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Bone Loss, Weight Loss, and Weight Fluctuation Predict Mortality Risk in Elderly Men and Women

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ABSTRACT: Low baseline BMD, rate of BMD loss, weight loss, and weight fluctuation are significant predictors of all-cause mortality in elderly men and women, independent of each other and of age, incident fracture, and concomitant diseases.

Introduction: Although low BMD has been shown to be associated with mortality in women, the effect of BMD is affected by weight and weight change and the contribution of these factors to mortality risk, particularly in men, is not known. This study examined the association between baseline BMD, rate of bone loss, weight loss, and weight fluctuation and all-cause mortality risk in elderly men and women.
Materials and Methods: Data from 1059 women and 644 men, ≥60 years of age (as of 1989), of white background who participated in the Dubbo Osteoporosis Epidemiology Study were analyzed. All-cause mortality was recorded annually between 1989 and 2004. BMD at the femoral neck was measured by DXA (GE-LUNAR) at baseline and at approximately every 2 yr afterward. Data on incident osteoporotic fractures and concomitant diseases, including cardiovascular diseases, all types of cancer, and type I/II diabetes mellitus, was also recorded.
Results: In the multivariable Cox's proportional hazards model with adjustment for age, incident fractures, and concomitant diseases, the following variables were independent risk factors of all-cause mortality in men: rate of BMD loss of at least 1%/yr, rate of weight loss of at least 1%/yr, and weight fluctuation (defined by the CV) of at least 3%. In women, in addition to the significant factors observed in men, lower baseline BMD was also an independent risk factor of mortality. In both sexes, baseline weight was not an independent and significant predictor of mortality risk. Approximately 36% and 22% of deaths in women and men, respectively, were attributable to the four risk factors.
Conclusions: These data suggest that, although low BMD was a risk factor of mortality in women, it was not a risk factor of mortality in men. However, high rates of BMD loss, weight loss, and weight fluctuation were also independent predictors of all-cause mortality in elderly men and women, independent of age, incident fracture, and concomitant diseases.
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Key words: bone loss, BMD, weight loss, weight fluctuation, mortality, fracture

INTRODUCTION

Fracture is a serious event in an individual's life, because apart from its association with increased morbidity and health care costs, it is also associated with an increased risk of death and reduced life expectancy.[1,2] Low BMD is a primary risk factor for fracture risk.[3,4] BMD is a dynamic variable and is known to decline with advancing age, especially in the late decades of life.[5,6] Although it has been shown that either low BMD or the greater the difference between two measurements in BMD is associated with all-cause mortality[7] in women, it is not known whether the rate of BMD loss contributes to mortality risk independent of baseline BMD. Furthermore, the associations between BMD and bone loss and mortality in men have not been studied.

Body weight is strongly related to BMD, such that higher weight is associated with higher BMD[8–11] and reduced fracture risk.[12,13] Numerous studies have suggested that weight loss[14–16] and weight fluctuation[14] are associated with an increased risk of mortality. Because previous studies have examined these risk factors in isolation, it is unknown whether the effect of weight loss or weight fluctuation on mortality is independent of baseline BMD and rate of bone loss.

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Given the interrelationships between weight, BMD, and fracture, it could be hypothesized that, in addition to low BMD, the rate at which BMD loss, weight loss, and weight fluctuation are independent risk factors for mortality in the elderly. This study was designed to test the hypothesis by assessing the independent association between bone loss, weight loss, and weight fluctuation in the prediction of all-cause mortality risk in elderly men and women.

MATERIALS AND METHODS

Study design

This study was part of the on-going Dubbo Osteoporosis Epidemiology Study (DOES), in which the study design and protocol have been described elsewhere.[1,3] Briefly, DOES is a longitudinal, population-based study of risk factors for fracture and mortality. The sampling frame is the city of Dubbo, New South Wales (Australia), a locality of ~32,000 people, 98.6% white, of which 1581 men and 2095 women were ≥60 years of age in 1989. The city is relatively isolated in terms of medical care, which allows virtually complete ascertainment of all fractures and mortality to be carried out. The study protocol was approved by the St Vincent's Hospital Ethics Committee. All participants gave written inform consent.

The participants have been continuously followed-up since 1989. During the period, participants were invited to have repeated examinations every ~2 yr. The median number of visits per subjects was four. In this study, only individuals who had at least three BMD measurements were included in the analysis.

