD_{age} = \alpha - \beta * age$$

using the appropriate values from table 4.

Table 4: Risk function values for lunar DPX-L, Hologic QDR-2000 and Norland XR26Mark ii densitometers

	Lunar DPX-L		Hologic QDR 2000		Norland XR26 Mark II	
	Women	Men	Women	Men	Women	Men
α	1.121284	1.08586	0.9293393424	0.89977896	1.040553924	1.00651146
β	0.00456	0.0031	0.00381216	0.0025916	0.00438216	0.0029791
SD	0.134	0.135	0.104024	0.10486	0.125074	0.126035

Using this conversion on the BMD data from women in our cohort, the relation of BMD with age became almost identical to the NHANES III data.[23] Unfortunately, no such widely accepted reference data are available for men.

For the derivation of the risk function, we used Dutch nationwide hip fracture registration to estimate the hip fracture incidence function by age and gender, and additionally, we used the assumption of a 2.6 relative risk per SD lower femoral neck bone density. Under those assumptions,[9] the one-year cumulative risk is given by:

$$p_{age,women,BMD} = \left(\frac{5.9 \cdot 10^{-15} \cdot age^{9.0731}}{1.578541} \right) \cdot 2.6^{\frac{\alpha - \beta * age - BMD}{SD}}$$

and

$$p_{age,men,BMD} = \left(\frac{9.3 \cdot 10^{-15} \cdot age^{8.8431}}{1.578541}\right) \cdot 2.6^{\frac{\alpha - \beta * age - BMD}{SD}}$$

again using the appropriate values from table 4.

Figures 1 and 2, adapted for use with either Hologic or Norland densitometers are added at the end of this chapter.

2.3 HIP FRACTURE PREDICTION IN THE INDIVIDUAL

INTRODUCTION

The association of bone mineral density (BMD) with subsequent hip fractures has been demonstrated in several studies, and in a meta-analysis the relative risk for women was estimated at 2.6 for 1 SD decrease in BMD measured at the femoral neck.[1] Previously, we showed that, for groups of individuals, the hip fracture risk can be estimated accurately by age, gender, and BMD,[2] using the risk functions that we developed based on Dutch data.[3] We also showed that the same relative risk estimate can be used for men,[2] and that men and women have the same risk for hip fractures at the same age and BMD level.[3]

For general prevention purposes predictability of fractures for groups of individuals is important. It is, however, less easy to predict which individual will suffer a hip fracture in the future.

Since it is part of the definition of osteoporosis, BMD can be used for the diagnosis of osteoporosis, and as such it will give an indication of individual risk, but it is not necessarily a good test to predict hip fractures in individuals, ie prognosis.[4] The World Health Organization defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviation (SD) below the mean for young adults. The number of SD's from this average for young adults is called a T-score.[5] BMD results can also be expressed as a Z-score. A Z-score corresponds to the number of SD from the age and gender specific average.

In this chapter, we evaluate the performance of our risk functions as an individual prognostic test for hip fractures within a large population based follow-up study, and compare it to the mere prediction by age and gender, and to the use of the conventional T-score and Z-score thresholds.

METHODS

For the risk estimation we used the risk functions for men and women that were described previously,[3] and that yield a one-year hip fracture risk estimate based on gender, BMD and age. The study was conducted within the Rotterdam Study, a population based prospective cohort study of the occurrence and determinants of disease and disability in the elderly.[6] For participants in whom BMD at the femoral neck was measured at baseline (Lunar DPX-L densitometer), we calculated the one-year cumulative risk according to the risk functions, as an individual and continuous risk estimate. Those participants were subsequently followed-up for the occurrence of hip fractures during on average 3.8 years. Details of procedures and partial results have been reported elsewhere (see also chapter 2.2).[2]

The performance of the risk function as an individual prognostic test was assessed by calculating the ROC area under the curve, and the sensitivity and specificity at various risk thresholds. To evaluate the additional value of the BMD measurement, we compared this with the performance of a test using just age and gender for risk prediction in the same group of participants. This was done by comparing the ROC area's under the curves, and by calculating the positive predictive value (PPV) at different risk thresholds.

Additionally, we compared sensitivity and specificity of the risk score to the sensitivity and specificity of a T-score ≤ -2.5 and of a Z-score ≤ -1. For the Z-scores, we used our

previously published Dutch reference data,[3] and for the T-score we used the same absolute value (0.675) in both men and women, based on Dutch reference data.[7] The argument for choosing the same value for men was first proposed in chapter 1.1 and further validated by our finding that hip fracture risk is similar in men and women at the same age and BMD level.[3]

The ROC area under the curve and its precision was calculated using the ROCFIT program.[8,9] The precision is presented as 95 % confidence intervals (CI).

RESULTS

Complete follow-up was achieved for 5305 participants (2227 men). In this group we observed 54 hip fractures during an average follow-up time of 3.8 years. Table 1 gives an overview of the risk estimates in 10-year age classes and the observed number of hip fractures.[2]

Table 1: *One-year risk estimate at baseline by age and gender (number of observed hip fractures).*

	Women				Men			
Age	< 0.1%	0.1 - < 1 %	≥ 1 %	Total	< 0.1%	0.1 - < 1 %	≥ 1 %	Total
< 60	472 (0)	74 (1)		546 (1)	371 (0)	15 (1)		386(1)
60-69	591 (1)	661 (1)	9 (0)	1261 (2)	667 (1)	365 (2)	1 (0)	1033(3)
70-79	85 (0)	736 (11)	141 (9)	962(20)	161 (0)	478 (6)	29 (0)	668(6)
≥ 80	7 (0)	148 (4)	154 (12)	309(16)	6 (0)	90 (1)	44 (4)	140(5)
Total	1155 (1)	1619 (17)	304 (21)	3078(39)	1205 (1)	948 (10)	74 (4)	2227(15)

Sensitivity and specificity at various threshold values of the risk estimate, in men and women, are shown in figures 1 and 2. Those figures show that, at a threshold risk estimate of 0.5 % one-year risk, sensitivity and specificity are around 80 % in both men and women.

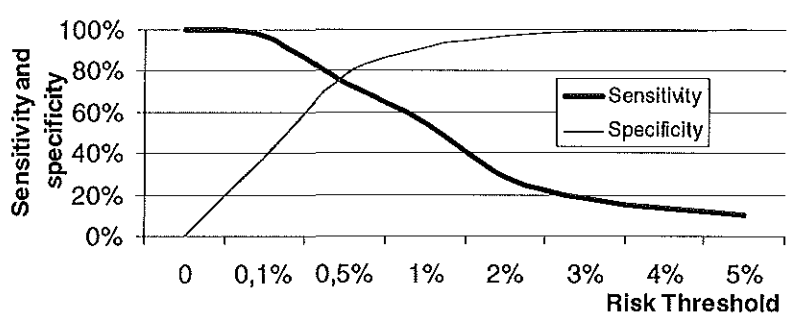


Figure 1: *Sensitivity and specificity at various risk thresholds in women.*

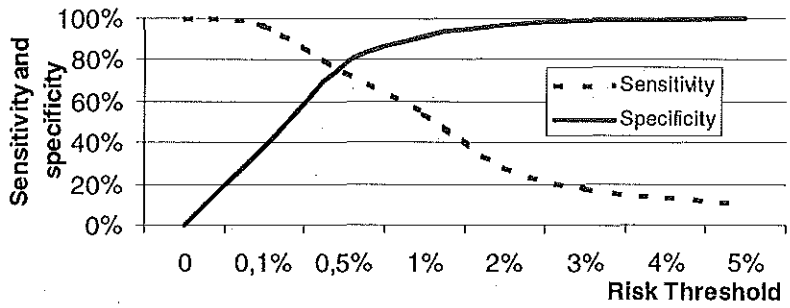


Figure 2: Sensitivity and specificity at various risk thresholds in men.

The overall ROC area under the curve for men and women combined was 0.86 (0.81 - 0.91). When BMD was excluded, using only age for risk prediction, the area under the curve decreased to 0.79 (0.73 - 0.85). For women the area under the curve was 0.85 (0.79 – 0.91) versus 0.81 (0.74 – 0.87) for age alone, and for men 0.87 (0.79-0.95) versus 0.74 (0.60 – 0.88).

In another representation of the same data, we compared the PPV of both tests. When no test is used, considering everybody at risk, the PPV is equal to the cumulative incidence for the total population. In women, this prior probability of a hip fracture, considering everybody at risk, was 1.3 %, while the sensitivity was obviously 100 %.

When we introduce testing, the aim is to increase this PPV while retaining acceptable sensitivity. By increasing the risk threshold of the test, the sensitivity decreases. But, at the same time the PPV increases. Figure 3 demonstrates this effect of changing the risk threshold level on the PPV and the sensitivity in women. The solid curve represents the risk function, including age and BMD, while the dotted curve shows what happens using only age as a risk indicator. On the graph we have indicated the corresponding ages: the area where the curves of both tests diverge, corresponds to the age of 75 years and older.

In men, the prior probability was 0.7 %. At all ages the probability of a hip fracture was lower than in women of the same age. As shown in figure 4, also in men the curves diverge in the area corresponding to the ages of 75 years and older. However, at ages above 80, results became unreliable.

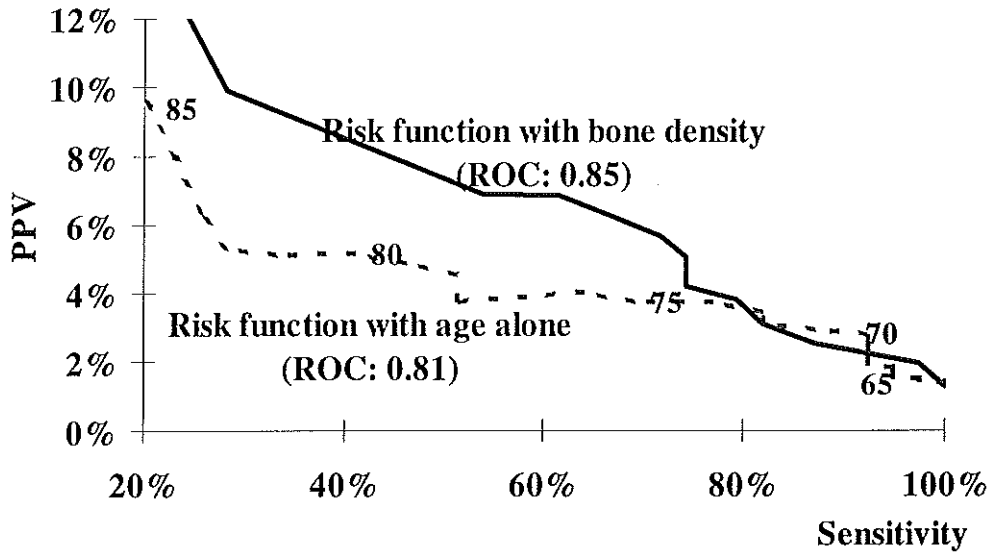


Figure 3: Positive Predictive Value and Sensitivity at various risk thresholds in women. The solid curve indicates the risk function including BMD and age, while the dotted line represents the use of only age as risk indicator. The corresponding ages are shown on the graph.

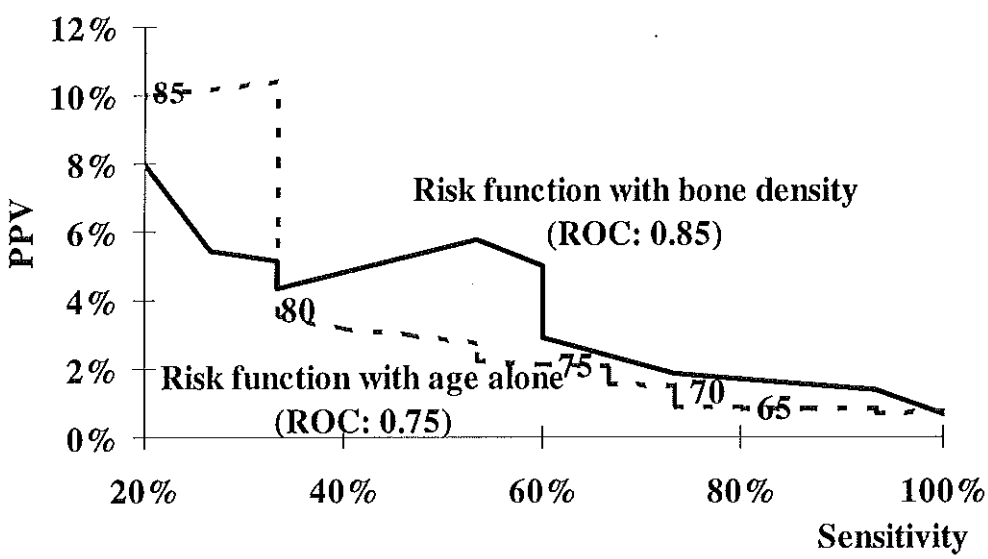


Figure 4: Positive Predictive Value and Sensitivity at various risk thresholds in men. The solid curve indicates the risk function including BMD and age, while the dotted line represents the use of only age as risk indicator. The corresponding ages are shown on the graph.

Subsequently, we compared the sensitivity and specificity of the risk function with the performance of using the conventional T- and Z-scores. Figures 5 and 6 show the threshold values used in women and men. They show that in women the use of the T-score or Z-score thresholds, yields the same absolute BMD value around the age of 70, After that age, a T-score of –2.5 corresponds to a higher BMD value than a Z-score of –1, and at later ages, a large proportion of women have BMD values lower than a T-score of –2.5.

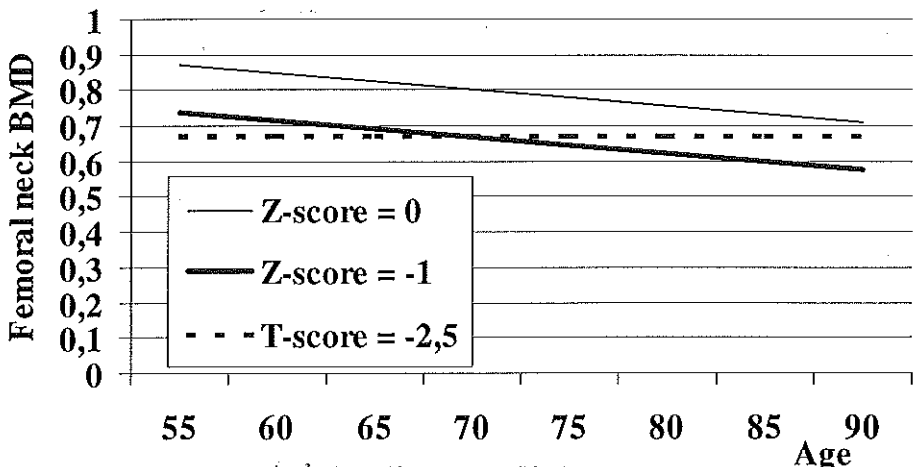


Figure 5: Absolute BMD (g/cm²) thresholds (Lunar DPX-L) in women.

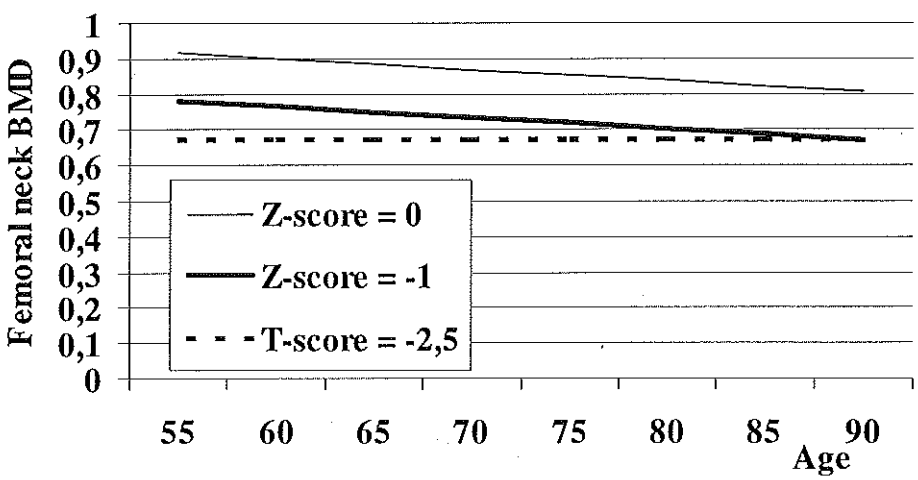


Figure 6: Absolute BMD (g/cm²) thresholds (Lunar DPX-L) in men.

