

## RESEARCH

# Can waist circumference be a predictor of bone mineral density independent of BMI in middle-aged adults?

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## Abstract

**Background:** Obesity and osteoporosis are major public health issues globally. The prevalence of these two diseases prompts the need to better understand the relationship between them. Previous studies, however, have yielded controversial findings on this issue. Therefore, our aim in this study was to evaluate the independent association between waist circumference (WC), as a marker of obesity, and the bone mineral density (BMD) of the lumbar spine among middle-aged adults using data from the National Health and Nutrition Examination Survey (NHANES).

**Methods:** Our analysis was based on NHANES data from 2011 to 2018, including 5084 adults, 40–59 years of age. A weighted multiple linear regression analysis was used to evaluate the association between WC and lumbar BMD, with smooth curve fitting performed for non-linearities.

**Results:** After adjusting for BMI and other potential confounders, WC was negatively associated with lumbar BMD in men ( $\beta = -2.8$ , 95% CI:  $-4.0$  to  $-1.6$ ) and premenopausal women ( $\beta = -2.6$ , 95% CI:  $-4.1$  to  $-1.1$ ). On subgroup analysis stratified by BMI, this negative association was more significant in men with a BMI  $\geq 30$  kg/m<sup>2</sup> ( $\beta = -4.1$ , 95% CI:  $-6.3$  to  $-2.0$ ) and in pre- and postmenopausal women with a BMI  $< 25$  kg/m<sup>2</sup> (premenopausal women:  $\beta = -5.7$ , 95% CI:  $-9.4$  to  $-2.0$ ; postmenopausal women:  $\beta = -5.6$ , 95% CI:  $-9.7$  to  $-1.6$ ). We further identified an inverted U-shaped relationship among premenopausal women, with a point of inflection at WC of 80 cm.

**Conclusions:** Our study found an inverse relationship between WC and lumbar BMD in middle-aged men with BMI  $\geq 30$  kg/m<sup>2</sup>, and women with BMI  $< 25$  kg/m<sup>2</sup>.

## Key Words

- ▶ central obesity
- ▶ bone health
- ▶ NHANES
- ▶ osteoporosis
- ▶ waist circumference

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## Introduction

Osteoporosis, characterized by a reduced bone mass and deterioration in the microarchitecture of bone (1), is a growing concern in aging societies (2). Osteoporosis is diagnosed using bone mineral density (BMD) measurements, most commonly obtained by dual-energy x-ray absorptiometry (DXA) (3). Considering the

increasing burden of osteoporosis with aging of the general population, identifying the risk factors for a lower BMD would be important for the prevention of osteoporosis.

Obesity is a major medical problem worldwide (4). Previous research provided evidence of a strong positive correlation between BMD and the BMI (5). Although this

relationship was first interpreted as a possible protective effect of obesity on bone health, more recent research has revealed a positive association between obesity and bone fractures (6). Waist circumference (WC), which is an easy-to-determine clinical parameter, has been proposed to assess central obesity in epidemiological surveys (7), with decrease in WC recommended as a critically important treatment target for reducing adverse health risks (8). However, studies regarding the relationship between WC and BMD are limited, with controversial findings having been reported (9, 10, 11, 12). What is known is that bone mass reaches its peak around the age of 30 years, followed by a slow rate decrease starting around the age of 40 years (13). Therefore, the loss of bone mass during middle-age may play a crucial role in the onset of osteoporosis at an older age. Hence, the objective of our study was to evaluate the independent association between WC and BMD among middle-aged adults using data from the National Health and Nutrition Examination Survey (NHANES).

