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The association between HDL-c levels and computed tomography-based osteosarcopenia in older adults

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Abstract

Objective Associations between serum lipid levels and osteoporosis and sarcopenia have been reported. However, few studies have reported a link between serum lipid levels and osteosarcopenia. In the present study, we investigated the association between serum high-density lipoprotein cholesterol (HDL-c) and osteosarcopenia.

Methods A total of 1995 participants aged 50 years and above who underwent chest CT physical examinations from 2016 to 2019 were included. Demographic information, including age, sex, and body mass index, and laboratory data, including liver and kidney function, blood lipids (HDL-c, low-density lipoprotein cholesterol (LDL-c), triglyceride (TG), total cholesterol (TC), blood glucose, and serum albumin, were collected from the medical records system. Osteosarcopenia was defined on the basis of the presence of low bone mass (bone CT values < 110 HU) and low muscle mass of bilateral erector spinae (< 25.0 cm^2 in men and < 20.0 cm^2 in women). The relationships between HDL-c (continuous data and categorical data) and osteosarcopenia were analyzed via multivariable logistic regression and restricted cubic spline analysis.

Results One hundred forty-one patients with osteosarcopenia (7.7%) were observed. The individuals with osteosarcopenia had significantly greater HDL-c levels than did those without osteosarcopenia (1.65 ± 0.30 vs. 1.49 ± 0.34 mmol/L, $P < 0.001$). Multivariate logistic regression revealed that HDL-c (odds ratio (OR) = 2.72, 95% confidence interval (CI): 1.30–5.69) was associated with osteosarcopenia. The third and fourth HDL-c quartiles were significantly related to a greater incidence of osteosarcopenia (OR = 3.36, 95% CI: 1.66–6.80; OR = 3.66, 95% CI: 1.67–8.01) than the first quartile was. Similar trends were observed in the male population. For female individuals, the fourth HDL-c quartile was significantly related to a greater incidence of osteosarcopenia than the first quartile was (OR = 2.73, 95% CI: 1.03–7.21). Restricted cubic splines revealed similar relationships between HDL-c and osteosarcopenia.

Conclusion High serum HDL-c levels were associated with the risk of osteosarcopenia in older adults.

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Keywords Osteoporosis, Sarcopenia, Osteosarcopenia, High-density lipoprotein cholesterol

Introduction

Osteoporosis and sarcopenia are two age-related conditions that can significantly impact the health and quality of life of older adults [1, 2]. Osteoporosis is a skeletal disorder characterized by reduced bone mass and deterioration of bone tissue, leading to an increased risk of fractures. Sarcopenia is a clinical syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with or without a decrease in muscle function [3]. It is an important geriatric syndrome that can lead to significant disability, poor quality of life, and increased mortality rates among older adults [4, 5]. The condition is often underdiagnosed because of its insidious onset and the lack of specific symptoms in its early stages. Both osteoporosis and sarcopenia can coexist in older adults, which leads to a new syndrome termed osteosarcopenia, and their combined effects can lead to a greater risk of falls and fractures [6, 7], particularly in elderly individuals. Recently, an increasing number of studies have focused on the effects of sarcopenia on health issues, such as falls, fractures and death [8–10] Osteosarcopenia is a serious global health burden [1].

Dyslipidemia is also a common health issue in older adults [11] Associations between serum lipid levels and osteoporosis or sarcopenia have been reported. Low-density lipoprotein cholesterol (LDL-c) and triglycerides (TGs) may be associated with decreased bone density (BMD) [12, 13], but high-density lipoprotein cholesterol (HDL-c) is positively associated with BMD [14] However, some studies have reported conflicting results. Zhang et al. [15] reported that LDL-c was positively associated with femoral neck BMD and that HDL-c was negatively associated with femoral neck BMD in postmenopausal women. For sarcopenia, HDL-c levels are positively associated with the incidence of sarcopenia [16]. In addition, a recent meta-analysis revealed that patients with sarcopenia have high levels of TC, HDL-c, LDL-c and TG [17]. Those conflicting conclusion indicates that further studies are needed.

