

# Association Between Bone Mineral Density and Lipid Profile in Chinese Women

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**Purpose:** Atherosclerotic cardiovascular disease may share the risk factors for low bone mineral density (BMD), one of which is dyslipidemia. The association between serum cholesterol and BMD remains controversial. Thus, the correlation between serum lipids and BMD in women was explored in the current study.

**Materials and Methods:** This cross-sectional study included 1116 Chinese female participants. Serum samples were collected to evaluate total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and other laboratory markers. Dual-energy X-ray absorptiometry was used to assess lumbar spine, femoral neck, and total hip BMD.

**Results:** In the postmenopausal women, a non-linear relationship was detected between TC, LDL-C, HDL-C, and lumbar spine BMD. Using segmented linear regression, the inflection points were 5.86 mmol/L, 3.52 mmol/L, and 2.37 mmol/L, respectively. To the left of the inflection point, the higher the serum lipid level, the lower the value for lumbar spine BMD. To the right of the inflection point, the higher the serum level of TC and LDL-C, the higher the value for lumbar spine BMD. In the premenopausal women, the association between HDL-C and femoral neck BMD was non-linear. In addition, LDL-C had a positive association with BMD of the femoral neck and HDL-C had an inverse association with BMD of the femoral neck in postmenopausal women.

**Conclusion:** In postmenopausal women, the relationship between TC, LDL-C, HDL-C, and lumbar spine BMD was non-linear. TC, LDL-C, and HDL-C were negatively associated with lumbar spine BMD when the values were less than 5.86 mmol/L, 3.52 mmol/L, and 2.37 mmol/L, respectively. The mechanisms of the association were unclear, and further research is warranted to clarify the relationship.

**Keywords:** serum lipids, bone mineral density, postmenopausal women, premenopausal women, cholesterol

## Introduction

Osteoporosis (OP), which leads to consequent fractures, has become a significant public health concern.<sup>1</sup> OP affects more than 200 million people globally, with approximately nine million osteoporotic fractures occurring annually of which 1.6 million affect the hip joint.<sup>2</sup> It is primarily caused by suboptimal bone mineral density (BMD). Risk factors for OP include aging, being female, reduced physical activity, low calcium intake, and hypothyroidism.<sup>3,4</sup>

OP and cardiovascular diseases lead to increased morbidity and fatalities in women. Patients with aortic calcification are at increased risk of hip and vertebral fractures.<sup>5</sup> OP patients were demonstrated to be at increased risk of atherosclerotic cardiovascular

events, compared to osteopenia patients, after adjusting for cardiovascular risk factors, age, and cardiovascular mortality.<sup>6</sup> Epidemiological studies have shown that the two diseases are closely related,<sup>7–9</sup> suggesting that there could be a possible link between OP and cardiovascular diseases.

Dyslipidemia is the leading risk factor of cardiovascular diseases and could be responsible for the association between the two disorders.<sup>10</sup> Mice studies found that low-density lipoprotein cholesterol (LDL-C) oxidation products suppressed bone formation by inhibiting osteoblast differentiation. LDL oxidation products also facilitated bone marrow stromal cell differentiation into adipocytes rather than osteoblasts.<sup>11</sup> In addition, dyslipidemia has been shown to weaken the synthesis and metabolism of parathyroid hormone in bone.<sup>12</sup>

Dyslipidemia is linked to abnormal bone mass.<sup>13–15</sup> However, there are considerable inconsistencies in the findings with regard to the way in which dyslipidemia affects bone mass. Cui et al reported a negative correlation between serum total cholesterol (TC), LDL-C levels, and BMD in premenopausal and postmenopausal women in South Korea.<sup>16</sup> Elsewhere, high-density lipoprotein cholesterol (HDL-C) levels were inversely associated with BMD in premenopausal women.<sup>17</sup> A population-based study in Spain showed that women taking lipophilic statins had higher bone density in the femoral neck.<sup>18</sup> Sivas et al demonstrated that TG was not related to BMD in Turkish postmenopausal women.<sup>19</sup> In other research, postmenopausal women with OP were demonstrated to have lower levels of TC and LDL-C and higher levels of HDL than postmenopausal women with normal BMD.<sup>20</sup>

The relationship between BMD and lipid levels remains unclear. A few large-scale community-based studies have indicated a potential link between BMD and lipids in different subgroups. Therefore, the objective of the current study was to evaluate the relationship between serum TC and other lipid indicators and BMD in pre- and postmenopausal women.

## Materials and Methods

### Study Population

A cross-sectional study was conducted in four cities in the east, north, south, and southernmost areas in Sichuan Province: Chengdu, Guangyuan, Luzhou, and Xichang from December 2012 to March 2013. Cluster random sampling was applied to urban and rural communities in each target city. From each city, permanent female residents aged approximately 30 years were randomly selected from two urban

communities and 1–2 rural communities for inclusion in the study.

After thorough screening, of 1511 potential participants, 1116 women were included in the final analysis. Exclusion criteria were women who (1) had been living in the city for less than 10 years ( $n = 137$ ), (2) were severely limited in their daily activities and function ( $n = 29$ ), (3) were cognitively impaired ( $n = 5$ ), (4) did not undergo a BMD test ( $n = 163$ ), and (5) did not undergo a lipoprotein test ( $n = 61$ ) (Figure 1).

The study participants provided written informed consent to participate in the research, which was conducted as per the Helsinki declaration after ethical permission was acquired from the Ethics Review Board of West China Hospital of Sichuan University.

### Research Methods

The researchers received standardized training prior to the study to ensure its objectivity and the accuracy of the data. Standardized questionnaires were used to collect the participants' basic data. The patients' medical history, which included liver disease, diabetes mellitus, chronic diarrhea, chronic obstructive pulmonary disease, hypertension, and kidney disease, and lifestyle factors (dietary calcium intake, outdoor exercise, smoking, and alcohol consumption) were also obtained. On completion of the questionnaire survey, the data were summarized, checked, reviewed and proofread. Database maintenance was also performed.

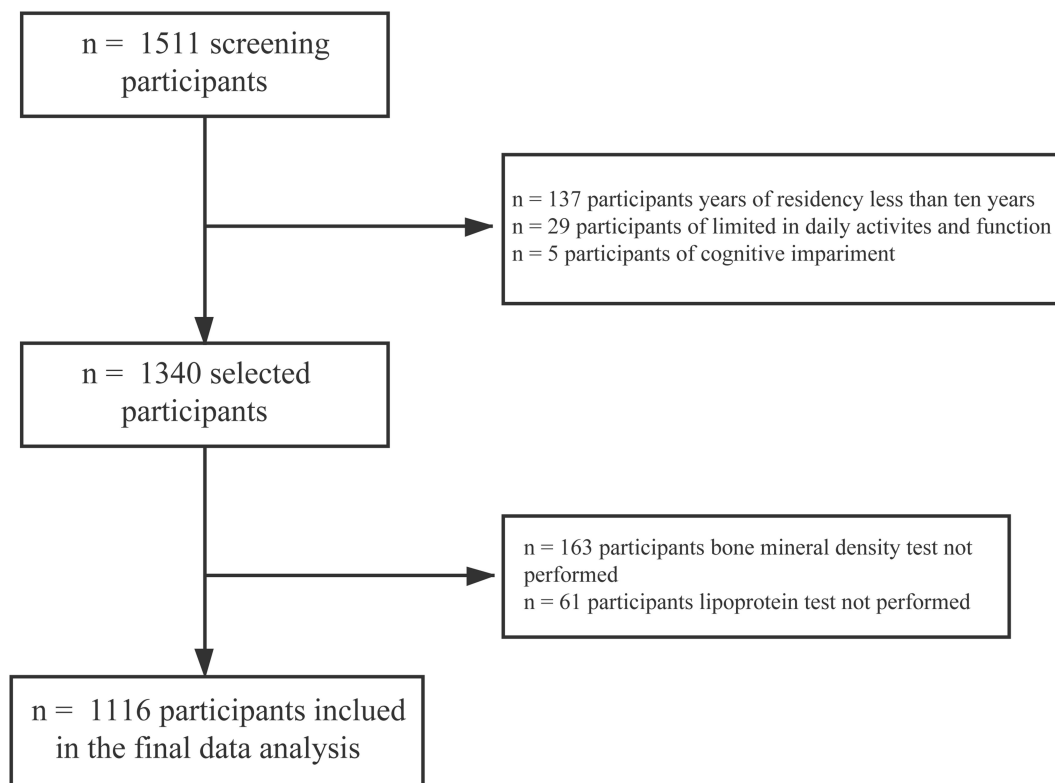
The height and weight of the enrolled subjects were measured in the morning on an empty stomach while wearing light clothing and without shoes. Their measurements were obtained twice and then averaged to reduce errors. Body mass index (BMI) was computed as weight divided by height<sup>2</sup> ( $\text{kg}/\text{m}^2$ ).

