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Risk Factors for Increased Bone Loss in an Elderly Population

The Rotterdam Study

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The association of bone loss with age, sex, and several prevalent and modifiable potential risk factors for osteoporosis was studied in 1,856 men and 2,452 women aged 55 years and over from the Rotterdam Study, a population-based cohort study in the Netherlands. The rate of change in femoral neck bone mineral density was estimated longitudinally between 1990 and 1995, after 2 years of follow-up on average. These rates, adjusted for age and body mass index, were −0.0025 (95% confidence interval −0.0038 to −0.0012) in men and −0.0045 (95% confidence interval −0.0056 to −0.0034) g/cm^2/year in women (p = 0.03). Bone loss accelerated with age, as seen more clearly in men than in women. Lower body mass index and cigarette smoking were associated with increased bone loss in both men and women. In men, higher calcium intake was associated with lower rates, and disability was associated with borderline significantly higher rates of bone loss (p = 0.07). In women, a nonsignificant relation was observed with disability, but not with dietary calcium intake. Alcohol intake was not consistently related to the rate of bone loss in either sex. It is concluded that in elderly people the rate of bone loss is higher in women, progresses with age, and is further determined by several modifiable risk factors, particularly in men. *Am J Epidemiol* 1998;147:871–9.

bone loss, age-related; longitudinal studies; men; risk factors; women

There is much literature documenting low bone mineral density as a risk factor for fractures (1–3). The sequelae of hip fractures are far more serious than those of other types of fracture (4). For the prediction of hip fracture, bone mineral density at the proximal femur appeared more precise than bone mineral density at various other sites (2, 3). Recently, longitudinal population-based studies showed progressive bone loss with age at the femoral neck in the elderly (5–7). This pattern of bone loss in the femur has not been observed in previous cross-sectional studies (8–10) and requires further confirmation from longitudinal data, particularly for men. Because of the foregoing, it is important to identify factors that set the rate of bone loss late in life. These risk factors should be both modifiable and prevalent to be of some use for preventing bone loss at the population level. Risk factors for osteoporosis may differ between men and women. Until now, population studies of gender differences in the relation of bone loss with age (8, 9) and other determinants (11–15) mostly assessed bone loss rates cross-sectionally.

We performed a follow-up study in 4,308 Dutch subjects aged 55 years and over to assess the rate of change in femoral neck bone mineral density in relation to sex, age, body mass index, lower limb disability, calcium intake, alcohol consumption, and cigarette smoking.

MATERIALS AND METHODS

Study population

This 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 (16). The focus is on cardiovascular, neurogeriatric, ophthalmologic, and locomotor diseases. All inhabitants of the district of Ommoord in Rotterdam, the Netherlands, aged 55 years and over were invited to participate. Of the 10,275 eligible persons, 9,161 (89 percent) were living independently. These independently living subjects form the target population for this study. The baseline examination of the Rotterdam Study was carried out between August 1990 and June 1993 and comprised an interview at home and extensive investigations at the research center.

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Within the independently living population, 7,086 persons (77 percent) completed the home interview and 6,494 (71 percent) persons also visited the research center. Written informed consent was obtained from each participant. The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical School in Rotterdam. This analysis was carried out among 5,823 persons (64 percent), who underwent baseline bone mineral density measurements. After a median duration of 1.9 years (range, 0.3–4.9 years), all participants were invited for follow-up assessments between September 1993 and December 1995. Of the group with baseline bone mineral density measurements, 227 had died, 31 could not be contacted, 675 refused, and 4,890 visited the research center. Because the densitometer was not available full time for this study, ultimately, 4,333 had follow-up bone mineral density measurement, i.e., 74 percent of the number of participants measured at baseline.

