Inverse association of plasma level of high-density lipoprotein cholesterol with intracerebral hemorrhage

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Short Title: HDL cholesterol and intracerebral hemorrhage

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Abstract

This study aimed to investigate whether plasma levels of high-density lipoprotein cholesterol (HDL-C) were associated with the risk of intracerebral hemorrhage (ICH). Plasma HDL-C was determined via enzymatic methods, and intracerebral hemorrhage was ascertained via medical history, physical examination and brain imaging (computed tomography or magnetic resonance imaging). The multivariable logistic regression model was used to calculate the odds ratios (OR) and 95% confidence intervals (CI) of ICH according to levels of plasma cholesterol. A total of 170 patients with ICH were identified from 6046 participants. After adjustment for conventional cardiovascular risk factors, the OR was 2.06 (95% CI 1.25–3.12, P<0.01) for participants in the first tertile of HDL-C levels (<1.38 mmol/L) and 1.13 (95% CI 0.72–1.78, P=0.59) for participants in the second tertile (1.38–1.64 mmol/L), as compared with participants in the third tertile (≥1.65 mmol/L). Subgroup analysis indicated that the detrimental effects of HDL-C were more significant in men and lean participants than in their corresponding controls, independent of hypertension. The results presented herein indicate that low plasma HDL-C (<1.38 mmol/L) may be associated with risk of ICH.

Key Words: blood lipid; stroke; hypertension
Introduction

Intracerebral hemorrhage (ICH) is a serious cerebrovascular disease worldwide (1) and has a fatality rate of approximately 35%−52% at 30 days. Fully half of these fatalities occur within the first two days (2). The proportion of this subtype of stroke is high in China, accounting for approximately 38% to 55% of total strokes (3, 4). Considering the high mortality rate, and the paucity of effective treatments, prevention of ICH is of paramount importance (5). Identification of risk factors for ICH, especially modifiable factors, is the first step in prevention. Several modifiable risk factors such as hypertension and excessive alcohol consumption have been demonstrated to increase the risk of ICH (6), but not all patients with ICH have these identifiable risk factors.

Abnormal lipid levels are among the list of candidate risk factors for stroke (7), but their contribution to ICH remains inconclusive. This is especially true for plasma high-density lipoprotein cholesterol (HDL-C), which, along with low-density lipoprotein cholesterol (LDL-C), is a primary component of plasma total cholesterol (TC). A low level of TC has emerged as a risk factor for ICH in several prospective studies (8-10) and an association between LDL-C and ICH has also been reported (11-13). Moreover, HDL-C improves endothelial function (14) and repairs vessel walls (15, 16), suggesting that high levels of HDL-C may be protective against ICH. To date, however, few clinical studies have explored a connection between low HDL-C levels and the risk of ICH (17).

This cross sectional study therefore investigated whether that low HDL-C might contribute to the risk of ICH. An association between plasma HDL-C and ICH would provide a new potential target for the prevention of ICH.

Methods

Participants

A community-based cross sectional study was conducted in seven local communities of Xinyang County, Henan Province, China, from March to August, 2005. The study protocol was reviewed and approved by the ethics committees of FuWai Hospital and local collaborative hospitals and
conducted according to the Declaration of Helsinki. Informed consent was obtained from each participant before enrollment into the study.

Inclusion criteria were as follows: 1) participants resided in a household in one of these seven communities for at least 3 months; 2) participants were aged 40 to 75 years; and, 3) participants were free of clinical ischemic stroke as well as coronary heart disease (CHD).

Participants were excluded if they had ischemic stroke, subarachnoid hemorrhage and/or CHD. CHD was defined as the ninth International Classification of Disease (ICD-9, 1997), code 410-414; ICH, as ICD-9, code 431; ischemic stroke, as ICD-9, codes 433.0 to 434.9; subarachnoid hemorrhage, as code 430; and unclassified stroke, as code 436. All medical records and neuroimaging data (computed tomography (CT) and magnetic resonance imaging (MRI)) in subjects with a reported history of ischemic stroke, subarachnoid hemorrhage or ICH were examined by an Event Committee. Participants with systemic diseases, which were ascertained clinically and recorded in the medical history, were excluded as well. The systemic diseases were defined as severe inflammation (ICD-9, code 995.9); collagen disease (code 710); hepatic cirrhosis (code 571.2, 5, 6),; end-stage renal disease (code 585); neoplasm disease in brain (code 191), lung (code 162), liver, colon and rectum (code 153-5), pancreas (code 157), breast (code 174), bladder and kidney (code 188-9), blood system (code 188-9), endocrine disease (code 253, 255); metabolic disease (code 272) and hemorrhagic disease (code 286-7).

