Associations Between Serum Total Cholesterol Level and Bone Mineral Density in Older Adults

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Abstract

Background: Osteoporosis is a major clinical problem in elderly people. The correlation between total cholesterol and bone mineral density remains controversial.

Methods: We obtained records from the National Health and Nutrition Examination Survey (NHANES) database for 4236 people aged over 60 without a diagnosis of cancer. We analyzed the relationship between total cholesterol and lumbar bone mineral density, using the statistical packages R and Empower Stats. We described the research population and performed stratified and single factor analysis, multiple equation regression analysis, smooth curve fitting, and threshold effect and saturation effect analysis.

Results: A significant negative association was found between serum cholesterol levels and bone mineral density of the lumbar spine in the study population. Older adults ≥ 70 years of age had an inflection point at 280 mg / dl, and those with moderate physical activity had an inflection point at 203 mg / dl. The smooth curves fitted were all U-shaped.

Conclusions: There is a negative association between total cholesterol and lumbar spine bone mineral density in people without cancer aged 60 or older.

Introduction

Estimates indicate that 50% of women and 20% of men aged over 50 years will experience osteoporosis, a major clinical problem in older people(1, 2). Studies have shown that increasing bone mineral density (BMD) reduces the risk of fracture(3). Therefore, research to discover the risk factors for low BMD is essential for osteoporosis prevention, early diagnosis, and treatment(4).

Several factors have been found to be closely related to BMD, including serum calcium(5), serum uric acid(4), calcium intake(6), osteoarthritis or rheumatoid arthritis(7), plasma total homocysteine level(8), diabetes mellitus(9), coffee drinking(10), serum iron(11), fibrinogen(12), and potassium intake(13). However, discovering further factors influencing BMD is still significant for osteoporosis prevention and treatment.

Total cholesterol levels are consistently associated with many diseases. Examples include the association between elevated total cholesterol levels and high cardiovascular disease risk in young adults(14), the association of total cholesterol and risk of a number of different cancers(15), and the increased the risk of severe acute pancreatitis with both low total cholesterol level (< 160 mg / dl) and high total cholesterol (> 240 mg / dl)(16). However, the relationship between total cholesterol and BMD has been less studied.

Makovey et al. (17) studied the relationship between cholesterol and BMD in women before and after menopause and found a modest inverse correlation. Yang et al.(18) found an inverse correlation between

BMD and serum cholesterol levels in patients with type 2 diabetes. Ackert-Bicknell (19) found an inverse correlation between serum HDL levels and bone status in vitamin D-deficient postmenopausal women. However, these were small, population-specific studies. We sought to explore the relationship between serum total cholesterol and BMD in normal elderly people without diabetes and cancer, in a large sample of normal cancer-free elderly people

Therefore, our aim in this study was to evaluate the relationship between total cholesterol and BMD using a representative sample of normal elderly people without diseases such as cancer, using a sample from the National Health and Nutrition Examination Survey (NHANES)(20). The NHANES is the cornerstone of national nutrition monitoring and informs nutrition and health policy. Nutritional assessment in NHANES is described with a focus on dietary data collection and analysis, and use of the data in nutrition monitoring(20).

Methods

Ethics statement

This study was approved by the ethics review board of the National Center for Health Statistics, and written consent was obtained from each case subject.

Study population

The NHANES is a population-based cross-sectional survey designed to collect information about the health and nutrition of the family population of the United States. The project surveys a nationally representative sample each year, and these populations are located in counties across the country. NHANES interviews collect demographic, socioeconomic, dietary, and health-related information. Physical examinations are conducted that include physiological measurements and laboratory examinations(21).

Our analysis is based on data recorded for the period 1999–2006, which represents the three cycles of the NHANES. The specific exclusion process is shown in the screening flowchart (Fig. 1). In the end, a total of 4236 cancer-free participants over 60 years of age were included in our analysis.

Variables

The exposure variable for this study was serum total cholesterol. In the mobile examination center (MEC) laboratory, blood specimens were processed, stored, and shipped to the Johns Hopkins University Lipoprotein Analytical Laboratory for analysis. The outcome variable was lumbar spine BMD, measured by dual-energy X-ray absorptiometry (DEXA) scan. The following categorical variables were included as covariates in our analysis: age, sex, race / ethnicity, and physical activity level. The following continuous covariates were included in our analysis: income poverty rate, blood urea nitrogen (BUN), total protein, serum uric acid, blood calcium, and body mass index (BMI). Detailed information on total cholesterol, lumbar spine BMD, and covariates is publicly available at <http://www.cdc.gov/nchs/nhanes/>.

Statistical analysis

Data were analyzed using statistical packages R version 3.6.3 (R Foundation, <http://www.r-project.org>) and Empower Stats (www.empowerstats.net, X&Y solutions Inc., Boston, Massachusetts). P values < 0.05 were considered statistically significant.

We performed weighted and variance estimation analyses to account for significant variance in our dataset. Weighted multiple logistic regression models were used to assess the association between total cholesterol and lumbar spine BMD. We calculated differences between groups using a weighted chi square test for categorical variables and a weighted linear regression model for continuous variables. Subgroup analysis was performed using stratified multiple regression analysis. In addition, smooth curve fitting and generalized additive models were used to address the nonlinear relationship between total cholesterol and lumbar spine BMD. A recursive algorithm was used to calculate the inflection point in the relationship between total cholesterol and BMD when non-linearity was detected, with a bi-segmented linear regression model on either side of the inflection point.

Results

A total of 4236 participants aged between 60 and 85 were included in our analysis. The weighted characteristics of the participants were subdivided according to the tertiles of serum total cholesterol (low: ≥ 75 mg/dL to 191 mg/dL; medium: ≥ 191 mg/dL to < 224 mg/dL; high: ≥ 224 mg/dL to < 704 mg/dL). As shown in Table 1, there were significant differences in baseline characteristics between the tertiles of total cholesterol, except for race / ethnicity. Compared with other subgroups, participants in the highest tertile of total cholesterol were more likely to be female, 60–69 years old, and sedentary. Participants in the top tertile of total cholesterol had lower income to poverty ratio, BUN, serum uric acid, and BMI levels but higher total protein and serum calcium levels.

