Relationship including nadir for low-density lipoprotein with all-cause and cause-specific mortality in a contemporary population: a cohort study

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Relationship including nadir for low-density lipoprotein with all-cause and cause-specific mortality in a contemporary population: a cohort study

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ABSTRACT

Objective: To determine the relationship between LDL-C and all-cause mortality and the LDL-C level associated with the lowest risk of all-cause mortality in individuals in the general population.


Setting: Danish population.

Participants: Individuals randomly selected from the national Danish Civil Registration System.

Exposure: Baseline LDL-C levels on risk of mortality were evaluated on a continuous scale (restricted cubic spline curves) and by a priori defined percentile categories using Cox proportional hazards regressions.

Main outcome measures: Main outcome was all-cause mortality. Secondary outcomes were cause-specific mortality (cardiovascular, cancer, and other mortality).

Results: In the study cohort of 108,243 individuals aged 20-100, 11,376 (10.5%) deaths occurred with a median age of 81 years at time of death. The association between LDL-C levels and risk of all-cause mortality was U-shaped with both low and high levels being associated with increased risk of all-cause mortality. Compared to individuals with LDL-C levels of 3.4-3.9 mmol/L (132-154 mg/dL; 61st-80th percentile), the multivariable adjusted hazard ratio for all-cause mortality was 1.42 (95% confidence interval 1.25 to 1.62) for individuals with LDL-C <1.8 mmol/L (<70 mg/dL; 1st-5th percentile) and 1.25 (1.07 to 1.46) for LDL-C >4.8 mmol/L (>189 mg/dL; 96th-100th percentile). The LDL-C level associated with the lowest risk of all-cause mortality was 3.6 mmol/L (140 mg/dL), consistent across sex and age-groups. Similar results were seen for cancer and other mortality, but not for cardiovascular mortality. Any increase in LDL-C levels was associated with increased risk of myocardial infarction.

Conclusions: In the general population, both low and high LDL-C levels were associated with increased risk of all-cause mortality and the lowest risk of all-cause mortality was found at an LDL-C level of 3.6 mmol/L (140 mg/dL).
Background

Low-density lipoprotein cholesterol (LDL-C) is a well-established causal risk factor for development of atherosclerosis and cardiovascular disease (1). High LDL-C consistently predicts risk of future atherosclerotic cardiovascular events in a wide variety of populations throughout the world. In addition, numerous randomized controlled trials with lipid-lowering therapy have clearly demonstrated that lowering LDL-C reduces the risk of future atherosclerotic cardiovascular events (1-4).

Because lowering of LDL-C reduces cardiovascular disease outcomes, it is the general perception that high LDL-C levels are associated with increased risk of mortality while low LDL-C levels are not. However, studies on the association between LDL-C levels and risk of all-cause mortality have provided diverging results where some studies have shown a counter-intuitive inverse association (lower mortality with increasing LDL-C) (5-7) and some no association (8-10). The majority of these studies have been conducted in individuals aged 65 and older and in historical population-based cohorts. Furthermore, a recent study on young Koreans not taking lipid-lowering medications showed a U-shaped relationship between LDL-C and mortality (11). Similarly, studies on the association between LDL-C and cardiovascular mortality have provided different results (8, 11, 12). Thus, the relationship between LDL-C levels and risk of all-cause and cause-specific mortality in individuals in the general population is unclear. It is also unclear at which level of LDL-C the risk of mortality is lowest.

In the present study we determined the relationship between LDL-C and risk of all-cause and cause-specific mortality. Further, we identified the LDL-C level associated with the lowest mortality in individuals in the contemporary Copenhagen General Population Study.
Methods

Study population

The study includes individuals of Danish descent from the Copenhagen General Population Study, an ongoing cohort study with first round of examination recruited in 2003-2015. Individuals invited were aged 20-100 and randomly selected from the national Danish Civil Registration System, thereby reflecting the Danish general population (43% participation rate). All participants filled out a self-administered questionnaire including lifestyle and medical therapy, showed up for physical examination, and had blood samples taken for biochemical measurements.

End points

Death from any cause was obtained through the Danish Civil Registration System, a complete register of all residents in Denmark since 1968 without losses at follow-up. The cause of death January 1977 and onwards was retrieved from the national Danish Causes of Death Registry in terms of International Classification of Disease (ICD) codes and classified into one of three major categories: cardiovascular, cancer, or other mortality. If one of the first three ranked causes of death had a cardiovascular diagnosis code (ICD-10: I00-I90) it was categorized as cardiovascular mortality. Remaining deaths were classified as cancer if one of the first three ranked causes of death had a cancer diagnosis (ICD-10: C00-C96) and other mortality if not classified as either cardiovascular or cancer mortality.

