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# Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage

## A prospective study

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## Abstract

### Objective

To prospectively examine the association between low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations and intracerebral hemorrhage (ICH) risk.

### Methods

The current cohort study included 96,043 participants (mean age 51.3 years) who were free of stroke, myocardial infarction, and cancer at baseline (2006). Serum LDL-C concentrations were assessed in 2006, 2008, 2010, and 2012. Cumulative average LDL-C concentrations were calculated from all available LDL-C data during that period. Incident ICH was confirmed by review of medical records.

### Results

We identified 753 incident ICH cases during 9 years of follow-up. The ICH risk was similar among participants with LDL concentrations of 70 to 99 mg/dL and those with LDL-C concentrations ≥100 mg/dL. In contrast, participants with LDL-C concentrations <70 mg/dL had a significantly higher risk of developing ICH than those with LDL-C concentrations of 70 to 99 mg/dL; adjusted hazard ratios were 1.65 (95% confidence interval [CI] 1.32–2.05) for LDL-C concentrations of 50 to 69 mg/dL and 2.69 (95% CI 2.03–3.57) for LDL-C concentrations <50 mg/dL.

### Conclusions

We observed a significant association between lower LDL-C and higher risk of ICH when LDL-C was <70 mg/dL, and the association became nonsignificant when LDL-C ≥70 mg/dL. These data can help determination of the ideal LDL range in patients who are at increased risk of both atherosclerotic disease and hemorrhagic stroke and guide planning of future lipid-lowering studies.

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## Glossary

**ASTEROID** = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; **BMI** = body mass index; **CI** = confidence interval; **CVD** = cardiovascular disease; **eGFR** = estimated glomerular filtration rate; **FOURIER** = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; **HDL-C** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **hs-CRP** = high-sensitivity C-reactive protein; **ICD-9** = *International Classification of Diseases, 9th revision*; **ICD-10** = *International Classification of Diseases, 10th revision*; **ICH** = intracerebral hemorrhage; **IMPROVE-IT** = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **JUPITER** = Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; **LDL-C** = low-density lipoprotein cholesterol; **NHANES** = National Health and Nutrition Examination Survey; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **PROVE-IT** = Pravastatin or Atorvastatin Evaluation and Infection Therapy; **REVERSAL** = Reversal of Atherosclerosis With Aggressive Lipid Lowering; **SPARCL** = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; **TC** = total cholesterol.

Intracerebral hemorrhage (ICH) is the second most common stroke type, with a high mortality and disability rate.[1–3] Although ICH is of special concern in developing countries[4] such as China,[5] the prevalence of hemorrhagic stroke is high in developed countries (particularly for blacks and Hispanics in the United States).[6] Because cholesterol has a key role in the structural formation of cell membranes, low cholesterol concentration has been proposed as a potential risk factor for ICH.[7] Some,[8,9] but not all,[10–17] epidemiologic studies reported an inverse association between low-density lipoprotein cholesterol (LDL-C) concentrations and risk of ICH. However, with 1 exception,[14] studies on this topic have been limited by a small number of incident ICH cases (<300). Furthermore, these studies were based on a single baseline LDL-C measurement, which could underestimate the association between LDL-C and ICH risk because of normal fluctuations and changes in LDL-C concentrations over time, particularly due to the initiation of lipid-lowering therapy. Because many older adults are at risk of hemorrhagic strokes, it is important to clarify the association between LDL-C concentration and ICH risk, knowing that lipid lowering is recommended for ischemic stroke prevention by all relevant guidelines. In particular, the 2018 American Heart Association/American College of Cardiology multisociety guideline on the management of blood cholesterol emphasized using maximally tolerated lipid-lowering medications to reduce LDL-C levels for patients with atherosclerotic cardiovascular disease.[18] However, long-term safety such as risk of hemorrhagic stroke after the more intensive lipid-lowering remains uncertain to date.[18]

To better understand the relationship between LDL-C and ICH, we prospectively examined the association between LDL-C concentrations, which were repeatedly assessed every 2 years, and subsequent risk of ICH among >95,000 adults.

## Methods

### Participants

As detailed elsewhere,[19] the Kailuan study is a community-based multicenter prospective cohort study in Tangshan, an industrial city in China, designed to investigate risk factors of chronic disease. From June 2006 to October 2007 (the cohort baseline, referred to as 2006 survey), a total of 101,510 participants (81,110 men and 20,400 women) from 11 centers underwent a standardized questionnaire, physical examination, and laboratory tests. Follow-up assessments were conducted biannually to update participant status on the aforementioned parameters. We excluded 1,306 participants due to missing baseline LDL-C concentration data and 4,161 participants due to a diagnosis of stroke, myocardial infarction, or cancer at the baseline. A total of 96,043 participants were included in the current analyses.

### Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee of the Kailuan General Hospital. The Kailuan study was registered at International Clinical Trials Registry Platform (apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-TNRC-11001489) with study identifying number ChiCTR-TNRC-11001489. Informed consent was obtained from the participants. Deidentified data were used for analyses.

### Assessment of incident ICH

The first occurrence of ICH was considered as the outcome, either the first nonfatal ICH or ICH death without a preceding nonfatal event. Ascertainment of incident ICH was described previously.[20] Briefly, all participants were linked to the Municipal Social Insurance Institution database and Hospital Discharge Register to identify potential cases of incident ICH, which cover all the Kailuan study participants. ICD-9 and ICD-10 were used to identify potential cases of ICH. Additional information on medical history of ICH was collected via questionnaire biennially in the Kailuan study since 2006. Information on death was collected from provincial vital statistics offices. For potential cases of ICH identified by the ICD code or questionnaire, a panel of 3 physicians examined their medical records. Fatal ICH was confirmed by medical records, autopsy reports, or death certificates with ICH listed as the cause of death. ICH events were diagnosed according to the World Health Organization criteria and either brain CT or MRI for confirmation. A total

