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Low and Decreasing Cholesterol Levels and Risk of All-Cause and Cause-Specific Mortality: A Prospective and Longitudinal Cohort Study



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ABSTRACT

This prospective study aimed to investigate the associations of untreated cholesterol levels and their longitudinal changes, especially low levels, with all-cause and cause-specific mortality in different populations. Participants were drawn from two Chinese cohorts and the UK Biobank, excluding those with lipid-lowering medications, coronary heart disease (CHD), stroke, cancer, clinically diagnosed chronic obstructive pulmonary disease, low body mass index ($<18.5 \text{ kg}\cdot\text{m}^{-2}$) at baseline, and deaths within the first two years to minimize reverse causality. Individual cholesterol changes were assessed in a subset who attended the resurvey after over four years. Mortality data were linked to registries, and risks were estimated using Cox proportional hazards models. A total of 163 115 Chinese and 317 305 UK adults were included (mean age, 49–61 years), with 43%, 81%, and 44% males in Dongfeng–Tongji, Kailuan, and UK Biobank cohorts, respectively. During a median follow-up of 9.7–12.9 years, 9553 and 15 760 deaths were documented in the Chinese cohorts and UK Biobank, respectively. After multivariate adjustments, nonlinear relationships were observed between total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) levels and mortality. In both populations, high cholesterol was primarily associated with CHD mortality, while low cholesterol associated with all-cause and cancer mortality ($P_{\text{nonlinear}} \leq 0.0161$). The optimal levels for all-cause mortality risk in Chinese adults (TC: $200 \text{ mg}\cdot\text{dL}^{-1}$; LDL-C: $130 \text{ mg}\cdot\text{dL}^{-1}$; non-HDL-C: $155 \text{ mg}\cdot\text{dL}^{-1}$) were lower than those in the UK Biobank but consistent with guideline recommendation. Additionally, decreasing cholesterol levels over four years were associated with higher all-cause and cancer mortality in the Chinese cohorts ($P_{\text{nonlinear}} \leq 0.0100$). Participants with low TC, LDL-C, or non-HDL-C levels at both baseline and resurvey experienced elevated all-cause mortality risks in both populations, as did those with low/medium baseline levels and $>20\%$ reductions over time in Chinese adults. In conclusion, higher TC, LDL-C, and non-HDL-C levels are associated with

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elevated CHD mortality. Importantly, low and/or longitudinally decreasing cholesterol levels are robustly associated with increased all-cause and cancer mortality, potentially serving as markers of premature death. Regular cholesterol monitoring, with attention to both high and low levels, is recommended to inform guideline updates and clinical strategies.

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1. Introduction

Cholesterol is essential for normal physiological functions, and low levels of blood cholesterol may impair health. Cholesterol also plays a crucial role in the development of both cardiovascular disease (CVD) and cancer. However, current lipid management guidelines primarily focus on CVD risk assessment based on randomized clinical trials (RCTs), which often involve participants with high cholesterol levels [1,2]. The potential risks of low cholesterol, particularly in the absence of lipid-lowering interventions, remain insufficiently addressed.

Emerging evidence from cohort studies has linked low-density lipoprotein cholesterol (LDL-C) levels below 70 mg·dL⁻¹ with elevated risks of all-cause, CVD (or its subtype), and cancer mortality. Such findings have been observed across multiple populations, including the general population of Copenhagen ($n = 108\,243$) [3], non-statin users in two Korean cohorts (both $n > 182\,000$) [4], and two Chinese populations with either low or high CVD risk (both $n > 820\,000$) [5]. Non-high-density lipoprotein cholesterol (non-HDL-C), a strong predictor of CVD, has shown inconsistent associations with mortality, with higher levels yielding opposite associations in different populations [6–8]. Moreover, high levels of HDL-C, traditionally regarded as “good cholesterol,” have been associated with elevated risks of CVD and mortality [9,10]. Notably, existing studies on high LDL-C and CVD mortality have been confounded by variations in baseline comorbidity exclusion [3,4,6]. Most previous studies failed to adequately exclude participants that were using lipid-lowering medications or suffering comorbidities such as cancer, chronic obstructive pulmonary disease (COPD), or preclinical diseases [3,7,11,12]. These methodological gaps could lead to spurious associations between both low and high cholesterol levels and mortality due to residual confounding or reverse causation.

Cholesterol levels fluctuate with aging, environmental factors, and behavioral determinants [13]. Guidelines recommend routine blood lipid screening every five years for adults over 20 years [1,14]. However, few studies have evaluated the association between longitudinal changes in cholesterol levels and mortality, with the exception of total cholesterol (TC) [11,15,16]. A Korean cohort study found that both two year increases and decreases in TC levels were linked to elevated all-cause mortality among participants without lipid-lowering medications and preexisting CVD or cancer [16]. However, lifestyle changes such as smoking and drinking were not accounted for [11,15,16]. Thus, the relationships of baseline levels and longitudinal changes in multiple cholesterol fractions with mortality require further investigation [3,7,11,12,15].

To address these gaps, we conducted a rigorous multicohort study in two Chinese cohorts to investigate associations between untreated baseline cholesterol levels and their longitudinal changes with all-cause and cause-specific mortality. We further evaluated the robustness and generalizability of our findings using data from the UK Biobank. This study focused exclusively on participants without lipid-lowering treatment, and its findings did not conflict with the efficacy of cholesterol-lowering therapies in high-risk CVD patients.

2. Methods

2.1. Study population

This study involved three population-based prospective cohorts, namely the Dongfeng–Tongji cohort ($n = 41\,129$, during 2008–2013), Kailuan study ($n = 159\,017$, during 2006–2013), and UK Biobank ($n = 502\,401$, during 2006–2010) [17–19]. To minimize reverse causality and pharmacological confounding, we excluded participants with lipid-lowering medication usage, coronary heart disease (CHD), stroke, cancer, clinically diagnosed COPD, or low body mass index ($BMI < 18.5\text{ kg}\cdot\text{m}^{-2}$) at baseline, or deaths within the first two years of follow-up. After further excluding those without lipid measurements or with extreme values ($< 0.1\text{th}$ or $> 99.9\text{th}$ percentiles), 25 523 (Dongfeng–Tongji), 137 592 (Kailuan), and 317 305 (UK Biobank) apparently healthy participants were included for the baseline analysis.

