# Effects of Low-density Lipoprotein Cholesterol on Cardiovascular Disease and All-cause Mortality in Elderly Patients (≥75 years old)

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# Abstract

**Background:** The associations of low-density lipoprotein cholesterol (LDL-C) with cardiovascular disease (CVD) and all-cause mortality are unclear in elderly(**≥75 years)** Chinese individuals.

**Methods:** A total of 3674 individuals aged 75 or older underwent medical examinations at the Kailuan Group in 2006. Participants were divided into three groups by LDL_C values: the ideal level (LDL-C <2.6 mmol/l), appropriate level (2.6 mmol/l≤ LDL-C≦3.4 mmol/l) and elevated level (LDL-C≥3.4 mmol/l) groups. CVD and all-cause mortality events were recorded during the follow-up period. The Cox proportional hazards regression model was applied to evaluate the effect of LDL-C on CVD and all-cause mortality events.

**Results:** The average follow-up time was 9.87±3.60 years.After adjustment for confounding factors, the multivariate Cox proportional hazards regression model showed that CVD risk in the elevated group was 1.46 (95% CI, 1.08-1.97), acute myocardial infarction risk was 2.08 (95% CI, 1.26-3.44), and all-cause mortality risk in the appropriate level group and elevated group was 1.12 (95% CI, 1.00-1.25) and 1.17 (95% CI, 1.00-1.36), respectively, compared with those in the ideal level group. For every standard deviation increase in LDL-C, CVD risk increased by 10%, acute myocardial infarction risk increased by 21%, and all-cause mortality event risk increased by 4%. No association was found between elevated LDL-C levels and the risk of stroke.

**Conclusions:** In the elderly population, elevated LDL-C levels are a risk factor for CVD and all-cause mortality.


# Key Messages

In age of subjects ≥75 years, elevated Low-density Lipoprotein Cholesterol (LDL-C) was observed as a risk factor for Cardiovascular Disease (CVD) and all-cause mortality.

Elevated LDL-C mainly increased the risk of myocardial infarction, and no association was found between increased LDL-C and stroke risk.

The target value of primary prevention in the elderly population is 2.6mmol/ L, which may not be appropriate. According to our research, the target value can be increased to 3.4mmol/ L.

# Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the global population,[1] animal experiments and clinical studies have confirmed that an increased low-density lipoprotein cholesterol (LDL-C) level is the main risk factor for the occurrence and development of atherosclerosis.[2,3] A number of randomized controlled trials using lipid-lowering drug interventions, such as a meta-analysis of 27 randomized controlled trials on the effectiveness and safety of reducing LDL-C treatments, have shown

that lowering LDL-C levels can reduce the risk of CVD in the future. The results showed that for every 1 mmol/l decrease in LDL-C levels, the risk of major coronary events decreased by 24%, and the risk of all-cause mortality decreased by 9%.[4] However, in randomized controlled trials on lipid-lowering therapy, none of the trials were specifically conducted in elderly individuals ≥ 75 years of age. Only some randomized controlled trials included some patients ≥ 75 years of age. Therefore, the various guidelines based on the results of randomized controlled trials were applicable only to adults aged < 75 years.

At present, with the improvement of living standards and medical standards, elderly individuals are healthier than before; therefore, the life expectancy of elderly individuals is significantly longer than before, which delays the onset of disease.[5] It is estimated that the proportion of the global elderly population that is over 75 years old will exceed 20% for the first time in 2046 and that the number will reach 410 million.[6] At present, there are approximately 73 million people over the age of 75 in China. With the advent of an ageing society, it is estimated that by 2030, there will be approximately 123 million people over the age of 75 in China.[7] With population growth and ageing, CVD events are expected to increase by 50% each year, and they mainly occur in the elderly population.[8] Therefore, it is urgent to address the issue of abnormal lipid metabolism in individuals aged 75 and over, especially regarding the influence of LDL-C on cardiovascular events and whether intervention is needed. For this reason, this article prospectively analysed the association of LDL-C with CVD and all-cause mortality in elderly individuals ≥ 75 years of age in the Kailuan study cohort.

# Methods

# Study population and follow-up

In the Kailuan study, since 2006, follow-up has been carried out once every 2 years. The questionnaire included items on sociodemographic information, lifestyle, past history of diseases, and so forth, and the basic physical examination measured LDL-C blood biochemical indicators, etc.

The inclusion criteria were as follows: persons aged 75 years old or over who participated in the 2006 Kailuan Group Medical Examination for the first time; persons who could complete the questionnaire; and persons who agreed to participate in the study and signed an informed consent form. The exclusion criteria were persons with a history of CVD or cancer and persons with limited mobility.This research complied with the Declaration of Helsinki and was approved by the ethics committee of Kailuan General Hospital (batch number: 200608).

The first physical examination of the Kailuan Group in 2006 was considered the starting point for the follow-up, and CVD and all-cause mortality were considered the endpoints. For those with 2 or more CVDs, the first occurrence of CVD was the endpoint. For those who died but did not have CVD, the time of death was the endpoint of follow-up. For those without CVD and those who died, the date of the last follow-up was December 31, 2019.

During the follow-up period, the trained medical staff verified the information of the observation subjects at the hospitals of the Kailuan Group and the designated hospitals of the municipal medical insurance every year, determined the diagnosis of cardiovascular disease according to the international disease classification code ICD-10, and recorded the endpoint events. All diagnoses were confirmed by professional physicians according to the patients' hospitalization records. Every year, information on deaths was obtained by consulting the Kailuan Social Security Information System.

# Data collection

Fasting venous blood was collected from all observation subjects after they had fasted for more than 8 hours to measure levels of LDL-C, fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), etc. LDL-C was measured by the direct surfactant removal method. The biochemical indicators were measured using a Hitachi 7600 automatic biochemical analyser (Hitachi, Japan).

