



OPEN Sex-specific associations between muscle-fat ratio and bone density in middle-aged adults

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Although the clinical importance of osteoporosis in middle-aged populations is widely recognized, the intricate relationships between body composition parameters, especially osteosarcopenic obesity, and bone health remain incompletely understood. This study aims to characterize the association between the skeletal muscle mass-to-visceral adipose tissue area ratio (SVR) and bone mineral density (BMD), while systematically evaluating potential variations by sex and menopausal status. Utilizing data from the National Health and Nutrition Examination Survey (2011–2018), we analyzed a cohort of 4,349 middle-aged adults (ages 40–59) with complete datasets on skeletal muscle mass (SMM), visceral adipose tissue area (VATA), and lumbar BMD. Dual-Energy X-ray Absorptiometry was employed for precise body composition analysis. Multivariate regression models were applied to analyze the relationships between SVR and BMD, with stratified analyses conducted to evaluate potential effect modifications by sex and menopausal status. Our findings revealed a significant positive correlation between SMM and BMD ($\beta = 12.8$, 95% CI: 11.2 to 14.4), while VATA exhibited an inverse relationship ($\beta = -0.5$, 95% CI: -0.6 to -0.4). Notably, men demonstrated a positive association between SVR and BMD ($\beta = 342.4$, 95% CI: 271.4 to 413.5), whereas premenopausal women displayed a non-linear, inverted U-shaped relationship between SVR and BMD, with a critical threshold identified at 0.31 kg/cm². This cross-sectional study highlights the association between SVR and lumbar BMD in middle-aged adults, revealing significant sex-specific differences. In men, higher SVR correlates with higher BMD, while in premenopausal women, BMD appears optimal when SVR falls within a specific range.

Keywords Osteoporosis, Body composition, Sarcopenic obesity, Sex-specific differences, Menopausal status

Bone mineral density (BMD) is a key biomarker for osteoporosis and fracture risk, gaining increasing relevance with population aging^{1,2}. Once considered an inevitable aspect of aging, bone loss is now understood as a modifiable process, with middle age representing a critical window for intervention—before the accelerated skeletal decline of later life^{3,4}. This period offers a strategic opportunity for proactive bone health management⁵. Identifying and targeting the physiological mechanisms underlying midlife bone metabolism could help mitigate age-related BMD deterioration, highlighting the importance of research in this demographic.

As metabolically active components of body composition, skeletal muscle and adipose tissue exhibit complex, often opposing interactions that significantly influence bone metabolism^{6,7}. While skeletal muscle enhances bone formation via mechanical loading and myokine secretion⁸, adipose tissue disrupts bone homeostasis through pro-inflammatory cytokines and metabolic dysfunction^{8–10}. Prior research has largely studied these tissues in isolation, overlooking their interdependent relationship. The skeletal muscle mass-to-visceral adipose tissue area ratio (SVR) provides a novel composite measure that reflects this physiological interplay, offering valuable insights into sarcopenic obesity and metabolic risk^{11,12}. However, the association between SVR and BMD remains poorly understood, representing a key gap in our knowledge of body composition's impact on bone health.

Sex hormones, particularly estrogen and testosterone, differentially regulate body composition and skeletal homeostasis^{13,14}, introducing sex-specific variations in the muscle-fat-bone relationship. The menopausal transition, marked by rapid estrogen depletion, highlights a key knowledge gap regarding SVR's influence on BMD, as current evidence lacks comprehensive sex- and menopause-stratified analyses. Using the National Health and Nutrition Examination Survey (NHANES) data with Dual-Energy X-ray Absorptiometry (DXA)

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-derived measurements, this study examines sex-specific associations between SVR and lumbar BMD in middle-aged adults.

Methods

Study design and population

NHANES is a comprehensive cross-sectional study conducted by the Centers for Disease Control and Prevention, offering a nationally representative assessment of the health and nutritional status of the U.S. population. Employing a rigorous methodology, NHANES integrates standardized household interviews with detailed physical examinations at Mobile Examination Centers, generating high-quality, multidimensional epidemiological data. In this investigation, we leveraged NHANES data from 2011 to 2018 to elucidate the intricate relationships between skeletal muscle mass (SMM), visceral adipose tissue area (VATA), and their compositional ratio with lumbar BMD among middle-aged adults. The research protocol received approval from the National Center for Health Statistics Research Ethics Review Board, with written informed consent obtained from all participants. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines¹⁵.

