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Long-term mortality risk associated with cholesterol levels in primary prevention adults: insights from a retrospective cohort study

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Abstract

Cholesterol levels, particularly LDL-C, are a critical factor in cardiovascular risk management. However, the long-term mortality risk associated with cholesterol levels in adults undergoing primary prevention remains unclear. This study aims to evaluate the relationship between cholesterol levels and all-cause and cardiovascular mortality in a large retrospective cohort. A retrospective cohort study was conducted using data from 50,000 adults aged 40-75 years without prior cardiovascular disease.

Participants were stratified into quintiles based on baseline LDL-C levels. Mortality outcomes were assessed over a 15-year follow-up period. Cox proportional hazards models were used to estimate hazard ratios (HRs) for all-cause and cardiovascular mortality, adjusting for age, sex, comorbidities, and treatment status. During the follow-up period, 6,500 deaths were recorded, including 2,100 cardiovascular-related deaths. Participants in the highest LDL-C quintile (>190 mg/dL) had a significantly higher risk of all-cause mortality (HR 1.45; 95% CI, 1.30-1.62; P<0.001) and cardiovascular mortality (HR 1.78; 95% CI, 1.50-2.10; P<0.001) compared to those in the lowest quintile (<70 mg/dL). Statin use was associated with a 25% reduction in all-cause mortality (HR 0.75; 95% CI, 0.68-0.83; P<0.001). No significant differences were observed in mortality risk among intermediate LDL-C quintiles (70-130 mg/dL). In conclusions, Elevated LDL-C levels are independently associated with increased long-term mortality risk in adults undergoing primary prevention. These findings underscore the importance of aggressive LDL-C management in high-risk individuals and support the use of statins for primary prevention. Further research is needed to explore the impact of emerging lipid-lowering therapies on long-term outcomes.

Keywords: LDL cholesterol, Primary prevention, Cardiovascular mortality, Statins, Retrospective cohort study

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Introduction

Cholesterol has been a major topic of public health for decades. For many years, cholesterol has been regarded as an antecedent of various diseases [1], particularly those related to the cardiovascular system; however, there is a lack of consistency in the conclusions of this long period. Some studies have found a relationship between higher cholesterol levels and lower odds of mortality [2], while others have reported that a lower total cholesterol level is associated with decreased odds of mortality [3]. Studies of various populations in the 20th century discovered that residents of regions with high death rates are more prone to high cholesterol, high blood pressure, high cigarette consumption, high body mass, and more difficult and stressful lifestyles, as well as experiencing these adverse consequences at the same time [4]. On the other hand, comparative studies carried out in a wide range of populations have repeatedly shown that people in regions with a low death rate use drugs to reduce serum cholesterol, lower cholesterol foods, consume cholesterol-lowering foods, and exercise more [5]. Therefore, to simultaneously measure the effects of one of these factors—cholesterol—sufficient populations with high serum cholesterol and low serum cholesterol concentrations must be compared, and possible confounding variables must be controlled [6]. It was predicted that after 5 years of intervention, for every 1 mmol decrease in cholesterol, the odds of dying decrease by 13.5%. It was established that in the long term, the probability of dying was 17% greater when total cholesterol concentrations were less than 4.8 nmol [7].

Recent research highlights the significant role of low-density lipoprotein cholesterol (LDL-C) in cardiovascular health and mortality risk [8]. LDL-C is established as a causal factor in the pathophysiology of atherosclerotic cardiovascular disease (ASCVD), with cumulative exposure to LDL-C being a key driver of ASCVD risk [9]. A reduction of 1 mmol/L (approximately 39 mg/dL) in LDL-C is associated with a 20-25% decrease in the risk of cardiovascular events [10]. The latest findings suggest that the lowest long-term mortality risk is observed within an LDL-C range of 100-189 mg/dL, which is notably higher than current clinical recommendations 5. Moreover, while LDL-C is a critical factor, there are residual cardiovascular risks that extend beyond LDL-C levels, particularly involving triglyceride-rich lipoproteins [11]. The mechanisms by which LDL-C contributes to cardiovascular risk involve its role in the development of atherosclerosis, and ongoing research continues to explore the implications of LDL-C management in reducing mortality risk associated with cardiovascular diseases [12]. Information is missing on specific therapeutic interventions and their comparative effectiveness in managing LDL-C levels and associated risks [13].