# Grouping method

According to the Chinese adult dyslipidaemia prevention and treatment guidelines[9] for the primary prevention of atherosclerotic cardiovascular disease, appropriate levels of blood lipids and abnormal stratification criteria were used for grouping. Because the marginal increase in LDL-C group (3.4 mmol/l ≤ LDL-C < 4.1 mmol/l) and the elevated group (LDL-C ≥ 4.1 mmol/l) in the population of this study were small, the LDL-C individuals with ≥ 3.4 mmol/l were combined into the elevated group. The participants were divided into three groups: an ideal level group (LDL-C < 2.6 mmol/l), an appropriate level group (2.6 mmol/l ≤ LDL-C < 3.4 mmol/l), and an elevated group (LDL-C ≥ 3.4 mmol/l).

# Related definitions or standards

Cardiovascular diseases included acute myocardial infarction (AMI) and stroke. Stroke included ischaemic stroke and haemorrhagic stroke, which included subarachnoid haemorrhage and cerebral haemorrhage. Diabetes[10] was defined as a standard fasting blood glucose level ≥ 7 mmol/l or a fasting blood glucose level < 7 mmol/l along with a history of clearly diagnosed diabetes or use of hypoglycaemic drugs. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg along with a history of clearly diagnosed hypertension or use of antihypertensive drugs. Smoking was defined as smoking at least 1 cigarette a day on average over the past year for at least 1 year. Drinking was defined as drinking liquor (alcohol content > 50%) ≥ 100 ml/d on average over the past year for a duration > 1 year. Regular physical exercise refers to physical exercise ≥ 3 times/week with a duration ≥ 30 min/session; body mass index = body weight (kg)/height 2 (m2). Use of lipid-lowering drugs was defined as statin use, which was obtained from questionnaires and medical record surveys.

# Statistical analysis

SAS (Version 9.4; SAS Institute, Cary, NC) was used for statistical analysis. Measurement data conforming to the normal distribution are expressed as ($\bar{x} \pm s$), and comparisons between multiple groups were expressed by single-factor analysis of variance. Measurement data with a skewed

distribution are expressed as the median (P25, P75), and comparisons between groups were expressed by the Kruskal-Wallis rank sum test. The count data are expressed as n (%), and the $\chi 2$ test was applied. The Kaplan-Meier method was used to calculate the cumulative incidence of endpoint events, and the log-rank test was performed; the Cox proportional hazards regression model was used to analyse the hazard ratio (HR) and 95% confidence interval (CI) of endpoint events in different LDL_C groups. To observe whether there was a dose-response relationship, each additional standard deviation (SD) of LDL-C was used as an independent variable to conduct Cox proportional hazards regression model analysis. Since the rate of all-cause mortality in this study population was as high as 54.49%, death competition risk model analysis was performed when analysing the impact of LDL-C on CVD events. Missing values of LDL_C were filled with the median. hs-CRP had a skewed distribution; thus, we converted it into a categorical variable(0–1,1–3□□3mg/dl) for further analyses. Missing values of covariates were filled by multiple imputation methods. A two-sided test was used, and $P < 0.05$ was considered statistically significant.

# Results

There were 3674 subjects, 3478 males (94.67%) and 196 females (5.33%), who participated in the 2006 health check-up and were ≥ 75 years old, with an average age of 79.40 ± 3.67 years old. Sixty-five missing LDL_C values were filled with the median. Of these, 2623, 727 and 324 were in the ideal level group, the appropriate level group and the elevated group, respectively. The median LDL-C of the three groups were respectively 1.89mmol/l□2.87mmol/l□3.88mmol/l. HDL-C and degree of education levels were the lowest ,SBP and hs-CRP levels were the highest in the elevated group (Table 1).

Table 1
Baseline characteristics according to different levels of LDL-C

| | Ideal group | Appropriate group | Elevated group | F/χ2 | *P* Value |
|---|---|---|---|---|---|
| | n = 2623 | n = 727 | n = 324 | | |
| Age (years,`x ± s) | 79.49 ± 3.71 | 79.20 ± 3.53 | 79.06 ± 3.65 | 3.33 | < 0.05 |
| Male [example, (%)] | 2492 (92.60) | 682 (93.81) | 304 (93.83) | 1.68 | 0.43 |
| BMI (kg/$m^2$,`x ± s) | 24.02 ± 3.71 | 24.73 ± 3.64 | 24.14 ± 3.46 | 10.46 | < 0.05 |
| SBP (mmHg,`x ± s) | 141.07 ± 21.20 | 143.63 ± 22.08 | 145.88 ± 24.49 | 9.66 | < 0.05 |
| DBP (mmHg,`x ± s) | 80.90 ± 10.90 | 82.92 ± 11.44 | 83.51 ± 11.57 | 15.15 | < 0.05 |
| MAP (mmHg,`x ± s) | 100.96 ± 12.97 | 103.16 ± 13.59 | 104.30 ± 14.61 | 14.76 | < 0.05 |
| LDL_C [ (mmol/L] | 1.89 (1.51,2.22) | 2.87 (2.71,3.07) | 3.88 (3.61,4.43) | 2305.51 | < 0.05 |
| HDL-C (mmol/L,`x ± s) | 1.60 ± 0.45 | 1.59 ± 0.42 | 1.53 ± 0.39 | 3.83 | < 0.05 |
| TC (mmol/L,`x ± s) | 4.61 ± 1.07 | 5.05 ± 1.21 | 5.67 ± 1.04 | 160.22 | < 0.05 |
| TG [ (mmol/L] | 1.13 (0.82,1.64) | 1.24 (0.91,1.74) | 1.19 (0.90,1.69) | 23.12 | < 0.05 |
| FBG [ (mmol/L] | 4.98 (4.48,5.62) | 5.22 (4.68,5.91) | 5.20 (4.74,5.96) | 51.16 | < 0.05 |
| hs-CRP [ (mg/l] | 1.45 (0.54,4.51) | 1.60 (0.56,4.66) | 3.23 (0.93,6.50) | 33.87 | < 0.05 |
| Drinking [*n*, (%)] | 632 (24.09) | 189 (26.00) | 77 (23.77) | 1.20 | 0.55 |
| Smoking [*n*, (%)] | 500 (19.06) | 151 (20.77) | 60 (18.52) | 1.22 | 0.54 |
| Education level [*n*, (%)] | | | | | |
| Junior high school or university | 1673 (63.78) | 378 (51.99) | 144 (44.44) | 67.47 | < 0.05 |

Values presented are the mean ± SD or median (interquartile range).

