High-density Lipoprotein Cholesterol Negatively Correlates with Bone Mineral Density and Has Potential Predictive Value for Bone Loss

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Abstract

Background: In recent years, it was demonstrated that high-density lipoprotein cholesterol (HDL-C), a critical lipid for human lipid metabolism, was not completely beneficial to human health, implying that extremely high HDL-C levels may also affect human health and contribute to various diseases. The correlation between HDL-C and bone metabolism was uncertain and controversial. This study aimed to explore the correlation between HDL-C level and bone mineral density (BMD), investigating whether this relationship is different in diverse populations by stratifying age and gender.

Method: The data utilized were extracted from 2005-2010 National Health and Nutrition Examination Survey (NHANES). We reviewed the data to exclude the participants aged over or equal to 20 years old or with missing core data. Multivariate linear regression analyses were conducted to estimate the association between HDL-C and BMD. A subgroup analysis was also utilized to estimate the difference in diverse populations by stratifying age and gender. Moreover, fitted smoothing curves and generalized additive models were also performed to address the nonlinear relationship between HDL-C levels and BMD.

Result: Multivariable-adjusted linear regression models demonstrated that HDL-C was negatively associated with BMD, especially in females. Meanwhile, smooth curve fittings and generalized additive models also suggested an inverted U-shaped curve among females aged 30-40 or over 60. A U-shaped curve was observed for the relationship between HDL-C and BMD in femoral regions in females aged 20 to 30 or 50 to 60. Besides, female participants aged over 40 at a higher than or equal to 71 mg/dL HDL-C level were more likely to have a high risk of osteopenia or osteoporosis.

Conclusion: HDL-C and BMD exhibited a negative correlation among females and different associations in diverse age groups. In addition, HDL-C can serve as a marker for osteopenia or osteoporosis.

Background

High-density lipoprotein cholesterol (HDL-C) is a type of cholesterol contained in or bound to high-density lipoproteins (HDL) [1]. HDL-C was believed to possess beneficial impacts on human health and was inversely associated with cardiovascular disease over a long time [2, 3]. For instance, Gordon et al. exhibited an independent inverse association of HDL-C levels and coronary heart disease event rates [4]. Rosenson et al. observed that low HDL-C levels below target may be beneficial in cardiovascular disease reduction [5]. However, over the past few years, some different voices increase. Madsen et al. reported that men and women with extremely high HDL cholesterol paradoxically have high all-cause mortality [6]. Hamer et al. observed a U-shaped association between HDL-C and mortality in a large general population sample [7]. These findings may indicate that we should reconsider our perspective on HDL-C.

Osteoporosis is a worldwide public health problem characterized by low bone mineral density (BMD) and a high risk of osteoporotic fracture [8]. According to International Osteoporosis Foundation, one-third of women and one-fifth of men aged over 50 years old have osteoporosis or low bone mass and are at risk

of osteoporotic fracture [9]. Simultaneously, as the population ages and grows, the prevalence of osteoporosis continues to rise [10]. At present, apart from genetic factors, age, or sex, the impact of other factors like lipid metabolism or lifestyle for bone metabolism has recently attracted considerable concern [11–13]. Meanwhile, researchers hope to discover novel modalities for osteoporosis prevention and treatment.

The correlation between HDL-C and BMD was uncertain and controversial. Some previous studies indicated that HDL-C level was elevated in post-menopausal women, negatively associated with bone mineral density (BMD). Maghbooli et al. found a negative correlation between HDL-C and BMD in post-menopausal Iranian women with vitamin D deficiency [14]. Zhang et al. observed that HDL-C was negatively associated with lumbar spine BMD in Chinese women [15]. Conversely, Cui et al. suggested that HDL-C level was not associated with BMD values at any of the sites in pre- and post-menopausal subjects [16]. Apart from the above, Jeong et al. observed that HDL-C was positively associated with BMD at the lumbar spine in Korean post-menopausal women [17]. Overall, the findings from these studies are contradictory. Meanwhile, since the participants in all the studies are usually from the same country or region, and most studies mainly focus on women, especially post-menopausal ones, it is difficult to say whether the relationship between HDL-C and BMD is different in diverse populations, like males or young adults. In addition, the relationship between HDL-C and BMD may be nonlinear, but the specific results require further investigation.

Accordingly, this study used a representative sample of adults aged over 20 years old from the National Health and Nutrition Examination Survey (NHANES), tried to explore linear or nonlinear relationship between HDL-C level and BMD, and investigated whether the relationship between them is different in diverse populations by stratifying age and gender.

Method

Study Population

The data analyzed in this study was extracted from National Health and Nutrition Examination Survey (NHANES), an ongoing study to assess the health and nutritional status of noninstitutionalized U.S. populations. We extracted the data for all participants from 2005–2010 [18–20]. The study was approved by the ethics review board of the National Center for Health Statistics, and written consent was obtained from each participant.

Data Extraction

1. We extracted the following information:
2. Demographic data (age, gender, race/ethnicity, education level, and income to poverty ratio)
3. Examination data (total femur BMD, femur neck BMD, trochanter BMD, intertrochanter BMD, total spine BMD, L1 BMD, L2 BMD, L3 BMD, and L4 BMD)

4. Laboratory data [HDL-C level (mg/dL), total cholesterol level (mg/dL), alanine aminotransferase (ALT) (U/L), asparate aminotransferase (AST) (U/L), and total calcium (mg/dL)]
5. Questionnaire data [drinking status (had at least 12 alcohol drinks past one year), smoking status (smoked at least 100 cigarettes in life), BMI (height and weight); diabetes (has a doctor told that you have diabetes), and hypertension (ever told you had high blood pressure)]
6. In addition, we selected the “Full Sample 2 Year MEC Exam Weight (WTMEC2YR)” to represent the weight value. Because we combine three two-year cycles of the continuous NHANES, the final weight we used was equal to one-third of the“Full Sample 2 Year MEC Exam Weight (WTMEC2YR)” according to the rule of constructing weights when combining survey cycles on the NHANES website [21].

Inclusion and Exclusion Criteria

The subjects aged over or equal to 20 with available BMD and HDL-C data were included in this study. The participants missing other variables data (data missing, answered "do not know" or refused to answer were also considered missing) are excluded.

Measurement of HDL-C

The Measurement of HDL-C was performed using Lipid Laboratory Johns Hopkins. Detailed information is accessible at NHANES website [22]. Based on the information provided at NHANES website, briefly, HDL-C is measured directly in serum. The basic principle of the method is as follows. The apolipoprotein-B (apoB) containing lipoproteins in the specimen are reacted with a blocking reagent that renders them non-reactive with the enzymatic cholesterol reagent under the assay conditions. The apoB containing lipoproteins are thus effectively excluded from the assay, and only HDL-C-cholesterol is detected under the assay conditions.

Assessment of BMD

The femur scans provide bone measurements for total femur, femoral neck, trochanter, and intertrochanter based on information provided on NHANES website. The DXA examinations were performed using Hologic QDR-4500A fan-beam densitometers (Hologic, Inc., Bedford, MA, USA) and software version Apex 3.2 by trained technologists. Further details of DXA examination protocol are documented in Body Composition Procedures Manual located on NHANES website [23].

Definition of Osteopenia and Osteoporosis

Mean femoral BMD of 20-29-year-old non-Hispanic white women from NHANES III was selected as the reference value. According to the research of Looker et al. [24].

(1) osteopenia: BMD value in any femoral regions between 1 and 2.5 SD below the mean of reference value [males (total femur BMD: 0.68–0.90 g/cm2, femur neck BMD: 0.59–0.79 g/cm2, trochanter BMD: 0.49–0.66 g/cm2, or intertrochanter BMD: 0.78–1.03 g/cm2); females (total femur BMD: 0.64–0.82

g/cm2, femur neck BMD: 0.56–0.74 g/cm2, trochanter BMD: 0.46–0.61 g/cm2, or intertrochanter BMD: 0.74–0.95 g/cm2)];

(2) osteoporosis: BMD value in any femoral regions > 2.5 SD below mean BMD of reference value [males (total femur BMD: < 0.68 g/cm2, femur neck BMD: < 0.59 g/cm2, trochanter BMD: < 0.49 g/cm2, or intertrochanter BMD: < 0.78 g/cm2); females (total femur BMD: < 0.64 g/cm2, femur neck BMD: < 0.56 g/cm2, trochanter BMD: < 0.46 g/cm2, or intertrochanter BMD: < 0.74 g/cm2)].

Statistical Analysis

We used mean (continuity variable) or proportion (categorical variable) to describe the baseline characteristics of participants. A weighted multivariate linear regression model was used to evaluate the association between HDL-C and BMD. A subgroup analysis was performed by stratified multivariate regression analysis. Furthermore, smooth curve fittings and generalized additive models were used to address the nonlinear relationship between HDL-C and BMD. For nonlinear models, the inflection point in this relationship was calculated using a recursive algorithm. A two-piecewise linear regression model was conducted on both sides of the inflection point when nonlinearity was detected. Multiple logistic regression analyses were performed to investigate the odds ratios (ORs) of osteopenia and osteoporosis. All analyses were performed using software R, V.4.0.3 [R: a language and environment for statistical computing (program). Vienna, Austria: R Foundation for Statistical Computing, 2016] and EmpowerStats (http://www.empowerstats. com), with a P-value < 0.05 considered statistically significant.

Results

Selection and Characteristics of Participants

A total of 31,034 participants were included in NHANES dataset from 2005 to 2010. Firstly, we excluded the participants without available BMD data (n = 14344). Secondly, we excluded the participants without available HDL-C data (n = 1080). Thirdly, the participants aged below 20 years old (n = 5516) and missing data on other variables (n = 1424, education level: 9, income to poverty ratio: 706, current BMI: 265, ALT: 60, AST: 1, diabetes: 5, hypertension: 9, smoking status: 2, drinking status: 367) were excluded. Finally, 8670 participants aged 20 years and over with complete data were analyzed. The detailed selection process is presented in Fig. 1.

The basic demographics of sample subjects are summarized in Table 1. A total of 8670 participants, 20–85 years of age, were included in our analysis, with weighted characteristics of participants subclassified based on gender. In this sample, subjects had a mean age of 44.39 ± 15.26; mean income to poverty ratio of 3.15 ± 1.62; mean ALT of 25.95 ± 18.18; mean AST of 25.66 ± 13.65; mean total calcium of 9.46 ± 0.35; mean total cholesterol of 197.61 ± 40.64. Most subjects were non-Hispanic whites (72.16%), received education above high school (60.07%), had at least 12 alcohol drinks past one year (77.97%), smoked less than 100 cigarettes in life (53.07%), had a BMI less than 25 kg/cm2 (37.69%). Diabetes and hypertension cases accounted for 6.02% and 25.45%, respectively.