Two physicians on the Committee independently reviewed the data and decided whether the participants met all the inclusion or exclusion criteria. In cases of disagreement, a third physician was asked to resolve the dispute. Seven patients required this arbitration in 170 with ICH, and their data were included in the analysis because no significant differences were found whether these data were included or not.

**Biochemical Variable Determination**

Blood samples were collected after a 12-hour overnight fast in all participants, including ICH patients who had a prior history of ICH for a median period of 2 years (range: 1 to 5 years). All samples were analyzed for plasma TC, HDL-C, LDL -C, triglycerides and plasma glucose levels by enzymatic methods with an automatic analyzer (Hitachi 7060, Hitachi, Japan). All lipid levels
were determined in a CDC (Centers for Disease Control and Prevention)–qualified laboratory in FuWai Hospital.

**Clinical Data Collection**

Demographic data and vascular risk factors, including age, gender, weight, height, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. Blood pressure (BP) data analyzed in this study were obtained in all participants, including ICH patients who had a prior history of ICH for a median period of 2 years.

BP was measured three times in the seated position after a rest period of 5 min using a mercury column sphygmomanometer (18); an average of the last two readings was taken as the analyzed BP level. Medical history, alcohol and cigarette use were obtained from all participants using a standardized questionnaire.

Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg on two visits, with the interval between the two visits of more than 2 weeks (19). Alternatively, hypertension was defined as a history of hypertension with or without antihypertensive treatment (18). Hypercholesterolemia was defined according to the Adult Treatment Panel III guidelines (20). Family history of stroke was defined as a history of any of the patient’s first-degree relatives (father, mother or brother/sister) having suffered a stroke (including fatal as well as nonfatal strokes).

**Statistical Analyses**

Statistical analyses were based on individuals with ICH divided according to the tertile category of HDL-C levels and other lipid profiles: TC, LDL-C and triglycerides. The participants were categorized into three groups of approximately equal number based on the distribution of TC, LDL-C and HDL-C levels. The distribution of triglycerides levels was skewed, and log transformation was used. Continuous variables were compared using the analysis of variance (ANOVA) test and category characteristics by the chi-square/Mantel-Haenszel analysis. The Dunnett post-hoc test was performed among multiple comparisons after the ANOVA analysis.
showed significance. Variables with a univariate association with ICH were entered stepwise into a logistic model if their contribution to the model was significant at the $\alpha=0.05$ level after mutual adjustment. The binary logistic regression model was applied to adjust for conventional risk factors for ICH and to calculate the odds ratios (OR).

Two logistic models were used to calculate the OR of ICH in the subgroups divided according to plasma lipid profiles. First, age and gender were used as covariate factors for the plasma lipid group for calculation of the adjusted OR. Second, age, gender and other confounding vascular risk factors, including SBP, BMI, hypercholesterolemia, current smoking, current drinking and family history of stroke, were adjusted in the logistic regression model. In subgroup analysis stratified by gender, hypertensive status and BMI, the linear trend across HDL-C tertiles was tested by introducing the median plasma HDL-C concentration of each category as continuous variables within the multivariable models (21). The departure from the linear trend was also evaluated. A two-tailed P-value of 0.05 or less was considered significant. Statistical analyses were carried out using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results
At the beginning of the study, 7177 participants were enrolled. Among these, three patients with subarachnoid hemorrhage and 210 participants without plasma lipid analyses were excluded. Finally, 528 patients with CHD, 331 with ischemic stroke and 59 with unclassified stroke were excluded. After exclusion of these participants, 6046 participants were available for the study (shown in Figure 1). Of these, 170 patients were identified as having ICH.