## Methods

### Data sources and study population

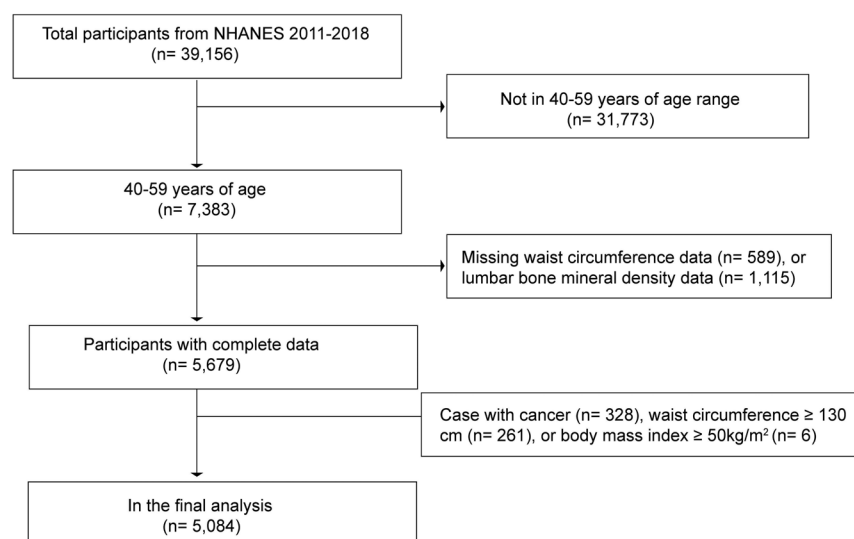
Since 1999, NHANES surveys have been conducted every 2 years to assess the health and nutritional status of the non-institutional population of the United States, using a complex, stratified, and multistage probability sampling design. NHANES survey obtained a nationally representative sample of about 5000 people each year, with data released in 2-year cycles. This survey combines interviews, which consists of demographic, socioeconomic, dietary, and

health-related questions, and physical examinations, which included medical, dental, physiological measurements, and laboratory tests. The data give researchers important clues to the causes of the disease and are publicly available on the internet by researchers throughout the world. We combined data from four waves of the NHANES, conducted between 2011 and 2018.

For our study, the population (total participants,  $n = 39,156$ ) was limited to middle-aged adults, 40-59 years of age ( $n = 7,383$ ). Cases with missing WC data ( $n = 589$ ), lumbar BMD data ( $n = 1,115$ ), as well as individuals with cancer ( $n = 328$ ), a WC  $\geq 130$  cm ( $n = 261$ ), or a BMI  $\geq 50$  kg/m<sup>2</sup> ( $n = 6$ ), were excluded. After screening, the data of 5084 individuals were included in the final analysis (Fig. 1). This observational study was approved by the National Center for Health Statistics, and each participant provided the written consent.

### Evaluation of exposure and outcome

Anthropometric data were collected by trained health technicians in the mobile examination center (MEC). Relevant to our study is the measure of WC, using a method previously described (14). WC was measured with individuals in the standing position, arms crossed across their chest (as to place their hands on opposite shoulders). The iliac crests were palpated bilaterally, and a horizontal line was drawn just above the uppermost lateral border of the right ilium. The midaxillary line was then drawn on the right. The measuring tape was positioned in the horizontal plane at the point of intersection between the two lines. WC was then measured (to the nearest 0.1 cm) at the end-point of the individual's normal expiration.



**Figure 1**  
Flowchart of sample selection.

Administered from 2011 to 2018, the whole body DXA measures were obtained using the hologic discovery model A densitometer (Hologic, Inc., Bedford, MA). With standard study-specific protocols and radiologic techniques, the scans were reviewed and analyzed by the shepherd research Lab (15).

### Covariates

The following covariates, part of the NHANES survey, were extracted for inclusion in the analysis: age, ratio of family income to poverty, BMI, diabetes status (defined as following criteria: participant has been told by a doctor to have diabetes or with a HbA1c  $\geq 6.5\%$ ), total protein, blood urea nitrogen, serum uric acid, serum phosphorus, and serum calcium levels, as continuous variables; and gender,

race, educational level, moderate recreational activities, and smoked at least 100 cigarettes in life as categorical variables. Details for obtaining these covariates are available on the NHANES website (<https://www.cdc.gov/nchs/nhanes/>).

### Statistical analysis

All data analyses were conducted using R version (3.4.3) and EmpowerStats (<http://www.empowerstats.com>), and with a *P*-value  $< 0.05$  were considered statistically significant. All estimates were calculated accounting for NHANES sample weights. Continuous variables were expressed as a mean  $\pm$  S.D. and categorical variables as percentage. Weighted linear regression models and weighted chi-square tests were used to evaluate between-group differences for continuous variables and categorical variables,

