BMC Geriatrics

RESEARCH

Open Access

The obesity paradox in osteoporosis risk among older adults is mostly driven by women: a population-based prospective study

Qingfeng Luo[1,2,3,4†], Shiyong Zhang[5†], Zixin Liang[6†], Danni Wang[9], Yanlin Zhong[5], Bin Xia[6], Peng Xie[7,8], Can Wang[1,2,3,4], Jinqiu Yuan[6,7,8*], Ziji Zhang[5*] and Xingsheng Li[1,2,3,4*]

Abstract

Objectives The obesity paradox is common among older adults at risk for various diseases. Although this paradox has also been observed in the association between obesity and osteoporosis, the available evidence remains controversial. This study aimed to investigate the association between obesity and OP risk in an older population.

Methods A cross-sectional and prospective study was conducted using data from 177,734 participants in the UK Biobank. The association of body mass index (BMI), waist circumference (WC), and fat percentage with BMD was examined using Spearman correlation analysis with baseline BMD data. Cox proportional hazards regression analysis was used to investigate the association between obesity and OP risk. Restricted cubic spline (RCS) were used to assess the nonlinear associations of BMI, WC, and fat percentage with OP.

Results Baseline cross-sectional analyses revealed a significant positive association between BMI, WC, and fat percentage with BMD in women, whereas this association was very weak in men. A total of 8,998 OP patients were identified during a median follow-up period of 13.7 years. Cox analyses showed that obesity as defined by BMI, WC, and fat percentage was associated with a 33%, 23%, and 31% reduction in the risk of OP in older women but not in men, respectively. Conjoint analysis showed that lower BMI was associated with increased risk of OP in older adults, whereas the lowest risk was observed in women with higher BMI and higher body fat. RCS revealed an inverse J-shaped nonlinear association between obesity metrics and OP risk in women.

Conclusion Lower BMI is an independent risk factor for OP in older adults, and the obesity paradox for OP risk exists only in women.

Keywords Obesity, Obesity paradox, Osteoporosis, Older adults

[†]Qingfeng Luo, Shiyong Zhang and Zixin Liang contributed equally to this work.

*Correspondence:
Jinqiu Yuan
yuanjq5@mail.sysu.edu.cn
Ziji Zhang
zhangziji@mail.sysu.edu.cn
Xingsheng Li
ptlxs@163.com
Full list of author information is available at the end of the article

Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by bone loss and fragility, leading to an increased risk of fracture [1]. According to the report published by the International Osteoporosis Foundation (IOF) in 2019, more than 30 million people were living with OP in the European Union plus Switzerland and the United Kingdom (UK), as well as over 200,000 related deaths [2]. Due to population aging, the number of osteoporotic fractures is estimated to increase by 25% per year by 2034 [3]. Age-related OP can be induced by environmental factors, unhealthy lifestyles, and other systemic interactions affecting the skeleton [4–6] . Endocrine disruption relating to aging and obesity and reduced exercise can cause imbalances in bone metabolism and bone loss, increasing the risk of OP [7]. However, the findings of recent studies have shown that obesity has a positive association with bone mineral density (BMD) and a negative association with the risk of OP, leading to an 'obesity paradox' in discussions around bone health [8].

Growing evidence suggests that the 'obesity paradox' is prevalent among the elderly, whereby individual obesity is paradoxically associated with health benefits. A recent cohort study has identified a causal association of higher body mass index (BMI) and waist circumference (WC) with reduced mortality in a longevity population (aged ≥ 80 years), whereas obesity has consistently been proven to increase cardiovascular risk [9] . Previous evidence has confirmed that obesity, as defined by BMI, is positively associated with BMD levels in older adults and exhibits a protective association with OP [10, 11]. In addition, two surveys utilizing data from the National Health and Nutrition Examination Survey (NHANES) have shown that obesity, defined by WC, also serves as a protective factor for OP in individuals over 60 years of age and that WC is nonlinearly associated with BMD [12, 13] . Regarding body fat, although WC can partially represent the fat accumulation in an individual's body, the association between obesity (defined by fat percentage alone) and OP remains controversial. Several studies have indicated that muscle-reducing obesity or normal-weight obesity (high body fat levels) is associated with an increased risk of OP [14, 15]. Therefore, the complex association between obesity and OP in older adults may be influenced by differences in the definition of obesity. Moreover, because the prevalence of OP is significantly higher in women, men have not received sufficient attention in related studies [16] . Given the significant health differences between women and men, sex may be a potential confounder in the relationship between obesity and bone health [17].

The present study using the UK Biobank data, focusing on individuals aged 60 years and older, to investigate the association between obesity and OP risk in older adults. We examined cross-sectional associations between measures of obesity (BMI, WC, and fat percentage) and ultrasound-measured BMD of the heel bone at baseline, and estimated the association between obesity and OP risk in a longitudinal cohort. Our aim was to identify the optimal range of BMI in the older adults and to elucidate the 'obesity paradox' in bone health.

Methods

Study population

The UK Biobank is a large-scale prospective cohort of over 500,000 participants aged 37–73 years who were enrolled between 2006 and 2010 [18]. All participants completed baseline data collection via touchscreen questionnaires and face-to-face interviews at assessment centers in England, Scotland, and Wales [19, 20]. Additionally, a subset of participants underwent further tests, including fat measurement and heel ultrasound bone density [19]. For the purposes of this study, we included only participants who were 60 years of age and older and had baseline physical measurements available. After excluding participants with missing covariates, lost to follow-up, or diagnosed with cancer, a total of 177,734 participants were included. Of these, 97,735 participants had available heel ultrasound BMD values. (Fig. 1).

Exposures

Participants underwent face-to-face body measurements at multiple assessment centers. Standing height was measured using a Seca 202 device, and weight was measured using various methods during the initial assessment center visit. BMI was calculated as weight (kg) divided by the square of height (m). Waist circumference was measured by trained staff using a tape measure. Body fat was measured by bioelectrical impedance (BI), and fat percentage was calculated. Obesity was defined according to different body metrics, including: obesity classified by BMI (≥ 30, with no distinction between genders); obesity classified by waist circumference (≥ 94 cm in men or ≥ 80 cm in women); and obesity classified by fat percentage (≥ 30% in men or ≥ 40% in women) [21, 22].