Information on diagnoses of nonfatal or fatal myocardial infarction (ICD-8: 410, ICD-10: I21-I22) was ascertained from the national Danish Patient Registry, comprising information on all hospital contacts in Denmark from January 1977 and onwards (outpatients and emergency wards from 1995), and the national Danish Causes of Death Registry (ICD-9 was never used in Denmark).

Laboratory analyses

All blood samples were collected in the non-fasting state (13). LDL-C was calculated using the Friedewald equation as total cholesterol – high-density-lipoprotein cholesterol – triglycerides/2.2 in mmol/L (total cholesterol – high-density-lipoprotein cholesterol – triglycerides/5 in mg/dL) when triglycerides were <4
mmol/L (350 mg/dL) and measured directly (Konelab) when triglycerides were >4 mmol/L (350 mg/dL). Total cholesterol, high-density-lipoprotein cholesterol, triglycerides, and direct LDL-C were measured using standard hospital assays (Roche and Konelab).

Covariates
Statistical analyses were adjusted for a priori defined covariates, that is, for well known risk factors for mortality (14). Sex and age derived from the Civil Registration Number. At the physical examination blood pressure was measured. In the questionnaire participants reported smoking status, cumulative number of pack-years, lipid-lowering therapy, and diabetes. Diagnoses on diabetes, cardiovascular disease, cancer, or chronic obstructive pulmonary disease before baseline were obtained through the national Danish Patient Registry. Individuals with diabetes were identified as those having a registered diagnosis in the national Danish Patient Registry, a non-fasting plasma glucose measurement >11 mmol/L (198 mg/dL), reporting taking antidiabetic medication, or self-reported diabetes from the questionnaire.

Statistical analyses
Only participants with an LDL-C measurement at baseline were included in the study; 847 individuals were excluded due to missing LDL-C measurement. Data on potential confounders was >99% complete. Remaining missing values were imputed using multivariable chained imputation with fully conditional specification; however, without imputation results were similar to those reported.

Associations between LDL-C and risk of all-cause mortality, cause-specific mortality, and myocardial infarction were estimated by Cox proportional hazards regressions with 95% confidence intervals (CI) using age as underlying time scale (age adjustment) and left truncation (delayed entry at study examination). Follow-up started at the day of examination and ended at the first occurrence of either death/myocardial infarction, emigration, or December 2018. For myocardial infarction, individuals with a previous event were excluded. Multivariate adjusted statistical analyses were adjusted for age (as timescale), sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline.
The associations between LDL-C and all endpoints were evaluated on a continuous scale using restricted cubic spline curves based on abovementioned Cox proportional hazards models. To balance best fit and overfitting, the number of knots, between 3 and 7, was chosen as the lowest value of Akaike information criteria, but if within two of each other for different knots, the lowest number of knots was chosen. The LDL-C level associated with the lowest risk of mortality was the level with the lowest hazard ratio on the spline curve. Furthermore, the associations between seven predefined LDL-C categories and all-cause mortality were examined. First, five equally distributed categories of LDL-C were defined by the 20\textsuperscript{th}, 40\textsuperscript{th}, 60\textsuperscript{th}, and 80\textsuperscript{th} percentile and second, to be able to evaluate extreme high and low levels of LDL-C two additional categories were defined by the 5\textsuperscript{th} and 95\textsuperscript{th} percentile. The reference category for these analyses was chosen as the one including the LDL-C level associated with the lowest all-cause mortality risk.

Hazard ratios and 95% CIs were corrected for regression dilution bias using a nonparametric method to correct for underestimation due to random measurements and long-term fluctuations (15). Using LDL-C measurements from 9604 individuals without atherosclerotic cardiovascular disease and lipid-lowering therapy participating in both the 2003-2015 examination and follow-up approximately 10 years later, a regression dilution ratio of 0.64 was determined for LDL-C.

In sensitivity analyses, pre-treatment LDL-C levels were estimated in individuals receiving lipid-lowering therapy as baseline LDL-C measurements multiplied by 1.43 for individuals with no concurrent diagnoses on ischemic heart disease or stroke and by 1.67 for individuals with known ischemic heart disease or stroke, corresponding to a 30% and 40% reduction, respectively (16).

All statistical analyses were performed in Stata/SE 15.1.

Patient and public involvement

No participants or the public were involved in defining the research question, outcome measures, study design, recruitment, or conduct. Nor were they asked to provide input for interpretation of results. There are no plans to disseminate the results of this study to the participants.
Results

This study included 108,243 individuals with 1,002,361 person-years of follow-up (median follow-up 9.4 years (range 0-15 years)). We observed 11,376 (10.5%) deaths during follow-up with a median age of 81 years (range 26-106 years) at time of death. Table 1 shows baseline characteristics by LDL-C percentile categories.

