Epidemiologic studies on bone mineral density and fractures

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Epidemiologisch onderzoek naar botmineraaldichtheid en fracturen

PROEFSCHRIFT
Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

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door

Huibert Burger
geboren te Hengelo (Ov)

Promotie-commissie

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	Prof. Dr. H.J. Stam
	Prof. Dr. J.M.J.P. van der Linden
Co-promotor:	Dr. H.A.P. Pols

If we can put helmets on motorcyclists, we ought to be able to find some effective way to reduce the incidence of osteoporotic fractures by prevention.

James F. Fries
The sunny side of aging (editorial). JAMA 1990;263:2354-2355.

Acknowledgements

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Publications and manuscripts based on studies described in this thesis

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Burger H, Daele PLA v, Algra D, Ouweland FA vd, Grobbee DE, Hofman A, Kuijk C v, Schütte HE, Birkenhäger JC, Pols HAP. The association between age and bone mineral density in men and women aged 55 years and over: The Rotterdam Study. Bone Miner 1994;25:1-13.

Chapter 3.2
Burger H, Daele PLA v, Algra D, Hofman A, Grobbee DE, Schütte HE, Birkenhäger JC, Pols HAP. Bone loss and the beneficial effect of high dietary calcium and vitamin D in an elderly population. (submitted)

Chapter 3.3
Burger H, Daele PLA v, Odding E, Valkenburg HA, Hofman A, Grobbee DE, Schütte HE, Birkenhäger JC, Pols HAP. Radiographic osteoarthritis is associated with higher bone mineral density and increased age-related bone loss: The Rotterdam Study. (accepted for publication in Arthritis & Rheumatism)

Chapter 4.1
Burger H, Daele PLA v, Grashuis K, Hofman A, Grobbee DE, Schütte HE, Birkenhäger JC, Pols HAP. Vertebral deformities and functional impairment in men and women. (accepted for publication in the Journal of Bone and Mineral Research)

Chapter 4.2
Burger H, Daele PLA v, Algra D, Hofman A, Grobbee DE, Schütte HE, Birkenhäger JC, Pols HAP. Vertebral deformities as predictors of non-vertebral fractures. BMJ 1994;309:991-992.

Chapter 1

Introduction

Chapter 1

Introduction

Osteoporosis is currently defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. The burden of fractures is substantial, both in terms of individual and public health. The most serious fracture, i.e. hip fracture, is associated with a high mortality rate of approximately 25% within one year and a considerable decline of physical and social functions [2,3]. Hip fracture is not a rare event. On average, the lifetime risk of a hip fracture for a 50 year old woman is approximately 16% [4]. The total number of incident hip fractures in the Netherlands was 10360 in 1987 and it is expected that, partly as a consequence of aging of the population, this number will have exceeded 20000 by the year of 2010 [5].

The general aim of the thesis is to study determinants of bone density and consequences of vertebral fractures or deformities.

Bone mineral density, which is currently thought to be an important determinant of fracture risk, has extensively been studied in women [6]. Studies of bone density in men, however, are sparse. In view of the exponential increase in hip fracture risk with age in both women and men, more research in men is warrantable.

Among several other potentially modifiable risk factors for osteoporosis, low dietary calcium and vitamin D intake have been proposed. The influence of these dietary factors on the skeleton in elderly people, again in particular for men, is unclear [7].

The issue of a possible inverse relationship between osteoporosis and osteoarthritis may provide insight into the etiology of both disorders and may have clinical implications as well. At present, this riddle is still unresolved [8].

Although hip fractures are without doubt the main outcome of osteoporosis, there is growing evidence that also vertebral fractures are among the determinants of disability in the elderly [9]. Different from hip fractures, the epidemiology as well as the nature of the health consequences of vertebral fractures is largely unknown, in particular in men [10].

The contents of this thesis constitute six epidemiologic studies on the above topics. All studies were conducted within the Rotterdam Study, a large prospective population-based study of subjects aged 55 years and over [11]. Chapter 2 briefly outlines the aim, design and methods of the Rotterdam Study. Chapter 3 is devoted to bone mineral density. Chapter 3.1 reports on a cross-sectional study on the associations of bone mineral density with age, age at menopause and body mass index. In chapter 3.2, the rate of decline of bone mineral density is studied longitudinally in relation to age, dietary calcium and vitamin D. The possibility of an inverse relation between osteoporosis and osteoarthritis is under discussion in chapter 3.3. Chapter 4 is on vertebral deformities and fractures. In chapter 4.1, a cross-sectional study on the prevalence and the association with functional impairment of vertebral deformities is described and chapter 4.2 reports on a nested case-control study on vertebral deformities as predictors of non-vertebral fractures. The thesis will be concluded with a general discussion including comments on clinical relevance and suggestions for further research in chapter 5.

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Chapter 2

The Rotterdam Study

Chapter 2

The Rotterdam Study

Aim and rationale

The Rotterdam Study aims at measuring the occurrence of disease in the elderly in relation to several potential determinants in order to enlarge our comprehension of the etiology and prognosis of disease and thereby finding clues for intervention [1]. The rationale of the study lies in the expectancy of an increasing number of elderly people with chronic diseases in many Western countries including the Netherlands. Research should therefore aim at postponing chronic disease and concomitant disability thereby compressing morbidity to the end of life [2]. In the Rotterdam Study, the centre of interest is at neurogeriatric, cardiovascular, locomotor and ophthalmologic diseases.

Design

The Rotterdam Study is a prospective single centre cohort study. This design allows estimating disease prevalence at baseline and incidence rate after follow-up and identifying potential risk factors in an efficient and precise way during follow-up by conducting case-referent studies within the cohort. The fixed cohort was defined as all inhabitants of Ommoord, a district of Rotterdam, the Netherlands, who were 55 years of age or older at January 1, 1990.

Methods

Cohort members were identified with the help of the municipality of Rotterdam. All eligible persons, 11854 in number, were invited to participate by means of a letter and were asked to sign an informed consent. The Rotterdam Study has obtained approval by the Medical Ethics Committee of Erasmus University Medical School.

The baseline survey was composed of an initial home interview followed by

two visits to the field centre in Ommoord for an extensive set of clinical examinations and laboratory assessments. Institutionalized persons in homes for the elderly and nursing homes made up 11% of the study population. These participants were not invited to visit the research center and were examined at their institutions. Consequently they did not have radiological assessments. In the independently living population, the overall response rate was 77% for the home interview and 71% for the center visit. The age-specific response rates for the interview and centre visit are depicted in figure 1. They were not meaningfully different for men and women.

The questions of the home interview addressed medical history, family history, dietary habits, alcohol consumption and smoking, socio-economic status, current complaints and medical consumption, mental status and activities of daily living.

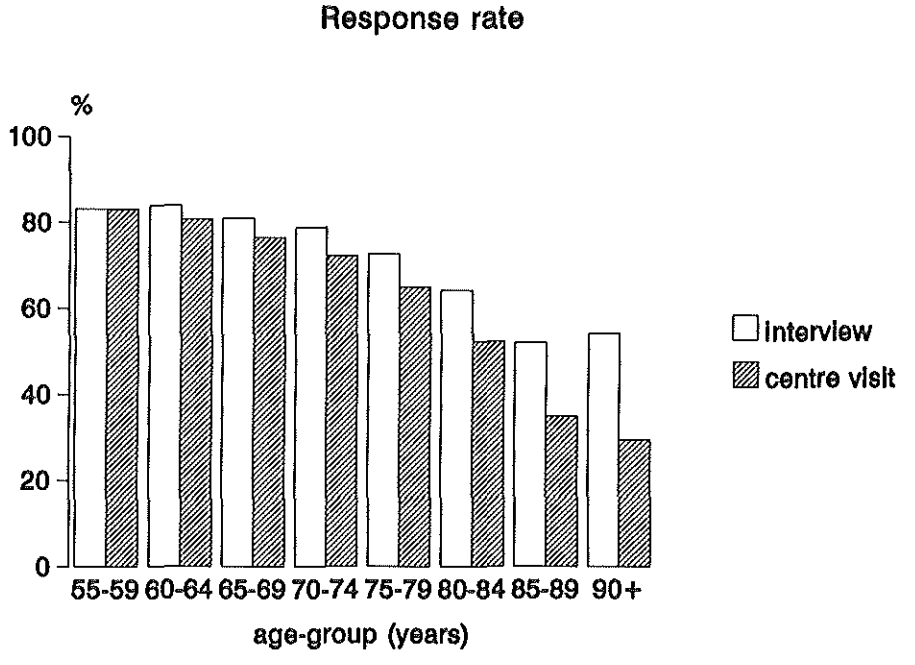

FIGURE 1. Age-specific response rates for interview and centre visit separately in independently living persons, expressed as proportions of the eligible population.

The clinical examinations comprised physical examination including eye examination, anthropometry, measurement of blood pressure, electrocardiography, ultrasonic measurements at the carotids and abdominal aorta, bone densitometry of the spine and proximal femur, radiography of the spine, pelvis, knees and hands, blood and urine analysis and measurement of cognitive function.

Follow-up data on morbidity and mortality is obtained through themostly automatized diagnosis registers of collaborating general practitioners and information on medication is provided by pharmacists.Many of the examinations at the research centre were repeated using identical procedures after approximately two years and were supplemented with several questions addressing issues that are not part of the follow-up data provided routinely by the general practitioners. As to the study of osteoporosis and fractures these issues comprise amongst others fall frequency, physical activity, alcohol consumption and smoking. The intention is to closely monitor the health status of the cohort in the future by biennial examinations.

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Chapter 3

Bone mineral density

Chapter 3.1

The association between age and bone mineral density in men and women aged 55 years and over

Introduction

It has been well documented that bone mass is inversely related to the risk of developing future fractures [1-7]. As the incidence of both hip [8-11] and vertebral [12,13] fractures increases with age, much attention has been paid to age-related bone loss [14-34]. Furthermore, the risk of fracture is greater in women than in men [10,12], as a result of which research has been focussed on bone loss in women, predominantly in the perimenopausal period [31]. Much less is known about the extent of bone loss in the elderly, especially after the age of seventy. In addition, very few data exist regarding age-related bone loss in men [21-24], despite the fact that fracture incidence is peaking in later life in men as well [8-12].

There is an increasing interest in the epidemiology of age-related bone loss in the elderly. To address this issue, it is essential to include a sufficiently large number of subjects. Especially cross-sectional studies require a large sample size to draw conclusions about age-related bone loss [34]. Furthermore, population based samples are needed combined with a high response rate to maximize external validity. If comparisons between bone loss in men and women are to be made, valid results are much more likely obtained if they were sampled from the same population.

In the light of the foregoing, there were two studies carried out in the U.S.A. concerning the epidemiology of bone loss in elderly subjects that deserve special attention [26,27]. In the Framingham Study [26], bone mass measurements of the proximal and ultradistal radius and proximal femur were performed in a large sample of elderly men and women aged 68 years and over. No bone mass measurements of the lumbar spine were made. The Study of Osteoporotic Fractures [27], although very large, was confined to measurements in women.

For Europe, no such studies are presently available. In the Netherlands, research concerning age-related phenomena is becoming more and more urgent since we are confronted with an increasingly ageing population. The age group of 80 years and over comprised 2.9% of the total population in 1991 compared to 2.2% in 1980[35], and the absolute number of hip fractures in people aged 65 and over in the Netherlands rose from 4,583 in 1972 to 10,360 in 1987[9].

In the present cross-sectional study, we analysed bone mineral density measurements at the lumbar spine and the proximal femur in an ambulatory, population based cohort of elderly men and women.

Methods

The Rotterdam Study is a prospective follow-up study of occurrence and determinants of disease and disability in the elderly[36]. The four main fields of interest are cardiovascular, neurogeriatric, ophthalmologic and locomotor diseases. Invited to participate in the study were all 11,854 inhabitants, men and women, aged 55 years and over of a district in Rotterdam, the Netherlands. In this study, institutionalized people (10% were not eligible for examination at the research center. The response rate was 80% and 69% of the total eligible population for the interview and center visit respectively. Every examination at the center included densitometry. Written informed consent was obtained from every participant. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical School.

Baseline data are obtained by interview at home, and physical examination, anthropometry, ultrasonography, radiography and blood and urine analysis at the research center as described previously[36]. For the evaluation of osteoporosis, dual energy X-ray absorptiometry (DXA) of the lumbar spine and proximal femur is performed together with lateral radiographs of the thoracic and lumbar spine.

Bone mineral density measurements were performed using a Lunar DPX-L densitometer (Lunar Radiation Corporation, Madison, WI). Standard positioning was used with anterior-posterior scans of the lumbar spine and the proximal femur. As for the femur, the right side was scanned unless there was a history

of hip fracture or prosthesis implantation. In the latter case, the left side was chosen. Using standard software, we analysed vertebrae L2 to L4, the femoral neck, Ward's triangle and greater trochanter. Quality assurance including calibration with the standard of the machine was performed routinely every morning. Duplicate measurements were performed in 12 randomly selected cohort members with a mean age of 66 years. The in vivo coefficient of variation calculated from these measurements was 3.2% in the femoral neck, 3.1% in the Ward's triangle, 2.5% in the greater trochanter and 0.9% in the lumbar spine.

Height and weight were measured in standing position without shoes. The body mass index (kg/m^2) was calculated for each individual as a measure of obesity.

The data presented in this cross-sectional analysis concern the first bone density and anthropometric measurements in 678 men and 1084 women.

Analysis

All analyses were carried out for each sex separately. Means and standard deviations of anthropometric and bone mineral density data were calculated in eight five-year age strata. Adjustment of mean bone mineral density values for age and body mass index was achieved by means of analysis of covariance. The average relation of bone density to age was quantified using linear regression analysis. Regression with polynomial models (quadratic and cubic) was performed to detect a possible non-linear association between age and bone mineral density. We examined periods of increased fall in bone mineral density by performing analyses in five-year periods separately. Examination of the age and bone mineral density plots revealed outliers in the L2-L4 measurements of both men and women (figure 1). These observations appeared to be more than three standard deviations above the mean value. These extreme values may represent a separate population of individuals with marked spinal osteoarthritis, vertebral deformities, or aortic calcification causing spuriously elevated spinal bone mineral density values. To verify this, we examined lateral radiographs of the lumbar spine of these participants and scored osteoarthritis according to

TABLE 1. Characteristics of the study population

	Age	Response (%)	N (%)	Height (cm) (SD)	Weight (kg) (SD)	Body mass index (kg/m^2) (SD)
Men	55-59	71	86 (13)	175.1 (6.2)	78.0 (10.4)	25.4 (3.0)
	60-64	78	131 (19)	174.8 (6.4)	80.8 (11.0)	26.4 (3.0)
	65-69	80	147 (22)	174.3 (5.8)	78.4 (10.5)	25.8 (2.9)
	70-74	77	132 (19)	173.1 (5.9)	77.0 (9.8)	25.7 (3.1)
	75-79	68	111 (16)	171.1 (5.8)	76.2 (9.4)	26.0 (3.0)
	80-84	61	54 (8)	169.8 (10.1)	74.2 (10.1)	26.1 (5.4)
	85 +	47	17 (3)	166.6 (7.5)	72.2 (8.1)	26.0 (2.8)
	Total	67	678 (100)	173.2 (6.8)	77.7 (10.3)	25.9 (3.3)
Women	55-59	80	130 (12)	163.7 (7.0)	70.0 (11.8)	26.2 (4.3)
	60-64	81	201 (19)	162.8 (5.9)	71.8 (12.0)	27.1 (4.2)
	65-69	78	196 (18)	162.7 (5.9)	70.9 (11.1)	26.8 (3.9)
	70-74	75	226 (21)	161.3 (5.9)	71.0 (11.0)	27.3 (4.1)
	75-79	70	186 (17)	158.4 (6.0)	67.3 (10.9)	26.8 (4.3)
	80-84	58	111 (10)	157.6 (5.6)	68.2 (10.6)	27.5 (4.3)
	85 +	46	34 (3)	156.1 (6.0)	67.3 (9.9)	27.6 (3.6)
	Total	70	1084 (100)	161.1 (6.4)	69.9 (11.3)	27.0 (4.1)

Kellgren [37]. Because of their potential influence on the slope of the regression line we did analyses without the outliers as well.

