Research Square

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A dose-dependent association of total cholesterol with all-cause and specific mortality: results from the National Health and Nutrition Examination Survey

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Abstract

Background: The link between total cholesterol (TC) and all-cause and specific mortality has not been elucidated. Herein, we aimed to evaluate the effect of TC levels on all-cause, cardiovascular disease (CVD), and cancer mortality.

Methods: All data analyzed were obtained from the National Health and Nutrition Examination Survey 1999-2014. The relationship between levels of TC and mortality was determined through Cox proportional hazard regression analysis coupled with multivariable adjustments. Two-piecewise linear regression model and Cox models with penalized splines were applied to explore non-linear and irregular shape relationships. Kaplan-Meier survival curve and subgroup analyses were conducted.

Results: The sample studied comprised 17853 men and 18922 women, categorized as 27927 adults aged 18–65 years and 8848 adults more than 65 years old. A total of 4441 deaths were recorded. All-cause, cardiovascular, and cancer mortality showed U-curve associations with nadir at 213 mg/dL, 200 mg/dL, and 218mg/dL after adjusting for confounding variables in the restricted cubic spline analysis. HRs of all-cause, CVD, and cancer mortality was particularly negatively related to TC levels in the lower range <200 mg/dL, especially in the range <120 mg/dL (HR 1.95; 95% CI 1.59, 2.38, HR 1.78; 95% CI 1.16, 2.72, HR 2.18; 95% CI 1.46, 3.25, respectively). The lowest cumulative survival rate was recorded in the lowest TC level group.

Conclusions: A U-curve association of TC level with all-cause, cancer, and CVD mortality in the American population was observed, suggesting that too low or too high serum total cholesterol levels might correlate with adverse outcomes.

Background

Cardiovascular disease (CVD) and cancer remain the main causes of mortality globally. Over 17 million people die every year, with the US accounting for almost 1 million deaths alone [1]. Moreover, the prevalence of cancer is on the increase globally [2]. Cholesterol is essential for several cellular processes and also participates in the pathogenesis of CVD and cancer [3–6]. Evidence from recent animal studies have linked impaired intracellular cholesterol metabolism to the development of many diseases. Prospective studies have explored the relationship between cholesterol and all-cause and specific mortality [6, 7].

Findings from such studies have been unreliable due to inconsistent results [8–11] and some are limited by small sample size [12–14]. Therefore, a strong link between cholesterol and all-cause and specific mortality remains obscure. Although cholesterol is one of the leading modifiable risk factors of CVD and cancer, the association between different ranges of total cholesterol (TC) with mortality is still controversial [15–18].

There has been an increasing interest to understand the impact of lower or higher cholesterol intake on the occurrence of different chronic diseases. Moreover, the optimal range of TC required for good health outcomes is still unknown. To answer these questions, we evaluated the effect of TC levels on all-cause and specific mortality in a large, nationwide US cohort.

Methods

Study population

This cohort study was based on prospective data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey program done in the United States by the National Center for Health Statistics (NCHS) that continually assesses the health status of civilians who are not institutionalized [19]. This study represents an analysis of data from the 1999–2014 cycles of NHANES collecting data from representative samples by either conducting interviews or laboratory tests. The Institutional Review Board of the National Center for Health Statistics, CDC, approved the protocol used by the NHANES. All participants provided informed consent.

We extracted data based on the time when TC test data were obtained. The entire data integration process is presented in Fig. 1. In total, 82,091 participants were enrolled in the NHANES from 1999 to 2014. First, considering that participants < 18 years of age could bring bias to the analysis, we excluded age < 18 years old individuals (N = 34735). Second, we excluded individuals missing TC data (N = 5159) and high-density lipoprotein cholesterol data (N = 3). In addition, individuals without blood pressure data (N = 1708), body mass index data (n = 592), past medical history (n = 3077) and follow-up data (n = 42) were all excluded. After missing entries were eliminated, 36775 subjects, including 980 women and 17853 men, were included in the final list.

Baseline Characteristics Of Data Collection

Baseline characteristics, such as age, sex, ethnicity, smoking status, and level of education were provided by the participants during the household interviews[20]. Hypertension referred to SBP (systolic blood pressures) more than or equal to 140 mmHg or/and DBP (diastolic blood pressure) more than or equal to 90 mmHg. This was verified by the record of antihypertensive drug usage or history of hypertension reported by the patient. Diabetes was confirmed by FBG ≥ 126 mg/dl, self-report, hemoglobin A1c (HbA1C) ≥ 6.5%, or hypoglycemic drug usage.

Serum lipids were evaluated at the Lipoprotein Analytic Laboratory of Johns Hopkins University. Total cholesterol was measured by a colorimetric method using a Hitachi 717 Analyzer (Boehringer Mannheim Diagnostics) in 1999–2005 and Hitachi 912 (Roche Diagnostics) since 2006. Details regarding other Laboratory tests can be obtained from the NHANES Laboratory. The quality control protocols and assurance met the 1988 Clinical Laboratory Improvement Act mandates.

Mortality And Follow-up

Mortality linkage methods used herein can be obtained from the NCHS. The anonymized data of individuals who participated in NHANES between 1999 to 2014 were allied to the longitudinal Medicare and mortality data based on the sequence number of NHANES. The NCHS classified mortality from CVD as follows: codes: I00–I09 (acute rheumatic fever and chronic rheumatic heart diseases), codes: I11 (hypertensive heart disease), codes: I13 (hypertensive heart and renal disease), codes: I20–I25 (ischemic heart diseases), codes: I26–I51 (other heart diseases), codes: I60–I69 (cerebrovascular disease), and codes: C00-C99 (mortality from cancer) according to ICD-10.

Data analysis

All the data analyses covered the complex, stratified, multistage, and cluster-sampling design (such as oversampling of some subpopulations) of NHANES based on the strata, sample weights, and primary sampling units incorporated in the NHANES data.

TC levels were divided into six groups < 120, 120–159, 160–199, 200–239, 240–279, and ≥ 280 mg/dL. The group which had the lowest mortality acted as a reference. Multivariable Cox proportional hazards model was applied to estimate the HRs (hazard ratios) and 95% CIs (confidence intervals). Cox proportional hazards regression models were utilized to understand the link between TC levels and total mortality and cause-specific mortality based on specific covariates: age, gender, and race (model II); model III plus education level, married, smoking, SBP, BMI, HDLC, estimated GFR, comorbidities (diabetes, hypertension, CVD, and cancer), and drug usage.

