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L-shaped association of the non-high-density lipoprotein to high-density lipoprotein ratio with low bone mass disorders

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Osteoporosis and osteopenia, collectively referred to as Low Bone Mass Disorders (LBMD), are characterized by decreased bone density and increased fracture risk. Studies have identified a potential link between cardiovascular disease and LBMD, and the role of lipid metabolism in this has attracted widespread attention. We analyzed participant information collected from multiple NHANES cycles using weighted multivariable logistic regression, subgroup analysis, restricted cubic splines (RCS) curve analysis, and causal mediation analysis. Non-high-density lipoprotein to high-density lipoprotein ratio (NHHR) was significantly negatively associated with low bone mass disorders in a fully adjusted model. We found that NHHR exhibited an L-shaped relationship with the prevalence of LBMD, with a negative association when NHHR < 3.38 and no significant association when NHHR > 3.38. So we could manage both disorders through NHHR. Causal mediation analysis demonstrated that NHHR was a partial mediator of the effect of body mass index (BMI) on low bone mass disorders (LBMD), accounting for 2.3% of the total effect. This suggests that part of the effect in weight affecting low bone mass disorders is mediated by the NHHR. This inspires us to utilize NHHR to guide weight management.

Keywords Low bone mass disorders, NHHR, NHANES, BMI

Abbreviations

NHANES	National Health and Nutrition Examination Survey
BMI	Body mass index
NCHS	The National Center for Health Statistics
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
SD	Standard deviation
OR	Odds ratio
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
NHHR	The non-high-density lipoprotein to high-density lipoprotein ratio
CKD	Chronic Kidney Disease
CVD	Cardiovascular disease
BMD	Bone mineral density
LBMD	Low bone mass disorders

Low Bone Mass Disorders (LBMD), including osteopenia and osteoporosis, refer to a group of disorders characterized by diminished levels of bone mineral density. This reduction makes bones more susceptible to weakness and increases the potential for fractures. As the world's population ages, the prevalence of LBMD continues to rise in the elderly population[1,2], which is prone to fragility fractures, resulting in limited mobility, deformity, chronic pain and even disability[3,4]. In particular, femoral fractures and fragility hip fractures due to osteoporosis in the elderly may lead to a variety of complications characterized by poor prognosis and

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high mortality[3,5]. Therefore, femoral BMD is widely used as an indicator for the diagnosis of osteopenia and osteoporosis and is an efficient tool for detecting LBMD[6,7]. Due to the current increase in the number of patients with LBMD and the severe impact of associated fractures on patients' quality of life and finances[8,9], it is essential for early LBMD diagnosis and intervention.

New research has revealed an association between obesity and LBMD, noting that populations with lower weight tend to have lower bone density and higher prevalence of LBMD[10,11]. Body mass index (BMI), a ratio of weight to height squared (kg/m^2), is the standard metric for weight status classification in epidemiological research. Previous studies have shown that body mass index (BMI)-mediated obesity has a protective effect on bone mineral density (BMD) and that optimal benefit is observed above a specific BMI threshold[12,13]. However, whether obesity directly affects or mediates the effects of BMD remains controversial. It is abundantly clear that obesity may predispose to a number of underlying diseases and increase the risk of cardiovascular disease (CVD). Therefore, non-strategic weight gain is not recommended to reduce LBMD risk. Further research should focus on safety thresholds to scientifically guide weight management.

To explore the relationship between lipid metabolism and osteoporosis, numerous studies have attempted to reveal a potential link between the two by analyzing various lipoprotein[14–16]. Some studies have suggested that high-density lipoprotein cholesterol (HDL-C) may be protective against osteoporosis, whereas low-density lipoprotein cholesterol (LDL-C) may increase the risk of this disease[14,15]. However, other studies have suggested the opposite, indicating that HDL may be a risk factor for osteoporosis, whereas LDL may be protective[16,17]. At present, the specific link between lipoproteins and osteoporosis remains unclear. Some studies have confirmed a significant association between cardiovascular disease and osteoporosis, particularly in the elderly population, suggesting that there may be a common pathophysiological mechanism or common risk factors for both[18]. As the population aged, the incidence of both cardiovascular diseases and osteoporosis has been increasing[19,20]. Studies have revealed that patients with cardiovascular diseases are more likely to develop osteoporosis and vice versa[21,22], prompting an increasing number of scholars to focus on clinical biomarkers with the aim of guiding the prevention and treatment of both diseases together[19,20,23]. NHHR is a composite indicator for cardiovascular diseases, particularly atherosclerosis, which integrates information on all lipid particles that both promote and inhibit atherosclerosis[24]. NHHR demonstrates superior predictive capacity for cardiovascular disease (CVD) risk stratification compared to conventional single-parameter biomarkers[25,26]. Therefore, in this study, we chose to use NHHR to comprehensively assess the effects of HDL cholesterol and non-HDL cholesterol lipoprotein to explore their relationship with LBMD, providing a new perspective for the combined management of cardiovascular disease (CVD) and LBMD, and offering scientific guidance for weight management in populations at risk of osteoporosis.

Methodology of the study

Study design and population

The data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES), a survey conducted by the National Center for Health Sciences (NCHS) of the Centers for Disease Control and Prevention (CDC). The health and nutritional status of the U.S. population is assessed by means of questionnaires, physical examinations, laboratory tests, and other records, and rigorous sampling and validation are used to ensure the accuracy of the data[27–30]. This survey was conducted with documented consent from every participant, and ethical authorization was secured through the Ethics Review Board of the U.S. Centers for Health Statistics.

A total of 56,769 individuals from NHANES 2005–2010, 2013–2014, and 2017–2020 were used in this study; the remaining years were not uploaded for femoral BMD and were therefore not included in this study. Initially, participants who had not undergone laboratory testing (and therefore lacked NHHR data) were excluded. Subsequently, those lacking data on femoral bone density, body mass index, smoking status, blood pressure status, kidney disease, diabetes or other diseases were also excluded. It should be noted that due to limitations in the availability of NHANES blood data, our study population only included adults aged 20 years and older. The study ultimately included a sample of 18,283 participants. Figure 1 illustrates the specific inclusion and exclusion process. All data were obtained from NHANES, and the study dataset, documents, and protocols are available free of charge on the NHANES website[31].