Outcomes

Participants (n = 278,764) initially underwent heel ultrasound bone densitometry (Sahara Clinical Bone Sonometer) at baseline. This non-invasive bone density assessment protocol does not directly measure bone mineral density but instead measures speed of sound (SOS in meters per second) and broadband ultrasound attenuation (BUA in decibels per megahertz). These results are combined to produce a quantitative ultrasound index (QUI) or 'hardness.' From these measurements, bone

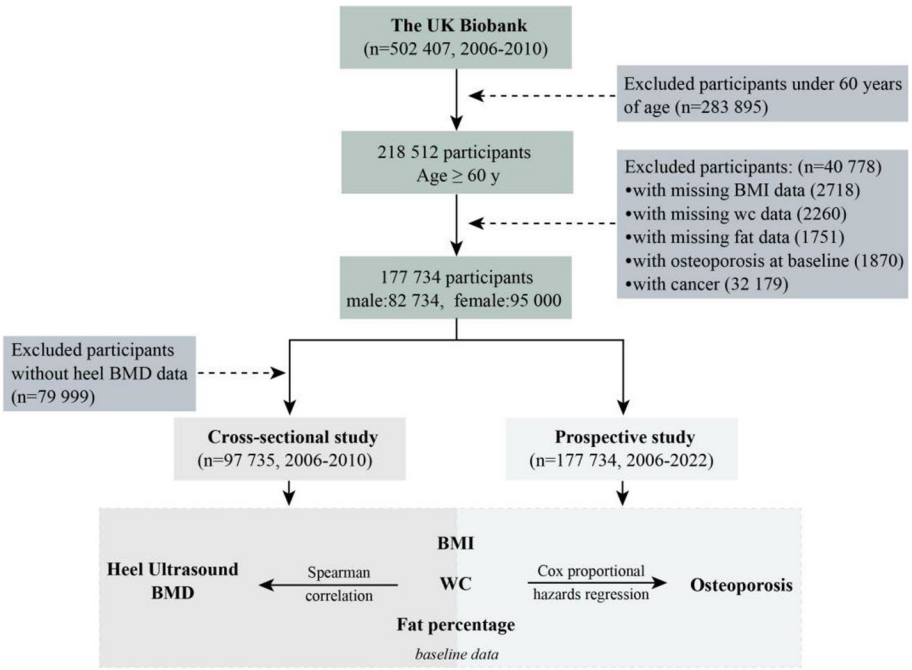

Fig. 1 Flow diagram and study design

mineral density (BMD in g/cm^2), which compares a person's bone density to the average peak bone density of a healthy young adult of the same sex, are estimated. Additionally, during follow-up, participants' status was determined as either OP diagnosis, death, or follow-up cutoff (December 31, 2022). According to the International Classification of Diseases (ICD, 10th Revision), the definition of OP includes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere). The diagnostic information primarily comes from primary care, hospital admission data, and self-reports. Some participants had multiple instances of diagnostic information, but we used the first diagnosis as the outcome event.

Confounders

Potential confounders are described in detail elsewhere [5]. These included age; deprivation (the Index of Multiple Deprivation, IMD); smoking status (never, previous, current); alcohol consumption (daily or almost daily, 1–4 times a week, 1–3 times a month, and special occasions only/never); physical activity (metabolic equivalent of task (MET), with MET < 600 min defining low levels and MET ≥ 600 min defining high levels); vegetable and fruit intake (≥ 5 portions per day or none); vitamin intake (yes or no, including vitamin D); and mineral intake (yes or no, including calcium).

Statistical analysis

Baseline characteristics based on OP diagnosis were summarized. The normality distribution of continuous variables was assessed using the Jarque–Bera test. Categorical variables were expressed using percentages and frequencies, while continuous variables were presented as mean (standard deviation, SD) for normally distributed variables and median (interquartile range, IQR) for skewed variables.

For cross-sectional analyses, Spearman rank correlation analyses were used to examine the correlation of BMI, WC, and fat percentage with BMD. To more accurately assess these relationships, partial Spearman correlations were also used, adjusting for potential confounders including age, sex, smoking status, alcohol consumption, diet (fruit, vegetable, vitamin, and mineral intake), and physical activity.

For longitudinal cohort analyses, Cox proportional hazards regression analyses were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between various definitions of obesity and OP risk. The proportional hazards assumption was tested using the Schoenfeld residual method. Two types of Cox models were used: the basic model (adjusted for gender and age only) and the full model (adjusted for gender, age, IMD, smoking, alcohol consumption, fruit and vegetable intake, vitamin intake, mineral intake, and physical activity). Restricted cubic spline (RCS) analysis was employed within the Cox models to explore potential nonlinear

relationships between BMI, WC, and fat percentage and OP risk. A three-part model at the 10th, 50th, and 90th percentiles was used to flexibly model these associations. Furthermore, to investigate the combined effect of the indicators, combinations of the two modalities (BMI + WC, BMI + fat percentage) were included in the analysis to model different body types. We used quartiles to categorize BMI into 'higher,' 'medium,' and 'lower' groups, representing the highest 25%, the middle 50%, and the lowest 25%, respectively. WC and fat percentage were categorized into 'higher' and 'lower' groups using the median as the threshold. The Cox model used the medium BMI + lower WC/fat percentage group as the reference group to explore this joint effect. Finally, we conducted replication analyses in multiple subgroups to test the robustness of these associations across different populations, including subgroups based on gender, chronic disease status (yes, primarily including diabetes and hypertension, or no), alcohol consumption, smoking status, and physical activity.

All analyses were performed using R software (Windows, version 4.4.0). Statistical tests were two-sided, and P values less than 0.05 were considered statistically significant differences.

Results

A total of 177,734 participants, with a mean age of 64.5 years, were enrolled in this study, including 82,734 men and 95,000 women. Over a median follow-up time of 13.7 years, 8998 osteoporotic participants were identified. At baseline, there were no significant differences between osteoporotic and non-osteoporotic participants in alcohol and smoking habits; osteoporotic participants consumed more fruits, vegetables, vitamins, and minerals, though. Concerning obesity, non-osteoporotic participants had significantly higher obesity rates than osteoporotic participants, with higher BMI and WC. However, although non-osteoporotic participants also had higher obesity rates based on fat percentage compared to osteoporotic participants, their overall fat percentage was lower. (Table 1).

Correlation between obesity indicators and BMD

In the present study, baseline heel ultrasound BMD data were available for 97,735 participants, with their baseline characteristics shown in eTable 1. All obesity indicators did not conform to a normal distribution, and the trends in their distribution and correlations with BMD are shown in Fig. 2. In the overall population, BMI ($r=0.12$, $p<0.01$) and WC ($r=0.19$, $p<0.01$) showed weak positive correlations with BMD, whereas fat percentage ($r=-0.14$, $p<0.01$) showed a weak negative correlation with BMD. However, significant differences were observed in gender subgroups. In men, BMI ($r=0.07$, $p<0.05$), WC ($r=0.02$, $p<0.05$), and fat percentage ($r=0.03$, $p<0.05$) showed very weak positive correlations with BMD. In women, these correlations were significantly stronger for BMI ($r=0.13$, $p<0.01$), WC ($r=0.10$, $p<0.01$), and fat percentage ($r=0.13$, $p<0.01$) compared to men. The partial Spearman correlation, adjusted for confounders, maintained the same trend as the Spearman rank correlation (eTable 2).

