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# Association between Non high density lipoprotein to high density lipoprotein cholesterol ratio and bone mineral density

Ying Zhou<sup>1,4</sup>, Ning Su<sup>1,4</sup>, Huimin Dai<sup>3,4</sup>, Guowei Ma<sup>2</sup>, Rui Yin<sup>2</sup>, Jiajia Sheng<sup>2</sup>, Mingxia Quan<sup>2</sup>, Liu Yang<sup>2</sup> & Jie Chen<sup>2</sup>✉

NHHR is the new composite lipid index. There are few studies on the relationship between NHHR and bone mineral density (BMD). This study aimed to investigate the correlation between the NHHR and BMD. Weighted multiple linear regression, threshold effects, and fitted smoothed-curve modeling were employed in this cross-sectional analysis, which comprised 3,138 participants in the 2011–2018 NHANES, to examine the relationship between NHHR and BMD. A total of 3,138 participants were analyzed and grouped by NHHR quartiles. Higher NHHR was associated with male gender, younger age, and increased cardiometabolic risk factors. NHHR was negatively correlated with BMD, and a significant non-linear relationship was observed, with an inflection point at 1.301. Below this threshold, NHHR was significantly inversely associated with BMD. Subgroup analyses revealed stronger associations in participants < 20 years and females. These findings suggest NHHR may be an independent biomarker for BMD, particularly in youth and women, offering insights into lipid–bone metabolism cross-talk. A U-shaped connection between NHHR and BMD was found in this study. As a novel lipid marker, NHHR can help diagnose osteoporosis early and direct treatment.

**Keywords** NHHR, Lipid metabolism, Bone density, Osteoporosis, NHANES

The systemic skeletal illness known as osteoporosis (OP) is typified by a reduction in bone mineral density (BMD)<sup>1</sup>. Currently, approximately 200 million people worldwide are affected by OP, impacting around 23% of women and 11% of men globally<sup>2,3</sup>, with significant economic implications for nations. BMD is crucial for bone formation in children and adolescents, as well as for maintaining bone mass in adults. BMD is a critical indicator of skeletal strength and fracture risk, influenced by a variety of physiological and metabolic factors<sup>4</sup>. While numerous studies have investigated the pathogenesis of osteoporosis, the specific role of lipid metabolism in this process remains insufficiently elucidated. Notably, dysregulated lipid metabolism has been strongly associated with a range of systemic inflammatory conditions, including cardiovascular disease, type 2 diabetes, and various cancers<sup>5</sup>. These disorders often share underlying features such as insulin resistance, chronic low-grade inflammation, and aberrant cellular metabolism—mechanisms that may also disrupt bone remodeling and accelerate bone loss<sup>6</sup>. Exploring the relationship between lipid metabolism and BMD could provide novel insights into the metabolic pathways contributing to osteoporosis, offering a theoretical foundation for early prevention and targeted interventions. Therefore, slowing the rate of BMD loss or delaying its onset is one of the primary strategies for maximizing the prevention of OP<sup>7–9</sup>. Meanwhile, the effects of lipid metabolism and lifestyle factors on BMD have garnered considerable attention.

The ratio of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol (NHHR) refers to the proportion between all atherogenic lipoproteins (non-HDL-C) and anti-atherogenic lipoproteins (HDL-C)<sup>10</sup>. It is a composite lipid parameter that has garnered increasing attention in recent years. Compared with traditional single lipid parameters such as LDL-C or HDL-C, NHHR provides a more comprehensive reflection of an individual's residual cardiovascular risk<sup>11–13</sup>. Recent epidemiological studies have further expanded the clinical implications of NHHR. In addition to cardiovascular diseases, NHHR has been found to

<sup>1</sup> Pharmacy Department, Xichang Munciple People's Hospital, Xichang 615000, Sichuan, China. <sup>2</sup>Pharmacy Department, Kunming Third People's Hospital/Yunnan Provincial Center for Clinical Pharmacy and Infectious Diseases, Kunming 650041, Yunnan, China. <sup>3</sup>Pharmacy Department, Chengdu Public Health Clinical Medical Center, Chengdu 610000, Sichuan, China. <sup>4</sup>These authors contributed equally: Ying Zhou, Ning Su and Huimin Dai. ✉email: chenjie\_0222@163.com

be significantly associated with various other conditions, including depression, nephrolithiasis, and abdominal aortic aneurysms<sup>14–16</sup>. Notably, several recent population-based studies suggest that elevated NHHR may serve as a potential risk predictor for angina pectoris, tinnitus, and sleep-disordered breathing, and has exhibited strong predictive performance across multiple machine learning models<sup>17–19</sup>. These findings indicate that NHHR, as a biomarker, has broadened its scope of application to encompass the cardiovascular, metabolic, and sensory systems.

