

Views & Comments

Cholesterol Levels and Mortality: Defining the Optimal Ranges

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In a large multicohort prospective study newly published in *Engineering*, Jiang et al. [1] investigated the associations between baseline cholesterol levels, their longitudinal changes, and the risk of all-cause and cause-specific mortality. The study included over 480 000 participants from three major cohorts, the Dongfeng–Tongji and Kailuan studies in China and the UK Biobank. To minimize reverse causation and confounding, participants with pre-existing chronic diseases or receiving lipid-lowering treatment were excluded. Over a median follow-up of nearly ten years, a U-shaped relationship was observed between total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) levels and mortality risk in the Chinese cohorts (Fig. 1). Specifically, both low and high cholesterol levels were associated with increased all-cause mortality and mortality due to causes other than cardiovascular diseases (non-cardiovascular disease (CVD) mortality) [1]. In the UK Biobank, an L-shaped relationship was observed, with low levels of TC, LDL-C, and non-HDL-C associated with elevated risks of all-cause, cancer-related, and non-CVD mortality. In both populations, low cholesterol was associated with higher all-cause and cancer mortality, particularly from gastrointestinal and urological cancers, while high levels were more strongly associated with CVD deaths. Declines in cholesterol over time were associated with increased mortality risks. The study identified optimal levels for all-cause mortality risk in Chinese adults (TC: 200 mg·dL⁻¹; LDL-C: 130 mg·dL⁻¹; non-HDL-C: 155 mg·dL⁻¹), which were significantly lower than those identified in the UK population.

The cardiovascular risks of elevated LDL-C are well-established in numerous randomized clinical trials (RCTs), which form the basis of current lipid-lowering guidelines [2,3]. However, this observational study reveals a more complicated picture of the relationship between cholesterol levels and mortality in the general population not receiving cholesterol-lowering therapy. The U-shaped and L-shaped association observed in this and other studies suggests that very low cholesterol levels may not be benign [4,5]. Both Chinese and UK adults with LDL-C levels below 70 mg·dL⁻¹ or non-HDL-C less than 100 mg·dL⁻¹ had significantly higher risks (18%–47%) of all-cause, cancer-related, and non-CVD mortality compared to those with medium levels of cholesterol (LDL-C: 100–130 mg·dL⁻¹; non-HDL-C: 130–160 mg·dL⁻¹) [1]. The authors

thoughtfully discuss several biological mechanisms that may explain the observed associations. Briefly, low cholesterol may impair cell membrane integrity and immune response, potentially contributing to carcinogenesis. It may also serve as a marker of underlying chronic disease or systemic inflammation, which could precede clinical manifestations of cancer or other non-CVD conditions. Alternatively, because cholesterol is essential for hormone synthesis and cellular signaling, its depletion might disrupt these processes in ways that promote malignancy or other pathologies, although this hypothesis needs to be further tested experimentally.

Nevertheless, these findings provide an interesting contrast with RCTs showing that further LDL-C reduction through statins and other cholesterol-lowering therapies below current targets continues to reduce CVD and mortality risks [6]. This discrepancy likely reflects differences in study design and causal inference. RCTs typically enroll healthier participants with fewer comorbidities and provide close clinical monitoring, thereby minimizing confounding by subclinical disease. Their relatively short duration of most RCTs may limit the ability to assess the risk of cancer development, which often requires decades. In contrast, low cholesterol in observational cohorts often reflects spontaneous decline due to underlying illness, frailty, or systemic inflammation, whereas in RCTs, low cholesterol is pharmacologically induced and accompanied by potential protective effects of statins (e.g., anti-inflammatory effect). Notably, meta-analyses of statin trials have consistently shown no significant association between statin use and cancer incidence or mortality [7–9], reinforcing the overall safety of therapeutic LDL-C reduction.

The observed association between low cholesterol and cancer mortality should therefore be interpreted with caution. Reverse causality is a major concern, as subclinical cancers may lower cholesterol levels rather than the reverse. Mendelian randomization studies using genetic variants as proxies for LDL-C exposure have found no evidence that genetically lower LDL-C is associated with increased cancer risk [10,11]. These findings suggest that observational associations are more likely to reflect underlying disease processes than a direct causal effect of low cholesterol. Mechanistic studies also indicate that cholesterol metabolism is altered in the early stages of malignancy [12,13]. Clinically, while intentional LDL-C lowering remains a cornerstone of cardiovascular prevention, unexpectedly low or declining cholesterol levels in untreated individuals should prompt careful evaluation for occult disease or other underlying health concerns. It is important to recognize that not all cholesterol declines are indicative of underlying