Osteosarcopenia and dyslipidemia may also coexist in older adults. However, to our knowledge, studies on the associations between serum lipid levels and the risk of osteosarcopenia are lacking [18]. Computed tomography (CT)-based muscle area and bone mass data have been used for evaluating sarcopenia [9, 10]. As serum lipid levels may be associated with both low BMD and sarcopenia, we hypothesized that serum lipids may also be associated with osteosarcopenia. Recent studies have shown that very high HDL-c may be not a protective factor for cardiovascular diseases [19]. Did such association exist between HDL-c and osteosarcopenia? In the present study we reported the relationship between HDL-c levels and computed tomography-based osteosarcopenia in older adults. Identifying associated factors of osteosarcopenia may be useful for osteosarcopenia management.

Methods

Participants

This retrospective study included individuals aged 50 years and above who underwent chest CT physical examinations at Nanjing University of Chinese Medicine from July 2016 to December 2019. The exclusion criteria were as follows: aged younger than 50 years, poor-quality CT images, severe osteoporotic and traumatic vertebral fractures, lumbar disc herniation, vertebral bone metastasis or bone tumors, history of malignant tumors, history of severe stroke, long-term use of glucocorticoids, and metabolic bone disease. Finally, a total of 1,995 participants were included in the current study.

Data collection

The following data were collected through the electronic medical system: demographic information, including age, sex, and body mass index; laboratory test results, including liver (aspartate aminotransferase, AST) and kidney (creatinine) function, blood lipids (HDL-c, low-density lipoprotein cholesterol (LDL-c), triglyceride (TG), total cholesterol (TC), blood glucose, and serum albumin (nutritional marker) data. All laboratory tests and CT scans were performed on the same day. Diabetes was diagnosed on the basis of fasting plasma glucose (≥7.0 mmol/L) or a self-reported medical history of diabetes.

Assessment of bone mass

Vertebral CT values reflect potential BMD [20, 21]. The CT scan parameters were as follows: tube voltage of 120 kV, tube current of 100–120 mAs, and slice thickness of 0.625 mm. The CT images were reconstructed using a slice thickness of 0.625 mm and an increment of 0.5 mm on the workstation. On axial CT images, vertebral CT values (Hounsfield unit, HU) were measured by placing an oval region of interest (ROI) of 2–3 cm^2 in the middle of the trabecular bone area at the T11 vertebral level, avoiding placing the ROI in areas that would distort BMD measurements (posterior venous plexus, focal heterogeneity or lesions, including compression fractures, and imaging-related artifacts). The results of the bone CT measurements are shown in Fig. 1A. Lower HU (lower CT values) indicates lower bone density, and patients were divided into two groups on the basis of vertebral CT values: low bone mass (vertebral CT value < 110 HU) and