Risk factors

Ascertainment of fracture: First incident nontraumatic and nonpathological fracture was considered a risk factor in this study. Fractures occurring during the study period were identified for residents of the Dubbo local government area through radiologists' reports from the two centers providing X-ray services as previously described.[3,17] Fractures were included only if the report of fracture was definite and, on interview, had occurred with minimal trauma (e.g., fall from standing height or less). Fractures clearly caused by major trauma (such as motor vehicle accidents) or underlying diseases (such as cancer or bone-related diseases) or digit or skull fractures were excluded from the analysis.

Clinical data: Individuals were interviewed by a nurse coordinator who administered a structured questionnaire to obtain data including age, lifestyle factors such as duration of smoking and alcohol consumption, physical activity, any history of falls in the preceding 12 mo, and any history of fractures in the past. Anthropometric variables (height, weight) were measured, and a dietary assessment was performed based on a frequency questionnaire for calcium intake as described elsewhere.[18] Information of concomitant diseases, including cardiovascular diseases (CVD), all types of cancer, and type I/II diabetes mellitus was also recorded based on the participant's self-report.

BMD measurements: BMD (g/cm^2) was measured at the lumbar spine and femoral neck by DXA using a LUNAR DPX densitometer (GE-LUNAR, Madison, WI, USA). The radiation dose with this method is <0.1 μGy. The coefficient of reliability of BMD in our institution in normal subjects is 0.96 and 0.98 at the proximal femur and lumbar spine, respectively.[19] Based on the actual measurement of femoral neck BMD (FNBMD), each subject was classified as "osteoporotic" with a BMD being 2.5 SD or more below the young normal level, "osteopenic" with a BMD between 2.5 and 1.1 SD below the young normal level, or as "normal." T-scores for the FNBMD were calculated by using the Australian BMD reference range.[20]

Ascertainment of mortality: During the follow-up period between 1989 and 2004, all deaths and dates of death were recorded.

Statistical analysis

The incidence of all-cause mortality was calculated as the number of deaths per 1000 person-years for the population at risk assuming that the occurrence of death followed the Poisson distribution. The study period used in the calculation of person years was defined as the interval between the baseline and follow-up visits, or in the case of death, between baseline and the date of death.

The annual percentage change in BMD and body weight was calculated for each individual using the linear regression. Quadratic and polynomial models were also considered; however, the goodness-of-fit did not significantly improve over the linear model; therefore, the simple linear model was selected as the basis for the analysis. In this approach, a linear regression equation was fitted to each individual's data, from which the intercept and slope for the individual were obtained. The percentage of change was estimated as the ratio of slope over the intercept.

Weight fluctuation can be quantified by two measures: the CV and the residual mean square error (RMSE) that is obtained from the linear regression model of each individual. In this study, two measures are highly correlated, with the correlation coefficient being 0.93. Therefore, in this study, CV was used as a measure of weight fluctuation. This approach has been used in previous study of mortality risk.[21] Specifically, the mean and SD of weight were estimated from multiple measurements of weight, and the CV was estimated as the ratio of SD over the mean. In preliminary analysis, the SD of weight fluctuation was ~3%; therefore, this value was used as a cut-off value to nominally define the stability of weight.

Cox's proportional hazards regression model was used to estimate relative hazard and 95% CI for each SD or unit change or in specified groups compared with reference group with categorized risk factors. The outcomes in this model were mortality incidence and time to death. The statistical significance of parameter estimates derived from the Cox's proportional hazards model was tested with the likelihood ratio statistics.[22,23] The assumptions of the proportional hazards model for the levels of each risk factor was checked by evaluating the linearity of plots of $\log\{-\log[S(t_i)_j]\}$, where $S(t_i)_j$ describes the jth survival time for the ith level ($i = 1, 2$) for each risk factor.