We compared the sensitivity and specificity of the risk score, as shown in figures 1 and 2, to the performance of the conventional T and Z-scores in 10-year age classes. In figures 7 and 8 this is shown for women, and in figure 9 and 10 for men. These figures show that both in men and in women, sensitivity and specificity of the use of BMD alone, not taking into account age, is good at low ages, but much lower at higher ages. Specificity remains acceptable at higher ages, but sensitivity drops to 50 % or lower. In interpreting

these figures, it should also be remembered that the number of hip fractures at the ages below 70, is extremely low.

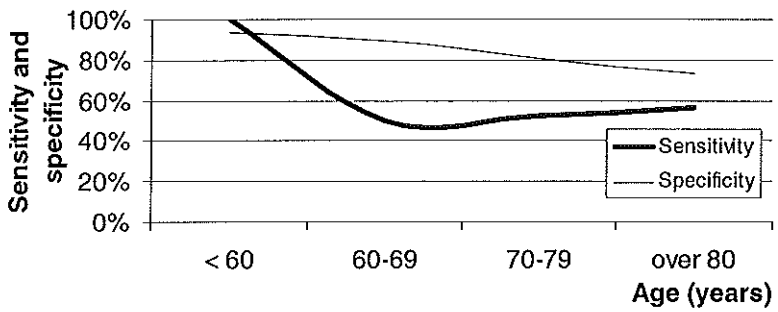


Figure 7: Sensitivity and specificity at various ages for T-score ≤ -2.5 in women.

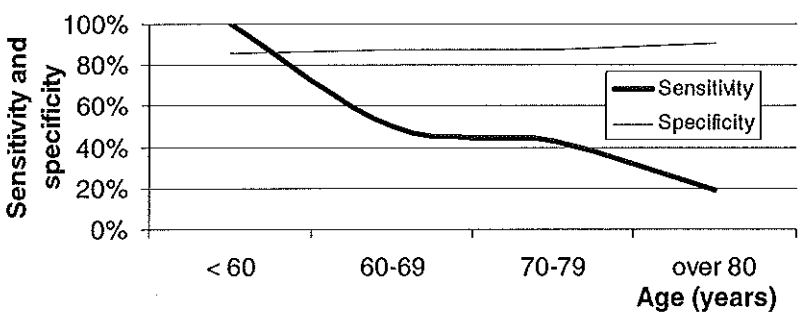


Figure 8: Sensitivity and specificity at various ages for Z-score ≤ -1 in women.

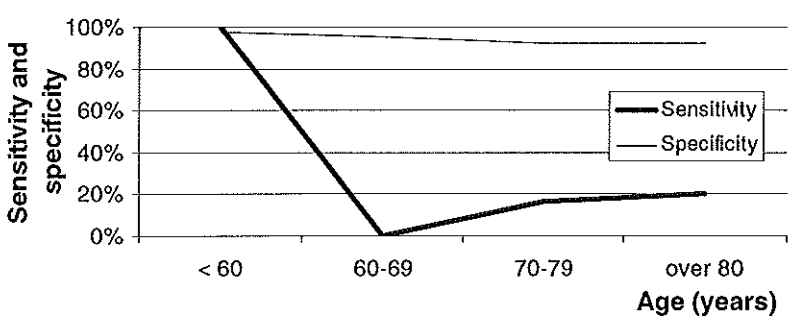


Figure 9: Sensitivity and specificity at various ages for T-score ≤ -2.5 in men.

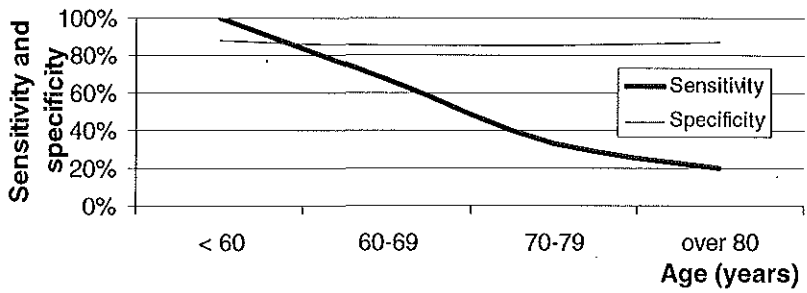


Figure 10: Sensitivity and specificity at various ages for Z-score ≤ -1 in men.

DISCUSSION

Main results

The choice of an optimal threshold is a trade-off between the cost and effects of the proposed intervention and the cost of missing a hip fracture. As a prognostic test, both the sensitivity and specificity of our risk function, incorporating both BMD and age, were around 80 % at a risk threshold level of 0.5 % one-year risk, regardless of age. The conventional T- and Z-scores, including only BMD, performed satisfactorily at ages up to 70, when the risk of hip fracture is trivial, both in men and women. At ages over 70, however, when hip fractures really become a problem, their performance is bad.

The risk function also performed better than age on its own, as demonstrated by the ROC area under the curve. A ROC area under the curve, however, describes the overall performance of a test at all thresholds, and does not provide information about the performance at specific thresholds. Our analysis showed that the better performance suggested by the ROC area under the curve, was due to a better performance from age 75 onward. In women this trend was stable, but in men the results became unreliable at ages over 80, due to the small number of elderly males, and therefore, the small number of events.

Implications

Conventionally, the results of BMD measurements are expressed as T-scores or Z-scores. They give an indication of the relative BMD level of that person, but in fracture prevention, we really need a tool for estimating the fracture risk of an individual. The risk functions that we evaluated in this study, appear to be a valid instrument for this, and the nomograms we presented elsewhere,[2] can assist in a better interpretation of BMD measurements taking age into account.

A threshold of 0.5 % annual risk appeared in this study to be a potentially interesting cutoff value, offering both high sensitivity and specificity, for the short term risk estimation. From the nomograms we can read that this risk thresholds corresponds to the risk of a 77 year old women with average BMD, but also to a 70 year old women with a T-score of –2.5. Women with high BMD only reach this risk level at later ages.

Our risk functions, and their performance were validated over a period of almost 4 years, and for estimating the individual short term hip fracture risk, including the measurement of BMD was only superior to age alone after the age of 75. At ages under 60, a low BMD had appeared to have both high sensitivity and specificity for predicting hip fractures, but past that age the performance of the BMD thresholds alone dropped dramatically This does not necessarily mean that BMD measurement at those ages is useless in clinical situations.

When we want to predict who will have a hip fracture when they will be older, we need to assume that individuals with low BMD for their age and gender, will remain on that same relative level in the future. Under this assumption, long term risk can be estimated by extrapolating their future BMD level. But, currently, little is known about the long term BMD evolution, since most studies of age related bone density decline are either cross-sectional or have limited follow-up time. The few long term studies available indicate indeed that the correlation of BMD measurements declines with time.[10] In the last part of this thesis, we will use modeling techniques to study the effects on the long-term risk, of different assumptions about correlation of BMD measurements over time.

Conclusion

Absolute BMD thresholds have limited value when age is not included in the assessment of hip fracture risk. The risk functions including age and BMD give more clinically relevant information than the commonly used T-scores and Z-scores. A threshold level of 0.5 % one-year risk had, in this study, both a high sensitivity and specificity, and is therefore, potentially, an interesting and clinically relevant cutoff point. However, confirmation and validation in other populations is desirable.

REFERENCES

1 Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Bmj 1996;312(7041):1254-9.

2 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998; 13:1587-93.

3 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Pols HAP. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997; 315:221-5.

4 Kanis JA, McCloskey EV. Evaluation of the risk of hip fracture. Bone 1996;18(3 Suppl):127S-132S.

5 Kanis JA 1994 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 4:368-381.

6 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA 1991 Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 7:403-422.

7 Erdtsieck RJ, Pols HA, Algra D, Kooy PP, Birkenhager JC. Bone mineral density in healthy Dutch women: spine and hip measurements using dual-energy X-ray absorptiometry. Neth J Med 1994;45:198-205.

8 Metz CE. LABROC and ROCFIT software. Available from Department of Radiology, University of Chicago, Chicago, IL, 1990.

9 Hajian-Tilaki KA, Hanley JA, Joseph L, Collet J. A comparison of parametric and nonparametric approaches to ROC analysis of quantitative diagnostic tests. Med Decis Making 1997; 17:94-102.

10 Hansen MA, Overgaard K, Christiansen C. Spontaneous postmenopausal bone loss in different skeletal areas followed up for 15 years. J Bone Miner Res 1995;10:205-10.

PART 3

MODELING PREVENTION

3.1 ESTIMATING LIFETIME RISK OF HIP FRACTURE IN WOMEN

INTRODUCTION

To target prevention of hip fractures at those with the highest risk, it is important to be able to predict hip fractures and to estimate the lifetime risk. The direct cause of a hip fracture is mostly a fall, but their occurrence is closely associated with osteoporosis.[1]

Although it has been shown that bone mineral density (BMD) can be used for estimating short term hip fracture risk,[1-3] less is known about the long-term risk. Ideally, we would like to have long-term data from follow-up studies to assess the long-term evolution of BMD and its predictive power for hip fracture incidence. Currently, we do not have those data, and we would have to wait unacceptably long before we would obtain them.[4] Modeling can, in those cases, be a solution, provided that there are reasonable assumption that can be made.

In this chapter we describe two models that were developed to assess the lifetime risk of hip fracture in the population at large at different ages, and at the conventional BMD thresholds as defined by T-scores and Z-scores.

THE STRUCTURE OF THE MODELS

Two separate models were used to estimate lifetime risk for hip fracture. The first model, that will be referred to as the *'individual model'* estimates the lifetime risk for a person with a given age, gender and BMD. This model is a lifetable-based spreadsheet, where a start age and a start BMD are defined. Every year, the probability to die and the probability of a hip fracture are calculated. Only the occurrence of first hip fractures is considered in the analysis.

The second model, that will be referred to as the *'population model'* basically performs the same analysis, whereby every year (or at other time intervals) the risk for a hip fracture or death is calculated, but rather than describing age and BMD as fixed starting points, they are entered as distributions. At the beginning of each simulation a virtual person is created with an age and BMD drawn from those distributions. Then this person is followed through the model till he or she dies. At each time interval the model calculates the age, BMD and subsequently the risk of events. From these risk distributions, either a hip fracture, death or no event, are randomly drawn. After the death of a virtual person, this is repeated for the next. The final results are the averages from the whole simulation run. Figure 1 graphically depicts the basic structure of both models.

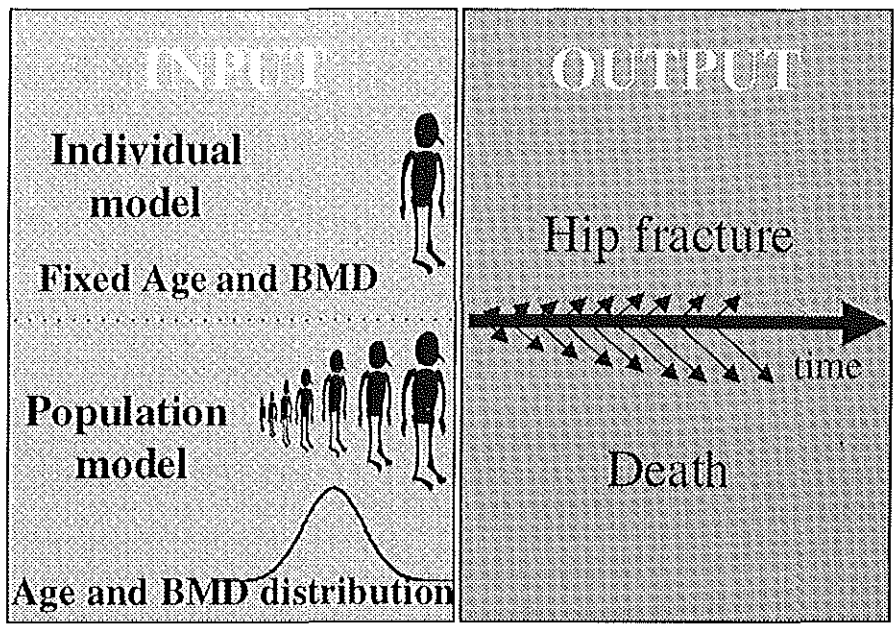


Figure 1: *Basic structure of the models. On the left side, the input is defined as either a fixed age and BMD (individual model) or as a distribution of age and BMD in the population model. On the right side, the number of events, and the moment when they occur in time are counted.*

During the simulation the virtual person ages, and future BMD is calculated. , While the calculation of future age is straightforward, estimating future BMD is less obvious. One possibility is to use the cross-sectionally measured BMD decline observed in a population and to apply this to the start BMD, assuming that the bone density at time 0 is perfectly correlated with bone density at time t, assuming the same rates of bone loss in different individuals. The few longitudinal studies that are available, however, show that this correlation is less than 1, partly due to different rates of bone loss and partly due to random error.[5-7]

Assuming that the correlation coefficient ρ that is less than 1, the average BMD at time t, given the baseline BMD (x) at time t, is given by: $BMD_{average} = \mu_t + \rho \frac{\sigma_t}{\sigma_0}(x - \mu_0)$, where μ_0 is the average BMD for the population at baseline age, σ_0 the SD at baseline age, and σ_t the SD at age+t. Assuming homoscedasticity, as found in the Rotterdam study, this becomes simply: $BMD_{average} = \mu_t + \rho\ (x - \mu_0)$. The standard deviation of BMD at time t is given by $SD = \sigma_t \sqrt{1 - \rho^2}$.

While testing the appropriateness of the bivariate normal model to describe the uncertainty of future BMD, we observed important regression-to-the mean phenomena when using low correlation coefficients, and extremely low baseline BMD values. Under those circumstances (T-score < -3.5 at age 55 and ρ < 0.7) we even observed small increases of average BMD with age. Since this only happened under extreme assumptions, we will limit the use of this model to more common BMD thresholds.

In the population model, a baseline BMD is randomly assigned for every individual from the distribution of BMD at that age. Then, based on the applied correlation coefficient and the assigned baseline BMD, a BMD value at time t is drawn from the calculated distribution. We assumed a linear evolution of BMD from the baseline value to this new value at time t. After time t, this linear decline is further extrapolated into the future.

In the individual model this distribution of future BMD was implemented in a similar way, using @Risk software as a simulation add-in tool for the spreadsheet.[8]

PARAMETERS FOR THE MODEL

Simulation characteristics

In the individual model we calculated the lifetime risk at different ages and for several clinically relevant BMD thresholds. We did this first assuming perfect correlation and then for correlation coefficients lower than 1.

To determine the lifetime risk at different ages for a population, we started with cohorts of equal ages in all the simulations with the population model. Those virtual persons were then assigned a BMD drawn from the bone density distribution at that age. To achieve high precision of the lifetime risk estimate, the model was run on cohorts of 1.000.000 women, leading to extremely small confidence intervals.

Baseline BMD and analysis thresholds

The input femoral neck BMD distribution at all ages was based on the distributions given in chapter 2.1.[9] We also used these distributions to calculate Z-scores at every age for the simulations in the individual model. As thresholds in the individual model, we used respectively a T-score = -2.5, and Z-scores equaling –1 and 0.

Average values for young adult women were obtained from a Dutch study, also using a Lunar DPX-L densitometer.[10] With those reference values, a T-score = - 2.5 corresponded to a BMD level of 0.675. This value was very similar to the threshold value in the machine specific USA Reference population.[11] In that population, a T-score of -2.5 corresponded to a BMD level of 0.681.