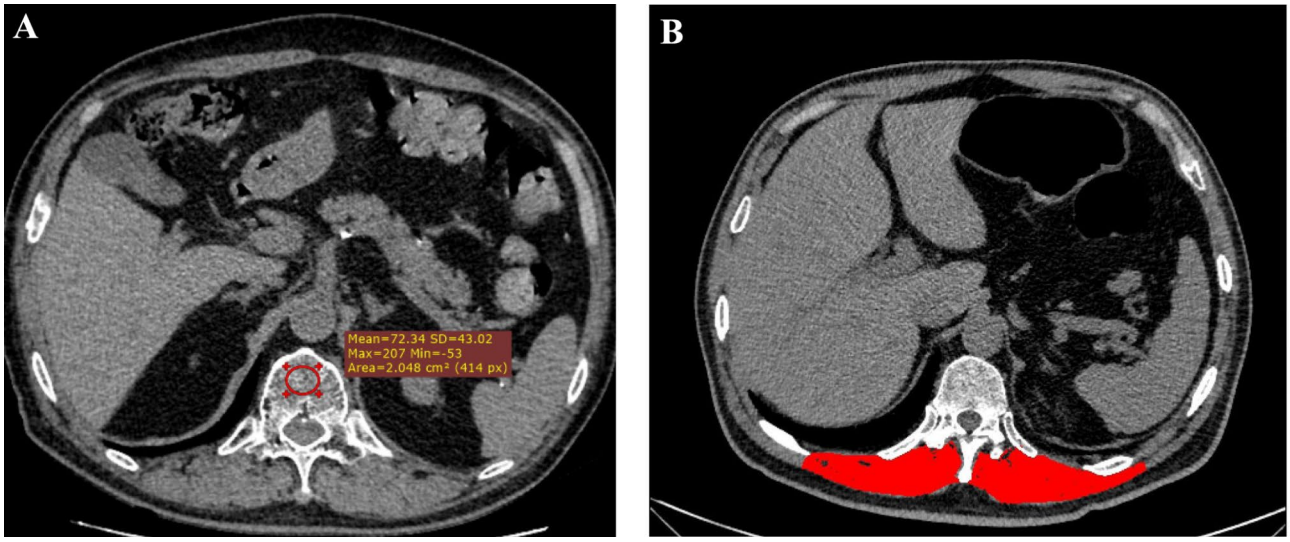


Fig. 1 Illustration of the measurement of bone mass and muscle area via computed tomography

the normal control group (vertebral CT value≥110 HU) [22, 23].

Assessment of muscle mass and sarcopenia

The participants' CT images were also used to assess the muscle mass of the erector spinae. The areas of the bilateral erector spinae muscles were measured on axial CT images at the midline level of the selected T11 vertebra via ImageJ software, as shown in Fig. 1B. Muscle area was divided into two groups on the basis of the critical values of 25.0 cm^2 in men and 20.0 cm^2 in women (calculated from the 25th percentile of muscle area in men and women). Osteosarcopenia was defined on the basis of low bone mass (bone CT values<110 HU) and muscle mass (<25.0 cm^2 in men and <20.0 cm^2 in women).

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine. Given that this study is retrospective, informed consent was waived. This study was performed in accordance with the Declaration of Helsinki.

Clinical trial number

Not applicable.

Statistical analysis

Quantitative data that had a normal distribution are expressed as the mean±standard deviation, and categorical data are expressed as the number (percentage). The participants were divided into two groups according to the presence of osteosarcopenia. HDL-c was divided into 4 groups on the basis of quartiles. Quantitative data were statistically compared via independent-samples t tests or one-way analysis of variance, and categorical data were compared via chi-square tests or Fisher's exact tests. HDL-c was categorized into quartiles: total population, Q1<1.25, Q2 1.25–1.47, Q3 1.47–1.71, and Q4>1.71; women, Q1<1.43, Q2 1.43–1.64, Q3 1.64–1.88, and Q4>1.88; men, Q1<1.18, Q2 1.18–1.36, Q3 1.36–1.56, and Q4>1.56. The relationships between HDL-c (continuous data and categorical data) and osteosarcopenia were analyzed via multivariable logistic regression and restricted cubic spline analysis, with age, sex, BMI, liver and kidney function, albumin, and diabetes as covariates. All the statistical analyses were performed via SPSS (version 22.0) or R (version 4.4.1). Statistical significance was assessed on the basis of a P value less than 0.05.

Results

Characteristics of the participants

The characteristics of the participants are shown in Table 1. There were 141 cases of osteosarcopenia. The participants with osteosarcopenia were older than people without osteosarcopenia were ($P<0.01$). The muscle area and bone CT attenuation were significantly lower in participants with osteosarcopenia than in those without osteosarcopenia ($P<0.01$). The BMI of participants without osteosarcopenia was greater than that of people with osteosarcopenia ($P=0.05$). A higher level of HDL-c was more common in participants with osteosarcopenia than in participants without osteosarcopenia ($P<0.01$). However, no significant differences were found in AST, albumin, creatinine, blood glucose, LDL-c, TC, TG or diabetes between the two groups. ($P>0.05$). The prevalence of osteosarcopenia in both men and women increased with increasing HDL-c levels (Fig. 2).

