Bone Mineral Density and Chronic Lung Disease Mortality: The Rotterdam Study

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Context: Low bone mineral density (BMD) has been associated with increased all-cause mortality. Cause-specific mortality studies have been controversial.

Objective: The aim of the study was to investigate associations between BMD and all-cause mortality and in-depth cause-specific mortality.

Design and Setting: We studied two cohorts from the prospective Rotterdam Study (RS), initiated in 1990 (RS-I) and 2000 (RS-II) with average follow-up of 17.1 (RS-I) and 10.2 (RS-II) years until January 2011. Baseline femoral neck BMD was analyzed in SD values. Deaths were classified according to International Classification of Diseases into seven groups: cardiovascular diseases, cancer, infections, external, dementia, chronic lung diseases, and other causes. Gender-stratified Cox and competing-risks models were adjusted for age, body mass index, and smoking.

Participants: The study included 5779 subjects from RS-I and 2055 from RS-II.

Main Outcome Measurements: We measured all-cause and cause-specific mortality.

Results: A significant inverse association between BMD and all-cause mortality was found in males [expressed as hazard ratio (95% confidence interval)]: RS-I, 1.07 (1.01–1.13), $P = .020$; RS-II, 1.31 (1.12–1.55), $P = .001$); but it was not found in females: RS-I, 1.05 (0.99–1.11), $P = .098$; RS-II, 0.91 (0.74–1.12), $P = .362$. An inverse association with chronic lung disease mortality was found in males [RS-I, 1.75 (1.34–2.29), $P < .001$; RS-II, 2.15 (1.05–4.42), $P = .037$] and in RS-I in females [1.72 (1.16–2.57); $P = .008$], persisting after multiple adjustments and excluding prevalent chronic obstructive pulmonary disease. A positive association between BMD and cancer mortality was detected in females in RS-I [0.89 (0.80–0.99); $P = .043$]. No association was found with cardiovascular mortality.

Conclusions: BMD is inversely associated with mortality. The strong association of BMD with chronic lung disease mortality is a novel finding that needs further analysis to clarify underlying mechanisms. **(*J Clin Endocrinol Metab* 99: 1834–1842, 2014)**

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CIC, cumulative incidence curve; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; DXA, dual-energy x-ray absorptiometry; GP, general practitioner; HR, hazard ratio; hsCRP, high-sensitivity CRP; RS-I, Rotterdam Study cohort 1; RS-II, Rotterdam Study cohort 2.

Osteoporosis is a condition characterized by low bone mineral density (BMD) and microarchitectural deterioration leading to decreased bone strength, which predisposes to fragility fractures and is associated with high morbidity and mortality (1). Low BMD has been linked to an increased risk of fracture-independent mortality and could be considered a predictor of survival (2, 3). Regarding cause-specific mortality, studies on the association between BMD and cardiovascular disease (CVD) mortality have not been consistent, with some showing an inverse relation with BMD (2, 4, 5), whereas others found no association (6, 7). Potential gender differences have been found for both CVD mortality and cancer-related mortality, but results remain inconclusive (5, 8, 9). An inverse association between the group of remaining unspecified causes of mortality and BMD has been found in both genders (2, 6).

Besides the association between low BMD and mortality, recent studies suggest that osteoporosis treatment reduces mortality, which could not be completely explained by a decrease in fracture-related mortality (10). Previously (3), we examined the relationship of femoral neck BMD with overall mortality in the first cohort of the Rotterdam Study (RS-I) and found an inverse association for all-cause mortality in men but not women after an average follow-up of 5.4 years. The aim of this study was to analyze the relationship between BMD and all-cause and detailed cause-specific mortality in males and females from two cohorts of the Rotterdam Study with long-term follow-up.

Subjects and Methods

Study population

The Rotterdam Study is a prospective cohort study of males and females designed to investigate the incidence and determinants of chronic disabling diseases. Rationale and design have been described previously (11). Inhabitants of the well-defined Ommoord district in the city of Rotterdam in The Netherlands were invited to participate; their names and addresses were drawn from the municipal register. The RS-I, initiated in 1990, consisted of 7983 subjects; the second cohort (RS-II), initiated in 2000, included 3011 subjects. All participants were >55 years old at recruitment and reside in Ommoord, a district in Rotterdam. Analyses were performed in 5779 and 2055 subjects from RS-I and RS-II, respectively—all with available BMD measured at baseline and signed informed consent. The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus MC.

Dual-energy x-ray absorptiometry (DXA) scanning

BMD was assessed using DXA. Trained radiographic technicians performed BMD measurements for participants with a GE Lunar DPX-L densitometer (GE Lunar Corp), as previously described (12). Femoral neck BMD was chosen because it is not affected by degenerative changes seen with age as lumbar spine is, and it has been proposed for defining osteoporosis in epidemiological studies (12, 13).