**LDL-C and all-cause mortality**

The association between LDL-C on a continuous scale and risk of all-cause mortality was U-shaped with both low and high LDL-C levels being associated with increased risk of all-cause mortality (Figure 1).

Compared to individuals with LDL-C levels of 3.4-3.9 mmol/L (132-154 mg/dL; 61st-80th percentile), the multivariable adjusted hazard ratio for all-cause mortality was 1.42 (95% CI, 1.25-1.62) for individuals with LDL-C <1.8 mmol/L (<70 mg/dL; 1st-5th percentile), 1.29 (1.16-1.43) for 1.8-2.3 mmol/L (70-92 mg/dL; 6th-20th percentile), 1.12 (1.02-1.23) for 2.4-2.8 mmol/L (93-112 mg/dL; 21st-40th percentile), 1.11 (1.01-1.22) for 2.9-3.3 mmol/L (113-131 mg/dL; 41st-60th percentile), 1.06 (0.98-1.17) for 4.0-4.8 mmol/L (155-189 mg/dL; 81st-95th percentile), and 1.25 (1.07-1.26) for >4.8 mmol/L (>189 mg/dL; 96th-100th percentile) (Figure 2).

Increased risk of all-cause mortality at low LDL-C levels were observed in both men and women, and the association was most pronounced in individuals not receiving lipid-lowering therapy and those aged ≤65 (both p for interaction <.001) (Figure 1, eFigures 1-5).

**LDL-C level with lowest risk of all-cause mortality**

The LDL-C level associated with the lowest risk of all-cause mortality in multivariable adjusted analyses was 3.6 mmol/L (140 mg/dL) in the overall population and in individuals not receiving lipid-lowering therapy, while it was 2.0 mmol/L (77 mg/dL) in individuals receiving lipid-lowering therapy (Figure 1). Similar levels were seen in both sexes and across age groups, except for individuals aged ≤65 receiving lipid-lowering therapy where the lowest risk of all-cause mortality was found at an LDL-C level of 2.5 mmol/L (97 mg/dL) (eFigures 1-2).
**LDL-C and cause-specific mortality**

In the overall population there was no association between LDL-C on a continuous scale and cardiovascular mortality, while the association with both cancer and other mortality appeared to be U-shaped (Figure 3, eFigure 6). In individuals not receiving lipid-lowering therapy, low LDL-C levels were associated with increased risk of cardiovascular mortality while the associations with both cancer and other mortality were U-shaped (eFigure 6). Likewise, among individuals receiving lipid-lowering therapy, low LDL-C levels were associated with increased cancer mortality, whereas no association was found for cardiovascular and other mortality (eFigure 6).

**LDL-C and myocardial infarction**

Any increase in LDL-C levels was associated with an increased risk for myocardial infarction in the overall cohort as well as in individuals not receiving lipid-lowering therapy (eFigure 7).

**Sensitivity analyses**

To assess whether the positive association between low levels of LDL-C and increased risk of all-cause mortality could be explained by reverse causation due to severe disease, we first excluded individuals with less than five years of follow-up (start of follow-up five years after baseline examination). This excludes individuals dying within five years from baseline and individuals with less than five years of follow-up. Results were similar to the main analyses, although the association attenuated slightly (Figure 4, eFigure 8). Excluding only those dying within five years from baseline examination yielded similar results. In other sensitivity analyses, we excluded individuals with baseline atherosclerotic cardiovascular disease, baseline cancer, or baseline chronic obstructive pulmonary disease, respectively. Overall results were similar to main analyses (Figure 4, eFigure 8).

Estimated pre-treatment LDL-C were examined to evaluate whether low LDL-C levels due to lipid-lowering therapy, representing a high-risk group with higher pre-treatment levels, could explain the association between low LDL-C levels and mortality. Results from these analyses yielded similar results for all-cause, cancer, and other mortality at low LDL-C levels while the association increased at high LDL-C
levels (eFigure 9). For cardiovascular mortality, results were similar at high LDL-C levels with no association while low LDL-C levels were associated with an increased risk.
Discussion

In the present study of 108,243 individuals from a contemporary general population cohort we found a U-shaped association between LDL-C levels and risk of all-cause mortality, with both low and high levels being associated with increased risk. Surprisingly, the lowest risk of all-cause mortality was found at an LDL-C level of 3.6 mmol/L (140 mg/dL) – well above what is generally considered optimal levels. These novel results are likely to have implications for the interpretation of LDL-C levels in clinical practice. As expected, risk of myocardial infarction increased with any increase of LDL-C.