However, despite separate studies having demonstrated associations between non-HDL-C and HDL-C with BMD, the results remain inconclusive<sup>20–23</sup>. This inconsistency may be attributable to variations in study design and population characteristics, leading to an overall lack of consensus. Nevertheless, the findings suggest that the influence of HDL-C and non-HDL-C on bone density warrants further investigation. Although the role of NHHR in various diseases has been extensively studied, its specific impact on bone health remains underexplored. As a composite indicator that incorporates both HDL-C and non-HDL-C, NHHR may offer a more stable and explanatory perspective to elucidate the complex and as-yet poorly understood relationship between lipid metabolism and bone metabolism.

## Materials and methods

### Data source and analysis sample

All participant data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES) database, which provides results from the U.S. Population Nutrition and Health Survey based on a cross-sectional study design. The data were updated and collected by the NHANES every two years. This study included 39,156 individuals who participated in the survey between 2011 and 2018. Participants with missing total BMD data ( $n=35,487$ ), missing NHHR data ( $n=299$ ), missing BMI data ( $n=9$ ), and those with thyroid disease ( $n=113$ ), cancer or malignant neoplasm ( $n=71$ ), or renal disease ( $n=39$ ) were excluded. Ultimately, 3,138 participants remained (Fig. 1).

### Study variables

In this study, the outcome variable was BMD, and the exposure variable was the NHHR. All participants included in the study were examined using dual-energy X-ray absorptiometry (DXA), the current gold standard for the diagnosis of osteoporosis. This examination was performed by certified radiological technicians using a Hologic QDR-4500 A device and Hologic APEX software (version 3.2) to determine and analyze BMD<sup>1,24</sup>. The data used for NHHR calculations were obtained from the laboratory data in NHANES specifically from “HDL.Doc,” which

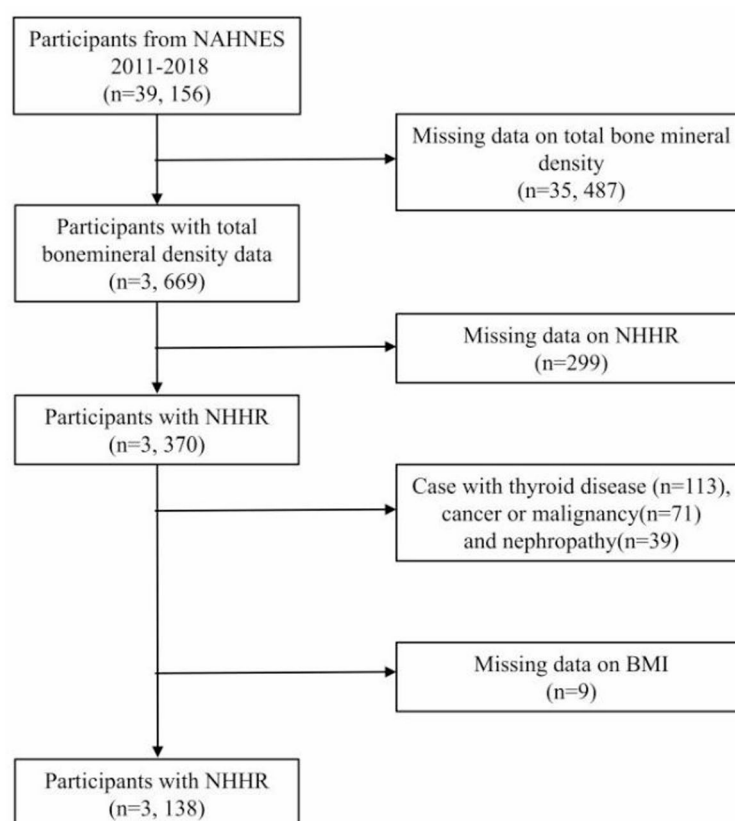


**Fig. 1.** NHANES 2011–2018 sample selection flowchart.

provided HDL data, and “TCHOL.Doc,” which provided total cholesterol data. The NHHR was calculated using the formula: (total cholesterol minus HDL) divided by HDL.

### Covariates

Considering the potential impact of other factors on BMD, multiple covariates were included in the analyses to ensure the reliability of the data in this study<sup>25,26</sup>. The covariates included gender, age, race, education, household income to poverty ratio (PIR), BMI, waist circumference (WC), height, hypertension status, systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes status, glycated haemoglobin (Hgb), and BMD. diastolic blood pressure (DBP), diabetes mellitus status, glycated haemoglobin (HbA1c), alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood potassium and blood sodium.

