Endocrine (2025) 88:446–456
https://doi.org/10.1007/s12020-025-04168-0

ORIGINAL ARTICLE

Nonlinear association between liver fat content and lumbar bone mineral density in overweight and obese individuals: evidence from a large-scale health screening data in China

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Received: 19 September 2024 / Accepted: 14 January 2025 / Published online: 27 January 2025

Abstract

Background The impact of fatty liver disease on lumbar bone mineral density (BMD) represents an intriguing area of study, particularly in light of established research linking obesity to bone metabolism. However, there remains limited investigation into the correlation between quantifying liver fat content (LFC) and lumbar BMD among overweight and obese populations, particularly within the Chinese demographic. This study aims to accurately quantify LFC and investigate its association with lumbar BMD in overweight or obese individuals.

Methods This cross-sectional study was conducted at the Health Management Center of Henan Provincial People's Hospital from January 2019 to February 2023, involving 6996 participants with a body mass index (BMI) of 24 kg/m² or higher. LFC and lumbar BMD were assessed using computed tomography. The study utilized one-way ANOVA, subgroup analysis, multifactor regression analysis, smooth curve fitting, and threshold and saturation effect analysis to explore the relationship between LFC and lumbar BMD. Furthermore, inflammatory cell analysis was included to investigate the potential mediating role of inflammatory cells in the association between LFC and lumbar BMD.

Results After adjusting for confounding variables, multivariate regression analysis revealed a significant negative association between LFC and lumbar BMD ($\beta = -0.323$, 95% CI: -0.464 to -0.183, $P < 0.001$). Particularly, participants in the highest baseline LFC quartile (Q4 group) exhibited a more pronounced negative impact on lumbar BMD compared to those in the lowest quartile (Q1 group) ($\beta = -5.026$, 95% CI: -7.040 to -3.012, $P < 0.001$). Threshold saturation effect analysis identified a turning point in the LFC-BMD relationship (K = 5.4). Below this point, LFC showed a positive correlation with lumbar BMD ($\beta = 0.962$, 95% CI: 0.016–1.907, $P < 0.05$), whereas above it, LFC was significantly negatively correlated with lumbar BMD ($\beta = -0.405$, 95% CI: -0.558 to -0.253, $P < 0.001$). Additionally, mediation analysis indicated that leukocytes and monocytes potentially mediated the association between LFC and lumbar BMD, with mediation ratios of -5.78 and -6.68%, respectively.

Conclusion Among individuals categorized as overweight or obese, elevated levels of LFC were associated with reduced lumbar BMD, particularly noticeable above a threshold of 5.4%. Additionally, various types of inflammatory cells are presumed to exert a substantial mediating influence on the correlation between LFC and lumbar BMD.

Keywords Bone mineral density · Osteoporosis · LFC · Adiposity · Chinese adults

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Introduction

Osteoporosis is characterized by decreased bone density and deterioration of microstructure. Its etiology is multifaceted and involves a variety of biological factors [1]. With global aging, osteoporosis incidence has risen notably, particularly in women experiencing postmenopausal osteoporosis [2]. A recent study in China reported osteoporosis prevalence among individuals aged 40 years and older as 5.0% in men and 20.6% in women [3]. This condition not only increases fracture risk but also leads to serious complications that significantly impact patients' quality of life, escalate medical costs, and can result in mortality [4]. Therefore, prevention and early screening are crucial. Lumbar bone mineral density (BMD) assessment is a widely used clinical screening tool for osteoporosis, and lumbar bone densitometry is commonly employed to monitor disease progression [5].

Hepatic steatosis, characterized by abnormal accumulation of triglycerides in liver cells, is implicated in various liver diseases such as cirrhosis and hepatocellular carcinoma. Recent research has increasingly explored the association between hepatic fat accumulation and BMD loss, particularly in relation to osteoporosis [6]. Studies indicate that elevated liver fat content (LFC) may initiate liver inflammation and fibrosis, potentially disrupting systemic metabolic balance and influencing osteoporosis risk [7]. Moreover, the research conducted by Chan et al. [8] proposes that the management of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) should incorporate strategies to prevent sarcopenia, as the development of sarcopenia is likely to contribute to the exacerbation of bone mineral density loss. Epidemiological evidence also underscores a negative correlation between increased LFC and decreased BMD, highlighting the significant role of hepatic fat accumulation in bone health. A large-scale cohort study in Korea utilized dual-energy X-ray absorptiometry (DXA) to assess BMD across multiple sites, revealing a link between nonalcoholic fatty liver disease (NAFLD) and reduced BMD in men [9]. Independently, Shen et al. employed DXA for BMD measurement and ultrasound for fatty liver assessment, reinforcing the association between NAFLD and heightened incidence of low BMD [10]. Additionally, the study also emphasized the substantial impact of obesity in this relationship. Despite the existence of prior research in this area, the quantification of hepatic steatosis and the specific dose-response relationship between LFC and lumbar bone mineral density in individuals with overweight and obesity have not been thoroughly investigated. Therefore, further studies are warranted to develop novel strategies for the effective prevention and management of osteoporosis.

Chronic inflammation plays a pivotal role in osteoporosis by stimulating the release of pro-inflammatory cytokines, inhibiting osteoblast function, and promoting osteoclast proliferation and differentiation [11]. These mechanisms contribute to decreased bone formation and increased bone resorption, ultimately resulting in reduced BMD. Additionally, the low-grade inflammation associated with obesity can induce the secretion of adipokines such as leptin and adiponectin, which indirectly affect bone metabolism and heighten the susceptibility to osteoporosis and fractures [12]. Given inflammation's critical involvement in metabolic disorders and osteoporosis-related conditions, this study utilized computed tomography to quantify LFC and lumbar BMD. The study aimed to explore the relationship between LFC and BMD among a cohort of overweight and obese individuals who underwent comprehensive physical assessments.