Definition of low bone mass disorders

LBMD include osteopenia and osteoporosis and are diagnosed on the basis of bone mineral density (BMD). The BMD data in the database is checked with a dual-energy X-ray absorptiometry instrument (Hologic, Bedford, MA, USA) for femoral neck, trochanter, intertrochanter and total femoral BMD. Based on the World Health Organization criteria[32], participants with BMD T-score between − 1.0 and − 2.5 standard deviation (SD) at any femoral measurement site were classified as having osteopenia, whereas those with T-score ≤ −2.5 SD were classified as having osteoporosis. Both conditions can be collectively referred to as LBMD, and if all the values of BMD in all regions are greater than or equal to the mean of the young population minus 1 SD, they are considered normal. The reference group for the young population in this study was people aged 20–29 years, and the corresponding thresholds for LBMD in each femoral region are shown in Supplementary Table 1.

Definition of NHHR and BMI measurement

Serum samples were analyzed to determine levels of high-density lipoprotein cholesterol (HDL-C) and total cholesterol. Total cholesterol (TC) was determined via the Wahlefeld method, HDL was determined via the magnesium sulfate/dextran method and non-HDL was obtained by subtracting HDL from total cholesterol. The non-high-density lipoprotein to high-density lipoprotein ratio (NHHR) was calculated as non-HDL divided by HDL, and the values were retained to two decimal places. Additionally, NHHR was considered as a meaningful

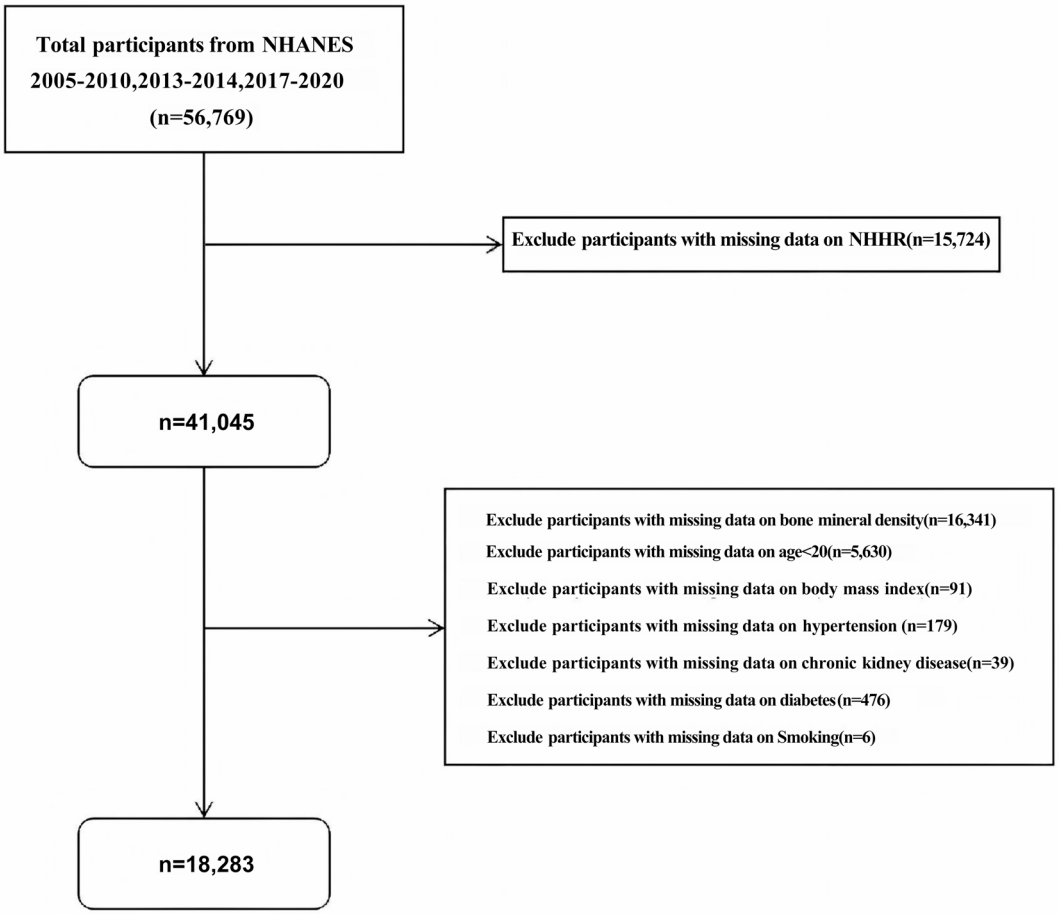

Fig. 1. Flowchart for inclusion and exclusion of NHANES 2005–2010, 2013–2014, and 2017–2020 participants.

mediator variable in this study. The body mass index (BMI) is determined by using a formula where weight in kilograms is divided by height in meters squared, expressed as BMI = weight (kg)/height^2 (m^2).

Ascertainment of covariates

The selection of covariates was based on previous studies[15,33] and clinical observations. This study incorporated a range of variables, including demographic risk factors, associated disease factors. Regarding demographic risk factors, factors like age, sex, education level, and racial/ethnic background were included. Education level was categorized as less than 9th grade, 9th-12th grade, high school grade, AA degree, college graduate or above, other grade. Race was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race. In addition, age was classified into two groups according to previous studies in subgroup analysis: those younger than 60 and those older than 60. The inclusion criteria for diabetes, hypertension and kidney disease in terms of underlying disease were considered. Additionally, the presence of smoking history was considered. To estimate the presence of smoking, the self-reported criterion was 'whether you have smoked at least 100 cigarettes in your lifetime'. Due to the limitations of the 2-hour oral glucose tolerance test measurement data, three complementary criteria were used to diagnose diabetes: physician diagnosis, fasting blood glucose ≥ 7.0 mmol/L, or glycated hemoglobin (HbA1c) ≥ 6.5%. Hypertension was determined by self-reported physician notification of hypertension or by three standardized measurements of arterial blood pressure of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic. Chronic kidney disease (CKD) was determined is determined by the eGFR value (eGFR < 60 mL/min/1.73 m^2). Self-reported information on the above diseases was collected through standardised NHANES interview questionnaires. For example, the diagnosis of hypertension was based on participants' responses to the question, 'Have you ever been told by a doctor or other health professional that you have high blood pressure?' Other diseases covered in the study (e.g., kidney disease, arthritis, diabetes, etc.) were defined in a similar way, and all NHANES survey interviews were conducted by trained health interviewers using scientifically validated questionnaires under strict quality control protocols.