**Table 1** Characteristics according to updated cumulative average blood LDL-C concentrations from 2006 to 2012 among 96,043 Kailuan participants

| | <50 mg/dL | 50–69 mg/dL | 70–99 mg/dL | 100–129 mg/dL | 130–159 mg/dL | ≥160 mg/dL |
|---|---|---|---|---|---|---|
| | <1.3 mmol/L | 1.3–1.7 mmol/L | 1.8–2.5 mmol/L | 2.6–3.3 mmol/L | 3.4–4.0 mmol/L | ≥4.1 mmol/L |
| **No.** | 2,867 | 10,183 | 42,824 | 31,907 | 6,367 | 1895 |
| **LDL-C,[a] mg/dL** | 39 | 62 | 89 | 112 | 143 | 189 |
| **Age, y** | 54.9 | 51.9 | 50.5 | 51.2 | 53.9 | 55.1 |
| **Women, %** | 17.8 | 22.4 | 20.8 | 19.8 | 22.2 | 18.5 |
| **Smoking status, %** | | | | | | |
| **Current** | 26.3 | 31.5 | 32 | 34.9 | 37.9 | 40.5 |
| **Past** | 4.1 | 5.1 | 5.2 | 5.2 | 5.9 | 5.5 |
| **Never** | 60.9 | 59.0 | 60.3 | 58.2 | 53.7 | 49.5 |
| **Alcohol intake,[b] %** | | | | | | |
| **Never** | 60 | 57.1 | 58.4 | 56.8 | 51.9 | 49.9 |
| **Past** | 3.5 | 3.5 | 3 | 3.3 | 4 | 3.9 |
| **Light** | 3.6 | 4.3 | 5.5 | 5.6 | 5 | 4.2 |
| **Moderate** | 3.3 | 4.4 | 3.7 | 3.9 | 4.6 | 5.2 |
| **Heavy** | 13.1 | 14 | 15.7 | 17.7 | 21.1 | 23 |
| **Physical activity, %** | | | | | | |
| **Never** | 5.0 | 5.22 | 7.6 | 10.2 | 10.5 | 12.6 |
| **1–2 times/wk** | 76.1 | 76.3 | 76.9 | 71.7 | 60.4 | 53.6 |
| **≥3 times/wk** | 9.2 | 12.8 | 12.2 | 15.6 | 25.5 | 28.2 |
| **Salt intake, %** | | | | | | |
| **≥10 g/d** | 6.7 | 9.0 | 9.2 | 11.2 | 14.0 | 14.5 |
| **6–9 g/d** | 77.9 | 77.4 | 79.1 | 77.1 | 71.1 | 66.7 |
| **<6 g/d** | 6 | 8.1 | 8.2 | 9.1 | 11.5 | 13.2 |
| **Education, %** | | | | | | |
| **Illiteracy or elementary school** | 11.0 | 9.3 | 8.6 | 10.4 | 14.4 | 15.9 |
| **Middle school** | 75.9 | 78.2 | 80.9 | 80.6 | 76.4 | 73.8 |
| **College/university** | 4.4 | 7.3 | 7.24 | 6.5 | 5.9 | 5.3 |
| **Average income, %** | | | | | | |
| **<500 ¥/mo** | 19.8 | 23.0 | 25.2 | 30.4 | 37.1 | 38.4 |
| **500–2,999 ¥/mo** | 66.5 | 64.8 | 64.8 | 60.9 | 53.2 | 50.6 |
| **≥3,000 ¥/mo** | 4.7 | 6.9 | 6.7 | 6.1 | 6.3 | 5.8 |
| **Use of antihypertensive agents,[c] %** | 14.8 | 17.4 | 17.6 | 20 | 23.6 | 25.1 |
| **Use of cholesterol-lowering agents,[c] %** | 1.2 | 1.9 | 1.7 | 2.3 | 2.7 | 4.3 |
| **Use of aspirin,[c] %** | 0.66 | 0.95 | 0.95 | 0.89 | 0.86 | 1.11 |
| **Use of anticoagulants, %** | 1.64 | 1.56 | 1.05 | 1.00 | 0.83 | 1.27 |
| **hs-CRP,[a] mg/L** | 0.59 | 0.09 | 0.004 | 0.05 | 0.25 | 0.41 |
| **BMI,[a] kg/m$^2$** | 24.3 | 24.4 | 24.9 | 25.3 | 25.5 | 25.5 |

Continued

**Table 1** Characteristics according to updated cumulative average blood LDL-C concentrations from 2006 to 2012 among 96,043 Kailuan participants *(continued)*

| | <50 mg/dL | 50–69 mg/dL | 70–99 mg/dL | 100–129 mg/dL | 130–159 mg/dL | ≥160 mg/dL |
|---|---|---|---|---|---|---|
| | <1.3 mmol/L | 1.3–1.7 mmol/L | 1.8–2.5 mmol/L | 2.6–3.3 mmol/L | 3.4–4.0 mmol/L | ≥4.1 mmol/L |
| **HDL-C,[a] mg/dL** | 59 | 58 | 58 | 59 | 60 | 62 |
| **TC,[a] mg/dL** | 163 | 168 | 185 | 204 | 232 | 256 |
| **Triglycerides,[a] mg/dL** | 172 | 145 | 143 | 151 | 154 | 160 |
| **SBP,[a] mm Hg** | 133 | 129 | 131 | 133 | 137 | 139 |
| **DBP,[a] mm Hg** | 84 | 83 | 84 | 85 | 86 | 87 |
| **eGFR,[a] mL/min/1.73 m$^2$** | 87.4 | 89 | 85.5 | 83.3 | 80.2 | 78.4 |

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high sensitive C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol.
[a] Updated cumulative average (see the Methods section).
[b] Light drinker: 0.1–0.4 servings a day for women and 0.1 to 0.9 serving a day for men; moderate: 0.5 to 1.5 servings a day for women and 1 to 2 servings a day for men; heavy: >1.5 servings a day for women and >2 serving a day for men (based on 15 g alcohol/serving).
[c] Use of antihypertensive, lipid-lowering agents, and aspirin (yes/no for each) was updated by every survey from 2006.

of 429 (57%) patients with incident ICH had clear information on parenchymal location of hematomas, as reviewed by an experienced radiologist.[21] The hematomas were categorized into 2 groups based on location: deep (i.e., hemorrhages that originated in the thalamus, basal ganglia, cerebellum, or brainstem) and nondeep (i.e., lobar) hematomas. Because the incident cases of epidural, subdural, and subarachnoid hemorrhages were rare (<0.02%), the ICH was the intraparenchymal hemorrhage in the current study.

## Assessment of lipid profile

Blood samples were collected in the morning of the survey after an overnight fast at the baseline (2006) and subsequent survey visits in 2008, 2010, and 2012. LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol (TC) were measured with the enzymatic colorimetric method (Mind Bioengineering Co Ltd, Shanghai, China). The interassay coefficient of variation for each measurement was <10% with the use of an autoanalyzer (Hitachi 747, Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital.