Table 1
Weighted characteristics of the study population.

Characteristics	Means or proportions
Age (years, mean ± SD)	44.39 ± 15.26
Sex, n (%)	4477 (50.53%)
Male	4193 (49.47%)
Female	
Race/ethnicity, n (%)	
Mexican American	1590 (7.92%)
Other Hispanic	710 (4.29%)
Non-Hispanic White	4347 (72.16%)
Non-Hispanic Black	1633 (9.84%)
Other Race	390 (5.79%)
Education level, n (%)	
Under high school	2195 (16.50%)
High school or equivalent	2026 (23.43%)
Above high school	4449 (60.07%)
Income to poverty ratio (mean ± SD)	3.15 ± 1.62
BMI, n (%)	
< 25	3024 (37.69%)
25–30	3248 (36.48%)
>=30	2398 (25.83%)
Diabetes, n (%)	
Yes	744 (6.02%)
No	7791 (92.67%)
Broadline	135 (1.31%)
Hypertension, n (%)	
Yes	2513 (25.45%)
No	6157 (74.55%)

BMI, body mass index; SD, standard deviation; n, numbers of subjects; %, weighted percentage.

Characteristics	Means or proportions
Smoked at least 100 cigarettes in life, n (%)	
Yes	4095 (46.93%)
No	4575 (53.07%)
Had at least 12 alcohol drinks past one year? n (%)	
Yes	6408 (77.97%)
No	2262 (22.03%)
ALT (U/L, mean ± SD)	25.95 ± 18.18
AST (U/L, mean ± SD)	25.66 ± 13.65
Total calcium (mg/dL, mean ± SD)	9.46 ± 0.35
Total cholesterol (mg/dL, mean ± SD)	197.61 ± 40.64
HDL-C (mg/dL, mean ± SD)	53.39 ± 16.17
Total femur BMD (g/cm2, mean ± SD)	0.98 ± 0.15
Femur neck BMD (g/cm2, mean ± SD)	0.84 ± 0.15
Trochanter BMD (g/cm2, mean ± SD)	0.74 ± 0.13
Intertrochanter BMD (g/cm2, mean ± SD)	1.16 ± 0.18
Total spine BMD (g/cm2, mean ± SD)	1.04 ± 0.14
L1 BMD (g/cm2, mean ± SD)	0.96 ± 0.15
L2 BMD (g/cm2, mean ± SD)	1.05 ± 0.15
L3 BMD (g/cm2, mean ± SD)	1.07 ± 0.15
L4 BMD (g/cm2, mean ± SD)	1.07 ± 0.15
BMI, body mass index; SD, standard deviation; n, numbers of subjects; %, weighted percentage.	

Association between HDL-C and BMD

The results of the multivariate regression analyses are presented in Table 2. In the unadjusted model, HDL-C was negatively correlated with BMD. After adjustment for age, gender, and race/ethnicity, this negative association was still present in model 2. After adjustment for age, sex, race/ethnicity, education level, income to poverty ratio, smoking status, drinking status, BMI, diabetes, hypertension, ALT, AST, total calcium, and total cholesterol, the negative association remained statistically significant. The nonlinear relationship using smooth curve fittings and generalized additive models, employed to characterize between HDL-C and BMD, was displayed in Fig. 2.

Table 2
The association between HDL-C (mg/dL) and BMD (g/cm2).

	Model 1	Model 2	Model 3
	β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Total femur BMD	-0.0025 (-0.0027, -0.0023) < 0.000001	-0.0013 (-0.0015, -0.0011) < 0.000001	-0.0004 (-0.0005, -0.0002) 0.000239
Femur neck BMD	-0.0019 (-0.0021, -0.0017) < 0.000001	-0.0011 (-0.0013, -0.0009) < 0.000001	-0.0003 (-0.0004, -0.0001) 0.006194
Trochanter BMD	-0.0018 (-0.0020, -0.0016) < 0.000001	-0.0008 (-0.0010, -0.0007) < 0.000001	-0.0002 (-0.0004, -0.0000) 0.037159
Intertrochanter BMD	-0.0030 (-0.0032, -0.0027) < 0.000001	-0.0016 (-0.0018, -0.0014) < 0.000001	-0.0005 (-0.0007, -0.0003) 0.000027
Total spine BMD	-0.0012 (-0.0014, -0.0010) < 0.000001	-0.0010 (-0.0012, -0.0008) < 0.000001	-0.0003 (-0.0005, -0.0001) 0.002281
L1 BMD	-0.0019 (-0.0021, -0.0017) < 0.000001	-0.0012 (-0.0014, -0.0010) < 0.000001	-0.0005 (-0.0007, -0.0002) 0.000016
L2 BMD	-0.0015 (-0.0017, -0.0013) < 0.000001	-0.0011 (-0.0013, -0.0009) < 0.000001	-0.0004 (-0.0006, -0.0002) 0.000079
L3 BMD	-0.0009 (-0.0011, -0.0007) < 0.000001	-0.0009 (-0.0011, -0.0007) < 0.000001	-0.0003 (-0.0005, -0.0001) 0.011329
L4 BMD	-0.0008 (-0.0010, -0.0006) < 0.000001	-0.0008 (-0.0010, -0.0006) < 0.000001	-0.0002 (-0.0004, 0.0001) 0.167819

Model 1: no covariates were adjusted. Model 2: age (40–49; 50–59; 60–69; ≥70), sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: age (40–49; 50–59; 60–69; ≥70), sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Subgroup analysis of the Associations between HDL-C and BMD

The subgroup analyses, stratified by age (20 ≤ Aged < 30; 30 ≤ Aged < 40; 40 ≤ Aged < 50; 50 ≤ Aged < 60; 60 ≤ Aged) and gender (male or female), were reported in Tables 3–4. After adjusting for confounders, the negative correlation of HDL-C with BMD remained present, especially the participants aged 30 to 40 or over 50 female participants.

Table 3
Subgroup analysis of the association between HDL-C and BMD stratified by age.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Total femur BMD	20 ≤ Aged < 30	-0.0019 (-0.0023, -0.0014) < 0.000001	-0.0008 (-0.0013, -0.0004) 0.000358	0.0001 (-0.0004, 0.0006) 0.604404
	30 ≤ Aged < 40	-0.0023 (-0.0027, -0.0019) < 0.000001	-0.0016 (-0.0021, -0.0012) < 0.000001	-0.0008 (-0.0012, -0.0003) 0.000564
	40 ≤ Aged < 50	-0.0020 (-0.0024, -0.0017) < 0.000001	-0.0012 (-0.0016, -0.0009) < 0.000001	-0.0003 (-0.0007, 0.0001) 0.119456
	50 ≤ Aged < 60	-0.0027 (-0.0031, -0.0022) < 0.000001	-0.0016 (-0.0020, -0.0011) < 0.000001	-0.0006 (-0.0010, -0.0001) 0.015563
	60 ≤ Aged	-0.0026 (-0.0031, -0.0022) < 0.000001	-0.0012 (-0.0016, -0.0008) < 0.000001	-0.0004 (-0.0007, 0.0000) 0.063049
Femur neck BMD	20 ≤ Aged < 30	-0.0015 (-0.0019, -0.0010) < 0.000001	-0.0008 (-0.0013, -0.0003) 0.000638	0.0002 (-0.0003, 0.0006) 0.508709
	30 ≤ Aged < 40	-0.0016 (-0.0020, -0.0012) < 0.000001	-0.0013 (-0.0018, -0.0009) < 0.000001	-0.0005 (-0.0010, -0.0001) 0.018517
	40 ≤ Aged < 50	-0.0014 (-0.0018, -0.0011) < 0.000001	-0.0012 (-0.0015, -0.0008) < 0.000001	-0.0004 (-0.0007, 0.0000) 0.066283
	50 ≤ Aged < 60	-0.0018 (-0.0022, -0.0014) < 0.000001	-0.0013 (-0.0017, -0.0009) < 0.000001	-0.0004 (-0.0009, -0.0000) 0.041834
	60 ≤ Aged	-0.0017 (-0.0021, -0.0014) < 0.000001	-0.0010 (-0.0013, -0.0006) < 0.000001	-0.0002 (-0.0005, 0.0002) 0.308122
Trochanter BMD	20 ≤ Aged < 30	-0.0014 (-0.0018, -0.0010) < 0.000001	-0.0005 (-0.0009, -0.0001) 0.007112	0.0000 (-0.0004, 0.0005) 0.868720

Model 1: no covariates were adjusted. Model 2: sex (male; female) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	30 ≤ Aged < 40	-0.0016 (-0.0020, -0.0012) < 0.000001	-0.0011 (-0.0014, -0.0007) < 0.000001	-0.0005 (-0.0009, -0.0001) 0.013278
	40 ≤ Aged < 50	-0.0015 (-0.0018, -0.0011) < 0.000001	-0.0008 (-0.0011, -0.0005) 0.000001	-0.0002 (-0.0006, 0.0001) 0.198229
	50 ≤ Aged < 60	-0.0020 (-0.0024, -0.0016) < 0.000001	-0.0010 (-0.0014, -0.0006) < 0.000001	-0.0003 (-0.0007, 0.0001) 0.166214
	60 ≤ Aged	-0.0019 (-0.0023, -0.0016) < 0.000001	-0.0006 (-0.0010, -0.0003) 0.000189	-0.0001 (-0.0004, 0.0003) 0.721758
Intertrochanter BMD	20 ≤ Aged < 30	-0.0022 (-0.0027, -0.0016) < 0.000001	-0.0010 (-0.0015, -0.0005) 0.000181	0.0001 (-0.0005, 0.0007) 0.729035
	30 ≤ Aged < 40	-0.0028 (-0.0033, -0.0023) < 0.000001	-0.0020 (-0.0025, -0.0015) < 0.000001	-0.0010 (-0.0015, -0.0005) 0.000263
	40 ≤ Aged < 50	-0.0024 (-0.0028, -0.0020) < 0.000001	-0.0014 (-0.0019, -0.0010) < 0.000001	-0.0003 (-0.0008, 0.0002) 0.207675
	50 ≤ Aged < 60	-0.0032 (-0.0037, -0.0026) < 0.000001	-0.0019 (-0.0024, -0.0013) < 0.000001	-0.0008 (-0.0013, -0.0002) 0.006320
	60 ≤ Aged	-0.0033 (-0.0037, -0.0028) < 0.000001	-0.0017 (-0.0021, -0.0012) < 0.000001	-0.0006 (-0.0011, -0.0001) 0.009357
Total spine BMD	20 ≤ Aged < 30	-0.0006 (-0.0010, -0.0002) 0.004010	-0.0007 (-0.0011, -0.0003) 0.000428	-0.0002 (-0.0006, 0.0003) 0.414071
	30 ≤ Aged < 40	-0.0005 (-0.0008, -0.0001) 0.022318	-0.0009 (-0.0013, -0.0005) 0.000025	-0.0005 (-0.0009, -0.0000) 0.033293

