

ONLINE-ONLY SUPPLEMENTS

Association between low density lipoprotein and all cause and cause specific mortality in Denmark:
prospective cohort study

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eTable 1. Distribution of cardiovascular mortality according to International Classification of Disease codes.

eFigure 1. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by lipid-lowering therapy.

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eFigure 10. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in individuals receiving lipid-lowering therapy with either start of follow-up at year 5 or after exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease at baseline, respectively.

eFigure 11. Multivariable adjusted hazard ratios for all-cause and cause-specific mortality according to estimated pre-lipid-lowering LDL cholesterol levels on a continuous scale.

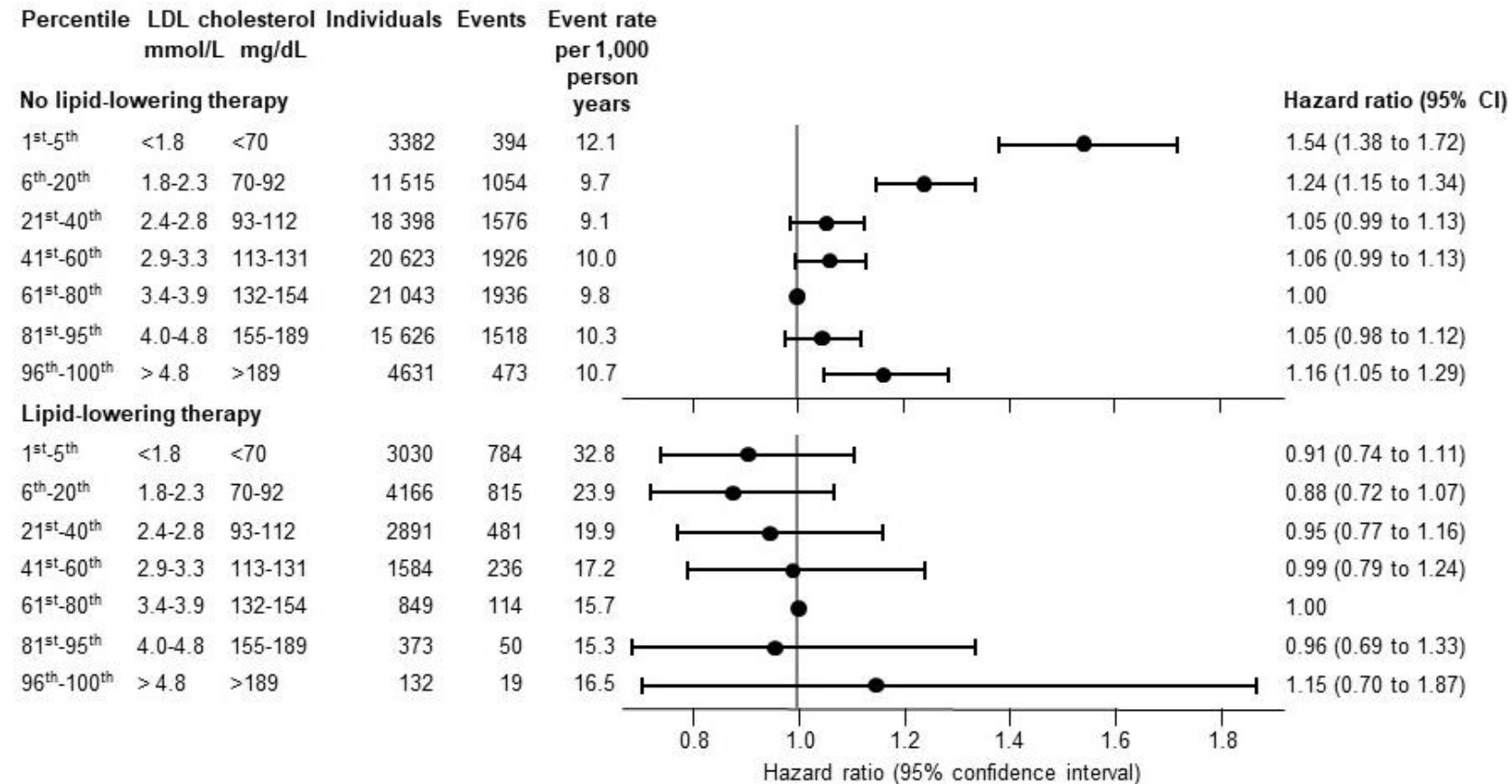
eFigure 12. Hazard ratios corrected for regression dilution bias for all-cause mortality according to categories of LDL cholesterol levels, sex and age adjusted and multivariable adjusted.

eTable 1. Distribution of cardiovascular mortality according to International Classification of Disease codes.

International Classification of Disease (ICD) codes	Numbers (%)
I00-I09: Acute rheumatic fever and chronic rheumatic heart diseases	13 (1)
I10-I15: Hypertensive diseases	118 (5)
I20, I23-I25: Ischemic heart diseases	344 (14)
I21-I22: Myocardial infarction	327 (13)
I26-I28: Pulmonary heart disease and diseases of pulmonary circulation	129 (5)
I30-I49, I51-I52: Other forms of heart disease	360 (15)
I50: Heart failure	327 (13)
I60-I64: Stroke, ischemic and hemorrhagic	596 (25)
I65-I69: Other cerebrovascular diseases	12 (0)
I70-I79: Diseases of arteries, arterioles and capillaries	170 (7)
I80-I89: Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	18 (1)
I95-I99: Other and unspecified disorders of the circulatory system	14 (1)