Table 1 Characteristics of the subjects

	Osteosarcopenia (*n* = 141)	Nonosteosarcopenia (*n* = 1854)	*P*
Age (years)	71.07 ± 8.87	61.68 ± 9.20	< 0.001
Sex (men)	32 (52.5%)	1126 (57.8%)	< 0.001
Muscle area (cm^2)	17.20 ± 2.39	27.66 ± 6.58	< 0.001
Bone CT attenuation (HU)	87.21 ± 23.14	146.0 ± 41.33	< 0.001
BMI (kg/m^2)	25.38 ± 2.96	25.79 ± 3.13	0.05
AST (mmol/L)	24.91 ± 6.74	23.97 ± 10.98	0.32
Albumin (mmol/L)	40.56 ± 3.15	40.78 ± 3.11	0.42
Creatinine (mmol/L)	74.17 ± 20.91	77.96 ± 23.93	0.07
Blood glucose (mmol/L)	5.65 ± 1.30	5.54 ± 1.40	0.37
HDL-c (mmol/L)	1.65 ± 0.30	1.49 ± 0.34	< 0.001
LDL-c (mmol/L)	2.96 ± 0.92	2.95 ± 0.82	0.90
TC (mmol/L)	4.84 ± 1.13	4.79 ± 1.01	0.52
TG (mmol/L)	1.41 ± 0.81	1.55 ± 1.13	0.17
Diabetes	14 (11.2%)	150 (10.7%)	0.45

AST: aspartate aminotransferase; BMI: body mass index; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride

Association between HDL-c and low bone/muscle mass

First, we observed an association between HDL-c levels and the risk of low bone mass and low muscle mass (Table 2). The risk of low bone mass increased with increasing HDL-c, but the difference was not statistically significant (odds ratio (OR) = 1.45, 95% confidence interval (CI): 0.93–2.27). High HDL-c levels (the third quartile and fourth quartile) were associated with a greater risk of low muscle mass (OR = 1.50, 1.08–2.09; OR = 1.93, 95% CI: 1.32–2.82) than low HDL-c levels (the first quartile) after adjusting for age, BMI, sex, liver and kidney function, diabetes, albumin, low-density lipoprotein cholesterol and total cholesterol.

Associations between HDL-c and osteosarcopenia

Multivariate logistic regression analyses were used to identify the association between HDL-c and the risk of osteosarcopenia (Table 3). Significant associations were found between HDL-c and the risk of osteosarcopenia in the total population (OR) = 2.27, 95% CI: 1.24–4.17)