Covariates

Several baseline covariates known to influence both BMD and mortality were included in the regression models, particularly age, gender, body mass index (BMI), and smoking status (14). BMI was calculated in kilograms per meter squared, from height and weight measured in a standing position without shoes. Smoking status was assessed by interview and coded as never, former, and current smokers. Other potential confounders were considered in additional analyses, such as physical activity, prevalent morbidity, medication, high-sensitivity C-reactive protein (hsCRP), and fracture incidence. For RS-I, a lower limb disability score was recorded using a modified version of the Stanford Health Assessment Questionnaire (15). For RS-II, a questionnaire on physical activity was collected. Baseline comorbidities were also assessed, such as prevalent myocardial infarction, dementia, type 2 diabetes mellitus, and chronic obstructive pulmonary disease (COPD); likewise, baseline medication use information was collected, such as bisphosphonate, hormone replacement therapy, and systemic corticosteroid use. Myocardial infarction prevalence was verified by a cardiologist, a general practitioner (GP), or electrocardiogram. Prevalent COPD, diabetes mellitus, and dementia were defined as previously described (11, 16). hsCRP was assessed as a marker of inflammation. Continuous covariates are described as mean and SD if there is normality of distribution; otherwise, median and interquartile range are shown. Fracture events were obtained from computerized records of GPs in the research area (covering 80% of the cohort); additionally, research physicians regularly followed participant information in GPs' records outside the research area. All reported events were verified by two trained research physicians, who independently reviewed and coded the information. Finally, all coded events were reviewed by a medical expert for final classification according to the International Classification of Diseases, 10th revision (ICD-10) (17). Participants were followed from the baseline visit until January 1, 2007, or until a first fracture or death occurred. In addition, thoracolumbar spine radiographs were collected at both the baseline visit and the second follow-up visit (between 1997 and 1999). All thoracolumbar spine radiographs of the follow-up visit were scored morphometrically for the presence of vertebral fractures using the McCloskey-Kanis method (18). If a vertebral fracture was diagnosed, the baseline radiograph was also evaluated, and if present, it was considered a prevalent vertebral fracture. If it was not present at baseline, the fracture was considered as incident. Information on spinal radiographs was available for 3145 subjects with baseline DXA information.

Assessment of cause-specific mortality

Information on vital status is obtained continuously from the municipal authorities in Rotterdam. The cohorts are monitored for major disease outcomes and mortality through computerized linkage of the study database to GPs' medical files. For subjects who moved outside Ommoord, these data are obtained from GPs, who report all important events through a computerized system (3). Two research physicians independently coded the mortality events according to ICD-10 (19). Medical specialists in the respective field reviewed the coded events and confirmed the diagnosis. Information on cause-specific mortality was available until January, 2011.

Different causes of mortality were recorded according to ICD-10 codes and first grouped into CVDs, cancer, and "other

causes" (5, 6). To perform comprehensive analyses, the group of other causes was further categorized into external causes, dementia, infections, chronic lung disease, and other causes, following a slightly modified previous approach (8). This categorization yielded seven groups: CVDs (cardio- and cerebrovascular diseases; ICD-10 codes I05-I30.0, I31, I32, I32.8, I34-I37, I42-I79, I81-I99, G95.1, F01), cancer (codes C00-D09.9), chronic lung diseases (COPD comprised 80% of this group; codes J21.9, J39.9, J40, J42-J84.9, J90-J96), dementia (mostly Alzheimer's disease; codes F00, F02, F03, F05.1), external causes (mainly fatal fractures; mostly hip fractures, but also accidents and suicides; codes S00-T98 except T82.7), infectious diseases (pneumonia and septic shock were the most common; codes A00-B99, G00-G09, I30.1, I32.0, I32.1, I33.0, J15-J18, J85–86, J41, K35-K38, K57.0, K75.0, I38-I41, I80, M00.9, M86, N71, T82.7), and other causes (heterogeneous group composed mainly of unspecified, unattended and sudden death and a minority of nontumoral gastrointestinal, renal, hematological, and cerebral diseases, senility, and cachexia; codes D10-D48.9, E00-E90, D50-D89.9, G10-G26, K22-K34, K40-K52, K55.0, K56, K64, K73, K80, K83, K92, L12, L88, M05, M06, M31, M35, N03, N04, N10,N17, N18, N28, R54, R64, R96, R98, R99).