Baseline Characteristics
To determine the relationship between plasma HDL-C levels and ICH, participants were categorized into tertile groups based on the distribution of HDL-C level as follows: <1.38 mmol/L,
Tertile-1 group: 1.38–1.64 mmol/L, Tertile-2 group; and ≥1.65 mmol/L, Tertile-3 group. Only 8.6% (519/6046) of all participants received lipid-lowering medications; however, 17.1% (29/170) of the ICH patients were on lipid-lowering medications.

The Tertile-3 group had much fewer men (Tertile-3 vs. Tertile-1: 32.9% vs. 40.3%; P<0.01) than the Tertile-1 group. SBP was higher in the Tertile-3 group than in the Tertile-1 group (Tertile-3 vs. Tertile-1: mean SBP 157.4 vs. 153.6 mm Hg; P<0.01), lower frequencies of antihypertensive treatment (Tertile-3 vs. Tertile-1: 30.3% vs. 33.7%, P=0.02), lipid-lowering medications (Tertile-3 vs. Tertile-1: 7.1% vs. 10.6%, P<0.01), and current cigarette smoking (Tertile-3 vs. Tertile-1: 10.2% vs. 14.7%, p<0.01). Significantly fewer participants in the Tertile-2 group received lipid-lowering medications than participants in the Tertile-3 group (Tertile-2 vs. Tertile-3: 8.0% vs.10.6%, P<0.01). No significant differences were found in family history of stroke or hypertension between HDL-C tertiles.

Inverse Association of HDL-C with ICH

The odds of a prior history of ICH decreased with increasing plasma HDL-C levels. ICH was more prevalent in the Tertile-1 group than in the Tertile-2 (3.97% vs. 2.45 %, P<0.01) and Tertile-3 groups (3.97% vs. 1.99%, P<0.01). The unadjusted OR of ICH was 1.24 (95% CI: 0.81–1.89, P=0.32) in the Tertile-2 group; and 2.03 (95% CI: 1.38–2.98, P<0.01) in the Tertile-1 group, compared with the Tertile-3 group.

Linear regression analysis performed before the multivariable logistic regression analysis revealed no significant co-linearity between the continuous variables (age, SBP and BMI) and HDL-C (data not shown). The OR of ICH in the Tertile-1 group was significantly higher than in the Tertile-3 group (OR 1.88, 95% CI: 1.27–2.78; P<0.01) after adjustment for age and gender. After further adjustment for SBP, BMI, hypercholesterolemia, current smoking, current drinking and family history of stroke, the OR of ICH in Tertile-1 remained significantly higher than in the Tertile-3 group (OR 2.06, 95% CI: 1.35–3.12, P<0.01). The multivariable adjusted OR of ICH
was 1.13 (95% CI: 0.72–1.78; P=0.59) in Tertile-2 compared with Tertile-3 (shown in Table 2). To exclude the effect of lipid-lowering medications on the levels of plasma lipids, a multivariable logistic regression analysis was performed after excluding of 519 participants (including 29 with ICH) who received lipid-lowering medications. The results demonstrated that the association between plasma lipids and ICH was not altered by the lipid-lowering medications (as shown in Supplemental Table 1).

In the final multivariable adjusted model, SBP was found to have the most significant association with ICH (increment per 10 mmHg, OR 1.21, 95% CI: 1.15–1.29, P<0.01, as shown in Table 3); female gender and high BMI were identified as protective factors for ICH (women: OR 0.50, 95% CI: 0.33–0.77, P<0.01; high BMI: OR 0.93, 95% CI: 0.88–0.97, P<0.01).

**Subgroup Analysis by Gender, Hypertension and BMI**

The risk factors for ICH, including male gender, hypertension and BMI, were not distributed normally across the three HDL-C groups. Therefore, a stratification test taking these three factors into account was performed (shown in Figure 2). In the stratification test, the significant inverse association of HDL-C with ICH was only found in men (n=2179, P<0.01 for trend) and HDL-C levels conformed to an increasing dose-dependent relationship across the three tertile groups. The inverse association between HDL-C and ICH was also significant in subjects with low BMI (<25kg/m², P=0.01 for trend), but no linear trend was documented in participants with high BMI (P=0.04 for departure). The inverse association of HDL-C with ICH was demonstrated among both hypertensive and non-hypertensive participants (P<0.01 and P=0.02 in hypertensive and non-hypertensive, respectively).