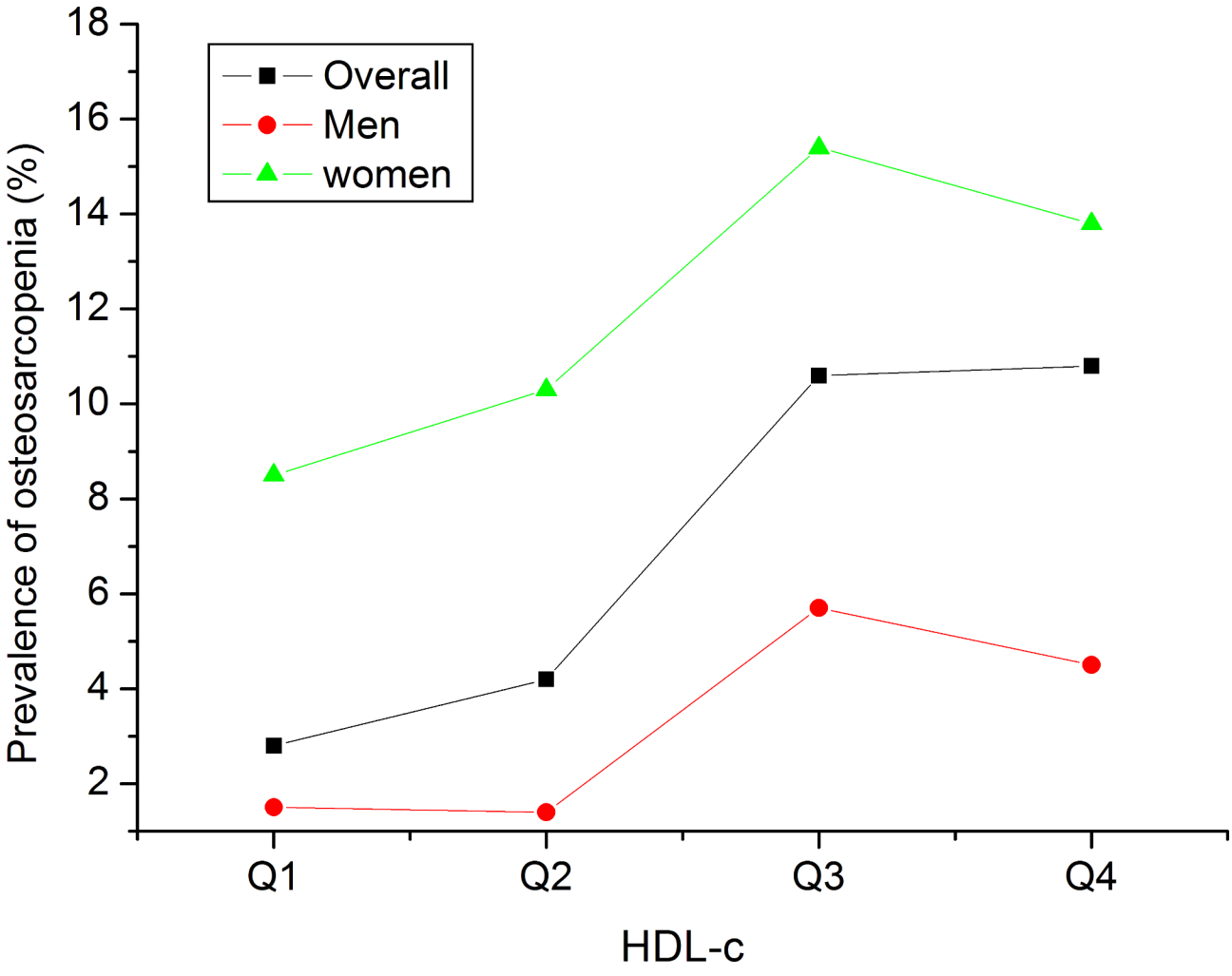


Fig. 2 Prevalence of osteosarcopenia in men and women on the basis of the interquartile range of high-density lipoprotein cholesterol (HDL-c)

Table 2 Association between HDL levels and the risk of low bone mass and low muscle mass

	Model 1	*p*	Model 2	*p*	Model 3	*p*
	OR (95%CI)		OR (95%CI)		OR (95%CI)	
Low bone mass						
HDL (continuous)	1.21 (0.80–1.83)	0.37	1.18 (0.76–1.82)	0.46	1.21 (0.75–1.96)	0.44
Q1 (< 1.25)	1		1		1	
Q2 (1.25–1.47)	1.00 (0.70–1.44)	0.99	1.00 (0.79–3.36)	0.99	1.01 (0.70–1.47)	0.94
Q3 (1.47–1.71)	1.20 (0.83–1.73)	0.32	1.20 (0.83–1.74)	0.33	1.25 (0.84–1.85)	0.28
Q4 (> 1.71)	1.37 (0.92–2.03)	0.12	1.38 (0.92–2.08)	0.12	1.45 (0.93–2.27)	0.10
Low muscle mass						
HDL (continuous)	2.05 (1.44–2.92)	< 0.001	2.18 (1.50–3.17)	< 0.001	2.25(1.45–3.40)	< 0.001
Q1 (< 1.25)	1		1		1	
Q2 (1.25–1.47)	1.21(0.89–1.63)	0.22	1.21 (0.90–1.64)	0.21	1.19(0.87–1.62)	0.27
Q3 (1.47–1.71)	1.50 (1.10–2.04)	0.01	1.52 (1.12–2.08)	0.008	1.50 (1.08–2.09)	0.016
Q4 (> 1.71)	1.89 (1.35–2.66)	< 0.001	1.94 (1.37–2.76)	< 0.001	1.93 (1.32–2.82)	0.001

Model 1 was adjusted for age, sex and body mass index; Model 2 was further adjusted for liver function, renal function, diabetes, and albumin. Model 3 was further adjusted for low-density lipoprotein cholesterol and total cholesterol