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, FBG: fasting blood sugar, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index

| | Ideal group | Appropriate group | Elevated group | F/χ2 | *P* Value |
|---|---|---|---|---|---|
| Physical exercises [*n*, (%)] | | | | | |
| None | 252 (9.61) | 75 (10.32) | 42 (12.96) | 16.14 | < 0.05 |
| Occasionally | 1776 (67.71) | 454 (62.45) | 190 (58.64) | | |
| Often | 595 (22.68) | 198 (27.24) | 92 (28.40) | | |
| Hypertension [*n*, (%)] | 1594 (60.77) | 486 (66.85) | 215 (66.36) | 11.27 | < 0.05 |
| Diabetes [*n*, (%)] | 296 (11.28) | 103 (14.17) | 38 (11.73) | 4.52 | 0.10 |
| Atrial fibrillation [*n*, (%)] | 68 (2.59) | 19 (2.61) | 8 (2.47) | 0.02 | 0.99 |
| Use of lipid-lowering drugs [*n*, (%)] | 44 (1.68) | 17 (2.34) | 3 (0.93) | 1.07 | 0.59 |
| Use of antihypertensive drugs [*n*, (%)] | 363 (13.84) | 118 (16.23) | 58 (17.90) | 5.56 | 0.06 |
| Values presented are the mean ± SD or median (interquartile range). | | | | | |
| SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, FBG: fasting blood sugar, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index | | | | | |

# Occurrence and comparison of CVD and all-cause mortality in different LDL-C level groups

The average follow-up time of the 3674 subjects was 9.87 ± 3.60 years. There were 24 subjects with 2 CVD events, of whom 10 had both AMI and stroke and 14 had both ischaemic stroke and haemorrhagic stroke. Considering the first occurrence of CVD as the endpoint, there were 439 cases in total, with 298, 89, and 52 cases in the ideal level group, appropriate level group, and elevated group, respectively. The incidence density was 12.00 per thousand person-years, 13.47 per thousand person-years, and 18.00 per thousand person-years. There were 122 cases of acute myocardial infarction events, with 79, 23, and 20 cases in the 3 groups, and the incidence density was 3.07 per thousand person-years, 3.32 per thousand person-years, and 6.61 per thousand person-years. There were 2002 cases of all-cause mortality, and the 3 groups had 1382, 422, and 198 cases; the incidence density was 52.94 per thousand person-years, 59.67 per thousand person-years, and 64.30 per thousand person-years (Table 2).

Table 2
Incidence density and adjusted risk ratio of CVD and all-cause mortality events in different LDL-C groups

| | Number of cases/Number of observers | Incidence density/thousand person-year (95%CI) | HR (95%CI)[a] | *P* value | HR (95%CI)[a,b] | *P* value |
|---|---|---|---|---|---|---|
| CVD | | | | | | |
| Ideal group | 298/2623 | 12.00 (10.71–13.44) | 1.00 | | 1.00 | |
| Appropriate group | 89/727 | 13.47 (10.95–16.58) | 1.07 (0.84–1.35) | 0.606 | 1.04 (0.81–1.32) | 0.781 |
| Elevated group | 52/324 | 18.00 (13.72–23.62) | 1.46 (1.08–1.97) | 0.015 | 1.42 (1.05–1.91) | 0.022 |
| SD | | | 1.10 (1.01–1.20) | 0.034 | | |
| AMI | | | | | | |
| Ideal group | 79/2623 | 3.07 (2.46–3.83) | 1.00 | | 1.00 | |
| Appropriate group | 23/727 | 3.32 (2.21-5.00) | 1.00 (0.63–1.60) | 0.988 | 0.98 (0.62–1.56) | 0.932 |
| Elevated group | 20/324 | 6.61 (4.27–10.25) | 2.08 (1.26–3.44) | 0.004 | 2.02 (1.23–3.32) | 0.006 |
| SD | | | 1.21 (1.05–1.39) | 0.010 | | |
| Stroke | | | | | | |
| Ideal group | 224/2623 | 8.89 (7.80-10.13) | 1.00 | | 1.00 | |
| Appropriate group | 68/727 | 10.06 (7.93–12.76) | 1.08 (0.82–1.42) | 0.585 | 1.06 (0.80–1.39) | 0.704 |

[a] Sex, age, smoking, drinking, physical exercise, education level, hypertension, diabetes, history of atrial fibrillation, hs-CRP, BMI, use of lipid-lowering drugs, and use of antihypertensive drugs.

[b] Adjusted for the competing risk of death.