Materials and methods

Participants and criteria for inclusion

The study was approved by the Ethics Committee of Henan Provincial People's Hospital (Approval No. 115, 2022). Informed consent was obtained from all participants following a comprehensive briefing on the study's objectives and methodologies.

Data for this study were extracted from the health records of individuals who underwent comprehensive physical assessments at the Health Management Center of Henan Provincial People's Hospital between 2019 and 2023. The inclusion criteria were: (1) individuals aged 20 to 80 years and body mass index (BMI) ≥ 24 kg/m², and (2) individuals with complete hematology tests and provided questionnaire information, and (3) individuals who underwent assessment of LFC and lumbar BMD. The exclusion criteria included: (1) history of any cancer, (2) previous or current thyroid disease and other endocrine disorders, (3) history of hepatic lobectomy, hepatic space-occupying lesions (excluding benign small cysts and small intrahepatic calcifications), and liver cirrhosis, and (4) previous or current use of drugs and lipid regulators for osteoporosis prevention, and (5) history of previous lumbar spine fracture or lumbar spine surgery, and, and (6) history of antibiotic use within the past two weeks. Trained personnel gathered fundamental participant data, including age, gender, nationality, marital status, medical and medication history.

Initially, 14,128 participants undergoing quantitative assessment of liver fat and lumbar bone densitometry were initially enrolled. Among them, 7879 participants satisfied the inclusion criteria, with 883 individuals being excluded. Consequently, the final analysis involved 6996 participants. The participant selection process is delineated in Fig. 1.

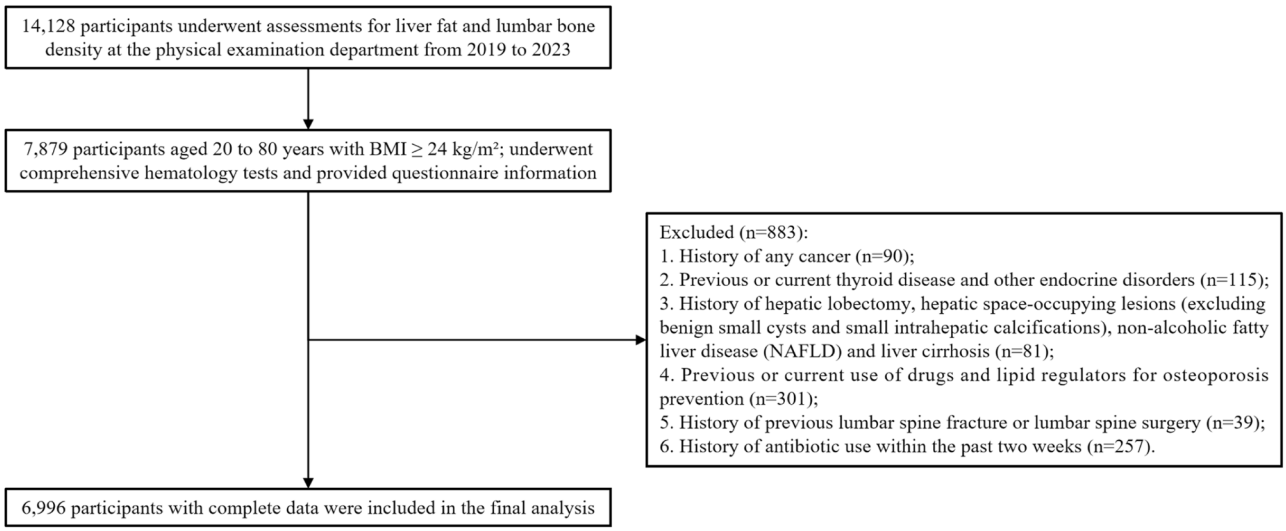

Fig. 1 Flowchart of participants selection

Laboratory tests

To ensure data accuracy and reliability, all investigators underwent standardized training in survey methodology before the commencement of this study. Basic participant data were collected via a comprehensive questionnaire, and measurements of height, weight, blood pressure, and other relevant indicators were recorded. To minimize errors, each measurement was conducted twice, with the final value calculated as the mean of the two readings.

Fasting blood samples were obtained from participants at 8 a.m., and various laboratory parameters were assessed, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hemoglobin (Hb), total protein (TP), total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), serum uric acid (SUA), and serum creatinine. An Olympus® AU 5400 automated biochemistry analyzer was used for lipid and blood glucose evaluations, while standard laboratory methods were employed for the analysis of the remaining variables. In addition, hematological cell counts were also collected using standardized laboratory methods.

LFC measurements

Utilizing a Lightspeed VCT 64-row CT scanner (General Electric), the study adhered to the standard low-dose chest CT scan protocol, with the tube voltage set to 120 kV and tube current at 100 mA. The scanning field was defined at 500 × 500 mm, with a slice thickness of 5 mm and a pitch of 0.984. Quantitative computed tomography (QCT) of liver fat was performed using the Measure Liver Fat module scanning analysis software, a specialized tissue measurement application. During this process, three circular regions of interest (ROIs) were positioned in the anterior and posterior segments of the left and right lobes, each with a cross-sectional area of 290–310 mm^2. The ROIs were positioned in the subcapsular area of the liver, avoiding bile ducts and blood vessels. If the left lobe of the liver was too small to be visualized on the section, the slice with the largest visible area of the left lobe was utilized for measurement. The mean of the three was taken as the final value to determine the liver fat percentage. All analyses using the QCT software were conducted by specially trained radiologists. Importantly, a previous publication confirmed the suitability of this technique for individuals of Chinese descent [13].

