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Association of obstructive sleep apnea with bone metabolism in older adults: a hospital-based study

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Abstract

Purpose Obstructive sleep apnea (OSA) significantly affects patients' quality of life; however, the mechanisms, such as its effects on bone mineral density (BMD) and bone turnover marker (BTM) expression, remain unclear. In this study, we investigated the relationships among OSA, BMD, and (BTMs) in older adults.

Methods This retrospective study enrolled 260 participants (114 women; 44.5%). Data of an established system (Alice NightOne) were used to diagnose OSA and analyze nocturnal hypoxia. Participants were divided into four groups according to respiratory event index (REI) (control, < 5 times/hour; mild OSA, 5–15 times/hour; moderate OSA 15–30 times/hour; severe OSA ≥ 30 times/hour). BMD were mesured by dual-energy x-ray absorptiometry. BTMs including bone specific alkaline phosphatase (BALP), tartrate-resistant acid phosphatase 5b (TRAP-5b) were collected.

Results Patients with OSA had higher BMD at first lumbar vertebra, left and right femur than those without (all $p < 0.05$). REI was positively correlated with BMD at the first lumbar vertebra ($r = 0.181$, $p = 0.006$), left femur ($r = 0.160$, $p = 0.014$), and right femur ($r = 0.243$, $p < 0.001$). In participants with body mass index (BMI) of 18–24 kg/m^2 ($N = 96$), the correlation between REI and BMD at the left femur($r = 0.251$, $p = 0.019$) and right femur ($r = 0.258$, $p = 0.018$) remained. Multiple regression analysis showed that OSA was significantly associated with osteoporosis ($p = 0.034$, 95% confidence interval, 0.092–0.100, odds ratio, 0.092). $MSaO_2$ was positively correlated with TRAP5b ($r = 0.560$, $p = 0.007$). In participants with a BMI of ≥ 24 kg/m^2($N = 164$), $MSaO_2$ was negatively correlated with BALP ($r = -0.331$, $p = 0.034$). No significant association between REI and BMD was observed.

Conclusions OSA and hypoxia were associated with higher BMD in older adults in BMI of 18–24 kg/m^2 but not in participants with a BMI of ≥ 24 kg/m^2. This study suggests a negative association between OSA and osteoporosis in non-overweight and obese population. BMI played an important role. The study's findings could help exploration mechanisms of osteoporosis and promoting its treatment.

Keywords Obstructive sleep apnea, Bone mineral density, Bone turnover markers, Older adults, Body mass index

Summary

Conflicting results existed regarding correlation between obstructive sleep apnea (OSA) and bone mineral density (BMD) in older adults. We found higher BMD in patients with OSA, and different bone turnover markers were involved in adults with different body mass indices, suggesting a role of hypoxemia and nocturnal hypopnea on bone remodeling.

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Background/introduction

Obstructive sleep apnea (OSA) is characterized by sleep disruption, recurrent apnea, and intermittent hypoxemia, which results in oxidative stress and increased sympathetic activity [1]. It is associated with an increased risk of multisystem diseases, such as hypertension, cardiovascular disease, and diabetes [1–4]. Regarding bone metabolism, intermittent hypoxia stimulates the formation and activation of monocytes and macrophages, triggering an oxidative stress response and causing high sympathetic nerve activity, resulting in abnormal bone metabolism and bone resorption [5, 6]. Animal models studies suggest that intermittent hypoxia may promote mesenchymal stem cells (MSC) mobilization from the bone marrow into the blood circulation, thus altering the bone remodeling process. Therefore OSA is associated with bone metabolism and osteoporosis in many ways. However, contradictory findings have arisen from human studies. Several studies have suggested that OSA is associated with decreased bone mass and is a risk factor for osteoporosis, particularly in men [7–10]. The related mechanism involves hypoxia, which can cause trophic effects on the activity of osteoclasts and upregulate the vascular endothelial growth factor and interleukin-6, leading to osteoclastogenesis, release of inflammatory cytokines, activation of sympathetic nervous systems, and disruption of the diurnal rhythm of bone turnover [11]. However, other studies have reported paradoxical results [12–14]. Studies by Sforza et al. [13] showed that OSA is associated with preserved bone mineral density (BMD) in healthy older participants. The oxygen desaturation index (ODI) was significantly positively correlated with femoral and lumbar T-scores. Participants with osteopenia and osteoporosis tended to have lower apnea–hypopnea index (AHI) and hypoxia indices. These results suggested that hypoxia may protect against osteoporosis. The study did not explore the changes in bone metabolism markers. The current study was conducted in the geriatric department (rather than sleep center) of a general hospital to investigate the correlation between OSA, nocturnal intermittent hypoxia, BMD, and bone turnover markers (BTMs) in older patients. which could provide insight into developing new approaches benefiting osteoporosis treatment.

Methods

Study participants/population

This retrospective study was conducted from December 2016 to October 2023. This study revruited older adults (≥60 years old) who visited the Geriatric Department of Peking University People's Hospital for regular examinations because of chronic diseases including hypertension and diabetes mellitus, were recruited in this study. The demographic information, medical history, medication, and anthropometric data, including weight and height were collected. Body mass index (BMI) was calculated as weight/height squared(kg/m^2). This study exclude participants with a history of chronic kidney disease, pulmonary diasease, rheumatic disorders and disease within one year that could result in malabsorption syndrome, impaired thyroid function, prolonged immobilization; chronic liver disease, inflammatory bowel disease, multiple myeloma, excessive drinking, cerebrovascular accidents, malignant tumors, and those who received therapy for osteoporosis or medications that could affect bone metabolism (steroids, thiazides, warfarin, heparin, and chemotherapy) were excluded. Initially, 648 patients completed the sleep study assessment. According to the inclusion and exclusion criteria, 260 patients (114 women, 44.5%) were eligible for further analysis.

The study was approved by the Ethics Committee of Peking University People's Hospital (Document ID: 2022PHB012-001). A study number instead of name was used for further exploration and all electronic data was stored on password protected system.