Statistical analysis

The data collected were analyzed according to the NHANES analytical guidelines, and continuous variables in the study were expressed as the mean ± standard deviation for those that conformed to a normal distribution and as the median and interquartile range for those that did not conform to normal distribution. Categorical variables

are expressed as number and percentage. To identify whether there was a potential nonlinear relationship between NHHR, BMI and LBMD, as well as to describe the difference in the effect relationship as the values of the two scales increased, we divided NHHR and BMI into four groups according to their respective interquartile sizes. Given the complex multistage probability sampling design used in NHANES, all analyses included sample weights (WTMEC2YR), clustering variables (SDMVPSU), and stratification variables (SDMVSTRA) to ensure that the estimated results were nationally representative.The association among NHHR, BMI and LBMD were analyzed via multifactorial logistic regression, which revealed the effect value and whether it was statistically significant according to the OR and 95% CI, with the lowest value group, Quartile 1, as a reference, in order to describe the associations between the different value groups. Based on the adjusted covariates, it was divided into three models. Model 1 was performed for univariate analysis without adjustment. Model 2 was adjusted for demographic variables to include age, sex, education, and racial/ethnicity. Model 3 further included smoking, hypertension, diabetes, and chronic kidney disease, and multiple study models were compared to test the associations and their stability. We also conducted subgroup analyses to investigate heterogeneity and potential association between NHHR and LBMD in different populations. In order to analyze the correlation between NHHR and LBMD prevalence, we performed smoothed curve fitting to investigate whether there was a linear or non-linear relationship between the two. All statistical analyses were performed with R software (version 4.4.0) and EmpowerStats (version 6.0). The main R packages used include: survey package, mediation package, rms package, and mgcv package.

Result

Baseline features of the subjects

This study utilized complex sampling weight analysis from the NHANES to include 18,283 adults aged ≥ 20 years with complete blood and bone density data, representing a weighted population of 140,351,693 in the United States. Characteristics of the weighted population showed: mean age of 51 years, 49.80% male, a smoking rate of 46.99%, and a prevalence of low bone mass disorder (LBMD) of 52.14%. Weighted comparisons revealed that the prevalence of LBMD was significantly lower in the fourth quartile of NHHR compared to the first quartile (45.99% vs. 59.48%, $p < 0.001$), while BMI was significantly higher (29.7 vs. 24.4 kg/m^2, $p < 0.001$); As detailed in Table 1 weighted results.

Logistic regression analysis

According to the analysis in Table 2, the weighted results indicate that there is a negative correlation between NHHR and LBMD prevalence regardless of whether confounding variables are adjusted for. In Model 1 (without adjustment for covariates), a negative correlation was found between NHHR levels and the prevalence of LBMD, and each unit increase in NHHR reduced the prevalence of LBMD by 13% (0.87 (0.84, 0.90), $p < 0.001$). In Model 3 (incorporating age, sex, education, race, hypertension, diabetes, smoking, and kidney disease covariates into the regression model), NHHR was negatively associated with LBMD, with each unit increase in NHHR decreasing the prevalence of LBMD by 13% (0.87, (0.85, 0.90), $p < 0.001$). Additionally, in Model 3, the NHHR and LBMD prevalence rates in the highest NHHR group (fourth quartile) were 0.55 times those in the lowest NHHR group (first quartile) (0.55, (0.49, 0.63), $p < 0.001$), and the difference between the fourth and first quartiles was statistically significant. In the NHHR quartile analysis, the p for trend was < 0.001.

When covariates are not considered, the weighted results indicate a significant correlation between BMI and LBMD, and for every unit increase in BMI, the prevalence of LBMD decreased by 10% (0.90, (0.80, 0.91), $p < 0.001$). When age, sex, education, race, hypertension, diabetes, smoking, and kidney disease covariates were included in the regression model, BMI and LBMD remained negatively and statistically significant (0.88, (0.87, 0.88), $p < 0.001$), with a 12% decrease in LBMD prevalence for each unit increase in BMI. In Model 3, the highest BMI group had an 84% decrease in LBMD prevalence compared with the lowest BMI group (Q1). The specific data are shown in Table 3.

Subgroup analysis

Weighting subgroup analysis was performed using model 3 to explore the association between NHHR and LBMD in different populations. Among the subgroups according to age (grouped with 60 as the cutoff), race, smoking status, and hypertension status, NHHR and LBMD were negatively correlated, and the correlation were statistically significant ($p < 0.001$). However, Fig. 2 shows that there was no significant interaction between the above subgroups (p for interaction > 0.05). In the diabetes subgroup, a significant negative correlation between NHHR and LBMD was observed in individuals without diabetes, whereas in diabetic patients, NHHR showed a non-significant negative correlation with LBMD. This phenomenon was also observed in the chronic kidney disease subgroup. There were significant interactions between the diabetes subgroup and the chronic kidney disease subgroup. In both sex subgroups, NHHR and LBMD showed significant negative correlation (0.83, (0.79, 0.87), 0.92, (0.89, 0.95)), and the p for interaction < 0.001, the correlation between gender and direction is negative, but there are significant differences in effect size (the protective effect is stronger in females), and there is a risk of false positives. Specific data are shown in Fig. 2.