Association between obesity and OP risk

Cox regression modeling indicated that obesity was associated with a reduced risk of OP in older adults. When compared to nonobese participants, individuals classified as obese based on BMI, fat percentage, and WC demonstrated a 29% (HR: 0.71, 95% CI: 0.67–0.75), 20% (HR: 0.80, 95% CI: 0.77–0.84), and 29% (HR: 0.71, 95% CI: 0.68–0.74) lower risk of OP, respectively (Table 2). This trend remained robust even after multivariate adjustment. The association between obesity and reduced risk of OP was observed across all subgroups, except for the gender subgroup (etable 2). Notably, the association was more pronounced in women, with a 33% (HR: 0.67, 95% CI: 0.64–0.72), 23% (HR: 0.77, 95% CI: 0.73–0.81), and 31% (HR: 0.69, 95% CI: 0.66–0.72) reduction in risk of OP across the three definitions of obesity, respectively. However, these associations were not significant in men. None of them reached statistical significance in the base model ($p \geq 0.05$), and only WC-defined obesity was associated with a reduced risk of OP in the fully adjusted model (HR: 0.82, 95% CI: 0.73–0.92) (Table 2).

Nonlinear association between obesity indicators and OP risk

The fully adjusted RCS model showed an inverse J-shaped association between BMI, WC, fat percentage, and OP risk. Compared to participants with lower weight or body fat, the risk of OP in obese participants decreased progressively with increasing BMI, WC, and fat percentage, demonstrating a clear dose-dependent relationship (Fig. 3, A). This OP-protective benefit was also observed in subgroups other than sex, with no significant interaction noted (efigure 1). In women, the risk of OP showed a sharp downward trend with increasing BMI, WC, and fat percentage, leveling off after exceeding 30 kg/m^2, 100 cm, and 42%, respectively (Fig. 3, B). However, in men, although the risk of OP initially decreased with increasing obesity indicators, it showed a significant upward trend after reaching critical values, indicating no significant protective effect (Fig. 3, C).

In examining the interaction between BMI and WC/fat percentage, we found no interaction between BMI and WC. The association between BMI and the risk of OP

Table 1 Baseline data of OP and non-OP participants identified during a median follow-up period of 13.7 years

Characteristics	Overall	Non-osteoporosis	Osteoporosis	*p*
Participants, n(%)	177734	168736 (94.9)	8998 (5.1)	<0.01
Age (years), mean (SD)	64.54 (2.85)	64.50 (2.84)	65.29 (2.88)	<0.01
Sex				
Male, n (%)	82734 (46.5)	81416 (48.3)	1318 (14.6)	<0.01
Female, n (%)	95000 (53.5)	87382 (52.7)	7680 (85.4)	<0.01
White, n (%)	172364 (97.0)	163612 (97.0)	8752 (97.3)	0.11
Education =high, n (%)	58321 (32.8)	55725 (33.0)	2596 (28.9)	<0.01
Smoking status				<0.01
Current, n(%)	14004 (7.9)	13220 (7.8)	784 (8.7)	
Never, n(%)	90854 (51.1)	86050 (51.0)	4804 (53.4)	
Previous, n(%)	72876 (41.0)	69466 (41.2)	3410 (37.9)	
Drinking habits				<0.01
Daily or almost daily, n(%)	41462 (23.3)	39823 (23.6)	1639 (18.2)	
1-4 times a week, n(%)	82107 (46.2)	78383 (46.5)	3724 (41.4)	
One to three times a month, n(%)	17781 (10.0)	16815 (10.0)	966 (10.7)	
Special occasions only/Never, n(%)	36384 (20.5)	33715 (20.0)	2669 (29.7)	
Fruits&Vegetables ≥ 5portion, n(%)	75516 (42.5)	71192 (42.2)	4324 (48.1)	<0.01
Vitamin intake, n(%)	29095 (16.4)	26697 (15.8)	2398 (26.7)	<0.01
Mineral intake, n(%)	37069 (20.9)	35058 (20.8)	2011 (22.3)	<0.01
Hypertension, n(%)	150156 (84.5)	142966 (84.8)	7190 (80.0)	<0.01
Diabetes, n(%)	39084 (25.1)	37188 (25.1)	1896 (24.3)	0.13
MET(minutes/week), median (IQR)	720 (480-1860)	720 (480-1920)	720 (480-1680)	<0.01
WC(cm), median (IQR)	91.0 (82.0-91.4)	91.0 (83.0- 100.0)	84.0 (76.0- 94.0)	<0.01
Fat percentage, median (IQR)	32.0 (26.1-38.4)	31.8 (26.0- 38.30)	35.2 (29.9- 40.2)	<0.01
BMI, median (IQR)	26.9 (24.5-29.9)	27.0 (24.6- 30.1)	25.5 (22.9- 28.8)	<0.01
Obesity classified by BMI, n(%)	43958 (24.7)	42283 (25.1)	1675 (18.6)	<0.01
Obesity classified by WC, n(%)	116556 (65.6)	111196 (65.9)	5360 (59.6)	<0.01
Obesity classified by fat percentage, n(%)	55114 (31.0)	52400 (31.1)	2714 (30.2)	0.08

remained consistent regardless of WC levels(efigure 2, A). However, there was a significant interaction between BMI and fat percentage in the overall population, with the protective effect of BMI on OP being significant only in individuals with high fat percentage. We hypothesize that this interaction stems from the difference in body fat between men and women, as it is supported by the consistent results observed in sex stratification(efigure 2, B).

Joint effect of BMI and WC/Fat percentage on OP risk

Given that BMI focuses more on the description of overall weight and muscle weight, whereas fat percentage and WC are more adept at describing whole-body fat and visceral fat, this joint analysis is more appropriate for describing the risk of OP in participants of different body types. BMI was categorized into three groups based on quartiles, whereas fat percentage and WC were categorized into two groups. Lower BMI was independently associated with an increased risk of OP compared with moderate BMI and lower fat percentage/WC (Fig. 4). Additionally, within the medium BMI category, higher fat percentage or WC was associated with an increased risk of OP in the whole population and in the men's group, but this association was not statistically significant in the women's group. At higher BMI levels, lower fat percentage or WC was not significantly associated with OP risk; however, higher fat percentage or WC was associated with reduced OP risk in women but, conversely, with increased OP risk in men. The number and statistical significance of the combined effect combinations can be seen in etable 4. Overall, lower BMI was an independent risk factor for OP, whereas there were sex differences in the associations of higher BMI and higher fat percentage/WC with OP risk.