In a further analysis, baseline BMD, rate of bone loss,

TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS

Variables	*Alive*	*Deceased*	*Diff.*	*(95% CI)*	*p*
Men					
Age (yr)	67.8 ± 5.1	72.2 ± 6.3	−4.3	(−5.2, −3.4)	0.0000
Weight (kg)	79.1 ± 12.1	77.9 ± 12.6	1.2	(−0.7, 3.2)	0.2239
Weight loss (%/yr)	0.27 ± 2.68	−0.60 ± 1.65	0.87	(0.50, 1.24)	0.0000
Weight fluctuation (%)	3.47 ± 2.36	4.20 ± 3.08	−0.74	(−1.16, −0.31)	0.0007
Height (cm)	173.9 ± 6.6	173.0 ± 6.5	0.9	(−0.2, 1.9)	0.1024
BMI (kg/m^2)	26 ± 4	26 ± 4	0.2	(−0.4, 0.7)	0.5710
FNBMD (g/cm^2)	0.94 ± 0.14	0.90 ± 0.15	0.03	(0.01, 0.06)	0.0033
Rate of BMD loss (%/yr)	−0.38 ± 1.15	−0.73 ± 1.96	0.35	(0.11, 0.59)	0.0045
Current/ex-smoking (yes)*	221 (56.7)	177 (69.7)			0.0010
Any fracture (yes)*†	48 (12.3)	60 (23.6)			0.0000
CVD (yes)*‡	118 (30.3)	84 (33.1)			0.4520
All types of cancer (yes)*	47 (12.1)	30 (11.8)			0.9270
Diabetes (type I and II) (yes)*	37 (9.5)	30 (11.8)			0.3540
Women					
Age (yr)	68.4 ± 5.8	73.9 ± 7.3	−5.5	(−6.3, −4.7)	0.0000
Weight (kg)	66.4 ± 12.1	63.2 ± 12.6	3.2	(1.6, 4.9)	0.0001
Weight loss (%/yr)	0.22 ± 1.61	−0.58 ± 2.10	0.80	(0.56, 1.04)	0.0000
Weight fluctuation (%)	4.18 ± 2.71	5.09 ± 3.70	−0.91	(−1.32, −0.50)	0.0000
Height (cm)	160.6 ± 6.0	159.1 ± 6.5	1.4	(0.6, 2.3)	0.0007
BMI (kg/m^2)	26 ± 5	25 ± 5	0.8	(0.1, 1.4)	0.0153
FNBMD (g/cm^2)	0.80 ± 0.12	0.74 ± 0.14	0.06	(0.04, 0.08)	0.0000
Rate of BMD loss (%/yr)	−0.54 ± 1.23	−0.93 ± 2.63	0.40	(0.17, 0.63)	0.0008
Current/ex-smoking (yes)*	223 (29.1)	88 (30.0)			0.7880
Any fracture (yes)*†	222 (29.0)	111 (37.0)			0.0050
CVD (yes)*‡	153 (20.0)	109 (37.0)			0.0000
All types of cancer (yes)*	78 (10.2)	32 (10.9)			0.7240
Diabetes (type I and II) (yes)*	51 (6.7)	26 (8.9)			0.2140

Values are mean ± SD, unpaired-*t*-test, unless otherwise specified.

* *n* (%), χ^2 test.

† Any fracture, any first incident fracture.

‡ CVD, cardiovascular diseases, including congestive heart failure, ischemic heart disease, myocardial infarction, chronic atrial fibrillation, pulmonary edema.

weight loss, weight fluctuation, age, lifestyle, and concomitant diseases were simultaneously considered in a multivariable Cox's proportional hazards model. Collinearity was also studied using previously published methods.[24] The plots of martingale residuals against covariates were used to detect nonlinearity.[25–27] Continuous variables included in the final multivariable model were categorized if their effects on the hazard function were nonlinear. The Akaike information criterion (AIC) was used to select the best fit model. Because each hazard ratio is subjected to sampling variability (as represented by the CI), it was also of interest to estimate the posterior probability that an association with a hazard ratio at a cut-point for defining "effect." In this study, the cut-point was selected as 1.2. To quantify the contribution of the risk factors, the partial population attributable risk (PAR_p) was estimated for each of the significant risk factors. All statistical analyses were performed with SAS and the R statistical environment.[28,29]

RESULTS

In total, 1059 women and 644 men 70 ± 6 (SD) yr of age as of 1989 have been followed for the median duration of 13 yr (interquartile range: 9–14 yr), yielding a total of 7168 person-years in men and 12,457 person-years in women. The median (interquartile range) of the number of measurements in BMD and body weight was 4 (3–5) in both sexes. During the follow-up period, 254 men and 293 women died, giving an incidence rate of 35.4 (95% CI, 25.5–49.2) per 1000 person-years for men and 20.4 (95% CI, 15.8–35.2) for women.