Weighted restricted cubic splines (RCS) curve fitting

Based on the weighted RCS curve fitting, we revealed an L-shaped association between NHHR and LBMD (see Fig. 3). There is an inflection point of 3.38 (log-likelihood ratio test $p < 0.001$) in the trend of the association between NHHR and LBMD. At < 3.38, the effect value is 0.77, indicating a significant negative correlation ((0.73, 0.81), $p < 0.001$). For every 1 unit increase in NHHR, the prevalence of LBMD was reduced by 23%. At > 3.5, the effect value was 1.00 ((0.96, 1.04), $p = 0.830$), NHHR was not associated with LBMD. Specific data from the threshold effect analysis are shown in Table 4.

Variables	Non-HDL-C/HDL-C ratio (NHHR)					p-value
	Overall Weighted $N = 140,351,693$ Unweighted $n = 18,283$	Q1 Weighted $N = 35,408,346$ Unweighted $n = 4,570$	Q2 Weighted $N = 34,863,849$ Unweighted $n = 4,571$	Q3 Weighted $N = 34,824,667$ Unweighted $n = 4,570$	Q4 Weighted $N = 35,254,831$ Unweighted $n = 4,572$	
Age, Median (Q1, Q3)	51 (39, 62)	51 (37, 65)	52 (39, 63)	51 (40, 61)	49 (39, 59)	< 0.001
Gender, n(%)						< 0.001
Female	70,459,970 (50.20%)	23,446,266 (66.22%)	19,968,427 (57.28%)	15,034,197 (43.17%)	12,011,080 (34.07%)	
Male	69,891,722 (49.80%)	11,962,080 (33.78%)	14,895,422 (42.72%)	19,790,470 (56.83%)	23,243,750 (65.93%)	
Race, n(%)						< 0.001
Mexican American	10,680,191 (7.61%)	1,778,426 (5.02%)	2,228,910 (6.39%)	3,051,201 (8.76%)	3,621,654 (10.27%)	
Other Hispanic	6,632,736 (4.73%)	1,221,070 (3.45%)	1,565,648 (4.49%)	1,848,489 (5.31%)	1,997,528 (5.67%)	
Non-Hispanic White	100,464,233 (71.58%)	25,669,345 (72.50%)	25,162,261 (72.17%)	24,533,233 (70.45%)	25,099,394 (71.19%)	
Non-Hispanic Black	13,504,251 (9.62%)	4,494,317 (12.69%)	3,595,249 (10.31%)	3,165,383 (9.09%)	2,249,302 (6.38%)	
Other Race	9,070,282 (6.46%)	2,245,188 (6.34%)	2,311,781 (6.63%)	2,226,360 (6.39%)	2,286,953 (6.49%)	
Education, n(%)						< 0.001
Less Than 9th Grade	7,895,288 (5.63%)	1,380,737 (3.90%)	1,739,728 (4.99%)	2,111,154 (6.06%)	2,663,670 (7.56%)	
9-12th Grade	15,319,986 (10.92%)	3,314,299 (9.36%)	3,251,359 (9.33%)	4,202,845 (12.07%)	4,551,484 (12.91%)	
High School Grade	33,838,805 (24.11%)	7,582,749 (21.42%)	7,820,526 (22.43%)	8,931,817 (25.65%)	9,503,713 (26.96%)	
AA degree	42,476,945 (30.26%)	10,527,290 (29.73%)	10,950,732 (31.41%)	10,134,001 (29.10%)	10,864,923 (30.82%)	
College graduate or above	40,717,701 (29.01%)	12,565,986 (35.49%)	11,091,234 (31.81%)	9,444,312 (27.12%)	7,616,169 (21.60%)	
Other grade	102,967 (0.07%)	37,285 (0.11%)	10,271 (0.03%)	538 (0.00%)	54,872 (0.16%)	
Body mass index, Median (Q1, Q3)	27.4 (24.0, 31.4)	24.4 (21.9, 28.1)	26.9 (23.8, 31.0)	28.3 (25.2, 32.2)	29.7 (26.7, 33.2)	< 0.001
Hypertension, n(%)						< 0.001
No	89,552,977 (63.81%)	24,061,495 (67.95%)	22,486,366 (64.50%)	21,492,247 (61.72%)	21,512,869 (61.02%)	
Yes	50,798,715 (36.19%)	11,346,851 (32.05%)	12,377,483 (35.50%)	13,332,419 (38.28%)	13,741,962 (38.98%)	
Glomerular Filtration Rate	74 (64, 84)	76 (65, 87)	75 (64, 85)	74 (63, 83)	73 (63, 83)	< 0.001
Chronic kidney disease, n(%)						0.019
No	112,875,330 (80.42%)	29,095,813 (82.17%)	28,075,434 (80.53%)	27,729,486 (79.63%)	27,974,597 (79.35%)	
Yes	27,476,363 (19.58%)	6,312,533 (17.83%)	6,788,415 (19.47%)	7,095,181 (20.37%)	7,280,234 (20.65%)	
Diabetes, n(%)						< 0.001
No	123,350,873 (87.89%)	31,739,887 (89.64%)	30,786,494 (88.30%)	30,463,736 (87.48%)	30,360,756 (86.12%)	
Yes	17,000,820 (12.11%)	3,668,460 (10.36%)	4,077,355 (11.70%)	4,360,930 (12.52%)	4,894,075 (13.88%)	
Smoking, n(%)						< 0.001
No	74,402,118 (53.01%)	19,741,162 (55.75%)	19,175,401 (55.00%)	18,544,300 (53.25%)	16,941,254 (48.05%)	
Yes	65,949,575 (46.99%)	15,667,184 (44.25%)	15,688,448 (45.00%)	16,280,367 (46.75%)	18,313,577 (51.95%)	
Femur neck BMD, (mg/dL)	0.81 (0.72, 0.92)	0.77 (0.68, 0.88)	0.80 (0.71, 0.91)	0.83 (0.73, 0.93)	0.84 (0.75, 0.94)	< 0.001
Trochanter BMD, (mg/dL)	0.72 (0.64, 0.81)	0.68 (0.61, 0.77)	0.72 (0.63, 0.80)	0.73 (0.65, 0.83)	0.76 (0.67, 0.84)	< 0.001
Intertrochanter BMD, (mg/dL)	1.14 (1.02, 1.26)	1.08 (0.96, 1.20)	1.13 (1.00, 1.25)	1.16 (1.04, 1.28)	1.19 (1.07, 1.31)	< 0.001
Total femur BMD, (mg/dL)	0.96 (0.86, 1.07)	0.91 (0.81, 1.01)	0.95 (0.84, 1.05)	0.98 (0.87, 1.08)	1.01 (0.91, 1.10)	< 0.001
Osteopenia, n(%)						< 0.001
No	67,952,909 (48.42%)	14,737,131 (41.62%)	16,351,496 (46.90%)	17,741,333 (50.94%)	19,122,948 (54.24%)	
Yes	72,398,784 (51.58%)	20,671,215 (58.38%)	18,512,353 (53.10%)	17,083,334 (49.06%)	16,131,883 (45.76%)	
Osteoporosis, n(%)						< 0.001
No	134,269,627 (95.67%)	33,197,868 (93.76%)	33,188,087 (95.19%)	33,470,247 (96.11%)	34,413,426 (97.61%)	
Yes	6,082,066 (4.33%)	2,210,478 (6.24%)	1,675,762 (4.81%)	1,354,420 (3.89%)	841,405 (2.39%)	
Low bone mass, n(%)						< 0.001
No	67,169,149 (47.86%)	14,348,854 (40.52%)	16,188,750 (46.43%)	17,589,890 (50.51%)	19,041,654 (54.01%)	
Yes	73,182,544 (52.14%)	21,059,492 (59.48%)	18,675,099 (53.57%)	17,234,776 (49.49%)	16,213,177 (45.99%)	