Discussion

In this prospective study based on the UK Biobank cohort of participants aged 60 years or more, we investigated the association between obesity and OP risk. Cox modeling demonstrated that BMI, WC, and fat percentage were

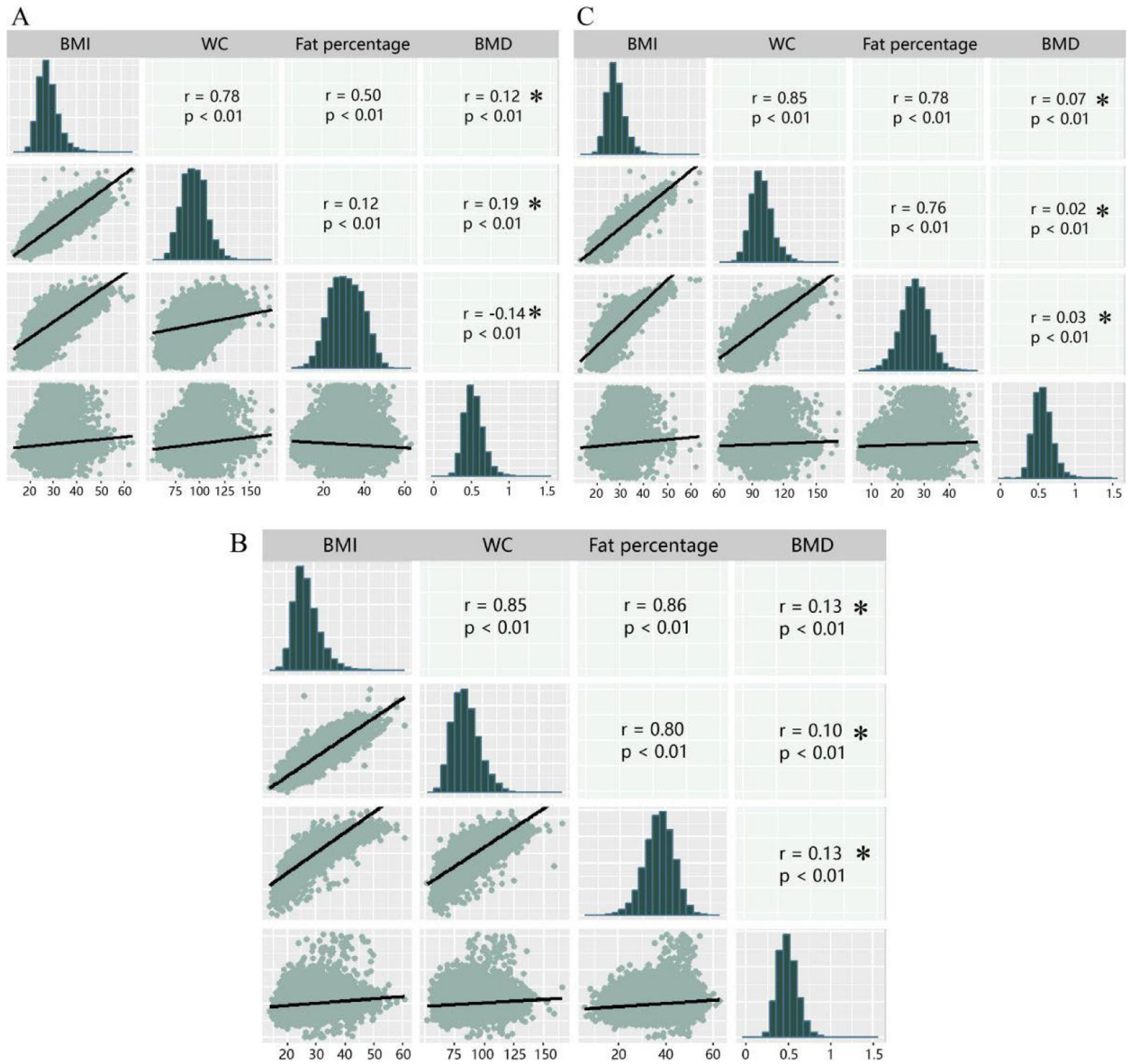

Fig. 2 Trends in the distribution of obesity indicators and Spearman rank correlation coefficients with BMD. **A** Overall; **B** Women; **C** Men

negatively correlated with the risk of OP, which seems to reconfirm the existence of the "obesity paradox" in older adults at OP. Subgroup analyses showed that the association between obesity and reduced OP risk was observed only in women, with no significant association in men. Baseline cross-sectional analyses confirmed that the association between obesity indicators and BMD was stronger in women than in men. However, lower BMI was positively associated with the risk of OP independently of body fat and showed consistent results between both sexes, suggesting that low body weight is a potential risk factor for OP in older adults.

Comparison with other studies

Bone loss is prevalent in the older population due to aging, endocrine, and dietary changes [23–26]. Previous studies on the association between obesity and BMD in older adults have shown a consistent trend, with slight differences in obesity definitions and gender [27–29]. In a retrospective study, Lavanya et al. found that the effect of weight on BMD was age-specific [30]. Weight was negatively associated with bone mass in men over 60 years and women over 55 years, whereas this association was not significant in the younger group. A cross-sectional analysis of older participants from the NHANES

Table 2 Association between obesity and the risk of osteoporosis

Obesity definition[a]	Model 1		Model 2	
	HR (95%CI)	p	HR (95%CI)	p
All participants (n = 177 734)				
BMI	0.71 (0.67, 0.75)	< 0.01	0.69 (0.65, 0.72)	< 0.01
Fat percentage	0.80 (0.77, 0.84)	< 0.01	0.79 (0.75, 0.82)	< 0.01
WC	0.71 (0.68, 0.74)	< 0.01	0.70 (0.67, 0.73)	< 0.01
Women (n = 95 000)				
BMI	0.67 (0.64, 0.72)	< 0.01	0.66 (0.62, 0.70)	< 0.01
Fat percentage	0.77 (0.73, 0.81)	< 0.01	0.76 (0.72, 0.80)	< 0.01
WC	0.69 (0.66, 0.72)	< 0.01	0.68 (0.65, 0.71)	< 0.01
Men (n = 82 734)				
BMI	0.93 (0.82, 1.06)	0.28	0.88 (0.77, 1.00)	0.05
Fat percentage	1.09 (0.96, 1.23)	0.18	1.02 (0.90, 1.15)	0.79
WC	0.87 (0.78, 1.00)	0.08	0.82 (0.73, 0.92)	< 0.01

[a] Obesity definition: BMI: body mass index (≥ 30); Fat percentage (female ≥ 40, male ≥ 30); WC: waist circumstance (female ≥ 80 cm, male ≥ 94 cm)

Model 1: adjusted for age and gender only

Model 2: adjusted for gender, age, IMD, smoking, alcohol consumption, fruit and vegetable intake, vitamin intake, mineral intake, and physical activity

database showed an inverted U-shaped association between WC and femoral neck BMD [12]. Although gender differences were observed after adjusting for BMI, adults over 60 years of age with abdominal obesity were more likely to benefit in terms of bone health. Lemoine et al. further demonstrated that, regardless of the obesity criteria (BMI, WC, or body fat), obese older adults had higher BMD parameters than non-obese individuals [31]. Our cross-sectional results support a positive correlation between obesity and BMD in older adults, with significant gender differences. Additionally, we found that fat percentage was negatively correlated with BMD in the overall population but positively correlated within each sex subgroup. We hypothesize that this typical Simpson's paradox [32], where associations in subgroups disappear or reverse in pooled data, may result from the large differences in fat percentage between genders (median: 37.6% female *vs*. 26.3% male).