Sleep study

All patients ($n=260$) in this study completed a nocturnal sleep assessment at the hospital using an established home sleep apnea testing system (HSAT), Alice Night-One (Philips-Respironics, Inc., Murrysville, PA, USA), which was approved by the Food and Drug Administration. Nasal airflow, chest and abdominal movements, and pulse oximetry results were recorded. The results were analyzed automatically using an analysis software and after that manually interpreted according to the the American Academy of Sleep Medicine definitions [15, 16]. Hypopnea was defined as a 50% or greater reduction in airflow from the baseline value lasting at least 10 s and associated with at least 3% oxygen desaturation or it was defined as a 30% or greater reduction in airflow from the baseline value lasting at least 10 s and associated with at least 4% oxygen desaturation. The total number of respiratory events; respiratory event index (REI), which is calculated as the number of sleep-associated apnea and hypopnea events per hour of recording; oxygen desaturation of ≥4% per hour of recording (ODI4), mean oxygen saturation (MSaO2, %), and lowest oxygen saturation (LSaO2, %) were calculated. Overtime in-lab polysomnography (PSG; Grael, Bestmed, China) was performed and scored according to current practice guidelines [15, 17] in 75 patients. The REI was used as the primary measure to classify patients into four groups. According to recent data on older adults, an REI cutoff of ≥5 events/hour combined with clinical symptoms and/or complications were used to define OSA. Furthermore,

the severity was classified as follows: mild OSA: REI of 5–15 with clinical symptoms and/or complications and 85% of events scored as obstructive, moderate OSA: REI of15–30 with clinical symptoms and/or complications and 85% of events scored as obstructive, and severe OSA: REI of > 30 with clinical symptoms and/or complications and 85% of events scored as obstructive [18–20].

BMD measurement

The BMD of the lumbar vertebrae (L1-4) and bilateral hip (includ- ing the femoral neck, trochanter, inside hip, Ward's triangle and total hip) was measured using the Discovery QDR SERIES dual-energy x-ray bone density instrument (Hologic Inc., Bedford, MA, USA) in the BMD examination room of Peking University People's Hospital. A standard quality control program was also carried out daily on the same machine, with a coefficient of variation of 1.0%. T-scores were calculated automatically by the built-in software, with the reference population being Asian. According to the World Health Organization's definition, osteoporosis was defined as a T-score of −2.5 SD or less at any site, and osteopenia was defined as a T-score between −1.0 and −2.5 [21]. The interval between BMD measurement and the sleep study was within two weeks.

BTMs

We collected levels of bone-specific alkaline phosphatase (BALP), tartrate-resistant acid phosphatase 5b (TRAP5b), osteocalcin (OCN), total procollagen I N-terminal propeptide (TP1NP), and β-cross-linked C-terminal telopeptide of type I collagen (β-CTX). Intact parathyroid hormone (iPTH) levels were also included considering their impact on calcium and phosphorus metabolism. Sixty-four participants completed BALP and TRAP5b assessments and 201 participants completed the evaluation of OCN, TP1NP, and β-CTX. The bone resorption marker tartrate-resistant acid phosphatase 5b (TRAP-5b) was measured using enzyme-linked immunosorbent assay, and the bone formation marker BALP was measured using enzyme immunoassay (EIA). TP1NP, β-CTX, and iPTH were assessed using electrochemiluminescence immunoassay (Roche, Basel, Switzerland). All procedures were performed by a professional laboratory staff following the manufacturer's instructions.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) and categorical variables are presented as percentages. Analysis of variance was used to compare the variables between the groups, while the Chi-square test was used to analyse categorical variables among the groups. The relationships among OSA data, BMD measurements, and BTMs were estimated using Pearson's correlation coefficients. Post hoc analysis (least significant difference, LSD) was used to compare BMD between different OSA groups. Multiple linear regression analysis was performed to analyze the association between femoral and lumbar T-scores (dependent variables) and age, sex, BMI, REI, MSaO2, LSaO2, or T-scores at different sites. All statistical results were significant when the P-value ≤ 0.05 (two-tailed).

Statistical Package for the Social Sciences (version 20.0) for Windows (SPSS Inc. IBM, Armonk, NY, USA) was used for data analyses.

Results

Two hundred and sixty participants aged 60 and above (60–94 years, 71.3 ± 8.5 years) were enrolled in this study and they were divided into four groups based on REI (control, $n = 35$; mild OSA, $n = 106$; moderate OSA, $n = 65$; severe OSA, $n = 54$). The data of the entire study population are summarised in Table 1. Among the total participants, 56.2% were male and 43.8% were female. According to the sleep study data, 86.5% of patients had an REI of ≥ 5 times/hour. A comparison between patients with different REIs revealed a higher proportion of men and a higher BMI in the group as the REI increased. No differences were observed regarding smoking, alcohol consumption, diabetes, and hypertension. The trend test results showed that REI grouping had a significant negative trend towards osteoporosis in all participants (P for trend = 0.038) and in women (P for trend = 0.019), but not in men (P for trend > 0.05).

The mean BMDs, T-scores, and prevalence of osteoporosis in participants with different REIs are shown in Table 2. Patients with OSA had a higher BMD at the first lumbar vertebra ($P < 0.05$), left femur ($P < 0.05$), and right femur ($P < 0.001$). The same trends were observed in the T-scores of the first lumbar vertebra and right femoral site. Post hoc analyses showed significant differences in L1 BMD between moderate OSA and control groups, as well as between the mild OSA and moderate OSA groups. The moderate OSA and severe OSA groups differed in left femur BMD and right femur BMD (Fig. 1). L1 BMD data for men and women are also presented separately in Table 2. As only a few subjects had bone metabolism markers measured, we combined subgroups of the control and mild OSA groups into a CON group, while moderate and severe OSA groups were combined into a moderate-to-severe (MTS) group. Levels of OCN in the CON group were higher than thosein the MTS group, while β-CTX showed a tendency to differ but was not statistically significant (Table 2).

Table 1 Demographic and polygraphic data for the entire study group

	Control ($n=35$)	Mild OSA ($n=106$)	Moderate OSA ($n=65$)	Severe OSA ($n=54$)	*P*
Age(year)	71.66 ± 8.17	70.50 ± 8.60	71.00 ± 8.35	72.78 ± 8.88	0.445
Male(n, %)	17 (48.6)	51 (48.1)	42 (64.6)	36 (66.7)	0.048*
BMI(kg/m^2)	24.23 ± 3.25	24.56 ± 3.17	25.81 ± 3.51	26.20 ± 4.15	0.006*
Smoking(n,%)	5 (14.3)	22 (20.8)	17 (26.2)	10 (18.5)	0.532
Alcohol(n,%)	7 (20)	20 (18.9)	14 (21.5)	12 (22.2)	0.963
Diabetes(n, %)	16 (45.7)	49 (46.2)	39 (60)	26 (48.1)	0.296
HT(n,%)	19 (54.3)	62 (58.5)	40 (61.5)	38 (70.4)	0.400
Ca(n,%)	12 (34.2)	24 (22.6)	17 (26.2)	14 (25.9)	0.599
VitD(n, %)	13 (37.1)	25 (23.6)	16 (24.6)	14 (25.9)	0.452
REI(n/h)	4.21 ± 4.00	9.50 ± 3.12	21.95 ± 5.72	34.57 ± 13.02	< 0.001#
AHI(n/h)	2.67 ± 1.0 ($n=3$)	11.20 ± 1.90 ($n=11$)	24.06 ± 7.67 ($n=25$)	51.77 ± 14.11 ($n=36$)	< 0.001#
OAI(n/h)	1.11 ± 1.38	2.78 ± 1.88	6.20 ± 3.36	10.71 ± 7.19	< 0.001#
CAI(n/h)	0.45 ± 0.54	2.09 ± 1.01	1.50 ± 1.5	2.61 ± 3.87	0.535
ODI4(n/h)	6.31 ± 14.92	8.18 ± 9.00	17.85 ± 6.89	29.45 ± 16.04	< 0.001#
$MSaO_2$(%)	93.51 ± 1.69	92.54 ± 8.56	93.19 ± 1.46	92.91 ± 2.01	0.800
$LSaO_2$(%)	83.7 ± 3.62	85.21 ± 3.39	81.88 ± 6.42	84.00 ± 4.44	0.920

