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ORIGINAL ARTICLE

Association between serum high-density lipoprotein cholesterol and bone health in the general population: a large and multicenter study

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Abstract

Summary This study was a cross-sectional study and enrolled 14,147 participants after excluding. We performed a large number of data analyses to indicate that HDL-C levels were related to bone health. A high HDL-C level is an independent risk factor for bone loss both in males and females.

Introduction Serum high-density lipoprotein cholesterol (HDL-C), usually called "good" cholesterol, is beneficial for preventing cardiovascular diseases. Previous studies have indicated that HDL-C levels may be related to bone mass. We performed a cross-sectional study to examine the relationship between HDL-C levels and bone mass, both in men and women.

Methods A total of 14,147 Chinese participants from five medical centers were enrolled in this study. Pearson's correlation analyses, linear regression analyses, one-way ANOVAs, and logistic regression analyses were performed to assess the relationship between HDL-C levels and bone mass in various cohorts.

Results Binary logistic regression analyses (after adjusting the confounding factors) indicated that a higher HDL-C level among males leads to a higher risk of at least osteopenia [OR (95% CI) = 1.807 (1.525, 2.142)] and osteoporosis [OR (95% CI) = 1.932 (1.291, 2.892)]. In the female group, the ORs of HDL-C for at least osteopenia [OR (95% CI) = 1.390 (1.100, 1.757)] and osteoporosis [OR (95% CI) = 1.768 (1.221, 2.560)] were still significant after adjusting for potential confounding factors except BMI. Data-standardized bivariate logistic regression analyses indicated that an increase in age is a stronger risk factor for osteoporosis and at least osteopenia than is higher HDL-C levels in females.

Conclusions A high HDL-C level is an independent risk factor for bone loss both in males and females. Compared with high HDL-C levels, an increase in age and menopause have a much more negative effect on bone mass in females.

Keywords High-density lipoprotein cholesterol · Risk factor · Bone mineral density · Osteoporosis

Abbreviations

HDL-C	high-density lipoprotein–C
BMI	body mass index
BMD	bone mineral density
UA	uric acid
ALB	albumin
Ca	serum–calcium
ALP	alkaline phosphatase
BUN	blood urea nitrogen
GLU	glucose
ALT	alanine transaminase
AST	aspartate transaminase
TBIL	total bilirubin
TC	total cholesterol
LDL-C	low-density lipoprotein cholesterol
TG	triglycerides
CKD–EPI	Chronic Kidney Disease Epidemiology Collaboration
GFR	glomerular filtration rate

Jiuzhou Jiang, Pengchen Qiu and Yiyun Wang contributed equally to this work.

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QC	quality control
SBP	systolic blood pressure
DXA	dual-energy x-ray absorptiometry
CV	coefficient of variation
eGFR	estimated renal function

Introduction

High-density lipoprotein (HDL-C) cholesterol is regarded as "good" cholesterol as it has been associated with a decreased risk of cardiovascular disease [1–3] and chronic kidney diseases [4]. Additionally, it also may be a protective factor in terms of overall survival in cancer patients [5]. However, recent studies have shown that a high HDL-C level in plasma does not always indicate a sign of health and longevity. A few epidemiological studies have suggested that high HDL-C levels increased the risk of premature death [6] and were associated with a high all-cause mortality [7], as well as a high risk of infectious disease [8].

Osteoporosis is described as an age-related disease which usually occurs in older adults [9]. Epidemiological investigations suggest that there is likely an association between bone mineral density (BMD) and serum lipids including HDL-C [10–22]. The conclusions are somewhat inconsistent since both positive and negative relationships were found. A few studies reported that HDL-C was beneficial for BMD in postmenopausal women [11, 12, 14] and men [11]. In contrast, some studies have shown a negative association between HDL-C and BMD [16–19, 21, 22], or a positive association between HDL-C and osteoporosis [15]. Despite these inconsistencies, some studies reported no significant relationship between HDL-C and osteoporosis [23–25]. Though a previous study found a possible negative relationship between HDL-C and bone mass in Chinese postmenopausal women, the study included only 790 participants from community centers in a single city [22].

Until now, an accurate understanding of the association between HDL-C and bone mass, including BMD and osteoporosis, has remained unclear. The present multicenter study, which involves a large cohort of many age groups, aimed to investigate the relationship between HDL-C and bone mass in a Chinese community population.