The findings on obesity and OP risk in older adults are somewhat controversial [8, 33]. Several population-based studies have found that higher BMI is strongly associated with a reduced risk of OP and can predict OP risk independent of BMD data [34–36]. For body fat, cohort studies based on NHANES data have shown that elevated WC is a potential protective factor for OP in older age groups [13]. Additionally, a study on older women suggested that adiposity has a protective effect on OP, potentially due to estrogenic effects produced by adipose tissue [37]. However, Scott et al. noted that both OP and fracture risk were significantly increased in obese older adults with either sarcopenic obesity or normal BMI [38, 39]. Overall, while the association between BMI-defined obesity and OP risk seems consistent, the association between body fat-defined obesity and OP risk is controversial. The present study supports that lower BMI is associated with an increased risk of OP, even among obese people with elevated WC or body fat percentage. However, with higher BMI, the effect of body fat on OP risk differed significantly between men and women. Men with higher body fat did not benefit from obesity, whereas women with higher BMI and higher body fat were significantly associated with a reduced risk of OP. This potential benefit appears to be the main source of the "obesity paradox" in OP risk among older adults.

Potential explanations

Although the exact mechanisms remain unclear, there may be gender differences in the effects of adiposity on bone [40, 41]. One explanation for the association between BMI and OP risk is that individuals with higher BMI tend to have greater muscle mass, which generates higher mechanical loads on bones [39]. Previous studies have shown that mechanical loading stimulates bone formation and maintains bone metabolism homeostasis [42, 43]. This explanation aligns with our observation that lower BMI is independently associated with an increased risk of OP. Mechanistically, mechanical loading effectively stimulates osteoblasts, enhancing their ability to regulate local calcium levels, which in turn strengthens bones and helps reduce bone loss [44]. In this process, mechanotransduction within osteocytes not only facilitates communication between osteocytes and their environment and neighboring cells, but also involves mechanosensors within individual cells [45]. As a result,

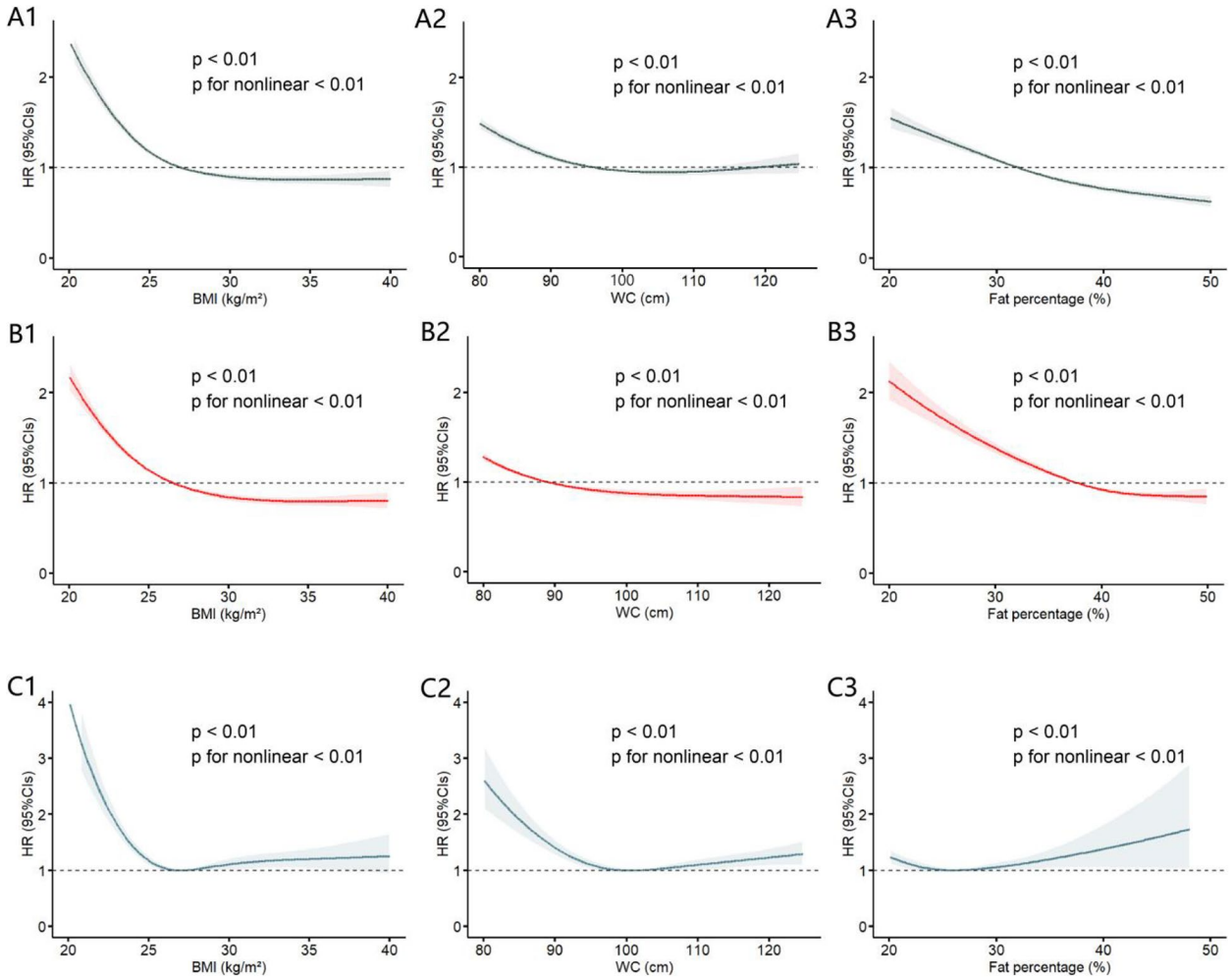

Fig. 3 Nonlinear association between obesity indicators and OP risk. The Restricted Cubic Splines (RCS) model showed a significant nonlinear relationship between OP risk and BMI, WC, and fat percentage in the elderly population. The fitted Cox regression models were fully adjusted for gender, age, IMD, smoking, alcohol consumption, fruit and vegetable intake, vitamin intake, mineral intake, and physical activity. Results were presented for the overall population (**A**), women (**B**), and men (**C**)

various regulatory factors are secreted to regulate osteoblast and osteoclast activity. However, estrogen receptors may play a key role in the osteogenic response to mechanical stimulation [46]. Estrogen receptor α regulation enhances the osteogenic response to loading in the cortical bone of female mice but reduces it in males, suggesting that sex differences exist in the regulation of bone by mechanical stimulation [47].