SD: standard difference. SD was used as the step size to analyse the harmful changes that occurred with each additional increase in SD. NA: not applicable, CVD: cardiovascular disease, AMI: acute myocardial infarction, HR: hazard ratio

| | Number of cases/Number of observers | Incidence density/thousand person-year (95%CI) | HR (95%CI)[a] | *P* value | HR (95%CI)[a,b] | *P* value |
|---|---|---|---|---|---|---|
| Elevated group | 35/324 | 11.89 (8.54–16.56) | 1.29 (0.90–1.86) | 0.169 | 1.25 (0.87–1.78) | 0.232 |
| SD | | | 1.06 (0.96–1.18) | 0.253 | | |
| Ischaemic stroke | | | | | | |
| Ideal group | 191/2623 | 7.54 (6.54–8.69) | 1.00 | | | |
| Appropriate group | 55/727 | 8.09 (6.21–10.53) | 1.03 (0.76–1.39) | 0.870 | 1.00 (0.74–1.35) | 0.985 |
| Elevated group | 29/324 | 9.79 (6.80-14.09) | 1.27 (0.85–1.89) | 0.243 | 1.22 (0.82–1.80) | 0.324 |
| SD | | | 1.04 (0.93–1.17) | 0.517 | | |
| Haemorrhagic stroke | | | | | | |
| Ideal group | 44/2623 | 1.70 (1.26–2.28) | 1.00 | | 1.00 | |
| Appropriate group | 14/727 | 1.99 (1.18–3.36) | 1.11 (0.60–2.03) | 0.742 | 1.09 (0.59–2.02) | 0.778 |
| Elevated group | 8/324 | 2.62 (1.31–5.25) | 1.46 (0.67–3.15) | 0.338 | 1.39 (0.65–2.99) | 0.397 |
| SD | | | 1.12 (0.92–1.37) | 0.263 | | |
| All-cause mortality | | | | | | |

[a] Sex, age, smoking, drinking, physical exercise, education level, hypertension, diabetes, history of atrial fibrillation, hs-CRP, BMI, use of lipid-lowering drugs, and use of antihypertensive drugs.

[b] Adjusted for the competing risk of death.

SD: standard difference. SD was used as the step size to analyse the harmful changes that occurred with each additional increase in SD. NA: not applicable, CVD: cardiovascular disease, AMI: acute myocardial infarction, HR: hazard ratio

| | Number of cases/Number of observers | Incidence density/thousand person-year (95%CI) | HR (95%CI)[a] | *P* value | HR (95%CI)[a,b] | *P* value |
|---|---|---|---|---|---|---|
| Ideal group | 1382/2623 | 52.94 (50.22–55.80) | 1.00 | | NA | |
| Appropriate group | 422/727 | 59.67 (54.24–65.65) | 1.12 (1.00-1.25) | 0.045 | NA | |
| Elevated group | 198/324 | 64.30 (55.94–73.90) | 1.17 (1.00-1.36) | 0.044 | NA | |
| SD | | | 1.04 (1.00-1.08) | 0.086 | | |

[a] Sex, age, smoking, drinking, physical exercise, education level, hypertension, diabetes, history of atrial fibrillation, hs-CRP, BMI, use of lipid-lowering drugs, and use of antihypertensive drugs.

[b] Adjusted for the competing risk of death.

SD: standard difference. SD was used as the step size to analyse the harmful changes that occurred with each additional increase in SD. NA: not applicable, CVD: cardiovascular disease, AMI: acute myocardial infarction, HR: hazard ratio

The cumulative morbidity rates of CVD in the different LDL-C groups were 14.08%, 14.90%, and 19.97% ($P < 0.05$). The cumulative morbidity rates of acute myocardial infarction were 3.51%, 3.73%, and 7.68% ($P < 0.05$). Moreover, the cumulative morbidity rates of stroke were 10.94%, 11.61%, 13.86% ($P > 0.05$), with cumulative morbidity rates of ischaemic stroke and haemorrhagic stroke of 9.47%, 9.59%, 11.67% ($P > 0.05$) and 2.11%, 2.41%, and 2.97%, respectively ($P > 0.05$). Finally, the cumulative mortality rates of all-cause mortality were 53.05%, 58.45%, and 61.31% ($P < 0.05$) (Fig. 1–6).

Cox proportional hazards regression analysis of the impact of different LDL-C groups on CVD and all-cause mortality events

The dependent variables were whether CVD, acute myocardial infarction, stroke, ischaemic stroke, haemorrhagic stroke, and all-cause mortality occurred during the follow-up period. The ideal level group was used as the control group for Cox proportional hazard regression analysis. After adjusting for age, sex, smoking, drinking, physical exercise, education level, hypertension, diabetes, atrial fibrillation history, hs-CRP level, BMI, use of lipid-lowering drugs, and use of antihypertensive drugs, the results showed that the risk of CVD in the appropriate level group and the elevated group was 1.07 (95% CI, 0.84–1.35) and 1.46 (95% CI, 1.08–1.97), the risk of acute myocardial infarction was 1.00 (95% CI, 0.63–1.60) and 2.08 (95% CI, 1.26–3.44), and the risk of all-cause mortality was 1.12 (95% CI, 1.00-1.25) and 1.17 (95% CI, 1.00-1.36). For every additional SD (0.93 mmol/l) in LDL-C, the risk of CVD was 1.10 (95% CI, 1.01–1.20), and the risk of acute myocardial infarction was 1.21 (95% CI, 1.05–1.39). The risk of death was 1.04

(95% CI, 1.00-1.08). After considering the competing risk of death to CVD, the results remained the same as before. There was no association between elevated LDL-C and the risk of stroke (Table 2).

# Discussion

We first confirmed that elevated LDL-C levels were a risk factor for CVD and all-cause mortality in Chinese individuals ≥ 75 years old, and the increased risk of CVD caused by high LDL-C levels was mainly seen in acute myocardial infarction, without an increase in the risk of stroke; moreover, the risk of haemorrhagic stroke and ischaemic stroke did not increase.

A total of 3674 patients aged ≥ 75 years in the Kailuan study were followed up for nearly 10 years. After possible confounding factors were adjusted, it was found that the risks of CVD and acute myocardial infarction events in the LDL-C elevated group were 1.46 times and 2.08 times that of the ideal group. The risk of all-cause mortality was 1.12 times and 1.17 times that of the ideal group. There may be a dose-response relationship between LDL-C and the risk of CVD and all-cause mortality. For every SD (0.93 mmol/l) increase in LDL-C, the risk of CVD increased by 10%, the risk of acute myocardial infarction increased by 21% and the risk of death increased by 4%. The above-mentioned associations still existed after the onset of CVD was adjusted for the competing risk of death.

