

**Osteoporosis: more than fractures  
alone**

An epidemiological approach

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**Osteoporosis: more than fractures alone**  
An epidemiological approach

**Osteoporose: meer dan alleen fracturen**  
Een epidemiologische aanpak

**Proefschrift**

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## Manuscripts based on studies described in this thesis

### *Chapter 2.1*

Van der Klift M, de Laet CEDH, McCloskey EV, Hofman A, Pols HAP The incidence of vertebral fractures in men and women: The Rotterdam Study. *J Bone Miner Res.* 2002;17(6):1051-6

### *Chapter 2.2*

Van der Klift M, de Laet CEDH, McCloskey EV, Johnell O, Kanis JA, Pols HAP Risk factors for incident vertebral fractures in men and women: the Rotterdam Study. Submitted

### *Chapter 3.1*

Van der Klift M, Seeman E, de Laet CEDH, Hofman A, Pols HAP Limits to the WHO definition of osteoporosis: the prevention paradox revisited. Submitted

### *Chapter 3.2*

De Laet CEDH, van der Klift M, Hofman A, Pols HAP Osteoporosis in men and women: a story about bone mineral density thresholds and hip fracture risk. *J Bone Miner Res.* In press

### *Chapter 4.1*

Van der Klift M, Pols HAP, Hak AE, Witteman JCM, Hofman A, de Laet CEDH Bone mineral density and the risk of peripheral arterial disease: the Rotterdam Study. *Calcified Tissue International.* In press

### *Chapter 4.2*

Van der Klift M, de Laet CEDH, Coebergh JWW, Hofman A, Pols HAP Bone mineral density and the risk of breast cancer: the Rotterdam Study. Submitted

### *Chapter 5.1*

Van der Klift M, Pols HAP, Geleijnse JM, van der Kuip DAM, Hofman A, de Laet CEDH Bone mineral density and mortality in elderly men and women: the Rotterdam Study. *Bone* 2002 30; 643-8

### *Chapter 6.1*

Van der Klift M, Pols HAP, Hofman A, Rutten FFH, de Laet CEDH Cost-effectiveness of fracture prevention and the effects on breast cancer in elderly women: the Rotterdam Study. Submitted





## Background

Osteoporosis is a systemic disease, which is characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. (1) Osteoporotic fractures, the clinical endpoint of osteoporosis, are associated with increased morbidity, mortality and high socio-economic costs. (2-8) The most important osteoporotic fractures are those of the vertebrae, the hip and the distal forearm. The diagnosis osteoporosis is made primarily on basis of measurement of bone mineral density (BMD), which is a measure of the amount of bone mass present. Around the age of 30 years, a peak in BMD is reached, after which BMD starts to decrease with age. For diagnostic use in clinical practice, a working group of the World Health Organisation (WHO) developed the T-score from the BMD. (9) The T-score reflects the number of standard deviations of the BMD below the average BMD in young adult individuals.

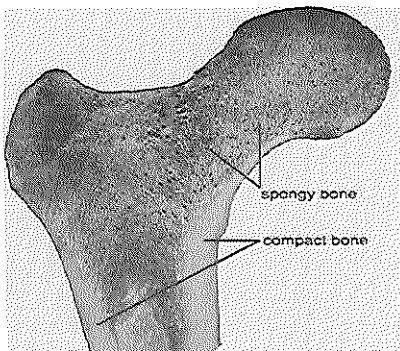
The diagnostic criteria for osteoporosis are given in Table 1.1.

**Table 1.1. Diagnostic criteria for osteoporosis**

T-score value	Diagnosis
Above - 1.0	Normal bone
Below - 1.0 and above -2.5	Osteopenia
Below - 2.5	Osteoporosis
Below - 2.5 and at least one fragility fracture	Established osteoporosis

There are two types of bone present in the human skeleton, namely cortical (“compact”) bone and trabecular (“spongy”) bone, the latter of which is the most metabolically active. (Fig 1.1) Therefore, the sudden decrease in estrogen exposure during menopause influences trabecular bone more than cortical bone. In the femoral neck, there is proportionally less trabecular bone than in the spine, and this suggests that factors that influence the turnover of bone may have stronger effects on spine BMD than on femoral neck BMD.

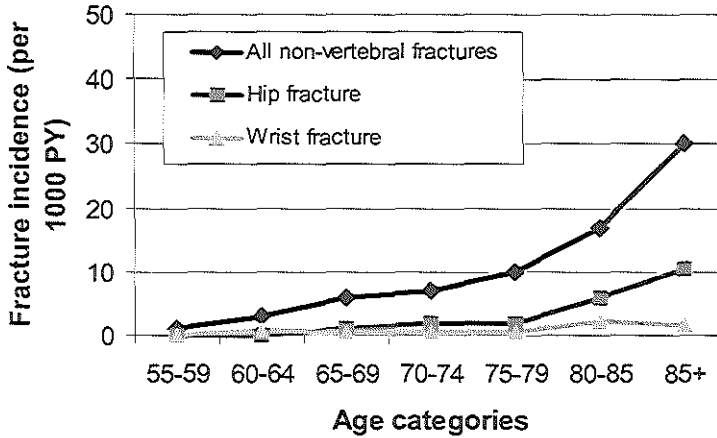
**Figure 1.1. Different types of bone**



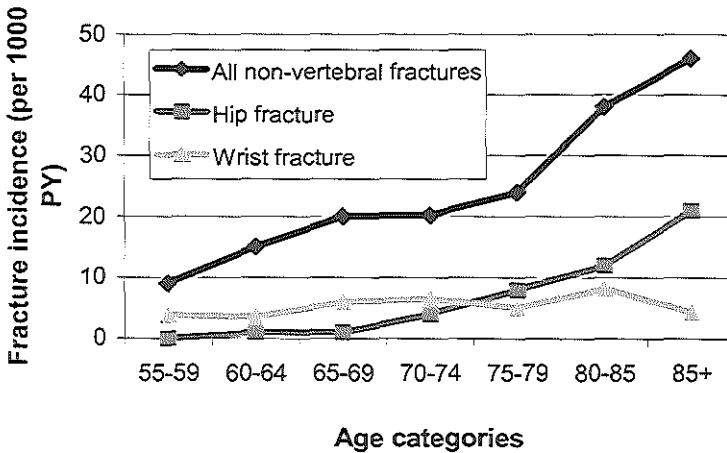
**Incidence of fractures**

Recently, Weel et al. studied the incidence of non-vertebral fractures in both men and women from the Rotterdam Study (Fig 1.2 and 1.3). (10)

**Figure 1.2.** The incidence of non-vertebral fractures per 1000 person years in men



**Figure 1.3.** The incidence of non-vertebral fractures per 1000 person years in women



In contrast to non-vertebral fractures, the incidence of vertebral fractures is not well known, especially in men. (11-14) In part, this is due to the fact that only about one third of vertebral fractures come to medical attention, whereas the majority remains unnoticed. (15) Vertebral fractures can be very debilitating, for they are associated with increased functional impairment, (16) back pain and kyphosis. (8,17) Furthermore, even in subjects without symptoms, vertebral fractures are associated with a decreased quality of life, which is not only the result of back problems, but also of other conditions, such as depression. (6,18) In addition, some studies have shown that the presence of a vertebral fracture is associated with an increased mortality risk. (4,19) Subjects with vertebral fractures have an increased risk of both new vertebral and non-vertebral fractures, such as hip fractures. (20-24) Thus, it is important to know how often these fractures occur in the general population. We studied the incidence of vertebral fractures in both men and women, as is described in chapter 2.1.

**Risk factors for osteoporotic fractures**

Several studies have investigated risk factors for incident fractures, but most of these studies have been focussed on hip fractures. (20,25-36) One of the most important risk factors for incident fractures is a low BMD. (25,29,31) With decreasing BMD, the risk of an incident non-vertebral fracture increases rapidly, both in men and in women. Besides BMD, the most important risk factors for non-vertebral fractures are age, female gender, low body weight, a history of prior fractures and family history of fractures, see Table 1.2. (26-35) For vertebral fractures, however, only two studies on risk factors for incident vertebral fractures were performed, and results were presented for women only. Ross et al. showed that both pre-existing vertebral fractures and a low bone mass were strong predictors for incident vertebral fractures in almost 900 elderly women. (21)

**Table 1.2. Risk factors for incident non-vertebral fractures**

Increased risk	Decreased risk
Increasing age	
Female gender	
Low body weight	
Early age at menopause	
Smoking	
Low BMD	
History of previous fractures	
Maternal history of fracture	
Low calcium intake	
Low physical activity	
Corticosteroid use	
	Statin use
	Thiazide diuretic use

Furthermore, Gregg et al. suggested that an increased physical activity is associated with a decreased incidence of vertebral fractures. (36) This prompted us to study risk factors for incident vertebral fractures in both men and women, as is described in chapter 2.2.

### **Fracture prevention**

Even though the above described definition of osteoporosis, a T-score at or below  $-2.5$ , was designed for diagnostic purposes only, it appears that in clinical practice this cut-off value of  $-2.5$  is often used as a treatment threshold. It is not known, however, what proportion of all fractures in the general population will be captured using such an approach. It is important that one can accurately identify subjects who will fracture, in order to optimally aim fracture prevention. Therefore, we studied the sensitivity of using a T-score at or below  $-2.5$  in order to identify subjects who will fracture, as is described in chapter 3.1.

Besides uncertainties about the sensitivity of the T-score, it is currently also unclear whether a same T-score should be used for both men and women, or whether a gender-specific T-score is to be preferred. This was studied in chapter 3.2.

### **The effects of endogenous estrogen on bone**

It is well known that women after menopause have an accelerated bone loss, suggesting that estrogen deficiency plays an important role in this loss. (37-39) Also, *in vitro* models have shown that estrogen stimulates osteoblast differentiation and enhances bone formation. (40) High estrogen exposure, both endogenous and exogenous, is associated with a high BMD. (41,42) Furthermore, since estrogens are thought to mainly affect the metabolically more active trabecular bone, lumbar spine BMD might be more influenced by estrogen exposure than femoral neck BMD is.

It is hypothesized that BMD can be regarded a marker for long-term estrogen exposure. (43) In addition, exposure to estrogens may stimulate the development and progression of breast cancer, by stimulating mitotic activity of mammary cells and thereby increasing mutation risk. (44) An association between endogenous estrogen levels and atherosclerosis is also suggested. (45-48) Bone density, reflecting estrogen exposure throughout life, may therefore be associated with both incident breast cancer and atherosclerosis risk. We therefore investigated the interrelationships between bone mineral density, atherosclerosis and breast cancer, as is described in chapters 4.1 and 4.2.

### **Therapeutical options for osteoporosis and fracture prevention**

One of the therapeutical options for osteoporosis is treatment with estrogens, in the form of hormone replacement therapy (HRT), to increased BMD and decrease fracture risk. In addition, there are also several other types of drugs, which can be offered to a patient for fracture prevention. The most important types of drugs, besides HRT are bisphosphonates and selective estrogen receptor modulators (SERMs). Bisphosphonates, such as risedronate and

alendronate, are compounds that inhibit osteoclast-mediated bone resorption. In addition, bisphosphonates have been shown to reduce fracture risk (both vertebral and non-vertebral) by as much as fifty percent. (50-57) Raloxifene, so far the only SERM available for osteoporosis treatment, is a nonsteroidal benzothiophene that binds to the estrogen receptor and inhibits bone resorption, thereby increasing BMD and decreasing (mainly vertebral) fracture risk. (49,50)

A brief summary of all randomized controlled trials (RCT) with fractures as an endpoint, that have been performed on HRT, SERMs and bisphosphonates, the drugs we will evaluate in this thesis in terms of fracture prevention, is shown in Tables 1.3, 1.4 and 1.5, respectively. (50-62)

### **Effects of HRT and SERMs on tissues other than bone**

Besides the anabolic effects on bone, estrogens are also thought to increase serum HDL-cholesterol levels, decrease serum LDL-cholesterol levels and influence the coagulation pathway resulting in an 2-3 times increased risk of thrombo-embolisms. (40,48,63-65) In addition, literature suggests that estrogen stimulates the occurrence and progression of breast cancer, increasing breast cancer risk by approximately 2 % per each additional year of taking HRT. (66-68) Finally, HRT is thought to increase the risk of endometrial cancer. (65)

SERMs are thought to have the same effects on bone and the cardiovascular system as estrogens have. (50,69,70) In contrast to estrogen, though, there is recent evidence that SERMs substantially decrease the risk of breast and endometrial cancer in women. (69,71)

Based on these observations, we compared the cost-effectiveness of HRT, SERMs and bisphosphonates for fracture prevention, taking into account the effects of HRT and SERMs on breast cancer risk in elderly women, as described in chapter 6.

### **Study population**

The results of the studies presented in this thesis were based on the Rotterdam Study, a prospective population-based cohort study, which was initiated to assess the prevalence, incidence, and determinants of diseases of the elderly. (72) The main focus was on cardiovascular disease, neurogeriatric disease, ophthalmologic disease, and locomotor disease. At baseline, between 1990 and 1993, all inhabitants aged 55 years and over (n=10,275) of the district of Ommoord in Rotterdam, were invited to take part in the study. A total of 7,983 subjects (response rate 78 %), 4878 of which were women, entered the study. At baseline, and again at the first and second follow-up visits (between 1994-1995 and 1997-1999, respectively), information was gathered concerning amongst others lifestyle habits, socio-economic status, medical history and pharmacotherapy history. In addition to an interview, all subjects were invited to visit our research centre for physical examination, including measurement of height and weight. BMD of the femoral neck and lumbar spine was measured by

Table 1.5. Summary of randomized controlled trials studying the effects of bisphosphonates on the occurrence of fractures

Authors	Year of publication	Study population	Drugs tested	Numbers of subjects	Effect on fracture incidence
Liberman et al.	1995	Osteoporotic women, 45-80 yr	A: 5 mg/d Alendronate B: 10 mg/d Alendronate C: 20 mg/d Alendronate, D: Placebo	526 (A+B+C)	For all Alendronate groups combined vs. placebo: Vertebral fractures RR 0.5 (0.3-1.0) Non-vertebral fractures RR 0.8 (0.5-1.2)
Cummings et al.	1998	Postmenopausal women, low FN BMD but no vertebral fractures, 54-81 yr	A: 5 mg/d Alendronate first 2 yr and 10 mg/d final 2 yr. B: Placebo	355 2214	In women with T-score $\leq$ -2.5: Clinical fractures RR 0.6 (0.5-0.8) Vertebral fractures RR 0.5 (0.3-0.8)
Pols et al.	1999	Postmenopausal women, low LS BMD, 39-84 yr	A: 10 mg/d Alendronate B: Placebo	950 958	Non-vertebral fracture RR 0.5 (0.3-0.9)
Harris et al.	1999	Postmenopausal women $\leq$ 85 yr with $\geq$ 1 vertebral fracture,	A: Risedronate 2.5 mg/d (stopped after 1 yr) B: Risedronate 5 mg/d C: Placebo	811 813 815	First yr: A Vertebral fractures RR 0.5 (0.3-0.9) B Vertebral fractures RR 0.4 (0.2-0.6) Third yr B vertebral fractures RR 0.6 (0.4-0.8) B non-vertebral fractures RR 0.6 (0.4-0.9)
Orwoll et al.	2000	241 osteoporotic men, 31-87 yr	A: 10 mg/d Alendronate B: Placebo	146 95	A lower incidence of vertebral fractures was observed in men taking Alendronate than in men taking Placebo
Reginster et al.	2000	Postmenopausal women with $\geq$ 2 prevalent vertebral fractures	A: Risedronate 2.5 mg/d B: Risedronate 5 mg/d C: Placebo	408 407 407	First yr: A vertebral fractures RR 0.5 (0.3-0.8) B vertebral fractures RR 0.4 (0.2-0.7) Third yr B vertebral fractures RR 0.5 (0.4-0.7) B non-vertebral fractures RR 0.7 (0.4-1.0)
McClung et al.	2001	1) Osteoporotic women aged 70-79 yr, with T-score $\leq$ -4 or -3 and hip-axis length $\geq$ 11.1 2) Osteoporotic women $\geq$ 80 yr with $\geq$ 1 non-skeletal risk factor	1A: 2.5 mg/d Risedronate 1B: 5.0 mg/d Risedronate 1C: Placebo 2A: 2.5 mg/d Risedronate 2B: 5.0 mg/d Risedronate 2C: Placebo	1812 1812 1821 1281 1292 1313	1A+B combined hip fracture RR 0.6 (0.4-0.9) 2A+B combined hip fracture RR 0.8 (0.6-1.2)

Dual Energy X-ray Absorptiometry (DEXA, Lunar DPX-L) and radiographs of the thoracolumbar spine were made.

For information on prevalent and incident vertebral fractures, all radiographs of the second follow-up visit were morphometrically evaluated for the presence of vertebral fractures by the McCloskey-Kanis method. (73) If a vertebral fracture was present at the follow-up radiographs, the baseline radiographs was additionally evaluated. If the fracture was already present at baseline, it was considered prevalent. Otherwise, the fracture was considered an incident vertebral fracture.

For the entire cohort, information on vital status was obtained continuously from the municipal authorities in Rotterdam. For subjects who moved outside the research area, mortality data are obtained from general practitioners (GPs). GPs in the research area (covering 80% of the cohort) reported all relevant fatal and non-fatal events, such as fractures, through a computerized system. Research physicians verified follow-up information by checking GPs' patient records. This is possible because in the Netherlands the GP has a gate keeper function, which means that the GP retains all medical information of his patients. For the remaining 20 % of the population, research physicians collected data from their GP's patient records. For hospitalised patients, discharge reports and letters from medical specialists were additionally used for verification. All non-fatal events, such as fractures, were coded independently by two research physicians according to the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10) (30). If there was disagreement, consensus was reached in a separate session. A medical expert in the field reviewed all coded events for a final classification.

### **Aim of this thesis**

The main purposes of this thesis are to study the incidence of and risk factors for vertebral fractures and to evaluate the interrelations between bone mineral density, atherosclerosis and breast cancer, all of which are considered to be influenced by estrogen exposure. We will look into fracture prevention; are the current methods for identifying subjects at risk for fractures adequate and should men and women be treated equally. Finally, the results of these studies are combined in a model on cost-effectiveness of fracture prevention.

### **Description of chapters**

In **Chapter 2**, vertebral fractures are investigated in both men and women. In *chapter 2.1*, the incidence of vertebral fractures will be described. In addition, the associations of incident vertebral fractures with both BMD and the presence of baseline prevalent vertebral fractures are studied. In *chapter 2.2*, we extended the analyses on risk factors for incident vertebral fractures for men and women. At first, we evaluated potential risk factors univariately for an association with incident vertebral fractures. Then, we evaluated whether univariately significant

risk factors were independent from BMD, prevalent vertebral fractures and from each other.

In **Chapter 3**, we study the value of a T-score of BMD in fracture prevention. In *Chapter 3.1* it is evaluated whether the current criterion for osteoporosis, as defined by the WHO, of a T-score at or below  $-2.5$ , is useful in accurately identifying women who will fracture within the coming years. *Chapter 3.2* discusses whether the association between BMD and fractures is similar for both men and women and if so, whether using a gender specific T-score of BMD is useful in describing the problem of osteoporosis in men.

**Chapter 4** describes the associations between BMD and diseases other than osteoporosis that are also considered to be influenced by estrogen exposure. First, in *Chapter 4.1*, the association between BMD and peripheral arterial disease, which is a measure for generalised atherosclerosis, is described. *Chapter 4.2* then shows the association between BMD and incident breast cancer in women.

Following the associations between BMD and morbidity, the association between femoral neck BMD and overall mortality is described for both men and women in **Chapter 5**.

The results of a mathematical model on the cost-effectiveness of fracture prevention are discussed in **Chapter 6**. This model is an example of how the results as described in the previous chapters can be used to evaluate the cost-effectiveness of fracture prevention. In this model, different treatment strategies of HRT, SERMs and bisphosphonates are compared.

Finally, in **Chapter 7** the overall results of this thesis are placed in perspective in a general discussion. We further discuss pitfalls, as well as the clinical relevance of the research that was presented in this thesis. The general discussion ends with some suggestions for further research.

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## *Chapter 2*

### *Epidemiology of vertebral fractures*



# *Chapter 2.1*

## *Incidence of vertebral fractures in elderly men and women*

*The Rotterdam Study*

## Abstract

Vertebral fractures are considered the most common fractures in osteoporosis. Nevertheless, little is known about the epidemiology of these fractures, especially in males. Therefore, the incidence of vertebral fractures was studied in 3469 men and women from the Rotterdam Study. Spinal radiographs were obtained at baseline and again after a mean follow-up of 6.3 years. The follow-up radiographs were scored for vertebral fractures using the McCloskey-Kanis assessment method. Whenever a vertebral fracture was detected the radiograph was compared with the baseline radiograph. If this fracture was not already present at baseline, it was considered an incident fracture. The incidence increased strongly with age, ranging from 7.8 per 1000 person years (PY) at ages 55-65 to 19.6 per 1000 PY at ages over 75 for women, and 5.2 to 9.3 per 1000 PY for men, respectively. Analyses repeated in strata of presence or absence of prevalent vertebral fractures showed that both in men and women, the increase in incidence with age was almost exclusively observed in subjects with one or more prevalent fractures present at baseline. For both genders, the incidence of vertebral fractures doubled per standard deviation (SD) decrease in lumbar spine or femoral neck bone mineral density (BMD). This study shows that overall the incidence of vertebral fractures is higher in women than in men. In both genders, the incidence increases with age. Furthermore, the presence of a prevalent vertebral fracture and a low BMD are strong independent predictors of incident vertebral fractures in men and women.



## **Introduction**

Vertebral fractures are the most common and yet least well investigated fractures in osteoporosis, especially in men. (1-4) In part, this is due to the fact that only about one third of vertebral fractures come to medical attention, whereas the majority remains unnoticed.(5) Vertebral fractures can be very debilitating, for they are associated with increased functional impairment, (6) back pain and kyphosis. (7,8) Furthermore, even in subjects without symptoms, vertebral fractures are associated with a decreased quality of life, which is not only the result of back problems, but also of other conditions, such as depression. (9,10) Several studies have shown that the presence of a vertebral fracture is associated with an increased mortality risk. (11,12) Furthermore, subjects with vertebral fractures have an increased risk of both new vertebral and non-vertebral fractures, such as hip fractures.(13-17) A limited number of other studies investigated the incidence of vertebral fractures. Cooper et al. studied the incidence of clinically detected vertebral fractures in Rochester, United States.(5) In the same population, Melton et al. estimated the incidence of all vertebral fractures from the prevalence.(3) Furthermore, some studies have shown cumulative incidence of vertebral fractures in women.(13,15,16) Several studies have investigated the prevalence of vertebral fractures.(18-21) The largest of those, the European Vertebral Osteoporosis Study, is currently also studying the incidence of vertebral fractures in European countries.

The present study is, to our knowledge, the first single-cohort study in both men and women to investigate the incidence of vertebral fractures in nearly 3500 subjects aged 55 years and over during more than 6 years of follow-up.

## **Materials and methods**

### **Study population**

The Rotterdam Study is a prospective population-based cohort study of men and women aged 55 and over and has the objective to investigate the incidence of, and risk factors for, chronic disabling diseases. Both the rationale and the study design have been described previously.(22) The focus of the Rotterdam Study is on neurologic, cardiovascular, ophthalmologic and locomotor diseases. All 10,275 inhabitants of Ommoord, a district in Rotterdam, the Netherlands, were invited to participate. Of these, 7,983 (4,878 women) participated in the study (resulting in a response rate of 78%). The Medical Ethics Committee of the Erasmus University Medical School has approved the Rotterdam Study.

### **Clinical examination**

Between 1990 and 1993, an extensive baseline home interview on medical history, risk factors for chronic diseases and medication use was performed on all participants by trained interviewers. After the home interview, the participants were invited to come to the research center for clinical examination and

laboratory assessments. Bone mineral density measurement of the femoral neck and lumbar spine was performed by dual energy X-ray absorptiometry (DXA) (Lunar DPX-L densitometer, Madison, Wisconsin, USA) as described previously.(23)

### **Vertebral deformity assessment**

Both at baseline, between 1990 and 1993, and at the second follow-up visit, between 1997 and 1999, a trained research technician obtained lateral radiographs of the thoracolumbar spine of subjects who were able to come to the research center. At baseline, there were two research technicians available, and one of them took all the radiographs at the follow-up visit. All radiographs were taken following a standard protocol, with a distance between source and plate of 120 cm, using a Solarize FV (General Electric CGR, Utrecht, the Netherlands). The follow-up radiographs were available for 3549 individuals (2022 women), who survived after an average 6.3 years after their baseline center visit and who were still able to come to our research center. The fact that all subjects had to survive to this point and still had to be mobile enough to visit the center caused a health selection bias in our study population, with participants being younger than non-participants (mean age of 65.5 (SD 6.6) in participants and 74.5 (SD 10.0) in non-participants, respectively). Overall, participants were generally more healthy than non-participants. All follow-up radiographs were evaluated morphometrically in Sheffield by the McCloskey-Kanis method, as described previously.(24) If a vertebral fracture was detected, the baseline radiograph was evaluated as well. If the fracture was already present at baseline it was considered a baseline prevalent fracture. If, however, the vertebra was determined to be normal at baseline and any of the three vertebral heights (anterior, central or posterior) showed a minimum decrease of at least 4.6 mm and 15% in absolute height on the later film; it was considered an incident fracture. All vertebral fractures were confirmed by visual interpretation by an expert in the field (EMC), to rule out artefacts and other etiologies, such as pathological fractures. We excluded 80 individuals who had not attended the baseline visit. Therefore, the population for analysis consisted of 3469 individuals (1971 women) with information on incidence of vertebral fractures.

### **Statistical analysis**

Differences in baseline characteristics were compared using student's t- test for continuous variables and Chi-square for categorical variables. Since we have no information on the exact date of fracture, we estimated this date by using the date halfway in between the baseline and follow-up radiograph dates. This date was also used to estimate the average age during follow-up for both cases and non-cases. For the calculation of follow-up time, the time between the two radiographs was used for non-cases, whereas for cases we used the time between

the date of the first radiograph and the date halfway in between the baseline and follow-up radiograph, the estimated date of fracture. In a first analysis, we calculated overall incidence rates, for men and women separately. Analyses were repeated in five- and ten-year age strata and we estimated an exponential curve through the incidence rates. Analyses were also repeated in strata of presence or absence of a prevalent vertebral fracture at baseline. To analyze the gender difference in vertebral fracture incidence, we calculated age adjusted odds ratios (OR) with 95% confidence intervals (CI) for the risk of an incident vertebral fracture for women compared to men with logistic regression analysis. Additionally we adjusted for lumbar spine BMD. To assess whether BMD measured at another site equally predicts incident vertebral fracture risk, we compared OR with 95% CI for incident vertebral fractures per standard deviation decrease in lumbar spine and femoral neck BMD.

For men and women separately, we modeled the association between lumbar spine BMD and incident vertebral fractures, adjusting for age and the presence of prevalent vertebral fractures, using logistic regression. SPSS 9.0 for windows was used for all analyses (SPSS Inc., Chicago, Illinois).

## Results

Figure 2.1.1 shows a radiograph on which a vertebral fracture is visible. During an average follow-up period of 6.3 years, 240 new vertebral fractures occurred in 176 individuals, 129 of which were females. The study generated a total of 22,046 person years (PY) (12,461 for females).

**Figure 2.1.1. Radiograph with vertebral fracture visible**

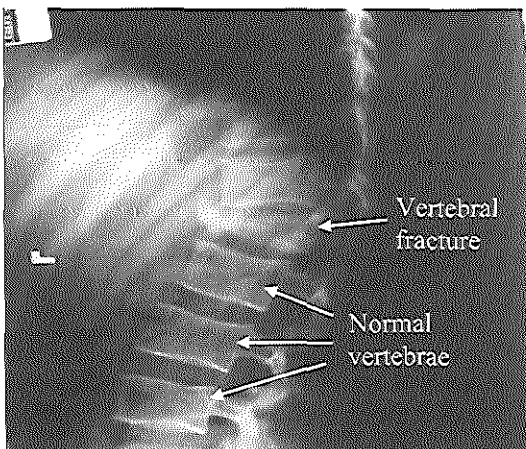
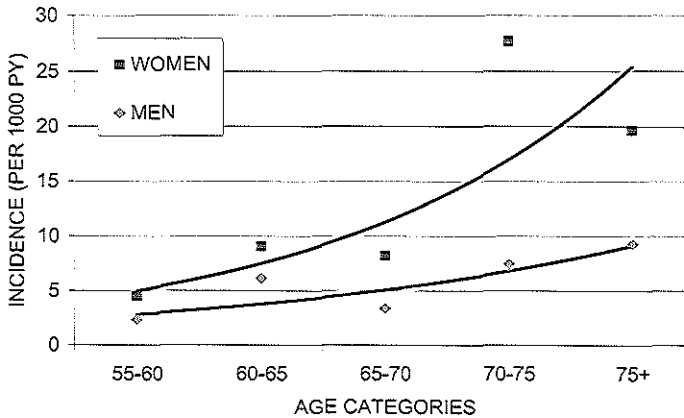


Table 2.1.1 shows the baseline characteristics for subjects with and without incident vertebral fractures. Individuals with incident fractures are older, thinner

Both in men and women, the incidence of vertebral fractures increases with age, even though this is most pronounced in women. This is again shown in 5-year age strata in figure 2.1.3.