The *P*-values given in the table refer to the analysis of variance (ANOVA) or Chi-square differences between the subjects with different REIs. Statistically significant ANOVA or Chi-square differences with and without OSA

REI respiratory event index, *BMI* body mass index, *HT* hypertension, *AHI* apnea–hypopnea index, *OAI* obstructive apnea index, *CAI* central apnea index, *ODI* oxyhaemoglobin desaturation index, $MSaO_2$ mean nocturnal oxygen saturation, $LSaO_2$ lowest nocturnal oxygen saturation

* $P<0.05$

\# $P<0.01$

In bivariate analysis (Table 3), the LSaO2 was positively correlated with BMD of the first lumbar vertebra ($r=0.214$, $p=0.046$). REI was positively correlated with BMD at the first lumbar vertebra ($r=0.181$, $p=0.006$), left femoral ($r=0.160$, $p=0.014$), and right femoral ($r=0.243$, $p<0.001$) sites. $MSaO_2$ was negatively correlated with BALP ($r=-0.358$, $p=0.004$). A particularly closely relationship between BMI and bone density was revealed. So in subsequent analyses, we adjusted for the effect of BMI and analysed the population in subgroups according to their BMI(< 24 kg/m^2 or ≥ 24 kg/m^2) [22].

In participants with BMI of ≥ 24 kg/m^2 ($N=164$), we analysed the correlation between BMIs, data of OSA and BMD, and T-scores at different sites. BMI was positively correlated with the left femoral T-score ($r=0.159$, $p=0.043$). The REI was also positively correlated with the BMD at the right femoral site ($r=0.175$, $p=0.036$) and the right femoral T-score ($r=0.168$, $p=0.044$). In bone metabolism, $MSaO_2$ was negatively correlated with BALP ($r=-0.331$, $p=0.034$). In participants with a BMI of < 24 kg/m^2 ($n=96$), the correlation between the REI and BMD at the left femoral ($r=0.251$, $p=0.019$) and right femoral sites ($r=0.258$, $p=0.018$) remaintabled. $MSaO_2$ was positively correlated with TRAP5b levels ($r=0.560$, $p=0.007$).

Multiple regression analysis was performed to examine the independent relationship between the REI and osteoporosis as well as the T-score at the femoral and lumbar sites after adjusting for confounding factors, including age, sex, BMI, hypertension, and smoking. Within the overall population, a significant relationship was found between BMI and osteoporosis when BMI (< 24 or ≥ 24 kg/m^2), OSA (divided into four groups by REI), and osteoporosis (yes or no) were used as categorical data. No significant correlation was found between OSA and osteoporosis after adjusting these factors in the overall population and in patients with a BMI of ≥ 24 kg/m^2. In the group with BMI of < 24 kg/m^2, OSA was significantly associated with osteoporosis ($p=0.034$; 95% confidence interval (CI) 0.092–0.010, odds ratio (OR) 0.092). We also conducted multiple linear regressions for T-scores at lumbar and femoral sites (continuous dependent variables), incorporating age, sex, BMI, REI, MSaO2, and $LSaO_2$ in the overall population and in populations with different BMIs (BMI < 24 kg/m^2 or ≥ 24 kg/m^2). A significant correlation was observed between the REIs and T-scores at different lumber and femur sites (Table 4). The REI was significantly associated with the T-scores at the L1, L3, L4, L1-L4, left femoral, and right femoral sites in total participants. REI was significantly related to T-scores at the L1, L4, left femoral, and right femoral sites in the group with a BMI of < 24 kg/m^2. In the group with a BMI of ≥ 24 kg/m^2, no significant association was found between the REI and T-scores at

Table 2 Comparison of bone mineral densities and bone metabolic indicators in participants with different respiratory event indices

	Control (*n* = 35)	Mild OSA (*n* = 106)	Moderate OSA (*n* = 65)	Severe OSA (*n* = 54)	*P*
L1 BMD (g/cm^2)	0.94 ± 0.18	0.97 ± 0.18	1.06 ± 0.22	1.03 ± 0.23	**0.012**
L1 T-score	−0.77 ± 1.57	−0.54 ± 1.59	0.18 ± 1.86	−0.10 ± 1.95	**0.029**†
L2 BMD (g/cm^2)	1.03 ± 0.23	1.05 ± 0.22	1.12 ± 0.28	1.06 ± 0.27	0.276
L2 T-score	−0.59 ± 1.94	−0.44 ± 1.87	0.14 ± 2.54	−0.06 ± 2.07	0.092†
L3 BMD (g/cm^2)	1.12 ± 0.28	1.16 ± 0.24	1.38 ± 0.27	1.17 ± 0.28	0.132
L3 T-score	−0.17 ± 2.42	0.13 ± 2.07	0.82 ± 2.19	0.38 ± 2.37	0.132†
L4 BMD (g/cm^2)	1.14 ± 0.28	1.17 ± 0.24	1.24 ± 0.26	1.18 ± 0.28	0.702
L4 T-score	0.13 ± 2.44	0.30 ± 2.68	1.02 ± 2.23	0.63 ± 2.34	0.161†
Total L BMD (g/cm^2)	1.07 ± 0.23	1.10 ± 0.21	1.17 ± 0.23	1.11 ± 0.27	0.122
Total L T-score	−0.31 ± 2.04	−0.04 ± 1.84	0.56 ± 2.00	0.27 ± 2.11	0.140†
Left F BMD (g/cm^2)	0.86 ± 0.18	0.89 ± 0.14	0.95 ± 0.18	0.93 ± 0.16	0.011
Left F T-score	−1.00 ± 1.33	−0.77 ± 1.01	−0.29 ± 1.36	−0.54 ± 1.08	0.053†
Right F BMD (g/cm^2)	0.84 ± 0.18	0.88 ± 0.14	0.98 ± 0.23	0.97 ± 0.20	**< 0.001**
Right F T-score	−1.11 ± 1.31	−0.79 ± 1.03	−0.07 ± 1.73	−0.19 ± 1.56	**0.004**†
Osteoporosis(n, %)	11 (31.4)	24 (22.6)	12 (18.5)	12 (22.2)	0.544
BALP	7.01 ± 1.61 (*n* = 4)	9.69 ± 3.56 (*n* = 17)	9.70 ± 2.28 (*n* = 17)	10.32 ± 4.17 (*n* = 26)	0.375
TRAP5b	2.80 ± 0.54 (*n* = 4)	3.56 ± 1.11 (*n* = 17)	3.40 ± 0.85 (*n* = 17)	3.71 ± 0.88 (*n* = 26)	0.291
TP1NP	58.10 ± 24.35 (*n* = 29)	56.84 ± 23.51 (*n* = 86)	53.84 ± 25.87 (*n* = 52)	48.71 ± 19.75 (*n* = 34)	0.320
β-CTX	0.54 ± 0.31 (*n* = 29)	0.54 ± 0.28 (*n* = 86)	0.46 ± 0.21 (*n* = 52)	0.49 ± 0.23 (*n* = 34)	0.293
OCN	16.97 ± 6.65 (*n* = 29)	16.67 ± 7.58 (*n* = 86)	14.57 ± 5.80 (*n* = 52)	14.60 ± 7.21 (*n* = 34)	0.191
iPTH	39.89 ± 13.96 (*n* = 29)	36.96 ± 14.10 (*n* = 86)	38.71 ± 18.86 (*n* = 52)	43.75 ± 22.35 (*n* = 35)	0.269