The association between low LDL-C levels and increased risk of all-cause mortality could possibly be explained by reverse causation. Debilitation and illness have been hypothesized to cause decline in cholesterol levels (17, 18) and indeed, in the present study, comorbidities were more frequent among individuals with the lowest LDL-C levels. Furthermore, consistent with the theory that low LDL-C is an indirect marker of severe disease, the association between low LDL-C levels and risk of all-cause mortality was strongest in the age and sex adjusted model and substantially attenuated when adjusting for baseline comorbidities. However, a strong association remained after this adjustment and after excluding individuals with known cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Further, the association was slightly attenuated when excluding individuals with less than five years of follow-up.

Whether the remaining association despite extensive comorbidity adjustment can be ascribed residual confounding in terms of alternative mechanisms is unclear. The more pronounced association seen among individuals aged ≤65 could for instance point to an epiphenomenon where a pathophysiological abnormality, possibly genetic, causes increased risk of mortality and decreased LDL-C levels in parallel.

Most studies investigating the relationship between LDL-C levels and risk of all-cause mortality have found either no association (8-10) or an inverse association (5-7). However, our study shows that the inverse association can be explained by the increased risk of all-cause mortality associated with low LDL-C levels rather than representing an actual decreased risk at high LDL-C levels. In addition, a recent study on young Koreans not taking lipid-lowering medication showed an association between low LDL-C levels and increased risk of all-cause mortality, cardiovascular mortality, and cancer mortality (11), similar to results from the subgroup of individuals not taking lipid-lowering therapy in the present study.
No previous study has examined the LDL-C level associated with the lowest risk of all-cause mortality in a general population setting. Though, one study has been published on subjects aged ≥65 reporting lowest all-cause mortality risk at an LDL-C level of 4.9 mmol/L (190 mg/dL) for women and 3.8 mmol/L (147 mg/dL) for men (19). In the present study, we consistently found the lowest risk of all-cause mortality at LDL-C levels of 3.6-3.7 mmol/L (140-143 mg/dL) across sex and age groups (≤ or >65 years).

Previous studies published on the association between total cholesterol and risk of mortality have shown a reversed J-shaped or U-shaped association with the highest risk of all-cause, cancer, and other mortality found at the lowest total cholesterol levels while both positive, inverse, and no association to cardiovascular mortality have been reported (17, 20, 21). Furthermore, we have recently demonstrated a similar U-shaped association between high-density lipoprotein cholesterol and risk of all-cause mortality (22).

The relatively low number of individuals receiving lipid-lowering therapy in Denmark may seem surprising, but have been confirmed by previous studies (23, 24). Among individuals receiving lipid-lowering therapy, the association between low LDL-C levels and increased risk of all-cause and cancer mortality was much weaker than for individuals not receiving lipid-lowering therapy, while no association was found between low LDL-C levels and cardiovascular or other mortality. Importantly, this indirectly indicates a non-causal association and suggests that it is not lowering of LDL-C levels by lipid-lowering therapy that explains the increased risk of mortality at low LDL-C levels. In other words, it would be incorrect to use our data as an argument against the use of lipid-lowering therapy in the prevention of atherosclerotic cardiovascular disease and mortality. Indeed, a recent meta-analysis of studies on individuals at high risk of atherosclerotic cardiovascular disease showed that more intensive lowering of LDL-C was associated with greater reduction in the risk of all-cause and cardiovascular mortality (4).

Our results may be of importance in understanding what a “normal and healthy” LDL-C level is in individuals in the general population, that is, when focus is not limited to myocardial infarction and atherosclerotic cardiovascular disease. The findings of the lowest risk of all-cause mortality at an LDL-C level of 3.6 mmol/L (140 mg/dL) implies that in individuals with otherwise low risk of atherosclerotic cardiovascular disease, an LDL-C level around this value is not necessarily hazardous per se. Though, it is important to notice that any increase in LDL-C was still associated with increased risk of myocardial infarction. All together, these results point to the importance of assessing the absolute risk of atherosclerotic
cardiovascular disease when deciding on whom to treat with lipid-lowering therapies (25, 26), rather than initiating treatment based solely on moderate LDL-C elevation.

Several strengths apply for our study. First, the size of the cohort in terms of the large number of individuals recruited without a single person lost to follow-up. Second, information on cause of death for every individual due to the use of Danish registries. Third, we were able to adjust for several confounders with an effect on mortality risk (14). Fourth, the strong positive association found between any increase in LDL-C and increased risk of myocardial infarction supports the validity of this study. Finally, it is a strength that we corrected for regression dilution bias.