### Statistical analysis

The NHANES was designed to generate data representative of the non-institutionalized civilian population within the United States, and all estimates were calculated using sample weights by the NCHS analytical guidelines<sup>27,28</sup>. To account for the complex sampling design of NHANES, all statistical analyses—including descriptive statistics, regression models, nonlinear curve fitting, threshold effect analysis, and stratified subgroup analyses—were conducted as weighted analyses. This was implemented using the survey package framework in R, based on the sample weights (WTMEC2YR) provided by the NCHS analytical guidelines. Statistical analyses were conducted using R software (version 4.3.2) and EmpowerStats 2.0 (<http://www.empowerstats.com>). EmpowerStats 2.0 is a graphical interface built on R and incorporates standard statistical packages such as survey, lm, glm, and segmented, allowing transparent and reproducible statistical modeling.

Continuous variables, including age, PIR, BMI, WC, height, SBP, DBP, HbA1c, ALP, AST, blood potassium, and blood sodium, were expressed as mean  $\pm$  standard deviation. Categorical variables including gender, race, education, hypertension, and diabetes status of the participants were expressed using percentages (%), and weighted linear regression models and weighted chi-square tests were used for continuous and categorical variables, respectively. The normality of the dependent variable BMD was assessed using a Q-Q plot (Supplementary Fig. 1), which demonstrated that BMD was approximately normally distributed and thus suitable for linear regression analysis. Weighted multiple linear regression was utilized to analyze the linear relationship between NHHR and BMD, encompassing three models: model 1 (unadjusted), model 2 (adjusted for age, sex, and ethnicity), and model 3 (adjusted for all covariates). Smoothed curve fitting and threshold effects were applied to evaluate the nonlinear relationship between NHHR and BMD, with inflection thresholds calculated. Stratified analyses were conducted to examine potential differences in the relationship between NHHR and BMD across gender and ethnic backgrounds. Differences were considered statistically significant at  $P < 0.05$ .

## Results

### Baseline characteristics

A total of 3,138 participants were enrolled in the study, with an average age of  $29.15 \pm 15.73$  years, comprising 50.19% males and 49.81% females. Participants were according to quartiles based on their NHHR levels (Q1:  $n = 785$ ; Q2:  $n = 782$ ; Q3:  $n = 786$ ; Q4:  $n = 785$ ). Table 1 provides a summary of the individuals' clinical characteristics. When comparing across NHHR quartiles, it is observed that participants in the highest quartile are more likely to be male and younger. Additionally, Mexican Americans and other Hispanic groups in the highest quartile exhibit a higher prevalence of diabetes and hypertension, along with increased levels of BMI, WC, AST, ALT, SBP, DBP, and HbA1c ( $P < 0.05$ ). Conversely, height and BMD levels show a decreasing trend in this group ( $P < 0.05$ ).

### The relationship between the NHHR and BMD

The correlation between NHHR and BMD is shown in Table 2, with significant negative correlations between BMD and NHHR in unadjusted Model 1 [ $-0.021$  ( $-0.025$ ,  $-0.017$ )] and in Model 2 [ $-0.006$  ( $-0.010$ ,  $-0.002$ )] after adjustment for the covariates sex, age, and race. This significant negative correlation remained after adjustment for all covariates, see Model 3 [ $-0.005$  ( $-0.009$ ,  $-0.001$ )]. Sensitivity analyses using NHHR as a categorical variable (quartiles) yielded consistent results. Find out more about the association between BMD and NHHR, a smoothed curve fitting was performed in this study after adjusting for all covariates. The results showed a significant non-linear relationship between NHHR and BMD ( $P < 0.05$ ) (Figure.2), with an inflection point of 1.301. For each unit increase in NHHR below 1.301, total BMD was expected to decrease by  $0.093 \text{ g/cm}^2$ . However, this relationship was not statistically significant above 1.301, as shown in Table 3.

### Subgroup analysis

To explore whether the association between the exposure and BMD differs across population subgroups, we conducted stratified analyses by age, gender, race, and BMI. These variables were selected because they are known biological and sociodemographic modifiers of bone metabolism and skeletal health, potentially influencing both BMD and individual vulnerability to environmental or lifestyle exposures. Age reflects developmental and degenerative stages of bone accrual; gender differences are largely mediated by sex hormones and skeletal structure; race may capture genetic predispositions and socioeconomic disparities; and BMI reflects mechanical loading as well as nutritional status, which are both critical for bone health.