Statistical analyses

For analysis of all-cause and cause-specific mortality, BMD was expressed in SD values, calculated as: (patient BMD − cohort BMD mean)/cohort BMD SD, specific for gender. For RS-I, BMD was further categorized according to the number of SD (T-scores)- below the mean BMD for young adults (age, 20–29 y), leading to three strata: osteoporosis (T-score ≤ -2.5), osteopenia ($-2.5 <$ T-score < -1.0), and normal BMD (T-score ≥ -1.0). Reference values for normal BMD were extracted from the Third National Health and Nutrition Examination Survey (NHANES III) for a non-Hispanic white population (20). To assess the relation between BMD and mortality, Cox proportional hazard regressions were used, adjusting for age, BMI, and smoking. The proportional hazard assumption of the Cox models was assessed using the Schoenfeld residuals-based test—the standard diagnostic test. Both the *P* value for the BMD covariate itself and the *P* value for the global model were taken into account. For cause-specific mortality, additional analyses were performed, running the competing-risk regressions based on the method of Fine and Gray (21) and taking into account informative censoring due to competing events. Proportionality was tested, evaluating interaction terms with time. All significant hazard ratios (HRs) reported here do not violate the proportionality assumption and thus are constant over follow-up time, unless stated otherwise. Analyses were sex-stratified because: 1) previous reports on gender differences have been described in the relation between BMD and mortality; and 2) Cox proportional hazards assumption violations were found due to gender. Because of fracture-related mortality (22), analyses were further adjusted for fracture incidence as a time-varying covariate. HRs with 95% confidence interval (CI) are expressed: 1) per decrease in SD of BMD; and 2) per category of osteopenia or osteoporosis, setting normal BMD as the reference. In a later step, analyses were repeated after exclusion of participants with fatal events within the first 3 years, taking into account that low BMD might be a marker of underlying illness.

The association between BMD and cause-specific mortality was evaluated through cumulative incidence curves (CICs) instead of Kaplan-Meier curves, which overestimate the risk probability when there are several types of possible events (21). CICs were calculated after running competing-risk regressions.

Results from individual cohorts were meta-analyzed.

SPSS version 17 (SPSS Inc) and Stata version 12 (StataCorp) were used for the individual analyses. Comprehensive Meta-Analysis version 2.0 (Biostat) was used for the meta-analysis.

Results

All-cause mortality

In total, 5779 RS-I and 2055 RS-II subjects were followed for a median of 17.1 years and a mean of 10.2 years, respectively. During the follow-up, 3117 deaths occurred in RS-I and 295 in RS-II. Baseline characteristics for both cohorts are presented in Table 1. In both cohorts, a significant and inverse association between BMD and overall mortality was found in males, expressed as HR (95% confidence interval [CI]): RS-I, 1.07 (1.01–1.13), $P = .020$; RS-II, 1.31 (1.12–1.55), $P = .001$. In females, there was no association with

Table 1. Baseline Characteristics of the Participants of the Rotterdam Study with Femoral Neck BMD Measurement Available

	RS-I		RS-II	
	Males	Females	Males	Females
n	2438	3341	954	1101
Age, y	66.5 (61.3–72.7)[a]	67.5 (61.5–74.0)[a]	61.5 (8.9)[b]	61.4 (7.9)[b]
BMI, kg/m^2	25.6 (23.8–27.6)[a]	26.2 (23.9–29.1)[a]	26.7 (4.2)[b]	26.8 (5.8)[b]
FN BMD, g/cm^2	0.91 (0.82–1.00)[a]	0.82 (0.73–0.91)[a]	0.97 (0.13)[b]	0.89 (0.14)[b]
Never smokers, n (%)	197 (8)	1706 (51)	502 (53)	861 (78)
Former smokers, n (%)	1517 (62)	961 (29)	206 (22)	3 (<0.1)
Current smokers, n (%)	711 (29)	646 (19)	243 (25)	234 (21)
Prevalent DM, n (%)	252 (10.3)	325 (9.7)	128 (13.4)	112 (10.2)
Prevalent MI, n (%)	258 (10.6)	419 (12.5)	62 (6.5)	19 (1.7)

Abbreviations: FN, femoral neck; DM, diabetes mellitus; MI, myocardial infarction.

[a] Median (interquartile range).

[b] Mean (SD).

Table 2. Description and Frequencies of Cause-Specific Mortality for Participants With BMD Available in RS-I and RS-II, up to 2011

Cause	Description	RS-I	RS-II
CVD	Cardio- and cerebrovascular pathology	1021 (32.8)	89 (30.1)
Cancer	All cancer-related deaths	829 (26.6)	110 (37.3)
Other causes	Noncancerous gastrointestinal, hematological, cerebral, and renal pathology; cachexia; senility; unattended, unspecified, and sudden death	640 (20.5)	45 (15.3)
Dementia	Dementia as final cause of death	241 (7.7)	18 (6.1)
Infectious diseases	All infection-related deaths	162 (5.2)	12 (4.1)
Lung diseases	COPD, interstitial diseases, respiratory failure	121 (3.9)	13 (4.4)
External causes	Mainly hip fractures, accidents, suicides	91 (2.9)	7 (2.4)
Missing causes	Cases without ICD-10 codification	12 (0.4)	1 (0.3)
Total		3117 (100)	295 (100)

Data are expressed as number (percentage).

overall mortality in either cohort. Adjustment for incident fractures yielded essentially the same results (data not shown).