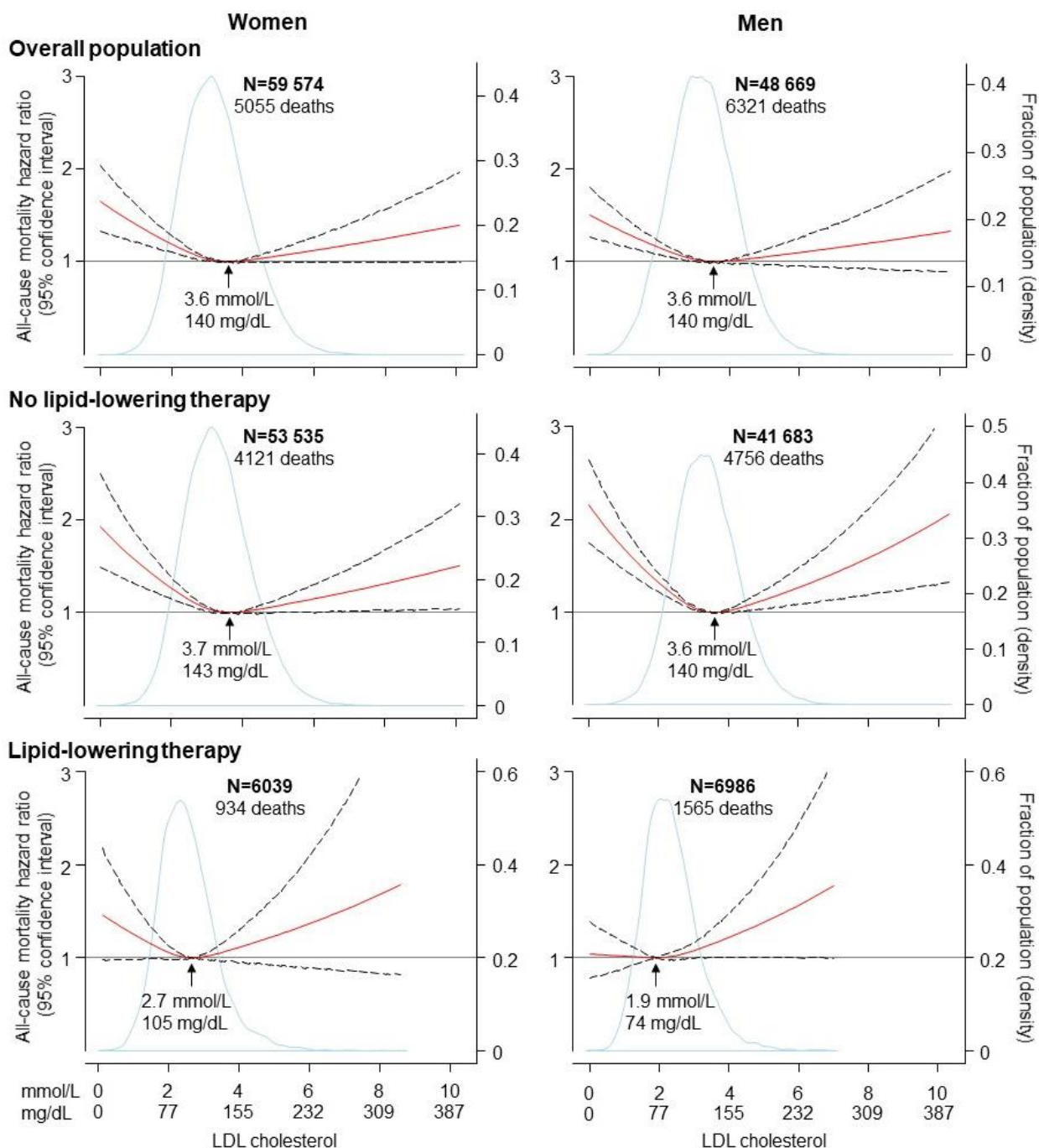
eFigure 1. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by lipid-lowering therapy.

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.