Our results revealed a significant interaction by age ( $P = 0.0027$ ), where participants under 20 years showed a stronger negative association ( $\beta = -0.020$ , 95% CI:  $-0.030$  to  $-0.010$ ) compared to those aged 20 and above ( $\beta = -0.004$ , 95% CI:  $-0.008$  to  $-0.001$ ). Gender also exhibited a significant interaction ( $P = 0.0193$ ), with females showing a significant inverse association ( $\beta = -0.011$ , 95% CI:  $-0.018$  to  $-0.005$ ), while no effect was observed

| Characteristic           | NHHR Quartiles       |                      |                      |                      | P value |
|--------------------------|----------------------|----------------------|----------------------|----------------------|---------|
|                          | Q1, n = 785 (25.02%) | Q2, n = 782 (24.92%) | Q3, n = 786 (25.05%) | Q4, n = 785 (25.02%) |         |
| Age (years)              | 26.91 ± 14.73        | 29.83 ± 14.91        | 33.49 ± 14.99        | 38.44 ± 12.53        | < 0.001 |
| Gender (%)               |                      |                      |                      |                      | < 0.001 |
| Males                    | 41.13                | 42.31                | 51.69                | 69.74                |         |
| Females                  | 58.87                | 57.69                | 48.31                | 30.26                |         |
| Race (%)                 |                      |                      |                      |                      | < 0.001 |
| Mexican American         | 11.84                | 11.80                | 13.46                | 16.03                |         |
| Other Hispanic           | 7.80                 | 7.69                 | 8.79                 | 9.71                 |         |
| Non-Hispanic White       | 58.03                | 55.6                 | 55.06                | 52.26                |         |
| Non-Hispanic Black       | 12.27                | 12.26                | 11.52                | 7.13                 |         |
| Other Race               | 10.07                | 12.65                | 11.17                | 14.88                |         |
| Educational level (%)    |                      |                      |                      |                      | 0.099   |
| High school and below    | 53.72                | 49.35                | 49.37                | 47.57                |         |
| More than high school    | 46.28                | 50.65                | 50.63                | 52.43                |         |
| PIR                      | 2.79 ± 1.60          | 2.94 ± 1.60          | 2.73 ± 1.59          | 2.67 ± 1.57          | < 0.001 |
| BMI (kg/m <sup>2</sup> ) | 23.02 ± 5.60         | 25.67 ± 6.54         | 31.23 ± 6.76         | 31.23 ± 6.76         | < 0.001 |
| WC (cm)                  | 80.21 ± 14.46        | 87.17 ± 16.68        | 95.67 ± 16.42        | 104.38 ± 15.53       | < 0.001 |
| Height (cm)              | 169.33 ± 9.52        | 165.88 ± 11.92       | 163.91 ± 12.08       | 162.78 ± 12.80       | < 0.001 |
| Diabetes status (%)      |                      |                      |                      |                      | < 0.001 |
| Yes                      | 1.43                 | 3.34                 | 5.93                 | 7.22                 |         |
| No                       | 98.57                | 96.66                | 94.07                | 92.78                | < 0.001 |
| Hypertension status (%)  |                      |                      |                      |                      | < 0.001 |
| Yes                      | 7.64                 | 9.03                 | 21.03                | 25.36                |         |
| No                       | 92.36                | 90.97                | 78.97                | 74.64                |         |
| AST (U/L)                | 20 (17, 24)          | 21 (18, 25)          | 21 (18, 25)          | 23 (19, 29)          | < 0.001 |
| ALT (U/L)                | 16 (13, 20)          | 18 (14, 24)          | 21 (16, 30)          | 25 (18, 36)          | < 0.001 |
| Serum potassium (mg/dl)  | 4.07 ± 0.28          | 4.07 ± 0.31          | 4.06 ± 0.33          | 4.06 ± 0.32          | 0.829   |
| Serum sodium (mg/dl)     | 140.21 ± 2.51        | 139.97 ± 2.45        | 140.07 ± 2.48        | 139.79 ± 2.58        | 0.017   |
| SBP (mmHg)               | 111.91 ± 12.87       | 112.53 ± 12.00       | 115.43 ± 13.59       | 119.80 ± 13.95       | < 0.001 |
| DBP (mmHg)               | 63.56 ± 16.45        | 66.81 ± 14.10        | 68.24 ± 13.92        | 73.40 ± 11.80        | < 0.001 |
| HbA1c (mg/dl)            | 5.29 ± 0.47          | 5.35 ± 0.55          | 5.48 ± 0.66          | 5.69 ± 1.00          | < 0.001 |
| BMD (g/cm <sup>2</sup> ) | 1.12 ± 0.11          | 1.09 ± 0.13          | 1.07 ± 0.15          | 1.05 ± 0.15          | < 0.001 |