The two-piecewise linear regression model and Cox models with penalized splines were used to examine the non-linear and irregular shape of the link between baseline TC and the risk of total mortality and cause-specific mortality using non-parametric smoothers. The survival probability of primary outcomes according to the different ranges of TC variability was calculated by using Kaplan–Meier curves for cause-specific mortality and all-cause mortality.

To determine whether the relationship varied by age at baseline (< 65 or ≥ 60 years), sex (female/male), race (white/non-white), CVDs (yes/no), cancer (yes or no) and lipid-lowering drugs (yes or no), we performed subgroup analyses.

All analyses were administrated with SAS 9.3 software (SAS Inc), and the alpha level for significance in statistical analysis was set as 0.05 in this study.

Results

Baseline characteristics

The demographic features of the study participants based on the six TC levels are listed in Table 1. The average age of the 36775 adults was 49.24 years, and about half of the sample were women (51.45%). Non-white race and white race adults accounted for 52.42% and 47.58%, respectively. Almost three-quarters of participants self-identified as high school or above. Half of the sample were married. 53.38%

of the sample were not current smokers. Women and higher education level persons were more likely to be with higher TC values. The levels of systolic and diastolic blood pressure increased across the TC levels. Hypertension and diabetes approximately accounted for 55% and 16%. However, only 27.04% and 8.98% were treated with antihypertensive drugs and hypoglycemic agents.

Table 1
Demographic and clinical characteristics according to total cholesterol levels

Characteristic	Total cholesterol, mg/dL							
	Total	< 120	120–159	160–199	200–239	240–279	≥ 280	P-value
Number	36775	544	6005	13598	11084	4217	1327	
Age, years	49.24 ± 18.18	48.35 ± 21.85	46.37 ± 20.28	47.91 ± 18.42	50.95 ± 16.87	52.41 ± 16.43	51.80 ± 16.55	< 0.001
Gender, n (%)								< 0.001
Male	17853 (48.55)	375 (68.93)	3244 (54.02)	6705 (49.31)	5179 (46.73)	1824 (43.25)	526 (39.64)	
Female	18922 (51.45)	169 (31.07)	2761 (45.98)	6893 (50.69)	5905 (53.27)	2393 (56.75)	801 (60.36)	
Race, n (%)								< 0.001
Non-white	19276 (52.42)	302 (55.51)	3230 (53.79)	7240 (53.24)	5789 (52.23)	2069 (49.06)	646 (48.68)	
White	17499 (47.58)	242 (44.49)	2775 (46.21)	6358 (46.76)	5295 (47.77)	2148 (50.94)	681 (51.32)	
Education level, n (%)								0.008
Less than high school	10285 (28.00)	158 (29.10)	1626 (27.11)	3722 (27.40)	3122 (28.19)	1261 (29.95)	396 (29.93)	
High school or above	26446 (72.00)	385 (70.90)	4372 (72.89)	9861 (72.60)	7951 (71.81)	2950 (70.05)	927 (70.07)	
Marital status, n(%)								< 0.001
Other	16708 (45.99)	305 (56.48)	3025 (50.80)	6328 (47.07)	4672 (42.68)	1801 (43.42)	577 (44.59)	
Married	19621 (54.01)	235 (43.52)	2930 (49.20)	7117 (52.93)	6275 (57.32)	2347 (56.58)	717 (55.41)	
Smoking, n (%)								< 0.001
No	19617 (53.38)	250 (45.96)	3247 (54.10)	7315 (53.84)	5971 (53.91)	2167 (51.41)	667 (50.26)	

Abbreviations: n, number; eGFR, estimated glomerular filtration rate.

Values are mean ± standardized differences or n (%).

Characteristic	Total cholesterol, mg/dL							
	Total	< 120	120–159	160–199	200–239	240–279	≥ 280	P-value
Yes	17132 (46.62)	294 (54.04)	2755 (45.90)	6271 (46.16)	5104 (46.09)	2048 (48.59)	660 (49.74)	
Body mass index, kg/m2	28.72 ± 6.55	28.30 ± 7.23	28.29 ± 7.17	28.63 ± 6.71	28.94 ± 6.29	29.01 ± 5.93	28.84 ± 5.31	< 0.001
Systolic blood pressure, mmHg	124.35 ± 19.44	121.50 ± 18.16	120.75 ± 18.15	123.15 ± 18.82	125.84 ± 19.55	128.15 ± 20.73	129.73 ± 22.25	< 0.001
Diastolic blood pressure, mmHg	69.95 ± 13.39	64.25 ± 14.95	67.06 ± 12.76	69.48 ± 12.98	71.30 ± 13.32	71.97 ± 14.04	72.46 ± 14.84	< 0.001
eGFR, mg/min/1.73 m2	88.15 ± 28.80	85.99 ± 33.32	88.36 ± 29.11	88.62 ± 27.65	87.69 ± 28.32	87.00 ± 30.32	90.86 ± 35.18	< 0.001
Serum lipid level								
High density lipoprotein cholesterol								< 0.001
mg/dL	52.88 ± 16.00	41.18 ± 10.09	48.42 ± 12.26	52.23 ± 14.76	54.86 ± 16.82	56.51 ± 18.83	56.51 ± 20.30	
mmol/L	1.37 ± 0.41	1.06 ± 0.26	1.25 ± 0.32	1.35 ± 0.38	1.42 ± 0.43	1.46 ± 0.49	1.46 ± 0.52	
Total cholesterol								< 0.001
mg/dL	197.89 ± 42.71	108.43 ± 9.78	144.57 ± 10.54	180.30 ± 11.39	217.45 ± 11.30	255.65 ± 11.18	309.07 ± 41.61	
mmol/L	5.12 ± 1.10	2.80 ± 0.25	3.74 ± 0.27	4.66 ± 0.29	5.62 ± 0.29	6.61 ± 0.29	7.99 ± 1.08	
Comorbidities, n (%)								
Hypertension								< 0.001
No	20510 (55.77)	257 (47.24)	3388 (56.42)	7889 (58.02)	6163 (55.60)	2146 (50.89)	667 (50.26)	
Yes	16265 (44.23)	287 (52.76)	2617 (43.58)	5709 (41.98)	4921 (44.40)	2071 (49.11)	660 (49.74)	

Abbreviations: n, number; eGFR, estimated glomerular filtration rate.

Values are mean ± standardized differences or n (%).