**Figure 2.1.3. The incidence of vertebral fractures per 5-year age strata in men and women**



The increased incidence with age in women is primarily observed in those with a baseline prevalent fracture present. In men, a similar pattern is observed though the incidence rates were significantly lower than in the women. At ages of 75 years and over, the incidence rate ratio between subjects with and without a prevalent vertebral fracture at baseline was very similar for both genders, about 6 for men and 8 for women.

After adjustment for age, the risk of an incident vertebral fracture was higher in women than in men (OR 2.1; 95% CI 1.5-3.0). After adjustment for age and lumbar spine BMD, these risk estimates dropped and were no longer statistically significant (OR 1.3; 95% CI 0.9-1.8). When adjustment was made for femoral neck BMD instead of lumbar spine BMD, odds ratios again dropped but remained higher and were still statistically significant (OR 1.6; 95% CI 1.1-2.3). Further adjustment for the presence or absence of baseline prevalent vertebral fractures did not essentially change these risk estimates.

**Table 2.1.3. Incidence per 1000 person years of vertebral fractures in elderly men**

	Nr of fractures	Person years	Incidence
Overall			
55-65	17	3294	5.2 (3.2-8.3)
65-75	24	4682	5.1 (3.4-7.7)
75+	16	1736	9.3 (5.7-15.1)
No vertebral fracture present			
55-65	16	3156	5.1 (3.1-8.3)
65-75	17	4359	3.9 (2.4-6.3)
75+	9	1534	5.9 (3.1-11.3)
Vertebral fracture present			
55-65	1	138	7.2 (1.0-51.3)
65-75	7	323	21.6 (10.3-45.4)
75+	7	193	36.4 (17.3-76.3)

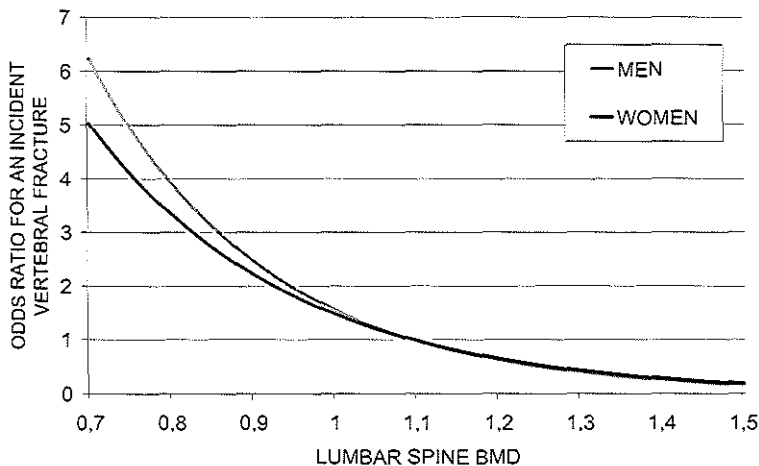
**Table 2.1.4. Incidence per 1000 person years of vertebral fractures in elderly women**

	Nr of fractures	Person years	Incidence
Overall			
55-65	33	4210	7.8 (5.6-11.0)
65-75	99	5811	17.0 (14.0-20.7)
75+	51	2598	19.6 (14.9-25.8)
No vertebral fracture present			
55-65	32	4064	7.9 (5.6-11.1)
65-75	61	5358	11.4 (8.8-14.6)
75+	26	2327	11.2 (7.6-16.4)
Vertebral fracture present			
55-65	1	146	6.9 (1.0-48.7)
65-75	38	454	83.7 (60.9-115.0)
75+	25	271	92.4 (62.4-136.7)

Especially in men, the age-adjusted relative risk of an incident vertebral fracture was higher per 1 SD decrease in lumbar spine BMD than per SD decrease in femoral neck BMD (OR 2.6; 95% CI 1.8-3.7 and 1.8; 95% CI 1.3-2.4, respectively; p-value for difference 0.061). A similar, but less obvious trend was observed for women (2.2; 95% CI 1.7-2.7 and 1.9; 95% CI 1.6-2.4, respectively; p-value for difference 0.225).

Figure 2.1.4 shows the odds ratios for incident vertebral fractures by absolute values of lumbar spine BMD for men and women separately. Adjustment was made for age and the presence of prevalent vertebral fractures at baseline. Especially for the higher BMD values, the lines completely overlapped for men and women. At very low BMD levels, the line for men was somewhat higher than for women. This is mainly due to the low numbers of men at very low BMD levels.

Figure 2.1.4. Age and prevalent vertebral fracture adjusted odds ratios for incident vertebral fractures by lumbar spine BMD, in men and women



### Discussion

In this large population-based cohort study, we found that both in men and in women, the incidence of vertebral fractures strongly increased with age. This increase with age occurred mainly in subjects who had a prevalent vertebral fracture present at baseline.

At higher ages, the incidence rate ratio between subjects with and without prevalent vertebral fractures was almost similar for men and women.

The absolute incidence of vertebral fractures is lower in men than in women, but after adjustment for age and the presence or absence of prevalent vertebral fractures, the risk of an incident vertebral fracture is similar at any given level of lumbar spine BMD in men and women. Therefore, the difference in absolute incidence in men and women may be due to the fact that overall, men have a higher peak bone mineral density and loose bone at a lower rate than women do.(25) In line with this finding, Lunt and colleagues also suggested that BMD, together with age, explain much of the differences in risk of vertebral fractures between men and women in a cross-sectional analysis. (26)

For both men and women, the presence of prevalent vertebral fractures as well as a low BMD were strong independent risk factors for incident vertebral fractures.

Ross et al. already showed prevalent vertebral fractures to be a strong risk factor for incident vertebral fractures in women. (13) This study shows that prevalent vertebral fractures are also important predictors for incident vertebral fractures in men.

A limited number of other studies investigated the incidence of vertebral fractures. Cooper et al. studied the incidence of clinically detected vertebral fractures during a 5 years period in the population of Rochester, Minnesota. (5) For women, these incidence rates were about one third of our incidence rates. This is similar to what could be expected from earlier studies, since it was estimated that only about one third of all vertebral fractures spontaneously come to clinical attention.(27) For men this was less obvious, probably due to low numbers. In a sample from the same study population, Melton et al. estimated the incidence of all vertebral fractures in women from the prevalence using the method of Leske et al.(3,28) Their estimated incidence is similar to our incidence at lower ages, but from around age 70 their incidence rates are higher than ours are. However, in order to estimate the incidence from the prevalence, it is assumed that subjects with vertebral fractures have a similar risk of mortality as subjects without a vertebral fracture. Several recent studies have shown that prevalent vertebral fractures are associated with an increased mortality risk. (11,12) Since the absolute mortality risk increases with age, this could explain why results deviate at higher ages.

Furthermore, some other studies reported the cumulative incidence of vertebral fractures in women.(13,15,16) The Study of Osteoporotic Fractures showed a vertebral fracture cumulative incidence of 5.4 % over an average follow-up time of 3.7 years in women aged 65 years and over, (16) whereas this was 6.8 % over 4.7 years in postmenopausal Japanese-American women. (13) Comparison with these studies is hampered, though, by the fact that different methods for defining vertebral fractures are used, and that large differences in duration of follow-up and age distribution of the subjects exist.

The absence of consensus about the definition of a vertebral fracture is indeed the major problem in studying the incidence of vertebral fractures. (24),(29-32) Several methods have been developed for the evaluation of spinal radiographs. For this study, we used the McCloskey-Kanis method, which is a method that is especially developed for assessing both the prevalence and incidence of vertebral osteoporosis in the population and in prospective studies. In contrast to other methods, this method predicts vertebral heights and ratios for the individual patient rather than comparing them exclusively to a reference population, resulting in a lower false positive rate. (24)

Even though this is a large population-based cohort study there are some weaknesses. There is a selection bias in our study population, since in order to be eligible for this study, subjects had to be able to come to our third center visit. Therefore, only the subjects who survived over 6 years of follow-up and were still mobile enough were included in this study. Due to this selection bias, our incidence rates are probably an underestimation of the true incidence in the population. However, since vertebral fractures only come to medical attention in one third of all cases, this is the only way to estimate the real incidence of vertebral fractures. Our assessment of vertebral deformities was based solely on morphometry, which is not commonly used in clinical practice. Because at older ages most vertebral fractures occur after minor or no trauma, (5) we assumed that most incident vertebral fractures in this group of elderly participants were caused by osteoporosis.

Altogether, we show that the incidence of vertebral fractures increases strongly with age in both men and women. Subjects with a prevalent vertebral fracture present at baseline primarily accounted for this increase of incidence with age. Even though overall incidence rates are higher in women than in men, the risk of an incident vertebral fracture at any given level of absolute BMD is similar for men and for women. The presence of a prevalent vertebral fracture and a low BMD are strong and independent risk indicators for incident vertebral fractures in both men and women.

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## *Chapter 2.2*

### *Risk factors for vertebral fractures in elderly men and women*

*The Rotterdam Study*

## Abstract

A low bone mineral density (BMD) and the presence of prevalent vertebral fractures have been reported as risk factors for incident vertebral fractures. Little is known, however, about other risk factors for incident vertebral fractures. We investigated potential risk factors for incident vertebral fractures in 3001 men and women aged 55 or over from the Rotterdam Study, a prospective population-based cohort study. Spinal radiographs were obtained at baseline and again after a mean follow-up of 6.3 years. Presence of incident vertebral fractures was evaluated morphometrically using the McCloskey-Kanis assessment method. For men and women separately, all potential risk factors were tested univariately, and when significant, tested for independence from age, BMD, and additionally from prevalent vertebral fractures. Finally all significant risk factors were entered into a multivariate model. For women age, early menopause (at or below age 45 years), current smoking and walking aid use were additional independent risk factors, apart from low BMD and presence of prevalent vertebral fractures. For men, only a history of non-vertebral fractures at or after age 50 years was a significant independent risk factor besides low BMD and prevalent vertebral fractures. Many of the risk factors studied here have more impact on the pathogenesis of incident vertebral fractures than either hypercholesterolemia or hypertension have on myocardial infarction. Finally, although a model including all risk factors best predicted incident vertebral fractures, a model with easily assessable risk factors only also resulted in good vertebral fracture prediction in women. For both genders, low BMD and prevalent vertebral fractures are strong independent risk factors for incident vertebral fractures. Increasing age, prevalent non-vertebral fractures, early menopause, current smoking and walking aid use are also associated with increased vertebral fracture risk.

## **Introduction**

Vertebral fractures are common fractures in osteoporosis, and they are associated with increased morbidity and mortality. (1-8) However, in contrast to other fractures, especially hip fractures, risk factors for incident vertebral fractures have not been extensively studied. The most important risk factors for non-vertebral fractures are age, gender, low bone mineral density (BMD), low body weight, a history of prior fractures and family history of fractures. (9-19) It is uncertain whether these same risk factors are equally important for vertebral fractures, or whether other factors play a role. We and others have previously reported that low BMD and the presence of baseline vertebral fractures are strong and independent risk factors for incident vertebral fractures. (20,21) Furthermore, Gregg et al. suggested that an increased physical activity is associated with a decreased incidence of vertebral fractures. (22) For men, no studies on other risk factors for incident vertebral fractures have been performed to our knowledge. Several cross-sectional studies have been performed on risk factors for prevalent vertebral fractures. (23-31) These studies suggest that age, low bone mass, smoking, alcohol intake and low physical activity are associated with an increased risk of vertebral fractures. However, these fractures may have occurred several years before, and conclusions on causality are less secure from these analyses.

In this study we evaluated potential risk factors for incident vertebral fractures in both elderly men and women from a large prospective population-based cohort study, the Rotterdam Study.

## **Materials and methods**

### **Study population**

The Rotterdam Study is a large prospective population-based cohort study of men and women aged 55 years and over. The study objective is to investigate the incidence of, and risk factors for, chronic disabling diseases. Both the rationale and the study design have been described previously. (32) All 10,275 inhabitants of Ommoord, a district in Rotterdam, the Netherlands, were invited to participate. Of these, 7,983 participated in the study (response rate 78%). All participants signed informed consent and the Medical Ethics Committee of the Erasmus Medical Centre has approved the Rotterdam Study.

### **Data collection for potential risk factors**

#### **Home interview**

Between 1990 and 1993, an extensive baseline home interview on medical history was performed by trained interviewers. Information on drug use, such as use of diuretics, systemic glucocorticoids, thyroid hormone, statins, hormone replacement therapy (HRT) and oral contraceptives (OC) was gathered. Calcium intake was assessed, as was total caloric intake. For the current analyses, calcium

intake was adjusted for total caloric intake. Smoking habits were categorized as current, former or never. Recent falling was described as at least one fall in the year before the baseline interview. Data on history of non-vertebral fractures at or after age 50 and use of a walking aid were obtained. Lower limb disability was assessed using a modified version of the Stanford Health Assessment Questionnaire, as described previously. (33,34) Information was obtained on age at and reason for menopause, defined as cessation of menses for 12 consecutive months. Natural menopause was defined as menopause occurring spontaneously, not after any intervention that would have stopped the menses. For non-natural menopause, we validated the date and indication of surgery by checking the GPs patient records and hospital discharge letters.

### **Clinical examination**

After the home interview, subjects visited the research center for a clinical examination and laboratory and BMD measurements. Height and weight were measured with subjects wearing indoor clothing and without shoes. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Subjects were classified as diabetics when they reported use of antidiabetic therapy (code A010 of the Anatomical Therapeutic Chemical classification index, WHO 1992), or when the pre- or postload serum glucose level was equal to or higher than 11.1 mmol/l. BMD measurements of the femoral neck and the lumbar spine (L2-L4) were performed by dual energy X-ray absorptiometry (DXA, Lunar DPX-L densitometer) as described previously. (34)

### **Vertebral deformity assessment**

Both at baseline, between 1990 and 1993, and at the second follow-up visit, between 1997 and 1999, a trained research technician obtained lateral radiographs of the thoracolumbar spine of subjects who were able to come to the research center. At baseline, there were two research technicians available, and one of them took all the radiographs at the follow-up visit. All radiographs were taken following a standard protocol, with a distance between source and plate of 120 cm, using a Solarize FV (General Electric CGR, Utrecht, the Netherlands). The follow-up radiographs were available for 3549 individuals (2022 women), who survived after an average 6.3 years after their baseline center visit and who were still able to come to our research center. All follow-up radiographs were evaluated morphometrically in Sheffield by the McCloskey-Kanis method, as described previously. (20,35) If a vertebral fracture was detected, the baseline radiograph was evaluated as well. If the fracture was already present at baseline it was considered a baseline prevalent fracture. If, however, the vertebra was determined to be normal at baseline and any of the three vertebral heights (anterior, central or posterior) showed a minimum decrease of at least 4.6 mm or 15 % in absolute height on the later film; it was considered an incident fracture. All vertebral fractures were confirmed by visual interpretation by an expert in the field, to rule out artifacts and other etiologies,

such as pathological fractures. We excluded 80 individuals who had not attended the baseline visit. We also excluded 468 men and women for whom data on one or more risk factors were missing. The final population for analysis consisted of 3001 individuals (1624 women) with information both on vertebral deformities and on potential risk factors.

### **Statistical analysis**

Differences in baseline characteristics were compared using student's t- test for continuous variables and Chi-square for categorical variables. Age was evaluated in 5-year strata, whereas BMD was evaluated per gender-specific standard deviation decrease. Height and weight were evaluated in quartiles. All potential risk factors were tested for significance in univariate models using logistic regression. To take account of those relatively weak potential risk factors that do not reach statistical significance at a p-value of 0.05 due to low numbers, risk factors were considered statistically significant when the p-value was below 0.10 (two-tailed). All risk factors that were statistically significant in the univariate analyses for either men or women were evaluated for independence from age, by adjusting for age in the model. When still significant, additional independence from BMD and subsequently from both BMD and the prevalence of baseline prevalent vertebral fractures was tested. This was done in order to test whether the risk factors studied reflect a low BMD and/or the presence of vertebral fractures, or whether these risk factors independently add to the etiology of incident vertebral fractures. The risk factors that were still in the model then were entered in a full multivariate model. All analyses were performed for men and women separately. Finally, attributable risks and population attributable risks were calculated for all independent risk factors. (36) The attributable risk ( $RR - 1 / RR$ ) expresses which fraction of the risk of incident vertebral fractures in the exposed is due to the exposure itself. The population attributable risk ( $R - R_0 / R$ , where  $R$  is the risk in the total population, and  $R_0$  is the risk in the non-exposed) expresses what proportion of all incident vertebral fractures in the total population is due to the exposure under study. Since age and BMD are continuous variables, these variables were dichotomized. Age was categorized as above or below 70 years. For lumbar spine BMD, we used a T-score of  $-2.5$  or below as a cut-off. The T-score is the number of standard deviations below the gender-specific young adult mean lumbar spine BMD. Attributable risks were based on age-adjusted odds ratios. We created three models for prediction of incident vertebral fractures: the first included easily assessable risk factors, age, weight, current smoking, use of a walking aid, history of non-vertebral fractures and, for women, age at menopause. The second model included only BMD and the presence of baseline prevalent vertebral fractures and the third model included all of the above. Differences in predictive value for incident vertebral fractures between the three models were evaluated by comparing the area under

the receiver operating characteristic curves (ROC area) with standard error. A ROC curve of a multivariate logistic regression model plots the sensitivity and 1-specificity at each consecutive threshold in the range of predicted probabilities of the model. The ROC area is a measure of the discriminative or predictive ability of the model that can range from 0.5 (no discrimination between subjects with and without incident vertebral fractures) to 1.0 (perfect discrimination). (37,38) SPSS 10.0 for Windows was used for all analyses.

## Results

Table 2.2.1 shows baseline characteristics of men and women with and without incident vertebral fractures. Both men and women with incident vertebral fractures had a lower BMD, more often had a history of fractures, both vertebral and non-vertebral, and tended to smoke more, even though this was not statistically significant in men. In addition, women with incident vertebral fractures were older, thinner, more frequently used a walking aid and had an earlier age at natural menopause. No differences in calcium intake, adjusted for caloric intake, were observed between subjects with and without incident vertebral fractures.

In a univariate analysis, incident vertebral fracture risk increased with age in women, but not in men (Table 2.2.2). Similarly, low body weight and small height were associated with increased incident vertebral fracture risk in women only. The presence of at least one prevalent vertebral fracture, however, was associated with an increased risk of new vertebral fractures in both genders, as was having had a prevalent non-vertebral fracture at or after age 50 years. As reported earlier, a low BMD at both the femoral neck and lumbar spine was associated with a strongly increased vertebral fracture risk. (30) Especially in men, the association with incident vertebral fractures appeared stronger for the site specific, lumbar spine BMD than for femoral neck BMD. Only in women, the use of a walking aid and a moderate or severe lower limb disability were univariate risk factors for incident vertebral fractures. Current smoking was associated with an increased vertebral fracture risk in both genders, although statistically significant in women only.

For women, several estrogen-related factors were univariate predictors for incident vertebral fractures. We stratified age at menopause into natural and non-natural menopause. Women in our cohort with a non-natural menopause (e.g. surgery) took HRT more often and longer (data not shown). Women with an early natural menopause, defined as an age at menopause at or before age 45, had a 2.7 times increased risk of an incident vertebral fractures, when compared with women who had their menopause above age 50.



Table 2.2.1. Baseline characteristic for men and women with and without incident vertebral fractures from the Rotterdam Study

	Men		Women	
	No incident vertebral fracture (n =1333)	Incident vertebral fracture (n =44)	No incident vertebral fracture (n =1511)	Incident vertebral fracture (n =113)
Age	65.2 (6.5)	66.3 (6.3)	65.7 (6.6)	68.6 (7.1)**
Weight	80.1 (10.5)	78.7 (10.2)	70.6 (10.7)	67.3 (11.9)**
Height	175.6 (6.8)	176.5 (7.8)	162.6 (6.4)	161.9 (7.1)
FN BMD	0.89 (0.12)	0.82 (0.10)**	0.83 (0.13)	0.75 (0.13)**
LS BMD	1.17 (0.19)	1.03 (0.18)**	1.01 (0.17)	0.93 (0.16)**
Calcium intake (g/day)	1161.5 (399.1)	1148.2 (340.9)	1107.5 (332.5)	1088.9 (304.8)
Smoking (%)				
<i>Current</i>	25.3 %	38.6 %	17.3 %	25.7 %*
<i>Former</i>	65.3 %	56.8 %	31.8 %	29.2 %
<i>Never</i>	9.4 %	4.5 %	51.0 %	45.1 %
Prevalent vertebral fracture (%)	6.5 %	20.5 %**	6.5 %	30.1 %**
Non-vertebral fracture $\geq$ age 50 years (%)	13.7 %	29.5 %**	21.7 %	30.1 %**
Use of walking aid (%)	2.6 %	2.3 %	3.2 %	9.7 %**
Age at natural menopause*	-	-	49.9 (4.4)	48.5 (4.8)**
HRT use (%)				
<i>Never</i>	-	-	57.7 %	70.0 %**
< 3 yr	-	-	26.6 %	17.3 %
$\geq$ 3 yr	-	-	15.7 %	12.7 %

Values are means with standard deviations or numbers with percentages

\*Spontaneous menopause not caused by any intervention

\*\* p-value < 0.05, \* p-value < 0.10

Table 2.2.2. Univariate analyses of potential risk factors for incident vertebral fractures

	Men		Women	
	Cases/ group	OR (95% CI)	Cases/ group	OR (95% CI)
Age (years)				
55-59	10/339	1 (reference)	11/366	1 (reference)
60-64	9/387	0.8 (0.3-2.0)	27/438	2.1 (1.0-4.3)**
65-69	11/330	1.1 (0.5-2.7)	28/366	2.7 (1.3-5.5)**
70-74	11/200	1.9 (0.8-4.6)	27/281	3.4 (1.7-7.0)**
75-79	3/90	1.1 (0.3-4.2)	13/128	3.6 (1.6-8.4)**
>= 80	0/31	DNC <sup>†</sup>	7/45	5.9 (2.2-16.2)**
Weight (quartiles)				
1 (lowest)	12/337	1.2 (0.5-2.9)	42/407	2.6 (1.5-4.7)**
2	10/353	1.0 (0.4-2.3)	31/402	1.9 (1.0-3.5)**
3	12/339	1.2 (0.5-2.8)	21/405	1.3 (0.7-2.4)
4	10/339	1 (reference)	17/406	1 (reference)
Height (quartiles)				
1 (lowest)	12/361	0.7 (0.3-1.5)	36/451	1.3 (0.8-2.2)
2	10/385	0.6 (0.2-1.2)	27/376	1.2 (0.7-2.1)
3	7/296	0.5 (0.2-1.2)	23/390	0.9 (0.5-1.7)
4	15/326	1 (reference)	25/403	1 (reference)
Baseline prevalent vertebral fracture				
None	35/1281	1 (reference)	79/1492	1 (reference)
>= 1	9/96	3.7 (1.7-7.9)**	34/132	6.2 (4.0-9.7)**
History of any non-vertebral fracture				
No	31/1150	1 (reference)	79/1262	1 (reference)
Yes	13/183	2.6 (1.4-5.1)**	34/362	1.6 (1.0-2.4)**
FN BMD (SD decrease)	43/1351	1.9 (1.3-2.6)**	108/1584	2.1 (1.7-2.6)**
LS BMD (SD decrease)	44/1377	2.6 (1.8-3.7)**	113/1624	2.2 (1.7-2.7)**
Use of a walking aid				
No	43/1342	1 (reference)	102/1564	1 (reference)
Yes	1/35	0.9 (0.1-6.6)	11/60	3.2 (1.6-6.4)**
Lower limb disability				
No	30/962	1 (reference)	50/878	1 (reference)
Moderate	6/178	1.1 (0.4-2.6)	29/393	1.4 (1.0-2.2)*
Severe	8/235	1.1 (0.5-2.4)	34/351	2.2 (1.1-4.6)**

Table 2.2.2. Univariate analyses of potential risk factors for incident vertebral fractures, continued

Smoking				
Current	17/354	3.1 (0.7-13.8)	29/290	1.7 (1.0-2.7)**
Former	25/896	1.8 (0.4-7.6)	33/513	1.0 (0.7-1.6)
Never	2/127	1 (reference)	51/821	1 (reference)
Recent falling				
No	33/1151	1 (reference)	90/1340	1 (reference)
Yes	3/86	1.2 (0.4-4.1)	23/281	1.2 (0.8-2.0)
Diabetes mellitus				
No	36/1119	1 (reference)	89/1349	1 (reference)
Yes	2/115	0.5 (0.1-2.2)	9/102	1.4 (0.7-2.8)
Age at <i>natural</i> menopause				
<= 45 yr	-	-	19/189	2.7 (1.6-4.6)**
46-50 yr	-	-	35/436	1.4 (0.8-2.2)
> 50 yr	-	-	31/513	1 (reference)
<i>Non-natural</i> menopause	-	-	19/486	0.6 (0.4-1.1)
Use of hormone replacement therapy (HRT)				
Never	-	-	77/917	1 (reference)
< 3 years	-	-	19/406	0.5 (0.3-0.9)**
>= 3 years	-	-	14/243	0.7 (0.4-1.2)
Ever use of oral contraceptives				
No	-	-	87/1021	1 (reference)
Yes	-	-	25/374	0.5 (0.3-0.8)**

\*\* P &lt; 0.05; \* p &lt; 0.10

†DNC = did not compute (due to lack of cases in this subgroup)

Women with a non-natural menopause had a somewhat decreased vertebral fracture risk. The use of HRT and OC were also univariately associated with a decreased vertebral fracture risk. Furthermore, the use of several other types of medications at baseline (diuretics, systemic glucocorticoids, thyroid hormone and statins) was evaluated in relation to incident vertebral fractures, but due to lack of power no significant associations were observed with incident vertebral fractures (data not shown).

Univariately significant risk factors were evaluated for independence from age. In women, the risk of an incident vertebral fractures in women with at least one baseline prevalent vertebral fracture decreased from 6.2 to 5.3, but remained statistically significant. Similarly, the OR for use of a walking aid at baseline

decreased, but remained significant. In contrast to men, a history of a non-vertebral fracture at or after age 50 was no longer a risk factor for incident vertebral fractures in women. In addition, a lower limb disability and the use of HRT or OC were no longer associated with increased vertebral fracture risk in women, suggesting that these factors may be merely markers for older age only in women.

We tested whether risk factors were independent of lumbar spine BMD and additionally of the presence of baseline prevalent vertebral fractures. When adjusting for BMD, weight was no longer a risk factor for incident vertebral fractures. For the association between the presence of a baseline prevalent vertebral fracture and incident vertebral fractures, however, ORs dropped from 3.6 [1.7-7.8] after adjusting for age, to 2.4 [1.1-5.4] after additionally adjusting for BMD in men. In women, a similar effect was observed (OR 5.4 [3.4-8.5] and 4.7 [2.9-7.6], respectively). The risk of an incident vertebral fracture in women with an early menopause decreased from 2.5 [1.4-4.3] after adjustment for age to 2.1 [1.2-3.7] after additional adjustment for BMD. All risk factors that were independent from BMD were also independent from the presence of a baseline prevalent vertebral fracture.

Finally, all remaining risk factors were entered into a multivariate model (Table 2.2.3). For women, age, low BMD, the presence of a prevalent vertebral fracture at baseline, use of a walking aid, (natural) menopause before or at age 45 and current smoking at baseline were all strong, independent risk factors for incident vertebral fractures. For men, only a low BMD and prevalent non-vertebral and vertebral fractures were independent risk factors for incident vertebral fractures, even though the presence of prevalent vertebral fractures was only borderline significant now, due to a low number of cases.

Table 2.2.4 shows attributable risks and population attributable risks for all independent risk factors. For men, low LS BMD contributed to 77.8% of incident vertebral fracture cases amongst all men with low BMD and was involved in the pathogenesis of 25% of all vertebral fracture cases in the total male study population. Similarly, in women low BMD contributed to 68.8% of cases in women with a low BMD, and was involved in the pathogenesis of 32.9% of all incident vertebral fracture cases in the general population. In terms of (population) attributable risks, low BMD and the presence of baseline prevalent vertebral fractures have the highest impact on the etiology of incident vertebral fractures in both men and women. Figure 2.2.1 shows the ROC curves for three models for incident vertebral fracture prediction for men and women separately. The first model includes only easily assessable risk factors, namely age, weight, current smoking, use of a walking aid, a history of prevalent non-vertebral fractures at or after age 50 years and, for women, age at menopause. The second model includes only BMD and the presence of a baseline prevalent vertebral fracture, whereas the third model includes all of these variables. In addition, table 2.2.5 shows the corresponding areas under the curves.

