Femoral bone mineral density and mortality risk in postmenopausal women: a National Health and Nutrition Examination Survey cohort study

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Abstract

Objective: Osteoporosis is highly prevalent among postmenopausal women. While previous studies have primarily focused on the relationship between bone mineral density (BMD) and fracture risk, the prognostic value of BMD with regard to mortality remains unclear.

Methods: A total of 2,977 postmenopausal women from the National Health and Nutrition Examination Survey (2005-2018) were included in this study. BMD at four femoral sites was assessed using dual-energy x-ray absorptiometry. The associations between BMD, osteoporotic fractures, and mortality were evaluated using Kaplan-Meier curves, receiver operating characteristic analysis, and multivariate Cox regression. Restricted cubic splines were applied to explore nonlinear relationships, and subgroup analyses were performed to evaluate the robustness of the results.

Results: Kaplan-Meier analysis revealed that mortality risk was significantly elevated when femoral BMD reached the osteoporotic threshold or in the presence of osteoporotic fractures ($P < 0.001$). Receiver operating characteristic curve analysis showed that the area under the curve for BMD at all femoral sites was greater than that for body mass index (area under the curve = 0.591). After full adjustment, osteoporosis was associated with a 47% increased risk of mortality (hazard ratio = 1.47, 95% CI: 1.16-1.86). Site-specific BMD was inversely correlated with mortality risk (all $P < 0.001$). The restricted cubic splines plots demonstrated a stronger inverse association between increased BMD and mortality risk within specific ranges: 0.46-0.71 g/cm² for total femur BMD and 0.33-0.54 g/cm² for trochanter BMD.

Conclusions: Femoral BMD and osteoporosis are independent predictors of all-cause mortality in postmenopausal women. The inverse relationship between BMD and mortality risk is more pronounced within specific BMD ranges, which may provide valuable insights for mortality risk stratification and clinical decision-making in this population.

Key Words: Bone mineral density, Mortality, National Health and Nutrition Examination Survey, Osteoporosis, Postmenopausal women.

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The studies involving human participants were reviewed and approved by the National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study. All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki).

Publicly available data sets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes

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As the global population ages, health issues among postmenopausal women have become increasingly prominent, particularly the high incidence of osteoporosis, which has garnered significant attention. According to a systematic review and meta-analysis published in 2022, the global prevalence of osteoporosis is 19.7%, with women exhibiting a significantly higher prevalence than men (23.1%).[1] A study projected that by 2030, the number of individuals affected by osteoporosis worldwide will reach 263 million, with 154 million of them being women.[2] It has been reported that postmenopausal women experience a significantly higher mortality rate within one year following hip or vertebral fractures compared with the general population,[3] which not only increases the risk of death but also leads to considerable functional impairment and a reduced quality of life.[4,5] Osteoporosis has thus emerged as a critical public health burden that warrants urgent attention on a global scale.

Menopause is a critical milestone in the maturation process of women, marking the gradual decline of ovarian function and a sharp reduction in estrogen levels. This change not only affects the reproductive system but also triggers physiological alterations across multiple systems, including bone metabolism, cardiovascular function, muscle mass, and fat distribution.[6–8] Estrogen plays a crucial regulatory role in female bone metabolism; its deficiency accelerates bone resorption and inhibits bone formation, leading to a rapid decrease in bone mineral density (BMD),[9] which in turn increases the risk of osteoporosis and fractures.[10] According to a systematic review and meta-analysis from Morocco, the prevalence of osteoporosis among postmenopausal women is 32%.[11] Numerous studies have confirmed that low bone density in the femoral region significantly increases the risk of fractures,[12] and fractures occurring in the femoral region are associated with a higher risk of mortality.[13] Some research has also indicated that individuals with low BMD exhibit a higher all-cause mortality rate,[14] suggesting that bone density may not only serve as an indicator of bone health but also impact overall systemic health. However, most existing research focuses on the relationship between low BMD and adverse outcomes,[15] with a lack of systematic studies examining whether increasing bone density in postmenopausal women can reduce the risk of death. We hypothesize that higher bone density may reflect better nutritional status, a healthy weight, and a more active lifestyle,[16] potentially correlating with a lower risk of mortality.

This study is based on the National Health and Nutrition Examination Survey (NHANES) database, which offers strong representation and comprehensive data across multiple dimensions. It focuses on postmenopausal women to investigate the potential association between BMD levels and mortality risk. This research provides a theoretical foundation for the clinical application of BMD as a predictive indicator of health and offers potential guidance for interventions in the health management of postmenopausal women.

METHODS

Data sources and study population

NHANES is a deinstitutionalized two-year survey conducted by the Centers for Disease Control and Prevention to assess the health and dietary status of the US population. The survey employs a multistage probability sampling design and collects data through face-to-face interviews, physical examinations, questionnaires, and laboratory tests. Participants are required to sign an institutional informed consent form during both the interview and examination phases. All procedures are standardized according to the US Department of Health and Human Services Human Research Protection Policy and reviewed by the National Center for Health Statistics Institutional Review Board. For detailed information on the NHANES survey methodology and data sources, please visit the website.[17]

Mortality data were obtained from the official website of the Centers for Disease Control and Prevention and linked to the NHANES database using a unique subject identifier. Mortality information is current through December 31, 2019.[18] Causes of death were defined according to the International Classification of Diseases, 10th Revision coding system.

This study employed a cross-sectional analysis using data from the 2005-2018 NHANES survey cycles. The 2011-2012 and 2015-2016 cycles were excluded due to a lack of testing data. The analysis was based on responses to relevant questionnaires and laboratory test results. A total of 50,463 participants were included across the entire survey period. Participants in this study were required to meet the following inclusion and exclusion criteria: (1) female sex, (2) well-documented causes of menopause, (3) complete BMD data, (4) complete survival data, (5) no missing data for failing kidneys, cancer, heart failure, stroke, liver disease, and diabetes, and (6) complete data on bilateral oophorectomy and hormone history. A total of 2,977 participants were included in the final analysis (Fig. 1).

Bone mineral density measurement, osteoporosis definition, and osteoporotic fractures definition

BMD measurements were performed using dual-energy x-ray absorptiometry (DXA) with the Hologic QDR-4500A fan-beam densitometer (Hologic, Inc.). According to the classification standards set by the World Health Organization, osteoporosis is defined as a BMD value lower than −2.5 SDs from the young adult reference group for any femoral region.[19] The femoral regions assessed in this study included the total femur, femoral neck, trochanter, and intertrochanteric region, with corresponding osteoporosis thresholds of 0.68 g/cm², 0.59 g/cm², 0.49 g/cm², and 0.78 g/cm², respectively.[20] To assess self-reported osteoporotic fractures, participants were asked, “Has a doctor ever told you that you had a hip/wrist/spine fracture?” Those who answered “yes” were considered positive for osteoporotic fractures.[21]

Covariates

Continuous covariates included age, body mass index (BMI), Healthy Eating Index 2020 (HEI-2020), and Charlson Comorbidity Index (CCI). In subgroup analyses, age was categorized as a dichotomous variable ($<65/\geq 65$). Race, education level (under high school/high school graduate/college degree or above), poverty-

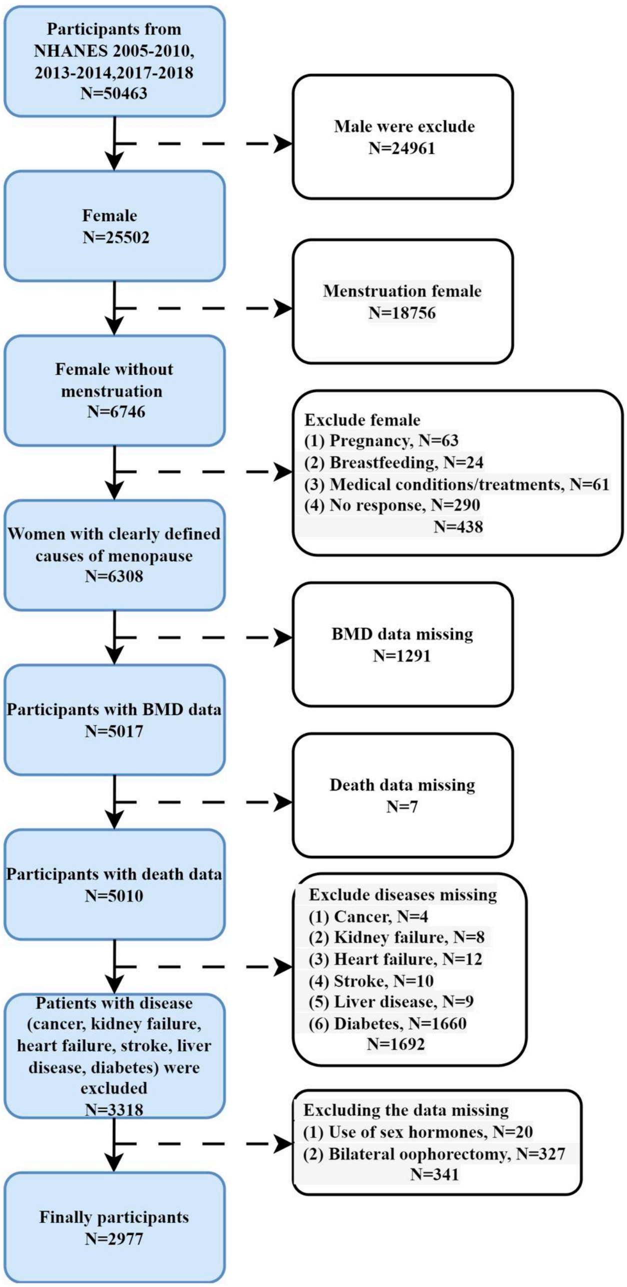

FIG. 1. The flowchart of participant selection. Exclusions at the same step were performed simultaneously. A single sample might meet multiple exclusion criteria or have missing data for multiple variables, thus the summarized value represents the final number of uniquely excluded samples at this step. BMD, bone mineral density; NHANES, National Health and Nutrition Examination Survey.

to-income ratio (PIR; not poor/poor), marital status (unmarried/married), smoking status, alcohol use, physical activity, depression, bilateral oophorectomy (no/yes), and hormone history (no/yes) were treated as categorical variables.

Race was self-reported by study participants based on fixed-category responses, including non-Hispanic White, non-Hispanic Black, Mexican American (self-identified, per NHANES data), other Hispanic, and other race (other race was not further defined). Smoking status was assessed as never smoked (smoked <100 cigarettes), former smoker (currently not smoking but smoked ≥ 100 cigarettes), or current smoker (smoked ≥ 100 cigarettes and currently smoking every day or some days). Alcohol use was categorized according to self-reported drinking data (non-drinker, 1-5 drinks/mo, 5-10 drinks/mo, 10+ drinks/mo). Physical activity levels (inactive, moderate, vigorous, or both moderate and vigorous) were evaluated based on participant-reported engagement in vigorous physical activity (high-intensity activities such as running or basketball) and moderate physical activity (eg, brisk walking, swimming, or regular cycling). Depression scores were calculated using the self-reported Patient Health Questionnaire-9 items (PHQ-9) scale and categorized as none, mild, moderate, severe, or extreme. The HEI-2020, established by the United States Department of Agriculture (USDA) and National Cancer Institute (NCI), is a metric used to assess diet quality in accordance with the Dietary Guidelines for Americans.[22,23] This study utilized 28 parameters from the NHANES data to compute this index using the dietaryindex R package.[24] The NHANES variables used to calculate the CCI score included chronic pulmonary disease (MCQ160K), heart failure (MCQ160B), stroke (MCQ160F), diabetes mellitus (DIQ010), diabetic retinopathy (DIQ080), hepatitis B (LBDHBG), hepatitis C (LBDHCV), kidney failure (KIQ022), kidney stones (KIQ026), and cancer (MCQ220, MCQ230A, MCQ230B, MCQ230C, MCQ230D).[25]

Missing data were imputed using the missForest R package, a random forest-based technique that is highly computationally efficient for high-dimensional data with both categorical and continuous predictors.[26]

Statistical analysis

This study presents the baseline characteristics of participants stratified by osteoporosis status. Categorical variables are reported as frequencies and percentages, while continuous variables are expressed as means with SDs. Between-group comparisons were conducted using χ^2 tests for categorical variables and one-way ANOVA for continuous variables. Post hoc pairwise comparisons were performed using Tukey test when ANOVA results were significant.

The Kaplan-Meier curves were first used to visualize the potential association between approaching osteoporotic threshold levels of femoral BMD and osteoporotic fractures with mortality risk in postmenopausal women. Subsequently, receiver operating characteristic (ROC) curves were generated to assess the predictive performance of femoral BMD at four anatomic subregions (total femur, femoral neck, trochanter, intertrochanter) compared with BMI for mortality risk assessment. Cox proportional hazards models were then employed to investigate the associations between BMD, osteoporosis, osteoporotic fractures, and mortality, using three progressively adjusted models: model 1 adjusted for age and race; model 2, in addition, adjusted for education level,

TABLE 1. Clinical characteristics of the study population

Variables	Osteoporosis			P
	Overall (n = 2,977)	No (n = 2,459)	Yes (n = 518)	
Age (y)	63.79 (10.03)	62.53 (9.73)	69.92 (9.15)	**< 0.001**
Race (%)				**< 0.001**
Non-Hispanic White	71.45	69.85	79.21	
Non-Hispanic Black	11.48	12.76	5.24	
Mexican American[a]	5.68	6.11	3.59	
Other Hispanic	4.91	5.01	4.46	
Other race[b]	6.49	6.28	7.50	
Educational level (%)				**0.038**
Under high school	6.48	5.98	8.89	
Completed high school	11.68	11.23	13.88	
College degree or above	81.84	82.79	77.24	
PIR level (%)				0.403
Not poor	90.30	90.52	89.20	
Poor	9.70	9.48	10.80	
Marital status (%)				**< 0.001**
Unmarried	42.87	40.69	53.41	
Married	57.13	59.31	46.59	
Smoking status (%)				0.181
Never	57.91	57.88	58.03	
Former	27.05	27.75	23.62	
Current	15.04	14.36	18.35	
Alcohol use (%)				**0.024**
Non-drinker	40.36	38.62	48.82	
1-5 drinks/mo	46.06	47.17	40.68	
5-10 drinks/mo	3.44	3.87	1.34	
10+ drinks/mo	10.14	10.34	9.17	
BMI (kg/m^2)	29.75 (6.32)	30.49 (6.25)	26.18 (5.39)	**< 0.001**
Physical activity (%)				0.246
Inactive	61.18	60.00	66.87	
Moderate	27.70	28.56	23.54	
Vigorous	2.14	2.33	1.25	
Both moderate and vigorous	8.98	9.12	8.35	
HEI-2020	54.54 (11.31)	54.39 (11.38)	55.26 (10.95)	0.331
CCI	1.09 (1.27)	1.04 (1.21)	1.30 (1.47)	**0.010**
Depression (%)				**0.018**
None	72.02	72.78	68.33	
Mild	18.96	18.44	21.46	
Moderate	5.65	5.75	5.19	
Severe	2.29	2.29	2.29	
Extreme	1.08	0.74	2.73	
Total femur BMD (g/cm^2)	0.87 (0.14)	0.91 (0.12)	0.67 (0.07)	**< 0.001**
Femoral neck BMD (g/cm^2)	0.73 (0.14)	0.77 (0.12)	0.55 (0.08)	**< 0.001**
Trochanter BMD (g/cm^2)	0.65 (0.12)	0.68 (0.10)	0.51 (0.08)	**< 0.001**
Intertrochanter BMD (g/cm^2)	1.03 (0.18)	1.08 (0.15)	0.81 (0.11)	**< 0.001**
Osteoporotic fractures (%)				**< 0.001**
No	85.66	87.50	76.73	
Yes	14.34	12.50	23.27	
Bilateral oophorectomy (%)				0.807
No	72.67	72.81	71.99	
Yes	27.33	27.19	28.01	
Hormone history (%)				**0.049**
No	58.44	57.25	64.18	
Yes	41.56	42.75	35.82	
Mortality status (%)				**< 0.001**
Alive	86.12	88.97	72.32	
Dead	13.88	11.03	27.68	

BMD, bone mineral density; BMI, body mass index; CCI, Charlson Comorbidity Index; HEI-2020, Healthy Eating Index-2020; NHANES, National Health and Nutrition Examination Survey; PIR, poverty-to-income ratio.

Bold values are statistically significant $P < 0.05$.

Number (n) matches the actual number of cases sampled, and all other analyses are weighted. Data were mean (SD) for continuous variables or proportions for categorical variables.

[a]Mexican American is a self-identified race/ethnicity category in the NHANES data.

[b]"Other" race was not further defined.

PIR, marital status, smoking status, alcohol use, physical activity, BMI, and HEI-2020; model 3 further adjusted for CCI, depression, bilateral oophorectomy, and hormone history. Potential nonlinear relationships between site-specific BMD and mortality were examined using restricted cubic splines (RCS) with four knots. Subgroup interaction analyses were performed to assess the robustness of the BMD-mortality associations across age, marital status, PIR, bilateral oophorectomy status, and hormone history.

All statistical analyses accounted for the complex multistage sampling design of NHANES, incorporating adjustments for strata, primary sampling units, and survey weights to ensure generalizability to the US population. Analyses were conducted using R software version 4.3.3, with two-tailed *P*-values <0.05 considered statistically significant.

RESULTS

Participant characteristics

This study included 2,977 postmenopausal women participants (Fig. 1). During a mean follow-up of 7.26 years (21,626.7 person-years), 471 deaths were recorded. Among the deceased participants, 83 had osteoporotic fractures. Table 1 presents baseline characteristics stratified by osteoporosis status. Compared with normal BMD participants, those with osteoporosis were significantly more likely to be older, non-Hispanic White, less educated, unmarried, non-drinkers, and have lower BMI (all $P<0.05$). The study also demonstrated a statistically significant increase in CCI scores, higher prevalence of depression, osteoporotic fractures, and elevated mortality rate (all $P<0.05$).

Preliminary links between femoral metrics and all-cause mortality

The distribution of participants with T-scores ≤ -2.5 across hip subregions was as follows (Fig. 2): total femur (n = 298), femoral neck (n = 423), trochanter (n = 239), and intertrochanteric region (n = 227). Kaplan-Meier analysis revealed that among postmenopausal women, those with osteoporosis (including a BMD T-score ≤ -2.5 at specific femoral sites) were associated

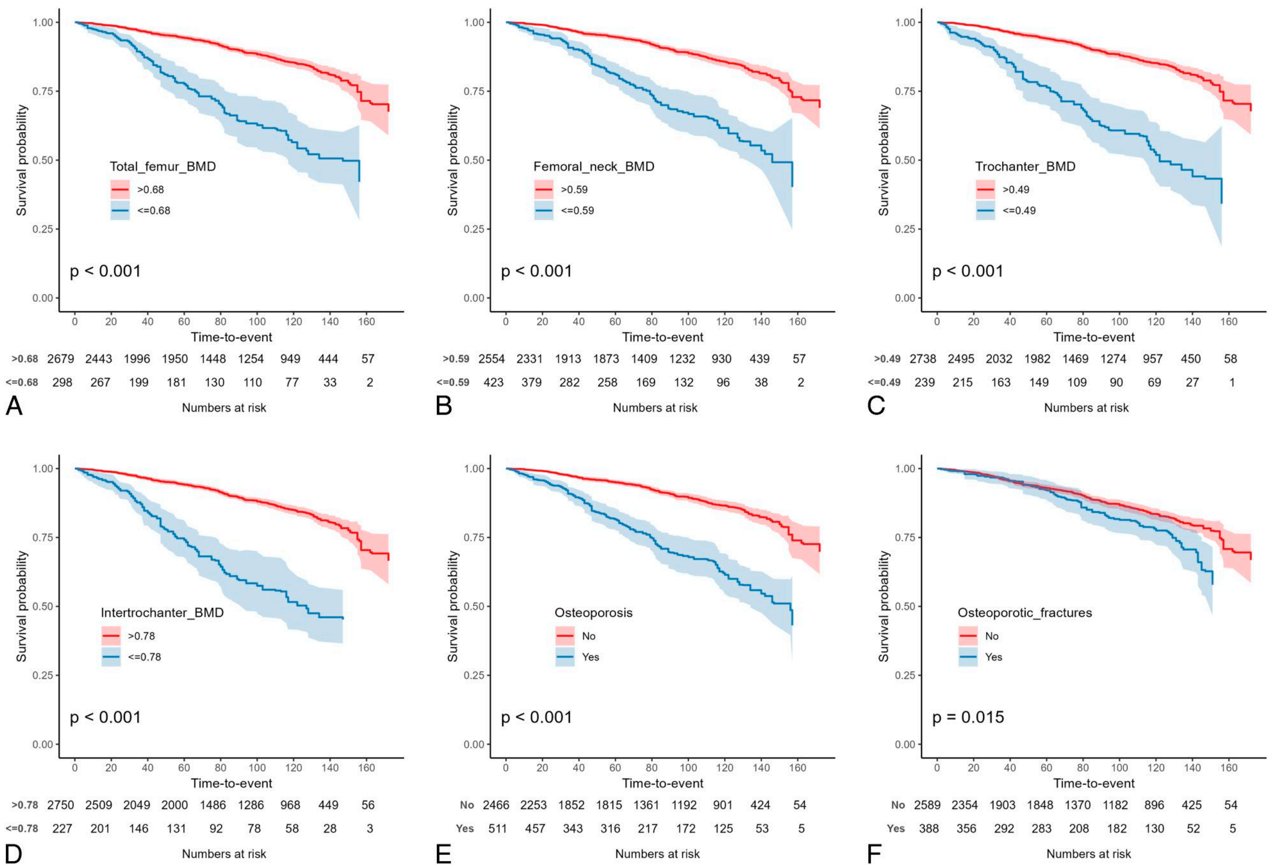

FIG. 2. Kaplan-Meier survival curves depicting all-cause mortality stratified by BMD metrics and osteoporosis status. **(A–D)** Illustrate survival probabilities stratified by site-specific BMD thresholds (total femur: >0.68 vs ≤ 0.68 g/cm²; femoral neck: >0.59 vs ≤ 0.59 g/cm²; trochanter: >0.49 vs ≤ 0.49 g/cm²; intertrochanter: >0.78 vs ≤ 0.78 g/cm²). **(E)** Presents survival probabilities by osteoporosis status (yes/no), while **(F)** shows survival probabilities stratified by osteoporotic fracture status (yes/no). BMD, bone mineral density.

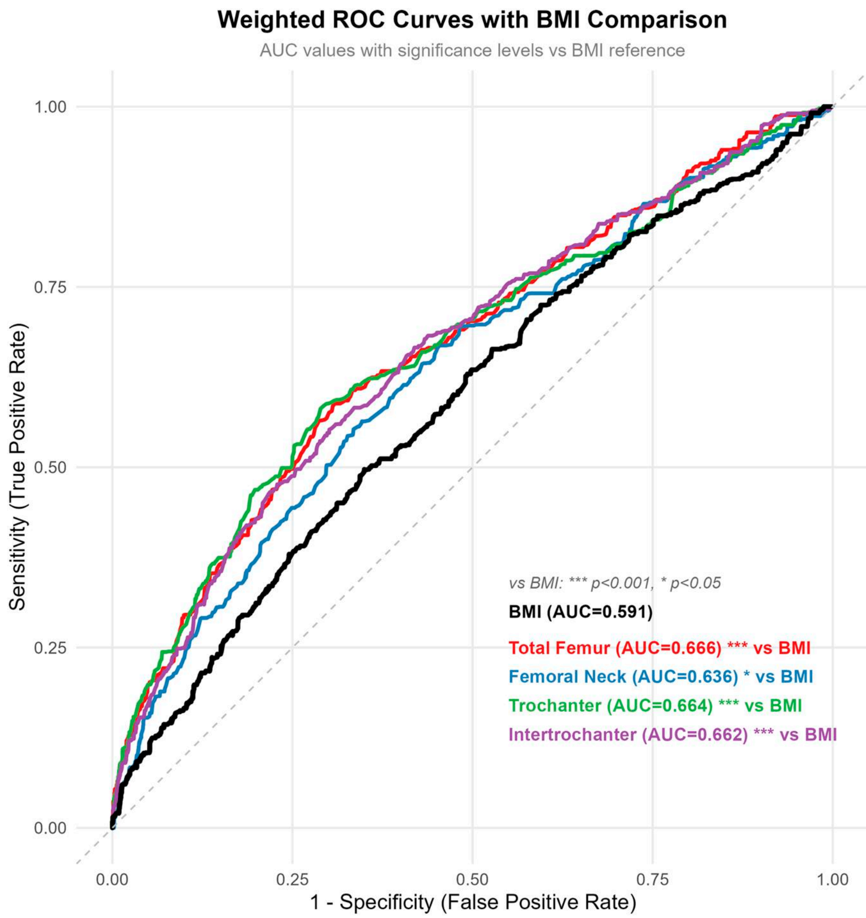

FIG. 3. Weighted ROC curves comparing the predictive performance of site-specific BMD metrics and BMI for all-cause mortality. Curves plot sensitivity (true positive rate) against 1-specificity (false positive rate) for BMI and four BMD measures (total femur, femoral neck, trochanter, intertrochanter). AUC values are reported for each metric, with significance levels (****P* < 0.001, **P* < 0.05) denoting differences relative to BMI (reference AUC = 0.591). AUC, area under the curve; BMD, bone mineral density; BMI, body mass index; ROC, receiver operating characteristic.

TABLE 2. Associations between site-specific BMD, osteoporosis, and mortality risk in postmenopausal women

	Model 1		Model 2		Model 3	
Variable	**HR (95% CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
BMD						
Total femur BMD	0.07 (0.04-0.14)	**< 0.001**	0.11 (0.05-0.24)	**< 0.001**	0.13 (0.06-0.27)	**< 0.001**
Femoral neck BMD	0.10 (0.05-0.21)	**< 0.001**	0.17 (0.07-0.43)	**< 0.001**	0.20 (0.08-0.51)	**< 0.001**
Trochanter BMD	0.04 (0.02-0.08)	**< 0.001**	0.07 (0.03-0.17)	**< 0.001**	0.08 (0.04-0.18)	**< 0.001**
Intertrochanter BMD	0.14 (0.08-0.25)	**< 0.001**	0.21 (0.12-0.38)	**< 0.001**	0.23 (0.12-0.42)	**< 0.001**
Osteoporosis						
No	—		—		—	
Yes	1.77 (1.40-2.24)	**< 0.001**	1.52 (1.20-1.93)	**< 0.001**	1.47 (1.16-1.86)	**0.001**
Osteoporotic fractures						
No	—		—		—	
Yes	1.27 (0.98-1.64)	0.072	1.32 (1.02-1.71)	**0.035**	1.16 (0.87-1.57)	0.312

BMD, bone mineral density; HR, hazard ratio.
Bold values are statistically significant $P < 0.05$.
Model 1: Age and race were adjusted.
Model 2: Age, race, education level, poverty-to-income ratio level, marital status, smoking status, alcohol use, physical activity, body mass index, and Healthy Eating Index-2020 were adjusted.
Model 3: Age, race, education level, poverty-to-income ratio level, marital status, smoking status, alcohol use, physical activity, body mass index, Healthy Eating Index-2020, Charlson Comorbidity Index, depression, bilateral oophorectomy, and hormone history were adjusted.

with a significantly higher risk of all-cause mortality ($P < 0.001$); in addition, osteoporotic fractures were also associated with increased mortality risk ($P = 0.015$).

ROC curve analysis (Fig. 3) showed areas under the curve of 0.666 (total femur), 0.636 (femoral neck), 0.664 (trochanter), and 0.662 (intertrochanter), all significantly greater than the 0.591 area under the curve value for BMI (all $P < 0.05$). Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/MENO/B511) demonstrates that the area under the ROC curve (area under the curve) of femoral neck BMD is significantly smaller than that of BMD at other femoral sites (all $P < 0.05$).

Multivariable analysis of bone metrics and all-cause mortality

Table 2 presents the associations between BMD/osteoporosis/osteoporotic fractures and mortality, with each association evaluated using three progressively adjusted models. The fully adjusted model 3 demonstrated significant inverse associations between BMD and mortality risk: Total femur BMD (hazard ratio [HR] = 0.13, 95% CI = 0.06-0.27, $P < 0.001$), femoral neck BMD (HR = 0.20, 95% CI = 0.08-0.51, $P < 0.001$), trochanter BMD (HR = 0.08, 95% CI = 0.04-0.18, $P < 0.001$), and intertrochanter BMD (HR = 0.23, 95% CI = 0.12-0.42, $P < 0.001$). In addition, reaching osteoporotic threshold at any site was associated with 47% higher mortality risk (HR = 1.47, 95% CI = 1.16-1.86, $P = 0.001$). Nevertheless, after adjusting for all covariates, no statistically significant link existed between osteoporotic fractures and mortality risk ($P = 0.312$).