Characteristic	Total cholesterol, mg/dL							
	Total	< 120	120–159	160–199	200–239	240–279	≥ 280	P-value
Diabetes								< 0.001
No	30753 (83.62)	371 (68.20)	4712 (78.47)	11465 (84.31)	9548 (86.14)	3588 (85.08)	1069 (80.56)	
Yes	6022 (16.38)	173 (31.80)	1293 (21.53)	2133 (15.69)	1536 (13.86)	629 (14.92)	258 (19.44)	
Cardiovascular disease								< 0.001
No	33230 (90.36)	426 (78.31)	5130 (85.43)	12307 (90.51)	10296 (92.89)	3869 (91.75)	1202 (90.58)	
Yes	3545 (9.64)	118 (21.69)	875 (14.57)	1291 (9.49)	788 (7.11)	348 (8.25)	125 (9.42)	
Cancer								0.004
No	33524 (91.16)	470 (86.40)	5480 (91.26)	12392 (91.13)	10122 (91.32)	3838 (91.01)	1222 (92.09)	
Yes	3251 (8.84)	74 (13.60)	525 (8.74)	1206 (8.87)	962 (8.68)	379 (8.99)	105 (7.91)	
Treatment, n (%)								
Hypoglycemic agents								< 0.001
No	33473 (91.02)	419 (77.02)	5114 (85.16)	12431 (91.42)	10328 (93.18)	3975 (94.26)	1206 (90.88)	
Yes	3302 (8.98)	125 (22.98)	891 (14.84)	1167 (8.58)	756 (6.82)	242 (5.74)	121 (9.12)	
Lipid-lowering drugs								< 0.001
No	31660 (86.09)	383 (70.40)	4609 (76.75)	11521 (84.73)	10002 (90.24)	3925 (93.08)	1220 (91.94)	
Yes	5115 (13.91)	161 (29.60)	1396 (23.25)	2077 (15.27)	1082 (9.76)	292 (6.92)	107 (8.06)	
Antiplatelet drugs								< 0.001

Abbreviations: n, number; eGFR, estimated glomerular filtration rate.

Values are mean ± standardized differences or n (%).

Characteristic	Total cholesterol, mg/dL							
	Total	< 120	120–159	160–199	200–239	240–279	≥ 280	P-value
No	36068 (98.08)	511 (93.93)	5781 (96.27)	13328 (98.01)	10962 (98.90)	4174 (98.98)	1312 (98.87)	
Yes	707 (1.92)	33 (6.07)	224 (3.73)	270 (1.99)	122 (1.10)	43 (1.02)	15 (1.13)	
Antihypertensive drugs								< 0.001
No	26830 (72.96)	314 (57.72)	4073 (67.83)	9997 (73.52)	8287 (74.77)	3149 (74.67)	1010 (76.11)	
Yes	9945 (27.04)	230 (42.28)	1932 (32.17)	3601 (26.48)	2797 (25.23)	1068 (25.33)	317 (23.89)	
Outcomes, n (%)								
Cardiovascular disease mortality								0.001
No	35833 (97.44)	520 (95.59)	5850 (97.42)	13280 (97.66)	10804 (97.47)	4104 (97.32)	1275 (96.08)	
Yes	942 (2.56)	24 (4.41)	155 (2.58)	318 (2.34)	280 (2.53)	113 (2.68)	52 (3.92)	
Cancer mortality								0.005
No	35800 (97.35)	517 (95.04)	5860 (97.59)	13248 (97.43)	10795 (97.39)	4099 (97.20)	1281 (96.53)	
Yes	975 (2.65)	27 (4.96)	145 (2.41)	350 (2.57)	289 (2.61)	118 (2.80)	46 (3.47)	
All-cause mortality								< 0.001
No	32334 (87.92)	438 (80.51)	5265 (87.68)	12098 (88.97)	9750 (87.96)	3670 (87.03)	1113 (83.87)	
Yes	4441 (12.08)	106 (19.49)	740 (12.32)	1500 (11.03)	1334 (12.04)	547 (12.97)	214 (16.13)	
Abbreviations: n, number; eGFR, estimated glomerular filtration rate.								
Values are mean ± standardized differences or n (%).								

During the follow-up of up to 15 years of NHANES 1999–2014, 3545 participants had CVD, and 3251 participants were diagnosed with cancer. Meanwhile, 4441 all-cause deaths were recorded, including 942

due to CVD and 975 cancer-related deaths.

Associations Between Total Cholesterol And Mortality

Follow-up data on mortality can be obtained from the date the survey was started (median follow-up: 96.06 ± 53.65 months). Cardiovascular, cancer and all-cause mortality showed U-curve associations after adjusting for confounding variables. Based on the restricted cubic spline analysis (Fig. 2), TC levels of 213(mg/dL), 200(mg/dL), and 218(mg/dL) were associated with the lowest all-cause, cardiovascular diseases, and cancer mortality, respectively. These were largely similar to the TC categorical analysis. There were significant non-linear relationships between the levels of TC and specific and all-cause mortality.

Table 2 shows the adjusted HRs (95% CIs) of specific and all-cause mortality in the six groups of TC levels. The association of TC levels with incidence and mortality were non-linear. In models I and II, TC levels < 120 (mg/dL) were strongly linked to all-cause, cardiovascular diseases, and cancer mortality. Similarly, TC levels ≥ 280 (mg/dL) were significantly related to all-cause, deaths associated with cardiovascular diseases. Analysis with multivariable adjustments (model III) showed the HRs of total mortality and cause-specific mortality was still particularly negatively correlated with TC levels in the lower range < 200 mg/dL, especially in the range < 120 mg/dL (HR 1.95; 95% CI 1.59, 2.38, HR 1.78; 95% CI 1.16, 2.72, HR 2.18; 95% CI 1.46, 3.25, respectively). In the upper range, a TC range of ≥ 280 mg/dL was correlated with mortality as a result of CVD (HR 1.40; 95% CI 1.03, 1.91).

Table 2
Multivariate Cox regression analysis of total cholesterol levels with cause-specific mortality

	Event/Total	Event rate/ 1000 person-years	Model I HR (95%CI), P-value	Model II HR (95%CI), P-value	Model III HR (95%CI), P-value
All-cause mortality					
Total cholesterol (per mmol/L increment)	4441/36775	15.09	0.97 (0.94, 0.99) 0.0155	0.93 (0.90, 0.96) < 0.0001	0.95 (0.92, 0.97) 0.0003
Total cholesterol group(mg/dL)					
< 120	106/544	30.08	2.23 (1.83, 2.71) < 0.0001	2.22 (1.82, 2.71) < 0.0001	1.95 (1.59, 2.38) < 0.0001
120–159	740/6005	17.09	1.25 (1.14, 1.36) < 0.0001	1.26 (1.15, 1.38) < 0.0001	1.19 (1.09, 1.30) 0.0002
160–199	1500/13598	13.96	1.0	1.0	1.0
200–239	1334/11084	14.47	1.03 (0.95, 1.11) 0.4789	0.94 (0.87, 1.01) 0.0768	0.97 (0.90, 1.05) 0.5152
240–279	547/4217	15.18	1.07 (0.97, 1.18) 0.1600	0.94 (0.85, 1.04) 0.2205	0.93 (0.84, 1.03) 0.1770
≥ 280	214/1327	18.08	1.27 (1.10, 1.46) 0.0012	1.19 (1.03, 1.37) 0.0188	1.12 (0.96, 1.30) 0.1528
P for trend			0.008	< 0.001	< 0.001
Cardiovascular mortality					

HR, hazard ratio; CI, confidence interval.