**Table 1** The weighted characteristics of middle-aged adults from NHANES 2011 to 2018.

	Men ( <i>n</i> = 2554)	Premenopausal women ( <i>n</i> = 1120)	Postmenopausal women ( <i>n</i> = 1206)	Unrecorded menstruation ( <i>n</i> = 204)	<i>P</i> value
Age (years)	49.3 $\pm$ 5.8	45.8 $\pm$ 4.0	52.9 $\pm$ 4.8	48.6 $\pm$ 5.6	<0.001
Race (%)					<0.001
Non-Hispanic White	64.1	61.1	66.1	50.7	
Non-Hispanic Black	10.7	12.3	13.1	13.3	
Mexican American	9.2	10.3	6.7	8.9	
Other race	16.0	16.3	14.0	27.1	
Education level (%)					<0.001
Less than high school	16.1	13.3	13.2	19.3	
High school	24.3	16.0	24.5	14.6	
More than high school	59.6	70.6	62.3	66.1	
Income-poverty ratio	3.2 $\pm$ 1.6	3.3 $\pm$ 1.6	3.2 $\pm$ 1.6	2.8 $\pm$ 1.7	0.005
BMI (kg/m <sup>2</sup> )	28.6 $\pm$ 4.4	28.6 $\pm$ 6.4	29.0 $\pm$ 5.8	28.1 $\pm$ 6.2	0.072
Smoked at least 100 cigarettes in life (%)					<0.001
Yes	49.6	34.6	42.3	25.8	
No	50.4	65.4	57.7	74.2	
Moderate recreational activities (%)					0.094
Yes	47.5	51.2	46.5	45.1	
No	52.5	48.8	53.5	54.9	
Diabetes status (%)					<0.001
Yes	10.4	7.6	9.7	8.1	
No	87.4	90.4	88.0	90.4	
Borderline	2.2	2.0	2.3	1.5	
Blood urea nitrogen (mmol/L)	5.1 $\pm$ 1.6	4.1 $\pm$ 1.3	4.8 $\pm$ 1.6	4.5 $\pm$ 1.5	<0.001
Total protein (g/L)	71.1 $\pm$ 4.4	70.2 $\pm$ 4.3	70.6 $\pm$ 4.4	70.9 $\pm$ 4.6	<0.001
Serum uric acid (umol/L)	354.4 $\pm$ 72.1	265.3 $\pm$ 60.7	285.7 $\pm$ 68.2	263.5 $\pm$ 62.3	<0.001
Serum phosphorus (mmol/L)	1.16 $\pm$ 0.18	1.18 $\pm$ 0.17	1.24 $\pm$ 0.16	1.20 $\pm$ 0.18	<0.001
Serum calcium (mmol/L)	2.34 $\pm$ 0.08	2.30 $\pm$ 0.08	2.35 $\pm$ 0.08	2.33 $\pm$ 0.09	<0.001
Waist circumference (cm)	101.5 $\pm$ 11.7	94.7 $\pm$ 14.0	97.4 $\pm$ 13.0	93.6 $\pm$ 14.7	<0.001
Lumbar bone mineral density (mg/cm <sup>2</sup> )	1024.6 $\pm$ 159.3	1070.7 $\pm$ 143.0	987.7 $\pm$ 155.5	1031.6 $\pm$ 132.0	<0.001

Mean  $\pm$  s.d. for continuous variables; *P* value was calculated by weighted linear regression model. % for categorical variables; *P* value was calculated by weighted chi-square test.

**Table 2** Association between waist circumference (cm) and lumbar bone mineral density (mg/cm<sup>2</sup>) among middle-aged adults from NHANES 2011 to 2018.