The association between elevated LDL-C and CVD in the adult population has been confirmed,[11,12] but there is still controversy in the elderly population ≥ 75 years old. The findings from the National Institutes of Health pooled cohort indicated that elevated LDL-C levels have nothing to do with the risk of CVD in the elderly population ≥ 75.[13] The results of a primary prevention cohort study in a 70 to 100 years old population showed that an elevated LDL-C level was associated with the risk of acute myocardial infarction and CVD. Every 1.0 mmol/L increase in the LDL-C level increased the risk of acute myocardial infarction and CVD by 25% and 12%, respectively.[14] This study obtained similar results. For every increase in the LDL-C level (0.93 mmol/l), the risk of acute myocardial infarction and CVD increased by 21% and 10%, respectively. Our results show that high LDL-C is not a risk factor for stroke. A recent Korean national longitudinal study showed that a high LDL-C level is a protective factor against ischaemic stroke among individuals ≥ 65 years of age. The results showed that compared with those in the first quartile, the risk of ischaemic stroke for subjects in the fourth quartile of LDL-C was reduced by 20%.[15]

The relationship between LDL-C in the elderly and all-cause mortality is also controversial. The results of clinical studies in a 75-year-old population by Nilsson et al. showed that there was no correlation between LDL-C and all-cause mortality,[16] while a study on the relationship between lipoprotein cholesterol levels and mortality found that there was a negative correlation between LDL-C and all-cause mortality in an elderly population ≥ 70 years old.[17] However, a number of current interventional trials of lipid-lowering drugs have confirmed that LDL-C-lowering therapy in elderly individuals ≥ 75 years old significantly reduces the risk of cardiovascular death or all-cause mortality.[18–23] Our results are consistent with the results of the intervention study.

Among our observation subjects, the average LDL-C level of the appropriate level group was 2.87 mmol/l, which was higher than the target LDL-C value of 2.6 mmol/l for primary prevention, but the CVD risk in the appropriate level group did not increase, while the risk of death increased by only 12% (P = 0.045). Therefore, a target value of 2.6 mmol/l for primary prevention among elderly patients may not be appropriate. According to our research, the target value can increase to 3.4 mmol/l.

Old age is an unchangeable risk factor, and elderly individuals often have multiple diseases. Therefore, randomized controlled trials often exclude elderly individuals. Even if elderly subjects are included, many conditions are set, and the results are not universal. The results of this research are derived from real-world data, so it has the value of promotion. Based on our research results, we support some guidelines, such as the 2018 Guideline for U.S. Blood Lipid Management[11] and the 2019 Guideline for the Management of Dyslipidaemia in European Society of Cardiology/European Atherosclerosis Association,[24] which are recommended for longer life expectancy (more than 1 year) and recommend that elderly patients ≥ 75 years old with elevated LDL-C levels should be given lipid-lowering treatment.

In our observation population, the risk of myocardial infarction was similar to all-cause mortality caused by high LDL-C levels, but the absolute number of all-cause deaths was much greater than the number of myocardial infarctions. Therefore, the greatest benefit of lipid-lowering intervention may be to reduce all-cause mortality. A study on the use of statins and all-cause mortality among veterans aged 75 years and over in the United States showed that the risk of all-cause mortality was reduced by 25% in those who took statins compared with those who did not take statins.[25] Moreover, moderate-intensity statin treatment can reduce LDL-C levels by 25%-50%.[9] According to this rough calculation, if the elevated group used statin drugs, LDL-C levels would drop to 1.94–2.91 mmol/l, which is close to the appropriate level. Therefore, adverse events, especially all-cause mortality, will be reduced.

Our results may underestimate the impact of high LDL-C levels on CVD and all-cause mortality in elderly people due to the deviation of healthy survival. Previous studies have found that exposure to high LDL-C levels at a young age is the main cause of early-onset CVD and early death. The average age in our observation population was 79 years old. These surviving individuals were relatively healthy compared to those with early-onset CVD or early death, and even the elevated LDL-C level was only 3.88 mmol/l,which was relatively small compared with the marginal increase of 3.4mmol/l in the primary prevention population of CVD in China, so we cannot observe the effect of higher LDL-C levels on CVD and all-cause mortality in the elderly populations, and this may underestimate the impact of LDL-C on CVD and all-cause mortality in elderly people.

# Strengths and limitations of the study

Advantages of research: our data are from a relatively large and stable cohort. The penetration rate of statins in China was not high in 2006, and this study was not affected by the use of lipid-lowering drugs.

Our research also has certain limitations. There is no cause of death provided in the data. The subjects of observation are retirees who enjoy public medical care, so it may not be applicable to other groups of people. The observation subjects have a high proportion of males. Point estimation of LDL-C was carried out, and the influence of LDL-C levels changes on CVD and all-cause mortality was not observed.

# Conclusions

Briefly, in the elderly population aged 75 years and older, the increase in LDL-C levels increases the impact on CVD and all-cause mortality. These results should strengthen the guidelines to recommend interventions for elderly individuals ≥ 75 years of age with elevated LDL-C levels and lipid-lowering treatment.

# Declarations


### Funding

None.

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### Author contributions

Y.M.L.and S.L.W.initiated the study concept and design, J.X.Y.,X.K.L.statistically analysed the data and wrote the first draft. S.H.C.,Y.L., H.M.L.,H.W.Z. and N.Y.acquired the data, analysed and interpreted the data and contributed to critical revision of the manuscript. All authors have read and approved the final submitted version of the manuscript. Y.M.L. is the study guarantor.

### Conflict of interest

None declared.

### Data availability statement

Data that support the findings of this study are available from the corresponding author upon reasonable request and approval.