The longitudinal change analysis included participants who attended both baseline and resurvey after four to five years. This was performed among 24 175 participants in the Dongfeng–Tongji cohort (baseline 2008–2010; resurvey in 2013), 68 746 participants in the Kailuan study (baseline 2006–2007; resurvey 2010–2011), and 20 343 participants in the UK Biobank (baseline 2006–2010; resurvey 2012–2013). The number of individuals with lipid-lowering medications increased from 4337 to 5820 in Dongfeng–Tongji, from 1923 to 2763 in Kailuan, and from 4366 to 6000 in the UK Biobank between the two surveys. Accordingly, we excluded those with lipid-lowering medication usage and above-mentioned diseases at or before resurvey, deaths within two years after the resurvey, and those with missing or extreme lipid values at either time point. This left 12 947 (Dongfeng–Tongji), 59 043 (Kailuan), and 11 738 (UK Biobank) participants for evaluating the associations between untreated cholesterol changes and mortality.

The sample selection criteria were consistent across all of the cohorts to ensure comparability. Detailed cohort descriptions and selection flowcharts are presented in [Figs. S1 and S2](#) in Appendix A. All of the participants provided written informed consent. The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (approval number, [2008] 03), the Ethics Committee of Kailuan General Hospital (ChiCTR-TNRC-11001489), and the North West Multi-Centre Research Ethics Committee (application number, 88159).

2.2. Measurement of blood lipids

Blood lipid profiles were measured using standard protocols at both baseline and resurvey ([Section S1](#) in Appendix A). LDL-C levels were determined using the Friedewald formula when triglyceride levels were below 400 mg·dL⁻¹ or were directly measured when triglyceride levels not lower than 400 mg·dL⁻¹. Non-HDL-C was derived by subtracting HDL-C from TC. Baseline cholesterol levels were categorized following guideline-defined cutoffs [1,2] and published studies [4–6,8,10], as low, slightly low, medium, slightly high, high, and very high. Specifically, TC levels were grouped as < 120 , 120–160, 160–200, 200–240, 240–280, and ≥ 280 mg·dL⁻¹,

HDL-C as <40, 40–50, 50–60, 60–70, 70–80, and ≥ 80 mg·dL⁻¹, LDL-C as <70, 70–100, 100–130, 130–160, 160–190, and ≥ 190 mg·dL⁻¹, and non-HDL-C as <100, 100–130, 130–160, 160–190, 190–220, and ≥ 220 mg·dL⁻¹. Longitudinal cholesterol changes were calculated with percent change from the baseline to resurvey, and classified into <–20%, –20% to –10%, $\pm 10\%$ (stable), 10% to 20%, and >20% groups, considering that the interquartile ranges (IQR) of changes in most cholesterol levels were around $\pm 20\%$ in the Chinese cohorts.

2.3. Ascertainment of deaths

Participants were followed until December 31, 2018 (Dongfeng–Tongji cohort); December 31, 2016 (Kailuan study); and December 31, 2021 (UK Biobank). In the Chinese cohorts, medical records and health status were tracked every one to three years using unique identification number via healthcare service and social security systems. The UK Biobank received death notifications regularly through linkage to national death registries. Therefore, death events were accurately and timely recorded, ensuring the ascertainment of the outcomes for all study participants. In line with the International Classification of Disease 10th Revisions (ICD-10), deaths from CVD were coded as I00–I99 and those from cancers were coded as C00–C97. Specific codes for their subtypes are presented in [Table S1](#) in Appendix A. We also evaluated non-CVD mortality and other mortality (non-CVD/cancer death).

2.4. Statistical analysis

All analyses were performed separately in each cohort due to the difference of cohort-specific characteristics. Associations between baseline and longitudinal changes in cholesterol levels and mortality were assessed using Cox proportional-hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Proportional-hazards assumption was checked using Schoenfeld residuals, with no violation observed. For cause-specific mortality, competing risks were considered using cause-specific hazard function models. Person-years (PYs) were calculated from baseline date (baseline analysis) or from resurvey date (longitudinal change analysis) to the date of death or end of follow-up, whichever came first. All models were stratified by baseline age (in five-year intervals) and gender [20], and adjusted for BMI, education, smoking, drinking, physical activity, and histories of hypertension and diabetes. We did not adjust for diet in the primary analysis due to lack of data in the Kailuan study. Multicollinearity among these covariates and cholesterol levels was assessed by calculating variance inflation factor (VIF) values and the results indicated no significant collinearity (all VIF < 3). The longitudinal change analyses additionally adjusted for the corresponding baseline cholesterol levels and changes in BMI, smoking, drinking, and physical activity. Covariate definitions were detailed in [Table S2](#) in Appendix A. Missing data of covariates (<3.5% overall) were excluded from the analysis. Restricted cubic splines (RCS) were performed to model the nonlinear associations of baseline cholesterol levels and their changes with mortality [21]. Optimal cholesterol levels for the lowest all-cause mortality risk were determined based on the lowest HR in the RCS models [4]. We also explored all-cause mortality risk by jointly grouping participants according to the baseline (low/medium/high) and resurvey (low/medium/high) cholesterol levels or longitudinal changes (decreasing/stable/increasing) in cholesterol levels.

To provide further insights into the potential associations, we investigated the relationships of baseline cholesterol levels with mortality from major CVD subtypes (myocardial infarction (MI), CHD, and stroke) and cancer deaths with case numbers contributing >0.5% of total deaths (gastrointestinal, respiratory, urological,

hematological). In secondary analyses, baseline cholesterol levels were grouped by the 5th, 20th, 40th, 60th, 80th, and 95th percentiles, accounting for the distributions of cholesterol in each cohort. Several sensitivity analyses were conducted to confirm the robustness of the findings, including ① replacement of the categorical covariates of drinking status, hypertension, and diabetes with their corresponding continuous measurements and medication usage; ② additional adjustments for income and dietary factors available in specific cohorts (namely, dietary habit in the Dongfeng–Tongji cohort, income level and habit of salt preference as a dietary proxy in the Kailuan study, and Townsend deprivation index and dietary habit in the UK Biobank); ③ additional adjustments for other lipid fractions, as well as C-reactive protein and apolipoproteins which were only available in the UK Biobank; and ④ additional exclusions of individuals who had self-reported chronic diseases (chronic hepatitis/liver cirrhosis, gastric ulcer/intestinal ulcer, chronic nephritis/nephrotic syndrome/renal failure/renal dialysis, pulmonary tuberculosis, hyperthyroidism, and anemia) at baseline or who developed cancer, died, or experienced a weight loss exceeding 5% (participants with resurvey data) within the first four years of follow-up. Additionally, we analyzed the mean cholesterol levels of the two measurements and their associations with mortality. The reproducibility of cholesterol levels between the two measurements was assessed using intra-class correlation coefficients (ICCs) to determine the consistency and reliability of the measurements over time.