Measurements

Clinical examinations at the research center included anthropometry and bone densitometry. Height and weight were measured in standing position without shoes, and 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 DPXL; Lunar Radiation, Madison, Wisconsin). These assessments were carried out by qualified radiographic technicians who were trained by the manufacturer of the machine. Standard positioning was used with anterior-posterior scans of the right proximal femur unless there was a history of hip fracture or prosthesis implantation on that side, in which case, the left side was scanned. Using standard software, we analyzed the femoral neck, Ward's triangle, and greater trochanter. The short-term in vivo coefficient of variation was 3.2 percent in the femoral neck, 3.1 percent in the Ward's triangle, and 2.5 percent in the greater trochanter, as assessed in 12 randomly selected cohort members, with repositioning between the two measurements. Follow-up bone mineral density was assessed by using identical measurement procedures and the same standard software for the analyses. Regular measurement of a phantom during the follow-up period showed that no machine drift had occurred.

As part of the baseline home interview, participants were asked about wrist and hip fractures during the previous 5 years, current cigarette smoking, and medication use that was verified by examining pills. They also received a checklist and were asked to indicate all foods and drinks consumed at least once a month in the previous year. During each participant's visit to the research center, this checklist served as a basis for a trained dietician, who filled out frequency and amount of consumption of the food items on a previously validated 170-item semiquantitative food frequency questionnaire (17). Average daily nutrient intake, including calcium and energy for this analysis, was calculated by multiplying the frequency and amount consumed for each food item by its nutrient content listed in an automated version of the Dutch Food Composition Table (18). The amount of alcohol consumed was calculated on the basis of 1 unit of alcoholic beverage containing 10 g of alcohol.

Lower limb disability was measured as the impairment in activities of daily living by using a questionnaire modified from the Stanford Health Assessment Questionnaire (19). The lower limb disability index we used was composed of the mean score (with zero indicating no impairment and three indicating unable to perform) for two questions about arising, two about walking, one about bending, and one about getting into and out of a car. Disability was defined as a lower limb disability index of 0.5 or over.

Data analysis

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. We excluded 25 participants who had extreme values for the rate of change, i.e., outside the mean $\pm$ four standard deviations range, leaving 4,308 participants for analyses. The rationale for exclusion of extreme values is that they most likely resulted from excessive measurement error. To evaluate the possibility of bias by nonresponse and loss to follow-up, we compared prevalences of some baseline characteristics between the study population and the target population, i.e., the independently living population. The prevalences in the target population were first adjusted for the age and sex distribution of the study population. All subsequent analyses were performed in men and women separately. The mean rate of change is presented for all three measurement sites at the proximal femur, but the associations with the determinants under study are shown for the femoral neck only. The findings at the Ward's triangle and greater trochanter were similar. Bone mineral density at the lumbar spine was not analyzed in this study because degenerative changes in elderly persons may seriously hamper valid measurement at this site (8). We studied the rate of change in bone mineral density according to sex; 5-year age strata; current cigarette smoking; lower limb disability; and categories of body mass index, dietary cal-

cium intake, and alcohol consumption. For categorization of continuous variables, prior to analyzing bone loss rates, we chose cutoff values at fixed intervals, while seeing to it that the numbers of participants in each category remained sufficient. All results were adjusted for age and body mass index except for the analysis of sex, which was also performed unadjusted, age that was adjusted for body mass index only, and body mass index that was adjusted for age only. The analyses of lower limb disability, current cigarette smoking, alcohol consumption, and dietary calcium intake were additionally adjusted for each other. The analyses involving dietary calcium intake were also adjusted for energy intake. Since body mass index can be considered a confounder, an intermediate variable, or both in the analyses of smoking and alcohol consumption, these analyses were repeated without adjustment for body mass index. The analyses were also redone while correcting for current use of medication known to influence bone metabolism. Finally, adjustment for duration of follow-up was performed. The *t* test was used for testing differences between crude mean values, and trends were evaluated for statistical significance using linear regression. Analysis of covariance was applied to calculate adjusted mean yearly rates of change in bone mineral density. All independent variables in these analyses were entered as discrete variables. Age- and sex-adjusted prevalences were calculated with logistic regression.