Table 1
Baseline characteristics of participants (N = 4236).

Total Cholesterol (mg/dL)	Total	Low (≥ 75 to 191)	Middle (≥ 191 to < 224)	High (≥ 224 to < 704)	P-value
Sex (%)					< 0.0001
Male	43.67	58.55	44.3	29.59	
Female	56.33	41.45	55.7	70.41	
Age (%)					0.0298
60–69 years	60.29	58.3	59.39	62.93	
≥ 70 years	39.71	41.7	40.61	37.07	
Race/ethnicity (%)					0.3112
Non-Hispanic White	83.16	81.85	84.77	82.86	
Non-Hispanic Black	8.62	9.29	7.78	8.80	
Mexican American	4.2	4.1	4.29	4.20	
Other races/ethnicities	4.02	4.76	3.16	4.14	
Physical activity (%)					0.0258
Sedentary	27.31	26.54	25.67	29.50	
Low	26.64	26.97	26.29	26.66	
Moderate	17.57	16.53	17.37	18.67	
High	28.49	29.96	30.67	25.17	
Income to poverty ratio	2.82 $\pm$ 1.52	2.90 $\pm$ 1.50	2.85 $\pm$ 1.53	2.71 $\pm$ 1.51	0.0044
Blood urea nitrogen (mg/dL)	16.24 $\pm$ 6.80	16.81 $\pm$ 7.91	15.99 $\pm$ 6.39	15.96 $\pm$ 5.99	0.0009
Total protein (mg/dL)	7.24 $\pm$ 0.50	7.17 $\pm$ 0.52	7.25 $\pm$ 0.49	7.30 $\pm$ 0.48	< 0.0001
Serum uric acid (mg/dL)	5.63 $\pm$ 1.44	5.83 $\pm$ 1.49	5.58 $\pm$ 1.41	5.50 $\pm$ 1.41	< 0.0001
Serum calcium (mg/dL)	9.51 $\pm$ 0.41	9.45 $\pm$ 0.43	9.50 $\pm$ 0.39	9.56 $\pm$ 0.39	< 0.0001
Body mass index	28.65 $\pm$ 5.73	29.50 $\pm$ 6.24	28.26 $\pm$ 5.55	28.24 $\pm$ 5.32	< 0.0001

Total Cholesterol (mg/dL)	Total	Low (≥ 75 to 191)	Middle (≥ 191 to < 224)	High (≥ 224 to < 704)	P-value
Lumber spine BMD (g/cm ²)	1.01 ± 0.18	1.05 ± 0.19	1.02 ± 0.18	0.98 ± 0.17	< 0.0001

Note: Mean +/- standard deviation for: age, income to poverty, ratio blood urea nitrogen, total protein, serum uric acid, serum calcium, BMI, total days drink year, total BMD, head BMD, lumber spine BMD, lumber pelvis BMD. P value was calculated using weighted linear regression model. % For: age, sex, race/ethnicity, education, physical activity. P value was calculated using weighted chi-square test. Weighted by: Full sample mobile examination center exam weight.

BMD, Bone mineral density; BMI, Body mass index.

Table 2 shows a stratified analysis of total cholesterol versus lumbar spine BMD. Except for non-Hispanic Black and Mexican American race / ethnicity, with the lowest tertile of total cholesterol as the reference, the β items in the highest tertile of total cholesterol were negative, and $P < 0.01$, a statistically significant difference.

Table 2
Stratified analysis between total cholesterol and lumbar bone mineral density.

	Total cholesterol (tertiles)		
	Low	Middle β (95%CI) P value	High β (95%CI) P value
Age			
60–69 years	Reference	-0.0271 (-0.0450, -0.0091) 0.0032	-0.0552 (-0.0727, -0.0378) < 0.0001
>= 70 years	Reference	-0.0236 (-0.0442, -0.0030) 0.0248	-0.0887 (-0.1095, -0.0680) < 0.0001
Sex			
Male	Reference	-0.0074 (-0.0260, 0.0112) 0.4376	-0.0359 (-0.0564, -0.0153) 0.0006
Female	Reference	-0.0115 (-0.0300, 0.0069) 0.2211	-0.0343 (-0.0518, -0.0169) 0.0001
Race ethnicity			
Non-Hispanic White	Reference	-0.0269 (-0.0422, -0.0117) 0.0005	-0.0737 (-0.0887, -0.0586) < 0.0001
Non-Hispanic Black	Reference	-0.0218 (-0.0580, 0.0143) 0.2370	-0.0319 (-0.0663, 0.0025) 0.0699
Mexican American	Reference	0.0205 (-0.0442, 0.0853) 0.5354	0.0183 (-0.0457, 0.0823) 0.5757
Other races/ethnicities	Reference	-0.0372 (-0.1150, 0.0406) 0.3501	-0.0861 (-0.1570, -0.0153) 0.0188
Physical activity			
Sedentary	Reference	-0.0458 (-0.0710, -0.0207) 0.0004	-0.0753 (-0.0992, -0.0515) < 0.0001
Low	Reference	-0.0564 (-0.0841, -0.0287) < 0.0001	-0.0818 (-0.1089, -0.0548) < 0.0001
Moderate	Reference	-0.0124 (-0.0490, 0.0242) 0.5057	-0.0859 (-0.1212, -0.0507) < 0.0001
High	Reference	0.0043 (-0.0217, 0.0303) 0.7443	-0.0360 (-0.0628, -0.0093) 0.0084
Income to poverty ratio (tertiles)			
0–1.38	Reference	-0.0281 (-0.0537, -0.0025) 0.0318	-0.0515 (-0.0758, -0.0272) < 0.0001