After separate analysis in each cohort, we applied the inverse-variance-weighted meta-analysis to combine the HR values from the two Chinese cohorts, facilitating comparison with the results from the UK Biobank. Heterogeneity tests demonstrated that most of the association patterns showed a proportion of total variation across studies due to heterogeneity rather than chance (I^2 below 50% and P values higher than 0.05 from Cochran's Q test, indicating low heterogeneity). Consequently, we used the fixed-effect models to present the combined HR estimates, consistent with prior studies involving these two cohorts [18]. All analyses were performed using SAS version 9.4 and R version 3.6.1.

3. Results

3.1. Baseline cholesterol levels and mortality

Basic characteristics of 480 420 participants were summarized in [Table 1](#). The median follow-up duration was 10.2 years in the Dongfeng–Tongji cohort, 9.7 years in the Kailuan study, and 12.9 years in the UK Biobank. During 5 415 868 PYs of follow-up, 25 313 deaths occurred, including 5 841 CVD deaths and 10 098 cancer deaths (3 292 and 2 484 in the Chinese cohorts, 2 549 and 7 614 in the UK Biobank, respectively).

After multivariate adjustments, nonlinear relationships of baseline cholesterol levels with all-cause and cause-specific mortality were observed in the three cohorts ([Table 2](#), [Fig. 1](#)). Compared with the medium group (160–200 mg·dL⁻¹) in the Chinese cohorts, participants with both low and high TC levels (<120, 120–160, and ≥ 280 mg·dL⁻¹) had higher all-cause mortality risks. Moreover, participants with TC < 120 or 120–160 mg·dL⁻¹ showed higher non-CVD, cancer, and other mortality risks, and those with TC ≥ 280 mg·dL⁻¹ had higher non-CVD and other mortality risks. The separate results of the three cohorts are presented in [Table S3](#) in Appendix A. The UK Biobank exhibited consistent trends. Namely, while the lowest group showed a lack of significance due to the limited sample size, the highest group showed a decreased mortality risk ([Table 2](#), [Fig. S3](#) in Appendix A). Additionally, Chinese adults with LDL-C < 70 mg·dL⁻¹ and non-HDL-C < 100 mg·dL⁻¹ had 18%–29% higher all-cause, non-CVD, cancer, and other

Table 1
Basic characteristics of the study population in the baseline analysis.

Characteristics	Dongfeng–Tongji cohort (n = 25 523)	Kailuan study (n = 137 592)	UK Biobank (n = 317 305)
Male, n (%)	10 967 (43.0)	110 717 (80.5)	140 367 (44.2)
Age (years)	61.3 ± 8.0	49.2 ± 13.6	54.9 ± 8.1
BMI (kg·m ⁻²) ^a	24.3 ± 3.1	25.0 ± 3.4	27.0 ± 4.5
Education level, n (%)			
Below high school	14 898 (58.5)	99 355 (75.4)	86 915 (27.7)
High school	7 740 (30.4)	19 686 (14.9)	57 081 (18.2)
Beyond high school	2 820 (11.1)	12 762 (9.7)	111 176 (35.4)
Other qualifications or none of the above	–	–	58 736 (18.7)
Smoking status, n (%)			
Never	18 417 (72.3)	83 412 (63.0)	193 436 (61.1)
Former	2 366 (9.3)	6 311 (4.8)	100 234 (31.6)
Current	4 707 (18.5)	42 764 (32.3)	23 078 (7.3)
Drinking status, n (%)			
Never	18 168 (71.3)	100 248 (75.9)	83 270 (26.3)
Former	1 057 (4.1)	3 794 (2.9)	9 696 (3.1)
Current	6 269 (24.6)	28 113 (21.3)	223 651 (70.6)
Physical activity, n (%) ^b			
Inactive	8 583 (33.6)	24 551 (17.8)	103 907 (32.7)
Less active	9 058 (35.5)	93 920 (68.3)	111 868 (35.3)
Active	7 882 (30.9)	19 121 (13.9)	101 530 (32.0)
Hypertension, n (%) ^c	12 318 (48.3)	56 004 (40.7)	168 355 (53.1)
Diabetes, n (%) ^d	3 813 (14.9)	11 567 (8.4)	6 760 (2.1)
TC (mg·dL ⁻¹)	194.3 ± 38.9	189.7 ± 40.8	227.4 ± 40.2
HDL-C (mg·dL ⁻¹)	56.7 ± 15.6	57.9 ± 15.0	56.8 ± 14.4
LDL-C (mg·dL ⁻¹)	114.9 ± 31.4	106.2 ± 34.7	141.4 ± 33.9
Non-HDL-C (mg·dL ⁻¹)	139.6 ± 34.6	133.1 ± 37.4	170.6 ± 38.9

Values are presented as mean ± SD for continuous variables and numbers (percentage) for categorical variables.

^a BMI was calculated as weight in kilograms divided by height in meters square.

^b Physical activity was defined based on the tertiles of exercise time per week in the Dongfeng–Tongji cohort and UK Biobank. According to the questionnaire in the Kailuan Study, active physical activity was defined as exercising > 4 times per week and ≥ 20 min per time in the first two surveys, while exercising > 3 times and ≥ 30 min in the third and fourth surveys, inactive was defined as no physical activity, and others as less active.

^c Hypertension was defined if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, taking anti-hypertensive medication, or self-reported physician diagnosis before the baseline survey.