RESULTS

When adjusted for age and sex, the baseline prevalence of a history of either a wrist or hip fracture during the previous 5 years was similar in the target and the study population (4 and 5 percent, respectively). For lower limb disability, these numbers were 21 and 20 percent, and for current cigarette smoking, they were 22 and 21 percent, respectively. Characteristics of the study population according to sex are displayed in table 1. The mean values and distributions of age and dietary calcium intake were similar in men and women, but women were clearly overrepresented in the highest category of body mass index. In addition, lower limb disability was more prevalent among women. Men were more frequently current cigarette smokers and also had a higher alcohol consumption than did women. As shown in table 2, the crude mean rate of bone loss was considerably higher in women, particularly for the femoral neck and the Ward's triangle, but none of these differences was statistically significant at the 0.05 alpha level. The gender differences were somewhat more pronounced after adjustment for age and body mass index and were statistically significant for the femoral neck. Expressed relative to the mean of the baseline and follow-up bone mineral density value, the crude rate of change at the femoral neck averaged −0.4 percent in men and −0.6 percent in women.

The yearly rate of change in bone mineral density according to age group is depicted in figure 1. It shows statistically significant acceleration of bone loss with age up to 80 years, most clearly in men. After age 80, we saw no further increase in the rate of bone loss. Figure 2 shows the association of the rate of change in bone mineral density with body mass index. In both men and women, a strong and statistically significant trend of decreasing rate of bone loss with increasing body mass index was observed. As can be seen in figure 3, lower limb disability was clearly associated with higher rates of bone loss but with only borderline significance in men and not significantly in women. In figure 4, a significant trend of lower rates of bone loss with increasing dietary calcium intake is demonstrated in men but not in women. The relation between bone loss and category of alcohol intake is depicted in figure 5. With increasing alcohol intake, a lower rate of bone loss was found except for the highest (>20 g/day) category in men. The overall trends in both men and women were not statistically significant, and in men, the trend in the three lowest categories was not significant either ($p = 0.105$). In all analyses of alcohol consumption, omitting body mass index did not alter the results. As is clear from figure 6, cigarette smoking was accompanied by a substantially as well as statistically significantly higher rate of bone loss in both men and women. When these analyses were not adjusted for body mass index, the associations became slightly stronger. None of the results were essentially different when corrected for use of thiazides (8 percent), loop diuretics (3 percent), corticosteroids (2 percent), and, in women, current use of estrogens (2 percent) and years since menopause (mean, 18 years) in the study population. Adjustment for duration of follow-up did not change the results.

DISCUSSION

This longitudinal study shows that bone loss progresses with age in elderly men and women. Further, high body mass index and, in men, high dietary calcium intake are associated with a reduced rate of decline in bone mineral density. Current cigarette smoking and lower limb disability (although the latter is not statistically significant) are associated with higher rates of bone loss. There was no convincing relation between alcohol consumption and bone loss.

A few limitations of this study are discussed first. Some selection in favor of the more mobile and healthy population with probably lower rates of bone

TABLE 1. Distribution of characteristics by sex, the Rotterdam Study, the Netherlands, 1990–1995

Characteristic	Men (n = 1,856)				Women (n = 2,452)			
	Mean	(SD*)	No.	%	Mean	(SD)	No.	%
Age (years)	66.7	(7.2)			67.2	(7.6)		
55–59			381	21			500	20
60–64			461	25			587	24
65–69			431	23			509	21
70–74			312	17			427	17
75–79			192	10			282	12
≥80			79	4			147	6
Body mass index (kg/m²)	25.9	(3.9)			26.8	(4.0)		
<24			485	26			631	26
≥24 to <26			507	27			525	21
≥26 to <28			443	24			444	18
≥28			421	23			852	35
Lower limb disability			249	13			626	26
Current cigarette smokers			427	23			451	19
Dietary calcium intake (mg/day)†	1,156	(436)			1,116	(366)		
<900			441	28			608	28
≥900 to <1,100			358	23			554	25
≥1,100 to <1,300			304	19			464	21
≥1,300			475	30			556	26
Alcohol consumption (g/day)†	16.9	(19.2)			6.4	(10.1)		
0			184	12			529	24
≥0.1 to <10			583	37			1,113	51
≥10 to <20			293	18			305	14
≥2			533	33			237	11

* SD, standard deviation.
† Data on dietary calcium and alcohol intake were available in 3,750 subjects (1,578 men) and 3,795 subjects (1,593 men). Major reasons for missing were reduced cognitive function, assessed by neuropsychological test, logistic reasons, and unreliable data, as judged by a dietician.