From an initial cohort of 39,156 individuals, we implemented rigorous inclusion and exclusion criteria to optimize data quality and research precision. Participant selection criteria were meticulously defined: individuals aged 40–59 years with complete datasets encompassing SMM, VATA, and lumbar BMD. We systematically refined the sample by excluding participants with: incomplete covariate information, ambiguous menstrual status, and documented cancer history. Following comprehensive screening, the final analytical sample comprised 4,349 participants (Fig. 1).

Measurements of SVR and lumbar BMD

DXA was employed for body composition analysis, enabling precise quantification of SMM, VATA, and lumbar BMD. SMM was calculated by aggregating lean mass from all four extremities using whole-body DXA scan data.

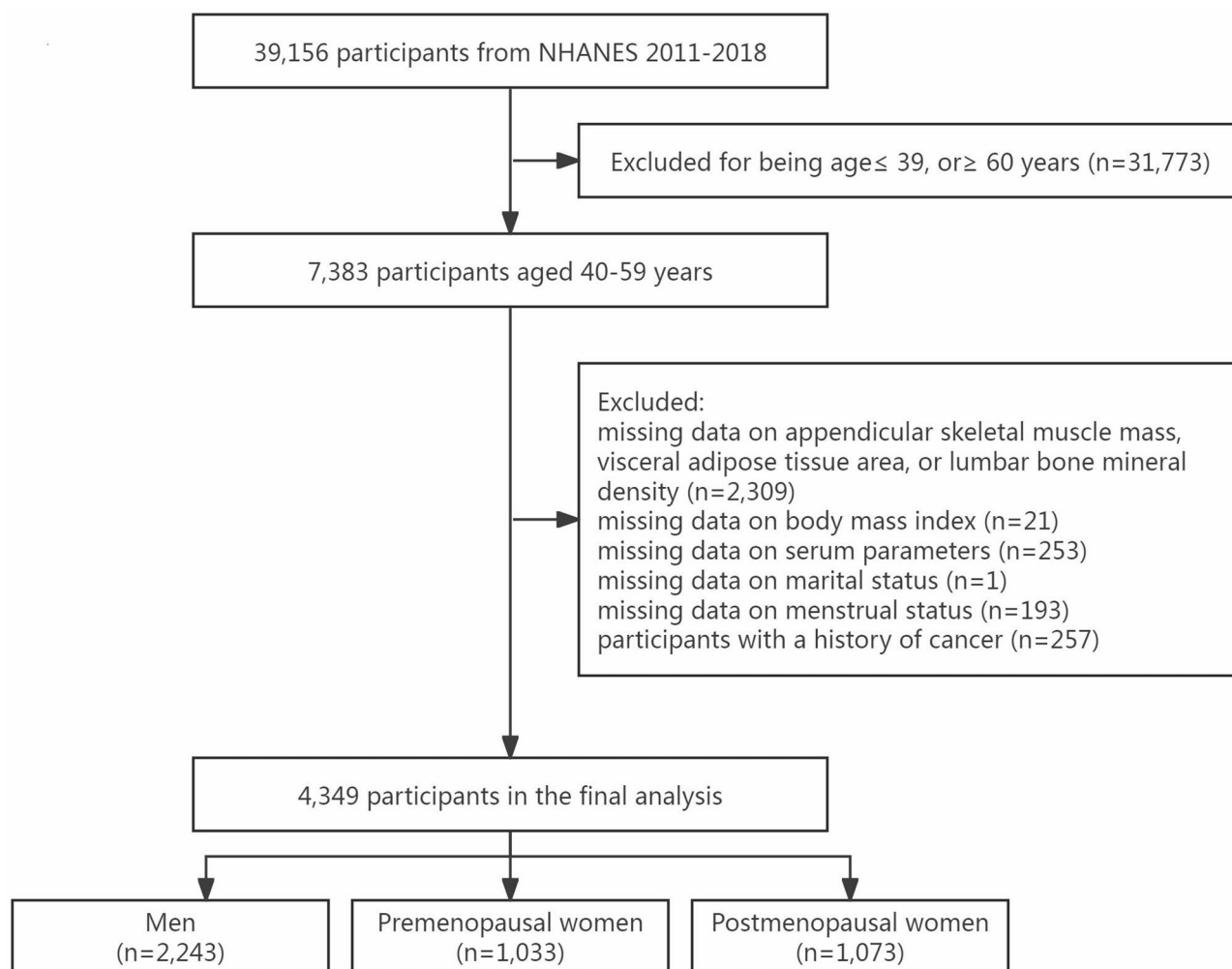


Fig. 1. Sample inclusion and exclusion flowchart.