^d Diabetes was defined if fasting glucose ≥ 7.0 mmol·L⁻¹, taking anti-diabetic agents, or self-reported physician diagnosis before the baseline survey, as well as HbA1c ≥ 6.5% or nonfasting glucose ≥ 11.1 mmol·L⁻¹ in the UK Biobank.

mortality risks, and those with LDL-C ≥ 190 mg·dL⁻¹ and non-HDL-C ≥ 220 mg·dL⁻¹ had 24%–38% higher all-cause, CVD, non-CVD, and other mortality risks (Table 2, Fig. S3). Similar results were observed in the UK Biobank, but high LDL-C and non-HDL-C levels were associated with significantly lower risks of all-cause, non-CVD, and other mortality rather than with higher risks as observed in the Chinese cohorts (Table 2, Fig. S3).

For CVD subtypes, the highest two groups of TC ≥ 240, LDL-C ≥ 160, and non-HDL-C ≥ 220 mg·dL⁻¹ were significantly associated with MI or CHD mortality in both the Chinese cohorts and UK Biobank (Fig. S4 in Appendix A). These cholesterol levels were mainly associated with CHD mortality at high levels and all-cause and cancer mortality at low levels (all $P_{\text{nonlinear}} \leq 0.0161$) (Fig. 1), but not with stroke mortality (Fig. S4). The cholesterol levels associated with the lowest all-cause mortality risks were nearly 200 and 250 mg·dL⁻¹ for TC, 130 and 175 mg·dL⁻¹ for LDL-C, and 155 and 200 mg·dL⁻¹ for non-HDL-C in the Chinese and UK populations, respectively (Fig. 1). Low cholesterol levels were also associated with gastrointestinal and urological cancer mortality in both populations (Figs. S5–S7 in Appendix A), and with hematological cancer mortality in the UK Biobank (Fig. S7). However, HDL-C levels < 40 and ≥ 80 mg·dL⁻¹ were associated with elevated all-cause, CVD, and non-CVD mortality only in the UK Biobank, with the lowest all-cause mortality risk at 60 mg·dL⁻¹ (Table 2, Fig. 1, Fig. S3).

Similar results were observed when cholesterol levels were classified by percentiles (Table S4 in Appendix A) and in the sensitivity analyses with additional adjustments for potential confounders including socioeconomic, dietary, or inflammatory factors (Tables S5–S8 in Appendix A). High cholesterol levels were

robustly associated with CHD mortality, and low cholesterol levels remained associated with high all-cause or cancer mortality risks, even after excluding individuals with baseline diseases likely related to inflammation, or those who developed cancer or died, or experienced significant weight loss within the first four years (Table S9 in Appendix A). Furthermore, we found higher cancer incidence in participants with low TC, LDL-C, and non-HDL-C levels in all three cohorts (all $P_{\text{overall}} \leq 0.0172$) (Fig. S8 in Appendix A).

3.2. Longitudinal changes in cholesterol and mortality

Basic characteristics of the participants are presented in Table S10 in Appendix A. Among 71 990 Chinese participants, the ICCs of cholesterol between baseline and resurvey ranged from 0.22 to 0.56 (Table S11 in Appendix A). During 422 733 PYs of follow-up (5.7–6.0 years), 2226 deaths (282 from CHD and 624 from cancer) occurred. A decrease of greater than 20% in TC, LDL-C, and non-HDL-C levels over four years exhibited 14%–26% higher all-cause mortality risks compared with the stable group (±10%) (Table 3, Table S12 in Appendix A). We found nonlinear relationships of these decreasing cholesterol levels with all-cause and cancer mortality (all $P_{\text{nonlinear}} \leq 0.0100$), as well as decreasing TC with CHD mortality ($P_{\text{nonlinear}} = 0.0392$) (Fig. S9 in Appendix A). Sensitivity analyses adjusting for additional factors confirmed these associations (Table S13 in Appendix A).

In the UK Biobank, blood cholesterol levels remained relatively stable over four years (ICCs ranging from 0.74 to 0.82) (Table S11). After a median follow-up of 8.9 years, 299 deaths (18 from CHD and 160 from cancer) occurred. An increase of greater than 20% in LDL-C levels over four years exhibited 46% elevated all-cause

Table 2
Adjusted hazard ratios of all-cause mortality by baseline cholesterol levels.

Cholesterol (baseline)	Dongfeng–Tongji cohort and Kailuan study		UK Biobank	
	Deaths/PYs	HR (95% CI)	Deaths/PYs	HR (95% CI)
TC (mg·dL⁻¹)				
Low (< 120)	330/35 779	1.22 (1.08–1.36)	14/2 336	1.66 (0.98–2.80)
Slightly low (120–160)	1 618/238 091	1.13 (1.07–1.20)	571/138 986	1.28 (1.17–1.41)
Medium (160–200)	3 674/564 166	Ref.	3 037/890 476	Ref.
Slightly high (200–240)	2 739/389 026	1.01 (0.96–1.06)	5 468/1 564 115	0.90 (0.86–0.94)
High (240–280)	860/114 062	1.05 (0.97–1.13)	3 765/1 027 873	0.87 (0.82–0.91)
Very high (≥ 280)	239/26 535	1.27 (1.12–1.46)	1 595/405 027	0.89 (0.84–0.95)
HDL-C (mg·dL⁻¹)				
Low (< 40)	807/113 933	1.05 (0.97–1.14)	1 890/377 566	1.17 (1.10–1.24)
Slightly low (40–50)	1 970/303 935	0.97 (0.91–1.02)	3 711/933 874	1.03 (0.99–1.09)
Medium (50–60)	2 732/416 569	Ref.	3473/1 016 610	Ref.
Slightly high (60–70)	1 940/285 647	0.99 (0.93–1.05)	2 223/717–282	1.00 (0.95–1.06)
High (70–80)	1 126/149 221	1.01 (0.94–1.09)	1 155/385 402	1.02 (0.95–1.10)
Very high (≥ 80)	940/105 513	1.04 (0.96–1.12)	840/253 471	1.15 (1.07–1.25)
LDL-C (mg·dL⁻¹)				
Low (< 70)	1 261/166 445	1.18 (1.10–1.26)	166/36 442	1.26 (1.08–1.49)
Slightly low (70–100)	2 708/400 437	1.05 (1.00–1.11)	1 263/338 013	1.18 (1.11–1.26)
Medium (100–130)	3 038/458 980	Ref.	3 680/1 057 539	Ref.
Slightly high (130–160)	1 625/234 573	1.00 (0.94–1.06)	4 465/1 243 238	0.93 (0.89–0.97)
High (160–190)	502/69 151	1.03 (0.94–1.14)	2 558/707 860	0.87 (0.83–0.92)
Very high (≥ 190)	200/20 870	1.24 (1.07–1.44)	1 214/304 904	0.93 (0.87–0.99)
Non-HDL-C (mg·dL⁻¹)				
Low (< 100)	1 651/217 690	1.19 (1.12–1.27)	288/80 391	1.47 (1.30–1.67)
Slightly low (100–130)	2 806/423 234	1.03 (0.98–1.09)	1 448/458 907	1.14 (1.07–1.22)
Medium (130–160)	2 735/411 154	Ref.	3 397/990 889	Ref.
Slightly high (160–190)	1 388/208 442	0.98 (0.92–1.05)	3 975/1 075 918	0.94 (0.90–0.99)
High (190–220)	510/65 913	1.10 (1.00–1.21)	2 582/681 522	0.90 (0.85–0.95)
Very high (≥ 220)	232/25 079	1.29 (1.13–1.48)	1 624/395 749	0.93 (0.88–0.99)