## Assessment of potential covariates

Information on age, sex, education level, income level, occupation, physical activity, smoking status, alcohol intake, and medical history (e.g., hypertension, diabetes mellitus, and active treatment such as hypoglycemic, antihypertensive, lipid-lowering agents, and aspirin) was collected via questionnaires, as detailed elsewhere.[20] Weight and height were measured by trained fieldworkers during surveys. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of height (meters squared). Systolic and diastolic blood pressures were measured twice from the seated position with a mercury sphygmomanometer. The average of the 2 readings was used for analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications in the last 2 weeks regardless of blood pressure status. Prehypertension was classified as systolic blood pressure between 120 and 139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg. Fasting blood glucose was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. Plasma high-sensitivity C-reactive protein (hs-CRP) concentrations were measured with high-sensitivity particle-enhanced immunonephelometry assay. Alanine aminotransferase was measured with an enzymatic rate method. Serum creatinine was assessed with the sarcosine oxidase assay method (Creatinine kit, BioSino Bio-Technology and Science Inc, Beijing, China). Estimated glomerular filtration rate (eGFR) was calculated with a modified 4-variable Chronic Kidney Disease Epidemiology Collaboration formula and adjusted for the Chinese population.[22] All the plasma samples were measured with the aforementioned autoanalyzer (Hitachi 747). The definition of diabetes mellitus was laboratory based and combined with medication use, that is, a concentration of fasting blood glucose ≥7.0 mmol/L or use of oral hypoglycemic agent or during active treatment with insulin, and prediabetes was defined as a concentration of fasting blood glucose between 5.6 and 6.9 mmol/L.

## Statistical analyses

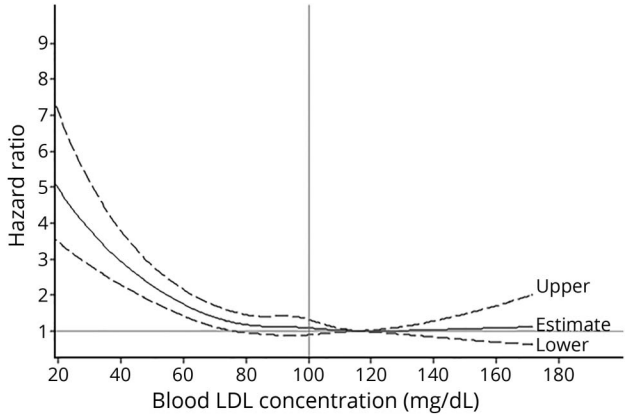
Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Inc, Cary, NC) and Stata 15 (StataCorp LLC, College Station, TX). Formal hypothesis testing was 2 sided with a significance level of 0.05. Person-years for each participant were calculated from the date the 2006 survey was completed to the diagnosed date of ICH or death, loss to follow-up (5%), or December 31, 2015, whichever came first. To represent long-term LDL-C patterns of individuals, we calculated updated cumulative average LDL-C concentrations from all available LDL-C measurement from 2006 to the end of follow up. For example, the incidence of ICH from 2006 to 2008 was related to the 2006 LDL-C concentrations, and the

**Table 2** Adjusted HRs (95% CIs) for risk of ICH according to blood LDL-C concentrations from 2006 to 2012 among 96,043 Kailuan participants

| | <50 mg/dL<br><1.3 mmol/L | 50–69 mg/dL<br>1.3–1.7 mmol/L | 70–99 mg/dL<br>1.8–2.5 mmol/L | 100–129 mg/dL<br>2.6–3.3 mmol/L | 130–159 mg/dL<br>3.4–4.0 mmol/L | ≥160 mg/dL<br>≥4.1 mmol/L |
|---|---|---|---|---|---|---|
| **Updated cumulative average blood LDL-C concentrations from 2006–2012** | | | | | | |
| **Cases/population, n** | 65/2,867 | 114/10,183 | 287/42,824 | 219/31,907 | 49/6,367 | 19/1,895 |
| **Incidence rate per 1,000 person-y** | 2.87 | 1.32 | 0.78 | 0.80 | 0.91 | 1.21 |
| **Age- and sex-adjusted HR** | 2.97 (2.27, 3.90) | 1.57 (1.27, 1.95) | 1 (Referent) | 1.00 (0.84, 1.19) | 1.06 (0.78, 1.44) | 1.33 (0.84, 2.12) |
| **Multivariate-adjusted HR[a]** | 2.69 (2.03, 3.57) | 1.65 (1.32, 2.05) | 1 (Referent) | 0.94 (0.78, 1.12) | 0.93 (0.69, 1.27) | 1.09 (0.68, 1.74) |
| **Excluding cholesterol-lowering agent users[a]** | 2.74 (2.06, 3.64) | 1.66 (1.33, 2.07) | 1 (Referent) | 0.93 (0.78, 1.11) | 0.91 (0.66, 1.24) | 1.06 (0.66, 1.72) |
| **Excluding anticoagulant users[a]** | 2.72 (2.05, 3.62) | 1.66 (1.33, 2.07) | 1 (Referent) | 0.92 (0.76, 1.10) | 0.92 (0.67, 1.25) | 1.10 (0.69, 1.75) |
| **Excluding participants with uncontrolled hypertension during follow-up[a]** | 2.61 (1.90, 3.60) | 1.73 (1.34, 2.23) | 1 (Referent) | 1.02 (0.83, 1.26) | 1.07 (0.75, 1.52) | 1.23 (0.71, 2.12) |
| **Excluding participants with hypertension during follow-up[a]** | 3.08 (1.77, 5.35) | 2.05 (1.35, 3.13) | 1 (Referent) | 1.18 (0.82, 1.70) | 1.02 (0.50, 2.06) | 0.81 (0.20, 3.33) |
| **Excluding participants with cancer, myocardial infarction, ischemic stroke, or hs-CRP >10 mg/L during follow-up[a]** | 2.58 (1.83, 3.65) | 1.71 (1.33, 2.21) | 1 (Referent) | 0.95 (0.77, 1.17) | 0.92 (0.64, 1.31) | 1.28 (0.76, 2.14) |
| **2-y lag analysis[a,b]** | 2.34 (1.62.3.38) | 1.76 (1.35.2.29) | 1 (Referent) | 0.98 (0.79, 1.21) | 0.98 (0.68.1.41) | 0.93 (0.50.1.71) |
| **Blood LDL-C concentrations in 2006** | | | | | | |
| **Cases/population, n** | 110/9,432 | 96/13,790 | 268/37,904 | 195/25,436 | 52/6,577 | 32/2,904 |
| **Incidence rate per 1,000 person-y** | 1.37 | 0.81 | 0.82 | 0.89 | 0.93 | 1.31 |
| **HR[a]** | 1.30 (1.01, 1.66) | 0.97 (0.77, 1.23) | 1 (Referent) | 1.02 (0.85, 1.23) | 0.91 (0.67, 1.24) | 1.06 (0.72, 1.56) |
| **Updated blood LDL-C concentrations** | | | | | | |
| **Cases/population, n** | 80/5,655 | 91/12,041 | 271/34,295 | 219/29,781 | 65/9,988 | 27/4,283 |
| **Incidence rate per 1,000 person-y** | 1.69 | 0.88 | 0.92 | 0.85 | 0.76 | 0.74 |
| **HR[a]** | 1.76 (1.36, 2.28) | 1.04 (0.81, 1.32) | 1 (Referent) | 0.88 (0.73.1.05) | 0.76 (0.58, 1.00) | 0.63 (0.43, 0.95) |