BMD measurement

Volumetric BMD (vBMD) was assessed using Mindways QCT Pro (Mindways Software, Inc., Austin, TX, USA). Specifically, trabecular vBMD (mg/cm^3) at the lumbar spine (L1–L2) was measured utilizing asynchronous BMD calibration and QCT Pro analysis (Mindways Software, Inc., Austin, TX, USA) [14]. Each vertebra underwent three measurements, with the average value considered representative of its bone density. The final BMD was derived from the average of these two vertebrae measurements. All assessments were conducted by experienced radiologists trained in QCT software. Notably, standard examination images were used for bone density measurement to avoid additional radiation exposure for participants. Additionally, continuous calibration and system cross-validation were performed using the European Spinal Phantom 145 (ESP-145) as a reference standard.

Definition

The BMI was determined by dividing the individual's weight by their height squared (kg/m²). Hypertension was characterized by a prior diagnosis of the condition or the current use of antihypertensive medications, or two consecutive daily blood pressure readings indicating elevated levels. The diagnosis of diabetes mellitus was established based on the criteria of the American Diabetes Association: self-reported diagnosis, use of insulin or oral hypoglycemic agents, HbA1c ≥ 6.5%, or fasting blood glucose (FBG) ≥ 7 mmol/L [15].

Variables

In this study, LFC was designated as the independent variable, while lumbar BMD was specified as the dependent variable. The covariates gathered included the following data: (1) demographic information, including age, gender, nationality, and marital status; (2) physical examination parameters, including BMI, systolic blood pressure, and diastolic blood pressure; (3) medical history, including the presence of diabetes, cancer, and other clinical conditions; (4) laboratory indicators, including TC, TG, LDL-C, HDL-C, Hb, TP, TB, AST, ALT, GGT, ALP, SUA, and serum creatinine. It is important to note that BMI classification was defined according to specific thresholds: individuals with a BMI of 24 kg/m^2 were classified as overweight, while those with a BMI of 28 kg/m^2 or above were classified as obese [16].

Treatment of missing data

In this study, 45 (0.64%), 234 (3.34%), 97 (1.39%), 73 (1.04%), 14 (0.20%), 123 (1.76%), and 365 (5.22%) participants were lacking data on age, BMI, TC, ALP, SUA, serum creatinine, and diabetes history. To address the missing data and reduce the uncertainty caused by missing variables, multiple imputations were performed [17, 18]. Age, BMI, TC, ALP, SUA, serum creatinine, and diabetes history were included in the inferential model (number of iterations 10; regression type linear). Missing data analysis utilized the missing at random (MAR) assumption.

Statistical analysis

Statistical analysis was performed using EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA) and R software (version 4.2.0). The mean ± standard deviation was used to represent the continuous variables with normal distribution, the median was used to represent the continuous variables with non-normal distribution, and the proportion was used to represent the categorical variables. Chi-square tests and ANOVA were used to identify significant differences in the dataset. To mitigate potential confounding factors, we employed a multifactorial regression analysis model to investigate the association between LFC and lumbar BMD. The initial model (coarse model) has no covariate adjustment. Model I adjusted for age, gender, nationality, marital status, and BMI, while Model II included all covariates. In addition, LFC was divided into quartiles, with the lowest quartile serving as a reference group to assess its association with lumbar BMD. The generalized additive model (GAM) of smooth curve fitting with the threshold saturation effect described the dose-response relationship between LFC and lumbar BMD, investigating any potential nonlinear associations. For the nonlinear condition in the model, the inflection point of the correlation between LFC and lumbar BMD was determined by objective calculation, and a two-stage linear regression model was established on both sides of the inflection point. Subgroup analysis further evaluated the association between LFC and lumbar BMD. Finally, multivariate linear regression models were employed to investigate the association between LFC and potential inflammatory markers. Causal mediation analysis was conducted to explore the intermediary role of inflammation cells in the relationship between LFC and lumbar BMD.

Result

Participant baseline characteristics

The study included 6996 participants from the Health Management Center of Henan Provincial People's Hospital, including 1853 women and 5143 men. For analysis, participants were divided into four groups based on LFC quartiles: Q1 ($0.2\% \le LFC < 6.9\%$, $n = 1725$), Q2 ($6.9\% \le LFC < 9.4\%$, $n = 1740$), Q3 ($9.4\% \le LFC < 12.8\%$, $n = 1750$), and Q4 ($12.8\% \le LFC \le 39.3\%$, $n = 1781$). Table 1 presents significant differences between the quartiles with respect to age, gender, BMI, TC, TG, LDL-C, HDL-C, Hb, TP, TB, AST, ALT, GGT, ALP, SUA, serum creatinine, hypertension, diabetes, white blood cell count, monocyte count, neutrophil count, lymphocyte count and lumbar BMD ($P < 0.05$). Notably, no significant differences were observed across LFC quartiles for nationality and marital status ($P > 0.05$).