**Table 1.** Analysis of general information on participants. Mean ± SD for continuous variables; the P value was calculated by the weighted linear regression model. (%) for categorical variables: the P value was calculated by the weighted chi-square test. PIR, Income to poverty ratio; BMI, Body mass index; WC, Waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, Hemoglobin A1c; BMD, bone mineral density; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

in males ( $\beta = -0.002$ , 95% CI:  $-0.007$  to  $0.003$ ). Although the interaction by race was not statistically significant ( $P = 0.3049$ ), subgroup estimates varied, with Other Hispanic individuals exhibiting the most pronounced negative association ( $\beta = -0.017$ , 95% CI:  $-0.030$  to  $-0.004$ ), and Mexican Americans showing no association. For BMI, no significant interaction was found ( $P = 0.1820$ ), but a stronger association was observed in individuals with normal BMI (18.5–24) ( $\beta = -0.014$ , 95% CI:  $-0.023$  to  $-0.005$ ), compared to those who were underweight or overweight. These findings suggest that age and gender may significantly modify the association between exposure and BMD, whereas race and BMI do not appear to exert significant effect modification (Fig. 3).

## Discussion

This study identified a significant U-shaped relationship between NHHR and BMD, with an inflection point at 1.301. Below this threshold, higher NHHR levels were negatively associated with BMD, indicating that increased NHHR corresponded to lower bone mineral density. However, beyond this point, the association was no longer statistically significant. These findings not only highlight the complex interplay between NHHR and bone metabolism but also offer new insights for the early identification of osteoporosis.

## Public health value of NHHR as a novel screening Indicator for osteoporosis

Although previous studies have established associations between individual lipid components (such as triglycerides and HDL-C) and bone mineral density (BMD), the conclusions have been inconsistent, limiting their practical utility in clinical diagnosis and treatment. Abnormal lipid metabolism is commonly observed in patients with OP, where dyslipidemia negatively impacts bone health, often due to vascular calcification and

|                | Model 1 $\beta$ (95% CI)<br><i>P</i> value | Model 2 $\beta$ (95% CI)<br><i>P</i> value | Model 3 $\beta$ (95% CI)<br><i>P</i> value |
|----------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|
| NHHR           | −0.021 (−0.025, −0.017)<br>< 0.001         | −0.006 (−0.010, −0.002)<br>< 0.001         | −0.005 (−0.009, −0.001) 0.0125             |
| NHHR Quartiles |                                            |                                            |                                            |
| Q1             | Reference                                  | Reference                                  | Reference                                  |
| Q2             | −0.020 (−0.034, −0.007)<br>< 0.001         | 0.010 (−0.022, −0.003)<br>0.1234           | −0.008 (−0.019, 0.004)<br>0.1801           |
| Q3             | −0.039 (−0.052, −0.025)<br>< 0.001         | −0.012 (−0.024, −0.001)<br>0.0639          | −0.016 (−0.028, −0.003) 0.0116             |
| Q4             | −0.074 (−0.088, −0.061)<br>< 0.001         | −0.025 (−0.038, 0.021)<br>< 0.001          | −0.018 (−0.031, −0.004)<br>< 0.001         |

**Table 2.** Association of NHHR with total BMD among NHANES participants, 2011–2018. Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3 was adjusted for age, gender, race, educational level, BMI, family income-to-poverty ratio, waist circumference, height, diabetes status, hypertension status, ALT, AST, serum potassium, serum sodium, SBP, DBP, and HbA1c.