VATA was meticulously measured at the intervertebral space between L4 and L5 vertebrae. To ensure optimal data quality, all DXA examinations were conducted by radiologic technologists with specialized training and certification in precision imaging techniques.

Confounding variables

The analytical framework incorporated a multidimensional set of covariates, stratifying participants by demographic characteristics including age, sex (men, premenopausal and postmenopausal women), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other), educational level (less than high school, high school, and more than high school), and marital status (married/living with partner, widowed/divorced/separated, and never married). Behavioral and physiological parameters were meticulously assessed, encompassing body mass index (BMI), sedentary lifestyle, hypertension and diabetes history, and serum biochemical markers (calcium, glucose, total protein, blood urea nitrogen, triglycerides, and total cholesterol). Demographic information was extracted from validated questionnaires. Sedentary status was determined through self-reported questionnaires, with participants classified as sedentary behavior if they reported no participation in either moderate or vigorous leisure-time physical activities. Menopausal status was classified based on self-reported absence of menstruation for ≥ 12 month. Hypertension and diabetes histories were systematically documented using specific questionnaire modules. Detailed methodological protocols are publicly accessible at www.cdc.gov/nchs/nhanes/.

Statistical analyses

Descriptive statistics were expressed as mean \pm standard deviation for continuous variables and percentages for categorical variables. Inter-group differences were rigorously evaluated using appropriate statistical tests: χ^2 tests for categorical data, one-way ANOVA for normally distributed continuous variables, and Kruskal-Wallis H tests for skewed distributions.

Multivariate linear regression analyses were employed to examine the correlations of SMM, VATA, and SVR with lumbar BMD, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines¹⁵. The analytical strategy comprised four progressive regression models: Model 1: unadjusted base model; Model 2: adjusted for age, sex, and race; Model 3: additional adjustment for BMI; Model 4: fully adjusted for all pre-screened covariates. Subgroup analyses were conducted using stratified linear regression models to explore potential effect modifications across demographic and clinical subpopulations. To comprehensively characterize the relationship, we applied advanced statistical techniques, including smooth curve fitting and generalized additive models, to investigate potential non-linear associations. We further employed a two-piecewise regression model to investigate the threshold effect of SVR on lumbar BMD. All statistical analyses were performed using R software (version 3.4.3) and EmpowerStats (X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as two-sided P values less than 0.05.

Results

The characteristics of participants across sex and menopausal status are presented in Table 1. BMI progressively increased from men (28.8 ± 5.5) to premenopausal (29.8 ± 7.5) to postmenopausal women (30.1 ± 7.0), with postmenopausal women experiencing notably higher hypertension (40.8%) and diabetes (14.3%) prevalence. Men exhibited the highest SMM (26.8 ± 5.0 kg), significantly surpassing premenopausal (18.6 ± 4.4 kg) and postmenopausal women (18.1 ± 4.0 kg). VATA was correspondingly higher in men (129.5 ± 54.9 cm²) compared to premenopausal (105.2 ± 55.7 cm²) and postmenopausal women (125.2 ± 59.5 cm²). SVR stratification revealed highest values in men (0.24 ± 0.11 kg/cm²), followed by premenopausal (0.23 ± 0.17 kg/cm²) and postmenopausal women (0.18 ± 0.13 kg/cm²). Lumbar BMD demonstrated significant variations, with postmenopausal women showing the lowest values (976.4 ± 158.5 mg/cm²) compared to premenopausal women (1065.5 ± 148.3 mg/cm²) and men (1023.5 ± 164.3 mg/cm²).

Correlation analyses unveiled significant associations between body composition components and lumbar BMD. SMM demonstrated a positive correlation with BMD, whereas VATA exhibited an inverse relationship (Table 2). SVR exhibited a progressive and systematic increase across sequential multivariate regression models. These intricate associations were comprehensively validated through advanced statistical modeling and graphical representations (Fig. 2).

Subgroup analysis revealed pronounced sex-specific interactions in the associations between SMM, VATA, and SVR with lumbar BMD (Fig. 3). Postmenopausal women demonstrated a positive relationship with SMM ($\beta = 15.3$, 95% CI: 11.4–19.2), while men exhibited an inverse relationship with VATA ($\beta = -0.7$, 95% CI: -0.9 to -0.6). The SVR revealed significant sex differences, with men demonstrating a stronger association ($\beta = 342.4$, 95% CI: 271.4–413.5) than postmenopausal women ($\beta = 156.6$, 95% CI: 78.1–235.1). Notably, this association remained statistically non-significant in premenopausal women ($\beta = 44.6$, 95% CI: -11.6–100.8). In racial/ethnic subgroup analyses, the most pronounced association between SVR and BMD was observed in Mexican American participants ($\beta = 305.9$, 95% CI: 160.1–451.6).