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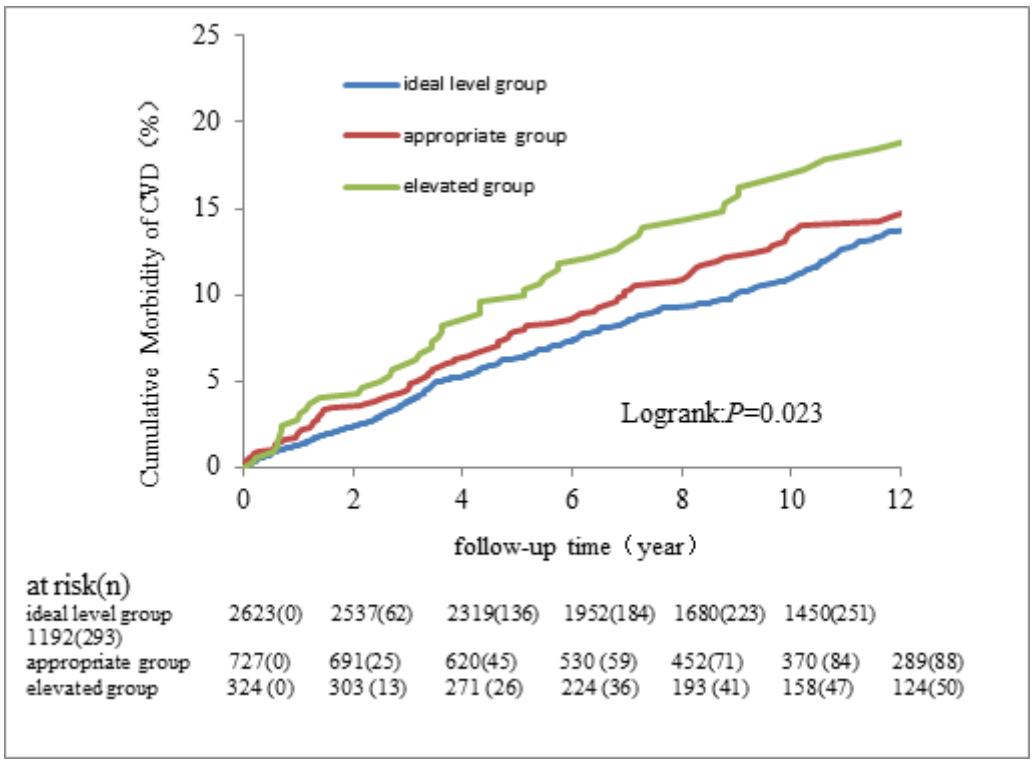
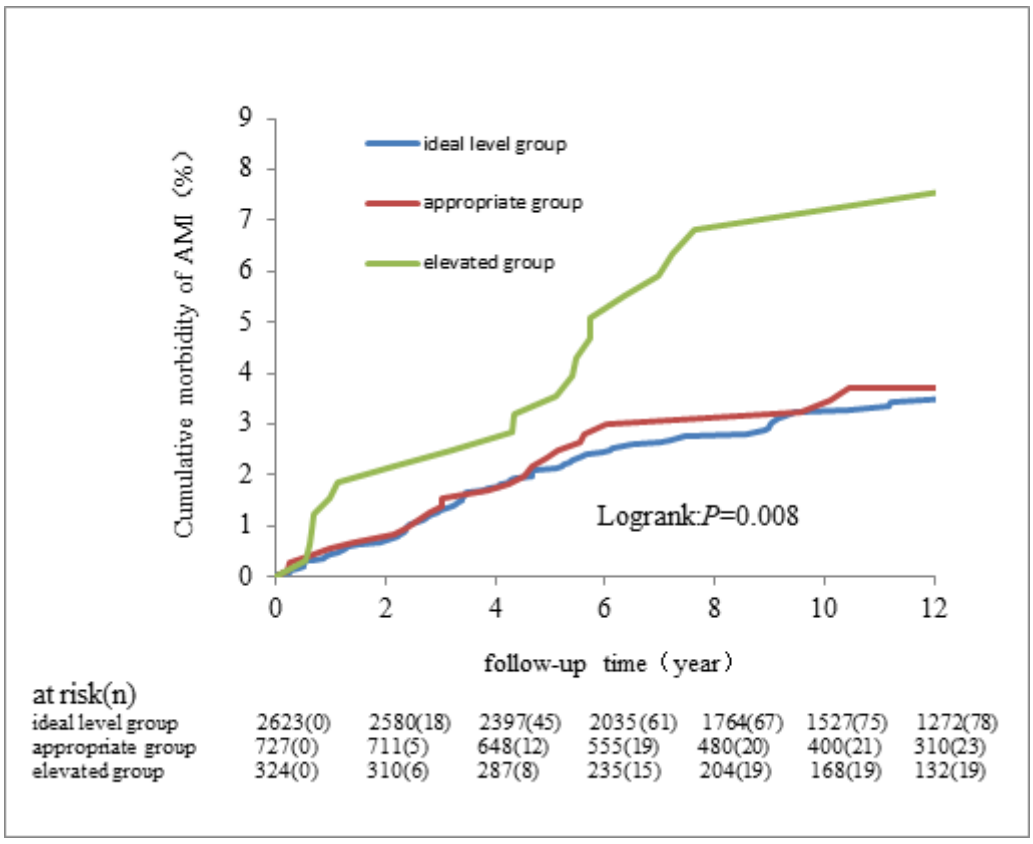
# Figures