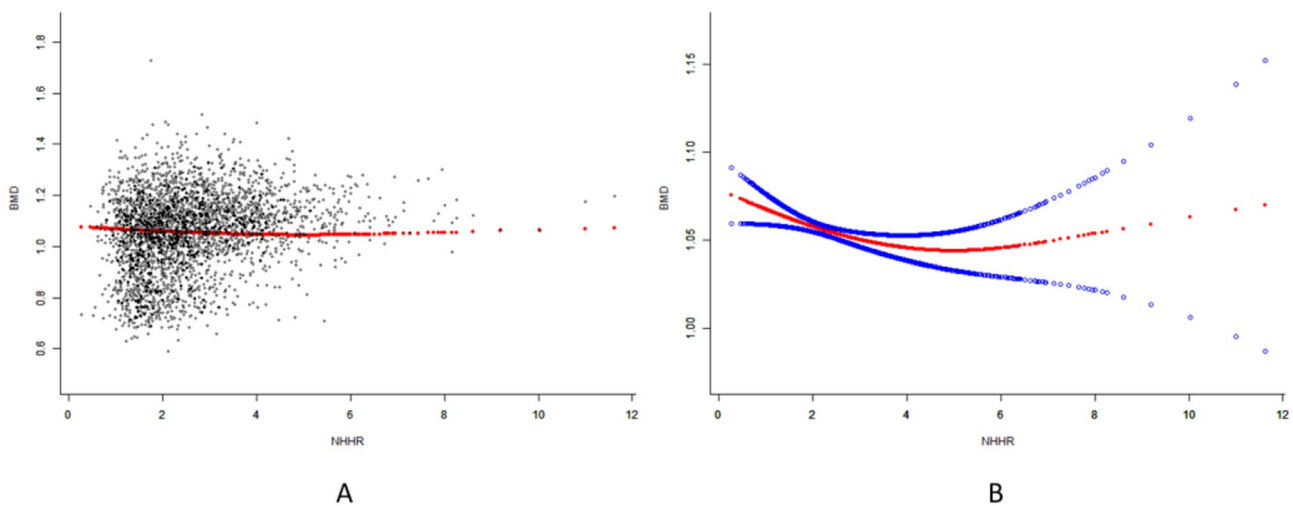


**Fig. 2.** Non-linear relationship between the NHHR and total BMD after adjusting for all variables. (A) Each black point represents a sample. (B) The solid red line indicates a smooth curve fit between the variables. The blue bars indicate the 95% confidence intervals for the fit. Age, gender, race, educational level, BMI, family income-to-poverty ratio, waist circumference, height, diabetes status, hypertension status, ALT, AST, serum potassium, serum sodium, SBP, DBP, and HbA1 were adjusted for.

| Inflection point     | BMD $\beta$ (95% CI)    | <i>P</i> -value |
|----------------------|-------------------------|-----------------|
| Inflection point     | 1.301                   |                 |
| <1.3                 | −0.093 (−0.145, −0.041) | <0.0001         |
| > 1.3                | −0.003 (−0.007, 0.001)  | 0.1333          |
| Log-likelihood ratio |                         | < 0.0001        |

**Table 3.** Two-stage linear regression analysis of the NHHR effect on total BMD thresholds. Note: Models adjusted for all covariates.

atherosclerosis<sup>29–31</sup>. One study identified a negative correlation between triglyceride (TG) levels and BMD. In contrast, another investigation reported a positive association between HDL-C levels and BMD, while finding no significant relationship between BMD and levels of total cholesterol (TC), LDL-C, or TG<sup>20,32</sup>. These contradictory findings have limited the clinical applicability of traditional lipid biomarkers in osteoporosis management, highlighting the urgent need for new lipid-based indicators to aid in prediction and treatment. Although direct studies on the association between NHHR and BMD remain scarce, a substantial body of research has explored the connections between BMD and various lipid-related factors. For example, an NHANES-based study found a positive association between HDL-C and BMD after adjusting for confounders<sup>33</sup>. A study focusing on hospitalized elderly patients examined the relationship between osteoporosis and age-related cardiovascular diseases, revealing

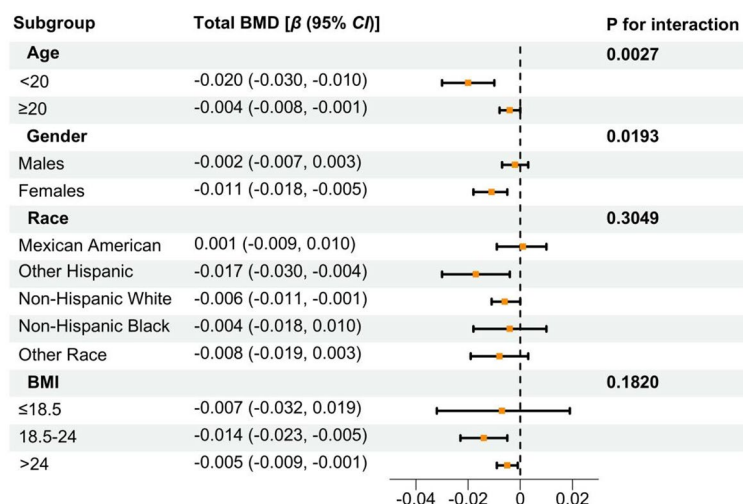


**Fig. 3.** Subgroup analysis of NHHR and BMD.

that elevated levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) are associated with an increased risk of osteoporosis in older adults<sup>34</sup>. Additionally, a retrospective analysis of elderly individuals with type 2 diabetes indicated that high-density lipoprotein cholesterol (HDL-C) serves as a protective factor against osteoporosis in both men and women, while elevated non-HDL-C levels are independently linked to a higher risk of osteoporosis in postmenopausal women<sup>35</sup>. These findings provide important clinical insights and support the relevance of NHHR in understanding the impact of lipid metabolism on bone density. This study is the first to approach the issue from the perspective of an integrative lipid metabolism marker, introducing NHHR as a parameter that reflects the balance between pro- and anti-atherogenic lipids within the field of bone metabolism. This novel perspective enriches the theoretical framework of lipid-bone interaction research and offers empirical support for further exploration of lipid dysregulation in the pathogenesis of osteoporosis.