Generalized additive models and smooth curve fittings substantiated these sex-stratified associations (Fig. 4), notably revealing an inverted U-shape relationship in premenopausal women between SVR and lumbar BMD. As initial linear regression analysis revealed no statistically significant association between SVR and BMD in premenopausal women, a two-piecewise linear regression model was conducted and identified a critical threshold at 0.31 kg/cm², demonstrating a significant positive association below this point ($\beta = 360.48$, 95% CI: 206.18–514.78) and a negative trend beyond it ($\beta = -47.05$, 95% CI: -116.66–22.55), with the log-likelihood ratio test confirming the model's statistical significance (Table 3).

	Men (<i>n</i> = 2243)	Premenopausal women (<i>n</i> = 1033)	Postmenopausal women (<i>n</i> = 1073)	<i>P</i> value
Age (years)	49.2 ± 5.7	45.5 ± 4.0	52.8 ± 4.7	< 0.001
Race/Ethnicity (%)				< 0.001
Non-Hispanic White	33.7	31.1	33.6	
Non-Hispanic Black	19.6	22.6	25.3	
Mexican American	14.7	17.4	14.2	
Other race/ethnicity	32.1	28.9	26.9	
Education level (%)				< 0.001
Less than high school	22.6	19.5	18.8	
High school	22.9	17.2	25.3	
More than high school	54.5	63.3	55.8	
Marital status (%)				< 0.001
Married/Living with Partner	73.0	65.9	60.0	
Widowed/Divorced/Separated	16.2	20.4	30.1	
Never married	10.8	13.6	9.9	
Sedentary behavior (%)				0.005
Yes	48.6	48.2	54.1	
No	51.4	51.8	45.9	
Hypertension (%)				< 0.001
Yes	33.3	26.8	40.8	
No	66.7	73.2	59.2	
Diabetes (%)				< 0.001
Yes	13.0	8.7	14.3	
No	87.0	91.3	85.7	
Body mass index (kg/m²)				< 0.001
Total protein (g/L)	71.7 ± 4.6	71.1 ± 4.4	71.6 ± 4.5	0.007
Blood urea nitrogen (mmol/L)	5.0 ± 1.8	4.1 ± 1.5	4.7 ± 1.6	< 0.001
Serum calcium (mmol/L)	2.34 ± 0.09	2.31 ± 0.08	2.35 ± 0.09	< 0.001
Serum glucose (mmol/L)	6.0 ± 2.7	5.7 ± 2.6	5.8 ± 2.4	< 0.001
Triglycerides (mmol/L)	2.1 ± 1.8	1.6 ± 1.3	1.7 ± 1.0	< 0.001
Total cholesterol (mmol/L)	5.1 ± 1.1	5.0 ± 1.0	5.4 ± 1.1	< 0.001
Skeletal muscle mass (kg)	26.8 ± 5.0	18.6 ± 4.4	18.1 ± 4.0	< 0.001
Visceral adipose area ratio (cm ²)	129.5 ± 54.9	105.2 ± 55.7	125.2 ± 59.5	
Skeletal muscle mass to visceral adipose area ratio (kg/cm ²)	0.24 ± 0.11	0.23 ± 0.17	0.18 ± 0.13	< 0.001
Lumbar bone mineral density (mg/cm ²)	1023.5 ± 164.3	1065.5 ± 148.3	976.4 ± 158.5	< 0.001

Table 1. The characteristics of participants.

Discussion

Our investigation found distinct associations between body composition and lumbar BMD in middle-aged adults. SMM showed a strong positive correlation with BMD, whereas VATA displayed a significant inverse relationship. Most strikingly, the SVR-BMD association demonstrated marked sexual dimorphism: men exhibited a robust linear correlation, while premenopausal women showed a characteristic inverted U-shaped relationship.