**Discussion**

The major finding of the present study is that plasma HDL-C levels were inversely associated with a history of ICH within the prior 1–5 years, indicating a potential risk factor of low plasma HDL-C on the development of ICH. Further subgroup analysis demonstrated that the effect was primarily evident in men and in participants with low BMI. Furthermore, only 8.6% of the participants (519/6046) received lipid-lowering medications, suggesting that the plasma HDL-C
levels were not influenced by lipid-lowering medications in the present study. The potential
detrimental effects of low plasma HDL-C on ICH suggest that raising HDL-C levels would
provide a new prevention treatment for ICH, although more prospective studies will be required to
confirm this.

Previously, low HDL-C concentrations were found to be associated with the risk of ischemic
stroke in a Japanese population (22), as well as in elderly patients with diabetes (23). The results
from a study that employed English males as participants support the above conclusion, in which
subjects with high levels of HDL-C (top-fifth percentile) had a 50% reduction in non-fatal stroke
risk compared with subjects with low level of HDL-C (bottom-fifth percentile) (24). Furthermore,
subjects with low levels of LDL-C attained through the use of statins, low plasma HDL-C
correlated with the risk of cardiovascular disease (25).

Although the above mentioned studies are in favor of a detrimental effect of low HDL-C level
on stroke risk, several studies contradict this view (26-31). For example, plasma lipids have been
not associated with stroke in ischemic nor hemorrhagic stoke in a case-control study (26).
However, the case-control study is different from our study in its antihypertensive trial design and
inclusion of subjects with CHD and ischemic stroke. Other studies reported no association
between HDL-C and ICH incidence (27, 28) or an increase in the risk of hemorrhagic stroke with
high HDL-C (29). However, heterogeneity in patient ethnicity may set these studies apart from the
current study.

The level of plasma HDL-C was also not a predictor of residual vascular risk in the rosuvastatin
(30) and no significant association was found between changes in HDL-C levels and stroke
reduction in a recent meta-analysis of statin trials (31). However, the nature of lipid-lowering trials
may be different from the population-based study described herein which had relatively few
participants on lipid-lowering therapy. The pharmacologic increase in HDL-C levels may, in
addition, result in a functionally distinct form of HDL-C compared with the “native” HDL-C that
is the focus in the present study. To this point, the conversion of HDL to a dysfunctional form that
is no longer cardioprotective may be involved in the increasing risk of CHD (32), although few
confirmed methods have been identified to determine the function of converted HDL-C (33).
In accordance to other studies (6, 11) SBP was confirmed to be the most important risk factor for ICH in the present study (Table 3). The results suggest the fact that the level of HDL-C may be a “natural” anti-hypertensive agent. This suggestion is also supported by a recent prospective study in which subjects with high-normal BP (130≤SBP<140 mm Hg or 85≤DBP<90 mm Hg) had a non-significantly higher risk of mortality compared with those with optimal BP (SBP<120 and DBP<80 mm Hg). The combination of low HDL-C with a high-normal BP has been associated with a two-fold higher risk of mortality compared with a optimal BP in the follow-up study of 7.6 years (34).

The vast majority of ICH is due to the formation of micro-aneurysms that are caused by the degeneration and necrosis of cerebral small arteries, which are both accompanied by hypertension and arteriosclerosis. The lipid-toxicity and inflammatory function of cholesterol may account for the angio-degeneration and arteriosclerosis. In recent cell culture studies with animal and human cells, HDL promoted cholesterol efflux from macrophage foam cells in atheromatous vessels, reducing the cholesterol burden and macrophage-driven inflammation (33, 35). HDL also inhibits the type I interferon response pathway independently of macrophage cholesterol stores (36) and activates the complement cascade (37, 38). Furthermore, HDL-C not only inhibits LDL-induced lipid hydro-peroxide formation, monocyte adherence, and monocyte chemotactic activity but also quenches the fluorescent signal of oxidized phospholipids in cell-based and cell-free studies (39).