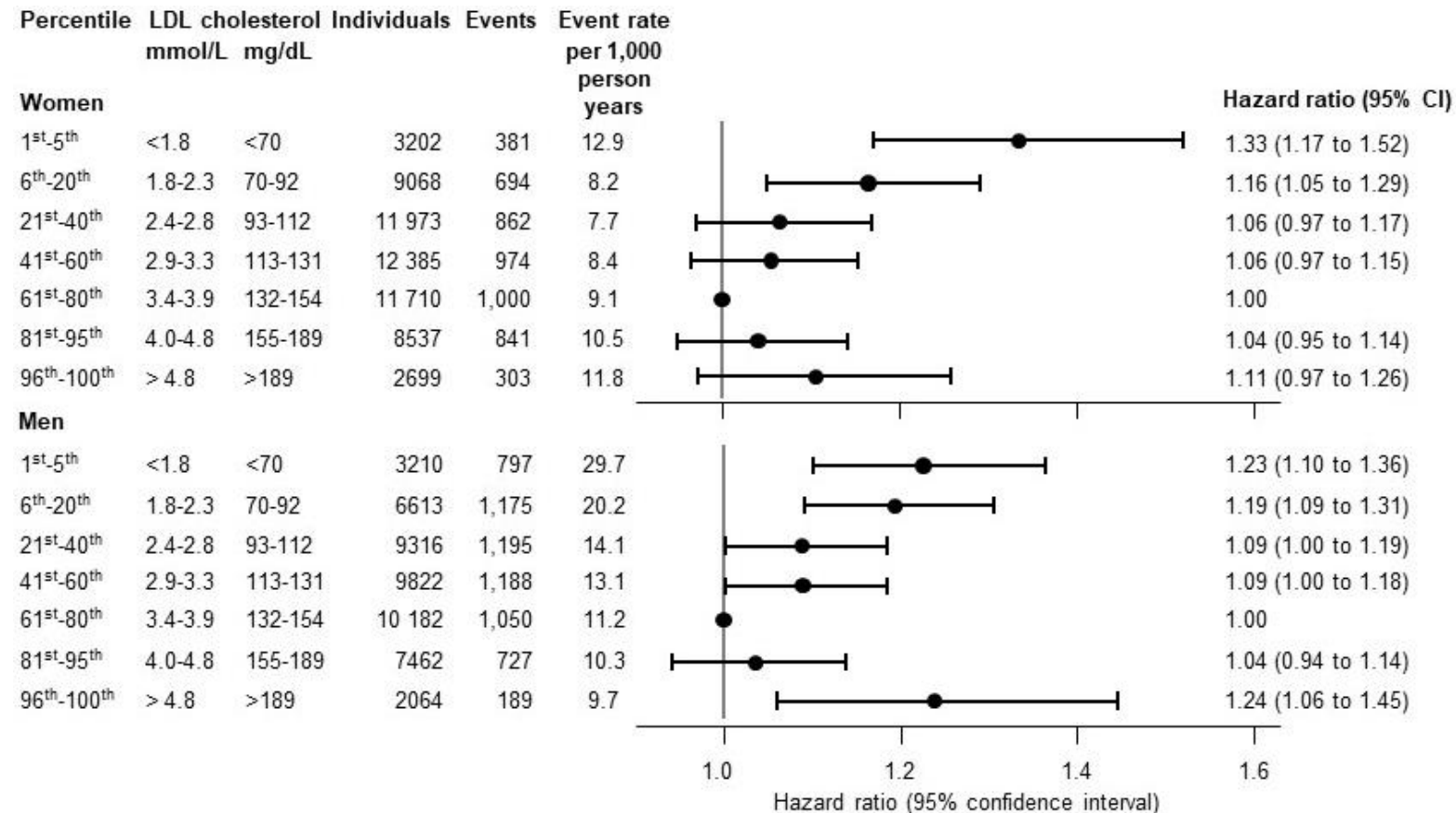
eFigure 2. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by sex.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions with three knots. 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.



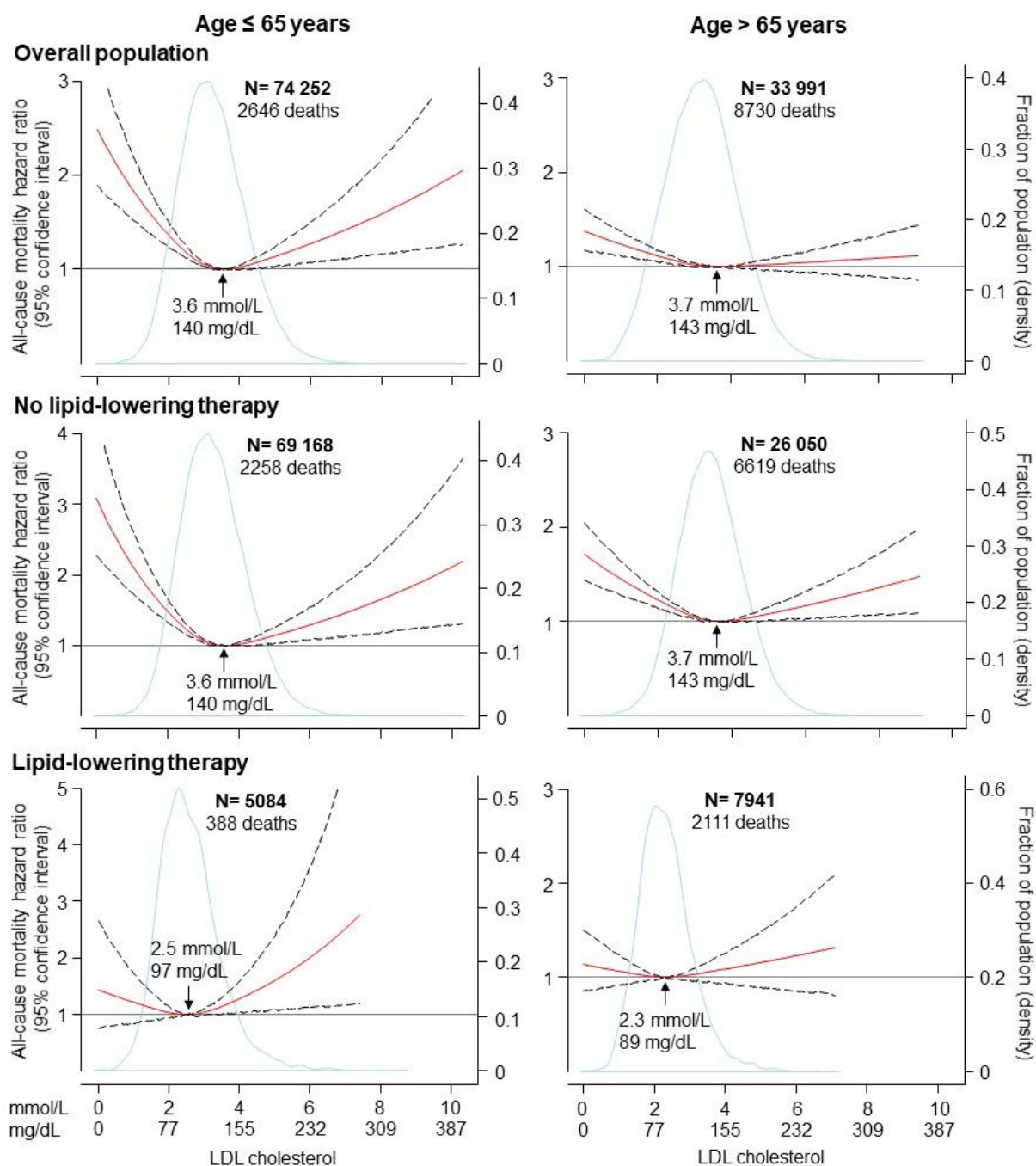
eFigure 3. Multivariable adjusted hazard ratios for all-cause mortality according to categories of LDL cholesterol levels stratified by sex.