Since obesity is well known to affect bone mineral density [38,39], and body mass index appeared to be related to age in this study, it might be a confounder in the relation between age and bone mineral density. Therefore, we also calculated the yearly fall in bone mineral density after adjustment for body mass index by using a multiple regression model. The measure of years since menopause represents a mixture of age and age of menopause and equals, after adjustment for age, age of menopause (AOM). Therefore, we decided to analyse the effect of AOM on bone mineral density by adding this variable to the model, thus separating the effect of age and menopause completely. The concept of a constant percentage bone reduction per year requires logarithmic transformation of bone mineral density. However, for the sake of clarity, we calculated the mean percentage change in bone density with aging by dividing the coefficients from the regression analyses by the overall mean bone density value. Mean rates of bone mineral density reduction, expressed as a percentage per year, were calculated from the unadjusted and the body mass index adjusted coefficients.

The interrelationship between bone density at the different sites of measurement was analysed by calculating Pearson's product moment correlation coefficients.

All results are presented with two-sided p-values. Statistical computations were made using the Statistical Analysis System (SAS Institute, Inc., Cary, North Carolina, USA) and Statgraphics (Statistical Graphics Corporation, Inc., Maryland, USA).

Results

General characteristics of the study population are shown in table 1. Response rates are given for bone mineral density measurement. Only at age 80 and over, the response rate declined in both sexes below 70%. Mean age in men was slightly lower than in women: 69.1 (SD = 7.9) and 69.8 (SD = 8.2) years respectively. Mean body mass index in women exceeded that in men.

TABLE 1. Site-specific mean values for bone mineral density by age and sex

	Age	Neck (g/cm^2) (SD)	Ward (g/cm^2) (SD)	Trochanter (g/cm^2) (SD)	L2-L4 (g/cm^2) (SD)
Men	55-59	0.912 (0.108)	0.771 (0.129)	0.882 (0.115)	1.138 (0.193)
	60-64	0.917 (0.124)	0.755 (0.143)	0.883 (0.122)	1.179 (0.186)
	65-69	0.880 (0.131)	0.713 (0.157)	0.836 (0.150)	1.140 (0.203)
	70-74	0.876 (0.142)	0.705 (0.154)	0.836 (0.139)	1.171 (0.213)
	75-79	0.874 (0.140)	0.708 (0.156)	0.835 (0.138)	1.165 (0.214)
	80-84	0.852 (0.157)	0.690 (0.193)	0.828 (0.167)	1.193 (0.249)
	85 +	0.835 (0.147)	0.675 (0.172)	0.838 (0.191)	1.344 (0.278)
	Total	0.886 (0.134)	0.724 (0.156)	0.851 (0.140)	1.166 (0.211)
	Adjusted *	0.892 (0.121)	0.730 (0.139)	0.860 (0.122)	1.176 (0.183)
Women	55-59	0.877 (0.131)	0.749 (0.150)	0.758 (0.128)	1.062 (0.141)
	60-64	0.840 (0.120)	0.695 (0.144)	0.746 (0.128)	1.007 (0.174)
	65-69	0.826 (0.128)	0.680 (0.143)	0.735 (0.128)	1.042 (0.184)
	70-74	0.811 (0.124)	0.668 (0.141)	0.734 (0.131)	1.040 (0.183)
	75-79	0.766 (0.132)	0.615 (0.143)	0.694 (0.144)	0.996 (0.193)
	80-84	0.760 (0.110)	0.613 (0.127)	0.696 (0.152)	1.038 (0.201)
	85 +	0.730 (0.125)	0.580 (0.145)	0.655 (0.140)	1.077 (0.224)
	Total	0.814 (0.131)	0.670 (0.149)	0.727 (0.136)	1.032 (0.183)
	Adjusted *	0.812 (0.120)	0.664 (0.139)	0.720 (0.122)	1.026 (0.183)

* Adjusted for age and body mass index

In men, the body mass index remained approximately constant throughout the age strata, while in women it slightly increased with age. Mean age at the last menstrual period was 48.6 (SD = 5.0) years.

Site-specific mean values for bone mineral density are displayed in table 2, stratified by age and sex. The overall mean bone mineral density as well as the age and body mass index adjusted mean values were higher in men than in women at all sites of measurement ($P < 0.0001$). At the femoral measurement sites, we observed a steady decrease of bone mineral density with age in both sexes, although more pronounced in women. At the lumbar spine, no relationship between age and bone mineral density could be observed in women, and a slight increase of spinal bone mineral density with age was found in the lumbar spine of men. Figure 1 depicts the bone mineral density of the lumbar spine and femoral neck by age in each sex together with the fitted regression lines. The eight outliers (> 3SD) of bone mineral density in the lumbar spine in men and six outliers in women could be recognized. Examination of the lateral radiographs of these participants showed severe spondylosis of the lumbar spine with large osteophytes and prominent sclerosis of the endplates (mean Kellgren score 3.75 in men and 2.4 in women). There was no significant aortic calcification or vertebral deformation in the outliers.

The results of both simple and multiple regression analyses are shown in table 3. The age-related decline in the lumbar spine bone mineral density of female subjects was not statistically significant. In men, a significant increase of spinal bone mineral density with age was observed. However, reanalysis of these data after outlier rejection resulted in a somewhat smaller, and no longer statistically significant, regression coefficient in men (0.0017, $P = 0.07$). After rejection of outliers in women, the slope became more negative (-0.0005, $P = 0.49$).

As to the femoral sites, all slopes were negative and statistically significant ($P < 0.01$, table 3). The strongest age-related decrease of bone mass was found at the Ward's triangle in both sexes. Within the proximal femur, all differences between the slopes of men and women were significant ($P < 0.05$). The female to male ratio of the slopes was 1.8 in the femoral neck, 1.6 in the Ward's

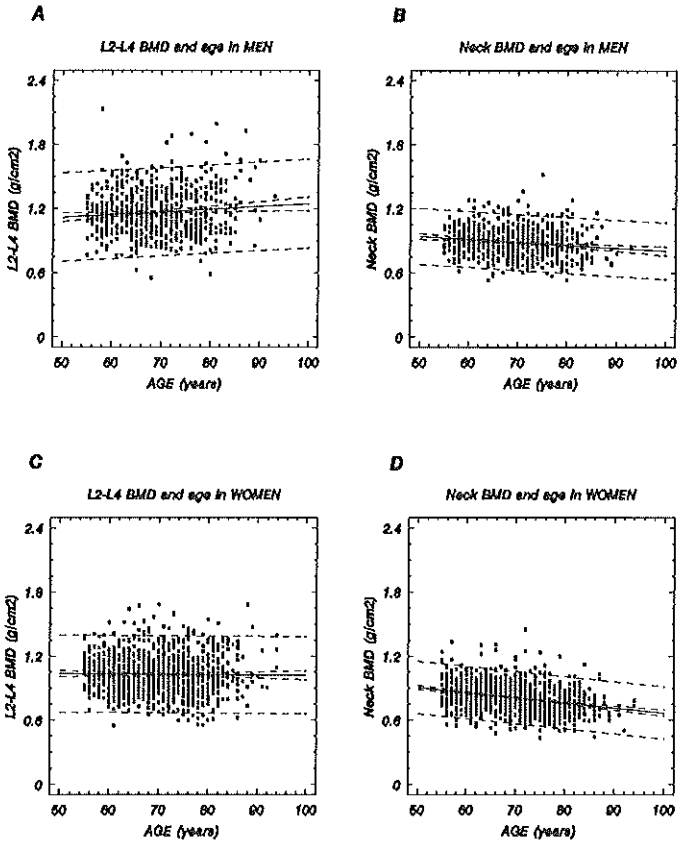

FIGURE 1. Bone mineral density in the lumbar spine (A and C) and femoral neck (B and D) by age in men (A and B) and women (C and D). Solid lines are fitted regression lines. Dotted lines are 95% confidence limits for the regression lines and 95% prediction bands.

triangle and 1.3 in the greater trochanter. Adjustment for body mass index did not influence the effect of age on bone mineral density in men whereas in women, the age-coefficient became more negative, thus enlarging the sex difference in age-related decline in bone mineral density to a female to male ratio of 1.9, 1.7 and 1.5 in the femoral neck, Ward's triangle and greater trochanter, respectively (table 3).

TABLE 3. Results of the regression analyses. Intercept (ic (g/cm^2)), age (g/cm^2/year), body mass index (BMI ($g/cm^2/(kg/m^2)$)) and age of menopause (AOM (g/cm^2/year)) coefficients and P-values, stratified by site of measurement and sex

		Univariate analysis			Multivariate analysis							
Men		ic	age	P		ic	age	P	BMI	P		
	Neck	1.075	-0.0027	0.00	Neck	0.797	-0.0028	0.00	0.011	0.00		
	Ward	0.956	-0.0034	0.00	Ward	0.665	-0.0034	0.00	0.011	0.00		
	Troch	1.013	-0.0024	0.00	Troch	0.632	-0.0024	0.00	0.015	0.00		
	L2-L4	0.992	0.0025	0.01	L2-L4	0.584	0.0024	0.02	0.016	0.00		
Women		ic	age	P		ic	age	P	BMI	P		
	Neck	1.146	-0.0048	0.00	Neck	0.798	-0.0052	0.00	0.012	0.00		
	Ward	1.044	-0.0054	0.00	Ward	0.623	-0.0059	0.00	0.013	0.00		
	Troch	0.934	-0.0030	0.00	Troch	0.464	-0.0036	0.00	0.017	0.00		
	L2-L4	1.053	-0.0003	0.64	L2-L4	0.448	-0.0009	0.17	0.017	0.00		
						ic	age	P	BMI	P	AOM	P
					Neck	0.798	-0.0051	0.00	0.012	0.00	0.0012	0.10
					Ward	0.623	-0.0058	0.00	0.013	0.00	0.0019	0.02
					Troch	0.464	-0.0034	0.00	0.017	0.00	0.0010	0.17
					L2-L4	0.448	-0.0007	0.29	0.016	0.00	0.0040	0.00

TABLE 4. Percentage bone reduction per year

		Unadjusted *	P	Adjusted †	P
Men	Neck	-0.30	0.00	-0.32	0.00
	Ward	-0.47	0.00	-0.47	0.00
	Troch	-0.28	0.00	-0.28	0.00
	L2-L4	0.21	0.01	0.21	0.00
Women	Neck	-0.59	0.00	-0.63	0.00
	Ward	-0.81	0.00	-0.87	0.00
	Troch	-0.41	0.00	-0.47	0.00
	L2-L4	-0.03	0.64	-0.07	0.29

* (unadjusted age coefficient / mean bone mineral density value) * 100
† (age coefficient adjusted for body mass index (and year of menopause in women) / mean bone mineral density value) * 100

Age of menopause was positively related to bone mineral density in the spine and Ward's triangle, independently of age and body mass index (table 3).

Percentage reduction in bone mineral density per year for the different sites are shown in table 4. Both methods of calculation of percentage loss per year showed the same patterns as the slopes from the regression analyses, although the sex differences became more prominent due to a lower mean bone mineral density in women. Again, the largest female to male ratio (1.9) was found in the femoral neck, followed by the Ward's triangle (1.7) and the greater trochanter (1.6). There was no evidence for a quadratic or cubic age-related decline, nor for periods of increased fall in bone mineral density in separate five-year periods, as none of the coefficients was substantially different from zero or statistically significant at the 0.05 level (results not shown).

Correlations between bone mineral density values at different sites are given in table 5. All correlation coefficients (r) were significantly different from zero. Within the femur, correlations are high in both sexes (r = 0.77-0.93). Between femoral sites and lumbar spine we observed a much lower correlation (r =0.51-0.56).

TABLE 5. Correlation between bone mineral density at different sites of measurement *

		Ward	Troch	L2-L4
Men	Neck	0.92	0.78	0.51
	Ward		0.77	0.52
	Troch			0.56
Women	Neck	0.93	0.78	0.56
	Ward		0.78	0.56
	Troch			0.54

* All correlation coefficients are significantly different from zero at $P < 0.001$

Discussion

In this population based study, there are two main findings. First, in both sexes, we could not demonstrate age-related decrease in bone mineral density in the lumbar spine. Second, we observed within one single population a statistically significant difference between men and women in the rate of decline in bone mineral density with aging at all femoral sites. The latter finding is, as far as we know, completely new. Age of menopause was an important independent determinant of bone mineral density in the Ward's triangle and the lumbar spine. body mass index was strongly related to bone mineral density at every site of measurement in both sexes and we found strong correlations within the proximal femur and modest correlations between the femoral sites and the lumbar spine measurements.

Since our study concerns cross-sectional data, the results might have been influenced by age-dependent selection and possibly also by cohort effects. Selection bias will occur in all age groups in the sense that more healthy subjects with higher bone mineral density values will be responders. If this is stronger in older age groups, the slope of the regression of bone mineral density on age will be biased upwards. The direction of the slope can be affected in the same direction due to cohort effects, if one assumes that persons with a recent year of birth, i.e. younger people, will have lower densities, adjusted for their age, compared to older subjects. This could be mediated through life-style

factors such as physical activity and diet [39,40]. Institutionalized cohort members did not have densitometry. This may have caused an underestimation of the rate of bone mineral density reduction.

With regard to our first finding, the lack of axial bone diminution in women is surprising since many studies have reported considerable decline in spinal bone mineral density with aging in women [17,19,27,31-33]. In these studies, selected subjects were relatively free of spinal abnormalities that may very well hamper bone mass measurements [41,42]. For men however, there are three studies [17,21,33] with results similar to ours. They could not detect any significant relation of spinal bone mineral density to age in men of 51 years and over, although there was a statistically non-significant tendency to a small reduction in younger (51-65 years [17,33], 40-69 years [21]) subjects and an increase of bone density with age in older men (66+ [17,33], 70+ [21]). In our study, we were not able to show such a biphasic pattern. With respect to age-related bone diminution in the proximal femur, we observed in women a rate of decline of femoral neck bone mineral density with aging expressed as grams/cm^2/year which appeared to be almost twice as high as that in men. The observed absolute rates of decline in the proximal femur of women is equal to the results of the Framingham Osteoporosis Study [26]. Another large study in women [27] also showed results that are almost similar to those observed in the present study. In men, on the other hand, we observed a rate of decline approximately two times lower compared to that observed in the Framingham Study. In the latter study, no statistically significant difference in femoral bone mineral density reduction between the sexes has been found. In two other important studies concerning sex differences in age-related bone reduction by Mazess et al. [19,21], the slopes in women were roughly similar to the slopes we observed, but they did not report any statistically significant difference in slopes between men and women aged 40 to 89 years. Comparison of percentage fall in bone mineral density between studies is difficult since it is affected by both level and slope. Within the femur, the steepest decline of bone mineral density with age was found in the Ward's triangle, in both men and women. This observation is consistent with findings from several other studies [19,21,26,27]. The effects of both body mass index [38,39] and

menopause [28,31,32] on bone mineral density we found is in agreement with data from other studies as well. Also the magnitude of correlation we observed between the different measurement sites is similar to that found by others [26,27].