### Laboratory Measurements

Fasting serum samples were obtained to evaluate TC, LDL-C, and HDL-C, and other laboratory markers, such as alanine aminotransferase (ALT), fasting plasma glucose (FBG), and aspartate aminotransferase (AST). Blood glucose and blood lipid were assessed using an Olympus<sup>®</sup> AU 5400 Automatic Biochemistry Analyser (Olympus Corporation, Japan). The remaining indicators were assessed using standard laboratory methods.

### BMD Measurement

The BMD assays were performed by experienced technicians using a GE<sup>®</sup> Lunar Prodigy Advance Bone



**Figure 1** Flow chart for selecting participants.

Densitometer (Lunar Corp, USA) that utilizes dual-energy X-ray absorptiometry (DXA). The DXA scans were obtained according to the standard scan and analysis protocol specifications of the manufacturer. Quality control was used to achieve stable results. The participants' femoral neck, lumbar spine (L1–L4), and total hip BMD ( $\text{g}/\text{cm}^2$ ) measurements were obtained.

## Statistical Analysis

The categorical variables are presented as percentages and frequencies, and the continuous variables are displayed as mean  $\pm$  standard deviation (SD). Univariate rectilinear regression was used to evaluate the association between LDL-C, TC, HDL-C and lumbar spine (L1–L4), femoral neck and total hip BMD. A non-adjusted model and a multivariate-adjusted model were utilized, and the results were reported using unadjusted, minimally adjusted, and fully adjusted analysis, according to the specifications of the STROBE statement.<sup>21</sup>

Variables in the crude model were not adjusted. However, age and BMI were controlled in the minimally adjusted model. In the fully adjusted model, age, BMI ( $\text{kg}/\text{m}^2$ ), FBG ( $\text{mmol}/\text{l}$ ), 25 (OH) D ( $\text{nmol}/\text{l}$ ), ALT (U/L), U/L, AST (U/L), calcium intake ( $\text{g}/\text{week}$ ), outdoor time (hours/day), walking time (hours/day), smoking,

drinking, hyperlipidemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus, hyperthyroidism, and chronic diarrhea were controlled.

The generalized additive model (GAM) was used to identify non-rectilinear relationships. If non-rectilinear correlations were identified, the threshold effects of TC, LDL-C, and HDL-C on lumbar spine (L1–L4), total hip, and femoral neck BMD were estimated using piecewise rectilinear regression smoothing. When the ratios of femoral neck, total hip, and lumbar spine BMD to TC, HDL-C, and LDL-C were shown on the smoothed curve, the recursive method was used to automatically calculate the inflection points; the maximum likelihood was used. The *p*-values were two-sided, and a *p*-value less than 0.050 denoted statistical significance. The analysis was conducted using R<sup>®</sup> Statistical Software (The R Foundation) and the Empower Stats (X&Y Solutions Inc., Boston, MA, USA).

## Results

### Basic Characteristics

The baseline features of the subjects are summarized in Table 1. One thousand one hundred and sixteen women were

**Table 1** Baseline Characteristics of Participants

	Total Patients (n = 1116)	Premenopausal (n = 360)	Postmenopausal (n = 756)	P value
Age (years)	58.2 ± 13.9	43.9 ± 8.3	64.9 ± 10.4	<0.001
BMI (kg/m <sup>2</sup> )	24.0 ± 3.4	23.5 ± 3.4	24.2 ± 3.5	0.002
Outdoor time (h/day)	2.0 (1.0–3.5)	2.000 (1.000–4.000)	2.000 (1.000–3.500)	0.048
Walking time (h/day)	2.0 (1.0–3.0)	2.000 (1.000–3.000)	2.000 (1.000–3.000)	0.709
Calcium intake, g/week	2325.7 (1622.0–3527.7)	2140.9 (1546.0–3250.8)	2420.4 (1664.9–3653.7)	0.004
Age at menopause (years)	–	–	48.3 ± 3.8	
Smoking				0.438
Never	1099 (98.5%)	356 (98.9%)	743 (98.3%)	
Current or ever	17 (1.5%)	4 (1.1%)	13 (1.7%)	
Drinking				0.004
Never	1062 (95.2%)	333 (92.5%)	729 (96.4%)	
Current or ever	54 (4.8%)	27 (7.5%)	27 (3.6%)	
Kidney disease				0.697
No	1085 (97.222%)	351 (97.5%)	734 (97.1%)	
Yes	31 (2.778%)	9 (2.5%)	22 (2.9%)	
Chronic obstructive pulmonary disease (COPD)				<0.001
No	1042 (93.4%)	351 (97.5%)	691 (91.4%)	
Yes	74 (6.6%)	9 (2.5%)	65 (8.6%)	
Diabetes				<0.001
No	1008 (90.3%)	352 (97.8%)	656 (86.8%)	
Yes	108 (9.7%)	8 (2.2%)	100 (13.2%)	
Hyperthyroidism				0.781
No	1102 (98.7%)	355 (98.6%)	747 (98.8%)	
Yes	14 (1.3%)	5 (1.4%)	9 (1.2%)	
Chronic diarrhea				0.978
No	1091 (97.8%)	352 (97.8%)	739 (97.8%)	
Yes	25 (2.2%)	8 (2.2%)	17 (2.2%)	
Hyperlipemia				<0.001
No	988 (88.6%)	346 (96.4%)	642 (84.9%)	
Yes	127 (11.4%)	13 (3.6%)	114 (15.1%)	
BMD Total lumbar (g/cm <sup>2</sup> )	0.937 ± 0.174	1.08 ± 0.138	0.869 ± 0.146	<0.001
BMD Femur neck (g/cm <sup>2</sup> )	0.805 ± 0.184	0.908 ± 0.162	0.756 ± 0.174	<0.001
BMD Total Hip (g/cm <sup>2</sup> )	0.855 ± 0.166	0.93 ± 0.185	0.82 ± 0.145	<0.001
TC, mmol/l	5.3 ± 1.1	4.9 ± 1.1	5.5 ± 1.1	<0.001
LDL-C, mmol/l	2.9 ± 0.8	2.7 ± 0.8	3.1 ± 0.8	<0.001

(Continued)

**Table 1** (Continued).

	Total Patients (n = 1116)	Premenopausal (n = 360)	Postmenopausal (n = 756)	P value
HDL-C, mmol/l	1.7 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	<0.001
FBG, mmol/l	5.8 ± 2.2	5.4 ± 1.3	6.0 ± 2.5	<0.001
25(OH)D, nmol/l	44.5 ± 19.0	43.4 ± 18.1	45.0 ± 19.4	0.179
AST, U/L	25.3 (21.0–30.3)	24.0 (20.0–28.2)	26.0 (22.0–31.0)	<0.001
ALT, U/L	20.4 (16.0–28.0)	19.1 (15.0–27.0)	21.0 (16.0–28.2)	0.053

enrolled (mean age of 58.2 ± 13.9 years), with a BMI of 24.0 ± 3.4 kg/m<sup>2</sup>. Of these, 360 were premenopausal, and 756 were postmenopausal (premenopausal: postmenopausal = 1.0:2.1). The mean levels of serum TC, LDL-C, and HDL-C were 5.3 ±

1.1, 2.9 ± 0.8, and 1.7 ± 0.4 mmol/L, respectively. The mean lumbar spine (L1–L4), femoral neck, and total hip BMD was 0.937 ± 0.174, 0.805 ± 0.184, and 0.855 ± 0.166 g/cm<sup>2</sup>, respectively.