A limitation of our study is that it only includes whites living in a Western country which may cause restrictions regarding generalizability to other ethnicities; however, we are not aware of data to suggest that our results are not applicable to other ethnicities living in countries with standard of living and health-care systems like the Danish. Indeed, a recent study on young Koreans of supposedly comparable affluence to people in Denmark showed similar results to the present study (11). Certainly, in less affluent and less developed countries the LDL-C level associated with the lowest mortality may differ from that shown in our study. We only had information on lipid-lowering therapy at baseline and cannot rule out that the results may be influenced by individuals initiating or discontinuing lipid-lowering therapy during follow-up. Finally, we were not able to address the question of causality given this is an observational study.

In conclusion, both low and high LDL-C levels were associated with increased risk of all-cause mortality in individuals in the general population. Similar results were seen for cancer and other mortality while no association was found for cardiovascular mortality. Furthermore, individuals in the general population with LDL-C of 3.6 mmol/L (140 mg/dL) live the longest. These findings support that use of lipid-lowering therapies should be based on absolute atherosclerotic cardiovascular disease risk rather than on moderately elevated LDL-C levels alone. Further research is needed to explore the association between low LDL-C and risk of all-cause mortality and the missing association with cardiovascular mortality.
What is already known on this topic

- Diverging results have previously been reported on the association between LDL-C and all-cause mortality.
- Majority of previous studies have been conducted in individuals aged above 65 years in historical populations.

What this study adds

- Both low and high levels of LDL-C are associated with increased risk of all-cause mortality in the general population.
- The lowest risk of all-cause mortality was found at an LDL-C level of 3.6 mmol/L (140 mg/dL).
- The use of lipid-lowering therapies should be based on absolute atherosclerotic cardiovascular disease risk rather than on moderately elevated LDL-C levels alone.

Acknowledgements

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Author contributions

All authors contributed to the study design, acquisition, analyses, and interpretation of the data. CDLJ drafted the initial manuscript and AL, MBM, and BGN critically revised the manuscript for important intellectual content. Final approval of the version to be published was given by all authors. BGN had full access to all the data in the study, takes responsibility for the work and conduct of the study, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interest declaration

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any
organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

The study was approved by Herlev Gentofte Hospital, the Ethics Committee of the Capital Region of Denmark (H-KF-01-144/01), and the Danish Data Protection Agency. Written informed consent was given by each participant.

Transparency statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Data sharing

Data is available from the corresponding author upon reasonable request.
References


Figure Legends

Figure 1. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale. Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.

Figure 2. Hazard ratios for all-cause mortality according to categories of LDL cholesterol levels, sex and age adjusted and multivariable adjusted. Multivariable adjusted analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: CI, confidence interval; LDL, low-density lipoprotein.

Figure 3. Multivariable adjusted hazard ratios for cause-specific mortality according to LDL cholesterol levels on a continuous scale in the overall population. Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.
Figure 4. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in the overall population with either start of follow-up at year 5 or exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease, respectively. Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; N, number.
### Table 1. Baseline characteristics of 108,243 individuals in the Copenhagen General Population Study.

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<td>mg/dL</td>
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<td>70-92</td>
<td>93-112</td>
<td>113-131</td>
<td>132-154</td>
<td>155-189</td>
<td>&gt;189</td>
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<tr>
<td>Number</td>
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<td>15,681 (14)</td>
<td>21,289 (20)</td>
<td>22,207 (21)</td>
<td>21,892 (20)</td>
<td>15,999 (15)</td>
<td>4,763 (4)</td>
<td>108,243</td>
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<td>Women</td>
<td>3,202 (50)</td>
<td>9,068 (58)</td>
<td>11,973 (67)</td>
<td>12,385 (56)</td>
<td>11,710 (53)</td>
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<td>56 (46-67)</td>
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<td>Lipid-lowering therapy</td>
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<td>563 (3)</td>
<td>401 (2)</td>
<td>169 (2)</td>
<td>83 (2)</td>
<td>4,605 (4)</td>
</tr>
<tr>
<td>Atherosclerotic cardiovascular disease</td>
<td>1,806 (28)</td>
<td>2,262 (14)</td>
<td>1,756 (8)</td>
<td>1,413 (6)</td>
<td>1,200 (5)</td>
<td>817 (5)</td>
<td>223 (5)</td>
<td>9,477 (9)</td>
</tr>
<tr>
<td>Cancer</td>
<td>557 (9)</td>
<td>1,093 (7)</td>
<td>1,393 (7)</td>
<td>1,474 (7)</td>
<td>1,508 (7)</td>
<td>1,081 (7)</td>
<td>327 (7)</td>
<td>7,433 (7)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1,218 (19)</td>
<td>2,517 (16)</td>
<td>3,224 (15)</td>
<td>3,324 (15)</td>
<td>3,246 (15)</td>
<td>2,331 (15)</td>
<td>666 (14)</td>
<td>16,526 (15)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.6 (1.4-1.7)</td>
<td>2.2 (2.0-2.3)</td>
<td>2.7 (2.6-2.8)</td>
<td>3.2 (3.1-3.3)</td>
<td>3.7 (3.6-3.9)</td>
<td>4.4 (4.2-4.6)</td>
<td>5.3 (5.1-5.7)</td>
<td>3.2 (2.6-3.8)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>62 (54-66)</td>
<td>85 (77-89)</td>
<td>104 (101-108)</td>
<td>124 (119-128)</td>
<td>143 (139-150)</td>
<td>170 (620-178)</td>
<td>205 (197-219)</td>
<td>124 (100-147)</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or numbers (%). Abbreviations: LDL, low-density lipoprotein.
Figure 1