Methods

Study population

Our research is based on the following five medical centers: Sir Run Run Shaw Hospital Affiliated to Zhejiang University, First Affiliated Hospital of Wenzhou Medical University, Taizhou Hospital, Shaoxing People's Hospital, and Shanghai Jiaotong University School of Medicine. A total of 22,409 participants were initially assessed for the study. Participants were the people who came to the five medical centers for health examinations and underwent widespread screening tests from October 2009 to December 2014. And we extract the information of the participants from the databases of the five medical centers. Those who had a history of alcohol consumption (over 10 g/day) or smoking (over 5 cigarettes per day) were excluded. Moreover, we also excluded women whose menopausal status was unknown and those with abnormal liver function, renal, or thyroid tests. Furthermore, participants who had recently taken drugs known to have an influence on bone metabolism were excluded. A total of 14,147 participants were enrolled after excluding.

Clinical measurements

The following physiological parameters were measured in the health examinations: serum uric acid (UA), total protein, albumin (ALB), blood urea nitrogen (BUN), serum calcium (Ca), serum phosphorus, alkaline phosphatase (ALP), liver function [which included alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin (TBIL)], blood glucose (GLU), and blood lipids [which included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)]. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate estimated renal function (eGFR) as an additional indicator, according to age, sex, race/ethnicity, and the serum creatinine level. The CKD-EPI equation is as follows: GFR (mL/min/1.73 m^2) = $141 \times \min(\mathrm{Scr}/\kappa, 1)\alpha \times \max(\mathrm{Scr}/\kappa, 1) - 1.209 \times 0.993\ \mathrm{age} \times 1.018$ [if female] $\times 1.159$ [if black] (κ: male, 0.9; female, 0.7; and α: male, −0.411; female, −0.329).

Lipids measurement

Blood lipids including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured after fasting for at least 12 h. Different kinds of blood lipids were measured using corresponding kits and biochemistry analyzer. Enzymatic assay was used to measure total cholesterol (TC); selective inhibition method was used to measure high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C); glycerol phosphate oxidase (GPO)–peroxidase (POD) method was used to measure triglycerides (TG).

BMD measurement

Dual-energy X-ray absorptiometry (DXA) with Lunar equipment (Prodigy; Lunar, Madison, WI) was used to measure

BMD (g/cm^2) of the lumbar spine (L1 to L4) which provides the T-score by comparing BMD values of same-sex healthy young Chinese adults, and the Z-score by comparing BMD values of the population with the same age, sex, and race. For postmenopausal women and men aged ≥ 50 years, the T-score can be considered part of the diagnostic criteria for osteoporosis and osteopenia: normal (T-score ≥ − 1.0), osteopenia (− 1.0 > T-score > − 2.5), and osteoporosis (T-score ≤ − 2.5), according to the World Health Organization. Participants were defined as "at least osteopenia" if they were diagnosed with osteoporosis or osteopenia. In the five medical centers, a program of standard quality control (QC) including calibrating machine-specific phantoms was used daily, and the five Lunar devices were cross-calibrated. We used the same densitometer and monitored the performance of the DXA scanner throughout our study. For QC BMD measurements, the coefficients of variation (CVs) in the five centers were reported as 0.91%, 0.85%, 0.82%, 0.95%, and 0.89%, respectively. In vivo reproducibility was reported as the CVs for BMD and estimated from duplicate scans. For lumbar spine BMD, the CVs were 1.15%, 1.07%, 0.95%, 1.22%, and 1.01%, respectively, in the five centers.

Potential confounder

The potential confounders involved in this study included age, weight, height, blood pressure, GLU, Ca, ALP, AST, ALB, ALT, TG, TBIL, and eGFR. In the multiple linear regression and multivariate logistic regression analyses, specific models were adjusted for confounding factors chosen from the potential confounders using Pearson's correlation analyses and univariate logistic regression analyses.