CI: confidence interval; OR: odds ratio

Table 3 Association between HDL levels and the risk of osteosarcopenia

	Model 1	*p*	Model 2	*p*	Model 3	*p*
	OR (95%CI)		OR (95%CI)		OR (95%CI)	
Total						
HDL (continuous)	2.27 (1.24–4.17)	0.008	2.50 (1.31–4.77)	0.006	2.72 (1.30–5.69)	0.008
Q1 (< 1.25)	1		1		1	
Q2 (1.25–1.47)	1.62 (0.79–3.34)	0.19	1.63 (0.79–3.36)	0.19	1.68 (0.80–3.51)	0.17
Q3 (1.47–1.71)	3.02 (1.56–5.86)	0.001	3.11 (1.60–6.08)	0.001	3.36 (1.66–6.80)	0.001
Q4 (> 1.71)	3.02 (1.52–6.01)	0.001	3.24 (1.59–6.59)	0.001	3.66 (1.67–8.01)	0.001
Women						
HDL (continuous)	1.97(0.95–4.09)	0.068	1.78 (0.85–3.73)	0.13	1.66 (0.71–3.88)	0.24
Q1 (< 1.43)	1		1		1	
Q2 (1.43–1.64)	1.85(0.72–4.76)	0.20	1.86 (0.72–4.82)	0.20	1.83 (0.70–4.83)	0.11
Q3 (1.64–1.88)	2.40 (1.01–5.69)	0.047	2.30 (0.96–5.47)	0.06	2.28 (0.92–5.67)	0.08
Q4 (> 1.88)	2.87 (1.19–6.90)	0.019	2.73(1.12–6.63)	0.026	2.73 (1.03–7.21)	0.043
Men						
HDL (continuous)	3.58 (1.17–10.99)	0.025	6.44 (1.76–23.64)	0.005	13.76(2.78–68.14)	0.001
Q1 (< 1.18)	1		1		1	
Q2 (1.18–1.36)	1.08 (0.32–3.65)	0.91	1.24 (0.36–4.29)	0.74	1.45 (0.40–5.21)	0.37
Q3 (1.36–1.56)	4.69 (1.69–13.04)	0.003	5.62 (1.92–16.41)	0.002	8.30(2.52–27.27)	< 0.001
Q4 (> 1.56)	2.94 (0.88–9.85)	0.08	4.55 (1.20-17.15)	0.025	8.04 (1.77–36.35)	0.007

Model 1 was adjusted for age, sex and body mass index; Model 2 was further adjusted for liver function, renal function, diabetes, and albumin. Model 3 was further adjusted for low-density lipoprotein cholesterol and total cholesterol

CI: confidence interval; OR: odds ratio

and men (OR = 3.58, 95% CI: 1.17–10.99) after adjusting for age, sex and body mass index. Similar results were found when more possible confounders were considered (OR = 2.72, 955 CI: 1.30–5.69; OR = 13.76, 95% CI: 2.78–68.14). We then divided HDL-c levels into categorical data. Compared with low HDL-c levels (the first quartile and fourth quartile), high HDL-c levels were associated with a greater risk of osteosarcopenia (OR = 3.36, 1.66–6.80; OR = 3.66, 95% CI: 1.67–8.01) after adjusting for age, BMI, sex, liver and kidney function, diabetes, albumin, low-density lipoprotein cholesterol and total cholesterol. Similar trends were observed in men (third quartile: OR = 8.30, 95% CI: 2.52–27.27; fourth quartile: OR = 8.04, 95% CI: 1.77–36.35). For women, high HDL levels (in the fourth quartile) were associated with the risk of osteosarcopenia in the fully adjusted model (OR = 2.73, 95% CI: 1.03–7.21).

Restricted cubic splines further showed adjusted odds ratios for the risk of osteosarcopenia according to HDL-c levels in the total population and in men and women (Fig. 3). A linear relationship was observed between HDL-c levels and the risk of sarcopenia, especially in the total population and men.

