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Views & Comments

Optimizing Cholesterol Management Strategies Based on Cholesterol–Mortality Associations

Jianxin Li, Xiangfeng Lu *

Department of Epidemiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

Clinical guidelines emphasize that lowering low-density lipoprotein cholesterol (LDL-C) levels is fundamental to the primary prevention of atherosclerotic cardiovascular disease (CVD) [1]. However, emerging evidence suggests that low LDL-C levels are associated with an elevated risk of incident cancer [2]. A previous study indicated a U-shaped association between LDL-C levels and all-cause mortality [3]. Inconsistent findings from studies may have been confounded by both lipid-lowering medication use and comorbidities. To address these uncertainties, comprehensive analyses are required to clarify the relation between mortality and all cholesterol indicators, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and non-HDL-C levels. In a recent study published in *Engineering*, Jiang et al. [4] provided critical insights by analyzing data from three prospective, longitudinal cohorts comprising 163 115 Chinese adults and 317 305 UK adults, with a median follow-up of nearly ten years. Their study examined the associations between untreated baseline cholesterol levels, longitudinal changes, and all-cause and cause-specific mortality. The research yielded several key findings with potential implications for public health policies and clinical practice.

First, the researchers specifically enrolled participants without severe chronic diseases or lipid-lowering treatments to minimize potential reverse causation and confounding effects. This revealed U-shaped associations between mortality and baseline levels of TC, LDL-C, and non-HDL-C in the Chinese population. Specifically, elevated cholesterol levels were significantly associated with coronary heart disease mortality, whereas decreased cholesterol levels were associated with increased all-cause and cancer mortality, especially gastrointestinal and urological cancer mortality. Elevated blood cholesterol is a well-established major pathogenic factor in atherosclerosis, and lower LDL-C levels show a significant dose-dependent association with reduced cardiovascular risk [1]. However, very low cholesterol levels (LDL-C < 70 mg·dL^{-1} and TC < 120 mg·dL^{-1}) appear to increase the risk of incident haemorrhagic stroke, independent of nutritional or obesity status [5,6]. Although randomized controlled trials have indicated that LDL-C reduction safely decreases cardiovascular risk even at very low levels [7], a previous study also reported a significant inverse association between on-treatment LDL-C levels and cancer incidence [2]. This study strengthens these findings by providing robust evidence that lower levels of TC, LDL-C, and non-HDL-C are significantly associated with increased risks of cancer incidence, cancer mortality, and all-cause mortality in participants free from lipid-lowering treatment and severe chronic diseases. In summary, this study challenges the "lower is better" paradigm in cholesterol management for primary CVD prevention, revealing a dual-risk pattern of cholesterol levels on mortality. A comprehensive understanding of the U-shaped relation between cholesterol levels and adverse health outcomes has significant implications for public health. These findings suggest that cholesterol management strategies should balance benefits and risks, considering their divergent effects on morbidity and mortality across different diseases.

Second, Jiang et al. highlighted the importance of individualized lipid management strategies by identifying optimal cholesterol levels of 200 mg·dL^{-1} for TC, 130 mg·dL^{-1} for LDL-C, and 155 mg·dL^{-1} for non-HDL-C in Chinese adults. The identified optimal cholesterol thresholds were closely aligned with the guideline-defined borderline-high cut-off points. Nevertheless, there were significant ethnic differences in the optimal cholesterol levels. Compared with the Chinese population, the UK population exhibited significantly higher optimal cholesterol thresholds—250 mg·dL^{-1} for TC, 175 mg·dL^{-1} for LDL-C, and 200 mg·dL^{-1} for non-HDL-C. These values correspond to the guideline-defined levels for high cholesterol. This may be attributable to population differences in cholesterol levels, with UK populations exhibiting approximately 20 mg·dL^{-1} higher cholesterol concentrations than those of Chinese populations. Furthermore, in contrast to the U-shaped relations found in Chinese populations, Jiang et al. revealed L-shaped dose–response curves for TC, LDL-C, and non-HDL-C in relation to all-cause mortality in UK populations. Surprisingly, high cholesterol levels were not associated with elevated mortality risk in this population. This phenomenon was attributed to the UK cohort's higher lipid levels, better lipid management, and overall healthier conditions compared with those of the Chinese cohorts. These factors collectively attenuated the adverse effects of elevated cholesterol levels on non-CVD and non-cancer mortality in the UK population. In addition, genetic heterogeneity may have

* Corresponding author.
E-mail address: luxf@pumc.edu.cn (X. Lu).