Table 2.2.3. Multivariate model of independent risk factors for incident vertebral fractures

	Men	Women
	Full model OR (95 % CI) <sup>†</sup>	Full model OR (95 % CI) <sup>†</sup>
Age (years)		
55-59	1	1
60-64	0.8 (0.3-1.9)	1.8 (0.9-3.8)
65-69	1.0 (0.4-2.5)	2.0 (1.0-4.3)*
70-74	1.9 (0.7-4.8)	2.2 (1.1-4.7)**
75-79	1.5 (0.4-6.2)	2.4 (0.9-5.9)*
>= 80	DNC <sup>‡</sup>	2.6 (0.8-8.5)
Baseline prevalent vertebral fracture		
None	1 (reference)	1 (reference)
>= 1	2.2 (0.9-5.0)*	4.1 (2.5-6.7)**
History of any non-vertebral fracture		
No	1 (reference)	1
Yes	2.4 (1.2-4.8)**	1.1 (0.7-1.8)
LS BMD (SD decrease)	2.3 (1.6-3.3)**	2.1 (1.6-2.6)**
Use of a walking aid		
No	1 (reference)	1 (reference)
Yes	1.0 (0.1-8.7)	2.5 (1.1-5.5)**
Age at <i>natural</i> menopause		
<= 45 yr	-	1.9 (1.1-3.5)**
46-50 yr	-	1.3 (0.7-2.2)
> 50 yr	-	1 (reference)
<i>Non-natural</i> menopause	-	0.7 (0.4-1.3)
Smoking		
Current	2.3 (0.5-10.5)	2.1 (1.2-3.5)**
Former	1.6 (0.4-6.9)	1.2 (0.7-2.0)
Never	1 (reference)	1 (reference)

<sup>†</sup>Multivariate model, adjusted for age, lumbar spine BMD, presence of a prevalent vertebral fracture, history of any non-vertebral fracture at or after age 50 years, age at menopause (for women only) and smoking habits. \*\* P < 0.05; \* p < 0.10

<sup>‡</sup>DNC = did not compute (due to lack of cases in this subgroup)

**Table 2.2.4. Attributable risk percentages and population attributable risk percentages for independent risk factors for incident vertebral fractures**

	Men			Women		
	OR <sup>†</sup>	AR (%)	PAR (%)	OR <sup>†</sup>	AR (%)	PAR (%)
Age >= 70	1.6	37.5 %	12.5 %	1.9	47.4 %	20.0 %
Prevalent vertebral fracture	3.4	70.6 %	15.6 %	5.3	81.1 %	24.3 %
Non-vertebral fracture >= age 50 yr	2.7	63.0 %	18.8 %	1.4	28.6 %	10.0 %
Lumbar spine T-score <= -2.5	4.5	77.8 %	25.0 %	3.2	68.8 %	32.9 %
Age at menopause <= 45	-	-	-	2.5	60.0 %	14.3 %
Walking aid use	0.9	0 %	0 %	2.4	58.3 %	7.1 %
Current smoking	3.3	69.7 %	50 %	2.3	56.7 %	11.4 %

<sup>†</sup>All odds ratio's (except for age over 70) were adjusted for age

AR = Attributable risk

PAR = Population attributable risk

Figure 2.2.1. ROC curves for incident vertebral fractures in men and women

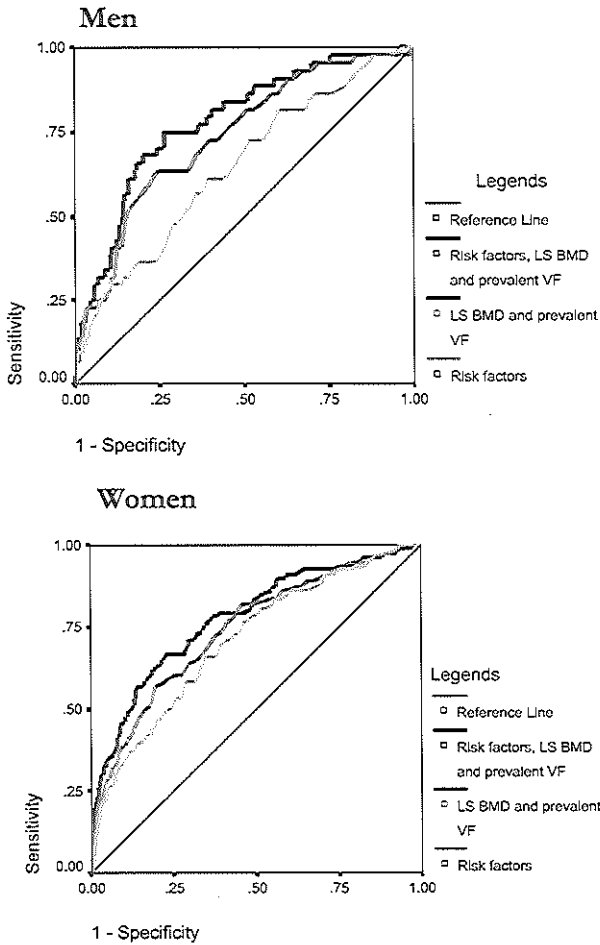


Table 2.2.5. Areas under the curves for men and women

	Men	Women
Model 1	0.65 (0.56-0.73)	0.71 (0.66-0.76)
Model 2	0.74 (0.66-0.81)	0.74 (0.69-0.79)
Model 3	0.78 (0.71-0.85)	0.78 (0.73-0.83)

Model 1 includes age, weight, current smoking, use of a walking aid, history of prevalent non-vertebral fractures at or after age 50 years and, for women, age at menopause. Model 2 includes BMD and the presence of prevalent vertebral fractures at baseline. Model 3 includes age, weight, current smoking, use of a walking aid, history of prevalent non-vertebral fractures at or after age 50 years

and, for women, age at menopause, as well as BMD and the presence of prevalent vertebral fractures at baseline.

Overall, both for men and for women, incident vertebral fracture prediction was strongest when combining all factors. In women, however, the clinical risk factors alone also provided a relatively good prediction model. For men, vertebral fracture prediction was much improved when (additional) information on BMD and prevalent vertebral fractures was present. This could be expected since in men, only a history of non-vertebral fractures was a significant risk factor for incident vertebral fracture.

## **Discussion**

In a previous study we have already shown that a low BMD and the presence of at least one baseline prevalent vertebral fracture are strong independent risk factors for incident vertebral fractures in both men and women. (20) In the present study we observed that age, current smoking, use of a walking aid and an early menopause are also strong, independent risk factors for incident vertebral fractures in women. In men, only a history of a prevalent non-vertebral fracture is an additional significant risk factor for incident vertebral fractures.

In the present study, our aim was to investigate potential risk factors for incident vertebral fractures. Those risk factors investigated are known risk factors for a low BMD, hip fractures or both. (11,13,15,17,19,34,39) To our knowledge, so far no studies on risk factors for incident vertebral fractures were performed, other than low BMD, prevalent vertebral fractures and physical activity. (21,22) Some cross-sectional studies on risk factors for prevalent vertebral fractures have been performed, but due to the cross-sectional design it is difficult to draw conclusions on causality and temporal relationships from these studies. (23-31)

In contrast to hip fractures, vertebral fractures mainly occur spontaneously. (40,41) Therefore, it was not surprising that recent falling before baseline was not associated with increased vertebral fracture risk. In addition, a lower limb disability was no longer associated with increased vertebral fracture risk after adjustment for age, suggesting that lower limb disability is merely a marker for older age.

In women, but not in men, incident vertebral fractures risk increased strongly with age. Cross-sectional data from the EVOS study already suggested that age was more strongly associated with prevalent vertebral fractures in women than in men. (42) The lack of association between increasing age and incident vertebral fractures in men is probably related to selective survival. To be eligible for this



study, subjects had to visit our research center for the second follow-up examination, resulting in a health selection bias. Men have a lower life expectancy than women do and vertebral fractures are associated with increased mortality. This could imply that primarily the older men with vertebral fractures would no longer be in our study, resulting in selection of healthier elderly men.

The effects of estrogen on bone are well established. (43-45) This study strengthens the importance of estrogen exposure further by showing that an early age at menopause is associated with an increased incident vertebral fracture risk. This effect appears limited to women whose age at menopause was before or at age 45 years, which was 11 percent of the whole female population. Women with a non-natural menopause more often took HRT, thereby supplementing their estrogen deficiency. Long-term and short-term HRT use and oral contraceptive use were all univariately associated with a decreased incident vertebral fracture risk, but these associations disappeared after adjusting for age. In the Netherlands oral contraceptives were not frequently prescribed until the mid sixties, resulting in only the younger women in our cohort ever using these drugs.

The impact of the risk factors described on overall vertebral fracture incidence was evaluated by calculating both attributable risks and population attributable risks. In comparison, Hak et al. recently reported that in women from the Rotterdam Study, the population attributable risks of hypercholesterolemia and hypertension in myocardial infarction were 18 % and 14 %, respectively. (46) Thus, many of the risk factors studied here have more impact on the pathogenesis of incident vertebral fractures than either hypercholesterolemia or hypertension have on myocardial infarction.

Overall, for both men and women, a model including both easily assessable risk factors, BMD and presence or absence of prevalent vertebral fractures best predicted incident vertebral fractures. For women, however, a model including only easily assessable risk factors resulted in approximately the same predictive value for incident vertebral fractures as known cardiovascular risk factors have in the prediction of cardiovascular and cerebrovascular disease (area's were 0.71 and 0.72, respectively). (37) This suggests that these risk factors might be used in a clinical setting as a first screening tool for incident vertebral fracture risk. On basis of the outcome of such a risk score, it can be assessed whether measuring BMD would be of additional value.

There are limitations to this study. Even though this is a large single-cohort population-based study, some health selection bias is present, as mentioned. In contrast to other types of fractures, vertebral fractures primarily occur spontaneously and only about one third of subjects has such complaints that they will come to clinical attention. (40,41) Thus, the only way to investigate all

incident vertebral fractures is to examine baseline and follow-up radiographs of the spine. Therefore, a selection bias is unavoidable in studies on incident vertebral fractures. Due to this selection bias, the subjects included in our study may not be representative for all subjects with vertebral fractures in the general population.

In conclusion, the results of this study show that in women, besides low BMD and the presence of baseline prevalent vertebral fracture, age, early menopause (at or below age 45), current smoking and use of a walking aid are strong and independent risk factors for incident vertebral fractures. In men, only a positive history of non-vertebral fractures is an additional independent risk factor. Current smoking was associated with an increased vertebral fracture risk, but in men this did not reach statistical significance.

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## *Chapter 3*

### *Value of the T-score in fracture prevention*



## *Chapter 3.1*

*Limits to the WHO  
definition of osteoporosis:  
the prevention paradox revisited*

## Abstract

Osteoporosis is defined by the World Health Organization as a bone mineral density (BMD) of 2.5 standard deviations or more below the young adult mean (T-score of  $-2.5$  or less).

We studied the sensitivity of using a T-score at or below  $-2.5$  in order to identify subjects who will fracture in 3357 women aged 55 years and over from the population-based Rotterdam Study. BMD of the femoral neck was measured by dual X-ray energy absorptiometry (DXA, Lunar, DPX-L). T-scores of BMD were calculated for women using the NHANES reference population. Follow-up of fractures was conducted by regularly checking the GPs patient records. Information on vertebral fractures was gathered by a morphometrical evaluation of both follow-up and baseline radiographs of the thoracolumbar spine. In total, 517 non-vertebral fractures and 120 vertebral fractures occurred during an average follow-up of 6.7 years for non-vertebral fractures and 6.3 years for vertebral fractures. Overall, two thirds of all fractures occurred in women with a T-score above  $-2.5$ . For hip fractures only, half of all fractures occurred in women with a T-score above  $-2.5$ .

Thus, although using a T-score of  $-2.5$  SD will help to identify individuals at high fracture risk, overall most fractures occur above this value. The public health burden of fractures will not be relieved using the current criterion for osteoporosis.



## **Introduction**

A working group of the World Health Organization (WHO) has defined osteoporosis as a bone mineral density of 2.5 standard deviations or more below the average bone mineral density in young adult women (the T-score).(1) This cut-off value was originally intended for diagnostic purposes only, and not, as is common practice nowadays, to be used as a treatment threshold. Given this development there is a clear need to investigate what the consequence of this approach will be for the reduction of the population burden of osteoporotic fractures.

Therefore, we studied the sensitivity of using a T-score at or below  $-2.5$  in order to identify subjects who will fracture in 3357 women aged 55 years and over from the population-based Rotterdam Study.

## **Methods**

At baseline, between 1990 and 1993, bone mineral density was measured at the femoral neck by DXA (Lunar DPX-L). From the bone mineral density, T-scores were calculated using the NHANES reference population. (2) Peak bone mass, as converted to Lunar values, was  $1.04 \text{ g/cm}^2$  (SD 0.14). The absolute bone mineral density cut-off value for osteoporosis (T-score =  $-2.5$ ) was  $0.69 \text{ g/cm}^2$ . The occurrence of incident non-vertebral fractures was continuously monitored through general practitioners. Each reported event was independently validated. All non-vertebral fractures were coded according to 10<sup>th</sup> revision of the International Classification of Diseases independently by two research physicians. If there was disagreement, consensus was reached in a separate session. A medical expert in the field reviewed all coded events for a final classification. During an average follow-up of 7.2 years, 517 women suffered at least one non-vertebral fracture.

For vertebral fractures, spinal radiographs were obtained at baseline and again after an average follow-up of 6.3 years. The follow-up radiographs were scored for vertebral fractures using the McCloskey-Kanis assessment method.(3) Whenever a vertebral fracture was detected the radiograph was compared with the baseline radiograph. If this fracture was not present at baseline, it was considered an incident fracture. Data on vertebral fractures were available for a subset of 1785 women, 120 of which suffered an incident vertebral fracture.

## **Results**

Figure 3.1.1 shows the prevalence of osteoporosis and osteopenia for women from the Rotterdam Study. Overall, the prevalence of osteoporosis in the Rotterdam Study was 16.9 % for women. The prevalence of osteoporosis increased with age, reaching 41.9 % in women aged 85 years or over.

randomized controlled trials have shown a 50% risk reduction with both hip and vertebral fractures for bisphosphonates. (5-11) In addition, several other therapeutical options for fracture prevention are available, such as hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs). (12-16) However, as the high-risk group of individuals with osteoporosis constitutes only 15 % of the population over 55 years, reducing the incidence of fractures in that group only will not be sufficient to adequately relieve the public health burden of fractures.

This study shows that using only a T-score at or below  $-2.5$  SD as a criterion for interventions will unfortunately not resolve the population burden of fractures. There is a clear need for the development of more sensitive risk tools, using not only bone mineral density, but also other clinical predictors of for fractures. Using such an approach, we might be able to more accurately identify those subjects who are at risk for fractures.

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## *Chapter 3.2*

### *Osteoporosis in men and women*

*a story about  
bone mineral density  
thresholds and fracture risk*

## Abstract

In post-menopausal women, the T-score for bone mineral density (BMD) is a well-accepted diagnostic criterion for osteoporosis. It is also used to assess fracture risk. It is unclear, however, whether in elderly men similar BMD thresholds should be used. Different hypotheses have been proposed for the relation of BMD with hip fracture risk in men. In this study we tested those hypotheses using a mathematical model and we compared the calculated results with observed prospective data from the Rotterdam Study. In the model, we combined the observed femoral neck BMD distribution for men and women with previously derived hip fracture risk functions based on age and BMD. For men, we tested different hypotheses for the relation of BMD with hip fracture risk. Either, the relation of BMD with hip fracture risk is similar in men and women (scenario 1), or the relative risk (RR) per standard deviation (SD) decrease of BMD is either larger or smaller in men than in women (scenario 2a and 2b), or at a similar absolute fracture risk, men have a higher BMD (scenario 3). In the prospective data men with a hip fracture had an average BMD that was  $0.070 \text{ g/cm}^2$  higher than women with a hip fracture. The calculated results from the first scenario were consistent with those data and were also consistent with the observed hip fracture incidence and the observed female to male (F/M) risk ratio (1.7). When the RR for each SD decrease of BMD was assumed to be either larger or smaller in men than in women (second scenario) the calculated average BMD difference in men and women became respectively smaller or larger than observed. When men would have a higher fracture risk at similar BMD levels (third scenario), the calculated total number of hip fractures increased and even exceeded that in women, with a F/M risk ratio of 0.94 in our example. In women a larger proportion of hip fractures occurs at a T-score below  $-2.5$  than in men using the same absolute BMD threshold, but using a male specific T-score largely solves this diagnostic problem. Taken together, the average hip fracture risk in men is much lower than in women, but appeared to be similar at the same BMD. Therefore, we propose the use of the same absolute BMD thresholds for decisions about interventions.

## Introduction

Osteoporotic fractures and mainly hip fractures cause major morbidity and mortality in the elderly. (1) Consequently, fractures generate substantial costs due to acute hospital treatment and subsequent rehabilitation. (2,3) Most of those fractures occur in women since they have a higher incidence of fractures at any given age and because of their higher life expectancy. (4) Therefore, most attention in hip fracture prevention was focused on women and only few epidemiological studies have investigated osteoporosis and fractures in men. (5-7) Recently, however, osteoporotic fractures in men have attracted more attention, also in intervention trials. (8-10) Even though the societal burden is smaller, osteoporotic fractures also have an important impact on men. Therefore, it is necessary to develop diagnostic and intervention standards for men.

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. (11) For diagnostic purposes osteoporosis in women was defined as a bone mineral density (BMD) of 2.5 standard deviations (SD) below the average for young adult women, the so-called T-score. (12)

There is uncertainty about how this definition should be used in men. Should the same T-score be used in men based on female reference values or should a gender-specific T-score be calculated, based on the BMD in young adult men and if so what are the appropriate thresholds? This debate was recently summarized in a review article published in this journal. (13) Some studies have suggested that men fracture at the same absolute BMD level as women do, (4,5,13,14) and that therefore the same absolute BMD threshold should be used. Other studies suggest a relation between BMD and hip fracture risk that is different in men and women. (13,15,16) Orwoll pointed out that in most studies on fracture patients, men have, on average, a higher BMD than women. (13) At first sight this appears to be at odds with a relation between BMD and fracture risk that is similar in men and women.

We studied whether the relation of BMD with hip fracture risk is similar in men and women, whether the gradient of risk per SD lower BMD is either higher or lower or whether men have a similar hip fracture risk at a higher BMD than women. We have approached this question by mathematical modeling, combining the different hip fracture risk assumptions with the known BMD distribution in men and women to calculate the hip fracture distribution by BMD. Subsequently we compared the calculated results with observed prospective data from the Rotterdam Study. We also used the results to discuss diagnostic and intervention BMD thresholds in men.

## Methods

### *Input data*

In a mathematical model we combined the relation of BMD and hip fracture risk with the BMD distribution to calculate the hip fracture distribution by BMD in the population. Previously, we estimated the hip fracture risk by gender, age and BMD, based on Dutch hip fracture registration data and the distribution of BMD. (4) The resulting risk functions (one-year cumulative hip fracture incidence) were validated over almost 4 years of follow-up in the prospective part of the Rotterdam Study. (5) This is a population-based prospective cohort study of the occurrence and determinants of disease and disability in 7983 elderly men and women in a suburb of Rotterdam, the Netherlands. Aims and design of this study were described previously. (17)

We also used the BMD distributions for men and women observed cross-sectionally in the Rotterdam Study in a sample of 5814 independently living men and women aged 55 years and over. (4) BMD was measured at the femoral neck using a Lunar DPX-L densitometer.

The model was developed using an Excel spreadsheet (Microsoft Corp. USA). Calculations were made for several ages between 65 and 80 years and results are described for age 70. We have chosen this age because at 70 the hip fracture risk begins to increase rapidly.

### *Modeling assumptions*

The baseline hip fracture risk functions by age, gender and BMD were described previously. (4,5) These risk functions show an exponential increase in hip fracture risk with lowering BMD and additionally an increase in risk with aging. The curves for men and women (at the same age) almost overlap. For women we used the baseline risk function. For men we used different scenarios reflecting the different hypotheses about the relation of BMD with hip fracture risk in men.

### **Scenario 1**

In scenario 1 we used the baseline risk function for men. In this scenario the relative risk (RR) for hip fracture per SD decrease in BMD is 2.6 for both men and women while the absolute risk level by BMD is very similar. (4)

### **Scenario 2**

In scenario 2 the risk function was modified to reflect either a higher or lower RR per SD decrease in BMD in men. Arbitrarily, we choose a RR of either 3.6 or 1.6 for men in this second scenario and they will be referred to as scenario 2a and 2b.

### **Scenario 3**

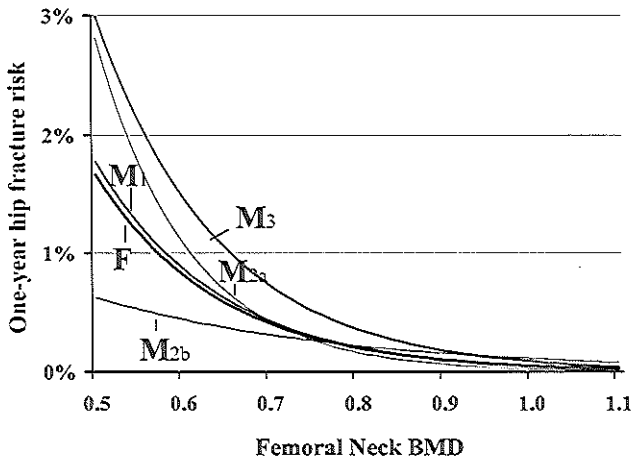
In scenario 3 the RR was assumed to be the same in men as in women but now the relation of BMD with fracture risk was shifted so that men had a similar



fracture risk at a BMD level  $0.070 \text{ g/cm}^2$  higher than in women. This shift corresponds to the average BMD difference between men and women at the same age. (4)

The relation of femoral neck BMD with the one-year hip fracture risk at age 70 for women and for the different scenarios in men is shown in-figure 3.2.1.

**Figure 3.2.1. One-year hip fracture risk by femoral neck BMD at age 70 in women (F), and for the three different scenarios in men (similar risk M1, higher or lower RR per SD M2a and M2b, or a higher risk at the same BMD M3).**



#### *Number of Hip Fractures*

From the BMD distribution at a given age we derived the proportion of the population at a specific BMD level. Next, we calculated the hip fracture risk that corresponds to this BMD level, as shown in figure 3.2.1. Finally, we multiplied the proportion of the population at a specific BMD level with the corresponding hip fracture risk to obtain the number of hip fractures at that specific BMD level. When this was done across the whole range of BMD values, we obtained the distribution of hip fractures. The sum of all these values corresponds to the one-year cumulative incidence at that age.

In women at age 70, for example, about 3% have a BMD of exactly  $0.80 \text{ g/cm}^2$ . This BMD corresponds to a one-year hip fracture risk of 0.2%. The calculated number of fractures, at age 70, contributed by women with a BMD of  $0.80 \text{ g/cm}^2$  was therefore 0.006% ( $3\% * 0.2\%$ ). When the same was done for all BMD values the total 1-year incidence for women at age 70 became 0.31% or 3.1/1000.

*Comparison with observed data*

We compared these distributions to the observed prospective data to determine which of the different scenarios are possible. Femoral neck BMD was measured at baseline between 1990 and 1993 and hip fracture follow-up was obtained as described previously. (5,18) For this analysis, follow-up started at the time of BMD measurement and ended either at the time of hip fracture, death or December 31, 1999, whichever occurred first.

We also used the hip fracture distributions to examine diagnostic and intervention BMD thresholds in men. To do this, we calculated at which threshold of BMD a similar proportion of hip fractures would be captured in men as would be in women at a T-score of -2.5.

**Results***Observed BMD in Hip Fracture cases and controls in the Rotterdam Study*

Valid hip fracture follow-up in individuals with femoral neck BMD measured at baseline was available for 5794 participants, and 156 hip fractures occurred during an average follow-up of 7 years (range 0.01 - 9.4). The average baseline BMD in men and women with and without hip fractures during follow-up is given in table 3.2.1. Average BMD was 0.070 g/cm<sup>2</sup> (95 % CI: 0.025-0.115) higher in male fracture cases than in females, and an almost similar difference of 0.065 g/cm<sup>2</sup> (0.058-0.072) was observed in controls.

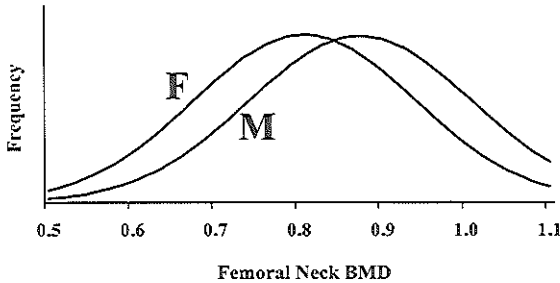
**Table 3.2.1. Observed average baseline femoral neck BMD (g/cm<sup>2</sup>) in men and women with and without hip fracture during follow-up.**

	Men		Women	
	Hip fracture	No hip fracture	Hip fracture	No hip fracture
Number	36	2401	120	3237
Average BMD	0.768	0.878	0.698	0.813
95 % CI	(0.739-0.797)	(0.872-0.883)	(0.675-0.721)	(0.808-0.817)

*Observed BMD distributions and Hip Fracture incidence rates*

Figure 3.2.2 shows the femoral neck BMD distribution for women and men aged 70 based on data from the Rotterdam Study. (4) The average BMD at age 70 was 0.802 g/cm<sup>2</sup> in women and 0.869 g/cm<sup>2</sup> in men. In Dutch national registration data the observed one-year cumulative hip fracture incidence at age 70 was 3.2/1000 in women and 1.9/1000 in men, and the female to male fracture incidence ratio was 1.7. (4)

Figure 3.2.2. The distributions of femoral neck BMD in men (M) and women (F) at age 70.



#### *Calculated Hip Fracture distributions by BMD*

The calculated hip fracture distributions at age 70 for women and for the different scenarios in men are shown in figure 3.2.3 and detailed results for all ages are shown in table 3.2.2. For women the calculated average femoral neck BMD in female fracture cases at age 70 was  $0.679 \text{ g/cm}^2$  and the calculated one-year hip fracture incidence was  $3.1/1000$ .

#### **Scenario 1**

Using the baseline scenario in men (similar fracture risk in men as in women, see figure 1), the calculated average BMD in 70 year old male fracture cases was  $0.743 \text{ g/cm}^2$ . This was  $0.064 \text{ g/cm}^2$  higher than in women. The calculated one-year incidence in men was  $1.9/1000$  and the female to male risk ratio was 1.7.

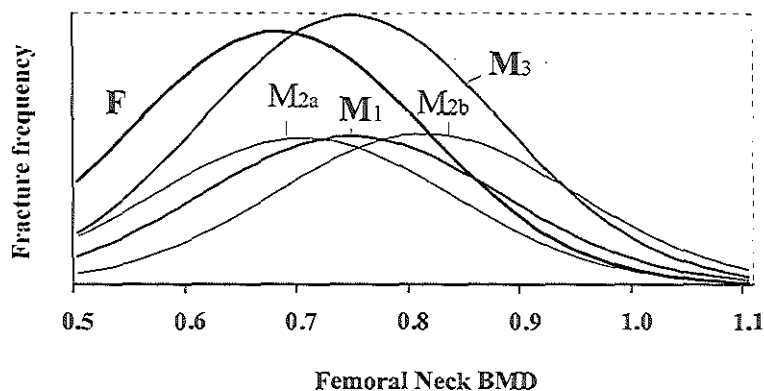
#### **Scenario 2**

In scenario 2a, assuming a higher RR in men than in women (RR 3.6 versus 2.6), the distribution of hip fractures by BMD in men shifts to the left, and the calculated average BMD at age 70 was only  $0.021 \text{ g/cm}^2$  higher than in women. In scenario 2b, assuming a lower RR in men (RR 1.6 versus 2.6) the average BMD difference at age 70 was  $0.126 \text{ g/cm}^2$ . With both assumptions the female to male ratio was 1.7.

#### **Scenario 3**

In the third scenario we assumed that the relation of BMD with fracture risk was shifted to the right in men by  $0.070 \text{ g/cm}^2$  and that the RR was similar in men and women. Here, the calculated average BMD in fracture cases was higher in men than in women and the same as in scenario 1. But, in scenario 3 the calculated number of hip fractures at the age of 70 increased to  $3.3/1000$ , exceeding that in women and the female to male incidence ratio was only 0.94.

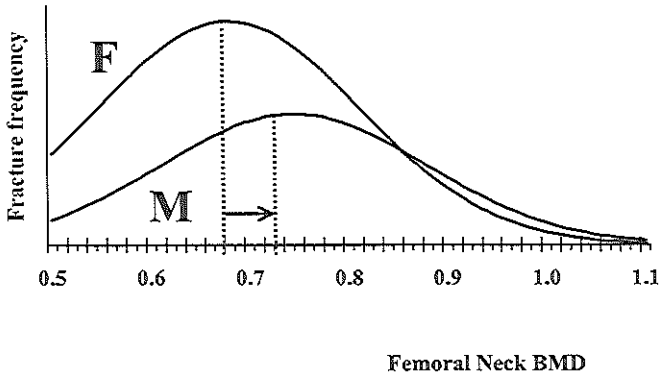
Figure 3.2.3. Hip fracture distribution by femoral neck BMD at age 70 in women (F), and for the three different scenarios in men (similar risk M1, higher or lower RR per SD M2a and M2b, and a higher risk at the same BMD M3).