Relationship between LFC and lumbar BMD

Supplementary Table 1 demonstrates that univariate analysis indicated a notable inverse relationship between LFC and lumbar BMD ($\beta = -0.17$, 95% CI: -0.32 to -0.02, $P < 0.05$). Multifactorial regression analysis model further

Table 1 Characteristics of the study population

Variables	Q1 (0.2–6.8)	Q2 (6.9–9.3)	Q3 (9.4–12.7)	Q4 (12.8–39.3)	*P*-value
Age (years)	52.02 ± 10.79	53.14 ± 11.11	53.55 ± 11.36	51.15 ± 11.57	<0.001
Gender [*n* (%)]					<0.001
Female	649 (37.62%)	483 (27.76%)	360 (20.57%)	361 (20.27%)	
Male	1076 (62.38%)	1257 (72.24%)	1390 (79.43%)	1420 (79.73%)	
Nationality [*n* (%)]					0.228
Non-Han nationality	25 (1.45%)	21 (1.21%)	16 (0.91%)	14 (0.79%)	
Han nationality	1700 (98.55%)	1719 (98.79%)	1734 (99.09%)	1767 (99.21%)	
Marital status [*n* (%)]					0.266
Not married	47 (2.72%)	44 (2.53%)	35 (2.00%)	54 (3.03%)	
Married	1678 (97.28%)	1696 (97.47%)	1715 (98.00%)	1727 (96.97%)	
BMI [kg/m^2, *n* (%)]					<0.001
<28	1499 (86.90%)	1420 (81.61%)	1259 (71.94%)	986 (55.36%)	
≥28	226 (13.10%)	320 (18.39%)	491 (28.06%)	795 (44.64%)	
TC (mmol/L)	4.98 ± 0.90	4.91 ± 0.96	4.82 ± 0.97	5.05 ± 0.97	<0.001
TG (mmol/L)	1.68 ± 0.98	1.81 ± 1.06	1.99 ± 1.27	2.60 ± 1.75	<0.001
LDL-C (mmol/L)	3.00 ± 0.75	2.96 ± 0.79	2.92 ± 0.79	3.06 ± 0.81	<0.001
HDL-C (mmol/L)	1.32 ± 0.27	1.28 ± 0.26	1.23 ± 0.24	1.17 ± 0.23	<0.001
Hb (g/L)	144.35 ± 14.54	145.99 ± 14.50	147.33 ± 13.45	149.90 ± 12.82	<0.001
TP (g/L)	71.11 ± 3.93	71.15 ± 3.94	71.34 ± 3.95	72.10 ± 3.79	<0.001
TB (g/L)	12.11 ± 5.23	12.42 ± 5.26	12.82 ± 5.27	12.70 ± 5.05	<0.001
AST (U/L)	20.82 ± 6.57	21.36 ± 6.77	22.16 ± 7.59	26.99 ± 11.80	<0.001
ALT (U/L)	21.23 ± 11.61	22.93 ± 11.90	25.18 ± 13.47	36.81 ± 21.82	<0.001
GGT (U/L)	29.70 ± 24.02	32.17 ± 25.81	35.69 ± 26.21	45.69 ± 32.05	<0.001
ALP (U/L)	68.99 ± 18.16	68.45 ± 17.33	69.89 ± 17.83	73.64 ± 19.49	<0.001
SUA (μmol/L)	329.91 ± 78.94	347.89 ± 80.63	359.54 ± 79.75	382.97 ± 84.23	<0.001
Serum creatinine (μmol/L)	66.66 ± 13.99	68.59 ± 14.07	69.43 ± 13.97	68.88 ± 13.65	<0.001
Hypertension [*n* (%)]					<0.001
No	526 (30.49%)	597 (34.31%)	661 (37.77%)	782 (43.91%)	
Yes	1199 (69.51%)	1143 (65.69%)	1089 (62.23%)	999 (56.09%)	
Diabetes [*n* (%)]					<0.001
No	141 (8.17%)	212 (12.18%)	325 (18.57%)	419 (23.53%)	
Yes	1584 (91.83%)	1528 (87.82%)	1425 (81.43%)	1362 (76.47%)	
Leukocytes (1000 cells/μL)	5.73 ± 1.31	5.96 ± 1.38	6.16 ± 1.36	6.33 ± 1.41	<0.001
Monocytes (1000 cells/μL)	0.36 ± 0.12	0.38 ± 0.13	0.40 ± 0.13	0.41 ± 0.13	<0.001
Neutrophils (1000 cells/μL)	3.28 ± 0.97	3.42 ± 1.01	3.59 ± 1.00	3.67 ± 1.02	<0.001
Lymphocytes (1000 cells/uL)	1.91 ± 0.53	1.97 ± 0.57	1.99 ± 0.57	2.06 ± 0.57	<0.001
BMD (mg/cm^3)	127.83 ± 35.52	124.61 ± 34.64	121.86 ± 34.17	122.84 ± 32.65	<0.001

BMI body mass index, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Hb* hemoglobin, *TP* total protein, *TB* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* glutamyl transpeptidase, *ALP* alkaline phosphatase, *SUA* serum uric acid

verified the independent association between LFC and lumbar BMD. As shown in Table 2, both Model I ($\beta = -0.339$, 95% CI: −0.468 to −0.211, $P < 0.001$) and Model II ($\beta = -0.323$, 95% CI: −0.464 to −0.183, $P < 0.001$) indicated that persistent increases in LFC were independently associated with decreases in lumbar BMD, even after adjusting for confounding variables. For the classification of continuous LFC levels, quartiles were used. Among the three models, individuals in the highest quartile (Q4) exhibited a more significant negative impact on lumbar BMD compared to those in the lowest quartile (Q1). In Q4, a 1% increase in LFC was associated with a 5.026 g/cm² reduction in lumbar BMD. Specifically, the estimates for the unadjusted model were: $\beta = -4.989$, 95% CI: −7.257 to −2.722, $P < 0.001$, and $P_{\text{for trend}} < 0.001$. For Model I: $\beta = -5.506$, 95% CI: −7.418 to −3.595, $P < 0.001$, and P