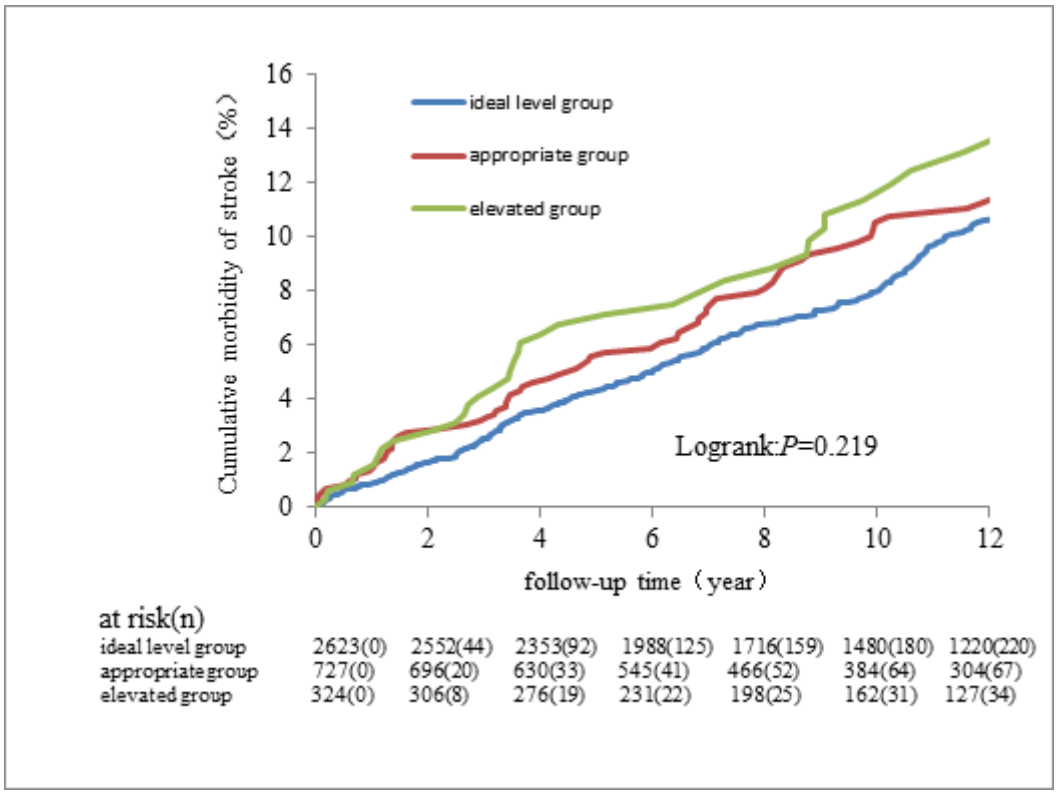

## Figure 1

Cumulative morbidity of CVD events in different LDL-C groups CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol



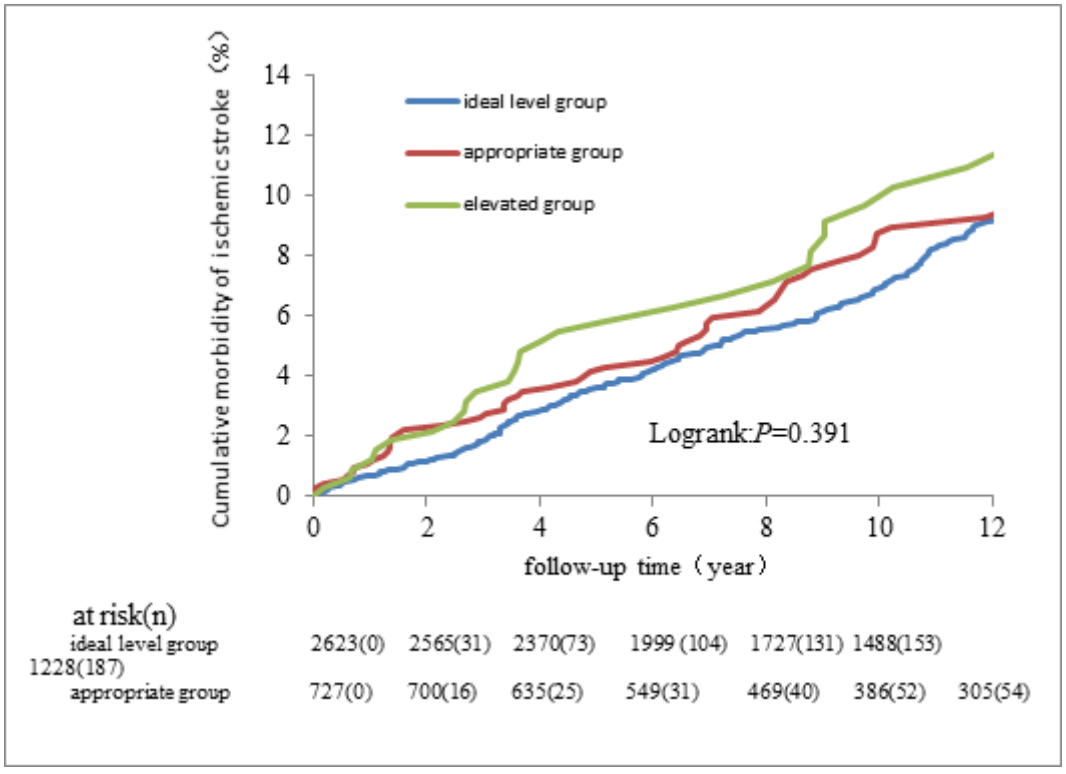

## Figure 2

Cumulative morbidity of acute myocardial infarction events in different LDL-C groups AMI: acute myocardial infarction; LDL-C: low-density lipoprotein cholesterol