Model 1: no covariates were adjusted. Model 2: sex (male; female) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	40 ≤ Aged < 50	-0.0005 (-0.0009, -0.0002) 0.004028	-0.0007 (-0.0011, -0.0004) 0.000105	-0.0001 (-0.0005, 0.0003) 0.560152
	50 ≤ Aged < 60	-0.0020 (-0.0025, -0.0016) < 0.000001	-0.0016 (-0.0020, -0.0011) < 0.000001	-0.0008 (-0.0013, -0.0003) 0.001722
	60 ≤ Aged	-0.0021 (-0.0026, -0.0017) < 0.000001	-0.0010 (-0.0014, -0.0005) 0.000011	-0.0002 (-0.0007, 0.0002) 0.333068
L1 BMD	20 ≤ Aged < 30	-0.0009 (-0.0013, -0.0005) 0.000020	-0.0007 (-0.0011, -0.0002) 0.002833	0.0000 (-0.0004, 0.0005) 0.953560
	30 ≤ Aged < 40	-0.0011 (-0.0015, -0.0007) < 0.000001	-0.0010 (-0.0014, -0.0006) 0.000007	-0.0005 (-0.0009, 0.0000) 0.053660
	40 ≤ Aged < 50	-0.0013 (-0.0017, -0.0009) < 0.000001	-0.0010 (-0.0014, -0.0006) < 0.000001	-0.0003 (-0.0007, 0.0001) 0.157263
	50 ≤ Aged < 60	-0.0028 (-0.0032, -0.0023) < 0.000001	-0.0019 (-0.0023, -0.0014) < 0.000001	-0.0011 (-0.0016, -0.0005) 0.000053
	60 ≤ Aged	-0.0030 (-0.0035, -0.0026) < 0.000001	-0.0015 (-0.0019, -0.0011) < 0.000001	-0.0006 (-0.0011, -0.0002) 0.004883
L2 BMD	20 ≤ Aged < 30	-0.0007 (-0.0011, -0.0003) 0.000763	-0.0008 (-0.0012, -0.0003) 0.000504	-0.0001 (-0.0006, 0.0003) 0.570538
	30 ≤ Aged < 40	-0.0007 (-0.0011, -0.0003) 0.001000	-0.0010 (-0.0014, -0.0006) 0.000007	-0.0006 (-0.0010, -0.0001) 0.018724
	40 ≤ Aged < 50	-0.0007 (-0.0011, -0.0004) 0.000098	-0.0009 (-0.0013, -0.0005) 0.000023	-0.0003 (-0.0007, 0.0002) 0.230465

Model 1: no covariates were adjusted. Model 2: sex (male; female) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	50 ≤ Aged < 60	-0.0023 (-0.0027, -0.0018) < 0.000001	-0.0017 (-0.0022, -0.0012) < 0.000001	-0.0010 (-0.0016, -0.0005) 0.000320
	60 ≤ Aged	-0.0024 (-0.0028, -0.0019) < 0.000001	-0.0011 (-0.0015, -0.0006) 0.000001	-0.0004 (-0.0008, 0.0001) 0.126408
L3 BMD	20 ≤ Aged < 30	-0.0004 (-0.0008, 0.0000) 0.069294	-0.0007 (-0.0012, -0.0003) 0.000635	-0.0003 (-0.0007, 0.0002) 0.266685
	30 ≤ Aged < 40	-0.0001 (-0.0005, 0.0003) 0.651313	-0.0008 (-0.0013, -0.0004) 0.000221	-0.0005 (-0.0010, -0.0000) 0.030862
	40 ≤ Aged < 50	-0.0001 (-0.0004, 0.0003) 0.730709	-0.0005 (-0.0009, -0.0001) 0.007935	-0.0000 (-0.0005, 0.0004) 0.954597
	50 ≤ Aged < 60	-0.0018 (-0.0023, -0.0013) < 0.000001	-0.0016 (-0.0021, -0.0011) < 0.000001	-0.0009 (-0.0015, -0.0004) 0.001325
	60 ≤ Aged	-0.0018 (-0.0023, -0.0014) < 0.000001	-0.0008 (-0.0013, -0.0004) 0.000389	-0.0001 (-0.0005, 0.0004) 0.822908
L4 BMD	20 ≤ Aged < 30	-0.0004 (-0.0008, 0.0000) 0.057092	-0.0007 (-0.0012, -0.0003) 0.000929	-0.0003 (-0.0008, 0.0002) 0.217005
	30 ≤ Aged < 40	-0.0001 (-0.0005, 0.0003) 0.740294	-0.0007 (-0.0011, -0.0003) 0.001378	-0.0004 (-0.0008, 0.0001) 0.126720
	40 ≤ Aged < 50	-0.0002 (-0.0006, 0.0002) 0.275874	-0.0007 (-0.0011, -0.0003) 0.001433	0.0000 (-0.0004, 0.0005) 0.925507
	50 ≤ Aged < 60	-0.0015 (-0.0020, -0.0011) < 0.000001	-0.0012 (-0.0017, -0.0007) 0.000003	-0.0004 (-0.0010, 0.0001) 0.113592
	60 ≤ Aged	-0.0016 (-0.0020, -0.0011) < 0.000001	-0.0006 (-0.0011, -0.0001) 0.010860	0.0000 (-0.0005, 0.0005) 0.866702

Model 1: no covariates were adjusted. Model 2: sex (male; female) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: sex (male; female), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Table 4
Subgroup analysis of the association between HDL-C and BMD stratified by sex.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Total femur BMD	Male	-0.0011 (-0.0014, -0.0008) < 0.000001	-0.0012 (-0.0015, -0.0009) < 0.000001	-0.0002 (-0.0005, 0.0001) 0.233455
	Female	-0.0016 (-0.0018, -0.0013) < 0.000001	-0.0014 (-0.0016, -0.0011) < 0.000001	-0.0005 (-0.0008, -0.0003) 0.000029
Femur neck BMD	Male	-0.0009 (-0.0012, -0.0006) < 0.000001	-0.0010 (-0.0012, -0.0007) < 0.000001	-0.0001 (-0.0003, 0.0002) 0.715642
	Female	-0.0015 (-0.0018, -0.0013) < 0.000001	-0.0013 (-0.0015, -0.0010) < 0.000001	-0.0004 (-0.0007, -0.0002) 0.000249
Trochanter BMD	Male	-0.0006 (-0.0008, -0.0003) 0.000011	-0.0007 (-0.0010, -0.0005) < 0.000001	-0.0000 (-0.0003, 0.0003) 0.894142
	Female	-0.0010 (-0.0013, -0.0008) < 0.000001	-0.0009 (-0.0011, -0.0007) < 0.000001	-0.0003 (-0.0006, -0.0001) 0.001941
Intertrochanter BMD	Male	-0.0014 (-0.0018, -0.0011) < 0.000001	-0.0015 (-0.0019, -0.0012) < 0.000001	-0.0003 (-0.0006, 0.0001) 0.093156
	Female	-0.0019 (-0.0022, -0.0016) < 0.000001	-0.0016 (-0.0019, -0.0014) < 0.000001	-0.0006 (-0.0009, -0.0004) 0.000012
Total spine BMD	Male	-0.0005 (-0.0007, -0.0002) 0.002124	-0.0007 (-0.0010, -0.0004) 0.000003	-0.0001 (-0.0004, 0.0002) 0.648678
	Female	-0.0013 (-0.0016, -0.0010) < 0.000001	-0.0012 (-0.0014, -0.0009) < 0.000001	-0.0005 (-0.0008, -0.0003) 0.000096
L1 BMD	Male	-0.0006 (-0.0009, -0.0004) 0.000014	-0.0008 (-0.0011, -0.0005) < 0.000001	-0.0001 (-0.0004, 0.0002) 0.698403
	Female	-0.0016 (-0.0019, -0.0014) < 0.000001	-0.0015 (-0.0017, -0.0012) < 0.000001	-0.0008 (-0.0010, -0.0005) < 0.000001
L2 BMD	Male	-0.0006 (-0.0009, -0.0003) 0.000236	-0.0008 (-0.0011, -0.0005) < 0.000001	-0.0002 (-0.0005, 0.0001) 0.252641
	Female	-0.0015 (-0.0018, -0.0012) < 0.000001	-0.0013 (-0.0016, -0.0011) < 0.000001	-0.0006 (-0.0009, -0.0003) 0.000011

Model 1: no covariates were adjusted. Model 2: age (40–49; 50–59; 60–69; ≥70) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: age (40–49; 50–59; 60–69; ≥70), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
L3 BMD	Male	-0.0003 (-0.0006, -0.0000) 0.037652	-0.0006 (-0.0009, -0.0003) 0.000206	-0.0000 (-0.0004, 0.0003) 0.864132
	Female	-0.0013 (-0.0015, -0.0010) < 0.000001	-0.0011 (-0.0014, -0.0009) < 0.000001	-0.0005 (-0.0008, -0.0002) 0.000399
L4 BMD	Male	-0.0003 (-0.0006, 0.0000) 0.071875	-0.0006 (-0.0009, -0.0003) 0.000176	0.0000 (-0.0003, 0.0003) 0.973395
	Female	-0.0010 (-0.0013, -0.0007) < 0.000001	-0.0009 (-0.0012, -0.0007) < 0.000001	-0.0003 (-0.0006, -0.0000) 0.029269

Model 1: no covariates were adjusted. Model 2: age (40–49; 50–59; 60–69; ≥70) and race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: age (40–49; 50–59; 60–69; ≥70), race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Association between HDL-C and BMD Stratified by Age in Males

In male participants, after adjustment for confounders, except for the subjects aged 30–40 years, where the results indicated that HDL-C level was negatively associated with BMD in the femoral region of intertrochanter (β = -0.0008, 95% CI: -0.0015 to -0.0000, P = 0.040346), no evidence demonstrated that HDL-C was associated with BMD. The detailed results are listed in Table 5. The smooth curve fittings and generalized additive models were also used to characterize the nonlinear relationship between HDL-C and BMD in male participants, Fig. 3.