Cause-specific mortality

A brief description of each cause and the frequencies are shown in Table 2. The HRs for BMD and cause-specific mortality adjusted for age, BMI, and smoking are shown in Table 3.

A relationship between lower BMD and higher chronic lung disease mortality was observed in RS-I and RS-II for males [RS-I, HR, 1.75 (95% CI, 1.34–2.29), $P < .001$; RS-II, 2.15 (1.05–4.42), $P = .037$] and in RS-I for females [1.72 (1.16–2.57), $P = .008$]; whereas for females in RS-II, a similar but nonsignificant trend was observed [1.77 (0.28–11.2); $P = .544$] with only two deaths due to chronic lung disease. Most cases of chronic lung disease mortality were due to COPD (RS-I and RS-II combined, 104 of 134 cases; 77.6%), whereas the non-COPD cases were mainly due to interstitial pulmonary disease, pneumonitis, and unspecified respiratory failure. When we restricted the analyses to COPD mortality, the association between BMD and COPD mortality showed similar or even higher HRs than for chronic lung disease mortality (data not shown). The HR magnitudes for chronic lung disease mortality were higher for males than females in

Table 3. All-Cause and Cause-Specific Mortality HRs for RS-I and RS-II per Decrease in SD of Femoral Neck BMD

	Males			Females		
	No. of Deaths	HR (95% CI)	*P*	No. of Deaths	HR (95% CI)	*P*
All-cause						
RS-I	1488	**1.07** (1.01–1.13)	.020	1629	1.05 (0.99–1.11)	.098
RS-II	177	**1.31** (1.12–1.55)	.001	118	0.91 (0.74–1.12)	.362
Cardiovascular						
RS-I	507	0.97 (0.88–1.07)	.576	514	0.99 (0.90–1.09)	.865
RS-II	52	1.24 (0.91–1.67)	.168	37	0.91 (0.63–1.32)	.615
Cancer						
RS-I	438	1.04 (0.94–1.15)	.453	391	**0.89** (0.80–0.99)	.043
RS-II	66	1.29 (0.99–1.68)	.060	44	0.91 (0.65–1.27)	.598
Other causes						
RS-I	266	**1.18** (1.02–1.35)	.021	374	**1.21** (1.07–1.37)	.003
RS-II	27	1.25 (0.82–1.91)	.293	18	0.66 (0.41–1.07)	.092
Dementia						
RS-I	67	1.08 (0.82–1.42)	.594	174	1.20 (0.99–1.45)	.060
RS-II	09	1.83 (0.93–3.60)	.081	09	0.91 (0.40–2.08)	.822
Infections						
RS-I	84	1.14 (0.89–1.46)	.295	78	0.93 (0.72–1.20)	.572
RS-II	06	0.84 (0.41–1.74)	.650	06	2.51 (0.81–7.78)	.111
Chronic lung disease						
RS-I	81	**1.75** (1.34–2.29)	<.001	40	**1.72** (1.16–2.57)	.008
RS-II	11	**2.15** (1.05–4.42)	.037	02	1.77 (0.28–11.2)	.544
External causes						
RS-I	37	1.26 (0.86–1.82)	.231	54	**1.87** (1.30–2.68)	.001
RS-II	05	1.58 (0.59–4.23)	.361	02	0.96 (0.18–5.12)	.958

Adjustments were made for age, smoking, and BMI. Boldface data corresponds to hazard ratios with statistically significant *P* values.

Table 4. Chronic Lung Disease Mortality HRs per SD Decrease in Femoral Neck BMD in RS-I

	Males				Females			
	All Cases (n = 81)		Excluding Prevalent COPD (n = 55)		All Cases (n = 40)		Excluding Prevalent COPD (n = 32)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Model I	**1.75** (1.33–2.29)	<.001	**1.55** (1.13–2.14)	.007	**1.72** (1.16–2.57)	.008	**1.79** (1.13–2.83)	.013
Model II	**1.73** (1.30–2.29)	<.001	**1.65** (1.16–2.33)	.005	**1.68** (1.12–2.54)	.012	**1.83** (1.14–2.93)	.013

Abbreviation: n, number of deaths. Model I was adjusted for age, BMI, and smoking. Model II was adjusted for age, BMI, smoking, lower limb disability, log CRP, baseline corticosteroid use, and prevalent and incident vertebral fractures. Boldface data corresponds to hazard ratios with statistically significant *P* values.