Comparison of BTMs in different group based on REI

	CON group (control and mild OSA)	MTS group (moderate-to- severe OSA)	*P*
BALP	10.00 ± 4.14(*n* = 21)	9.67 ± 3.12 (*n* = 43)	0.724
TRAP5b	3.41 ± 1.00 (*n* = 21)	3.60 ± 0.90 (*n* = 43)	0.462
TP1NP	56.67 ± 23.94 (*n* = 115)	51.80 ± 23.09 (*n* = 86)	0.149
β-CTX	0.54 ± 0.29 (*n* = 115)	0.47 ± 0.21 (*n* = 86)	0.050
OCN	16.68 ± 7.39 (*n* = 115)	14.54 ± 6.35 (*n* = 86)	0.034*
iPTH	37.67 ± 13.94 (*n* = 115)	40.26 ± 20.71 (*n* = 86)	0.319

Comparison of bone mineral densities and bone metabolic indicators in **men** with different respiratory event indices

	Control (*n* = 17)	Mild OSA (*n* = 51)	Moderate OSA (*n* = 42)	Severe OSA (*n* = 36)	*P*
L1 BMD (g/cm^2)	1.06 ± 0.14	1.05 ± 0.20	1.14 ± 0.21	1.09 ± 0.22	0.155
L1 T-score	0.27 ± 1.20	0.13 ± 1.74	0.93 ± 1.76	0.35 ± 2.0	0.186†
L2 BMD (g/cm^2)	1.19 ± 0.16	1.15 ± 0.22	1.24 ± 0.22	1.12 ± 0.29	0.130
L2 T-score	0.74 ± 1.43	0.42 ± 1.90	1.22 ± 1.78	0.56 ± 2.08	0.220†
L3 BMD (g/cm^2)	1.30 ± 0.24	1.25 ± 0.24	1.56 ± 0.55	1.23 ± 0.27	0.292
L3 T-score	1.52 ± 2.07	1.12 ± 2.05	1.71 ± 2.00	1.05 ± 2.34	0.458†
L4 BMD (g/cm^2)	1.30 ± 0.28	1.27 ± 0.25	1.32 ± 0.25	1.25 ± 0.26	0.605
L4 T-score	1.64 ± 2.37	1.41 ± 2.10	1.86 ± 2.07	1.28 ± 2.23	0.665†

Table 2 (continued)

Total L BMD (g/cm^2)	1.22 ± 0.19	1.19 ± 0.21	1.26 ± 0.22	1.17 ± 0.28	0.328
Total L T-score	1.10 ± 1.65	0.84 ± 1.84	1.40 ± 1.81	0.85 ± 2.04	0.475†
Left F BMD (g/cm^2)	0.97 ± 0.14	0.95 ± 0.13	1.02 ± 0.18	0.97 ± 0.149	0.129
Left F T-score	−0.15 ± 1.03	−0.34 ± 0.952	0.19 ± 1.35	−0.30 ± 1.013	**0.112**†
Right F BMD (g/cm^2)	0.95 ± 0.14	0.95 ± 0.11	1.07 ± 0.22	0.96 ± 0.13	**0.003**
Right F T-score	−0.34 ± 1.05	−0.33 ± 0.82	0.61 ± 1.72	−0.22 ± 0.98	**0.003**†
Osteoporosis(n, %)	1 (5.9)	5 (9.8)	3 (7.1)	6 (16.7)	0.580
BALP	6.74 ± 1.86 (*n* = 3)	9.50 ± 3.60 (*n* = 12)	10.05 ± 4.61 (*n* = 14)	10.04 ± 4.61 (*n* = 19)	0.562
TRAP5b	2.54 ± 0.13 (*n* = 3)	3.57 ± 1.25 (*n* = 12)	3.37 ± 1.00 (*n* = 14)	3.48 ± 0.74 (*n* = 19)	0.402
TP1NP	46.89 ± 14.87 (*n* = 13)	48.49 ± 17.56 (*n* = 39)	47.64 ± 18.78 (*n* = 32)	44.29 ± 16.30 (*n* = 24)	0.807
β-CTX	0.43 ± 0.28 (*n* = 13)	0.45 ± 0.21 (*n* = 39)	0.41 ± 0.20 (*n* = 32)	0.45 ± 0.20 (*n* = 24)	0.815
OCN	13.62 ± 3.87 (*n* = 13)	12.87 ± 5.53 (*n* = 39)	12.46 ± 4.14 (*n* = 32)	12.89 ± 6.07 (*n* = 24)	0.923
iPTH	37.31 ± 12.42 (*n* = 13)	35.81 ± 14.47 (*n* = 39)	34.05 ± 14.31 (*n* = 32)	42.52 ± 22.05 (*n* = 24)	0.253

Comparison of bone mineral densities and bone metabolic indicators in **women** with different respiratory event indices