Our results indicate that NHHR levels below 1.301 are significantly associated with increased risk of low BMD, suggesting strong predictive value within this range. Compared with conventional bone densitometry techniques, NHHR derives from routine lipid testing, offering advantages such as low cost, high accessibility, and ease of implementation. It is especially well-suited for preliminary screening in primary care and community health settings, potentially enhancing the early detection rate of osteoporosis<sup>36</sup>. Therefore, NHHR holds promise as a novel, easily obtainable serum biomarker for bone health assessment and osteoporosis risk stratification, particularly among populations with high osteoporosis prevalence.

The observed U-shaped relationship suggests that both excessively low and high levels of NHHR may negatively impact bone health, highlighting the importance of maintaining lipid homeostasis. Compared to traditional single lipid markers such as triglycerides (TG) or high-density lipoprotein cholesterol (HDL-C), NHHR better reflects the balance between pro- and anti-atherogenic lipoproteins and may more comprehensively capture the lipid-related inflammatory and oxidative stress environment influencing bone metabolism. Studies have demonstrated that lipids are essential for maintaining skeletal homeostasis<sup>37</sup>. The impact of lipid metabolism on BMD may be mediated through various mechanisms. Firstly, abnormal lipid metabolism may trigger inflammatory responses, whereby atherosclerosis promotes the release of pro-inflammatory cytokines, thereby affecting osteoclast activation or function, altering bone metabolism, and resulting in decreased BMD; Secondly, oxidative stress is another potential pathway through which lipid metabolism influences BMD. Oxysterols are essential for osteoblast formation, and elevated HDL-C levels can inhibit this differentiation process. Lipid metabolites can activate PPAR $\gamma$ , and elevated PPAR $\gamma$  levels suppress osteoblast activity, thereby increasing bone resorption<sup>38–40</sup>. Although several studies suggest that lipid metabolism affects BMD through multiple pathways, direct evidence supporting this theory remains limited and warrants further investigation.

Given that osteoporosis is often a “silent” disease diagnosed only after a fracture occurs, early identification of high-risk individuals is crucial. Incorporating NHHR into the biochemical assessments of routine physical examinations may assist clinicians in screening individuals at risk of reduced bone mass before overt clinical symptoms appear. This is particularly valuable in women over the age of 40, who are more susceptible to dyslipidemia and bone loss due to significant hormonal fluctuations. Dynamic monitoring of NHHR in this population may thus offer important clinical utility.

### Clinical implications of gender differences

Stratified analysis revealed a U-shaped relationship between NHHR and BMD among female participants, while no such association was observed in males. This difference may be attributed to the pivotal role of sex hormones in bone growth and maturation<sup>41</sup>. Specifically, estrogen stimulates periosteal bone deposition and inhibits cortical bone resorption, whereas testosterone increases bone diameter by enhancing periosteal apposition<sup>41,42</sup>. Therefore, the influence of sex hormones on bone health may be greater in women than in men. Perimenopausal women often experience a decline in BMD and an increase in bone resorption rates<sup>43</sup>. Li et al. reported that

annual changes in lipid levels significantly decrease in women after age 40, potentially due to age-related changes in basal metabolism, growth hormone levels, and peroxisome proliferator-activated receptor alpha activity<sup>44</sup>. Based on this, clinicians are advised to intensify interventions for lipid abnormalities in women around the age of 40. This finding suggests the need for strengthened assessment and intervention in middle-aged women, particularly those with dyslipidemia but without overt osteoporosis symptoms. When a female patient's NHHR approaches or exceeds the inflection point of 1.3, timely BMD screening, lifestyle modifications, and appropriate pharmacological treatment should be considered to reduce future fracture risk.