both cohorts, and this difference remained after further adjustments for baseline medication use, such as bisphosphonates and hormone replacement therapy use (data not shown). Furthermore, adjustments for corticosteroid use, prevalent and incident radiographic and clinical vertebral fractures, log C-reactive protein (CRP) and lower limb disability score, and exclusion of COPD prevalent cases yielded similar results (Table 4). Figure 1A shows RS-I CICs (ie, the probability of dying of a chronic lung disease taking into account competing risks) for participants of median age, according to baseline BMD in SD values and adjusted for gender, BMI, lower limb disability, and smoking. Figure 1, B–D, shows the CICs stratified by smoking status in RS-I. Figure 1, E–H, shows correspondent CICs for RS-II.

There was a significant relationship between BMD and mortality due to other causes in RS-I [for males, HR, 1.18 (95% CI, 1.02–1.35), $P = .021$; for females, 1.21 (1.07–1.37), $P = .003$]; whereas it was not significant in RS-II. Subanalysis of this group in RS-I attributed mortality mainly to unattended death, sudden death–cause unknown, and unspecified cause of mortality. For females in RS-I, there was a significant relationship between external causes of mortality and BMD [1.87 (1.30–2.68); $P = .001$], driven mainly by hip fracture mortality and a significant positive association between BMD and cancer mortality [0.89 (0.80–0.99); $P = .043$], whereas no associations were found in men.

There were no significant associations between BMD and mortality due to CVD, dementia, or infectious diseases.

Results from competing-risk regression models were similar to Cox models (data not shown).

The HRs from combined analysis of the two cohorts mostly reflected the results from the much larger RS-I cohort, both in all-cause and in cause-specific mortality analysis (data not shown).

Further adjustments for baseline comorbidity, bisphosphonate use, log CRP, and physical exercise did not substantially change the results in either cohort or gender (data not shown).

Risk of all-cause and cause-specific mortality in subjects with osteopenia and osteoporosis compared to those with normal BMD in RS-I

When analyzing the mortality in subjects with osteopenia and osteoporosis compared to those with normal BMD in RS-I, similar trends were found as with BMD in SD, except that females with osteoporosis also had increased risk of death. For all-cause mortality in RS-I, the HR for males with osteopenia was 1.26 (95% CI, 1.10–1.43; $P < .001$); and the HR for males with osteoporosis was 2.40 (1.39–4.16; $P = .002$), compared with those with normal BMD (Figure 2). Females with osteoporosis had 1.66 (1.17–2.35; $P = .004$) times increased risk of death. For chronic lung disease mortality, males with osteopenia had 2.21 (1.34–3.62; $P = .002$) times increased risk, whereas for those with osteoporosis, the risk was increased 16.6 times (5.84–47.0; $P < .001$). Females with osteoporosis had 5.91 (1.20–29.0; $P = .029$) times increased risk for chronic lung disease mortality. Figure 2, A and B, shows the HRs for all-cause mortality and mortality due to chronic lung disease in males and females with normal BMD, osteopenia, and osteoporosis. These analyses have been adjusted for age, BMI, and smoking. Further adjustments for incidental fractures yielded similar results (data not shown).

Exclusion of participants with early fatal events

Analyses excluding participants who died within the first 3 years of follow-up did not change results essentially (data not shown).

Discussion

In these analyses in two large prospective cohorts of elderly subjects from the Rotterdam Study, femoral neck BMD in SD was significantly inversely related to overall mortality in males but not in females. This relationship was not driven by fracture-related mortality because adjustment for incident fractures yielded similar results.