Our findings aligned with and extend existing literature on the complex interplay between body composition and bone health. Previous research has consistently demonstrated the protective role of skeletal muscle on bone health, with studies revealing positive associations between muscle mass and BMD across diverse age groups, including both adults and adolescents^{16–18}. Concurrently, visceral adipose has been substantiated as a negative predictor of BMD, reinforcing the detrimental metabolic impact of excess adiposity^{19,20}. Our sex-stratified analyses revealed distinct sexual dimorphism in body composition-BMD relationships: postmenopausal women showed the strongest positive association between SMM and BMD, whereas men exhibited the most marked inverse relationship between VATA and BMD. These differential associations suggest fundamental sex-specific regulatory pathways in bone metabolism, supporting the implementation of sex-differentiated clinical approaches.

The innovative application of SVR as a composite metric addresses a critical limitation of isolated tissue analyses by revealing a sophisticated inverted U-shaped association in premenopausal women, thereby challenging the linear assumptions of previous models. Evidence suggests that increased visceral adiposity and decreased muscle mass are associated with various metabolic and cardiovascular risks, including dyslipidemia, insulin resistance, and metabolic syndrome^{21–23}. We hypothesized that a moderate SVR optimizes the mechanical and metabolic synergy essential for bone health, while extremes may disrupt this equilibrium, potentially affecting bone health.

	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 β (95% CI)
Skeletal muscle mass	5.8 (5.0, 6.5) ***	7.7 (6.6, 8.7) ***	13.2 (11.6, 14.8) ***	12.8 (11.2, 14.4) ***
Q1	Reference	Reference	Reference	Reference
Q2	31.3 (17.9, 44.7)	36.6 (22.9, 50.3)	46.3 (31.3, 61.4)	44.4 (29.4, 59.4)
Q3	35.1 (21.7, 48.5)	56.3 (40.0, 72.7)	73.1 (53.5, 92.8)	70.6 (51.0, 90.2)
Q4	85.6 (72.2, 98.9)	101.3 (83.1, 119.6)	126.1 (101.7, 150.5)	119.4 (94.9, 143.9)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001
Visceral adipose tissue area	-0.3 (-0.3, -0.2) ***	-0.1 (-0.2, 0.0)	-0.5 (-0.6, -0.3) ***	-0.5 (-0.6, -0.4) ***
Q1	Reference	Reference	Reference	Reference
Q2	-16.9 (-30.4, -3.4)	-5.6 (-18.6, 7.4)	-25.2 (-38.7, -11.7)	-23.6 (-37.1, -10.0)
Q3	-40.6 (-54.1, -27.0)	-20.0 (-33.2, -6.8)	-52.5 (-67.2, -37.8)	-50.9 (-65.9, -36.0)
Q4	-49.5 (-63.0, -35.9)	-21.8 (-35.3, -8.3)	-76.3 (-93.7, -58.8)	-77.6 (-95.6, -59.7)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001
Skeletal muscle mass to visceral adipose tissue area ratio	219.1 (184.3, 254.0)	113.6 (78.0, 149.2) ***	174.7 (136.3, 213.1) ***	168.6 (129.5, 207.7) ***
Q1	Reference	Reference	Reference	Reference
Q2	36.6 (23.3, 49.9)	24.0 (10.7, 37.2)	34.0 (20.8, 47.3)	35.4 (22.2, 48.7)
Q3	62.0 (48.8, 75.3)	39.7 (26.0, 53.4)	57.4 (43.3, 71.5)	58.9 (44.6, 73.1)
Q4	99.2 (85.9, 112.4)	59.0 (44.7, 73.3)	89.2 (73.7, 104.8)	89.9 (73.9, 105.9)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001

Table 2. Correlations of skeletal muscle mass (kg), visceral adipose tissue area (cm²) and their ratio with lumbar bone mineral density (mg/cm²). Model 1: no covariates were adjusted. Model 2: age, sex and race were adjusted. Model 3: age, sex, race and body mass index were adjusted. Model 4: age, sex, race, educational level, marital status, sedentary behavior, history of hypertension, history of diabetes, body mass index, total protein, blood urea nitrogen, serum calcium, serum glucose, triglycerides and total cholesterol were adjusted. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