Existing evidence suggests that body fat contributes to bone health in women but not in men [48]. The potential mechanism is that adipocytes may promote the secretion of bone-active hormones such as estrogen and prolactin [49, 50]. Estrogen has been found to induce the expression of osteoprotegerin and estrogen receptor proteins in human osteoblasts, which in turn exerts an antiresorptive effect on bone [51]. Jia et al. suggested that estrogen may stimulate the expression of osteoprotegerin by inhibiting the expression of miR-145 in human osteoblast-like MG63 cells [52]. Studies have shown that estrogen can regulate gene expression in osteoclasts through estrogen receptor α, thereby inducing apoptosis and preventing bone loss [53]. However, Wang et al. found that the effects of 17β-estradiol and testosterone on osteoclast gene expression are gender-specific [54]. Of the 18 genes responsive to 17β-estradiol, 15 exhibited differential expression between male and female osteoclasts, with two genes being regulated in opposite directions in the two sexes. This suggests that the conversion of testosterone into 17β-estradiol has a limited effect on osteoclast inhibition in males. These findings suggest that women may indirectly benefit from obesity due to their hormonal levels, which could help explain the obesity paradox in OP. For men, it has been reported that visceral fat accumulation is often associated with androgen deficiency,

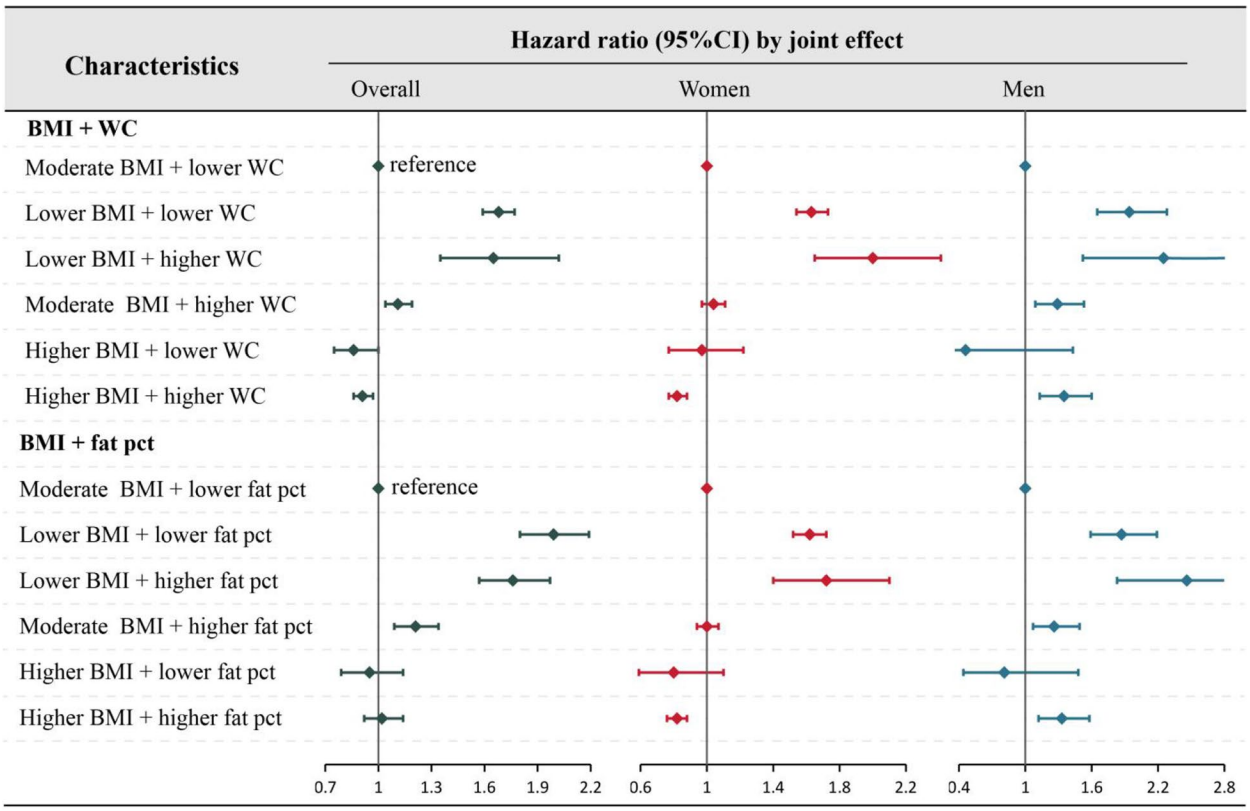

Fig. 4 Joint effect of BMI and WC/Fat percentage on OP risk. BMI was stratified according to quartiles, with the lowest 25% categorized as lower, the middle 50% as moderate, and the highest 25% as higher. WC and fat percentage were stratified into higher and lower tiers according to the median. The Cox regression model was adjusted for gender, age, IMD, smoking, alcohol consumption, fruit and vegetable intake, vitamin intake, mineral intake, and physical activity. The results are presented for the overall population on the left, women in the center, and men on the right

which may have negative effects on bone [55]. Additionally, some studies have explored the roles of resistin, leptin, lipocalin, and interleukin-6 (IL-6) in the association between obesity and OP, but these do not fully explain the observed gender differences [56].

Strengths and limitations

The study has several strengths. First, it is based on a large cohort from the UK Biobank database with available BMD data and diagnostic text messages. Second, data on obesity indicators were collected using a standardized process at multiple UK Biobank centers, minimizing data errors due to differences in facilities. Finally, this study employed both cross-sectional and prospective approaches. It first explored the association between obesity metrics and BMD at baseline, and then examined the relationship with OP risk over time. Consistency between the two analyses increased the confidence in the results.

The study also has some limitations. First, due to the nature of the health cohort, "volunteer bias" is difficult to avoid completely. Second, the BMD measured by heel ultrasound was only a reference value, not the actual BMD of the participants, which may influence the judgment of the actual situation. Third, participants' obesity indicators were all collected at baseline, making it difficult to consistently reflect obesity status during follow-up, which may affect the observation of OP risk associations. Fourth, The effect of chronic disease on bone metabolism was significant. Although we adjusted for chronic disease at baseline, any chronic diseases that developed during follow-up were not included in this analysis. Fifth, the inherent limitations of observational studies, such as the lack of randomization and the potential influence of confounding variables, make it difficult to establish causal relationships, despite allowing for the observation of associations. Sixth, this study was based primarily on a white population of European ancestry, and the results may not be extrapolated to other populations, such as those in Asia and Africa.

Conclusion

In cross-sectional analyses, significant sex differences were observed in the correlations of BMI, WC, and fat percentage with BMD. Prospective analyses further confirmed that obesity was associated with a reduced risk of OP in older women, whereas this association was absent in older men. The joint analysis suggested that lower BMI is an independent risk factor for OP in older adults, whereas high BMI and high body fat may be protective factors for OP in women. In conclusion, the obesity paradox in OP risk among older adults is only applicable to women and not relevant for men. Optimal body weight and body composition should be considered separately based on sex when developing OP risk management strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05704-3.