Statistics

All continuous variates were calculated using the mean and standard deviation. Correspondingly, two classification variates were used to calculate quantity and proportion of one classification. χ^2 tests and Wilcoxon signed rank tests were performed to compare categorical variables and continuous variables, respectively. Pearson's correlation analyses were performed to screen out the variates related to bone loss including BMD, T-score, and Z-score. Multiple linear regression analyses were performed to determine the effect of HDL-C on BMD and T-score. One-way ANOVA analyses were performed to compare the HDL-C levels of the three participant groups (normal, osteopenia, and osteoporosis). Binary logistic regression analyses were performed to investigate the relationship between HDL-C and osteoporosis and at least osteopenia. In addition to unadjusted models, univariate-adjusted and multivariable-adjusted models were also established. The adjusted variates in the multivariable-adjusted models came from the potential confounding factors which were significant in the univariate logistic regression models (p value < 0.05). Data-standardized bivariate logistic regression analyses were performed to compare the influence of age and HDL-C on osteoporosis. The odds ratios (OR) and corresponding 95% confidence interval (CI) were calculated. All the analyses were performed by using SPSS 23.0 software (IBM, Armonk, NY). A two-sided P value < 0.05 was considered significant.

Results

Baseline characteristics

A large population of 14,147 participants (8864 males and 5483 females) was used for our study (Fig. 1). The descriptive characteristics of the study population are shown in Table 1. The mean age of the total participants was 49.059 ± 10.382. The mean BMD levels in males aged < 50 ($n = 5186$) and males aged ≥ 50 ($n = 3478$) were significantly different (1.149 ± 0.135 vs 1.121 ± 0.17 g/cm^2, $p < 0.001$). The BMD levels gradually decreased from 2070 pre-menopausal females to 1856 menopausal females and then to 1557 postmenopausal females (1.202 ± 0.13 vs 1.135 ± 0.154 vs 0.941 ± 0.147 g/cm^2, respectively, $p < 0.001$). The mean BMD level in males was higher than in females (1.138 ± 0.15 vs 1.105 ± 0.179 mmol/L, respectively, $p < 0.001$). But the mean HDL-C level in males was lower than in females (1.300 ± 0.306 vs 1.540 ± 0.339 mmol/L, respectively, $p < 0.001$). The males had higher mean values of the majority of biochemical characteristics (TG, GLU, Ca, ALP, UA, ALT, AST, TBIL, ALB) than females. And the osteoporosis ratio of female participants was higher than that of male participants (5.7% vs 2.3%, $p < 0.001$).

Relationship between HDL-C levels and BMD

In Pearson's correlation analyses of the total participants, a negative correlation was observed between HDL-C and BMD ($p < 0.001$) along with HDL-C and T-score ($p < 0.001$) (Supplementary Table 1). Apart from HDL-C, the following variates had significant correlations with both BMD and T-score: age, weight, height, BMI, SBP, Ca, UA, ALP, and ALB. These variates, with the exception of weight, height, and ALB, were adjusted in the linear regression models which were used to investigate the association between HDL-C and BMD, as well as the association between HDL-C and T-scores in various populations. Because BMI is calculated from weight and height and because ALB was extremely insignificant in the multiple linear regression models, these three variates were not included. As shown in Fig. 2 and Supplementary Table 2, after adjusting for potential confounding factors, the results of the multiple linear regression models proved that BMD and T-score would linearly increase with a decrease of HDL-C in male participants. However, the coefficients of HDL-C in the models for females were insignificant.