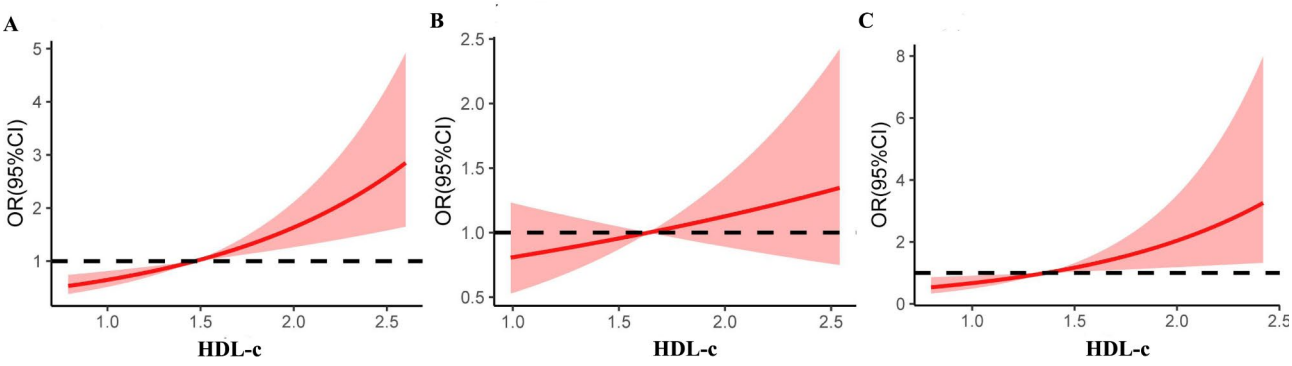


Fig. 3 Restricted cubic splines show the multivariable adjusted odds ratio for the risk of osteosarcopenia according to high-density lipoprotein cholesterol in the total population (**A**), women (**B**) and men (**C**). Age, sex and body mass index, liver function, renal function, diabetes, low-density lipoprotein cholesterol, albumin and total cholesterol were adjusted

Discussion

Osteosarcopenia and dyslipidemia are common health issues in older adults. However, the associations between serum lipid levels and the risk of osteosarcopenia have rarely been investigated. In the present study, we reported the relationship between serum HDL-c levels and osteosarcopenia in a general Chinese population. Our results revealed that individuals with osteosarcopenia had higher HDL-c levels than did those without osteosarcopenia. High HDL-c levels were associated with an increased risk of osteosarcopenia after adjusting for multiple covariates, such as age, BMI, and diabetes status. Restricted cubic spline analysis further revealed that the risk of osteosarcopenia increased with increasing HDL-c levels. This study raises the possibility that high HDL-c levels may be an associated factor for increased risk of osteosarcopenia.

Many studies have reported the associations between serum lipid levels and the risk of low bone mass/osteoporosis [24] and sarcopenia. However, those studies yielded controversial results. For example, Cao et al. [12] reported that high LDL-c levels may be associated with decreased BMD, but Zhang et al. [15] reported that LDL-c was positively associated with femoral neck BMD. Similar conflicting results have also been reported concerning the relationship between serum lipid levels and sarcopenia. Jiang et al. [25] reported that low TC and TG levels and high LDL levels were risk factors for sarcopenia. However, Gong et al. [26] reported that TC, TG, and LDL-c were all negatively correlated with the skeletal muscle index (SMI). In our study, we found that HDL-c levels were positively associated with both a high risk of low bone mass and low muscle mass, especially low muscle mass ($P<0.01$). Our results were in accordance with those of a recent study that revealed that older adults with high HDL-C levels (>70 mg/dl) had a significantly greater risk of sarcopenia than those with low HDL-c levels (40–60 mg/dl) [27]. Interestingly, recent studies have also shown the unfavorable effects of high HDL-c levels on health issues, such as cardiovascular disease, fracture and mortality [28–30].

Osteosarcopenia is a syndrome characterized by a combination of low bone mass and low muscle mass or function [1]. Osteosarcopenia is an associated factor for falls, fractures and death.1 However, to our knowledge, the associations between osteosarcopenia and serum lipid levels, especially HDL-c, have not been well studied. Fahimfar et al. [18] reported that the prevalence of high HDL-c in individuals with osteosarcopenia was greater than that in those without osteosarcopenia. However, they did not observe an association between lipid profiles and osteosarcopenia via multivariable analysis. One possible reason is that Fahimfar and colleagues [18] divided HDL-c into only two groups: low (<40 mg/dl in men and <50 mg/dl in women) and high levels. Another reason is that we used a different method to define osteosarcopenia and used a stricter standard to define low bone mass.

