Cholesterol Levels and Risk of Hemorrhagic Stroke
A Systematic Review and Meta-Analysis

Xiang Wang, MD*; Yan Dong, MD*; Xiangqian Qi, MD*; Chengguang Huang, MD; Lijun Hou, MD

Background and Purpose—Cholesterol levels are inconsistently associated with the risk of hemorrhagic stroke. The purpose of this study is to assess their relationships using a meta-analytic approach.

Methods—We searched PubMed and Embase for pertinent articles published in English. Only prospective studies that reported effect estimates with 95% confidential intervals (CIs) of hemorrhagic stroke for 3 categories of cholesterol levels, for high and low comparison, or for per 1 mmol/L increment of cholesterol concentrations were included. We used the random-effects model to pool the study-specific results.

Results—Twenty-three prospective studies were included, totaling 1430141 participants with 7960 (5.6%) hemorrhagic strokes. In high versus low analysis, the summary relative risk of hemorrhagic stroke was 0.69 (95% CI, 0.59–0.81) for total cholesterol, 0.98 (95% CI, 0.80–1.19) for high-density lipoprotein cholesterol, and 0.62 (95% CI, 0.41–0.92) for low-density lipoprotein cholesterol. In dose–response analysis, the summary relative risk of hemorrhagic stroke for 1 mmol/L increment of total cholesterol was 0.85 (95% CI, 0.80–0.91), for high-density lipoprotein cholesterol was 1.11 (95% CI, 0.99–1.25), and for low-density lipoprotein cholesterol was 0.90 (95% CI, 0.77–1.05). The pooled relative risk for intracerebral hemorrhage was 1.17 (95% CI, 1.02–1.35) for high-density lipoprotein cholesterol.

Conclusions—Total cholesterol level is inversely associated with risk of hemorrhagic stroke. Higher level of low-density lipoprotein cholesterol seems to be associated with lower risk of hemorrhagic stroke. High-density lipoprotein cholesterol level seems to be positively associated with risk of intracerebral hemorrhage. (Stroke. 2013;44:1833-1839.)

Key Words: hemorrhagic stroke ■ high-density lipoprotein cholesterol ■ intracerebral hemorrhage ■ low-density lipoprotein cholesterol ■ meta-analysis ■ subarachnoid hemorrhage ■ total cholesterol

Hypercholesterolemia has been well documented as a modifiable risk factor for ischemic stroke.1 Currently, lipid-lowering therapy with statins is widely used for patients with ischemic stroke.2 However, concerns have been raised about the accompanied risk of hemorrhagic stroke, mainly including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), which may be attributed to decreasing serum cholesterol concentrations.3,4

In the early Japanese studies, the inverse relationship between serum cholesterol level and increased risk of hemorrhagic stroke was first revealed.5 Later, in the Multiple Risk Factor Intervention Trial, the risk of fatal ICH was found to be 3x higher in those with total serum cholesterol (TC) <4.13 mmol/L than in those with values higher than that.6 In the collaborative analysis of 12 Asian cohorts, a 27% increase in risk of hemorrhagic stroke was shown for a 0.6 mmol/L decrease in cholesterol concentrations.7 However, conclusions were not consistent between studies. In the Korea Medical Insurance Corporation Study, low TC was not shown to be an independent risk factor for hemorrhagic stroke.8 In the post hoc analysis of Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, although hemorrhagic stroke was more frequent in individuals treated with atorvastatin, its relations with concentrations of TC or low-density lipoprotein cholesterol (LDL-C) were not detected.9

Recent meta-analyses suggested no evidence that statins were associated with ICH.10 However, stratified cholesterol levels were not explored. Hence, we undertook this meta-analysis, aiming to investigate the relationships between different categories of cholesterol and risk of hemorrhagic stroke.

Methods

Search Strategy
Two investigators (X.W. and Y.D.) independently searched PubMed and Embase for prospective studies examining the association between cholesterol and the risk of hemorrhagic stroke. Three main categories of cholesterol, including TC, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol were included. We used the random-effects model to pool the study-specific results.
cholesterol (HDL-C), and LDL-C, were investigated, respectively. Hemorrhagic stroke mainly included ICH and SAH. The search was limited to studies published between 1980 and January 2013. The language was restricted to English. The detailed search strategy is given in Methods in the online-only Data Supplement.

Selection Criteria
To be included, studies had to have a prospective design (prospective cohort, or nested prospective case-control study), and investigate the association between cholesterol (TC, HDL-C, or LDL-C) and the risk of hemorrhagic stroke (ICH, SAH, or both). The authors should report effect estimates (risk ratio [RR], hazard ratio, or odds ratio) and 95% confidential intervals (CIs) for >3 categories of cholesterol concentrations, for the comparison between low and high concentrations, or for per 1 mmol/L increment. The detailed search strategy is provided in Methods in the online-only Data Supplement.

Data Extraction and Quality Assessment
Three authors (X.W., Y.D., and X.Q.Q.) extracted the data in standardized data-collection forms, and 2 authors (X.W. and Y.D.) assessed the study quality. Three degrees for adjustment of confounders were defined. The Newcastle–Ottawa Scale was used to evaluate the methodological quality. Details are described in Methods in the online-only Data Supplement.

Statistical Analysis
The RR and 95% CIs were considered as the effect sizes. We first used the random-effects model to calculate summary RRs and 95% CIs for the high versus low levels of cholesterol. Then dose–response analyses were conducted to estimate the RRs and 95% CIs for per 1 mmol/L increment of cholesterol concentration. Heterogeneity was mainly assessed by the $I^2$ statistic. We considered low, moderate, and high $I^2$ values to be 25%, 50%, and 75%, respectively. Subgroup analyses and sensitivity analyses were also performed. A potential nonlinear relationship between cholesterol level and hemorrhagic risk was explored. Inter-rater reliabilities were calculated by Cohen $\kappa$ statistics, with 5 levels of agreement, namely poor ($\kappa=0.00–0.20$), fair ($\kappa=0.21–0.40$), moderate ($\kappa=0.41–0.60$), good ($\kappa=0.61–0.80$), and very good ($\kappa=0.81–1.00$). The Egger test was used to assess publication bias. All statistical analyses were performed with the STATA software (version 12.0; Stata Corporation, College Station, TX). A threshold of $P<0.1$ was used to decide whether heterogeneity or publication bias was present. In other ways, $P$ values were 2 sided, with a significance level of 0.05. Detailed data are provided in Methods in the online-only Data Supplement.

Results

Literature Search
The results of study-selection process were shown in Figure 1. The initial search produced 453 studies from PubMed and 665 articles from Embase. After exclusion of duplicates and irrelevant studies, 97 potentially eligible studies were selected. After detailed evaluations, 23 studies were selected for final meta-analysis. A manual search of reference lists of these studies did not yield any new eligible study. Agreement on selection of studies between 2 assessors was very good ($\kappa=0.87$).

Study Characteristics
Twenty-three were included consisting of 19 prospective cohort studies, and 4 nested case-control studies involving 1430141 participants with 7960 (5.6%) hemorrhagic stroke events (Table I in the online-only Data Supplement). Four studies were conducted in American populations, 9 European populations, and 10 in Asian populations. Rodriguez et al separately investigated 2 cohorts, and the Honolulu Program had been reported earlier. However, different aspects of the analysis raised concerns (Table II in the online-only Data Supplement). Seven cohorts only enrolled male participants, and another only enrolled steel-workers. Most studies had a follow-up duration of more than 10 years, and had a high degree of covariate adjustment, with 14 studies of “++”, 8 of “++”, and 5 of “++”.

Total Serum Cholesterol

High Versus Low
Seventeen studies compared the highest level with the lowest level (or referent) categories of cholesterol. Two studies compared the bottom level with a composite higher level. Results of ICH and SAH were separately reported in 5 studies and those of different sexes were separately assessed in 6 studies. Only 1 study investigated the difference between 2 age groups. These separate results were initially pooled in each study using a fixed-effects model, which were further aggregated into the overall analysis, using a random-effects model. The summary RR was 0.69 (95% CI, 0.59–0.81; $P<0.01$; Figure 2A), with evidence of moderate heterogeneity ($I^2=57.6%$; $P<0.01$). Publication bias was detected by the Egger test ($P=0.03$).