**Table 2** Multivariate Regression for Effect of TC, LDL-C, and HDL-C on Lumbar BMD in Postmenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
TC, mmol/l	-0.006 (-0.018, 0.006)	0.31121	-0.004 (-0.015, 0.007)	0.47136	-0.003 (-0.014, 0.008)	0.59432
TC (quartile)						
Q1	Ref		Ref		Ref	
Q2	-0.009 (-0.043, 0.026)	0.6238	-0.008 (-0.041, 0.024)	0.61999	-0.002 (-0.036, 0.031)	0.8829
Q3	-0.044 (-0.078, -0.011)	0.00995	-0.040 (-0.072, -0.008)	0.0134	-0.040 (-0.073, -0.008)	0.01454
Q4	-0.011 (-0.045, 0.023)	0.51295	-0.010 (-0.042, 0.023)	0.5552	-0.008 (-0.041, 0.025)	0.63312
P for trend	0.23902		0.28444		0.3348	
LDL-C, mmol/l	0.004 (-0.012, 0.020) 0.63116		-0.002 (-0.017, 0.013)	0.8322	-0.000 (-0.015, 0.015)	0.97906
LDL-C (quartile)						
Q1	Ref		Ref		Ref	
Q2	-0.011 (-0.045, 0.024)	0.54488	-0.019 (-0.052, 0.014)	0.25845	-0.019 (-0.052, 0.014)	0.26571
Q3	-0.019 (-0.052, 0.014)	0.26184	-0.035 (-0.067, -0.004)	0.02951	-0.032 (-0.064, -0.001)	0.04686
Q4	0.001 (-0.033, 0.035)	0.95179	-0.014 (-0.046, 0.019)	0.40944	-0.011 (-0.044, 0.021)	0.49887
P for trend	0.99904		0.3373		0.4537	
HDL-C, mmol/l	-0.056 (-0.084, -0.028) 0.00009		-0.031 (-0.059, -0.003)	0.02951	-0.033 (-0.061, -0.004)	0.02387
HDL-C (quartile)						
Q1	Ref		Ref		Ref	
Q2	-0.016 (-0.050, 0.017)	0.33577	-0.012 (-0.045, 0.020)	0.45378	-0.011 (-0.043, 0.021)	0.50464
Q3	-0.023 (-0.057, 0.010)	0.17403	-0.013 (-0.046, 0.019)	0.42993	-0.012 (-0.045, 0.021)	0.47561
Q4	-0.057 (-0.089, -0.025)	0.00046	-0.031 (-0.063, 0.000)	0.05077	-0.033 (-0.065, -0.001)	0.04141
P for trend	0.00031		0.04836		0.04347	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea. CI, confidence interval; Ref, reference.

**Table 3** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on Lumbar Spine BMD in Premenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
<b>TC, mmol/l</b>	-0.012 (-0.027, 0.004)	0.13301	-0.007 (-0.021, 0.007)	0.34509	-0.006 (-0.021, 0.008)	0.39137
<b>TC (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	-0.012 (-0.052, 0.027)	0.53523	-0.022 (-0.056, 0.013)	0.21969	-0.020 (-0.056, 0.015)	0.26229
Q3	0.008 (-0.034, 0.050)	0.7106	0.023 (-0.014, 0.061)	0.22072	0.018 (-0.020, 0.057)	0.35113
Q4	-0.043 (-0.088, 0.002)	0.06327	-0.025 (-0.066, 0.016)	0.22777	-0.024 (-0.065, 0.018)	0.26182
<b>P for trend</b>	0.19723		0.61577		0.63612	
<b>LDL-C, mmol/l</b>	-0.017 (-0.038, 0.004)	0.11166	-0.016 (-0.035, 0.003)	0.10843	-0.015 (-0.034, 0.005)	0.13521
<b>LDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.006 (-0.032, 0.045)	0.74357	-0.012 (-0.047, 0.022)	0.4852	-0.012 (-0.047, 0.023)	0.50624
Q3	-0.011 (-0.053, 0.031)	0.61911	-0.008 (-0.045, 0.030)	0.69855	-0.008 (-0.047, 0.030)	0.67465
Q4	-0.041 (-0.085, 0.003)	0.07132	-0.037 (-0.077, 0.004)	0.08139	-0.033 (-0.074, 0.008)	0.11109
<b>P for trend</b>	0.08862		0.12741		0.15223	
<b>HDL-C, mmol/l</b>	-0.016 (-0.058, 0.026)	0.44464	0.004 (-0.035, 0.043)	0.83793	0.002 (-0.038, 0.042)	0.91381
<b>HDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	-0.017 (-0.059, 0.026)	0.44213	-0.006 (-0.044, 0.032)	0.75195	-0.004 (-0.042, 0.035)	0.85452
Q3	-0.006 (-0.046, 0.034)	0.77564	-0.000 (-0.036, 0.036)	0.98853	0.004 (-0.033, 0.040)	0.84452
Q4	-0.022 (-0.067, 0.024)	0.34715	-0.002 (-0.043, 0.040)	0.93498	-0.002 (-0.044, 0.040)	0.93073
<b>P for trend</b>	0.46474		0.9971		0.9536	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

## Correlation Between Serum HDL-C, TC, LDL-C and Lumbar Spine BMD (L1–L4)

The relationship between serum levels of HDL-C, TC, LDL-C and BMD at the lumbar spine (L1–L4), femoral neck, and total hip in postmenopausal and premenopausal women was assessed using univariate rectilinear regression. In postmenopausal women, an association was not found between either TC or LDL-C and lumbar spine BMD (L1–L4) in the crude model ( $\beta = -0.006$ , 95% confidence interval [CI]:  $-0.018$  to  $0.006$ ,  $p = 0.311$ ;  $\beta = 0.004$ , 95% CI:  $-0.012$  to  $0.02$ ,  $p = 0.631$ , respectively). Similarly, a correlation between TC and lumbar spine BMD [L1–L4] was not shown in either the minimally adjusted model (controlled for age and BMI) or the fully adjusted model ( $\beta = -0.004$ , 95% CI:  $-0.015$  to  $0.007$ ,  $p = 0.471$ ;  $\beta = -0.003$ , 95% CI:  $-0.014$  to  $0.008$ ,  $p = 0.594$ , respectively).