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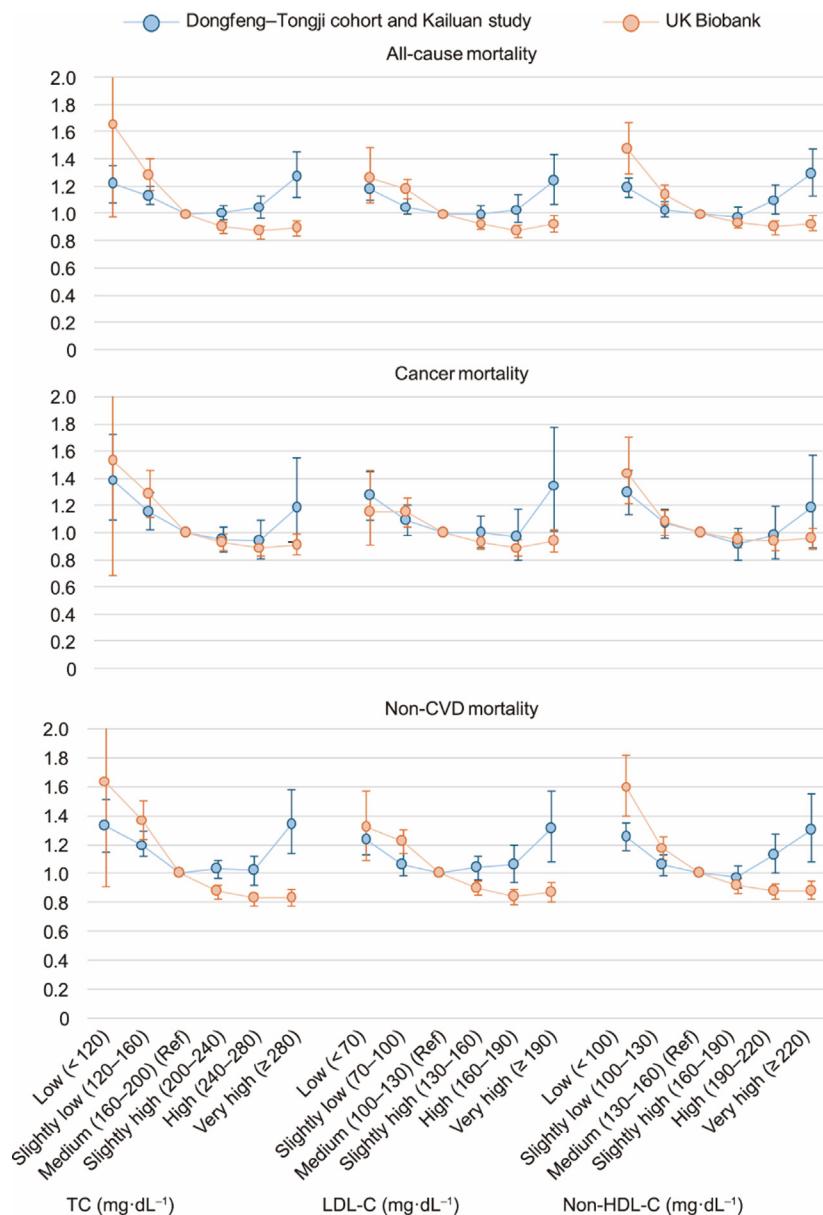


Fig. 1. Schematic summary of key findings on associations between different cholesterol at baseline and the risk of all-cause, cancer-related, and non-CVD mortality among participants of the Chinese and UK cohorts. CVD: cardiovascular disease. Adapted from Ref. [1] with permission.

pathology. Some reductions may result from healthy lifestyle changes, such as improved diet, increased physical activity, or smoking cessation, while others may reflect normal aging processes. Distinguishing between beneficial and concerning declines requires careful clinical judgment and consideration of the patient’s overall health status, the trajectory and magnitude of change, and the presence of other risk factors.

This study raises questions about whether it is appropriate to aggressively lower cholesterol in individuals who are generally healthy and not at high risk of CVD. For primary prevention, clinicians may need to be cautious in pursuing very low cholesterol targets and should consider the broader health context of each patient. This indicates a personalized approach to lipid management, considering individual differences in overall health status, comorbidities, and functional status. For example, closer monitoring may be warranted in older adults with frailty, undernutrition, or unexplained weight loss, as these conditions may signal under-

lying conditions associated with low cholesterol [14–16]. A sudden decline in LDL-C below 70 mg·dL⁻¹ or non-HDL-C below 100 mg·dL⁻¹, particularly in the absence of lipid-lowering therapy, could serve as a monitoring threshold and should raise concern for possible subclinical disease or systemic inflammation. In contrast, LDL-C levels below 70 mg·dL⁻¹ can serve as a therapeutic target for patients with established atherosclerotic cardiovascular disease (ASCVD), familial hypercholesterolemia, or high calculated CVD risk, where intensive lipid-lowering treatment is beneficial, as supported by robust RCT evidence. Tailoring LDL-C targets based on age, comorbidities, and overall risk profile rather than applying uniform thresholds can help optimize outcomes and minimize unintended harm.