Table 5
The association between HDL-C and BMD in male participants stratified by age.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Total femur BMD	20 ≤ Aged < 30	-0.0006 (-0.0013, 0.0001) 0.115524	-0.0009 (-0.0016, -0.0002) 0.017402	0.0002 (-0.0006, 0.0010) 0.615178
	30 ≤ Aged < 40	-0.0014 (-0.0021, -0.0008) 0.000014	-0.0015 (-0.0022, -0.0009) 0.000002	-0.0008 (-0.0014, -0.0001) 0.018263
	40 ≤ Aged < 50	-0.0007 (-0.0013, -0.0001) 0.021800	-0.0009 (-0.0015, -0.0003) 0.002213	0.0001 (-0.0006, 0.0007) 0.839256
	50 ≤ Aged < 60	-0.0012 (-0.0020, -0.0005) 0.001535	-0.0015 (-0.0023, -0.0008) 0.000073	-0.0003 (-0.0011, 0.0005) 0.447713
	60 ≤ Aged	-0.0013 (-0.0019, -0.0006) 0.000056	-0.0014 (-0.0020, -0.0008) 0.000011	-0.0005 (-0.0011, 0.0001) 0.113393
Femur neck BMD	20 ≤ Aged < 30	-0.0006 (-0.0013, 0.0002) 0.138530	-0.0008 (-0.0015, -0.0001) 0.026261	0.0002 (-0.0006, 0.0009) 0.649731
	30 ≤ Aged < 40	-0.0010 (-0.0017, -0.0004) 0.002045	-0.0011 (-0.0017, -0.0005) 0.000692	-0.0004 (-0.0011, 0.0002) 0.208086
	40 ≤ Aged < 50	-0.0006 (-0.0012, -0.0001) 0.023136	-0.0009 (-0.0015, -0.0004) 0.001203	-0.0001 (-0.0007, 0.0005) 0.690638
	50 ≤ Aged < 60	-0.0006 (-0.0012, 0.0001) 0.075347	-0.0009 (-0.0015, -0.0002) 0.007817	0.0003 (-0.0004, 0.0009) 0.466506
	60 ≤ Aged	-0.0010 (-0.0016, -0.0004) 0.000462	-0.0011 (-0.0017, -0.0006) 0.000065	-0.0004 (-0.0009, 0.0002) 0.211866
Trochanter BMD	20 ≤ Aged < 30	-0.0003 (-0.0010, 0.0003) 0.330555	-0.0005 (-0.0011, 0.0001) 0.105673	0.0001 (-0.0006, 0.0008) 0.865177

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	30 ≤ Aged < 40	-0.0008 (-0.0014, -0.0003) 0.004085	-0.0009 (-0.0014, -0.0004) 0.001311	-0.0004 (-0.0010, 0.0002) 0.188158
	40 ≤ Aged < 50	-0.0003 (-0.0008, 0.0002) 0.216489	-0.0005 (-0.0010, 0.0000) 0.074508	0.0002 (-0.0004, 0.0007) 0.600983
	50 ≤ Aged < 60	-0.0008 (-0.0015, -0.0002) 0.016474	-0.0011 (-0.0018, -0.0004) 0.001514	-0.0002 (-0.0009, 0.0006) 0.620892
	60 ≤ Aged	-0.0005 (-0.0010, 0.0000) 0.071928	-0.0006 (-0.0011, -0.0000) 0.032413	-0.0001 (-0.0007, 0.0004) 0.709963
Intertrochanter BMD	20 ≤ Aged < 30	-0.0007 (-0.0016, 0.0001) 0.096844	-0.0011 (-0.0019, -0.0002) 0.011457	0.0002 (-0.0007, 0.0011) 0.618908
	30 ≤ Aged < 40	-0.0018 (-0.0026, -0.0011) 0.000003	-0.0019 (-0.0027, -0.0012) < 0.000001	-0.0011 (-0.0019, -0.0003) 0.005125
	40 ≤ Aged < 50	-0.0008 (-0.0015, -0.0001) 0.018369	-0.0011 (-0.0018, -0.0004) 0.001913	0.0001 (-0.0007, 0.0008) 0.853152
	50 ≤ Aged < 60	-0.0015 (-0.0024, -0.0006) 0.000849	-0.0019 (-0.0028, -0.0010) 0.000050	-0.0005 (-0.0014, 0.0005) 0.330337
	60 ≤ Aged	-0.0018 (-0.0025, -0.0011) 0.000001	-0.0019 (-0.0027, -0.0012) < 0.000001	-0.0008 (-0.0015, -0.0001) 0.028094
Total spine BMD	20 ≤ Aged < 30	-0.0002 (-0.0009, 0.0004) 0.430869	-0.0005 (-0.0011, 0.0002) 0.140474	0.0000 (-0.0007, 0.0007) 0.991680
	30 ≤ Aged < 40	-0.0006 (-0.0012, 0.0000) 0.051732	-0.0007 (-0.0013, -0.0001) 0.025491	-0.0003 (-0.0009, 0.0004) 0.384966
	40 ≤ Aged < 50	0.0000 (-0.0006, 0.0006) 0.956595	-0.0002 (-0.0008, 0.0004) 0.470854	0.0006 (-0.0001, 0.0012) 0.073739

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	50 ≤ Aged < 60	-0.0011 (-0.0019, -0.0003) 0.006953	-0.0015 (-0.0023, -0.0007) 0.000173	-0.0006 (-0.0014, 0.0003) 0.195890
	60 ≤ Aged	-0.0007 (-0.0014, -0.0000) 0.041374	-0.0009 (-0.0015, -0.0002) 0.011893	-0.0004 (-0.0011, 0.0003) 0.255188
L1 BMD	20 ≤ Aged < 30	-0.0002 (-0.0008, 0.0005) 0.611215	-0.0003 (-0.0010, 0.0003) 0.288404	0.0003 (-0.0004, 0.0010) 0.421029
	30 ≤ Aged < 40	-0.0005 (-0.0012, 0.0001) 0.091467	-0.0006 (-0.0012, 0.0000) 0.056638	-0.0001 (-0.0008, 0.0005) 0.729167
	40 ≤ Aged < 50	-0.0002 (-0.0008, 0.0005) 0.622394	-0.0004 (-0.0010, 0.0003) 0.247077	0.0005 (-0.0001, 0.0012) 0.126636
	50 ≤ Aged < 60	-0.0014 (-0.0021, -0.0006) 0.000389	-0.0018 (-0.0025, -0.0010) 0.000006	-0.0007 (-0.0015, 0.0001) 0.098942
	60 ≤ Aged	-0.0012 (-0.0018, -0.0006) 0.000266	-0.0013 (-0.0020, -0.0007) 0.000078	-0.0006 (-0.0013, 0.0001) 0.071599
L2 BMD	20 ≤ Aged < 30	-0.0003 (-0.0010, 0.0003) 0.355879	-0.0005 (-0.0012, 0.0001) 0.119616	-0.0000 (-0.0007, 0.0007) 0.951247
	30 ≤ Aged < 40	-0.0006 (-0.0013, -0.0000) 0.049876	-0.0007 (-0.0014, -0.0001) 0.025488	-0.0003 (-0.0010, 0.0004) 0.377686
	40 ≤ Aged < 50	-0.0001 (-0.0007, 0.0005) 0.775438	-0.0003 (-0.0009, 0.0003) 0.312485	0.0004 (-0.0003, 0.0011) 0.251953
	50 ≤ Aged < 60	-0.0013 (-0.0021, -0.0005) 0.002333	-0.0017 (-0.0025, -0.0008) 0.000067	-0.0009 (-0.0018, 0.0000) 0.057990
	60 ≤ Aged	-0.0006 (-0.0013, 0.0000) 0.064998	-0.0008 (-0.0015, -0.0001) 0.021833	-0.0004 (-0.0012, 0.0003) 0.230982

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
L3 BMD	20 ≤ Aged < 30	-0.0002 (-0.0009, 0.0004) 0.471605	-0.0005 (-0.0011, 0.0002) 0.167605	-0.0001 (-0.0008, 0.0006) 0.740059
	30 ≤ Aged < 40	-0.0006 (-0.0013, 0.0001) 0.072596	-0.0007 (-0.0014, -0.0000) 0.036172	-0.0004 (-0.0011, 0.0003) 0.239139
	40 ≤ Aged < 50	0.0002 (-0.0005, 0.0008) 0.596499	-0.0001 (-0.0007, 0.0006) 0.838056	0.0007 (-0.0000, 0.0014) 0.062945
	50 ≤ Aged < 60	-0.0010 (-0.0018, -0.0001) 0.026701	-0.0014 (-0.0022, -0.0005) 0.001307	-0.0005 (-0.0014, 0.0004) 0.293799
	60 ≤ Aged	-0.0004 (-0.0011, 0.0003) 0.272922	-0.0006 (-0.0013, 0.0001) 0.117742	-0.0001 (-0.0008, 0.0007) 0.873756
L4 BMD	20 ≤ Aged < 30	-0.0003 (-0.0009, 0.0004) 0.423373	-0.0005 (-0.0012, 0.0001) 0.128665	-0.0001 (-0.0008, 0.0007) 0.834089
	30 ≤ Aged < 40	-0.0005 (-0.0012, 0.0001) 0.097663	-0.0006 (-0.0013, 0.0000) 0.053291	-0.0002 (-0.0009, 0.0005) 0.535861
	40 ≤ Aged < 50	0.0001 (-0.0006, 0.0007) 0.778714	-0.0002 (-0.0008, 0.0005) 0.625760	0.0007 (0.0000, 0.0014) 0.047933
	50 ≤ Aged < 60	-0.0008 (-0.0017, 0.0000) 0.060838	-0.0013 (-0.0021, -0.0004) 0.003298	-0.0003 (-0.0012, 0.0007) 0.555758
	60 ≤ Aged	-0.0005 (-0.0013, 0.0003) 0.194689	-0.0007 (-0.0015, 0.0001) 0.071464	-0.0004 (-0.0012, 0.0004) 0.310063

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Association between HDL-C and BMD Stratified by Age in Females

In female participants, after adjustment for confounders, multivariate linear regression results indicated that HDL-C level was negatively correlated with BMD in all age groups. Especially in females aged 30 to 40 or 50 to 60, the results revealed that HDL-C levels were negatively correlated with BMD in both femoral regions and spinal areas, Table 6.