The results of our spinal bone mineral density measurements could be explained in part by selection bias and cohort effects. However, the response rate in the present study remained high up to age 85 thus limiting the possible influence of selection. Furthermore, we observed from interview data that the frequency of hip and wrist fracture history between those who were included in this study and those who refused to come to the center was not significantly different. From those who were included in this study, 1% reported a hip fracture and 6% reported a wrist fracture in the past five years. These frequencies were 1% and 4% in those who refused to come to the center for hip and wrist fractures respectively. Most importantly, these biases would have influenced femoral measurements as well. Since we clearly observed age-related bone reduction in the femur and selection would almost certainly not affect spinal bone mineral density selectively, the explanation of selection bias or cohort effects is unlikely. We believe that age-related local factors limited the possibility to study cross-sectional bone diminution with aging in the spine such as the presence of marked spinal osteoarthritis in the region of interest [41-43]. This suggestion was also supported by the fact that in participants with extremely high lumbar spine bone mineral density (more than 3 standard deviations above the mean value), severe spondylosis in the measurement area was found. These factors may have decreased the correlation between spinal and femoral density as well. The discrepancy between the results of our femoral measurements and those of the Framingham Study, can be explained in part by the fact that the mean age of the population in the Framingham Study was higher (76 years) than in our study (69 years). This would have resulted in a more negative slope in men in the Framingham Study if bone loss in the male femur is accelerating with increasing age, thus diminishing the difference. Such an assumption is supported by the findings of Mazess et al. [19,21]. In these studies, the decrease of bone mineral density was stronger in women than in men in the age group 40-69 years at all femoral sites measured but this relation inverted in the older age

group. Other factors, such as differences in distribution of body mass index over age strata or different cohort effects, may have contributed to the different findings as well. The large sex difference in age-related bone reduction we found in the proximal femur, predominantly concerns cortical bone since the largest female to male ratio was found for the femoral neck. The steepest decline was found in the Ward's triangle suggesting that aging particularly affects trabecular bone. The effect of the age of onset of menopause underlines the special vulnerability of trabecular bone to relative estrogen deficiency after menopause. However, the mean bone reduction due to early menopause was modest compared to the effect of age. In our population, one year of age-related bone reduction in the Ward's triangle could be compensated by a three years later onset of menopause.

From this population based study in the elderly we conclude that spinal bone mass measurements from cross-sectional studies can not be used for the accurate assessment of age-related bone reduction in elderly men and women. As to the proximal femur, the rate of age-related bone reduction in the femoral neck is almost two times higher in women than in men.

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Chapter 3.2

Bone loss and the beneficial effect of high dietary calcium and vitamin D in an elderly population

Introduction

It has been convincingly shown that low bone mineral density is a risk factor for fractures [1,2]. Recently, a progressive rate of bone loss in the femoral neck with age was seen in a population based longitudinal study of osteoporosis in elderly men and women [3]. This pattern of bone loss has not been observed in previous cross-sectional studies [4,5] and requires further confirmation from longitudinal data.

Nutritional factors that may prevent bone loss include calcium and vitamin D intake [6,7]. Although both substances appear to have a beneficial effect on bone in elderly women [8], conflicting results for calcium intake were obtained in men [9,3].

The current study was performed to longitudinally assess the rate of change of femoral neck bone mineral density in relation to age, dietary calcium and vitamin D in elderly men and women.

Methods

The present study was conducted as part of the Rotterdam Study, a prospective population based cohort study of determinants and prognosis of chronic diseases in the elderly [10]. The focus is on cardiovascular, neurogeriatric, ophthalmologic and locomotor diseases. Eligible for the study were all inhabitants aged 55 years or over of the district Ommoord in Rotterdam, the Netherlands. In total 10275 persons, of whom 9161 (89%) were living independently, were invited for the study. The baseline examination of the Rotterdam Study comprised an interview at home and extensive investigations at the research center. In the independently living

population, the response rate for the baseline phase was 77% for the home interview and 71% for the center visit. Written informed consent was obtained from each participant. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical School.

The investigations at the research center included anthropometry and bone mineral density measurements. Height and weight were measured in standing position without shoes. Body mass index (kg/m^2) was calculated for each individual as a measure of obesity. Bone mineral density measurements were performed using dual energy x-ray absorptiometry (Lunar DPX-L). Standard positioning was used with anterior-posterior scans of the right proximal femur unless there was a history of hip fracture or prosthesis implantation. In the latter case, the left side was scanned. Using standard software, we analyzed the femoral neck, Ward's triangle and greater trochanter. The in vivo coefficient of variation was 3.2% in the femoral neck, 3.1% in the Ward's triangle, and 2.5% in the greater trochanter. During the baseline phase, bone mineral density values were obtained in 2440 men and 3367 women. As part of the second survey approximately 2 years after the baseline phase, follow-up bone mineral density measurements were performed using identical procedures. A phantom was regularly scanned to be sure that no machine drift had occurred. The study population for the present study comprised all 1859 men and 2459 women (76 and 73% of the baseline numbers, respectively) with both baseline and follow-up bone mineral density measurements. In these participants, the yearly rate of change in bone mineral density was calculated as the difference between baseline and follow-up bone mineral density divided by the duration of follow-up in years. The median duration of follow-up was 1.9 years.

At the research center, trained dietitians used a semiquantitative food frequency questionnaire to obtain information on food intake during the past year. The conversion from foods to energy and nutrient intakes was established using the Dutch Food Composition Table (NEVO, 1993). Food supplements were not included in the computation of nutrients in the current study.

TABLE 1. Age distribution and mean values (SD) or quartiles for baseline characteristics of the study population by gender.

	Men	Women
Number	1859	2459
Age-group (years)		
55-59	380	502
60-64	462	589
65-69	429	510
70-74	314	428
75-79	194	282
80+	80	148
Age (years)	66.7 (7.2)	67.2 (7.6)
Body mass index (kg/m^2)	25.8 (2.9)	26.7 (4.0)
Baseline bone mineral density (g/cm^2)	0.883 (0.13)	0.817 (0.13)
Energy intake (kcal/day)	2247 (497)	1783 (385)
Dietary calcium (mg/day)		
Quartile 1	≤ 864	≤ 874
Quartile 2	865 - 1092	875 - 1073
Quartile 3	1093 - 1363	1074 - 1307
Quartile 4	≥ 1364	≥ 1308
Dietary vitamin D (μg/day)		
Quartile 1	≤ 1.38	≤ 0.99
Quartile 2	1.39 - 2.15	1.00 - 1.62
Quartile 3	2.16 - 3.35	1.63 - 2.49
Quartile 4	≥ 3.36	≥ 2.50

Analysis

Baseline characteristics and the mean yearly rate of change in bone mineral density were compared between men and women. The rate of change was stratified according to five-year age strata and gender and tested for linear trends with age using regression analysis. In order to assess the influence of the nutritional factors, the rate of change in bone mineral density was

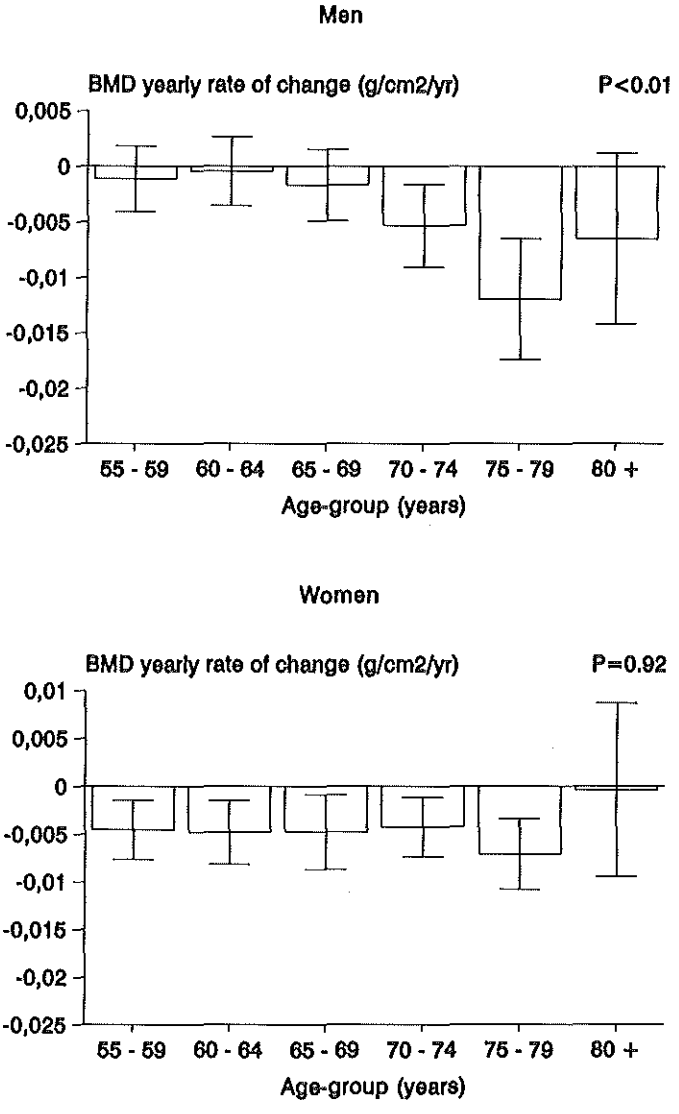


FIGURE 1. The mean (95% confidence interval) yearly rate of change of bone mineral density (BMD) according to age-group and gender. P-values are for linear trends.

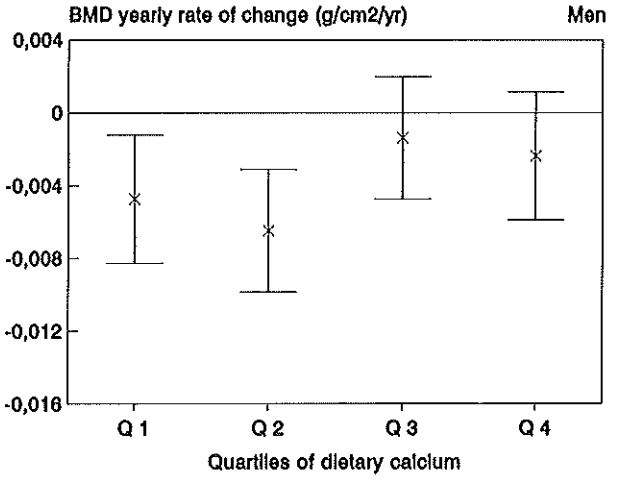
calcutated according to quartiles of dietary calcium and vitamin D. Differences in bone loss between the first and fourth quartiles of dietary calcium and vitamin D were tested for statistical significance. As the intakes of nutritional factors may be interrelated, the analyses with calcium were adjusted for vitamin D and vice versa. The possibility of interaction between calcium and vitamin D and between age and nutrition was addressed by including interaction terms in a multiple regression model. Additionally, the rate of change in subjects who were in the highest quartiles as well as in the lowest quartiles for both nutritional factors were calculated. All analyses of nutrition were carried out while adjusting for age, body mass index and energy intake. The adjustments were made using analysis of covariance. The results for the femoral neck are presented. The findings in the analyses of the Ward's triangle and greater trochanter were similar.

Results

The baseline characteristics according to gender are displayed in table 1. Compared to women, the energy and dietary vitamin D intake were considerably higher in men while for calcium intake this difference was modest. The mean (95% confidence interval) rate of change in bone mineral density was -0.0032 (-0.0047, -0.0017) g/cm^2/yr in men and -0.0047 (-0.0062, -0.0032) g/cm^2/yr in women. This difference was not statistically significant (P=0.16).

The rate of change according to age-group and gender is depicted in figure 1. In men, a substantial increase with age was observed in the age range 65 to 79 years. In the oldest age-group, the rate of change diminished. The overall linear trend was significant. The rate of change in women remained approximately constant over age strata except for the oldest age-group where the rate of change was almost zero.

Figure 2 shows the rate of change in bone mineral density according to quartiles of dietary calcium. In both men and women a trend of lower rates of change with higher calcium intake was found. The differences in bone loss were not statistically significant between the first and fourth quartiles. The



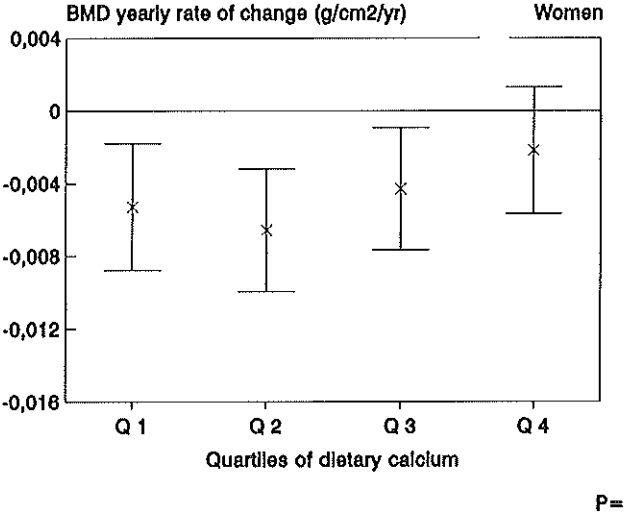


FIGURE 2. The mean (95% confidence interval) yearly rate of change of bone mineral density (BMD) according to quartiles of dietary calcium and gender. Values are adjusted for age and body mass index. P-value refers to the difference in rates between the first and the fourth quartile.