*Hip fractures and BMD thresholds: men compared to women*

Figure 3.2.3 shows that for all scenarios, the proportion of fractures occurring below any specific BMD value was higher in women than in men. In figure 3.2.4 this is illustrated for a female T-score of -2.5 comparing the calculated hip fracture distributions at age 70 for women and for the first scenario in men. The bone densities measured in our female population corresponded to the Lunar US Female Reference Data Base used by the machine (Lunar Corp, Madison, WI, USA), and a female-specific T-score of -2.5 corresponded to a BMD of  $0.675 \text{ g/cm}^2$ . In the model, half of the hip fractures in women occurred at or below this threshold at the age of 70. Using the same absolute BMD value in men only 32 % of the hip fractures were captured. If we wanted a threshold that also captures half of the hip fractures in men the threshold needed to move upward and became  $0.740 \text{ g/cm}^2$ . Based on female reference values this corresponded to a T-score of -2.0, but using male reference data this corresponded to a T-score of -2.7. With a male specific T-score equaling -2.5 ( $0.769 \text{ g/cm}^2$ ) almost 60 % of the hip fractures were captured.

Figure 3.2.4. BMD threshold that captures the same proportion of hip fractures in men (M) as a T-score=-2.5 in women (F).



#### *Other ages*

The above results were described for men and women aged 70. Table 3.2.2 also gives these results at other ages. At those other ages we obtained similar results but at other levels of absolute incidence and average BMD. The general conclusions, however, are similar to those at age 70.

#### **Discussion**

In participants from the Rotterdam Study who suffered a hip fracture during follow-up, the average baseline BMD was 0.070 g/cm<sup>2</sup> higher in men than it was in women. Assuming a similar relation between femoral neck BMD and hip fracture risk in men and women the difference in the calculated average BMD was almost the same in the model. Moreover, the results were also consistent with the observed hip fracture incidence in the Netherlands and with the observed female to male (F/M) risk ratio of 1.7. (4)

Table 3.2.2. Women compared to men at different ages: calculated average femoral neck BMD ( $\text{g}/\text{cm}^3$ ) in hip fracture cases, calculated one-year hip fracture incidence (/1000), female to male (F/M) hip fracture incidence ratio and proportion of hip fractures occurring at or below a female T-score of -2.5.

	Age							
	65 yr				70 yr			
	Mean BMD	Inc.	F/M	T<-2.5	Mean BMD	Inc.	F/M	T<-2.5
<b>Women</b>	0.70	1.6		44%	0.68	3.1		50%
<b>Men</b>								
<i>Scenario 1 (RR=2.6)</i>	0.76	0.96	1.7	28%	0.74	1.9	1.7	32%
<i>Scenario 2a (RR=3.6)</i>	0.72	0.96	1.7	39%	0.70	1.8	1.7	44%
<i>Scenario 2b (RR=1.6)</i>	0.82	0.95	1.7	14%	0.81	1.9	1.7	17%
<i>Scenario 3</i> <i>(shifted 0.07 g/cm<sup>3</sup>)</i>	0.76	1.7	0.92	28%	0.74	3.3	0.94	32%

	Age							
	75 yr				85 yr			
	Mean BMD	Inc.	F/M	T<-2.5	Mean BMD	Inc.	F/M	T<-2.5
<b>Women</b>	0.66	5.9		57%	0.63	10.5		64 %
<b>Men</b>								
<i>Scenario 1 (RR=2.6)</i>	0.73	3.4	1.7	36%	0.71	6.0	1.7	40%
<i>Scenario 2a (RR=3.6)</i>	0.69	3.4	1.7	48%	0.67	6.0	1.8	53%
<i>Scenario 2b (RR=1.6)</i>	0.79	3.4	1.7	20%	0.78	6.1	1.7	23%
<i>Scenario 3</i> <i>(shifted 0.07 g/cm<sup>3</sup>)</i>	0.73	6.2	0.95	36%	0.71	10.9	0.96	40%

When we assumed that the RR per SD decrease in BMD was either higher or lower in men than in women, the calculated difference in average BMD was respectively smaller or higher than observed. Therefore, we consider this hypothesis less likely and, even if the RR is different in men and women, this difference can only be small

Assuming that men have a similar hip fracture risk at a higher BMD the calculated incidence of hip fractures seriously increased and the female to male hip fracture risk ratio even reversed. This does not correspond to observations in the Netherlands and in most other countries, (4,5,19) making this third scenario highly unlikely.

When we repeated the calculations at ages other than 70 we confirmed that the scenario where the relation of BMD with hip fracture risk is very similar in men and women is the most consistent with the prospective observations in our population.

This conclusion is important for the definition of a BMD threshold in men. We illustrated this using a T-score of -2.5, the agreed definition of osteoporosis in women. (12) In women at age 70, only half of the hip fractures occurred below that threshold. This is so because hip fractures also occur in women who do not have osteoporosis. At the age of 70 this group of non-osteoporotic women is relatively large. With aging the proportion of women with a T-score below -2.5 increases and as a consequence the calculated proportion of hip fractures occurring below that threshold also increased up to 64% at the age of 80 (table 3.2.2). In men, using the same absolute BMD threshold, the proportion of hip fractures below that female specific value was much lower.

Capturing a similar proportion of fractures in a population is important if we have the intention to evenly reduce the burden of illness in both men and women. Our analyses show that, whatever the proportion of fractures we want to capture, the absolute BMD cutoff value will always be higher in men than in women. The use of a gender-specific T-score largely solves this diagnostic problem. (12)

However, when cost-effectiveness of interventions is the goal, and assuming equal efficacy in men and women, absolute fracture risks are more important since the numbers needed to treat with an intervention are directly influenced by the fracture incidence in those in whom an intervention is undertaken. This is demonstrated in intervention trials where including populations with a different fracture incidence leads to different numbers needed to treat even with the same intervention. (20,21) Since men have a lower hip fracture incidence than women, fewer men than women reach the required fracture risk threshold to make an intervention cost-effective. Therefore, when cost-effectiveness is the main





# *Chapter 4*

## *Bone mineral density and morbidity*



## *Chapter 4.1*

### *Bone mineral density and the risk of peripheral arterial disease:*

*The Rotterdam Study*

## Abstract

Low estrogen exposure throughout life is thought to result in low bone mineral density (BMD) and an increased incidence of cardiovascular disease. In the Rotterdam Study, we cross-sectionally examined the relation between BMD and peripheral arterial disease (PAD), as assessed by an ankle-arm index (AAI) of < 0.9 in either leg. Data on BMD and PAD were available for 5268 individuals (3053 women). From the BMD, Z-scores were calculated, which were subsequently divided into tertiles. Logistic regression analysis was used to compute odds ratios (OR) for PAD in tertiles of BMD, using the upper tertile as a reference. When adjusting for age, women with a low femoral neck BMD had a significantly increased risk of PAD (OR = 1.49, 95% CI 1.16-1.91). This could not be found for men (1.14, 0.84-1.53). The mid tertile did not differ from the reference in either men or women. In women, additional adjustment for several potential confounders resulted in a somewhat lowered risk estimate (1.35, 1.02-1.79). In contrast, no association between lumbar spine BMD and PAD could be observed in either men or women. Our study shows an association between low femoral neck BMD and PAD in women only. This association is unlikely to be causal. Estrogen deficiency may be the common denominator in osteoporosis and PAD, resulting in clustering of these two major diseases in postmenopausal women.

## **Introduction**

Recently, an association between osteoporosis and atherosclerosis, two frequent diseases of the elderly has been suggested in women. (1-6) Since both osteoporosis and atherosclerosis share major risk factors such as low estrogen exposure, low physical activity, body mass index and smoking, it is relevant to study these common etiological factors. These factors may at least in part explain the suggested relation between these two major diseases.

In women, the association between bone mineral density (BMD) and atherosclerosis at different sites has been investigated in several studies, (1,2,4-6) whereas in men only one small study has been performed. (3)

In elderly women, Vogt et al. found that after adjusting for age, BMD decreased with a decreasing ankle-arm index (AAI). (4) However, after additional adjustment for smoking and body mass index this relationship disappeared. In addition, women with a decrease in AAI during a year lost more bone than women whose AAI remained stable. Furthermore, in women, studies have been performed focussing on other sites of atherosclerosis, such as in the coronary arteries, (1) the aortic wall, (2,5) or in the carotid arteries. (6) Although most of these studies have found an association between BMD and atherosclerosis as well, not all potential confounders (such as age at menopause and exercise) have been fully investigated. Furthermore, these studies have all assumed the relationship between BMD and atherosclerosis to be linear, which is not necessarily the case. One small study has observed a local effect of atherosclerosis on bone mineral density in men with asymmetrical peripheral arterial disease (PAD). (3)

In the present study, we investigate the association between BMD measured at the femoral neck and PAD, a marker of both local and generalized atherosclerosis. (7,8) This study is the first large population based study of osteoporosis and PAD to include both elderly Caucasian men and women.

## **Materials and methods**

### **Study population**

The Rotterdam Study is a prospective cohort study of individuals aged 55 years and over. Its aim is to investigate the incidence of, and risk factors for, chronic disabling diseases in the elderly. The rationale and study design have been described previously. (9) The focus of the Rotterdam Study is on neurologic, cardiovascular, ophthalmologic and locomotor diseases. All 10,275 inhabitants of Ommoord, a district in Rotterdam, the Netherlands, were invited to participate. Of these participants, 7,983 entered the study (response rate 78%). At baseline, between 1990 and 1993, 6,451 were able to visit the research center. Of those, BMD was measured in 5,819 participants (3,374 women), all of whom were

living independently. Of these, information on AAI was available for 5,268 persons, of whom 3,053 were females. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus Medical Center.

### **Clinical examination**

#### Peripheral arterial disease measurement.

The presence of PAD was evaluated by measuring the systolic blood pressure level of the posterior tibial artery at both legs using an 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer. (10,11) For each leg, a single blood pressure reading was taken with the subject in supine position. The blood pressure in the arm was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index (AAI) in either leg was used in the current analysis. In agreement with the approach used by Fowkes et al. and by Schroll and Munck, peripheral arterial disease was considered present when the AAI was lower than 0.90 in at least one leg. (12,13) We excluded 178 participants with an AAI > 1.50, since this AAI usually reflects arterial rigidity preventing arterial compression, leading to spuriously high ankle blood pressure values. (14)

#### Bone mineral density measurement.

Bone mineral density measurement of the femoral neck and lumbar spine (L2-L4) was performed by dual energy X-ray absorptiometry (DXA, Lunar DPX-L densitometer) as described previously. (15) BMD of the femoral neck was measured in one leg only.

#### Measurement of covariates.

A trained interviewer performed an extensive home interview on medical history, risk factors for chronic diseases and medication use, such as estrogen replacement therapy and diuretics. We categorized subjects as current, former or never smokers. Information on menopause, such as age and its cause, was obtained. Intermittent claudication was diagnosed according to the criteria of WHO/Rose- questionnaire, which was included in the home interview. (16) Walking ability was assessed as a combination of questions on ability to walk outdoors and ability to climb stairs as scored in the Stanford Health Assessment Questionnaire. (17) After the home interview, subjects were invited to the research center for clinical examination and laboratory measurements. Height and weight were measured with subjects wearing indoor clothing without shoes. Body mass index was computed as weight in kilograms divided by height in meters squared. Subjects were classified as diabetics when they reported use of antidiabetic therapy (code a010 of the Anatomical Therapeutic Chemical classification index, WHO 1992), or when the pre- or postload serum glucose

level was equal to or higher than 11.1 mmol/l. Serum total cholesterol levels were assessed by an automated enzymatic procedure in a non-fasting blood sample.

## **Statistics**

At first, we compared continuous variables between subjects with and without PAD with the student's T-test. For categorical variables, a chi-square test was used. Subsequently, we calculated Z-scores of both femoral neck and lumbar spine BMD for men and women separately. These were then divided into tertiles. The Z score is the number of standard deviations from the gender- and age-adjusted mean. In all our analyses, we used the upper tertile as a reference. We used stepwise logistic regression to compute odds ratios for PAD in tertiles of Z-score, adjusting for age. Analyses were repeated additionally adjusting for body mass index, blood pressure, smoking (current, past, never), serum cholesterol levels and walking ability in men. In women, besides these additional confounders, we also adjusted for age at menopause and use of hormone replacement therapy. We also computed odds ratios in strata of age (< 65, 65-75, >75 years). For women, odds ratios were also calculated in strata of age at menopause. Analyses were repeated additionally adjusting for presence or absence of diabetes mellitus and after exclusion of subjects using diuretics, who had suffered a myocardial infarction or who reported the presence of intermittent claudication.

## **Results**

Baseline characteristics are shown in Table 4.1.1. Both men and women with PAD are older, have diabetes mellitus more often, use diuretics more often, and are more likely to be current smokers. Women with PAD have a lower BMD than women without PAD, whereas in men this is absent.

When adjusting for age only, women in the lower tertile of femoral neck BMD had a significantly increased risk of PAD (OR = 1.49, 95% CI 1.16,1.91), whereas this could not be found for men (OR = 1.14; 0.84,1.53). The mid tertile did not significantly differ from the reference in women (OR = 1.05; 0.81,1.37) or in men (OR = 1.13; 0.83,1.53). (Table 4.1.2) Additional adjustment for body mass index, systolic blood pressure, smoking (current, past, never), serum cholesterol levels and walking ability was made. In women, we also adjusted for age at menopause and use of estrogen. This resulted in somewhat lower odds ratios for women and men respectively (OR = 1.35; 1.02,1.79 and OR = 0.89; 0.64,1.23). Again, the mid tertile did not significantly differ from the reference. These analyses were repeated for lumbar spine bone density. However, neither in men, nor in women a relationship between lumbar spine BMD and PAD could be observed (data not shown).

Table 4.1.1. Baseline characteristics for subjects with and without PAD

	Men		Women	
	No PAD	PAD	No PAD	PAD
Number	1787	329	2507	477
Age	66.4 (7.1)	71.3 (8.4)	67.2 (7.8)	72.1 (8.9)
FN BMD	0.88 (0.13)	0.87 (0.14)	0.82 (0.13)	0.78 (0.14)
LS BMD	1.16 (0.19)	1.16 (0.20)	1.03 (0.18)	1.03 (0.18)
FN BMD Z-score	0.001 (0.97)	0.008 (1.02)	0.010 (0.97)	-0.11 (1.06)
LS BMD Z-score	-0.013 (0.97)	-0.031 (1.03)	-0.011 (0.98)	-0.019 (1.02)
Body mass index	25.8 (2.9)	25.4 (3.0)	26.7 (1.0)	26.7 (4.2)
Weight	79.2 (10.7)	76.4 (10.0)	70.1 (10.9)	68.3 (11.2)
Age at menopause	-	-	49.0 (4.9)	48.0 (4.9)
Serum cholesterol	6.3 (1.1)	6.4 (1.1)	6.9 (1.2)	7.0 (1.2)
Systolic blood pressure	137.5 (20.9)	149.0 (21.9)	137.6 (21.4)	150.7 (24.3)
Diabetes mellitus (%)	9.5	18.6	9.3	18.1
Prevalent myocardial infarction (%)	15.8	27.0	6.2	14.0
Diuretic users (%)	7.9	16.4	14.0	26.0
Intermittent claudication (%)	0.7	9.8	0.5	4.9
Walking disability (%)				
<i>No</i>	78.5	55.2	61.4	41.6
<i>Moderate</i>	20.5	41.8	36.2	53.1
<i>Severe</i>	1.1	3.0	2.4	5.3
Smoking (%)				
<i>Current</i>	26.1	45.7	18.3	25.3
<i>Former</i>	65.8	50.0	29.7	25.9
<i>Never</i>	8.2	4.3	52.1	48.7

Values are means with standard deviations or percentages



In women, analyses were repeated in strata of age at menopause (Table 4.1.3). The risk of PAD in women with a BMD in the lowest tertile is similar in women with an early menopause and in women with a late menopause (OR 1.36; 0.96,1.94 and 1.42; 0.90,2.25, respectively). Additionally, both for men and for women, analyses were repeated in age strata of below 65 years, between 65 and 75 years and 75 years and above (Table 4.1.4 and 4.1.5). In men, the risk of PAD was similar in all age categories. For women, however, the risk estimate in the youngest group was somewhat higher than in the two older groups. All analyses were repeated with adjustment for presence of diabetes mellitus and after exclusion of subjects with a prevalent myocardial infarction, intermittent claudication or current use of diuretics. All these analyses yielded similar risk estimates.

## **Discussion**

The results of our study show that women with a BMD in the lowest tertile have a 30 % increased risk of peripheral arterial disease as compared to women with a high BMD, whereas subjects with an average BMD did not have an increased risk as compared to the reference. This suggests that there is some threshold in BMD below which an increased risk of PAD arises. In men, neither crude, nor after adjustment for potential confounders did we observe a relation between BMD and PAD.

In women, previous studies have already shown an inverse relationship between BMD and ankle-arm index or with the prevalence of various other measures of atherosclerosis. (1,2,4-6) In men, however, only one small study within 17 men with asymmetrical severe peripheral arterial disease has been performed. (3) They found that the bone mineral content of the affected leg was significantly lower than in the unaffected leg and, therefore, they suggested that arterial disease could lead to local bone mineral loss. However, our study population consists of mainly asymptomatic subjects.

PAD, as measured by an ankle-arm index of  $< 0.90$ , is a measure for both local and generalised atherosclerosis. (7,8) Both osteoporosis and atherosclerosis are related to several risk factors, some of which are similar for both diseases. For instance aging, smoking and physical inactivity both lower the BMD, (18) and increase the risk of atherosclerosis. (19) In our analyses, adjusting for these potential confounders did not fundamentally affect the calculated risk estimates. Furthermore, analyses were repeated excluding subjects with intermittent claudication, which also yielded similar risk estimates. The results of these additional analyses suggest that the relation found is unlikely to be explained by these factors.

Table 4.1.2. Risk of peripheral arterial disease in tertiles of Z score of femoral neck BMD

	Tertiles of Z-score of femoral neck BMD		
	Lower tertile OR (95% CI)	Middle tertile OR (95% CI)	Upper tertile OR (95 % CI)
<b>Men</b>			
Nr of cases	119	109	101
<i>Crude</i>	1.1 (0.8-1.5)	1.0 (0.8-1.4)	1.0
<i>Age adjusted</i>	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.0
<i>Full model</i>	0.9 (0.6-1.2)	1.1 (0.8-1.5)	1.0
<b>Women</b>			
Nr of cases	200	146	130
<i>Crude</i>	1.5 (1.2-1.9)	1.1 (0.8-1.4)	1.0
<i>Age adjusted</i>	1.5 (1.2-1.9)	1.1 (0.8-1.4)	1.0
<i>Full model†</i>	1.4 (1.0-1.8)	1.0 (0.8-1.4)	1.0

\* Additional adjustment was made for body mass index, systolic blood pressure, smoking (current, former, never), serum cholesterol levels and walking ability.

† Additional adjustment was made for body mass index, systolic blood pressure, smoking (current, former, never), serum cholesterol levels, walking ability, age at menopause and use of estrogen.

Table 4.1.3. Relationship between femoral neck BMD and PAD in strata of age at menopause

	Tertiles of Z-score of femoral neck BMD		
	Lower tertile OR (95% CI)	Middle tertile OR (95% CI)	Upper tertile OR (95 % CI)
<b>50 years and below</b>			
Nr of cases	125	100	84
<i>Age adjusted</i>	1.3 (1.0-1.8)	1.1 (0.8-1.5)	1.0
<i>Full model†</i>	1.4 (1.0-1.9)	1.2 (0.9-1.7)	1.0
<b>Over 50 years</b>			
Nr of cases	65	42	45
<i>Age adjusted</i>	1.6 (1.1-2.4)	0.9 (0.6-1.4)	1.0
<i>Full model†</i>	1.4 (0.9-2.3)	0.8 (0.5-1.3)	1.0

† Additional adjustment was made for body mass index, systolic blood pressure, smoking (current, former, never), serum cholesterol levels, walking ability and use of estrogen.

Table 4.1.4. Risk of peripheral arterial disease in tertiles of Z-score of femoral neck BMD in women, divided in strata of age

	Tertiles of Z-score of femoral neck BMD		
	Lower tertile	Middle tertile	Upper tertile
	OR (95% CI)	OR (95% CI)	OR (95 % CI)
<b>&lt; 65</b>			
Nr of cases	56	46	29
<i>Crude</i>	1.8 (1.1-2.9)	1.5 (0.9-2.4)	1.0
<i>Full model†</i>	1.8 (1.1-3.0)	1.4 (0.8-2.4)	1.0
<b>65-75</b>			
Nr of cases	61	46	43
<i>Crude</i>	1.4 (0.9-2.2)	1.0 (0.7-1.6)	1.0
<i>Full model†</i>	1.3 (0.8-2.1)	1.1 (0.7-1.8)	1.0
<b>&gt; 75</b>			
Nr of cases	83	54	58
<i>Crude</i>	1.3 (0.9-2.0)	0.8 (0.5-1.2)	1.0
<i>Full model†</i>	1.2 (0.7-1.9)	0.7 (0.5-1.2)	1.0

† Additional adjustment was made for body mass index, systolic blood pressure, smoking (current, former, never), serum cholesterol levels, walking ability, age at menopause and use of estrogen.

**Table 4.1.5. Risk of peripheral arterial disease in tertiles of Z-score of femoral neck BMD in men, divided in strata of age**

<b>Tertiles of Z-score of femoral neck BMD</b>			
	<b>Lower tertile</b>	<b>Middle tertile</b>	<b>Upper tertile</b>
	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>	<b>OR (95 % CI)</b>
<b>&lt; 65</b>			
Nr of cases	30	38	21
<i>Crude</i>	1.3 (0.7-2.3)	1.5 (0.9-2.7)	1.0
<i>Full model†</i>	1.0 (0.5-1.9)	1.4 (0.8-2.5)	1.0
<b>65-75</b>			
Nr of cases	43	39	40
<i>Crude</i>	1.0 (0.6-1.5)	0.9 (0.6-1.5)	1.0
<i>Full model†</i>	0.7 (0.4-1.2)	0.9 (0.5-1.5)	1.0
<b>&gt; 75</b>			
Nr of cases	46	32	40
<i>Crude</i>	1.3 (0.8-2.2)	1.0 (0.6-1.7)	1.0
<i>Full model†</i>	1.2 (0.7-2.1)	1.1 (0.6-2.0)	1.0

† Additional adjustment was made for body mass index, systolic blood pressure, smoking (current, former, never), serum cholesterol levels and walking ability

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## *Chapter 4.2*

### *Bone mineral density and the risk of breast cancer in women*

*The Rotterdam Study*

## Abstract

Estrogens play an important role in the development of breast cancer, but studies on serum levels of estrogens have shown inconsistent results. Bone mineral density is considered to be a marker for lifetime estrogen exposure. Some studies have suggested that a higher bone mass is associated with an increase in breast cancer risk. We investigated the association between bone mineral density, as measured at the lumbar spine and femoral neck, and the risk of breast cancer in women aged 55 or over in the Rotterdam Study, a population-based cohort study in the Netherlands. Information on baseline lumbar spine and femoral neck bone mineral density, as measured by DEXA (Lunar DPX-L), and cancer incidence was available for 3107 women. The Rotterdam Cancer Registry provided information on follow-up of incident cancer. After an average follow-up time of 6.5 years, 74 new cases of breast cancer occurred. Z-scores of lumbar spine and femoral neck BMD were divided into tertiles and risk estimates for breast cancer were computed by Cox' proportional hazards model, using the middle tertile as a reference. Breast cancer risk in the upper tertile of lumbar spine BMD was doubled as compared to the reference after adjustment for age, weight and age at menopause (HR = 2.1 [1.1-3.8]), whereas risk estimates for women in the lower tertile did not significantly differ from the reference (HR = 1.5 [0.8-2.9]). For femoral neck BMD, neither women with a low BMD nor women with a high BMD had an increased breast cancer risk as compared to the reference. The results of this study suggest that in elderly women an association between lumbar spine BMD and incident breast cancer exists. Stimulating effects of estrogen on both trabecular bone and mammary cells may be responsible.

## **Introduction**

Both osteoporosis and breast cancer are common diseases in elderly women. There are two main reasons for studying the association between these diseases. First of all, exposure to estrogens may stimulate the development and progression of breast cancer, by stimulating mitotic activity of mammary cells and thereby increasing mutation risk. (1) Studies on serum estrogen levels, however, have shown inconsistent results, because these levels strongly vary over time, especially in premenopausal women. (2,3) Therefore, it is difficult to classify a woman's long-term exposure to endogenous estradiol by a single measurement. Bone mineral density, in contrast, is regarded to be a marker for lifelong estrogen exposure. (4) A high bone density, reflecting high estrogen exposure throughout life, may therefore be a predictor of incident breast cancer. The second reason for studying the association between BMD and breast cancer is that hormone replacement therapy (HRT) is one of the therapeutical options for osteoporosis. Simultaneously, these drugs are thought to increase breast cancer risk. (5) Therefore, it is important to know how these two diseases interrelate to one another.

Several studies have already shown a high BMD to be associated with an increased breast cancer risk. (6-12) Most of these studies, however, were performed in US populations. In these studies, the percentage of current hormone replacement therapy (HRT) users was much higher than in the Netherlands. (7,9,12) Although often either current users at baseline were excluded, or adjustment was made for use of HRT for in the analyses of these studies, we have to take into account that the percentage of current HRT users is much higher than observed in the Netherlands. This might affect the generalisability of these results. Furthermore, the incidence of breast cancer varies between countries. At age 65 or over, the breast cancer incidence rate was 4.1 per 1000 PY in the US and 2.8 per 1000 PY in Western Europe. (13)

The aim of this study was to investigate the association between BMD and breast cancer in over 3000 Dutch women from the Rotterdam Study.

## **Materials and methods**

### **The Rotterdam Study**

The Rotterdam Study is a prospective population-based cohort study that was initiated in 1990 to assess the prevalence, incidence, and determinants of diseases of the elderly. (14) The study focuses on cardiovascular, neurogeriatric, ophthalmologic, and locomotor diseases. All inhabitants aged 55 and over (n=10,275) of the district of Ommoord in Rotterdam, were invited to take part in the study. A total of 7,983 subjects (78%), 4,878 of which were women,

entered the study. The Medical Ethics Committee of the Erasmus Medical Centre has approved the Rotterdam Study.

### **Baseline data collection**

#### *Home interview and research centre visit*

A trained research assistant interviewed all participants at home. Information was obtained on medical history, surgical interventions, current health, and medication use. Detailed information was obtained on lifestyle and other potential risk indicators for chronic diseases. Lower limb disability was assessed using a modified version of the Stanford Health Assessment Questionnaire, as described previously. (15) Smoking status was assessed, and classified as current, former or never.

At the research centre, an extensive clinical examination was performed, and non-fasting blood samples were taken. Amongst various other measurements, weight was measured at the research centre with the subject wearing indoor clothing without shoes. Bone mineral density measurements of the lumbar spine and femoral neck were performed by dual energy X-ray absorptiometry (DXA, Lunar DPX-L densitometer) as described previously. (16) In addition, lumbar spine and femoral neck bone mineral density were also measured at the first follow-up visit, between 1994 and 1995, using the same methods.

#### *Hormone-related determinants*

Data on age at and type of menopause (spontaneous or artificial) were collected during the home interview. Menopause was defined as the cessation of menses for at least one year. For women reporting natural menopause, age at menopause was defined as the self-reported age of last menstruation. For all women who reported menopause after gynecologic surgery and radiotherapy, and for those who reported any other operations before age 50 that might have induced menopause, information on the exact date and type of operation were verified using general practitioners (GP) patient records. Every individual is registered in the practice of one specific GP, who offers the only access to specialist and hospital care, and centralizes physician and hospital notes. The GP thus has a gatekeeper function in the Netherlands. Data on hormone replacement therapy (HRT) were obtained during the home interview. For all women who reported ever use of female hormones, data were verified in GP records. For the present analysis, HRT comprises hormonal substitutes for the indication of menopausal complaints or after oophorectomy (with or without hysterectomy) and excludes oral contraceptives.

## **Follow-up procedures**

### *Follow-up within the Rotterdam Study*

The present analysis is based on follow-up data collected from baseline (1990-1993) until December 31<sup>st</sup> 1998, comprising an average follow-up period of 6.5 (SD 1.5) years (20,229 person-years for women). Information on vital status was obtained continuously from the municipal population registry. Additionally, follow-up events were reported by general practitioners (GPs) in the research area (covering 80% of the cohort) by means of a computerized system. Information from GPs outside the research area was obtained by regular checking of the patient records by research physicians. All reported events were verified by research physicians who independently reviewed and coded the information. Subsequently all coded events were reviewed by a medical expert in the field for final classification.