Overall population

N=108,243
11,376 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.6 mmol/L
140 mg/dL

No lipid-lowering therapy

N=95,218
8,877 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.6 mmol/L
140 mg/dL

Lipid-lowering therapy

N=13,025
2,499 deaths

All-cause mortality hazard ratio
(95% confidence interval)

2.0 mmol/L
77 mg/dL

mmol/L
mg/dL
0 2 4 6 8 10
0 77 155 232 309 387
LDL cholesterol
Figure 2

Percentile LDL cholesterol (mmol/L, mg/dL) and event rates (per 1,000 person years).

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL Cholesterol</th>
<th>Individuals</th>
<th>Events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-5th</td>
<td>&lt;1.8</td>
<td>6412</td>
<td>1178</td>
<td>1.89 (1.69-2.11)</td>
</tr>
<tr>
<td>6th-20th</td>
<td>1.8-2.3</td>
<td>15681</td>
<td>1863</td>
<td>1.45 (1.35-1.64)</td>
</tr>
<tr>
<td>21st-40th</td>
<td>2.4-2.8</td>
<td>21289</td>
<td>2057</td>
<td>1.17 (1.07-1.29)</td>
</tr>
<tr>
<td>41st-60th</td>
<td>2.9-3.3</td>
<td>22207</td>
<td>2162</td>
<td>1.10 (1.00-1.21)</td>
</tr>
<tr>
<td>61st-80th</td>
<td>3.4-3.9</td>
<td>21892</td>
<td>2050</td>
<td>1.00</td>
</tr>
<tr>
<td>81st-95th</td>
<td>4.0-4.8</td>
<td>15999</td>
<td>1568</td>
<td>1.03 (0.93-1.15)</td>
</tr>
<tr>
<td>96th-100th</td>
<td>&gt;4.8</td>
<td>4763</td>
<td>492</td>
<td>1.25 (1.07-1.46)</td>
</tr>
</tbody>
</table>

Age and sex-adjusted hazard ratios (95% confidence interval).
Figure 3

Cardiovascular mortality

N=108 243
2428 deaths

3.4 mmol/L
132 mg/dL

Cancer mortality

N=108 243
3226 deaths

3.7 mmol/L
143 mg/dL

Other mortality

N=108 243
5722 deaths

3.5 mmol/L
136 mg/dL

LDL cholesterol
Figure 4

Start follow-up at year 5

N=97 810
7390 deaths

3.7 mmol/L
143 mg/dL

Atherosclerotic cardiovascular diseases excluded

N=98 766
6675 deaths

3.6 mmol/L
139 mg/dL

Cancer excluded

N=100 810
9335 deaths

3.7 mmol/L
143 mg/dL

COPD excluded

N=91 588
7724 deaths

3.4 mmol/L
132 mg/dL

Fraction of population (density)
ONLINE-ONLY SUPPLEMENTS

Relationship including nadir for low-density lipoprotein with all-cause and cause-specific mortality in a contemporary population: a cohort study

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\textsuperscript{2}The Copenhagen General Population Study, Herlev Gentofte Hospital, Copenhagen University Hospital, Denmark
\textsuperscript{3}The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark
\textsuperscript{4}Faculty of Health and Medical Science, University of Copenhagen, Denmark
\textsuperscript{5}Department of Cardiology, Aarhus University Hospital, Denmark
eFigure 1. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by sex.

eFigure 2. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by age.

eFigure 3. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by lipid-lowering therapy.

eFigure 4. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by sex.