Table 2 Relationship between LFC and lumbar BMD

	Crude model		Model I		Model II	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
LFC	−0.170 (−0.320, −0.020)	0.026	−0.339 (−0.468, −0.211)	<0.001	−0.323 (−0.464, −0.183)	<0.001
Q1	Reference		Reference		Reference	
Q2	−3.221 (−5.502, −0.940)	0.006	−0.978 (−2.801, 0.846)	0.294	−1.281 (−3.068, 0.507)	0.160
Q3	−5.973 (−8.250, −3.695)	<0.001	−2.661 (−4.515, −0.808)	0.005	−2.810 (−4.646, −0.974)	0.003
Q4	−4.989 (−7.257, −2.722)	<0.001	−5.506 (−7.418, −3.595)	<0.001	−5.026 (−7.040, −3.012)	<0.001
P for trend		<0.001		<0.001		<0.001
Stratifed by ages						
<45	−0.536 (−0.762, −0.309)	<0.001	−0.445 (−0.679, −0.211)	<0.001	−0.383 (−0.664, −0.101)	0.008
≥45, <60	−0.404 (−0.581, −0.228)	<0.001	−0.350 (−0.532, −0.167)	<0.001	−0.354 (−0.557, −0.152)	<0.001
≥60	−0.061 (−0.349, 0.227)	0.680	−0.015 (−0.304, 0.274)	0.919	−0.359 (−0.669, −0.049)	0.534

Crude model: no covariates were adjusted

Model I: Age, gender, Nationality, Marital status and BMI were adjusted

Model II: Age, gender, Nationality, Marital status, BMI, TC, TG, LDL-C, HDL-C, Hb, TP, TB, AST, ALT, GGT, ALP, SUA, serum creatinine, hypertension and diabetes were adjusted

$_{\text{for trend}} < 0.001$. For Model II: $\beta = -5.026$, 95% CI: −7.040 to −3.012, $P < 0.001$, and $P_{\text{for trend}} < 0.001$. Furthermore, stratified analysis by age reveals that the negative correlation between LFC and lumbar spine BMD is more pronounced in the population aged < 45 years ($\beta = -0.383$, 95% CI: −0.664 to −0.101, $P < 0.05$). Figure 2 illustrates a significant nonlinear relationship between LFC and lumbar BMD after adjusting for all confounders. Through the threshold saturation effect, we identified an inflection point between LFC and lumbar BMD (K = 5.4). To the left of the inflection point, a positive association between LFC and lumbar BMD was observed ($\beta = 0.962$, 95% CI: 0.016 to 1.907, $P < 0.05$), while a significant negative association was evident to the right of the inflection point ($\beta = -0.405$, 95% CI: −0.558 to −0.253, $P < 0.001$) (Table 3).

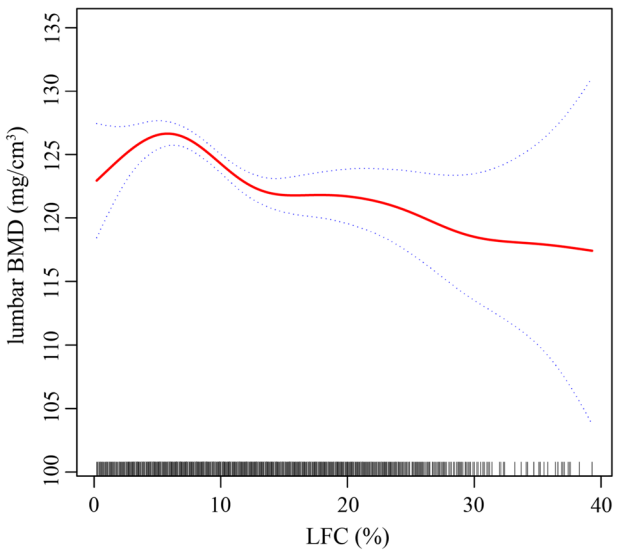

Fig. 2 Generalized additive model with fitting smoothness for the dose-response relationship between LFC and lumbar BMD

Subgroup analysis

Subgroup analysis demonstrated consistency, as shown in Fig. 3 and Supplementary Fig. 1. By age, gender, nationality, marital status, TC, TG, LDL-C, HDL-C, Hb, TP, TB, AST, ALT, GGT, ALT, SUA, serum creatinine, hypertension and diabetes, there was no significant interaction between LFC and lumbar BMD. The relationship between LFC and lumbar BMD was consistent among different subgroups ($P_{\text{for interaction}} > 0.05$).

Examination of the mediating effects of inflammatory cells

In this study, multiple linear regression models were used to investigate the relationship between inflammatory cells and LFC. As shown in Table 4, LFC and White blood cell count ($\beta = 0.227$, 95%CI: 0.147–0.307, $P < 0.001$), monocyte count ($\beta = 1.818$, 95%CI: 0.962–2.675, $P < 0.001$), neutrophil count ($\beta = 0.278$, 95% CI: 0.170–0.386, $P < 0.001$) and lymphocyte count ($\beta = 0.319$, 95% CI: 0.126–0.511, $P < 0.05$) showed a significant positive correlation. These findings suggest an association between inflammatory cells and LFC.

The study employed a mediation analysis to ascertain the role of inflammatory cells as a mediator in the association between LFC and lumbar BMD. Table 5 demonstrates that leukocytes and monocytes significantly mediate the relationship between LFC and lumbar BMD (P <0.001), with mediation rates of −5.78% and −6.68%, respectively.