Models were stratified by the five-year intervals of baseline age and gender, and adjusted for BMI, education level, smoking status, drinking status, physical activity, and history of hypertension and diabetes at baseline. Bold value indicates HRs and the 95% CIs all ≥ 1.00.

mortality risk than the stable group (±10%). There was no significant increase in mortality risks in participants with decreasing cholesterol levels, possibly due to sample size limitation (Table 3, Table S12).

When examining mean cholesterol levels of the two measurements, low LDL-C and non-HDL-C levels remained associated with higher all-cause and cancer mortality in both populations (Table S14 in Appendix A). In the Chinese cohorts, participants with low or medium levels of TC, LDL-C, or non-HDL-C at baseline and low levels at resurvey (low/medium + low groups) experienced 17%–29% higher all-cause mortality risk than those maintaining medium levels (Fig. S10 in Appendix A). Moreover, participants with either low or medium levels at baseline and decreases > 20% in LDL-C and non-HDL-C over four years or those with medium but decreasing TC levels (low/medium + decreasing groups) had significantly higher all-cause mortality than those with stable cholesterol levels. Individuals with a high + increasing pattern in LDL-C and non-HDL-C levels experienced twofold higher risks (Fig. 2). Similar associations were observed in the UK Biobank for decreasing patterns of low + low/stable or medium + low levels of TC, LDL-C, and non-HDL-C, and increasing patterns of medium + increasing LDL-C and high + increasing TC, despite limited sample sizes (Fig. 2, Fig. S10).

4. Discussion

In this prospective study of Chinese and UK adults without lipid-lowering medications or severe chronic diseases, nonlinear relationships of TC, LDL-C, and non-HDL-C levels with mortality were observed. In both populations, high cholesterol levels were primarily associated with CHD mortality, while low cholesterol levels were linked to all-cause and cancer (including gastrointesti-

nal and urological cancers, rather than cardiovascular mortality). We determined population-specific optimal cholesterol levels associated with the lowest all-cause mortality risk in the Chinese and UK participants. Low and high HDL-C levels were associated with all-cause and CVD mortality only in the UK Biobank. In the Chinese cohorts, decreasing TC, LDL-C, and non-HDL-C levels over four years exhibited elevated all-cause or cancer mortality risks. Furthermore, participants with low levels of TC, LDL-C, or non-HDL-C at both baseline and resurvey (low + low) in both populations, and those with initially low or medium levels and decreases over time (low/medium + decreasing) in Chinese adults, experienced higher all-cause mortality risks compared with those maintaining medium levels.

4.1. Comparison to prior studies

The U-shaped relationship between TC and mortality has long been recognized [12]. Subsequent studies with larger sample sizes and more refined cholesterol groups have further supported U-shaped relationships of TC [12,22], LDL-C [3–5], and HDL-C [9,10] with all-cause, CVD, or cancer mortality. Additionally, non-HDL-C has been positively associated with CVD morbidity and mortality [6,14], although several studies reported elevated all-cause mortality risk at low levels (< 100 mg·dL⁻¹) [7,8]. However, these studies were limited by incomplete sample exclusions, such as lipid-lowering medications or comorbidities that could introduce reverse causation bias. In contrast, in our study strictly based on apparently healthy adults from both Chinese and UK populations, low cholesterol levels (TC < 160, LDL-C < 100, and non-HDL-C < 130 mg·dL⁻¹) were associated with increased all-cause and cancer mortality risks.

Although high LDL-C levels (> 130 mg·dL⁻¹) have been linked to elevated CVD incidence [1,2], its associations with CVD mortal-