What high levels of HDL-c affect osteosarcopenia is not completely understood. HDL particles are also important in addition to the HDL-c concentration. It has been shown that there may be differences in HDL particles between individuals with low HDL-c and those with high HDL-c, which may explain the different roles of HDL-c in health [31]. HDL-c function is also a critical factor for the role of HDL in cardiovascular disease [32]. The function of HDL may be more important than elevating HDL cholesterol levels [32]. In addition, high levels of HDL-c play a proinflammatory role and are linked to cellular senescence [33]. Cellular senescence is a common pathway for age-related musculoskeletal diseases [34]. An in vitro study demonstrated that high concentrations of HDL (400–800 μg/ml) accelerated endothelial progenitor cell senescence via activation of the Rho-associated kinase pathway [35]. In addition, it has been shown that HDL from the elderly group caused more severe cellular senescence in human dermal fibroblasts [36] and human umbilical vein endothelial cells [37]. The effect of HDL-c on cellular senescence may play a critical role in

osteosarcopenia. A Study reported subclasses of human HDL could induce smooth muscle cell apoptosis [38]. Moreover, high HDL-c level was associated with risk of fracture [28]. Spine fracture may affect the back muscle which caused muscle loss in erector spinae. As for bone loss, a study showed that oxidized HDL at 100 μg/mL protein could inhibit osteoblast mineralization [39], which may contribute to bone loss. In addition, impaired and/or dysfunctional HDL may activate T lymphocytes and enhance the production and secretion of cytokines which can suppress the Wnt/β-catecinin signaling axis [40]. Consequently, osteoblast number and activity were impaired [40]. However, to our knowledge, few in vivo or in vitro studies have shown the role of HDL-c on musculoskeletal system. The exact mechanisms should be investigated in future studies.

Our study has several advantages. This may be the first study to explore the association between CT-based osteosarcopenia and serum HDL-c levels in a Chinese population. Furthermore, the sample size of our study was relatively large. Several limitations should be acknowledged. First, osteosarcopenia is defined on the basis of CT rather than dual-emission X-ray absorptiometry, which is more widely used. However, CT-based osteosarcopenia has been used in some studies. Second, we did not investigate the possible mechanism by which HDL-c affects osteosarcopenia. Third, our study is a cross-sectional study. Longitudinal studies are needed to show the causal relationship between HDL-c and risk of osteosarcopenia. Fourth, this study was conducted on a Chinese population. While the results are relevant for this group, it is unclear whether our conclusion was generalizable to populations with different genetic backgrounds and lifestyles. Finally, even though we had controlled some covariates, some confounders which may affect HDL-c level and osteosarcopenia, such as smoking, drinking, physical exercise, dietary habits and medicines, were not considered in our study. Our results showed a strong association between HDL-c and osteosarcopenia ($p<0.01$ or 0.001). Therefore, we speculated that the results may not be changed even though considering more confounders. Moreover, we conducted the risk of bias assessment based on Agency for Healthcare Research and Quality (AHRQ) form. The score for AHRQ was 7 which mean the study quality is acceptable.

In conclusion, our study showed that subjects with osteosarcopenia had high levels of HDL-c and HDL-c level was positively associated with low muscle mass and osteosarcopenia after controlling for age, diabetes, BMI, and other potential confounders. Further studies are needed to establish a causal relationship and to investigate the mechanisms by which HDL-c affects osteosarcopenia.

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None.

Author contributions
XC participated in the design of the study. RW, YW and XC wrote the manuscript. RW, YW, ZW, JW, HT, XG, CZ, JW and XC collected and analyzed the data. RW, YW, CZ and XC contributed to the interpretation of the data and the preparation of the manuscript. All the authors have read and approved the final manuscript.

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Data availability
All the data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from the Affiliated Hospital of Nanjing University of Chinese Medicine. The study was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine because of the retrospective nature of the study.

Consent for publication
Not applicable.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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