Associations between high-density lipoprotein cholesterol and both stroke and coronary heart disease in the Asia Pacific region

Mark Woodward*, Federica Barzi, Valery Feigin, Dongfeng Gu, Rachel Huxley, Koshi Nakamura, Anushka Patel, Suzanne Ho, and Konrad Jamrozik for the Asia Pacific Cohort Studies Collaboration

Introduction

High values of total cholesterol (TC) and low values of high-density lipoprotein (HDL) cholesterol are well-recognized as being associated with increased risk of coronary heart disease (CHD). However, there is no such concordance regarding their relationship to stroke, due, in part, to limited epidemiological data (particularly for HDL cholesterol) and to the heterogeneity of this disease. Even analyses confined to epidemiological data (particularly for HDL cholesterol) and to regarding their relationship to stroke, due, in part, to limited epidemiological data (particularly for HDL cholesterol) and to the heterogeneity of this disease. Even analyses confined to epidemiological data (particularly for HDL cholesterol) and to the heterogeneity of this disease.

Methods and results

Cox survival models were applied to individual participant data from 25 cohort studies (about 80,000 subjects), with a median of 6.8 years follow-up. After adjustment for age and regression dilution, hazard ratios (95% confidence intervals) for a 1 standard deviation (SD) lower level of HDL cholesterol (0.4 mmol/L) were: for CHD events, 1.39 (1.22–1.57); for ischaemic stroke, 0.90 (0.75–1.07), and for haemorrhagic stroke, 0.89 (0.74–1.07). As total cholesterol (TC) increased relative to HDL cholesterol, the risk of CHD increased, the risk of ischaemic stroke was unchanged but the risk of haemorrhagic stroke decreased. A 1 SD increase in TC/HDL cholesterol (1.63 units) was associated with a 27% decrease in the risk of haemorrhagic stroke (95% confidence interval, 7–44%).

Conclusion

There is clear evidence of potential benefit for CHD of increases in HDL cholesterol and decreases in TC relative to HDL cholesterol, but no evidence of an association between either HDL cholesterol or TC/HDL cholesterol and ischaemic stroke. Increasing HDL cholesterol relative to TC may increase the risk of haemorrhagic stroke.

Background

The inverse relationship between high-density lipoprotein (HDL) cholesterol and coronary heart disease (CHD) is well established. Questions remain about the association between HDL cholesterol and stroke, particularly for stroke subtypes.

Methods and results

Cox survival models were applied to individual participant data from 25 cohort studies (about 80,000 subjects), with a median of 6.8 years follow-up. After adjustment for age and regression dilution, hazard ratios (95% confidence intervals) for a 1 standard deviation (SD) lower level of HDL cholesterol (0.4 mmol/L) were: for CHD events, 1.39 (1.22–1.57); for ischaemic stroke, 0.90 (0.75–1.07), and for haemorrhagic stroke, 0.89 (0.74–1.07). As total cholesterol (TC) increased relative to HDL cholesterol, the risk of CHD increased, the risk of ischaemic stroke was unchanged but the risk of haemorrhagic stroke decreased. A 1 SD increase in TC/HDL cholesterol (1.63 units) was associated with a 27% decrease in the risk of haemorrhagic stroke (95% confidence interval, 7–44%).

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Introduction

High values of total cholesterol (TC) and low values of high-density lipoprotein (HDL) cholesterol are well-recognized as being associated with increased risk of coronary heart disease (CHD). However, there is no such concordance regarding their relationship to stroke, due, in part, to limited epidemiological data (particularly for HDL cholesterol) and to the heterogeneity of this disease. Even analyses confined to ischaemic stroke, which might be expected to share a common aetiology with CHD, have not yielded consistent results. Haemorrhagic stroke, which is relatively unusual in Western countries, has rarely been studied with large numbers.

The Asia Pacific Cohort Studies Collaboration (APCSC) includes several studies from Asia and Australia. Due to its large overall sample size and its wide range of lipid levels, this makes it an excellent vehicle for the study of lipid subfractions and their associations with CHD and stroke. For example, levels of TC tend to be relatively low in Asia compared with Australasia. