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Body Mass Index and Bone Mineral Density in Postmenopausal Women: Nonlinear Associations and Discriminatory Performance for Osteoporosis at Three Skeletal Sites

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Article

Keywords: Osteoporosis, Osteopenia, Bone Density, Body Mass Index, Postmenopause

Posted Date: November 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11373555/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Body mass index (BMI) is positively associated with bone mineral density (BMD), but its shape, usefulness, and variation across skeletal sites remain uncertain.

Methods

In this cross-sectional study, 1,707 postmenopausal women undergoing dual-energy X-ray absorptiometry in Isfahan, Iran (April 2022–March 2023) were analyzed after excluding secondary causes of bone loss and bone-active medications. BMD was measured at the lumbar spine, femoral neck, and total hip. Logistic and ordinal logistic regression, adjusted for age, current smoking, exercise, number of pregnancies, years of menstruation, and fragility fracture history, compared BMI categories (< 25, 25–<30, 30–<35, ≥ 35 kg/m²). RCS assessed nonlinearity; receiver operating characteristic analysis with the Youden index evaluated BMI for identifying absence of osteoporosis.

Results

Mean age and BMI were 61.1 ± 8.0 years and 29.7 ± 4.7 kg/m²; 606 women (35.5%) had osteoporosis at one or more sites. BMD increased across BMI categories at all sites. Compared with BMI < 25 kg/m², BMI ≥ 35 kg/m² was associated with lower adjusted odds of osteoporosis overall (OR 0.21; 95% CI 0.13–0.32) and at the total hip (OR 0.04; 95% CI 0.01–0.19). Splines showed significant nonlinearity overall and at each site (all P ≤ 0.007). AUCs for absence of osteoporosis were 0.64 (lumbar spine), 0.65 (femoral neck), and 0.76 (total hip), with Youden cut-offs of 28.0–29.1 kg/m².

Conclusions

BMI was nonlinearly and positively associated with BMD across skeletal sites. A BMI of approximately 28–29 kg/m² provided the best discrimination for absence of osteoporosis, particularly at the total hip, warranting prospective validation.

1. Introduction

Osteoporosis is a systemic skeletal metabolic disorder characterized by reduced bone mineral density (BMD) and structural deterioration of bone tissue, leading to increased risk of fractures [1, 2]. It is considered a major global public health concern, associated with disability, reduced quality of life, increased mortality, and substantial social and economic costs, affecting approximately one-third of postmenopausal women [2, 3]. In postmenopausal women, estrogen deficiency is the primary driver of bone loss, as estrogen normally limits bone resorption and promotes bone formation [4]. Following estrogen deficiency and other unmodifiable determinants such as aging, family history, and genetics, the strongest modifiable risk factor for osteoporosis is low body mass, followed by prior fractures, smoking, excessive alcohol consumption, physical inactivity, inadequate nutrition, and long-term corticosteroid therapy [5, 6].

While many studies indicate that higher body mass index (BMI) is directly associated with higher BMD, primarily due to the mechanical loading on bones and the hormonal contribution of adipose tissue–mediated estrogen synthesis, emerging evidence suggests that this relationship may not be strictly linear [7–11]. For example, a cross-sectional study in older Asian adults found an inflection point in BMI at 25.2 kg/m² for lumbar spine BMD and 27.3 kg/m² for femoral neck BMD, beyond which the increase in BMD slows [9]. Although the reason for the presence of a BMI inflection point remains unclear, it may be explained by several physiological mechanisms, including increased bone marrow adiposity, chronic inflammation, and obesity-related comorbidities such as diabetes and vitamin D deficiency [6, 12, 13].

Moreover, the effect of BMI on osteoporosis risk is not uniform across different skeletal sites. For instance, a large meta-analysis found that while higher BMI is generally associated with increased BMD at weight-bearing sites such as the trochanteric part of the hip, total hip, and femoral neck this protective effect is less pronounced in lumbar spine and calcaneal bone potentially due to differences in bone composition, marrow fat content, and site-specific mechanical loading [14].

Given the complex and potentially nonlinear relationship between BMI and bone health, as well as the heterogeneity of this association across skeletal sites and the inconsistent findings of previous studies, there remains uncertainty regarding the BMI range associated with better bone health and lower osteoporosis risk in postmenopausal women. Therefore, we conducted this study to comprehensively evaluate the association between BMI and bone health in postmenopausal women, examining BMD and osteoporosis status at the lumbar spine, femoral neck, and total hip. We further assessed the association across BMI categories, evaluated potential nonlinear relationships between BMI and the ordered spectrum of bone health, and determined the discriminatory performance and BMI thresholds that optimally discriminated the absence of osteoporosis, while accounting for relevant demographic, lifestyle, and clinical factors.

2. Methods

2.1. Study Design and Participants:

This cross-sectional study, was conducted on all the postmenopausal women who were referred to the Bone Mineral Density Evaluation Center, Shariati Hospital, Isfahan, Iran from April 2022 to March 2023. Considering the ethical guidelines, approved by the Islamic Azad University–Najafabad Branch ethics committee (IR.IAU.NAJAFABAD.REC.1402.076), informed written consent was obtained from each individual.

2.2 Data collection:

Participants were recruited at the time of their scheduled bone mineral density evaluation and completed a structured questionnaire specifically developed for this study, which collected information on demographic characteristics, past medical history (including menopausal status, age at menarche, age at menopause, number of full-term pregnancies, history of fragility fractures, and frequent use of medications or calcium and vitamin D supplements), as well as lifestyle factors such as current smoking status(cigarettes and/or opioids), persistent alcohol consumption (3 or more units of alcohol per day), and engagement in weight-bearing aerobic exercise (≥ 2 times/week for at least 20–30 minutes per session).

Anthropometric measurements (weight, height, and BMI) were obtained with participants wearing light clothing and no shoes. Weight was measured to the nearest 0.1 kg using a calibrated beam scale, and height was

recorded to the nearest 1 cm using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Dual-energy X-ray absorptiometry (DXA) scans were used to assess BMD in the three WHO-standard sites for diagnosing osteoporosis (Femoral neck, Total hip, and Lumbar spine). BMD was measured using a daily calibrated Horizon® machine (Hologic Inc., USA) with software version Apex 5. The percentage coefficient of variation in BMD for the DXA machine used in the present study was 1.0%. DXA measurements were performed by certified radiologic technologists trained in standard scanning protocols, with patient positioning following established guidelines. All scans were subsequently reviewed and validated by a radiology specialist. Lumbar spine BMD (LS-BMD) was assessed at L1–L4, with any vertebra that deemed unreliable or inconclusive due to artifacts excluded from the average. For hip measurements, the non-dominant leg was used to determine femoral neck BMD (FN-BMD) and total hip BMD (TH-BMD). Osteoporosis at each skeletal site was defined as a T-score ≤ − 2.5, osteopenia as a T-score > − 2.5 and < − 1.0, and normal bone-health status as a T-score ≥ − 1.0. Participants were classified according to the lowest bone-health status observed across the three skeletal sites: osteoporosis was defined as osteoporosis at any site; osteopenia was defined as the absence of osteoporosis but the presence of osteopenia at at least one site; and normal bone-health status was defined as normal T-scores at all three sites [15].

Following completion of data collection, predefined eligibility and exclusion criteria were applied to determine the final study population. Participants were excluded if they had: (1) induced menopause by bilateral oophorectomy or androgen deprivation therapy, (2) Frequent use of medications known to affect bone metabolism, including bisphosphonates, RANKL inhibitors, selective estrogen receptor modulators, aromatase inhibitors, parathyroid hormone analogues, Estrogen–Progestogen therapy, calcitonin, strontium ranelate, systemic glucocorticoids, hormone replacement therapy, anticonvulsants, and anti-obesity medications, (3) accompanying diseases that may cause secondary osteoporosis, such as hyperparathyroidism, Cushing syndrome, malabsorptive disorders, inflammatory bowel disease, rheumatoid arthritis, lupus erythematosus, chronic renal failure, and malignancies.

2.3 Statistical Analysis

All the mentioned data were entered and analyzed by SPSS software version 26 (SPSS Inc, Chicago, IL), and R statistical software 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Missing values for continuous variables were replaced using the median value of the corresponding variable. Categorical variables with missing responses were handled as missing and were not imputed. Categorical variables were summarized as frequencies and percentages and compared between groups using Chi-square test or Fisher's exact test (when the expected frequencies in the contingency table were less than 5.). Continuous variables were expressed as the mean ± standard deviation and were first assessed for normality using the Kolmogorov–Smirnov and Shapiro-Wilk tests. Normally distributed variables were compared across groups using one-way ANOVA, while non-normally distributed variables were compared using the Kruskal–Wallis test. *P*-values below 0.05 were considered statistically significant.

Logistic regression analyses were performed to examine the association between BMI categories and osteoporosis at each skeletal site and overall. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using three models: an unadjusted model, a model adjusted for age, and a multivariable model adjusted for age, current smoking, weight-bearing aerobic exercise, number of pregnancies, years of menstruation, and history of fragility fractures.

Potential confounders were identified based on their clinical relevance and associations with BMI and bone-health outcomes in the study population. Multicollinearity among candidate covariates was assessed using variance inflation factors (VIFs) (Table S1). Because of substantial collinearity among anthropometric variables (BMI, weight, and height) and among reproductive variables (age at menarche, age at menopause, years of menstruation, and years since menopause), highly correlated variables were not simultaneously included in the multivariable models. The final adjusted models included age, current smoking, weight-bearing aerobic exercise, number of pregnancies, years of menstruation, and history of fragility fractures.

For descriptive analyses, BMI was categorized into six groups according to the World Health Organization classification: underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obesity class I (30.0–34.9 kg/m²), obesity class II (35.0–39.9 kg/m²), and obesity class III (≥ 40 kg/m²). For regression analyses, BMI categories were combined into four groups (Q1: <25 kg/m²; Q2: 25–<30 kg/m²; Q3: 30–<35 kg/m²; Q4: ≥35 kg/m²) because of the relatively small numbers of participants in the extreme BMI categories, particularly those with BMI < 18.5 and ≥ 40 kg/m², which could compromise the stability of the regression estimates.

Ordinal logistic regression models were additionally used to assess the association between BMI categories and bone-health status as an ordered outcome (normal bone-health status, osteopenia, and osteoporosis). This approach accounted for the ordinal nature of BMD classification and estimated the odds of being in a worse bone-health status across BMI groups.

Restricted cubic spline ordinal logistic regression models were fitted to further assess potential nonlinear associations between BMI and ordered bone-health status overall and at each of the three major skeletal sites. Models incorporating three to six knots were evaluated, and model fit was compared using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The model with the lowest BIC and greater parsimony was selected for the final analyses. Predicted probabilities of normal bone-health status, osteopenia, and osteoporosis across the BMI spectrum were estimated from the selected models.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of BMI for identifying the absence of osteoporosis overall and at each skeletal site. The area under the ROC curve (AUC) and corresponding 95% CIs were calculated to assess the discriminatory performance of BMI. For the ROC analyses, absence of osteoporosis was defined as the positive outcome. Optimal BMI cutoff values were determined using the Youden index (J), calculated as sensitivity + specificity − 1, with the threshold maximizing the combined sensitivity and specificity selected as the optimal cutoff. Corresponding sensitivity and specificity values were reported for each optimal cutoff

3. Results

3.1 Baseline characteristics

Among the 2,734 women referred to the Bone Mineral Density Evaluation Center during the study period, 1,707 participants met the eligibility criteria and were included in the analysis (Fig. 1). The mean age and BMI of the study population were 61.1 ± 8.0 years and 29.7 ± 4.7 kg/m², respectively. Based on DXA measurements, 606 participants (35.5%) were diagnosed with osteoporosis in at least one of the major skeletal sites. Among

participants with osteoporosis, the largest proportion (42.2%) belonged to the overweight BMI category (Table S2).

Baseline characteristics according to overall bone-health status are presented in Table 1. Older age, current smoking, history of fragility fractures, greater number of pregnancies, older age at menarche, and more years since menopause were significantly associated with a higher likelihood of osteoporosis. Conversely, greater height, weight, BMI, older age at menopause, longer duration of menstruation, and engagement in weight-bearing aerobic exercise were significantly associated with a lower likelihood of osteoporosis (Table 1).

Table 1
Baseline characteristics of the participants

Age, (Mean ± SD) (years)	**Overall (N = 1707)**	**Normal bone-health status (N = 319, 18.7%)**	**Osteopenia (N = 782, 45.8%)**	**Osteoporosis (N = 606, 35.5%)**	**P-value**
	61.14 ± 8.02 [41–96]	**56.97 ± 6.92**	**60.43 ± 7.60**	**64.25 ± 7.87**	**< 0.001[a]**
Height (Mean ± SD) (cm)	153.77 ± 5.89 [137.1–191.0]	156.07 ± 5.89	154.18 ± 5.56	152.02 ± 5.81	< 0.001[a]
Weight (Mean ± SD) (Kg)	70.23 ± 11.59 [35–122]	76.81 ± 11.25	71.20 ± 10.52	65.52 ± 11.11	< 0.001[a]
BMI (Mean ± SD) (Kg/M^2)	29.71 ± 4.71 [14.78–52.46]	31.56 ± 4.50	30.0 ± 4.52	28.36 ± 4.65	< 0.001[a]
Number of pregnancies (Mean ± SD)	3.86 ± 2.08 [0–14]	3.17 ± 2.28	3.70 ± 1.81	4.45 ± 2.37	< 0.001[a]
Age at menopause (Mean ± SD)	48.61 ± 4.304 [38–60]	49.18 ± 4.05	48.54 ± 4.2	48.39 ± 4.53	0.036[a]
Age at menarche (Mean ± SD)	13.36 ± 1.62 [9–19]	13.17 ± 1.72	13.37 ± 1.56	13.45 ± 1.64	0.036[a]
Years of menstruation (Mean ± SD)	35.24 ± 4.56 [22–48]	36.00 ± 4.61	35.17 ± 4.46	34.93 ± 4.61	0.008[a]
Years after menopause (Mean ± SD)	12.53 ± 8.60 [0–47]	7.79 ± 6.93	11.88 ± 8.18	15.85 ± 8.57	< 0.001[a]
Current smoking	80 (4.7%)	11 (3.4%)	30 (3.8%)	39 (6.4%)	0.039[b]
Persistent alcohol consumption*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

(a=Kruskal-Wallis/ one-way ANOVA Test, b= Pearson Chi-Square Test)

* Alcohol consumption could not be analyzed as a risk factor because none of the participants reported chronic drinking, consistent with cultural norms of the study population.

Age, (Mean ± SD) (years)	Overall (N = 1707)	Normal bone-health status (N = 319, 18.7%)	Osteopenia (N = 782, 45.8%)	Osteoporosis (N = 606, 35.5%)	P-value
	61.14 ± 8.02 [41–96]	**56.97 ± 6.92**	**60.43 ± 7.60**	**64.25 ± 7.87**	**< 0.001[a]**
History of fragility fractures	66 (3.9%)	10 (3.1%)	17 (2.2%)	39 (6.4%)	< 0.001[b]
Weight-bearing aerobic exercise	236 (13.8%)	59 (18.5%)	111 (14.2%)	66 (10.9%)	0.006[b]
Vitamin D supplementation	1352 (79.2%)	261 (81.8%)	624 (79.8%)	467 (77.1%)	0.204[b]
Ca supplementation	874 (51.2%)	175 (54.9%)	396 (50.6%)	303 (50.0%)	0.340[b]
(a=Kruskal-Wallis/ one-way ANOVA Test, b= Pearson Chi-Square Test)					
* Alcohol consumption could not be analyzed as a risk factor because none of the participants reported chronic drinking, consistent with cultural norms of the study population.					

3.2 BMD and T-scores across BMI categories

Assessment of BMD and T-scores at the three principal skeletal sites across WHO classified BMI categories demonstrated significant positive associations at all sites, with both BMD and T-scores increasing progressively as BMI category increased (Table 2; Figure S1).

Table 2

Bone mineral density and T-scores of participants classified by BMI categories in the three major skeletal sites

LS-BMD (L1-L4)	Overall (N = 1707)	BMI < 18.5 (N = 8, 0.5%)	BMI 18.5–24.9 (N = 240, 14.1%)	BMI 25–29.9 (N = 676, 39.6%)	BMI 30–34.9 (N = 575 (33.7%)	BMI 35-39.9 (N = 164, 9.6%)	BMI ≥ 40 (N = 44, 2.6%)	P-Value
	0.858 ± 0.148 [0.442–1.552]	**0.581 ± 0.114**	**0.785 ± 0.140**	**0.849 ± 0.144**	**0.882 ± 0.138**	**0.919 ± 0.145**	**0.921 ± 0.166**	**< 0.001[a]**
FN-BMD	0.680 ± 0.118 [0.315–1.288]	0.504 ± 0.089	0.618 ± 0.106	0.672 ± 0.112	0.702 ± 0.113	0.722 ± 0.129	0.745 ± 0.130	< 0.001[a]
TH-BMD	0.848 ± 0.128 [0.411–1.279]	0.583 ± 0.053	0.766 ± 0.113	0.833 ± 0.119	0.877 ± 0.118	0.911 ± 0.120	0.967 ± 0.134	< 0.001[a]
LS T-Score (L1-L4)	-1.639 ± 1.362 [-5.5–4.6]	-4.200 ± 1.014	-2.298 ± 1.292	-1.733 ± 1.316	-1.418 ± 1.279	-1.079 ± 1.338	-1.089 ± 1.534	< 0.001[a]
FN T-Score	-1.506 ± 1.082 [-4.8–4.0]	-3.100 ± 0.807	-2.066 ± 0.962	-1.574 ± 1.037	-1.316 ± 1.034	-1.151 ± 1.146	-0.909 ± 1.200	< 0.001[a]
TH T-Score	-0.762 ± 1.050 [-4.4–2.8]	-2.938 ± 0.434	-1.435 ± 0.934	-0.885 ± 0.977	-0.530 ± 0.978	-0.236 ± 0.966	0.207 ± 1.108	< 0.001[a]

a=Kruskal-Wallis/ one-way ANOVA Test, BMI=Body Mass Index, BMD= Bone Mineral Density, LS= Lumbar Spine, FN= Femoral Neck, TH= Total Hip)

3.3 Association between BMI and osteoporosis

Univariable and multivariable logistic regression analyses were performed to evaluate the association between BMI categories and osteoporosis overall and at each skeletal site (Table 3). In the adjusted models, patients with BMI ≥ 35 kg/m² had approximately one-fifth the odds of overall osteoporosis compared with those with BMI < 25 kg/m², while participants in the overweight category had approximately half the odds.

Table 3
Association between BMI categories and the risk of osteoporosis in the three major skeletal sites using univariable logistic regression analysis (osteoporosis Vs osteopenia & normal bone-health status).

		Q1: BMI < 25	Q2: BMI 25-29.9	Q3: BMI 30-34.9	Q4: BMI ≥ 35	Trend
LS Risk of Osteoporosis [OR (95% CI)]	**Crude**	**1**	**0.47(0.35,0.64)**	**0.27(0.20,0.37)**	**0.21(0.13,0.33)**	**0.89(0.87,0.92)**
	Model1	**1**	**0.46(0.33,0.62)**	**0.26(0.19,0.36)**	**0.20(0.13,0.31)**	**0.89(0.87,0.91)**
	Model2	**1**	**0.47(0.34,0.64)**	**0.24(0.17,0.34)**	**0.19(0.12,0.29)**	**0.89(0.86,.0.91)**
FN Risk of Osteoporosis [OR (95% CI)]	Crude	1	0.49(0.36,0.68)	0.27(0.19,0.39)	0.27(0.17,0.45)	0.89(0.86,0.91)
	Model1	1	0.45(0.31,0.65)	0.24(0.16,0.36)	0.25(0.15,0.42)	0.88(0.85,0.91)
	Model2	1	0.47(0.33,0.68)	0.23(0.15,0.35)	0.24(0.14,0.41)	0.87(0.85,0.90)
TH Risk of Osteoporosis [OR (95% CI)]	Crude	1	0.25(0.15,0.41)	0.11(0.06,0.21)	0.05(0.01,0.21)	0.77(0.73,0.82)
	Model1	1	0.24(0.15,0.41)	0.11(0.06,0.22)	0.05(0.01,0.22)	0.77(0.72,0.81)
	Model2	1	0.25(0.14,0.42)	0.09(0.05,0.19)	0.04(0.01,0.19)	0.75(0.71,0.80)
Overall Risk of Osteoporosis [OR (95% CI)]	Crude	1	0.47(0.35,0.63)	0.29(0.21,0.39)	0.25(0.17,0.37)	0.90(0.88,0.93)
	Model1	1	0.43(0.31,0.59)	0.25(0.18,0.35)	0.22(0.14,0.34)	0.89(0.87,0.92)
	Model2	1	0.44(0.32,0.60)	0.23(0.17,0.33)	0.21(0.13,0.32)	0.89(0.87,0.91)

Model1: adjusted for age.

Model2: adjusted for age, current smoking, weight-bearing aerobic exercise, number of pregnancies, years of menstruation, and history of fragility fractures.

BMI= Body Mass Index, LS= Lumbar Spine, FN= Femoral Neck, TH= Total Hip, OR= Odds Ratio, CI= Confidence Interval

Similar patterns were observed for lumbar spine and femoral neck osteoporosis. For total hip osteoporosis, the inverse association was particularly pronounced: participants with BMI ≥ 35 kg/m² had substantially lower odds of osteoporosis (OR = 0.04) compared with those with BMI < 25 kg/m². All reported associations were statistically significant, with 95% CIs excluding 1.0.

3.4. Association between BMI and ordered bone-health status

Ordinal logistic regression was performed to evaluate the association between BMI and progressively worse bone-health status (normal bone-health status → osteopenia → osteoporosis) at the lumbar spine, femoral neck, total hip, and overall levels (Table S3). Overall, the adjusted odds of being in a worse bone-health status were 0.16 (95% CI, 0.11–0.24) among participants with BMI ≥ 35 kg/m² and 0.42 (95% CI, 0.31–0.56) among those who were overweight, compared with participants with BMI < 25 kg/m². Similar inverse associations were observed for lumbar spine and femoral neck BMD. For total hip BMD, participants with BMI ≥ 35 kg/m² had substantially lower odds of being in a worse bone-health status (OR = 0.08), while the odds among overweight participants were approximately one-third those of the reference group. All corresponding 95% CIs excluded 1.0.

3.5. Nonlinear association between BMI and bone-health status

To further investigate the shape of the association between BMI and ordered bone-health status, restricted cubic spline ordinal logistic regression demonstrated a statistically significant nonlinear association between BMI and ordered bone-health status overall and at each of the three major skeletal sites. Based on model comparison, the three-knot model was selected for all four outcomes according to BIC and model parsimony (Table S4). The overall association and nonlinear component were statistically significant for all outcomes (Table S4; Figure S2). The overall association was significant for overall bone-health status, lumbar spine, femoral neck, and total hip (all $P < 0.001$), while the nonlinear component was also significant for all four outcomes ($P = 0.001$, 0.007, < 0.001, and < 0.001, respectively).

The predicted-probability curves demonstrated a consistent shift toward normal bone-health status with increasing BMI, accompanied by declining probabilities of osteoporosis. At the lumbar spine, the probability of osteoporosis was highest at lower BMI values and declined progressively with increasing BMI, while normal bone-health status became the predominant classification at higher BMI levels. At the femoral neck, increasing BMI was similarly associated with a marked decline in the probability of osteoporosis and an increase in the probability of normal bone-health status, whereas the probability of osteopenia showed a curvilinear pattern. The total hip demonstrated the most pronounced nonlinear pattern, with increasing BMI associated with a marked increase in the probability of normal bone-health status and a rapid decline in the probability of osteoporosis (Figure S2).

3.6. Discriminatory performance of BMI

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of BMI for identifying absence of osteoporosis at different skeletal sites. The area under the curve (AUC) demonstrated modest to acceptable diagnostic performance, with the highest accuracy observed for total hip (AUC = 0.76; 95% CI: 0.71–0.81), followed by femoral neck (AUC = 0.65; 95% CI: 0.61–0.68) and lumbar spine (AUC = 0.64; 95% CI: 0.61–0.67) (Table 4).

Table 4
Diagnostic performance of BMI as a predictor of absence of osteoporosis, using ROC (Receiver Operating Characteristic) curve analysis, overall and separately for the three major skeletal sites.

LS-Osteoporosis	**Cut off value for BMI**	**Youden Index (J)**	**specificity**	**sensitivity**	**AUC (95%CI)**
	28.28	**0.217**	**0.67**	**0.55**	**0.64(0.61,0.67)**
FN-Osteoporosis	28.39	0.231	0.63	0.60	0.65(0.61,0.68)
TH-Osteoporosis	28.00	0.419	0.65	0.76	0.76(0.71,0.81)
Overall Osteoporosis	29.13	0.193	0.60	0.60	0.63(0.60,0.66)

Optimal BMI thresholds, determined using the Youden index, ranged from 28.00 to 29.13 kg/m² across skeletal sites. The corresponding sensitivity and specificity values were moderate. The ROC curves demonstrated better-than-chance discrimination for the absence of osteoporosis, with the greatest discriminatory performance observed at the total hip (Figure S3).

4. Discussion

In this study of postmenopausal women, higher BMI categories showed a positive association with BMD at the lumbar spine, femoral neck, and total hip. Furthermore, adjustment for possible confounders (i.e., demographic, lifestyle, reproductive, and clinical factors) indicated that higher BMI was associated with lower odds of osteoporosis and significantly lower odds of worse bone-health status. Additionally, the association between BMI and BMD was not strictly linear, with restricted cubic spline analyses demonstrating significant nonlinear relationships across all evaluated skeletal sites. Although the strength of these associations varied across skeletal sites, the highest probability of normal bone health was observed at the total hip. Furthermore, BMI demonstrated modest-to-acceptable discriminatory ability for identifying the absence of osteoporosis, with the best performance observed at the total hip and Youden index–derived thresholds ranging from approximately 28 to 29 kg/m².

Ordinal logistic regression analysis showed that higher BMI was associated with lower odds of worse bone-health status, with higher BMI categories corresponding to significantly lower odds of osteoporosis. Our findings align in part with a study of postmenopausal women using generalized additive models (GAMs), which showed a decreasing risk of osteoporosis with rising BMI; however, that study observed a U-shaped reversal after a threshold of 25.74 kg/m² [11]. Furthermore, our adjusted analyses revealed site-specific differences in osteoporosis risk, with higher BMI conferring a substantially lower risk at the total hip than at the lumbar spine or femoral neck. This site specificity is consistent with a prior meta-analysis demonstrating a stronger positive association between BMI and BMD at the total hip compared to other skeletal regions [14]. Although a positive association between BMI and the BMD at the total hip, femoral neck, and lumbar spine is widely reported across diverse postmenopausal populations [11, 16–20], a Mendelian randomization study demonstrated a positive effect of BMI on lumbar spine BMD but not on the femoral neck BMD [21]. Furthermore, some reports demonstrated that there is not even a significant association between BMI and BMD [22, 23]. These discrepancies are likely due to variations in study design, population characteristics, and statistical methods.

Anthropometric measures, including height and body weight, were positively associated with BMD in our population of postmenopausal women, consistent with previous studies reporting higher bone density among women with greater body size and weight [24, 25]. The positive association with height may partly reflect differences in skeletal size, whereas the relationship with body weight may be attributable to greater mechanical loading on the skeleton and, potentially, metabolic effects of adipose tissue on bone remodeling [25]. There is broad consensus that advancing age, an older age at menarche, and a greater number of years since menopause are associated with declining BMD in postmenopausal women, a pattern clearly reflected in our population [25–28]. These associations are biologically plausible, as both later menopause and longer reproductive lifespan indicate prolonged exposure to endogenous estrogen, which contributes to the maintenance of bone remodeling balance and may attenuate postmenopausal bone loss [28]. In line with our results, smoking has been shown to adversely affect bone health through multiple direct and indirect pathways, contributing to bone loss and increased fracture risk [17, 29]. Similarly, a history of fragility fracture was negatively associated with BMD across all measured skeletal sites in our study, consistent with evidence identifying previous fragility fracture as an important clinical marker of skeletal fragility and fracture risk, partly independent of BMD [30]. Physical activity was also positively associated with BMD, supporting the well-established role of regular exercise in preserving bone mass after menopause[25, 31]. Furthermore, our findings showed that higher parity was associated with lower BMD, consistent with some previous studies [32, 33]. However, the literature remains inconsistent, with other studies reporting no association or even a protective effect of parity on BMD [34, 35]. These discrepancies may reflect differences in study populations and methodology.

Notably, the association between BMI and BMD appears to be nonlinear rather than strictly linear [11]. Ma et al. reported that in women over 50 years of age, each unit increase in BMI below 26 kg/m² was associated with a substantially greater increase in BMD compared with BMI values above 26 kg/m² [18]. A similar nonlinear pattern was observed in another study of postmenopausal women in which femoral neck BMD increased with BMI up to a threshold, beyond which further BMI elevation was associated with a negative correlation [7]. Our findings are consistent with these reports, as BMI was positively associated with BMD at all measured skeletal sites, with a clearly nonlinear relationship. Several biological mechanisms have been proposed to explain the positive association between BMI and BMD. Increased body mass results in greater mechanical loading on weight-bearing bones, which stimulates bone formation and contributes to higher BMD [36]. In addition, individuals with higher BMI often exhibit elevated circulating levels of estrogen and insulin, both of which may favor bone preservation by reducing bone resorption and enhancing bone remodeling [8]. Conversely, obesity has also been linked to increased oxidative stress and chronic low-grade inflammation, which can promote osteoclast activity and contribute to bone loss [37, 38]. Furthermore, excess adiposity may shift mesenchymal stem cell differentiation toward adipocyte rather than osteoblast lineages, thereby reducing bone formation potential [39]. The balance between these protective and detrimental pathways may underlie the observed nonlinear relationship between BMI and BMD.

The nonlinear relationship between BMI and BMD was discussed above, and it was shown in previous studies that beyond a certain amount of BMI, further increases are associated with only minimal gains in BMD or may even have an inverse association [7, 11, 18]. Furthermore, elevated BMI plays a role as a well-established risk factor for several chronic conditions, including cardiovascular disease, type 2 diabetes, and metabolic dysfunction–associated steatotic liver disease [40–42]. Therefore, identifying a BMI threshold that balances optimal osteoporosis risk discrimination against obesity-related diseases is crucial. For instance, a nationwide study of postmenopausal women found that although a BMI ≥ 30 kg/m² was associated with the lowest osteoporosis risk, the optimal BMI range for simultaneously minimizing the risk of osteoporosis at the lumbar spine, total hip, and femoral neck, as well as type 2 diabetes, was 23.0–24.9 kg/m² [43]. In our study the Youden index showed that a BMI of approximately 28–29 kg/m² has the best discriminatory performance for the absence of osteoporosis across the measured skeletal sites, with the highest performance at the total hip. A prior study reported comparable threshold effects: using the Youden index on femoral neck BMD, the lowest combined risk of osteoporosis and osteopenia occurred at a BMI of approximately 27 kg/m² [7]. These discrepancies among the reported thresholds likely are due to the differences in study design, covariates, population characteristics, skeletal sites analyzed, and statistical methodology.

Our study has several notable strengths. First, to our knowledge, it is among the few studies to comprehensively evaluate the nonlinear association between BMI and BMD and to identify site-specific BMI thresholds across the spectrum of bone health in postmenopausal women. To the best of our knowledge, no previous study has simultaneously examined these relationships across multiple skeletal sites using this analytical framework. Methodologically, the use of advanced statistical approaches, including restricted cubic spline and ordinal logistic regression models, enabled a more nuanced assessment of nonlinear associations and ordered categories of bone health beyond conventional linear analyses. Second, our analysis utilized a large, well-characterized cohort across a wide age spectrum, with BMD evaluated at all three standard diagnostic skeletal sites to maximize clinical relevance. Third, the strict collection of detailed clinical and reproductive data permitted comprehensive adjustments for key potential confounders.

It should be noted that our study has several limitations which should be considered while interpreting our findings. First, the cross-sectional design precludes evaluating causal relationships between variables. Second, the single-center nature of the study may expose our results to selection bias, which may limit generalizability to broader community populations. Third, although BMI is widely used as an indicator of adiposity, it does not distinguish between fat mass and lean body mass and therefore may not fully reflect body composition. Fourth, BMD measurement in obese individuals using DXA may be less accurate, as excess adipose tissue can artifactually increase measured BMD values [44]. Finally, several potentially important confounders, including family history of osteoporosis and metabolic comorbidities such as diabetes mellitus and components of metabolic syndrome, were not assessed, and local cultural norms precluded the evaluation of chronic alcohol consumption within this cohort, which may have influenced the observed associations [6, 45].

In conclusion, BMI demonstrated a significant, nonlinear positive association with BMD across all measured skeletal sites in postmenopausal women. Furthermore, a BMI threshold of approximately 28–29 kg/m² provided optimal diagnostic discrimination for the absence of osteoporosis, and the highest discriminatory performance was observed at the total hip. In addition, age, height, body weight, age at menopause, duration of menstruation, physical activity, smoking status, and history of fragility fractures were associated with BMD. These findings may contribute to a better understanding of strategies for maintaining bone health in postmenopausal women. Future longitudinal prospective studies are warranted to elucidate causal mechanisms and evaluate whether BMI thresholds can enhance individualized osteoporosis screening strategies.

Declarations

Acknowledgements

The authors gratefully acknowledge all the patients who generously gave their time and participated in this study. The authors also thank the nursing staff and administrative personnel at the Bone Mineral Density Evaluation Center, Shariati Hospital, affiliated to Iranian Social Security Organization for their invaluable assistance with patient recruitment.

The authors used ChatGPT (OpenAI, GPT-5.5) solely to assist with language editing, including grammar, clarity, and readability of the manuscript. The authors reviewed and verified all edits and take full responsibility for the content of the manuscript.

Authors' contributions

ES: Conceptualization, investigation, data curation, methodology, formal analysis, visualization, writing – original draft.

MR: Investigation, data curation, project administration, writing – original draft.

MT: Formal analysis, visualization, writing – review & editing.

FS: Investigation, data curation, writing – original draft.

BS: Conceptualization, supervision, writing – review & editing.

Funding

This research received no specific grant from any funding agency.

Data availability

The datasets used and/or analyzed during the present study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committees of Islamic AZAD University- Najafabad Branch (Approval ID: IR.IAU.NAJAFABAD.REC.1402.076). Informed consent was obtained from all individual participants included in the study. All data were handled confidentially and analyzed anonymously to protect participants' privacy. The rights, safety, and well-being of all participants were safeguarded throughout the study.

Consent for publication

Not applicable.

Competing interests

Banafsheh Sedaghat, Mobin Rasapour, Marzieh Taheri, Fatemeh Salehi, and Erfan Sabouri declare that they have no conflict of interest.

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Figures

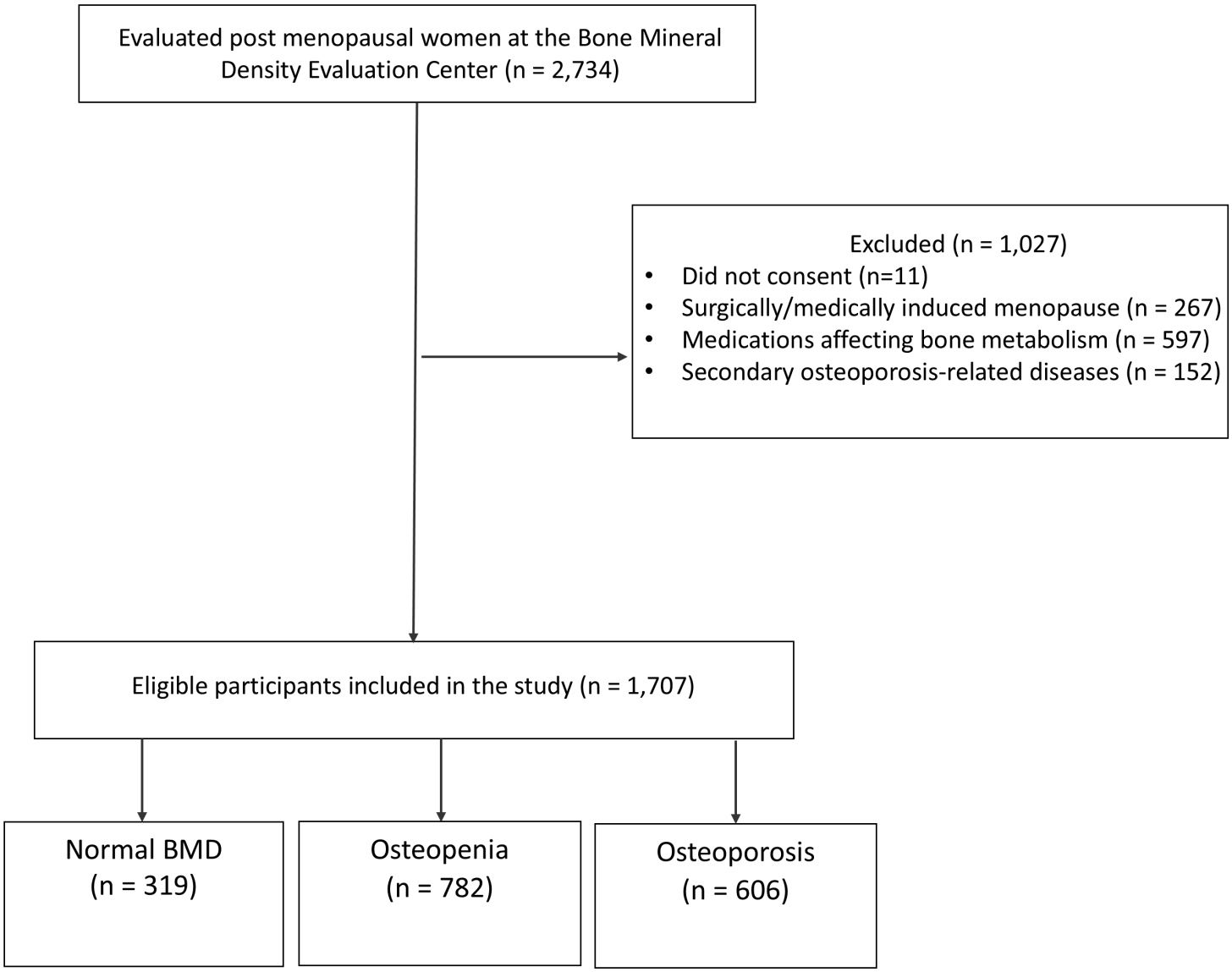


Figure 1

Flow diagram of participant selection and bone mineral density classification.

Supplementary Files

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