Total cholesterol (tertiles)			
	Low	Middle	High
		β (95%CI) P value	β (95%CI) P value
1.39–2.99	Reference	-0.0381 (-0.0636, -0.0126) 0.0034	-0.0784 (-0.1033, -0.0536) < 0.0001
3.01–5.00	Reference	-0.0236 (-0.0466, -0.0007) 0.0440	-0.0572 (-0.0803, -0.0342) < 0.0001
Blood urea nitrogen (tertiles, mg/dL)			
2.00–12.00	Reference	-0.0356 (-0.0601, -0.0110) 0.0046	-0.0527 (-0.0768, -0.0286) < 0.0001
13.00–16.00	Reference	-0.0261 (-0.0507, -0.0016) 0.0369	-0.0627 (-0.0867, -0.0386) < 0.0001
17.00–122.00	Reference	-0.0182 (-0.0400, 0.0036) 0.1015	-0.0805 (-0.1020, -0.0590) < 0.0001
Total protein (tertiles, mg/dL)			
5.40–7.00	Reference	-0.0177 (-0.0425, 0.0070) 0.1601	-0.0631 (-0.0887, -0.0374) < 0.0001
7.10–7.40	Reference	-0.0363 (-0.0602, -0.0124) 0.0030	-0.0529 (-0.0757, -0.0301) < 0.0001
7.50–11.00	Reference	-0.0253 (-0.0480, -0.0026) 0.0293	-0.0834 (-0.1055, -0.0613) < 0.0001
Serum uric acid (tertiles, mg/dL)			
1.50–4.80	Reference	-0.0054 (-0.0287, 0.0179) 0.6491	-0.0559 (-0.0783, -0.0334) < 0.0001
4.90–6.00	Reference	-0.0086 (-0.0323, 0.0151) 0.4757	-0.0466 (-0.0700, -0.0233) < 0.0001
6.10–13.70	Reference	-0.0399 (-0.0624, -0.0175) 0.0005	-0.0656 (-0.0882, -0.0430) < 0.0001
Serum calcium (tertiles, mg/dL)			
6.70–9.20	Reference	-0.0441 (-0.0693, -0.0188) 0.0007	-0.0611 (-0.0878, -0.0343) < 0.0001
9.30–9.50	Reference	-0.0015 (-0.0259, 0.0229) 0.9040	-0.0673 (-0.0909, -0.0438) < 0.0001
9.60–12.50	Reference	-0.0286 (-0.0502, -0.0070) 0.0096	-0.0638 (-0.0847, -0.0429) < 0.0001
Body mass index (tertiles)			

	Total cholesterol (tertiles)		
	Low	Middle	High
		β (95%CI) P value	β (95%CI) P value
15.18–25.91	Reference	-0.0008 (-0.0233, 0.0218) 0.9476	-0.0532 (-0.0757, -0.0307) < 0.0001
25.93–30.04	Reference	-0.0135 (-0.0376, 0.0106) 0.2733	-0.0630 (-0.0864, -0.0395) < 0.0001
30.05–58.58	Reference	-0.0360 (-0.0587, -0.0133) 0.0019	-0.0604 (-0.0826, -0.0382) < 0.0001

We performed a univariate analysis of lumbar BMD (Table 3). Compared with men, women's lumbar spine BMD was reduced by 0.15, a relatively large difference that was statistically significant ($P < 0.001$). Other results are shown in Table 3.

Table 3
Univariate analysis for lumbar spine bone mineral density.

	Statistics	β (95%CI)	P-value
Total cholesterol	209.81 ± 42.95	-0.00 (-0.00, -0.00)	< 0.0001
Total cholesterol quartiles			
Low	1405 (33.17%)	Reference	
Middle	1388 (32.77%)	-0.02 (-0.04, -0.01)	0.0008
High	1443 (34.07%)	-0.06 (-0.08, -0.05)	< 0.0001
Sex			
Male	2062 (48.68%)	Reference	
Female	2174 (51.32%)	-0.15 (-0.16, -0.15)	< 0.0001
Race/ethnicity			
Non-Hispanic white	3231 (76.27%)	Reference	
Non-Hispanic black	740 (17.47%)	0.08 (0.07, 0.09)	< 0.0001
Mexican American	144 (3.40%)	-0.04 (-0.07, -0.02)	0.0002
Other races/ethnicities	121 (2.86%)	-0.01 (-0.03, 0.02)	0.4821
Age			
60–69 years	2294 (54.15%)	Reference	
>= 70 years	1942 (45.85%)	-0.02 (-0.03, -0.00)	0.0109
Income to poverty ratio	2.46 ± 1.51	0.02 (0.02, 0.02)	< 0.0001
Income to poverty ratio (tertile)			
Low	1277 (33.31%)	Reference	
Middle	1279 (33.36%)	0.03 (0.02, 0.04)	< 0.0001
High	1278 (33.33%)	0.06 (0.05, 0.07)	< 0.0001
Blood urea nitrogen	16.46 ± 7.46	-0.00 (-0.00, 0.00)	< 0.0001
Blood urea nitrogen (tertile)			
Low	1178 (27.92%)	Reference	
Middle	1348 (31.95%)	-0.00 (-0.01, 0.01)	0.9751
High	1693 (40.13%)	-0.01 (-0.02, 0.00)	0.0886

	Statistics	β (95%CI)	<i>P</i> -value
Total protein	7.33 $\pm$ 0.52	-0.01 (-0.01, 0.00)	0.1642
Total protein (tertile)			
Low	1249 (29.62%)	Reference	
Middle	1345 (31.89%)	-0.00 (-0.01, 0.01)	0.8438
High	1623 (38.49%)	-0.01 (-0.02, -0.00)	0.0254
Serum uric acid	5.66 $\pm$ 1.47	0.02 (0.02, 0.03)	< 0.0001
Serum uric acid (tertile)			
Low	1304 (30.91%)	Reference	
Middle	1412 (33.47%)	0.05 (0.04, 0.06)	< 0.0001
High	1503 (35.62%)	0.08 (0.07, 0.09)	< 0.0001

Continued Table 3.