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contributed to the differences observed between Chinese and European populations. Blood cholesterol levels are predominantly influenced by genetic factors through polygenic inheritance patterns, with most cholesterol-associated coding variants being population-specific [8,9]. Therefore, cholesterol management strategies should be tailored to specific populations based on their unique characteristics and optimal cholesterol levels. Implementing these strategies should maximize the benefits and minimize the risks in the primary prevention of chronic diseases.

Third, by utilizing largescale longitudinal cohorts with repeated cholesterol measurements, this study further elucidated the effects of longitudinal cholesterol changes on subsequent all-cause and cause-specific mortality. This indicates that Chinese adults with persistently low levels of TC, LDL-C, or non-HDL-C, as well as those showing decreasing trends from initial low or medium levels, demonstrated a significantly higher all-cause mortality risk than those maintaining stable medium levels. These findings highlight the clinical importance of monitoring longitudinal cholesterol patterns, as significant decreases may indicate underlying health deterioration, including ageing, malnutrition, and frailty progression. Consequently, individuals presenting with either unexpectedly low or decreased cholesterol levels, particularly those not receiving lipid-lowering therapy, require close clinical monitoring for potential health issues. However, no significant increase in mortality risk was observed in UK participants with decreasing cholesterol levels, potentially owing to sample size limitations. Previous epidemiological studies have demonstrated age-dependent variations in both absolute cholesterol levels and their longitudinal changes [10,11]. Moreover, older individuals in the lowest LDL-C level group had a significantly higher risk of all-cause mortality than that of their middle-aged counterparts [12]. Therefore, it is necessary to elaborate on the age-specific effects of longitudinal cholesterol changes on all-cause mortality, an important consideration that warrants further investigation.

Although the authors acknowledged some inevitable limitations and potential biases in their study, the investigation by Jiang et al. provided robust and generalizable findings because of several key strengths: ① three prospective cohorts involving nearly 500 000 participants with ethnic diversity, ② long-term follow-up duration, ③ focus on participants without severe chronic diseases and lipid-lowering treatment, ④ repeated cholesterol measurements, and ⑤ comprehensive analyses of cholesterol–mortality relations. Significant sex-specific differences in cholesterol levels and their changing patterns have been identified in previous studies, with women exhibiting the most pronounced changes in the age group of 40–49 years, while men showed the greatest variation before the age of 40 years [10,11]. However, sex-specific effects of cholesterol levels and longitudinal changes on all-cause mortality remain unclear. Furthermore, individuals with low cholesterol polygenic risk scores demonstrate stable or decreasing cholesterol levels, whereas those with high genetic risk scores exhibit accelerated progression towards unhealthy conditions [11]. However, evidence regarding the potential heterogeneity in the dose–response relations between cholesterol and cause-specific mortality across polygenic risk strata remains limited. Consequently, future studies should prioritize the characterization of precise dose–response relations and establish subpopulation-specific optimal thresholds to enable targeted prevention and management of chronic diseases.

In conclusion, this study advances our understanding of the associations between cholesterol, longitudinal changes, and cause-specific mortality, providing critical evidence to inform the development of population-tailored strategies for reducing the cholesterol-related disease burden. It identified a U-shaped cholesterol–mortality relation, with both low and high cholesterol levels showing an increased all-cause mortality risk, underscoring the importance of precision cholesterol management approaches based on optimal thresholds. These results could optimize clinical cholesterol management strategies in practice, underscoring the importance of regularly monitoring populations exhibiting high, low, or decreasing cholesterol levels.

CRediT authorship contribution statement

Jianxin Li: Writing – review & editing, Writing – original draft. **Xiangfeng Lu:** Writing – review & editing.

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