Overall, survivors were on average younger, heavier, and had lower baseline BMD, lower rate of bone loss, lower rate of weight loss, and lower weight fluctuation than deceased individuals in both sexes, except for men, where there was no difference in body weight between survivors and deceased individuals. In men, compared with the deceased, survivors had a significantly lower prevalence of ever smoking and lower incidence of fracture (23.6% versus 12.3%, $p = 0.0002$); however, no significant differences in the prevalence of concomitant diseases between survivors and deceased were observed. In women, survivors had a lower incidence of fractures and lower prevalence of cardiovascular disease than the deceased (Table 1).

Bivariate analysis

Results of unadjusted analysis and age-adjusted analysis of risk factor for all-cause mortality results are shown in Table 2. As expected, advancing age and low femoral neck

TABLE 2. HAZARD RATIO OF BONE LOSS, WEIGHT LOSS, WEIGHT FLUCTUATION, AND OTHER FACTORS FOR ALL-CAUSE MORTALITY RISK BY BIVARIATE ANALYSIS

Variables	Unit of comparison	Unadjusted		Age-adjusted	
		HR	(95% CI)	HR	(95% CI)
Men					
Age	+5 yr	**1.7**	**(1.6, 1.9)**		
Weight	–10 kg	**1.1**	**(1.0, 1.2)**	**1.1**	**(1.0, 1.2)**
Weight loss	+2%/yr	**2.0**	**(1.7, 2.4)**	**1.7**	**(1.4, 2.0)**
Weight fluctuation	+3%	**1.2**	**(1.1, 1.4)**	**1.2**	**(1.1, 1.4)**
Height	–5 cm	**1.1**	**(1.0, 1.2)**	**1.1**	**(1.0, 1.2)**
BMI	–5 kg/m^2	1.0	(0.9, 1.2)	0.8	(0.7, 1.0)
Baseline FNBMD	–0.12 g/cm^2	**1.2**	**(1.1, 1.4)**	1.1	(0.9, 1.2)
Bone loss	+5%/yr	**2.5**	**(1.6, 3.9)**	**1.6**	**(1.1, 2.5)**
Ever smoking*	Yes	**1.6**	**(1.2, 2.1)**	**1.6**	**(1.2, 2.1)**
Any fracture†	Yes	**1.9**	**(1.4, 2.5)**	**1.3**	**(1.0, 1.8)**
CVD‡	Yes	1.1	(0.9, 1.5)	1.1	(0.8, 1.4)
All types of cancer	Yes	0.9	(0.6, 1.4)	1.0	(0.7, 1.5)
Diabetes (type I and II)	Yes	1.2	(0.8, 1.7)	1.3	(0.9, 1.9)
Women					
Age	+5 yr	**1.8**	**(1.7, 2.0)**		
Weight	–10 kg	**1.2**	**(1.1, 1.4)**	**1.1**	**(1.0, 1.2)**
Weight loss	+2%/yr	**1.4**	**(1.3, 1.5)**	**1.3**	**(1.2, 1.5)**
Weight fluctuation	+3%	**1.2**	**(1.1, 1.4)**	**1.2**	**(1.1, 1.3)**
Height	–5 cm	**1.3**	**(1.1, 1.4)**	**1.1**	**(1.0, 1.2)**
BMI	–5 kg/m^2	**1.1**	**(1.0, 1.3)**	1.0	(0.9, 1.1)
Baseline FNBMD	–0.12 g/cm^2	**1.5**	**(1.4, 1.7)**	**1.3**	**(1.1, 1.4)**
Bone loss	+5%/yr	**2.3**	**(1.7, 3.2)**	**1.8**	**(1.2, 2.5)**
Ever smoking*	Yes	1.1	(0.8, 1.4)	**1.3**	**(1.0, 1.7)**
Any fracture†	Yes	**1.4**	**(1.1, 1.8)**	**1.4**	**(1.1, 1.8)**
CVD‡	Yes	**2.0**	**(1.6, 2.6)**	**1.5**	**(1.2, 2.0)**
All types of cancer	Yes	1.2	(0.8, 1.4)	1.1	(0.8, 1.6)
Diabetes (type I and II)	Yes	1.4	(0.9, 2.1)	**1.7**	**(1.1, 2.6)**

Bold numbers represent statistical significance at $p < 0.05$ level.