	Statistics	β (95%CI)	P-value
Serum calcium	9.48 $\pm$ 0.42	-0.01 (-0.02, -0.00)	0.0087
Serum calcium (tertile)			
Low	1172 (27.78%)	Reference	
Middle	1301 (30.84%)	0.01 (-0.00, 0.02)	0.1108
High	1746 (41.38%)	-0.00 (-0.01, 0.01)	0.5408
Physical activity			
Sedentary	1328 (31.35%)	Reference	
Low	1026 (24.22%)	0.04 (0.03, 0.05)	<0.0001
Moderate	619 (14.61%)	0.05 (0.04, 0.06)	<0.0001
High	997 (23.54%)	0.06 (0.05, 0.08)	<0.0001
Not recorded	266 (6.28%)	0.07 (0.05, 0.09)	<0.0001
BMI	28.60 $\pm$ 5.65	0.00 (0.00, 0.01)	<0.0001
BMI (tertile)			
Low	1383 (33.32%)	Reference	
Middle	1382 (33.29%)	0.05 (0.04, 0.06)	<0.0001
High	1386 (33.39%)	0.06 (0.05, 0.07)	<0.0001

Abbreviations: CI, confidence interval; BMI, Body mass index.

The results of the multiple regression equation analysis are shown in Table 4. In the unadjusted model, total cholesterol was negatively correlated with lumbar spine BMD (β =-0.0007, 95% confidence interval [CI]: -0.0008, -0.0005, $P < 0.001$). After adjusting for confounding factors, this correlation still existed in Model 2 (β =-0.0004, 95% CI: -0.0005, -0.0002, $P < 0.001$), and Model 3 (β =-0.0003, 95% CI: -0.0004, -0.0001, $P < 0.001$), with P for trend < 0.001 . We also stratified by continuous variables (third quantiles) and categorical variables; The results are shown in Table 4.

Table 4
Relationship between total cholesterol and lumbar spine bone mineral density.

Outcome	Crude Model		Model 1		Model 2	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Total cholesterol	-0.0007 (-0.0008, -0.0005)	< 0.0001	-0.0004 (-0.0005, -0.0002)	< 0.0001	-0.0003 (-0.0004, -0.0001)	< 0.0001
Total cholesterol (tertiles)						
Low	Reference		Reference		Reference	
Middle	-0.0255 (-0.0390, -0.0119)	0.0002	-0.0079 (-0.0208, 0.0050)	0.2312	-0.0016 (-0.0151, 0.0118)	0.8147
High	-0.0669 (-0.0802, -0.0535)	< 0.0001	-0.0344 (-0.0474, -0.0214)	< 0.0001	-0.0195 (-0.0330, -0.0060)	0.0047
P for trend	< 0.001		< 0.001		< 0.001	
Sex						
Male	-0.0004 (-0.0006, -0.0002)	< 0.0001	-0.0004 (-0.0006, -0.0002)	0.0001	-0.0003 (-0.0005, -0.0001)	0.0013
Female	-0.0003 (-0.0005, -0.0002)	0.0001	-0.0003 (-0.0005, -0.0002)	< 0.0001	-0.0002 (-0.0003, -0.0000)	0.0460
Age						
60–69 years	-0.0006 (-0.0007, -0.0004) <	< 0.0001	-0.0003 (-0.0005, -0.0002)	< 0.0001	-0.0002 (-0.0003, 0.0000)	0.0590
>= 70 years	-0.0008 (-0.0010, -0.0006)	< 0.0001	-0.0004 (-0.0006, -0.0002)	< 0.0001	-0.0003 (-0.0005, -0.0001)	0.0007
Race/ethnicity						
Non-Hispanic White	-0.0007 (-0.0009, -0.0006)	< 0.0001	-0.0004 (-0.0005, -0.0003)	< 0.0001	-0.0003 (-0.0004, -0.0002)	< 0.0001
Non-Hispanic Black	-0.0004 (-0.0007, -0.0000)	0.0267	-0.0002 (-0.0005, 0.0002)	0.3208	-0.0001 (-0.0004, 0.0003)	0.6625

Outcome	Crude Model		Model 1		Model 2	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Mexican American	-0.0001 (-0.0008, 0.0005)	0.7457	-0.0000 (-0.0007, 0.0006)	0.9187	0.0004 (-0.0003, 0.0011)	0.3169
Other races/ethnicities	-0.0006 (-0.0013, 0.0001)	0.0902	-0.0004 (-0.0011, 0.0003)	0.2223	-0.0003 (-0.0010, 0.0004)	0.3774
Serum uric acid (tertiles)						
Low	-0.0006 (-0.0008, -0.0004)	< 0.0001	-0.0004 (-0.0006, -0.0002)	0.0005	-0.0003 (-0.0005, -0.0001)	0.0093
Middle	-0.0007 (-0.0009, -0.0004)	< 0.0001	-0.0004 (-0.0007, -0.0002)	0.0001	-0.0004 (-0.0006, -0.0002)	0.0012
High	-0.0005 (-0.0007, -0.0003)	< 0.0001	-0.0003 (-0.0005, -0.0001)	0.1351	-0.0001 (-0.0003, 0.0001)	0.3774
Physical activity (tertiles)						
Sedentary	-0.0007 (-0.0009, -0.0005)	< 0.0001	-0.0004 (-0.0006, -0.0002)	0.0003	-0.0003 (-0.0005, -0.0000)	0.0231
Low	-0.0007 (-0.0009, -0.0004)	< 0.0001	-0.0004 (-0.0007, -0.0002)	0.0007	-0.0002 (-0.0005, 0.0000)	0.0978
Moderate	-0.0010 (-0.0014, -0.0007)	< 0.0001	-0.0006 (-0.0010, -0.0003)	0.0006	-0.0004 (-0.0007, -0.0000)	0.0432
High	-0.0005 (-0.0008, -0.0003)	0.0001	-0.0003 (-0.0005, -0.0001)	0.0186	-0.0002 (-0.0005, 0.0000)	0.1155

Continued Table 4.