Table 1. Weighted baseline characteristics of the study population based on Non-HDL-C/HDL-C ratio. *Notes: Median (IQR) for continuous variables; N (%) for categorical variables. BMD: Bone mineral density; HDL-C: High-density lipoprotein cholesterol. .*

Exposure	Model 1		Model 2		Model 3	
	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
NHHR(continuous)	0.87(0.84,0.90)	< 0.001	0.87((0.84,0.90)	< 0.001	0.87(0.85,0.90)	< 0.001
NHHR(quartile)						
Quartile 1	1.0(Ref.)		1.0(Ref.)		1.0(Ref.)	
Quartile 2	0.79(0.71,0.87)	< 0.001	0.72(0.63,0.81)	< 0.001	0.72(0.63,0.82)	< 0.001
Quartile 3	0.67(0.61,0.73)	< 0.001	0.61(0.54,0.67)	< 0.001	0.61(0.55,0.68)	< 0.001
Quartile 4	0.58(0.52,0.65)	< 0.001	0.54(0.48,0.62)	< 0.001	0.55(0.49,0.63)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Table 2. Weighted multiple logistic regression of the association between NHHR and low bone mass Disorders. *Notes: NHHR was converted from a continuous variable to a categorical variable (quartiles) in multiple logistic regression analyses. . OR: odds ratio; 95% Cl: 95% confidence interval; NHHR: The non-high-density lipoprotein to high-density lipoprotein ratio. . Model 1: no adjustment for covariates. . Model 2: adjusted for sex, age, race/ethnicity and education. Model 3: adjusted for sex, age, race/ethnicity, education, hypertension, diabetes, chronic kidney disease, smoking.*

Exposure	Model 1		Model 2		Model 3	
	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
BMI(continuous)	0.90(0.80,0.91)	*P* < 0.001	0.87(0.87,0.88)	*P* < 0.001	0.88(0.87,0.88)	*P* < 0.001
BMI(quartile)						
Quartile 1	1.0(Ref.)		1.0(Ref.)		1.0(Ref.)	
Quartile 2	0.61(0.54,0.70)	< 0.001	0.43(0.38,0.49)	< 0.001	0.43(0.37,0.49)	< 0.001
Quartile 3	0.46(0.40,0.52)	< 0.001	0.28(0.24,0.33)	< 0.001	0.29(0.25,0.33)	< 0.001
Quartile 4	0.25(0.22,0.29)	< 0.001	0.15(0.13,0.18)	< 0.001	0.16(0.14,0.18)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Table 3. Weighted multiple logistic regression of the association between BMI and low bone mass Disorders. *Notes: BMI was converted from a continuous variable to a categorical variable (quartiles) in multiple logistic regression analyses. . OR: odds ratio; 95% Cl: 95% confidence interval; BMI: Body mass index. . Model 1: no adjustment for covariates. . Model 2: adjusted for gender, age, race and education. Model 3: adjusted for gender, age, race, education, hypertension, diabetes mellitus, chronic kidney disease, smoking.*

Causal mediation analysis

Causal mediating effect analysis, revealed that the NHHR mediated the negative association of BMI with LBMD, with an indirect effect of −0.0007 ((−0.0011, −0.0001), $p = 0.020$). Figure 4 shows the multiple pathways by which BMI affects LBMD, as well as the influence of mediating factor. The direct effect of BMI on the prevalence of LBMD continued to be significantly negatively correlated after controlling for NHHR (−0.0273 (−0.0283, −0.0261), $p < 0.001$). According to Table 5, the effect of BMI on LBMD includes both direct and indirect effects, where the mediating effect is 2.3%.

Discussion

In recent years, a large number of studies have centered around biological and lipid markers associated with LBMD and have gradually reported the potential links between LBMD and various factors such as metabolism and the environment. This research explored the potential link between NHHR lipid markers and LBMD, revealing an L-shaped association between NHHR levels and LBMD prevalence. Multifactorial logistic analyses revealed that a negative correlation was observed between NHHR levels and the incidence of low bone mineral density among adult individuals, and the negative association remained stable after adjusting for multiple covariates, with Q4 showing a significant more negative association compared with Q1. An important interaction was observed between diabetes and gender categories, showing a strong negative correlation between NHHR and low bone mineral density (LBMD) in individuals without diabetes, a negative relationship was observed between NHHR and low bone mineral density (LBMD) in individuals with diabetes. This phenomenon was also observed in the chronic kidney disease subgroup. And a negative correlation between NHHR and LBMD was noted in both male and female subgroups, nevertheless, variations in effect magnitude or variance may induce statistical interactions despite consistent effect directions, potentially leading to false positives. Our study revealed a significant negative correlation between BMI and LBMD, which remained stable even after adjusting for multiple covariates. Specifically, the prevalence of LBMD was 84% lower in the high BMI group compared than in the low BMI group. To further explore this relationship, we conducted a mediation effect analysis, using NHHR as the mediating variable. The results revealed not only a direct effect between BMI and the prevalence of LBMD in adults, but also a partial indirect effect mediated through NHHR, with a mediated effect size of 2.3%. This finding provides a new perspective for an in-depth study of how BMI affects LBMD prevalence. Through