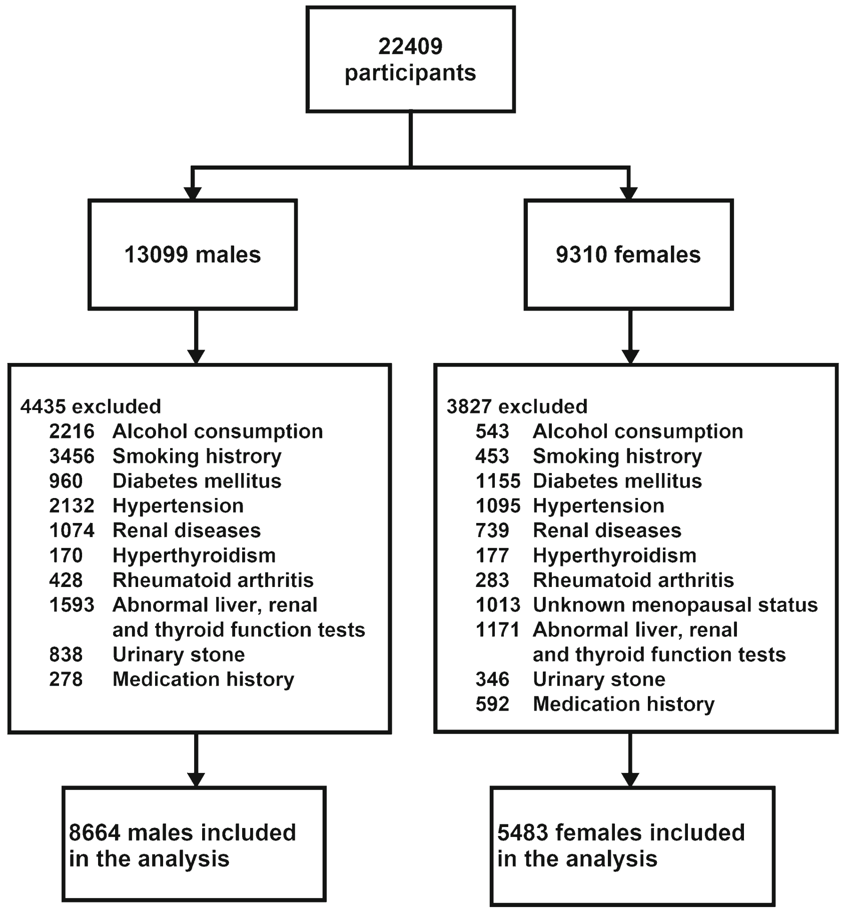

Fig. 1 The participant flow chart

Prevalence of osteopenia and osteoporosis for different HDL-C levels

The mean serum HDL-C level of osteoporotic participants was higher than participants with osteopenia and normal participants. The mean serum HDL-C level of normal participants was lower than participants with bone loss (including osteopenia and osteoporosis). These findings were applicable to the males (age ≥ 50) and postmenopausal females as shown as Fig. 3 and Supplementary Table 3.

Univariate logistic regression analyses showed that the following variates have a significant influence on ‘at least osteopenia’ and ‘osteoporosis’ among all the participants; males aged ≥ 50 and postmenopausal females: age, weight, height, BMI, UA, ALP, and HDL-C. To investigate the influence HDL-C had on bone loss, we performed multivariate logistic regression analyses which revealed a positive correlation. After adjusting for age, BMI, UA, and ALP, a higher HDL-C level among males led to a higher risk of at least osteopenia, [all males: OR (95% CI) = 1.807(1.525, 2.142); males aged ≥ 50: OR (95% CI) = 1.409 (1.113, 1.785)] and osteoporosis [all males: OR (95% CI) = 1.932 (1.291, 2.892); males aged ≥ 50: OR (95% CI) = 2.325 (1.489, 3.629)], as shown in Fig. 4 and Supplementary Table 4. In the female group, when BMI was removed from the adjusted variates, the significant ORs for at least osteopenia [all females: OR (95% CI) = 1.390 (1.100, 1.757); postmenopausal females: OR (95% CI) = 1.418 (1.013, 1.985)] and osteoporosis [all females: OR (95% CI) = 1.768 (1.221, 2.560); postmenopausal females: OR (95% CI) = 1.749 (1.184, 2.585)] could be obtained, as shown in Fig. 4 and Supplementary Table 5.

Data-standardized bivariate logistic regression analyses revealed that age has much higher ORs than HDL-C for at least osteopenia [6.508 (5.849, 7.242) vs 1.148 (1.064, 1.238)] and osteoporosis [4.402 (3.835, 5.054) vs 1.302 (1.155, 1.468)] among females. This phenomenon was inconspicuous among males for at least osteopenia [1.373 (1.307, 1.443) vs 1.287 (1.226, 1.352)] and osteoporosis [1.782 (1.578, 2.012) vs 1.394 (1.244, 1.562)], as shown in Fig. 5 and Supplementary Table 6.

Discussion

In the present study, we found a negative association between HDL-C levels and bone mass. In general, a high level of HDL-C was related to a low level of BMD and T-score and high ORs for at least osteopenia and osteoporosis.