An association was also not established between LDL-C and lumbar spine BMD [L1–L4] in either the minimally adjusted model (controlled for age and BMI) or the fully adjusted model ( $\beta = -0.002$ , 95% CI:  $-0.017$  to  $0.013$ ,  $p = 0.832$ ;  $\beta = -0.000$ , 95% CI:  $-0.015$  to  $0.015$ ,  $p = 0.979$ , respectively). In addition, HDL-C was shown to negatively correlate with lumbar spine BMD (L1–L4) in the crude model ( $\beta = -0.056$ , 95% CI:  $-0.084$  to  $-0.028$ ,  $p = < 0.001$ ). A similar relationship was identified in the minimally adjusted and fully adjusted models ( $\beta = -0.031$ , 95% CI:  $-0.059$  to  $-0.003$ ,  $p = 0.03$ ;  $\beta = -0.033$ , 95% CI:  $-0.061$  to  $-0.004$ ,  $p = 0.024$ , respectively). TC, LDL-C, and HDL-C were treated as categorical variables (categorized into quartiles) in the sensitivity assessments. Similar trends were identified using this approach ( $p$ -values of 0.239, 0.284, and 0.335; 0.999,

**Table 4** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on Femur Neck BMD in Postmenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
<b>TC, mmol/l</b>	0.010 (-0.003, 0.023)	0.12125	0.011 (-0.001, 0.024)	0.07885	0.011 (-0.001, 0.024)	0.08357
<b>TC (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.041 (0.002, 0.080)	0.0422	0.045 (0.007, 0.083)	0.02153	0.049 (0.011, 0.087)	0.01227
Q3	0.033 (-0.006, 0.071)	0.09935	0.035 (-0.003, 0.072)	0.06976	0.039 (0.001, 0.076)	0.04314
Q4	0.045 (0.007, 0.084)	0.02136	0.047 (0.010, 0.084)	0.0141	0.047 (0.010, 0.085)	0.01329
<b>P for trend</b>	0.0631		0.0541		0.05938	
<b>LDL-C, mmol/l</b>	0.030 (0.012, 0.047)	0.00104	0.024 (0.007, 0.041)	0.00619	0.023 (0.006, 0.040)	0.00838
<b>LDL-C (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.031 (-0.008, 0.070)	0.11541	0.024 (-0.014, 0.062)	0.21553	0.020 (-0.018, 0.058)	0.3032
Q3	0.043 (0.005, 0.080)	0.02683	0.028 (-0.009, 0.065)	0.1351	0.026 (-0.011, 0.063)	0.1738
Q4	0.061 (0.023, 0.099)	0.0016	0.047 (0.010, 0.084)	0.01249	0.044 (0.007, 0.081)	0.01931
<b>P for trend</b>	0.00158		0.01483		0.01935	
<b>HDL-C, mmol/l</b>	-0.068 (-0.100, -0.037)	0.00002	-0.047 (-0.078, -0.015)	0.00386	-0.041 (-0.073, -0.009)	0.01257
<b>HDL-C (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	-0.002 (-0.038, 0.035)	0.92649	-0.000 (-0.036, 0.036)	0.99442	0.006 (-0.029, 0.042)	0.72717
Q3	-0.018 (-0.055, 0.019)	0.34158	-0.010 (-0.047, 0.026)	0.57426	-0.003 (-0.040, 0.033)	0.87126
Q4	-0.070 (-0.105, -0.035)	0.00009	-0.048 (-0.083, -0.013)	0.00698	-0.041 (-0.077, -0.005)	0.02434
<b>P for trend</b>	0.00003		0.00415		0.01436	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea. CI, confidence interval; Ref, reference.

0.337 and 0.454; 0.001, 0.048 and 0.043, respectively) (Table 2).

In premenopausal women, TC, LDL-C, and HDL-C were not shown to have a correlation with lumbar spine BMD (L1–L4) in all the models. These findings were supported using sensitivity analyses (Table 3).

### Correlation Between Serum TC, LDL-C, HDL-C Levels and Femoral Neck BMD

In postmenopausal women, there was no association between TC and femoral neck BMD in the crude model ( $\beta = 0.01$ , 95% CI: -0.003 to 0.023,  $p = 0.121$ ). LDL-C was positively associated with femoral neck BMD of ( $\beta = 0.03$ , 95% CI: 0.012 to 0.047,  $p = 0.001$ ). In contrast, HDL-C was negatively correlated with femoral neck BMD ( $\beta = -0.068$ , 95% CI: -0.1 to -0.037,  $p < 0.001$ ). In the minimally and fully adjusted models and after sensitivity analysis (Table 4),

the same relationships were established. In premenopausal women, TC, LDL-C, and HDL-C showed no correlation with femoral neck BMD in all the models. Similar trends were reported using sensitivity analysis (Table 5).

### Correlation Between Serum TC, LDL-C, HDL-C Levels and Total Hip BMD

In postmenopausal women, either TC or LDL-C showed no correlation with total hip BMD in all the models. Similar trends were reported using the sensitivity analysis. In the crude model, HDL-C was shown to have a negative association with total hip BMD ( $\beta = -0.044$ , 95% CI: -0.072 to -0.015,  $p = 0.003$ ). In the minimally and fully adjusted models, an association was not identified. Similar trends were observed using sensitivity analysis (Table 6). In premenopausal women, TC, LDL-C, and HDL-C showed no correlation with total hip BMD in all the

**Table 5** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on Femur Neck BMD in Premenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
<b>TC, mmol/l</b>	-0.009 (-0.027, 0.008)	0.30044	-0.002 (-0.019, 0.014)	0.78328	-0.002 (-0.018, 0.015)	0.84657
<b>TC (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.050 (0.007, 0.093)	0.02214	0.048 (0.009, 0.087)	0.01714	0.038 (-0.002, 0.078)	0.06266
Q3	0.012 (-0.034, 0.058)	0.61486	0.028 (-0.016, 0.071)	0.21376	0.027 (-0.018, 0.071)	0.23796
Q4	-0.041 (-0.092, 0.009)	0.10951	-0.022 (-0.070, 0.025)	0.35497	-0.016 (-0.063, 0.032)	0.52242
<b>P for trend</b>	0.24644		0.77539		0.91687	
<b>LDL-C, mmol/l</b>	-0.009 (-0.032, 0.015)	0.48305	-0.004 (-0.027, 0.018)	0.70946	-0.005 (-0.027, 0.018)	0.68306
<b>LDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.010 (-0.033, 0.054)	0.63435	-0.006 (-0.046, 0.034)	0.77209	-0.015 (-0.055, 0.026)	0.47553
Q3	0.000 (-0.046, 0.047)	0.98436	0.007 (-0.036, 0.051)	0.74103	0.000 (-0.044, 0.044)	0.99301
Q4	-0.041 (-0.092, 0.009)	0.11023	-0.031 (-0.080, 0.017)	0.20738	-0.027 (-0.075, 0.021)	0.26675
<b>P for trend</b>	0.19074		0.39877		0.40591	
<b>HDL-C, mmol/l</b>	-0.028 (-0.076, 0.019)	0.24415	-0.007 (-0.052, 0.038)	0.761	0.005 (-0.041, 0.051)	0.82518
<b>HDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.015 (-0.031, 0.062)	0.51079	0.024 (-0.019, 0.067)	0.27658	0.026 (-0.017, 0.069)	0.237
Q3	-0.006 (-0.050, 0.038)	0.78824	0.005 (-0.037, 0.046)	0.82301	0.015 (-0.027, 0.056)	0.48213
Q4	-0.038 (-0.089, 0.013)	0.14781	-0.018 (-0.067, 0.031)	0.47038	-0.009 (-0.058, 0.040)	0.72792
<b>P for trend</b>	0.15712		0.48112		0.84693	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

models. Similar trends were reported using sensitivity analysis (Table 7).