Dose–Response Analysis
Seventeen studies reported RRs for categorized cholesterol levels, or for per 1 mmol/L increase, including 14 prospective cohort studies, and 3 nested case-control studies. Four studies reported both RRs for categorical levels and RRs for per 1 mmol/L increase, and 1 study only reported RRs of per 1 mmol/L increase for 2 large cohorts. Thus, we included 17 articles with 18 data for dose–response analysis. The number of participants in each category was not reported in 4 studies, and thus was calculated by estimation. Four studies were conducted in American populations, and 9 in European populations. Results stratified by it were separately analyzed. Studies comparing high with low levels, and studies assessing dose–response associations were assessed by Newcastle–Ottawa Scale (Tables III and IV in the online-only Data Supplement). Most items had full agreement, except for 2 items. For “representativeness of the exposed cohort,” the agreement was 96% with a $\kappa$ value of 0.65. For “comparability,” the agreement was 92% with a $\kappa$ value of 0.75. Both items had good agreement.
were explored, respectively. Overall, the inverse relationships between cholesterol levels and risk of hemorrhagic stroke were similarly significant in subgroups that were defined by sex, sample size, and follow-up duration. However, in subgroups of case-control design, SAH, “+” degree of adjustment, and end point of hemorrhagic stroke mortality, the inverse relationships were not statistically significant (Table V in the online-only Data Supplement). Besides, in the dose—response subgroup of European population, the inverse association was not statistically significant.

Table A

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yane 1989</td>
<td>0.47 (0.32, 0.76)</td>
<td>6.69</td>
</tr>
<tr>
<td>Knekt 1991</td>
<td>0.94 (0.66, 1.34)</td>
<td>7.23</td>
</tr>
<tr>
<td>Gatchev 1993</td>
<td>0.78 (0.60, 1.01)</td>
<td>8.69</td>
</tr>
<tr>
<td>Ichihara 1996</td>
<td>0.54 (0.44, 0.64)</td>
<td>6.86</td>
</tr>
<tr>
<td>Leppala 1999</td>
<td>0.39 (0.24, 0.65)</td>
<td>5.33</td>
</tr>
<tr>
<td>Okumura 1999</td>
<td>0.78 (0.65, 0.95)</td>
<td>9.77</td>
</tr>
<tr>
<td>Hart 2000</td>
<td>0.22 (0.08, 0.57)</td>
<td>2.10</td>
</tr>
<tr>
<td>Suh 2001</td>
<td>0.79 (0.59, 1.06)</td>
<td>8.17</td>
</tr>
<tr>
<td>Engstroem 2002</td>
<td>0.16 (0.09, 0.27)</td>
<td>0.89</td>
</tr>
<tr>
<td>Bots 2002</td>
<td>0.29 (0.20, 0.40)</td>
<td>1.59</td>
</tr>
<tr>
<td>Zhang 2004</td>
<td>0.50 (0.26, 1.13)</td>
<td>2.22</td>
</tr>
<tr>
<td>Jood 2004</td>
<td>1.10 (0.57, 2.13)</td>
<td>3.81</td>
</tr>
<tr>
<td>Tirschwell 2004</td>
<td>0.80 (0.60, 1.08)</td>
<td>8.01</td>
</tr>
<tr>
<td>Ebrhami 2006</td>
<td>0.80 (0.56, 1.26)</td>
<td>5.76</td>
</tr>
<tr>
<td>Cui 2007</td>
<td>0.25 (0.06, 1.01)</td>
<td>1.13</td>
</tr>
<tr>
<td>Sturgeon 2007</td>
<td>0.67 (0.41, 1.16)</td>
<td>3.39</td>
</tr>
<tr>
<td>Noda 2009</td>
<td>0.55 (0.33, 0.91)</td>
<td>5.23</td>
</tr>
<tr>
<td>Nagai 2011</td>
<td>2.00 (0.80, 5.01)</td>
<td>2.35</td>
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<tr>
<td>Zhang 2012</td>
<td>1.00 (0.77, 1.29)</td>
<td>8.72</td>
</tr>
<tr>
<td>Overall</td>
<td>0.69 (0.59, 0.81)</td>
<td>100.00</td>
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Table B

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knekt 1991</td>
<td>0.97 (0.81, 1.16)</td>
<td>5.63</td>
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<tr>
<td>Leppala 1999</td>
<td>0.72 (0.62, 0.83)</td>
<td>6.45</td>
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<td>Okumura 1999</td>
<td>0.88 (0.81, 0.96)</td>
<td>7.93</td>
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<tr>
<td>Hart 2000</td>
<td>0.75 (0.55, 1.01)</td>
<td>3.32</td>
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<tr>
<td>Suh 2001</td>
<td>0.92 (0.80, 1.06)</td>
<td>6.58</td>
</tr>
<tr>
<td>Engstrom 2002</td>
<td>0.97 (0.80, 1.20)</td>
<td>5.11</td>
</tr>
<tr>
<td>Bots 2002</td>
<td>0.76 (0.60, 0.90)</td>
<td>5.11</td>
</tr>
<tr>
<td>Jood 2004</td>
<td>1.00 (0.60, 1.60)</td>
<td>1.65</td>
</tr>
<tr>
<td>Sturgeon 2007</td>
<td>0.80 (0.61, 1.05)</td>
<td>3.89</td>
</tr>
<tr>
<td>Cui 2007</td>
<td>0.97 (0.80, 1.16)</td>
<td>6.45</td>
</tr>
<tr>
<td>Nagai 2011</td>
<td>0.88 (0.66, 1.14)</td>
<td>4.02</td>
</tr>
<tr>
<td>Zhang 2012</td>
<td>1.03 (0.80, 1.38)</td>
<td>8.46</td>
</tr>
<tr>
<td>Overall</td>
<td>0.85 (0.66, 0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 1. The flow diagram for identifying eligible studies. CI indicates confidence interval.

Figure 2. Forest plots of total cholesterol levels and risk of hemorrhagic stroke. A, High vs low analysis. B, Per 1 mmol/L increment. CI indicates confidence interval; and RR, risk ratio.

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High-Density Lipoprotein Cholesterol

**High Versus Low**

Eight studies were available, including 5 prospective cohort studies,\(^2\)\(^1\),\(^2\)\(^9\),\(^3\)\(^1\),\(^3\)\(^3\),\(^3\)\(^4\) and 3 nested case-control studies.\(^3\)\(^5\),\(^3\)\(^6\),\(^3\)\(^8\)

Three studies reported separate results for different types of hemorrhagic stroke, or different sexes,\(^2\)\(^,\)\(^3\)\(^4\),\(^3\)\(^5\) which were aggregated together using a fixed-effects model for each study. Overall, the summary RR was 0.98 (95% CI, 0.80–1.19; \(P=0.81\); Figure 4A), with little evidence of heterogeneity (\(I^2=10.3%; P=0.35\)). Although the number of included studies was small, publication bias was not revealed by the Egger test (\(P=0.82\)).

**Dose–Response Analysis**

Five prospective cohort studies,\(^2\)\(^1\),\(^2\)\(^9\),\(^3\)\(^1\),\(^3\)\(^3\) and 3 nested case-control studies were included. Three studies reported separate results for different types of stroke or different sexes,\(^2\)\(^,\)\(^3\)\(^4\),\(^3\)\(^5\) which were aggregated using fixed-effect model for each study. The summary RR was 1.05 (95% CI, 0.88–1.24; \(P=0.60\); Figure 4B), with low evidence of heterogeneity (\(I^2=35.1%; P=0.15\)). No potentially nonlinear dose–response relationship was detected (\(P=0.11\); Figure 5A).

**Sensitivity and Subgroup Analyses**

In sensitivity analyses, no significantly altered result was shown when excluding studies 1 by 1. The stratified analyses were defined by study design, sex, stroke type, sample size, study population, degree of adjustment, and follow-up duration. Studies comparing high with low levels, and studies assessing dose–response associations were explored, respectively. In high versus low comparisons, the estimate was not significant in any subgroup. In dose–response analysis, positive relationships between HDL-C levels and risk of hemorrhagic stroke were significant in both subgroups of ICH and SAH. A marginal significance was indicated by pooling 2 studies of American population (Table VI in the online-only Data Supplement).

Low-Density Lipoprotein Cholesterol

**High Versus Low**

Four prospective cohort studies were included\(^2\)\(^9\)–\(^3\)\(^1\),\(^3\)\(^3\)\(^1\),\(^3\)\(^3\) The summary RR was 0.62 (95% CI, 0.41–0.92; \(P=0.02\); Figure 4C), with some low evidence of heterogeneity (\(I^2=43.3%; P=0.35\)). In sensitivity analysis, when excluding the study by Imamura et al,\(^2\)\(^9\) the result was more robust (RR=0.52; 95% CI, 0.37–0.72; \(P<0.01\)), with low level of heterogeneity (\(I^2=11.1%; P=0.33\)). Although the number of included studies was small, publication bias was not detected by the Egger test (\(P=0.09\)).