* Ever smoking, current, or ex-smoking vs. nonsmoking.

† Any fracture, any first incident fracture.

‡ CVD, cardiovascular diseases, including congestive heart failure, ischemic heart disease, myocardial infarction, chronic atrial fibrillation, and pulmonary edema.

BMD were each significantly associated with all-cause mortality risk for both sexes. The magnitude of association was similar for women and men. Each 5-year increase in age was associated with a hazard ratio (HR) of 1.7 and 1.8 increase in the hazard (risk) of death for men and women, respectively.

After adjusting for age, lower baseline BMD was associated with increased risk of mortality in women (HR per SD: 1.3; 95% CI: 1.0–1.7), but not in men (HR 1.1; 95% CI: 0.9–1.2). Each 5%/yr increase in BMD loss was associated with a 1.6-fold (95% CI: 1.1–2.5) increase in the hazard of death in men, which was comparable with that in women (HR: 1.8, 95% CI: 1.2–2.5). Lower body weight, excessive weight loss, and weight fluctuation were each associated with increased risk of all-cause mortality (after adjusting for age) with an average HR ranging between 1.1 and 1.7.

Men and women with osteoporotic BMD (i.e., T-scores ≤ -2.5) had a significantly reduced survival probability compared with men and women with either osteopenic or normal BMD (Figs. 1A and 1B). Furthermore, men and women whose BMD loss was ≥1%/yr also had reduced survival probability compared with those with rate of bone loss <0.5%/yr (Figs. 1C and 1D).

Individuals with a weight loss of 1%/yr or higher had a reduced survival probability compared with those with less weight loss (Figs. 2A and 2B). In addition, weight fluctuation of 3% or more was also associated with an increased risk of mortality in both sexes (Figs. 2C and 2D).

Multivariable analysis

In a further analysis, all risk factors, including baseline FNBMD, rate of FNBMD loss, weight change, and weight fluctuation were simultaneously considered in the multivariable Cox's proportional hazards model, with age, smoking status, and concomitant diseases (including incident fracture, cardiovascular diseases, all type of cancers, and type I and II diabetes mellitus) being covariates. Analysis of martingale residuals showed that the effects of baseline BMD, rate of bone loss, weight loss, and weight fluctuation on the hazard function were nonlinear (data not shown); therefore, these variables were categorized and reanalyzed. In both sexes, the nonlinear model exhibited a better fit than the linear model.

In men with rate of BMD loss of 1% of higher, weight loss of 1% or higher, and high weight fluctuation (≥3%)

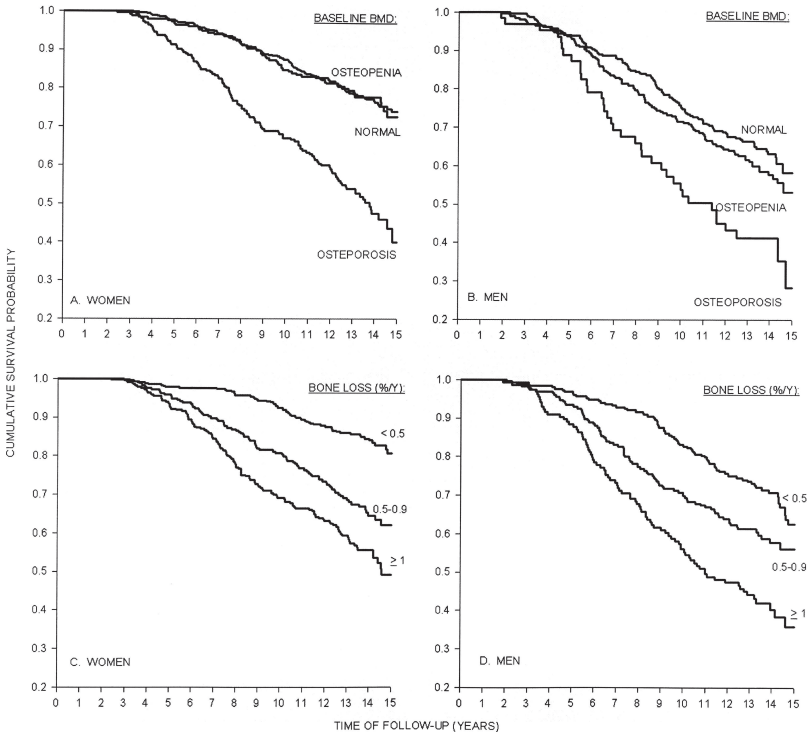

FIG. 1. Cumulative survival probability stratified by baseline BMD, osteoporosis, T-scores ≤ –2.5; osteopenia, T-scores –2.4 to –1.1; and normal, T-scores ≥ –1.0 (A for women and B for men), and by BMD change (%/yr) category, <0.5, 0.5–0.9, and ≥1.0 (C for women and D for men).