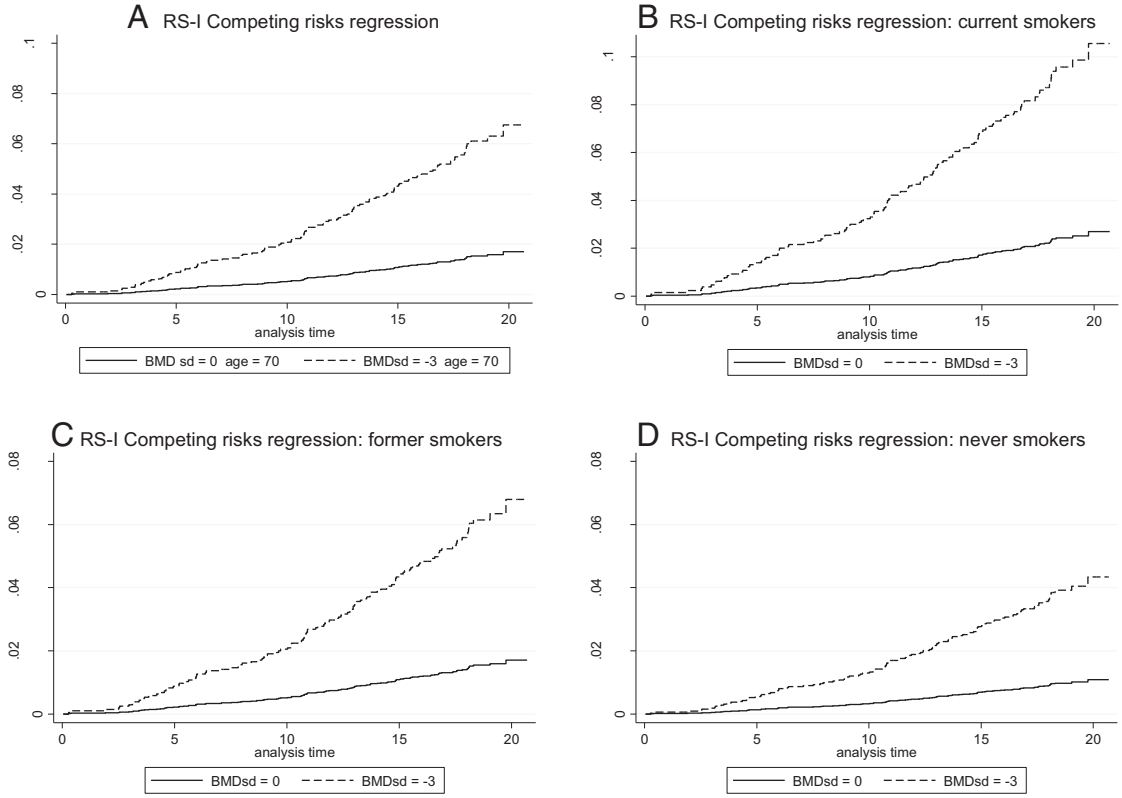

Figure 1. A, CIC for chronic lung disease mortality according to baseline BMD expressed in SD values (BMDsd), adjusted for gender, BMI, lower limb disability and smoking, for participants of median age of RS-I cohort. B–D, CIC according to baseline smoking status: current smokers (B), former smokers (C), and never smokers (D). The solid line represents participants with average BMD (BMDsd = 0), and the dashed line represents participants with 3 SD below average BMD (BMDsd = −3). The analysis time is in years. E, CICs for chronic lung disease mortality according to baseline BMD expressed in BMDsd, adjusted for gender, BMI, physical activity, and smoking, for participants of median age of RS-II cohort. F–H, CIC according to baseline smoking status: current smokers (F), former smokers (G), and never smokers (H). The solid line represents participants with average BMD (BMDsd = 0), and the dashed line represents participants with 3 SD below average BMD (BMDsd = −3). The analysis time is in years.

However, both males and females with osteoporosis had increased risk of death compared to those with normal BMD. When assessing cause-specific mortality in detail, we found a novel and inverse relation in both genders between BMD and mortality related to chronic lung diseases (mainly COPD). In RS-I, there was a significant inverse relationship between BMD and other causes of mortality in both genders, which was mainly observed in participants with unattended, unspecified, and sudden deaths. An inverse association of BMD with external causes of mortality (mainly due to hip fracture) was found in females in RS-I. No association was found between BMD and CVD mortality, dementia-related mortality, and death due to infectious diseases in either cohort. To the best of our knowledge, the relation we found between baseline BMD and chronic lung disease mortality has not been described before. The direction of association was consistent between genders and study cohorts and was not explained by prevalent COPD. Males and females with osteoporosis in RS-I had a 17 and 6 times increased risk of death due to chronic lung disease, respectively. It has been known that patients with COPD are at increased risk for low BMD and fractures (23, 24), partly related to factors such as older age, smoking, physical inactivity, corticosteroid use, and low BMI (25), the latter being one of the more important determinants of low BMD according to a recent systematic review (26). All of these factors have been taken into account in our analyses, and the HRs did not change, suggesting that other, yet unknown factors explain this relationship between BMD and COPD mortality. Chronic inflammation, associated to COPD, may induce low BMD, but additional adjustments for hsCRP did not modify the associations. Likewise, smoking, the most recognized environmental trigger for COPD (27), produces profound bone loss, mainly through increased osteoclast activity (28). Smoking induces IL-17 production, which is related to the development of emphysema (29) and is a potent inductor of inflammatory bone loss via stimulation of receptor activator of nuclear factor-κB ligand (30). Nevertheless, adjusting for smoking did not modify the association, and competing risk regression analyses showed similar associations in smokers as in nonsmokers.