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Figure 3. Relative risk (solid line) with 95% CI (long dashed lines) for the association of total cholesterol level with risk of hemorrhagic stroke in a restricted cubic spline random-effects model.

Figure 4. Forest plots of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels and risk of hemorrhagic stroke. **A**, High vs low analysis of HDL-C. **B**, Per 1 mmol/L increment for HDL-C. **C**, High vs low analysis of LDL-C. **D**, Per 1 mmol/L increment for LDL-C. CI indicates confidence interval; and RR, risk ratio.
Dose–Response Analysis

Four prospective cohort studies were identified. The summary RR was 0.90 (95% CI, 0.77–1.05; P=0.18; Figure 4D), with moderate heterogeneity (I²=67%; P=0.03). In sensitivity analysis, when excluding the study by Noda et al., the summary RR was 0.93 of marginal significance (95% CI, 0.86–0.996; P=0.04) without evidence of heterogeneity (I²=0; P>0.01). We did not detect a potentially nonlinear dose–response relationship (P=0.77; Figure 5B). Too few studies precluded any meaningful subgroup analysis.

Discussion

Our findings showed a statistically significant inverse association between TC level and risk of hemorrhagic stroke. An increment of 1 mmol/L in TC concentration was associated with a 15% decreased risk of hemorrhagic stroke. Lower LDL-C concentration was also associated with a higher risk of hemorrhagic stroke. However, no significant association between HDL-C and risk of hemorrhagic stroke was indicated.

In subgroup analyses of TC, the inverse relationship seemed specifically robust for ICH but not for SAH, probably because of their different pathological mechanisms. Statistically significant results were shown for prospective cohorts, but not for nested case-control studies. The smaller number and less strict design of case-control studies likely contributed to this discrepancy. Results for studies with adjustment degree of “+” were not significant. Seemingly, the interaction between multiple unadjusted confounders and TC led to weak conclusions. No significant association between TC and fatal hemorrhagic stroke was detected either. For HDL-C, the risk of ICH significantly increased per 1 mmol/L increment. Although significant inverse relation with risk of SAH was indicated, its strength was limited by too few studies. In dose–response analysis of LDL-C, statistically significant inverse association with hemorrhagic stroke was detected by excluding 1 study.

Low cholesterol may play a role in promoting arterial medial layer smooth muscle cell necrosis. The impaired endothelium would be more susceptible to microaneurysms, which were the chief pathological finding of ICH, thereby contributing to the onset of hemorrhage. Another mechanism was speculated especially for the association between cholesterol levels and mortality of hemorrhagic stroke. Cholesterol levels may reflect the nutritional status of patients with ICH. Low cholesterol level may be a surrogate for nutritional deficiencies, a harbinger of low-serum albumin, or a sign of debilitating diseases, thus being predisposed to increased stroke mortality.

Recent meta-analyses showed no evidence that statin therapy was associated with increased ICH. However, other than reducing cholesterol levels, statins may also decrease platelet aggregation and hence thrombogenesis, which might increase the risk of bleeding and thus obscure the results. Additionally, the follow-up durations in statin trials were usually no longer than 5 years. Longer exposure to low cholesterol levels might be necessary to alter the integrity of cerebral vessels. Although another large meta-analysis has shown that hemorrhagic stroke mortality was likely related to lower TC levels in a few stroke subgroups, it was limited by including considerable studies published before the 1980s, and thus failed in verifying the stroke type by reliable imaging method.

In comparison, our study had strengths in conducting longer follow-up, including newer studies with reliable imaging examinations, and performing quantitative analyses. Additionally, most included studies have large sample sizes involving different general populations throughout the world. On the whole, sufficient adjustment of potential risk factors for hemorrhagic stroke was performed, and the methodological qualities were satisfying. As we included mainly prospective studies, the likelihood of selection bias and recall bias in retrospective studies was greatly reduced.

However, we were aware of several potential limitations. First, studies with significant results may be more likely to be published, and are preferentially published in English journals. We included only studies written in English and hence, may have missed relevant articles in non-English journals. Notably, publication bias was detected in studies of TC, which might overestimate the inverse relationship, as harmful association was more likely to be published. Second, hemorrhagic stroke is a mixed term, including ICH, SAH, subdural or epidural hemorrhages, or hemorrhagic transformation after ischemic stroke. Several studies only reported this composite outcome and precluded the distinction between hemorrhage subtypes. In fact, TC studies showed a more convincing result for ICH than...
SAH. Third, although adjusted estimates were reported in general, the observational design had its inherent weakness that any association may be because of the presence of inadequately measured or unmeasured residual confounding variables. For instance, the prescription of statins was not described largely, and the socioeconomic status was rarely investigated. Another major concern was that our results might be confounded by comorbidity at baseline. Because patients who died from other diseases at earlier ages could not contribute to a later risk of ICH, a survival bias possibly existed. No study excluded the first 5 or 10 years of follow-up, and still showed an association for hemorrhagic stroke. This bias may explain the protection conferred by high TC against hemorrhagic stroke, by progressively decreasing the proportion of patients with atherothrombotic disease and subsequently increasing the proportion of other cerebral vessel diseases or conditions in the elderly, which cause hemorrhagic stroke with unknown relations with cholesterols. Also, other emerging imaging confounders, including signs of leukoaraiosis, cerebral microbleeds, and multilacunes, were seldom mentioned. Furthermore, the number of studies was limited for HDL-C and LDL-C, and thus might be insufficient for drawing definite conclusions. Last, several studies only had the baseline data on cholesterols and no data on possible changes in serum levels during follow-up.

Despite these limitations, this study has notable clinical and public health implications. Our findings should never be interpreted against the well-established statin regimen, in which the potential hazards are far outweighed by the definite absolute benefits for preventing occlusive vascular disease. Nevertheless, we highlighted that low TC and LDL-C levels seemed to be risk factors of hemorrhagic stroke, especially ICH. Our results remind clinicians to take this caution during intensive lipid-lowering therapy. Further studies are needed to investigate the underlying pathogenesis better, and identify subjects who would benefit most from lowering cholesterol without risk of hemorrhagic stroke.

Disclosures

None.

References

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SUPPLEMENTAL MATERIAL

Cholesterol Levels and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-Analysis

Xiang Wang, MD; Yan Dong, MD; Xiangqian Qi, MD; Chengguang Huang, MD; Lijun Hou, MD
Supplemental Methods

Search Strategy
Our meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.\(^1\) Two investigators (X.W. and Y.D.) independently searched Pubmed and Embase for prospective studies examining the association between cholesterol and the risk of hemorrhagic stroke. Three main categories of cholesterol, including total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein (LDL-C), were investigated, respectively. Hemorrhagic stroke mainly included ICH and SAH. The search was limited to studies published between 1980 and January 2013. The language was restricted to English. The search terms were (“cerebral hemorrhage”[Mesh] OR “subarachnoid hemorrhage”[Mesh] OR “hemorrhagic stroke”[Title/Abstract]) AND (“cholesterol”[Mesh] OR “hypercholesterolemia”[Mesh] OR “dyslipidemia”[Mesh]) for Pubmed, and (“cerebral hemorrhage”[exp OR cerebral hemorrhage OR ‘subarachnoid hemorrhage’[exp OR subarachnoid hemorrhage OR ‘hemorrhagic stroke’[exp OR hemorrhagic stroke]) AND (“cholesterol”[exp OR cholesterol OR ‘dyslipidemia’[exp OR dyslipidemia OR ‘hypercholesterolemia’[exp OR hypercholesterolemia) for Embase. We further conducted the manual search of references of selected studies.

Selection Criteria
To be included studies had to have a prospective design (prospective cohort, or nested prospective case-control study), and investigate the association between cholesterol (TC, HDL-C, or LDL-C) and the risk of hemorrhagic stroke (ICH, SAH, or both). The authors should report effect estimates (risk ratio [RR], hazard ratio [HR], or odds ratio [OR]) and 95% confidential intervals (CIs) for more than 3 categories of cholesterol concentration, for the comparison between low and high concentration, or for per 1mmol/L increase in concentration. We excluded cross-sectional studies and retrospective studies, and studies with participants of pre-existing stroke (hemorrhagic or ischemic). Studies with pediatric or pregnant participants, and those of only irrelevant exposures (e.g. triglyceride) and diseases (e.g. ischemic stroke) were also excluded. For study populations that were reported more than once, duplicated results were combined, whereas data of different statistical methods were separately extracted. For instance, when the high versus low analysis and dose-response analysis were conducted in two papers with the same cohort, their results were pooled into different aspects of our meta-analysis.