Abbreviations: CI = confidence interval; HR = hazard ratio; hs-CRP = high sensitive C-reactive protein; ICH = intracerebral hemorrhage; LDL-C = low-density lipoprotein cholesterol.
[a] Model adjusted for age; sex; smoking (current, past, or never); alcohol intake (never, past, light, moderate, or heavy); education (illiteracy or elementary school, middle school, college/university); physical activity (never, sometimes, or active); average monthly income of each family member (<500, 500–2,999, or ≥3,000 ¥); salt intake (≥10.0, 6.0–9.9, or <6.0 g/d); updated diabetes status (no, prediabetes, or diabetes mellitus); use of antihypertensive, lipid-lowering agents, aspirin, and anticoagulants (yes/no for each); updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m$^2$); triglycerides (<150, 150–199, 200–240, or ≥240 mg/dL), high-density lipoprotein cholesterol (≥60, 40–59, or <40 mg/dL), hs-CRP (<1.00, 1.00–2.99, or ≥3.00 mg/L), and alanine aminotransferase (for men: <47 or ≥47 U/L; for women <36 or ≥36 U/L) levels; systolic blood pressure (quintile); diastolic blood pressure (quintile); and estimated glomerular filtration rate (quintile).
[b] Excluded ICH events in the first 2 years of follow-up.

**Figure** Hazard ratios for intracerebral hemorrhage according to updated cumulative average blood LDL cholesterol from 2006 to 2012 among 96,043 Kailuan participants




Model was adjusted for age; sex; smoking (current, past or never); alcohol intake (never, past, light, moderate, or heavy); education (illiteracy or elementary school, middle school, or college/university); physical activity (never, sometimes, or active); average monthly income of each family member (<500, 500–2,999, or ≥3,000 ¥); salt intake (≥10.0, 6.0–9.9 or <6.0 g/d); updated diabetes status (no, prediabetes, or diabetes mellitus); use of antihypertensive, lipid-lowering agents, aspirin, and anticoagulants (yes/no for each); updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m$^2$); triglycerides (<150, 150–199, 200–240, or ≥240 mg/dL), high-density lipoprotein cholesterol (≥60, 40–59, or <40 mg/L), and high-sensitivity C-reactive protein (<1.00, 1.00–2.99, or ≥3.00 mg/mL) concentrations; alanine aminotransferase (for men <47 or ≥47 U/L; for women <36 or ≥36 U/L); systolic blood pressure (quintile); diastolic blood pressure (quintile); and estimated glomerular filtration rate (quintile). Data were fitted by a restricted cubic spline Cox proportional hazards model. The 95% confidence intervals are indicated by the dashed lines. LDL = low-density lipoprotein.

incidence from 2008 to 2010 was related to the average LDL-C concentrations in 2006 and 2008. In secondary analyses, we used a single measure of LDL-C in 2006 and updated LDL-C and cumulative average TC, HDL-C, and triglycerides as the exposure.

LDL-C concentrations were categorized as <50, 50 to 69, 70 to 99, 100 to 129, 130 to 159, and ≥160 mg/dL. TC concentrations were categorized as <120, 120 to 199, 200 to 239, and ≥240 mg/dL. HDL-C concentrations were categorized as ≥60, 40 to 59, and <40 mg/dL. Triglycerides concentrations were categorized as <150, 150 to 199, and ≥200 mg/dL. All categories were based on the definition of hypocholesterolemia/hypercholesterolemia and the current targets for statin treatment.[18,23,24] We used the category with LDL-C concentration of 70 to 99 mg/dL, TC concentration of 120 to 199 mg/dL, HDL-C concentration ≥60 mg/dL, and triglycerides concentration <150 mg/dL as the reference groups. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of total and subtypes of ICH based on the updated cumulative average LDL-C, after adjustment for potential cofounders.

For more detailed analyses of the dose-response trends, the continuous measure of cumulative average LDL-C was used to fit a restricted cubic spline model[25] and to obtain a smooth representation of the hazard ratio as a function of LDL-C concentrations with adjustment for the effects of potential confounders. We used 5 knots defined at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles to divide continuous LDL-C concentration into 5 intervals.

To explore whether the potential LDL-ICH relation was confounded by cholesterol-lowering agents (e.g., statins), we conducted a sensitivity analysis by excluding the participants who used cholesterol-lowering agents. Because anticoagulants would increase the risk of ICH, we excluded participants with atrial fibrillation or flutter, deep venous thrombosis, pulmonary infarction, or heart valve disease, which are major indications for use of anticoagulants. These participants were referred to as anticoagulant users in this report. Because incident cancer, myocardial infarction, incident ischemic stroke, or high-grade inflammation might be associated with low LDL-C and higher risk of ICH, we excluded participants who developed these conditions during follow-up. We also excluded individuals with hypertension and uncontrolled hypertension (i.e., treated hypertension with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) during the follow-up. Because the altered LDL-C concentration may be the consequence of impending ICH (i.e., reverse causality), we conducted a 2-year lag analysis by excluding those with ICH onset during the first 2 years of follow-up.