Supplementary Material 1.

Acknowledgements
This work was conducted using the UK Biobank Resource and we thank the participants and staff of the UK Biobank for their valuable contributions.

Clinical trial number
Not applicable.

Authors' contributions
Q.L., S.Z. and Z.L. contributed equally to this work. Q.L. and S.Z. conceived the ideas. J.Y. and Z.L. obtained and analyzed the data. Y.Z. and B.X. provided software support. C.W. and P.X. provided literature support. Z.Z., C.W. and X.L. acquired funds. Q.L., S.Z. and Z.L. wrote the manuscript. D.W., X.L and Z.Z. edited and reviewed the manuscript.

Funding
This study was supported by the National Natural Science Foundation of China (82302219), China Postdoctoral Science Foundation (2022MD723741), Postdoctoral Project of Chongqing Natural Science Foundation (CSTB2022NSCQ-BHX0638), the Natural Science Foundation of Guangdong Province (2022A1515012279), and the Natural Science Foundation of Chongqing Municipality (2023NSCQ-MSX0742).

Data availability
This work was conducted using the UK Biobank Resource.UK Biobank is an open-access resource, and the study website https://www.ukbiobank.ac.uk/ has information on available data and access procedures.Data sets used for the analysis will be made available under reasonable requests.

Declarations

Ethics approval and consent to participate
This study was approved by the North West Multi-center Research Ethics Committee, the England and Wales Patient Information Advisory Group, and the Scottish Community Health Index Advisory Group (application number 51671). All participants provided written informed consent prior to data collection.

Conflict of interest
The authors declare no competing interests.

Author details
[1]Department of Gerontology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China. [2]Chongqing Municipality Clinical Research Center for Geriatrics, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China. [3]State Key Laboratory of Ultrasound in Medicine and Engineering, Chongqing Medical University, Chongqing 400016, China. [4]Chongqing Key Laboratory of Ultrasound Molecular Imaging, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China. [5]Department of Joint Surgery, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong, China. [6]Department of Epidemiology and Biostatistics, Clinical Big Data Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, Guangdong, China. [7]Guangdong Provincial Key Laboratory of Gastroenterology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China. [8]Digestive Diseases Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, Guangdong, China. [9]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

Received: 11 September 2024 Accepted: 14 January 2025
Published online: 27 January 2025

References

1. Ensrud KE, Crandall CJ. Osteoporosis [J]. Ann Intern Med. 2017;167(3):17–32.
2. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe[J]. Arch Osteoporos. 2021;16(1):82.
3. Willers C, Norton N, Harvey NC, et al. Osteoporosis in Europe: a compendium of country-specific reports[J]. Arch Osteoporos. 2022;17(1):23.
4. Liang W, Chen Q, Cheng S, et al. Skin chronological aging drives age-related bone loss via secretion of cystatin-A[J]. Nat Aging. 2022;2(10):906–22.
5. Zhang S, Wu S, Xia B, et al. Association of coffee and tea consumption with osteoporosis risk: A prospective study from the UK biobank. Bone. 2024;186:117135.
6. Tan T, Tang L, Guo X, et al. Associations of residential greenness with bone mineral density and osteoporosis: the modifying effect of genetic susceptibility[J]. Ann Rheum Dis. 2024;83(5):669–76.
7. Imerb N, Thonusin C, Chattipakorn N, et al. Aging, obese-insulin resistance, and bone remodeling[J]. Mech Ageing Dev. 2020;191: 111335.
8. Liu Y, Liu Y, Huang Y, et al. The effect of overweight or obesity on osteoporosis: A systematic review and meta-analysis[J]. Clin Nutr. 2023;42(12):2457–67.
9. Lv Y, Zhang Y, Li X, et al. Body mass index, waist circumference, and mortality in subjects older than 80 years: a Mendelian randomization study. Eur Heart J. 2024;45(24):2145–54.
10. Qiao D, Li Y, Liu X, et al. Association of obesity with bone mineral density and osteoporosis in adults: a systematic review and meta-analysis[J]. Public Health. 2020;180:22–8.
11. Lloyd JT, Alley DE, Hawkes WG, et al. Body mass index is positively associated with bone mineral density in US older adults[J]. Arch Osteoporos. 2014;9:175.
12. Chen J, Zhu L, Yao X, et al. The association between abdominal obesity and femoral neck bone mineral density in older adults[J]. J Orthop Surg Res. 2023;18(1):171.
13. Pan R, Wang R, Zhang Y, et al. The association of waist circumference with bone mineral density and risk of osteoporosis in US adult: National health and nutrition examination survey[J]. Bone. 2024;185: 117134.
14. Kim J, Kang S, Kang H. Association between normal-weight obesity and bone mineral density in older Korean adults: A population-based cross-sectional study[J]. Maturitas. 2024;180: 107891.
15. Scott D, Seibel M, Cumming R, et al. Sarcopenic Obesity and Its Temporal Associations With Changes in Bone Mineral Density, Incident Falls, and Fractures in Older Men: The Concord Health and Ageing in Men Project[J]. J Bone Miner Res. 2017;32(3):575–83.
16. Zhu B, Hu S, Guo J, et al. Differences in the global exposure, mortality and disability of low bone mineral density between men and women: the underestimated burden in men[J]. BMC Public Health. 2023;23(1):991.