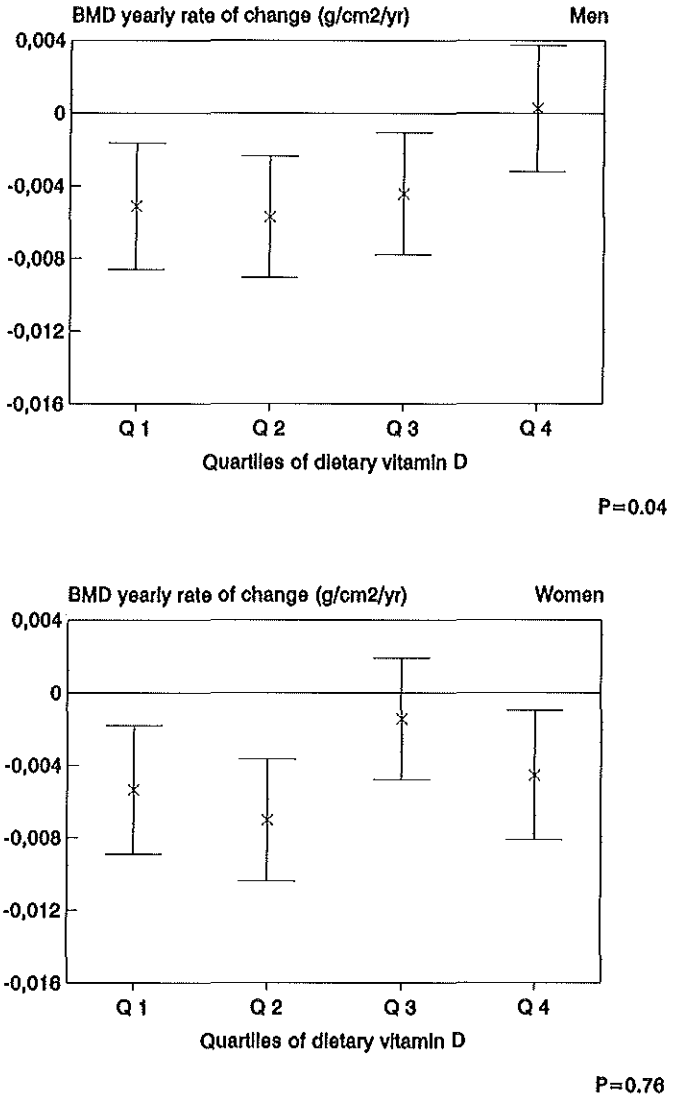


FIGURE 3. *The mean (95% confidence interval) yearly rate of change of bone mineral density (BMD) according to quartiles of dietary vitamin D and gender. Values are adjusted for age and body mass index. P-value refers to the difference in rates between the first and the fourth quartile.*

relationship with vitamin D is depicted in figure 3. In both men and women a lower rate of change was seen with higher vitamin D intake. The difference in bone loss between the first and fourth quartile was more pronounced in men and statistically significant. The adjustments for energy intake did not influence the results. Interaction was not present between age and dietary factors nor between calcium and vitamin D intake. The rates of change (95% confidence interval) in men and women with both the highest quartile for calcium intake and vitamine D intake were 0.0020 (-0.0042, 0.0082) and -0.0053 (-0.0119, 0.0014) g/cm^2/yr, respectively.

Discussion

The current study shows progressive bone loss with age in men and approximately constant rates in women. Men in the highest quartile of dietary vitamin D had a significantly lower rate of bone loss than those in the lowest quartile. Further, we observed modestly lower rates of bone loss with higher intakes of dietary calcium in men and both calcium and vitamin D in women. The effects of having both the highest quartile for dietary calcium and vitamin D were approximately additive in men but not in women.

Some methodological issues should be discussed before the findings of this study can be accepted. The participation in the Rotterdam Study is voluntary. Therefore, some selection in favour of the more mobile and healthy population with probably lower rates of bone loss may have occurred both at baseline and during follow-up. The result is an underestimation of the true rate of bone loss. As such non-response bias is likely to become more pronounced with increasing age, the progression of the rate of change with age is probably also underestimated as the analysis of the progression with age is cross-sectional. The low rates of bone loss in the highest age-groups in both men and women suggests such a non-response bias. Overall, however, the high response rates set bounds to selection bias. Selective non-response may also have influenced the association between dietary factors and the rate of change. However, the magnitude of these associations were not different between the younger and older age-groups. Assuming that the true

association does not vary with age, this suggests that selection by non-response did not influence the associations under study as non-response bias becomes probably more pronounced with increasing age. The nutrients intake was assessed using a semiquantitative questionnaire. Some misclassification is therefore inevitable. In our view, however, it is likely that this misclassification is random, i.e. not dependent on the rate of change in bone mineral density and would therefore result in some dilution of the associations.

The rate of bone loss as estimated cross-sectionally in the Rotterdam Study [4] was of similar magnitude, though in men somewhat lower than estimated longitudinally. The high longitudinal rate of change in the age-group 75-79 years was not found in the cross-sectional analysis. We believe, however, that the longitudinal data are more valid as they are less subject to cohort effects and selection bias. The progressive rate of change in men from the Rotterdam Study was also seen in men from the Dubbo Study [3]. In women from our study, however, no progression was observed as opposed to the Dubbo Study showing an approximately similar progression in men and women. Within age strata, the rates of loss were substantially lower in the Rotterdam Study. Possibly, the higher weight in women from our study population (70.1 kg versus 65.3 kg) and considerably higher mean dietary calcium intake in both men (1156 mg/day versus 627 mg/day) and women (1113 mg/day versus 645 mg/day) may explain the lower rates of bone loss. In men, three studies showed no or minor effects of high calcium intake on the rate of bone loss [3,9,11]. In the placebo-controlled trial presented by Orwoll et al, the absence of a preventive effect of calcium supplementation on the rate of loss may be explained by the fact that the mean calcium intake at entry was approximately already as high as the mean value in our study. In the study by Slemenda et al, the proportion of men with high calcium intake was probably too low to detect any effect. In women, several experimental studies showed a minor beneficial effect on the rate of bone loss of calcium [12,13], calcium combined with vitamin D [8] or with exercise [14]. In the only study in men, as far as we know, supplementation with vitamin D combined with

calcium was not effective [9].

The data in the present study are well compatible with the current knowledge on the etiology of bone loss in the elderly. Naturally, calcium absorption has to keep up with calcium excretion to maintain sufficient mineral content of the skeleton. The relative vitamin D deficiency in the elderly [15] may, by its crucial role in the absorption of calcium [16], deplete the bone in the absence of sufficient intake of these nutrients. Some caution, however, is needed interpreting the data. As inherent to the observational design of the study, residual confounding may have distorted the results. Low rates of bone loss in persons with high calcium or vitamin D intake could well be the result of a lifestyle that is more beneficial to the bones or merely the absence of comorbidity in these persons rather than effects of the nutrients themselves. For instance, high physical activity, which in itself may have a beneficial effect on the bone, either directly [17] or indirectly through higher solar exposure and consequent higher vitamin D synthesis [7], may be associated with dietary habits that are favourable to the skeleton including high calcium and vitamin D intake. This mechanism, however, could not be supported by our finding that adjustment for energy intake, which is likely to be a correlate of physical activity, did not affect the results. Although not very likely in our view, the weaker associations with dietary factors in women may, at least in part, be explained if women were, more than men, already before they had the dietary interview aware of their osteoporosis, or an increased risk of this condition, and subsequently altered their eating habits.

The clinical implication of the results may be that the current advice on calcium intake in the USA of 1000 mg/day [17] may be relatively low. The present study also underlines the importance of sufficient dietary vitamin D. In particular men seem to benefit from a combined high intake of calcium and vitamin D as the effects appeared to be approximately additive.

In summary, the present study shows that bone loss with age in elderly men tends to increase with age and that high dietary intake of calcium and high dietary vitamin D intake is associated with slightly lower rates of bone

loss.

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Chapter 3.3

Radiographic osteoarthritis is associated with higher bone mineral density and increased bone loss with age

Introduction

Osteoarthritis and osteoporosis are major health problems in the elderly [1,2]. However, the coexistence of both disorders in one patient has been considered to be rare [3]. Hence, an inverse relationship between osteoarthritis and osteoporosis has been proposed. Evidence for such a relationship may give rise to etiological clues [4].

The presently available studies do not allow definite conclusions. Studies that are in favor of an inverse relationship [5-10], as well as studies in which there was no sufficient support for such a relationship [11,12], have been published. The relation between osteoarthritis and femoral bone loss with age has not been investigated so far.

In the present study, we investigated the relationship of radiographic osteoarthritis of the knees and hips with the level of bone mineral density and the rate of bone loss with age in a sample from the general population.

Methods

The present study was conducted as part of the Rotterdam Study, a prospective population based cohort study of determinants and prognosis of chronic diseases in the elderly [13]. The focus is on cardiovascular, neurogeriatric, ophthalmologic and locomotor diseases. Eligible for the study were all inhabitants aged 55 years or over of the district Ommoord in Rotterdam, the Netherlands. 10275 persons, of whom 9161 (89%) were living independently, were invited for the study. The baseline examination of the Rotterdam Study comprised an interview at home and extensive investigations at the research center. In the independently living population,

the response rate was 77% for the home interview and 71% for the center visit. Written informed consent was obtained from each participant. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical School.

As a measure of mobility of the participant, the degree of lower limb disability was assessed as the impairment in activities of daily living (ADL) using a questionnaire modified from the Stanford Health Assessment Questionnaire [14]. The lower limb disability index used was composed of the mean score (zero indicating no impairment and three indicating unable to perform) for six questions on arising, walking, bending and getting in and out of a car. Disability was defined as a lower limb disability index of 0.5 or over.

The investigations at the research center included anthropometry, bone mineral density measurement and radiography. Height and weight were measured in standing position without shoes. The body mass index (kg/m^2) was calculated for each individual as a measure of obesity. Bone mineral density measurements were performed using dual energy X-ray absorptiometry (Lunar DPX-L densitometer). Standard positioning was used with anterior-posterior scans of the right proximal femur unless there was a history of hip fracture or prosthesis implantation. In the latter case, the left side was scanned. Using standard software, we analyzed the femoral neck, Ward's triangle and greater trochanter. The in vivo coefficient of variation was 3.2% in the femoral neck, 3.1% in the Ward's triangle, and 2.5% in the greater trochanter as assessed in 12 randomly selected cohort members with repositioning between the two measurements.

Osteoarthritis of the hip and knee joints was assessed on weight-bearing anterior-posterior radiographs of the pelvis and knees, respectively. Grading of osteoarthritis was performed without knowledge of other data by two independent observers (EO and HAV) on a five point scale (0-4), according to Kellgren [15]. Whenever the scores differed more than 1 point or was 1 for one reader and 2 (or more) for the other, a consensus score was agreed upon. Consensus reading was necessary in approximately 10% of all X-rays.

The highest score or, in case of a consensus reading, the consensus-score was entered as the final score. The maximum of the left and right side Kellgren score was used for the analyses. Definite radiographic osteoarthritis was defined as Kellgren score 2 or over.

By the time of this analysis, the reading of baseline knee and pelvis radiographs of a sample comprising 1121 ambulatory men and 1624 women was completed. Among them, 714 men and 1009 women had follow-up bone mineral density measurements using identical procedures. In these participants, the yearly rate of change of bone mineral density was calculated as the difference between baseline and follow-up bone mineral density divided by the duration of follow-up in years. Baseline measurements were performed between August 1990 and September 1993 and follow-up measurements between October 1993 and November 1994. The median duration of follow-up for the current study population was 2.2 years (range 1.2 - 3.2).

Analysis

The total study population and the group that had follow-up bone mineral density measurements were compared with regard to baseline characteristics. Bone mineral density level and rate of bone loss, expressed as the absolute or percentage yearly change of bone mineral density, were compared in subjects with and without site-specific radiographic osteoarthritis. Linear regression analysis was performed to test whether there was a statistically significant trend of increasing bone mineral density level and increasing rate of bone loss with the number of affected sites (none, knee or hip, both), as well as with the Kellgren score. Kellgren scores 3 and 4 were collapsed to one category (3+) for numerical reasons. Linear regression was also used to assess the influence of radiographic osteoarthritis and disability on the rate of bone loss by entering the Kellgren score and lower limb disability index into the regression model as independent variables, both separately and simultaneously. The coefficients from the separate and simultaneous analyses were compared to investigate whether the rate of bone loss associated with

TABLE 1. Sex-specific mean values (standard deviation) and proportions (%) of baseline characteristics of the total study population and the subgroup with follow-up bone mineral density measurements.

		Total population	Follow-up group
Men	Number	1121	714
	Age (yrs)	68.6 (7.6)	68.1 (7.2)
	Body mass index (kg/m^2)	25.7 (2.9)	26.0 (2.9)
	Femoral neck bone mineral density (g/cm^2)	0.876 (0.14)	0.882 (0.13)
	Disability (%)	19	17
	Radiographic osteoarthritis (%)		
	Knee	14	14
	Hip	10	11
	Knee and hip	3	3
Women	Number	1624	1009
	Age (yrs)	69.1 (8.0)	68.1 (7.5)
	Body mass index (kg/m^2)	26.7 (4.0)	26.8 (4.1)
	Femoral neck bone mineral density (g/cm^2)	0.806 (0.13)	0.817 (0.13)
	Disability (%)	29	25
	Radiographic osteoarthritis (%)		
	Knee	23	22
	Hip	7	7
	Knee and hip	5	4

radiographic osteoarthritis was independent of disability. All analyses were carried out in men and women separately, while controlling for age and body mass index. The results presented concern bone mineral density measurements in the femoral neck only as the bone mineral density of the

Ward's triangle and greater trochanter showed a similar relationship to radiographic osteoarthritis. This is in agreement with the relatively high correlation coefficients that were found between on the one hand the femoral neck density and on the other hand the Ward's triangle and greater trochanter, 0.9 and 0.8 ($P < 0.01$), respectively. The correlation coefficients for the rate of loss were 0.8 and 0.6 ($P<0.01$), respectively.

Results

Table 1 shows the baseline characteristics of the study population. The characteristics of participants who had follow-up measurements were similar to those of the total study population although they were slightly younger and had somewhat higher bone mineral density. In table 2, baseline bone mineral density level and rate of change are presented according to site-specific osteoarthritis. As to bone mineral density level, 3-8% higher values were observed in the presence of osteoarthritis of the knee or hip or both as compared to subjects without osteoarthritis. However, the higher level in men with knee osteoarthritis was not statistically significant. In both men and women, there was a significant trend of increasing bone mineral density level with increasing number of affected sites. The rate of bone loss, either expressed as the absolute yearly change or as a percentage of the baseline value, was higher in subjects with osteoarthritis. In women, the differences in the absolute rate of change were statistically significant for all sites. Expressed as a percentage, the difference in women was not statistically significant for osteoarthritis of the hip. In men, the difference in rate of loss, either absolute or as a percentage, was statistically significant for hip osteoarthritis only. A trend of increasing absolute rate of bone loss with the number of affected sites was statistically significant in both men and women. As to the percentage bone loss, the trend was significant in women only.

Bone mineral density level according to Kellgren score is depicted in figure 1. Higher bone mineral density levels were observed with increasing Kellgren score, except for the highest knee Kellgren score category in women. The observed trend was significant for both sites in men and

TABLE 2. Mean baseline bone mineral density level and mean yearly rate of change of bone mineral density by site-specific radiographic osteoarthritis and sex.

		No ROA	Knee ROA	P*	Hip ROA	P*	Knee and hip ROA	P*	P†
Men	BMD Level‡	0.868 (0.005)	0.890 (0.011)	0.07	0.895 (0.013)	0.05	0.920 (0.023)	0.03	<0.01
	BMD rate§	-0.008 (0.001)	-0.009 (0.003)	0.67	-0.0018 (0.003)	<0.01	-0.016 (0.007)	0.21	0.02
	Percentage¶	-0.87	-0.96	0.79	-2.00	<0.01	-1.42	0.48	0.07
Women	BMD Level‡	0.793 (0.004)	0.821 (0.006)	<0.01	0.847 (0.011)	<0.01	0.857 (0.013)	<0.01	<0.01
	BMD rate§	-0.005 (0.001)	-0.010 (0.002)	0.04	-0.013 (0.004)	0.04	-0.023 (0.005)	<0.01	<0.01
	Percentage¶	-0.52	-1.11	0.04	-1.40	0.06	-2.50	<0.01	<0.01

Values (standard error) are adjusted for age and body mass index.