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.



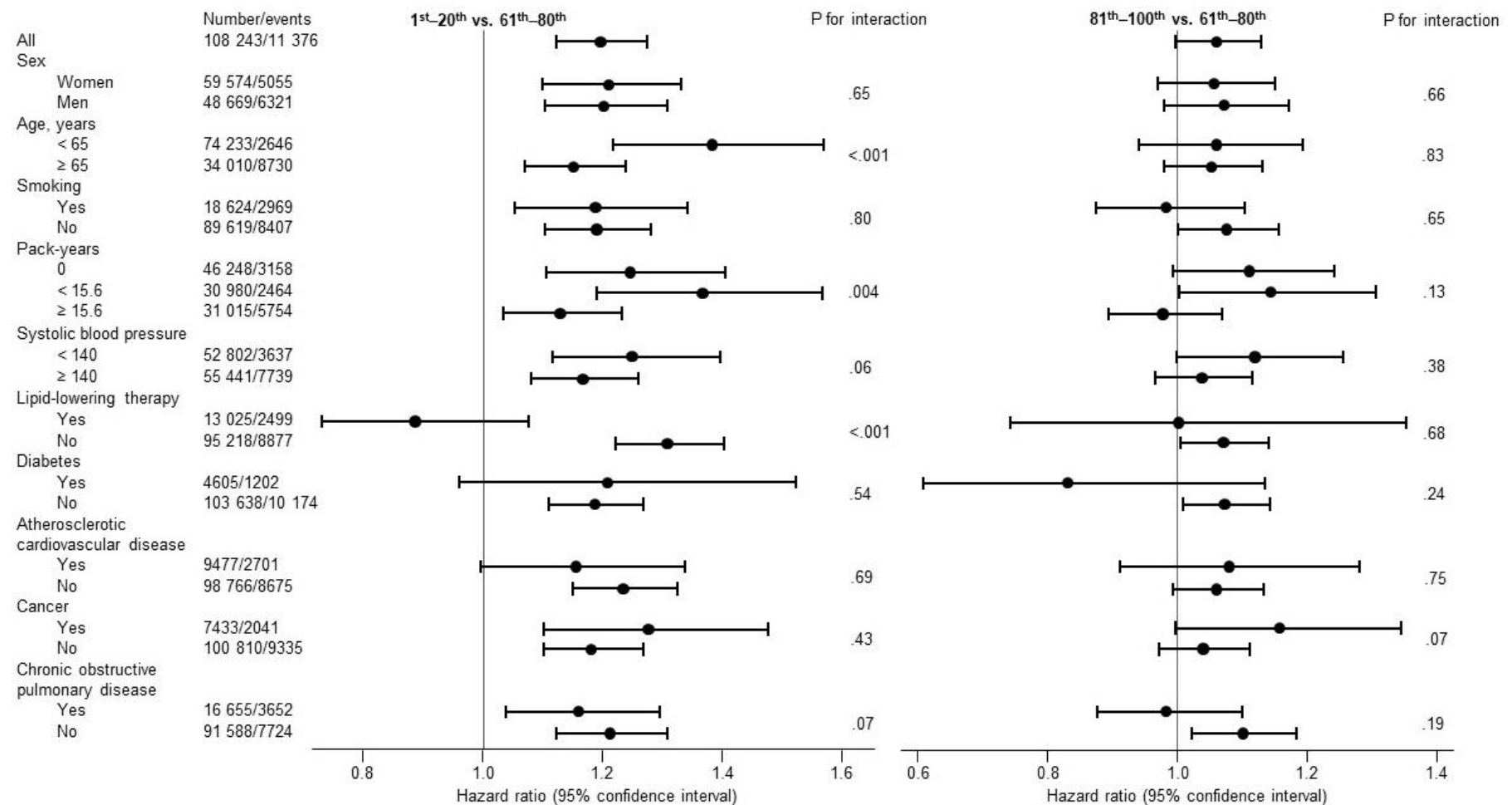
eFigure 4. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale stratified by age.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions with three knots. 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.