Nonlinear relation

After full adjustment for covariates, RCS analyses (Fig. 4) revealed significant nonlinear associations of total femur BMD and trochanter BMD with mortality risk (p for nonlinear < 0.05), whereas femoral neck BMD and intertrochanter BMD only exhibited linear relationships (P for nonlinear > 0.05). Furthermore, the RCS plots showed a stronger inverse association between BMD increase and mortality risk within specific ranges: 0.46-0.71 g/cm² for total femur BMD and 0.33-0.54 g/cm² for trochanter BMD (Fig. 5).

Subgroup analysis

We performed subgroup interaction analyses stratified by age, marital status, PIR level, bilateral oophorectomy status, and hormone history (Fig. 6). The inverse associations between site-specific BMD and mortality risk remained consistent across all subgroups, with no significant interaction effects observed (all interaction P-values > 0.05).

DISCUSSION

This investigation, utilizing the NHANES database, systematically explores the association between BMD and all-cause mortality risk in postmenopausal women. The study reveals a significant inverse correlation between femoral BMD and mortality, providing novel epidemiological evidence for BMD as a prognostic biomarker of systemic health.

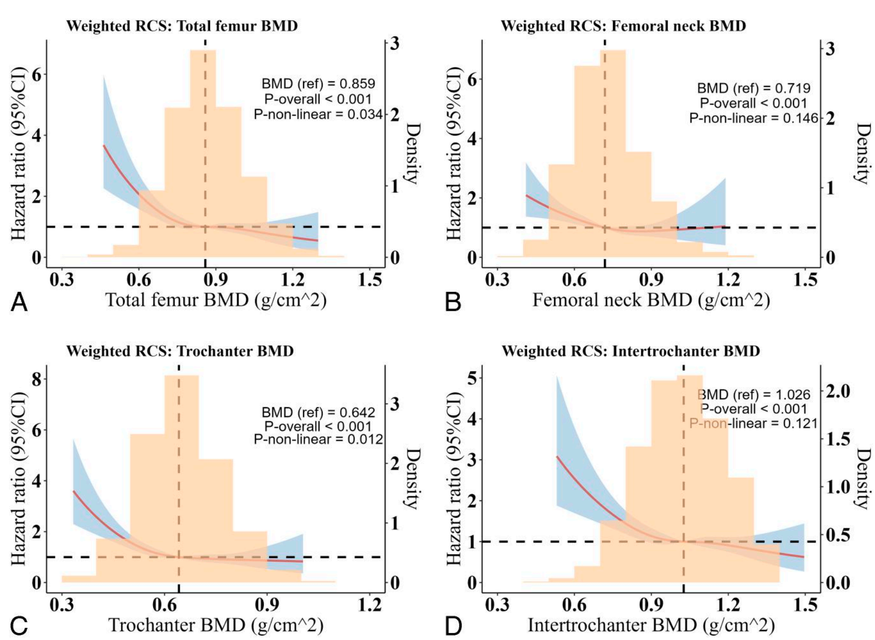

FIG. 4. Weighted RCS models evaluating the dose-response relationship between site-specific BMD (g/cm²) and all-cause mortality HR. (**A–D**) Display HRs (95% CIs, solid red line) and BMD distribution densities (right *y*-axis, shaded bars) for total femur, femoral neck, trochanter, and intertrochanter BMD, respectively. Reference BMD values, along with *P*-values for overall association (*P*-overall) and nonlinearity (*P*-nonlinear), are annotated for each model; the dashed line denotes the null effect (HR = 1). BMD, bone mineral density; HR, hazard ratio; RCS, restricted cubic spline.

Findings demonstrate that postmenopausal women with osteoporosis exhibit a constellation of deleterious baseline characteristics across demographic, clinical, and lifestyle domains when compared with non-osteoporotic counterparts. Aging is associated with a physiological decline in bone formation, coupled with enhanced osteoclastic resorption, leading to progressive BMD attrition. Mechanistically, senescence-induced adipogenic differentiation of bone marrow mesenchymal stem cells, augmented osteocyte apoptosis, and dysregulated bone remodeling contribute to this trajectory.[27] Notably, osteoporotic women exhibit a significantly higher burden of chronic comorbidities, including end-stage renal disease, congestive heart failure, cerebrovascular accidents, and major depressive disorder—conditions independently associated with elevated mortality risk.[28–30] For instance, chronic kidney disease is accompanied by bone mineral metabolic derangements, characterized by abnormal bone turnover and mineralization defects that potentiate fracture risk and mortality.[31] Cardiac failure is associated with reduced BMD and upregulation of RANKL in bone marrow, indicative of heightened osteoclast activity.[32] Post-stroke hemiplegia is associated with regional BMD loss in affected limbs, equivalent to over two decades of skeletal aging in healthy individuals. Antidepressant use in depressive disorders confers a 44% increased risk of osteoporosis[33] and a 2.5-fold increase in fracture susceptibility,[34] with selective serotonin/norepinephrine reuptake inhibitor users demonstrating a 32% higher incidence of osteoporotic fractures.[35] Collectively, these data suggest that osteoporosis clusters with a "high-risk phenotypic profile" that mechanistically underlies its association with mortality, while also supporting BMD as a surrogate marker of survival prognosis.

Lifestyle correlates of osteoporosis include lower alcohol consumption and reduced BMI. Hypothetically, reduced body weight accelerates bone loss by diminishing mechanical loading and estrogenic signaling.[36] While heavy alcohol use is a known risk factor for osteoporosis and mortality, the observed association between low-volume drinking and osteoporosis, consistent with prior reports, warrants further investigation given potential sampling constraints.[37]

Central to this inquiry is the finding that osteoporotic BMD thresholds in any femoral subregion are associated with a significant elevation in all-cause mortality, corroborating results from large-scale population studies.[38] Although BMI has historically been used as a