TABLE 2. Mean values and 95% confidence intervals for the yearly rate of change in bone mineral density (g/cm²/year) at specific sites according to sex, the Rotterdam Study, the Netherlands, 1990–1995

	Men		Women		p value†
	Mean	95% CI*	Mean	95% CI	
Femoral neck					
Crude	−0.0028	−0.0042 to −0.0014	−0.0044	−0.0056 to −0.0032	0.07
Adjusted‡	−0.0025	−0.0038 to −0.0012	−0.0045	−0.0056 to −0.0034	0.03
Ward's triangle					
Crude	−0.0037	−0.0051 to −0.0023	−0.0050	−0.0063 to −0.0037	0.20
Adjusted‡	−0.0033	−0.0048 to −0.0018	−0.0051	−0.0064 to −0.0038	0.07
Greater trochanter					
Crude	−0.0020	−0.0035 to −0.0005	−0.0023	−0.0035 to −0.0011	0.74
Adjusted‡	−0.0019	−0.0034 to −0.0004	−0.0022	−0.0034 to −0.0010	0.81

* CI, confidence interval.
† Significance level for difference in rate of change in bone mineral density between men and women.
‡ Adjusted for age and body mass index.

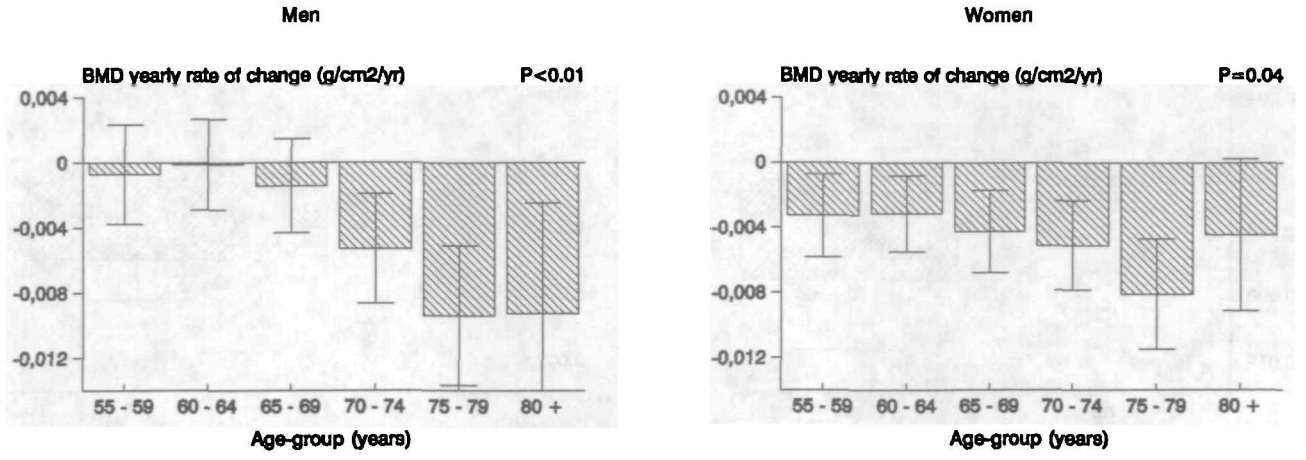

FIGURE 1. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to age group and sex, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