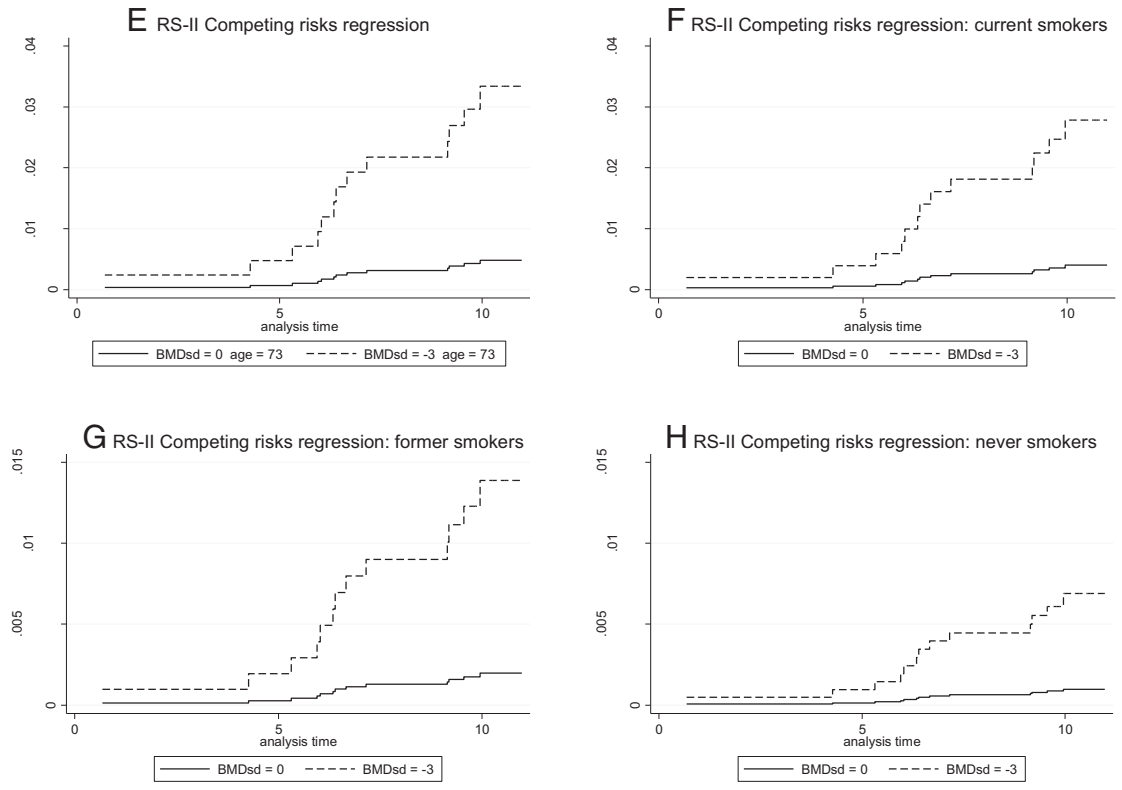

Figure 1. Continued.

Although vertebral fractures could compromise lung function and thus mortality (31, 32), we did not find this to be an explanation for our findings because adjustment for prevalent and incident vertebral fractures did not modify results. Alternative explanations may be low vitamin D levels, which may lead to decreased BMD, as well as impaired lung function, or sarcopenia, and/or physical inactivity. COPD patients have a high prevalence of hypovitaminosis D and sarcopenia (33, 34). Unfortunately, vitamin D levels were not available at baseline, but adjusting for disability index, which might be expected to associate with both low vitamin D and physical inactivity, did not change results. It was recently reported that the presence of anti-citrullinated protein antibodies is related to bone loss years before the occurrence of rheumatoid arthritis (35, 36), while also being related to the develop-