	Control (*n* = 18)	**Mild OSA (*n* = 55)**	**Moderate OSA (*n* = 23)**	**Severe OSA (*n* = 18)**	***p***
L1 BMD (g/cm^2)	0.83 ± 0.16	0.89 ± 0.13	0.90 ± 0.16	0.91 ± 0.20	0.408
L1 T-score	−1.76 ± 1.23	−1.19 ± 1.12	−1.15 ± 1.23	−1.04 ± 1.51	0.282†
L2 BMD (g/cm^2)	0.90 ± 0.19	0.96 ± 0.17	0.91 ± 0.24	0.95 ± 0.20	0.522
L2 T-score	−1.86 ± 1.47	−1.25 ± 1.47	−1.79 ± 2.57	−1.26 ± 1.44	0.426†
L3 BMD (g/cm^2)	0.95 ± 0.18	1.07 ± 0.21	1.05 ± 0.18	1.03 ± 0.24	0.185
L3 T-score	−1.76 ± 1.48	−0.79 ± 1.63	−0.81 ± 1.46	0.94 ± 1.87	0.163†
L4 BMD (g/cm^2)	1.00 ± 0.19	1.09 ± 0.20	1.08 ± 0.21	1.06 ± 0.28	0.517
L4 T-score	−1.22 ± 1.57	−0.75 ± 2.76	−0.48 ± 1.66	−0.59 ± 2.07	0.763†
Total L BMD (g/cm^2)	0.92 ± 0.17	1.01 ± 0.17	1.02 ± 0.16	1.00 ± 0.23	0.317
Total L T-score	−1.63 ± 1.41	−0.88 ± 1.41	−0.94 ± 1.36	0.95 ± 1.74	0.291†
Left F BMD (g/cm^2)	0.74 ± 0.14	0.82 ± 0.12	0.82 ± 0.11	0.84 ± 0.14	0.075
Left F T-score	−1.8 ± 1.07	−1.17 ± 0.90	−1.17 ± 0.86	−1.04 ± 1.06	0.062†
Right F BMD (g/cm^2)	0.74 ± 0.15	0.82 ± 0.13	0.82 ± 0.13	0.96 ± 0.31	**0.004**
Right F T-score	−1.79 ± 1.15	−1.18 ± 1.03	−1.22 ± 0.96	−0.13 ± 2.34	**0.005**†
Osteoporosis(n, %)	10 (55.6)	19 (34.5)	9 (39.1)	6 (33.3)	0.447
BALP	7.84 (*n* = 1)	10.16 ± 3.83 (*n* = 5)	9.04 ± 2.24 (*n* = 5)	11.51 ± 5.12 (*n* = 13)	0.664
TRAP5b	3.59 (*n* = 1)	3.52 ± 0.75 (*n* = 5)	3.10 ± 0.68 (*n* = 5)	4.16 ± 1.07 (*n* = 13)	0.195
TP1NP	66.96 ± 26.23 (*n* = 17)	64.29 ± 25.65 (*n* = 48)	64.87 ± 34.17 (*n* = 22)	57.64 ± 23.40 (*n* = 11)	0.849
β-CTX	0.62 ± 0.31 (*n* = 17)	0.61 ± 0.31 (*n* = 48)	0.52 ± 0.22 (*n* = 22)	0.57 ± 0.28 (*n* = 11)	0.629
OCN	19.37 ± 7.17 (*n* = 17)	19.85 ± 7.57 (*n* = 48)	17.64 ± 7.20 (*n* = 22)	18.22 ± 8.09 (*n* = 11)	0.684

Table 2 (continued)

iPTH	40.38 ± 14.91 (*n* = 17)	37.88 ± 13.72 (*n* = 48)	44.57 ± 23.94 (*n* = 22)	40.36 ± 17.66 (*n* = 11)	0.513

The *P*-values given in the table refer to the analysis of variance (ANOVA) or Chi-square differences between the subjects with different REIs. Statistically significant ANOVA or Chi-square differences with and without OSA

BMD bone mineral density, *OSA* obstructive sleep apnea, *BALP* bone specific alkaline phosphatase, *TRAP5b* tartrate-resistant acid phosphatase 5b, *TP1NP* total procollagen I N-terminal propeptide, *β-CTX* β-cross-linked C-terminal telopeptide of type I collagen, *OCN* osteocalcin, *iPTH* intact parathyroid hormone

[*] $P < 0.05$

[#] $P < 0.001$

[†] non-parametric test

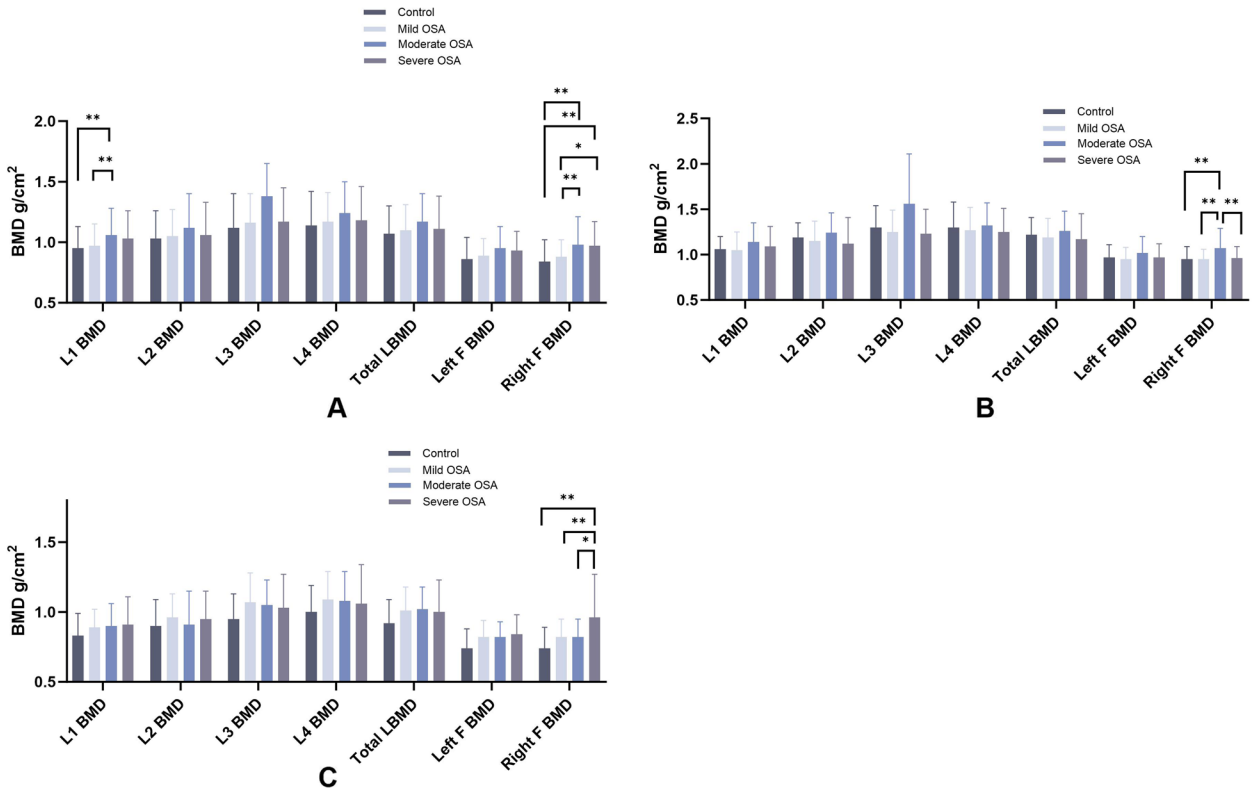

Fig. 1 Comparison of bone mineral densities in the different obstructive sleep apnea groups. **A** whole participents; **B** men, **C** women. [*] $P < 0.05$, BMD, bone mineral density; OSA, obstructive sleep apnea

different sites. BMI was associated with the left femoral T-score in the total population (OR = 0.096, 95%CI 0.005–0.188, $p = 0.039$). No significant relationship was found between femoral and lumbar T-scores with ODI4, $MSaO_2$ and $LSaO_2$.