Outcome	Crude Model		Model Ⅹ		Model Ⅹ	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Income to poverty ratio (tertiles)						
Low	-0.0004 (-0.0006, -0.0002)	0.0003	-0.0002 (-0.0004, -0.0000)	0.0252	-0.0001 (-0.0003, 0.0001)	0.2724
Middle	-0.0007 (-0.0010, -0.0005)	<0.0001	-0.0004 (-0.0007, -0.0002)	0.0002	-0.0003 (-0.0005, -0.0001)	0.0121
High	-0.0007 (-0.0009, -0.0004)	<0.0001	-0.0004 (-0.0006, -0.0001)	0.0034	-0.0003 (-0.0006, -0.0001)	0.0062
Blood urea nitrogen (tertiles)						
Low	-0.0005 (-0.0008, -0.0003)	<0.0001	-0.0002 (-0.0004, 0.0000)	0.0584	-0.0002 (-0.0004, 0.0000)	0.1151
Middle	-0.0007 (-0.0009, -0.0004)	<0.0001	-0.0004 (-0.0006, -0.0002)	0.0010	-0.0003 (-0.0005, -0.0001)	0.0181
High	-0.0007 (-0.0009, -0.0005)	<0.0001	-0.0005 (-0.0007, -0.0003)	<0.0001	-0.0003 (-0.0005, -0.0001)	0.0062
Total protein (tertiles)						
Low	-0.0006 (-0.0008, -0.0003)	<0.0001	-0.0003 (-0.0005, -0.0001)	0.0103	-0.0002 (-0.0004, 0.0001)	0.1457
Middle	-0.0006 (-0.0008, -0.0004)	<0.0001	-0.0003 (-0.0005, -0.0001)	0.0060	-0.0003 (-0.0005, -0.0001)	0.0171
High	-0.0008 (-0.0010, -0.0006)	<0.0001	-0.0004 (-0.0006, -0.0002)	<0.0001	-0.0003 (-0.0005, -0.0001)	0.0018
Serum calcium (tertiles)						
Low	-0.0007 (-0.0009, -0.0004)	<0.0001	-0.0004 (-0.0007, -0.0002)	0.0007	-0.0004 (-0.0007, -0.0001)	0.0026
Middle	-0.0005 (-0.0007, -0.0003)	<0.0001	-0.0002 (-0.0004, 0.0001)	0.1429	-0.0001 (-0.0003, 0.0001)	0.2873

High	-0.0007 (-0.0009, -0.0005)	<0.0001	-0.0005 (-0.0007, -0.0003)	<0.0001	-0.0003 (-0.0005, -0.0001)	0.0071
BMI (tertiles)						
Low	-0.0006 (-0.0009, -0.0004)	<0.0001	-0.0004 (-0.0006, -0.0002)	0.0002	-0.0004 (-0.0007, -0.0002)	<0.0001
Middle	-0.0006 (-0.0008, -0.0003)	<0.0001	-0.0002 (-0.0004, 0.0000)	0.1046	-0.0001 (-0.0003, 0.0002)	0.6275
High	-0.0007 (-0.0009, -0.0004)	<0.0001	-0.0004 (-0.0006, -0.0001)	0.0012	-0.0004 (-0.0007, -0.0002)	0.0002

Outcome variable: Total BMD. Exposure variable: Total cholesterol.

The crude model is not adjusted. Model 1 adjusted for age, sex, and serum uric acid. Model 2 adjusted for age, sex, serum uric acid, race ethnicity, education, income to poverty ratio, blood urea nitrogen, total protein, serum uric acid, serum calcium, physical activity, BMI.

Abbreviations: CI, confidence interval; BMD, bone mineral density BMI, body mass index.

We also performed weighted generalized additive models and smooth curve fitting to assess their association (Fig. 2). Figure 2 shows that total cholesterol was linearly negatively correlated with lumbar BMD. We also performed smooth curve fitting in subgroups stratified by categorical variables (Fig. 3). Figure 3a shows a turning point in the fitting curve for elderly people 70 years or older, at a total cholesterol of 280 mg/dL (Table 5). Figure 3d shows that the fitting curve of older people with more than moderate physical activity had a turning point at a total cholesterol of 203 mg/dL (Table 5). Other turning points are shown in Fig. 4 and Table 5.