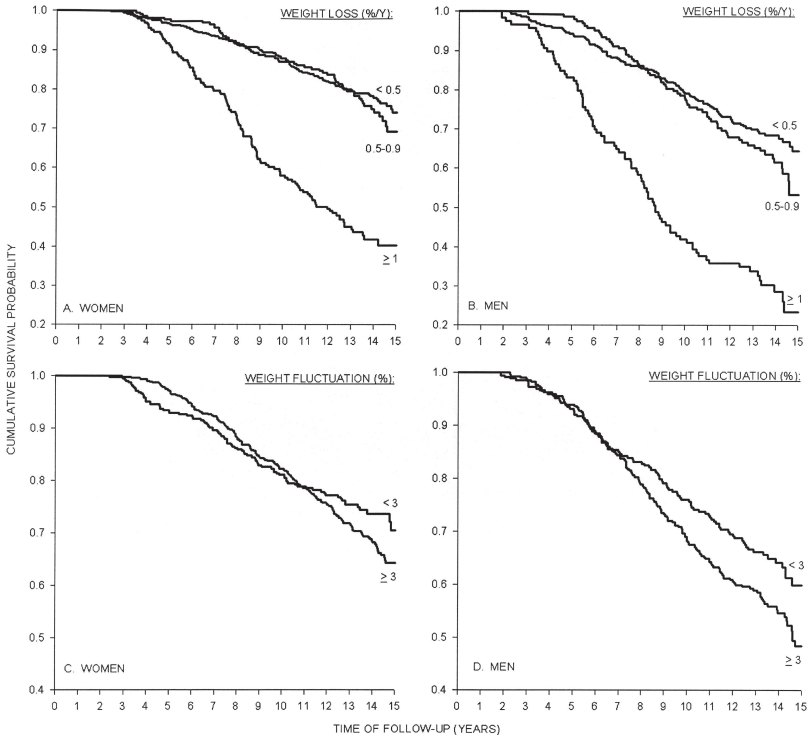

FIG. 2. Cumulative survival probability stratified by weight loss (%/yr) category, <0.5, 0.5–0.9, and ≥1.0 (A for women and B for men), and by weight fluctuation (%), <3% and ≥3% (C for women and D for men).

were independent predictors of all-cause mortality. However, baseline BMD was not a significant risk factor of mortality (Table 3). The magnitude of effect of weight loss on mortality was more pronounced than either weight fluctuation or bone loss. The probability that HR of mortality associated with weight loss (of at least 1%/yr) being >1.2 was 100%.

In women, all four factors (e.g., low baseline BMD, high rate of BMD loss, weight loss, and weight fluctuation) were independently and significantly associated with a greater risk of all-cause mortality. As observed in men, there was a 100% probability that weight loss (of at least 1%/yr) increased the hazard of mortality by at least 1.2.

The partial population attributable risk analysis (Table 4)

Table 3. Independent Risk Factors for All-Cause Mortality (Multivariable Cox's Proportional Hazards Model)

	HR	*(95% CI)*	*Probability that HR ≥ 1.2*
Men			
Baseline FNBMD			
Normal	1.0		
Osteopenia	0.9	(0.7, 1.2)	0.02
Osteoporosis	1.2	(0.8, 1.8)	0.57
Rate of bone loss			
<0.5%/yr	1.0		
0.5–0.9%	0.8	(0.5, 1.1)	0.01
≥1%	**1.3**	**(1.0, 1.7)**	0.66
Rate of weight loss			
<0.5%/yr	1.0		
0.5–1%	1.3	(0.9, 2.0)	0.72
≥1%	**2.6**	**(1.9, 3.7)**	1.00
Weight fluctuation			
<3%	1.0		
≥3%	**1.5**	**(1.1, 2.0)**	0.91
Women			
Baseline FNBMD			
Normal	1.0		
Osteopenia	0.8	(0.5, 1.1)	0.00
Osteoporosis	**1.5**	**(1.0, 2.1)**	0.86
Rate of bone loss			
<0.5%/yr	1.0		
0.5–0.9%	0.9	(0.6, 1.3)	0.05
≥1%	**1.3**	**(1.0, 1.7)**	0.70
Rate of weight loss			
<0.5%/yr	1.0		
0.5–1%	1.2	(0.8, 1.7)	0.45
≥1%	**2.2**	**(1.7, 2.9)**	1.00
Weight fluctuation			
<3%	1.0		
≥3%	**1.3**	**(1.0, 1.7)**	0.66