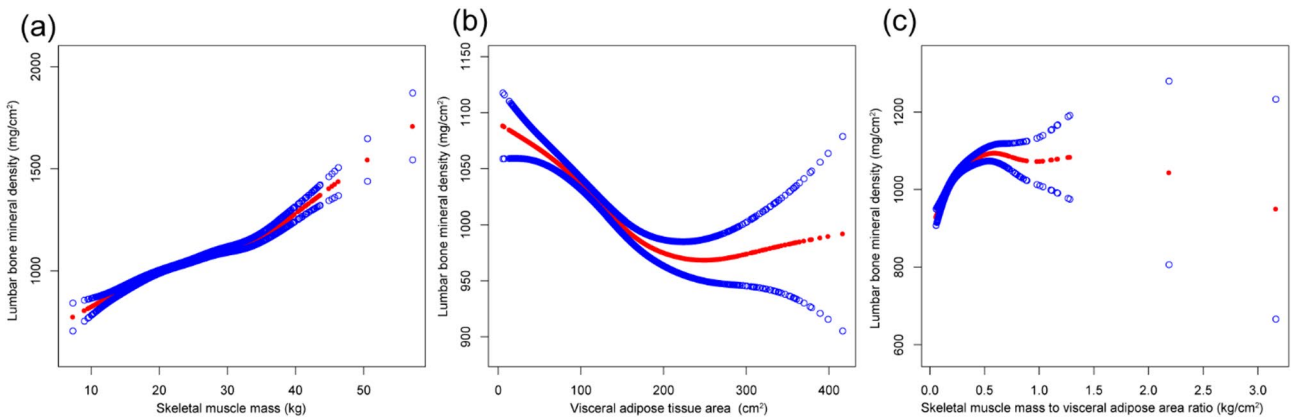


Fig. 2. The correlations of skeletal muscle mass, visceral adipose tissue area and their ratio with lumbar bone mineral density. Age, sex, race, educational level, marital status, sedentary behavior, history of hypertension, history of diabetes, body mass index, total protein, blood urea nitrogen, serum calcium, serum glucose, triglycerides and total cholesterol were adjusted.

indirectly by altering metabolic pathways and hormonal balance^{24,25}. The stronger association between SVR and BMD in men likely reflects their inherently greater muscle mass and lower estrogen levels, which enhance the relative contribution of mechanical loading to bone maintenance^{26,27}. The threshold effect observed in premenopausal women indicates a dynamic interplay between anabolic muscle-driven and catabolic fat-driven signals, influenced by the hormonal stability characteristic of this phase^{28,29}. Future studies should investigate whether interventions targeting SVR optimization can improve BMD in this population.

The intricate balance between SMM and VATA emerges as a pivotal determinant of optimal BMD. Robust SMM confers both mechanical and metabolic advantages that safeguard against osteoporosis, whereas excessive VATA precipitates adverse metabolic and inflammatory cascades detrimental to bone health. Mechanistically, skeletal muscle exerts direct mechanical forces on bone tissue, stimulating osteogenesis and remodeling processes essential for BMD maintenance³⁰. Furthermore, myokines secreted by skeletal muscle, particularly irisin, play a crucial role in enhancing bone formation, with specific effects on cortical bone architecture^{31,32}. Concurrently,