Table 3 The result of the two-piecewise multivariate regression analysis

	Linear regression β (95%CI) *P*-value	Break point (K)	<K β (95%CI) *P*-value	> K β (95%CI) *P*-value	LLR test *P* value
LFC	−0.323 (−0.464, −0.183) <0.001	5.4	0.962 (0.016, 1.907) 0.046	−0.405 (−0.558, −0.253) <0.001	0.007

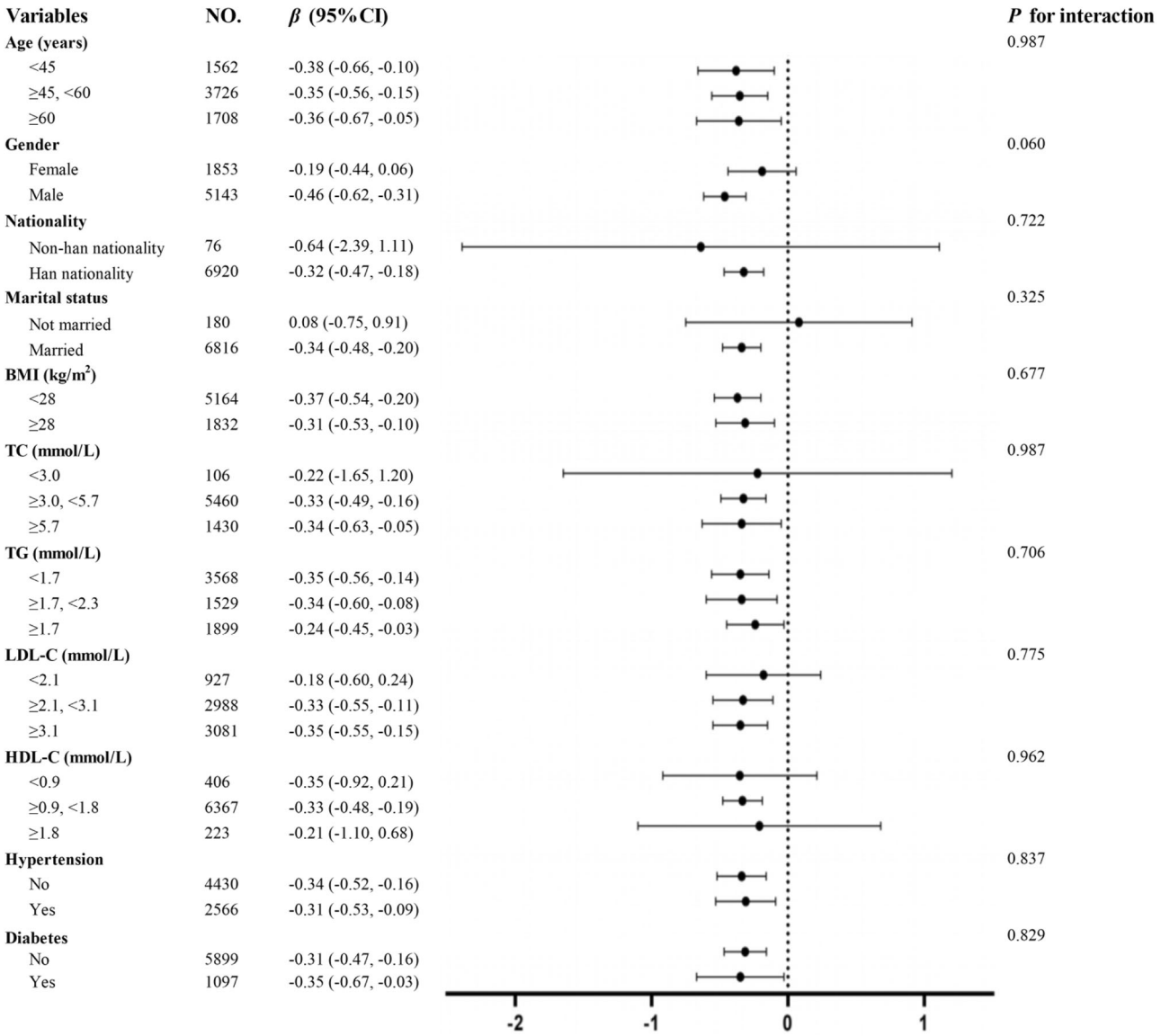

Fig. 3 The relationship between LFC and lumbar BMD according to different subgroups. BMI body mass index, TC total cholesterol, TG triglycerides, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol

Discussion

Low bone mass and osteoporosis often present without characteristic clinical manifestations in early stages. As the disease progresses, patients may develop low back or joint pain, potentially leading to spinal curvature or fractures in severe cases. With osteoporosis prevalence increasing globally, early and effective screening methods and interventions are crucial to slowing its progression and improving metabolic health outcomes. This study enrolled 6996 participants from the Health Management Center of Henan Provincial People's Hospital, utilizing computed tomography to quantify LFC and lumbar BMD. Following adjustment for potential confounders, a linear association between LFC and lumbar BMD was identified ($\beta = -0.323$, 95% CI: −0.464 to −0.183, $P < 0.001$). Quartile analysis

revealed a significant correlation (Q4 vs Q1: $\beta = -5.026$, 95% CI: −7.040 to −3.012, $P < 0.001$; $P_{\text{for trend}} < 0.001$), indicating a pronounced relationship. Notably, a nonlinear effect was observed, with an inflection point of 5.4 for LFC; positive associations were seen below this threshold, while above it, the negative impact on lumbar BMD intensified ($P < 0.05$). Additionally, the study found a positive correlation between LFC and inflammatory marker levels, with leukocytes and monocytes significantly mediating the LFC-lumbar BMD relationship ($P < 0.05$). These findings underscore liver fat's potential role as a risk factor for lumbar BMD and highlight inflammatory factors' mediating influence on BMD progression. Moreover, this study pioneers the use of QCT for direct LFC assessment in overweight and obese individuals, exploring its implications for lumbar BMD. QCT emerges as a practical, well-tolerated, highly effective, and cost-efficient method for assessing both LFC and lumbar BMD, suitable for large-scale population screening and comprehensive health assessments targeting fatty liver disease and osteoporosis risks.