* *P*-value for difference refers to comparison with the group without radiographic knee or hip osteoarthritis.

† *P*-value for linear trend of increasing values with increasing number of sites affected.

‡ Baseline bone mineral density level at the femoral neck (g/cm^2).

§ Yearly rate of change at the femoral neck ($g/cm^2/yr$).

¶ Yearly rate of change at the femoral neck as a proportion of the baseline value expressed as a percentage (%/yr).

women. The yearly rate of change, as shown in figure 2, also increased with higher Kellgren score, although this trend was not statistically significant for knee osteoarthritis in men.

Table 3 shows the relationship between the lower limb disability index as well as site-specific Kellgren score and the rate of bone loss. The coefficients indicate the mean change in the yearly rate of femoral neck bone mineral density per unit increase of the independent variable, i.e. lower limb disability index and Kellgren score. Disability was associated with an increased rate of bone loss in both men and women. The higher rate of bone loss associated with increasing Kellgren score was independent of disability since the coefficients for the Kellgren scores in the simultaneous analyses were almost the same as those observed in the separate analyses. Analyses with the Kellgren score at either the right or left joint were similar.

Discussion

The present population based study shows that both bone mineral density level and rate of bone loss is increased in the presence of radiographic osteoarthritis of the knee or hip. As far as we know, this is the first study of the relationship between osteoarthritis and the rate of bone loss in the proximal femur. A graded relationship between on the one hand the number of affected sites as well as the Kellgren score and on the other hand both bone mineral density level and rate of bone loss was demonstrated. The relationship between osteoarthritis and rate of bone loss appeared to be independent of lower limb disability.

Some limitations of the study have to be discussed. Selective non-response of subjects with impaired mobility may have caused an underestimation of the prevalence of osteoarthritis and an overestimation of the mean bone mineral density. It is, however, unlikely that selective non-response would have produced the observed association. In that case, it has to be assumed that impaired mobility in the presence of osteoarthritis would lead to a lower response rate than other conditions with impaired mobility. Regarding the assessment of radiographic osteoarthritis, one may argue that the degree of

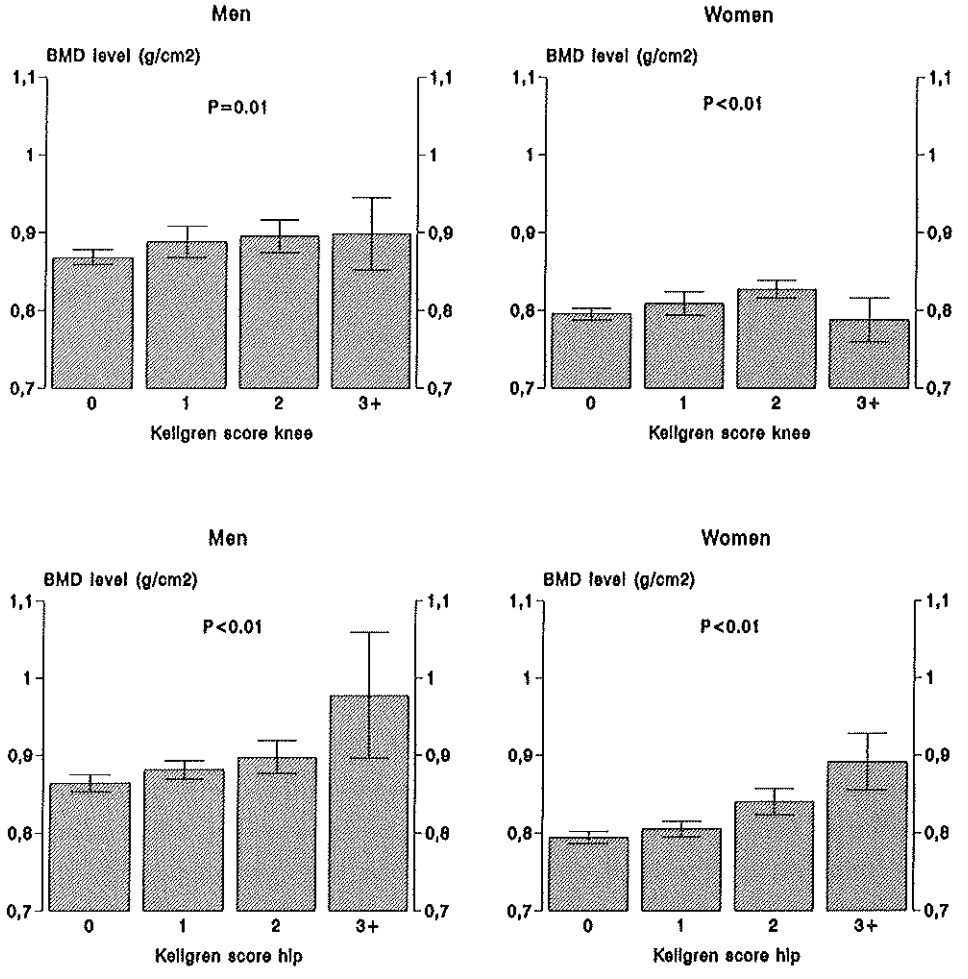

FIGURE 1. Femoral neck bone mineral density (BMD) level according to Kellgren score. P-values are for linear trends. All values are adjusted for age and body mass index.

osteoporosis was estimated on the radiographs of the knees and pelvis and that accordingly the Kellgren scores were influenced. This also seems unlikely as the readers were not aware of the present study question at the

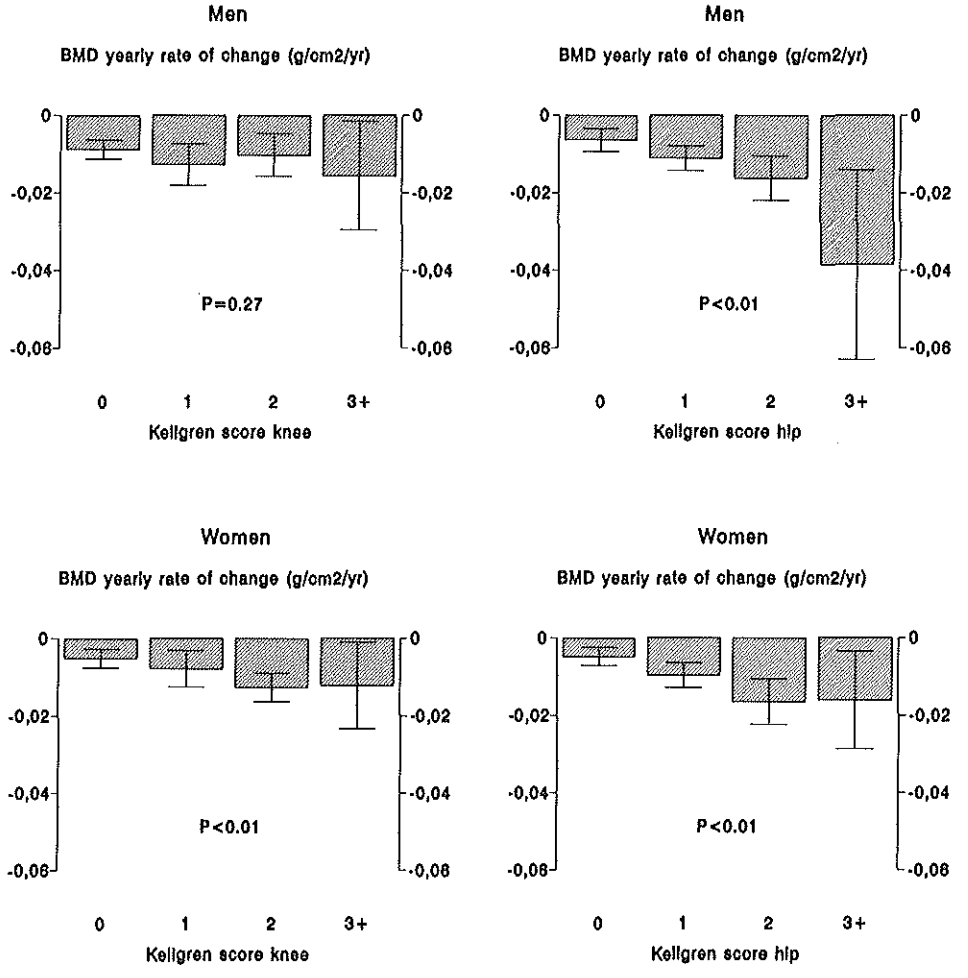

FIGURE 2. The rate of bone loss expressed as the yearly rate of change of femoral neck bone mineral density according to Kellgren score. P-values are for linear trends. All values are adjusted for age and body mass index.

time of the assessment of osteoarthritis. Occasionally, hip osteophytes may have been in the scanning field of the densitometer causing spuriously elevated values. On the other hand, since in almost all subjects the right side

TABLE 3. Regression of the yearly rate of change of femoral neck bone mineral density ($g/cm^2/yr$) on disability and Kellgren score, analysed both separately and simultaneously.

		Separate analyses	Simultaneous analyses	
			Disability & Kellgren score Knee	Disability & Kellgren score Hip
Men	Disability	-0.0022 (-0.0083, 0.0039)	-0.0026 (-0.0089, 0.0037)	-0.0019 (-0.0080, 0.0042)
	Kellgren-score knee	-0.0015 (-0.0040, 0.0010)	-0.0015 (-0.0040, 0.0010)	
	Kellgren-score hip	-0.0054 (-0.0083, -0.0025)		-0.0055 (-0.0084, -0.0026)
Women	Disability	-0.0047 (-0.0090, -0.0004)	-0.0042 (-0.0085, 0.0001)	-0.0033 (-0.0078, 0.0012)
	Kellgren-score knee	-0.0034 (-0.0054, -0.0014)	-0.0032 (-0.0052, -0.0012)	
	Kellgren-score hip	-0.0050 (-0.0074, -0.0026)		-0.0047 (-0.0072, -0.0022)

Values are regression coefficients with 95% confidence intervals in parentheses adjusted for age and body mass index.

was scanned and bone mineral density was equally increased in subjects with either right- or left-sided hip osteoarthritis, this is not likely to explain our results.

As to the inverse relationship between osteoarthritis and osteoporosis, the results between studies vary greatly [5-12]. Firstly, this may be due to the fact that most studies included small numbers of patients. Secondly, both osteoarthritis and osteoporosis were assessed in various ways. Thirdly, not all analyses were carried out while adjusting for age and weight or body mass index. As to bone mineral density level, our results are similar to the results obtained in another population based study presented by Hannan et al [9]. In this study, a higher bone mineral density in women with knee osteoarthritis and, to a lesser extend, also in men was demonstrated using similar methodology. The only study, as far as we know, on the relationship between osteoarthritis and bone loss with age conducted by Sowers et al [16], also showed an increased bone mineral density level and an increased rate of bone loss in the presence of osteoarthritis. However, comparison with the present study is complicated as both method and site of bone mineral density measurement as well as the site of osteoarthritis was different: osteoarthritis of the hand was related to metacarpal bone loss as assessed by measurement of the cortical area.

Several explanations for the inverse relation between osteoarthritis and osteoporosis may be given. In our study as well as in other studies [5,6,8,9], the association exceeds the single joint, and this suggest that generalized factors play a role. Elevated insulin-like growth factors have been measured in iliac crest bone of patients with osteoarthritis of the hand [17] and serum insulin-like growth factor-1 has been shown to affect the prognosis of knee osteoarthritis by stimulating osteophyte formation [18]. Since insulin-like growth factors seem to have an anabolic effect on bone [19], these factors may mediate the inverse relation between osteoarthritis and osteoporosis. In addition to high body mass index [20], we suggest that physical activity early in life may produce the association since high physical activity during youth has shown to be of key importance in reaching peak bone mass [21] and may also lead to an increased

risk of osteoarthritis later in life [22,23].

Besides an increased level, we also found an increased rate of bone loss with age in subjects with radiographic osteoarthritis. The increased rate of bone loss was not proportional to the increased level since the percentage loss was also elevated. The most plausible explanation for this, i.e. reduced mobility, is not supported by our finding that the rate of bone loss was independent of lower limb disability. Metabolic factors, e.g. cytokines, may mediate the relationship between osteoarthritis and the rate of bone loss as well. For example, elevated interleukin-6 levels have been found in experimental canine osteoarthritis [24] and may also be an important mediator in conditions associated with an increased bone resorption [25].

An important implication of the observation of both an elevated level and an increased rate of bone loss is that earlier in life the difference in bone mineral density between subjects with and without osteoarthritis must have been even more pronounced, probably before the development of osteoarthritis. This notion is in concordance with the hypothesis that high bone mineral density through an increased stiffness of the subchondral bone promotes the development of osteoarthritis [26]. Clinically, the question arises whether subjects with osteoarthritis, who also appear to have a lower risk of fractures in some studies [3,7], continue to have this benefit with advancing age.

In conclusion, the present study shows a graded relationship of osteoarthritis of the knees and hips with a higher bone mineral density and an increased age-related bone loss in men and women aged 55 years or over. Taken together, this suggests a more pronounced difference in bone mineral density earlier in life.

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Chapter 4

Vertebral deformities and fractures

Chapter 4.1

Vertebral deformities and functional impairment in men and women

Introduction

The impact of hip fractures on present-day health care systems in Western countries is considerable [1,2]. The frequency and consequences of vertebral fractures are, however, not as clear [3]. Yet, it may be expected that the number of vertebral deformities will grow in all aging populations. As a considerable proportion of vertebral deformities do not come to medical attention, population based research is needed to determine the size and consequences of this health problem [4]. Although vertebral fractures are considered uncommon in men, studies on the prevalence in men are deficient [5,6]. Investigations that allow comparison of the prevalence in men and women are virtually non-existent. In women, severe deformities appear to contribute substantially to pain and disability [4]. For men, however, no such data are available. The present study shows the prevalence of vertebral deformities in persons from the general population in relation to age, gender, and several measures of functional impairment.

Methods

The present study was conducted as part of the Rotterdam Study, a prospective population based cohort study of determinants and prognosis of chronic diseases in the elderly [7]. The focus of the study is on cardiovascular, neurogeriatric, ophthalmologic and locomotor diseases. The eligible population comprised all inhabitants aged 55 years or over of the district of Ommoord in Rotterdam, the Netherlands. Altogether, 10275 persons, of whom 9161 (89%) were living independently, were invited for the study. The baseline examination of the Rotterdam Study included an interview at home

and extensive investigations at the research center. In the independently living population, the response rate was 77% for the home interview and 71% for the center visit. Written informed consent was obtained from every participant. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical School. The present study was performed in a stratified sample from independently living participants of the Rotterdam Study composed of 750 men and 750 women with X-rays and with balanced numbers (150) in the age-groups 55-59, 60-64, 65-69, 70-74 and 75 years or over. The response rates in these age-groups for participants with radiographs were 73, 74, 69, 63 and 47% respectively.