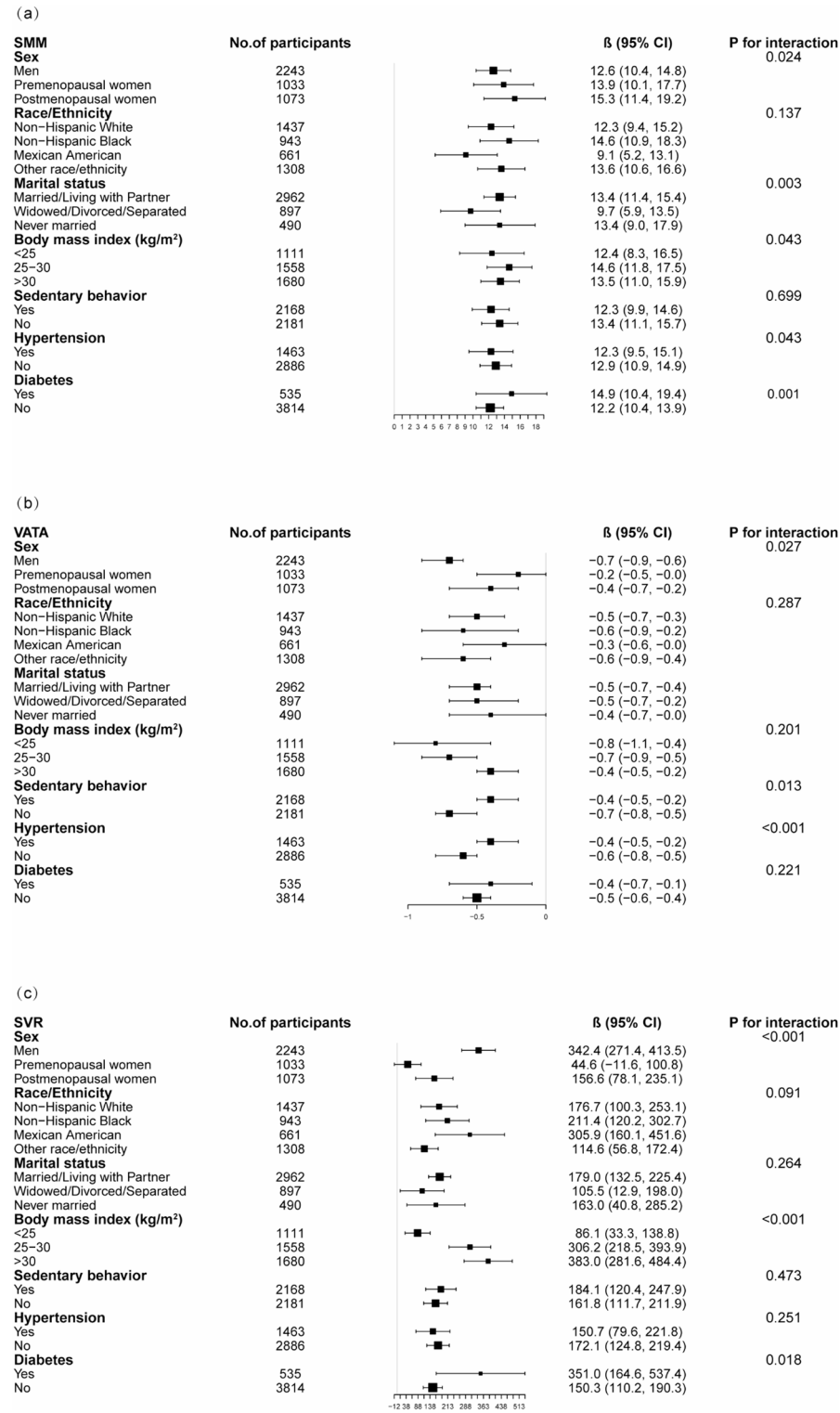


Fig. 3. Subgroup analysis of the correlations of skeletal muscle mass, visceral adipose tissue area and their ratio with lumbar bone mineral density. Age, sex, race, educational level, marital status, sedentary behavior, history of hypertension, history of diabetes, body mass index, total protein, blood urea nitrogen, serum calcium, serum glucose, triglycerides and total cholesterol were adjusted. In the subgroup analysis, the model is not adjusted for the stratification variable itself. SMM: skeletal muscle mass VATA: visceral adipose tissue area SVR: skeletal muscle mass to visceral adipose tissue area ratio.

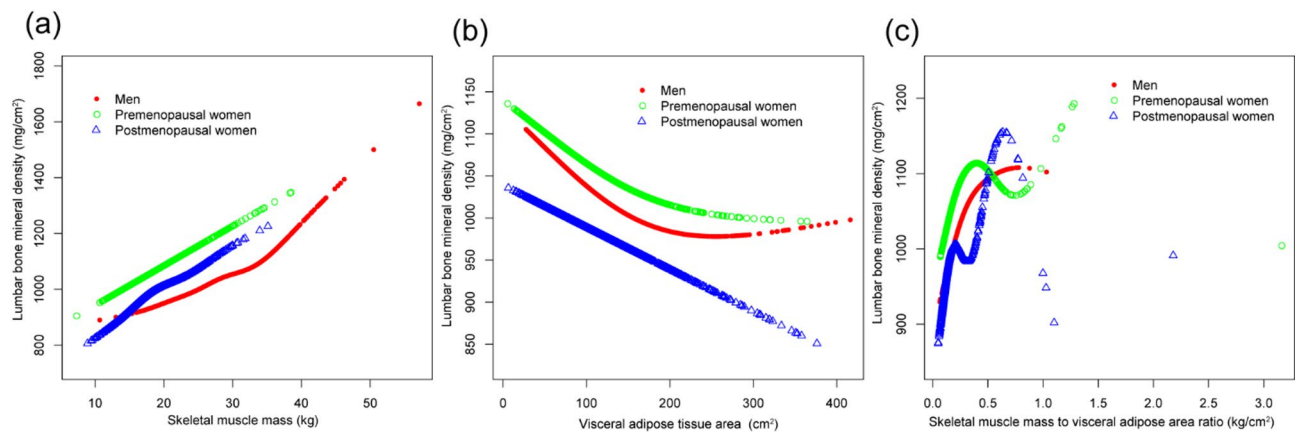


Fig. 4. Sex-stratified smooth curve analysis of the the correlations of skeletal muscle mass, visceral adipose tissue area and their ratio with lumbar bone mineral density. Age, race, educational level, marital status, sedentary behavior, history of hypertension, history of diabetes, body mass index, total protein, blood urea nitrogen, serum calcium, serum glucose, triglycerides and total cholesterol were adjusted.