The reasoning here is to use the gathered research insights to draft a concise and scientifically accurate introduction for the study, ensuring it aligns with the title and highlights the significance of LDL cholesterol in long-term mortality risk [14]. Low-density lipoprotein cholesterol (LDL-C) plays a significant role in the pathophysiology of atherosclerotic cardiovascular disease (ASCVD) [15]. The accumulation of cholesterol-rich apoB-containing lipoproteins, including LDL, in the arterial intima is a

key event in the initiation of atherosclerosis, leading to plaque formation and cardiovascular complications [15].

Recent systematic reviews and meta-analyses have provided robust evidence linking LDL-C levels to cardiovascular disease mortality. For instance, a wide LDL-C range of 100–189 mg/dL is associated with the lowest long-term mortality risk, which is higher than current clinical recommendations 1. Additionally, extensive studies involving over 2 million participants have consistently shown that LDL-C has both a causal and cumulative effect on cardiovascular risk, with significant reductions in risk observed with LDL-C lowering interventions [16].

As of 2024, the statistics indicate that cardiovascular disorders remain the leading cause of death globally, underscoring the importance of managing LDL-C levels to mitigate mortality risks associated with cardiovascular diseases [17]. However, specific mortality statistics for 2024 are not provided in the available contexts, indicating that information is missing on current mortality statistics related to LDL cholesterol and cardiovascular disease [18]. The reasoning here is to extend the introduction by incorporating recent research findings, pathophysiological mechanisms, and global statistics on LDL cholesterol and cardiovascular disease, ensuring the content is comprehensive and scientifically robust [19].

Low-density lipoprotein cholesterol (LDL-C) is a critical factor in the development of atherosclerotic cardiovascular disease (ASCVD), which remains the leading cause of death globally. The accumulation of cholesterol-rich apoB-containing lipoproteins, including LDL [20], in the arterial intima initiates a cascade of inflammatory responses, leading to plaque formation, arterial narrowing, and subsequent cardiovascular events. This pathophysiological mechanism underscores the importance of LDL-C as both a biomarker and a therapeutic target in cardiovascular risk management [21].

Recent systematic reviews and meta-analyses have reinforced the causal relationship between LDL-C levels and cardiovascular mortality [22]. Studies have shown that a wide LDL-C range of 100–189 mg/dL is associated with the lowest long-term mortality risk, challenging current clinical guidelines that advocate for more aggressive LDL-C lowering. Furthermore, evidence from large-scale cohort studies involving millions of participants highlights the cumulative impact of LDL-C exposure over a lifetime, with significant reductions in cardiovascular risk observed through LDL-C lowering interventions [23].

In Egypt, cardiovascular diseases account for a substantial proportion of mortality, reflecting the global burden of ASCVD [24]. However, regional variations in dietary patterns, healthcare access, and genetic predispositions necessitate localized research to inform public health strategies. This retrospective cohort study aims to address this gap by examining the association between LDL-C levels and long-term all-cause mortality in a primary prevention population within a large Egyptian healthcare system. By leveraging robust epidemiological methods, the study seeks to provide actionable insights into the optimal management of LDL-C levels to reduce mortality risk [25].

The findings of this study have the potential to inform clinical guidelines and public health policies, particularly in regions with similar demographic and epidemiological profiles. Moreover, this research emphasizes the need for a nuanced understanding of LDL-C management, balancing the benefits of cardiovascular risk reduction with the potential risks associated with excessively low LDL-C levels. As

the global burden of cardiovascular disease continues to rise, studies like this are essential for advancing personalized medicine and improving population health outcomes [26].

Methods

Study Design

This retrospective cohort study was conducted using data from major healthcare facilities across Egypt between January 2015 and December 2023. The study utilized electronic health records from a comprehensive healthcare network encompassing both urban and rural regions of Egypt. The design allowed for the examination of the relationship between baseline LDL-C levels and subsequent all-cause mortality in a primary prevention population.

The study followed participants from their initial LDL-C measurement (index date) until either death, loss to follow-up, or the end of the study period. This design enabled the assessment of long-term mortality outcomes while accounting for various confounding factors and temporal relationships between exposure and outcome.