Table 1 Baseline characteristics and comparison of male and female

	All	Male	Female	*P*
Age (year)	49.059 ± 10.382	48.774 ± 10.414	49.511 ± 10.317	< 0.001
Weight (kg)	65.702 ± 11.306	70.635 ± 10.117	57.906 ± 8.299	< 0.001
Height (cm)	164.135 ± 8.165	168.516 ± 6.282	157.213 ± 5.606	< 0.001
BMD (g/cm^2)	1.125 ± 0.163	1.138 ± 0.15	1.105 ± 0.179	< 0.001
T-score	−0.025 ± 1.402	−0.013 ± 1.346	−0.044 ± 1.486	0.165
Z-score	0.158 ± 1.335	0.059 ± 1.43	0.314 ± 1.153	< 0.001
BMI (kg/m^2)	24.29 ± 3.14	24.835 ± 3.005	23.43 ± 3.156	< 0.001
SBP (mmHg)	123.28 ± 16.042	124.94 ± 15.187	120.66 ± 16.98	< 0.001
DBP (mmHg)	78.84 ± 10.468	80.96 ± 10.091	75.5 ± 10.177	< 0.001
TG (mmol/L)	1.804 ± 1.518	2.063 ± 1.683	1.395 ± 1.095	< 0.001
HDL-C (mmol/L)	1.393 ± 0.34	1.3 ± 0.306	1.54 ± 0.339	< 0.001
GLU (mmol/L)	5.573 ± 1.422	5.65 ± 1.521	5.451 ± 1.238	< 0.001
Ca (mmol/L)	2.362 ± 0.127	2.372 ± 0.128	2.348 ± 0.124	< 0.001
ALP (U/L)	74.397 ± 22.083	76.156 ± 20.171	71.618 ± 24.551	< 0.001
UA (mmol/L)	332.039 ± 93.901	375.247 ± 82.498	263.765 ± 66.217	< 0.001
ALT (U/L)	29.521 ± 39.127	34.624 ± 45.371	21.458 ± 24.315	< 0.001
AST (U/L)	25.37 ± 19.774	26.917 ± 22.607	22.926 ± 13.842	< 0.001
TBIL (μmol/L)	13.544 ± 5.89	14.475 ± 6.293	12.074 ± 4.838	< 0.001
ALB (g/L)	46.863 ± 2.746	47.309 ± 2.751	46.159 ± 2.587	< 0.001
e-GFR (mL/min/1.73 m^2)	92.133 ± 17.418	91.982 ± 15.623	92.372 ± 19.927	0.001
At least Osteopenia	3402 (24%)	1995 (23%)	1407 (25.7%)	< 0.001
Osteoporosis	511 (3.6%)	198 (2.3%)	313 (5.7%)	< 0.001

Continuous variates are reported as mean ± SD (standard deviation); two classification variates are reported as numbers and percentage

BMD bone mineral density, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *GLU* glucose, *Ca* serum calcium, *ALP* alkaline phosphatase, *UA* serum uric acid, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *TBIL* total bilirubin, *e-GFR* estimated glomerular filtration rate

For males, HDL-C is inversely related to BMD and T-score after adjusting for potential confounding factors. Correspondingly, male participants with osteopenia or osteoporosis had a higher mean level of HDL-C than did participants without osteopenia and osteoporosis. Meanwhile, high HDL-C levels is an independent risk factor for at least osteopenia and osteoporosis in males.

Some previous studies found a negative relationship between HDL-C levels and BMD values in postmenopausal women [16, 17]. However, our analyses found this relationship to be insignificant after adjusting for BMI. A study by Li et al. found that a higher HDL-C level was a risk factor for osteoporosis after adjusting for confounding factors including age and BMI in central south Chinese postmenopausal women [22]. They divided HDL-C levels into two groups (lower ≤ 1.54 and higher ≥ 1.55 mmol/L) as a categorical variable. Our study analyzed HDL-C as a continuous variable and found that a higher HDL-C level was a risk factor for at least osteopenia and osteoporosis in both female and postmenopausal female participants, after adjusting for confounding factors except BMI. Previous studies found BMI to be positively correlated with bone mass including increased BMD and a low risk of osteoporosis [26–29]. BMI was an important confounder in our regression models; however, studies show that there is inverse association between BMI and HDL-C levels [30, 31] and we found a significant linear correlation between BMI and the HDL-C value in our data. As we know, multicollinearity can lead to inaccurate regression models. In consideration of the linear correlation between BMI and HDL-C, we cannot ignore the association between HDL-C levels and bone mass in females, even though it was stronger in males. From the above, the association between HDL-C levels and bone mass in females is not distinct as it is in males and depends on BMI. However, a high HDL-C level is still related to a lower BMD and T-score, along with a higher risk of at least osteopenia and osteoporosis.