Likelihood ratio tests were conducted to examine statistical interactions between LDL-C concentrations and sex, age, hypertension during the follow-up (yes/no), hypertension in 2006 (yes/no), diastolic blood pressure in 2006 (<90 mm Hg/≥90 mm Hg), BMI (<28/≥28 kg/m$^2$), and drinking status (current drinkers/noncurrent drinkers in 2006) in relation to ICH risk by comparing −2 log likelihood $\chi^2$ between nested models with and without the cross-product terms.

## Data availability

Deidentified data are available to researchers on request by contacting with Dr. Wu or Dr. Gao.

## Results

During the 9-year follow-up period (2006–2015), we identified 753 cases of incident ICH. In general, participants with higher LDL-C concentrations were more likely to smoke and report heavy alcohol intake; to engage in more physical activity; to have higher salt intakes, higher BMIs, higher TC concentrations, and lower eGFR levels; and to use antihypertensive, cholesterol-lowering agents, and aspirin (table 1).

The ICH risk was similar for participants with LDL-C concentrations of 70 to 99 mg/dL and those with LDL-C concentrations >100 mg/dL. In contrast, participants with LDL-C concentrations <70 mg/dL had a significantly higher risk of developing ICH than those with LDL-C

**Table 3** Adjusted HRs and 95% CIs for risk of ICH according to blood LDL-C concentrations from 2006 to 2012, stratified by age, sex, hypertension, diastolic blood pressure, BMI, and drinking status[a]

| | <50 mg/dL<br><1.3 mmol/L | 50–69 mg/dL<br>1.3–1.7 mmol/L | 70–99 mg/dL<br>1.8–2.5 mmol/L | 100–129 mg/dL<br>2.6–3.3 mmol/L | 130–159 mg/dL<br>3.4–4.0 mmol/L | ≥160 mg/dL<br>≥4.1 mmol/L | *p* Interaction |
|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | 0.89 |
| **Cases/population** | 33/1,914 | 63/7,556 | 172/33,933 | 133/24,961 | 30/4,618 | 9/1,289 | |
| **<60 y** | 3.02 (2.05, 4.46) | 1.78 (1.33, 2.38) | 1 (Referent) | 0.93 (0.74, 1.16) | 1.01 (0.68, 1.50) | 0.96 (0.49, 1.89) | |
| **Cases/population** | 32/953 | 51/2,627 | 115/8,891 | 86/6,946 | 19/1,749 | 10/606 | |
| **≥60 y** | 2.37 (1.56, 3.59) | 1.51 (1.08, 2.12) | 1 (Referent) | 0.93 (0.70, 1.23) | 0.80 (0.49, 1.31) | 1.15 (0.60, 2.22) | |
| **Sex** | | | | | | | 0.56 |
| **Cases/population** | 60/2,356 | 100/7,899 | 245/33,915 | 196/25,579 | 43/4,955 | 18/1,544 | |
| **Men** | 2.82 (2.09, 3.80) | 1.68 (1.32, 2.12) | 1 (Referent) | 0.99 (0.82, 1.19) | 1.01 (0.72, 1.40) | 1.24 (0.77, 2.02) | |
| **Cases/population** | 5/511 | 14/2,284 | 42/8,909 | 23/6,328 | 6/1,412 | 1/351 | |
| **Women** | 2.05 (0.77, 5.44) | 1.48 (0.80, 2.75) | 1 (Referent) | 0.62 (0.37, 1.04) | 0.57 (0.24, 1.37) | 0.34 (0.05, 2.47) | |
| **Hypertension during follow-up** | | | | | | | 0.41 |
| **Cases/population** | 47/1,269 | 79/3,765 | 223/16,493 | 166/14,161 | 40/3,277 | 17/1,062 | |
| **Yes** | 2.52 (1.81, 3.51) | 1.52 (1.17, 1.98) | 1 (Referent) | 0.87 (0.71, 1.06) | 0.89 (0.63, 1.25) | 1.13 (0.69, 1.86) | |
| **Cases/population** | 18/1,598 | 35/6,418 | 64/26,331 | 53/17,746 | 9/3,090 | 2/833 | |
| **No** | 3.08 (1.77, 5.35) | 2.05 (1.35, 3.13) | 1 (Referent) | 1.18 (0.82, 1.70) | 1.02 (0.50, 2.06) | 0.81 (0.20, 3.33) | |
| **Hypertension in 2006** | | | | | | | 0.25 |
| **Cases/population** | 17/1,501 | 38/6,163 | 68/24,428 | 56/16,189 | 10/2,922 | 1/782 | |
| **Yes** | 2.86 (1.64, 5.00) | 2.12 (1.41, 3.17) | 1 (Referent) | 1.20 (0.84, 1.71) | 1.06 (0.54, 2.09) | 0.37 (0.05, 2.65) | |
| **Cases/population** | 48/1,363 | 76/4,014 | 218/18,369 | 163/15,693 | 39/3,436 | 18/1,112 | |
| **No** | 2.60 (1.87, 3.61) | 1.50 (1.15, 1.96) | 1 (Referent) | 0.87 (0.71, 1.06) | 0.88 (0.62, 1.25) | 1.21 (0.75, 1.97) | |
| **Diastolic blood pressure in 2006** | | | | | | | 0.48 |
| **Cases/population** | 27/1,889 | 52/7,572 | 126/29,905 | 92/20,689 | 19/3,910 | 4/1,084 | |
| **<90 mm Hg** | 2.31 (1.49, 3.58) | 1.53 (1.10, 2.12) | 1 (Referent) | 0.98 (0.75, 1.29) | 0.97 (0.60, 1.59) | 0.62 (0.23, 1.69) | |
| **Cases/population** | 38/964 | 62/2,548 | 160/12,706 | 127/11,050 | 30/2,430 | 15/801 | |