	Model 1	Model 2	Model 3	Model 4
Waist circumference	-0.3 (-0.6, 0.1)	-0.2 (-0.5, 0.1)	-2.2 (-3.0, -1.4)***	-2.2 (-3.0, -1.4)***
Stratified by gender				
Men (n = 2554)	-0.6 (-1.1, -0.1)*	-0.4 (-1.0, 0.1)	-3.0 (-4.2, -1.8)***	-2.8 (-4.0, -1.6)***
Premenopausal women (n = 1120)	-0.1 (-0.7, 0.5)	-0.3 (-0.9, 0.3)	-2.7 (-4.2, -1.3)**	-2.6 (-4.1, -1.1)***
Postmenopausal women (n = 1206)	0.8 (0.1, 1.5)*	0.7 (-0.0, 1.3)	-0.7 (-2.2, 0.8)	-0.7 (-2.2, 0.8)
Unrecorded menstruation (n = 204)	-0.4 (-1.7, 0.8)	-0.6 (-1.9, 0.6)	-0.7 (-3.8, 2.5)	0.2 (-3.0, 3.4)
Stratified by race				
Non-Hispanic White (n = 1621)	-0.6 (-1.1, 0.0)	-0.3 (-0.9, 0.2)	-2.5 (-3.8, -1.1)***	-2.4 (-3.8, -1.1)***
Non-Hispanic Black (n = 1183)	-0.3 (-1.0, 0.5)	0.0 (-0.7, 0.7)	-3.2 (-4.9, -1.5)***	-3.7 (-5.4, -2.0)***
Mexican American (n = 735)	-0.3 (-1.2, 0.5)	-0.1 (-0.9, 0.7)	-1.1 (-3.0, 0.8)	-1.7 (-3.5, 0.2)
Other race (n = 1545)	0.5 (-0.1, 1.1)	0.7 (0.0, 1.3)*	0.4 (-1.1, 2.0)	0.4 (-1.2, 1.9)
Diabetes status				
Yes (n = 655)	0.8 (-0.2, 1.7)	0.1 (-0.9, 1.0)	-1.5 (-3.6, 0.5)	-1.2 (-3.2, 0.8)
No (n = 4297)	-0.6 (-0.9, -0.2)**	-0.4 (-0.8, -0.0)*	-2.6 (-3.4, -1.7)***	-2.4 (-3.2, -1.5)***
Borderline (n = 132)	1.4 (-0.8, 3.5)	0.7 (-1.6, 2.9)	-1.7 (-6.1, 2.7)	-1.1 (-5.9, 3.7)

Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: model 2 plus BMI were adjusted. Model 4: model 3 plus education level, income-poverty ratio, moderate recreational activities, smoked at least 100 cigarettes in life, diabetes status, blood urea nitrogen, total protein, serum uric acid, serum phosphorus, and serum calcium were adjusted. In the subgroup analysis stratified by gender, race or diabetes status, the model is not adjusted for the stratification variable itself.

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

respectively. A weighted multiple linear regression analysis was performed to evaluate the independent association between WC and lumbar BMD. Four models were built to provide statistical inference: model 1, no adjustment for covariates; model 2, adjusted for age, gender, and race; model 3, adjusted for covariates in model 2 plus BMI; and model 4, adjustment for all covariates. Smooth curve fitting was used to address local non-linearities in the models. If the relationship between WC and BMD was non-linear, a two-piecewise regression was performed to determine the threshold effect of WC on lumbar BMD.

## Results

### Characteristics of the study population

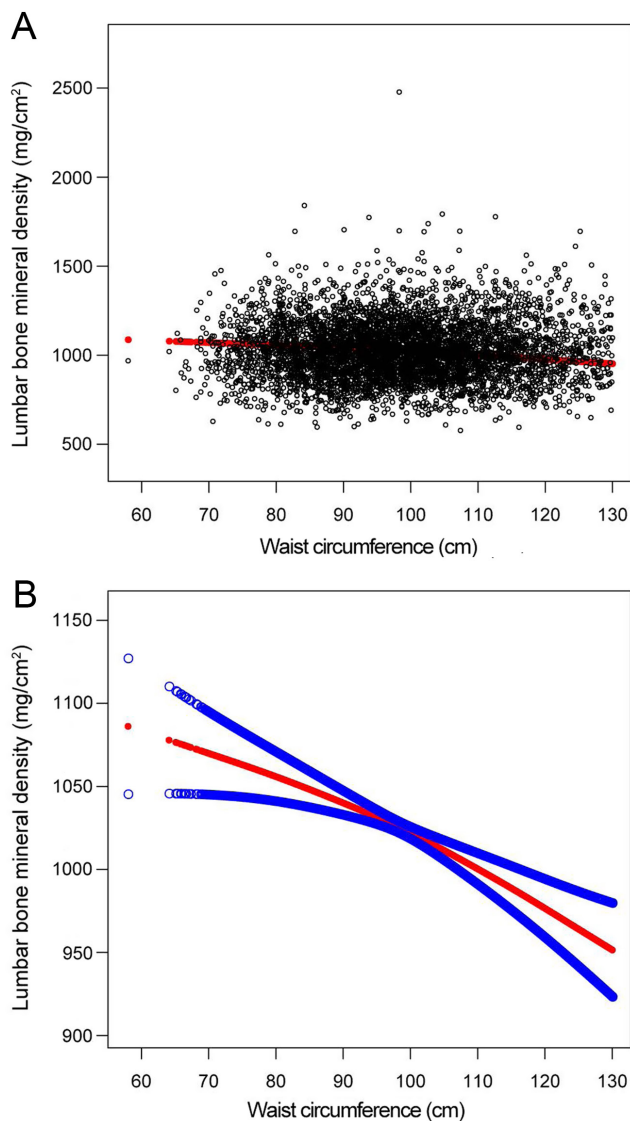
The weighted characteristics of the study sample are presented in Table 1. The study sample of 5084 individuals included 2554 men (mean age, 49.3 years), 1120 premenopausal women (mean age, 45.8 years), 1206 postmenopausal women (mean age, 52.9 years), and 204 women with unrecorded menstrual status. Compared to premenopausal women, men and postmenopausal women had higher levels of total protein, blood urea