Subgroup	N	Adjusted OR (95% CI)*	P value	P for interaction
Overall	140,351,693 (100%)	0.88 (0.86, 0.91)	<0.001	
Age				0.298
Below 60	98,327,685 (70%)	0.88 (0.84, 0.91)	<0.001	
Over 60	42,024,008 (30%)	0.91 (0.86, 0.97)	0.003	
Gender				0.001
Female	70,459,970 (50%)	0.83 (0.79, 0.87)	<0.001	
Male	69,891,722 (50%)	0.92 (0.89, 0.95)	<0.001	
Diabetes				0.004
No	123,350,873 (88%)	0.87 (0.85, 0.90)	<0.001	
Yes	17,000,820 (12%)	0.98 (0.92, 1.06)	0.675	
Hypertension				0.640
No	89,552,977 (64%)	0.89 (0.87, 0.92)	<0.001	
Yes	50,798,715 (36%)	0.89 (0.84, 0.94)	<0.001	
Chronic kidney diease				0.004
No	112,875,330 (80%)	0.87 (0.84, 0.90)	<0.001	
Yes	27,476,363 (20%)	0.97 (0.91, 1.03)	0.325	
Education				0.094
Less than 9th grade	7,895,288 (5.6%)	0.90 (0.82, 0.99)	0.036	
9-12th Grade	15,319,986 (11%)	0.83 (0.78, 0.90)	<0.001	
High school grade	33,838,805 (24%)	0.88 (0.83, 0.94)	<0.001	
AA Degree	42,476,945 (30%)	0.89 (0.84, 0.95)	<0.001	
College graduate or above	40,717,701 (29%)	0.88 (0.83, 0.92)	<0.001	
Other grade	102,967 (<0.1%)	0.56 (0.31, 1.01)		
Race				0.811
Mexican American	10,680,191 (7.6%)	0.87 (0.80, 0.94)	0.001	
Other Hispanic	6,632,736 (4.7%)	0.86 (0.77, 0.95)	0.004	
Non-Hispanic White	100,464,233 (72%)	0.87 (0.84, 0.90)	<0.001	
Non-Hispanic Black	13,504,251 (9.6%)	0.85 (0.79, 0.91)	<0.001	
Other Race	9,070,282 (6.5%)	0.88 (0.80, 0.98)	0.018	
Smoking				0.864
No	74,402,118 (53%)	0.87 (0.84, 0.91)	<0.001	
Yes	65,949,575 (47%)	0.88 (0.84, 0.92)	<0.001	

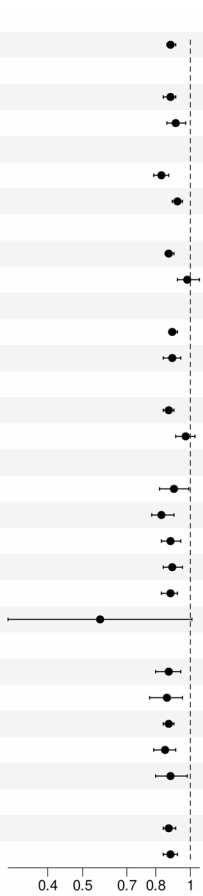

Fig. 2. Weighted Subgroup analysis of the association between NHHR and Low bone mass disorders.

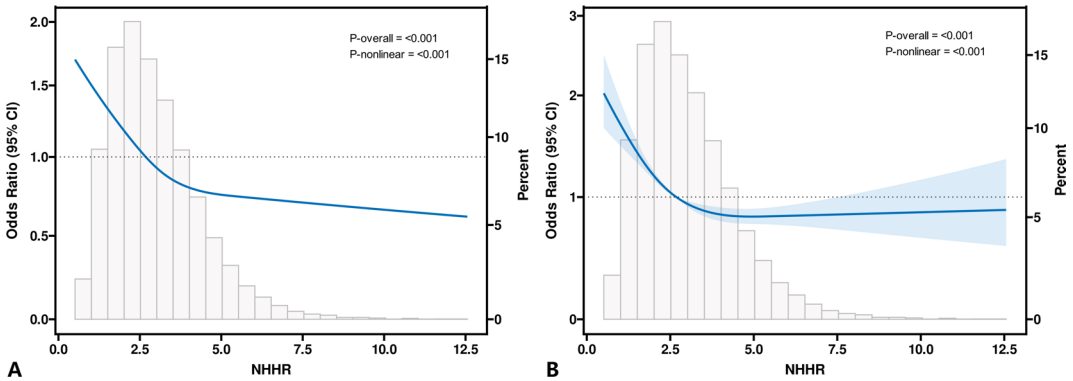

Fig. 3. **Weighted Restricted Cubic Splines (RCS) Curve Fitting**. *Notes: Subfigure A: Association between NHHR and LBMD without adjusting for confounding factors; Subfigure B: Association between NHHR and LBMD after full adjustment for confounding factors.*

the restricted cubic splines (RCS) curve fitting technique, we also observed a negative correlation between NHHR and adult LBMD prevalence, with an L-shaped distribution of the curve. When NHHR was less than 3.38, there was a significant negative correlation between NHHR and LBMD prevalence, with a 23% decrease in LBMD prevalence for each unit increase in NHHR. However, when NHHR exceeded 3.38, NHHR was not correlated with LBMD prevalence.