Table 6
The association between HDL-C and BMD in female participants stratified by age.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Total femur BMD	20 ≤ Aged < 30	-0.0009 (-0.0015, -0.0003) 0.002740	-0.0009 (-0.0014, -0.0003) 0.002334	-0.0000 (-0.0006, 0.0006) 0.956497
	30 ≤ Aged < 40	-0.0017 (-0.0023, -0.0011) < 0.000001	-0.0017 (-0.0023, -0.0012) < 0.000001	-0.0010 (-0.0016, -0.0003) 0.002547
	40 ≤ Aged < 50	-0.0014 (-0.0019, -0.0009) < 0.000001	-0.0014 (-0.0019, -0.0009) < 0.000001	-0.0005 (-0.0010, -0.0000) 0.043755
	50 ≤ Aged < 60	-0.0016 (-0.0022, -0.0011) < 0.000001	-0.0016 (-0.0021, -0.0010) < 0.000001	-0.0006 (-0.0012, -0.0000) 0.033738
	60 ≤ Aged	-0.0010 (-0.0015, -0.0005) 0.000071	-0.0011 (-0.0016, -0.0006) 0.000011	-0.0004 (-0.0009, 0.0001) 0.098618
Femur neck BMD	20 ≤ Aged < 30	-0.0009 (-0.0014, -0.0003) 0.004488	-0.0009 (-0.0014, -0.0003) 0.003061	0.0001 (-0.0005, 0.0007) 0.721703
	30 ≤ Aged < 40	-0.0015 (-0.0020, -0.0009) < 0.000001	-0.0015 (-0.0021, -0.0010) < 0.000001	-0.0008 (-0.0015, -0.0002) 0.007730
	40 ≤ Aged < 50	-0.0013 (-0.0018, -0.0009) < 0.000001	-0.0013 (-0.0018, -0.0008) < 0.000001	-0.0005 (-0.0010, 0.0000) 0.054536
	50 ≤ Aged < 60	-0.0016 (-0.0021, -0.0011) < 0.000001	-0.0016 (-0.0021, -0.0011) < 0.000001	-0.0007 (-0.0012, -0.0001) 0.016750
	60 ≤ Aged	-0.0007 (-0.0012, -0.0003) 0.001014	-0.0009 (-0.0013, -0.0004) 0.000074	-0.0001 (-0.0006, 0.0003) 0.527758
Trochanter BMD	20 ≤ Aged < 30	-0.0006 (-0.0011, -0.0001) 0.011943	-0.0006 (-0.0011, -0.0002) 0.010425	-0.0001 (-0.0006, 0.0005) 0.802236

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	30 ≤ Aged < 40	-0.0012 (-0.0017, -0.0007) 0.000004	-0.0012 (-0.0017, -0.0007) 0.000001	-0.0007 (-0.0013, -0.0002) 0.010806
	40 ≤ Aged < 50	-0.0010 (-0.0014, -0.0005) 0.000009	-0.0010 (-0.0014, -0.0006) 0.000003	-0.0004 (-0.0009, 0.0000) 0.080617
	50 ≤ Aged < 60	-0.0010 (-0.0015, -0.0006) 0.000022	-0.0010 (-0.0015, -0.0005) 0.000030	-0.0003 (-0.0008, 0.0002) 0.234918
	60 ≤ Aged	-0.0006 (-0.0010, -0.0001) 0.008169	-0.0007 (-0.0011, -0.0002) 0.002373	-0.0001 (-0.0006, 0.0003) 0.520647
Intertrochanter BMD	20 ≤ Aged < 30	-0.0011 (-0.0017, -0.0004) 0.001673	-0.0010 (-0.0017, -0.0004) 0.001610	-0.0001 (-0.0008, 0.0006) 0.702295
	30 ≤ Aged < 40	-0.0019 (-0.0026, -0.0012) < 0.000001	-0.0020 (-0.0027, -0.0013) < 0.000001	-0.0011 (-0.0018, -0.0004) 0.002608
	40 ≤ Aged < 50	-0.0016 (-0.0022, -0.0011) < 0.000001	-0.0016 (-0.0022, -0.0010) < 0.000001	-0.0005 (-0.0011, 0.0001) 0.102820
	50 ≤ Aged < 60	-0.0020 (-0.0027, -0.0013) < 0.000001	-0.0019 (-0.0026, -0.0013) < 0.000001	-0.0009 (-0.0016, -0.0002) 0.016607
	60 ≤ Aged	-0.0014 (-0.0020, -0.0008) 0.000009	-0.0015 (-0.0021, -0.0009) 0.000002	-0.0007 (-0.0013, -0.0001) 0.033965
Total spine BMD	20 ≤ Aged < 30	-0.0009 (-0.0015, -0.0004) 0.000836	-0.0010 (-0.0015, -0.0005) 0.000254	-0.0004 (-0.0010, 0.0002) 0.190767
	30 ≤ Aged < 40	-0.0009 (-0.0015, -0.0004) 0.000962	-0.0011 (-0.0016, -0.0005) 0.000166	-0.0008 (-0.0014, -0.0002) 0.011145
	40 ≤ Aged < 50	-0.0010 (-0.0015, -0.0005) 0.000099	-0.0011 (-0.0016, -0.0006) 0.000011	-0.0005 (-0.0010, 0.0001) 0.085278

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
	50 ≤ Aged < 60	-0.0017 (-0.0023, -0.0011) < 0.000001	-0.0017 (-0.0023, -0.0011) < 0.000001	-0.0009 (-0.0015, -0.0002) 0.009989
	60 ≤ Aged	-0.0009 (-0.0014, -0.0003) 0.002841	-0.0010 (-0.0016, -0.0005) 0.000342	-0.0002 (-0.0008, 0.0004) 0.541538
L1 BMD	20 ≤ Aged < 30	-0.0009 (-0.0015, -0.0003) 0.002901	-0.0010 (-0.0015, -0.0004) 0.001059	-0.0002 (-0.0008, 0.0004) 0.547791
	30 ≤ Aged < 40	-0.0013 (-0.0019, -0.0007) 0.000047	-0.0014 (-0.0020, -0.0008) 0.000010	-0.0010 (-0.0016, -0.0003) 0.004785
	40 ≤ Aged < 50	-0.0013 (-0.0019, -0.0008) < 0.000001	-0.0014 (-0.0019, -0.0009) < 0.000001	-0.0008 (-0.0014, -0.0002) 0.006333
	50 ≤ Aged < 60	-0.0020 (-0.0026, -0.0014) < 0.000001	-0.0020 (-0.0026, -0.0014) < 0.000001	-0.0011 (-0.0018, -0.0005) 0.000860
	60 ≤ Aged	-0.0014 (-0.0020, -0.0009) < 0.000001	-0.0016 (-0.0021, -0.0010) < 0.000001	-0.0007 (-0.0013, -0.0001) 0.015418
L2 BMD	20 ≤ Aged < 30	-0.0010 (-0.0015, -0.0004) 0.001366	-0.0010 (-0.0016, -0.0004) 0.000528	-0.0003 (-0.0009, 0.0003) 0.395872
	30 ≤ Aged < 40	-0.0011 (-0.0017, -0.0005) 0.000200	-0.0013 (-0.0018, -0.0007) 0.000032	-0.0009 (-0.0016, -0.0003) 0.006432
	40 ≤ Aged < 50	-0.0011 (-0.0016, -0.0006) 0.000042	-0.0012 (-0.0018, -0.0007) 0.000004	-0.0005 (-0.0011, 0.0000) 0.069252
	50 ≤ Aged < 60	-0.0018 (-0.0024, -0.0011) < 0.000001	-0.0018 (-0.0024, -0.0011) < 0.000001	-0.0010 (-0.0017, -0.0003) 0.007973
	60 ≤ Aged	-0.0011 (-0.0017, -0.0005) 0.000249	-0.0013 (-0.0018, -0.0007) 0.000023	-0.0004 (-0.0010, 0.0002) 0.213659

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

		Model 1	Model 2	Model 3
		β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
L3 BMD	20 ≤ Aged < 30	-0.0009 (-0.0015, -0.0004) 0.001420	-0.0010 (-0.0016, -0.0005) 0.000365	-0.0004 (-0.0010, 0.0002) 0.197957
	30 ≤ Aged < 40	-0.0008 (-0.0014, -0.0002) 0.006788	-0.0009 (-0.0015, -0.0004) 0.001369	-0.0008 (-0.0014, -0.0001) 0.018031
	40 ≤ Aged < 50	-0.0007 (-0.0013, -0.0002) 0.005685	-0.0009 (-0.0014, -0.0004) 0.001043	-0.0003 (-0.0009, 0.0002) 0.254036
	50 ≤ Aged < 60	-0.0018 (-0.0025, -0.0012) < 0.000001	-0.0019 (-0.0025, -0.0012) < 0.000001	-0.0011 (-0.0018, -0.0004) 0.003002
	60 ≤ Aged	-0.0008 (-0.0014, -0.0002) 0.007618	-0.0010 (-0.0016, -0.0004) 0.001248	-0.0001 (-0.0008, 0.0005) 0.693671
L4 BMD	20 ≤ Aged < 30	-0.0009 (-0.0015, -0.0003) 0.001687	-0.0010 (-0.0015, -0.0004) 0.000783	-0.0006 (-0.0012, -0.0000) 0.048496
	30 ≤ Aged < 40	-0.0006 (-0.0012, -0.0001) 0.025961	-0.0008 (-0.0013, -0.0002) 0.008134	-0.0006 (-0.0012, 0.0001) 0.078155
	40 ≤ Aged < 50	-0.0009 (-0.0014, -0.0004) 0.001001	-0.0010 (-0.0015, -0.0005) 0.000156	-0.0003 (-0.0009, 0.0002) 0.250199
	50 ≤ Aged < 60	-0.0013 (-0.0019, -0.0006) 0.000081	-0.0013 (-0.0019, -0.0007) 0.000068	-0.0004 (-0.0011, 0.0003) 0.239878
	60 ≤ Aged	-0.0004 (-0.0010, 0.0002) 0.202832	-0.0006 (-0.0011, 0.0000) 0.065270	0.0002 (-0.0004, 0.0009) 0.482683

Model 1: no covariates were adjusted. Model 2: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races) were adjusted. Model 3: race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

The smooth curve fittings and generalized additive models were also utilized to characterize the nonlinear relationship between HDL-C and BMD in female participants. After adjustment for confounders, this association was different among different age groups. (i) An inverted U-shaped curve of the relationship between HDL-C and BMD in femoral regions was observed among participants aged 30 to 40 or over 60. When HDL-C was less than the inflection point, BMD increased with increasing HDL-C; when HDL-C was

greater than the inflection point, BMD decreased with increasing HDL-C. (ii) A U-shaped curve of the relationship between HDL-C and BMD in femoral regions in females aged 20 to 30 or 50 to 60. When HDL-C was less than the inflection point, BMD decreased with increasing HDL-C; when HDL-C was greater than the inflection point, BMD increased with increasing HDL-C. Besides, the inflection point was identified using a two-piecewise linear regression model. The inflection points for each group (20–30, 30–40, 50–60, ≥ 60) were about 65–67, 35–37, 71–83, 54-61mg/dL, respectively. The specific values can be found in Fig. 4 and Table 7.