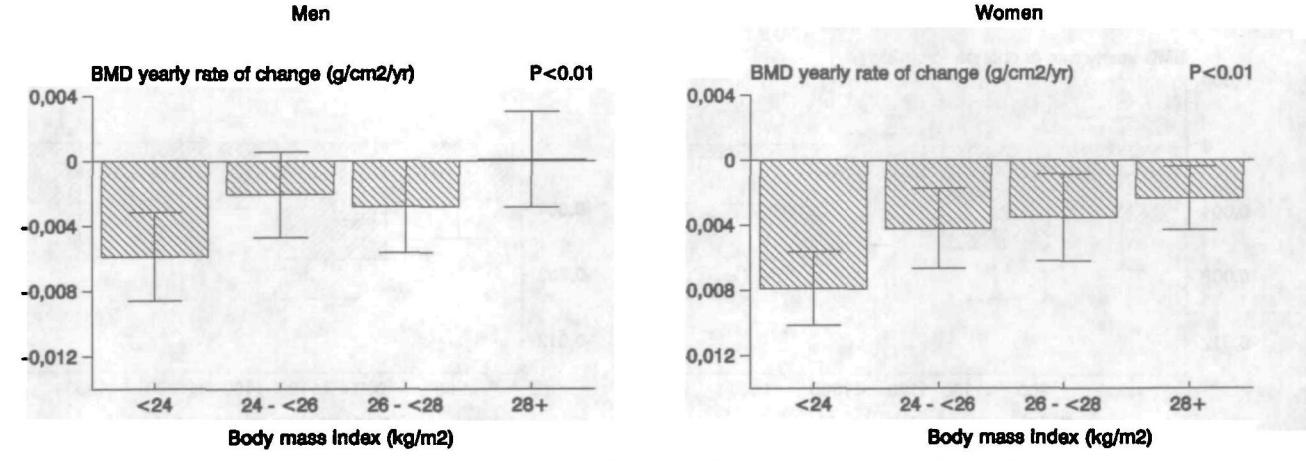

FIGURE 2. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to body mass index and sex, adjusted for age, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

loss may have occurred, particularly for the visit to the examination center. Further, loss to follow-up is most likely related to illness. After adjustment for age and sex, there was, however, no evidence that the target population, i.e., all independently living participants, differed much from the current study population with respect to baseline fracture history, lower limb disability, and current cigarette smoking. Age-dependent nonresponse bias would have resulted in an underestimation of the progression of bone loss with age. Therefore, the true progression has probably been underestimated in this study. Misclassification of the determinants is probably nondifferential, i.e., not dependent on the rate of change in bone mineral density since bone loss itself is not accompanied by any signs or symptoms. As nondifferential misclassification of the determinant results in dilution of an association, the conclusion is again that the true association would be stronger. The same can be said for nondifferential misclassification of the outcome. In short-term follow-up studies on bone loss, this source of error may be relatively large since the variability in the assessment of the rate of bone loss tends to decrease with increasing duration of follow-up (20). Although, in our study, adjustments were made for potential confounders, it remains an observational study so that it is still possible that other, unknown determinants of bone loss confound the relations observed. Consequently, no causal relations can be inferred with certainty. A further limitation of the study is that we did not analyze bone loss according to change in risk factors during follow-up, but only according to baseline levels of risk factors. We could not, therefore, directly show that modification of a certain risk factor