There exist intricate connections between ectopic fat deposition, particularly the escalation in visceral and hepatic fat, and the reduction in BMD. Research indicates that visceral fat accumulation releases various pro-inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin-6 (IL-6), which impede osteoblast differentiation and function while promoting osteoclastogenesis, thereby increasing bone resorption and decreasing BMD [19]. Moreover, excess abdominal fat accumulation can alter mechanical loading on bones; initially, this may enhance BMD. However, the adverse effects of ectopic fat accumulation typically outweigh these benefits, leading to an overall decline in BMD [20]. Furthermore, hepatic fat accumulation correlates with insulin resistance and metabolic disorders, exacerbating bone loss. Given the liver's pivotal role in systemic metabolism, heightened LFC may elevate circulating free fatty acids and disrupt hormone secretion, both detrimental to bone health [21]. In conclusion, these mechanisms highlight the complex interaction between ectopic fat deposition and bone metabolism, thereby emphasizing the importance of targeted interventions to ameliorate its detrimental effects on BMD.

The interrelation between liver fat accumulation and BMD has been a focal point in recent literature. Prior investigations have consistently demonstrated a significant correlation between fatty liver disease and decreased BMD. Notably, heightened levels of LFC have been identified as a potential risk factor for osteoporosis. In a study involving middle-aged and older men as well as postmenopausal women, Xia et al. discovered an inverse relationship between LFC and BMD, which persisted even after adjusting for other potential confounders [22]. Similarly, Labayen et al. observed a direct link between liver fat accumulation, increased bone marrow fat content, and reduced BMD among obese children, suggesting that liver fat may influence BMD through its impact on bone marrow fat accumulation [23]. Du et al. further supported these findings by noting significantly lower lumbar BMD in patients with NAFLD compared to those without, reinforcing the negative relationship between liver fat and BMD [24]. It is noteworthy that certain studies have highlighted the potential mediating role of obesity and BMI in the relationship between LFC and BMD. Higher BMI has been closely associated with increased LFC, which in turn correlates negatively with BMD. Specifically, obesity may influence bone metabolism by promoting hepatic fat accumulation, thereby contributing to decreased bone density. Both Li et al. and Labayen et al. have shown that BMI elevation significantly modifies the association between liver fat and BMD, suggesting obesity as a pivotal mediator in this pathway [23, 25]. Consistent with previous research,

Table 4 Multivariate linear regression of LFC with inflammatory cells

Inflammatory factors	*n*	*β*	95%CI	*P* value
Leukocytes (1000 cells/μL)	6996	0.227	(0.147–0.307)	<0.001*
Monocytes (1000 cells/μL)	6996	1.818	(0.962–2.675)	<0.001*
Neutrophils (1000 cells/μL)	6996	0.278	(0.170–0.386)	<0.001*
Lymphocytes (1000 cells/uL)	6996	0.319	(0.126–0.511)	0.001*

All covariates were adjusted in this model

CI confidence interval

*$P < 0.05$

Table 5 The mediating effects of inflammatory cells on the association between LFC and lumbar BMD

Inflammatory factors	Mediation effects *β* (95%CI)	Direct effects *β* (95%CI)	Mediated proportion (%)	*P* value
Leukocytes	0.110 (0.045, 0.187)	−2.018 (−2.845, −1.170)	−5.78%	<0.001*
Monocytes	0.128 (0.062, 0.209)	−2.035 (−2.873, −1.180)	−6.68%	<0.001*
Neutrophils	0.034 (−0.007, 0.083)	−1.942 (−2.763, −1.095)	−1.80%	0.102
Lymphocytes	−0.003 (−0.040, 0.031)	−1.904 (−2.732, −1.080)	0.16%	0.836

All covariates were adjusted in this model

CI confidence interval

*$P < 0.05$

the present study demonstrates a significant negative association between LFC and lumbar BMD among overweight and obese individuals. Consequently, future investigations should delve deeper into the specific mechanisms through which obesity and BMI mediate the association between liver fat and BMD, aiming to devise more effective clinical interventions.

The pathogenesis of osteoporosis involves multiple cellular processes. Extensive research indicates that inflammation plays a key role in the etiology of osteoporosis. Liu et al. [26] demonstrated that pro-inflammatory cytokines (e.g., IL-6 and TNF-α) secreted by inflammatory cells during bone remodeling affect bone cell function, leading to increased bone resorption and consequent BMD decline. Mazzaferro et al. [27] further noted that in chronic inflammation, the disruption of bone metabolism is closely associated with inflammatory cell infiltration, particularly notable in elderly patients, linking increased inflammatory cell presence with osteoporosis occurrence. Similarly, Goodnough et al. [28] provided evidence of inflammatory cells in bone marrow significantly influencing fracture healing, where excessive activation inhibits bone formation and leads to decreased BMD. These findings underscore the detrimental impact of inflammatory cells on BMD, necessitating strategies targeting inflammation-related bone loss. Besides direct effects on BMD, emerging evidence suggests inflammatory cells mediate the link between obesity and reduced BMD. Suzuki [29] emphasizes that in individuals with obesity, the expansion of adipose tissue results in the infiltration of inflammatory cells that secrete pro-inflammatory cytokines, promote bone resorption, and inhibit formation, thereby reducing BMD. Furthermore, Kuhn et al. [30], using an obese mouse model, linked inflammatory cell activation to osteoporosis, suggesting chronic low-grade inflammation from obesity as a key mechanism in BMD reduction. Additionally, obesity is frequently accompanied by hepatic steatosis and disturbances in liver-related metabolism. Notably, multiple studies have presented evidence of the association between inflammatory factors mediating hepatic fat accumulation and decreased bone mass [31, 32]. Consistent with the aforementioned research, this study further validates that inflammatory cells may contribute to the development of osteoporosis through various pathways influenced by disruptions in hepatic fat metabolism, as confirmed by the quantification of hepatic fat content.