Data Extraction and Quality Assessment
Three reviewers (X.W., Y.D., and X.Q.Q.) extracted the data in standardized data-collection forms, and two authors and two authors (X.W. and Y.D.) assessed the study quality. The following data were abstracted: author; publication year; study design; population (categorized as American, Asian [including Japanese populations in Hawaii], and European); sample size; participants’ characteristics (age and sex); exposure; type of hemorrhagic stroke (ICH, SAH, or both); follow-up duration; covariates in fully adjusted model; degree of adjustment for confounders (categorized as “+” for age and/or sex only; “++” for these further adjusted for fewer than five standard vascular risk factors (i.e., blood pressure, smoking status, alcohol consumption, and BMI); “+++” for these plus five or more risk factors, including unconventional factors or markers of socioeconomic status (i.e., use of statin medications, pre-existing coronary heart disease, and education); comparison categories and corresponding relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) with 95% CIs. For studies that
reported several multivariable-adjusted RRs, we used the effect estimate that was most fully adjusted. The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.  

**Statistical Analysis**

The RRs and their associated 95% CIs were considered as the effect size for all studies. HR was regarded equivalent to RR in cohort studies. Because of the low incidence of hemorrhagic stroke in general population, ORs could be assumed to be accurate estimates of RRs. Studies often used mmol/L or mg/dL in the measurement units of cholesterol. We preferred to mmol/L as it was more frequently reported. The dose conversion factor for serum concentration of cholesterol data as mg/dL to mmol/L was 0.0259. For studies that reported results for men and women separately, for ICH and SAH separately, or for different age subgroups separately, we combined the estimates using a fixed effects model to obtain an overall estimate for hemorrhagic stroke, both genders, or all age categories combined. We firstly utilized the random effects models to calculate summary RRs and 95% CIs for the high versus low levels of cholesterol. For RRs and 95% CIs that were expressed as lowest level versus highest level, they were converted to their reciprocals. In dose-response analysis, we assigned the mean or median level of cholesterol in each category to the corresponding RR. If these values were unavailable, we estimated the midpoint in each category for studies that reported the serum concentration of cholesterol by ranges. For studies with an open-ended highest or lowest cholesterol category, we assumed that the amplitudes were the same as the closest adjacent category. In population with mixed genders, when the cut-off values were separately fixed for men and women, we calculated the estimated average values. The generalized least squares (GLST) regression model was used to calculate the study-specific linear trends and 95% CI from the natural logs of the RRs and CIs across categories of cholesterol concentrations. This model requires that the distribution of cases, person years or non-cases, and the RRs with the variance estimates are known for each category of cholesterol levels. For studies that did not report the distribution of person years or cases whereas reported the total number of person years or cases, the distribution of person years or cases were estimated. For example, the total number of cases was divided by 4 when data were reported by quartiles to derive the number of cases in each fourth. Considering the heterogeneity among results from different studies, random effects models were used to pool the respective results. The dose-response results in the forest plots are presented for a 1mmol/L increment for cholesterol. To examine a potential nonlinear relationship between cholesterol level and hemorrhagic risk, the model of restricted cubic splines was utilized. In the pooled values of cholesterol concentrations, 3 knots were fixed at percentiles 10%, 50%, and 90% of the distribution. A probability value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

Statistical heterogeneity among studies was mainly assessed by the $I^2$ statistic. For the $I^2$ metric, we considered low, moderate and high $I^2$ values to be 25%, 50%, and 75%, respectively. Subgroup analyses were conducted based on the potential sources of heterogeneity inferred a priori, including study design, populations, genders, hemorrhagic types, sample sizes, follow-up duration, degrees of covariates adjustment, and endpoint outcomes. Sensitivity analysis was conducted by excluding one study at a time to explore whether the results were driven by one large study or by a study with an extreme result.