### *Cancer follow-up at Rotterdam Cancer Registry (IKR)*

The Netherlands Cancer Registry is population-based, i.e. a systematic collection of data on all malignant neoplasms and in situ malignancies occurring in a geographically defined population. (17) In the mid-1980s, a nation-wide cancer registry was set up based on nine autonomous regional registries, including the Rotterdam Cancer Registry (IKR) where data collection started in 1986. Since January 1<sup>st</sup> 1989, all Dutch hospitals are associated with one of the regional cancer registries and all registry data are submitted to a national database. Ascertainment takes place through the nation-wide pathology registration system (PALGA), which is the basis for tracing medical records in hospitals. Cases with a clinical diagnosis only are found through the computerized hospital discharge registry (LMR). Co-workers of the cancer registry perform the coding of data according to a strict protocol. Repeated diagnoses or hospitalizations for the same cancer are not recorded separately, so all registered events are true incident cases.

### *Incident cancer*

Information on cancer incidence in women was obtained by linking the Rotterdam Study data files to the Rotterdam Cancer Registry (IKR). The IKR obtains data from hospitals in the Rotterdam City area and near surroundings. Incident cancers were coded according to the ICD-9 system. The present study focuses on first-ever incident breast cancers (ICD-9 code 174). Ascertainment of cancer was complete till December 31, 1998.

### **Data available for analysis**

Of the 4878 women in our cohort, 151 did not sign the informed consent form for the retrieval of follow-up information, and were therefore excluded from the study population. Of the remaining 4727 women, 125 had been diagnosed with breast cancer before baseline. For 1495 women, no information on either BMD

(lumbar spine or femoral neck), age at menopause or body weight was available. This was primarily due to the fact that these women were not able to come to our research centre. Thus, these women were also excluded from the analyses, leaving data on 3107 women available for the present study.

### Statistical analysis

Differences in baseline characteristics were compared using student's t- test for continuous variables and Chi-square for categorical variables. For all other analyses, Cox's proportional hazard regression analysis was used. We calculated follow-up time as the number of days from BMD measurement until the first-ever incident breast cancer, death or December 31<sup>st</sup> 1998, whichever occurred first. First, hazard ratios for incident first-ever breast cancer were calculated per standard deviation increase in absolute femoral neck and lumbar spine BMD, both crude and after adjustment for age.

Since BMD is strongly age-dependent, we thereafter corrected for age by expressing BMD (both lumbar spine and femoral neck) as Z-scores; the deviation from the age adjusted average expressed in standard deviations (SD). This Z-score was then divided into tertiles.

Age at menopause was divided into quartiles, using the lowest quartile as a reference, since these women had the shortest time of estrogen exposure. Potential confounders were tested for univariate association with breast cancer and BMD.

Relative risks for the lower and upper tertiles of BMD were computed univariately and multivariately. We used the middle tertile as the reference, since these subjects have an average ('normal') BMD in the population. In the base analysis, adjustment was made for age only. In a second analysis, we additionally adjusted for other potential confounders, namely weight and age at menopause. Analyses were repeated with additional adjustment for smoking habits, physical activity and ever use of HRT.

Yearly percentages of bone loss between the baseline and first follow-up visit were calculated, and the average loss was compared between women with and without breast cancer. Women who had their breast cancer before the first follow-up visit or women who did not have their BMD measured at the follow-up visit were excluded from these analyses (35 breast cancer cases). Adjustment was made for age and weight, and subsequently for baseline BMD.

SPSS 10.0 for windows was used for all analyses.

## Results

After an average follow-up time of 6.5 years (SD 1.5), 74 new breast cancer cases occurred in 3107 individuals. Thus, the overall incidence in our study population is 3.7 per 1000 person years.

Table 4.2.1 shows the baseline characteristics of the study group. Women with breast cancer are on average nearly three years younger. They are also somewhat heavier, older at menopause and have a higher BMD (both femoral neck and lumbar spine) than non-cases. No differences in physical activity, smoking and other relevant lifestyle factors could be observed.

**Table 4.2.1. Baseline characteristics of women with and without breast cancer during follow-up**

	Breast cancer	No breast cancer	p-value
Number	74	3033	
Age (yrs)	65.5 (6.9)	68.1 (8.1)	< 0.01
Weight (kg)	71.4 (10.7)	69.8 (10.8)	0.21
Age at menopause (yrs)	50.2 (4.6)	48.8 (4.9)	0.01
Lumbar spine BMD (g/cm <sup>2</sup> )	1.08 (0.18)	1.03 (0.18)	0.05
Femoral neck BMD (g/cm <sup>2</sup> )	0.83 (0.12)	0.81 (0.13)	0.15
Ever use of HRT	8 (11.1 %)	310 (10.4 %)	0.85
Smoking habits			
Current	15 (20.3 %)	598 (19.7 %)	0.92
Former	23 (31.1 %)	887 (29.3 %)	
Never	36 (48.6 %)	1543 (51.0 %)	
Lower limb disability			
No	37 (50.0 %)	1402 (46.3 %)	0.25
Moderate	34 (45.9 %)	1326 (43.8 %)	
Severe	3 (4.1 %)	299 (9.9 %)	

Values are means with standard deviations or numbers with percentages.

Table 4.2.2 shows relative risks per standard deviation decrease in femoral neck or lumbar spine BMD. Both crude and after adjustment for age was a standard deviation decrease in lumbar spine BMD associated with a decreased risk of breast cancer, even though after adjustment for age this was only just failed to reach statistical significance (p-value 0.06), possibly due to low power. For femoral neck, no clear association between absolute BMD and incident breast cancer could be observed.

**Table 4.2.2. Relative risk of breast cancer per standard deviation decrease in femoral neck or lumbar spine BMD**

	FN BMD per SD decrease	LS BMD per SD decrease
Breast cancer		
Crude	0.9 (0.7-1.1)	0.8 (0.6-1.0)**
Age adjusted	1.1 (0.9-1.4)	0.8 (0.6-1.0) *

\*\* p-value < 0.05, \* p-value < 0.10

**Table 4.2.3. Hazard ratio of incident first ever breast cancer in tertiles of Z-score of lumbar spine BMD**

	Tertiles of Z-score of LS BMD		
	Lower tertile	Mid tertile	Upper tertile
Cases/total group	22/1020	16/1024	36/989
Crude	1.4 (0.7-2.6)	1	2.3 (1.3-4.2)
Age adjusted	1.4 (0.7-2.7)	1	2.3 (1.3-4.2)
Age and weight	1.4 (0.7-2.8)	1	2.3 (1.3-4.1)
Full model <sup>¶</sup>	1.5 (0.8-2.9)	1	2.1 (1.1-3.8)
Exclusion of women who ever used HRT before baseline <sup>¶</sup>	1.9 (0.9-3.8)	1	2.5 (1.3-4.9)
Exclusion of first year of follow-up <sup>¶</sup>	1.3 (0.6-2.8)	1	2.3 (1.2-4.3)

<sup>¶</sup>Adjustment was made for age, weight and age at menopause

Table 4.2.3 shows hazard ratios for breast cancer in tertiles of Z score of lumbar spine BMD, both crude and after adjustment for age, weight and age at menopause. After adjustment for possible confounders women with a lumbar spine BMD in the highest tertile have a 2.1 times increased risk of breast cancer as compared to the reference. The risk is also somewhat increased in the lowest



tertile but this is not statistically significant. To further test for a potential U-shaped curve, Z-scores of lumbar spine BMD were added to the model both continuously and squared simultaneously. These terms are not statistically significant in the model, suggesting that no clear U-shape is present.

With femoral neck BMD no significant differences were observed between tertiles, especially after exclusion of women who had ever used HRT (Table 4.2.4). There was a slight trend, however, towards a decreased risk of incident breast cancer in women with a Z-score of femoral neck in the lower tertile as compared to the reference.

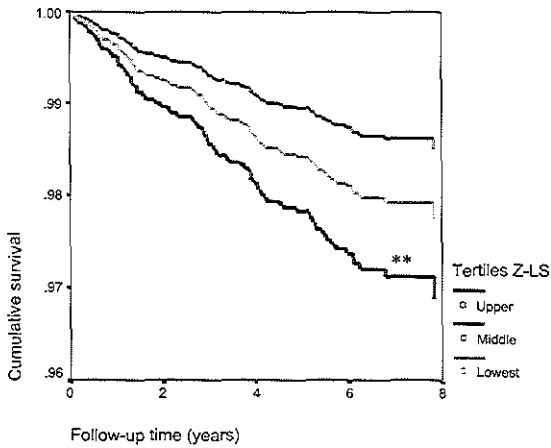
**Table 4.2.4. Hazard ratio of incident first ever breast cancer in tertiles of Z-score of femoral neck BMD**

	Tertiles of Z-score of FN BMD		
	Lower tertile	Mid tertile	Upper tertile
Cases/total group	18/1009	27/1008	29/1016
Crude	0.7 (0.4-1.2)	1	1.1 (0.6-1.8)
Age adjusted	0.7 (0.4-1.2)	1	1.1 (0.6-1.8)
Age and weight	0.7 (0.4-1.3)	1	1.0 (0.6-1.7)
Full model <sup>†</sup>	0.7 (0.4-1.4)	1	1.0 (0.6-1.7)
Exclusion of women who ever used HRT before baseline <sup>†</sup>	0.9 (0.4-1.6)	1	1.1 (0.6-1.9)
Exclusion of first year of follow-up <sup>†</sup>	0.7 (0.4-1.4)	1	0.9 (0.5-1.7)

<sup>†</sup>Adjustment was made for age, weight and age at menopause

Figure 4.2.1 and 4.2.2 show differences in time until breast cancer between tertiles of Z score of lumbar spine and femoral neck BMD, respectively. Women with a lumbar spine BMD in the highest tertile have a significantly shorter time till incident breast cancer as compared to women with an average BMD. Women with a femoral neck BMD in the lower tertile have a somewhat longer time until breast cancer as compared with women in the mid tertile, even though this was not statistically significant. For women with a femoral neck BMD in the highest tertile, the survival curve completely overlaps with that of women in the mid tertile.

**Figure 4.2.1. Survival curve for breast cancer in tertiles of Z-score of lumbar spine BMD**



Adjustment was made for age, weight and age at menopause  
 \*\* p-value < 0.05

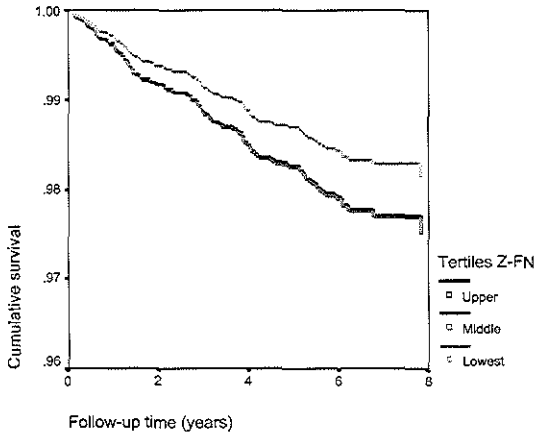
Analyses repeated excluding women who ever used HRT (never, less than three years and more than three years) did not essentially change risk estimates (Tables 4.2.3 and 4.2.4). Additional adjustment for smoking status or physical activity (as assessed by a lower limb disability score) yielded similar results (data not shown).

To further investigate the increase in breast cancer risk in the lowest tertile of lumbar spine BMD, we repeated the analyses after exclusion of the first year of follow-up after bone mineral density measurement. We did this in order to exclude breast cancer potentially present at baseline (19 cases).

For lumbar spine BMD, the hazard ratio in the lowest tertile now decreased, whereas the hazard ratio in the upper tertile was slightly increased (Table 4.2.3). For femoral neck BMD, hardly any changes were observed (Table 4.2.4).

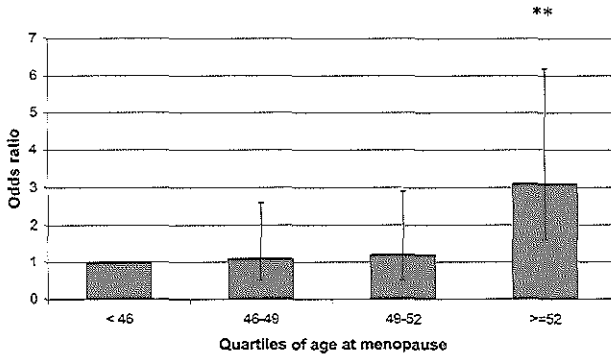
Finally we analyzed the association between age at menopause in quartiles and incident first ever breast cancer, using the lowest quartile as the reference category. Women whose menopause was at age 52 or above (the highest quartile) had a three times increased risk of developing breast cancer as compared to women whose menopause started before age 46 (the lowest quartile), whereas no difference could be observed for women in the two middle quartiles (Fig 4.2.3). No significant interaction between BMD and age at menopause was observed.

Figure 4.2.2. Survival curve for breast cancer in tertiles of Z-score of femoral neck BMD



Adjustment was made for age, weight and age at menopause

Figure 4.2.3. Hazard ratio for first ever breast cancer in quartiles of age at menopause



\*\* = p-value < 0.05 (two-tailed)

starts to increase, whereas below that threshold the relative risk remains around one. In theory, vitamin D may also play a role in the observed association. One of the causes of low BMD in the elderly is a vitamin D deficiency. Vitamin D is known to be a stimulator of cell differentiation and an inhibitor of cell division, thereby decreasing tumor cell growth. (20) Therefore, a lack of vitamin D could be associated with on the one hand a somewhat increased cancer risk and on the other hand a lower BMD.

Some studies showed breast cancer to be associated with physical activity, even though these results were conflicting. (2,21) When we adjusted for physical activity in our analyses, by means of a lower limb disability index, we did not observe any change in risk estimates, suggesting that in our cohort low physical activity is not a likely explanation for the observed association between BMD and breast cancer. Smoking is thought to be associated with an increased breast cancer risk and a low BMD, (22) whereas ever use of HRT is associated with an increased breast cancer risk and high BMD. (5,17) Adjustment for smoking, HRT use or both did not change the risk estimates, suggesting that these factors do not play an important role in explaining the observed association either.

A high BMD appeared to be associated with increased breast cancer risk, independent from higher age at menopause, suggesting that BMD is not an intermediary factor in the association between age at menopause and breast cancer risk. Also, no interaction existed between high BMD and high age at menopause on breast cancer risk.

Of course, BMD is not merely a marker for estrogen exposure. Other metabolic pathways and many growth factors and interleukins may be involved in the association between BMD and breast cancer, either alone or through stimulation of the estrogen pathway. For instance, both insulin and insulin-like growth factor type 1 (IGF-1) are thought to have anabolic effects on bone, and could also be related to the risk of breast cancer. (23-26) Also, interaction may exist between the IGF and estrogen metabolic pathways. (27) Furthermore, abnormalities in the transforming growth factor  $\beta$  (TGF- $\beta$ ) pathway may be involved in oncogenesis, particularly of breast cancer, (28) whereas they are also associated with an increased BMD. (29)

There are some limitations to our study. First of all, in order to have BMD measurements, subjects had to be able to come to the research centre. This could introduce a health selection bias. Breast cancer incidence rates in our study (3.7 per 1000 woman-years) were quite similar, however, to the incidence rate in women in the same age range from the general Dutch population (3.3 per 1000 woman-years). Furthermore, a program for regular breast cancer screening in all women over age 50 was started in Rotterdam area in 1990. This could result in a relatively young age at diagnosis and therefore a higher BMD. Therefore, we

expressed the BMD as Z-scores, thereby adjusting for the potential confounding effect of age.

The results of this study suggest that women with a lumbar spine BMD in the highest tertile are at a doubled risk of breast cancer as compared to women with an average BMD. For baseline femoral neck BMD, we could not observe a strong association with incident breast cancer. However, both for femoral neck and lumbar spine BMD, in contrast to women without breast cancer, women with breast cancer on average gained bone.

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## *Chapter 5*

### *Bone mineral density and overall mortality*





# *Chapter 5.1*

## *Bone mineral density and mortality in elderly men and women*

*The Rotterdam Study*

## Abstract

Recent studies have shown that a low bone mineral density (BMD) is associated with a higher risk of mortality. Most studies only investigated this relationship in women and presented their risk estimates per standard deviation change in BMD. However, when using this approach a threshold in BMD might be missed when relative risks are presented in the traditional way. Therefore, our aim was to model the relation between BMD and all cause mortality. In the Rotterdam Study, follow-up was complete for 5819 men and women aged 55 and over for whom BMD data were available. During an average follow-up of 5.4 years, 399 men and 317 women died. We calculated BMD Z-scores as measured at the femoral neck. Cox' proportional hazards regression was used to fit the model. An average BMD, reflected by a Z score of zero, was used as the reference. For women, no significant relationship between BMD and overall mortality was observed. For men, however, a cubic model best fitted the relationship under study, also after adjusting for age and body mass index. The risk of mortality increased when BMD was below average. Similar results were found when separate curves were made for diabetics and non-diabetics, smokers (ever or never), and tertiles of BMI. Excluding subjects who had suffered hip fractures or adjusting for the number of drugs used and for lower limb disability did not essentially change results. This suggests that low BMD is not mainly due to morbidity and impaired mobility in our cohort, which makes this a less likely explanation for the observed relation with mortality. The results of our study suggest that in men a non-linear relationship between BMD and mortality exists, which is independent of co-morbidity, whereas in women no significant relationship can be observed.

## **Introduction**

It is well known that a low bone mineral density (BMD) is a predictor for osteoporotic fractures (10,11,13,18). Furthermore, a positive association between BMD and incidence of breast cancer has been observed, which might indicate that BMD reflects lifetime exposure to estrogen (6,31). Recent studies suggested that a low BMD is associated with an increased mortality risk (3,15,27). In addition, Kado et al. recently showed that an increased rate of bone loss at the femoral neck is associated with an increased mortality risk, especially from pulmonary causes in elderly women (16).

Besides estrogen exposure, many other factors might affect the relationship between BMD and mortality, such as body mass index, smoking, or comorbidity (1,4,7,12,19-21,26,28). These might affect the association between BMD and mortality in several different ways. Therefore, it may not be biologically plausible to express the relationship between BMD and mortality in relative risks per standard deviation change in BMD, as done in previous studies (3,15,27). If a threshold in BMD exists below which the risk increases, this will not be found when relative risks are expressed in the traditional way.

Our aim was to investigate whether an association exists between BMD and mortality and if so, what the nature of this relationship is in nearly 6000 elderly men and women from the Rotterdam Study.

## **Materials and methods**

### **Study population**

The Rotterdam Study is a prospective cohort study of men and women aged 55 and over and has the objective to investigate the incidence of, and risk factors for, chronic disabling diseases. The rationale and study design have been described previously (14). The focus of the Rotterdam Study is on neurologic, cardiovascular, ophthalmologic and locomotor diseases. All 10,275 inhabitants of Ommoord, a district in Rotterdam, the Netherlands, were invited to participate. Of these, 7,983 participated in the study (response rate 78%). BMD was measured in 5819 participants (3374 women), all of whom were living independently and were able to visit the research center. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus University Medical School.

## Clinical examination

Between 1990 and 1993, an extensive baseline home interview on medical history, risk factors for chronic diseases and medication use was performed by trained interviewers. Lower limb disability was assessed using a modified version of the Stanford Health Assessment Questionnaire (22). A lower limb disability index was obtained by calculating the mean score of answers to questions concerning rising, walking, bending and getting in and out of a car. It is a continuous score ranging from zero to three, where a score of zero indicates no impairment and a score of three indicates severe impairment (4).

After the home interview, subjects were invited to the research center for clinical examination and laboratory measurements. Height and weight were measured with subjects wearing indoor clothing without shoes. Body mass index was computed as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Subjects were classified as diabetics when they reported use of antidiabetic therapy (code A010 of the Anatomical Therapeutic Chemical classification index, WHO 1992), or when the pre- or postload serum glucose level was equal to or higher than 11.1 mmol/l. Serum albumin was measured in g/l by standard laboratory methods. Bone mineral density measurement of the femoral neck was performed by dual energy X-ray absorptiometry (DXA, Lunar DPX-L densitometer) as described previously (5).

## Follow-up procedures

For the entire cohort, information on vital status is obtained continuously from the municipal authorities in Rotterdam. For subjects who moved outside the research area, mortality data are obtained from general practitioners (GPs). GPs in the research area (covering 80% of the cohort) reported all relevant fatal and non-fatal events, such as fractures, through a computerized system. Research physicians verified follow-up information by checking GPs' patient records. This is possible because in the Netherlands the GP has a gate keeper function, which means that the GP retains all medical information of his patients. For the remaining 20 % of the population, research physicians collected data from their GP's patient records. For hospitalized patients, discharge reports and letters from medical specialists were additionally used for verification. All non-fatal events, such as fractures, were coded independently by two research physicians according to the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10) (30). If there was disagreement, consensus was reached in a separate session. A medical expert in the field reviewed all coded events for a final classification. Data for overall mortality were available until 31st December 1997.

## Statistical analysis

Differences in baseline characteristics were compared using student's t- test for continuous variables and Chi-square for categorical variables. For all other analyses, Cox's regression analysis was used (9). We calculated survival time as the number of days from BMD measurement until death or December 31st 1997, whichever occurred first. Outcome was overall mortality. First, we calculated hazard ratios in the traditional way, per standard deviation decrease in femoral neck BMD, in a full model with all potential confounders for both genders. Variables were considered confounders when statistically significant when tested univariately with both BMD and mortality, and when they remained significant upon entering into the model.

Then, in order to optimally correct for age, BMD was expressed as Z-scores, the age adjusted deviation from the average expressed in standard deviations (SD) for men and women separately. We divided the Z-score in tertiles. This resulted (as expected from normal theory) in a lower cut-off level of  $Z = -0.42$  and a higher cut-off level of  $Z = 0.42$ . At 55 years, the cut-off for the lower tertile of Z-score for women was on average at a BMD level of  $0.80 \text{ g/cm}^2$ , and for the upper tertile at a level of  $0.92 \text{ g/cm}^2$ . For men, corresponding cut-off values were  $0.87$  and  $0.96 \text{ g/cm}^2$ , respectively. The corresponding values at other ages are listed in table 5.1.1. Furthermore, we divided the Z-score of BMD into quintiles, whereafter we calculated mortality incidence rates per quintile, to compare results to other studies.

**Table 5.1.1. Age-specific cut-off values in men and women for BMD at the femoral neck ( $\text{g/cm}^2$ ), which correspond to the Z-score tertile cut-off values.**

	Men		Women	
	Lower cut-off	Upper cut-off	Lower cut-off	Upper cut-off
55 yr	0.87	0.96	0.80	0.92
60 yr	0.85	0.95	0.79	0.89
65 yr	0.81	0.92	0.77	0.87
70 yr	0.80	0.91	0.74	0.84
75 yr	0.79	0.92	0.72	0.82
80 yr	0.77	0.91	0.68	0.79
85 yr	0.75	0.88	0.70	0.80

Hazard ratios for the lower and upper tertiles were computed univariately and multivariately, using the mid tertile as the reference. In the base analysis, adjustment was made for age only.

In a second analysis, we additionally adjusted for body mass index (BMI) ( $\text{kg}/\text{m}^2$ ). Furthermore, we repeated the analysis with adjustment for all potential confounders, namely the presence or absence of diabetes mellitus type II, physical activity, as represented by the lower limb disability index, the use of diuretics and smoking habit.

In order to fit the model that optimally reflects the true relationship between BMD and mortality, Z-scores were first entered continuously into the model, and more terms were added until statistical significance ( $p < 0.05$ ) was no longer reached. This was considered the optimal model. In these analyses, adjustment was made for age and BMI. All analyses were performed for men and women separately.

We used SPSS for windows 9.0 in all our analyses.

## Results

Follow-up on overall mortality was achieved for 2445 men and 3374 women after an average follow-up time of 5.4 years. Of these subjects, 399 men (16.3 %) and 317 women (9.4 %) died. Table 5.1.2 a and b show baseline characteristics of the study population. The study generated 31.705 person years of follow-up. Since not all subjects had information on all confounders available, the population for study consisted of 2106 men and 2945 women for the multivariate model, whereas for all other analyses, the entire cohort was used.

Fig 5.1.1 shows mortality incidence rates per 1000 person years in quintiles of Z-score of femoral neck BMD for men and women separately. For men, more deaths occurred in the lowest quintile, whereas in women, there was no difference between quintiles.

Hazard ratios for mortality were calculated per standard deviation (SD) decrease of femoral neck BMD, both age-adjusted and with adjustment for all potential independent confounders. After adjustment for age only, mortality risk increased per SD decrease in BMD in men (hazard ratio (HR) = 1.14; 95% confidence interval 1.04-1.26), but not in women (HR = 1.06; 95% CI 0.95-1.19). Hazard ratios after adjustment for potential confounders are shown in Table 5.1.3. For men, the risk of mortality increases with a decrease in BMD, whereas this is not observed for women.

**Table 5.1.2a. Baseline characteristics of 2445 men of the Rotterdam Study in tertiles of the Z-score of femoral neck BMD**

	Lower tertile (n = 867)	Middle tertile (n = 814)	Upper tertile (n = 765)
Age	67.9 (7.6)	66.7 (7.4)	67.9 (7.9)
Follow-up time (yr.)	5.1 (1.4)	5.4 (1.3)	5.4 (1.3)
Body mass index (kg/m <sup>2</sup> )	24.7 (2.8)	26.0 (2.9)	26.5 (2.9)
BMD femoral neck (g/cm <sup>3</sup> )	0.74 (0.07)	0.88 (0.04)	1.03 (0.08)
Smoking status (%)			
Current	35.6	27.6	23.9
Former	58.2	64.6	65.4
Never	6.1	7.8	10.6
Disability (%)			
No	70.0	79.0	73.4
Moderate	27.6	20.4	25.4
Severe	2.4	0.6	1.2
5 year history of hip fractures	3 (0.3)	2 (0.2)	5 (0.7)
Incident hip fractures	23 (2.7)	7 (0.9)	-
Diuretics users (all types, %)	73 (8.4)	73 (9.0)	74 (9.7)
Diabetes mellitus (%)	75 (10.0)	66 (9.2)	97 (14.6)
Serum albumin level (mmol/L)	43.0 (2.7)	43.2 (2.6)	43.2 (2.9)

Values are means with standard deviations or numbers with percentages

\* Data on smoking status were missing for 11 subjects; † Data on diabetes mellitus were missing for 316 subjects; ‡ Data on mobility were missing for 14 subjects

In order to optimally adjust for age, we hereafter analysed Z-scores of BMD instead of the absolute BMD.

When the mortality risk was analysed in tertiles of Z-score of BMD for men and women separately in a multivariate model using Cox' proportional hazards, men in the lower tertile of BMD had a hazard ratio of 1.4 (95 % confidence interval 1.1-1.8), after adjustment for age. In the upper tertile mortality risk was not significantly different from the reference group (Table 5.1.4). For women, we did not find a significant increase in the lower tertile (HR=1.1 [0.8-1.4]).

**Table 5.1.2b. Baseline characteristics of 3374 women of the Rotterdam Study in tertiles of the Z-score of femoral neck BMD**

	Lower tertile (n = 1164)	Middle tertile (n = 1149)	Upper tertile (n = 1062)
Age	68.3 (8.3)	68.3(8.1)	68.3 (8.3)
Follow-up time (yr.)	5.5 (1.2)	5.6 (1.2)	5.6 (1.2)
Body mass index (kg/m <sup>2</sup> )	25.1 (3.5)	26.9 (3.8)	28.3 (4.1)
BMD femoral neck (g/cm <sup>2</sup> )	0.68 (0.07)	0.81 (0.05)	0.95 (0.09)
Smoking status (%)			
Current	23.0	17.7	17.5
Former	28.7	28.3	30.4
Never	48.4	54.0	52.2
Disability (%)			
No	56.9	60.3	55.9
Moderate	27.1	29.4	31.9
Severe	11.6	8.4	9.8
History of hip fractures	25 (2.1)	7 (0.6)	3 (0.3)
Incident hip fractures	59 (5.1)	20 (1.8)	16 (1.5)
Diuretics users (all types, %)	156 (13.4)	183 (15.9)	215 (20.3)
Diabetes mellitus (%)	98 (9.6)	96 (9.4)	133 (14.0)
Serum albumin level (mmol/L)	42.8 (2.4)	43.0 (2.5)	42.9 (2.5)

Values are means with standard deviations or numbers with percentages  
 Data on smoking status were missing for 23 subjects; † Data on diabetes mellitus were missing for 381 subjects; ‡ Data on mobility were missing for 27 subjects

Subsequently, we modelled the true relationship between BMD and mortality. For men, the model was optimal when Z-scores were entered into the model continuously ( $\beta = -0.042$ ,  $p = 0.52$ ), squared ( $\beta = 0.101$ ,  $p = 0.00$ ) and cubic ( $\beta = -0.022$ ,  $p = 0.04$ ) simultaneously. Adjustment was made for age and body mass index. (Fig. 5.1.2). For women, even the continuous Z score was not significant upon entering into the model ( $\beta = -0.048$ ,  $p = 0.45$ ).

A model that included all potential confounders resulted in a similar model. ( $\beta$ 's now were  $-0.009$ ,  $0.121$  and  $-0.046$  for men, respectively, and  $-0.057$  for women). We also repeated the analyses in strata of high and low BMI and smoking status. This resulted in similar results. (Data not shown).



Figure 5.1.1. Mortality incidence per 1000 person years during an average of 5,4 years of follow-up for men and women separately.