**Table 3** Association between waist circumference (cm) and lumbar bone mineral density (mg/cm<sup>2</sup>) among middle-aged adults from NHANES 2011 to 2018, stratified by BMI.

	Model 1	Model 2	Model 3	Model 4
Men				
BMI (< 25 kg/m <sup>2</sup> ) (n = 608)	-2.7 (-4.3, -1.0)**	-1.3 (-3.1, 0.4)	-1.6 (-4.1, 0.9)	-2.0 (-4.5, 0.6)
BMI (25–29.9 kg/m <sup>2</sup> ) (n = 1,091)	-1.3 (-2.8, 0.2)	-1.6 (-3.1, -0.1)*	-2.5 (-4.5, -0.5)*	-1.8 (-3.8, 0.2)
BMI (≥30 kg/m <sup>2</sup> ) (n = 855)	-1.3 (-2.8, 0.1)	-1.5 (-2.9, -0.1)*	-4.5 (-6.5, -2.4)***	-4.1 (-6.3, -2.0)***
Premenopausal women				
BMI (< 25 kg/m <sup>2</sup> ) (n = 359)	-1.2 (-3.9, 1.5)	-0.9 (-3.7, 1.8)	-6.2 (-9.7, -2.7)***	-5.7 (-9.4, -2.0)**
BMI (25–29.9 kg/m <sup>2</sup> ) (n = 317)	-0.8 (-3.3, 1.7)	-0.6 (-3.1, 1.8)	-1.5 (-4.3, 1.3)	-0.9 (-3.8, 2.0)
BMI (≥30 kg/m <sup>2</sup> ) (n = 444)	-0.0 (-1.4, 1.3)	-0.6 (-2.0, 0.7)	-2.1 (-4.1, -0.2)*	-2.1 (-4.2, 0.0)
Postmenopausal women				
BMI (< 25 kg/m <sup>2</sup> ) (n = 299)	1.2 (-1.7, 4.1)	0.8 (-2.0, 3.5)	-5.9 (-9.7, -2.1)**	-5.6 (-9.7, -1.6)**
BMI (25–29.9 kg/m <sup>2</sup> ) (n = 370)	0.2 (-2.1, 2.5)	0.6 (-1.7, 2.9)	-0.3 (-3.3, 2.6)	-1.4 (-4.4, 1.7)
BMI (≥30 kg/m <sup>2</sup> ) (n = 537)	0.2 (-1.3, 1.6)	-0.0 (-1.5, 1.5)	0.2 (-1.8, 2.1)	0.5 (-1.5, 2.5)

Model 1: no covariates were adjusted. Model 2: age and race were adjusted. Model 3: model 2 plus BMI were adjusted. Model 4: model 3 plus education level, income-poverty ratio, moderate recreational activities, smoked at least 100 cigarettes in life, diabetes status, blood urea nitrogen, total protein, serum uric acid, serum phosphorus, and serum calcium were adjusted.

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.



**Figure 2** Association between waist circumference and lumbar bone mineral density. (A) Each black point represents a sample. (B) Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% CI from the fit. Age, gender, race, BMI, education level, income-poverty ratio, moderate recreational activities, smoked at least 100 cigarettes in life, diabetes status, blood urea nitrogen, total protein, serum uric acid, serum phosphorus, and serum calcium were adjusted.

nitrogen, serum uric acid, serum calcium, a greater WC, and lower lumbar BMD.