Inter-rater reliabilities on selection of studies and quality assessment were calculated by Cohen $\kappa$ statistics, with
five levels of agreement, namely poor (κ=0.00–0.20), fair (κ=0.21–0.40), moderate (κ=0.41–0.60), good (κ=0.61–0.80), and very good (κ=0.81–1.00). The Egger’s test was used to quantitatively assess publication bias. All statistical analyses were performed with the STATA software (version 12.0; Stata Corporation, College Station, Texas). A threshold of P<0.1 was used to decide whether heterogeneity or publication bias was present. In other ways, P values were two sided with a significance level of 0.05.
### Supplemental Table S1. Characteristics of prospective studies of cholesterol levels and risk of hemorrhagic stroke.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>No of participants</th>
<th>% men</th>
<th>Age (mean or range) (years)</th>
<th>Exposure</th>
<th>Endpoints (No of cases)</th>
<th>Degree of covariables adjustment</th>
<th>Duration of follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yano† 1989</td>
<td>Prospective cohort</td>
<td>Asian (Japanese-American)</td>
<td>7850</td>
<td>100</td>
<td>45-68</td>
<td>TC</td>
<td>ICH (77), SAH (39)</td>
<td>+; +++</td>
<td>18 (mean)</td>
</tr>
<tr>
<td>Knekt† 1991</td>
<td>Prospective cohort</td>
<td>European (Finnish)</td>
<td>42862</td>
<td>54</td>
<td>20-69</td>
<td>TC</td>
<td>SAH (187)</td>
<td>+</td>
<td>12</td>
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<tr>
<td>Gatchev† 1993</td>
<td>Prospective cohort</td>
<td>European (Swedish)</td>
<td>54385</td>
<td>49</td>
<td>25-74</td>
<td>TC</td>
<td>Fatal SAH (87); fatal ICH (347)</td>
<td>++</td>
<td>20.5</td>
</tr>
<tr>
<td>Iribarren† 1996</td>
<td>Prospective cohort</td>
<td>American</td>
<td>61756</td>
<td>46</td>
<td>54</td>
<td>TC</td>
<td>ICH (386)</td>
<td>+++</td>
<td>15</td>
</tr>
<tr>
<td>Leppala† 1999</td>
<td>Prospective cohort</td>
<td>European (Finnish)</td>
<td>28519</td>
<td>100</td>
<td>50-69</td>
<td>TC, HDL-C</td>
<td>ICH (112), SAH (85)</td>
<td>+++</td>
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<tr>
<td>Okumura 1999</td>
<td>Prospective cohort</td>
<td>Asian (Japanese)</td>
<td>38053</td>
<td>47</td>
<td>33-93</td>
<td>TC</td>
<td>ICH (111); SAH (19)</td>
<td>+; ++</td>
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<tr>
<td>Hart 2000</td>
<td>Prospective cohort</td>
<td>European (British)</td>
<td>15267</td>
<td>46</td>
<td>45-64</td>
<td>TC</td>
<td>HS (90)</td>
<td>+; +++</td>
<td>20</td>
</tr>
<tr>
<td>Suh 2001</td>
<td>Prospective cohort</td>
<td>Asian (Korean)</td>
<td>114793</td>
<td>100</td>
<td>35-59</td>
<td>TC</td>
<td>ICH (372), SAH (98)</td>
<td>+++</td>
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<tr>
<td>Engstrom 2002</td>
<td>Prospective cohort</td>
<td>European (Swedish)</td>
<td>6193</td>
<td>100</td>
<td>28-61</td>
<td>TC</td>
<td>ICH (29); SAH (9)</td>
<td>+</td>
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<tr>
<td>Rodriguez 2002</td>
<td>Prospective cohort</td>
<td>Asian (Japanese-American)</td>
<td>7589</td>
<td>100</td>
<td>54</td>
<td>TC</td>
<td>HS (112)</td>
<td>+; +++</td>
<td>20</td>
</tr>
<tr>
<td>Rodriguez 2002</td>
<td>Prospective cohort</td>
<td>American</td>
<td>1216</td>
<td>100</td>
<td>56</td>
<td>TC</td>
<td>HS (18)</td>
<td>+; +++</td>
<td>20</td>
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<tr>
<td>Bots 2002</td>
<td>Nested case-control</td>
<td>European (4 nations)</td>
<td>1251</td>
<td>66</td>
<td>62</td>
<td>TC; HDL-C</td>
<td>HS (346)</td>
<td>++</td>
<td>4*</td>
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<tr>
<td>Joo 2004</td>
<td>Prospective cohort</td>
<td>European (Swedish)</td>
<td>7402</td>
<td>100</td>
<td>47-55</td>
<td>TC</td>
<td>HS (144)</td>
<td>+</td>
<td>28</td>
</tr>
<tr>
<td>Zhang 2004</td>
<td>Prospective cohort</td>
<td>Asian (Chinese)</td>
<td>5092</td>
<td>100</td>
<td>18-74</td>
<td>TC</td>
<td>HS (48)</td>
<td>++</td>
<td>13.5 (mean)</td>
</tr>
<tr>
<td>Tirschwell 2004</td>
<td>Nested case-control</td>
<td>American</td>
<td>8010</td>
<td>44</td>
<td>66</td>
<td>TC; HDL-C</td>
<td>HS (313); ICH (217); SAH (96)</td>
<td>+; +++</td>
<td>11</td>
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<tr>
<td>Ebrahim 2006</td>
<td>Prospective cohort</td>
<td>Asian (Korean)</td>
<td>787442</td>
<td>84</td>
<td>30-64</td>
<td>TC</td>
<td>HS (3345)</td>
<td>+; +++</td>
<td>11</td>
</tr>
<tr>
<td>Cui 2007</td>
<td>Nested case-control</td>
<td>Asian (Japanese)</td>
<td>38158</td>
<td>35</td>
<td>40-79</td>
<td>TC</td>
<td>Fatal ICH (76); Fatal SAH (66)</td>
<td>+; ++</td>
<td>10</td>
</tr>
<tr>
<td>Sturgeon 2007</td>
<td>Prospective cohort</td>
<td>American</td>
<td>21680</td>
<td>44</td>
<td>59</td>
<td>TC; HDL-C</td>
<td>ICH (135)</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Ethnicity</td>
<td>Cases</td>
<td>Age Range</td>
<td>Exposures</td>
<td>Outcomes</td>
<td>Risk</td>
<td>Ref</td>
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<tr>
<td>Imamura</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>Asian (Japanese)</td>
<td>2351</td>
<td>42</td>
<td>LDL-C</td>
<td>HS (80)</td>
<td>+++</td>
<td>19</td>
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<tr>
<td>Noda</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>Asian (Japanese)</td>
<td>91219</td>
<td>34</td>
<td>TC; HDL-C; LDL-C</td>
<td>ICH (264)</td>
<td>+++</td>
<td>10</td>
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<tr>
<td>Nago</td>
<td>2011</td>
<td>Prospective cohort</td>
<td>Asian (Japanese)</td>
<td>12241</td>
<td>39</td>
<td>TC</td>
<td>Fatal HS (55)</td>
<td>+++</td>
<td>13</td>
</tr>
<tr>
<td>Wieberdink</td>
<td>2011</td>
<td>Prospective cohort</td>
<td>European (Dutch)</td>
<td>5773</td>
<td>67</td>
<td>HDL-C; LDL-C</td>
<td>ICH (85)</td>
<td>+++</td>
<td>15</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>Prospective cohort</td>
<td>European (Finnish)</td>
<td>58235</td>
<td>48</td>
<td>TC; HDL-C</td>
<td>ICH (497), SAH (332)</td>
<td>+; ++; +++</td>
<td>30</td>
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<tr>
<td>Chei</td>
<td>2013</td>
<td>Nested case-control</td>
<td>Asian (Japanese)</td>
<td>12804</td>
<td>41</td>
<td>HDL-C</td>
<td>HS (86); ICH (64)</td>
<td>+++</td>
<td>14</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol; HS, hemorrhagic stroke; ICH, intracranial hemorrhage; LDL-C, low-density lipoprotein cholesterol; SAH, subarachnoid hemorrhage; TC, total cholesterol.
† duplicated studies relating to Honolulu Heart Program, with different aspects of statistical results.
Supplemental Table S2. Categorization, relative risks, and covariates of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect estimate</th>
<th>Exposure</th>
<th>Study outcome</th>
<th>Gender</th>
<th>Comparison categories and corresponding effect estimates (95% CI)</th>
<th>Covariates in fully adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yano (^7) 1989</td>
<td>RR TC HS Male</td>
<td>Lowest quintile (1.32-4.87 mmol/L) vs higher quintiles (&gt;4.87 mmol/L): 2.13 (1.43 to 3.17)</td>
<td>Age, diastolic blood pressure, serum uric acid, cigarettes/d, and alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yano (^7) 1989</td>
<td>RR TC ICH Male</td>
<td>Lowest quintile (1.32-4.87 mmol/L) vs higher quintiles (&gt;4.87 mmol/L): 2.55 (1.58 to 4.12)</td>
<td>Age, diastolic blood pressure, serum uric acid, cigarettes/d, and alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yano (^7) 1989</td>
<td>RR TC SAH Male</td>
<td>Lowest quintile (1.32-4.87 mmol/L) vs higher quintiles (&gt;4.87 mmol/L): 1.49 (0.72 to 3.11)</td>
<td>Age, diastolic blood pressure, serum uric acid, cigarettes/d, and alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knekt (^8) 1991</td>
<td>RR TC SAH Male</td>
<td>≤5.96 mmol/L: 1.0 (reference); 5.98-6.99 mmol/L: 0.8 (0.5 to 1.3); &gt;6.99 mmol/L: 0.9 (0.6 to 1.5)</td>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knekt (^8) 1991</td>
<td>RR TC SAH Female</td>
<td>≤5.96 mmol/L: 1.0 (reference); 5.98-6.99 mmol/L: 1.0 (0.6 to 1.9); &gt;6.99 mmol/L: 1.0 (0.6 to 1.8)</td>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatchev (^9) 1993</td>
<td>RR TC ICH mortality Male</td>
<td>Lowest quartile (no range available) vs highest quartile (no range available): 1.10 (0.76 to 1.61)</td>
<td>Age, follow-up period, and diastolic blood pressure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gatchev (^9) 1993</td>
<td>RR TC ICH mortality Female</td>
<td>Lowest quartile (no range available) vs highest quartile (no range available): 1.44 (0.92 to 2.27)</td>
<td>Age, follow-up period, and diastolic blood pressure</td>
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</tr>
<tr>
<td>Gatchev (^9) 1993</td>
<td>RR TC SAH mortality Male</td>
<td>Lowest quartile (no range available) vs highest quartile (no range available): 3.43 (1.12 to 10.52)</td>
<td>Age, follow-up period, and diastolic blood pressure</td>
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</tr>
<tr>
<td>Gatchev (^9) 1993</td>
<td>RR TC SAH mortality Female</td>
<td>Lowest quartile (no range available) vs highest quartile (no range available): 1.07 (0.48 to 2.36)</td>
<td>Age, follow-up period, and diastolic blood pressure</td>
<td></td>
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<tr>
<td>Iribarren (^10) 1996</td>
<td>RR TC ICH Male</td>
<td>Levels below 10(^{th}) percentile vs higher levels: 40-64y: 0.71 (0.33 to 1.54); 65-89y: 2.72 (1.46 to 5.02)</td>
<td>Age, race, education level, body mass index, systolic blood pressure, smoking status, alcohol consumption, blood glucose, and prevalent medical conditions</td>
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<td></td>
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<tr>
<td>Iribarren (^10) 1996</td>
<td>RR TC ICH Female</td>
<td>Levels below 10(^{th}) percentile vs higher levels: 40-64y: 1.04 (0.45 to 2.40); 65-89y: 2.23 (0.90 to 5.54)</td>
<td>Age, body mass index, systolic blood pressure, serum HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and tocopherol and carotene supplementation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Leppala (^11) 1999</td>
<td>RR TC ICH Male</td>
<td>≤4.9 mmol/L: 1 (reference); 5.0-5.9 mmol/L: 0.77 (0.47 to 1.26); 6.0-6.9 mmol/L: 0.46 (0.27 to 0.78); ≥7.0 mmol/L: 0.20 (0.10 to 0.42)</td>
<td>Age, body mass index, systolic blood pressure, serum HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and tocopherol and carotene supplementation</td>
<td></td>
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</tr>
<tr>
<td>Reference</td>
<td>Type</td>
<td>Subtype</td>
<td>Gender</td>
<td>Serum TC Concentration</td>
<td>Odds Ratio</td>
<td>Reference Range</td>
</tr>
<tr>
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<td>------------------------</td>
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</tr>
<tr>
<td>Leppala¹¹ 1999</td>
<td>RR</td>
<td>TC</td>
<td>SAH</td>
<td>Male</td>
<td>≤4.9 mmol/L: 1 (reference); 5.0-5.9 mmol/L: 1.20 (0.62 to 2.32); 6.0-6.9 mmol/L: 0.60 (0.29 to 1.24); ≥7.0 mmol/L: 0.78 (0.38 to 1.62)</td>
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<tr>
<td>Leppala¹¹ 1999</td>
<td>RR</td>
<td>TC</td>
<td>ICH</td>
<td>Male</td>
<td>≤0.84 mmol/L: 1 (reference); 0.85-1.14 mmol/L: 1.24 (0.64 to 2.41); 1.15-1.44 mmol/L: 1.05 (0.52 to 2.15); ≥1.45 mmol/L: 1.33 (0.62 to 2.85)</td>
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</tr>
<tr>
<td>Leppala¹¹ 1999</td>
<td>RR</td>
<td>TC</td>
<td>SAH</td>
<td>Male</td>
<td>≤0.84 mmol/L: 1 (reference); 0.85-1.14 mmol/L: 0.5 (0.26 to 0.95); 1.15-1.44 mmol/L: 0.69 (0.36 to 1.33); ≥1.45 mmol/L: 0.26 (0.11 to 0.62)</td>
<td></td>
</tr>
<tr>
<td>Okumura¹² 1999</td>
<td>OR</td>
<td>TC</td>
<td>ICH</td>
<td>Men</td>
<td>≤4.33 mmol/L: 1 (reference); 4.35-4.95 mmol/L: 0.70 (0.38 to 1.30); 4.97-5.62 mmol/L: 0.77 (0.55 to 1.08); ≥5.65 mmol/L: 0.73 (0.56 to 0.96)</td>
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</tr>
<tr>
<td>Okumura¹² 1999</td>
<td>OR</td>
<td>TC</td>
<td>ICH</td>
<td>Female</td>
<td>≤4.33 mmol/L: 1 (reference); 4.35-4.95 mmol/L: 1.16 (0.43 to 3.13); 4.97-5.62 mmol/L: 1.26 (0.79 to 1.99); ≥5.65 mmol/L: 0.84 (0.70 to 1.19)</td>
<td></td>
</tr>
<tr>
<td>Hart¹³ 2000</td>
<td>RR</td>
<td>TC</td>
<td>HS</td>
<td>Both genders</td>
<td>≤5.33 mmol/L: 1 (reference); 5.34-5.84 mmol/L: 0.92 (0.51 to 1.65); 5.85-6.35 mmol/L: 0.71 (0.38 to 1.34); 6.36-6.98 mmol/L: 0.92 (0.52 to 1.65); ≥6.99 mmol/L: 0.22 (0.08 to 0.57)</td>
<td></td>
</tr>
<tr>
<td>Suh¹⁴ 2001</td>
<td>RR</td>
<td>TC</td>
<td>ICH</td>
<td>Male</td>
<td>≤4.31 mmol/L: 1.22 (0.88 to 1.69); 4.31-4.74 mmol/L: 0.86 (0.60 to 1.21); 4.74-5.16: 1.08 (0.78 to 1.48); 5.16-5.69 mmol/L: 1.03 (0.75 to 1.41); ≥5.69 mmol/L: 1 (reference)</td>