Table 5
Threshold effect and saturation effect analysis.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Total							
Adjusted β (95% CI)	-0.0003 (-0.0004, -0.0002)	146	0.0003 (-0.0011, 0.0017)	-0.0003 (-0.0005, -0.0002)	-0.0006 (-0.0020, 0.0009)	1.0584 (1.0461, 1.0706)	0.430
P-value	< 0.0001		0.7028	< 0.0001	0.4308		
Stratification variables							
<i>Age</i>							
60–69 years							
Adjusted β (95% CI)	-0.0002 (-0.0004, -0.0001)	256	-0.0001 (-0.0003, 0.0001)	-0.0007 (-0.0011, -0.0002)	-0.0006 (-0.0012, -0.0000)	1.0010 (0.9858, 1.0161)	0.034
P-value	0.0057		0.4673	0.0027	0.0350		
>= 70 years							
Adjusted β (95% CI)	-0.0003 (-0.0006, -0.0001)	280	-0.0005 (-0.0007, -0.0002)	0.0006 (-0.0002, 0.0014)	0.0011 (0.0001, 0.0020)	0.9196 (0.8978, 0.9415)	0.023
P-value	0.0016		0.0001	0.1672	0.0236		
<i>Sex</i>							
Male							
Adjusted β (95% CI)	-0.0004 (-0.0006, -0.0002)	138	0.0012 (-0.0013, 0.0037)	-0.0004 (-0.0007, -0.0002)	-0.0017 (-0.0042, 0.0009)	1.1131 (1.0957, 1.1305)	0.196
P-value	0.0001		0.3336	< 0.0001	0.1985		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	> K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Female							
Adjusted β	-0.0002	207	0.0003	-0.0004	-0.0006	0.9638	0.033
(95% CI)	(-0.0003, 0.0000)		(-0.0002, 0.0007)	(-0.0007, -0.0001)	(-0.0012, -0.0001)	(0.9511, 0.9765)	
<i>P</i> -value	0.0658		0.2311	0.0050	0.0337		
<i>Race/ethnicity</i>							
Non-Hispanic White							
Adjusted β	-0.0004	146	0.0007	-0.0004	-0.0011	1.0505	0.216
(95% CI)	(-0.0005, -0.0002)		(-0.0010, 0.0023)	(-0.0006, -0.0002)	(-0.0027, 0.0006)	(1.0371, 1.0639)	
<i>P</i> -value	<0.0001		0.4327	<0.0001	0.2171		
Non-Hispanic Black							
Adjusted β	-0.0001	154	-0.0009	-0.0000	0.0009	1.1161	0.544
(95% CI)	(-0.0004, 0.0003)		(-0.0038, 0.0019)	(-0.0004, 0.0004)	(-0.0021, 0.0039)	(1.0867, 1.1455)	
<i>P</i> -value	0.7282		0.5234	0.9422	0.5485		
Mexican American							
Adjusted β	0.0001	181	-0.0033	0.0005	0.0038	0.9334	0.045
(95% CI)	(-0.0006, 0.0008)		(-0.0070, 0.0003)	(-0.0003, 0.0013)	(-0.0001, 0.0078)	(0.8814, 0.9854)	
<i>P</i> -value	0.8348		0.0730	0.2362	0.0621		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Other races/ethnicities							
Adjusted β	-0.0001	132	-0.0016	-0.0000	0.0016	1.0036	0.701
(95% CI)	(-0.0009, 0.0007)		(-0.0100, 0.0068)	(-0.0009, 0.0008)	(-0.0071, 0.0103)	(0.9288, 1.0783)	
<i>P</i> -value	0.8128		0.7060	0.9332	0.7219		
<i>Physical activity</i>							
Sedentary							
Adjusted β	-0.0003	146	0.0008	-0.0003	-0.0011	1.0338	0.403
(95% CI)	(-0.0005, -0.0000)		(-0.0017, 0.0032)	(-0.0005, -0.0001)	(-0.0035, 0.0014)	(1.0119, 1.0556)	
<i>P</i> -value	0.0238		0.5397	0.0161	0.4063		
Low							
Adjusted β	-0.0003	272	-0.0005	0.0008	0.0013	0.9424	0.006
(95% CI)	(-0.0006, -0.0000)		(-0.0008, -0.0002)	(-0.0000, 0.0017)	(0.0004, 0.0023)	(0.9163, 0.9684)	
<i>P</i> -value	0.0271		0.0010	0.0614	0.0069		
Moderate							
Adjusted β	-0.0002	203	0.0007	-0.0008	-0.0015	1.0491	0.011
(95% CI)	(-0.0006, 0.0001)		(-0.0001, 0.0015)	(-0.0014, -0.0002)	(-0.0027, -0.0003)	(1.0237, 1.0745)	
<i>P</i> -value	0.2225		0.0917	0.0063	0.0118		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
High							
Adjusted β (95% CI)	-0.0003 (-0.0006, -0.0001)	256	-0.0002 (-0.0005, 0.0002)	-0.0008 (-0.0014, -0.0001)	-0.0006 (-0.0014, 0.0002)	1.0021 (0.9797, 1.0245)	0.133
P-value	0.0115		0.3555	0.0163	0.1358		
<i>Income to poverty ratio (tertiles)</i>							
Low							
Adjusted β (95% CI)	-0.0002 (-0.0004, -0.0000)	208	-0.0000 (-0.0005, 0.0004)	-0.0003 (-0.0007, -0.0000)	-0.0003 (-0.0010, 0.0003)	0.9847 (0.9684, 1.0010)	0.329
P-value	0.0307		0.9188	0.0309	0.3320		
Middle							
Adjusted β (95% CI)	-0.0004 (-0.0006, -0.0002)	145	0.0008 (-0.0022, 0.0039)	-0.0004 (-0.0007, -0.0002)	-0.0013 (-0.0044, 0.0018)	1.0795 (1.0571, 1.1019)	0.416
P-value	0.0010		0.5864	0.0008	0.4196		
High							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0000)	150	-0.0016 (-0.0040, 0.0009)	-0.0002 (-0.0005, 0.0001)	0.0013 (-0.0012, 0.0039)	1.0692 (1.0483, 1.0901)	0.294
P-value	0.0369		0.2090	0.1192	0.2978		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Blood urea nitrogen (tertiles)							
Low							
Adjusted β (95% CI)	-0.0003 (-0.0006, -0.0000)	146	0.0011 (-0.0013, 0.0035)	-0.0004 (-0.0006, -0.0001)	-0.0015 (-0.0040, 0.0010)	1.0490 (1.0263, 1.0717)	0.246
P-value	0.0197		0.3696	0.0096	0.2495		
Middle							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0000)	281	-0.0003 (-0.0006, -0.0001)	0.0004 (-0.0008, 0.0016)	0.0007 (-0.0006, 0.0020)	0.9554 (0.9299, 0.9808)	0.285
P-value	0.0357		0.0188	0.5471	0.2890		
High							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0001)	143	0.0016 (-0.0009, 0.0040)	-0.0003 (-0.0005, -0.0001)	-0.0019 (-0.0044, 0.0006)	1.0752 (1.0557, 1.0946)	0.139
P-value	0.0072		0.2138	0.0025	0.1413		
Total protein (tertiles)							
Low							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0001)	142	0.0023 (-0.0001, 0.0047)	-0.0004 (-0.0006, -0.0001)	-0.0027 (-0.0052, -0.0002)	1.0742 (1.0524, 1.0960)	0.031
P-value	0.0138		0.0586	0.0024	0.0321		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Middle							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0000)	187	-0.0009 (-0.0017, -0.0001)	-0.0001 (-0.0004, 0.0002)	0.0008 (-0.0002, 0.0018)	1.0134 (0.9952, 1.0316)	0.105
P-value	0.0216		0.0243	0.5513	0.1076		
High							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0001)	152	-0.0008 (-0.0028, 0.0012)	-0.0002 (-0.0005, -0.0000)	0.0006 (-0.0015, 0.0027)	1.0448 (1.0249, 1.0648)	0.588
P-value	0.0152		0.4247	0.0408	0.5907		
<i>Serum uric acid (tertiles)</i>							
Low							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0000)	218	0.0000 (-0.0004, 0.0005)	-0.0006 (-0.0010, -0.0002)	-0.0006 (-0.0014, 0.0001)	0.9576 (0.9406, 0.9745)	0.089
P-value	0.0198		0.8597	0.0072	0.0912		
Middle							
Adjusted β (95% CI)	-0.0003 (-0.0006, -0.0001)	278	-0.0002 (-0.0005, 0.0001)	-0.0009 (-0.0016, -0.0002)	-0.0007 (-0.0015, 0.0002)	0.9699 (0.9460, 0.9939)	0.113
P-value	0.0068		0.1472	0.0170	0.1157		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
High							
Adjusted β (95% CI)	-0.0003 (-0.0005, -0.0000)	279	-0.0004 (-0.0007, -0.0001)	0.0005 (-0.0003, 0.0012)	0.0008 (-0.0000, 0.0017)	1.0041 (0.9806, 1.0276)	0.055
P-value	0.0223		0.0033	0.2482	0.0568		
<i>Serum calcium (tertiles)</i>							
Low							
Adjusted β (95% CI)	-0.0006 (-0.0009, -0.0003)	141	0.0005 (-0.0020, 0.0029)	-0.0006 (-0.0009, -0.0004)	-0.0011 (-0.0037, 0.0014)	1.0856 (1.0619, 1.1092)	0.384
P-value	<0.0001		0.7064	<0.0001	0.3882		
Middle							
Adjusted β (95% CI)	-0.0001 (-0.0003, 0.0001)	268	-0.0002 (-0.0005, 0.0001)	0.0005 (-0.0003, 0.0012)	0.0007 (-0.0002, 0.0016)	0.9699 (0.9467, 0.9930)	0.114
P-value	0.4314		0.1298	0.2171	0.1170		
High							
Adjusted β (95% CI)	-0.0002 (-0.0004, -0.0000)	208	0.0003 (-0.0002, 0.0007)	-0.0005 (-0.0008, -0.0002)	-0.0007 (-0.0014, -0.0001)	1.0152 (0.9998, 1.0305)	0.028
P-value	0.0408		0.2825	0.0029	0.0294		