Variables included in the multivariable model were baseline BMD, rate of bone loss, rate of weight loss, weight fluctuation, age, smoking status, and concomitant diseases (i.e., incident fracture, cardiovascular diseases, all type of cancers, and type I/II diabetes mellitus).

Posterior probability of HR ≥ 1.2 was computed from the Bayesian analysis, in which the prior information was given a uniform distribution (i.e., nonuniformed prior).

Bold numbers represent statistical significance at the $p > 0.05$ level.

Table 4. Partial Population Attributable Risk Fraction (PAR_p) of Risk Factors for All-Cause Mortality

	PAR_p (%)	*(95% CI)*
Men		
Osteoporotic BMD (T-scores ≤ –2.5)	2.5	(–0.5, 5.5)
Rate of bone loss (>1%/yr)	6.5	(1.1, 12.0)
Rate of weight loss (>1%/yr)	11.6	(0.5, 17.9)
Weight fluctuation (>3%)	1.4	(0.0, 5.1)
Total	22.0	
Women		
Osteoporotic BMD (T-scores ≤ –2.5)	11.1	(5.6, 16.7)
Rate of bone loss (>1%/yr)	10.5	(4.4, 16.7)
Rate of weight loss (>1%/yr)	10.9	(5.2, 16.5)
Weight fluctuation (>3%)	3.4	(0.0, 7.8)
Total	35.9	

Partial population attributable risks were computed under the condition of multiple risk exposures with adjustment for age and concomitant diseases, including any osteoporotic fracture, cardiovascular disease, all-cause cancer, diabetes mellitus, and smoking.

showed that ~36% and 22% of deaths in women and men, respectively, was attributed to osteoporosis, rate of bone loss, weight loss, and weight fluctuation. In women, the attributable risks caused by osteoporosis, bone loss, and weight loss were comparable, with estimates being around 11%. However, in men, most of the attributable risk was caused by weight loss (11.6%). Despite the fact that bone loss in men conferred a comparable HR to women, there were fewer men with this risk factor than women (26% versus 33%), yielding lower attributable risk.

DISCUSSION

Weight and BMD are known to be correlated.[8–11] Furthermore, weight loss and BMD loss are also correlated.[30] Each of the measures has been shown to be associated with mortality risk,[7,14–16] but no previous studies have simultaneously examined their independent effects on mortality risk. By analyzing all of the risk factors together, this study showed for the first time that low baseline BMD, high rate of BMD loss, high rate of weight loss, and weight fluctuation independently and additively contributed to the increased risk of mortality in women. Furthermore, this study showed that in men, low baseline BMD was not an independent risk factor of mortality, but high rate of BMD loss, high rate of weight loss, and weight fluctuation were independently associated with increased risk of all-cause mortality.

Although BMD measurements were measured at different sites, the strength of association between baseline BMD and mortality in women in this study was comparable with an earlier report,[31] in which each SD lower in baseline BMD was associated with an ~30% increase in all-caused mortality rate. The magnitude of the association between baseline BMD and all-cause mortality risk in this study was slightly lower than in a previous study,[7] perhaps because this study adjusted for weight change and weight fluctuation.

Loss of BMD is observed in most elderly women and men, with women having a greater rate of loss than men.[5,32] Interestingly, rapid BMD loss was found to be an independent predictor for the all-cause mortality risk in both men and women after adjustment for baseline BMD and other risk factors, as well as concomitant diseases. The strength of association between BMD loss and mortality in men and women is highly comparable, such that mortality risk among those with a rate of bone loss being 1%/yr or above increased by 1.3-fold compared with those with a rate of BMD loss <0.5%/yr. The attributable risk analysis showed that loss of BMD was a major risk factor of death (with partial attributable risk fraction of 10.5% in women and 6.5% in men). If the association between BMD loss and mortality is causal, this finding suggests that anti-osteoporosis intervention not just reduces fracture risk (which has been found in most clinical trials), but can also reduce mortality risk.