Table 7
Threshold effect analysis of HDL-C on bone mineral density in female.

20 ≤ Aged < 30	Index	Total femur BMD	Femur neck BMD	Trochanter BMD	Intertrochanter BMD
	Fitting by the standard linear model	-0.0007 (-0.0013, -0.0002) 0.0140	-0.0007 (-0.0013, -0.0001) 0.0320	-0.0006 (-0.0011, -0.0000) 0.0330	-0.0009 (-0.0016, -0.0003) 0.0075
	Fitting by the two-piecewise linear model				
	Inflection point (mg/dL)	66	65	67	66
	HDL-C < Infection point	-0.0020 (-0.0029, -0.0011) < 0.0001	-0.0017 (-0.0027, -0.0008) 0.0004	-0.0016 (-0.0023, -0.0008) < 0.0001	-0.0024 (-0.0034, -0.0013) < 0.0001
	HDL-C > Infection point	0.0015 (0.0001, 0.0028) 0.0314	0.0010 (-0.0003, 0.0024) 0.1241	0.0014 (0.0001, 0.0026) 0.0297	0.0016 (0.0000, 0.0031) 0.0500
	Log likelihood ratio	< 0.001	0.004	< 0.001	< 0.001
30 ≤ Aged < 40	Index	Total femur BMD	Femur neck BMD	Trochanter BMD	Intertrochanter BMD
	Fitting by the standard linear model	-0.0018 (-0.0024, -0.0012) < 0.0001	-0.0016 (-0.0022, -0.0010) < 0.0001	-0.0013 (-0.0019, -0.0008) < 0.0001	-0.0021 (-0.0028, -0.0014) < 0.0001
	Fitting by the two-piecewise linear model				
	Inflection point (mg/dL)	36	35	37	37
	HDL-C < Infection point	0.0073 (0.0004, 0.0143) 0.0383	0.0073 (-0.0006, 0.0152) 0.0703	0.0065 (0.0012, 0.0119) 0.0162	0.0074 (0.0003, 0.0145) 0.0412

Race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

	HDL-C > Infection point	-0.0021 (-0.0028, -0.0015) < 0.0001	-0.0019 (-0.0025, -0.0012) < 0.0001	-0.0016 (-0.0022, -0.0011) < 0.0001	-0.0025 (-0.0033, -0.0017) < 0.0001
	Log likelihood ratio	0.008	0.024	0.003	0.007
50 ≤ Aged < 60	Index	L1 BMD	L2 BMD	L3 BMD	L4 BMD
	Fitting by the standard linear model	-0.0015 (-0.0021, -0.0008) < 0.0001	-0.0013 (-0.0020, -0.0006) 0.0003	-0.0014 (-0.0021, -0.0007) < 0.0001	-0.0008 (-0.0015, -0.0001) 0.0215
	Fitting by the two-piecewise linear model				
	Inflection point (mg/dL)	83	72	72	71
	HDL-C < Infection point	-0.0024 (-0.0032, -0.0015) < 0.0001	-0.0025 (-0.0036, -0.0013) < 0.0001	-0.0026 (-0.0038, -0.0015) < 0.0001	-0.0019 (-0.0031, -0.0008) 0.0009
	HDL-C > Infection point	0.0013 (-0.0005, 0.0032) 0.1569	0.0002 (-0.0012, 0.0017) 0.7431	0.0003 (-0.0011, 0.0017) 0.6573	0.0006 (-0.0007, 0.0020) 0.3425
	Log likelihood ratio	0.001	0.013	0.005	0.012
60 ≤ Aged	Index	Total femur BMD	Femur neck BMD	Trochanter BMD	Intertrochanter BMD
	Fitting by the standard linear model	-0.0013 (-0.0018, -0.0008) < 0.0001	-0.0009 (-0.0014, -0.0005) < 0.0001	-0.0008 (-0.0012, -0.0004) 0.0002	-0.0017 (-0.0023, -0.0011) < 0.0001
	Fitting by the two-piecewise linear model				
	Inflection point (mg/dL)	55	60	61	54

Race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

HDL-C < Infection point	0.0007 (-0.0007, 0.0021) 0.3442	0.0001 (-0.0008, 0.0011) 0.7926	0.0004 (-0.0005, 0.0013) 0.3638	0.0007 (-0.0011, 0.0025) 0.4399
HDL-C > Infection point	-0.0021 (-0.0029, -0.0014) < 0.0001	-0.0016 (-0.0024, -0.0009) < 0.0001	-0.0018 (-0.0025, -0.0010) < 0.0001	-0.0026 (-0.0035, -0.0017) < 0.0001
Log likelihood ratio	0.002	0.017	0.002	0.004

Race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Association between HDL-C and Low Bone Density in Females

According to the lowest threshold of HDL-C in subjects aged 50 to 60, we used a threshold of 71 mg/dL to investigate whether a high HDL-C level could increase the bone loss risk. After adjustment for confounders. The results of multiple logistic regression models displayed that participants with an equal to or higher than 71 mg/dL HDL-C levels had a significantly elevated prevalence of osteoporosis or osteopenia, especially in subjects aged over 40 (since the sample size of osteoporosis or osteopenia group were much smaller than those of the normal BMD group after weighting, the OR value and 95%CI could not be calculated, so the sample numbers are not weighted in this analysis). No statistically significant associations were found in other age groups. The detailed results are displayed in Table 8.

Table 8
The associations between HDL-C and bone loss (osteopenia or osteoporosis) in female participants.

	20 ≤ Aged < 30	30 ≤ Aged < 40	40 ≤ Aged < 50	50 ≤ Aged < 60	60 ≤ Aged
Non-adjusted					
HDL-C < 71 mg/dL	Reference	Reference	Reference	Reference	Reference
HDL-C >= 71 mg/dL	0.9961 (0.6172, 1.6078) 0.987290	1.3181 (0.8361, 2.0780) 0.234326	2.0106 (1.4439, 2.7997) 0.000036	2.1462 (1.4648, 3.1445) 0.000089	1.5311 (1.1042, 2.1230) 0.010636
Adjust					
HDL-C < 71 mg/dL	Reference	Reference	Reference	Reference	Reference
HDL-C >= 71 mg/dL	1.0532 (0.6220, 1.7832) 0.847032	1.3787 (0.8409, 2.2605) 0.203053	1.9732 (1.3614, 2.8599) 0.000332	2.1305 (1.4041, 3.2327) 0.000377	1.7778 (1.2381, 2.5529) 0.001828

Race/ethnicity (Mexican American; other Hispanic; non-Hispanic white; non-Hispanic black; other Races), Education (under high school; high school or equivalent; above high school), income to poverty ratio (quartile groups), BMI (obese, overweight, normal), drink status (had at least 12 alcohol drinks past one year; don not have at least 12 alcohol drinks past one year), smoking status (less than 100 cigarettes; greater than or equal to 100 cigarettes), diabetes (yes; no), hypertension (yes; no), ALT (quartile groups), AST (quartile groups), total calcium (quartile groups) and total cholesterol (quartile groups) were adjusted.

Discussion

Osteoporosis is a worldwide public health problem characterized by low BMD and a high risk of osteoporotic fracture [8]. At present, apart from genetic factors, age, or sex, the impact of other factors like lipid metabolism or lifestyle for bone metabolism has recently garnered increasing attention [11–13]. Meanwhile, HDL-C, a critical lipid for human lipid metabolism, has recently been demonstrated to be detrimental to human health, implying that extremely high HDL-C levels can also affect human health and contribute to several diseases [6, 7]. This study demonstrated that HDL-C was negatively associated with BMD, especially in females. Additionally, HDL-C might have a potential predictive value for osteopenia or osteoporosis in females. As a result, we conclude that our findings complement existing research and provide guidance for future studies.

This study results exhibited a negative correlation between HDL-C and BMD, mainly among females but not males. This finding may suggest that correlation is affected by hormone levels, and we found some evidence for this hypothesis. Jirapinyo et al. observed that combined oral estrogen/progestogen

increased BMD of spine and hip in post-menopausal women but decreased HDL-C [25]. Han et al. found that tanshinol exerted a bone-protective function by modulating bone turnover markers via blocking NF-κB pathway and decreased HDL-C levels [26]. However, although this phenomenon was observed in some studies, the specific mechanism is yet unclear. Meanwhile, the relationships between HDL-C and BMD were different in diverse age groups. Especially in females aged 20 to 30, although the results of the multivariate regression analyses manifested a negative correlation between HDL-C and BMD, a nonlinear relationship by smooth curve fittings and generalized additive models suggested that BMD increased with increasing HDL-C as HDL-C exceeded the inflection point. The specific reason for such a discrepancy is unclear, and future mechanism studies are required. Besides, we stated that elevated HDL-C levels might be predictive of osteoporosis or osteopenia, implying that patients with a high HDL-C level needed to monitor BMD, especially among females aged over 40. Meanwhile, because of different inflections in diverse age groups, the threshold choices may require adjustments, and More studies will be required to further investigate this aspect.