Methodologically, the study by Jiang et al. [1] is robust in its design and data analyses. A major strength of the study is that it is based on several large, well-characterized cohorts from both Eastern and Western populations, which allows for cross-cultural

comparisons. The large sample sizes and long-term follow-up provide strong statistical power for the advanced statistical analyses. The exclusion of individuals with pre-existing chronic diseases, low body mass index, or early deaths helps to reduce reverse causation and confounding. However, residual confounding remains a concern in any observational analysis. One concern is that low cholesterol levels may reflect unmeasured factors such as under-nutrition or undiagnosed illnesses that were not fully captured in the available data. This phenomenon may lead to artificially elevated mortality among individuals with very low cholesterol levels and who have experienced a significant reduction in cholesterol levels over time. Moreover, the association between cholesterol reduction and mortality may be influenced by time-varying confounders such as weight loss, inflammation, or emerging comorbidities. While the present study adjusted for baseline covariates, it did not employ time-varying Cox models or other longitudinal methods to account for changes in health status over time. Future studies should apply these dynamic modeling approaches to better capture temporal changes and disentangle causal relationships from reverse causation or confounding by declining health.

Another important consideration is whether optimal cholesterol levels associated with mortality may vary across different populations. This study reveals notable differences between the Chinese and UK cohorts: Chinese participants had much lower baseline cholesterol levels and a stronger association between low cholesterol and cancer mortality, while participants in the UK Biobank had higher baseline lipid levels than their Chinese counterparts and better lipid management compared to the general UK population, and showed a weaker association between low cholesterol levels and mortality risk. The observed differences in optimal cholesterol levels between Chinese and UK populations underscore the importance of tailoring clinical guidelines to specific population contexts. Ethnicity, dietary patterns, and healthcare system structures can all influence baseline lipid profiles and associated risks, particularly given that genetic predispositions, dietary patterns, statin use, and comorbidity profiles differ substantially between Chinese and Western populations. These findings suggest that uniform cholesterol targets may not be appropriate across diverse populations. Clinical guidelines should incorporate region-specific evidence and consider stratified risk thresholds that account for local epidemiology, healthcare access, and cultural factors.

One unique aspect of this study is the availability of repeated measures of cholesterol levels longitudinally, which allows for examining changes in cholesterol levels over time on subsequent mortality risk. The finding that decreasing cholesterol levels over four years was associated with higher mortality, independent of lifestyle changes, suggests that dynamic lipid trends may be at least as informative as static measurements. However, the intra-class correlation coefficients (ICCs) for cholesterol changes were relatively low in the Chinese cohorts, which could reflect both biological fluctuations and potential laboratory variabilities. In contrast, the higher ICCs observed in the UK Biobank may reflect better standardization of lipid measurements or a healthier baseline population. These differences highlight the need for careful interpretation of longitudinal lipid data. Future studies should explore the clinical utility of cholesterol trajectories in risk predictions.

This study has significant implications for both clinical practice and future research. One key takeaway is the need for a more personalized approach to lipid management by considering each patient's overall risk profile, comorbidities, and racial and ethnic background when determining optimal cholesterol targets. For example, while LDL-C levels below 70 mg·dL⁻¹ may be appropriate for secondary prevention for high-risk cardiovascular patients, such low targets may not be necessary or suitable for individuals

in primary prevention, particularly for those with low baseline risk. This study suggests that cholesterol levels should be interpreted in the context of age, sex, race, ethnicity, nutritional status, and longitudinal health trends, rather than as standalone health markers.

In addition to informing clinical guidelines, the study suggests the potential value of tracking cholesterol changes over time in risk assessment. Traditional risk calculators rely on single time-point measurements, which do not capture dynamic changes in health status. The observation that decreasing cholesterol levels over time are associated with increased mortality, in the absence of lipid-lowering therapy, suggests that such declines could signal early stages of diseases or physiological decline. Future research should explore the integration of longitudinal lipid data into machine learning models and electronic health record-based decision tools to improve early detection of individuals at higher risk of chronic diseases, particularly non-CVD outcomes such as cancer, given the nuanced findings on cancer-related and non-CVD mortality.

Further research is needed to better understand the relationship between low cholesterol levels and certain adverse health outcomes, especially cancer. Although reverse causation remains a possibility, the consistency of the findings across cohorts and evidence from some mechanistic studies suggests that very low cholesterol may play a role in disease processes than previously appreciated. More robust Mendelian randomization studies and large randomized controlled trials conducted in populations with relatively low cholesterol could help clarify whether the observed associations are likely to be causal or spurious. In addition, future studies should also examine the role of cholesterol subfractions and functionality.

In summary, Jiang et al.'s study provides new insights into the complex relationship between cholesterol levels and mortality across different populations. The findings that both high and low cholesterol levels, and particularly declining levels over time, are associated with increased risk of mortality, and challenge the notion of "the lower cholesterol, the better." This underscores why it is important to consider individuals' overall health status, risk factors, and racial and ethnic background in lipid management. In practice, clinicians should pay close attention to unexpectedly low or decreasing cholesterol levels in patients who are not on lipid-lowering therapy, because these changes may signal potential underlying health issues. As the field moves toward more personalized healthcare, personalized approaches to lipid management are more important than ever.

CRediT authorship contribution statement

Mengxi Du: Writing – original draft, Conceptualization, Investigation. **Frank B. Hu:** Writing – review & editing, Conceptualization, Investigation, Supervision.

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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