Several studies have revealed a strong link between obesity and bone density[33–35]. Specifically, obese individuals or those with a high body mass index (BMI) typically exhibit greater bone density and a lower risk of fracture. However, patients who are overly obese or have an abnormally high BMI may experience a decrease in BMD along with an increased risk of fragility fractures. This phenomenon may be associated with metabolic abnormalities and high risk of falling[11]. This suggests that BMI, as an indicator of body weight status, has a dual

	Non-HDL-C/HDL-C ratio (NHHR)	Adjusted model	
		OR(95%CI)	P-value
Low bone mass disorders	Fitting by the standard linear model	0.89(0.87,0.91)	$P<0.001$
	Fitting by the two-piece wise linear model		
	Infection point	3.38	
	NHHR<3.50	0.77(0.73,0.81)	$P<0.001$
	NHHR ≥ 3.50	1.00(0.96,1.04)	$P=0.830$
	Log likelihood ratio	<0.001	

Table 4. Threshold effect analysis of NHHR and low bone mass Disorders. *Notes: Adjusted for gender, age, race/ethnicity, education, hypertension, diabetes, chronic kidney disease, smoking. OR: odds ratio; 95% Cl: 95% confidence interval; NHHR: The non-high-density lipoprotein to high-density lipoprotein ratio; HDL-C: High-density lipoprotein cholesterol.*

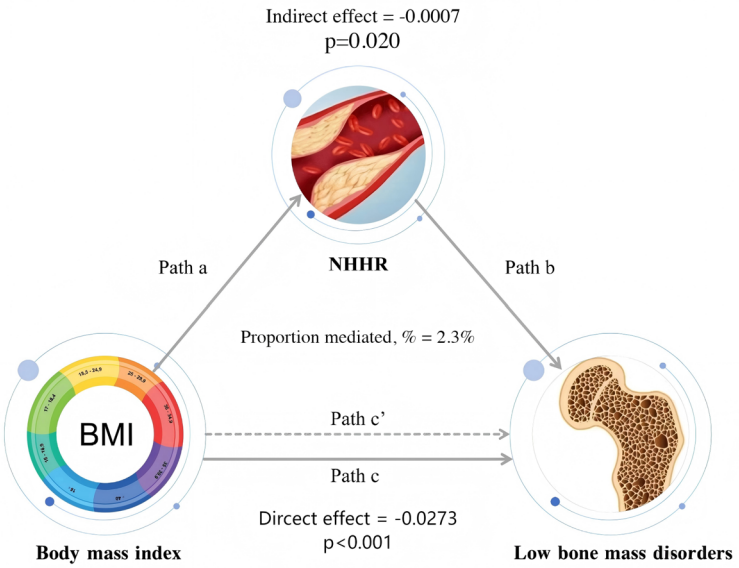

Fig. 4. Mediated analysis model path diagram.*Notes: Body mass index was defined as the independent variable; Low bone mass disorders as the dependent variable; and NHHR as the mediating variable. Path a represents the regression coefficient of the association between BMI and NHHR. Path b represents the regression coefficient of the association between NHHR and Low bone mass disorders. Path c represents the simple total effect of NHHR on Low bone mass disorders. Path c' represents the direct effect of BMI on Low bone mass disorders when controlling for NHHR.*

Variable	Mediator	Total effect		Mediation effect		Direct effect		Proportion mediated,%
		Coefficient(95%CI)	*P* value	Coefficient(95%CI)	*P* value	Coefficient(95%CI)	*P* value	
BMI	NHHR	−0.0280(−0.0287,−0.0270)	<0.001	−0.0007(−0.0011,−0.0001)	0.020	−0.0273(−0.0283,−0.0261)	<0.001	2.3

Table 5. Mediating effects of NHHR in the association between BMI and LBMD. *Notes: NHHR: The non-high-density lipoprotein to high-density lipoprotein ratio; BMI: Body mass index; LBMD: Low bone mass disorders. .*

effect on BMD: within a certain range, an elevated BMI contributes to higher BMD and a lower incidence of LBMD; however, when the BMI is too high, it instead decreases BMD and contributes to fragility fractures[36–38]. The effect of BMI on BMD is exerted by both adipose tissue and muscle tissue, with muscle tissue affected mainly through mechanical loading. Adipose tissue, on the other hand, can affect bone density through lipid metabolism, and its effects have received increasing attention[11,39]. Previous studies have shown that HDL-C is positively correlated with bone density and is considered a protective factor, whereas LDL-C show a negative correlation with bone density and is considered a risk factor[14,15,40]. However, some studies have also shown a negative correlation between HDL-C and BMD[16,17,41], there are conflicting conclusions about the effects of lipid

metabolism on BMD, and no basic research has conducted to clarify the exact mechanisms of the effects of lipoproteins on BMD.

The preponderance of evidence suggests that there may be a complex link between CVD and LBMD[22,42], and the mechanisms and indicators of the link between the two diseases are of particular importance for their joint prevention and management. NHHR, the ratio of non-HDL-C to HDL-C, is a combined indicator of CVD, particularly atherosclerosis, and collects information about all atherogenic and antiatherogenic lipid particles[25,26], with high early warning value in CVD. This indicator collects information on all atherogenic and anti-atherogenic lipid particles and has high early warning value in CVD. In this study, the non-high-density lipoprotein cholesterol ratio (NHHR) was used as a combined index to comprehensively assess the effects of including LDL-C and HDL-C on the prevalence of LBMD and bone density. We hope to explore the potential clinical link between CVD and LBMD by studying the association between NHHR and LBMD, and to provide safe and effective strategies for the prevention and treatment of both diseases.