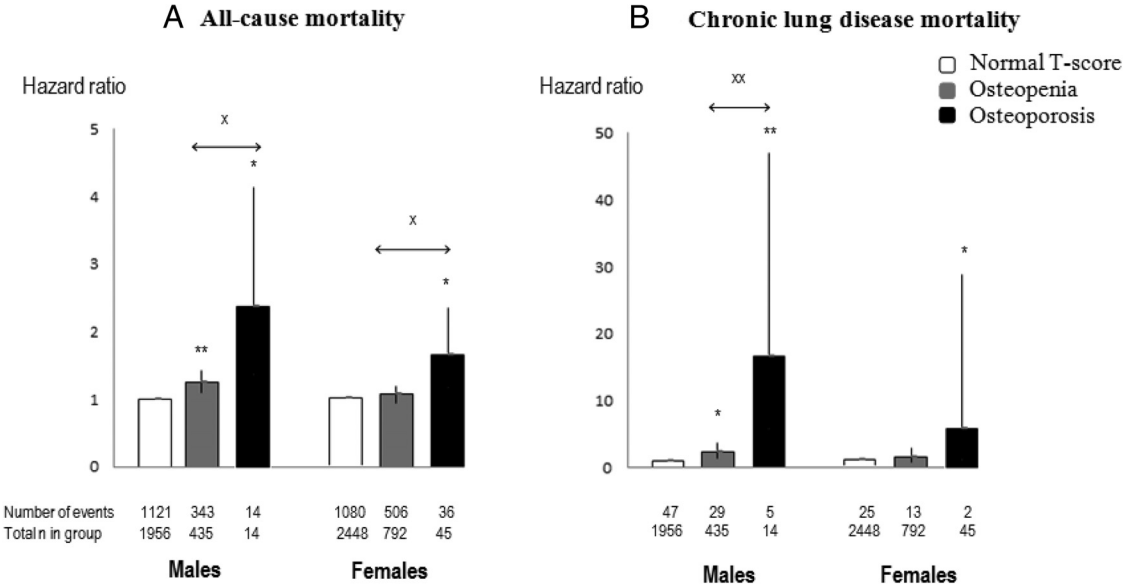

Figure 2. All-cause (A) and chronic lung disease (B) mortality HRs for participants from RS-I, according to T-score, adjusted for age, BMI, and smoking status. *, $P < .05$; **, $P < .001$ compared to normal T-score. x, $P < .05$; xx, $P < .001$ osteoporosis compared to osteopenia.

ment of airway abnormalities (37). This or other common factors might underlie our findings. Alternatively, a causal relationship between osteoporosis and (deaths from) other diseases like COPD cannot be ruled out because bone influences multiple other tissues and organs, eg, through its endocrine and immune-modulating properties as has been shown by multiple recent studies (38).

Future studies should investigate a potential role of vitamin D, body composition, muscle strength, physical activity, and potential common factors such as anti-citrullinated protein antibodies. Also, based on our findings, it would be of public health importance to study further whether treatment of osteoporosis in patients with COPD would influence their mortality and potential pulmonary function.

In both studies, we found that femoral neck BMD was significantly inversely related to overall mortality in males but not in females. However, female subjects with osteoporosis also had increased risk of death. The relation between BMD and mortality in males was explained by an association with mortality from several causes, and similar findings were seen in females, except in the relation with cancer mortality. We found a decreased HR for cancer mortality with decreasing BMD in females, which may explain the absence of an association with overall mortality in females. A gender difference in cancer mortality was found in the NHANES I cohort (5), with a significantly increased HR for males but not females. Possible diverging associations between BMD and cancer mortality will have to be further investigated in well-powered studies.

We did not find a consistent association between BMD and CVD mortality, adding to the inconsistent literature findings of such a relationship. We found no association between BMD and dementia-related mortality. There is always the possibility that a low bone mass reflects a poor pre-existing health status, which may lead to increased mortality. We tried to account for this by excluding participants with mortality within the first 3 years of follow-up, but results were essentially the same.

This study has several limitations and strengths. A potential selection bias may have occurred because subjects who came to the research center at baseline for tests were healthier; however, if present, a dilution of the observed effects would be expected. Also, residual confounding cannot be excluded. Another weakness is that baseline COPD diagnosis was made based on clinical grounds and not in all cases on spirometry data, which is the "gold standard" method. Therefore, we cannot exclude the possibility of misclassification of COPD status at baseline, but it is not likely that this explains our finding. Also, we had no information on cumulative dose of corticosteroids in the past, only current use at baseline. Another potential limitation stems from the fact that the entire cohort is composed of European Caucasians, limiting the generalizability of our findings to other populations or ethnic groups.

One strength is the availability of two large prospective and similarly well-characterized, population-based prospective studies with accurate determination of causes of death. In general, data of The Netherlands registers is recognized as reliable and consistent (39), and more than 85% of the death registries in these cohorts were coded with high certainty level. As with any survival analysis, the completeness of follow-up is important, because when low it produces biased estimates (40). For both cohorts, the corresponding values for completeness of follow-up were higher than 90%, reassuring us that effect estimates obtained are valid.

In summary, we found an inverse relationship between BMD and all-cause mortality in males and an increased risk of death for male and female subjects with osteoporosis compared to those with normal BMD. This relationship was explained by several underlying causes, such as chronic lung disease mortality, trauma, and other causes. A potential gender difference in the relation between BMD and cancer-related mortality with a positive association between BMD and cancer-related mortality in females may explain the absence of an inverse relation between BMD and all-cause mortality in females. The consistent finding in both genders in both studies of an inverse and strong association between baseline BMD and chronic lung disease mortality has not been reported before and needs further study into the underlying pathophysiological mechanisms.

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