Lateral radiography of the spine from the fourth thoracic to the fifth lumbar vertebra was performed in each participant. Vertebral deformities were diagnosed according to Eastell [8]. The degree of deformity of each vertebra was assessed by measurement of the anterior height (AH), central height (CH) and posterior height (PH) of the vertebrae T4 to L4 using a cross-wired cursor and an illuminated digitizing board. The following ratios were calculated: AH / PH, CH / PH, PH / $PH_{\text{upper adjacent vertebra}}$, PH /$PH_{\text{lower adjacent vertebra}}$. The coefficient of variation for these ratios was about 3% for repeated measurements on the same radiograph. Deviation of one of these ratios below a given cutoff value indicates vertebral deformity. Cutoff values were calculated as the vertebra specific mean reference value for each ratio minus 3 and 4 SD. A deviation of any ratio between the 3 and 4 SD cutoff value was recorded as a moderate (grade I) deformity. A severe (grade II) deformity was recorded in case of a deviation below the 4 SD cutoff value. The reference values were obtained from 50 men and 50 women aged 55 to 60 years. From this group 2 men were excluded because they had clinically visible vertebral deformities according to an expert radiologist. No distinction between wedge, biconcave or compression deformities was made in the present study. Subsequently, the degree of vertebral deformity was calculated for each participant. Moderate vertebral deformity was defined as at least one moderate deformity without severe deformities. Severe vertebral deformity in a participant was defined as one or more severe deformities.

The measures of functional impairment in the present study were self-perceived health, disability, use of a walking aid, back complaints, impaired rising and impaired bending. Disability was assessed as the impairment in activities of daily living (ADL) using a questionnaire adapted from the Stanford Health Assessment Questionnaire as part of the home interview [9]. The questionnaire measured the amount of difficulty in eight components: dressing and grooming, rising, reaching, hygiene, eating, walking, grip and activity. Each component was addressed by two to four component questions. The answers to these questions were scored on a four-point scale ranging from zero to three meaning (0) without difficulty, (1) some difficulty, (2) much difficulty and (3) unable to do. The component score was defined by the highest score on any component question. The mean score of the eight component scores is the disability index. Disability was defined by an index of 0.5 or over. The interview also assessed self-perceived general health compared with people of the same age, the use of a walking aid and back complaints during the past five years. As part of the physical examination at the research center, the study physician judged the difficulty in rising from a low chair without using the arm-rests and bending down to the floor to pick up an object [10]. The same four-point scoring scale as for the disability assessments was used. Impaired rising and impaired bending was defined as score two or over.

Data analysis

For reasons of poor technical quality, the radiographs of 26 men and 33 women did not allow reliable measurements of all vertebral heights, leaving 724 men and 717 women for the analyses. First, we compared some characteristics of the study population between men and women. In addition to the crude prevalence, the prevalence of vertebral deformities adjusted for the age distribution of the Dutch population at January 1, 1994 [11] was calculated. The relation of vertebral deformities with age was examined using logistic regression. Similarly, the association between vertebral deformity and functional impairment was studied while adjusting for age. A dose-response

TABLE 1. Characteristics of the study population by gender. Values are mean (SD) or percentage

	Men	Women	P
Age (years)	68 (8)	68 (8)	-
Moderate vertebral deformity (%)	13	11	0.25
Severe vertebral deformity (%)	6	9	0.02
Poor self-perceived health (%)	9	11	0.11
Disability (%)	21	31	<0.01
Use of a walking aid (%)	4	6	0.11
Back complaints (%)	37	59	<0.01
Impaired rising (%)	3	5	0.07
Impaired bending (%)	6	5	0.71

* Refers to the comparison between men and women

relationship was investigated by specifying a variable indicating the number of deformities in the logistic regression model. As the data suggested that gender modifies the effect of vertebral deformity on the outcomes, the data were also analyzed in men and women combined with an interaction term for gender.

Results

Table 1 shows the crude prevalence of some characteristics of the study population stratified by gender. Moderate and severe deformities taken together were equally frequent among men and women. The prevalence of moderate vertebral deformity was somewhat higher in men whereas the prevalence of severe vertebral deformity was considerably and statistically significant higher in women. After adjustment for the age distribution of the Dutch population at January 1 1994, the prevalence of moderate or severe vertebral deformity was 18% in men (12% moderate and 6% severe) and 22% in women (11% moderate and 11% severe). All aspects of functional impairment were more frequent among women than men, except for impaired bending. The differences were statistically significant for disability and back

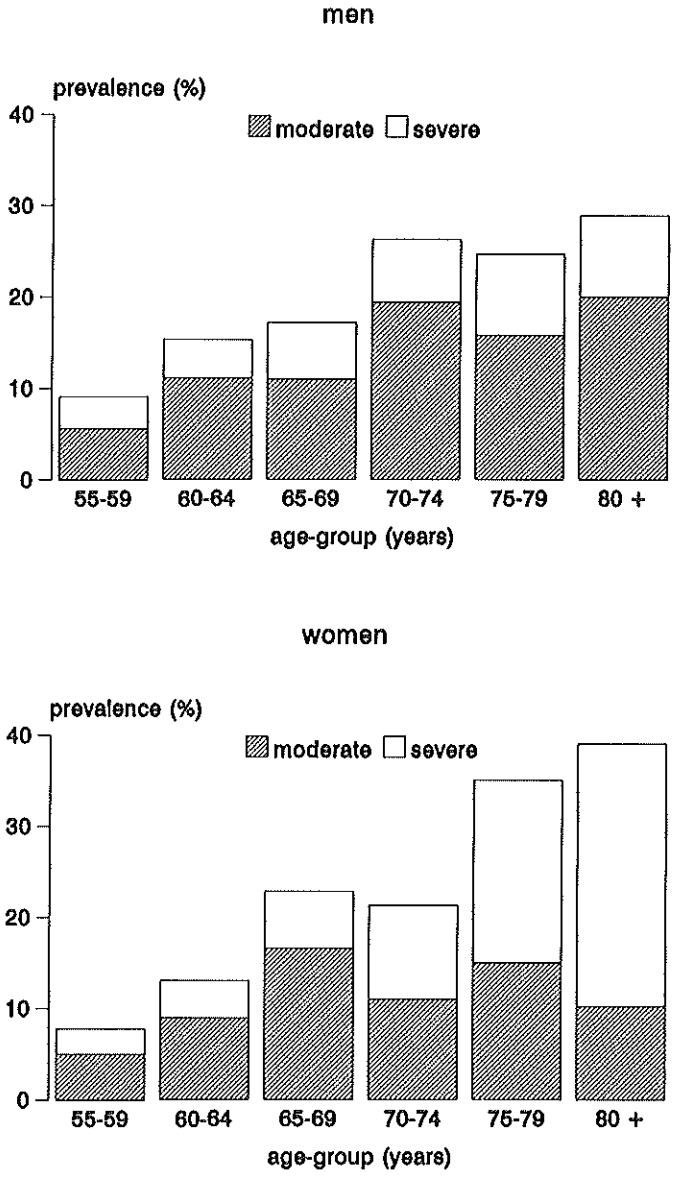

FIGURE *The prevalence of moderate and severe vertebral deformities according to age and gender.*

complaints during the past five years.

The prevalence of deformity according to gender, age and severity is depicted in the figure. The prevalence of both moderate ($P<0.01$) and severe deformity ($P=0.03$) increased proportionally with age in men. In women, no rise with age was found for moderate deformity ($P=0.11$) whereas the prevalence of severe deformity increased markedly with age ($P<0.01$).

The association between functional impairment and vertebral deformity is presented in table 2 according to gender and severity of deformity. Moderate vertebral deformity was in general not related to impaired functional status, although in men a statistically non-significant two times higher risk of impaired rising was observed. Severe vertebral deformity, on the other hand, was related to all measures of functional status in men, with the exception of back complaints. The associations were statistically significant for disability, impaired rising and impaired bending. In women, the relative risks for measures of functional impairment of severe vertebral deformity were generally lower and the only statistically significant association was observed for the use of a walking aid. From those with moderate deformities, 12% had more than 1 deformity. For severe deformities this percentage was 27. No consistent relationship between the number of deformities and impaired functional impairment was found. The magnitude of the relationship between vertebral deformity and functional impairment was not significantly affected by gender.

Discussion

To our knowledge, this is the first population-based study to compare the prevalence and health consequences of vertebral deformity between men and women. The overall prevalence was similar in men and women. Moderate vertebral deformity, however, was slightly more frequent among men whereas the prevalence of severe deformity was considerably higher in women. With advancing age, the prevalence of the two grades of vertebral deformity increased proportionally in men. In women, by contrast, the frequency of moderate deformity remained approximately constant while the

TABLE 2. The association between functional impairment and vertebral deformity by gender and grade. Values are age-adjusted relative risks with 95% confidence intervals between parentheses.

	Men		Women	
	Moderate	Severe	Moderate	Severe
Poor self-perceived health	1.0 (0.4 - 2.1)	1.8 (0.7 - 4.6)	0.6 (0.3 - 1.6)	1.7 (0.8 - 3.6)
Disability	0.7 (0.4 - 1.3)	2.4 (1.2 - 4.6)	1.0 (0.6 - 1.7)	1.6 (0.9 - 2.8)
Use of a walking aid	0.5 (0.2 - 1.9)	2.2 (0.7 - 6.8)	0.7 (0.2 - 2.1)	2.4 (1.1 - 5.1)
Back complaints	1.2 (0.7 - 2.1)	0.9 (0.4 - 2.2)	1.0 (0.5 - 2.0)	1.7 (0.8 - 3.8)
Impaired rising	2.6 (0.8 - 8.0)	5.5 (1.5 - 19.8)	0.8 (0.2 - 3.0)	2.2 (0.8 - 5.9)
Impaired bending	0.9 (0.3 - 2.6)	4.0 (1.4 - 10.9)	1.0 (0.3 - 3.4)	1.2 (0.4 - 3.7)

prevalence of severe deformity rose sharply. Finally, a marked association was observed between severe vertebral deformity and functional impairment, most clearly so in men.

Two limitations of the present study are to be discussed. Firstly, an underestimation of the true prevalence may have occurred if persons with vertebral deformities were, probably through concomitant health problems, less likely to participate. As such a non-response bias tends to become more prominent with age, an underestimation of the increase with age may have resulted as well. However, an influence on the association of vertebral deformities with functional impairment is unlikely as this would only occur if those with functional impairment would be more likely to be non-responders if they had vertebral deformities. Secondly, the cross-sectional design of the study does not allow conclusions about the time relationship of deformities and health outcomes. It remains therefore possible that impairment of locomotor functions preceded rather than followed the vertebral deformities. This sequence may have been realized through immobility inducing elevated bone resorption [12] and subsequent deformities.

The comparison of the prevalence of vertebral deformities between studies is seriously complicated by the use of widely divergent methodologies.

Therefore, we compared our results with the results from studies using similar methodology only. Melton et al. reported prevalence data from a population-based study of vertebral deformities in women [13]. After standardization to the age distribution of our sample, the prevalence of vertebral deformities in this survey was identical to the overall prevalence we found (20%). The Chingford study also showed similar prevalence for moderate (16%) and severe deformities (3%) among women aged 60 to 69 years [14]. In women aged 65-70 years from a very large population-based study these prevalence were 13% and 6%, respectively [4]. As far as we know, only one study assessed the prevalence of vertebral deformities in men using vertebral morphometry [6]. In this study the mean age was 64 years and the prevalence of moderate and severe deformities taken together was only 10%. This may, at least in part, be explained by the fact that approximately half of the participants were healthy volunteers. The results of studies on the relationship between vertebral deformities and detrimental health outcomes vary considerably [4,14-17]. Among these, at least two investigators also conclude that severe rather than moderate deformities are associated with impaired health status [4,17].

The strong increase in severe deformities in women after the age of 75 years was not accompanied by an increase in moderate vertebral deformities. This observation suggests that in elderly women moderate deformities further progress to severe vertebral deformities. Alternatively, although less likely in our view, a severe deformity in elderly women may result from a sudden collapse without being preceded by a moderate deformity. In men, no such pattern was found suggesting less fragile vertebral bone than women. Apart from their higher bone mineral density [18], male vertebrae may remain stronger as a result of the continued bone deposition during adulthood resulting in a larger diameter as compared with women [5]. In addition, a lower rate of decline of trabecular connectivity in aging men may play an important role in maintaining vertebral strength [19]. Convincingly, vertebral deformities do not appear to be associated with functional impairment until they deteriorate to grade II. Possible mechanisms for the development of impaired

locomotor function comprise an increased kyphoscoliosis, altered tension of the paravertebral musculature as well as an impaired flexibility of the spine. Surprisingly, no consistent dose-response relationship was observed. This is probably due to the relatively low number of participants with multiple deformities. While the prevalence of both severe deformities and detrimental health outcomes was higher in women, a stronger association was found in men. It is unclear what explains this discrepancy. Possibly, men are loading their spines more heavily or in a different way that is not compatible with the altered shape of the spine. Nevertheless, vertebral osteoporosis appears to be a health problem in men as well, and clinicians should therefore be aware of this possibility when they encounter men with complaints that possibly relate to vertebral deformities.

In conclusion, (1) vertebral deformities are about equally common in non-selected elderly men and women, with severe progression with age predominantly in women and (2) severe vertebral deformities are, particularly in men, related to functional impairment.

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Chapter 4.2

Vertebral deformities as predictors of non-vertebral fractures

Introduction

The estimated number of people fracturing a hip will increase from 1.7 million in 1990 to 6.3 million in 2050 [1]. It is therefore important to identify risk factors [2]. Previous vertebral fractures have been shown to increase the risk of subsequent vertebral fractures [3]. The degree of spinal deformity may, however, indicate the bone quality of the whole skeleton. We investigated the association between vertebral deformities and incident non-vertebral fractures.

Methods

This nested case-control analysis was carried out within the Rotterdam Study [4]. We studied 40 subjects who had a non-vertebral fracture on average 582 (range 287-1028) days after baseline assessments. Controls were subjects who had not had a non-vertebral fracture during 648 (range 113-1072) days of follow-up and who were patients of the general practitioners of the patients with fracture.

On entering the study participants were asked about hip and wrist fractures in the past five years, history of hip fracture in parents or siblings, and frequent falling (more than once a month). Vertebral heights were measured from lateral radiographs and ratios were calculated according to Melton et al [5]. A grade 1 or grade 2 deformity was recorded in a vertebra if one of the ratios was smaller than a reference value minus 2 SD or 3 SD, respectively. A mild spinal deformity was arbitrarily defined as one to three grade 1 vertebral deformities and at most one grade 2 deformity, and a severe spinal deformity as more than three grade 1 or more than one grade 2 deformities. Radiographs of the spine were unavailable in one case and in two controls. Bone mineral density was measured at the femoral neck by dual energy X-ray absorptiometry. The associations of baseline variables with incident non-vertebral fractures were

TABLE Relative risk of baseline spinal deformation for incident non-vertebral fractures.