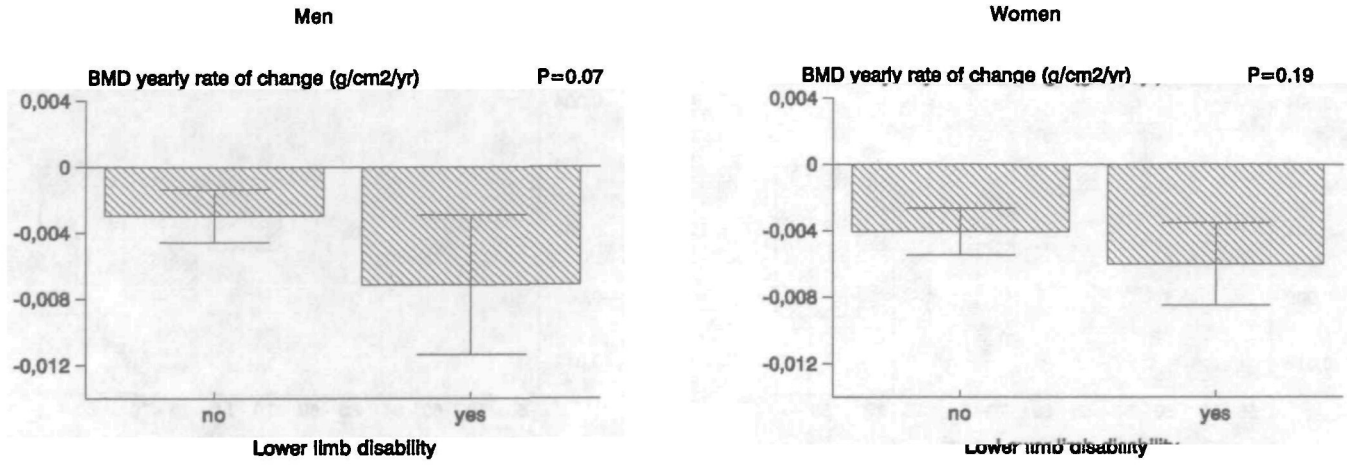

FIGURE 3. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to lower limb disability and sex, adjusted for age, body mass index, current cigarette smoking, dietary calcium and energy intake, and alcohol consumption, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

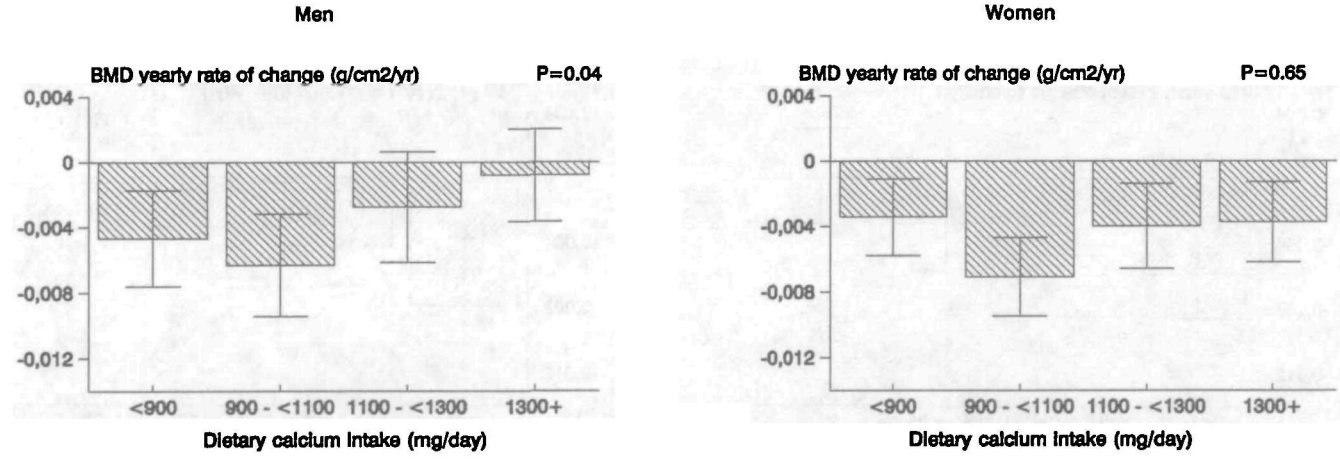

FIGURE 4. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to dietary calcium intake and sex, adjusted for age, body mass index, current cigarette smoking, lower limb disability, energy intake, and alcohol consumption, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

is accompanied by a change in the rate of bone loss.