Discussion

The association between OSA and osteoporosis remains controversial and warrants further investigation. This study aimed to explore the correlation among OSA, hypoxemia, BMD, BTM, and the risk of osteoporosis in older adults. The results showed that the BMD of lumbar and femoral in patients with OSA were significantly higher than those of the control group, and with an increase in REI, which represented the severity of OSA, the lumbar and femoral bone densities and T-values tended to increase. Post hoc analyses and trend testing demonstrated similar results. Patients with moderate OSA tend to have the highest BMD, especially in femur. The correlation between OSA and femoral bone density was significant in both male and female older individuals. Multiple regression analysis revealed similar results. These observations are consistent with the findings of a large-sample study by Sforza et al. [12, 13], which showed

Table 3 Pearson correlation coefficients of BMI, bone metabolism, and nocturnal intermittent hypoxemia data in total participants

	BMI	REI	$MSaO_2$	$LSaO_2$
L1 BMD	**0.226**$^{\#}$	**0.181**$^{\#}$	0.023	**0.214***
L2 BMD	**0.159***	0.029	0.013	0.170
L3 BMD	0.060	0.078	−0.008	0.180
L4 BMD	**0.171**$^{\#}$	0.081	0.025	0.105
L1-L4 BMD	**0.226**$^{\#}$	0.117	0.014	0.136
Left femoral BMD	**0.309**$^{\#}$	**0.160***	−0.076	0.101
Right femoral BMD	**0.273**$^{\#}$	**0.243**$^{\#}$	−0.075	0.054
OCN	**−0.203**$^{\#}$	−0.081	0.060	0.184
BALP	**0.248***	−0.002	**−0.358**$^{\#}$	0.081

BMI body mass index, *REI* respiratory event index, $MSaO_2$ mean nocturnal oxygen saturation, $LSaO_2$ lowest nocturnal oxygen saturation, *BMD* bone mineral density, *BALP* bone specific alkaline phosphatase, *OCN* osteocalcin

* $P<0.05$, $^{\#}$ $P<0.001$

Table 4 Multiple regression analysis of the relationship between REI and T-scores at lumbar vertebra and femoral site in total population and in the subgroup with a body mass index of < 24 kg/m^2

Site	Coefficient	95% CI	*P*
Total population			
L1 T-score	0.054	0.009–0.098	0.019
L3 T-score	0.055	0.001–0.109	0.045
L4 T-score	0.060	0.008–0.111	0.026
L1-L4 T-score	0.054	0.004–0.104	0.033
Left femoral T-score	0.027	0.002–0.052	0.035
Right femoral T-score	0.029	0.003–0.055	0.032
Group with a BMI of < 24 kg/m^2			
L1 T-score	0.161	0.017–0.303	0.031
L4 T-score	0.207	0.053–0.362	0.011
Left femoral T-score	0.116	0.047–0.184	0.002
Right femoral T-score	0.115	0.044–0.186	0.003

BMI Body mass index, *95% CI* 95% confidence interval

significant differences in L1 BMD between moderate OSA and control groups, as well as between the mild OSA and moderate OSA groups. The moderate OSA and severe OSA groups also differed in left femur BMD and right femur BMD. Many studies have shown that oxidative stress can affect the process of bone metabolism involving the expression of receptor activator for nuclear factor-κ b ligand (RANKL) and osteoprotegerin (OPG) [23, 24], the cytochrome c (Cyto-c) and thioredoxin (Trx)-apoptosis signal regulated kinase 1 (ASK1) -c-Jun N-terminal kinase (JNK) pathway [25]. But antioxidant supplementation did not prevent or treat osteoporosis as expected which, combining with the results of this study, suggests a complex role for oxidative stress in bone metabolism. Moderate OSA patients tend to have highest BMD compared to the other groups possibly suggesting that different levels of oxidative stress have differing effects on BMD. Appropriate levels of oxidative stress may be beneficial in maintaining BMD. Meanwhile, many studies have found that OSA is associated with low bone density [7, 8]. After reviewing the mechanisms by which OSA may influence bone metabolism [11], we hypothesise that this contradictory result may be related to the differences in study populations (young, middle-aged, and older individuals), BMI, and gender. To address this issue, we conducted subgroup analyses and observed a possitive association between OSA and BMD in both male and female older adults. However, this correlation was not present in those with a BMI ≥ 24 kg/m^2, suggesting the important role of BMI in the correlation between OSA and BMD in an older population. However, these results still need to be confirmed by larger prospective studies and the mechanisms deserve further exploration.

Gender and BMI is strongly associated with osteoporosis [28–31], and low body weight is an independent risk factor for osteoporosis [32, 33]. In the current study, BMI had a close relationship with BMD at the lumbar vertebra and femoral site. According to the results of a large-scale epidemiological survey conducted in China [22], the Chinese population with a BMI of ≥ 24 kg/m^2 has a significantly increased risk of related diseases. Therefore, we conducted subgroups analyses for patients with a BMI of ≥ 24 kg/m^2 or higher. In men and women, OSA correlates consistently with BMD. However, the relationship between OSA and BMD was slightly distinct in people with different BMI. In participants with a BMI of ≥ 24 kg/m^2, correlation between REI and BMD disappears while in whole participants and these with BMI of < 24 kg/m^2. It is suggested that in the elderly population, weight is closely related to BMD, and the role of OSA and oxidative stress is attenuated in those with a BMI > 24 kg/m^2. BMI may be one of the reasons for the current inconsistency in the correlation between OSA and BMD and should be taken into consideration. Further there may be a role for nutrition in the prevention of osteoporosis in the older population.

Futhermore, bone metabolism is associated with OSA-related pathogenic factors, such as nocturnal intermittent hypoxemia, fragmented sleep, and sympathetic activation. The incidence of OSA also shows an increasing trend with age [29]. However, OSA in the older population has different characteristics from those in the middle-aged and young populations. Older adults experience muscle relaxation, increased fat accumulation around the upper airway, reduced airway diameter, and worsened upper airway collapse [20, 34]. In addition, they may

experience reduced lung function and decreased diaphragmatic contractions, which may worsen nocturnal hypoxemia [35]. Sleep disorders are more severe in older patients than in middle-aged or young patients with OSA [34]. As age increases, bone resorption is enhanced and its formation decreases, leading to osteoporosis. Alterations in hormonal and biochemical factors with age are also involved [36]. These characteristics may partially explain the difference in the correlation between OSA and BMD in older adults compared to middle-aged and young populations. It should be noted that although this study observed an association between OSA and higher BMD, this does not imply a protective effect of OSA on osteoporosis. The association suggests that some OSA-related pathological mechanisms, such as oxidative stress, may affect the process of bone metabolism. Exploring the development of osteoporosis from the perspective of oxidative stress may provide valuable insights for its prevention and treatment. Considering the effects of OSA on multiple organs throughout the body, it should be treated and diagnosed aggressively.