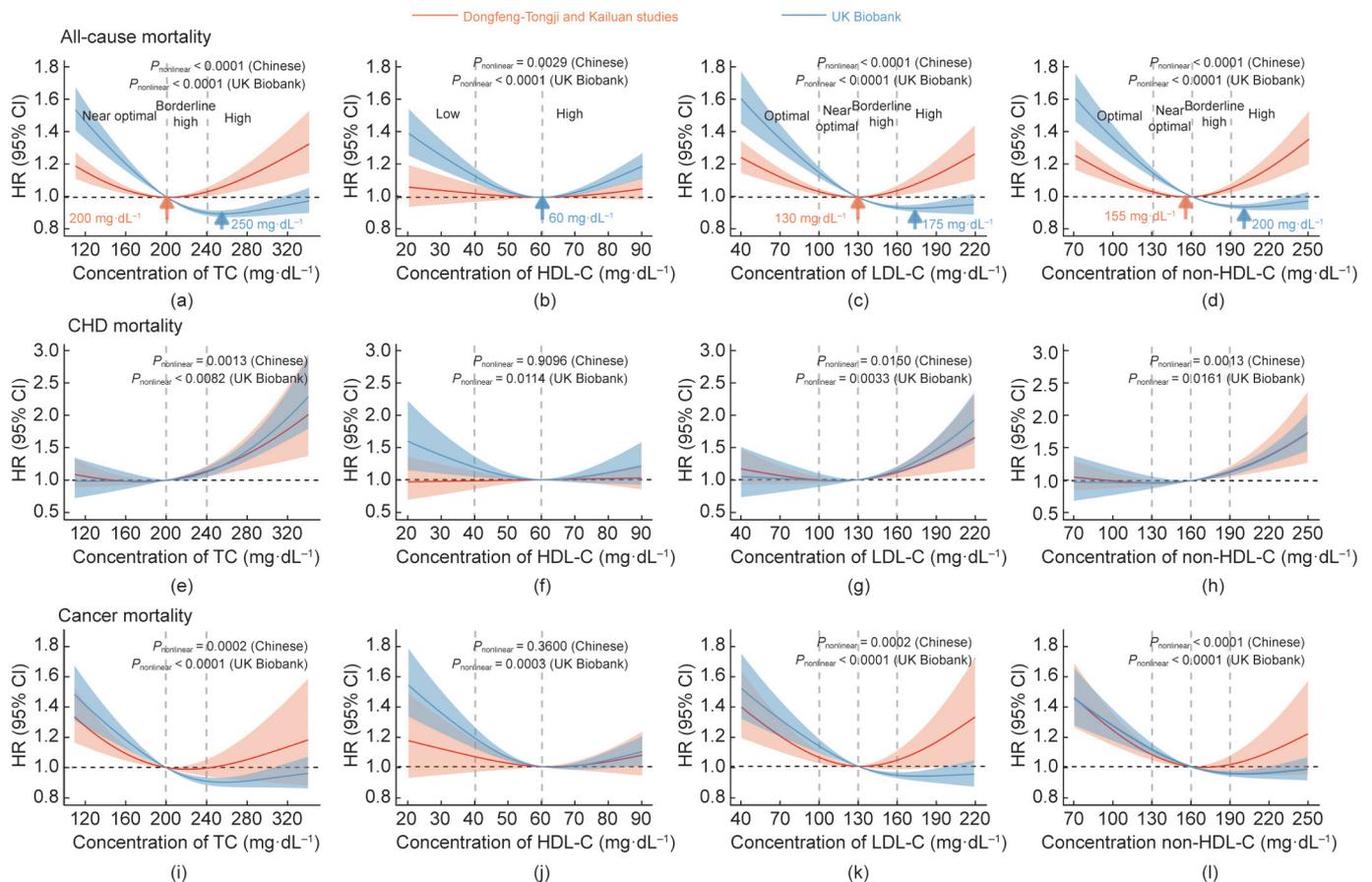


Fig. 1. Dose–response associations between baseline cholesterol levels and all-cause, CHD, and cancer mortality. The curves and the areas represent point estimates and 95% CIs of the HRs of mortality from (a–d) all causes, (e–h) CHD, and (i–l) cancer estimated by restricted cubic splines for the Dongfeng–Tongji cohort, Kailuan study, and the UK Biobank. The vertical dotted gray lines show the cutoffs to define blood cholesterol levels as low, optimal, near optimal, borderline high, and high, in line with the Adult Treatment Panel III guidelines. The models were adjusted for age, gender, BMI, education, drinking status, smoking status, physical activity, and history of hypertension and diabetes at baseline. Knots were set at the 5th, 50th, and 95th percentiles of the distribution of cholesterol levels, with the reference value set at 200, 60, 130, and 160 mg·dL⁻¹ for TC, HDL-C, LDL-C, and non-HDL-C, respectively.

ity are inconsistent [3–6,23]. In participants with a ten-year CVD risk below 10%, a study conducted in the United States showed positive linear trends [6], whereas another study in China reported U-shaped relationships [5]. Our study revealed no significant association was observed between lower LDL-C levels and CVD mortality after strict exclusion. Conversely, high levels of TC ≥ 240 , LDL-C ≥ 160 , and non-HDL-C ≥ 220 mg·dL⁻¹ were associated with increased MI or CHD mortality, rather than stroke mortality, in both populations, consistent with prior studies [4,6,23].

In contrast to our Chinese cohorts, high cholesterol levels in the UK Biobank were not associated with elevated all-cause or non-CVD mortality. This discrepancy may be partly explained by population-level differences. European populations generally exhibit higher lipid levels than East Asians [13]. Moreover, the UK Biobank participants tend to have better lipid management and overall healthier conditions than the general UK population [24]. These factors may have mitigated the adverse impact of elevated baseline cholesterol on non-CVD and non-cancer mortality within the UK Biobank, which may also explain the higher optimal cholesterol levels observed in the UK Biobank than in the Chinese adults. In our study, the optimal TC (200 mg·dL⁻¹), LDL-C (130 mg·dL⁻¹), and non-HDL-C (155 mg·dL⁻¹) levels determined in Chinese adults were close to the guidelines [1,2] recommended for low cardiovascular risk and consistent with previous findings from the Copenhagen [3] and Chinese [5] studies. These observations emphasize the necessity of considering population-specific

characteristics in the formulation of optimal cholesterol thresholds. Additionally, we found insignificant association between HDL-C and mortality in the Chinese cohorts, consistent with previous results from the Kailuan study [25].

Repeated blood lipid measurements have shown that persistently low and high-to-low TC, HDL-C, and persistently high TC are associated with higher mortality [11,15,16,26]. Consistently, our study showed that both Chinese and UK adults with low/medium + low and low + stable patterns of TC, LDL-C, or non-HDL-C levels had higher all-cause mortality. In Chinese participants, those with low/medium baseline cholesterol levels and decreases over time experienced higher mortality risk. A recent Chinese study has suggested that aging, being male, and genetic factors may contribute to decreases in lipid levels [27]. In the UK Biobank, increasing cholesterol levels exhibited higher all-cause mortality, although baseline cholesterol levels showed null risk. Together, these findings underscore the clinical value of monitoring cholesterol changes, as both significant increases or decreases over time may signal underlying health risk.

4.2. Possible explanation of the associations

The causal association between higher LDL-C levels with increased risks of all-cause and CVD mortality are well-established [28,29]. However, low LDL-C or non-HDL-C levels in relation to all-cause and cancer mortality remains controversial. Cohort studies [30] have shown elevated cancer incidence at low

Table 3
Adjusted hazard ratios of all-cause mortality by longitudinal changes in cholesterol levels.