As rates of bone loss differ markedly between sites (21), comparison of our results should be restricted to data from proximal femur measurements. The rate of bone loss as estimated cross-sectionally in the Rotterdam Study (8) was of the same order of magnitude, although somewhat lower than estimated longitudinally. The high longitudinally assessed rate of bone loss 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 since they are less subject to cohort effects and selection bias. In the highest age group, the progression stopped. This is most likely due to selection on health at baseline and loss to follow-up of those who developed serious illnesses, which predominantly occur at the oldest ages. Acceleration of bone loss with age was also seen in the Dubbo Study (5). Within age strata, however, the rates of bone loss in that study were substantially higher than in the Rotterdam Study. This may be partly due to the much lower calcium intakes of the Dubbo Study participants. Further, for women in our study, the higher weight (70.1 kg vs. 65.3 kg for Dubbo study participants) in the presence of identical mean height (1.62 m) may in part explain the lower rates of bone loss. Data from a 1-year follow-up study of community-dwelling women showed a somewhat lower rate of change for their age compared with our study (6). In that study, there was no evidence of acceleration of bone loss, possibly because of limited statistical power. The Study of Osteoporotic Fractures (7) showed progression of the rate of bone loss with age in elderly women similar to that in the Rotterdam Study.

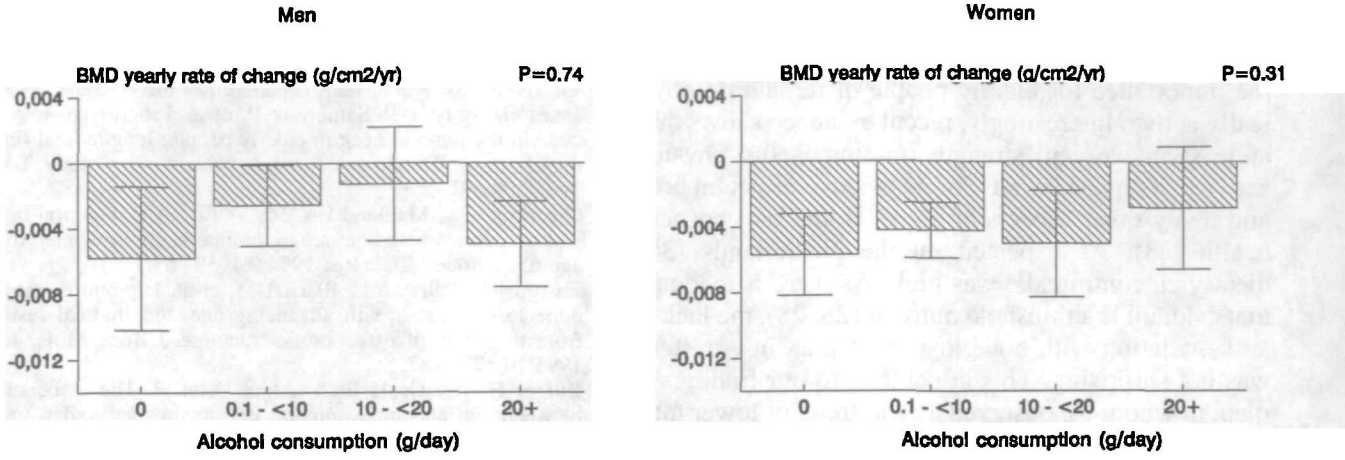

FIGURE 5. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to alcohol consumption and sex, adjusted for age, body mass index, current cigarette smoking, dietary calcium and energy intake, and lower limb disability, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