As a previous study has shown, postmenopausal women are much more likely to develop osteoporosis than others as a result of a sharp decrease in estrogen [32]. Compared with males, data-standardized analyses indicated that age increase is a stronger risk factor for osteoporosis and at least osteopenia than higher HDL-C levels in females in our study. Since

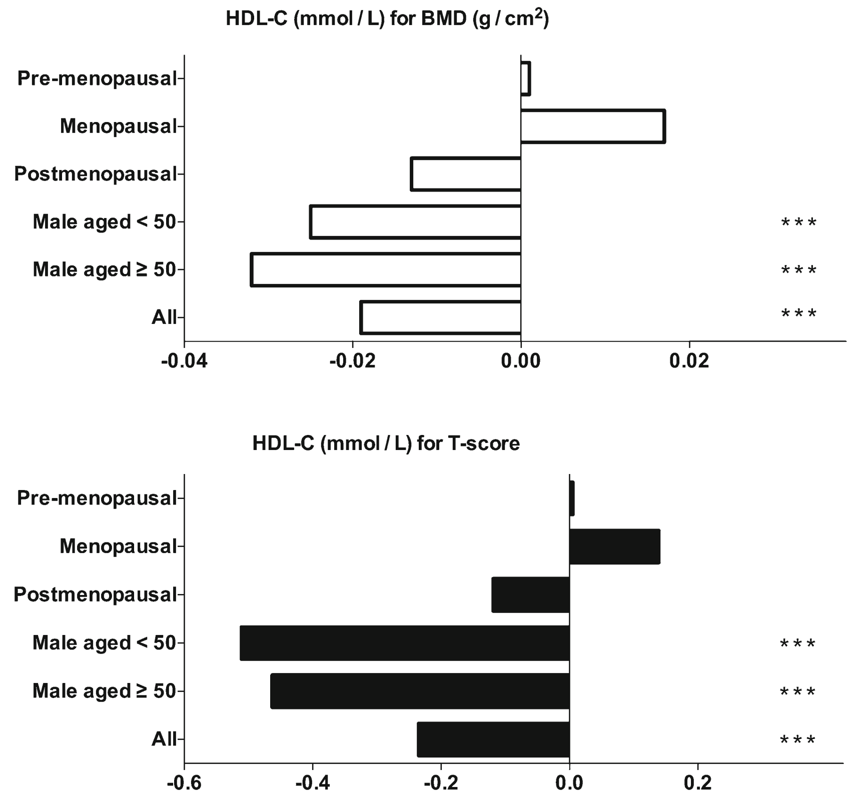

Fig. 2 Linear regression analyses of HDL-C for BMD and T-score. The graph shows the linear regression coefficients of HDL-C for BMD and T-score adjusted for age, BMI, SBP, Ca, ALP, UA, and ALB. The multiple linear regression analyses were performed in six cohorts: all participants, males aged < 50, males aged ≥ 50, pre-menopausal females, menopausal females, and postmenopausal females. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$

postmenopausal women would not be affected by an increase in age when compared to those who are pre-menopausal, the OR gap between age and HDL-C in the postmenopausal female cohort was smaller than in the whole female cohort. As we just discussed, the association between HDL-C levels and bone mass in females is not as strong as in males. In females, age increase is a much stronger risk factor.

In general, the relationship between HDL-C and bone mass varied in previous epidemiological studies and the participants of these studies came from different countries and regions [10–25, 33, 34]. According to the study by Ackert-Bicknell [35], the relationship between HDL-C and BMD is genetically linked. Papachristou et al. elaborated on the molecular basis of the interaction between HDL-C and bone [36]. However, the complex genetic relationship and interaction could not illustrate the exact association between HDL-C levels and bone mass clearly.