## Non-Rectilinear Relationship Analysis

The non-rectilinear relationship between continuous variables, TC, LDL-C, and HDL-C, was evaluated. Consequently, the association between TC, LDL-C, HDL-C and lumbar spine BMD (L1–L4) was found to be non-rectilinear in postmenopausal women (after adjusting for age, BMI, FBG [mmol/l], 25 [OH] D [nmol/l], ALT [U/L], AST [U/L], calcium intake (g/week), outdoor time (hours/day), walking time (hours/day), smoking, drinking, hyperlipidemia, CKD, diabetes mellitus, hyperthyroidism, COPD, and chronic diarrhea). The inflection points were established to be 5.86 mmol/L, 3.52 mmol/L, and 2.37 mmol/L, respectively, using piecewise rectilinear regression. To the left of the inflection

points, the  $\beta$  and 95% CI values were -0.029, -0.047 to -0.011; -0.022, -0.044 to -0.001; -0.046, -0.077 to -0.014, respectively. To the right of the inflection points in the relationship curve between either TC or LDL-C and lumbar spine BMD (L1–L4), the  $\beta$  and 95% CI values were 0.046, 0.016 to 0.076; 0.061, 0.013 to 0.109, respectively. However, an association was not found between HDL-C and lumbar spine BMD (L1–L4) to the right of the inflection point ( $\beta$  of 0.094, 95% CI: -0.025 to 0.213). Similarly, a non-rectilinear relationship was not identified between TC, LDL-C, HDL-C and femoral neck BMD, nor between TC, LDL-C, HDL-C and total hip BMD (Table 8 and Figure 2).

In premenopausal women, a non-rectilinear relationship was not established between either TC and LDL-C and lumbar spine (L1–L4), femoral neck and total hip BMD, nor between HDL-C and either lumbar spine



**Table 6** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on Total Hip BMD in Postmenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
<b>TC, mmol/l</b>	-0.001 (-0.012, 0.011)	0.93165	0.000 (-0.011, 0.011)	0.99993	-0.001 (-0.012, 0.011)	0.89663
<b>TC (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.017 (-0.017, 0.052)	0.32308	0.014 (-0.019, 0.047)	0.4126	0.009 (-0.024, 0.042)	0.59727
Q3	-0.003 (-0.037, 0.031)	0.84906	-0.004 (-0.037, 0.029)	0.79858	-0.005 (-0.038, 0.028)	0.76657
Q4	0.006 (-0.028, 0.040)	0.73376	0.004 (-0.029, 0.037)	0.82476	-0.003 (-0.035, 0.030)	0.88118
<b>P for trend</b>	0.86489		0.81617		0.61671	
<b>LDL-C, mmol/l</b>	0.005 (-0.011, 0.021)	0.51524	0.001 (-0.014, 0.017)	0.86301	0.000 (-0.015, 0.015)	0.97492
<b>LDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.003 (-0.032, 0.038)	0.87251	-0.010 (-0.043, 0.024)	0.58368	-0.014 (-0.048, 0.020)	0.4246
Q3	0.020 (-0.014, 0.054)	0.24238	0.004 (-0.029, 0.037)	0.80731	0.000 (-0.033, 0.034)	0.98198
Q4	0.008 (-0.026, 0.042)	0.6391	-0.006 (-0.039, 0.028)	0.74078	-0.010 (-0.043, 0.023)	0.54066
<b>P for trend</b>	0.46764		0.98147		0.7939	
<b>HDL-C, mmol/l</b>	-0.044 (-0.072, -0.015)	0.00262	-0.024 (-0.052, 0.004)	0.09856	-0.023 (-0.052, 0.005)	0.10896
<b>HDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	-0.041 (-0.074, -0.007)	0.01752	-0.032 (-0.065, 0.001)	0.05519	-0.030 (-0.062, 0.003)	0.07363
Q3	-0.041 (-0.074, -0.008)	0.01624	-0.026 (-0.059, 0.007)	0.12215	-0.026 (-0.059, 0.007)	0.12196
Q4	-0.056 (-0.087, -0.024)	0.00056	-0.034 (-0.066, -0.003)	0.03351	-0.035 (-0.066, -0.003)	0.03187
<b>P for trend</b>	0.00139		0.07073		0.05952	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

BMD (L1–L4) or total hip BMD. By contrast, the association between HDL-C and femoral neck BMD was non-rectilinear. The inflection point was 1.36 mmol/L. To the left of the inflection point, the  $\beta$  and 95% CI values were 0.205 and 0.058 to 0.351, respectively. To the right of the inflection point, an association linking HDL-C and femoral neck BMD was not established (Table 9 and Figure 3).

## Discussion

The current study objective was to evaluate the relationship between serum cholesterol profile and BMD in women. To the best of our knowledge, this is the first study to have established a link between serum cholesterol levels and BMD in apparently healthy women via a curvilinear relationship.

Interestingly, in the primary results, TC, LDL-C, and HDL-C were associated with lumbar spine BMD (L1–L4) in postmenopausal women (L1–L4) and this was reflected

in a non-rectilinear relationship. The different correlations of LDL-C, TC, and HDL-C with lumbar spine (BMD) (L1–L4) were reported on the two sides of the inflection points. LDL-C, TC, and HDL-C, assessed against the baseline values, were negatively associated with lumbar spine BMD (L1–L4) to the left of the inflection points. However, correlations to the right of the inflection points were positive, except HDL-C. In addition, the non-rectilinear models showed that TC, LDL-C, and HDL-C were not related to femoral neck and total hip BMD, even using sensitivity analysis. In premenopausal women, the association between HDL-C and femoral neck BMD was non-rectilinear, and the correlation to the left of the inflection point was positive.

However, previous studies have mostly focused on the linear relationship between serum lipids and BMD, and overall consensus has not been reached.<sup>22–25</sup> The results of a case-control study in which 452 postmenopausal women

**Table 7** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on Total Hip BMD in Premenopausal Women

Variables	Crude Model		Minimally Adjusted Model		Fully Adjusted Model	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
<b>TC, mmol/l</b>	0.013 (-0.009, 0.035)	0.24955	0.010 (-0.012, 0.032)	0.37078	0.005 (-0.017, 0.027)	0.63903
<b>TC (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.057 (0.003, 0.112)	0.03957	0.039 (-0.013, 0.090)	0.14703	0.028 (-0.026, 0.081)	0.3096
Q3	0.051 (-0.007, 0.109)	0.08405	0.052 (-0.004, 0.108)	0.06877	0.045 (-0.013, 0.103)	0.13171
Q4	0.017 (-0.047, 0.082)	0.60022	0.011 (-0.052, 0.074)	0.72654	0.002 (-0.062, 0.067)	0.94179
<b>P for trend</b>	0.25874		0.3031		0.49422	
<b>LDL-C, mmol/l</b>	0.008 (-0.021, 0.038)	0.58375	-0.001 (-0.030, 0.029)	0.96844	-0.003 (-0.033, 0.026)	0.82975
<b>LDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	0.057 (0.002, 0.111)	0.04211	0.035 (-0.017, 0.088)	0.18721	0.030 (-0.024, 0.083)	0.27481
Q3	0.052 (-0.006, 0.111)	0.0823	0.046 (-0.010, 0.103)	0.10831	0.032 (-0.025, 0.090)	0.27317
Q4	0.008 (-0.055, 0.072)	0.79249	-0.007 (-0.069, 0.055)	0.82618	-0.007 (-0.070, 0.056)	0.83041
<b>P for trend</b>	0.40574		0.65212		0.80914	
<b>HDL-C, mmol/l</b>	-0.032 (-0.090, 0.026)	0.28283	-0.002 (-0.060, 0.055)	0.93745	-0.002 (-0.061, 0.056)	0.93483
<b>HDL (quartile)</b>						
Q1	Ref		Ref		Ref	
Q2	-0.005 (-0.064, 0.055)	0.8786	0.012 (-0.045, 0.069)	0.68109	0.007 (-0.050, 0.064)	0.81428
Q3	-0.020 (-0.076, 0.037)	0.49717	-0.003 (-0.057, 0.052)	0.92356	0.010 (-0.046, 0.065)	0.73139
Q4	-0.007 (-0.070, 0.056)	0.83167	0.024 (-0.038, 0.086)	0.44444	0.026 (-0.037, 0.089)	0.42218
<b>P for trend</b>	0.66455		0.61964		0.44521	