Hip fracture risk

The risk functions based on age, gender, and femoral neck BMD are described in chapter 2.1.[9] These theoretical one-year risk functions were validated over a period of almost 4 year in a large cohort from the Rotterdam Study as described in chapter 2.2.[12] We extrapolated those risk functions into the future, and we assumed them to remain valid through life.

Mortality

Mortality was based on Dutch cross-sectional mortality data for 1993[13]. Mortality was modeled as a continuous function with the SPSS curved fitting function.[14] Best fitting was an exponential function, and the one year mortality risk in women by age (/1000) was given by: $d_{age} = 0.008 * e^{(0.11 \cdot age)}$

Estimating future BMD

In a first analysis, we assumed perfect correlation of baseline BMD with BMD later in life. To determine future BMD, we used a linear decline based on the cross-sectionally measured BMD decline with age described in chapter 2.1.[9] Subsequently we tested the effect of non-perfect correlation of BMD measurements using correlation coefficients lower than 1. We changed the correlation of baseline BMD with BMD 20 years later between 0.6 and 1 corresponding to the orders of magnitude of previous estimates of this correlation.[5-7] The rate of decline of BMD was assumed to be linear over those 20 years and the same rate of decline was further extrapolated into the future.

RESULTS

The individual model

The calculated lifetime risk of hip fracture for women at different ages and with various BMD thresholds, assuming perfect correlation of BMD measurements is shown in figure 2. It was remarkably similar at all ages when Z-scores were used: at every age the lifetime risk was about 11% in women with average BMD, and about 25% in women with BMD at – 1SD for that age.

However, when T-scores were used as thresholds, the lifetime risk was higher at younger ages for the same T-score, reflecting the fact that a T-score is a fixed cutoff level of BMD. The BMD thresholds correspond to the threshold values used in chapter 2.3 and they are discussed in more detail there. As shown in figure 5 of that chapter, a T-score = -2.5 and a Z-score = -1 become equal around the age of 70 in women. Therefore, risk estimates based on both scores will cross at that age. Lifetime risk before this age was higher when the T-score threshold was used, afterwards the opposite happened.

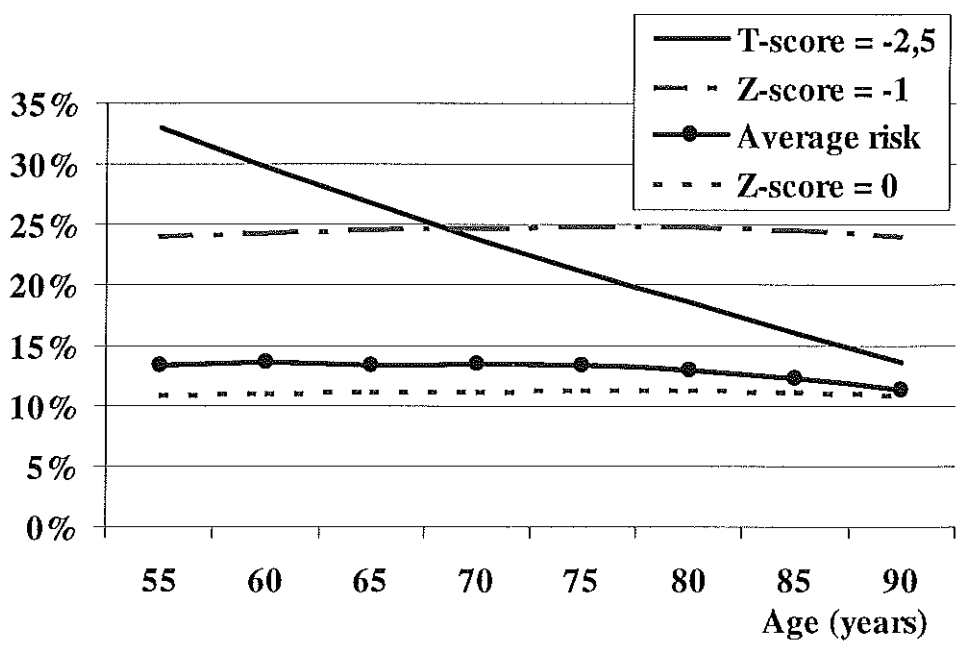


Figure 2: *Life time risk for hip fracture for women at different ages assuming perfect correlation. The estimates for BMD thresholds were obtained with the individual model, the average risk was estimated with the population model.*

The previous calculation assumed perfect correlation between BMD measured at one moment in life, and bone density measured later. Figure 3 shows the effect on the lifetime risk at age 55 of less than perfect correlation, assuming correlation coefficients ρ ranging from 1 to 0.6. When a correlation coefficient lower than one was assumed, we found that the lifetime risk calculated previously, was overestimated in women with low baseline BMD.

When the T-score was -2.5, the estimated lifetime risk at age 55, that was 33 % assuming perfect correlation went down to 24 % when correlation was 0.6. With a Z-score = –1 at age 55, the estimated lifetime risk declined from 24 % to 20 %.

In women with average and high baseline BMD, however, the previously estimated lifetime risk assuming perfect correlation, appeared underestimated. For women with average BMD, estimated lifetime risk went up from 10.9 % to 14.3 %.

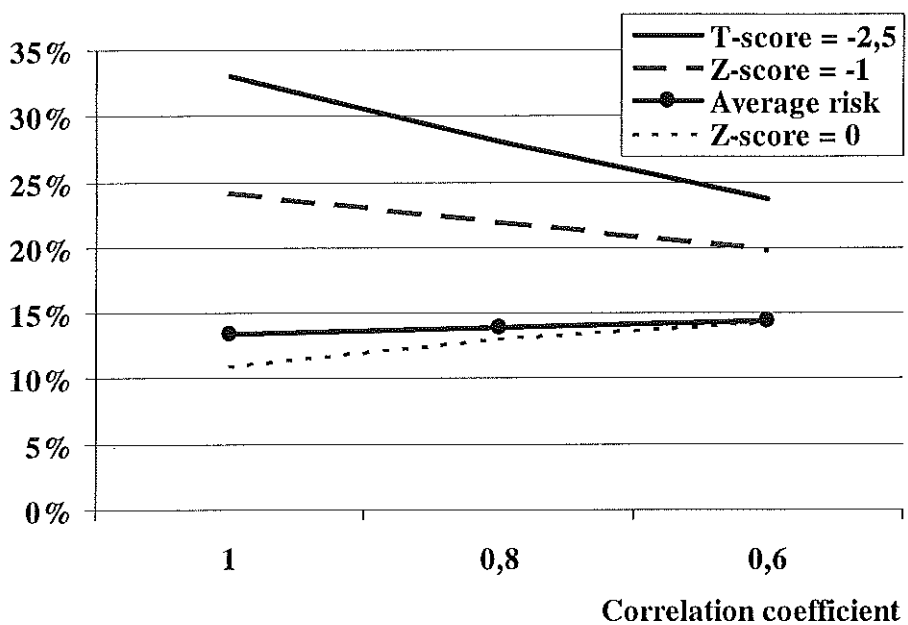


Figure 3: Lifetime risk at age 55 for different baseline levels of BMD and different levels of correlation. The estimates for BMD thresholds were obtained with the individual model, the average risk was estimated with the population model.

Figure 4 shows the same analysis for lifetime risk estimated at age 70. We observed similar effects, but with a smaller magnitude, since there is less uncertainty about future BMD when BMD is measured later in life.

As mentioned earlier, Z-score = -1 and T-score = -2.5 correspond to almost the same absolute BMD level at age 70. Therefore, lifetime risk estimates are very close at this age. The estimate for Z-score, assuming perfect correlation is 24.8 % while the estimate for T-score is 23.8 %. When correlation coefficient 0.6 is assumed these estimates go down to 21.6 % and 21.5 % respectively.

In women with average and high baseline BMD at age 70, the lifetime risk was again underestimated, but less pronounced than at age 55. For women with average BMD, estimated lifetime risk went up from 11.2 % to 12.4 %.

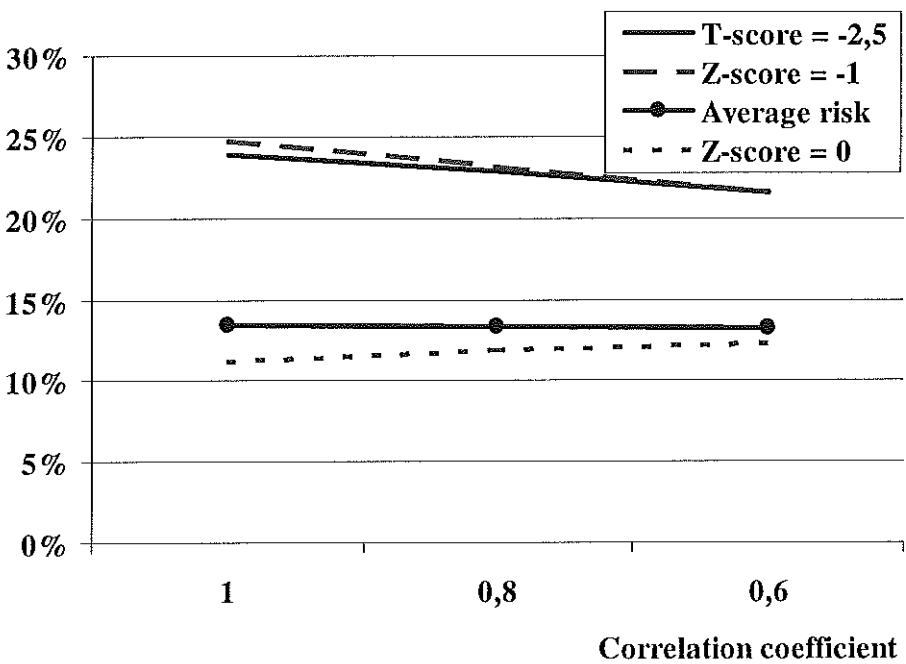


Figure 4: *Lifetime risk at age 70 for different baseline levels of BMD and different levels of correlation. The estimates for BMD thresholds were obtained with the individual model, the average risk was estimated with the population model.*

The population model

The population model estimates the lifetime hip fracture risk for a population with a BMD distribution corresponding to the distribution of the Dutch population at that age. The lifetime risk at different ages, and assuming perfect correlation of BMD measurements over time is given in figure 2 as the average risk curve. At age 55 the average lifetime hip fracture risk is estimated at 13.3 %, slightly higher then the risk for an individual with average BMD, due to the combination of an exponential increase of risk with lower BMD, together with a normal distribution of this BMD. This lifetime risk remained stable when estimated at later ages. This is due to the exponential increase of both the incidence of hip fractures and death, as competing risks. Only at ages over 80 the lifetime risk decreases slightly.

The average lifetime hip fracture risk at ages 55 and 70, but assuming less than perfect correlation is included in figures 3 and 4 as the average risk curve. At the age of 55, the average lifetime risk, previously estimated at 13.3 %, went slightly up to 14.4 % as shown in figure 3. This phenomenon was due to the exponential increase of risk with lower BMD. Therefore, the effect on lifetime risk in people with high baseline BMD loosing more bone than expected outweighed the lower than expected risk in people with a low BMD at baseline, but loosing less than expected.

When we estimate lifetime risk at age 70, we observe similar phenomena, but smaller in magnitude. The population lifetime risk assuming perfect correlation was estimated at 13..4 % and it remained at the same level with decreasing correlation.

DISCUSSION

Main findings

Assuming perfect correlation of BMD now and in the future, the average lifetime hip fracture risk at age 55 was estimated at 13.3 %, a risk comparable to previous estimates of the lifetime risk by other groups.[15-18] Moreover, this lifetime risk remained stable regardless of age. Only at ages over 80 this lifetime risk decreased slightly. Also when Z-scores are used to evaluate BMD, the lifetime risk remained similar at all ages. The reason for both phenomena is that, although hip fracture risk increases exponentially with age, this phenomenon is matched by a similar exponential increase of mortality, and the ratio of hip fracture risk and mortality risk is relatively stable through aging.

A T-score on the other hand, is a fixed threshold value, and therefore the lifetime risk is much higher when T-score is low at a younger age. The consequences of this and the discussion about whether a T-score or a Z score is to be preferred for screening purposes will further be addressed in the chapter 3.2. At ages around 70, both scores have the same absolute meaning in this population and with the reference values used.

When non-perfect correlation of BMD over time was assumed, we conclude that the lifetime risk in women labeled at high risk was overestimated. On the contrary, in women considered at low risk, the lifetime risk was underestimated. This is most prominent when screening occurred at younger ages. At age 70 this phenomenon is still present, but

much less pronounced. This, again, might have important consequences, since it means that the performance of screening at an early age will be overestimated when this declining correlation is not considered.

The lifetime risk at age 55 for the population at large was found to be 13.3 % assuming perfect correlation. But assuming a lower correlation, this lifetime risk increased slightly. Apparently, the underestimated risk in women at low risk outbalances the overestimated risk in women at high risk.

Strengths and limitations

One of the main limitations of any modeling study lies in its assumptions. The relation of hip fractures with age and bone density was derived theoretically, but validated in a 4-year follow-up study. But, this distribution of bone density related to age was only observed in a cross-sectional way. This might lead to observation biases. Ideally, we would prefer long term longitudinal bone density data. In the future, studies such as the Rotterdam Study are expected to provide those.

The use of a correlation coefficient to express the uncertainty about the long-term evolution of BMD has not been validated and might indeed present some problems at extreme BMD values, as indicated in the methods section. Whether this is caused by a bias in observational cross-sectional studies caused by surplus mortality in persons with lower BMD or whether the bivariate normal model is not completely suited for describing the relation of BMD density measurements remains to be investigated in long-term follow-up studies of bone density. However, with the BMD thresholds used here this problem appears to be minor compared to the uncertainty surrounding the correlation coefficient itself.

Conclusions

We estimated lifetime risk of hip fracture at several ages. At all ages this risk is around 13.3 %, and it only declines slightly after the age of 80. But, when taking into account the uncertainty about future rates of bone loss, this lifetime risk estimates appears slightly underestimated. When using specific BMD thresholds for risk estimation, the lifetime risk is overestimated at low BMD values, but underestimated at average or high BMD. Measuring BMD later in life partly circumvents these problems, since the uncertainty about future BMD diminishes.

REFERENCES

1 Cummings SR, Black DM, Nevitt MC, et al Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993;341:72-75.

2 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998;13:1587-93.

3 Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Bmj 1996;312:1254-9.

4 Jönsson B. Targeting High-Risk Populations. Osteoporos Int 1998;8: Suppl 1

5 Hansen MA, Overgaard K, Christiansen C. Spontaneous postmenopausal bone loss in different skeletal areas followed up for 15 years. J Bone Miner Res 1995;10:205-10.

6 Falch JA, Sandvik L. Perimenopausal appendicular bone loss: a 10-year prospective study. Bone 1990;11:425-8.

7 Nordin BE, Cleghorn DB, Chatterton BE, Morris HA, Need AG. A 5-year longitudinal study of forearm bone mass in 307 postmenopausal women. J Bone Miner Res 1993;8:1427-32.

8 Palisade Corporation. 31 Decker Road, Newfield, NY 14867 USA

9 De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997;315:221-5.

10 Erdtsieck RJ, Pols HA, Algra D, Kooy PP, Birkenhager JC. Bone mineral density in healthy Dutch women: spine and hip measurements using dual-energy X-ray absorptiometry. Neth J Med 1994;45:198-205.

11 Lunar Corp., Madison, WI, U.S.A.

12 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998;13:1587-93.

13 CBS, Statistisch Jaarboek 1994.

14 SPSS for windows, Release 6.1.

15 Lauritzen JB, Schwarz P, Lund B, McNair P, Transbol I. Changing incidence and residual lifetime risk of common osteoporosis-related fractures. Osteoporos Int 1993;3:127-32.

16 Black DM, Cummings SR, Melton LJ 3th Appendicular bone mineral and a woman's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639-46.

17 Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact Arch Intern Med 1991;151:2026-32.

18 Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med 1989;149:2445-8.