17. Patwardhan V, Gil GF, Arrieta A, et al. Differences across the lifespan between females and males in the top 20 causes of disease burden globally: a systematic analysis of the Global Burden of Disease Study 2021[J]. Lancet Public Health. 2024;9(5):e282–94.
18. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age[J]. PLoS Med. 2015;12(3):e1001779.
19. Montgomery G, Yusuf M, Cooper R, et al. Are associations between physical activity and bone mineral density in adults sex- and age-dependent? An analysis of the UK Biobank study[J]. J Bone Miner Res. 2024;39(4):399–407.
20. Zhang S, Wang D, Zhao J, et al. Metabolic syndrome increases osteoarthritis risk: findings from the UK Biobank prospective cohort study[J]. BMC Public Health. 2024;24(1):233.
21. Lemieux S, Mongeau L, Paquette MC, et al. Health Canada's new guidelines for body weight classification in adults: challenges and concerns[J]. CMAJ. 2004;171(11):1361–3.
22. Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index[J]. Am J Clin Nutr. 2000;72(3):694–701.
23. Fan Y, Li Q, Liu Y, et al. Sex- and Age-Specific Prevalence of Osteopenia and Osteoporosis: Sampling Survey[J]. JMIR Public Health Surveill. 2024;10: e48947.
24. Kan B, Guo D, Yuan B, et al. Dietary carotenoid intake and osteoporosis: the National Health and Nutrition Examination Survey, 2005–2018[J]. Arch Osteoporos. 2021;17(1):2.
25. Dogan A, Nakipoglu-Yuzer GF, Yildizgoren MT, et al. Is age or the body mass index (BMI) more determinant of the bone mineral density (BMD) in geriatric women and men?[J]. Arch Gerontol Geriatr. 2010;51(3):338–41.
26. Pignolo RJ. Aging and Bone Metabolism[J]. Compr Physiol. 2023;13(1):4355–86.
27. Ning HT, Du Y, Zhao LJ, et al. Racial and gender differences in the relationship between sarcopenia and bone mineral density among older adults[J]. Osteoporos Int. 2021;32(5):841–51.
28. Dolan E, Swinton PA, Sale C, et al. Influence of adipose tissue mass on bone mass in an overweight or obese population: systematic review and meta-analysis[J]. Nutr Rev. 2017;75(10):858–70.
29. Evans AL, Paggiosi MA, Eastell R, et al. Bone density, microstructure and strength in obese and normal weight men and women in younger and older adulthood[J]. J Bone Miner Res. 2015;30(5):920–8.
30. Cherukuri L, Kinninger A, Birudaraju D, et al. Effect of body mass index on bone mineral density is age-specific[J]. Nutr Metab Cardiovasc Dis. 2021;31(6):1767–73.
31. Lemoine L, Buckinx F, Aidoud A, et al. Relationships between obesity markers and bone parameters in community-dwelling older adults[J]. Aging Clin Exp Res. 2024;36(1):49.
32. Marang-van de Mheen PJ, Shojania KG. Simpson's paradox: how performance measurement can fail even with perfect risk adjustment[J]. BMJ Qual Saf. 2014;23(9):701–705.
33. Pinar-Gutierrez A, Garcia-Fontana C, Garcia-Fontana B, et al. Obesity and Bone Health: A Complex Relationship. Int J Mol Sci. 2022;23(15):8303.
34. Zhang X, Lin J, Yang Y, et al. Comparison of three tools for predicting primary osteoporosis in an elderly male population in Beijing: a cross-sectional study[J]. Clin Interv Aging. 2018;13:201–9.
35. Chiu CT, Lee JI, Lu CC, et al. The association between body mass index and osteoporosis in a Taiwanese population: a cross-sectional and longitudinal study[J]. Sci Rep. 2024;14(1):8509.
36. Wu CL, Nfor ON, Tantoh DM, et al. Associations Between Body Mass Index, WNT16 rs2908004 and Osteoporosis: Findings from Taiwan Biobank[J]. J Multidiscip Healthc. 2022;15:2751–8.
37. Mathieu M, Guillot P, Riaudel T, et al. Association between Bone Mineral Density and Fat Mass Independent of Lean Mass and Physical Activity in Women Aged 75 or Older. Nutrients. 2021;13(6):1994.
38. Scott D, Chandrasekara SD, Laslett LL, et al. Associations of Sarcopenic Obesity and Dynapenic Obesity with Bone Mineral Density and Incident Fractures Over 5–10 Years in Community-Dwelling Older Adults[J]. Calcif Tissue Int. 2016;99(1):30–42.
39. Scott D, Johansson J, Ebeling PR, et al. Adiposity Without Obesity: Associations with Osteoporosis, Sarcopenia, and Falls in the Healthy Ageing Initiative Cohort Study[J]. Obesity (Silver Spring). 2020;28(11):2232–41.
40. Jain RK, Vokes T. Fat Mass Has Negative Effects on Bone, Especially in Men: A Cross-sectional Analysis of NHANES 2011–2018[J]. J Clin Endocrinol Metab. 2022;107(6):e2545–52.
41. Charoenngam N, Apovian CM, Pongchaiyakul C. Increased fat mass negatively influences femoral neck bone mineral density in men but not women[J]. Front Endocrinol (Lausanne). 2023;14:1035588.
42. Li X, Liu D, Li J, et al. Wnt3a involved in the mechanical loading on improvement of bone remodeling and angiogenesis in a postmenopausal osteoporosis mouse model[J]. FASEB J. 2019;33(8):8913–24.
43. Carina V, Della Bella E, Costa V, et al. Bone's Response to Mechanical Loading in Aging and Osteoporosis: Molecular Mechanisms[J]. Calcif Tissue Int. 2020;107(4):301–18.
44. Robling AG, Castillo AB, Turner CH. Biomechanical and molecular regulation of bone remodeling[J]. Annu Rev Biomed Eng. 2006;8:455–98.
45. Qin L, Liu W, Cao H, et al. Molecular mechanosensors in osteocytes[J]. Bone Res. 2020;8:23.
46. Windahl SH, Saxon L, Borjesson AE, et al. Estrogen receptor-alpha is required for the osteogenic response to mechanical loading in a ligand-independent manner involving its activation function 1 but not 2[J]. J Bone Miner Res. 2013;28(2):291–301.
47. Saxon LK, Galea G, Meakin L, et al. Estrogen receptors alpha and beta have different gender-dependent effects on the adaptive responses to load bearing in cancellous and cortical bone[J]. Endocrinology. 2012;153(5):2254–66.
48. Moayyeri A, Luben RN, Wareham NJ, et al. Body fat mass is a predictor of risk of osteoporotic fractures in women but not in men: a prospective population study[J]. J Intern Med. 2012;271(5):472–80.
49. Beranger GE, Pisani DF, Castel J, et al. Oxytocin reverses ovariectomy-induced osteopenia and body fat gain[J]. Endocrinology. 2014;155(4):1340–52.
50. Reid IR. Relationships between fat and bone[J]. Osteoporos Int. 2008;19(5):595–606.
51. Bord S, Ireland DC, Beavan SR, et al. The effects of estrogen on osteoprotegerin, RANKL, and estrogen receptor expression in human osteoblasts[J]. Bone. 2003;32(2):136–41.
52. Jia J, Zhou H, Zeng X, et al. Estrogen stimulates osteoprotegerin expression via the suppression of miR-145 expression in MG-63 cells[J]. Mol Med Rep. 2017;15(4):1539–46.
53. Nakamura T, Imai Y, Matsumoto T, et al. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts[J]. Cell. 2007;130(5):811–23.
54. Wang J, Stern PH. Sex-specific effects of estrogen and androgen on gene expression in human monocyte-derived osteoclasts[J]. J Cell Biochem. 2011;112(12):3714–21.
55. Donner DG, Elliott GE, Beck BR, et al. The effects of visceral obesity and androgens on bone: trenbolone protects against loss of femoral bone mineral density and structural strength in viscerally obese and testosterone-deficient male rats[J]. Osteoporos Int. 2016;27(3):1073–82.
56. Zhao LJ, Jiang H, Papasian CJ, et al. Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis[J]. J Bone Miner Res. 2008;23(1):17–29.

Publisher's Note