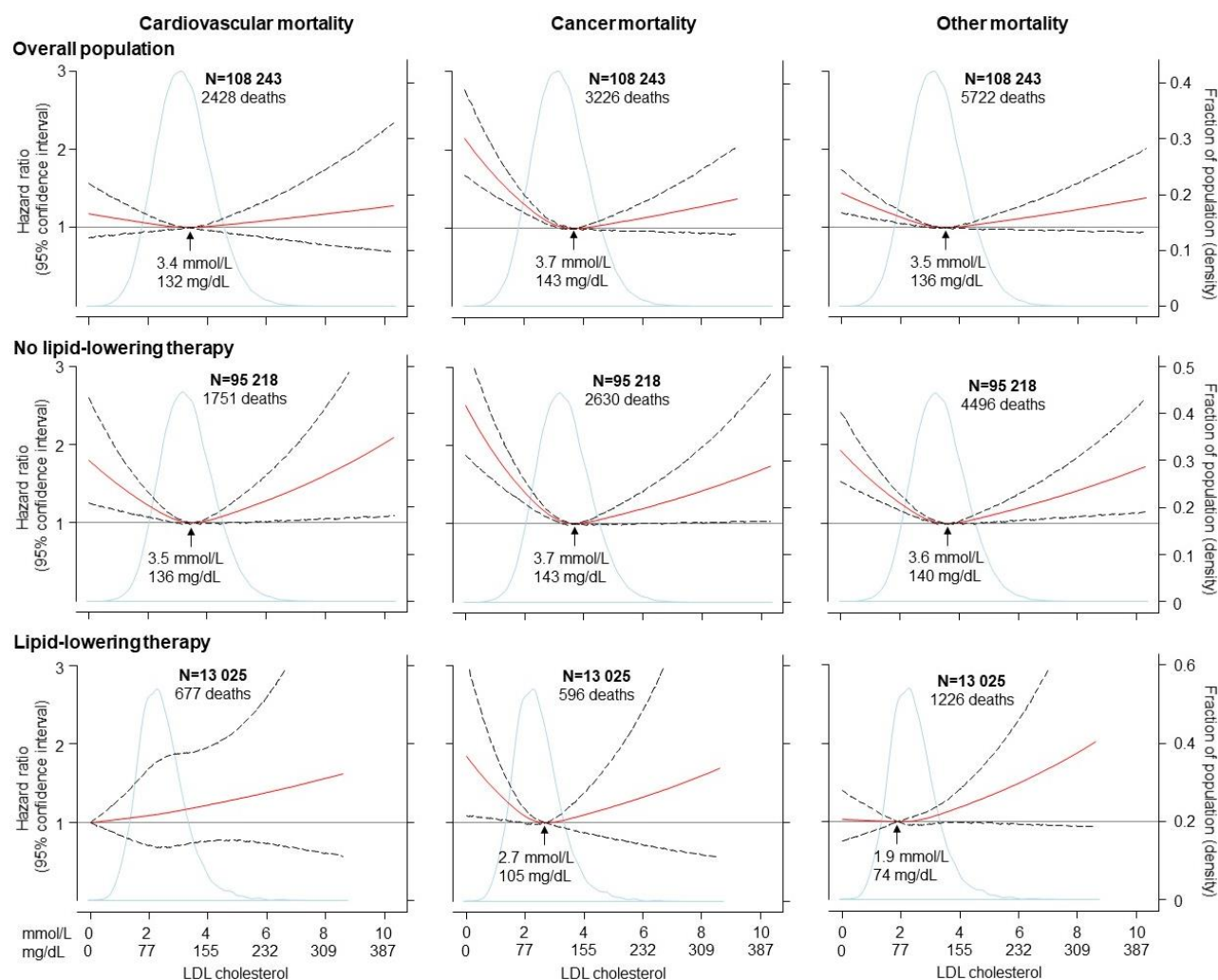
eFigure 5. Multivariable adjusted hazard ratios with 95% confidence intervals for all-cause mortality for the highest 20% and lowest 20% of LDL cholesterol.

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. P for interaction was examined by including a two-factor interaction term between the examined LDL cholesterol percentiles and each covariate in the Cox proportional hazards regression. 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.

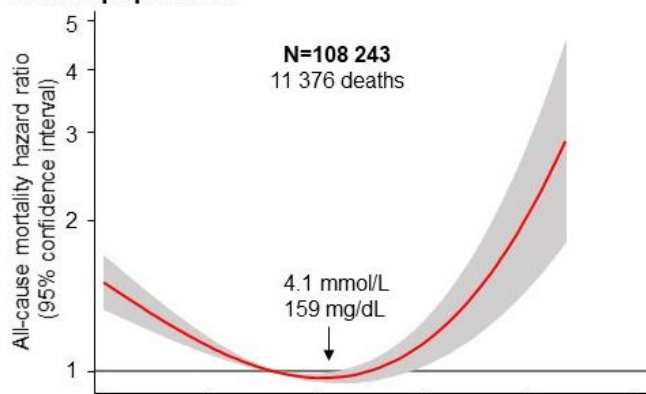
Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions with three knots. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines while solid light blue lines show fraction 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.



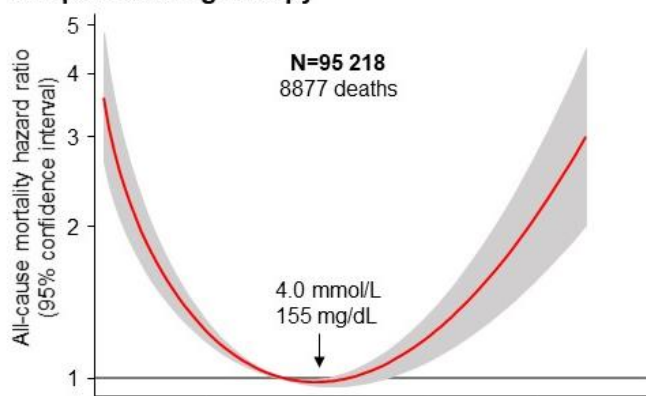
eFigure 7. Fractional polynomials showing multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale.

Solid red lines are multivariable adjusted hazard ratios and light gray areas show 95% confidence intervals derived from fractional polynomials. Reference line for no association (hazard ratio of 1.0) is indicated by solid gray lines. 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.