### Association between WC and lumbar BMD

Table 2 represents the association between WC and lumbar BMD for the four linear regression models. In models 1 and 2, there was no significant association between WC and lumbar BMD. However, this association became negative

after adjusting for BMI and all other covariates (model 3:  $\beta = -2.2$ , 95% CI:  $-3.0$  to  $-1.4$ ; model 4:  $\beta = -2.2$ , 95% CI:  $-3.0$  to  $-1.4$ ).

On a subgroup analysis stratified by gender, WC was negatively associated with lumbar BMD in men ( $\beta = -2.8$ , 95% CI:  $-4.0$  to  $-1.6$ ) and premenopausal women ( $\beta = -2.6$ , 95% CI:  $-4.1$  to  $-1.1$ ) in the fully adjusted model. On subgroup analysis stratified by race, the negative association between WC and lumbar BMD was retained in Non-Hispanic Whites ( $\beta = -2.4$ , 95% CI:  $-3.8$  to  $-1.1$ ) and Non-Hispanic Blacks ( $\beta = -3.7$ , 95% CI:  $-5.4$  to  $-2.0$ ). In the subgroup analysis stratified by diabetes status, this negative association remained significant in non-diabetic participants ( $\beta = -2.4$ , 95% CI:  $-3.2$  to  $-1.5$ ).

As the BMI was a strong confounding factor, we performed a subgroup analysis stratified by BMI (Table 3). In this subanalysis, the negative association between WC and lumbar BMD was more significant in men with a BMI  $\geq 30$  kg/m<sup>2</sup> ( $\beta = -4.1$ , 95% CI:  $-6.3$  to  $-2.0$ ) and in pre- and postmenopausal women with a BMI  $< 25$  kg/m<sup>2</sup> (premenopausal women:  $\beta = -5.7$ , 95% CI:  $-9.4$  to  $-2.0$ ; postmenopausal women:  $\beta = -5.6$ , 95% CI:  $-9.7$  to  $-1.6$ ).

As BMI and WC are collinear in nature, we further evaluated the association between BMI and WC and lumbar BMD, respectively (Supplementary Figs 1 and 2).

### Non-linearity in the association between WC and lumbar BMD

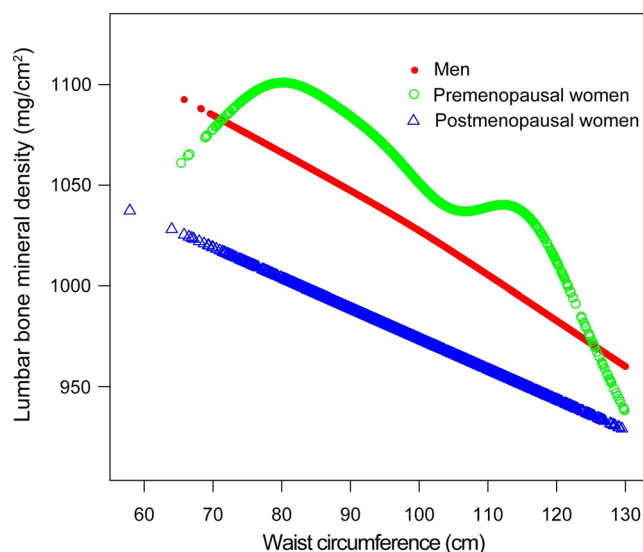
Smooth curve fittings were performed to characterize the non-linear relationship between WC and lumbar BMD (Figs 2 and 3). Among premenopausal women, the association between WC and lumbar BMD was an inverted U-shaped curve. The point of inflection was identified at 80 cm using a two-piecewise linear regression model (Table 4).

### Discussion

Our data revealed an inverse relationship between WC and lumbar BMD among middle-aged men and premenopausal women, and with an inverted U-shaped relationship among premenopausal women, with a point of inflection at a WC of 80 cm.

Obesity and osteoporosis have become major health issues globally. The prevalence of these two diseases prompts the need to better understand the relationship between them. To date, evidence on the relationship between WC and BMD has remained controversial. In a recent cross-sectional study of 4663 Chinese males, Chen *et al.* (9) identified WC to be a





**Figure 3** Association between waist circumference and lumbar bone mineral density, stratified by gender. Age, race, BMI, education level, income-poverty ratio, moderate recreational activities, smoked at least 100 cigarettes in life, diabetes status, blood urea nitrogen, total protein, serum uric acid, serum phosphorus, and serum calcium were adjusted.