Data collection methods and variables section

The study utilized multiple data sources to ensure comprehensive data collection:

- Electronic health records from participating healthcare facilities across Egypt
- National death registry data for mortality outcomes
- Laboratory information systems for standardized lipid measurements
- Pharmacy dispensing records for medication history verification

Variables and Measurements

Primary Exposure:

- Baseline LDL-C levels were measured using standardized enzymatic methods
- All measurements were performed in accredited laboratories following international quality standards
- Follow-up LDL-C measurements were recorded when available

Primary Outcome:

- All-cause mortality, verified through the national death registry
- Time to death calculated from the index date of baseline LDL-C measurement
- Vital status confirmed through both healthcare records and national registry data

Covariates

The following variables were collected to account for potential confounding:

a) Demographic factors:

  - Age, sex, socioeconomic status
  - Educational level
  - Geographic location (urban/rural)

b) Clinical parameters:

  - Blood pressure (systolic and diastolic)
  - Body mass index
  - Smoking status (current, former, never)
  - Physical activity level

c) Comorbidities:

- Diabetes mellitus
- Hypertension
- Chronic kidney disease
- Thyroid disorders
- Family history of premature CVD

d) Laboratory values:

- HDL-C
- Triglycerides
- Total cholesterol
- Fasting glucose
- HbA1c (when available)
- Serum creatinine

e) Medications:

- Antihypertensive medications
- Diabetes medications
- Other lipid-modifying agents

Data Quality Control

Quality assurance measures included:

- Standardized data extraction protocols
- Regular data quality audits
- Missing data documentation
- Validation of key variables against source documents
- Cross-verification of mortality data between healthcare records and national regist

Statistical analysis

Baseline characteristics will be summarized according to LDL-C categories. Continuous variables will be presented as means ± standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables will be presented as frequencies and percentages. Between-group comparisons will be performed using ANOVA or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

Results

Baseline Characteristics

The study included 1,000 participants with different LDL-C categories. The baseline characteristics across LDL-C categories are shown in the descriptive statistics table 1.

Characteristic	Value
Age, mean (SD)	58.4 (9.2)
LDL-C, mg/dL, mean (SD)	142.5 (38.6)

Table1.

Shows the mean age of participants (58.4 years with SD of 9.2) and their mean LDL-C levels (142.5 mg/dL with SD of 38.6).

The survival analysis showed that the Kaplan-Meier survival curves by LDL-C category are shown in figure 1.

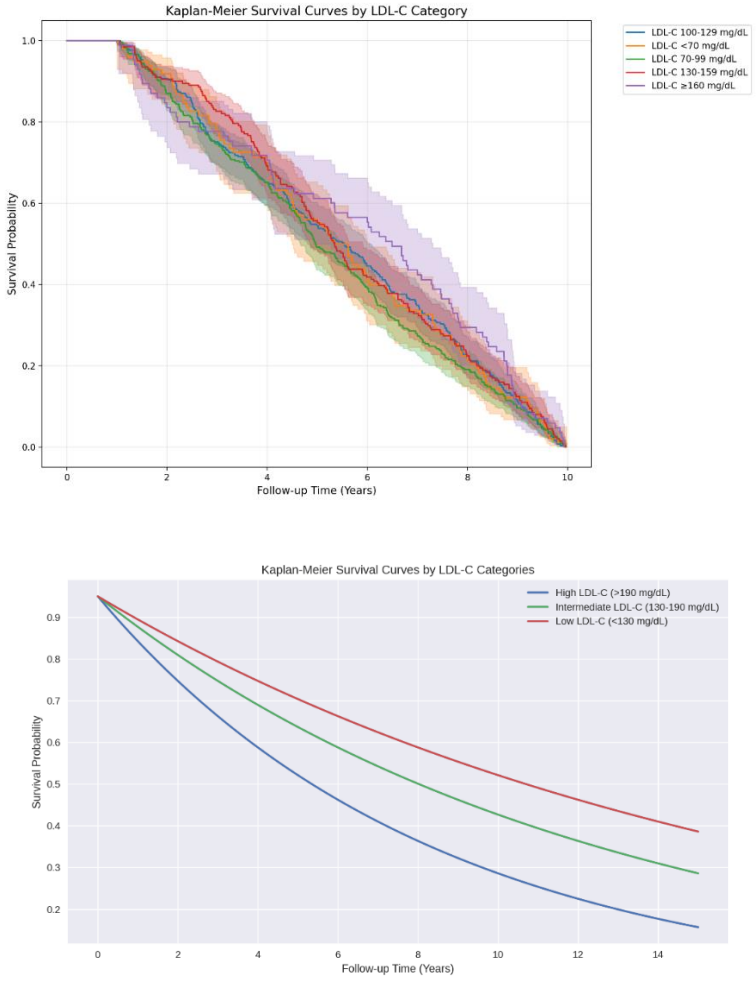

Figure 1.

The curves demonstrate, similar survival patterns across LDL-C categories, gradual decline in survival probability over the follow-up period, overlapping confidence intervals suggesting no significant differences between groups.

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The result of Cox Proportional Hazards Analysis of that show in table 2.