Continued

**Table 3** Adjusted HRs and 95% CIs for risk of ICH according to blood LDL-C concentrations from 2006 to 2012, stratified by age, sex, hypertension, diastolic blood pressure, BMI, and drinking status[a] *(continued)*

| | <50 mg/dL<br><1.3 mmol/L | 50–69 mg/dL<br>1.3–1.7 mmol/L | 70–99 mg/dL<br>1.8–2.5 mmol/L | 100–129 mg/dL<br>2.6–3.3 mmol/L | 130–159 mg/dL<br>3.4–4.0 mmol/L | ≥160 mg/dL<br>≥4.1 mmol/L | *p* Interaction |
|---|---|---|---|---|---|---|---|
| ≥90 mm Hg | 2.77 (1.90, 4.03) | 1.80 (1.33, 2.42) | 1 (Referent) | 0.91 (0.72, 1.15) | 0.90 (0.60, 1.33) | 1.33 (0.78, 2.27) | |
| **Body mass index** | | | | | | | 0.47 |
| Cases/population | 52/2,462 | 89/8,764 | 217/36,367 | 174/26,196 | 38/5,112 | 13/1,529 | |
| <28 kg/m$^2$ | 2.65 (1.92, 3.65) | 1.66 (1.29, 2.13) | 1 (Referent) | 1.02 (0.84, 1.25) | 1.03 (0.73, 1.47) | 1.04 (0.59, 1.82) | |
| Cases/population | 13/390 | 24/1,389 | 69/6,379 | 44/5,666 | 10/1,244 | 4/369 | |
| ≥28 kg/m$^2$ | 3.01 (1.62, 5.57) | 1.54 (0.96, 2.48) | 1 (Referent) | 0.68 (0.46, 0.99) | 0.62 (0.32, 1.22) | 0.85 (0.31, 2.36) | |
| **Current drinkers in 2006** | | | | | | | 0.56 |
| Cases/population | 40/1,736 | 57/5,853 | 184/25,148 | 133/18,219 | 29/3,325 | 7/953 | |
| Yes | 2.52 (1.76, 3.61) | 1.33 (0.98, 1.79) | 1 (Referent) | 0.91 (0.73, 1.14) | 0.98 (0.66, 1.46) | 0.76 (0.36, 1.64) | |
| Cases/population | 18/885 | 43/3,880 | 96/16,635 | 79/13,144 | 19/2,881 | 11/856 | |
| No | 3.04 (1.80, 5.12) | 1.93 (1.34, 2.77) | 1 (Referent) | 0.95 (0.70, 1.28) | 0.87 (0.53, 1.44) | 1.50 (0.80, 2.83) | |

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; LDL-C = low-density lipoprotein cholesterol.
[a] Model adjusted for age; sex; smoking (current, past, or never); alcohol intake (never, past, light, moderate, or heavy); education (illiteracy or elementary school, middle school, college/university); physical activity (never, sometimes, or active); average monthly income of each family member (<500, 500–2,999, or ≥3,000 ¥); salt intake (≥10.0, 6.0–9.9, or <6.0 g/d); updated diabetes status (no, prediabetes, or diabetes mellitus); use of antihypertensive, lipid-lowering agents, aspirin, and anticoagulants (yes/no for each); updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m$^2$); triglycerides (<150, 150–199, 200–240, or ≥240 mg/dL), high-density lipoprotein cholesterol (≥60, 40–59, or <40 mg/dL), hs-CRP (<1.00, 1.00–2.99, or ≥3.00 mg/L), and alanine aminotransferase (for men: <47 or ≥47 U/L; for women <36 or ≥36 U/L) levels; systolic blood pressure (quintile); diastolic blood pressure (quintile); and estimated glomerular filtration rate (quintile).

**Table 4** Adjusted HRs and 95% CIs for risk of deep and nondeep ICH according to updated cumulative average blood LDL-C concentrations from 2006 to 2012 among 96,043 Kailuan participants

| | <50 mg/dL <1.3 mmol/L | 50–69 mg/dL 1.3–1.7 mmol/L | 70–99 mg/dL 1.8–2.5 mmol/L | 100–129 mg/dL 2.6–3.3 mmol/L | 130–159 mg/dL 3.4–4.0 mmol/L | *p* Trend |
|---|---|---|---|---|---|---|
| **Deep hemorrhagic stroke** | | | | | | |
| **Cases/population** | 39/2,867 | 53/10,183 | 141/42,824 | 108/31,907 | 27/8,262 | |
| **Incidence rate per 1,000 person-y** | 1.72 | 0.61 | 0.38 | 0.39 | 0.39 | |
| **HR**[a] | 3.40 (2.34, 4.95) | 1.59 (1.16, 2.19) | 1 (Referent) | 0.91 (0.71, 1.18) | 0.72 (0.48, 1.10) | <0.001 |
| **Nondeep hemorrhagic stroke** | | | | | | |
| **Cases/population** | 9/2,867 | 8/10,183 | 21/42,824 | 17/31,907 | 6/8,262 | |
| **Incidence rate per 1,000 person-y** | 0.40 | 0.09 | 0.06 | 0.06 | 0.09 | |
| **HR**[a] | 4.22 (1.81, 9.82) | 1.52 (0.67, 3.49) | 1 (Referent) | 1.02 (0.53, 1.94) | 1.08 (0.43, 2.73) | 0.005 |

Abbreviations: CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; LDL-C = low-density lipoprotein cholesterol.
[a] Model adjusted for age; sex; smoking (current, past, or never); alcohol intake (never, past, light, moderate, or heavy); education (illiteracy or elementary school, middle school, college/university); physical activity (never, sometimes, or active); average monthly income of each family member (<500, 500–2,999, or ≥3,000 ¥); salt intake (≥10.0, 6.0–9.9, or <6.0 g/d); updated diabetes status (no, prediabetes, or diabetes mellitus); use of antihypertensive, lipid-lowering agents, aspirin, and anticoagulants (yes/no for each); updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m$^2$); triglycerides (<150, 150–199, 200–240, or ≥240 mg/dL), high-density lipoprotein cholesterol (≥60, 40–59, or <40 mg/dL), hs-CRP (<1.00, 1.00–2.99, or ≥3.00 mg/L), and alanine aminotransferase (for men: <47 or ≥47 U/L; for women <36 or ≥36 U/L) levels; systolic blood pressure (quintile); diastolic blood pressure (quintile); and estimated glomerular filtration rate (quintile).

concentrations of 70 to 99 mg/dL (adjusted HR 1.65 [95% CI 1.32–2.05] for LDL-C concentrations of 50 to 69 mg/dL and 2.69 [95% CI 2.03–3.57] for LDL-C concentrations of <50 mg/dL) (table 2). In the restricted cubic spline model, we observed a cutoff point of LDL-C at 75.7 mg/dL (HR 1.24, 95% CI 1.00–1.54) at which the association between lower LDL-C and higher risk of ICH became significant (figure). Results did not change materially in the sensitivity analyses by excluding participants who used cholesterol-lowering agents or anticoagulants during the follow-up; participants who developed cancer, myocardial infarction, ischemic stroke, or high-grade inflammation (hs-CRP>10 mg/L) during the follow-up; participants with hypertension or uncontrolled hypertension during the follow-up; or participants with ICH onset during the first 2 years of follow-up. Similar patterns were observed when baseline or updated LDL-C concentration was used as the exposure, although the strength of the associations between low LDL-C concentrations and high ICH risk was attenuated (table 2).