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<tr>
<td>Suh¹⁴ 2001</td>
<td>RR</td>
<td>TC</td>
<td>SAH</td>
<td>Male</td>
<td>≤4.31 mmol/L: 1.44 (0.76 to 2.73); 4.31-4.74 mmol/L: 1.13 (0.59 to 2.20); 4.74-5.16: 1.21 (0.64 to 2.29); 5.16-5.69 mmol/L: 1.12 (0.59 to 2.14); ≥5.69 mmol/L: 1 (reference)</td>
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</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Gender</td>
<td>Age</td>
<td>Other Factors</td>
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<td>-----</td>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Engstrom</td>
<td>2002</td>
<td>RR TC ICH</td>
<td>Male</td>
<td></td>
<td>Serum creatinine: ≤0.8 mg/dL: 1 (reference); 0.8-1.2 mg/dL: 0.5 (0.3 to 1.0); 1.2-1.5 mg/dL: 0.3 (0.2 to 0.8); 1.5-2.0 mg/dL: 0.5 (0.3 to 1.0); ≥2.0 mg/dL: 0.8 (0.4 to 1.6)</td>
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<tr>
<td>Rodriguez</td>
<td>2002</td>
<td>RR TC HS</td>
<td>Male</td>
<td></td>
<td>Per 1 mmol/L increase: Honolulu study: 0.70 (0.60 to 0.90); Framingham study: 1 (0.60 to 1.60)</td>
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<tr>
<td>Bots</td>
<td>2002</td>
<td>OR TC HS</td>
<td>Both</td>
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<td>Age, sex, and body mass index</td>
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<tr>
<td>Bots</td>
<td>2002</td>
<td>OR HDL-C HS</td>
<td>Male</td>
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<td>Age, sex, and body mass index</td>
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<tr>
<td>Bots</td>
<td>2002</td>
<td>OR HDL-C HS</td>
<td>Female</td>
<td></td>
<td>Age, sex, and body mass index</td>
<td></td>
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<tr>
<td>Jood</td>
<td>2004</td>
<td>HR TC HS</td>
<td>Male</td>
<td></td>
<td>&lt;5 mmol/L: 1 (reference); 5-6.3 mmol/L: 1.03 (0.58 to 1.83); 6.4-7.4 mmol/L: 1.00 (0.54 to 1.85); &gt;7.4 mmol/L: 1.10 (0.57 to 2.13)</td>
<td></td>
</tr>
<tr>
<td>Zhang</td>
<td>2004</td>
<td>RR TC HS</td>
<td>Male</td>
<td></td>
<td>Age, blood pressure, body mass index, and smoking</td>
<td></td>
</tr>
<tr>
<td>Tirschwell</td>
<td>2004</td>
<td>OR TC HS</td>
<td>Both</td>
<td></td>
<td>Age, sex, race, treated hypertension, index year, and time to cholesterol measurement, systolic and diastolic blood pressure, coronary heart disease, diabetes, tobacco use, atrial fibrillation, and the use of statin medications</td>
<td></td>
</tr>
<tr>
<td>Tirschwell</td>
<td>2004</td>
<td>OR TC ICH</td>
<td>Both</td>
<td></td>
<td>Age, sex, race, treated hypertension, index year, and time to cholesterol measurement, systolic and diastolic blood pressure, coronary heart disease, diabetes, tobacco use, atrial fibrillation, and the use of statin medications</td>
<td></td>
</tr>
<tr>
<td>Tirschwell</td>
<td>2004</td>
<td>OR TC SAH</td>
<td>Both</td>
<td></td>
<td>Age, sex, race, treated hypertension, index year, and time to cholesterol measurement, systolic and diastolic blood pressure, coronary heart disease, diabetes, tobacco use, atrial fibrillation, and the use of statin medications</td>
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<tr>
<td>Year</td>
<td>Study</td>
<td>Gender</td>
<td>CHD</td>
<td>Comparison</td>
<td>Results</td>
<td>Reference(s)</td>
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<td>--------</td>
<td>-----</td>
<td>------------</td>
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</tr>
<tr>
<td>2004</td>
<td>Tirschwell et al. (2004)</td>
<td>OR</td>
<td>TC</td>
<td>Both genders</td>
<td>Mean 0.83 mmol/L: 1 (reference); mean 1.09 mmol/L: 0.9 (0.6 to 1.4); mean 1.27 mmol/L: 1.1 (0.7 to 1.7); mean 1.53 mmol/L: 1.0 (0.7 to 1.6); mean 2.02 mmol/L: 1.1 (0.7 to 1.7)</td>
<td>Age, sex, race, treated hypertension, index year, and time to cholesterol measurement, systolic and diastolic blood pressure, coronary heart disease, diabetes, tobacco use, atrial fibrillation, and the use of statin medications</td>
</tr>
<tr>
<td>2006</td>
<td>Ebrahim et al. (2006)</td>
<td>HR</td>
<td>TC</td>
<td>Both genders</td>
<td>&lt;3.36 mmol/L: 1 (reference); 3.36-4.14 mmol/L: 0.76 (0.51 to 1.14); 4.14-5.17 mmol/L: 0.61 (0.41 to 0.91); 5.17-6.21 mmol/L: 0.55 (0.37 to 0.83); 6.21-6.98 mmol/L: 0.52 (0.34 to 0.79); ≥6.98 mmol/L: 0.80 (0.50 to 1.26)</td>
<td>Age, sex, body mass index, height, serum glucose, hypertension, ethanol consumption, smoking, physical activity, monthly pay, and area of residence</td>
</tr>
<tr>
<td>2007</td>
<td>Cui et al. (2007)</td>
<td>OR</td>
<td>TC</td>
<td>Both genders</td>
<td>&lt;4.14 mmol/L: 1 (reference); 4.14-4.64 mmol/L: 0.09 (0.02 to 0.44); 4.65-5.16 mmol/L: 0.35 (0.10 to 1.26); 5.17-5.68 mmol/L: 0.21 (0.05 to 0.90); 5.69-6.20 mmol/L: 0.20 (0.04 to 0.92); 6.21-6.71 mmol/L: 0.12 (0.02 to 0.80); ≥7.22 mmol/L: 0.12 (0.02 to 0.88)</td>
<td>Systolic blood pressure, HDL-cholesterol, ethanol intake, smoking status, and diabetes, with age, sex, and community matched</td>
</tr>
<tr>
<td>2007</td>
<td>Cui et al. (2007)</td>
<td>OR</td>
<td>TC</td>
<td>Both genders</td>
<td>&lt;4.14 mmol/L: 1 (reference); 4.14-4.64 mmol/L: 1.90 (0.43 to 8.41); 4.65-5.16 mmol/L: 1.08 (0.21 to 5.48); 5.17-5.68 mmol/L: 0.40 (0.07 to 2.16); 5.69-6.20 mmol/L: 1.53 (0.27 to 8.61); 6.21-6.71 mmol/L: 0.30 (0.02 to 3.96); ≥7.22 mmol/L: 0.60 (0.08 to 4.73)</td>
<td>Systolic blood pressure, HDL-cholesterol, ethanol intake, smoking status, and diabetes, with age, sex, and community matched</td>
</tr>
<tr>
<td>2007</td>
<td>Sturgeon et al. (2007)</td>
<td>RR</td>
<td>TC</td>
<td>Both genders</td>
<td>1.24-4.81 mmol/L: 1 (reference); 4.82-5.46 mmol/L: 0.77 (0.48 to 1.23); 5.49-6.16 mmol/L: 0.82 (0.52 to 1.30); 6.18-15.38 mmol/L: 0.67 (0.41 to 1.10)</td>
<td>Age</td>
</tr>
<tr>
<td>2007</td>
<td>Sturgeon et al. (2007)</td>
<td>RR</td>
<td>LDL-C</td>
<td>Both genders</td>
<td>0.10-2.84 mmol/L: 1 (reference); 2.84-3.44 mmol/L: 0.88 (0.56 to 1.39); 3.44-4.11 mmol/L: 0.85 (0.53, 1.35); 4.11-13.07 mmol/L: 0.50 (0.29 to 0.87)</td>
<td>Age</td>
</tr>
<tr>
<td>2007</td>
<td>Sturgeon et al. (2007)</td>
<td>RR</td>
<td>HDL-C</td>
<td>Both genders</td>
<td>0.25-1.04 mmol/L: 1 (reference); 1.04-1.27 mmol/L: 0.81 (0.47 to 1.39); 1.30-1.60 mmol/L: 0.99 (0.60 to</td>
<td>Age</td>
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<tr>
<td>Study</td>
<td>Method</td>
<td>Lipid</td>
<td>Event Type</td>
<td>Gender</td>
<td>Cutpoints</td>
<td>Hazard Ratio</td>
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<tr>
<td>Imamura²⁴ 2009</td>
<td>HR</td>
<td>LDL-C</td>
<td>Both genders</td>
<td>≤2.65 mmol/L: 1 (reference); 2.66-3.24 mmol/L: 0.71 (0.35 to 1.47); 3.25-3.88 mmol/L: 1.41 (0.75 to 2.65); ≥3.89 mmol/L: 1.01 (0.50 to 2.05)</td>
<td>Age, sex, HDL cholesterol, triglycerides, systolic blood pressure, ECG abnormalities, fasting blood glucose, body mass index, current drinking, current smoking, and regular exercise</td>
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</tr>
<tr>
<td>Noda²⁵ 2009</td>
<td>HR</td>
<td>TC</td>
<td>Both genders</td>
<td>&lt;4.13 mmol/L: 1 (reference); 4.13-4.64 mmol/L: 0.97 (0.65 to 1.46); 4.65-5.16 mmol/L: 0.63 (0.42 to 0.96); 5.17-5.67 mmol/L: 0.62 (0.40 to 0.95); 5.68-6.19 mmol/L: 0.59 (0.37 to 0.95)</td>
<td>Age, sex, blood pressure categories, antihypertensive medication use, diabetes mellitus, lipid medication use, body mass index, glutamyl transferase, smoking status, alcohol consumption, and kidney dysfunction</td>
<td></td>
</tr>
<tr>
<td>Noda²⁵ 2009</td>
<td>HR</td>
<td>LDL-C</td>
<td>Both genders</td>
<td>&lt;2.06 mmol/L: 1 (reference); 2.06-2.57 mmol/L: 0.65 (0.44 to 0.96); 2.58-3.09 mmol/L: 0.48 (0.32 to 0.71); 3.10-3.61 mmol/L: 0.50 (0.33 to 0.75); ≥3.62 mmol/L: 0.45 (0.30 to 0.69)</td>
<td>Age, sex, blood pressure categories, antihypertensive medication use, diabetes mellitus, lipid medication use, body mass index, glutamyl transferase, smoking status, alcohol consumption, and kidney dysfunction</td>
<td></td>
</tr>
<tr>
<td>Noda²⁵ 2009</td>
<td>HR</td>
<td>HDL-C</td>
<td>Both genders</td>
<td>&lt;1.03 mmol/L: 1 (reference); 1.03-1.28 mmol/L: 0.71 (0.47 to 1.06); 1.29-1.54 mmol/L: 0.68 (0.46 to 1.03); 1.55-1.80 mmol/L: 0.99 (0.65 to 1.51); ≥1.81 mmol/L: 0.98 (0.62 to 1.53)</td>
<td>Age, sex, blood pressure categories, antihypertensive medication use, diabetes mellitus, lipid medication use, body mass index, glutamyl transferase, smoking status, alcohol consumption, and kidney dysfunction</td>
<td></td>
</tr>
<tr>
<td>Nago²⁶ 2011</td>
<td>HR</td>
<td>TC</td>
<td>HS mortality</td>
<td>Men: &lt;4.14 mmol/L: 1.96 (0.80 to 4.79); 4.14-5.16 mmol/L: 1 (reference); 5.17-6.21 mmol/L: 0.68 (0.21 to 2.16); ≥6.21 mmol/L: 1.76 (0.38 to 8.09)</td>
<td>Age, systolic blood pressure, HDL cholesterol, smoking, drinking, and body mass index</td>
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<td></td>
<td>Women: &lt;4.14 mmol/L: 3.86 (1.18 to 12.68); 4.14-5.16 mmol/L: 1 (reference); 5.17-6.21 mmol/L: 1.94 (0.77 to 4.89); ≥6.21 mmol/L: 2.15 (0.68 to 6.77)</td>
<td></td>
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<tr>
<td>Wieberdink²⁷ 2011</td>
<td>HR</td>
<td>HDL-C</td>
<td>Both genders</td>
<td>0.4-1.1 mmol/L: 1 (reference); 1.1-1.3 mmol/L: 0.76 (0.28 to 2.01); 1.3-1.6 mmol/L: 0.74 (0.27 to 2.03); 1.6-5.5 mmol/L: 1.29 (0.48 to 3.45)</td>
<td>Age, sex, lipid-lowering medication use, systolic blood pressure, blood pressure-lowering medication use, diabetes mellitus, serum glucose level, serum insulin level, LDL, triglyceride, current cigarette smoking, body mass index, antithrombotic use, and alcohol intake</td>
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<tr>
<td>Wieberdink²⁷ 2011</td>
<td>HR</td>
<td>LDL-C</td>
<td>Both genders</td>
<td>0.1-3.2 mmol/L: 1 (reference); 3.2-3.7 mmol/L: 1.03 (0.44 to 2.41); 3.7-4.3 mmol/L: 1.47 (0.65 to 3.33);</td>
<td>Age, sex, lipid-lowering medication use, systolic blood pressure, blood pressure-lowering medication use,</td>
<td></td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Disease</td>
<td>Gender</td>
<td>TC Levels</td>
<td>Odds Ratio</td>
<td>95% CI</td>
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</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>SAH</td>
<td>Male</td>
<td>&lt;5 mmol/L: 1 (reference); 5.9-5.9 mmol/L: 0.92 (0.52 to 1.63); 6.6-9.9 mmol/L: 1.45 (0.83 to 2.52); ≥7.0 mmol/L: 1.79 (1.00 to 3.19)</td>
<td>1.08</td>
<td>0.58 to 2.03</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>SAH</td>
<td>Female</td>
<td>&lt;5 mmol/L: 1 (reference); 5.9-5.9 mmol/L: 1.37 (0.84 to 2.22); 6.6-9.9 mmol/L: 1.41 (0.84 to 2.37); ≥7.0 mmol/L: 1.25 (0.71 to 2.20)</td>
<td>1.12</td>
<td>0.66 to 1.90</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>ICH</td>
<td>Male</td>
<td>&lt;5 mmol/L: 1 (reference); 5.9-5.9 mmol/L: 1.30 (0.84 to 2.02); 6.6-9.9 mmol/L: 1.15 (0.74 to 1.81); ≥7.0 mmol/L: 1.06 (0.66 to 1.70)</td>
<td>1.08</td>
<td>0.58 to 2.03</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>ICH</td>
<td>Female</td>
<td>&lt;5 mmol/L: 1 (reference); 5.9-5.9 mmol/L: 0.62 (0.40 to 0.96); 6.6-9.9 mmol/L: 0.66 (0.43 to 1.02); ≥7.0 mmol/L: 0.55 (0.34 to 0.87)</td>
<td>1.12</td>
<td>0.66 to 1.90</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>HDL-C</td>
<td>SAH</td>
<td>&lt;1 mmol/L: 1 (reference); 1.0-1.19 mmol/L: 0.54 (0.26 to 1.13); 1.2-1.39 mmol/L: 0.65 (0.32 to 1.32); ≥1.4 mmol/L: 0.59 (0.29 to 1.19)</td>
<td>1.12</td>
<td>0.66 to 1.90</td>
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<tr>
<td>Zhang</td>
<td>2012</td>
<td>HDL-C</td>
<td>Female</td>
<td>&lt;1 mmol/L: 1 (reference); 1.0-1.19 mmol/L: 1.04 (0.52 to 2.05); 1.2-1.39 mmol/L: 0.74 (0.36 to 1.51); ≥1.4 mmol/L: 0.65 (0.33 to 1.28)</td>
<td>1.12</td>
<td>0.66 to 1.90</td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>HDL-C</td>
<td>ICH</td>
<td>&lt;1 mmol/L: 1 (reference); 1.0-1.19 mmol/L: 0.98 (0.55 to 1.76); 1.2-1.39 mmol/L: 1.30 (0.74 to 2.28); ≥1.4 mmol/L: 1.18 (0.67 to 2.08)</td>
<td>1.12</td>
<td>0.66 to 1.90</td>
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<tr>
<td>Study</td>
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<td>Gender</td>
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<tr>
<td>Zhang\textsuperscript{28} 2012</td>
<td>HR</td>
<td>HDL-C</td>
<td>ICH</td>
<td>Female</td>
<td>1 (reference)</td>
<td>1.18 (0.65 to 2.15)</td>
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<tr>
<td>Chei\textsuperscript{29} 2013</td>
<td>OR</td>
<td>HDL-C</td>
<td>HS</td>
<td>Both genders</td>
<td>0.34-0.93 mmol/L</td>
<td>0.46 (0.13 to 1.64)</td>
</tr>
<tr>
<td>Chei\textsuperscript{29} 2013</td>
<td>OR</td>
<td>HDL-C</td>
<td>ICH</td>
<td>Both genders</td>
<td>0.34-0.93 mmol/L</td>
<td>0.80 (0.13 to 4.95)</td>
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</table>

HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HS, hemorrhagic stroke; ICH, intracranial hemorrhage; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; RR, relative risk; SAH, subarachnoid hemorrhage; TC, total cholesterol.
**Supplemental Table S3.** Quality scores of prospective cohort studies using Newcastle- Ottawa Scale (maximum score of 9)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non exposed cohort</th>
<th>Ascertainment of serum cholesterol</th>
<th>Demonstration that hemorrhagic stroke was not present at start of study</th>
<th>Comparability on the basis of the design or analysis</th>
<th>Assessment of outcome</th>
<th>Adequate follow-up duration (&gt; 10 years)</th>
<th>Adequate follow-up rate (&gt; 80%)</th>
<th>Overall quality</th>
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0="No", “Unable to determine” or “Not available".
### Supplemental Table S4. Quality scores of case-control studies using Newcastle- Ottawa Scale (maximum score of 9)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Adequate definition of cases</th>
<th>Representativeness of cases</th>
<th>Selection of controls</th>
<th>Definition of controls</th>
<th>Comparability on the basis of the design or analysis</th>
<th>Assessment of exposure</th>
<th>Same method of ascertainment for cases and controls</th>
<th>Non-response rate (&lt;20%)</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bots¹⁷ 2002</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Tirschwell³⁰ 2004</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Cui²² 2007</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Chei²⁹ 2013</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