3.2 MODELING INTERVENTIONS

INTRODUCTION

In the previous chapters we have developed models to estimate short-term and long-term hip fracture risk by age and bone mineral density. The aim of interventions on osteoporosis is to reduce this fracture risk. In this chapter, we will use the previously described models to study the dynamics of interventions on osteoporosis and fracture prevention, with a special focus on their potential cost-effectiveness. Designing a cost-effective intervention means that we not only need to select the most suited treatment but also the right target population and the age at which intervention result is optimal.

Many treatments have been proposed for osteoporosis, ranging from general healthy living recommendations such as diet, exercise and smoking cessation, over the use of pharmaceutical drugs such as calcium or vitamin D supplementation, hormone replacement therapy (HRT), bisphosphonates, up to the use of hip protectors. But, in the most optimistic scenarios, the hip fracture risk reduction is not larger than 50 %, and most often it is smaller.[1] For most interventions it is also unclear what happens with the effect after treatment cessation, although it is assumed that there will be an offset of effect in the following years, and in some cases such as HRT it is likely that lifelong treatment is needed.[1]

In a perfect world, we would like to possess long-term data from clinical trials to assess the long-term effectiveness of different interventions. If we want to study the effect of early intervention on long-term hip fracture risk there are, however, long delays between the start of the intervention and the occurrence of the event, so unacceptably long follow-up would be needed to reach conclusions.[2] Modeling allows for the simulation of reality but should be used with caution. It is important that the assumptions used are reasonable and supported by the best available evidence.

Recently there has been some debate about whether osteoporosis should be targeted to the whole population, a public health approach, rather than to high risk groups.[3,4] Attractive as it may seem at first, it seems unlikely that this type of intervention, unless very effective and inexpensive, could ever be cost-effective.[5] Therefore, it can be expected that the focus of osteoporosis will, at least for a while, be on a high-risk approach where individuals at high risk will need to be identified.

An important predictor of hip fracture risk is bone mineral density (BMD), leading the WHO to define osteoporosis as a T-score < -2.5.[6] But, the short- and long-term hip fracture risk is very much dependent upon the age at which this T-score is reached as we showed in part 2 of this thesis, [7,8] and in chapter 3.1. Nevertheless, this threshold has evolved into an intervention threshold in many guidelines around the world, regardless of age.[9-12]

In this chapter we will compare the effect of a population approach without screening with a screening approach. We will also assess the effect of age at intervention on effectiveness and the potential cost-effectiveness of hip fracture prevention in women. As an example of a screening approach we will use the conventional bone density thresholds. Rather than focus on specific therapies, we choose a generic approach where we compare theoretical interventions leading to a preset risk reduction, without

specifying whether this was obtained through a pharmaceutical or any other intervention. Additionally we will address the uncertainties about the duration of effect after treatment cessation. In doing so, we will try to clarify the dynamics of intervention scenarios in hip fracture prevention.

METHODS

The mathematical model used for the intervention modeling was a purpose written model described in chapter 3.1 as the *'population model'*. We used this model to estimate the lifetime risk for hip fracture at different ages with changing assumptions about the correlation between BMD measured at one moment and BMD measured 20 years later.

In this chapter, we will use the same model to assess the effect of theoretical preventive interventions in various situations of screening and non-screening and at different ages. The model was fitted with exactly the same parameters as described in chapter 3.1. Each of the intervention scenarios was compared with the baseline scenario of no intervention.

Baseline scenarios

In the baseline scenarios we estimated the lifetime risk for hip fracture in a cohort of 55-year-old women that were followed up for a lifetime without any intervention. The results for these baseline scenarios were described in chapter 3.1.

Interventions

We assumed two theoretical interventions:

Intervention 1: lifelong treatment having lifelong full effect

Intervention 2: a 5-year treatment period with full effect, followed by a linear decline of the effect over a period of 5 year after treatment cessation.

For each of these two interventions we assumed 2 different effectiveness assumptions, so that each intervention lead to a hip fracture risk reduction of either 20% or 50% during the period of its full effect. Those levels of risk reductions were arbitrary, but chosen to correspond to clinically relevant risk reductions. With risk reduction lower than 20 %, intervention would probably not be envisaged, unless the treatment is both save and inexpensive. A risk reduction of 50% corresponds to the highest estimates to date of intervention effectiveness. [1]

The interventions were all assumed to have an immediate effect. Using this approach also implies that we assume that intervention effectiveness was equal at all ages.

Targeting the interventions

We modeled the effect of timing by starting the theoretical intervention at different ages. For each of these ages we either applied the intervention directly to everybody without screening, or only to a high-risk group.

As examples of risk thresholds we used either a T-score < -2.5 or a Z-score < -1. The Z-score was calculated from Dutch age specific BMD distribution data.[7] Average values for young adult women were obtained from a Dutch study.[13] As described previously in this thesis, a T-score of - 2.5 corresponded to a BMD level of 0.675 measured on a Lunar DPX-L densitometer.[14]

It was assumed that screening was followed immediately by treatment when appropriate. Since we assessed the effect of preventive strategies on the occurrence of a first hip fracture, we did not allow the model to start intervention when a hip fracture had occurred previously.

Correlation of BMD over time

For each of the interventions, we assessed the effect of the uncertainty of future BMD evolution, given a baseline value. First the interventions will be analyzed assuming perfect correlation. Next, we will assess the effect on treatment effectiveness and cost-effectiveness assuming a lower correlation, as described in chapter 3.1. For the purpose of this analysis we will present the results for a correlation coefficient $\rho = 0.6$.

Number of treatment years

In the lifelong treatment scenarios, treatment years were counted as the number of years until the occurrence of either death or a hip fracture. When 5 year of treatment was assumed, this was counted as 5 years unless either death or a hip fracture occurred before.

Analysis

To achieve high precision for the baseline scenarios (no intervention with either perfect correlation or with $\rho = 0.6$), these were run on cohorts of 5.000.000 women, leading to extremely small confidence intervals (CI) for the parameters of interest. The intervention scenarios were run on cohorts of 250.000 women. It was felt that when, after this number of simulations, results did not become precise and statistically different from no effect, they were probably irrelevant anyway. When the effect is not statistically different from no effect after 250.000 simulations, it will not be shown in the tables. When the lower limit of the 95 % CI was lower than half the point estimate or the upper limit over double the point estimate this will be indicated in the tables.

Presentation of the results

The main results will be presented as proportion of first hip fractures avoided and treatment years per hip fracture avoided. Additionally, we will describe the number needed to screen to avoid one hip fracture, as a measure of the screening burden.

First we will present the results for both interventions assuming perfect correlation of BMD over time. Subsequently, we will present the results for the same intervention, now assuming that the correlation of BMD over 20 years time is only 0.6.

In a sensitivity analysis the original 5-year offset of treatment period was modified to 0 and to 10 year linear decline of the protective effect after treatment cessation.

RESULTS

1. Baseline scenarios (no intervention)

In the baseline scenario we estimated the lifetime risk for a cohort of 55 year old women at 13.3%, assuming a BMD distribution equal to the Dutch population of that age, in the absence of intervention, and assuming the same linear BMD decline for every participant. When lower correlation coefficients were assumed for these rates of loss, this lifetime risk estimate increased slightly, to 14.4 % as was shown previously in chapter 3.1. Therefore, in each of the intervention scenarios, the intervention was compared to what would have happened without intervention with the same correlation coefficient assumption. Full results of the baseline scenarios can be found in chapter 3.1.

2. Intervention assuming perfect correlation

Intervention 1: lifelong treatment

In the most optimistic scenario, we assumed lifelong treatment and lifelong effectiveness, perfect correlation of BMD over time and a 50 % risk reduction. With the no-screening approach, when the total cohort would receive this intervention at baseline (age 55), 44 % of first hip fractures would be avoided in this population, compared to the situation without intervention. The intervention with a 20 % risk reduction resulted in a 16 % reduction in hip fractures. When intervention occurred at a later age, the proportion of hip fractures avoided declined, as can be expected with lifelong effectiveness. This is illustrated in figure 1.

When screening was used, the proportion of hip fractures avoided in the population declined markedly, but the effect of age became more complicated. For the Z-score threshold, the proportion hip fractures avoided declined with age, but with the T-score threshold it first increased until the age of 75, with a subsequent decline. When intervention occurred at older ages, the difference between the screening and the-no screening strategies became smaller. In this intervention simulation, and in all other simulation in this chapter, the curves for Z-scores and T-scores come together at the age of 70 since, as we showed in chapter 2.3, both scores represent the same absolute BMD level at that age.

Since intervention 1 involves lifelong treatment, treating at age 55 involved many treatment years. With 50 % risk reduction, treating everybody at age 55 meant that we needed almost 500 treatment-years to prevent one hip fracture. For the 20 % risk reduction this went up to almost 1300 treatment years. Treating at later ages, or introducing screening reduced the number of treatment years to avoid a hip fracture. These effects are shown in figure 2. The full results for both outcome measures are listed in table 1.

The number needed to screen to avoid one hip fracture (50 % risk reduction) decreased for the T-score from 100 at age 55 to 40 at age 85. For the Z-score it was around 50 at age 55 and remained at that level. After the age of 70 is slowly increased to about 70 at the age of 85.

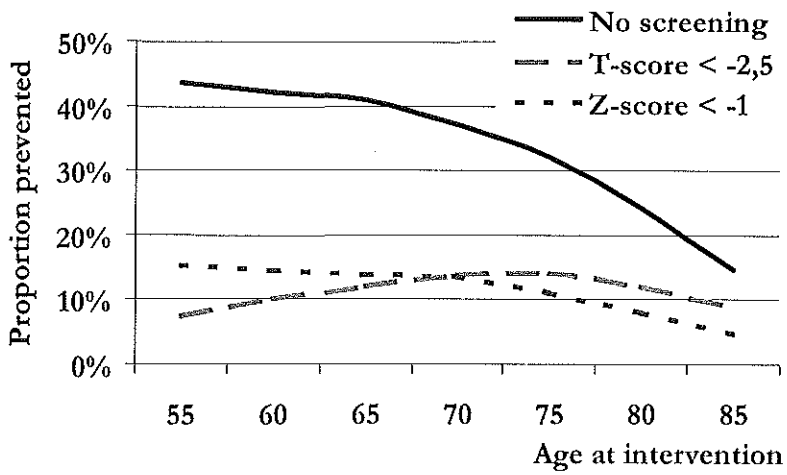


Figure 1: Proportion of hip fractures prevented in the population with intervention 1, assuming 50 % risk reduction (lifelong treatment and perfect correlation of bone density).

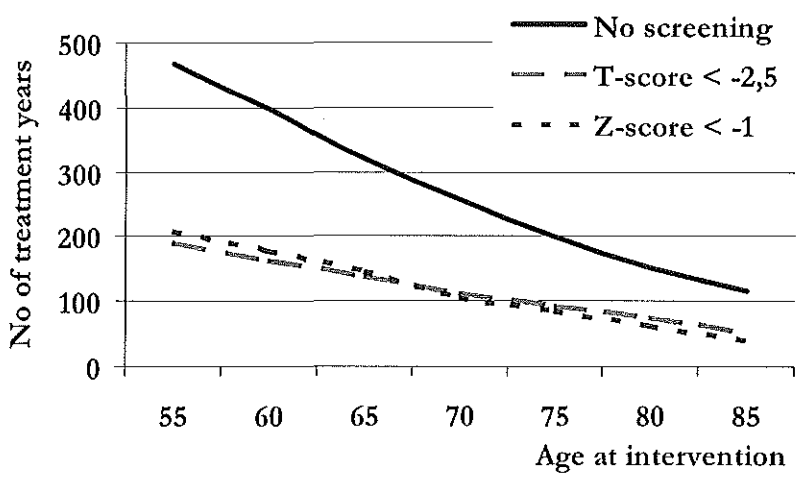


Figure 2: Number of treatment years needed to avoid one hip fracture with intervention 1, assuming 50 % risk reduction (lifelong treatment and perfect correlation of bone density).

Table 1. Results for intervention 1 by level of risk reduction and age (lifelong treatment and perfect correlation of bone density).

	Treatment years to avoid one hip fracture							Proportion of hip fractures avoided						
Age	55	60	65	70	75	80	85	55	60	65	70	75	80	85
no screening														
50%	467	397	318	257	199	152	115	44%	42%	41%	37%	32%	24%	15%
20%	1292	995	885	673	512	500	371	16%	17%	15%	14%	12%	7%	5%
T-score<-2.5														
50%	196	165	139	113	92	75	53	7%	10%	12%	14%	14%	12%	9%
20%	436	464	349	483	264	222	163	3%	4%	5%	3%	5%	4%	3%
Z-score<-1														
50%	225	174	146	107	85	63	41	14%	15%	14%	14%	11%	8%	5%
20%	558	619	405	327	229	209	144[+]	6%	4%	5%	4%	4%	2%	1%

[+] upper 95 % CI limit exceeds double of this estimate

Table 2. Results for intervention 1 by level of risk reduction and age (lifelong treatment and assuming a bone density correlation of 0.6).

	Treatment years to avoid one hip fracture							*Proportion of hip fractures avoided*						
Age	55	60	65	70	75	80	85	55	60	65	70	75	80	85
no screening														
50%	462	385	321	252	186	150	114	41%	40%	38%	35%	32%	23%	14%
20%	1282	1088	781	670	507	428	306	15%	14%	15%	13%	12%	8%	5%
T-score<-2.5														
50%	251	189	159	117	116	72	66	5%	7%	8%	11%	11%	13%	7%
20%	473	425	477	307	310	234	135	3%	3%	3%	4%	4%	4%	4%
Z-score<-1														
50%	295	216	152	100	81	63	45	10%	10%	10%	12%	11%	9%	6%
20%	600	440	382	695	360	156	98	5%	5%	4%	2%	3%	4%	3%

[+] upper 95 % CI limit exceeds double of this estimate
[-] lower 95 % CI limit is lower than half this estimate

Intervention 2: 5-year treatment period

When using intervention 2, assuming a 5-year treatment period during which full effect is obtained, followed by a linear decline of the effect over a period of 5 year after treatment cessation, the results changed dramatically.

Figure 3 shows the proportion of hip fractures prevented in the population with a 50 % effective intervention. Treating the whole cohort at age 55 would result in the prevention of only 2 % of the hip fractures in that population. Applying this same intervention at later ages increased the effectiveness of this intervention, and the optimal age for effectiveness was around 80 years of age, when 12 % of the hip fractures in the population could be prevented.

In this scenario, we assumed treatment during only 5 years. Therefore, the total number of treatment years was obviously much lower. Figure 4 shows the years needed to treat to

avoid one hip fracture. As in the intervention 1, the intervention is most cost-effective in terms of treatment years per hip fracture prevented at later ages, but this effect is much more pronounced than in the previous scenario. The full results for both outcome measures are listed in table 3.

The number needed to screen to avoid one hip fracture (50 % risk reduction) decreased only below 250 at the age of 70 for both scores. From there on it quickly decreased with age, arriving at 70 for the T-score and at 100 for the Z-score at age 85.

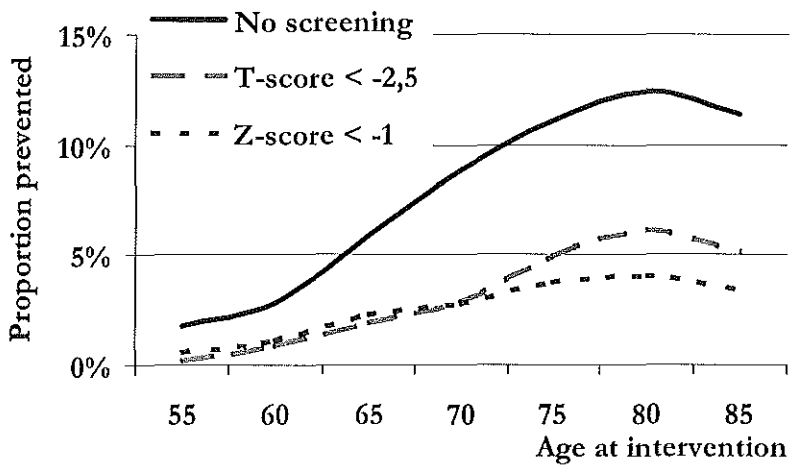


Figure 3: Proportion of hip fractures prevented in the population with intervention 2, assuming 50 % risk reduction (5-year treatment and perfect correlation of bone density).