The association between LDL-C concentrations and ICH risk was not significantly modified by age, sex, hypertension status, diastolic blood pressure, BMI, and drinking status ($p$ for interaction ≥ 0.1 for all) (table 3). When we further examined the location of ICH, the association between lower LDL-C concentration and higher risk persisted consistently for both deep and nondeep hematoma ($p$ trend < 0.0001 for both) (table 4).

Lower (<120 mg/dL) TC concentrations were associated with higher ICH risk compared with TC concentrations of 120 to 199 mg/dL. In contrast, the associations between HDL-C, triglycerides, and ICH risk were not significant (table 5).

## Discussion

In this community-based prospective study of 96,043 participants with 9 years of follow-up, individuals with average LDL-C <70 mg/dL had a higher risk of ICH relative to those with LDL-C of 70 to 99 mg/dL, independently of potential codeterminants, including age, sex, BMI, hypertension, and drinking status. Excluding participants using cholesterol-lowering agents and anticoagulants did not change the results. Our study used currently recommended cutoffs in estimating the risk[18,23]; thus, the findings provide potentially actionable results. In patients at higher ICH risk, the use of a less stringent LDL-C target, that is, 70 to 99 mg/dL, might be more appropriate to obtain a better balance between cardiovascular disease and ischemic and hemorrhagic risks.

Unlike our study, previous studies on this topic were based on a single-time measurement of LDL-C at baseline. Nevertheless, most of them showed a similar trend between low LDL-C concentrations and high ICH incidence or ICH mortality, although the results frequently did not reach a level of statistical significance. For example, in a pooled prospective cohort study with 135 cases of incident ICH (n = 21,680), the adjusted HR was 0.50 (95% CI 0.29–0.87) for the highest vs the lowest quartile of LDL-C.[8] In another prospective cohort study, participants with LDL-C concentration ≥140 mg/dL had a 50% lower risk of ICH mortality relative to those with an LDL-C <80 mg/dL.[9]

**Table 5** Adjusted HRs and 95% CIs for risk of ICH according to updated cumulative average blood lipid profile from 2006 to 2012 among 96,043 Kailuan participants

| TC | <120 mg/dL <3.1 mmol/L | 120–199 mg/dL 3.1–5.1 mmol/L | 200–239 mg/dL 5.2–6.1 mmol/L | ≥240 mg/dL ≥6.2 mmol/L | *p* Trend |
|---|---|---|---|---|---|
| **Cases/population** | 24/936 | 449/59,102 | 189/27,548 | 91/8,457 | |
| **Incidence rate, per 1,000 person-y** | 3.29 | 0.88 | 0.80 | 1.27 | |
| **Fully adjusted[a]** | 2.24 (1.48, 3.40) | 1 (Referent) | 0.82 (0.69, 0.98) | 1.17 (0.93, 1.48) | 0.46 |
| **HDL-C** | **≥60 mg/dL (≥1.6 mmol/L)** | **40–59 mg/dL (1.0–1.5 mmol/L)** | | **<40 mg/dL (<1.0 mmol/L)** | ***p* Trend** |
| **Cases/population** | 382/44,144 | 343/49,219 | | 28/2,674 | |
| **Incidence rate per 1,000 person-y** | 1.01 | 0.81 | | 1.25 | |
| **Fully adjusted[a]** | 1 (Referent) | 0.86 (0.74, 1.00) | | 1.05 (0.71, 1.55) | 0.05 |
| **Triglycerides** | **<150 mg/dL (<1.7 mmol/L)** | **150–199 mg/dL (1.7–2.1 mmol/L)** | | **≥200 mg/dL (≥2.2 mmol/L)** | ***p* Trend** |
| **Cases/population** | 498/64,838 | 102/13,097 | | 153/18,108 | |
| **Incidence rate per 1,000 person-y** | 0.90 | 0.90 | | 0.99 | |
| **Fully adjusted[a]** | 1 (Referent) | 0.99 (0.80, 1.24) | | 0.97 (0.80, 1.18) | 0.96 |

Abbreviations: CI = confidence interval; HR = hazard ratio; HDL-C = high-density lipoprotein cholesterol; ICH = intracerebral hemorrhage; TC = total cholesterol.
[a] Model adjusted for age; sex; smoking (current, past, or never); alcohol intake (never, past, light, moderate, or heavy); education (illiteracy or elementary school, middle school, college/university); physical activity (never, sometimes, or active); average monthly income of each family member (<500, 500–2,999, or ≥3,000 ¥); salt intake (≥10.0, 6.0–9.9, or <6.0 g/d); updated diabetes status (no, prediabetes, or diabetes mellitus); use of antihypertensive, lipid-lowering agents, aspirin, and anticoagulants (yes/no for each); updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m$^2$); triglycerides (<150, 150–199, 200–240, or ≥240 mg/dL), high-density lipoprotein cholesterol (≥60, 40–59, or <40 mg/dL), hs-CRP (<1.00, 1.00–2.99, or ≥3.00 mg/L), and alanine aminotransferase (for men: <47 or ≥47 U/L; for women <36 or ≥36 U/L) levels; systolic blood pressure (quintile); diastolic blood pressure (quintile); and estimated glomerular filtration rate (quintile).