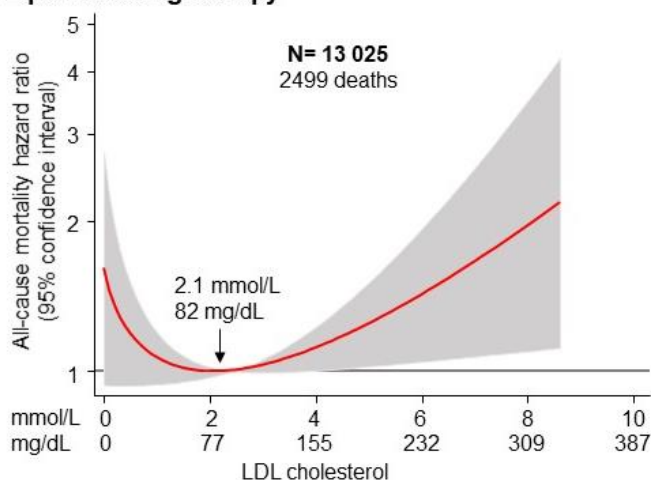
Overall population



No lipid-lowering therapy

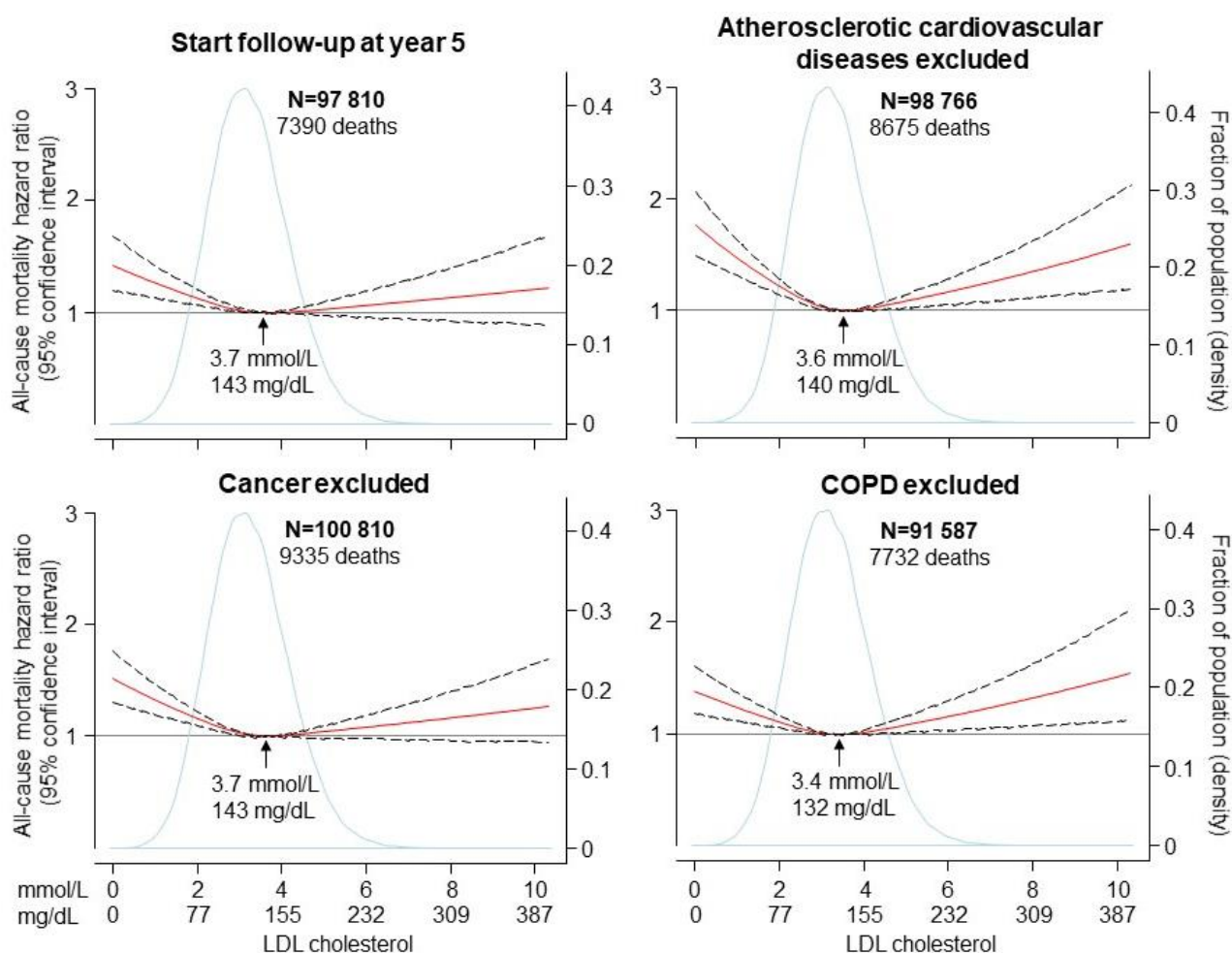


Lipid-lowering therapy



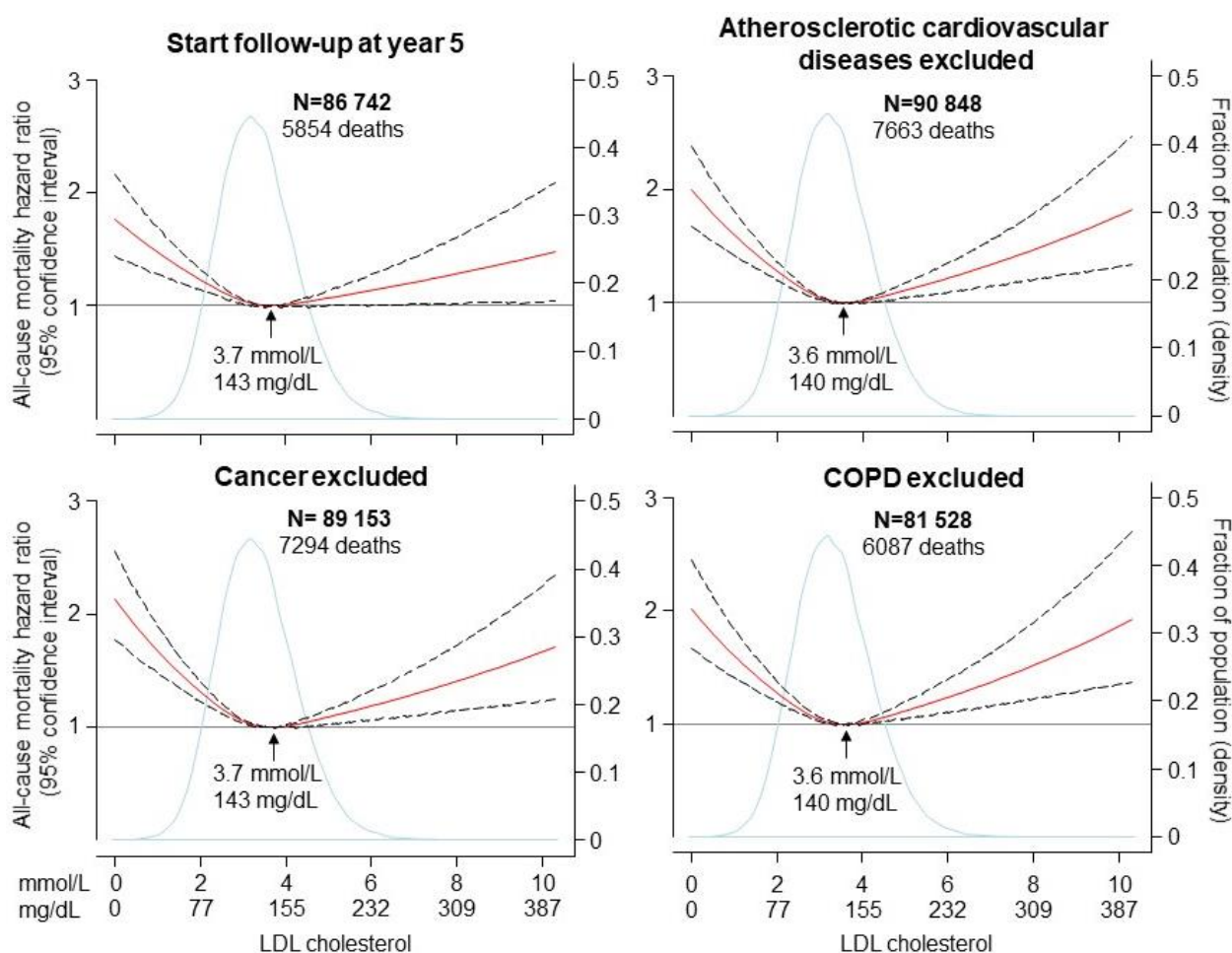
eFigure 8. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in the overall population with either start of follow-up at year 5 or after exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease at baseline, respectively.

Solid red lines are multivariable adjusted hazard ratios and dashed lines show 95% confidence intervals derived from restricted cubic spline regressions with three knots. 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.