Some previous studies also explored the association between HDL-C and BMD [14–17]. For example, Maghbooli et al. found in Iranian women that HDL-C levels were negatively correlated with BMD in post-menopausal women with vitamin D deficiency [14]. Zhang et al. demonstrated in Chinese women a negative correlation between HDL-C and BMD in the population above 50 [15]. Makovey et al. observed a modest inverse relationship between hip BMD and HDL-C in post-menopausal women [27]. Jeong et al. found that HDL-C was positively associated with BMD at the lumbar spine in post-menopausal women, but a positive correlation was too weak ($\beta < 0.001$) [17]. Cui et al. demonstrated that HDL-C levels were not linked to BMD values at any of the sites in pre- and post-menopausal women [16]. In summary, because the conclusions remain controversial, and we considered some limitations in these studies, like the small sample size, selected population, or adjusted variables, we improved these shortcomings. First, we used a nationally representative sample of NHANES, with huge sample size. Second, since previous studies usually considered the relationship between HDL-C and BMD in females, especially post-menopausal females, this study also considered the potential impact of gender and age. Third, this study adjusted more variables that might potentially influence BMD. As expected, we demonstrate not only a correlation between HDL-C and BMD except in post-menopausal females but also a potential predictive value of HDL-C for osteoporosis or osteopenia.

For a long time, numerous researchers and studies have believed that HDL-C is beneficial to health [28, 29]. Especially in the field of cardiovascular disease [2, 4], HDL-C is considered to be negatively correlated with adverse cardiovascular events [2–5]. However, numerous research results indicated that HDL-C contribution to human health might be highly overestimated. Several years ago, it was demonstrated that drugs that increased HDL-C did not prevent adverse cardiovascular events [30]. Other recent studies reported an inverted U-shaped relationship between HDL-C level and all-cause mortality [7, 31]. All of this indicates that elevated HDL-C levels may detrimental to health and may even cause some adverse events. This study established an inverse relationship between HDL-C and BMD in adult females, corroborating this view. Besides, it is worth mentioning that most basic studies usually focus on the impact of low HDL-C but not high HDL-C on bone metabolism [32, 33]. Other studies published in the last few years have

revealed an inverted U-shaped association between HDL-C levels and all-cause mortality. All of this indicates that elevated HDL-C levels can be detrimental to health and may even be a source of some adverse events. This study established an inverse relationship between HDL-C and BMD in adult females, corroborating this view. Additionally, it is worth noting that most basic research focuses on low HDL-C effect on bone metabolism but not on high HDL-C impact. As a result, future research may focus on the specific mechanism underlying elevated HDL-C levels.

Several limitations of this study should be noted:

1. Our research is based on American participants, so it is hard to say whether our conclusion applies to other countries or races. In subgroup analysis for race, we can also observe that HDL-C and BMD of the relevance between different races afforded different results, implying that our conclusion has some unavoidable limitations.
2. Our study excluded participants who did not have BMD or HDL-C data, introducing potential bias even though it was inevitable for subsequent analysis.
3. Part of the data we collected was questionnaire data. The subjects may refuse to answer for personal reasons or make wrong judgments due to recall bias. All these are factors that may potentially affect the research conclusion.
4. There will inevitably be missing values in the data set. When we deal with these missing values, we choose to exclude rather than fill them indirectly. Although both methods produce certain biases, the accuracy of the conclusion will inevitably be affected.
5. There remains the possibility of bias caused by other potential confounding factors that were not adjusted.

Conclusion

We concluded that HDL-C and BMD were negatively correlated among females and were different in diverse age groups. Moreover, HDL-C might be predictive for osteopenia or osteoporosis.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All analyses were based on data of the National Health and Nutrition Examination Survey (NHANES). The study was approved by the ethics review board of the National Center for Health Statistics. The detailed information located on the NHANES website.

Consent for publication

Not applicable.

Availability of data and materials

The datasets obtained and analysed during the current study are available in the NHANES [https://www.cdc.gov/nchs/nhanes/index.htm].

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contribution

YT and SW contributed equally to this work. YT and BG contributed the central idea, YT and SW analyzed most of the data. YT wrote the initial draft of the paper. The remaining authors contributed to refining the ideas, carrying out additional analyses and finalizing this paper.

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Figures

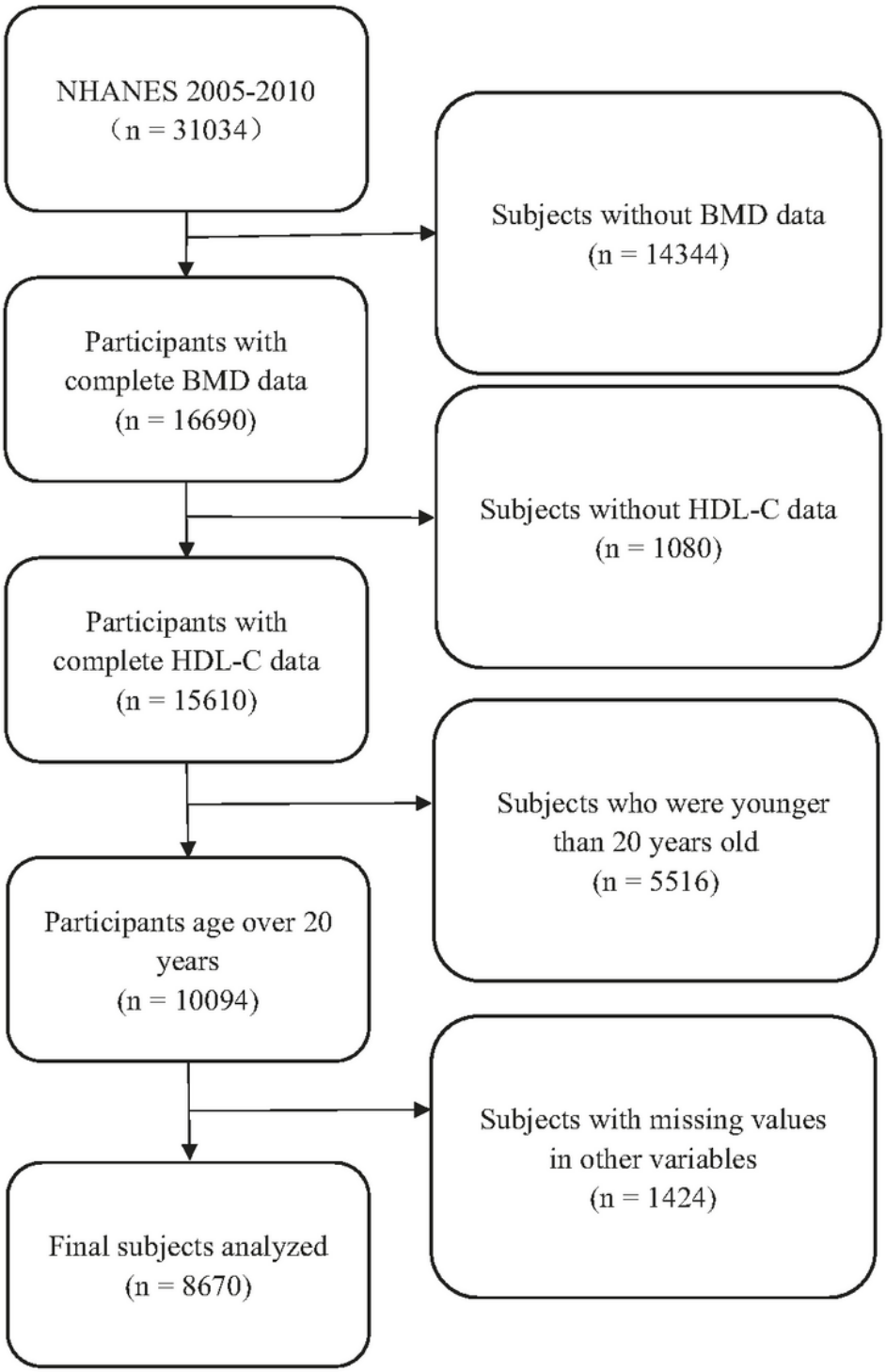

Figure 1

Flow chart of participants selection.

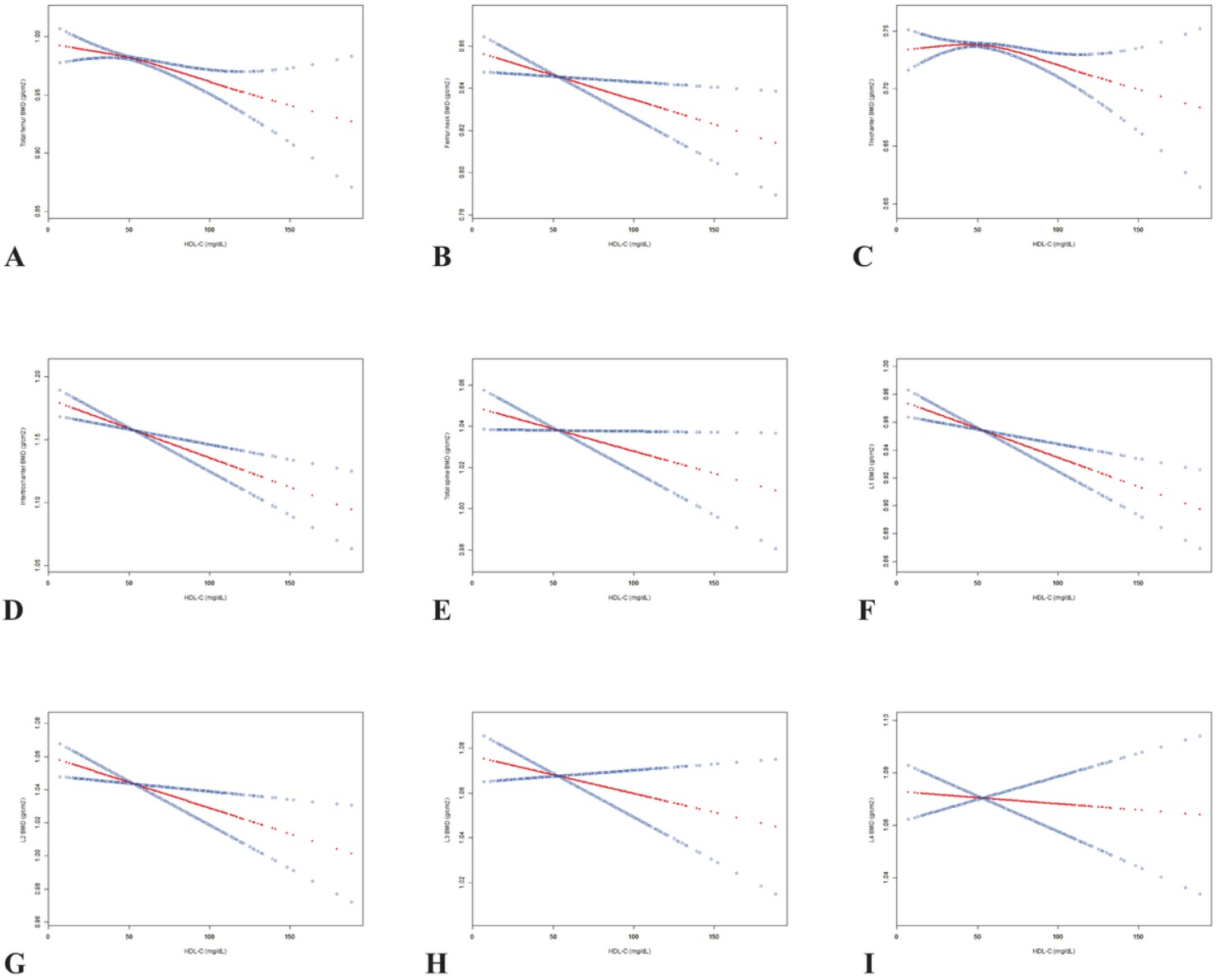

Figure 2

The association between HDL-C and BMD. Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Age, sex, Race/ethnicity, education level, income to poverty ratio, smoking status, drinking status, BMI, diabetes, hypertension, ALT, AST, total calcium, and total cholesterol were adjusted. (a) Total femur BMD; (b) Femur neck BMD; (c) Trochanter BMD; (d) Intertrochanter BMD; (e) Total spine BMD; (f) L1 BMD; (g) L2 BMD; (h) L3 BMD; (i) L4 BMD.