**Notes:** Crude model: we did not adjust other covariates. Minimally adjusted model: we adjusted age and BMI. Fully adjusted model: we adjusted Age; BMI; FBG, mmol/l; 25 (OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

were assessed between January 2012 and January 2015 indicated that lumbar spine BMD was negatively correlated with LDL levels.<sup>26</sup> The findings of a cross-sectional study on 136 postmenopausal Caucasian women who were in good health also revealed that TC levels and hip BMD were positively correlated. Even after controlling for age, BMI, physical activity, energy, calcium, and alcohol intake, the finding remained significant.<sup>27</sup> In another cross-sectional study on 170 postmenopausal women aged 50 to 70 years in Iran, performed from March 2013 to September 2013, it was shown that serum lipid levels were independent of lumbar and femoral neck BMD after controlling for BMI.<sup>28</sup>

The results of numerous studies have demonstrated that the association between serum cholesterol levels and BMD was influenced by gender and ethnicity and whether or not menopause had occurred.<sup>29–32</sup> Hence, it was necessary to

establish the effect of serum cholesterol levels on BMD in premenopausal and postmenopausal Chinese women.

In the current study, it was established that high level of serum lipids to the left of the inflection point correlated with low lumbar spine BMD in postmenopausal women. Our findings in postmenopausal women are consistent with the data from a different cross-sectional study in which an inverse association was reported between lumbar spine BMD and HDL-C in women of broad-ranging ages.<sup>33</sup> The study involved two cohort subjects, a clinical group of women (n = 236) aged 35–81 years in an OP assessment group and a community cohort (n = 265 men, n = 481 women) aged 68–75 years participating in a population-based epidemiological survey. A marked inverse relationship between HDL-C and spinal BMD was reported in the clinical cohort group.

An epidemiological study in South Korea on 355 postmenopausal and 375 premenopausal women showed that

**Table 8** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on BMD in Postmenopausal Women

	Linear Regression	Break Point (K)	< K	> K	LLR Test
	$\beta$ (95% CI)		$\beta$ (95% CI)	$\beta$ (95% CI)	P
Total lumbar BMD, g/cm <sup>2</sup>					
TC, mmol/l	-0.004 (-0.015, 0.007)	5.86	-0.029 (-0.047, -0.011)	0.046 (0.016, 0.076)	<0.001
LDL-C, mmol/l	-0.001 (-0.016, 0.014)	3.52	-0.022 (-0.044, -0.001)	0.061 (0.013, 0.109)	0.009
HDL-C, mmol/l	-0.033 (-0.062, -0.005)	2.37	-0.046 (-0.077, -0.014)	0.094 (-0.025, 0.213)	0.036
Femur neck BMD, g/cm <sup>2</sup>					
TC, mmol/l	0.011 (-0.002, 0.023)	5.4	0.027 (0.001, 0.053)	-0.004 (-0.024, 0.016)	0.149
LDL-C, mmol/l	0.022 (0.005, 0.039)	4.24	0.022 (0.003, 0.041)	0.041 (-0.140, 0.221)	0.81
HDL-C, mmol/l	-0.041 (-0.073, -0.009)	2.34	-0.057 (-0.094, -0.020)	0.077 (-0.065, 0.220)	0.133
Total Hip BMD, g/cm <sup>2</sup>					
TC, mmol/l	-0.001 (-0.012, 0.010)	6.8	0.047 (-0.001, 0.094)	0.081 (-0.008, 0.171)	0.06
LDL-C, mmol/l	0.000 (-0.015, 0.015)	4.22	-0.003 (-0.020, 0.014)	0.075 (-0.094, 0.243)	0.366
HDL-C, mmol/l	-0.023 (-0.052, 0.005)	2.26	-0.041 (-0.075, -0.007)	0.098 (-0.031, 0.228)	0.063

**Notes:** Multivariate-Adjusted Model adjust for: Age; BMI; FBG, mmol/l; 25(OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

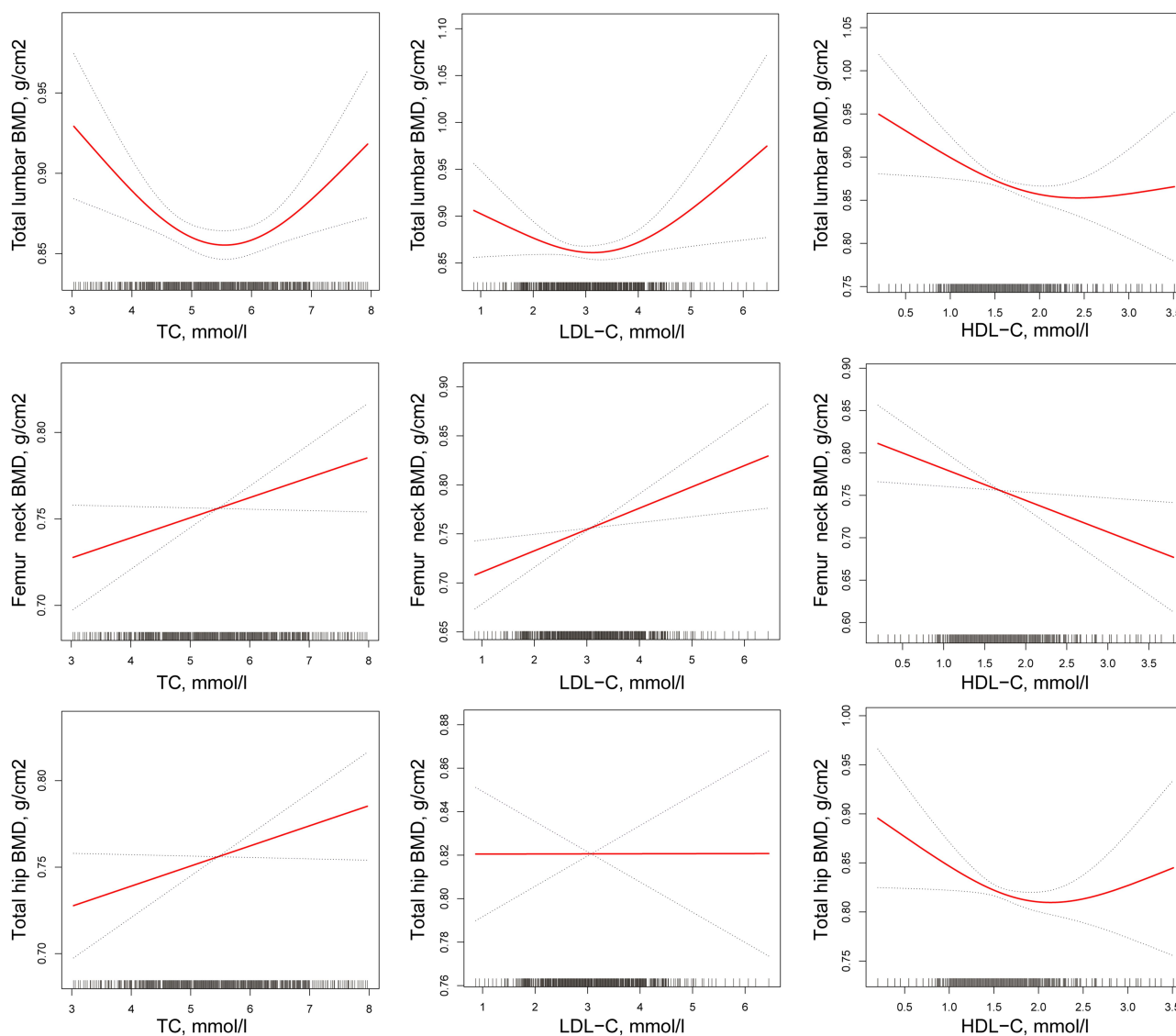
serum TC and LDL-C levels had a negative correlation with BMD.<sup>16</sup> There were many similarities between the study by Cui et al and the current study. Their study included 867 South Korean women and the current study recruited 1116 Chinese women. Compared with their study, the participants in the current study were drawn from different sources, represented different sectors of the population, and the number of participants was slightly greater.