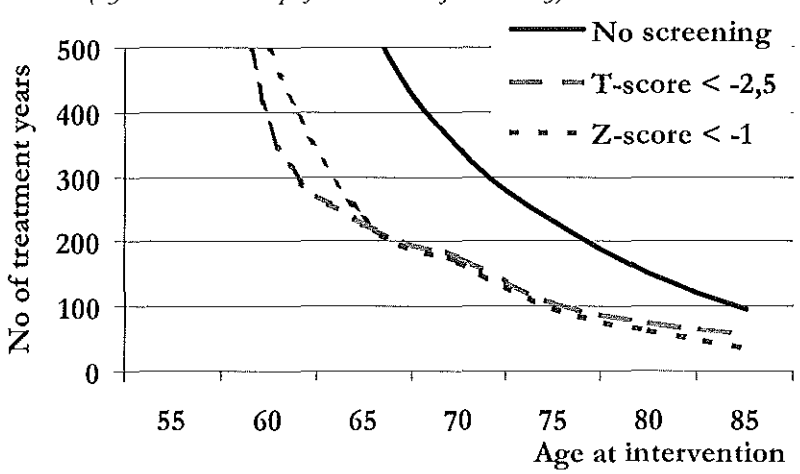


Figure 4: Number of treatment years needed to avoid one hip fracture with intervention 2, assuming 50 % risk reduction (5-year treatment and perfect correlation of bone density).

Table 3. Results for intervention 2 by level of risk reduction and age (5-year treatment and perfect correlation of bone density).

	Treatment years to avoid one hip fracture							*Proportion of hip fractures avoided*						
Age	55	60	65	70	75	80	85	55	60	65	70	75	80	85
no screening														
50%	2050⁺	1266	575	344	231	151	96	2%⁻	3%	6%	9%	11%	12%	11%
20%			2256	1055	767	450	235			1%⁻	3%	3%	4%	5%
T-score<-2.5														
50%		380⁺	229	177	106	75	59		1%⁻	2%	3%	5%	6%	5%
20%				500±	278	196	129					2%⁻	2%⁻	2%
Z-score<-1														
50%		497⁺	233	167	99	63	38		1%⁻	2%	3%	4%	4%	3%
20%				299⁺	189	204	98				2%⁻	2%⁻	1%⁻	1%⁻

⁺ upper 95 % CI limit exceeds double of this estimate
⁻ lower 95 % CI limit is lower than half this estimate

Table 4. Results for intervention 2 by level of risk reduction and age (5 year treatment and assuming a bone density correlation of 0.6).

	Treatment years to avoid one hip fracture							*Proportion of hip fractures avoided*						
Age	55	60	65	70	75	80	85	55	60	65	70	75	80	85
no screening														
50%	2045⁺	1373	884	381	237	134	98	2%⁻	2%	4%	7%	10%	13%	10%
20%			1877	752	505	418	269			2%⁻	4%⁻	5%⁻	4%	4%
T-score<-2.5														
50%		504	198⁺	152	181	59	54		1%⁻	2%⁻	3%	3%	8%	6%
20%				250⁺	294⁺	102	121				2%⁻	2%⁻	5%⁻	3%⁻
Z-score<-1														
50%		422⁺	298	181	97⁺	67	37		1%⁻	1%	2%	4%⁻	4%	4%
20%				344⁺	197⁺	128	62				1%	2%⁻	2%⁻	3%⁻

⁺ upper 95 % CI limit exceeds double of this estimate
⁻ lower 95 % CI limit is lower than half this estimate

3. Interventions assuming a lower correlation coefficient for future BMD evolution ($\rho = 0.6$)

With the population approach (no-screening), the differences with the baseline scenarios were negligible and within the margins of variation, as could be expected. The effectiveness of the screening approaches, however, decreased, notably for early post-menopausal interventions. At older ages, this effect became smaller. Therefore, this effect is only observed in intervention 1, were the efficiency of the screening approach was lower up to the age of 70. In intervention 2, the efficiency of early post-menopausal interventions was low anyhow, so differences were obscured. The results for both scenarios for a correlation coefficient of 0.6 are shown in tables 2 and 4.

For intervention 1, the number needed to screen to avoid one hip fracture (50 % risk reduction) decreased for the T-score from 130 at age 55 to 40 at ages 80 and 85. For the

Z-score it was around 70 at age 55 and decreased to 50 at the age 70. After the age of 75 is slowly increased to about 60 at the age of 85. For intervention 2, the numbers only decreased below 250 after the age of 70 and its further pattern was similar to that of intervention 2 assuming perfect correlation.

4. Sensitivity analysis assuming different offset of treatment periods in intervention 2

For intervention 2, we assumed that after the 5-year treatment period, the protective effect gradually declined over a period of the 5 following years (the offset of treatment period). To assess the importance of this assumption, we changed in a sensitivity analysis this baseline scenario to an offset of treatment period of 0 and 10 years.

When we increased the offset of treatment period to 10 years, the age of optimal effectiveness was slightly younger than in the baseline scenario (between 75 and 80) and more hip fractures were prevented. Similarly, assuming a 10-year offset of treatment period decreased the number of treatment years needed to avoid one hip fracture at every age. When immediate loss of effect was assumed the opposite happened. The effect on the proportion of hip fractures prevented in the population and on years to treat to prevent one hip fracture is illustrated in figures 5 and 6 for the scenario of the population approach (no-screening), 50 % risk reduction and perfect correlation of bone density over time.

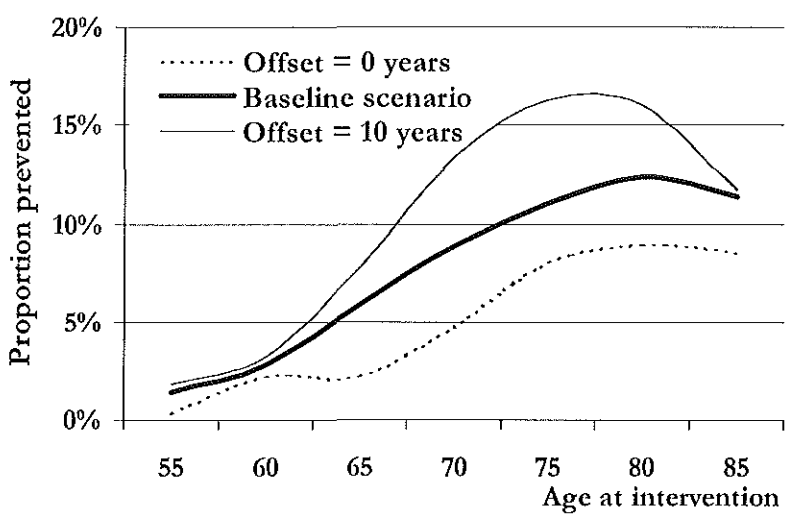


Figure 5: *Effect of changing the offset of treatment effect on the proportion of hip fractures prevented in the population with intervention 2, assuming 50 % risk reduction and without screening (5-year treatment and perfect correlation of bone density).*

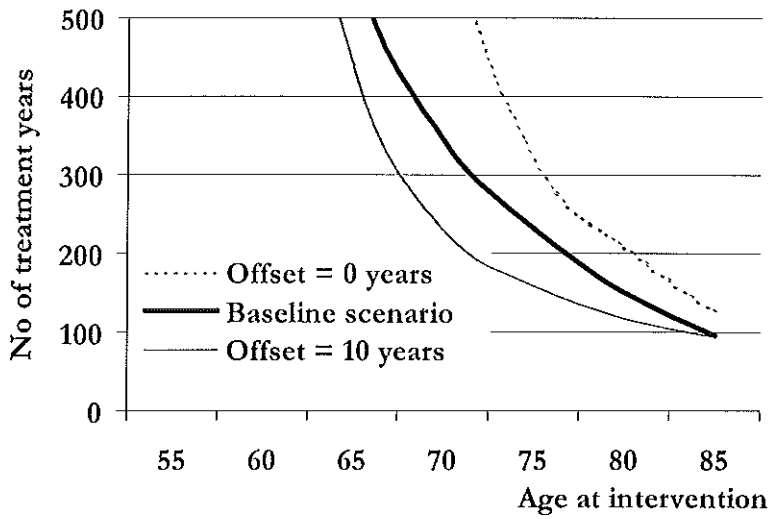


Figure 6: *Effect of changing the offset of treatment effect on the number of treatment years needed to avoid one hip fracture with intervention 2, assuming 50 % risk reduction and without screening (5-year treatment and perfect correlation of bone density).*

DISCUSSION

Main findings

In this modeling study, we concluded that in a population approach and in the most optimistic scenario of lifelong effectiveness (intervention 1) and 50 % risk reduction, 44 % of hip fractures could be avoided by applying this intervention to everybody at the age of 55. This means that in some people hip fractures would indeed be prevented early on by the intervention, but occurred later in life. However, with 500 treatment years to avoid one hip fracture this would probably only be an option for an intervention that is both very effective and inexpensive. Applying this same intervention at later ages improved the cost-effectiveness balance, as expressed by treatment years needed to prevent one hip fracture. At the age of 70, only 250 treatment years would be needed to avoid one hip fracture, while we would still be able to avoid 35 % of hip fractures.

In a screening scenario, the effectiveness (number of hip fractures avoided) was better for the Z-score threshold approach before the age of 70 and better for the T-score threshold above that age, reflecting the fact that the more people are selected the more hip fractures can be avoided. The number of treatment years to avoid one hip fracture was much lower in the screening than in the population approach, but cost-effectiveness differences between both screening approaches were slight. However, the cost-effectiveness was again much better when treating at later ages.

With intervention 2, assuming a more realistic scenario of treatment during 5 years, followed by a gradual decline of effect during the next 5 years, effectiveness of intervention increased with age reaching an optimum around the age of 80, both in the population and in the screening approach. Again, cost-effectiveness was much better in the screening than in the population approach and improved with age.

In both interventions the cost-effectiveness difference between the screening and the population approach became relatively small at ages over 80. When screening would be an important cost, or unfeasible, the population approach might become the best alternative for women over 80, depending upon the burden of the proposed intervention.

From the sensitivity analysis, changing the offset of treatment assumptions, it became clear that these are important parameters. When residual effect would last for 10 years after treatment cessation, more hip fractures would be prevented by intervention at a younger age, and the cost-effectiveness balance would improve. The opposite occurred when effect stopped immediately after treatment cessation.

When we introduced the assumption that BMD evolution over time was not perfectly predictable, the effectiveness and cost-effectiveness of the population approach were not affected, but it did negatively influence the effectiveness and cost-effectiveness of the screening scenarios at younger ages. Past the age of 70, however, the effect of this assumption became negligible. If we intend lifelong treatment starting at a peri-menopausal age, this assumption has important consequences. If, however, we propose a 5-year treatment similar to intervention 2 starting after the age of 70, the effect becomes unimportant.

The number needed to screen to avoid one hip fracture varied between 50 and 100 shortly after menopause in intervention 1, a lifelong treatment that could correspond to lifelong HRT. However, when short-term treatment is what we have in mind, the number needed to screen stayed well above 250 before the age of 70.

Strengths and limitations

As indicated before, the main limitation of any modeling study lies in its assumptions. It is important to underline that the interventions that were modeled here were theoretical. Rather than focussing on specific therapies, we choose a generic approach where we compared theoretical interventions leading to a preset risk reduction, without specifying whether this was obtained through a pharmaceutical or through any other treatment. We tested these interventions at various ages and in screening and non-screening conditions thereby implicitly assuming that intervention were equally effective at all ages. This is probably not true for all types of interventions. However, it is plausible that different interventions could be conceived at different ages, such as HRT early postmenopausal, specific bone resorption inhibitors later on, and hip protectors at old age.

Ultimately, this study was intended to show the dynamics of intervention in a cohort of women. Therefore, effectiveness and cost-effectiveness were expressed as proportion of hip fractures avoided and treatment years needed to avoid a hip fracture. In a real cost-effectiveness analysis we would need to discount both costs and effects. However, this

would only help to reinforce the conclusion that intervention should be postponed until older ages.

Conclusions

In modeling the dynamics of osteoporosis interventions, we observed that lifelong treatment of the entire population starting at an early post-menopausal age with a theoretical intervention with 50 % risk reduction for hip fractures, and assuming lifelong effectiveness, would prevent 44 % of first hip fractures in women. Apart from being unrealistic, however, this intervention would also be extremely expensive. Testing more realistic scenarios with a shorter treatment period and declining effect, it became evident that early postmenopausal intervention is both less effective and especially less cost-effective in terms of years needed to treat to prevent a hip fracture. From ages 70 onwards, however, the effectiveness and cost-effectiveness of such interventions markedly improved for persons at high risk After the age of 80, a population approach, treating everybody with an effective intervention and without screening, might become cost-effective.

REFERENCES

1 Eddy DM, Johnston CC, Cummings SR, Dawson-Hughers B, Lindsay R, Melto LJ. Et al. Osteoporosis: Review of the Evidence for Prevention, Diagnosis and Treatment and Cost-Effectiveness Analysis. Osteoporos Int 1998;8 Suppl 4.

2 Jönsson B. Targeting High-Risk Populations. Osteoporos Int 1998;8: Suppl 1

3 Barrett-Connor E, Gore R, Browner WS, Cummings SR. Prevention of Osteoporotic Hip Fracture: Global versus High-Risk Strategies. Osteoporos Int 1998;8 S2-7.

4 Cummings SR. Prevention of Hip Fractures in Older Women: A Population-Based Perspective. Osteoporos Int 1998;8 S8-12.

5 Jönsson B. Targeting High-Risk Populations. Osteoporos Int 1998;8 S13-6.

6 Kanis JA Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 1994;4:368-381.

7 De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997;315:221-5.

8 De Laet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP. Hip Fracture Prediction in Elderly Men and Women: Validation in the Rotterdam Study. J Bone Miner Res 1998;13:1587-93.

9 Anonymous. Clinical practice guidelines for the diagnosis and management of osteoporosis. Scientific Advisory Board, Osteoporosis Society of Canada. Can Med Assoc J 1996;155:1113-33.

10 Johnston C, Jr. Development of clinical practice guidelines for prevention and treatment of osteoporosis. Calcif Tissue Int 1996;59:S30-3.

11 Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1997;7(4):390-406.

12 Royal College of Physicians 1999. Clinical guidelines for strategies to prevent and treat osteoporosis. Royal College of Physicians, London.

13 Erdtsieck RJ, Pols HA, Algra D, Kooy PP, Birkenhager JC. Bone mineral density in healthy Dutch women: spine and hip measurements using dual-energy X-ray absorptiometry. Neth J Med 1994;45:198-205.

14 Lunar Corp., Madison, WI, U.S.A.

PART 4

DISCUSSION AND SUMMARY

GENERAL DISCUSSION

Since the number of elderly is increasing and the elderly are becoming older, there is growing attention for the prevention of those diseases that typically affect elderly people. There is a need for the definition of not only effective, but also cost-effective strategies for the prevention of those diseases and notably for osteoporosis, as indicated by various organizations within the Dutch healthcare (CBO, NHG, Gezondheidsraad, Ministry of Health).[1,2] However, there is a variety of options that have not yet been properly assessed regarding their associated costs and benefits.

We showed that osteoporosis and fractures are an important burden to society. Of the fractures related to osteoporosis, the hip fractures are the most important public health problem. They invalidate patients physically and psychologically and they induce high costs. We estimated the yearly cost of osteoporotic fractures in the Netherlands at € 200 million, and this cost was for 85 % related to hip fractures. This thesis therefore focuses on the prediction and prevention of hip fractures. A study conducted in the United States attributed a larger proportion of the total cost to fractures other than the hip, [3] but this study considered a large proportion of all fractures as osteoporosis related, while we only included vertebral, wrist an hip fractures. However, even in this US study, the cost of fractures was mainly determined by hip fractures.