Our study has several advantages over similar research. First, 14,147 participants were enrolled in the present study. The large population and the wide spectrum of variates are infrequent in similar studies. Second, the participants were assigned to specific groups according to sex and age for more detailed subgroup analysis. Third, our analyses of association between HDL-C and bone mass were comprehensive and diverse. The bone mass was measured by four indicators including BMD,

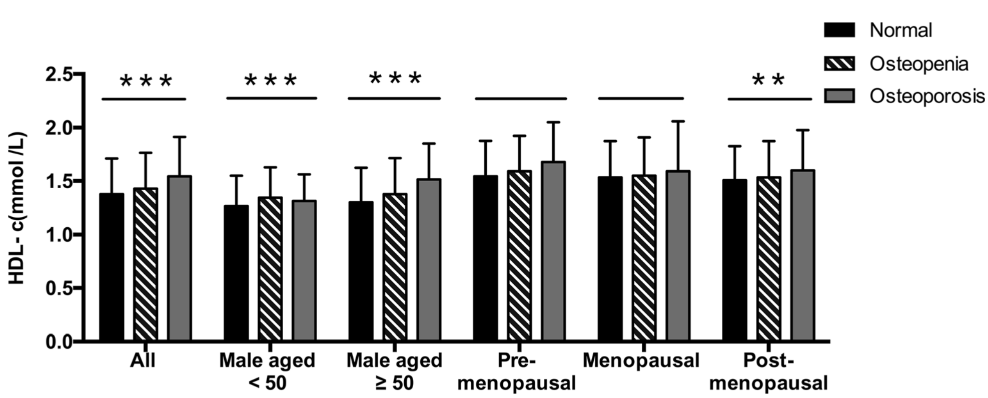

Fig. 3 One-way ANOVA analyses of HDL-C. The graph shows the mean and standard deviation of HDL-C levels in normal, osteopenia, and osteoporosis participants. One-way ANOVA analyses were performed in six cohorts: all participants, males aged < 50, males aged ≥ 50, pre-menopausal females, menopausal females, and postmenopausal females. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$