To our knowledge, this study represents the first cross-sectional study to examine the relationship between NHHR and LBMD, and the mediating effects of NHHR, which have not been explored in depth in large-scale epidemiological studies before. We found a negative correlation between NHHR and the prevalence of LBMD, suggesting that elevated NHHR decreases the prevalence of LBMD. A possible mechanism for this is, on the one hand, through the influence of HDL-C on BMD, which can be influenced by estrogens that have a significant biological effect on lipid metabolism in the blood and bone[43]. Moreover, HDL and BMD may have a greater genetic influence. Several animal experiments have shown that HDL-C and BMD are simultaneously influenced by the *Apoe* gene, with gene expression being reflected in a decrease in HDL-C levels and an increase in BMD[44,45]. On the other hand, BMD is affected by LDL-C, which can affect osteoclast activity by preventing apoptosis and mediating cholesterol transfer, thus affecting BMD[46–48]. To further investigate the association between NHHR and LBMD prevalence, we performed restricted cubic splines (RCS) curve fitting to investigate linear or nonlinear associations between the two, and the graphs showed an L-shaped association between the two. Threshold effect analysis revealed an inflection point at 3.38, and NHHR at <3.38, NHHR and LBMD were significantly negatively correlated, with a 23% decrease in LBMD for every 1 unit increase in NHHR. At NHHR >3.38 NHHR was not correlated with LBMD. That is, the prevalence decreased with increasing in NHHR, and there was no further decrease in the prevalence beyond a certain value. As an early warning indicator, elevated NHHR is often elevated NHHR serves as an early warning sign and is frequently linked to a higher likelihood of developing conditions such as CVD and diabetes[25,26]. However, the results of this study suggest that elevated NHHR was negatively associated with the prevalence of LBMD, but its effect on the prevalence of LBMD was no longer significant when NHHR exceeded a specific threshold. This finding provides important guidelines for the prevention and treatment of both CVD and LBMD in the clinic. We can adjust dietary and pharmacological strategies based on the basis of the values of NHHR within the threshold range of NHHR to modulate lipid metabolism to achieve the joint prevention and treatment of these two diseases. In addition, chronic metabolic diseases such as cardiovascular disease may negatively affect BMD when NHHR exceeds the threshold, which may be related to the role of various components of the bone matrix, like type I collagen, proteoglycans, in osteogenesis and atherosclerosis[49]. Nonetheless, the relationship between NHHR and the prevalence of LBMD needs to be validated by further basic studies and the underlying mechanisms thoroughly explored.

In our study of the association between BMI and LBMD, the mediation effect analysis showed that there were direct and indirect effects in the pathway of BMI affecting LBMD, in which NHHR, as a mediator, mediated the indirect effect of BMI on LBMD, with a mediating effect of 2.3%. These findings suggest that some of the effects of BMI on LBMD and BMD indirectly affect the prevalence of BMD and LBMD by influencing lipid metabolism, and several studies have validated the results we derived[50–52]. This result has clinical and dietary recommendations, and when considering BMD or LBMD control through BMI, the NHHR index can be derived from laboratory blood biochemistry tests and used to guide clinical management of BMD and LBMD. In addition to this, previous studies have demonstrated a similar inflection point in the association between BMI and BMD[36], so we can hypothesize that the saturation effect between BMI and BMD is mediated by NHHR in the BMI and LBMD association. This may be because after the BMI threshold is exceeded, the effects of other underlying diseases[37,38,53–55], excessive mechanical loading, and lipid metabolism due to high BMI lead to a decrease in BMD, increased occurrence of LBMD, and an increase in fragility fractures. This finding has important clinical implications for LBMD and CVD in the clinic, and while individuals with low weight and BMI are at high risk for low BMD and LBMD, blindly increasing weight and BMI poses a risk to dietary health and underlying disease. From our results, it can be concluded that the inflection point of NHHR can be referred to control BMI and lipid metabolism levels to reduce the risk of LBMD while considering CVD and other underlying diseases, providing reference for clinical nutritional diet and scientific prevention and treatment.

We further conducted subgroup analyses to investigate the potential relationship between NHHR and LBMD in different populations, and to determine whether the association between NHHR and LBMD was stable in different populations. The results of the analyses showed that, in the diabetes group, NHHR showed a significant negative correlation with LBMD among non-diabetics, and a non-significant negative correlation was observed among diabetics and there was a significant interaction between suffering from diabetes and not suffering from diabetes. There was a significant interaction between diabetics and non-diabetics; diabetes altered the association between NHHR and LBMD. This result may be related to the fact that insulin signaling can activate osteoblasts[56,57], and microangiopathy in diabetes also leads to changes in bone mineral density. In addition, insulin and insulin-like growth factors affect bone metabolism itself, which may influence bone metabolism in diabetic patients and may determine changes in bone metabolism in diabetic patients[58].

This study has several significant strengths. Compared with other cross-sectional studies, this study not only has a larger sample size but also has a greater degree of accuracy in representing U.S. national characteristics.

We have further enhanced the credibility of the findings by including multiple covariates that account for a wide range of potential confounders. For the first time to our knowledge, this study synthesized the correlation between NHHR and LBMD, and the mediating effect of NHHR was also exhaustively explored in this study, which provides new research perspectives on preventive strategies and the clinical diagnosis and treatment of LBMD.

There are several limitations to this study. First, given its cross-sectional study design, we were unable to establish an exact causal relationship between NHHR and LBMD; therefore, the association needs to be verified by subsequent prospective studies or basic experiments. In assessing LBMD, this study was based only on BMD data in the femoral region and did not include sites such as the lumbar spine and forearm, which may have led to some omissions in LBMD. Second, although multiple covariates were included to ensure the stability of the association between NHHR and LBMD, it was not possible to exclude the effects of all confounding factors. In addition, as the study sample was limited to U.S. adults, it lacks representation of the underage population and other countries and ethnicities, necessitating larger population data to further test these associations.

Conclusion

In conclusion, our study revealed that NHHR was significantly negatively associated with the prevalence of low bone mass disorders, and there was an L-shaped relationship with an inflection point of 3.38, which facilitates our simultaneous intervention and early warning of low bone mass disorders and CVD. Moreover, we found that NHHR mediated the negative association between BMI and low bone mass disorders. This provides valuable suggestions for the prevention and diagnosis of low bone mass disorders and suggest that healthcare professionals should pay attention to lipid metabolism factors for the management of low bone mass disorders.

Data availability

All data for this study was obtained from the official NHANES website (https://www.cdc.gov/nchs/nhanes/).

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Author contributions

XTC, WYD: Data collection, Investigation, Software, Design, Original manuscript. JW, HL, YKW: Conception, Graphing, Review, Data analysis. XTC: Wrote the paper. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Data for this study were obtained from the NHANES data builder and ethical approval was obtained from the Ethics Review Board of the Center for Health Statistics.

Additional information

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