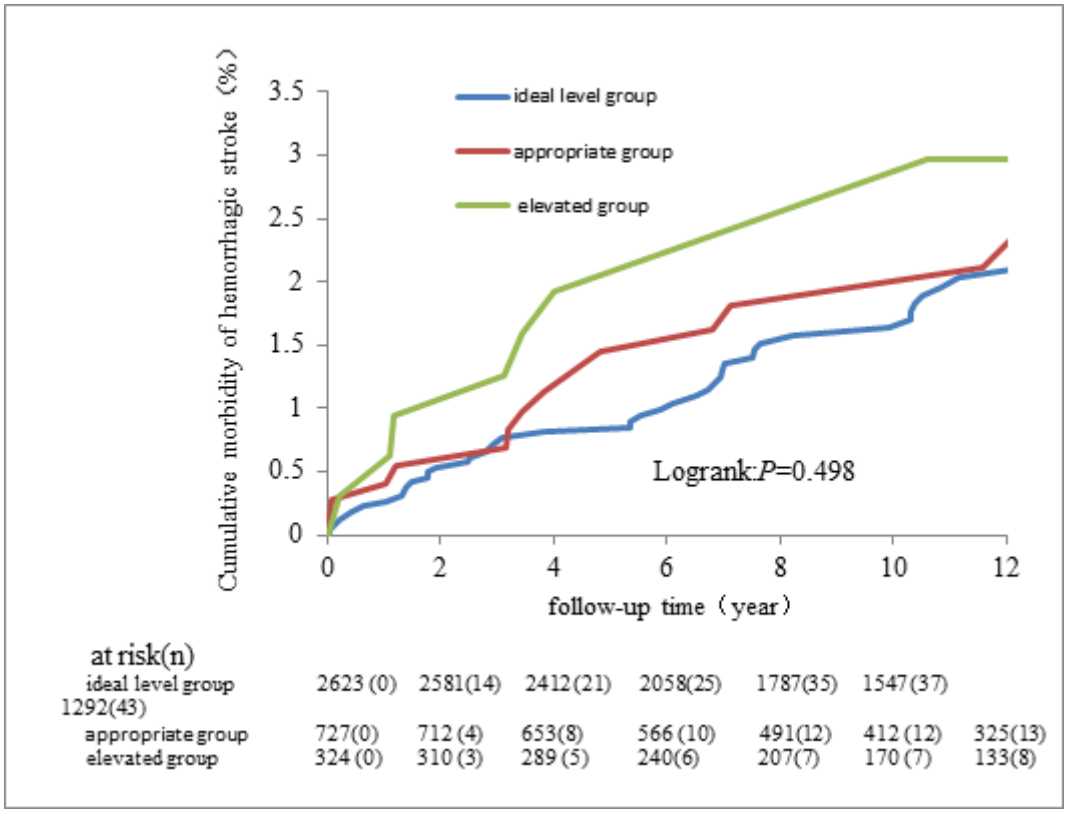

## Figure 3

Cumulative morbidity of stroke events in different LDL-C groups LDL-C: low-density lipoprotein cholesterol



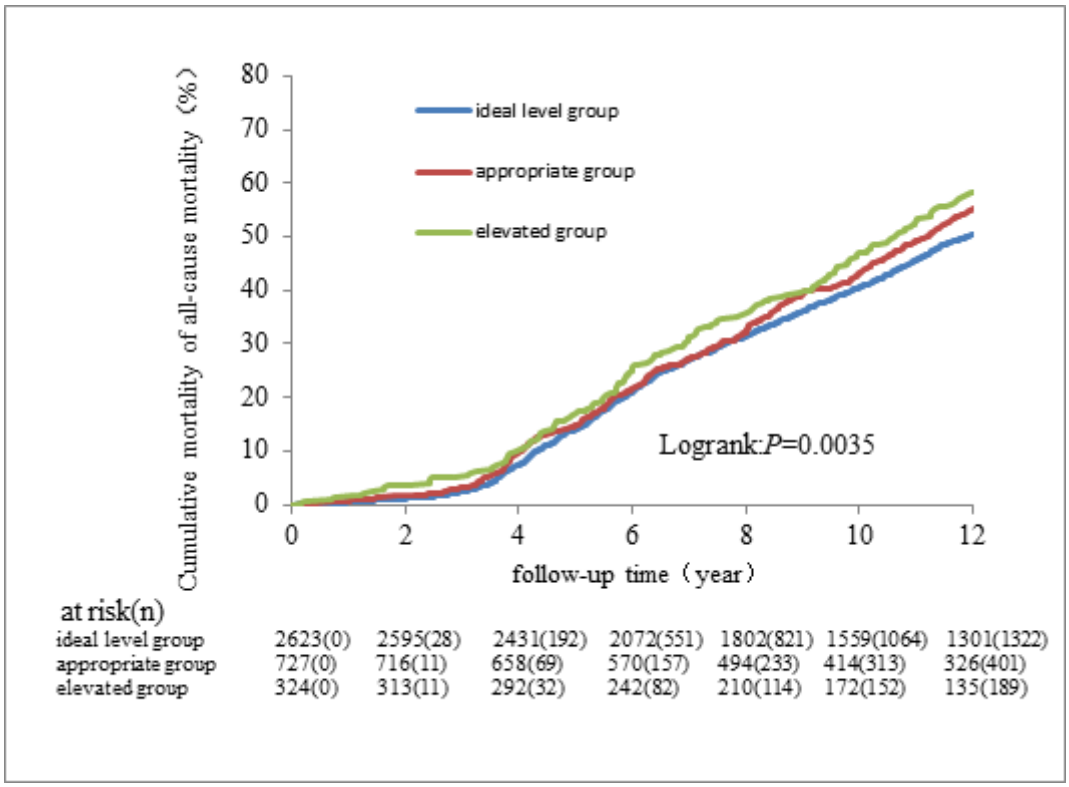
## Figure 4

Cumulative morbidity of ischaemic stroke events in different LDL-C groups LDL-C: low-density lipoprotein cholesterol




## Figure 5

Cumulative morbidity of haemorrhagic stroke events in different LDL-C groups LDL-C: low-density lipoprotein cholesterol




## Figure 6

Cumulative mortality of all-cause mortality in different LDL-C groups LDL-C: low-density lipoprotein cholesterol