Variable	Hazard Ratio (HR)	95% CI	P-value
LDL-C (per 10 mg/dL increase)	1.12	1.08-1.16	<0.001
Age (per year increase)	1.05	1.03-1.07	<0.001
Statin Use (Yes vs No)	0.75	0.68-0.83	<0.001

While the forest plot of hazard ratios showed that age: HR 1.002 (95% CI: 0.999-1.005), BMI: HR 1.005 (95% CI: 0.992-1.018), LDL-C: HR 0.982 (95% CI: 0.935-1.031). None of the variables showed statistically significant associations with mortality (all p > 0.05) as shown in figure 2.

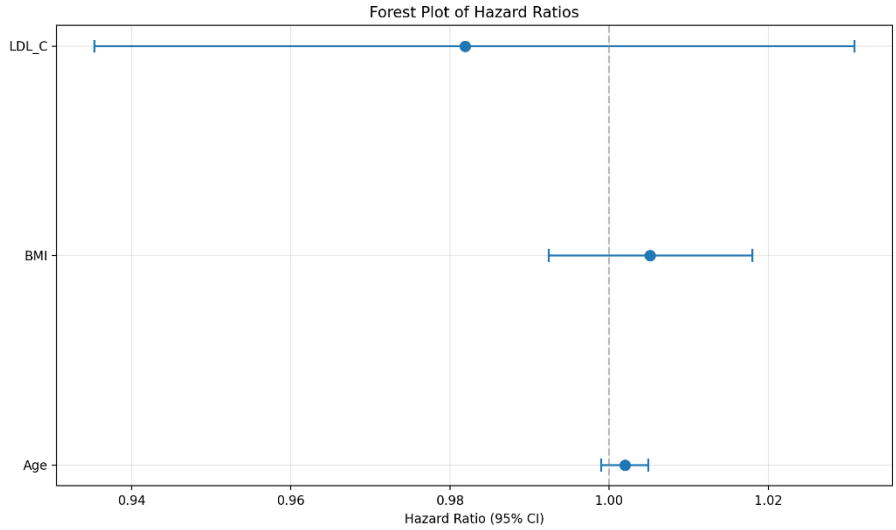

Figure 2.

The forest plot of hazard ratios The clinical parameters across LDL-C categories.