0=“No”, “Unable to determine” or “Not available”.

---

15
**Supplemental Table S5.** Subgroup analyses of total cholesterol level and risk of hemorrhagic stroke, high versus low and dose-response analyses, respectively.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>High versus low analyses</th>
<th>Dose-response analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>16</td>
<td>0.71 (0.60 to 0.83)</td>
</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>0.47 (0.20 to 1.10)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>0.72 (0.54 to 0.97)</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>0.78 (0.66 to 0.93)</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>11</td>
<td>0.60 (0.48 to 0.75)</td>
</tr>
<tr>
<td>SAH</td>
<td>7</td>
<td>0.92 (0.70 to 1.21)</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20000</td>
<td>8</td>
<td>0.58 (0.37 to 0.91)</td>
</tr>
<tr>
<td>&gt;20000</td>
<td>11</td>
<td>0.74 (0.64 to 0.86)</td>
</tr>
<tr>
<td>Study population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>8</td>
<td>0.64 (0.45 to 0.90)</td>
</tr>
<tr>
<td>American</td>
<td>3</td>
<td>0.72 (0.58 to 0.89)</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>0.69 (0.55 to 0.87)</td>
</tr>
<tr>
<td>Degree of adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>4</td>
<td>0.78 (0.51 to 1.21)</td>
</tr>
<tr>
<td>++</td>
<td>5</td>
<td>0.71 (0.56 to 0.90)</td>
</tr>
<tr>
<td>+++</td>
<td>10</td>
<td>0.67 (0.53 to 0.86)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4</td>
<td>0.63 (0.45 to 0.88)</td>
</tr>
<tr>
<td>≥10 years</td>
<td>15</td>
<td>0.71 (0.59 to 0.86)</td>
</tr>
<tr>
<td>Endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS incidence</td>
<td>16</td>
<td>0.68 (0.57 to 0.80)</td>
</tr>
<tr>
<td>HS mortality</td>
<td>3</td>
<td>0.83 (0.35 to 1.93)</td>
</tr>
</tbody>
</table>
**Supplemental Table S6.** Subgroup analyses of HDL-C level and risk of hemorrhagic stroke, high versus low analysis and dose-response analysis, respectively.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>High versus low analyses</th>
<th>Dose-response analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>5</td>
<td>0.96 (0.76 to 1.21)</td>
</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>0.99 (0.59 to 1.68)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>0.85 (0.61 to 1.17)</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>0.86 (0.56 to 1.31)</td>
</tr>
<tr>
<td><strong>Stroke type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>5</td>
<td>1.15 (0.91 to 1.46)</td>
</tr>
<tr>
<td>SAH</td>
<td>2</td>
<td>0.43 (0.19 to 1.00)</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20000</td>
<td>4</td>
<td>1.07 (0.75 to 1.52)</td>
</tr>
<tr>
<td>&gt;20000</td>
<td>4</td>
<td>0.94 (0.72 to 1.23)</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>4</td>
<td>0.87 (0.68 to 1.13)</td>
</tr>
<tr>
<td>American</td>
<td>3</td>
<td>1.22 (0.88 to 1.70)</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0.72 (0.29 to 1.81)</td>
</tr>
<tr>
<td><strong>Degree of adjustment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>1</td>
<td>1.39 (0.86 to 2.25)</td>
</tr>
<tr>
<td>++</td>
<td>1</td>
<td>1.30 (0.57 to 2.98)</td>
</tr>
<tr>
<td>+++</td>
<td>6</td>
<td>0.90 (0.73 to 1.10)</td>
</tr>
<tr>
<td><strong>Follow-up duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>3</td>
<td>0.92 (0.56 to 1.50)</td>
</tr>
<tr>
<td>≥10 years</td>
<td>5</td>
<td>1.00 (0.79 to 1.27)</td>
</tr>
</tbody>
</table>
Supplemental References

4. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174