Model I adjust for none

Model II adjust for age, gender, and race

Model III adjust for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

	Event/Total	Event rate/ 1000 person-years	Model I HR (95%CI), P-value	Model II HR (95%CI), P-value	Model III HR (95%CI), P-value
Total cholesterol (per mmol/L increment)	942/36775	3.20	0.98 (0.92, 1.03) 0.4026	0.97 (0.91, 1.03) 0.2851	1.02 (0.96, 1.09) 0.5710
Total cholesterol group, mg/dL					
< 120	24/544	6.81	2.36 (1.56, 3.57) < 0.0001	2.18 (1.43, 3.30) 0.0003	1.78 (1.16, 2.72) 0.0080
120–159	155/6005	3.58	1.23 (1.01, 1.49) 0.0368	1.18 (0.98, 1.44) 0.0853	1.03 (0.84, 1.26) 0.7670
160–199	318/13598	2.96	1.0	1.0	1.0
200–239	280/11084	3.04	1.02 (0.87, 1.20) 0.8182	0.96 (0.82, 1.13) 0.6275	1.09 (0.92, 1.28) 0.3329
240–279	113/4217	3.14	1.05 (0.85, 1.30) 0.6690	0.97 (0.78, 1.20) 0.7812	1.01 (0.81, 1.27) 0.9204
≥ 280	52/1327	4.39	1.46 (1.09, 1.96) 0.0116	1.47 (1.09, 1.98) 0.0107	1.40 (1.03, 1.91) 0.0310
P for trend			0.395	0.249	0.557
Cancer mortality					
Total cholesterol (per mmol/L increment)	975/36775	3.31	0.96 (0.90, 1.02) 0.1579	0.93 (0.88, 0.99) 0.0206	0.94 (0.88, 1.00) 0.0457
Total cholesterol group, mg/dL					

HR, hazard ratio; CI, confidence interval.

Model I adjust for none

Model II adjust for age, gender, and race

Model III adjust for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

	Event/Total	Event rate/ 1000 person-years	Model I HR (95%CI), P-value	Model II HR (95%CI), P-value	Model III HR (95%CI), P-value
< 120	27/544	7.66	2.41 (1.63, 3.56) < 0.0001	2.35 (1.58, 3.48) < 0.0001	2.18 (1.46, 3.25) 0.0001
120–159	145/6005	3.35	1.04 (0.86, 1.26) 0.6803	1.05 (0.87, 1.28) 0.6133	1.04 (0.85, 1.27) 0.7274
160–199	350/13598	3.26	1.0	1.0	1.0
200–239	289/11084	3.13	0.96 (0.82, 1.12) 0.5754	0.89 (0.76, 1.04) 0.1295	0.87 (0.74, 1.02) 0.0869
240–279	118/4217	3.27	1.00 (0.81, 1.23) 0.9665	0.90 (0.73, 1.12) 0.3477	0.90 (0.73, 1.12) 0.3598
≥ 280	46/1327	3.89	1.18 (0.86, 1.60) 0.3022	1.14 (0.84, 1.56) 0.3997	1.13 (0.83, 1.56) 0.4384
P for trend			0.24	0.0496	0.073
HR, hazard ratio; CI, confidence interval.					
Model I adjust for none					
Model II adjust for age, gender, and race					
Model III adjust for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).					

Kaplan-Meier survival curve (Fig. 3) for all-cause, cardiovascular, and cancer mortality showed that the lowest cumulative survival rate was observed in the lowest TC level group.

We observed that the cutoff values were 145 mg/dL,143 mg/dL, and 149 mg/dL for cancer, cardiovascular, and all-cause mortality, respectively, by using a two-piecewise linear regression model (Table 3). When TC levels were < 149 mg/dL, 145 mg/dL, and 143 mg/dL, a 1-unit decrease in the TC level was associated with a 51%, 55%, and 55% greater adjusted hazard ratio of all-cause, cancer, and cardiovascular mortality, respectively (HR 0.49; 95% CI 0.42, 0.58, HR 0.45; 95% CI 0.31, 0.66, HR 0.45; 95% CI 0.29, 0.68, respectively). Cancer and all-cause mortality were not related when TC levels were ≥ 149 mg/dL and 143 mg/dL, respectively. When TC levels were ≥ 145 mg/dL, a 1-unit increase in the TC

level was linked to a 7% greater adjusted hazard ratio of cardiovascular mortality (HR 1.07; 95% CI 1.00, 1.15).

Table 3
The results of two-piecewise linear regression model between total cholesterol and cause-specific mortality

	All-cause mortality HR (95% CI) P-value	Cardiovascular disease mortality HR (95% CI) P-value	Cancer mortality HR (95% CI) P-value
Cutoff value, mmol/L	3.85(149 mg/dL)	3.75(145 mg/dL)	3.70 (143 mg/dL)
<Cut-off value	0.49 (0.42, 0.58) < 0.0001	0.45 (0.31, 0.66) < 0.0001	0.45 (0.29, 0.68) 0.0002
≥Cut-off value	0.99 (0.96, 1.03) 0.7614	1.07 (1.00, 1.15) 0.0469	0.98 (0.91, 1.05) 0.4897
P for log likelihood ratio test	< 0.001	< 0.001	0.001
HR, hazard ratio; CI, confidence interval.			
The two-piecewise linear regression model were adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).			

Subgroup Analyses

Subgroup analyses according to age, gender, race, with or without CVD, with or without cancer, and lipid-lowering drugs of diabetes are presented in Table 4.

Table 4
Subgroups analyses for mortality.