negative predictor of calcaneal BMD among males  $\geq 40$  years of age, with a normal weight to minimize the influence of BMI on the measured relationship between WC and BMD. In a Korean community-based, cross-sectional study including 3042 adults  $>40$  years of age, Kim *et al.* (10) identified a negative association between WC and BMD after adjusting for age and weight. This negative association between WC and BMD was confirmed in another community-based study in Korea, including individuals aged  $\geq 50$  years (16). By comparison, a cross-sectional study conducted in Turkey reported a significant positive association between WC and total hip BMD, but a negative association with non-weight-bearing sites (11). A community-based study

**Table 4** Threshold effect analysis of waist circumference (cm) on lumbar bone mineral density ( $\text{mg}/\text{cm}^2$ ) in premenopausal women using two-piecewise linear regression model.

Lumbar bone mineral density	Adjusted $\beta$ (95% CI)
Premenopausal women	
Fitting by standard linear model	-2.6 (-4.1, -1.1)
Fitting by two-piecewise linear model	
Inflection point	80
Waist circumference $<80$ (cm)	2.4 (-2.7, 7.4)
Waist circumference $>80$ (cm)	-3.1 (4.7, -1.5)
Log likelihood ratio	0.041

Age, race, BMI, education level, income-poverty ratio, moderate recreational activities, smoked at least 100 cigarettes in life, diabetes status, blood urea nitrogen, total protein, serum uric acid, serum phosphorus, and serum calcium were adjusted.

conducted in rural regions of Taiwan reported a positive association between WC and lumbar, hip and femoral neck BMD among elderly women (12). Noted differences reflect differences in study design, study population, method for BMD quantification and site of measurement, and control of confounding variables.

WC has been used as a measure of abdominal obesity, with the BMI providing a measure of general obesity. It is widely accepted that abdominal obesity is a better predictor for several adverse health outcomes (17). This might explain differences in findings between our study and those from a recent meta-analysis that showed that a higher BMD, both at the lumbar spine and the femoral neck, among adults with obesity (defined by the BMI) compared to those with a healthy weight (18). BMI and WC are collinear in nature, however, individual with a normal BMI but a large waist is at a higher risk of metabolic disorders (19). Our findings indicate that the inverse association between WC and BMD was independent of BMI. Moreover, this association tends to be different among men and women according to BMI. It may be related to the inherent differences between men and women in fat mass and distribution. Further prospective intervention trials are warranted to confirm this association.

The exact mechanisms of the deleterious effects of obesity on bone are unclear. Replacement of osteoblasts by adipocytes in bone marrow is a possible explanation. Osteoblasts and adipocytes are both derived from bone marrow mesenchymal stem cells, and, thus, increasing adipogenic differentiation decreases osteogenic differentiation (20). Another possible explanation is that obesity-induced hypermetabolism caused by enhanced insulin signaling leads to accelerated metabolic senescence of bone marrow stromal stem cells (21). Despite these possibilities, further studies are needed to explore the molecular mechanism towards the association of WC with BMD. Moreover, our results revealed that men and postmenopausal women had higher levels of serum calcium and lower lumbar BMD than premenopausal women. In another NHANES study for the elderly adults, a similar negative relationship between serum calcium level and BMD has also been reported (22).

The results of our study have a high degree of generalizability as the NHANES survey provides data from a nationally representative sample. Furthermore, the large sample size of our study allowed us to perform subgroup analyses. The limitations of our study also need to be acknowledged. First, the main study limitation is its cross-sectional design. We were unable to assess the causal association between WC and lumbar BMD. Large sample prospective studies are warranted to address causality.

Second, the NHANES database does not include the prevalence of osteoporosis and there were many missing data on hip BMD in the NHANES database from 2011 to 2018. Therefore, we could only use lumbar BMD and not hip BMD or prevalence of osteoporosis. Third, direct measurements of visceral adiposity were not available in this study, which is an inherent limitation. Fourth, we excluded participants with cancer or with a WC  $\geq 130$  cm or a BMI  $\geq 50$  kg/m<sup>2</sup>; therefore, the findings of our study cannot be generalized to these specific populations.

In conclusion, our study found an inverse relationship between WC and lumbar BMD in middle-aged men with BMI  $\geq 30$  kg/m<sup>2</sup>, in pre- and postmenopausal women with BMI  $< 25$  kg/m<sup>2</sup>.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0352>.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Ethical statement

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

#### Author contribution statement

All authors made a significant contribution to the work reported, and agreed to be accountable for all aspects of the work.

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