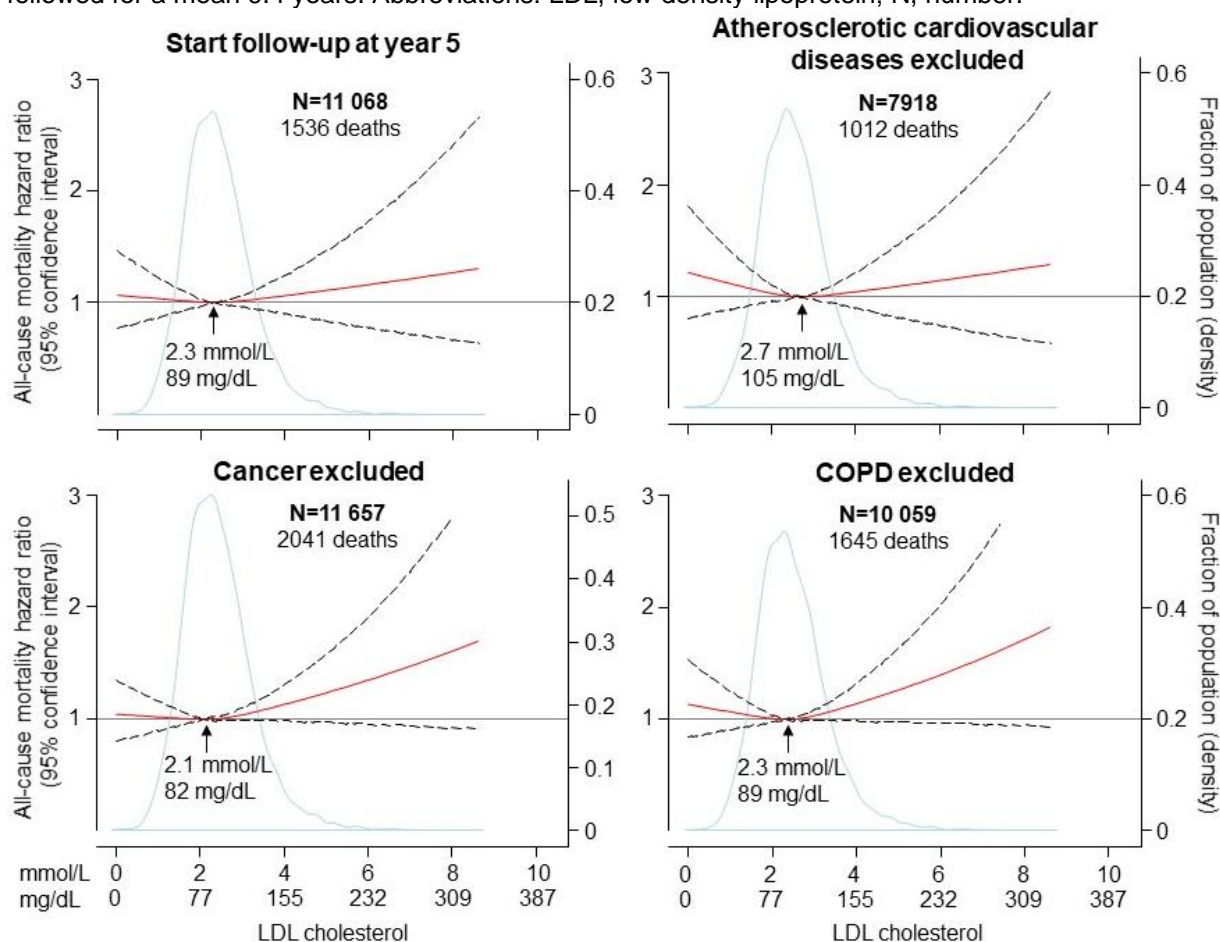
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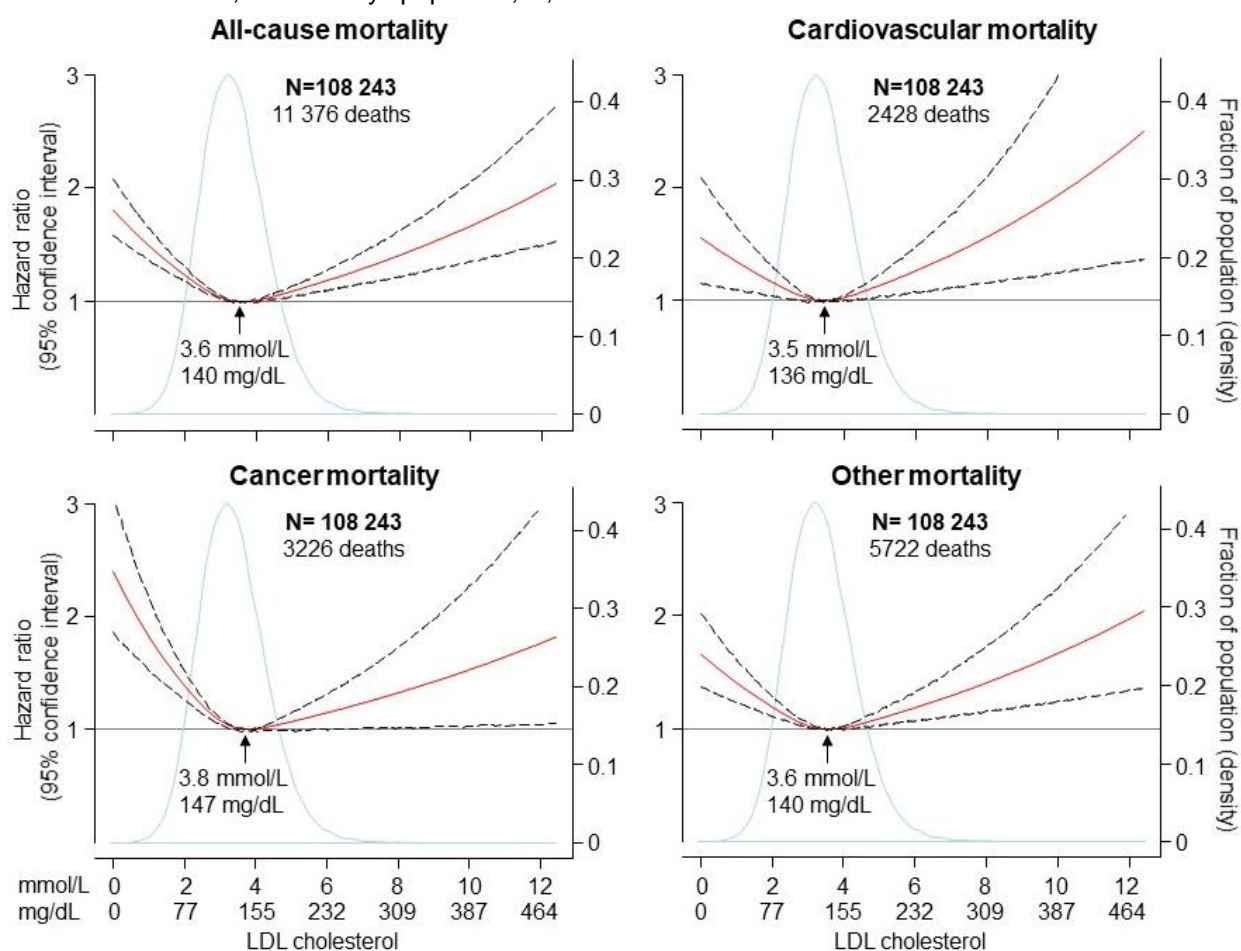
eFigure 10. Multivariable adjusted hazard ratios for all-cause mortality according to LDL cholesterol levels on a continuous scale in individuals receiving lipid-lowering therapy with either start of follow-up at year 5 or after exclusion of individuals with known atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease at baseline, respectively.

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eFigure 11. 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 with three knots. 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.



eFigure 12. Hazard ratios corrected for regression dilution bias 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.