In this study, we also analysed changes in bone metabolism markers; however, the sample size was small, and the analyses revealed no significant differences in other data for study participants with missing information. Hence, we combined subgroups due to the small sample resulting from missing data. OCN level was found to be lower in patients with moderate and severe OSA. In the current study, $MSaO_2$ was negatively correlated with BALP. BALP is produced by osteoblasts, and its production is positively correlated with the bone formation rate [37] and currently used as a marker for bone formation. On the other hand, $MSaO_2$ was positively correlated with TRAP5b in those with a BMI of < 24 kg/m^2. TRAP5b is secreted by osteoclasts and is a marker of osteoclastic activity and an indicator of bone resorption [38]. The $MSaO_2$ was found to be significantly associated with osteocalcin levels and femoral neck BMD [8]. However, this correlation is inconsistent with the results of the present study. Given the small sample size of this study and the lack of significant differences in $MSaO_2$ between different subgroups, the above results may only suggest that nocturnal blood oxygen levels are involved in the regulation of bone metabolism. Bone formation may be promoted during in the process of hypoxemia in older adults with a BMI of ≥ 24 kg/m^2, and in the population with a BMI of < 24 kg/m^2, bone absorption may be inhibited with higher REI. This correlation may partially explain the positive relationship between OSA and BMD [39].

This study had some limitations that should be acknowledged. First, this was a retrospective cross-sectional study based on hospital patients, and all participants completed sleep and bone metabolism measurements within two weeks. Although OSA was found to be statistically associated with BMD, a causal relationship cannot be established. Prospective cohort studies that account for factors related to CPAP may help to explain the causal relationship between OSA and BMD, particularly with follow-up studies start from middle-aged population. Additionally, the results cannot be generalised to all older or middle-aged populations in the community. This study included an older cohort with stable control of chronic diseases. The prevalence of hypertension and diabetes mellitus in this study was higher than that reported in epidemiological data [26, 27], primarily because the data were obtained from a hospital setting. It is important to consider the correlation between OSA and osteoporosis in older individuals attending hospitals. Some participants had missing data for bone metabolism markers; therefore, the correlation between bone metabolism markers and hypoxemia requires further confirmation. Third, although HSCT has high accuracy for OSA [40], the use of REI instead of AHI may reduce the accuracy of sleep apnea testing. Meanwhile, we lacked data on the sleep structure and duration of the participants. Previous studies have suggested that long sleep duration may be associated with a higher risk of osteoporosis [41, 42]. Data on the correlation between sleep structure and osteoporosis warrants further exploration based on PSG results.

In conclusion, this study evaluated the association between OSA and BMD and analysed the influencing factors, including BMI, hypertension, diabetes, and BTM. OSA was closely correlated with T-score and BMD in the femur especially in older population with a BMI < 24 kg/m^2. Nocturnal hypoxemia is associated with different markers of bone metabolism including BALP and TRAP5b. BMI is an important factor for study of osteoporosis in older adults. These findings could help develop new strategies for improving the management and treatment of osteoporosis. Large-scale prospective cohort studies are needed to clarify the causal relationship between OSA and osteoporosis, further to provide new perspectives for the prevention and treatment of osteoporosis and OSA in the older population.