Continued table 5.

	Model I	Model II					
	A straight-line effect	Fold points (K)	< K-segment effect 1	>K-segment Effect 2	Effect size difference of 2 versus 1	Equation predicted values at break points	Log likelihood ratio tests
Body mass index (<i>tertiles</i>)							
Low							
Adjusted β (95% CI)	-0.0004 (-0.0006, -0.0002)	259	-0.0003 (-0.0006, 0.0000)	-0.0007 (-0.0013, -0.0001)	-0.0004 (-0.0011, 0.0003)	0.9217 (0.9020, 0.9414)	0.261
P-value	0.0010		0.0597	0.0198	0.2648		
Middle							
Adjusted β (95% CI)	-0.0002 (-0.0005, 0.0000)	203	0.0001 (-0.0005, 0.0007)	-0.0004 (-0.0008, -0.0000)	-0.0005 (-0.0013, 0.0003)	1.0288 (1.0116, 1.0461)	0.238
P-value	0.0651		0.7904	0.0358	0.2419		
High							
Adjusted β (95% CI)	-0.0004 (-0.0006, -0.0002)	282	-0.0004 (-0.0007, -0.0002)	0.0001 (-0.0011, 0.0013)	0.0005 (-0.0007, 0.0018)	1.0071 (0.9833, 1.0310)	0.406
P-value	0.0009		0.0010	0.8715	0.4095		

Note: Adjusted β (95% CI), P-value. Outcome variables: lumbar spine BMD. exposure variables: total cholesterol. Adjustment variables: age, sex, race/ethnicity, income to poverty ratio, blood urea nitrogen, total protein, serum uric acid, serum calcium, physical activity and body mass.

Discussion

Samelson et al.(22) believe that the cholesterol levels of people in young adulthood to middle age do not have long-term clinical significance for later osteoporosis. However, the research of Zolfaroli(23) suggests that there is a positive correlation between cholesterol and BMD in the lumbar spine and femoral neck in postmenopausal women. Other researchers have found a moderate negative correlation between BMD and serum cholesterol levels(17). Therefore, the relationship between BMD and serum total cholesterol level is complex and unclear.

The primary objective of this study was to investigate whether total cholesterol was independently associated with lumbar spine BMD. We used a nationally representative sample of 4326 older Americans without cancer. Our results suggest a significant inverse association between serum cholesterol levels and BMD of the lumbar spine in US non-cancer-affected adults aged 60 years or older. Adults ≥ 70 years of age had an inflection point at 280 mg / dl, with a log likelihood ratio of 0.023. Those with moderate physical activity had an inflection point at 203 mg / dl, with $p = 0.011$ from the log likelihood ratio test. There was an inflection point at 279 mg / dl for older adults in the highest tertile of serum uric acid ($p = 0.055$ from the log likelihood ratio test) and at 268 mg / dl for older adults in the middle tertile of serum calcium ($p = 0.114$ from the log likelihood ratio test). The fitted smooth curves were all U-shaped, with statistical significance for the first two but not for the latter two.