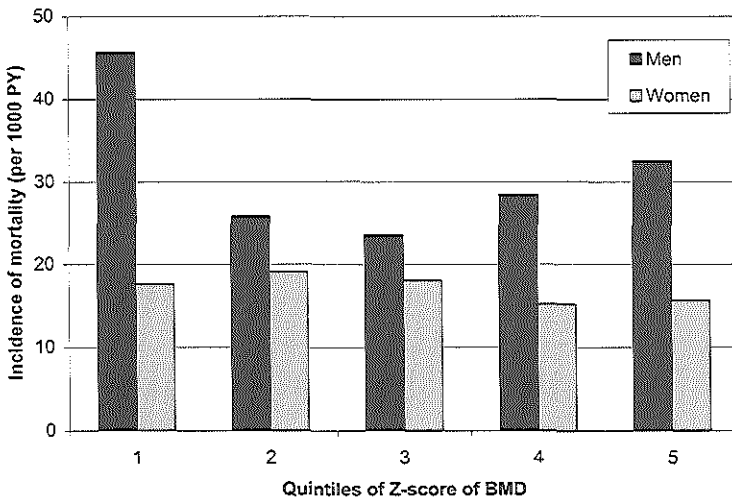


Table 5.1.3. Hazard ratio of all-cause mortality in a multivariate model for men and women separately

	Men		Women	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Femoral neck BMD (per SD)	1.14 (1.02-1.28)	0.024	1.04 (0.91-1.19)	0.521
Age (per yr)	1.09 (1.07-1.10)	0.000	1.10 (1.08-1.12)	0.000
BMI	0.96 (0.92-0.99)	0.026	0.97 (0.94-1.00)	0.055
Presence of diabetes mellitus	1.74 (1.33-2.28)	0.000	1.82 (1.37-2.42)	0.000
Use of diuretics	1.98 (1.51-2.60)	0.000	1.56 (1.18-2.05)	0.001
Lower limb disability				
No	1 (reference)		1 (reference)	
Moderate	1.74 (1.33-2.28)	0.000	1.28 (0.91-1.80)	0.162
Severe	1.95 (1.49-2.57)	0.000	1.48 (1.07-2.03)	0.017
Smoking				
Current	1.50 (0.91-2.48)		1.80 (1.31-2.48)	
Former	1.21 (0.75-1.97)	0.113	1.13 (0.85-1.52)	0.000
Never	1 (reference)	0.436	1 (reference)	0.399

†All covariates are independent predictors for mortality

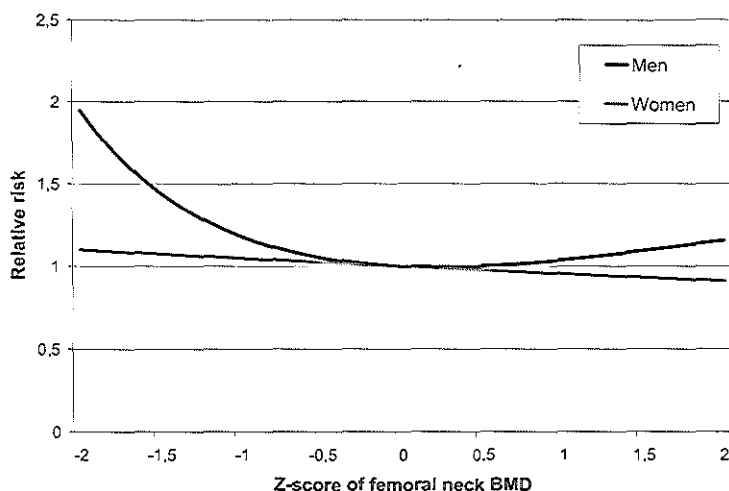
Table 5.1.4. Hazard ratio of all-cause mortality by tertiles of Z-score of BMD of femoral neck

	Z-score in tertiles		
	Lower tertile	Middle tertile	Upper tertile
<b>Men</b>			
No. of cases	163/867	106/814	136/765
Adjusted for age	1.42 (1.11-1.81)	1	1.18 (0.92-1.53)
Adjusted for age and BMI	1.33 (1.03-1.70)	1	1.21 (0.94-1.57)
Full model†	1.33 (1.01-1.74)	1	1.17 (0.89-1.55)
<b>Women</b>			
No. of cases	118/1164	109/1149	94/1062
Adjusted for age	1.09 (0.84-1.41)	1	0.90 (0.68-1.19)
Adjusted for age and BMI	1.06 (0.81-1.39)	1	0.92 (0.69-1.22)
Full model†	1.04 (0.78-1.38)	1	0.89 (0.66-1.21)

RR = relative risk for mortality obtained by Cox' proportional hazard analysis, 95 % confidence interval between parentheses

†Full model additionally included presence of diabetes mellitus, use of diuretics, lower limb disability and smoking status

Figure 5.1.2. Relative risk of all-cause mortality in men and women. Adjustment was made for age and body mass index.



Analyses repeated with the exclusion of subjects who died during the first year of follow-up, with the objective to exclude serious diseases at baseline, yielded similar results. Also, analyses repeated after exclusion of diuretics-users or subjects who suffered a hip fracture or any clinical fracture during follow-up yielded similar results. The inclusion of serum albumin, as a proxy of health status, had no additional effect on the risk estimates for mortality by BMD (8,29). Neither inclusion of the number of drugs used nor the lower limb disability index caused a significant change in relative risks.

## **Discussion**

The results of our study show that in men, low BMD is associated with an increased risk of mortality. There seems to be a threshold around the age-adjusted average of BMD (Z-score of zero). Above this threshold, there is no further decrease in relative risk. If anything, the risk appears to go up again in men with a high Z-score of BMD. In women, however, we could not identify a relationship between BMD and mortality.

Bone mineral density may be regarded as a marker of general health and ageing, representing lifelong effects of hereditary, endocrine and life style factors. Therefore, when studying BMD in relation to mortality, it is important to take confounders such as body mass index, presence of diabetes mellitus type II, lower limb disability and use of thiazide diuretics into consideration. These confounders do not all have the same effect on the relation between BMD and mortality and possibly have counteracting effects on the risk estimates. A higher body mass index is associated with an increase in BMD (4,21), but also with increased mortality (12,42). Also, presence of diabetes mellitus type II and use of thiazide diuretics are both associated with a higher BMD (7,26,28) and an increased mortality risk (1,19). Disability and smoking are associated with a higher mortality risk, but are inversely associated with BMD (4,20). Because of these opposing effects, we decided to study their effect not only by simply adjusting for it in the model, but also by fitting our model for separate groups, in a separate analysis.

In men, we found that a low BMD was significantly associated with an increased mortality in the total population, but also in subgroups. There appears to be threshold at a Z-score of zero below which the risk of mortality increases rapidly. When the BMD was analysed per standard deviation decrease, such thresholds were missed.

In women, Browner et al. found an inverse relationship between BMD as measured at the radius and calcaneus, and mortality, especially from stroke in 9704 elderly women, with a mean follow-up time of 2.8 years (3). The age

adjusted relative risk per standard deviation decrease in BMD was around 1.2. However, they also show that when BMD is divided in quintiles, more deaths occur in the lowest quintile, whereas the three mid quintiles have similar numbers of deaths. In the highest quintile less deaths are observed. Von der Recke et al. studied the relationship between bone mineral content (BMC) and mortality in a group of women soon after menopause and in a group late after menopause (27). They also found that relative risks of mortality increase when BMC is below the average, whereas under condition of BMC above average, the risk of mortality remains constant. An inverse relationship of BMD, measured at the calcaneus, with mortality in a general population of men and women aged 70 years and older, was observed by Johansson et al. (15). They found a stronger relationship in men than in women, which was confirmed in this study. However, all these previous studies have presented their relative risks only per standard deviation change in absolute BMD.

Unlike these previous studies, we did not observe a significant relationship between low BMD and mortality in women. It might be postulated that women with a low estrogen exposure during life have a lower BMD and have an increased risk of cardiovascular disease, but a decreased risk of estrogen related cancers, such as breast- and endometrial cancer (2,17,23,25). Therefore, our findings may be due to the fact that the increased risk of cardiac mortality and the decrease in risk of cancer mortality counteract each other in the analysis of the relationship between BMD and all-cause mortality. Furthermore, it could also be that in order to observe such a relationship in women, we have to follow them up for a longer period since women have a longer life expectancy.

When studying the association between BMD and mortality, it is important to thoroughly investigate whether a low BMD is not merely a marker for underlying illness. There are several possible reasons for this to occur. First of all, when a person is very ill, quite often he or she will have less physical activity, resulting in a lower BMD. In order to see whether this explained our results, we repeated the analyses excluding persons who had died during the first year of follow-up or excluding subjects who had a history of clinical fractures. Furthermore, we tried to correct for potential indicators for morbidity, by repeating the analyses adjusting for the number of drugs used and for lower limb disability. None of these analyses essentially changed the risk estimates.

Another possibility is that unfavourable lifestyle habits, such as a low physical activity and smoking play a role. Therefore, we also adjusted for this in our analyses. All these analyses suggest that a low BMD is not mainly due to morbidity and impaired mobility in our cohort, which makes these factors less plausible to explain the observed relation with mortality. There are, however, several other factors that may still play a role in the relationship between BMD and mortality, for instance low estrogen exposure and genetic factors.

A potential limitation of our study is that selection bias may have occurred. Our study population consists of 5819 healthy independently living subjects, who were able to come to our research centre. Therefore, it is likely that there is an underrepresentation of persons with severe lower limb disability in our cohort. However, this potential selection bias would only dilute the observed association.

In conclusion, the results of this study suggest that in men a non-linear relationship between BMD and mortality exists, which is independent of comorbidity and impaired mobility. In women, no significant relationship between BMD and all-cause mortality was observed.

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# *Chapter 6*

## *Cost-effectiveness of fracture prevention*





## *Chapter 6.1*

### *Cost-effectiveness of fracture prevention and the effects on breast cancer in elderly women*

*The Rotterdam Study*

## Abstract

Osteoporotic fractures, especially fractures of the hip, are associated with high morbidity, mortality and economic costs. Several therapeutical options for fracture prevention are available, some of which might also influence breast cancer and cardiovascular disease risk. The aim of this study was to evaluate cost-effectiveness of hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs) and bisphosphonates on fracture prevention, taking into account the effect of these drugs on breast cancer risk. We used a mathematical model, based on a life-table approach. Whenever possible, we used Dutch reference data. Essentially, four treatment strategies were evaluated. For HRT, a hip fracture risk reduction of 10 % and 50 %, respectively, and a vertebral fracture risk reduction of 50 % were assumed. For SERMs and bisphosphonates the assumed risk reductions were 10 % and 50 % for hip fractures, respectively and 50 % for vertebral fractures. We evaluated women at ages 55, 65 and 75 years at various intervention thresholds. The results of this model suggest that when the effects of drugs on breast cancer are taken into account, SERMs are more cost-effective than either HRT or bisphosphonates, especially before the age of 75 years. Only at age 75, bisphosphonates become more cost-effective. In conclusion, the results of this model suggest that in terms of cost-effectiveness SERMs are to be preferred over HRT, mainly because of the potential effects on breast cancer. At older ages, bisphosphonates become more cost effective than SERMs, due to their large hip fracture risk reduction.

## **Introduction**

Osteoporotic fractures, especially hip fractures, are associated with increased morbidity, mortality, and substantial economic costs. (1-7) Due to demographic changes, the incidence of fractures is increasing over time, hereby increasing the population burden of fractures. (6) We and others have previously found that bone mineral density and fracture risk are associated with the risk of breast cancer and atherosclerosis, as was described in detail in chapters 4.1 and 4.2. (8-19)

Several therapeutical options are available for the prevention of fractures. Estrogens, both endogenous and exogenous, are known to have bone-sparing effects. (20-26) Various studies have suggested that hormone replacement therapy (HRT) prevents the age-related loss in bone mineral density (BMD) (27-32) and decreases fracture risk in postmenopausal women. (31-44) Most of these studies, however, were designed as a case-control or cohort study, (34,37-44) whereas only few randomised controlled trials have been performed on HRT with fractures as an endpoint. (31-33,36) Even though HRT has favourable effects on bone, it is thought that women who use HRT are at increased risk of breast cancer (45,46), endometrial cancer (for unopposed estrogens) (23) and thrombo-embolism (47,48). Furthermore, although not expected, the Heart Estrogen/progestin Replacement Study (HERS) trial showed an increased myocardial infarction risk in women during the first year of taking HRT. (49) Selective Estrogen Receptor Modulators (SERMs) are also drugs that have estrogen-like effects on bone, (50) but, in contrast to HRT, these drugs appear not to have the negative effects on breast and endometrial cells. (51,52) In fact, there is evidence for a risk reduction of breast cancer. (53) In terms of costs, however, SERMs are more than 4 times as expensive as HRT. Finally, bisphosphonates also increase bone density and decrease fracture risk, and are frequently described drugs for fracture prevention. (54-57) Bisphosphonates are not known to have an effect on either breast cancer or cardiovascular disease.

When comparing different treatment strategies in terms of cost-effectiveness, it is important that besides numbers and costs of osteoporotic fractures, the loss in quality of life (QOL) after an event is also taken into account. Therefore, cost-effectiveness will be expressed in Euros (€) per Quality Adjusted Life Year (QALY) gained.

The aim of this study was to investigate the cost-effectiveness of prevention of osteoporotic fractures in elderly women from the Rotterdam Study, using several different scenarios and taking the effects of the different treatment strategies on breast cancer into account.

## Materials and methods

### *Model development*

For the economic evaluation of different treatment strategies of fracture prevention, we developed a model based on a life-table design.

### *Baseline incidence rates*

The baseline age-adjusted hip fractures incidence was derived from the Dutch hip fracture incidence data, based on nationwide hospital registration data gathered for the year 1999. (58) The baseline incidence of vertebral fractures was derived from the recent Dutch guidelines on osteoporosis. (59) The incidence of breast cancer was based on data from the Dutch cancer registry. (60)

### *Baseline BMD and thresholds for analysis*

The femoral neck BMD distributions used were derived from the Rotterdam Study, as published previously. (61) A T-score of BMD was calculated, using average values for young adult women from a Dutch study, which were also measured using a Lunar DPX-L densitometer. (62) With those reference values, a T-score of -2.5 corresponded to a BMD level of 0.675 g/cm<sup>2</sup> in women. (63) This value was very similar to the threshold value in the machine specific USA Female Reference population, which was 0.681 g/cm<sup>2</sup>. (64) In the cost-effectiveness analysis, we used a T-score of -2.5, and -1 as treatment thresholds as these thresholds are commonly used in clinical practice and well-accepted thresholds for the WHO definition of osteoporosis and osteopenia, respectively. (65)

### *Interrelation of events*

To describe the relation between BMD and the endpoints of interest, the relative risk (RR) of the event at various levels of BMD was calculated in reference to the average risk in the population. We previously described this technique for hip fracture risk. (61) When the risk is described as a fixed relative risk per unit change (decline) of BMD, such as was done for hip fractures, the relative risk compared to the average in the population is obtained by  $RR = a^{-z} / C$ . Here “a” represents the risk per unit change of BMD (2.6 in the case of the relation of hip fracture with femoral neck BMD) and “z” represents the Z-score of BMD. The correction factor “C” is given by

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

The relation of vertebral fractures with BMD was derived from the incident vertebral fracture data from the Rotterdam Study, as was described in chapter 2.1. (66) Similarly, the interrelation of BMD with breast cancer was modeled based on data from the Rotterdam Study as described in this thesis (chapter 4.2).

Both for vertebral fractures and for breast cancer, a cubic model best described the association with BMD. In this case, the relative risk of an event compared to the average in the population can be calculated similarly by dividing the calculated risk by the correction factor “C”. The relative risk compared to the average population will be given by:

$$RR = e^{(\alpha + \beta_1 z + \beta_2 z^2 + \beta_3 z^3)} / C$$

where C is given by

$$C = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \cdot e^{-0.5z^2} \cdot e^{(\alpha + \beta_1 z + \beta_2 z^2 + \beta_3 z^3)} \cdot dz$$

The specific betas and correction factors are shown in Table 6.1.1

#### *Mortality*

General mortality was based on Dutch cross-sectional mortality data from 1999, (67) and modeled as a continuous function with the SPSS curve fitting function (SPSS for Windows, version 9.0). For the cost-effectiveness analysis, we estimated the increased mortality after hip fractures and after breast cancer. For hip fractures we used the in-hospital mortality after hip fracture obtained from Dutch registration data as a proxy for the hip fracture specific mortality. (67) For breast cancer, the tumor specific mortality in the first 5 years after diagnosis, and again in years 6 until 20 after diagnosis was based on the relative survival in the Netherlands as described by Dutch cancer registration data. (68) For vertebral fractures, no excess mortality was assumed.

Table 6.1.1. Overview of the parameters and assumptions used in the model

<b>Baseline Incidences</b>		
Hip fracture	$9.2 \cdot 10^{-15} \cdot \text{age}^{8.9456}$	
Vertebral fracture	$1765.9 + 31.7876 \cdot \text{age} + 0.0514 \cdot \text{age}^2$	
Breast Cancer	$-3.4864 + 0.1679 \cdot \text{age} - 0.001 \cdot \text{age}^2$	
<b>Femoral Neck BMD</b>		
Average Femoral Neck BMD (g/cm <sup>2</sup> )	$1.121284 - 0.00456 \cdot \text{age}$	
SD Femoral Neck BMD (g/cm <sup>2</sup> )	0.134	
<b>Risk by femoral neck BMD Z-Score (z)</b>		
Hip fracture	$2.6^{-z}/C$	C=1.578541
Vertebral fracture	$(-0.652 \cdot z + 0.113 \cdot z^2 + 0.002 \cdot z^3)/C$	C=1.46
Breast Cancer	$(-0.1015 \cdot z - 0.2277 \cdot z^2 + 0.0631 \cdot z^3)/C$	C=0.832
<b>Mortality (per year)</b>		
General Mortality	$0.0508 \cdot e^{(0.086 \cdot \text{age})}$	
Hip fracture specific mortality (first year only)	$1/(1 + e^{(-9.4444 + 0.0812 \cdot \text{age})})$	
Breast Cancer specific mortality (1-5 year)	$31.6375 + 0.5664 \cdot \text{age} - 0.005 \cdot \text{age}^2$	
Breast Cancer specific mortality (6-20 year)	$15.3793 + 0.2753 \cdot \text{age} - 0.0024 \cdot \text{age}^2$	
<b>Quality of life (QOL)</b>		
Average QOL under 65	0.8	
Average QOL 65 and over	0.715	
<b>Costs (€)</b>		
	<b>First Year</b>	<b>Subsequent years</b>
Hip fracture	9000	1700
Vertebral fracture	500	100
Breast Cancer	9500	170
<b>Utility loss (QALY loss)</b>		
	<b>First Year</b>	<b>Subsequent years</b>
Hip fracture (under age 65)	0.2413	0.1284
Hip fracture (65 and over)	0.2279	0.1284
Vertebral fracture	0.0387	0.0227
Breast Cancer	0.1	0.1

## **Costs and Utilities**

### **Cost of event**

Overall, in 1993 the healthcare costs due to osteoporotic fractures in the Netherlands were estimated at around € 210 million. (69) Over 85 % of these costs are due to hip fractures. In this estimation, only direct medical costs, as made in the hospital, the nursing homes and the ambulant clinical care are taken into account. The average hip fracture costs are estimated at € 9000 for the first year after fracture and € 1700 for the years thereafter. (70) (Table 6.1.1) In the current model, all costs were incremental costs only. For vertebral fractures, it is difficult to estimate costs, and cost estimates differ between studies. The main reason for this is that there is no consensus about the definition of vertebral fractures. (71-75) Furthermore, about two-thirds of all vertebral fractures remain clinically unnoticed. The costs for vertebral fractures as used in this model were estimated in the Netherlands at € 500 in the first year and € 100 in the years thereafter (table 6.1.1). (70) For breast cancer, cost estimates were taken from a Swedish modeling study, since we did not have reliable Dutch cost estimates available. (76)

### **Cost of intervention**

For interventions costs we used the average public prices of the drugs. (77) We did not take diagnostic and monitoring costs into account, because the aim of the study was to compare different drug regimens. We therefore assumed that all costs, other than the costs of the drugs would be the same for all treatment strategies. This is also the reason why we did not take the additional costs of calcium and vitamin D suppletion into account. In our model, treatment costs per year were thus estimated as € 100 for HRT and € 450 for both SERMs and bisphosphonates.

### **Effects of fractures and breast cancer on Quality of Life**

The effect of fractures on health related quality of life (QOL) was expressed as Quality Adjusted Life Years lost (QALY). In this measure the QOL loss is expressed as going from 0 (death) to 1 (perfect health). The loss in QOL is then multiplied by the time spent in this condition, resulting in a QOL measure weighted by time, the Quality Adjusted Life Year (QALY). A Dutch expert panel (Table 6.1) estimated the QALY loss in the first and subsequent years after both hip and vertebral fractures. A detailed overview of how this panel arrived at these estimates is described in the Dutch Guideline for Osteoporosis. (59) We used Swedish data to estimate the QALY loss related to breast cancer. (76) Again, estimates are shown in Table 6.1.1.

### **Cost-effectiveness**

In general, thresholds for cost-effectiveness are disputable and there is currently no consensus. Two thresholds are often used, one of € 20.000/QALY gained and one of € 30.000 /QALY gained. The first is the cost-effectiveness threshold

that was used in the Dutch guidelines for Osteoporosis, as well as in other Dutch guidelines. (78-81) The second is based on the definition of cost-effectiveness that is used in the NOF guidelines for osteoporosis. (82)

**Intervention scenarios**

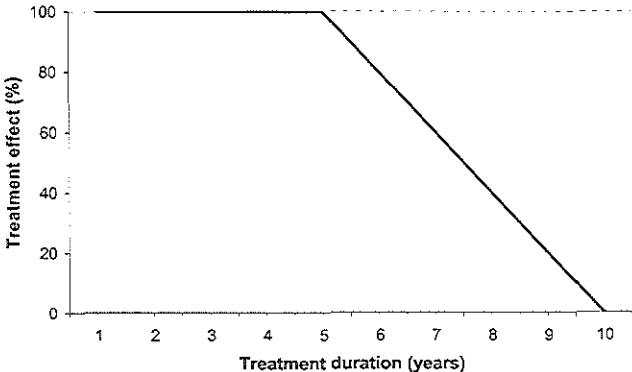
The effects of the different intervention scenarios were expressed as the relative risk reduction for each of the outcomes under study and based on a literature review. (28,31-44,49,50,54-57,83-86) Because HRT risk estimates for hip fracture prevention are not straightforward in literature, we used 2 alternative scenarios, one with a hip fracture risk reduction of 10 % and another with a risk reduction of 50 %. The assumed risk reductions for different treatment strategies that were used in the model are presented in table 6.1.2

**Table 6.1.2. Assumed risk reduction in various intervention scenarios**

	Risk reduction		
	Hip fractures	Vertebral fractures	Breast cancer
HRT	10 % / 50 %	50 %	-10 % (risk increase)
SERMs	10 %	50 %	50 %
Bisphosphonates	50 %	50 %	0 %

We assumed an intervention for the duration of 5 years, corresponding to the time period for which data are available from most clinical trials. (Fig 6.1.1) We also assumed an offset of treatment effect period of 5 years.

**Fig 6.1.1. Assumed treatment effect over time**



We assumed that through this offset of treatment period the risk reduction due to treatment linearly declined towards zero. Although little is known about this period of declining effect, it is widely believed that the effect of treatment does



not stop immediately after the cessation of treatment. On the other hand it is improbable that treatment effects would continue throughout life.

### **Discounting**

In economic evaluations, it is common practice to discount all costs and effects of treatment. In short, discounting is a way to adjust for the fact that costs and effects are less valuable when they occur in the future as compared to current costs and effects. This difference in value is in part due to inflation, but also due to personal appreciation of both costs and events. (87) In concordance with those guidelines, all results are shown with a discount rate of 4% per year for both costs and effects.

### **Treatment scenarios**

We calculated the cost-effectiveness ratios for different scenarios of intervention in women with a T-score of BMD of  $-2.5$  and for women with a T-score of  $-1.0$ . All analyses were performed for women aged 55, 65 and 75 years.

We present the cost-effectiveness results for different situations:

Scenario 1: the intervention has an effect on fracture risk only. In this scenario we do not include any effects on breast cancer.

Scenario 2: the intervention not only has an effect on fracture risk, but also has an effect on breast cancer. To model this, we used the assumptions that are described in detail in table 6.1.1. In this scenario, however, we assume that breast cancer is not related to BMD, and is thus unrelated to fracture risk.

Scenario 3: the intervention has an effect on both breast cancer and fracture risk, In contrast, we now assume that breast cancer is related to fracture risk through femoral neck BMD. This association is described in figure 6.1.3.

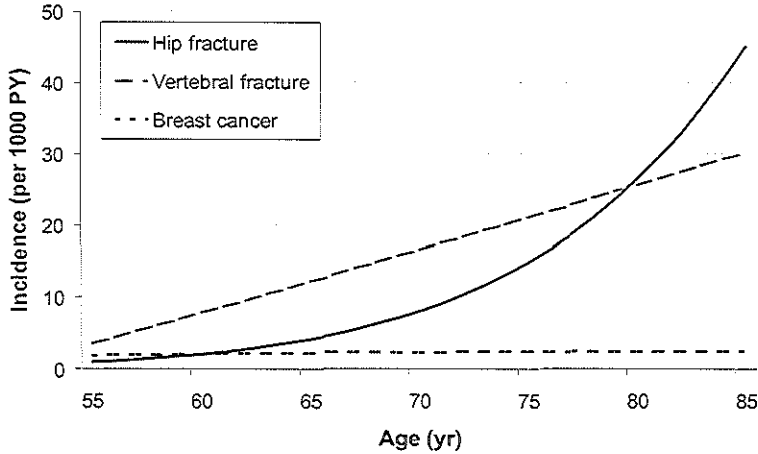
### **Results**

Figure 6.1.2 shows the baseline incidence rates of the various outcome events by age, as they were used in the model. These incidence rates were derived from the data sources as described in the materials and methods section.

In the previous chapters of this thesis we examined the relation of these outcome events with BMD (chapters 2.1 and 4.2, for vertebral fractures and breast cancer, respectively).

These associations were recalculated to reflect the relative risk compared to the average in the population. In figure 6.1.3 we show the associations between femoral neck BMD and hip fractures, vertebral fractures and breast cancer. The risk of both hip and vertebral fractures increases exponentially with decreasing BMD. Furthermore, in subjects at low BMD, the risk of breast cancer is lower than the average in the population. These analyses were repeated with lumbar spine BMD instead of femoral neck BMD, and similar risk functions were observed (data not shown).

Figure 6.1.2. Baseline incidences in women of the various outcome events by age used in the model.



Excess mortality in the first year after diagnosis of hip fractures and breast cancer is shown in figure 6.1.4.

We calculated the cost-effectiveness ratios for the different scenarios. Values are given for women with a T-score of femoral neck BMD of both  $-1.0$  and  $-2.5$ .

Figure 6.1.3. Relation of relative risk of different outcome events with femoral neck BMD in women (relative risk relative to average of population)

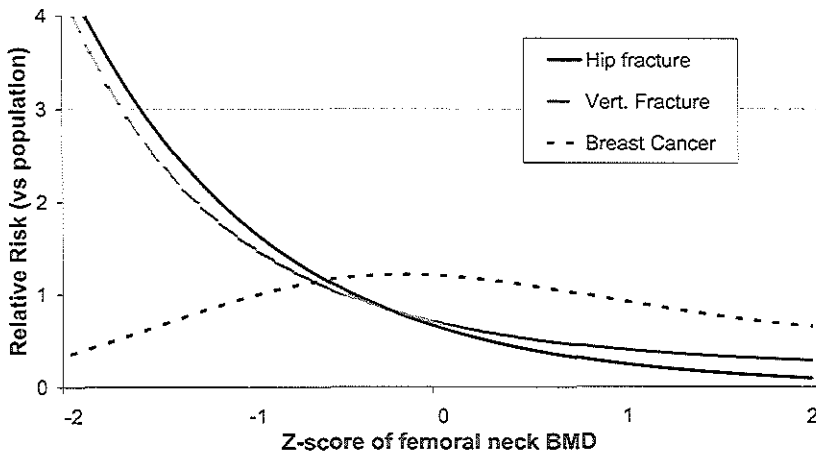


Figure 6.1.4. Excess mortality in the first year after diagnosis for hip fractures and breast cancer

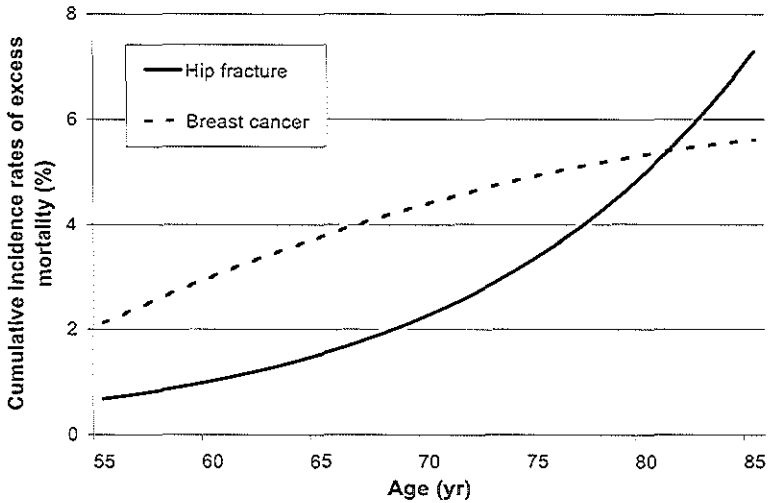


Table 6.1.3 shows cost-effectiveness ratios for various treatment options in scenario 1. In scenario 1, the intervention has an effect on fracture risk only. In this scenario we do not include any effects on breast cancer.