In terms of differences between the studies, most importantly, they used a general linear model to evaluate the linear relationship between BMD and serum lipids, whereas GAM was used in the present research to determine the non-rectilinear relationship between them; this was perhaps the greatest difference between the two studies. The inflection point of the relationship between serum lipids and BMD was identified in the current study, which was considered to be of invaluable significance and may constitute the real relationship between the two. It is hoped that this will form the basis in future studies for an exploration of the non-linear relationship between serum lipids and BMD.

In the study by Cui et al, the levels of serum TC and LDL-C were inversely associated with BMD in both pre- and postmenopausal women. However, we established that the relationship between TC, LDL-C, HDL-C and lumbar spine BMD was non-linear in postmenopausal women, while in premenopausal women, the association between HDL-C and femoral neck BMD was non-linear.

Elsewhere, a weak negative association was found between BMD and TC in older women.<sup>34</sup> Although the association between TC and BMD was found to be inversely correlated in other studies, dissimilar to our results, the researchers failed to provide a possible explanation for their findings. To some extent, our results provide evidence of the lipid hypothesis for OP that suggests that LDL atherogenic lipid distribution and oxidation facilitate bone loss. The suppression of cholesterol biosynthesis has also been demonstrated to prevent osteogenic differentiation by inhibiting the mRNA expression of stromal bone marrow cells, which are precursors of osteoblasts, thereby improving BMD and fracture risk.<sup>35,36</sup>

Paraonase is a calcium-dependent esterase and confers HDL antioxidant properties by inhibiting the accumulation of lipid peroxidation products. A study on 100 healthy postmenopausal women found that the concentration of paraonase in the osteopenic group was significantly lower than that in the normal group.<sup>37</sup> The mechanisms for the negative relationship between serum HDL-C and BMD are unclear. A study on the differentiation of mesenchymal stem cells showed that hydroxysterol stimulated the osteogenic differentiation of bone marrow mesenchymal stem cells, while HDL-C removed oxysterol in the surrounding tissue, indicating that high HDL-C level is not conducive to osteogenic differentiation.<sup>38</sup> This may elucidate the negative correlation between serum HDL-C and BMD.



**Figure 2** Multivariate-adjusted smoothing spline plots of BMD by TC, HDL-C, and LDL-C in postmenopausal women. Red dotted lines represent the spline plots of TC, HDL-C, and LDL-C and blue dotted.

The current study demonstrated that the high levels of serum TC and LDL-C correlated with high lumbar spine BMD to the right of the inflection points. Jeong et al also observed a positive correlation between TC and BMD at different skeletal sites in women.<sup>39</sup> This suggests that common mechanisms connect lipids to bone metabolism. Research evidence shows that oxysterols regulate the specialization of mesenchymal stem cells, and this is beneficial to osteoblast differentiation. The researchers hypothesized that osteogenesis of the oxidized sterol was partly moderated by the activation of cyclo-oxygenase and phospholipase A2 in the arachidonic acid cascade and their metabolism to osteogenic prostaglandins and other eicosanoids.<sup>38</sup>

Subgroup analysis is fundamental in scientific research.<sup>40</sup> Unfortunately, most previous studies only used gender as a stratified factor for subgroup analysis, and only a few segregated premenopausal and postmenopausal women, which hindered our exploration of the relationship between serum lipids and BMD. In the present study, a completely different relationship was demonstrated between BMD and serum lipids in pre- and postmenopausal women. In postmenopausal women high LDL-C concentrations correlated with high femoral neck BMD; and high HDL-C concentrations reflected low femoral neck BMD. However, TC, LDL-C, and HDL-C showed no correlation with femoral neck BMD in premenopausal women.

**Table 9** Multivariate Regression for Effect of TC, HDL-C, and LDL-C on BMD in Premenopausal Women

	Linear Regression	Break Point (K)	< K	> K	LLR Test
	$\beta$ (95% CI)		$\beta$ (95% CI)	$\beta$ (95% CI)	P
Total lumbar BMD, g/cm <sup>2</sup>					
TC, mmol/l	-0.006 (-0.021, 0.008)	4.35	-0.047 (-0.097, 0.002)	0.005 (-0.014, 0.025)	0.073
LDL-C, mmol/l	-0.015 (-0.034, 0.005)	1.66	-0.237 (-0.492, 0.019)	-0.009 (-0.030, 0.012)	0.156
HDL-C, mmol/l	0.002 (-0.038, 0.042)	2.24	0.020 (-0.026, 0.066)	-0.177 (-0.408, 0.054)	0.085
Femur neck BMD, g/cm <sup>2</sup>					
TC, mmol/l	-0.002 (-0.018, 0.015)	5.57	0.008 (-0.018, 0.034)	-0.025 (-0.076, 0.025)	0.295
LDL-C, mmol/l	-0.005 (-0.027, 0.018)	3.37	0.004 (-0.026, 0.035)	-0.038 (-0.119, 0.043)	0.371
HDL-C, mmol/l	0.005 (-0.041, 0.051)	1.36	0.205 (0.058, 0.351)	-0.049 (-0.108, 0.010)	0.005
Total Hip BMD, g/cm <sup>2</sup>					
TC, mmol/l	0.005 (-0.017, 0.027)	5.93	0.014 (-0.014, 0.043)	-0.037 (-0.123, 0.050)	0.286
LDL-C, mmol/l	-0.003 (-0.033, 0.026)	1.81	-0.127 (-0.377, 0.122)	0.004 (-0.029, 0.037)	0.329
HDL-C, mmol/l	-0.002 (-0.061, 0.056)	1.53	0.026 (-0.108, 0.160)	-0.020 (-0.112, 0.073)	0.564