In addition to hypertension, other major causes of ICH include anticoagulants, bleeding disorders, cerebral amyloid angiopathy (CAA), ruptured arterial aneurysms, arteriovenous malformations and other vascular anomalies (40). Hypertensive degenerative changes in small cerebral arteries coexist with CAA in the patients with ICH (41). A sudden elevation of BP can result in ruptured micro-aneurysm in such patients, resulting in a greatly enhanced risk of ICH. High HDL-C levels might reduce the risk of ICH by decreasing CAA, given that two-fold increases in plasma HDL-C levels attenuated CAA by approximately 50% in mice (42).

**Strengths and Limitations of the Current Study**

The collection of BP and HDL-C data at a median time of 2 years after the onset of ICH can be

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**Table 3**

<table>
<thead>
<tr>
<th>BP Range</th>
<th>Mortality Risk</th>
</tr>
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<tbody>
<tr>
<td>130≤SBP&lt;140 mm Hg or 85≤DBP&lt;90 mm Hg</td>
<td>Non-significantly higher</td>
</tr>
<tr>
<td>SBP&lt;120 and DBP&lt;80 mm Hg</td>
<td>Optimal</td>
</tr>
</tbody>
</table>

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**References**

6. Other study (year).
11. Another study (year).
33. Latest cell culture study (year).
34. Follow-up study (year).
35. Atheromatous vessels study (year).
36. Type I interferon response study (year).
37. Complement cascade study (year).
38. LDL-induced lipid hydro-peroxide study (year).
39. Oxidized phospholipids study (year).
40. Major causes of ICH (year).
41. CAA with small cerebral arteries study (year).
42. Plasma HDL-C levels study (year).
considered as a drawback of the present study. Because this is a cross sectional study, the low levels of plasma HDL-C identified in patients with ICH may have been either the cause or the result of ICH. The causal relationship between plasma HDL-C and ICH cannot be established in this kind of study design, but can only be drawn in prospective studies with large number of samples free of ICH at baseline.

Second, survivor bias is a limitation of the present study, and the results must be interpreted with caution. The hypothesis may be advanced that the patients with ICH who survived to participate in the study had lower plasma HDL-C levels than did dead patients who died from the disorder and were consequently excluded from the study. However, the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study showed that low baseline HDL-C was the strongest predictor of recurrent stroke, including fatal stroke, in patients without a prior history of CHD disease (43) attenuating the hypothesis. Survivor bias can be reduced through the use of time-dependent covariate analyses in the follow-up studies.

The strength of present study is that it was performed in a large community-based sample of participants who did not employ many interventions to alter lipids profiles and/or blood pressure. These interventions would likely have impact on the nature of relationship between HDL-C levles and ICH risk.

In conclusion, this study showed that HDL-C levels were inversely associated with a history of prior ICH. Hence, low plasma levels of HDL-C (<1.38mmol/L) may be associated with the development of ICH especially in men and in lean participants.
Acknowledgement

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References


Figure Legends

**Figure 1.** Flow chart of subject enrollment and exclusion

**Figure 2.** Multivariable adjusted odds ratios of intracerebral hemorrhage (ICH) at different HDL-C categories, stratified by gender, hypertension status and BMI

Solid square points indicate multivariable ORs of ICH in Tertile-2 and in Tertile-3 as compared with that in Tertile-1 (reference), and bars indicate 95% CIs. Median HDL-C values of different group were indicated in horizontal axis. (A) The OR of ICH significantly decreased as median plasma HDL-C increased in men. (B) The linear trend of association between HDL-C and ICH remained non-significant in women. (C) The inverse trend of association between ICH and HDL-C in hypertensive participants was significant. (D) The inverse trend of association between ICH and HDL-C in non-hypertensive participants was also significant. (E) No linear association was found between ICH and HDL-C in participants with BMI ≥25 kg/m² (P=0.04 for departure from linear trend). (F) The inverse trend of association in participants with BMI<25 kg/m² was significant.

Multivariable OR was adjusted by gender, age, SBP, BMI, hypercholesterolemia, current smoking, current drinking and family history of stroke, excluding the stratifying factor.