Lumbar bone mineral density	Adjusted β (95% CI), p -value
Skeletal muscle mass to visceral adipose area ratio	
Fitting by standard linear model	44.6 (-11.6, 100.8), 0.120
Fitting by two-piecewise linear model	
Inflection point	0.31 (kg/cm ²)
< 0.31 (kg/cm ²)	360.48 (206.18, 514.78) < 0.001
> 0.31 (kg/cm ²)	-47.05 (-116.66, 22.55) 0.186
Log likelihood ratio	< 0.001

Table 3. Threshold effect analysis of skeletal muscle mass to visceral adipose area ratio (kg/cm²) on lumbar bone mineral density (mg/cm²) in premenopausal women using two-piecewise linear regression model. Age, race, educational level, marital status, sedentary behavior, history of hypertension, history of diabetes, body mass index, total protein, blood urea nitrogen, serum calcium, serum glucose, triglycerides and total cholesterol were adjusted.

skeletal muscle-derived adipokines, including leptin and adiponectin, modulate glucose metabolism and systemic inflammation, thereby indirectly influencing bone metabolism through complex endocrine pathways^{33,34}. In contrast, visceral fat accumulation triggers the release of pro-inflammatory cytokines such as IL-6 and TNF- α , which disrupt bone homeostasis and promote osteoclastogenesis^{35,36}. While animal and in vitro studies suggest that myokines and adipokines modulate bone metabolism, these biomarkers were not available in our dataset to directly test their roles. Thus, the observed associations may reflect broader muscle-fat-bone interactions warranting further investigation. Notably, the inverted U-shaped association in premenopausal women suggests a hormonally sensitive equilibrium. While moderate SVR optimizes the anabolic effects of muscle-derived mechanical loading on bone formation, excessively high SVR could disrupt endocrine homeostasis in this population. On the other hand, for clinical settings lacking DXA capabilities, SVR may be approximated using widely available tools such as bioelectrical impedance analysis for muscle mass assessment and waist circumference measurements for visceral fat estimation, though with acknowledged limitations in precision compared to DXA.

To the best of our knowledge, this is one of the first studies to employ the SVR metric for characterizing a non-linear, inverted U-shaped relationship between body composition and lumbar BMD in premenopausal women, while also highlighting sex-specific differences in middle-aged adults. The large sample size enhances the reliability of our findings and allows for meaningful statistical analyses. Furthermore, the standardized data collection process ensures high-quality and consistent measurements of the variables. However, several limitations should be noted. First, the study's reliance on NHANES data precludes causal inference, as temporal relationships between SVR and BMD cannot be established. Longitudinal studies are required to delineate dynamic changes in body composition and bone health trajectories. Second, although we adjusted for several covariates, residual confounding may still exist due to unmeasured factors such as hormonal levels, measurements of key biomarkers (e.g., myokines, adipokines, inflammatory cytokines), dietary habits and genetic predispositions, which could modulate muscle-fat-bone interactions. Third, menopausal status was determined solely by self-reported menstrual history, which may misclassify women with irregular cycles. Fourth, our study, focused on middle-aged adults and excluding individuals with a history of cancer, enhances

internal validity while inherently limiting the generalizability of the findings to younger and older populations, as well as cancer survivors, who may possess differing body composition and bone health profiles.

Conclusion

In conclusion, this study found significant associations between SVR and lumbar BMD in middle-aged adults, with notable sex-specific variations. Notably, men exhibited a positive correlation between elevated SVR and higher BMD, whereas in premenopausal women, BMD appeared to peak within an specific SVR range. These results advocate for a personalized approach to osteoporosis prevention, emphasizing the importance of considering individual body composition profiles in clinical practice.

Data availability

The data of this study are publicly available on the NHANES website (<https://www.cdc.gov/nchs/nhanes/>).

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Author contributions

FJ, STG and XCY contributed to data collection, analysis and writing of the manuscript. ZXX contributed to study design, analysis, writing and editing of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The ethics review board of the National Center for Health Statistics approved all NHANES protocols and written informed consents were obtained from all participants.

Additional information

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