Authors' contributions

DLH, JR and WJT devised and designed the study and contributed to the analysis. DLH, XQ, LMH, YGY, JJ and WYN collected data. DLH and JR wrote the initial draft of the manuscript. LJ and WJT revised the manuscript. All authors have read and approved the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Peking University People's Hospital (Document ID: 2022PHB012-001). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Adderley NJ, Subramanian A, Toulis K, et al. Obstructive sleep apnea, a risk factor for cardiovascular and microvascular disease in patients with type 2 diabetes: findings from a population-based cohort study. Diabetes Care. 2020;43(8):1868–77. http://dx.doi.org/10.1016/j.sleep.2018.12.017.
2. Abud R, Salgueiro M, Drake L, Reyes T, Jorquera J, Labarca G. Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis. Sleep Med. 2019;62:14–21. http://dx.doi.org/10.1016/j.sleep.2018.12.017.
3. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. Eur Respir J. 2021;57(1). http://dx.doi.org/10.1183/13993003.02258-2020.
4. Al-Jahdali H, Ahmed AE, Abdullah AH, et al. Comorbidities in clinical and polysomnographic features of obstructive sleep apnea: a single tertiary care center experience. J Epidemiol Glob Health. 2022;12(4):486–95.
5. Utting JC, Robins SP, Brandao-Burch A, Orriss IR, Behar J, Arnett TR. Hypoxia inhibits the growth, differentiation and bone-forming capacity of rat osteoblasts. Exp Cell Res. 2006;312(10):1693–702. http://dx.doi.org/10.1016/j.yexcr.2006.02.007.
6. Orriss IR, Knight GE, Utting JC, Taylor SE, Burnstock G, Arnett TR. Hypoxia stimulates vesicular ATP release from rat osteoblasts. J Cell Physiol. 2009;220(1):155–62. http://dx.doi.org/10.1002/jcp.21745.
7. Wang C, Zhang Z, Zheng Z, et al. Relationship between obstructive sleep apnea-hypopnea syndrome and osteoporosis adults: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2022;13:1013771.
8. Terzi R, Yılmaz Z. Bone mineral density and changes in bone metabolism in patients with obstructive sleep apnea syndrome. J Bone Miner Metab. 2016;34(4):475–81. http://dx.doi.org/10.1007/s00774-015-0691-1.
9. Uzkeser H, Yildirim K, Aktan B, et al. Bone mineral density in patients with obstructive sleep apnea syndrome. Sleep Breath. 2013;17(1):339–42. http://dx.doi.org/10.1007/s11325-012-0698-y.
10. Ma XR, Wang Y, Sun YC. Imbalance of osteoprotegerin/receptor activator of nuclear factor-κB ligand and oxidative stress in patients with obstructive sleep apnea-hypopnea syndrome. Chin Med J (Engl). 2019;132(1):25–9.
11. Swanson CM, Shea SA, Stone KL, et al. Obstructive sleep apnea and metabolic bone disease: insights into the relationship between bone and sleep. J Bone Miner Res. 2015;30(2):199–211.
12. Sforza E, Saint Martin M, Thomas T, et al. Risk factors of osteoporosis in healthy elderly with unrecognized obstructive sleep apnea: role of physical activity. Sleep Med. 2016;22:25–32. http://dx.doi.org/10.1016/j.sleep.2016.04.010.
13. Sforza E, Thomas T, Barthélémy JC, Collet P, Roche F. Obstructive sleep apnea is associated with preserved bone mineral density in healthy elderly subjects. Sleep. 2013;36(10):1509–15.
14. Chen DD, Huang JF, Lin QC, Chen GP, Zhao JM. Relationship between serum adiponectin and bone mineral density in male patients with obstructive sleep apnea syndrome. Sleep Breath. 2017;21(2):557–64. http://dx.doi.org/10.1007/s11325-017-1492-7.
15. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499–521. http://dx.doi.org/DOI 10.1093/sleep/28.4.499.
16. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619. http://dx.doi.org/10.5664/jcsm.2172.
17. Berry RB, Brooks R, Gamaldo CE, et al. For the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Darien: American Academy of Sleep Medicine; 2012. Version 2.0.
18. Li CX, Zhang YF, Zhu Z, et al. Diagnosis of obstructive sleep apnea using a bio-radar contact-free system compared with an established HST device in older adults. Sleep Health. 2023;9(3):381–6. http://dx.doi.org/10.1016/j.sleh.2023.01.001.
19. Pavlova MK, Duffy JF, Shea SA. Polysomnographic respiratory abnormalities in asymptomatic individuals. Sleep. 2008;31(2):241–8.
20. Chan MTV, Wang CY, Seet E, et al. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery. JAMA. 2019;321(18):1788–98.
21. Orimo H, Hayashi Y, Fukunaga M, et al. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab. 2001;19(6):331–7. http://dx.doi.org/10.1007/s007740170001.
22. Zhou B. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. Zhonghua Liu Xing Bing Xue Za Zhi. 2002;23(1):5–10.
23. Domazetovic V, Marcucci G, Iantomasi T, Brandi ML, Vincenzini MT. Oxidative stress in bone remodeling: role of antioxidants. Clin Cases Miner Bone Metab. 2017;14(2):209–16. http://dx.doi.org/10.11138/ccmbm/2017.14.1.209.
24. Filaire E, Toumi H. Reactive oxygen species and exercise on bone metabolism: friend or enemy? Joint Bone Spine. 2012;79(4):341–6. http://dx.doi.org/10.1016/j.jbspin.2012.03.007.
25. Feng H, Li Z, Du J, et al. Dual function of peroxiredoxin I in lipopolysaccharide-induced osteoblast apoptosis via reactive oxygen species and the apoptosis signal-regulating kinase 1 signaling pathway. Cell Death Discov. 2018;4:47. http://dx.doi.org/10.1038/s41420-018-0050-9.
26. Li Y, Teng D, Shi X, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ (Clinical research ed). 2020;369:m997. http://dx.doi.org/10.1136/bmj.m997.
27. World Health O. Global report on hypertension: the race against a silent killer. Geneva: World Health Organization; 2023.
28. Tang G, Feng L, Pei Y, Gu Z, Chen T, Feng Z. Low BMI, blood calcium and vitamin D, kyphosis time, and outdoor activity time are independent risk factors for osteoporosis in postmenopausal women. Front Endocrinol (Lausanne). 2023;14:1154927. http://dx.doi.org/10.3389/fendo.2023.1154927.
29. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog Cardiovasc Dis. 2009;51(4):285–93. http://dx.doi.org/10.1016/j.pcad.2008.08.001.
30. Lopes MP, Robinson L, Stubbs B, et al. Associations between bone mineral density, body composition and amenorrhoea in females with eating disorders: a systematic review and meta-analysis. J Eat Disord. 2022;10(1):173.
31. Ouyang Y, Quan Y, Guo C, et al. Saturation effect of body mass index on bone mineral density in adolescents of different ages: a population-based study. Front Endocrinol (Lausanne). 2022;13:922903.
32. Lane JM, Russell L, Khan SN. Osteoporosis. Clin Orthop Relat Res. 2000;372:139–50. http://dx.doi.org/10.1097/00003086-200003000-00016.
33. Wildner M, Peters A, Raghuvanshi VS, Hohnloser J, Siebert U. Superiority of age and weight as variables in predicting osteoporosis in postmenopausal white women. Osteoporos Int. 2003;14(11):950–6. http://dx.doi.org/10.1007/s00198-003-1487-z.

34. Subramanian S, Hesselbacher S, Mattewal A, Surani S. Gender and age influence the effects of slow-wave sleep on respiration in patients with obstructive sleep apnea. Sleep Breath. 2013;17(1):51–6. http://dx.doi.org/10.1007/s11325-011-0644-4.
35. Roman MA, Rossiter HB, Casaburi R. Exercise, ageing and the lung. Eur Respir J. 2016;48(5):1471–86. http://dx.doi.org/10.1183/13993003.00347-2016.
36. Syed FA, Ng AC. The pathophysiology of the aging skeleton. Curr Osteoporos Rep. 2010;8(4):235–40. http://dx.doi.org/10.1007/s11914-010-0035-y.
37. Nakayama M, Gorai I, Minaguchi H, Rosenquist C, Qvist P. Purification and characterization of bone-specific alkaline phosphatase from a human osteosarcoma cell line. Calcif Tissue Int. 1998;62(1):67–73. http://dx.doi.org/10.1007/s002239900396.
38. Halleen JM, Alatalo SL, Suominen H, Cheng S, Janckila AJ, Väänänen HK. Tartrate-resistant acid phosphatase 5b: a novel serum marker of bone resorption. J Bone Miner Res. 2000;15(7):1337–45. http://dx.doi.org/10.1359/jbmr.2000.15.7.1337.
39. López-Gómez JJ, Pérez-Castrillón JL, de Santos García I, et al. Influence of obesity on bone turnover markers and fracture risk in postmenopausal women. Nutrients. 2022;14(8):1617.
40. Wang J, Zhang C, Xu L, et al. Home monitoring for clinically suspected obstructive sleep apnea in pregnancy. J Clin Sleep Med. 2023;19(11):1951–60. http://dx.doi.org/10.5664/jcsm.10726.
41. Tian Y, Shen L, Wu J, et al. Sleep duration and timing in relation to osteoporosis in an elderly Chinese population: a cross-sectional analysis in the Dongfeng-Tongji cohort study. Osteoporos Int. 2015;26(11):2641–8. http://dx.doi.org/10.1007/s00198-015-3172-4.
42. Moradi S, Shab-Bidar S, Alizadeh S, Djafarian K. Association between sleep duration and osteoporosis risk in middle-aged and elderly women: a systematic review and meta-analysis of observational studies. Metabolism. 2017;69:199–206. http://dx.doi.org/10.1016/j.metabol.2017.01.027.

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