eFigure 5. Multivariable adjusted hazard ratios with 95% confidence intervals for all-cause mortality for the highest 20% and lowest 20% of LDL cholesterol.

eFigure 6. Multivariable adjusted hazard ratios for cause-specific mortality according to LDL cholesterol levels on a continuous scale in the overall population and stratified by lipid-lowering therapy.

eFigure 7. Multivariable adjusted hazard ratios for myocardial infarction according to LDL cholesterol levels on a continuous.

eFigure 8. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in individuals not receiving lipid-lowering therapy with either start of follow-up at year 5 or exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease, respectively.

eFigure 9. Multivariable adjusted hazard ratios for all-cause and cause-specific mortality according to estimated pre-lipid-lowering LDL cholesterol levels on a continuous scale.
eFigure 1. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by sex.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.

Overall population

Women

N=59,574
5055 deaths

Men

N=48,669
6321 deaths

No lipid-lowering therapy

Women

N=53,535
4121 deaths

Men

N=41,683
4765 deaths

Lipid-lowering therapy

Women

N=6039
934 deaths

Men

N=11,373
1666 deaths
eFigure 2. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by age.
Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.

Overall population

Age ≤ 65 years

N= 74 252
2646 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.6 mmol/L
140 mg/dL

Age > 65 years

N= 33 991
8730 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.7 mmol/L
143 mg/dL

No lipid-lowering therapy

N= 89 188
2256 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.6 mmol/L
140 mg/dL

N= 26 060
6619 deaths

All-cause mortality hazard ratio
(95% confidence interval)

3.7 mmol/L
143 mg/dL

Lipid-lowering therapy

N= 5084
368 deaths

All-cause mortality hazard ratio
(95% confidence interval)

2.5 mmol/L
97 mg/dL

N= 7941
2111 deaths

All-cause mortality hazard ratio
(95% confidence interval)

1.9 mmol/L
73 mg/dL
**eFigure 3. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by lipid-lowering therapy.**

Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: CI, confidence interval; LDL, low-density lipoprotein.

### No lipid-lowering therapy

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL cholesterol mmol/L</th>
<th>Individuals</th>
<th>Events</th>
<th>Event rate per 1,000 person years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-5th</td>
<td>&lt;1.8</td>
<td>3362</td>
<td>394</td>
<td>12.1</td>
<td>1.57 (1.66-2.34)</td>
</tr>
<tr>
<td>6th-20th</td>
<td>1.8-2.3</td>
<td>11,516</td>
<td>1064</td>
<td>9.7</td>
<td>1.40 (1.25-1.58)</td>
</tr>
<tr>
<td>21st-40th</td>
<td>2.4-2.8</td>
<td>18,398</td>
<td>1576</td>
<td>9.1</td>
<td>1.09 (0.98-1.20)</td>
</tr>
<tr>
<td>41st-60th</td>
<td>2.9-3.3</td>
<td>20,623</td>
<td>1926</td>
<td>10.0</td>
<td>1.10 (0.99-1.21)</td>
</tr>
<tr>
<td>61st-80th</td>
<td>3.4-3.9</td>
<td>21,043</td>
<td>1936</td>
<td>9.8</td>
<td>1.00</td>
</tr>
<tr>
<td>81st-95th</td>
<td>4.0-4.8</td>
<td>16,262</td>
<td>1518</td>
<td>10.3</td>
<td>1.07 (0.97-1.19)</td>
</tr>
<tr>
<td>96th-100th</td>
<td>&gt;4.8</td>
<td>4631</td>
<td>473</td>
<td>10.7</td>
<td>1.26 (1.08-1.48)</td>
</tr>
</tbody>
</table>

### Lipid-lowering therapy

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL cholesterol mmol/L</th>
<th>Individuals</th>
<th>Events</th>
<th>Event rate per 1,000 person years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-5th</td>
<td>&lt;1.8</td>
<td>3030</td>
<td>784</td>
<td>32.8</td>
<td>0.85 (0.62-1.17)</td>
</tr>
<tr>
<td>6th-20th</td>
<td>1.8-2.3</td>
<td>4166</td>
<td>815</td>
<td>23.9</td>
<td>0.81 (0.60-1.11)</td>
</tr>
<tr>
<td>21st-40th</td>
<td>2.4-2.8</td>
<td>2691</td>
<td>431</td>
<td>19.9</td>
<td>0.91 (0.66-1.26)</td>
</tr>
<tr>
<td>41st-60th</td>
<td>2.9-3.3</td>
<td>1684</td>
<td>236</td>
<td>17.2</td>
<td>0.98 (0.69-1.39)</td>
</tr>
<tr>
<td>61st-80th</td>
<td>3.4-3.9</td>
<td>849</td>
<td>114</td>
<td>16.7</td>
<td>1.00</td>
</tr>
<tr>
<td>81st-95th</td>
<td>4.0-4.8</td>
<td>373</td>
<td>50</td>
<td>15.3</td>
<td>0.93 (0.55-1.57)</td>
</tr>
<tr>
<td>96th-100th</td>
<td>&gt;4.8</td>
<td>132</td>
<td>19</td>
<td>16.5</td>
<td>1.23 (0.57-2.63)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% confidence interval)
eFigure 4. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by sex.

Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: CI, confidence interval; LDL, low-density lipoprotein.

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL cholesterol Individuals</th>
<th>Event rate per 1,000 person years</th>
<th>Hazard ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st-5th</td>
<td>&lt;1.8 &lt;70</td>
<td>3202 381</td>
<td>12.9</td>
</tr>
<tr>
<td>6th-20th</td>
<td>1.8-2.3 70-92</td>
<td>9066 694</td>
<td>0.2</td>
</tr>
<tr>
<td>21st-40th</td>
<td>2.4-2.8 93-112</td>
<td>11973 862</td>
<td>7.7</td>
</tr>
<tr>
<td>41st-60th</td>
<td>2.9-3.3 113-131</td>
<td>12365 974</td>
<td>6.4</td>
</tr>
<tr>
<td>61st-80th</td>
<td>3.4-3.9 132-154</td>
<td>11710 1000</td>
<td>9.1</td>
</tr>
<tr>
<td>81st-95th</td>
<td>4.0-4.8 155-189</td>
<td>8537 841</td>
<td>10.5</td>
</tr>
<tr>
<td>96th-100th</td>
<td>&gt; 4.8 &gt; 189</td>
<td>2699 303</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st-5th</td>
<td>&lt;1.8 &lt;70</td>
<td>3210 797</td>
<td>29.7</td>
</tr>
<tr>
<td>6th-20th</td>
<td>1.8-2.3 70-92</td>
<td>6613 1175</td>
<td>20.2</td>
</tr>
<tr>
<td>21st-40th</td>
<td>2.4-2.8 93-112</td>
<td>9316 1195</td>
<td>14.1</td>
</tr>
<tr>
<td>41st-60th</td>
<td>2.9-3.3 113-131</td>
<td>9822 1188</td>
<td>13.1</td>
</tr>
<tr>
<td>61st-80th</td>
<td>3.4-3.9 132-154</td>
<td>10182 1050</td>
<td>11.2</td>
</tr>
<tr>
<td>81st-95th</td>
<td>4.0-4.8 155-189</td>
<td>7462 727</td>
<td>10.3</td>
</tr>
<tr>
<td>96th-100th</td>
<td>&gt; 4.8 &gt; 189</td>
<td>2064 189</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Hazard ratio (95% confidence interval)
Figure 5. Multivariable adjusted hazard ratios with 95% confidence intervals for all-cause mortality for the highest 20% and lowest 20% of LDL cholesterol.

The highest 20% (> 3.9 mmol/L; 154 mg/dL) vs the 61st-80th percentile (3.4-3.9 mmol/L; 132-154 mg/dL) of LDL cholesterol and the lowest 20% (< 2.4 mmol/L; 93 mg/dL) vs the 61st-80th percentile (3.4-3.9 mmol/L; 132-154 mg/dL) of LDL cholesterol, respectively. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years.
eFigure 6. Multivariable adjusted hazard ratios for cause-specific mortality according to LDL cholesterol levels on a continuous scale in the overall population and stratified by lipid-lowering therapy. Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.
eFigure 7. Multivariable adjusted hazard ratios for myocardial infarction according to LDL cholesterol levels on a continuous scale. Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.
eFigure 8. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in individuals not receiving lipid-lowering therapy with either start of follow-up at year 5 or exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease, respectively.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, lipid-lowering therapy, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.
eFigure 9. Multivariable adjusted hazard ratios for all-cause and cause-specific mortality according to estimated pre-lipid-lowering LDL cholesterol levels on a continuous scale.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction of population with different LDL cholesterol levels. The arrows indicate the LDL cholesterol level with the lowest all-cause mortality. Analyses were adjusted for age, sex, current smoking, cumulative number of pack-years, systolic blood pressure, diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease at baseline. Pre-lipid-lowering LDL cholesterol levels were estimated in individuals receiving lipid-lowering therapy as baseline LDL cholesterol measurements multiplied by 1.43, corresponding to a 30% reduction. Based on individuals from the Copenhagen General Population Study followed for a mean 9.4 years. Abbreviations: LDL, low-density lipoprotein; N, number.