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
All-cause mortality								
Age, years								0.888
< 65	27927	1.91 (1.32, 2.78) 0.0006	1.16 (0.98, 1.38) 0.0939	1.0	1.08 (0.94, 1.24) 0.2865	1.11 (0.93, 1.32) 0.2694	1.50 (1.19, 1.90) 0.0007	
≥ 65	8848	1.83 (1.44, 2.33) < 0.0001	1.16 (1.04, 1.30) 0.0058	1.0	0.95 (0.86, 1.04) 0.2498	0.86 (0.75, 0.97) 0.0160	0.95 (0.78, 1.15) 0.5767	
Gender								0.150
Male	17853	1.93 (1.53, 2.45) < 0.0001	1.24 (1.11, 1.39) 0.0001	1.0	1.01 (0.91, 1.11) 0.8981	0.99 (0.85, 1.14) 0.8520	1.22 (0.97, 1.54) 0.0961	
Female	18922	2.20 (1.45, 3.32) 0.0002	1.10 (0.94, 1.30) 0.2309	1.0	0.93 (0.83, 1.04) 0.2074	0.88 (0.76, 1.01) 0.0709	1.03 (0.85, 1.26) 0.7519	
Race								0.513

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
Non-white	19276	2.29 (1.68, 3.13) < 0.0001	1.21 (1.04, 1.40) 0.0115	1.0	0.97 (0.86, 1.09) 0.5882	0.96 (0.82, 1.12) 0.5732	1.12 (0.89, 1.41) 0.3273	
White	17499	1.75 (1.34, 2.29) < 0.0001	1.16 (1.03, 1.30) 0.0157	1.0	0.98 (0.89, 1.09) 0.7458	0.93 (0.81, 1.06) 0.2904	1.13 (0.93, 1.38) 0.2261	
Cardiovascular disease								0.002
No	33230	1.89 (1.41, 2.52) < 0.0001	1.24 (1.10, 1.39) 0.0003	1.0	0.92 (0.84, 1.00) 0.0569	0.86 (0.77, 0.97) 0.0138	1.06 (0.89, 1.27) 0.4988	
Yes	3545	2.05 (1.54, 2.73) < 0.0001	1.15 (0.99, 1.34) 0.0699	1.0	1.18 (1.01, 1.37) 0.0403	1.17 (0.96, 1.44) 0.1259	1.27 (0.95, 1.71) 0.1041	
Cancer								0.076
No	33524	2.23 (1.75, 2.85) < 0.0001	1.24 (1.12, 1.38) < 0.0001	1.0	0.98 (0.90, 1.07) 0.7196	0.95 (0.85, 1.07) 0.3905	1.12 (0.95, 1.31) 0.1935	

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
Yes	3251	1.61 (1.12, 2.32) 0.0109	1.04 (0.85, 1.27) 0.6921	1.0	0.96 (0.81, 1.13) 0.5972	0.85 (0.67, 1.09) 0.1964	1.18 (0.82, 1.71) 0.3628	
Lipid-lowering drugs								< 0.001
No	31660	2.75 (2.10, 3.59) < 0.0001	1.22 (1.09, 1.37) 0.0009	1.0	0.94 (0.87, 1.03) 0.1795	0.92 (0.82, 1.02) 0.1180	1.05 (0.90, 1.24) 0.5273	
Yes	5115	1.35 (0.99, 1.84) 0.0575	1.14 (0.99, 1.33) 0.0759	1.0	1.14 (0.96, 1.36) 0.1277	1.04 (0.75, 1.44) 0.8015	1.79 (1.22, 2.62) 0.0031	
Cardiovascular mortality								
Age, years								0.164
< 65	27927	2.18 (0.86, 5.51) 0.0985	1.52 (0.98, 2.36) 0.0615	1.0	1.54 (1.08, 2.21) 0.0171	1.42 (0.89, 2.25) 0.1384	3.05 (1.88, 4.95) < 0.0001	
≥ 65	8848	1.64 (1.02, 2.65) 0.0423	0.95 (0.76, 1.19) 0.6625	1.0	0.96 (0.79, 1.16) 0.6697	0.85 (0.66, 1.11) 0.2381	0.84 (0.55, 1.28) 0.4126	
Gender								0.623

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
Male	17853	1.86 (1.16, 3.00) 0.0104	1.11 (0.88, 1.40) 0.3650	1.0	1.05 (0.84, 1.30) 0.6890	1.12 (0.82, 1.53) 0.4712	1.65 (1.06, 2.55) 0.0252	
Female	18922	1.74 (0.63, 4.79) 0.2808	0.85 (0.56, 1.28) 0.4395	1.0	1.11 (0.86, 1.44) 0.4262	0.88 (0.63, 1.22) 0.4357	1.19 (0.77, 1.84) 0.4342	
Race								0.284
Non-white	19276	1.30 (0.52, 3.22) 0.5724	1.25 (0.90, 1.73) 0.1872	1.0	1.19 (0.92, 1.55) 0.1929	1.15 (0.82, 1.61) 0.4298	1.44 (0.90, 2.28) 0.1273	
White	17499	1.91 (1.17, 3.11) 0.0093	0.91 (0.71, 1.17) 0.4479	1.0	1.02 (0.82, 1.27) 0.8396	0.92 (0.68, 1.25) 0.6033	1.36 (0.90, 2.06) 0.1397	
Cardiovascular disease								0.908
No	33230	0.80 (0.30, 2.17) 0.6646	1.05 (0.79, 1.40) 0.7129	1.0	0.98 (0.80, 1.20) 0.8582	0.91 (0.69, 1.21) 0.5238	1.32 (0.90, 1.92) 0.1512	
Yes	3545	2.32 (1.42, 3.79) 0.0008	1.02 (0.77, 1.36) 0.8706	1.0	1.26 (0.95, 1.67) 0.1140	1.14 (0.76, 1.70) 0.5324	1.49 (0.87, 2.55) 0.1479	
Cancer								0.262

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
No	33524	1.40 (0.77, 2.52) 0.2684	1.04 (0.83, 1.30) 0.7507	1.0	1.12 (0.93, 1.34) 0.2317	1.13 (0.89, 1.44) 0.3261	1.38 (0.98, 1.93) 0.0647	
Yes	3251	2.35 (1.21, 4.57) 0.0114	1.01 (0.64, 1.57) 0.9767	1.0	0.93 (0.63, 1.39) 0.7389	0.49 (0.23, 1.04) 0.0645	1.71 (0.81, 3.58) 0.1569	
Lipid-lowering drugs								0.851
No	31660	2.38 (1.21, 4.68) 0.0122	1.10 (0.83, 1.45) 0.5067	1.0	1.12 (0.92, 1.36) 0.2487	1.02 (0.80, 1.31) 0.8560	1.34 (0.95, 1.89) 0.0918	
Yes	5115	1.37 (0.79, 2.39) 0.2615	0.94 (0.70, 1.25) 0.6728	1.0	1.00 (0.70, 1.42) 0.9819	0.83 (0.42, 1.65) 0.5895	1.75 (0.84, 3.64) 0.1367	
Cancer mortality								
Age, years								< 0.001
< 65	27927	2.10 (1.10, 4.01) 0.0247	0.83 (0.59, 1.18) 0.2988	1.0	0.94 (0.73, 1.21) 0.6306	1.03 (0.75, 1.42) 0.8608	1.50 (0.98, 2.29) 0.0599	
≥ 65	8848	2.03 (1.22, 3.39) 0.0065	1.11 (0.86, 1.42) 0.4288	1.0	0.87 (0.70, 1.08) 0.1984	0.85 (0.63, 1.14) 0.2861	0.88 (0.54, 1.44) 0.6118	