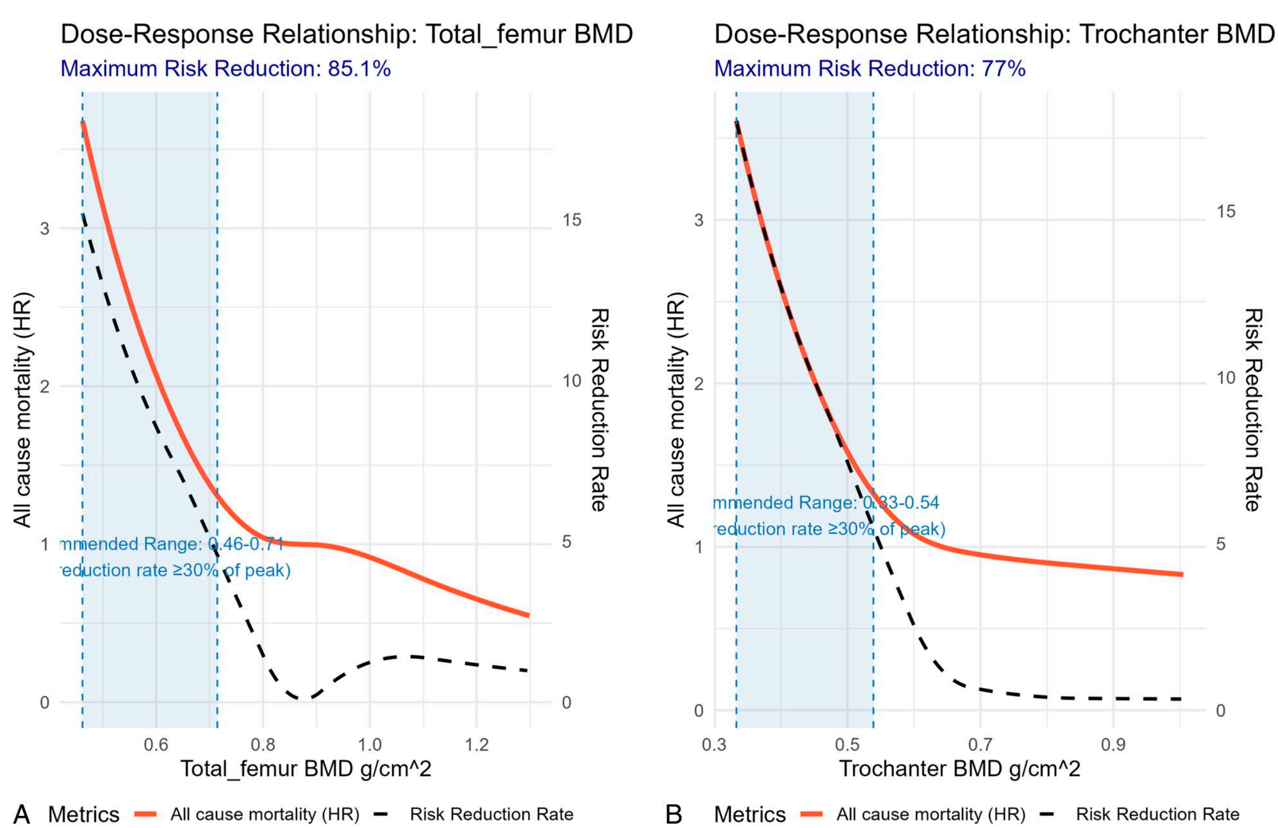

FIG. 5. Dose-response relationship between BMD (g/cm²) and all-cause mortality HR, incorporating risk reduction rates. (**A and B**) Depict HRs (solid red line) and corresponding risk reduction rates (dashed black line) for total femur and trochanter BMD, respectively. Key annotations include maximum risk reduction rates (85.1% for total femur; 77% for trochanter) and recommended BMD ranges associated with ≥ 30% of the peak risk reduction. BMD, bone mineral density; HR, hazard ratio.