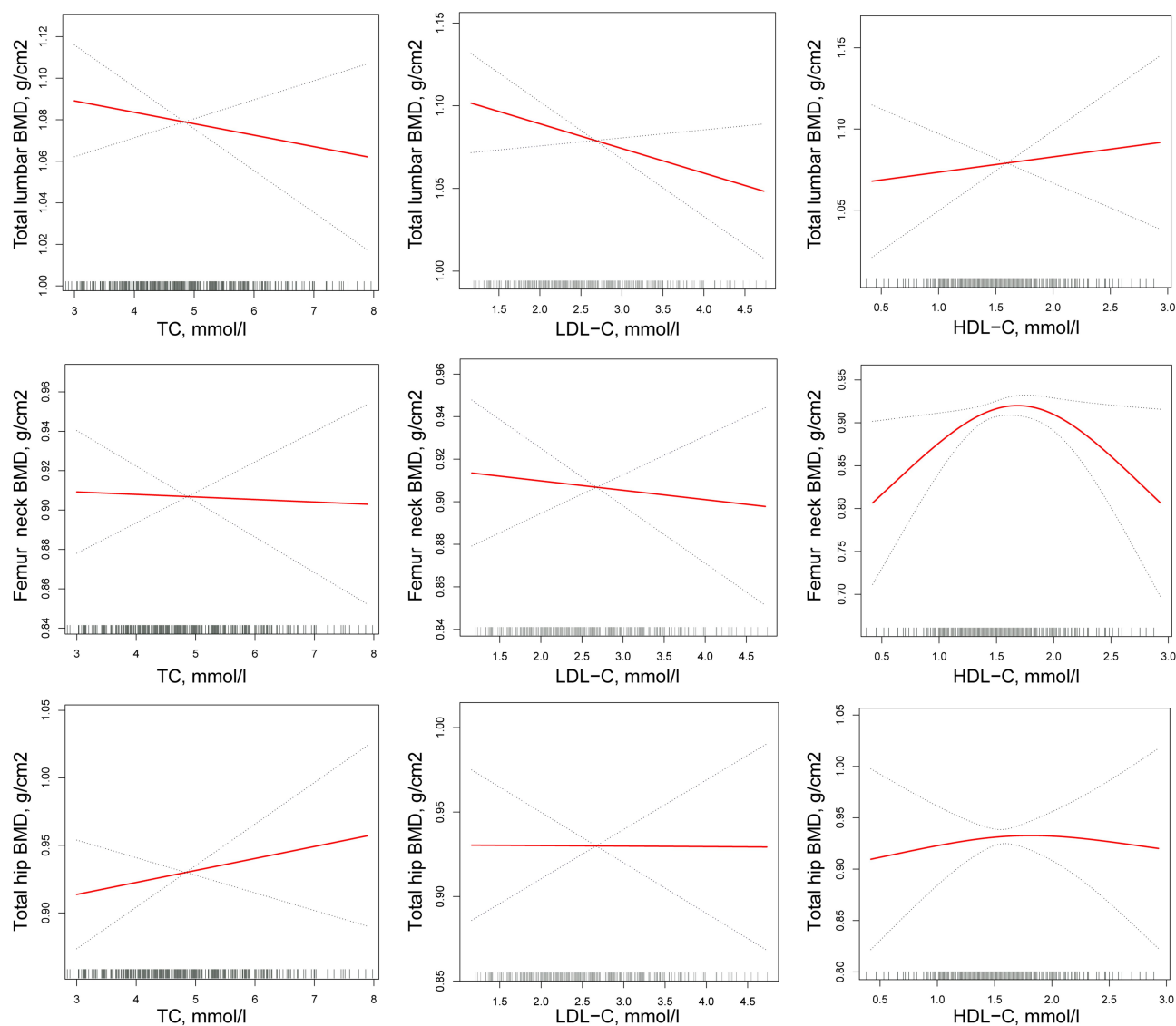
**Notes:** Multivariate-Adjusted Model adjust for: Age; BMI; FBG, mmol/l; 25(OH)D, nmol/l; ALT, U/L; AST, U/L; Calcium intake, g/week; Outdoor time, h/day; Walking time, h/day; Smoking; Drinking; Chronic Kidney disease (CKD); Chronic obstructive pulmonary disease (COPD); Diabetes; Hyperthyroidism; Hyperlipemia and Chronic diarrhea.

In the study by Cui et al,<sup>16</sup> serum TC levels were negatively associated with lumbar BMD in premenopausal women. In the study by Garg et al, a declining trend was demonstrated in relation to the relationship between femoral and lumbar spine BMD and LDL-C in premenopausal women.<sup>10</sup> These findings indicate that serum lipids have different effects on BMD at different bone sites in premenopausal women. However, it is difficult to elucidate the effects of serum lipids on BMD in premenopausal women in cross-sectional studies. In addition, there is a scarcity of literature on the impact of serum lipids on BMD in premenopausal women. The differences in the findings of the relationship between serum lipids and BMD between pre- and postmenopausal women may be explained by the following reasons. Firstly, estrogen concentrations in different subjects play an important role. In addition, it is difficult to measure the BMD of lumbar vertebrae in the elderly due to degenerative changes, such as hyperosteoegeny, which may cause changes in lumbar BMD unrelated to serum lipids in postmenopausal women. Therefore, it is necessary to evaluate the role of different bone sites and aging when evaluating the relationship between serum lipids and BMD.

Our research had many strengths. Firstly, a generalized rectilinear model was used to assess the rectilinear association between serum lipids and BMD; in addition, a GAM was utilized to assess the non-rectilinear relationship between the two. GAM is advantageous with respect to evaluations of non-rectilinear relationships between response variables and multiple explanatory variables, and it can be effective in the

analysis of large data sets.<sup>41,42</sup> It accomplishes non-parametric smoothing and fits the spline regression data. In addition, GAM can be effectively applied to analyzing the interaction between influential factors and response variables.<sup>43</sup> By contrast, traditional statistical methods are not as effective at determining complex non-linear relationships.<sup>44</sup> GAM is also more successful at pinpointing the actual relationship between serum lipids and BMD. Secondly, the data collection, in addition to the estimations made and assessments of the participants, was performed consistently and meticulously in the current study, which was part of a larger project. Thirdly, this was an observational study, with the potential for inevitable potential confounding; thus, rigorous statistical adjustments were utilized to minimize residual confusion. Finally, the use of subgroup analysis achieves better use of the data compared to primary analysis only. In subgroup analysis, the relationship between serum lipids and BMD was different in different groups.

This research also had numerous limitations. Firstly, it utilized a cross-sectional design without a prospective follow-up; thus, the support between the exposure and the outcomes was weak. Secondly, the study population comprised Chinese women only, which limits generalization to other groups. Thirdly, only a small number of patients with hyperlipidemia were used anti-lipid drugs in this research. Adjustments were made for hyperlipidemia but not for the use of anti-lipid drugs. Finally, although adjustments were made for diabetes mellitus, the effects of impaired glucose tolerance were overlooked, which was a limitation of this study.



**Figure 3** Multivariate-adjusted smoothing spline plots of BMD by TC, HDL-C, and LDL-C in premenopausal women. Red dotted lines represent the spline plots of TC, HDL-C, and LDL-C and blue dotted.

## Conclusion

In postmenopausal women, TC, LDL-C, and HDL-C concentrations were shown to relate negatively to lumbar spine BMD when their respective concentrations were less than 5.86 mmol/L, 3.52 mmol/L, and 2.37 mmol/L. In addition, a non-linear relationship was demonstrated between HDL-C and femoral neck BMD in premenopausal women. The mechanisms that underlie these associations remain unclear; therefore, more well-controlled prospective studies are warranted to establish the actual associations between serum lipids and BMD in women.

## Abbreviations

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OP, Osteoporosis; BMI, Body Mass Index; ALT, alanine aminotransferase; FBG, fasting plasma glucose; AST, aspartate aminotransferase; SD, standard deviation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; GAM, generalized additive model; CI, confidence interval.

## Data Sharing Statement

Restrictions apply to the availability of data generated or analyzed during this study to preserve participant confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

## Ethics Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical permission was acquired from the Ethics Review Board of West China Hospital of Sichuan University (MISP-40407). Informed consent was obtained from all individual participants included in the study. Consent for publication: Informed consent was obtained from all individual participants included in the study.

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## Author Contributions

Decai Chen, Chunyan Lu and Qin Wang: designed and conducted the research and critically revised the manuscript. Yong Xu, Hongyi Cao, Xiaohua Xie, Xueyan Wu and Jing Li: collected data, analyzed and interpreted data and critically review article. Qi Zhang and Junteng Zhou: collected data, analyzed the data and performed the statistical analyses, wrote the manuscript and substantially revised the article. We all agreed on the journal to which the article will be submitted, and reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. In addition, we all agree to take responsibility and be accountable for the contents of the article.

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## Disclosure

The authors have no conflicts of interest to disclose.

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