Since hip fractures are related to important direct medical cost and excess mortality, the prevention of hip fractures would probably avoid those. The yearly number of hip fractures in this country is rising and based solely on the demographic evolution (CBS), we predicted that, without intervention, the number of hip fractures will double by the year 2040. One might even expect a sharper increase when we take into account the fact that the incidence of hip fractures, corrected for age, increased significantly in the Netherlands during the last 20 years.

Hip fractures in the Netherlands almost always lead to a hospitalization, and the average length of stay was 26 days in 1993. This appears to be too long, and we concluded that the most direct way for cost reduction was to accelerate the discharge from hospital by either providing adequate facilities at home or by making the transfer to a nursing home easier.

Compiling numbers and costs from national registration gives a good overview of the total medical consumption after a fracture has occurred. It is, however, also important to know the real incremental cost in fracture patients. Therefore, we compared cost with and without a fracture. In the follow-up phase of the Rotterdam Study we did this for hip and vertebral fractures, using a nested case-cohort design. This pilot study confirmed the high cost of a hip fracture (around € 10.000 during the first year). For vertebral fractures, on the contrary, we found no evidence of important acute care cost but we observed a yearly incremental cost of € 1.000. Part of this incremental cost, however, was pre-existing and might therefore be caused by co-morbidity. The additional incremental cost was mainly caused by the use of pharmaceutical drugs. It is therefore unlikely that prevention of vertebral fractures will eliminate all the incremental cost. This was, however, only a small study and it needs to be repeated in a larger population.

At this moment there is no coherent strategy for fracture prevention, and in daily life osteoporosis and fracture prevention is mainly carried out through sporadic individual case identification in general practice and specialist care. But, at the same time, there is a growing awareness of osteoporosis in the general public, partly generated by information from the pharmaceutical industry, and there is no guarantee that this growing awareness and demand from the general public will automatically lead to optimal intervention.

For the prevention of osteoporotic fractures it is important to know who are at risk as well as which preventive strategy is most effective and cost-effective for different risk categories. In the modeling of fractures and fracture risk we concentrated on the predictive value of bone mineral density (BMD) and age. A limitation, however, was that there are currently almost no prospective data about the long term evolution of BMD within individuals, and the bone mineral density data in our prediction models were measured cross-sectionally. Therefore, we needed to make assumptions about this individual evolution, evaluating different correlation coefficients. The Rotterdam study will, over time, provide these follow-up data on BMD evolution and fractures, allowing more detailed estimates for the incidence of those fractures in the Netherlands, and its relation to BMD.

BMD is, however, not the only element involved in fractures. The observed and relatively modest decline in bone density with age can not fully explain the exponential increase of hip fracture incidence with age. This shows that also other factors are important contributors to the fracture risk, including bone quality but also non-bone specific determinants. A trauma, most often a fall from standing height, is the direct cause of the fracture. Propensity to fall increases with age due to a variety of reasons such as a decrease in mobility, the use of sedative drugs, visual impairment etc.. The impact of those non-bone-density-related factors have, in the current models, been taken into account by using age as a surrogate.

These other risk indicators could, of course, be contemplated for fracture prediction. Some of these have indeed been included in risk scores developed around the world, and also in our own study population.[4,5] They include risk indicators such as visual impairment, low body weight, smoking, use of walking aids, drug usage and also co-morbidity in general. But, as is clear from our validation studies, both in subgroups as in the individual, the performance of age, gender and BMD is already quite high, making it very difficult to improve the predictive value of those functions substantially. Risk can well be estimated for groups of individuals, but since a fracture also remains a chance event, it will most likely remain difficult to predict in which individual and when it will occur.

We do not expect that adding other fractures will change our overall conclusions, but we will add them into the model, since they too will be affected by prevention and they too are associated with increased costs and impairment of quality of life. No nationwide data are available, but we recently obtained estimates of the incidence of non-hip peripheral fractures and their relation to BMD from the fracture follow-up within the Rotterdam study.[6] The incidence of vertebral fractures is, however, more difficult to evaluate, since these fractures often do not come to clinical attention. But, since we have estimates of

the prevalence of vertebral fractures from the first cross-sectional phase of the Rotterdam Study, where the spinal radiographs were analyzed,[7] we were able to estimate incidence, taking into account the increased mortality risk when a vertebral fracture is present.[8] In the future we will obtain the cumulative incidence of vertebral fractures by comparing spinal radiographs made at baseline in the Rotterdam study with radiographs made at later return visits. Currently, the third round of return visits in the Rotterdam Study is being completed, which will lead to an average follow-up period of 6 years.

Over the years, the Rotterdam Study will continue to offer a unique opportunity to study the combined risk indicators and outcomes in the same population and in both men and women. Although these additional risk indicators were measured at baseline, additional follow-up time and more events are needed before more precise estimates can be obtained.

The current models perform well, and the simulated incidences were equal to the observed incidence in the Netherlands as, obviously, they should. The estimated lifetime risk was also similar to previously published estimates, although the methods to arrive at it were different.[9] Since the risk equations are based on Dutch data, they can be used to effectively help in reviewing the Dutch osteoporosis guidelines, where this model can be used to simulate any proposed interventions. Additionally, we feel confident that they can also be used for other populations, fitted with local data when needed and available.

Many pharmaceutical treatments have been proposed to prevent osteoporotic fractures with various evidence of effectiveness:[4] calcium or vitamin D supplementation, hormone replacement therapy (HRT), bisphosphonates, calcitonin, and recently also the "selective estrogen receptor modulators" (SERM's). Other strategies have focused on lifestyle interventions, the removal of risk factors in the home or on interventions to reduce the propensity to fall by training, or by the avoidance of sedative drugs. Yet another strategy is the use of external hip protectors in individuals at high risk, such as nursing home patients.

But, whatever the choice of the intervention, the important question that remains is when to intervene and in whom. Overall one-year hip fracture incidence only rises above 1 % after the age of 80 for women and 85 for men. When the moment of intervention is at or soon after the menopause, we can expect that even with an effective therapy, the expected benefit is so far off that the compliance with medication will be poor. This issue is further complicated by the problem that, even when data about short-term effectiveness may be readily available, long-term effectiveness data are lacking. Additionally, effectiveness data often concern intermediate endpoints such as bone mineral density rather than the "harder" endpoints such as fracture incidence. It is therefore preferable, if possible, to bring the preventive intervention nearer to the adverse outcome.

In our modeling studies, we observed that even a very effective intervention, with 50 % risk reduction and assuming lifelong effectiveness, would not prevent more than 44 % of first hip fractures in women when the whole population were treated at an early post-menopausal age. This was due to the fact that prevention, on average, leads to a postponement of the occurrence of a hip fracture, but not always to the avoidance of it. Assuming more realistic scenarios, with shorter treatment periods and with declining

effect after discontinuation of treatment, it became evident that early postmenopausal intervention is both less effective and therefore surely less cost-effective.

We also observed that a T-score lower than –2.5 in early post-menopausal women, represents an extremely high lifetime risk, and we should probably design strategies to detect those women at an early stage as was also advised by the 'Gezondheidsraad'.[2] At ages past 70 years, however, a large proportion of women will have a T-score below this threshold. This means that the current definition of osteoporosis is possibly not the best threshold for treatment. As an alternative we suggest our one-year risk estimate taking into consideration both age and BMD. At a risk threshold of 0.5 % this estimate had both a high sensitivity and specificity for predicting hip fractures in the 4 following years. At those higher ages screening followed by selective treatment of women at high risk might become the most cost-effective option. After the age of 80, however, our modeling experiments indicate that treating everybody with an effective intervention and without screening might be more cost-effective than a screening approach.

Current guidelines for the prevention of osteoporosis are relatively vague,[1] reflecting the uncertainties. Recently the 'Gezondheidsraad' advised to investigate different prevention scenarios.[2] Those scenarios should not only define how to treat, but especially who and when. To support this decision making, information about the balance between costs and effects - from a societal point of view - is needed. Given the time horizons that need to be considered, a model is the most productive instrument to bring together knowledge and uncertainties about the epidemiology, and about the expected costs and benefits of various preventive strategies. Currently, the CBO guideline for osteoporosis is being revised and, with our models, we will try and contribute to the assessment of the cost-effectiveness of the strategies proposed, both in the definition of the target population and strategies for case finding, as in the evaluation of the interventions chosen.

The overall picture of fracture prevention is indeed complex. Optimal and cost-effective strategies will probably be combinations of several types of interventions, each focused on a specific target population with specific risk indicators. The aim of our research was to provide the tools to design such strategy. The questions that we put forward at the start of this research were simple but important: who should be treated, and when and how should this be done? With the models we developed in this thesis, we provided the framework to answer those questions for every proposed intervention.

FUTURE RESEARCH

In this thesis we developed basic models to analyze costs and effects of prevention and treatment of osteoporosis. Since the prevention of osteoporosis, and its cost-effectiveness will also be influenced by the impact of interventions (e.g. HRT scenarios or the use of SERM's) on other diseases such as cardiovascular disease and cancers, these need to be included in a more global model. We need to clarify whether these diseases occur independently, allowing for simple models, or whether their occurrence is related either directly, or through the same risk factors. There might, for example, be a positive relation between fracture risk and heart disease reflecting estrogen exposure during a life. There might also be an inverse relation between the risk of fracture and that of breast cancer as has been suggested in the literature.[10] The data from the Rotterdam Study will, in the future, be used to study these relations.

Around the world there are a few prospective cohort studies that are comparable to the Rotterdam Study, and that also study osteoporosis and some of the other outcomes of interest. Only one of those other cohorts also includes men. At this moment, we are preparing to collaborate with some of those large cohort studies, to try and cross validate our findings. When successful, this cross validation would greatly enhance the generalizability of the results.

REFERENCES

1 Centraal Bureau Onderlinge Toetsing: CBO Concensus Osteoporose, Eerste herziening 1992

2 Gezondheidsraad: Commissie Osteoporose. Preventie van aan osteoporose gerelateerde fracturen. Rijswijk. Gezondheidsraad, 1998; publicatie nr 1998/05

3 Ray NF, Chan JK, Thamer M, Melton LJ. Medical Expenditures for the Treatment of Osteoporotic Fractures in the United States in 1995: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24-35.

4 Eddy DM, Johnston CC, Cummings SR, Dawson-Hughers B, Lindsay R, Melto LJ. Et al. Osteoporosis: Review of the Evidence for Prevention, Diagnosis and Treatment and Cost-Effectiveness Analysis. Osteoporos Int 1998;8 Suppl 4.

5 Burger H, De Laet CEDH, Weel AEAM, Hofman A, Pols HAP. Added value of bone mineral density in hip fracture risk scores (submitted)

6 Weel AEAM, Burger H, De Laet CEDH, Hofman A, Van Leeuwen JPTM, Pols HAP. Fractures in Elderly Men and Women: Incidence and Association with Bone Mineral Density (submitted)

7 Burger H, Van Daele PLA, Grashuis K et al. Vertebral deformities and functional impairment in men and women. Bone Miner Res 1997;12:152-7.

8 De Laet CEDH, Van Hout BA, Hofman A, Pols HAP. Incidence of Vertebral Fractures estimated from Dutch cross-sectionally measured prevalence: the influence of differential mortality. (submitted)

9 Black DM, Cummings SR, Melton LJ 3d. Appendicular bone mineral and a woman's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639-46.

10 Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group. Jama 1996;276:1404-8.

SUMMARY

In this thesis on the cost-effectiveness of osteoporosis and fracture prevention, the first part deals with the burden of illness and the cost of osteoporosis in the Netherlands, both in terms of morbidity and mortality as in financial terms. In the second part models for estimating the short-term hip fractures risk are developed. The last part is devoted to simulation models that estimate lifetime hip fracture risk and the effect of theoretical interventions.

PART 1: BURDEN OF ILLNESS OF OSTEOPOROSIS

Osteoporosis and related fractures are a major source of morbidity and health care costs both today as in the foreseeable future (chapters 1.1 and 1.2). The most serious fracture, the hip fracture, occurs frequently in the Netherlands, and its incidence is increasing with time. The incidence increases exponentially with age, and men reach the same hip fracture incidence at a 5 year older age than women.

The total number of hip fractures will inevitable rise if no serious preventive efforts are undertaken. Based solely on the demographic evolution, we predict that, without intervention, the number of hip fractures will be around 30.000 by the year 2040. One might even expect a sharper increase when we take into account the fact that the incidence of hip fractures, corrected for age, has increased significantly in the Netherlands during the last 20 years.

Mortality associated with hip fracture is strongly age dependent and related to concomitant illnesses and in-hospital complications. In a case cohort study (chapter 1.3), we were able to directly confirm the finding that after a hip fracture mortality rates are elevated in the first few months following the event, but return to normal after about 6 months. Although osteoporosis and hip fractures are often thought of as related solely to women, mortality rates after a hip fracture are much higher in men.(chapters 1.1 and 1.2) In-hospital mortality is twice that of women, but it remains unclear whether this is related to co-morbidity in men or to other factors.

The average hospital length of stay after a hip fracture was 26 days in 1993, and this was much longer than necessary from a medical point of view. From the data, we concluded that notably persons waiting for a nursing home admission stayed in the hospital for too long. Therefore, we concluded that, besides prevention, a more efficient hospital stay and discharge strategy is the most obvious way to control costs in the near future.

Nursing home care was often needed after the acute phase of the hip fracture. We detected that 21 % of men and 27 % of women were discharged directly towards nursing homes. This difference could partly be explained by the higher in-hospital mortality of men, but also to the fact that, at the age when hip fractures occur, more women live alone than men, and they are therefore more in need of outside help. Although nursing home stays were sometimes very long, the majority of patients left the nursing home within 3 months.

Precise incidence rates for non-hip fractures could not be obtained for the Netherlands at the start of this research, and we derived those from international data. Since the focus of this thesis was on cost and personal illness burden, this uncertainty for non-hip fractures was not perceived as a major problem. Later on, however, we were able to confirm those data with data from the Rotterdam Study. Wrist and vertebral fractures (when diagnosed) are most frequently treated in an outpatient setting. Based on the literature it was estimated that about one third of the vertebral fractures came to clinical attention.

We estimated the direct cost associated with fractures at older age. The majority of these fractures were probably osteoporosis related, but not all. We concluded that the cost of osteoporosis is mainly related to hip fractures. We used two approaches to calculate the yearly cost of osteoporosis and fractures in the population aged 50 and over in the Netherlands in 1993. The results of both the top-down and the bottom-up approach were comparable, and indicated a yearly cost between € 180 million and € 210 million. The main difference between both approaches was the cost of nursing home care that was not included in the top-down approach. Indirect costs were excluded since osteoporosis mainly affects the elderly and their production losses can be neglected.

The contribution of the oldest patients in the total cost was very striking. Although people from 85 years and older constituted only 1,3% of the Dutch population (1993), this group contributed to more than one third of the cost of osteoporotic fractures. The most important cause was, besides the higher incidence of hip fractures, the longer length of stay in the hospital and the higher incidence of admissions to a nursing home. With an aging population this situation may worry health policy planners.

When comparing the cost in the Netherlands with international figures, we found both higher and lower estimates. Several studies indicated a cost of US$ 7 - 10 billion for the United States resulting in a yearly cost per capita of € 20 - 30 for osteoporosis related fractures. A more recent study estimated the cost in the US for all osteoporosis related fractures at almost US$ 14 billion, but this study included a large proportion of all fractures as osteoporosis related. Our maximum cost estimate is equivalent to about € 15 per head of the population in the Netherlands. The US estimates however did include the indirect costs that we choose not to include. The estimates for France, however, were much lower with a global cost of FF 3.5 billion (€ 500 million) and a per capita cost of € 9.