Table 6.1.4 then shows cost-effectiveness ratios for scenario 2: the intervention not only has an effect on fracture risk, but also has an effect on breast cancer. In this scenario, however, we assume that breast cancer and fracture risks are unrelated.

Finally, the results of scenario 3 (the intervention has an effect on both breast cancer and fracture risk, and breast cancer is related to fracture risk via femoral neck BMD) are shown in Table 6.1.5.

As an example of how these results should be interpreted, we go through the results for women aged 55 years at a T-score of  $-1.0$ .

When HRT is chosen for fracture prevention, and we assume that the hip fracture risk reduction is 10 % and vertebral fracture risk reduction is 50 %, costs per QALY gained are € 166,833 when only effects of treatment on fracture risk are taken into account (scenario 1, table 6.1.3). If we now assume that indeed there is a negative effect of HRT on breast cancer risk, and we assume that fracture risk and breast cancer risk are interrelated via femoral neck BMD, HRT now actually results in negative QALYs, and thus an overall *decrease* of QALYs (scenario 3, table 6.1.5).

If the HRT analyses are repeated with assumed risk reductions for both hip and vertebral fractures of 50 %, we again find negative QALYs, suggesting that at age 55, the effects of HRT on breast cancer outweigh the effects on osteoporotic fractures in women.

When we assume that SERMs only have effects on fracture risk, the costs per QALY gained are € 776,340 (scenario 1, table 6.1.3). Thus, overall SERMs are expensive drugs, and if no effect on breast cancer is assumed, this type of drug is far less cost-effective than HRT. However, if we now assume that indeed SERMs result in a 50 % breast cancer risk reduction, and that fracture risk and breast cancer risk are associated via femoral neck BMD, the costs per QALY gained drop dramatically to a cost-effective value of € 24,773. Thus, when the effects of drugs on breast cancer are taken into account, SERMs become favourable over HRT (scenario 3, table 6.1.5).

For bisphosphonates, no effect on breast cancer risk is assumed. Thus, costs per QALY gained are € 416,390 at age 55 years, which is the same for all three scenarios.

**Table 6.1.3. Results from scenario 1: treatment effect only on fracture risk, no effect on breast cancer risk**

	Age		
	55	65	75
<b>HRT (10/50/-)<sup>1</sup></b>			
T-Score -1	€ 166,833	€ 94,989	€ 77,248
T-Score -2.5	€ 42,281	€ 22,392	€ 15,550
<b>HRT (50/50/-)<sup>2</sup></b>			
T-Score -1	€ 84,201	€ 36,187	€ 18,715
T-Score -2.5	€ 14,003	€ 438	Net savings
<b>SERMs (10/50/-)<sup>3</sup></b>			
T-Score -1	€ 776,340	€ 456,240	€ 381,596
T-Score -2.5	€ 217,173	€ 131,970	€ 107,301
<b>Bisphosphonates (50/50/-)<sup>4</sup></b>			
T-Score -1	€ 416,390	€ 203,866	€ 128,635
T-Score -2.5	€ 102,339	€ 45,377	€ 23,506

Values are costs (€) per QALY gained

<sup>1</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

<sup>2</sup> 50 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

<sup>3</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

<sup>4</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

**Table 6.1.4: Results from scenario 2: treatment effect on fracture risk and breast cancer risk, but fracture risk and breast cancer are unrelated**

	Age		
	55	65	75
<b>HRT (10/50/-10)<sup>1</sup></b>			
T-Score -1	Neg QALYs	Neg QALYs	Neg QALYs
T-Score -2.5	Neg QALYs	€ 62,094	€ 26,373
<b>HRT (50/50/-10)<sup>2</sup></b>			
T-Score -1	Neg QALYs	€ 953,038	€ 35,931
T-Score -2.5	€ 45,062	€ 1,502	Net savings
<b>SERMs (10/50/50)<sup>3</sup></b>			
T-Score -1	€ 29,779	€ 37,815	€ 51,316
T-Score -2.5	€ 27,154	€ 30,428	€ 36,011
<b>Bisphosphonates (50/50/0)<sup>4</sup></b>			
T-Score -1	€ 416,390	€ 203,866	€ 128,635
T-Score -2.5	€ 102,339	€ 45,377	€ 23,506

Values are costs (€) per QALY gained

<sup>1</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, -10 % breast cancer risk reduction (increased risk)

<sup>2</sup> 50 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, -10 % breast cancer risk reduction (increased risk)

<sup>3</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 50 % breast cancer risk reduction

<sup>4</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

**Table 6.1.5. Results of scenario 3: treatment effect on fracture risk and breast cancer risk, and fracture risk and breast cancer are related to each other via femoral neck BMD**

	Age		
	55	65	75
<b>HRT (10/50/-10)<sup>1</sup></b>			
T-Score -1	Neg QALYs	Neg QALYs	Neg QALYs
T-Score -2.5	€ 583,213	€ 55,323	€ 28,138
<b>HRT (50/50/-10)<sup>2</sup></b>			
T-Score -1	Neg QALYs	Neg QALYs	€ 36,437
T-Score -2.5	€ 27,868	€ 1,400	Net savings
<b>SERMs (10/50/50)<sup>3</sup></b>			
T-Score -1	€ 24,773	€ 33,734	€ 50,546
T-Score -2.5	€ 37,124	€ 32,381	€ 33,620
<b>Bisphosphonates (50/50/0)<sup>4</sup></b>			
T-Score -1	€ 416,390	€ 203,866	€ 128,635
T-Score -2.5	€ 102,339	€ 45,377	€ 23,506

Values are costs (€) per QALY gained

<sup>1</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, -10 % breast cancer risk reduction (increased risk)

<sup>2</sup> 50 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, -10 % breast cancer risk reduction (increased risk)

<sup>3</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 50 % breast cancer risk reduction

<sup>4</sup> 10 % hip fracture risk reduction, 50 % vertebral fracture risk reduction, 0 % breast cancer risk reduction

## Discussion

The results of this model show that in fracture prevention the inclusion of effects on breast cancer of the various intervention alternatives has an important influence on the cost-effectiveness balance. SERMs are, in this model, more cost-effective for fracture prevention than either HRT or bisphosphonates in women aged 55 or 65 years. Only at age 75 years and over, bisphosphonates become more cost-effective.

When testing different drugs for cost-effectiveness of fracture prevention only, HRT is favourable over both SERMs and bisphosphonates at all ages and for both a T-score of BMD of  $-1.0$  and  $-2.5$ . This is due to fact that effects of HRT on vertebral fracture risk and perhaps on hip fracture risk are substantial and costs are low.

However, when breast cancer was added to the model, at age 55 years, a 5-year treatment strategy of HRT results in a QALY loss rather than a gain due to the increase in breast cancer incidence. An important part of the loss of QALYs is due to the actual loss of life years. This can be explained by the fact that although at age 55 years, incidence rates of breast cancer, hip fracture and vertebral fractures are comparable, there are substantial differences in reduction in quality of life (QOL) due to these diseases. Most importantly, the mortality rate after breast cancer is higher than after hip fracture and that breast cancer mortality occurs at younger age, resulting in much more life years lost. This strongly influences the total QALY lost due to breast cancer cases. Since the health related QOL is age dependent, we adjusted for this by using the average health related QOL during the lost life years. (88)

A scenario with SERMs now becomes much more attractive, and, depending on the definition used, might even be considered cost-effective. These results suggest that especially at younger ages, the effects on breast cancer outweigh the effects on fracture prevention. At age 65 years, results are still quite comparable to those at age 55 years.

At age 75 years, however, bisphosphonates become more cost-effective than SERMs are. At this age, the incidence of hip fractures is increasing rapidly, and as of age 80, hip fracture incidence rates are higher than either vertebral fracture and breast cancer incidence rates.

In contrast to SERMs, bisphosphonates largely reduce hip fracture risk (estimated risk reductions 50 % and 10 %, for bisphosphonates and SERMs, respectively). Hip fractures are associated with higher costs than either vertebral fractures or breast cancer. At younger ages, breast cancer played an important role in determining cost-effectiveness ratios, but at age 75, the total number of life years lost is no longer as high as it was at ages 55 and 65. Thus, due to the strong effects on hip fractures, as well as the diminished effect of breast cancer on total cost per QALY gained, it is not surprising that at older ages, bisphosphonates, are more cost-effective than SERMs.

It should be noted that HRT was more cost-effective at age 75 years, but the compliance of HRT is likely to be low at old age, given the fact that with opposed estrogens a withdrawal bleeding is also reintroduced into a woman's life.

There are disadvantages to using modelling to test cost-effectiveness of different treatment scenarios for fracture prevention. The main problem is that the model is based on various assumptions. We estimated the effectiveness of the various drugs in terms of both fracture prevention and breast cancer risk by a thorough review of existing medical literature.

For HRT, only few and relatively small trials have been performed. (28,31-33,36,49) In the larger trials, which often were not primarily designed for osteoporosis research, a hip fracture risk reduction of about 5 to 15 % was observed, (28,49) whereas from smaller trials and population-based cohort studies a risk reduction of around 50 % was observed. (31-44) A recent meta-analysis showed an overall risk reduction of 27 % that was statistically significant. (35) Since such large discrepancies were observed, we decided to use different scenarios for HRT on fracture prevention.

For SERMs, we assumed a 10 % hip fracture risk reduction. The MORE trial, however, suggested that SERMs did not significantly reduce hip fracture risk (RR 1.1; 95 % C.I. 0.6-1.9), whereas for all non-vertebral fractures, a non-significant 10 % risk reduction was observed. (50) The fact that no effect on hip fractures was observed may be due to low power, and indeed a higher femoral neck BMD was observed in women taking SERMs as compared to the placebo group. If, however, there truly is no hip fractures risk reduction, this still would not essentially change our results, especially at ages 55 and maybe at 65, since results are mainly driven by breast cancer.

For SERM breast cancer risk reduction, we again based risk estimates on the MORE trial, which showed a 70 % breast cancer risk reduction. (53) However, because these results were obtained from one trial only, and because this trial did not have breast cancer as a primary outcome, we used a somewhat conservative breast cancer risk reduction of 50 %. True risk reductions may be somewhat different, but when higher, this would only strengthen our results.

Furthermore, for this model, we assumed that for all drugs a similar wear-off pattern lasting five years, after which no effects of the drug were present. The true wear-off pattern is not exactly known for any of the drugs studied, and may differ from the assumed pattern. If the wear-off pattern were similar for all drugs, but different from what we assumed, this would not alter the message of this study. In addition, 100 % compliance is assumed in this study, although this may not be very realistic. Again, as long as compliance rates are comparable between drugs, this will not change the message of the paper.

It is known that besides breast cancer, both SERMs and HRT also influence cardiovascular risk factors. (23,47,48) (51,89) The Heart and Estrogen/progestin Replacement Study (HERS) trial, however, overall did not show a risk reduction on cardiovascular disease. (49) In the first year, even an increased risk of myocardial infarctions was observed. Ongoing trials, including the Women's Health Initiative (WHI) and the Women's International Study of Long Duration



Estrogen after Menopause (WISDOM), will determine whether HRT is or is not effective in primary coronary heart disease prevention. (90,91) For SERMs, the Multiple Outcomes of Raloxifene Evaluation (MORE) trial recently showed that in women at increased cardiovascular risk, SERMs reduced cardiovascular disease risk by 40 %. (92) This trial, however, was not designed to study cardiovascular endpoints. In the Raloxifene Use for The Heart (RUTH) trial, coronary heart disease is a primary endpoint, but this trial is currently still ongoing. (93) Since there are currently so many uncertainties about the potential protective effect of both HRT and SERMs on cardiovascular disease, we decided not to consider any potential effect on cardiovascular disease in the current model.

It is not feasible to give preventive treatment to entire elderly population with a T-score at or below  $-1.0$ . This would be far too expensive, side effects would be considerable, individual effects and consequently compliance would be very low. Thus, tools are needed to identify subjects who are eligible for fracture prevention. For this model, we examined the costs and effects of the different treatment scenarios in women at different values of T-score of BMD. We used the values of a T-score of  $-1.0$  and  $-2.5$  since these values represent the cut-off values for definitions of osteopenia and osteoporosis, respectively. The T-score was developed by a working group of the World Health Organisation (WHO) and the definition on osteoporosis was originally intended for diagnostic purposes only. In clinical practice, though, it is currently often used as a treatment threshold. As described in chapters 3.1 and 3.2, there are also disadvantages to the use of T-scores in fracture prevention. When using a T-score of BMD of  $-2.5$  as a threshold for fracture prevention, two thirds of all non-vertebral and vertebral fractures and about 50 % of hip fractures would be missed. Thus, from a public health point of view, a screening strategy based on bone mineral density alone is unlikely to be sufficient for prevention of fractures. Thus, there is a need to develop more adequate tools for identification of subjects who will fracture.

In conclusion, the results of this model suggest that at ages 55 and 65 years, SERMs are more cost-effective for fracture prevention than HRT, mainly because of the effects on breast cancer. At older ages, bisphosphonates become more cost-effective than SERMs. As soon as the results of trials on cardiovascular effects become available, further study is necessary to extend the model with effects of drugs on cardiovascular disease.

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# *Chapter 7*

## *General discussion*



In this thesis, we investigated several aspects of osteoporosis, as osteoporosis is more than just fractures alone. All studies were performed in the Rotterdam Study, which is a large population-based cohort study among men and women aged 55 years and over from Ommoord, a suburb of Rotterdam, the Netherlands.

First, we evaluated the incidence of, and risk factors for vertebral fractures. Then, we studied fracture prevention, and examined whether current methods for identifying subjects at risk for fractures are adequate. We investigated the interrelations between bone mineral density, atherosclerosis and breast cancer, and also the association between BMD and overall mortality was studied. The thesis ends with a comparison of the cost-effectiveness of hormone replacement therapy (HRT), Selective Estrogen Receptor Modulators (SERMs) and bisphosphonates for fracture prevention.

## **Main findings**

### **Vertebral fractures**

Vertebral fractures are common fractures in osteoporosis, and these fractures are associated with increased functional impairment, (1) back pain and kyphosis. (2,3) Furthermore, even in subjects without symptoms, vertebral fractures are associated with a decreased quality of life, which is not only the result of back problems, but also of other conditions, such as depression. (4,5) Several studies have shown that the presence of a vertebral fracture is associated with increased mortality, as well as with an increased risk of both new vertebral and non-vertebral fractures, such as hip fractures. (6-12)

Nonetheless, in contrast to non-vertebral fractures, only few studies on incidence of vertebral fractures have been performed, especially in men. (8-10,13-15)

This is because three important factors complicate the study of vertebral fractures.

First of all, in contrast to non-vertebral fractures, vertebral fractures mainly occur spontaneously (or without major trauma), and only in about one third of all cases clear symptoms, leading to clinical recognition of a fracture, are present. (13) Thus, many vertebral fractures remain clinically unnoticed. This means that for the follow-up of vertebral fractures, it does not suffice to regularly check with General Practitioners' patient records and hospital records to find all new cases, as is standard procedure for non-vertebral fracture follow-up. Instead, one has to evaluate radiographs of the thoracolumbar spine at (at least) two points in time, if one wants to assess vertebral fracture incidence.

Here a second complication becomes evident. Currently, there is no consensus about the definition of a vertebral fracture. (16-20) Several methods have been developed for the evaluation of spinal radiographs. Every method uses slightly

different cut-off values in loss of vertebral height. In this thesis, we used the McCloskey-Kanis method, which is especially developed for assessing both the prevalence and incidence of vertebral osteoporosis in the population and in prospective studies. (16) In contrast to other methods, this method predicts vertebral heights and ratios for the individual patient rather than comparing them exclusively to a reference population, resulting in a lower false positive rate. However, it may well be that some misclassification has occurred due to the method used for fracture identification.

The fact that we chose for a morphometrical assessment instead of a visual semiquantitative assessment by an experienced radiologist might result in higher numbers of both false positive and false negative vertebral fractures. (21) To reduce numbers of false positives, all fractures were confirmed by visual interpretation by an expert in the field, in order to rule out artefacts and other etiologies, such as pathological fractures. Therefore, we will mainly have false negatives, because, as compared to the semiquantitative approach, the ability to detect the milder vertebral fractures is supposedly lower for the morphometrical approach. (21) Consequently, this will result in a potential underestimation of the true incidence of vertebral fractures in our population.

A third important complication when studying the incidence of vertebral fractures is that a substantial selection bias arises in the study population. This is due to the fact that subjects had to survive up to the second follow-up visit in order to have a second radiograph of their spine taken. Because of this bias, it is likely that the incidence rates, as described in chapter 2.1, are an underrepresentation of the true incidence of vertebral fractures, especially at older ages. Also, the generalisability of our results to the general population may be hampered by this selection bias.

### **Incidence of vertebral fractures**

The results of our study showed that although the absolute incidence of vertebral fractures is lower in men than in women, the risk of an incident vertebral fracture is similar at any given level of lumbar spine BMD in men and women after adjustment for age and the presence or absence of prevalent vertebral fractures (chapter 2.1). Therefore, the difference in absolute incidence in men and women may be due to the fact that overall, men have a higher peak bone mineral density and loose bone at a lower rate than women do. (22) In line with this finding, Lunt and colleagues also suggested that BMD, together with age, explain much of the differences in risk of vertebral fractures between men and women in a cross-sectional analysis. (23)

### **Risk factors for incident vertebral fractures**

In chapter 2.1 we show that both a low BMD and the presence of baseline prevalent vertebral fractures are strong and independent risk factors for incident

vertebral fractures. For women only, one previous study has suggested that both these risk factors were indeed predictors for incident vertebral fractures. (8) For men, no evidence was available thus far.

The main problem for both BMD and prevalent vertebral fracture assessment is that expensive methods of measurement are required, which currently cannot be performed in the general practice. In addition, the patient is exposed to irradiation. Thus, there is a clear need for more easily measurable risk factors for incident vertebral fractures, as was described in chapter 2.2.

We tested whether risk factors are independent from BMD and prevalent vertebral fractures, to assess whether these factors yield additional information other than that provided by BMD and prevalent vertebral fractures. The results of this study provide new insight in the etiology of incident vertebral fractures. In women, the risk of incident vertebral fractures increased strongly with age. In men, however, no clear association between age and incident vertebral fractures could be observed. Cross-sectional data from the multi-centre European Vertebral Osteoporosis Study (EVOS) study have already suggested that age was more strongly associated with prevalent vertebral fractures in women than in men. (24) The lack of association between increasing age and incident vertebral fractures in men is probably partly related to the health selection bias during follow-up that was described above.

Low body weight was a univariate risk factor for incident vertebral fractures, but this association disappeared after adjustment for BMD. This suggests that weight, at least in part, is a reflection of BMD. Burger et al previously showed this to be true for hip fractures. (25) Therefore, when the aim is to create a risk assessment tool for prediction of vertebral fractures, weight might be used as a measure of BMD, instead of actually measuring BMD.

Current smoking at baseline was associated with an increased incident vertebral fracture risk in both men and women, even though only statistically significant in women. Several studies have suggested an inverse relation between smoking and BMD. (26-28) The mechanism through which smoking influences BMD and fracture risk is not fully elucidated. Some research suggests that nicotine directly influences bone metabolism. (29) Smoking might also influence BMD and fracture risk through its effect on body weight, sex steroid hormone levels and other hormones and enzymes involved in bone regulation or overall lifestyle. (30-37) Finally, there is indirect evidence that smoking may damage blood supply to bone. (38-40) Other risk indicators for incident vertebral fractures in women were the use of a walking aid, probably as a measure of low physical activity and co-morbidity, and an early age at menopause (at or before age 45). For men, the only additional significant risk factor besides low BMD and the presence of prevalent vertebral fractures was a positive history of non-vertebral fractures at or after age 50.

We evaluated the predictive power of only the easily assessable risk factors (age, weight, use of a walking aid, history of non-vertebral fractures, current smoking and — for women — early age at menopause), only BMD and the presence of prevalent vertebral fractures or all factors combined. Overall, incident vertebral fracture prediction was strongest when combining all factors. In women, though, the clinical risk factors alone also provided a relatively good prediction model. For men, vertebral fracture prediction was much improved when (additional) information on BMD and prevalent vertebral fractures was present. This could be expected since in men, only a history of non-vertebral fractures was a significant and independent risk factor for incident vertebral fracture.

Based on these and perhaps also other easily assessable risk factors, it would be very interesting to develop a risk score for vertebral fractures, which can be used by the general practitioner to screen for subjects who are eligible for fracture prevention or for bone strength assessment. The aim would be to create a risk score, which the general practitioner can fill out together with the patient. The odds ratios, as presented in this thesis, might be used to create a weighted risk score, on basis of which an estimate of the patient's absolute vertebral fracture risk can be calculated, in a similar way as was previously presented for hip fractures by Burger et al. (25) This might help the physician to decide whether or not it is informative to have the patient's BMD measured or a radiograph taken, or even just to initiate therapy. Once a risk score is developed, it has to be validated in other population-based cohort studies with data on incident vertebral fractures present, such as the Study of Osteoporotic Fractures. It might well be that, especially for men, there is insufficient power to create stable risk scores. However, there are several possibilities available to increase power.

First of all, it might be worthwhile to evaluate the radiographs of the third follow-up visit, which is currently ongoing, for the presence of incident vertebral fractures.

Furthermore, now only radiographs of subjects who visited both the baseline and second follow-up examination were evaluated, but it would also be of interest to evaluate their first follow-up radiographs to see whether the incident vertebral fracture was already present at that time.

To substantially increase power in this respect, we could also evaluate radiographs of subjects who only went to the baseline and first follow-up visit, again using the McCloskey-Kanis method. Based on these data, it will be possible to study differences in risk factors for incident vertebral fractures soon after the baseline visit and those that occurred after a longer time period. Such an analysis will provide additional information on the etiology of vertebral fractures.

Given recent technological developments, it is currently also possible to evaluate the spine for vertebral fractures by the same machine that is used for BMD

measurement. Using this approach, one can assess both BMD and the presence of prevalent vertebral fractures, the strongest risk factors for incident vertebral fractures, during a single measurement session. There are disadvantages of using such an approach for assessing the presence of vertebral fractures, for it is uncertain whether the sensitivity of detecting vertebral fractures is quite as high as when using the morphometrical approach based on radiographs. It might give a good first impression on whether a vertebral fracture is present or not, especially in those subjects in whom BMD measurement will be performed anyway. Since we already have data on morphometrically assessed vertebral fractures available, we should consider studying the sensitivity and specificity of using the DXA to assess presence or absence of prevalent and / or incident vertebral fractures in a pilot study within the Rotterdam Study.

### **Interrelations between bone mineral density, atherosclerosis and breast cancer**

Estrogen levels, both endogenous and exogenous, are widely considered to influence bone mineral density and fracture risk, as well as breast cancer and cardiovascular disease risk. (37,41-60) It is difficult, however, to classify a woman's long-term exposure to endogenous estradiol by a single measurement, since these levels strongly vary over time, especially in premenopausal women. Bone mineral density, in contrast, might be regarded as a crude marker for lifelong estrogen exposure, with high bone density reflecting high estrogen exposure throughout life. (43) Based on this, we hypothesized that a *low* BMD would be associated with an increased risk of atherosclerosis, whereas a *high* BMD would be associated with an increased breast cancer risk.

### **BMD and peripheral arterial disease**

As a marker of generalised atherosclerosis, we studied peripheral arterial disease (PAD) in association with BMD. In women, low femoral neck BMD was associated with an increased risk of peripheral arterial disease, which is in line with the hypothesis that BMD is a marker for life-time estrogen exposure, since both could be a reflection of estrogen deficiency. (Chapter 4.1) (45,56,58,61,62) Several other studies have also reported similar associations between BMD and PAD, as well as between BMD and atherosclerosis at several other sites, such as in the coronary arteries, and the aorta. (63-65) We did not, however, observe an association between lumbar spine BMD and PAD.

There are some methodological considerations. First of all, in contrast to the other studies presented in this thesis, this was a cross-sectional study. Therefore, no conclusions on causes or consequences can be made. Therefore, the association observed might be due to low physical activity or co-morbidity. The prevalence of intermittent claudication in subjects with PAD was low (around 10 % for men and 5 % for women). Thus, most subjects with PAD were asymptomatic. In addition, adjustment for walking ability did not essentially

change results. Unfortunately, we do not have detailed information on physical activity for the entire cohort. Thus, there might still be some residual confounding due to physical activity. To test whether co-morbidity plays an important role in explaining the observed association, the analyses were repeated excluding diabetics, subjects who had suffered a myocardial infarction before baseline or subjects who used diuretics. Again this did not change risk estimates, suggesting that co-morbidity does not play an important role in this association. Also, there is a possibility that measurement error amongst various potential confounding factors exists, but this would only have biased results towards no effect.

There are several possible explanations for the fact that the association was observed for femoral neck BMD only. In contrast to femoral neck BMD, both spinal osteoarthritis and aortic calcification influence lumbar spine BMD. (66-68) Especially the latter, which is also a marker of generalised atherosclerosis, may dilute the association between lumbar spine BMD and PAD. In addition, it might be that, since the presence of PAD is a marker for generalised atherosclerosis, in PAD cases also atherosclerosis of the renal arteries exists. (69) This, in turn, could result in both lower serum vitamin D and higher serum parathyroid hormone (PTH) levels (secondary hyperparathyroidism) due to renal dysfunction, and PTH is known to mainly affect cortical bone. (70) High levels of PTH are also associated with increased risk of cardiovascular disease. (71,72) However, the association between femoral neck BMD and PAD might also be due to the fact that atherosclerosis of the arteries in the femoral neck result in a locally reduced blood flow, affecting bone remodelling. Vogt et al. showed that the relationship between the ankle-arm index and BMD also exists when BMD is measured at the wrist, hereby suggesting that the association between BMD and PAD is not based solely on a localised process. (65)

### **BMD and breast cancer risk**

For incident breast cancer, we found that a high lumbar spine BMD was associated with increased breast cancer risk, and that a low femoral neck BMD was associated with a decreased breast cancer risk, even though the latter was not statistically significant (chapter 4.2). In support of this finding, several other studies also showed that a high BMD, as measured at several sites, was associated with increased breast cancer risk in elderly women. (73-76) Higher BMD is associated with higher body weight. (77,78) It is known that aromatization of adrenal androgens in peripheral fatty tissue is the main source of estrogen in post-menopausal women. The fact that results remained similar after adjustment for body weight suggests that the observed association is not explained by the fact that women with a high BMD have a higher rate of estrogen production in fatty tissue. In addition, the association observed was also independent from age at menopause.



The main disadvantages of this study were the relatively low power and short follow-up period. It might well be that, when power is increased, the association between femoral neck BMD and breast cancer does become statistically significant. Therefore, it would be very interesting to repeat the analysis when follow-up of breast cancer is complete until the beginning of this century.

Furthermore, in order to have BMD measurements, subjects had to be able to come to the research centre. This could introduce a health selection bias. However, breast cancer incidence rates in our study (3.7 per 1000 woman-years) were quite similar to the incidence rate in women in the same age range from the general Dutch population (3.3 per 1000 woman-years). Finally, a program for regular breast cancer screening in all women over age 50 was started in the Rotterdam area in 1990. This could result in a relatively young age at diagnosis and therefore a higher BMD. We tried to correct for this issue by expressing the BMD as Z-scores, thereby adjusting for the potential confounding effect of age. Similar to the analysis performed on the association between BMD and breast cancer, it would also be interesting to study the association between BMD and endometrial cancer. Because of the low incidence of this specific type of cancer, power is currently too low to really study that association.

Overall, the results of the associations between BMD, PAD and breast cancer suggest that BMD can indeed be regarded as a crude marker for long-term estrogen exposure.

### **BMD and cardiovascular endpoints**

Besides effects on atherosclerosis, estrogens are thought to influence other cardiovascular disease risk factors. (58) High estrogen exposure has been reported to be associated with decreased LDL-cholesterol, increased HDL-cholesterol, and lower blood pressure. Thus, if BMD is indeed a marker for long-term estrogen exposure, we might expect that women with a low BMD would be at increased risk of both MI and stroke. Preliminary analyses, however, did not reveal any clear association between baseline BMD, MI and stroke risk. It is too soon to really exclude that there is an association between BMD and cardiovascular disease, given the limited power of our current study. It might be relevant to study the association between rates of bone loss and cardiovascular endpoints. It is known that estrogen deficiency results in increased bone loss. (45,61) In addition, trials have shown that HRT inhibits the bone loss. (42,49,59,79-83) Therefore, it is of interest to study whether a change in sex steroid hormones over time, and estrogen in particular, is associated with the rate of bone loss. In strata of change in sex steroid hormones, one could study the rate of bone loss during the same period. In addition, as soon as the data, which are currently being collected at the third follow-up visit, become available, one could study rates of loss in sex steroid hormones in the elderly in relation to absolute BMD, BMD change over time, and also body composition values.