	Cases	Controls	RR *	RR †
No spinal deformity	12	94	1.0 (reference)	1.0 (reference)
Mild spinal deformity	19	100	1.6 (0.7 - 3.5)	1.5 (0.6 - 3.4)
Severe spinal deformity	8	16	4.4 (1.5 - 13.3)	4.1 (1.3 - 12.4)
Total	39	210	P=0.026 ‡	P=0.015 ‡

* Relative risk (RR) with 95% confidence interval adjusted for age and sex.
† Relative risk (RR) with 95% confidence interval adjusted for age, sex, and bone mineral density in the femoral neck.
‡ Mantel test for trend.

expressed as relative risks adjusted for age and sex.

Ten patients had fractures in the hip, 17 in the radius or ulna, and 13 elsewhere. Mean age was 74.4 (SD 8.5) years in cases and 74.4 (SD 7.6) in controls; 90% of subjects were women. Subjects with a history of a wrist or hip fracture had a significantly higher risk (relative risk 3.1, 95% confidence interval 1.1 to 8.6) of fracture. A family history of hip fracture (2.0, 0.6 to 5.9) and frequent falling (4.7, 0.8 to 26.2) did not significantly increase the risk of fracture. The highest quartiles of bone mineral density (0.3, 0.1 to 1.1) and body mass index (0.8, 0.3 to 2.4) were associated with a non-significantly decreased risk.

The table shows the increasing relative risk of incident non-vertebral fractures with increasing spinal deformity. Adjustment for bone mineral density did not affect the relative risk estimates. The relative risks were also similar after other variables were adjusted for.

Discussion

We found a strong relation between spinal deformity and subsequent non-vertebral fractures that was independent of bone mineral density. Our findings agree with the observations by Ross et al that previous vertebral fractures predict future vertebral fractures [3].

There are at least two explanations of our findings. Firstly, an increased

thoracic kyphosis caused by multiple vertebral deformities could shift the centre of gravity forward increasing the frequency of falling over. However, the relation of vertebral deformities with risk of fracture was independent of frequency of falling. Secondly, and we believe more likely, vertebral deformities may reflect impaired bone strength in the whole skeleton since the relation was independent of bone mineral density. We conclude that by assessing the degree of spinal deformity patients with a fourfold increased risk of future non-vertebral fractures can be identified.

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Chapter 5

General discussion

Chapter 5

General discussion

Methodological considerations

Design

Several relations described in this thesis are cross-sectional, i.e. the determinant and outcome were measured simultaneously. The implications of such an approach for inference depend heavily on the actual study question. From the nine original Hill's criteria for causality of an association, the only necessary criterium is temporality [1] meaning that a supposed cause needs to precede the effect in time (possibly with the exception of some situations in theoretical physics where time can behave oddly so that effects precede causes [2]). In cross-sectional studies it may be unclear whether the determinant preceded or followed the disease leaving this criterium unapplicable. In chapter 3.3 for instance, the higher bone mineral density and osteoarthritis were assessed simultaneously. Consequently, no evidence for the sequence of the development of these conditions was available, thus hampering inferences about causality. The same problem was encountered when trying to infer from the association between vertebral deformities and functional impairment described in chapter 4.1. It is, indeed, possible that the impairment, most likely through accelerated bone loss, preceded rather than followed the deformities of the vertebral column.

On the other hand, at least with respect to the criterium of temporality, a causal relationship can be inferred from cross-sectional associations if it is reasonable to assume that the determinant by its nature must have preceded the outcome. This is, for instance, the case for the associations with gender presented in this thesis.

In addition to the discussion of temporality in cross-sectional studies, the question arises whether the observed determinants of a prevalence rate also

reflect differential survival. For example, the true difference in the occurrence of vertebral deformities between men and women may not accurately be estimated from prevalence data if the mortality rate in men with vertebral deformities is different from that in women.

The cross-sectional design of the studies on the relation of bone mineral density, and prevalence of vertebral deformities with age implicates susceptibility to cohort effects. Such an influence is not unlikely in view of the trend of an increasing age-adjusted incidence of hip fractures with calender time without an increased frequency of falling suggesting that past cohorts had stronger bones for their age [3]. The consequence would therefore be an underestimation of the decrease of bone mineral density and increase of vertebral deformities with age.

Precision and validity

All measurements either in epidemiology or in any other discipline involve error. Generally, two types of error are distinguished. The most important error is denoted as bias, i.e. systematic error and affects the validity of the study. The other type of error is random error which is completely unpredictable by available information and affects the precision of the study.

In general, the precision of a study can be increased by enlarging the study size or by using a more efficient design. An example of increasing the efficiency of a study from this thesis is the use of the case-control design to assess the relationship between vertebral deformities and non-vertebral fractures. Suppose that a random sample of the same size as the total number of cases and referents, i.e. 249, was followed for an equally long period in the Rotterdam Study. It is obvious that the number of incident fractures in that case would have been very low. A considerably less precise estimation of the relationship as reflected in substantially wider confidence intervals would then have been obtained.

Some comment on the measurement of bone mineral density and vertebral deformity is due here. As to the assessment of bone mineral density, the in vivo precision of dual energy X-ray absorptiometry is reported excellent [4]. In the

Rotterdam Study, the precision as assessed by determining the reproducibility of this measurement and expressed as the coefficient of variation ranged from 2.5 to 3.2% in the femoral neck and was 0.9% in the lumbar spine. These estimations were obtained by performing duplicate measurements on 12 participants whose mean age was 66 years. The participants were asked to dismount the table of the system between the measurements to assure realistic reproducibility, since a large proportion of measurement error is caused by variation in positioning of the patient. A frequently emerging discussion, possibly also relating to validity, concerns the question whether measurement of bone mineral content or, theoretically more appealing, volumetric measurement of bone density would be superior compared with the standard projected, essentially two-dimensional, density. As to the predictive value for hip fracture incidence, this question was addressed by a large study in women [5]. It was concluded that the conventional projected density and volumetric bone density had similarly stronger predictive value than bone mineral content. Certainly in view of the objectives and size of the Rotterdam Study, we conclude that the precision of dual energy X-ray absorptiometry is more than sufficient.

Vertebral deformities are visualized using lateral radiography of the spine and assessed either in a qualitative or quantitative way. As the qualitative approach is, by its nature, relatively subjective, the prevalence of vertebral deformities was estimated by measuring vertebral dimensions and detecting deformities according to an algorithm developed by Eastell [6]. This method meets the majority of guidelines suggested by a recent report on vertebral fractures [7] and the reproducibility of the measurements in the Rotterdam Study was satisfactory as described in chapter 4.1. The use of a cut-off value in the assessment of vertebral deformities, however, may introduce a systematic overestimation of its prevalence as discussed below under the heading information bias. Before the implementation of the Eastell algorithm, arbitrarily less stringent criteria for deformities were used in the study of vertebral deformities as predictors of non-vertebral fractures. In our view it is, however, unlikely that the use of the Eastell criteria would have shown less pronounced results as particularly the

more severe spinal deformity was associated with the increased risk of a non-vertebral fracture.

The validity of the studies in this thesis will be discussed briefly by evaluating the most prominant categories of bias: selection bias, information bias and confounding.

Selection bias occurs when the actual study population is different as to the effect measure under study from those who are considered to be the target population. Almost inherent to voluntary participation in a study is a lower than 100% response. Although in itself not threatening validity, this non-response may be selective, i.e. not random and, depending on the study question, introduce bias. The issue of non-response bias with respect to the particular study questions has been extensively evaluated in the discussion sections of the manuscripts incorporated in this thesis. Another type of selection bias is socalled diagnostic bias. Although almost exclusively of theoretical interest, as it is very unlikely that it factually occurred, diagnostic bias could have played a role in the study on the relation between vertebral deformities and non-vertebral fractures. Suppose that the general practitioners were somehow aware of the vertebral deformities in their patients and that they, in case of the suspicion of a non-vertebral fracture, were more inclined to refer them to a hospital for X-ray evaluation if the patient had vertebral deformities, then a bias would result. It is, however, very unlikely that the general practitioners knew about their patients having vertebral deformities and it is even more unlikely that their decision to refer them to a hospital would depend on this knowledge.

Information bias occurs whenever determinant classification depends on the outcome classification or vice versa. Misclassification of determinant or outcome status is in most instances inevitable. It will, in case it is nondifferential, introduce some bias toward the null condition of no association [1]. An example of nondifferential misclassification is related to random error in assessing vertebral dimensions. Specifically, the large number of measurements in one spine increases the probability of finding a deformity in one subject solely on the basis of measurement error. The consequence would therefore be an overestimation of the prevalence of vertebral deformities. As it is likely that

this error is independent of the outcomes studied, we consider this misclassification random and therefore likely to have reduced the strength of the associations observed. On the other hand, misclassification of self-reported intake of foods known to have a high calcium or vitamin D content may have been differential, that is spuriously high in case the participants were aware of osteoporosis. This, however, would have produced an association opposite to that was observed. A similar mechanism may have influenced the association in the study of vertebral deformities and functional impairment. It is, however, not clear in which direction the bias would have operated. Both exaggerating and masking of functional impairment in case of awareness of deformities may have occurred. A fourth example of information bias was encountered in the study described in chapter 3.1 where spinal osteoarthritis hampered valid measurement of bone mineral density at the lumbar spine.

Confounding occurs if a third factor is (1) independent of the exposure predictive for the disease and (2) is also associated with the exposure under study. Principally different from other types of bias, control for confounding may be accomplished to a degree that is dependent on the accuracy of measurement of confounders. The most important confounders in the relationships described in this thesis namely age, gender and body mass index was controlled for by using statistical modeling (age and body mass index) or stratification (gender). A complex situation was noted in the study of dietary factors and bone loss where persons with high intakes of calcium and vitamin D may also have been more physically active and consequently at a decreased risk of bone loss. Although an attempt was made to control for this factor by controlling for energy intake, an equal distribution of all known and unknown confounders can only be accomplished by random assignment to different levels of calcium and or vitamin D exposure. An important notion is that if the aim is mere prediction instead of understanding etiology, confounding is not an issue. In the study of vertebral deformities as predictors of non-vertebral fractures, a crude analysis of the association between baseline deformities and incident non-vertebral fractures would have been sufficient if the only aim was prediction. In that case, it is not of interest whether deformities, in part, reflect

age or low bone density. Adjustment for these factors, however, could provide information on the question whether deformities have, independent of age and bone density, additional value for estimating bone strength thereby possibly acting as indicators of bone structure.

In chapter 3.3 both a higher level and a higher rate of change of bone mineral density was observed in the presence of osteoarthritis. This might raise the question whether there is in general a relationship between level and change of bone mineral density. It has been proposed that those with the highest bone mineral density level also have the highest rate of bone loss and, consequently, the rate of bone loss has frequently been expressed as percentage of the (initial) level. As was pointed out in chapter 3.1, an exponential rate of decline of bone mineral density with age would be expected if the rate of loss occurred at a constant percentage of the level. Evidence for exponential loss is, however, limited to the first postmenopausal years. The problems in the analysis of the relationship between level and rate of change relate to statistical phenomena such as regression to the mean, biological questions whether initial bone mass reflects bone surface, proportional to which bone is lost, and logical matters such as the socalled horse racing effect which means that the attained level is the result instead of the determinant of the rate of change [8]. In the study of osteoarthritis, described in chapter 3.3, the higher rates of loss can not be be explained by regression to the mean as erroneously high bone mineral density values will have occurred equally likely in both the group with and without osteoarthritis. Finally and most importantly, there is no evidence of a clear relationship between level and rate of bone loss in a study that adequately deals with the above problems [9].

Clinical relevance

Bone mineral density measurements at the lumbar spine are probably not reliable in elderly subjects as a result of degenerative disease. Consequently, bone mineral status should be measured elsewhere. For the prediction of hip fractures, bone mineral density at the proximal femur has been shown to have

superior predictive value compared with the radial sites, the calcaneus and the spine [10].

Bone loss with age appears to be present not only in women but also in men, though on average at a lower rate. In addition, bone loss continues in both sexes with increasing age. It is therefore no longer warranted to consider bone loss as a problem of perimenopausal women only and intervention aiming at reducing bone loss may be useful even in the highest age-groups. In the clinical situation, the aim is to identify those who are most likely to end up at the lower part of the bone density distribution. Although the variation in the rate of change is substantial, women and those with low intakes of calcium and vitamin D seem to be at the highest risk. If the higher dietary intakes of calcium and vitamin D were truly the cause of the lower rates, not confounded by exercise, solar exposure or supplement usage, the clinical implication is that diet changes instead of supplementation may already be sufficient.

Though important in the search for etiological clues, the clinical relevance of the association between osteoarthritis and both a high level and high rate of change of bone mineral density is unclear in the absence of information on the long-term consequences. If subjects with osteoarthritis continue to have higher rates of bone loss, the difference in the level of bone mineral density will be diminished or even reversed at high age. This pattern was not observed in the cross-sectional analysis of this relationship, possibly as a result of cohort effects. A second issue relates to intervention. If it were true that high bone mineral density level induces or promotes the development of osteoarthritis, this may have implications for preventive or therapeutic strategies aiming at higher bone density.

Vertebral deformities are not only frequent among elderly men and women, severe spinal deformity is also associated with several aspects of functional impairment. The fact that vertebral deformities may also result from other conditions such as spinal osteoarthritis or trauma will have consequences for intervention.

Severe spinal deformity is associated with a four times increased risk of non-vertebral fractures. As vertebral deformities are common, they are clinically

useful to identify high risk patients. Depending on the underlying mechanism, secondary prevention may be started. If vertebral deformities do not so much reflect bone strength of the total skeleton and rather cause fractures by increasing the patients tendency to fall, rational intervention should primarily aim at improving posture instead of systemic bone treatment.

Future research

The epidemiology of fractures including its sequelae is well known nowadays. In the future, two broad categories of research are needed: (1) research primarily concerned with fracture prediction with the aim to identify those at the highest risk and to find out where and when intervention will be most effective and (2) research dealing with the etiology of decreased bone strength in close collaboration with the basic sciences. Obviously, these categories can not completely be separated and both issues can be addressed in the same study.

As to fracture prediction, the focus has to change from bone density, which role is well known by now, to falls as they constitute, of course, an important cause of fracture. Especially the effects of drugs that suppress the central nervous system are to be studied in relation to fall frequency [11]. Although disabled persons are at a greater risk for falling [12,13], the precise role of disability is not clear yet. Visual [11] and cognitive [14] impairment may be risk factors less open to intervention. Succesful intervention in this field has already been shown by Tinetti et al [15].

As already stated, the cross-sectional association between vertebral deformities and functional impairment does not provide sufficient evidence for definite conclusions and should be addressed longitudinally in future studies.

As to etiology, there is a great challenge to find out what factor causes some individuals to lose bone at the highest rate. Longitudinal information on bone loss in the present study was obtained over a relatively short period. Elongation of the observation time is needed as the variability in bone loss rates decreases dramatically with follow-up time [16]. The study on the relation between bone density and osteoarthritis should be extended to the study of incident osteoarthritis to find out whether high density really precedes the development

of osteoarthritis as this inference was in our study only based on backward extrapolation. Genetic determinants like vitamin D receptor polymorfisms and their interactions with the environment may provide further clues in understanding bone status [17].