P<0.05 for departure indicates non-linearity across three groups. The $x^2$ statistics was obtained by subtracting the trend chi-square from the overall chi-square with one (k-2) degree of freedom.
### Tables

#### Table 1. Baseline characteristics according to HDL cholesterol tertiles

<table>
<thead>
<tr>
<th>Variables</th>
<th>HDL Cholesterol</th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile-3</td>
<td>Tertile-2</td>
<td>Tertile-1</td>
<td>P&lt;sup&gt;a&lt;/sup&gt; value</td>
<td>P&lt;sup&gt;b&lt;/sup&gt; value</td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>2008</td>
<td>1996</td>
<td>2042</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Men, %&lt;sup&gt;(n)&lt;/sup&gt;</td>
<td>32.9 (660)</td>
<td>34.9 (696)</td>
<td>40.3 (823)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.18</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>Mean(SD)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>58.0 (9.1)</td>
<td>56.9 (9.8)</td>
<td>56.2 (10.0)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>24.8 (3.6)</td>
<td>25.9 (3.6)</td>
<td>26.7 (3.5)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>157.4 (28.1)</td>
<td>154.6 (28.6)</td>
<td>153.6 (29.5)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>DBP, mm Hg</td>
<td>94.5 (13.8)</td>
<td>93.9 (14.2)</td>
<td>93.5 (14.4)</td>
<td>0.51</td>
<td>0.06</td>
<td></td>
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<tr>
<td>TC, mmol/L</td>
<td>5.82 (1.11)</td>
<td>5.42 (1.04)</td>
<td>4.98 (1.06)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>LDL-C, mmol/L</td>
<td>3.11 (0.94)</td>
<td>3.11 (0.85)</td>
<td>2.85 (0.82)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.00</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.93 (0.25)</td>
<td>1.52 (0.08)</td>
<td>1.21 (0.13)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>TG, mmol/L</td>
<td>1.63 (1.33)</td>
<td>1.52 (0.92)</td>
<td>2.10 (1.90)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>FBG, mmol/L</td>
<td>5.39 (1.71)</td>
<td>5.39 (1.73)</td>
<td>5.46 (1.82)</td>
<td>0.06</td>
<td>0.06</td>
<td></td>
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<tr>
<td>%&lt;sup&gt;(n)&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Hypertension</td>
<td>59.3 (1191)</td>
<td>59.2 (1181)</td>
<td>58.5 (1194)</td>
<td>0.92</td>
<td>0.59</td>
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<td>Antihypertensive treatment</td>
<td>30.3 (608)</td>
<td>33.1 (660)</td>
<td>33.7 (688)</td>
<td>0.06</td>
<td>0.02</td>
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<tr>
<td>Diabetes</td>
<td>2.0 (20)</td>
<td>3.4 (68)</td>
<td>4.7 (96)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>Tertile-1</td>
<td>Tertile-2</td>
<td>Tertile-3</td>
<td>P&lt;sub&gt;a&lt;/sub&gt;</td>
<td>P&lt;sub&gt;b&lt;/sub&gt;</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>9.5 (191)</td>
<td>12.6 (252)</td>
<td>16.4 (334)**</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>7.1 (143)</td>
<td>8.0 (160)</td>
<td>10.6 (216)**</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>15.2 (305)</td>
<td>14.6 (292)</td>
<td>15.8 (322)</td>
<td>0.62</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>10.2 (204)</td>
<td>10.2 (203)</td>
<td>14.7 (300)**</td>
<td>0.69</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Current drinker</td>
<td>14.9 (300)</td>
<td>13.8 (276)</td>
<td>15.7 (321)**</td>
<td>0.38</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

P<sup>a</sup> value compared Tertile-2 with Tertile-3; P<sup>b</sup> values compared Tertile-1 with Tertile-3.

*indicates P<0.05, **P<0.01 for the comparison of Tertile-1 with Tertile-2.

Comparisons were performed between different groups of continuous variables using AVONA analysis; category characteristics were compared using the Mantel-Haenszel chi-square test. TG levels were determined using the log-transformed value.

To covert mmol/L (values) for TG to mg/dL, values were multiplied by 88.54; To convert mmol/L (values) for cholesterol to mg/dL, values were multiplied by 38.67.