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
Gender								0.994
Male	17853	2.18 (1.37, 3.47) 0.0010	1.25 (0.98, 1.58) 0.0685	1.0	0.92 (0.74, 1.14) 0.4439	0.98 (0.72, 1.32) 0.8777	1.41 (0.90, 2.22) 0.1339	
Female	18922	2.65 (1.16, 6.05) 0.0209	0.60 (0.39, 0.92) 0.0180	1.0	0.80 (0.62, 1.02) 0.0742	0.84 (0.61, 1.15) 0.2738	0.93 (0.59, 1.46) 0.7544	
Race								0.081
Non-white	19276	2.50 (1.38, 4.56) 0.0027	1.07 (0.79, 1.44) 0.6648	1.0	0.85 (0.67, 1.08) 0.1828	0.73 (0.52, 1.02) 0.0679	1.04 (0.64, 1.68) 0.8808	
White	17499	2.00 (1.16, 3.44) 0.0126	1.00 (0.76, 1.31) 0.9765	1.0	0.88 (0.71, 1.10) 0.2659	1.06 (0.80, 1.40) 0.6954	1.21 (0.79, 1.85) 0.3836	
Cardiovascular disease								0.073
No	33230	2.55 (1.57, 4.15) 0.0002	1.04 (0.82, 1.32) 0.7462	1.0	0.83 (0.70, 1.00) 0.0449	0.83 (0.65, 1.06) 0.1319	1.16 (0.82, 1.64) 0.4133	
Yes	3545	1.83 (0.90, 3.73) 0.0977	1.09 (0.75, 1.58) 0.6632	1.0	1.02 (0.70, 1.49) 0.9081	1.27 (0.79, 2.03) 0.3211	0.96 (0.43, 2.12) 0.9136	

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Characteristic	Number	Total cholesterol, mg/dL Hazard ratios (95%CI)						P-interaction
		< 120	120–159	160–199	200–239	240–279	≥ 280	
Cancer								0.342
No	33524	2.13 (1.21, 3.76) 0.0090	1.09 (0.86, 1.38) 0.4784	1.0	0.82 (0.68, 0.99) 0.0395	0.88 (0.69, 1.13) 0.3188	1.06 (0.73, 1.53) 0.7564	
Yes	3251	2.47 (1.37, 4.44) 0.0026	0.96 (0.65, 1.41) 0.8327	1.0	1.02 (0.75, 1.39) 0.8887	0.97 (0.63, 1.51) 0.9049	1.40 (0.74, 2.67) 0.3015	
Lipid-lowering drugs								0.038
No	31660	3.25 (2.02, 5.22) < 0.0001	1.08 (0.85, 1.39) 0.5261	1.0	0.81 (0.67, 0.97) 0.0194	0.93 (0.74, 1.17) 0.5363	1.13 (0.81, 1.58) 0.4825	
Yes	5115	1.17 (0.55, 2.46) 0.6812	0.95 (0.67, 1.35) 0.7715	1.0	1.29 (0.89, 1.86) 0.1783	0.49 (0.18, 1.35) 0.1676	1.17 (0.43, 3.24) 0.7570	

CI, confidence interval.

When analyzing a subgroup variable, age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs) were all adjusted except the variable itself.

Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

Strong links between the lowest range of TC level and all-cause mortality were observed in all subgroups except for using lipid-lowering drugs. When the range of TC level was 120–159 mg/dL, significant associations were also observed in patients aged ≥ 65 years, male, all races, without CVD, without cancer or without using lipid-lowering drugs. When the range of TC range was 200–239 mg/dL, we only found a significant association in patients with CVD. However, In the range 240–279 mg/dL, there was a substantial association in patients without CVD or aged ≥ 65 years. In the groups aged < 65 years and

using lipid-lowering drugs, the associations between the highest rang of TC level and all-cause mortality was significant. There were substantial interactions with CVD and lipid-lowering drugs in the association of TC level with all-cause mortality (P for interaction = 0.002 and, < 0.001, respectively)

The significant associations between the lowest range of TC and cardiovascular mortality were observed in patients aged ≥ 65 years, male, white, with CVD, with cancer or without using lipid-lowering drugs. Similarly, the significant association was also found in patients aged < 65 years with a TC range of 200–239 mg/dL and aged < 65 years or male with the highest range of TC level. However, no significant interaction was observed in cardiovascular mortality.

The associations of the lowest range of TC range with cancer mortality were significant in all subgroups except for CVD and using lipid-lowering drugs. Interestingly, female with a TC range 120–159 mg/dL was inclined to have lower all- cancer mortality. Besides, the significant associations of TC level range 200–239 mg/dL with cancer mortality were observed in patients without CVD, without cancer or without using lipid-lowering drugs. There were significant interactions with age and lipid-lowering medications in the association of TC level with cancer mortality (P for interaction < 0.001 and, = 0.038, respectively)

Discussion

Herein, we revealed that there was a dose-dependent association of TC with all causes and specific mortality using data from the US NHNES. U-curve relationships between TC and mortality were found. Negative correlations in the lower TC range were strong in all-cause and specific mortality, whereas positive correlations in the upper TC range were only found in CVD mortality. The occurrence of a TC range of < 120 mg/dL was strongly predictive of enhanced death risk from all causes, whereas a TC range of ≥ 280 mg/dL was not except for CVD mortality.

Until recently, it was thought that TC is a biomarker of cholesterol metabolism and a significant contributor to atherosclerotic CVD, especially for the risk of CVDs. However, findings from previous studies have been inconsistent. Varied association shapes for TC versus all-cause mortality were obtained, including positive linear, U-curve, reverse-L-curve (or reverse-J-curve), and negative associations [15, 21, 22].