Cholesterol (change)	Dongfeng–Tongji cohort and Kailuan study		UK Biobank	
	Deaths/PYs	HR (95% CI)	Deaths/PYs	HR (95% CI)
TC				
< -20%	261/39 568	1.26 (1.09–1.46)	7/1 665	1.40 (0.65–3.03)
-20% to -10%	373/68 427	1.10 (0.97–1.24)	25/7 937	1.17 (0.76–1.81)
±10%	917/184 985	Ref.	138/50 969	Ref.
10% to 20%	211/50 602	0.87 (0.74–1.01)	49/16 549	1.20 (0.86–1.68)
> 20%	258/59 366	0.99 (0.85–1.15)	27/8 286	1.40 (0.91–2.18)
HDL-C				
< -20%	489/95 635	1.08 (0.95–1.24)	4/1 665	0.92 (0.34–2.53)
-20% to -10%	283/54 533	1.04 (0.90–1.20)	20/6 540	1.10 (0.68–1.78)
±10%	550/108 356	Ref.	104/36 470	Ref.
10% to 20%	189/39 307	0.94 (0.80–1.11)	40/14 264	1.07 (0.74–1.55)
> 20%	527/108 023	0.98 (0.86–1.11)	32/10 418	1.23 (0.81–1.86)
LDL-C				
< -20%	526/100 509	1.14 (1.01–1.30)	12/4 457	0.99 (0.54–1.81)
-20% to -10%	271/52 432	1.05 (0.90–1.22)	32/9 196	1.22 (0.81–1.85)
±10%	514/101 909	Ref.	88/32 548	Ref.
10% to 20%	169/37 387	0.86 (0.72–1.02)	23/11 256	0.78 (0.49–1.24)
> 20%	492/102 420	0.92 (0.80–1.06)	49/11 884	1.46 (1.01–2.12)
Non-HDL-C				
< -20%	448/76 025	1.24 (1.10–1.41)	10/2 867	1.25 (0.65–2.42)
-20% to -10%	309/59 051	1.12 (0.97–1.29)	28/8 282	1.17 (0.76–1.80)
±10%	597/128 566	Ref.	105/36 268	Ref.
10% to 20%	219/44 733	1.06 (0.91–1.24)	32/12 385	0.97 (0.65–1.45)
> 20%	399/86 636	1.02 (0.89–1.17)	28/9583	1.03 (0.66–1.61)

Models were stratified by the five-year intervals of baseline age and gender, and adjusted for the corresponding lipid levels, BMI, smoking status, drinking status, and physical activity at baseline, and changes in BMI, smoking status, drinking status, and physical activity from baseline to resurvey, education level, and history of hypertension and diabetes before resurvey. Bold value indicates HRs and the 95% CIs all ≥ 1.00.

LDL-C levels, but genetic analyses [30] and nonlinear Mendelian randomization (MR) studies [31] suggest no such association. Nonetheless, limited proportion of cholesterol variation explained by current genetic instruments may result in insufficient statistical power. A common belief is that low cholesterol is likely a consequence or marker of poor health conditions, such as aging, malnutrition, and frailty [32]. In our study, participants in low LDL-C groups had slightly higher proportions of males, smokers, drinkers, and patients with diabetes (Tables S15–S17 in Appendix A). However, through rigorous exclusion of potentially ill participants and comprehensive adjustments for covariates, we largely mitigated reverse causation and can therefore suppose the potential biological mechanisms.

Biologically, cholesterol is crucial for membrane integrity, hormone synthesis, and immune system [33]. It is plausible that untreated low cholesterol levels may impair these processes and contribute to all-cause and cancer-specific deaths through multiple pathways. First, lipoproteins can neutralize endotoxins and inactivate toxic products from microorganisms, thereby protecting against endotoxins-induced death in animal models [34,35]. Second, disrupted cholesterol metabolism may disrupt lipid raft organization, weakening immune surveillance and increasing cancer susceptibility, including liver cancer and kidney tumorigenesis [36–38]. This may partly explain the observed associations between low cholesterol and increased gastrointestinal and urological cancer mortality in our study. Third, low LDL-C levels in relation to all-cause mortality might involve chronic inflammation, as suggested by elevated levels of high-sensitivity CRP in previous research [39]. Although long-term trials lowering LDL-C to < 20 mg·dL⁻¹ have not identified significant safety concerns regarding cancer or non-CVD death [40], the causal relationships and explicit mechanisms linking low cholesterol and all-cause and cancer mortality remain to be clarified. Further rigorous MR studies using stronger instruments and RCTs conducted in low-cholesterol populations are warranted. Moreover, the association

of higher HDL-C levels with all-cause and CVD mortality might involve various aspects, including the efflux and anti-inflammatory capacities, as well as the size and number of HDL particles [41].

4.3. Strengths and limitations

The strengths of this study include its prospective design, stringent participant selection, large sample size, and long follow-up involving three cohorts. Inclusion of nearly 500 000 individuals enhanced the generalizability of our findings. Exclusions of participants with lipid-lowering medications, pre-existing chronic diseases, low BMI, and early deaths minimized reverse causation bias. Extensive sensitivity analyses ensured robustness of the findings. Furthermore, the availability of repeated measurements allowed for the examination of longitudinal changes and their associations with subsequent mortality. To the best of our knowledge, this study probably represents the most rigorous and comprehensive analysis of cholesterol-related mortality to date. Several limitations need to be noted. First, due to the observational design, residual confounding might exist and causality remains to be established by future RCTs. Nevertheless, our findings provide stronger evidence than previous studies, supporting elevated mortality risks at low and/or decreasing LDL-C and non-HDL-C levels, which may serve as a marker of premature death. Second, factors like particle sizes, sub-classes, or function of blood cholesterol were not examined, but routine blood lipid tests have direct clinical implications. Third, the relatively short follow-up duration, particularly among younger UK Biobank participants, resulted in a small number of death events in the cholesterol change–mortality analyses. Fourth, residual confounding cannot be entirely ruled out due to inherent limitations in observational studies. However, results remained consistent after adjusting for traditional risk factors and information on socioeconomic, dietary, and inflammatory factors using available data.