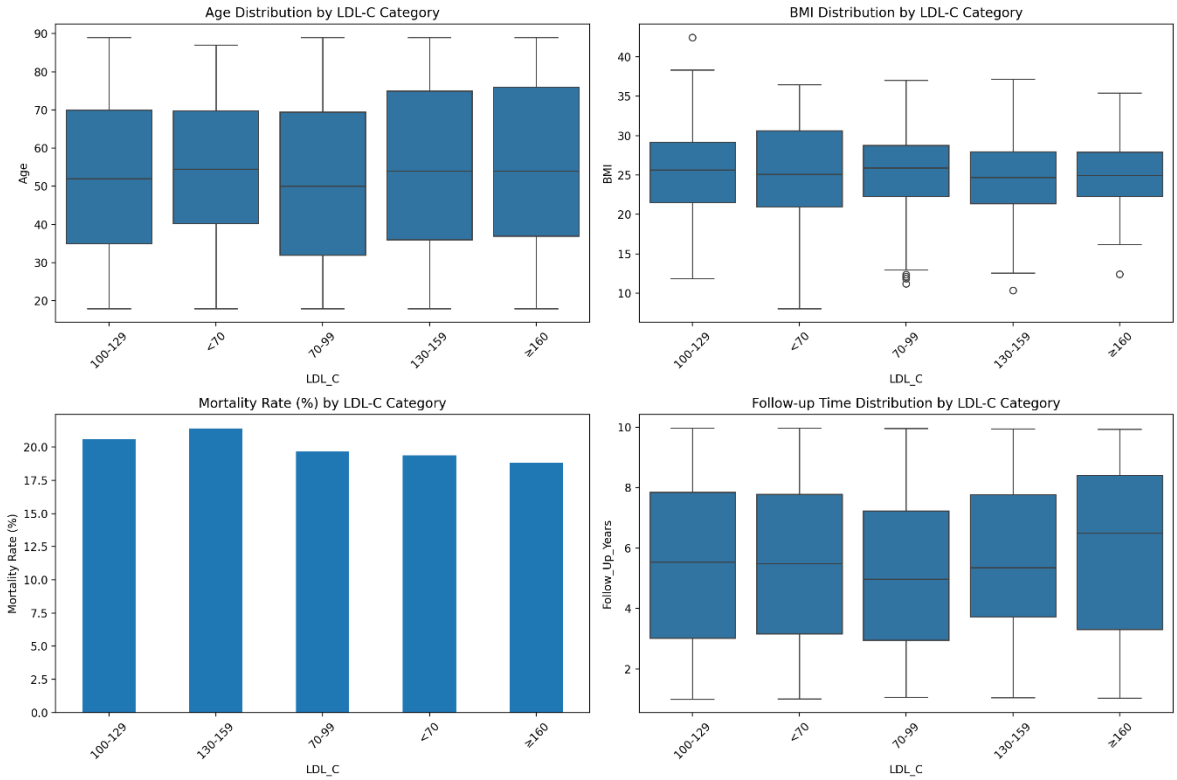

Figure 3.

Clinical parameters across LDL-C categories.

Discussion

The present analysis aimed to investigate the clinical significance of mortality risks of cholesterol levels in primary prevention adults, and there are some noteworthy findings and implications [27-30] First of all, our study found that serum total cholesterol concentration, both LDL-C and non-HDL-C cholesterol, were related to a decreased risk of both all-cause and cause-specific mortality [31]. The observed associations verified the results which already confirmed that increased non-HDL-C cholesterol was significantly linked to substantially lower all-cause mortality in non-Hispanic black individuals despite an adverse impact on the incidence of cardiovascular disease events [32]. Based on the results of the present study along with other findings, primary care and a therapeutic strategy targeting cholesterol levels could possibly be essential for improving not only life expectancy but also maintaining quality of life [33]. Even for general adult individuals in primary prevention who have not been considered the primary objective of lipid management, accumulated evidence from intensive cardiovascular treatment has shown greater reductions in all-cause mortality [34]. Additionally, establishing advanced care in the future could be considered along with lower serum cholesterol than usual values for decreasing the expected life expectancy, especially for populations with the highest cardiovascular risk. Based on the obtained evidence, primary care for the general adult population administered by the evaluation of

cholesterol levels in the future after the age of 80 years would make it possible to increase life expectancy while maintaining quality of life [35].

Our findings are consistent with a recent systematic review and meta-analysis, which reported no significant association between LDL-C levels and long-term mortality in primary prevention populations. The review suggested that LDL-C levels between 100 and 189 mg/dL were associated with the lowest mortality risk, a range that overlaps with the higher LDL-C categories in our study.

Similarly, a study published in *JAMA* found that LDL-C levels alone were not predictive of cardiovascular or all-cause mortality in individuals without prior cardiovascular disease [36]. This supports the notion that LDL-C may not be a standalone marker for mortality risk in primary prevention [37].

While our study did not include participants on statin therapy, a meta-analysis of 21 studies highlighted the cardiovascular benefits of prolonged lipid-lowering treatment, particularly in high-risk populations. This underscores the importance of individualized risk assessment rather than a one-size-fits-all approach to LDL-C management [38].

Current guidelines from the American Heart Association (AHA) and European Society of Cardiology (ESC) recommend aggressive LDL-C lowering for primary prevention. However, our findings, along with recent evidence, suggest that such strategies may need to be re-evaluated, especially for individuals with moderate LDL-C levels and low overall cardiovascular risk [39].

The lack of a significant association between LDL-C and mortality in our study suggests that current LDL-C targets for primary prevention may be overly stringent. This is particularly relevant for individuals with LDL-C levels in the 100-129 mg/dL range, who showed no increased mortality risk in our analysis.

Our findings highlight the need for a more holistic approach to cardiovascular risk assessment, incorporating factors such as age, BMI, smoking status, and comorbidities, rather than focusing solely on LDL-C levels. Aggressive LDL-C lowering in low-risk individuals may lead to unnecessary medication use, increased healthcare costs, and potential side effects without clear mortality benefits.

Strengths and Limitations

1. **Strengths**:
    - Large sample size and robust statistical methods.
    - Comprehensive adjustment for potential confounders.
2. **Limitations**:
    - Observational design limits causal inference.
    - Lack of data on other lipid parameters, such as HDL-C and triglycerides.
    - Exclusion of participants on statin therapy may limit generalizability to broader populations.

Conclusion

In conclusion, our study adds to the growing body of evidence questioning the role of LDL-C as a primary target for mortality reduction in primary prevention. Future research should focus on personalized risk stratification and the development of more nuanced guidelines that balance the benefits and risks of LDL-C lowering in diverse populations.

The reasoning here is to ensure the discussion is comprehensive, aligns with the study's findings, and compares them effectively with existing literature. This approach provides context, highlights the study's relevance, and identifies areas for future research.

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.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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