The findings of this study indicate a significant inflection point between LFC and BMD, which explains the contradictory relationship observed in the existing literature between hepatic steatosis and low bone mass (including osteoporosis). Based on previous related research findings, individuals with a history of fatty liver disease typically exhibit higher body weight and BMI, which can increase skeletal loading and serve as a protective factor against bone density loss [33, 34]. Thus, the detrimental impact of hepatic steatosis on BMD might be counterbalanced by the beneficial effects of elevated BMI. Nevertheless, conflicting outcomes from various studies suggest an independent adverse correlation between fatty liver and BMD. From a mechanistic perspective, this may involve the development of hepatic steatosis-induced insulin resistance and obesity-mediated inflammation [35, 36]. This study corroborates these conflicting findings, demonstrating that lumbar BMD rises with mild hepatic steatosis but declines once LFC surpasses 5.4%. With the gradual progression of hepatic steatosis, lumbar spine bone density decreases, leading to an increased risk of low bone mass and osteoporosis. Previous clinical explorations of treatment in NAFLD suggest that factors contributing to low bone mass and osteoporosis risk in NAFLD include cell factors released by hepatic fat deposition that may affect the bone microenvironment, vitamin D deficiency, and limited physical activity [31, 37]. Interventions targeting obesity and fatty liver disease, vitamin D supplementation, and long-term exercise may be essential therapeutic approaches against both NAFLD and osteoporosis, two prevalent conditions. Therefore, the application of QCT technology for hepatic fat quantification is crucial for early clinical intervention and treatment of fatty liver disease and osteoporosis.

In comparison to previous studies, this study focused on overweight and obese individuals who underwent health screening. Its geographic homogeneity also enhanced the generalizability of its results. Furthermore, the consistent approach to these health screenings ensures the wider applicability of the findings. Additionally, this study quantified liver fat in relation to lumbar BMD and conducted subgroup analyses, consistently yielding reliable outcomes across different demographic subgroups, a feature not addressed in earlier research. Furthermore, the quantification of liver fat and lumbar BMD in this study was performed using existing low-dose chest CT scan data, minimizing scanning time and radiation exposure, thereby facilitating large-scale population health screening. Despite efforts to control for potential confounding factors inherent in cross-sectional studies, certain limitations must be acknowledged. First, covariates such as dietary habits, smoking and alcohol use history, and physical activity were not fully accounted for, although participants with alcoholic fatty liver disease were excluded based on medical records. Second, due to the cross-sectional design, causal relationships between LFC and prediabetes cannot be determined. Lastly, the study was conducted at a single health examination center, potentially limiting the diversity of the sample, warranting future multicenter studies to further explore and elucidate the relationship between LFC and lumbar BMD.

Conclusion

In summary, this study revealed a non-linear association between LFC and lumbar BMD in overweight and obese individuals who underwent physical examination. Notably, there was a significant association between elevated LFC (above 5.4%) and reduced BMD in the lumbar spine. In addition, inflammation has been identified as a potential mechanism mediating the relationship between LFC and lumbar BMD. Therefore, future research should focus on identifying mechanisms and interventions for hepatic steatosis to reduce the risk of developing osteoporosis and improve metabolic health outcomes for affected individuals.

Data availability

The relevant data are available from the corresponding author upon reasonable request.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s12020-025-04168-0.

Acknowledgements This study was supported by the National Natural Science Foundation of China (82071884); Central Plains Science and Technology Innovation Leading Talents (244200510016); the National Key R&D Program of China (2022YFC2010000, 2022YFC2010001); Henan Provincial Medical Science and Technology Program Funding (SBGJ202302011); and the Henan Provincial Science and Technology Research Program (242102311121, 242102311018, 242102310299). At the meantime, we would also like to express our appreciation for the language editing services (https://m.essaystar.com/service.html) provided by the American journal experts.

Author contributions A.L. and Y.L. contributed to the central idea. Y.S., X.Q. and Y.Z. analyzed most of the data. A.L. drafted the initial version of the manuscript. J.Z. assisted in revising the manuscript. Z.L., X.W., and Z.Z. contributed to data collection. X.L. and H.L. contributed to refining opinions, conducting supplementary analysis, and finalizing the paper. All authors reviewed and approved the final manuscript.

Funding This study was supported by the National Natural Science Foundation of China (82071884); Central Plains Science and Technology Innovation Leading Talents (244200510016); the National Key R&D Program of China (2022YFC2010000, 2022YFC2010001); Henan Provincial Medical Science and Technology Program Funding (SBGJ202302011); and the Henan Provincial Science and Technology Research Program (242102311121, 242102311018, 242102310299).

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval The study protocol adhered to the Declaration of Helsinki and received approval from the Ethics Committee of Henan Provincial People's Hospital (Approval No. 115, 2022). Informed consent was obtained from all participants.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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