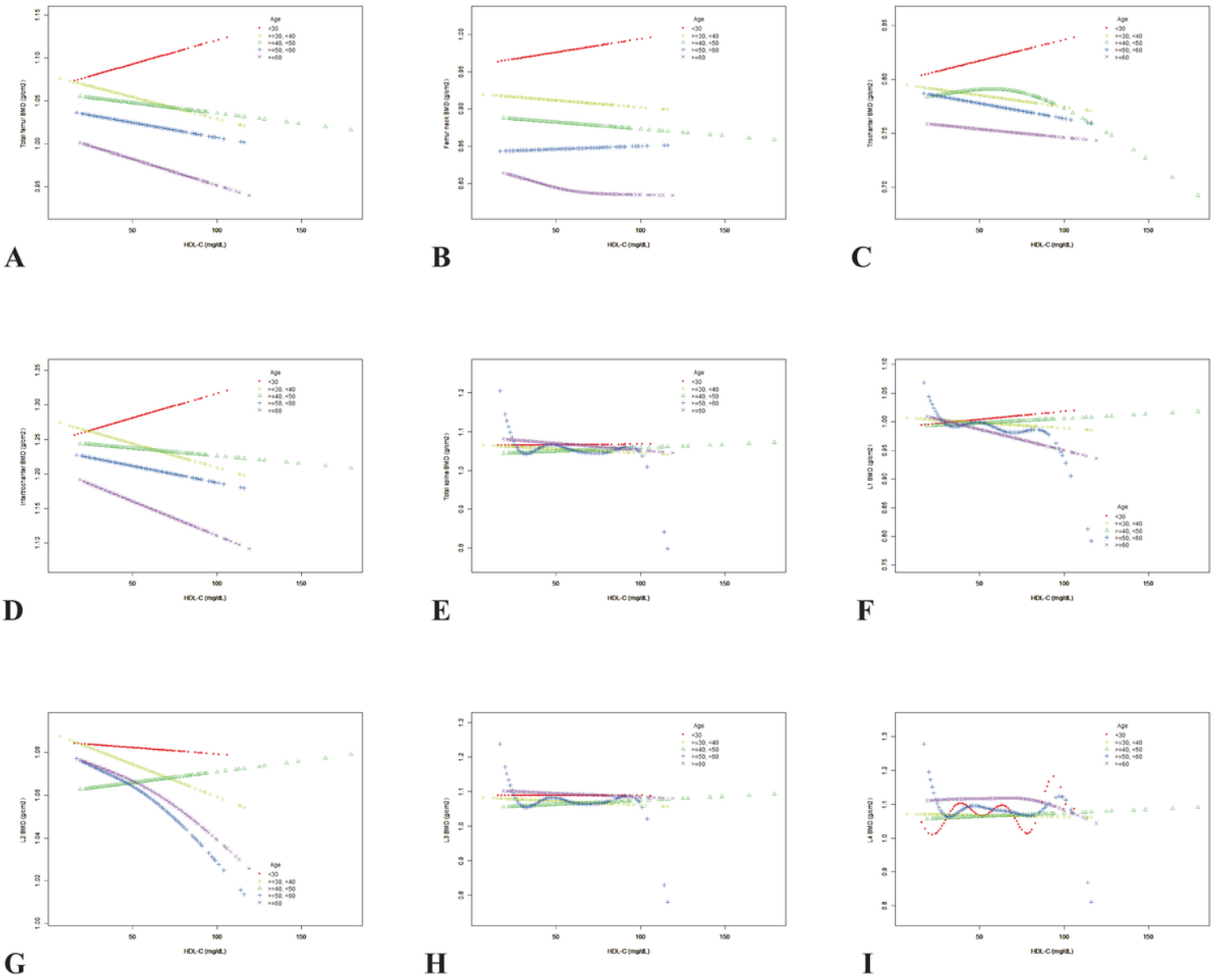

Figure 3

The association between HDL-C and BMD in male participants stratified by age. Race/ethnicity, education level, income to poverty ratio, smoking status, drinking status, BMI, diabetes, hypertension, ALT, AST, total calcium, and total cholesterol were adjusted. (a) Total femur BMD; (b) Femur neck BMD; (c) Trochanter BMD; (d) Intertrochanter BMD; (e) Total spine BMD; (f) L1 BMD; (g) L2 BMD; (h) L3 BMD; (i) L4 BMD. Red line: 20≤Aged<30; Yellow line: 30≤Aged<40; Green line: 40≤Aged<50; Blue line: 50≤Aged<60; Purple line: 60≤Aged.

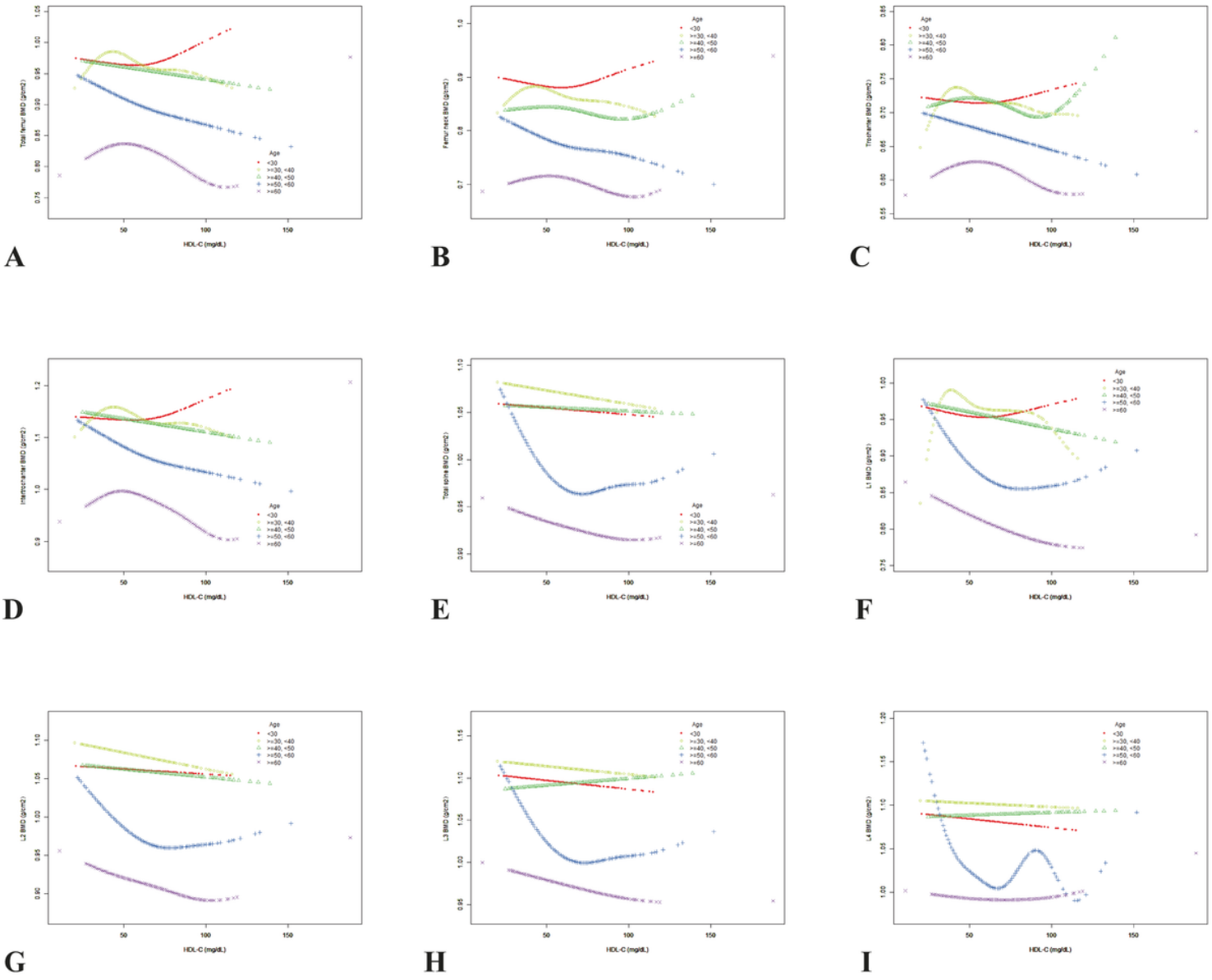

Figure 4

The association between HDL-C and BMD in female participants stratified by age. Race/ethnicity, education level, income to poverty ratio, smoking status, drinking status, BMI, diabetes, hypertension, ALT, AST, total calcium, and total cholesterol were adjusted. (a) Total femur BMD; (b) Femur neck BMD; (c) Trochanter BMD; (d) Intertrochanter BMD; (e) Total spine BMD; (f) L1 BMD; (g) L2 BMD; (h) L3 BMD; (i) L4 BMD. Red line: 20≤Aged<30; Yellow line: 30≤Aged<40; Green line: 40≤Aged<50; Blue line: 50≤Aged<60; Purple line: 60≤Aged.