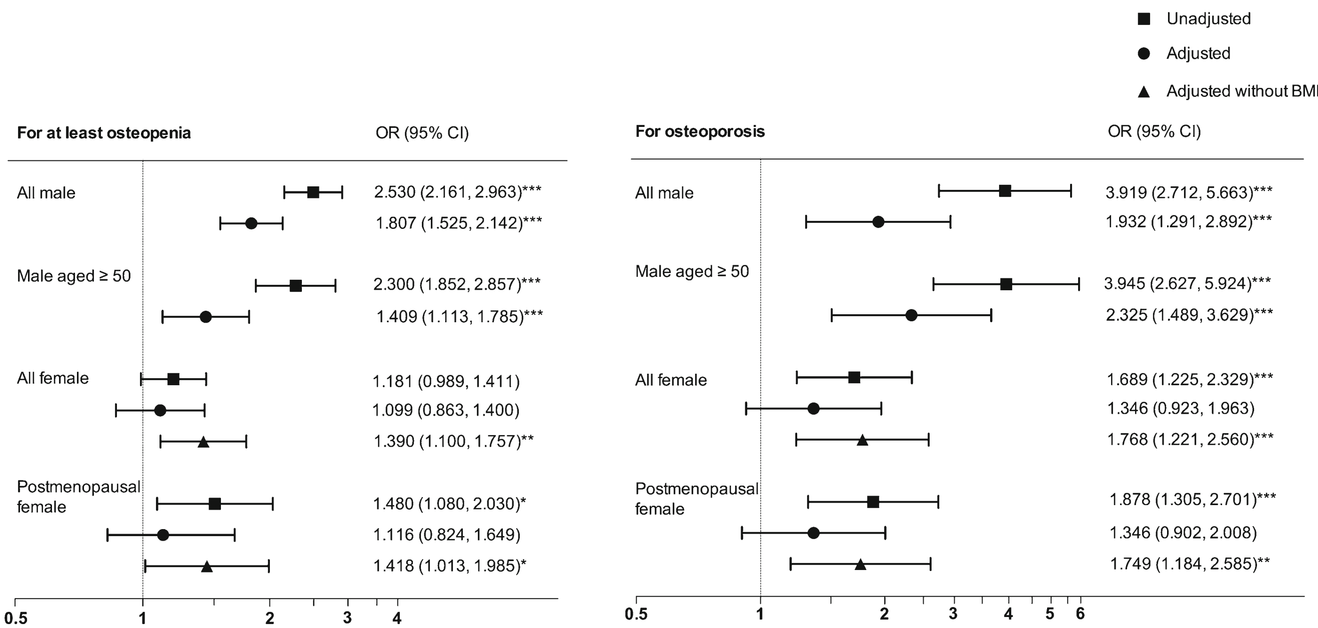

Fig. 4 Logistic regression analyses of HDL-C. The graph shows the odd ratios (ORs) and 95% confidence intervals (CIs) for at least osteopenia and osteoporosis according to HDL-C in four cohorts: males, females, males aged ≥ 50, and postmenopausal females. Including both unadjusted models and adjusted models. The adjusted model includes age, BMI, UA, and ALP. Analyses adjusted without BMI were performed in all females and postmenopausal females. *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$

T-score, at least osteopenia, and osteoporosis. Fourth, our analyses were precise with adjusting variables in multivariate analyses.

Furthermore, comparison of standardized ORs is an innovative and effective method to assess and compare the variables related to bone loss. Using this method, we found that, in females, an increase in age is a stronger risk factor for bone loss than is a higher HDL-C level.

Our study has some limitations. First, lifestyle habits that likely affect bone mass such as diet, smoking, and intake of alcohol were not evaluated in our study. Second, another effective indicator of bone mass is fracture, which was not considered in our study. Furthermore, we only measured the BMD of the lumbar spine. The BMD of other parts of the body could have been considered in our study.

In conclusion, HDL-C is associated with bone mass. For both males and females, there is a significant negative association between HDL-C and BMD as well as T-score. A higher HDL-C level is an independent risk factor for osteoporosis and at least osteopenia. Compared with high HDL-C levels, age increase and menopause have a much more significant effect on bone mass in females.

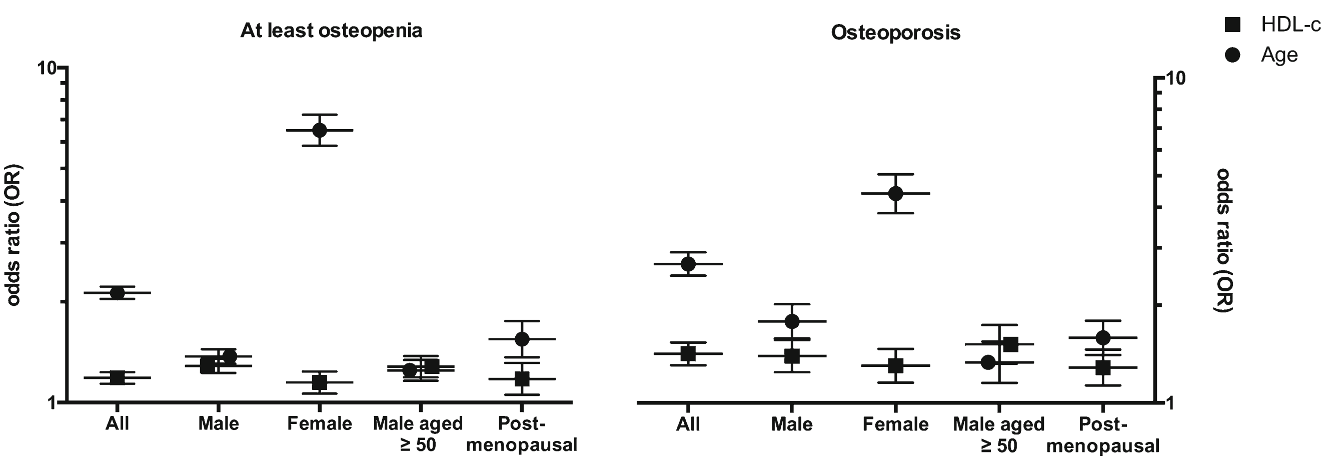

Fig. 5 Standardized logistic regression analyses of age and HDL-C. The graph shows the standardized odd ratios (ORs) and 95% confidence intervals (CIs) for at least osteopenia and osteoporosis according to age and HDL-C. The standardized logistic regression analyses were performed in five cohorts: all participants, males, females, males aged ≥ 50, and postmenopausal females

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Compliance with ethical standards

Conflicts of interest None.

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