Current guidelines on cholesterol levels are largely based on CVD risk, and they all suggest a TC range of < 200 mg/dL. However, our study demonstrated that a TC range of < 200 mg/dL TC was strongly linked to a higher risk of death from all causes, including CVD. It is no surprise that TC range < 200 mg/dL does not usually indicate good health with regards to the presence of other diseases. A recent national guideline on nutrition also did not recommend a reduction in dietary cholesterol[23]. Additionally, previous studies mainly focus on elderly populations. Our study showed the stronger effect size associated with TC range < 120 mg/dL at age ≥ 65 years as well as age < 65 in all-cause and cancer mortality. However, interpreting the connection between CVD mortality and cholesterol has been an intractable clinical challenge. In this study, TC range < 120 mg/dL was negatively linked to cardiovascular mortality in patients age ≥ 65 years. In contrast, the TC range of ≥ 280 mg/dL was positively related to cardiovascular and all-cause mortality

in patients age < 65 years. Since people with low cholesterol levels exhibited higher rates of all-cause and cancer mortality, we postulated that low TC may partially reflect frailty. However, for CVD mortality, aged people (age ≥ 65 years) with TC range < 120 mg/dL had a higher risk of death, and those below 65 years of age with TC range ≥ 280 mg/dL were more likely to die relative to aged people. Similarly, the association between low TC and higher occurrence rate of serious adverse cardiovascular events in men aged ≥ 70 years has also been reported [24].

TC levels were classified into three categories: desirable (less than 200) borderline high (between 200 to 239), and high level (≥ 240 mg/dL). However, the categories were suggested according to the interactions between IHD and TC. In this study, 213(mg/dL), 200(mg/dL), and 218(mg/dL) TC levels were linked to the lowest all-cause, cardiovascular, and cancer mortality in the spline analyses, respectively. Our data indicated that the optimal overall survival (OS) ranges were higher relative to those for IHD. The previous studies have shown a higher optimal body-mass index range for OS relative to IHD mortality [25]. Cholesterol levels may reflect the general health status but not specific for CVD [26].

The association of low cholesterol levels with higher mortality may be explained by reverse causality. However, a study that involved long-term follow-up of the Japanese-American population indicated that people with low cholesterol levels that last for more than 20 years were likely to have the worst all-cause mortality. It suggested that reverse causality was not likely to be fully responsible for the higher mortality linked to low cholesterol [27].

Besides, a key finding in cancer of our study suggested that low cholesterol could be linked to high cancer-associated deaths. Although a few studies of statins indicated that statin therapy increases cancer incidence [28–30], it was still challenging to elucidate the connection between low cholesterol and cancer disease mortality. Previous studies on liver cancer reported an increased level of cholesterol[31, 32]. However, in this study, a higher rate of cancer mortality in the group with the lowest cholesterol was also significant, and the effects of malnutrition should be considered. This suggested that screening the low cholesterol levels of patients with cancers was needed.

A large-scale, long-term complete follow-up study evaluating the influence of TC on all-cause and specific mortality are clear strengths of this study, and a large sample size used can ensure statistical efficiency. The NHANES database represented the entire US population, and this study was showing that low TC is a significant risk factor, not only in patients but also in the general population. Another advantage of this study is that it estimated all causes, CVD, and cancer mortality risk related to TC levels as low as < 120 mg/dL. However, this study had some limitations. Firstly, we could not understand the reason behind the link between TC and mortality risk in a cross-sectionally designed study. Secondly, we might have underestimated the risk associated with high cholesterol. Also, we could not verify that low cholesterol levels induced by statin increase mortality. Thirdly, this study was based on American participants; as such, its findings may not apply to other populations. Although the U-curve associations can apply to other ethnic groups, the level of relative risk related to TC, as well as the optimal TC range with the lowest mortality, could differ among various ethnic groups.

Conclusions

In summary, a U-curve association of TC level with CVD, cancer, and all-cause mortality risks was observed in the American population, suggesting that too low or too high cholesterol levels in the serum might increase the opportunity of adverse outcomes. Besides, high TC levels were linked to CVD mortality, and positive correlations in the upper TC range were enhanced in age <65 years and reduced in advanced age. However, a low TC level was liked to more adverse outcomes. Our findings indicated that TC levels might be a critical risk factor in the general population, and TC levels <200 mg/dL might not be indicative of good health. However, there is a need to conduct further studies to verify our findings. This will aid in the appropriate management of the disorders that are linked to low TC levels, and hence improve survival.

List Of Abbreviations

total cholesterol (TC); cardiovascular disease (CVD); the National Health and Nutrition Examination Survey (NHANES); the National Center for Health Statistics (NCHS); systolic blood pressures (SBP); diastolic blood pressure (DBP); hemoglobin A1c (HbA1C); hazard ratios (HRs); confidence intervals (CIs)

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

HGD, LXC, HYQ and FYQ designed the study. HGD, LXC and HYQ draft the manuscript. All authors participated in reviewing and editing the manuscript. LK, LXC and HYQ participated in data analysis. HGD, LXC, HYQ, LK, LL, YYL, CCL and HJY participated in data downloading and collection. FYQ is the guarantor of this work. All authors read and approved the final draft of the manuscript for publication.