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose.
Table 2. ORs (95% CI) of ICH according to plasma lipid tertiles

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tertiles of plasma lipid</th>
<th>P&lt;sup&gt;a&lt;/sup&gt; value</th>
<th>P&lt;sup&gt;b&lt;/sup&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile-3</td>
<td>Tertile-2</td>
<td>Tertile-1</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>≥3.20</td>
<td>2.61–3.19</td>
<td>&lt;2.61</td>
</tr>
<tr>
<td>ICH (n)</td>
<td>69</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>0.78(0.5–1.11)</td>
<td>0.66(0.45–0.96)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.0</td>
<td>0.77(0.53–1.11)</td>
<td>0.62(0.42–0.92)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>0.83(0.57–1.22)</td>
<td>0.72(0.48–1.10)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>≥1.65</td>
<td>1.38–1.64</td>
<td>&lt;1.38</td>
</tr>
<tr>
<td>ICH (n)</td>
<td>40</td>
<td>49</td>
<td>81</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>1.24(0.81–1.89)</td>
<td>2.03(1.38–2.98)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.0</td>
<td>1.21(0.79–1.85)</td>
<td>1.88(1.27–2.78)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>1.13(0.72–1.78)</td>
<td>2.06(1.35–3.12)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>≥5.77</td>
<td>4.87–5.76</td>
<td>&lt;4.87</td>
</tr>
<tr>
<td>ICH (n)</td>
<td>57</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>1.06(0.73–1.53)</td>
<td>0.95(0.65–1.38)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.0</td>
<td>1.07(0.73–1.55)</td>
<td>0.88(0.60–1.31)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>1.14(0.77–1.70)</td>
<td>1.11(0.73–1.67)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>≥1.24</td>
<td>1.03–1.23</td>
<td>&lt;1.03</td>
</tr>
<tr>
<td>ICH (n)</td>
<td>63</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>0.92(0.64–1.33)</td>
<td>0.79(0.54–1.16)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.85(0.58–1.23)</td>
<td>0.87(0.58–1.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.75(0.51–1.10)</td>
<td>0.86(0.55–1.33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

$P^a$ values were calculated using the multivariable logistic regression model and compared Tertile-2 with Tertile-3; $P^b$ values were compared Tertile-1 with Tertile-3 (In each case, Tertile-3 was the reference group).

Model 1 was used to adjust for age and gender.

Model 2 was used to adjust for age, gender, and other vascular risk factors including SBP, BMI, hypercholesterolemia, current smoking, current drinking, and family history of stroke.

Abbreviations are the same as for Table 1.
<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (increment per year)</td>
<td>1.00</td>
<td>0.99–1.02</td>
<td>0.66</td>
</tr>
<tr>
<td>Female (0, 1)</td>
<td>0.50</td>
<td>0.33–0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.93</td>
<td>0.88–0.97</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (increment per 10 mmHg)</td>
<td>1.21</td>
<td>1.15–1.29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C (increment per 1 mmol/L)</td>
<td>0.47</td>
<td>0.28–0.78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia (0, 1)</td>
<td>1.85</td>
<td>1.24–2.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoking, (0, 1)</td>
<td>1.02</td>
<td>0.63–1.64</td>
<td>0.95</td>
</tr>
<tr>
<td>Current drinking (0, 1)</td>
<td>1.29</td>
<td>0.81–2.04</td>
<td>0.28</td>
</tr>
<tr>
<td>Family history of stroke (0, 1)</td>
<td>1.06</td>
<td>0.69–1.61</td>
<td>0.80</td>
</tr>
</tbody>
</table>

OR indicates odds ratios; 95% CI, 95% confidence interval; 0, no; 1, yes.

Abbreviationa are the same as for Table 1.
At the beginning, 7177 subjects were enrolled

- 3 with subarachnoid hemorrhage
- 210 subjects reluctant to lipid analysis

6964 subjects among which 188 with intracerebral hemorrhage

- 528 with coronary heart disease including 16 with ICH
- 331 with ischemic stroke including 2 with ICH
- 59 with unclassified stroke

Finally, 6046 subjects including 170 with intracerebral hemorrhage
2F  BMI<25

P=0.63 for departure
P=0.01 for trend
n=2745

<table>
<thead>
<tr>
<th>Median HDL-C (mmol/L)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>383</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td>524</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td>693</td>
<td>466</td>
</tr>
</tbody>
</table>