Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis

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CRD summary
This review examined the association between cholesterol and risk of haemorrhagic stroke, concluding that higher total cholesterol and higher low-density lipoprotein cholesterol seem to be associated with a lower risk of haemorrhagic stroke. Although the evidence base was large and details were limited making it difficult to assess the reliability of the findings, the authors’ cautious conclusions seem reasonable.

Authors' objectives
To examine the association between cholesterol and the risk of haemorrhagic stroke.

Searching
PubMed and EMBASE were searched for articles published in English from 1980 up to January 2013. Search terms were reported. Reference lists of eligible studies were manually screened.

Study selection
Eligible for inclusion were prospective cohort or nested case-control studies that assessed the association between cholesterol (including total cholesterol, high-density and low-density lipoprotein cholesterol) and the risk of haemorrhagic stroke (intracerebral haemorrhage and/or subarachnoid haemorrhage). Eligible studies had to report effect estimates (risk ratios, hazard ratios, or odds ratios) for at least three categories of cholesterol concentrations to compare low and high concentrations, or per 1mmol/L increments of cholesterol. Studies in children, pregnant women, or participants with pre-existing stroke were excluded from the review.

Included studies were conducted in America, Asia, and Europe (one in the UK) from 1989 to 2013. Some studies included only men. Participant ages ranged from 18 to 93 years, where reported. The categorisation of high and low cholesterol levels varied across studies. Some study characteristics were available in separate online-only supplementary tables.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two reviewers assessed study quality using the Newcastle-Ottawa Scale, including criteria on participant selection, comparability of study design or analysis, and outcome assessment and follow-up. Studies could score a maximum of 9.

Data extraction
Three reviewers extracted effect estimates and their 95% confidence intervals. Hazard ratios and odds ratios were considered to be equivalent to risk ratios. Studies that measured cholesterol concentrations using mg/dL were converted to mmol/L (as reported in the review). Where several variable-adjusted models were reported, data from the most fully adjusted model were used.

Methods of synthesis
Where original studies reported separate data by sex, age, and type of stroke, effect estimates were pooled using a fixed-effect model to obtain overall estimates for haemorrhagic stroke, both sexes, and all ages.

A random-effects model was then used to pool risk ratios, and their 95% confidence intervals, by cholesterol type. Separate analyses were conducted to compare the effects of high versus low levels of cholesterol on the risk of haemorrhagic stroke and the effects of 1mmol/L increments of cholesterol concentration on risk (dose-response analysis). Statistical heterogeneity was assessed using $I^2$ ($I^2=25\%$ indicated low, $I^2=50\%$ indicated moderate, and $I^2=75\%$ indicated high statistical heterogeneity).

Subgroup and sensitivity analyses were also performed (as detailed in the review).
The Egger test was used to assess publication bias.

**Results of the review**

Twenty-three studies (over 1.4 million participants, range 1,216 to 787,442) were included in the review, comprising 19 prospective cohort studies and four nested case-control studies. Cohort studies scored from 7 to 9 on the quality scale; all case-control studies scored 9. Four studies adjusted for one covariate (age), while the remaining studies adjusted for at least three covariates. The duration of follow-up ranged from four to 30 years, where reported.

A statistically significant relationship was reported between risk for haemorrhagic stroke and total cholesterol (RR 0.69, 95% CI 0.59 to 0.81; 19 studies; I²=57.6%) and between risk and low-density lipoprotein cholesterol (RR 0.62, 95% CI 0.41 to 0.92; four studies; I²=43.3%), which indicated that lower levels of total cholesterol and low-density lipoprotein cholesterol increased risk. There was no statistically significant relationship between risk of haemorrhagic stroke and high-density lipoprotein cholesterol (eight studies; I²=10.3%).

A statistically significant relationship was reported for per 1mmol/L increment in total cholesterol and risk of haemorrhagic stroke (RR 0.85, 95% CI 0.80 to 0.91; 17 studies; I²=81%), but not for low-density or high-density lipoprotein cholesterol and risk of stroke.

Results from subgroup and sensitivity analyses were reported in the review.

There was evidence of publication bias for analysis comparing high versus low total serum cholesterol.

**Authors' conclusions**

Higher total cholesterol and higher low-density lipoprotein cholesterol seem to be associated with a lower risk of haemorrhagic stroke.

**CRD commentary**

The review question was broad but supported by appropriate inclusion criteria. The literature review was somewhat limited and restricted by language, and it was unclear whether unpublished data were sought. Therefore, potentially relevant data may have been missed; the authors noted the potential for publication bias in the results. Each stage of the review process was performed in duplicate, which minimised the potential for reviewer error and bias.

Study quality was assessed using previously published criteria; the included studies seemed to meet most criteria. However, all studies were observational designs (with their own inherent limitations). A large number of participants were included in the review, but few study/participant characteristics were reported and studies were published over a large time span. There was evidence of statistical heterogeneity for some outcomes; the authors went some way to explore the underlying sources.

The authors acknowledged some of the limitations of the evidence, including potential confounding factors, unclear loss to follow-up, and limited number of studies assessing low-density and high-density lipoprotein density. Although the uncertainties regarding the data make it difficult to assess the reliability of the findings, the authors' cautious conclusions seem reasonable.

**Implications of the review for practice and research**

**Practice:** The authors stated that when considering lipid-lowering therapy, clinicians should be aware that low total cholesterol and low-density lipoprotein cholesterol levels seem to be risk factors of haemorrhagic stroke, but this should not be interpreted as going against the well-established statin regimen.

**Research:** The authors stated that further studies were required to investigate risk for stroke and identify participants who would benefit most from lowering cholesterol without the risk of haemorrhagic stroke.

**Funding**

Not stated.

**Bibliographic details**

Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and
meta-analysis. Stroke 2013; 44(7): 1833-1839

**PubMedID**
23704101

**DOI**
10.1161/STROKEAHA.113.001326

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Cerebral Hemorrhage /blood /epidemiology; Cholesterol /blood; Cholesterol, HDL /blood; Cholesterol, LDL /blood; Humans; Stroke /blood /epidemiology

**AccessionNumber**
12013029788

**Date bibliographic record published**
17/06/2013

**Date abstract record published**
29/10/2013

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.