Finally, it is also well possible that BMD is simply too crude a measure of estrogen exposure to reveal an association with cardiovascular disease, especially

since many factors other than estrogen exposure also play a role in the etiology of cardiovascular disease.

### **Bone mineral density and overall mortality**

In addition to studies into the potential interrelations between BMD and diseases, which are potentially estrogen-related, the association between BMD and overall mortality in both men and women was investigated. In men, low femoral neck BMD is associated with an increased risk of mortality. There seems to be a threshold around the age-adjusted average of BMD (Z-score of zero). Below this threshold, mortality risk starts to increase rapidly. Above this threshold, though, there is no further decrease in relative risk. If anything, the risk appears to go up again in men with a high Z-score of BMD. This association appears to be independent from co-morbidity. In women, however, we could not identify a relationship between BMD and mortality. We hypothesized that the absence of an association between BMD and mortality in women could be due to counteracting associations with cardiovascular and cancer mortality. As discussed above, high BMD is associated with increased breast cancer risk, and extrapolating from this result it is not unthinkable that high BMD is also associated with increased cancer mortality. Following the hypothesis that low BMD, as a measure of low estrogen exposure, is associated with increased cardiovascular disease, it might also be that low BMD is associated with increased cardiovascular mortality. Unfortunately, at the time this study was performed, data on cause of death were not available, but when they will become available it will be interesting to test whether the hypothesis postulated is correct. In addition, here also a relatively low power in women might play a role, since men on average die at a younger age than women do.

### **Fracture prevention**

As described in the general introduction (chapter 1), osteoporosis is a common disease in the elderly. Osteoporotic fractures, the clinical endpoint of osteoporosis, are associated with increased morbidity, mortality and high socio-economic costs. (3,5,7,84-87) Therefore, there is a clear need for adequate fracture prevention. Several therapeutical options are available for fracture prevention, and overall efficacy is considerable. However, before prevention can be initiated, sensitive screening tools are necessary to accurately identify subjects who are most likely to fracture.

A working group of the World Health Organisation (WHO) has defined osteoporosis as a bone mineral density of 2.5 standard deviations or more below the average bone mineral density in young adult women (the T-score). (88) This cut-off value was originally intended for diagnostic purposes only, and not, as is common practice nowadays, for use as a treatment threshold. In chapter 3.1, we evaluated the sensitivity of using such a threshold for fracture prevention. Overall, about two-thirds of subjects who will sustain a fracture will not be offered treatment when a T-score of  $-2.5$  is used as a treatment threshold. For hip fractures only, approximately 50 % of all fractures occurred in women with a

T-score at or below  $-2.5$ . This is probably due to the fact that hip fractures on average occur at an older age than either vertebral fractures or wrist fractures do, and the prevalence of osteoporosis also increases with age. Thus, although subjects with a T-score at or below  $-2.5$  are at a highly increased fracture risk, using only a T-score at or below  $-2.5$  alone is not a tool that is sensitive enough for identifying subjects who should receive fracture prevention.

Geoffrey Rose already spoke about the prevention paradox: a large number of people at a small risk may give rise to more cases than the small number of people who are at high risk. (89) He proposed that two strategies for prevention are available: the population-based approach and the high-risk approach. Ideally, the population-based approach is preferable over the high-risk approach, but a treatment often is expensive, and probably results in an extremely low compliance with a high percentage of adverse effects. One way to implement the population-based approach in practice would be to promote a change to a healthier life-style. Even though this might work in theory, there is not much evidence that this would substantially reduce the population-burden of fractures in the general population. Thus, practically speaking, the high-risk approach is more feasible at present in general practice.

Therefore, since BMD measurement alone clearly is not enough, it is necessary that more sensitive tools than the T-score alone are developed for identification of subjects at high risk. Burger et al. have previously created risk assessment models for short-term hip fracture risk estimation, both with and without BMD. (25) These analyses merit further research, using an extended follow-up. In addition, risk scores for osteoporotic fractures, other than hip fractures, should be developed in order to identify subjects who would benefit from preventive treatment.

The Rotterdam Study provides a good basis for such an analysis, especially now that follow-up time is extended to an average of 10 years. In addition, it might be worthwhile to consider conducting a meta-analysis of all large population-based cohorts, in order to have optimal power.

Of course, it should be noted that the prevention paradox does not diminish the value of the T-score in identifying subjects at high risk for fractures. This 'high-risk' approach offers these individuals the opportunity to reduce their fracture risk substantially through intervention.

In chapter 3.2 we showed that, when using the same absolute BMD threshold in men as in women, in men the proportion of hip fractures below that (female specific) value was much lower than in women. Therefore, if we have the intention to evenly reduce the burden of illness in both men and women, the absolute BMD cut-off value will always be higher in men than in women. The use of a gender-specific T-score largely solves this diagnostic problem. (88)

In contrast, when cost-effectiveness of interventions is the goal, absolute fracture risks are more important since the numbers needed to treat with an

intervention are directly influenced by the fracture incidence in those in whom an intervention is undertaken. This is demonstrated in intervention trials where including populations with a different fracture incidence leads to different numbers needed to treat even with the same intervention. (90,91) Since men have a lower hip fracture incidence than women, fewer men than women reach the required fracture risk threshold to make an intervention cost-effective. Therefore, when cost-effectiveness is the main concern, a similar BMD threshold in men and women should be used to assess the need for intervention. Therefore, fewer men than women will now be treated.

### **Economic evaluation of therapeutical options**

Of course, there is no use in identifying subjects eligible for fracture prevention, unless (cost-) effective interventions can be offered. There are currently many pharmaceutical treatments available for fracture prevention, amongst which are: hormone replacement therapy (HRT), Selective Estrogen Receptor Modulators (SERMs) and Bisphosphonates. In our modelling study, we compared the cost-effectiveness of these three drugs on fracture prevention in women, assuming a 5-year treatment period with a subsequent 5-year offset period. For HRT, a hip fracture risk reduction of 10 % or 50 %, and a vertebral fracture risk reduction of 50 % were assumed. For SERMs, the assumed reductions were 10 % for hip fractures and 50 % for vertebral fractures. Finally, for bisphosphonates, a 50 % risk reduction was assumed for both hip fractures and vertebral fractures.

It is thought that both HRT and SERMs also have an effect on the incidence of breast cancer. (46,53,92) To take these effects into account in our model, we assumed a 10 % breast cancer risk increase for HRT, a 50 % breast cancer risk decrease for SERMs, and no effect on breast cancer risk for bisphosphonates. We evaluated women at ages 55, 65 and 75 years at T-scores of femoral neck BMD of  $-2.5$  and  $-1.0$ .

When we consider an effect present on fractures only, HRT is very cost-effective, whereas especially SERMs are very expensive, with relatively few Quality Adjusted Live Years (QALYs) gained. When, however, effects of HRT and SERMs on breast cancer are taken into account, results change dramatically. Especially at younger ages, HRT actually results in a decrease in QALYs instead of an increase. An important part of the loss of QALYs is due to the actual loss of life years. Although incidence rates of breast cancer, hip fracture and vertebral fractures are comparable at 55 years, breast cancer mortality rates are much higher than hip fracture mortality rates and breast cancer mortality occurs on average at younger ages, resulting in much more life years lost. This strongly influences the total QALY loss due to breast cancer cases. Instead, due to a breast cancer sparing effect, SERMs now become the most cost-effective drug at ages 55 and 65 years in the model.

At older ages, bisphosphonates become more cost-effective than SERMs. This is mainly due to the fact that at older ages, hip fracture incidence rates increase

rapidly, and bisphosphonates are thought to prevent hip fractures more adequately than SERMs do. Furthermore, at older ages, there are less life-years lost due to breast cancer.

These results could be important for determining the clinical approach to fracture prevention. But of course, one has to bear in mind that this is only one study, and that it is based on a mathematical model, which involves several assumptions.

For instance, even though we assumed SERMs to result in a 10 % hip fracture risk reduction, the MORE study reported a non-significant relative risk of 0.97 for hip fractures. However, even if our risk estimate were an overestimation, the cost-effectiveness ratios would still remain similar since results are primarily driven by the strong breast cancer risk reduction, especially at younger ages. Similarly, a different HRT hip fracture risk reduction would also hardly affect the cost-effectiveness ratios.

For this thesis, the model was confined to women only. This was mainly done because we included the effects of therapy on breast cancer. In addition, for bisphosphonates only few and relatively small trials have been performed on the effects on fracture prevention in men, and for SERMs no trials in men have been performed at all. (93-95) Still, it would be interesting to study the cost-effectiveness of bisphosphonates on fracture prevention in men, assuming the same effect size on fracture prevention as in women.

### **Overall methodological considerations**

Apart from the methodological issues that have been discussed in the appropriate sections, there is an overall issue that warrants some further discussion.

An appropriate study design is essential for epidemiological research. Most of the studies presented in this thesis are follow-up studies. Follow-up studies are widely believed to have many advantages over cross-sectional and case-control designs, mainly because a follow-up design is the design that optimally enables the researcher to follow the course of a disease from exposure to disease, thus allowing to make inferences in terms of causes and consequences. The precision of the effect estimates observed are directly dependent on both the study size and the total numbers of cases, which in the case of the Rotterdam Study are quite large (given that the disease of interest is not rare).

In addition, it is thought that follow-up studies have fewer disturbances due to bias.

Generally speaking, there are three types of bias, namely selection bias, information bias and confounding. Whenever we felt that results could have

been distorted by such a bias or confounder, we have described this in the previous section of the general discussion.

In general, it is thought that the longer the follow-up, and the more cases are available, the stronger the results of the study are. However, now that the follow-up within the Rotterdam Study is more than a decade long, it is time to re-evaluate the methods of analysis that are so commonly used.

Of course, the further away we get from the baseline of the study, the more factors can be of influence on the exposure status that was measured at baseline. For instance, in the case of osteoporosis research, it may well be that those subjects who had a high BMD at baseline might be the ones who loose more bone during follow-up. This might, in time, dilute the results of associations under study. This phenomenon probably will not have a big influence in studies with a relatively short follow-up time, but the larger the follow-up time gets, the stronger the influence becomes. It would be of interest to perform our analysis for both a short-term and a long-term follow-up, to study the magnitude of this problem.

However, primarily in etiologic research, more and more we will have to additionally evaluate changes in exposure in relation to different outcomes of interest, such as rates of bone loss besides studying a baseline measurement only. Such an analysis might provide us with more insight in the pathophysiology of fractures. For instance, is it really the status of low bone mineral density itself, or perhaps more the state of rapid bone loss that results in fragile and therefore fracture-prone bones?

In this respect, it is also very much of interest to study interactions between bone mineral density and other exposures related to fracture risk, on overall fracture risk.

In addition, whenever possible, we may have to consider taking the change in exposure status over time into account in our analysis, by using a time-varying exposure analysis or other analyses allowing for changes in exposure over time.

Nevertheless, especially for longer-term prediction models and for intervention studies, analysis of a baseline measurement alone in relation to events during follow-up remains of extremely important.

As an example of how important it is to take changes in exposure over time into account, in chapter 4.2 we presented the association between BMD and breast cancer both using merely the baseline BMD levels and the rates of loss between the baseline and first follow-up visits. Although using the baseline femoral neck BMD, no strong association could be observed, a clear association was apparent when studying the change in BMD over time. Now, it was apparent that women who were to suffer from breast cancer had gained bone in the years prior to diagnosis, a finding which was consistent for both femoral neck and lumbar spine BMD. These additional analyses provided strong extra support for an association between BMD and breast cancer, an association that is potentially

explained by differences in estrogen exposure between women with and without breast cancer.

### **Suggestions for further research**

The results of the studies presented in this thesis give rise to new hypotheses for further research. Many of those have already been presented in the course of this general discussion.

Apart from those suggestions, we here present some additional ideas for further research following the results presented in this thesis.

For the cost-effectiveness model described in this thesis, the association between BMD and breast cancer has been taken into account. It is thought, however, that both HRT and SERMs also influence cardiovascular risk factors. (58,96,97) (98,99) Since there are currently so many uncertainties about the potential protective effect of both HRT and SERMs on cardiovascular disease, we decided not to consider any potential effect on cardiovascular disease in the present model. Several trials are currently being performed on the effects of HRT and SERMs on cardiovascular disease. Trials, such as the Women's Health Initiative (WHI) and the Women's International Study of Long Duration Estrogen after Menopause (WISDOM), will determine whether HRT is effective in primary coronary heart disease prevention. (100,101) For SERMs, the Multiple Outcomes of Raloxifene Evaluation (MORE) trial recently showed that in women at increased cardiovascular risk, SERMs reduced cardiovascular disease risk by 40 %. (102) This trial, however, was not originally designed to study cardiovascular endpoints. In the Raloxifene Use for The Heart (RUTH) trial, coronary heart disease is a primary endpoint, but this trial is currently still ongoing. (103) As soon as the results of these trials become available, the model can be extended further, to also take the potential protective effect on MI and/or stroke into account.

In addition to this, it would be interesting to also evaluate the associations between BMD and dementia, and BMD and depression in the Rotterdam Study, as recent literature suggests that both these diseases are also associated with estrogen exposure. (104-106) Eventually, it would then be interesting to take the potential effects of HRT and SERMs on both dementia and depression into account. But as for cardiovascular disease, double-blind randomized trials will first have to provide us with reliable evidence before this can actually be implemented into our model.

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# *Chapter 8*

## *Summary & samenvatting*





# *Chapter 8.1*

## *Summary*



Osteoporosis is a systemic disease that is characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Fractures, the clinical outcome of osteoporosis, and hip fractures in particular, are associated with increased morbidity, mortality and substantial economic costs.

The overall aims of this thesis were to study the incidence of and the risk factors for vertebral fractures, and to evaluate the interrelations between bone mineral density, atherosclerosis and breast cancer. Furthermore, we evaluated the sensitivity of using a T-score of bone mineral density (BMD) at or below  $-2.5$  as a treatment threshold for fracture prevention. We also investigated whether in elderly men a similar BMD threshold should be used as is currently used in women. The results of all these studies were combined to investigate the cost-effectiveness of fracture prevention in women.

For all analyses that were presented in this thesis, we used data from the Rotterdam Study, a large prospective population-based cohort study in the Netherlands. Participants of this study were men and women aged 55 years or over living in Ommoord, a suburb of Rotterdam.

In **Chapter 2**, the epidemiology of vertebral fractures was studied. In **chapter 2.1** we showed that in subjects with a baseline prevalent vertebral fracture, the incidence of vertebral fractures increases strongly with age. Although overall incidence rates are higher in women than in men, the risk of an incident vertebral fracture at any given level of absolute bone mineral density (BMD) is similar for men and for women. Furthermore, the presence of a prevalent vertebral fracture and a low BMD are strong and independent risk indicators for incident vertebral fractures in both men and women.

In **chapter 2.2** we continued on this subject and showed that besides prevalent vertebral fractures and low BMD, in women age, early menopause (at or below age 45), current smoking and the use of a walking aid are also strong independent risk factors for incident vertebral fractures. In men, only a positive history of non-vertebral fractures at or after age 50 is an additional independent risk factor. Current smoking was associated with an increased vertebral fracture risk in men, but this did not reach statistical significance.

In **chapter 3** we evaluated whether the T-score should be used in the identification of subjects who will fracture, and if so, whether the same threshold should be used for men and women. As described in **chapter 3.1**, two thirds of all fractures occurred in women with a T-score above  $-2.5$ . Thus, although a T-score of  $-2.5$  SD (and below) identifies individuals at high fracture risk, overall most fractures occur in subjects with a BMD above this threshold. The public health burden of fractures will not be alleviated using the current WHO criterion for osteoporosis. In **chapter 3.2** we then studied whether the association between BMD and fracture risk is similar in men and women and whether the

same T-score of BMD should be used for men and women or whether a gender-specific T-score would be better. Overall, hip fracture risk in men and women of the same age and at the same absolute BMD is very similar but, due to the different BMD distribution, the average BMD in men who fracture their hip is higher than in women. To capture the same proportion of hip fractures in men the threshold BMD needs to be higher than in women but the use of a gender-specific T-score largely solves this for diagnostic purposes. The overall hip fracture incidence is lower in men than in women and we propose the use of the same absolute BMD thresholds in men and women for decisions about interventions.

In **chapter 4** the interrelations between BMD, atherosclerosis and breast cancer are investigated. Both atherosclerosis and breast cancer are also considered to be related to estrogen exposure. The underlying hypothesis was that BMD may be regarded as a marker for lifetime estrogen exposure.

First, in **chapter 4.1** the association between BMD and peripheral arterial disease (PAD) was described. PAD is a marker for generalized atherosclerosis. We observed an association between low BMD and PAD in women, but not in men. Possibly, part of this difference between men and women may be explained by the direct and indirect influences of the sudden decrease in estrogen following menopause.

In **chapter 4.2** we investigated the association between BMD and incident first-ever breast cancer in women. The results of this study suggest that women with a lumbar spine BMD in the highest tertile are at a doubled risk of breast cancer as compared to women with an average BMD. For femoral neck BMD, even though not statistically significant, women with a low BMD were at a somewhat decreased breast cancer risk.

In **chapter 5** we studied the association between BMD and overall mortality in both men and women. In men a non-linear relationship between BMD and mortality exists, which is independent of comorbidity and impaired mobility. In women, no significant relationship between BMD and all-cause mortality was observed.

The results of the studies as described in all previous chapters were now combined and used to develop a model on cost-effectiveness of fracture prevention. This model and the results were described in **chapter 6**. In the model, the cost-effectiveness of fracture prevention was evaluated for hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs) and bisphosphonates in women at the ages of 55, 65 and 75 years. For HRT, we assumed a risk reduction of 10 % or 50 % for hip fractures and a risk reduction of 50 % for vertebral fractures. For SERMs and bisphosphonates the assumed hip fracture risk reductions were 10 % and 50 %, respectively. For both these drugs, a 50 % risk reductions for vertebral fractures was assumed. We assumed a 5-year treatment period and a 5-year offset period for all treatment strategies. In

addition, the effects of HRT and SERMs on breast cancer were taken into account. The results of this model strongly suggest that in terms of cost-effectiveness SERMs compare favorably with HRT for fracture prevention, mainly because of the effects on breast cancer. At older ages, bisphosphonates become more cost-effective than SERMs. This is mainly due to the fact that at older ages, hip fracture incidence rates increase rapidly, and bisphosphonates are thought to prevent hip fractures more adequately than SERMs do. Furthermore, at older ages, there are less life-years lost due to breast cancer.

Finally, in **chapter 7** a general discussion of the results described in this thesis is presented. We discuss the main pitfalls in studying vertebral fractures. Furthermore, we elaborate on strategies for fracture prevention. What would be the best approach to optimally identify subjects who will fracture in the near future. Finally, we further discuss the results and pitfalls of the cost-effectiveness model described in chapter 6. We finish the discussion by giving some suggestions for further research following the results that were presented in this thesis.



## *Chapter 8.2*

### *Samenvatting*





Osteoporose, oftewel botontkalking, is een aandoening die wordt gekenmerkt door een lage bot massa en een achteruitgang van de microarchitectuur van het bot weefsel. Dit leidt tot een verhoogde botfragiliteit, welk resulteert in een verhoogde kans op botbreuken. Fracturen (oftewel botbreuken), de klinische uitkomst van osteoporose, en dan met name heup fracturen, gaan gepaard met een verhoogde kans op ziekte en sterfte, maar ook met hoge sociaal-economische kosten voor de maatschappij.

In dit proefschrift, hebben we ook gekeken naar het vóórkomen van wervelinzakkingen, waarbij we ook de belangrijkste risicofactoren voor deze inzakkingen hebben bestudeerd. Daarnaast bestudeerden we de onderlinge relaties tussen botmineraal dichtheid, atherosclerose (oftewel slagaderverkalking) en borst kanker. Tevens hebben we onderzoek verricht naar preventie van fracturen; zijn de huidige methoden die gebruikt worden voor de identificatie van mensen met een hoge kans op een fractuur goed genoeg en zo ja: zouden beslissingen over interventie gemaakt moeten worden bij eenzelfde drempel in botmassa bij mannen als bij vrouwen. Tot slot werden de resultaten van alle voorgaande hoofdstukken gecombineerd in een model naar de kosten-effectiviteit van fractuur preventie bij vrouwen, rekening houdend met potentiële effecten van de geneesmiddelen op het voorkomen van borstkanker.

Voor dit onderzoek hebben we gebruik gemaakt van gegevens van het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek. Dit is een grote populatie-gebaseerde studie onder mannen en vrouwen van 55 jaar en ouder uit Ommoord, Rotterdam.

In **hoofdstuk 2** wordt de epidemiologie van wervelinzakkingen bestudeerd. In **hoofdstuk 2.1** laten we zien dat in mensen die aan het begin van de studie reeds een wervelinzakking hadden, het vóórkomen van wervelinzakkingen sterk toeneemt met de leeftijd. Hoewel algemeen genomen wervelinzakkingen vaker voorkomen bij vrouwen dan bij mannen, was de absolute kans op inzakkingen gelijk bij eenzelfde absolute botmineraal dichtheid (BMD). Daarnaast bleken zowel de aanwezigheid van een wervelinzakking aan het begin van de studie als een lage BMD sterke voorspellers te zijn voor nieuwe wervelinzakkingen.

In **hoofdstuk 2.2** toonden we aan dat naast reeds bestaande wervelinzakkingen en een lage BMD, in vrouwen leeftijd, een vroege menopauze (voor of tijdens het 45e levensjaar), roken en het gebruik van hulpmiddelen bij het lopen ook sterke voorspellers zijn voor nieuwe inzakkingen. In mannen was alleen een voorgeschiedenis van een botbreuk op of na het 50e levensjaar een additionele voorspellende factor. Hoewel dit niet statistisch significant was, leek roken ook in mannen gerelateerd te zijn aan meer wervelinzakkingen.

In **hoofdstuk 3** bestudeerden we of de T-score van de BMD gebruikt kan worden voor identificatie van personen die een fractuur zullen krijgen, en zo ja, of eenzelfde drempelwaarde zou moeten worden gebruikt voor mannen als voor vrouwen.

Zoals beschreven in **hoofdstuk 3.1**, komt twee-derde van alle fracturen voor in personen met een T-score boven de  $-2.5$ . Dit suggereert dat, hoewel een T-score van  $-2.5$  of lager mensen met een hoge kans op fracturen wel identificeert, de meeste fracturen voorkomen in mensen met een BMD boven deze drempelwaarde. De totale ziektelast ten gevolge van fracturen voor de populatie wordt niet sterk verminderd wanneer de huidige criteria voor osteoporose worden gehanteerd voor fractuur preventie.

In **hoofdstuk 3.2** bekeken we of de relatie tussen BMD en fractuur kans gelijk is voor mannen en vrouwen, en of we beter een geslachtsspecifieke of een gelijke BMD T-score kunnen gebruiken. De kans op een heup fractuur is zeer vergelijkbaar voor mannen en vrouwen met eenzelfde leeftijd en BMD, maar door een andere BMD verdeling in de mannelijke bevolking, is de gemiddelde BMD bij mannen met een fractuur hoger dan bij vrouwen. Wanneer we eenzelfde proportie heup fracturen willen voorkomen bij mannen als bij vrouwen, moet de drempelwaarde in BMD voor mannen hoger zijn dan voor vrouwen, en het gebruiken van een geslachtsspecifieke BMD T-score zal dit probleem grotendeels oplossen. Echter, wanneer het doel is beslissingen te nemen aangaande interventie, lijkt het beter eenzelfde drempel in absolute BMD te hanteren voor zowel mannen als vrouwen.

In **hoofdstuk 4** worden de onderlinge relaties tussen BMD, atherosclerose en borstkanker, welke ook gerelateerd zijn aan blootstelling aan oestrogenen (vrouwelijk hormoon), nader onderzocht. De onderliggende hypothese is dat BMD beschouwd mag worden als een maat voor oestrogeen blootstelling gedurende het leven.

In **hoofdstuk 4.1** wordt de relatie tussen BMD en perifere vaatlijden beschreven. Perifere vaatlijden is een maat voor gegeneraliseerde atherosclerose. We vonden een relatie tussen een lage BMD en perifere vaatlijden in vrouwen, maar niet in mannen. Mogelijk wordt dit verschil ten dele verklaard door de directe en indirecte invloeden van de snelle daling van oestrogenen ten gevolge van de menopauze.

In **hoofdstuk 4.2** beschreven we de relatie tussen BMD en borstkanker in vrouwen. Vrouwen met een hoge BMD, zoals gemeten aan de lage wervelkolom, hebben een twee keer zo hoge kans op het krijgen van borstkanker dan vrouwen met een gemiddelde BMD. Hoewel niet statistisch significant, hadden vrouwen met een lage BMD, zoals gemeten aan de heup, een wat verlaagde kans op het krijgen van borstkanker.

In **hoofdstuk 5** bestudeerden we de relatie tussen BMD en sterfte in mannen en vrouwen. In mannen is er een niet-lineaire relatie tussen BMD en sterfte, welke onafhankelijk is van co-morbiditeit en verminderde lichamelijke activiteit. In vrouwen werd geen duidelijke relatie tussen BMD en sterfte gevonden.

De resultaten van bovenstaande hoofdstukken werden gecombineerd en gebruikt om een model te ontwikkelen ter bestudering van kosten effectiviteit van fractuur preventie, welk beschreven werd in **hoofdstuk 6**. In het model wordt de kosten-effectiviteit van fractuur preventie vergeleken voor hormoon substitutie therapie (HRT), selectieve oestrogeen receptor modulators (SERMs) en bisfosfonaten in vrouwen van 55, 65 en 75 jaar. Voor alle drie de geneesmiddelen schatten we de effecten op fractuur kans. Voor HRT werd een risico reductie van 10 % of 50 % voor heup fracturen en een risico reductie van 50 % op wervelinzakkingen aangenomen. Voor SERMs en bisfosfonaten waren de geschatte heup fractuur risico reducties respectievelijk 10 % en 50 %. Voor beide geneesmiddelen werd een 50 % vermindering van wervelinzakkingen geschat. In het model was de behandelduur 5 jaar, waarna er nog 5 jaar een na-effect zichtbaar bleef. Tevens werden de effecten van HRT en SERMs op borstkanker meegenomen in de analyses. De resultaten van het model suggereren dat op de leeftijd van 55 en 65 jaar, SERMs kosten-effectiever zijn dan HRT. Dit wordt met name verklaard door de borstkanker verlagende effecten van SERMs. Op latere leeftijd zijn de bisfosfonaten het meest kosten-effectief. Dit wordt verklaard door het feit dat op oudere leeftijd het voorkomen van heup fracturen sterk toeneemt, en bisfosfonaten een groter effect hebben op heup fracturen dan SERMs. Bovendien zijn er op oudere levensjaren minder levensjaren die verloren gaan ten gevolge van borstkanker.

In **hoofdstuk 7** worden alle resultaten samen besproken in de algemene discussie. We bespreken de grootste problemen bij het bestuderen van wervelinzakkingen. Verder gaan we wat gedetailleerder in op strategieën voor fractuur preventie. Tot slot gaan we dieper in op de resultaten en problemen van het kosten-effectiviteitsmodel, zoals beschreven in hoofdstuk 6. We eindigen de discussie met het aanreiken van suggesties voor verder onderzoek volgend uit het onderzoek wat beschreven is in dit proefschrift.



**List of publications**

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3. Van der Klift M, Pols HAP, Hak AE, Witteman JCM, Hofman A, de Laet CEDH Bone mineral density and the risk of peripheral arterial disease: the Rotterdam Study. *Calcif Tissue Int* (In press)
4. De Laet CEDH, van der Klift M, Hofman A, Pols HAP Osteoporosis in men and women: a story about bone mineral density thresholds and hip fracture risk. *J Bone Miner Res* (In press)
5. Geusens P, Hochberg MC, van der Voort DJM, Pols HAP, van der Klift M, Siris E, Melton ME, Turpin J, Byrnes C, Ross PD. Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clinic Proc* (In press)

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## **About the author**

Marjolein van der Klift was born on September 3, 1977 in Rotterdam, the Netherlands. In 1995 she passed secondary school at the “Maarten Luther Scholengemeenschap” in Rotterdam (atheneum).

In September 1999 she obtained her doctoral degree in medicine at the Erasmus University in Rotterdam. In 1996, during the second year of her study, she began a Masters of Science Program in Clinical Epidemiology from the Netherlands Institute for Health Sciences in Rotterdam, which she finished in 1999. As part of this program, she followed courses at the Epidemiology Research Institute in Boston, USA.

In October 1999, she started the work presented in this thesis at the Institute for Medical Technology Assessment, in close collaboration with the Departments of Internal Medicine and Epidemiology & Biostatistics. In May 2000 and May 2002 she received “Young Investigator Awards” from the European Calcified Tissue Society, and in June 2001 she received a “Travel Award” from the same organization. In November 2001 she received a “Young Investigator Award” from the Dutch Society for Calcium and Bone Metabolism.

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