It is noted that weight loss in the elderly is often associated with ill health,[33] and it is possible that changes in bone and weight are indications of serious or advanced ill health likely to lead increased mortality. Several studies have shown that weight loss[33–35] and weight fluctuation[14,21,36,37] were associated with increased mortality in older people. One potential complicated issue of the association between weight loss and mortality is the problem of intentional weight loss. Although this study could not separate intentional from unintentional weight loss, unintentional weight loss is common in the elderly[38] and may be a marker for frailty.[39] In this study, the attributable risk analysis showed that the contribution of weight loss to the mortality in community was comparable or higher to bone loss in women and men. Therefore, prevention for weight loss could be also beneficial in terms of reducing mortality risk in the elderly.

The weight loss–mortality association could also be mediated by sarcopenia that has been suggested as an independent risk factor for mortality in the elderly.[40] Sarcopenia is indirectly estimated from BMI[40,41] and defined as a reduction of 2 SD below the sex-specific means of the reference data for the young adults.[41] In this study, it was not possible to estimate the prevalence of sarcopenia because of the lack of a reference database. However, in this population BMI was not significantly associated with mortality risk in both sexes after adjustment for age.

The weight fluctuation–mortality association found in this study is consistent with previous findings.[21,37,42,43] It was further shown in this study that the association was independent of baseline BMD, bone loss, weight loss, concomitant diseases, and smoking status, albeit with the modest contribution in terms of population attributable risk. The association can be partially explained by confounding factors and the presence of pre-existing disease[14,44] or by the disadvantageous lifestyle factors.[14]

It is not possible in this epidemiology study to dissect the underlying mechanism of the excess of mortality associated with changes in BMD and with weight loss and weight fluctuation; however, the effects of lifestyle factors and other concomitant diseases cannot be ruled out. Indeed, male smokers tended to have higher risk of all-cause mortality (HR = 1.4; 95% CI, 1.0–1.6), and there was a similar trend in women but not significantly so. CVD and diabetes (type I and II) were significant associated with mortality risk in women with hazard ratios of 1.4 (95% CI: 1.1–1.8) and 1.7 (95% CI: 1.1–2.6), respectively. However, in this study, there was no significant association between bone change and weight change with concomitant diseases, such as CVD, cancer, and diabetes. However, weight fluctuation was associated with CVD in which women who had higher weight fluctuation were more likely to suffer of CVD (data not shown). Nevertheless, as previously mentioned, the effects of bone change and weight change on all-cause mortality risk, was independent of concomitant diseases, including CVD.

The study was conducted in a stable population, which enabled the recording of deaths and risk factor to be completely ascertained. The large sample size and prospective design increase the chance to detect small differences, which not be detected in case-control studies. More importantly, in this study, BMD and its change, weight, and weight changes, including fluctuations, were measured more frequently than in previous studies, which enabled the delineation of association to be more accurately estimated. However, this study should be interpreted within the context of several limitations. The population is of a white background; therefore, extrapolation to other populations should be made with caution. Selection bias was likely to be present in this study, in that participants were healthier than nonparticipants. For instance, although the relative distribution of subjects with respect to age in the sample was comparable with that in the target population,[3] the mortality rate in the DOES sample was lower than in the general population,[1] which might reflect the bias toward healthy subjects in the study. Therefore, these results may underestimate, rather than overestimate, the effects of BMD and weight change on mortality. As mentioned above, the causes of death in this study were not defined; therefore, it is not possible to make inference regarding the causal link between BMD and weight change and mortality.

In conclusion, these data suggest that lower BMD was an independent predictor of mortality in women but not in men. Furthermore, in addition to low baseline BMD, rate of BMD loss and weight fluctuation were also significant predictors of all-cause mortality in elderly men and women, independent from age and concomitant diseases. Although the risk factors found to be associated with mortality in this study probably reflect the underlying frailty or the presence of other wasting diseases in the elderly, these findings partly re-emphasize the public health burden of osteoporosis in the general population. Reducing bone loss, weight loss, and maintaining stable weight may have beneficial effects on the survival of elderly individuals.

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