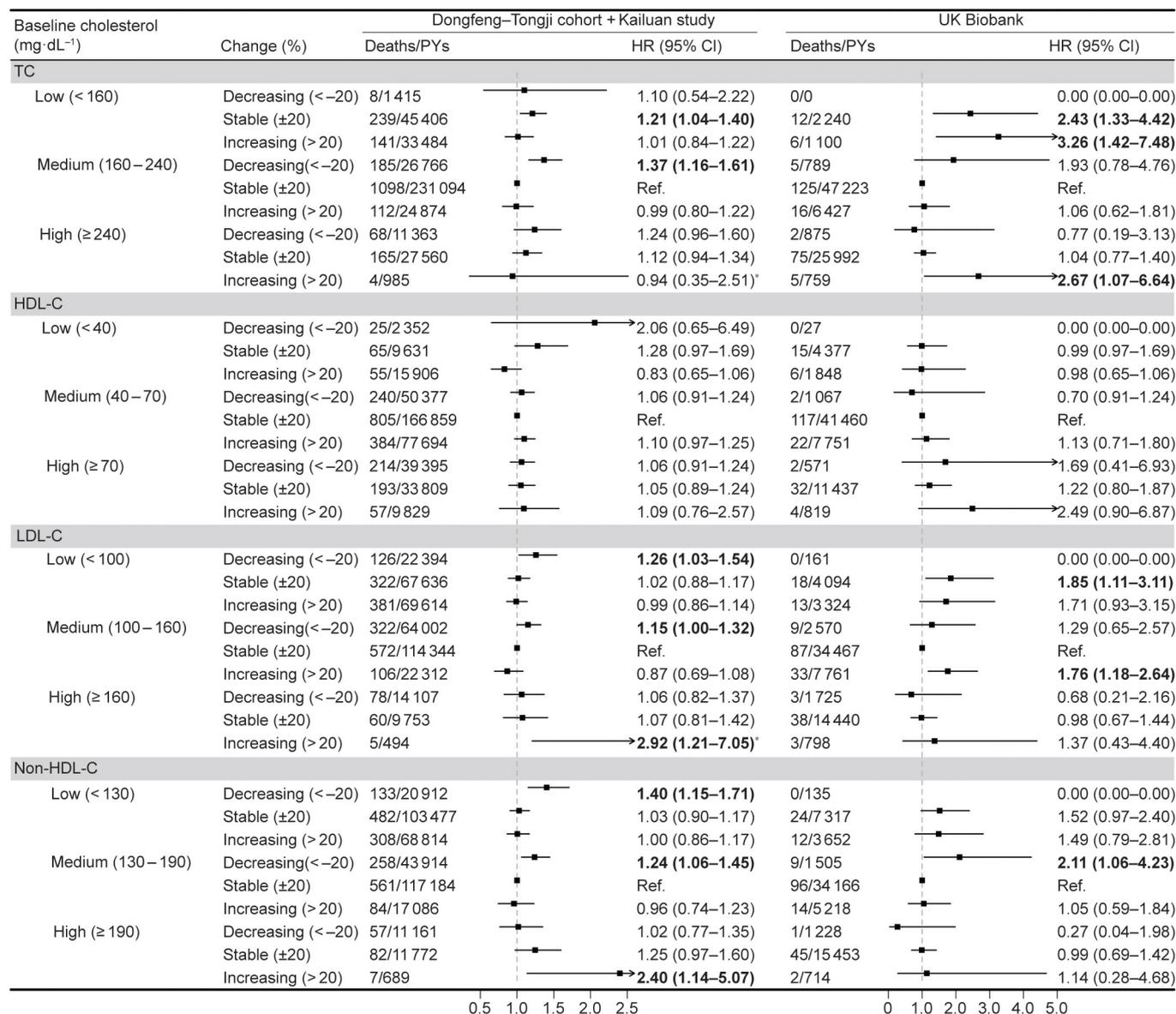


Fig. 2. Adjusted hazard ratios of all-cause mortality by joint patterns of cholesterol levels at baseline and resurvey. Models were stratified by the five-year intervals of baseline age and gender, and adjusted for BMI, smoking status, drinking status, and physical activity at baseline, and changes in BMI, smoking status, drinking status, and physical activity from baseline to resurvey, education level, and history of hypertension and diabetes before resurvey. Bold value indicates the HRs and the 95% CIs all ≥ 1.00. *The HRs from the Dongfeng-Tongji cohort were not included because no death occurred in these groups.

5. Conclusions and implications

The present study, in addition to the established link between high cholesterol levels and elevated CHD mortality, provides strong evidence that low and/or decreasing TC, LDL-C, and non-HDL-C levels are associated with elevated risks of all-cause and cancer mortality in untreated Chinese and UK adults. The optimal cholesterol levels for all-cause mortality in Chinese adults align with guideline recommendations. These findings underscore the dual risk pattern of cholesterol levels, emphasizing that both high and low levels may be harmful depending on death causes and suggesting the need for individualized lipid management strategies. Our findings may also inspire future studies on the health impacts of low cholesterol levels in other populations, a largely overlooked area that may indicate premature death. Integrating low cholesterol levels and longitudinal changes into risk prediction models may facilitate earlier identification of high-risk individuals. It is

crucial to emphasize that our study focused on untreated cholesterol levels and should not be interpreted as contradicting the efficacy of cholesterol-lowering therapies for CVD prevention and treatment.

CRedit authorship contribution statement

Qin Jiang: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Jiachen Wu:** Writing – review & editing. **Yu Yuan:** Writing – review & editing, Investigation. **Xingjie Hao:** Writing – review & editing, Resources, Project administration. **Pinpın Long:** Writing – review & editing, Investigation. **Kang Liu:** Writing – review & editing, Investigation. **Shihe Liu:** Software, Investigation. **Rong Peng:** Writing – review & editing, Investigation. **Kuai Yu:** Writing – review & editing, Investigation. **Rui Zeng:** Validation,

Investigation. **Shuohua Chen:** Resources, Project administration, Investigation. **Handong Yang:** Resources, Project administration, Investigation, Data curation. **Xiulou Li:** Resources, Project administration, Investigation. **Xiaomin Zhang:** Writing – review & editing, Resources, Investigation. **Meian He:** Writing – review & editing, Resources, Investigation. **Lin Wang:** Writing – review & editing. **Xiang Cheng:** Writing – review & editing. **An Pan:** Writing – review & editing, Investigation. **Shouling Wu:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Data curation. **Chaolong Wang:** Writing – review & editing, Resources, Project administration, Methodology, Data curation. **Tangchun Wu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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