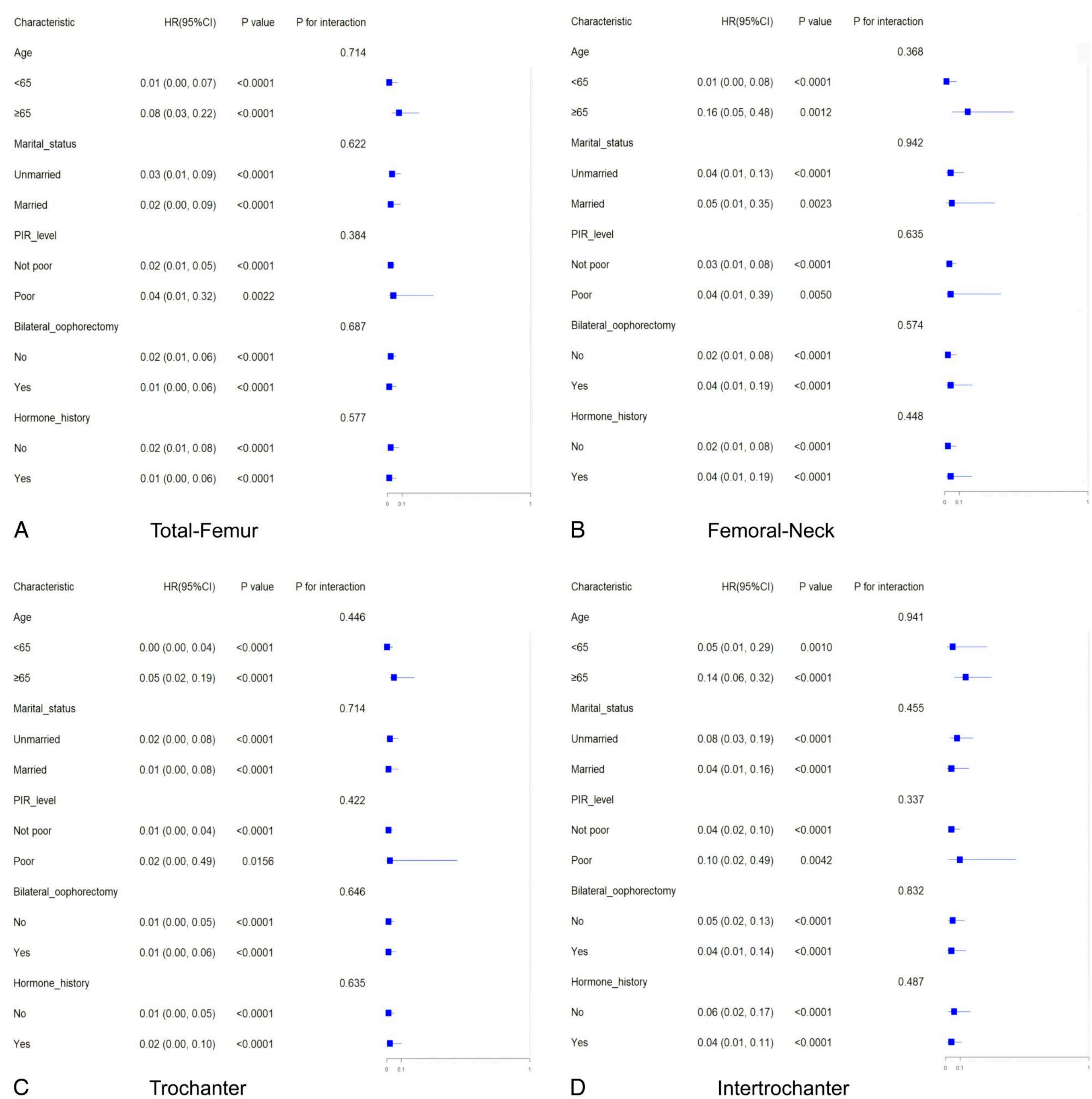

FIG. 6. Subgroup analyses assessing the association between site-specific BMD and all-cause mortality HRs, stratified by baseline characteristics. (**A–D**) Present subgroup results for total femur, femoral neck, trochanter, and intertrochanter BMD, respectively. For each subgroup (age, marital status, PIR level, bilateral oophorectomy, hormone history), the analysis reports HRs (95% CIs), *P*-values (for the BMD-mortality association), and *P* for interaction (for subgroup heterogeneity). Blue squares denote HR point estimates, with horizontal lines representing 95% CIs. BMD, bone mineral density; HR, hazard ratio; PIR, poverty-to-income ratio.

surrogate marker for mortality risk,[39] its U-shaped association with mortality in menopausal women[40] may reflect limitations in capturing skeletal health, lean body mass, and overall body composition. Indeed, overweight BMI was not associated with mortality across most racial subgroups, a finding consistent with multicenter studies demonstrating the suboptimal predictive utility of BMI in postmenopausal women.[41] ROC curve analysis confirmed the superior discriminative capacity of femoral BMD (across anatomic sites) compared with BMI for mortality prediction, likely attributable to BMD's sensitivity to functional status, chronic disease burden, and nutritional homeostasis.[8,42] Even after adjustment for multiple comorbidities, low BMD independently predicts elevated mortality,[43] suggesting that skeletal demineralization may serve as a sentinel marker of systemic senescence. These findings underscore the clinical utility of incorporating BMD assessment into comprehensive health risk stratification for postmenopausal women, facilitating early intervention.

Supporting these conclusions, investigations in elderly Japanese and Brazilian women have linked reduced femoral neck and trochanteric BMD to increased mortality.[44] Employing RCS modeling, we observed nonlinear BMD-mortality relationships: femoral neck and intertrochanteric BMD exhibited linear associations, whereas total femoral and trochanteric BMD demonstrated nonlinear trends. This discrepancy may be attributed to biomechanical and metabolic heterogeneity across skeletal sites: femoral neck fractures, owing to their anatomic location and tenuous blood supply, are associated with poor healing and severe secondary complications,[45] driving a linear risk gradient. Although the trochanteric region is also a common site of femoral fractures,[46] the trabecular-rich trochanteric region—characterized by robust vascularity, muscular attachments, and mechanical stress responsiveness[47] exhibits adaptive remodeling, explaining its nonlinear relationship with mortality. Notably, incremental increases in total femoral and trochanteric BMD were associated with disproportionate reductions in mortality risk, suggesting that early preservation of BMD may confer maximal protective benefit and underscoring the sensitivity of femoral BMD to systemic health status.

Subgroup analyses stratified by age, marital status, PIR, history of bilateral oophorectomy, and hormone therapy exposure consistently demonstrated negative BMD-mortality associations, with no evidence of effect modification. These findings support femoral BMD as a universal biomarker of health across diverse sociodemographic and hormonal exposure profiles, reinforcing its utility as a stratified risk indicator in postmenopausal women.

Strengths and limitations

This study has several key strengths. First, the large sample size ensures robust national representativeness, allowing the findings to be generalized to a broader US population. Second, this is the first cohort study in the United States to systematically assess the association between femoral BMD and all-cause mortality risk in postmenopausal women.

It is important to note several limitations of this study. Although NHANES employs a rigorous sampling methodology to represent the US adult population, certain subgroups may still be underrepresented. For example, individuals living in remote areas or those with unique lifestyles that limit survey accessibility may not be adequately included. Such potential sampling biases may limit the generalizability of the findings to the entire US adult population. Despite adjustments for age, sex, race, lifestyle factors, dietary habits, and genetic variables, unmeasured confounders may still affect the results. Future studies should assess the consistency of findings across different populations. In addition, the cross-sectional nature of the BMD assessment through a single DXA scan does not capture longitudinal changes in bone mass. Thus, the external validity of these findings should be further validated through multicohort studies and longitudinal designs. Lastly, this study did not investigate cause-specific mortality but focused on all-cause mortality, and did not differentiate the mortality risk associated with specific diseases. More critically, the database lacks explicit data on fracture-related mortality. Therefore, the current study's findings may be confounded by the direct consequences of fractures and the indirect effects of osteoporosis as a marker of systemic frailty and comorbidities. Future research should include detailed cause-of-death classification data to clarify the exact mechanisms.

CONCLUSONS

Femoral BMD and osteoporosis are independent predictors of all-cause mortality in postmenopausal women. The inverse relationship between BMD and mortality risk is more pronounced within specific BMD ranges, which may provide valuable insights for mortality risk stratification and clinical decision-making in this population.

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