The exact mechanism between total cholesterol and bone metabolism is unclear, and the correlation between total cholesterol and BMD remains controversial(24–26). Bones are highly innervated and vascularized. The seemingly closed system of the skeleton, tightly linked to systemic metabolic homeostasis, is dynamically regulated by hormones and nutrients. A large number of epidemiological studies have demonstrated a positive association between the risk of cardiovascular disease and osteoporosis(27–30). Bone metabolism is a continuous cycle of bone formation and resorption, which is coordinated by osteoblasts, osteocytes, and osteoclasts. Free cholesterol may inhibit BMP2, blocking *Runx2*, *Alpl*, and *COL 1A1* expression in osteoblasts and subsequently inhibiting osteoblast differentiation(26, 31). Cholesterol and its metabolites influence bone homeostasis by modulating the differentiation and activation of osteoblasts and osteoclasts(26). Treatment of rodents with the cholesterol-lowering drugs simvastatin and lovastatin increased bone formation in one study(32). In another animal study, a high cholesterol diet resulted in a decrease in femoral BMD accompanied by an increase in serum osteocalcin (OCN) and carboxy terminal collagen cross-linking, suggesting that high cholesterol may increase bone turnover(31, 32). A high fat diet induced cathepsin K-positive osteoclasts and RANKL expression in another study, leading to enhanced osteoclastogenesis, resulting in decreased BMD(33).

In this study, we analyzed a representative sample of a multi-ethnic population to better generalize the American population. The large sample size allowed us to perform subgroup analysis, an important advantage of this research. Our findings suggest that older adults should be advised that cholesterol be controlled at an appropriate level and that older patients with hypercholesterolemia will have reduced BMD. Our study results can inform governments to enable them to develop suitable policies. Appropriate and individualized measures for the prevention of osteoporosis should be developed for older people of all ethnicities, genders, ages, and levels of physical activity.

Our study had some limitations. First, confounding factors not identified in this study may have had an impact on the results. Second, because this study used a cross-sectional design, determining whether there is a causal relationship between total cholesterol and lumbar spine BMD is difficult. Therefore, the role of total cholesterol in bone metabolism requires further studies with large samples.

Conclusions

There is a negative association between total cholesterol and lumbar spine BMD in people without cancer ages 60 years and older.

Abbreviations

BMD: Bone mineral density; BMI: Body mass index; NHANES, National Health and Nutrition Examination Survey; BUN: blood urea nitrogen.

Declarations

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Availability of data and materials

All data and materials were sourced from public databases. The datasets for this study can be found at www.cdc.gov/nchs/nhanes/.

Ethics approval and consent to participate

The Ethical Review Committee of the National Center for Health Statistics approved all NHANES protocols and obtained written informed consent from all participants.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Authors' contributions

SH and WYP contributed to data collection, analysis, and writing of the manuscript. SH, WXZ, JYY, DYZ, YZ1, SLW, QG, LS, DLY, JHP, YPW, and JJX contributed to study design and writing of the manuscript. All

authors read and approved the final manuscript.

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Figures

Figure 1
Flow chart of sample selection from the NHANES.

Figure 2

The association between serum total cholesterol and lumbar bone mineral density. (a) Each black dot represents a sample. (b) The solid arc line represents the smooth curve fit between the variables. The blue bar represents the 95% confidence interval of the fit. Adjustments were made for age, gender, race / ethnicity, physical activity, income poverty rate, blood urea nitrogen, serum urea, total protein, blood phosphorus, and blood calcium.

Figure 3

The association between serum total cholesterol and lumbar spine bone mineral density stratified by categorical variables. (a) Stratified by age. Sex, race / ethnicity, physical activity, income poverty rate, blood urea nitrogen (BUN), total protein, serum uric acid, blood calcium, and body mass index (BMI) were adjusted. (b) Stratified by sex. Age, race / ethnicity, physical activity, income poverty rate, BUN, total protein, serum uric acid, blood calcium, and BMI were adjusted. (c) Stratified by race / ethnicity. Age, sex,

physical activity, income poverty rate, BUN, total protein, serum uric acid, blood calcium, and BMI were adjusted. (d) Stratified by physical activity. Age, sex, race / ethnicity, income poverty rate, BUN, total protein, total protein, serum uric acid, blood calcium, and BMI were adjusted.

Figure 4

The association between serum total cholesterol and lumbar spine BMD stratified by tertiles of different continuous variables. (a) Stratified by income poverty rate tertiles. Age, sex, race / ethnicity, physical

activity, blood urea nitrogen (BUN), total protein, serum uric acid, blood calcium, and body mass index (BMI) were adjusted. (b) Stratified by blood urea nitrogen tertiles. Age, sex, race / ethnicity, physical activity, income poverty rate, total protein, serum uric acid, blood calcium, and BMI were adjusted. (c) Stratified by total protein tertiles. Age, sex, race / ethnicity, physical activity, income poverty rate, BUN, serum uric acid, blood calcium, and BMI were adjusted. (d) Stratified by serum uric acid tertiles. Age, sex, race / ethnicity, physical activity, income poverty rate, BUN, total protein, blood calcium, and BMI were adjusted. (e) Stratified by blood calcium tertiles. Age, sex, race / ethnicity, physical activity, income poverty rate, BUN, total protein, serum uric acid, and BMI were adjusted. (f) Stratified by body mass index tertiles. Age, sex, race / ethnicity, physical activity, income poverty rate, BUN, total protein, serum uric acid, and blood calcium were adjusted.