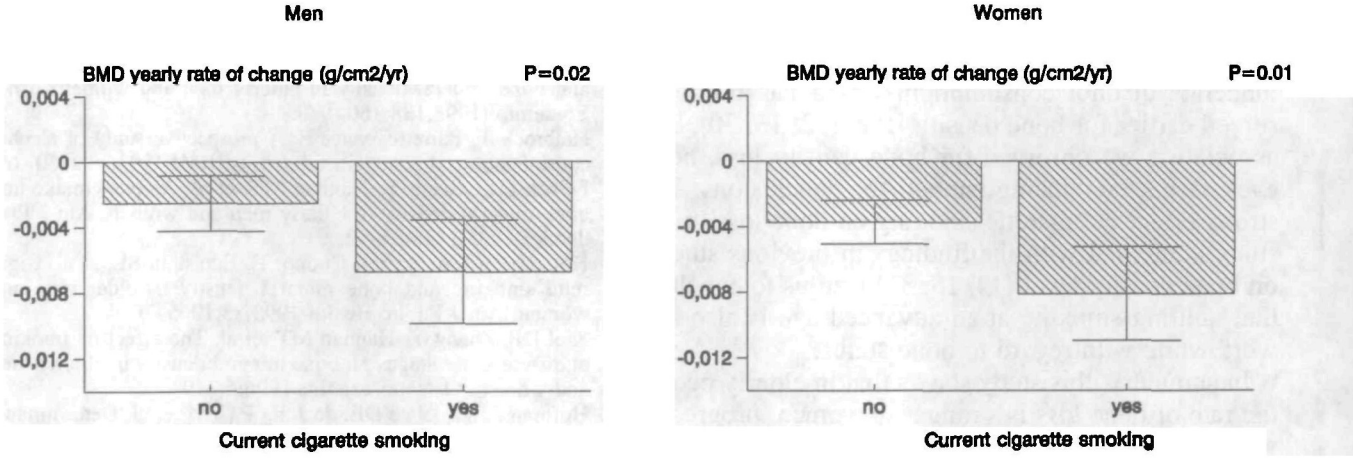

FIGURE 6. Mean yearly rate of change in bone mineral density (BMD) and 95% confidence interval according to current cigarette smoking and sex, adjusted for age, body mass index, lower limb disability, dietary calcium and energy intake, and alcohol consumption, the Rotterdam Study, the Netherlands, 1990–1995. *p* values are for linear trends.

Determinants were generally more clearly associated with bone loss in men than in women, in particular, dietary calcium intake. As the women in our study were on average more than 18 years postmenopausal, they would have lost a relatively great part of their bone reserve. The weaker association in women may therefore be due to limited potential for environmental factors to further influence bone loss rates. We could not, however, demonstrate that associations were any stronger in younger than in older women. An alternative explanation is that some women, more than men, were already aware of their osteoporosis before the time of their dietary interview and had altered their lifestyle accordingly.

Body mass index, calcium intake, physical inactivity, smoking, and, more controversially, alcohol intake as well have been shown to be determinants of bone mineral density level (11–15, 22–31). Our data are largely in concordance with these findings and indicate that these determinants, if causal, exert their effect on bone density level late in life, at least in part through their effect on the rate of bone loss. Body mass index in our population was similar to that found in other population-based studies (11, 13). The strong relation of lower rates of bone loss with higher body mass index underlines the importance of not becoming underweight as far as bone density is concerned (11, 22, 23). The prevalence of lower limb disability is well in line with the prevalence of disability assessed using comparable methodology in the 1994 National Long-Term Care Surveys (21.3 percent) in persons aged 65 years and over (32). We did not collect data on physical activity and assumed that disability may serve as a proxy. Lower limb disability was associated with

higher rates of bone loss, probably through its association with reduced physical activity. This is in accordance with previous studies (24–27) and emphasizes the importance for elderly people of remaining physically active. Interestingly, recent evidence shows that, at least in women, strength training is the physical activity of choice because of its positive effect on bone and many other aspects of physical and psychosocial health (33). As expected, in the Netherlands (34), dietary calcium intake was high. As there is evidence that calcium is a threshold nutrient (28, 28), the lack of an association with bone loss in women in our study was not surprising. This in contrast to our findings in men, in whom we observed a clear trend of lower rates with increasing dietary calcium intake. Since subjects in calcium studies were mostly women, we suggest that a threshold in men may be at a higher level of calcium intake. Our findings stress the importance of the Recommended Daily Allowance in the United States of 1,500 mg/day for elderly people (35). For alcohol, in men, our data suggest a beneficial effect of moderate alcohol consumption, which has been observed earlier for bone density level (12, 13, 30). The association we observed for bone density loss, however, is not convincing enough for conclusions. The strong effect of cigarette smoking on bone loss in our study combined with the findings in previous studies on bone density level (14, 15, 31) lead us to conclude that quitting smoking at an advanced age is also still worthwhile with regard to bone status.

In summary, this study shows that in elderly people the rate of bone loss is stronger in women, progresses with age, and is further determined by several modifiable risk factors, particularly in men.

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