### Clinical implications of age differences

In our subgroup analysis, the negative correlation between NHHR and whole-body BMD varied significantly across age groups, with an interaction *P*-value of 0.0027, suggesting age may be an important modifier of this association. Specifically, in individuals under 20 years of age, each unit increase in NHHR was associated with a significant BMD reduction ( $\beta = -0.020$ , 95% CI:  $-0.030$  to  $-0.010$ ), while in those aged 20 years and older, the association was attenuated ( $\beta = -0.004$ , 95% CI:  $-0.008$  to  $-0.001$ ). This phenomenon may be closely related to the physiological characteristics of bone metabolism at different ages. Adolescence and early adulthood are critical periods for rapid bone accumulation and peak bone mass formation, during which bone metabolism is more sensitive to external influences<sup>45</sup>. The dyslipidemia indicated by elevated NHHR may more profoundly affect bone formation and remodeling through mechanisms such as increased inflammatory cytokines, oxidative stress, or disrupted hormonal signaling, leading to decreased BMD<sup>46,47</sup>. Conversely, in adulthood and particularly in middle to old age, bone metabolism stabilizes, with bone resorption becoming predominant, and the mechanisms linking lipid metabolism and BMD become more complex and multifactorial, involving hormonal fluctuations, reduced basal metabolic rate, and accumulation of chronic diseases<sup>48,49</sup>. Thus, although NHHR remains statistically associated with BMD in adults, the effect size is smaller, suggesting its predictive value may be weaker compared to younger populations.

### Recommendations at the public health policy level

From a public health perspective, NHHR into preliminary screening mechanisms for osteoporosis holds substantial significance. This is particularly relevant in regions where resources for BMD testing are limited. NHHR, as a biomarker obtainable from routine lipid profiles, offers advantages of low cost and high accessibility. It is recommended to apply NHHR-based stratified management in middle-aged and elderly women. For example, in women aged 40 and above with  $\text{NHHR} \geq 1.3$ , primary care providers in community health services can initiate further BMD screening or deliver bone health education. This approach could improve early detection rates and promote efficient allocation of medical resources. The observed association between NHHR and BMD also suggests potential avenues for prevention and treatment. Evidence has demonstrated that lifestyle interventions targeting lipid levels—such as the Mediterranean diet, regular physical activity, and weight control—may improve both cardiovascular and bone health<sup>50</sup>.

In conclusion, this study identifies a U-shaped association between NHHR and BMD, indicating the potential utility of NHHR as a novel and accessible biomarker for assessing osteoporosis risk. This research not only bridges a gap in understanding the link between lipid and bone metabolism but also provides a theoretical basis and practical strategy for developing simplified early detection methods. Future research should explore the integration of NHHR into clinical decision-support systems to guide personalized prevention and treatment strategies, enabling precise interventions and comprehensive care for high-risk populations.

### Strengths and limitations of the study

The investigation's evaluation of the relationship between the NHHR and BMD has a number of advantages. The study's foundation is a large sample size and reliable clinical data from a national survey conducted in the United States. In order to investigate the connection between lipid metabolism and BMD, this study offers a novel, workable composite lipid index. Multiple confounding variable adjustment guaranteed the validity of the study findings.

However, there are nevertheless a few restrictions on this study. First off, despite every effort to include participants of various ages in the study, data from those over 70 years of age is still lacking, which could skew the study's findings. Additionally, the cross-sectional design complicates the establishment of causal relationships due to difficulties in verifying the temporal associations between changes in NHHR and BMD. Lastly, the NHANES database's design necessitated the implementation of certain exclusion criteria, which may have introduced selection bias. Therefore, it is recommended to conduct longitudinal cohort studies to explore the causal relationship between changes in NHHR and dynamic alterations in bone mineral density. Additionally, interventional trials should be undertaken to assess whether improving NHHR through lifestyle modifications or pharmacological agents can directly enhance bone density or reduce fracture incidence. Furthermore, strengthening basic research on the cross-talk between lipid metabolism and bone metabolism may help identify novel therapeutic targets and provide a theoretical foundation for the prevention and treatment of metabolic bone diseases.

### Conclusions

This study revealed a U-shaped correlation between NHHR and BMD. The NHHR can serve as a novel lipid biomarker for the early diagnosis and treatment guidance of osteoporosis. However, no evidence currently exists to elucidate NHHR's effect on bone metabolism; thus, future studies should explore the specific mechanisms by which lipid metabolism influences bone metabolism.

## Data availability

The data for this research can be accessed on the following websites: <https://www.cdc.gov/nchs/nhanes/>.

Received: 24 February 2025; Accepted: 7 July 2025

Published online: 17 July 2025

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## Acknowledgements

We are thankful to all the study participants for their contribution and cooperation toward this work.

## Author contributions

YZ, NS and HD: collected the data; YZ, GM, RY: performed the statistical analysis; JS, MQ and LY: did the statistical analysis and wrote the article; YZ and NS: wrote the article; JC: designed the study, provided senior supervision, and reviewed and wrote the article.

## Funding

No specific funding for this work.

## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics statement

The protocols of the NHANES were approved by the National Center for Health Statistics Research Review Board. All participants provided written informed consent. This study used publicly available deidentified data and did not require additional ethical approval.

## Additional information

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-10908-z>.

**Correspondence** and requests for materials should be addressed to J.C.

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