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Figures

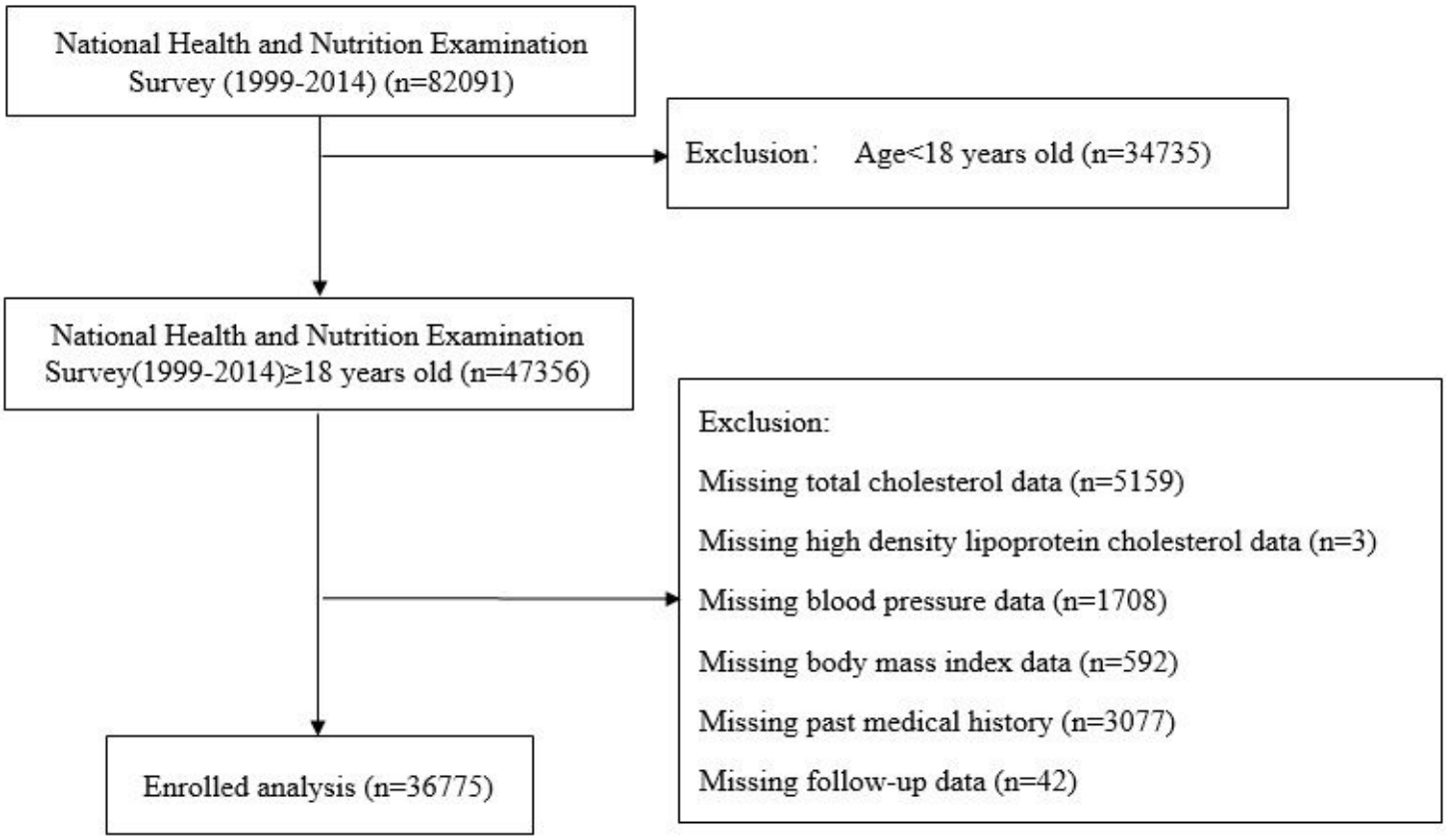

Figure 1

Study cohort.

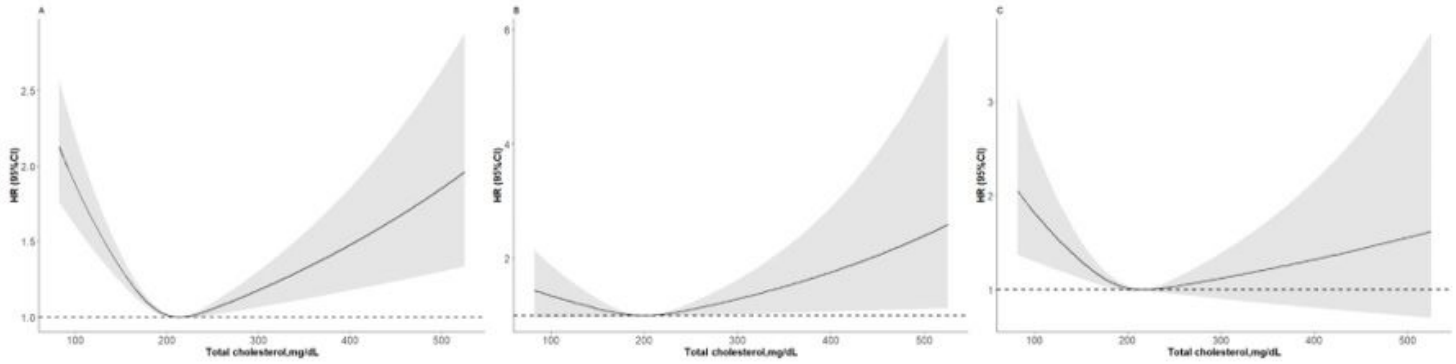

Figure 2

Spline analyses of mortality by total cholesterol levels. Spline analyses of all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol levels. Adjusted for age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, comorbidities (hypertension, diabetes, cardiovascular disease, and cancer), and medication use(antihypertensive drugs, hypoglycemic agents, antiplatelet drugs, and lipid-lowering drugs).

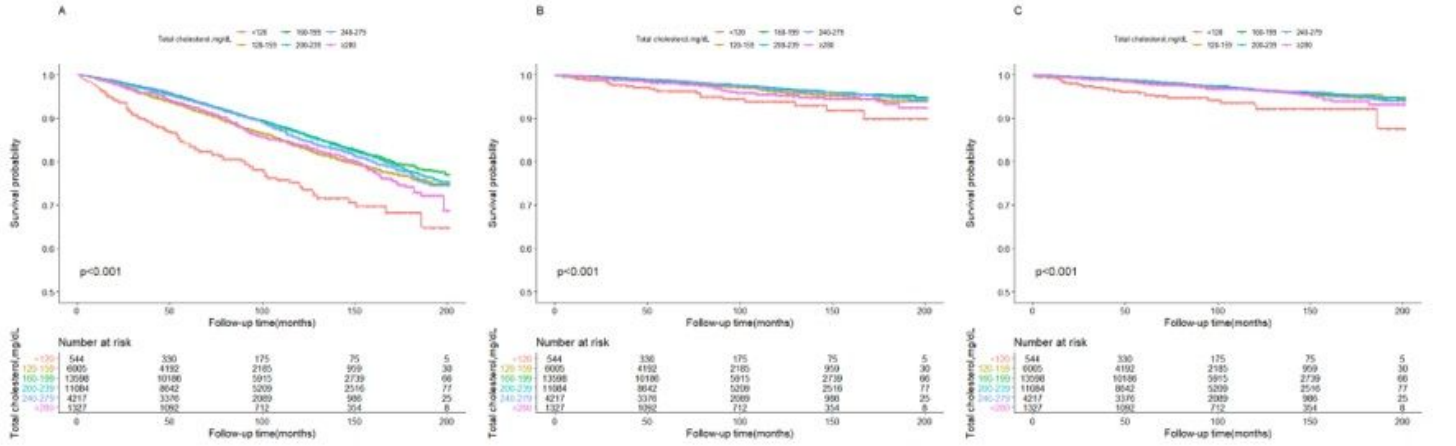

Figure 3

Kaplan-Meier survival curve for all-cause (A), cardiovascular (B), and cancer (C) mortality by total cholesterol groups.