In a case cohort study within the Rotterdam Study, we estimated the incremental health care consumption and its associated cost directly (chapter 1.3). For hip fractures, the cost estimate of € 10.000 for the first year largely confirmed our previous cost estimates in the Netherlands and those made for other countries. But, the results for vertebral fractures were unexpected. For vertebral fractures we could not detect important acute health care costs, but we did observe a yearly incremental cost of € 1000. Almost half of this incremental cost, however, was present even before the occurrence of the vertebral fracture, while an important part of the additional incremental cost after the fracture was caused by use of pharmaceutical drugs, mostly anti-ulcer drugs. This appears to point to co-morbidity, and it is therefore unlikely that prevention of vertebral fractures will eliminate all the incremental cost.

PART 2: MODELING THE RISK OF HIP FRACTURES

For the modeling of fractures (chapter 2.1), we concentrated on the predictive value of bone mineral density (BMD), while the impact of other, non-bone density related risk indicators were accounted for by using age as a surrogate indicator.

BMD is the indicator that is most commonly used to determine fracture risk, especially BMD measured at the femoral neck. BMD at the hip appears to be more strongly related to the risk of hip fracture than bone density measured at other sites. In the literature, the age-adjusted relative risk for hip fracture was estimated at 2.6 per SD decrease in bone density at the femoral neck in women. We were able to confirm this estimate in the Rotterdam study, not only for women but also for men.

From this relative risk, combined with Dutch incidence data and BMD distribution from the Rotterdam Study, we theoretically derived risk functions by age, gender and BMD to calculate one-year cumulative incidence.

Subsequently we conducted a validation study within the Rotterdam Study, to test the performance of these theoretically derived risk functions for hip fracture risk prediction (chapter 2.2). The majority of hip fractures (61 out of 110) occurred either in the high risk group or in the residential care group, even though these groups accounted for barely 14 % of the study population. In the community dwelling individuals, the high risk group consisted mainly of individuals aged 70 years and older, predominantly women. The low and moderate risk groups taken together identified a large proportion of the study group with low hip fracture incidence, even at ages over 80. However, a smaller group of individuals with high hip fracture incidence starting at age 70, could be identified a priori by using the risk function.

Therefore, we concluded that we can accurately estimate hip fractures risk in population subgroups. The risk functions performed well for the prediction over a period of 4 years in both men and women. Longer follow-up will be needed to validate those risk functions for use over longer time periods.

As an additional tool to estimate hip fracture risk in daily routine, we constructed, based on the risk functions, a nomogram to derive the hip fracture risk based on age, gender and BMD measured at the femoral neck. Although our risk functions were developed with data from a Lunar machine we have also converted them for use with other brands of bone densitometers.

For the prediction of hip fractures in the individual (chapter 2.3), absolute BMD thresholds appear to have limited value when age is not included in the assessment of hip fracture risk. Our risk functions including age and BMD gave more clinically relevant information than the commonly used T-scores and Z-scores. A threshold level of 0.5 % one-year risk had, in this study, both a high sensitivity and specificity, and is therefore, potentially, an interesting and clinically relevant cutoff point.

PART 3: MODELING PREVENTION

In two models, we evaluated lifetime risk of hip fracture extrapolating risk from the previous fracture risk models, and assuming BMD decline with perfect correlation over time. The average lifetime risk in women aged 55 was estimated at 13.3 %, comparable to previous estimates by others. Subsequently, we evaluated the performance of specific threshold values of BMD for predicting long term and lifetime risk. When Z-scores were used to evaluate the BMD, the lifetime risk remained similar at all ages. The reason for this is that, although hip fracture risk increases exponentially with age, this phenomenon is matched by a similar exponential increase in mortality rates. The ratio of hip fracture risk and mortality risk is almost stable through aging. A T-score on the other hand, is a fixed threshold value, and therefore the lifetime risk was much higher when T-scores are low at younger ages.

Subsequently, we assumed that the BMD decline is not the same in every individual and that the correlation between BMD now and BMD in the future is not perfect. When taken into account, average lifetime risk increased slightly, with decreasing correlation. We also concluded that the lifetime risk in women considered at high risk is seriously overestimated when this phenomenon is disregarded. On the contrary, in women considered at normal or at low risk, the lifetime risk is underestimated. This, again, might have important consequences, since it means that the benefits of screening at an early age will be overestimated when this phenomenon is not considered.

We simulated the effect of theoretical interventions leading to a risk reduction of 20 % and 50 % respectively. In this intervention simulation study, we found that in the most optimistic scenario of lifelong effectiveness and 50 % risk reduction, only 44 % of hip fractures would be avoided by applying this intervention to everybody at the age of 55 (the population approach). However, with 500 treatment years to avoid one hip fracture this would only be an option for a very inexpensive intervention.

Applying this same intervention at later ages improved the cost benefit balance considerably. With the same intervention at the age of 70, only 250 treatment years would be needed to avoid one hip fracture, while we would still be able to avoid 35 % of hip fractures.

As examples of a screening approach we used the Z-score and T-score thresholds. Most hip fractures were prevented using the Z-score before the age of 70 and by using the T-score threshold past that age, reflecting the fact that the more people are selected the more hip fractures can be avoided. Cost-effectiveness was much better for the screening approaches than for the population approach but the difference between both screening approaches was small. However, the cost-effectiveness was again much better when treating at later ages.

When the more realistic scenario of treating for 5 years, followed by a linear offset of effect during the next 5 years was assumed, effectiveness of intervention increased with age reaching an optimum around the age of 80, both in the population and in the screening approaches. The effect of treatment shortly after menopause was almost

In both interventions, the cost-effectiveness difference between the screening and the population approach became relatively small at ages over 80. When screening would be an important cost, or when using it would be impractical such as for nursing home residents, the population approach is likely to become the best alternative for women at those ages.

From the sensitivity analysis it became clear that the offset of treatment assumptions are important parameters. When residual effect would last for 10 years after treatment cessation, more hip fractures would be prevented by intervention at a younger age, and the cost-effectiveness balance would improve. The opposite occurred when effect stopped immediately after treatment cessation.

Assuming a less than perfect correlation did not influence the effectiveness or cost-effectiveness of the no-screening approaches, but it did negatively influence the effectiveness and cost-effectiveness of the screening scenarios at younger ages. After the age of 70, however, this effect became negligible. Again, this is an argument for screening and intervention at later ages.

Overall, the cost-effectiveness of fracture prevention appears better in screening approaches than in the population approach, although this difference becomes smaller late in life. The cost-effectiveness is also improved when intervention occurs at later ages. Therefore, optimal and cost-effective strategies will probably be a combination of several types of interventions, each focused on specific target populations with a specific risk profile. The aim of our research was to provide the tools to design such strategy. The questions that we put forward at the start of this research were simple: who should be treated, and when and how should this be done? With the models we developed in this thesis, we provided the framework to answer those questions for every proposed intervention.

SAMENVATTING

In dit proefschrift over de kosteneffectiviteit van de preventie van osteoporose en fracturen, is het eerste deel gewijd aan de ziektelast van osteoporose in Nederland. In het tweede deel worden modellen ontwikkeld om het korte termijn risico op heupfracturen te schatten. In het derde deel worden deze modellen gebruikt om het lange termijn risico op een heupfractuur en het effect van theoretische interventies op dit risico te simuleren.

DEEL 1: ZIEKTELAST VAN OSTEOPOROSE IN NEDERLAND

Osteoporose en aan osteoporose gerelateerde fracturen zijn een belangrijke oorzaak van ziekte en van kosten, zowel vandaag als in de nabije toekomst (hoofdstukken 1.1 en 1.2). De meest ernstige fractuur, de heupfractuur, komt veel voor in Nederland en de incidentie ervan neemt nog steeds toe. De incidentie stijgt exponentieel met de leeftijd, en de incidentie bij mannen bereikt vergelijkbare waarden op een 5 jaar hogere leeftijd dan bij vrouwen.

Indien geen preventieve acties worden ondernomen zal het totaal aantal heupfracturen nog verder toenemen. Wanneer we enkel rekening houden met de demografische evolutie zullen rond 2040 jaarlijks 30.000 heupfracturen optreden in Nederland. Wanneer we bovendien de trend extrapoleren dat in Nederland de leeftijdsspecifieke incidentie van heupfracturen de laatste 20 jaar sterk is toegenomen kan dit aantal nog scherper stijgen.

Aan heupfracturen gerelateerde sterfte is sterk leeftijdsafhankelijk, en bovendien afhankelijk van co-morbiditeit en complicaties die optreden na een chirurgische interventie in het ziekenhuis. In een case-cohortonderzoek (hoofdstuk 1.3) hebben we aangetoond dat de sterftekans verhoogd is gedurende 6 maanden na de heupfractuur, maar daarna terugkeert naar normale waarden. Alhoewel osteoporose en heupfracturen meestal beschouwd worden als een aandoening van vrouwen, is de ziekenhuismortaliteit na een heupfractuur bij mannen twee keer zo groot (hoofdstukken 1.1 en 1.2). De reden hiervoor is onbekend.

De gemiddelde duur van de opname in het ziekenhuis bedroeg 26 dagen in 1993. Dit lijkt een flink stuk langer dan noodzakelijk vanuit medisch oogpunt. Uit de gegevensanalyse bleek dat vooral die personen die uiteindelijk naar een verpleeghuis gingen veel te lang in het ziekenhuis verbleven. Een voor de hand liggende conclusie is dat, naast preventie, ook een tijdige voorbereiding van het ziekenhuisontslag kan bijdragen tot het terugdringen van de kosten in de nabije toekomst.

Na de acute fase van de heupfractuur was er dikwijls behoefte aan verpleeghuiszorg. Bij mannen ging 21 % en bij vrouwen 27 % na de ziekenhuisopname direct naar het verpleeghuis. Dit verschil werd deels verklaard door de hogere sterfte bij mannen, maar ook door het feit dat op deze leeftijd veel meer vrouwen alleen leven dan mannen en daarom ook meer behoefte hebben aan hulp van buitenaf. Alhoewel het verblijf in het verpleeghuis in sommige gevallen erg lang was, kon de meerderheid van de patiënten toch binnen 3 maanden terug naar huis.

Nauwkeurige incidentiegegevens van andere dan heupfracturen waren niet beschikbaar voor Nederland en voor ons onderzoek hebben we deze geëxtrapoleerd vanuit

Amerikaanse gegevens. Vermits de klemtoon van dit proefschrift lag op de kosten en het persoonlijk lijden ten gevolge van osteoporose, beschouwden we de mindere betrouwbaarheid van deze gegevens niet als een belangrijk probleem. Bovendien konden we, achteraf, deze schattingen valideren aan de hand van gegevens uit ERGO. Polsfracturen en wervelfracturen worden meestal poliklinisch behandeld, en uit de literatuur konden we afleiden dat slechts ongeveer een derde van de vertebrale fracturen ook echt onder de aandacht komt van een arts. De resultaten van ons case-cohortonderzoek bevestigden dit.

We hebben een schatting gemaakt van de kosten gerelateerd aan het optreden van fracturen op oudere leeftijd. De meerderheid van deze fracturen was waarschijnlijk toe te schrijven aan osteoporose. We kwamen tot de conclusie dat de kosten van osteoporose vooral bepaald worden door de heupfracturen. We kozen twee benaderingen om de jaarlijkse kosten van osteoporose en fracturen te berekenen in de bevolking ouder dan 50 jaar, en beide benaderingen gaven vergelijkbare cijfers. De schatting van de kosten voor de verzorging van fracturen, voor het jaar 1993, lag tussen € 180 miljoen en € 210 miljoen. Het belangrijkste verschil tussen beide benaderingen was dat de kosten van verpleeghuizen niet meegenomen waren in de laagste schatting. Indirecte kosten werden ook niet meegenomen, vermits osteoporose en daaraan gerelateerde fracturen voorkomen bij een oudere bevolking waar de productieverliezen verwaarloosbaar zijn.

Het aandeel van de oudste patiënten in de totale kosten was erg opvallend. Alhoewel personen van 85 jaar en ouder maar 1.3 % uitmaken van de Nederlandse bevolking (1993), droeg deze groep voor meer dan een derde bij aan de kosten van osteoporotische fracturen. De voornaamste reden hiervoor was, behalve een hogere heupfractuur incidentie, het langere verblijf in het ziekenhuis en de grotere kans op opname in een verpleeghuis. Met een snel verouderende bevolking is dit fenomeen verontrustend.

Wanneer we onze schattingen van de kosten vergeleken met internationale gegevens vonden we zowel hogere als lagere schattingen. Verschillende onderzoeken rapporteren voor de Verenigde Staten jaarlijkse kosten van US$ 7 - 10 miljard, wat per capita overeenkomt met € 20 - 30 voor osteoporose en gerelateerde fracturen. Een recent onderzoek schatte de kosten van osteoporose in de Verenigde Staten zelfs op US$ 14 miljard, maar dit onderzoek beschouwde een belangrijk deel van alle fracturen als gerelateerd aan osteoporose. Onze maximale schatting komt overeen met een per capita kost van ongeveer € 15, maar de Amerikaanse schattingen bevatten ook de indirecte kosten die wij buiten beschouwing hebben gelaten. Schattingen voor Frankrijk waren lager, met een globale kostprijs van € 500 miljoen, per capita € 9.

In een case-cohortonderzoek binnen het ERGO-onderzoek (hoofdstuk 1.3) hebben we ook rechtstreeks het verschil in medische consumptie en kosten onderzocht tussen patiënten met een fractuur en vergelijkbare personen zonder fractuur. Voor heupfracturen vonden we bijkomende kosten van € 10.000 voor het eerste jaar, hetgeen grotendeels onze vroegere schattingen bevestigde. De resultaten voor wervelfracturen waren echter onverwacht. Alhoewel we geen belangrijke acute medische kosten konden detecteren, vonden we toch een jaarlijks kostenverschil van ongeveer € 1000. Bijna de helft van dit kostenverschil was echter al aanwezig in de jaren voor het optreden van de wervelfractuur. Van de bijkomende kosten na de fractuur was een belangrijk deel toe te schrijven aan het gebruik van geneesmiddelen, vooral van maagzuursecretieremmers. Dit

lijkt te wijzen op co-morbiditeit, en het is daarom onwaarschijnlijk dat de preventie van wervelfracturen ook alle bijkomende kosten zal vermijden.

DEEL 2: MODELLEREN VAN HET RISICO OP EEN HEUPFRACTUUR

Voor het modelleren van het risico op een heupfractuur (hoofdstuk 2.1), hebben we ons geconcentreerd op het voorspellend vermogen van botmineraaldichtheid (BMD). De invloed van andere, niet aan de botdichtheid gerelateerde indicatoren werd in beschouwing genomen door leeftijd te gebruiken als een surrogaatindicator.

BMD is de meest gebruikte indicator voor het risico op fracturen, en vooral de BMD gemeten ter hoogte van de femurhals blijkt sterk gerelateerd te zijn aan het risico op een heupfractuur. In de internationale literatuur wordt het, voor de leeftijd gecorrigeerde, relatief risico op een heupfractuur bij vrouwen geschat op 2.6 per standaard deviatie vermindering van de BMD gemeten aan de femurhals. Binnen het ERGO-onderzoek konden we deze schatting bevestigen, niet alleen bij vrouwen maar ook bij mannen.

Met dit geschatte relatieve risico, Nederlandse incidentie gegevens en de BMD verdeling binnen het ERGO cohort hebben we theoretische risicofuncties afgeleid die het één-jaars cumulatieve risico op een heupfractuur geven naar leeftijd, geslacht en BMD.

Vervolgens hebben we, binnen het prospectieve deel van het ERGO-onderzoek, deze functies gevalideerd ten aanzien van hun voorspellend vermogen voor heupfracturen (hoofdstuk 2.2). De meerderheid van de heupfracturen (61 van de 110) kwamen inderdaad voor bij de hoogrisico groep, ofwel bij de geïnstitutionaliseerde deelnemers in verpleeg- en verzorgingshuizen, ook al maakten deze groepen samen maar 14 % uit van de onderzoekspopulatie. Bij de niet-geïnstitutionaliseerde deelnemers bestond de hoog risico groep vooral uit personen van 70 jaar en ouder, en ook vooral uit vrouwen. De groepen met een laag of gemiddeld risico identificeerden een belangrijk deel van de bevolking waarbij we een lage incidentie van heupfracturen vaststelden, zelfs op de leeftijd van 80 jaar en ouder. Een kleinere groep van personen met een hoog risico op een heupfractuur kon correct gedetecteerd worden met onze risicofuncties.