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Chapter 6

Summary

Chapter 6.1

Summary

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in fracture risk. The impact of the most prominent clinical outcome of this disease in terms of morbidity and mortality, i.e. hip fracture, is substantial. It is expected that the number of hip fractures will rise dramatically in the next decades. The general aim of the thesis is to study determinants of bone density and consequences of vertebral deformities.

All studies were conducted as part of the Rotterdam Study, a large population-based prospective study of disease in subjects aged 55 years and over. Chapter 2 gives a brief outline of its aim, rationale, design and methods. Dual energy x-ray absorptiometry was used to measure bone mineral density at the lumbar spine and proximal femur. Vertebral deformities were assessed by measurement of vertebral dimensions on lateral x-rays of the spine and subsequent comparison with reference values.

Chapter 3.1 describes the pattern of bone reduction with age from cross-sectional data on bone mineral density in the first 1762 subjects with dual energy x-ray absorptiometry. No age-related decline in bone mineral density could be observed in the lumbar spine as elderly subjects with severe osteoarthritis in the scanning field, known to be associated with spuriously high values, biased the slope upwards. Yearly bone mineral density reduction in men and women was 0.003 and 0.005 g/cm^2 in both the femoral neck and the Ward's triangle, and 0.002 and 0.003 g/cm^2 in the trochanter respectively. It was concluded that accurate assessment of age-related bone reduction in the spine from cross-sectional data is hampered by spinal osteoarthritis in elderly subjects and that the apparent rate of age-related bone reduction in the femoral neck appears to be approximately two times higher in women than in men.

The cross-sectional estimation of bone mineral density diminution with age may be affected by cohort effects. In order to put limits to these effects, the rate of change of bone mineral density was assessed longitudinally in chapter 3.2. In addition, bone loss with age was studied in relation to dietary calcium and vitamin D. The study population comprised 1859 men and 2459 women with follow-up bone mineral density measurements after a median period of 1.9 years. A semiquantitative food frequency questionnaire was used to obtain information on nutrient intake. The overall rate of change of femoral neck bone mineral density was similar to that observed in the cross-sectional study, namely -0.003 and -0.005 g/cm^2 per year in men and women, respectively. In men, a substantial increase in the rate of loss with age was observed. Independently of energy intake, high dietary calcium and vitamin D was, particularly in men, associated with lower rates of bone loss. The results from this study suggest that prevention of bone loss could still be worthwhile in the elderly and that high dietary calcium and vitamin D may play a beneficial role.

Evidence for the possible inverse relationship between osteoporosis and osteoarthritis may give rise to etiological clues. Chapter 3.3 deals with the relationship of radiographic osteoarthritis of the knees and hips with femoral neck bone mineral density and the rate of change with age. Baseline data on osteoarthritis, defined as Kellgren-score 2+, were available for 2745 persons of whom 1723 subjects also had follow-up bone mineral density measurement. Radiographic osteoarthritis was associated with higher baseline bone mineral density level and higher rate of change. In addition, a graded relationship of the number of affected sites and Kellgren-score with baseline bone mineral density level and the rate of change was observed. The association with the rate of change appeared to be independent of lower limb disability as assessed by the Stanford Health Assessment Questionnaire and remained present when expressed as a percentage of the baseline value. It was suggested that shared metabolic factors such as insulin-like growth factor-1 may explain the relation between the two disorders. Tentatively, the observation of both an elevated level and an increased rate of bone loss could suggest that the difference in bone mineral density level between subjects with and without osteoarthritis must

have been greater earlier in life, which is compatible with the hypothesis that high bone mineral density promotes the development of osteoarthritis.

Different from hip fractures, the prevalence and consequence of vertebral deformities is largely unknown, particularly for men. The objective of the study presented in chapter 4.1 was to assess the prevalence and concomitant functional impairment of vertebral deformities. The study was carried out in a random sample of 750 men and 750 women. Information on several measures of functional impairment were obtained by interview as well as judgement by the study physician. The prevalence of moderate vertebral deformities was 13% and 11% in men and women, respectively. For severe deformities, these percentages were 6 and 9. Adjusted for the age distribution of the Dutch population in 1994, the prevalence of spinal deformity was 18% in men (12% moderate and 6% severe) and 22% in women (11% moderate and 11% severe). In men, the prevalence of moderate and severe deformities increased proportionally with age. In women, the prevalence of moderate vertebral deformities remained constant, opposite to a marked increase in severe deformities. Moderate vertebral deformities were not associated with functional impairment. Severe vertebral deformities, however, were, particularly in men, associated with a considerably increased risk of general disability, impaired rising, impaired bending and the use of a walking aid. It was concluded that vertebral deformities are approximately equally common in men and women from the general population though severe progression with age occurs in women only. In addition, severe spinal deformity is, particularly in men, related to functional impairment.

Previous vertebral deformities have been shown to increase the risk of subsequent vertebral deformities. The degree of spinal deformity may, however, indicate the bone quality of the total skeleton. In chapter 4.2, the association between vertebral deformities and future non-vertebral fractures was investigated by performing a nested case-referent analysis within the Rotterdam Study. The degree of spinal deformity was assessed on baseline radiographs of 40 incident non-vertebral fracture cases and 212 age- and sex-matched controls. Two arbitrarily chosen exposure categories were defined: mild and severe spinal

deformity. The relative risk (95% confidence interval) of non-vertebral fractures increased from 1.6 (0.7 - 3.5) in subjects with mild deformity to 4.4 (1.5 - 13.3) in those with severe spinal deformity. The most likely explanation in our view is that vertebral deformities reflect impaired bone strength in the whole skeleton. As the association was independent of bone mineral density, they may be viewed as a measure for bone quality or bone structure. From this study it was concluded that by assessing the degree of spinal deformity, patients with a fourfold increased risk of future non-vertebral fractures can be identified.

Methodological issues are described in chapter 5 and followed by some remarks on the clinical relevance of the findings and suggestions for future research.

Chapter 6.2

Samenvatting

Osteoporose wordt gekenmerkt door een lage botmassa in combinatie met een slechte botstructuur. Dit leidt tot een verminderde sterkte van het bot met als gevolg een verhoogd risico op fracturen. De gevolgen van de heupfractuur zijn aanzienlijk, zowel voor wat betreft de morbiditeit als de mortaliteit. Het aantal heupfracturen zal naar het zich laat aanzien sterk toenemen in de komende decennia. Het doel van de onderzoeken in dit proefschrift was het bestuderen van determinanten van botmineraaldichtheid en gevolgen van werveldeformaties.

Alle onderzoeken werden verricht binnen een populatieonderzoek naar ziekten bij personen ouder dan 55 jaar, het "Erasmus Rotterdam gezondheid en ouderen" (ERGO)-onderzoek. Hoofdstuk 2 beschrijft in het kort de achtergrond, de opzet en methoden van dit onderzoek. Voor het onderzoek naar osteoporose werd de botmineraaldichtheid gemeten in de lumbale wervelkolom en het proximale femur middels 'dual energy x-ray absorptiometry'. Werveldeformaties werden vastgesteld door het meten van de wervelcontouren op de laterale röntgenfoto van de wervelkolom en deze vervolgens te vergelijken met referentiewaarden.

Hoofdstuk 3.1 beschrijft het botverlies met de leeftijd geschat uit gegevens van dwarsdoorsnede onderzoek bij de eerste 1762 deelnemers aan het ERGO-onderzoek die een botmineraaldichtheidsmeting hadden ondergaan. In de lumbale wervelkolom kon geen afname van de botmineraaldichtheid met de leeftijd worden vastgesteld, waarschijnlijk als gevolg van extreem hoge waarden bij vooral ouderen met artrose in het meetgebied. Gemiddeld daalde per jaar de botmineraaldichtheid in de femurhals bij mannen met 0.003 g/cm^2 en bij vrouwen met 0.005 g/cm^2. Uit dit onderzoek werd geconcludeerd dat een betrouwbare schatting van het botverlies met de leeftijd in de wervelkolom niet

mogelijk is door artrose in het meetgebied bij met name ouderen. Verder bleek dat de afname van de botmineraaldichtheid in de femurhals bij vrouwen bijna twee keer zo groot is als bij mannen.

De schatting van botverlies met de leeftijd uit gegevens van dwarsdoorsnede onderzoek wordt mogelijk vertroebeld door cohort effecten en selectieve non-respons die beide met de leeftijd kunnen samenhangen. In hoofdstuk 3.2 wordt het botverlies geschat uit longitudinale gegevens waarbij deze effecten beperkt worden. Daarbij werd tevens onderzocht of er een relatie bestaat tussen de hoeveelheid calcium en vitamine D in de voeding en de snelheid van botverlies. Het onderzoek werd verricht bij 1859 mannen en 2459 vrouwen die tevens een follow-up botmineraaldichtheidsmeting ondergingen. De mediane follow-up duur bedroeg 1.9 jaar. Een semiquantitatieve voedingsvragenlijst werd gebruikt om de inname van de verschillende bestanddelen te schatten. Gemiddeld was de afname van de botmineraaldichtheid per jaar even groot als uit het dwarsdoorsnede onderzoek werd geschat, namelijk 0.003 g/cm^2 bij mannen en 0.005 g/cm^2 bij vrouwen. Het botverlies werd bij mannen aanzienlijk sterker op hogere leeftijd. Gecorrigeerd voor de hoeveelheid energie uit de voeding was het botverlies geringer bij hoge calcium en vitamine D inname. Dit was het meest uitgesproken voor mannen. De gegevens uit dit onderzoek wijzen erop dat preventie van botverlies ook op hogere leeftijd zin kan hebben en dat een relatief hoge inname van calcium en vitamine D gepaard gaat met geringer botverlies.

Osteoporose en artrose zijn volgens de literatuur wellicht omgekeerd aan elkaar gerelateerd. De bevestiging van deze relatie kan aanwijzingen geven omtrent de etiologie van één of beide aandoeningen. Hoofdstuk 3.3 gaat over de relatie tussen enerzijds artrose van het heup- en kniegewricht en anderzijds zowel het niveau als de verandering van botmineraaldichtheid met de leeftijd. Bij 2745 personen werd in de eerste fase van het ERGO onderzoek artrose (Kellgren 2+) alsmede de botmineraaldichtheid gemeten. Van deze groep hadden 1723 personen tevens een follow-up botmineraaldichtheidsmeting. Het bleek dat personen met artrose gemiddeld een hogere botmineraaldichtheid en een sterker botverlies hadden. Tevens bleek er een graduele relatie te bestaan

tussen enerzijds het aantal aangedane gewrichtsgroepen en de Kellgrenscore en anderzijds het niveau van de botmineraaldichtheid en de mate van botverlies. De relatie tussen artrose en botverlies was onafhankelijk van beperkingen in het dagelijks leven volgens een vragenlijst en bleef ook bestaan indien het botverlies uitgedrukt werd als percentage van het niveau van de botmineraaldichtheid. Mogelijk kunnen gemeenschappelijke metabole factoren zoals 'insulin-like growth factor-1' de bevindingen verklaren. Met enig voorbehoud zouden deze bevindingen kunnen wijzen op een groter verschil in botmineraaldichtheid tussen personen met en zonder artrose op jongere leeftijd hetgeen past bij de hypothese dat een hoge botmineraaldichtheid de ontwikkeling van artrose stimuleert.

In tegenstelling tot heupfracturen zijn van werveldeformaties de frequentie en gezondheidseffecten grotendeels onbekend, in het bijzonder bij mannen. Hoofdstuk 4.1 is gewijd aan dit onderwerp. Het onderzoek werd gedaan bij een steekproef van 750 mannen en 750 vrouwen. Beperking in het functioneren werd gemeten middels een vragenlijst en middels de beoordeling door een arts van de prestaties bij een tweetal testen. De prevalentie van matige werveldeformaties was bij mannen en vrouwen respectievelijk 13 en 11 procent. Ernstige deformaties kwamen bij 6 procent van de mannen en 9 procent van de vrouwen voor. Na correctie voor de leeftijdsopbouw van de Nederlandse bevolking in 1994 is de prevalentie van werveldeformaties 18% bij mannen (12% matig en 6% ernstig) en 22% (11% matig en 11% ernstig) bij vrouwen. Bij mannen werd een evenredige toename van matige en ernstige deformaties met de leeftijd gevonden terwijl bij vrouwen uitsluitend een sterke toename van de ernstige deformaties werd gezien. Alleen de ernstige deformaties gingen samen met een aanzienlijk verhoogd risico op beperkingen in het dagelijks leven, opstaan uit een lage stoel, buigen naar de tenen en het gebruik van een hulpmiddel bij het lopen. In het algemeen was de samenhang tussen werveldeformaties en beperkingen bij mannen sterker dan bij vrouwen. De conclusie van dit onderzoek is dat werveldeformaties ongeveer even vaak voorkomen bij mannen als bij vrouwen maar dat met de leeftijd de progressie van deformaties van matig naar ernstig vooral bij vrouwen optreedt. Verder

werd geconcludeerd dat ernstige deformaties, vooral bij mannen, samen gaan met een verhoogd risico op functionele beperkingen.

Werveldeformaties duiden vanzelfsprekend op een verminderde draagkracht van het bot der wervellichamen. De mate van deformatie van de wervelkolom zou eveneens de botkwaliteit in het gehele skelet kunnen reflecteren. In hoofdstuk 4.2 wordt het verband tussen reeds aanwezige werveldeformaties en nieuwe niet-wervel fracturen onderzocht middels een patiënt-controle onderzoek binnen ERGO. De mate van deformatie van de wervelkolom werd vastgesteld bij 40 patiënten met een nieuwe niet-vertebrale fractuur en 212 controles met dezelfde leeftijds- en geslachtsverdeling. De mate van deformatie werd arbitrair verdeeld in de klassen matig en ernstig. Het relatief risico (95% betrouwbaarheidsinterval) op niet-vertebrale fracturen nam toe van 1.6 (0.7 - 3.5) voor matige tot 4.4 (1.5 - 13.3) voor ernstige deformatie van de wervels. Zoals gezegd kunnen de werveldeformaties een verminderde botsterkte van het gehele skelet reflecteren. Een minder waarschijnlijke verklaring is dat werveldeformaties via een toegenomen kyfose een verhoogde kans op vallen geven. Aangezien het verband onafhankelijk bleek van de botmineraaldichtheid kan de werveldeformatie, gegeven een bepaalde botmineraaldichtheid, gezien worden als een maat voor botkwaliteit of botstructuur. De conclusie luidt dat door het meten van de graad van deformatie van de wervelkolom patiënten met een viervoudig verhoogd risico op niet-vertebrale fracturen kunnen worden geïdentificeerd.

Het proefschrift wordt afgesloten met de bespreking van enkele methodologische kwesties en enige opmerkingen over de klinische relevantie. Tevens worden suggesties voor verder onderzoek gedaan.

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About the author

The author was born on February 16, 1963 in Hengelo (Ov), the Netherlands. After general education at the Bataafse Kamp in Hengelo (Gymnasium-β) he started his medical study in Groningen 1982 and graduated in 1989. In 1989 he started military service and went on long furlough in 1991. From 1991 to 1995 the author worked as a research associate at the department of Epidemiology & Biostatistics (head Prof. A. Hofman) in close collaboration with the departments of Radiology (Prof. H.E. Schütte) and Internal Medicine III (Prof. J.C. Birkenhäger). The latter period was devoted to teaching students and writing this thesis.