Because hypercholesterolemia is directly related to increased cardiovascular morbidity and mortality,[26] statins are recommended by the American Heart Association/American College of Cardiology and European Society of Cardiology/European Atherosclerosis Society for the primary and secondary prevention of atherosclerotic cardiovascular disease.[18,23] A recent analysis of National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2010 reported that the number of people eligible for statin therapy would rise from 43.2 million US adults (37.5%) to 56.0 million (48.6%) on the basis of the aforementioned guidelines for management of LDL-C.[27] The net number of new statin prescriptions could potentially raise by 12.8 million, including 10.4 million for primary prevention.[28] Clinical trials such as Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL), A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID), and Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) showed that lowering LDL-C to <70 mg/dL halted or even reversed the development of atherosclerotic plaque and reduced heart attack and stroke rates.[29–32] However, concerns persist that a reduction of LDL-C might entail some risk. A post hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) clinical trial indicated that atorvastatin use was associated with an increased risk of ICH in patients enrolled after experiencing a hemorrhagic stroke.[33] Furthermore, the latest meta-analysis of statin clinical trials showed that there was an insignificant association between statin therapy and the risk of hemorrhagic stroke (pooled relative risk 1.14 for per 1.0-mmol/L LDL-C reduction, 95% CI 0.96–1.36).[34] A latest meta-analysis of nonstatin clinical trials of further lowering of LDL-C in patients starting with very low levels showed a nonsignificant positive association between LDL-C lowering and increased risk of hemorrhagic stroke, with 250 total cases (pooled relative risk 1.11, 95% CI 0.87–1.43).[35] Meanwhile, a recent pooled analysis including 2 trials of antiproprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors did not find evidence for the use of PCSK9 and altered subsequent risk of ICH; those investigators did not identify any hemorrhagic stroke cases in either study.[36] Similar results of insignificant association between LDL-C and hemorrhagic stroke were also observed in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial (92 incident ICH cases)[37] and the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (53 incident ICH case).[38] However, these currently available limited data should be interpreted with caution because of the short follow-up durations (1.0–6.0 years) and small sample size of hemorrhagic stroke incident cases. As suggested by another meta-analysis of PCSK9 trials, the potential effects of PCSK9 "remain inconclusive for rarer CVD [cardiovascular disease] and non-CVD events such as haemorrhagic stroke,"[39] which could be due to lack of statistical power. In the current study with ≈96,000

participants, we observed that ICH risk was inversely associated with LDL-C concentration <70 mg/dL. This observation suggests that maintaining LDL-C concentration in a range of 70 to 100 mg/dL might be optimal for ICH prevention. A recent meta-analysis of 34 randomized clinical trials showed that more intensive LDL-C–lowering therapy was associated with a reduced total mortality only for participants with higher baseline LDL-C concentrations, not for those with baseline LDL-C levels <100 mg/dL.[40]

Studies supported the notion that low TC concentration was associated with increased ICH risk. For example, in a prospective study with 77 cases of ICH (n = 23,867), participants in the lowest quintile of TC (≤188 mg/dL) had a significantly higher ICH incidence rate relative to those with higher TC concentrations ($p$ trend = 0.001).[41] A similar pattern was observed in the current study. The possibility cannot be ruled out that the association between TC and ICH risk could be, at least in part, driven by LDL-C. This is suggested by an insignificant relationship between HDL-C/triglycerides and ICH risk in the current analyses.

Although the mechanisms explaining how low LDL-C could promote hemorrhagic stroke are unclear, there are some possible explanations. These include erythrocyte fragility due to low cholesterol in erythrocyte membrane,[42] LDL-related platelet activation and tissue factor expression,[43] and impaired coagulation function.[43,44] Furthermore, low LDL-C concentrations were strongly related to a higher number of microbleeds,[45] a well-known risk factor for ICH.[46] Previous studies also demonstrated that the *APOE* ε4 genotype was associated with cerebral amyloid angiopathy–related ICH (i.e., nondeep ICH),[47,48] and *APOE* ε4 carriers manifested higher rates of decline in LDL-C concentration over time.[49] Collectively, these data suggest that low LDL-C concentration and elevated ICH risk might involve both amyloid- and non–amyloid-related mechanisms.

Our study has several strengths and limitations. First, the large number of ICH incident cases in our cohort provides great statistical power to study the LDL-C/ICH relationship, resulting from the unique study setting in the area with a relatively high frequency of ICH. According to the recent findings from the Global Burden of Disease Study, the incidence of hemorrhagic stroke in China ranked the highest globally,[5] which might be due to the increased prevalence of risk factors for this stroke type (e.g., high blood pressure and alcohol intake) and an aging population. Second, the availability of repeated measurements for LDL-C concentrations reduced random errors and captured fluctuations and normal changes of LDL-C over time not possible in prior investigations of the topic. We consistently observed a stronger association between cumulative average LDL-C and ICH risk relative to baseline or updated LDL-C. Third, LDL-C concentration was determined directly with the same series of kits consistently throughout the study. Fourth, we had information on the location of hematoma for many incident ICH cases, which provided valuable clues for investigating the underlying mechanisms of the relationship between LDL-C and ICH. Fifth, we collected comprehensive information repeatedly and rigorously such as obesity, hs-CRP and alanine aminotransferase concentrations, eGFR status, and medication use, which could minimize possible residual confounding to the extent possible. Generalizability to other settings and populations (e.g., whites) might be a limitation because the current study was conducted in Tangshan, an industrial city in northern China. In addition, only 54% of patients with incident ICH had clear information on parenchymal location of hematomas. However, we still observed a significant association of LDL-C with both deep and nondeep ICH. Furthermore, the identification of potential ICH with ICD coding might induce misclassification of ICH, especially when ICH was a complication of other disease. However, reviewing medical records by a panel of 3 physicians could reduce the possibility.

In this population-based prospective study, we observed a significant association between lower LDL-C and higher ICH risk when LDL-C was <70 mg/dL, and the risk decreased to a nonsignificant level and stabilized when LDL-C was ≥70 mg/dL. Similar patterns were observed for both deep and nondeep ICH. These results could be important in determining a target of LDL-C range, especially in patients with atherosclerotic disease who might be at higher baseline ICH risk such as aging individuals, those with hypertension, and people with high alcohol drinking. Future studies with large sample sizes with categorical information on parenchymal hematoma location and conducted among other populations would be appropriate to further investigate this association.

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## Disclosure

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## Publication history

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Continued

## Appendix *(continued)*

| Name | Location | Role | Contribution |
|---|---|---|---|
| **M. Edip Gurol, MD, MSc** | Hemorrhagic Stroke Research Program, Massachusetts General Hospital and Harvard Medical School, Boston | Author | Revised the manuscript for intellectual content |
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| **Alice H. Lichtenstein, DSc** | Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA | Author | Revised the manuscript for intellectual content |
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| **Yuzhen Wang, MD** | Kailuan General Hospital, Tangshan, China | Author | Major role in the acquisition of data; interpreted the data |
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| **Xiang Gao, MD, PhD** | Department of Nutritional Sciences, Pennsylvania State University, University Park | Corresponding author | Supervised the study; design and conceptualized study |

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