Hieruit concludeerden we dat dit risicomodel accuraat de incidentie van heupfracturen kan voorspellen in deelgroepen van de bevolking. De risicofunctie werkte adequaat over een periode van 4 jaar, zowel bij mannen als bij vrouwen. Een verdere follow-up is nodig om het voorspellend vermogen over langere periodes te valideren.

Als extra instrument om het risico op een heupfractuur in te schatten in de dagelijkse praktijk, hebben we op basis van onze risicofuncties een nomogram gemaakt waarop gemakkelijk is af te lezen wat het één-jaars risico is gebaseerd op leeftijd, geslacht en BMD. Deze risicofuncties werden ontwikkeld met gegevens van een Lunar DPX-L densitometer. We hebben ze ook geconverteerd voor gebruik met andere densitometers.

Een vast afkappunt voor de BMD lijkt weinig waarde te hebben om bij individuen een heupfractuur te voorspellen wanneer de leeftijd buiten beschouwing blijft (hoofdstuk 2.3). Onze risicofuncties die zowel leeftijd als BMD gebruiken geven meer klinisch relevante informatie dan de in de praktijk gebruikelijke T- en Z-scores. Een afkappunt

van 0.5 % één-jaars risico resulteerde in zowel een hoge sensitiviteit als een hoge specificititeit, en dit is daarom potentieel een interessante en klinisch relevant afkappunt.

DEEL 3: HET MODELLEREN VAN PREVENTIE

In twee aparte modellen hebben we het 'life-time' risico op heupfracturen gemodelleerd uitgaande van de genoemde risicofuncties met de aanname dat de BMD lineair afneemt met de leeftijd en met een perfecte correlatie in de tijd. Het gemiddelde 'life-time' risico voor een 55-jarige vrouw werd geschat op 13.3 %, vergelijkbaar met vroegere schattingen van andere onderzoekers. We hebben bovendien het belang geëvalueerd van specifieke BMD afkapwaarden voor het 'life-time' risico. Wanneer Z-scores werden gebruikt bleef het 'life-time' risico op een heupfractuur gelijk op alle leeftijden. De reden hiervoor is dat, alhoewel het risico op een heupfractuur exponentieel stijgt met de leeftijd, dit tegengegaan wordt door een vergelijkbare stijging van de sterfte met de leeftijd. Hierbij is de verhouding tussen het risico op een heupfractuur en het sterfterisico stabiel over alle leeftijden. Een T-score daarentegen is een vaste afkappunt en daarom was het 'life-time' risico veel hoger bij een lage T-score op jonge leeftijd.

Vervolgens namen we aan dat de daling van de BMD niet gelijk is bij alle personen en dat de correlatie tussen BMD nu en BMD in de toekomst niet perfect zal zijn. Wanneer we dit fenomeen in beschouwing namen steeg het 'life-time' risico licht bij dalende correlatie. We kwamen bovendien tot de conclusie dat het 'life-time' risico op een heupfractuur behoorlijk overschat wordt bij vrouwen met een hoog risico wanneer we dit fenomeen niet in beschouwing nemen. Bij vrouwen met een gemiddeld of een laag risico, daarentegen, wordt het risico onderschat. Het voorspellend effect van screening op een vroege leeftijd zal dus overschat worden indien we hiermee geen rekening houden.

We simuleerden theoretische interventies die aanleiding geven tot een risicoreductie van respectievelijk 20 % en 50 %. Bij het simuleren van deze interventies vonden we dat met het meest optimistische scenario dat 'life-time' interventie koppelt aan 'life-time' effectiviteit met 50 % risico reductie, slechts 44 % van de heupfracturen vermeden kan worden, ook al wordt deze interventie aan iedereen gegeven vanaf 55 jarige leeftijd (de bevolkingsstrategie). Om dit te doen zijn echter 500 behandelingsjaren nodig voor elke vermeden heupfractuur, wat alleen een optie kan zijn voor een behandeling die erg goedkoop is.

Wanneer we dezelfde interventie op latere leeftijd toepassen verbetert de kosteneffectiviteit aanzienlijk. Op de leeftijd van 70 jaar zijn er voor de preventie van een heupfractuur slechts 250 behandelingsjaren nodig, terwijl toch nog 35 % van de heupfracturen vermeden kan worden.

Als voorbeeld van een mogelijke screeningsstrategie gebruikten we afkappunten voor de Z-score en de T-score. Het grootste aantal heupfracturen werd vermeden door gebruik te maken van een Z-score vóór de leeftijd van 70 jaar en door gebruikt te maken van de T-score na die leeftijd. Dit reflecteert uiteraard het feit dat rond de leeftijd van 70 jaar beide afkappunten corresponderen met dezelfde BMD. De kosteneffectiviteit van screening was veel beter dan voor de algemene interventie zonder screening, maar toch was ook

hier de kosteneffectiviteit veel beter op hogere leeftijd. Het verschil in kosteneffectiviteit tussen beide screeningsbenaderingen was gering.

Met het meer realistische scenario waarbij uitgegaan wordt van een behandelingsperiode van 5 jaar die gevolgd wordt door een periode van 5 jaar waarbij het effect van de behandeling uitdooft, steeg de effectiviteit van de interventie met de leeftijd en bereikte een optimum rond de leeftijd van 80 jaar. Zowel bij de algemene bevolkingsbenadering als in het screeningsscenario werd dit optimum bereikt op dezelfde leeftijd. Het effect van deze interventie kort na de menopauze was zelfs verwaarloosbaar. Opnieuw nam de kosteneffectiviteit toe met de leeftijd en was deze beter in de screeningsscenarios dan in de algemene bevolkingsbenadering.

Bij alle bestudeerde interventies werd het verschil in kosteneffectiviteit tussen de screenings- (hoogrisico) en de algemene bevolkingsscenarios relatief klein na de leeftijd van 80 jaar. Het valt daarom te verwachten dat, indien de kosten voor screening hoog zijn, of wanneer screening moeilijk te organiseren is zoals voor verpleeghuisbewoners, een interventie zonder screening het beste alternatief is op deze leeftijd.

Uit de gevoeligheidsanalyse bleek dat de assumpties over de uitdoving van het beschermend effect belangrijk zijn. Wanneer we veronderstellen dat het effect 10 jaar aanwezig blijft in plaats van 5 jaar, worden meer heupfracturen vermeden en ligt het optimum van de interventie op een iets jongere leeftijd. Wanneer daarentegen het effect onmiddellijk stopt bij het staken van de interventie worden er minder fracturen vermeden en moet er zo laat mogelijk behandeld worden.

Wanneer we ervan uitgaan dat het verloop van de BMD bij het verouderen niet perfect voorspeld kan worden verandert er niets aan de efficiëntie van de algemene bevolkingsinterventies, maar de efficiëntie van de screening benaderingen vermindert sterk, vooral op lagere leeftijd. Dit is opnieuw een argument om screening en interventie uit te stellen tot latere leeftijden.

De preventie van fracturen is inderdaad ingewikkeld. Over het algemeen lijkt een scenario waarbij een hoogrisico groep behandeld wordt kosteneffectiever dan een bevolkingsbenadering, maar het verschil tussen beide benaderingen wordt klein op hogere leeftijd. De kosteneffectiviteit van interventies verbetert ook wanneer ze wordt toegepast op latere leeftijd. Een optimale, en hopelijk kosteneffectieve strategie, zal waarschijnlijk een combinatie zijn van verschillende interventies die elk gericht zijn op een specifieke doelgroep met een eigen risicoprofiel. Het belangrijkste doel van dit onderzoek was het ontwikkelen van hulpmiddelen om deze strategie te ontwerpen. Bij het begin van dit onderzoek hadden we een eenvoudige vraagstelling: wie moet behandeld worden, en wanneer en hoe moet dit gebeuren? Met de door ons ontwikkelde modellen hebben we het kader geschetst om deze vragen te beantwoorden voor elke interventie die overwogen wordt.

DANKWOORD

Het is zover, het boekje ligt er, en dat is zeker niet alleen mijn verdienste. Mijn oprechte dank gaat uit naar allen die hieraan, direct of indirect, hebben bijgedragen. Maar, hoewel ik hiermee het gevaar loop iemand te vergeten, wil ik toch graag enkele personen heel specifiek bedanken.

Huib ('grote Huib'), toen ik je voor het eerst ontmoette begreep ik dat je iemand bent die voorzichtig maar vastberaden naar het doel kan gaan. Je hebt me op je eigen typische manier overtuigd om dit onderzoek te doen. Ik ben blij dat ik al die jaren met jou heb kunnen samenwerken en dat we daarbij ook vrienden zijn geworden. Ik hoop dat deze samenwerking nog lang duurt en dat je me daarbij blijft aansporen de biologie ook af en toe een kans te geven te midden van het computergeweld.

Bert, toen eind 1994 de onderzoeker van dit onderzoeksproject vertrok vroeg jij mij of ik geïnteresseerd was om het over te nemen, ook al wist je dat ik niet op zoek was naar dit soort werk. Ik zei uiteindelijk toch 'ja' en ik heb er nooit spijt van gehad.

Ben, onze samenwerking begon moeilijk maar ik heb redelijk snel je gebruiksaanwijzing gevonden en na een paar maanden verliep het uitstekend. Ik heb ontzettend veel van jou geleerd en je hebt me behoed voor ontelbare flaters.

Frans, vanaf het begin was je bij dit project betrokken als promotor, maar uiteindelijk heb je Ben naar voren geschoven. Het werd inderdaad een beetje dringen, en ik stelde het erg op prijs. Sinds ik bij jou werk, heb ik wel ondervonden hoe goed je kan delegeren.

John, from the beginning of my work in the field of Osteoporosis your name was familiar to me from scientific literature. Later on I have come to know you more personally and I have learned a lot from our discussions. I am honored that you have accepted to be a member of this promotion committee.

Robert, als voorzitter van het UPT Verouderingsvraagstukken was jij officieel mijn werkgever. Je hebt je al die jaren erg betrokken getoond bij het goede verloop van het onderzoek, en het contact met onderzoekers van andere faculteiten was stimulerend. Ik ben blij dat je nu ook bij de promotie zelf betrokken bent.

Paul en Huib ('kleine Huib'), mijn twee kamergenoten bij het begin van dit project. Jullie hebben me ingewijd in de geheimen van de epidemiologie van osteoporose en ik weet dat ik uren van jullie tijd heb verbruikt met mijn ontelbare vragen. Jullie hebben natuurlijk ook wraak genomen door op het enige moment in die drie jaar dat we moesten verhuizen samen te vertrekken naar Australië voor een congres. Maar ik had na 8 jaar bij IBM veel ervaring met het verhuizen en ik heb de gelegenheid gebruikt om ontzettend veel troep weg te gooien. Gelukkig heeft niemand die ooit gemist.

Paul ging na 1 jaar al weg, maar Huib was zo vriendelijk te blijven tot ik ook wegging. Gedurende die tijd was het erg prettig om met jou de meest absurde ideeën te bedenken, ze meestal ook weer te verwerpen, maar heel af en toe kwam er toch iets bruikbaars uit. Bedankt ook dat je bij dat kleine groepje Rotterdamse BV's hoorde,[1] zodat we niet alleen in de witte toren deze gesprekken hebben gevoerd. Overigens ook nog onze gezamenlijke dank aan dr. Moortgat en aan dr. De Koninck voor hun creatieve hulp.

Angélique, jij kwam pas later bij het clubje en bovendien had je in het begin erg veel werk buiten de afdeling. Ik vrees dat het in die beginperiode soms lastig voor je was wanneer Huib en ik weer eens heftige gesprekken voerden, maar je hoorde er al snel helemaal bij. Ik vind het erg leuk om met jou samen te werken.

Marianne, jou heb ik pas laat beter leren kennen. Nu we aan dezelfde projecten werken en daarbij dezelfde kastelen bezoeken heb ik jouw manier van werken erg leren waarderen, en ook het feit dat je me, in de aanloop naar dit proefschrift, zoveel met rust hebt gelaten en zoveel in mijn plaats hebt gedaan. Ik hoop dat we nog lang en goed kunnen samenwerken op het terrein van de 'suggestions for further research'.

Anu, Alejandro, Alexei, Rueben, Jama, Sara, and the other NIHES fellows, the year we spent together at the Master of Science course is unforgettable. Especially for an older boy, this direct contact with a bunch of eager young people that were fascinated by the same scientific spirit was a unique experience. Now, when everybody is spread out over the world again, we are still good friends. Thanks to the Net.

Hanne, Peter, Pascale en Marc, mijn ex-collega's bij Lasion. Toen ik daar vertrok wisten jullie ook dat het zeker niet omwille van de collega's was. Het was een sprong in het onbekende en jullie hebben me, ieder op jullie eigen manier, prima ondersteund bij dit proefschrift.

Een speciale dank gaat verder uit naar Maiwenn. Dankzij het voorbeeldprogramma dat zij schreef in Turbo-Pascal kon ik een vliegende start nemen bij het programmeren van de simulatiemodellen. Patrick en Hilde leenden me de antieke schrijfmachine die ik nodig had om de standaardformulieren voor deze promotie in te vullen.

Beide paranimfen werden al genoemd, maar toch nog eens extra bedankt dat jullie dit voor mij willen doen.

Erna, met jou heb ik dit wilde idee om een leuke en goedbetaalde baan in te ruilen voor een onzeker bestaan in de wetenschap voor het eerst besproken. We wisten toen niet waar we beiden, nu meer dan 7 jaar later, zouden staan, maar de vele gesprekken die ik met jou hierover gevoerd heb, hebben me enorm geholpen om de juiste keuze te maken. Ik hoop dat je hier vandaag aanwezig kan zijn.

En dan is er natuurlijk het gezin, en dat heeft me erg goed geholpen om alles toch maar te relativeren. Hannah kan het nog niet zo goed verwoorden, maar toen ik Lisa trots vertelde dat een artikel van mij gepubliceerd was in de BMJ vroeg ze me nuchter, "En..., ben je nu beroemd ?"

Rita, bedankt voor je geduld, en voor al de rest.

Mijn moeder is helaas veel te vroeg gestorven. Ze zou apetrots zijn geweest.

1 BV: 'Bon Vivant'. Arana A, Rotterdam 1994.

ABOUT THE AUTHOR

Chris De Laet was born on September 26, 1956 in Antwerp and he still lives there. After a fascinating but otherwise uneventful youth he graduated as a Medical Doctor from Antwerp University Medical School in 1981.

He fulfilled a civil service at the Antwerp Free Clinic from late 1981 till early 1983, caring mainly for adolescents and illegal-drug users. Afterwards, he worked for some time both as a general practitioner and in a hospital emergency ward. In 1984 he decided that clinical work was not what he intended to do in life, and after some travelling through South America he joined IBM in September 1984. There, he was a witness and participant in the, than evolving, science and business of medical informatics. He was especially involved in the concepts and implementation of the electronic patient record.

At the end of 1992, when IBM was reorganizing its worldwide operations and strategic objectives, he got a nice offer to leave and he did not refuse this. He took a sabbatical leave in 1993, and during that year, he mainly enjoyed himself, but he also took some steps back to science. This included attending the Florence epidemiology summer course. Thereafter, however, he joined a small Belgian company, as editor-in-chief of medical CD-ROM's.

But, still looking for new challenges, he decided in 1994 to come to Rotterdam to attend the NIHES Master of Science Epidemiology Course. After a couple of months, he was offered the opportunity to conduct the present research at the Institute of Epidemiology and Biostatistics of the Erasmus University. Currently he is involved in the Dutch guidelines project, working at the institute for Medical Technology Assessment of the same University.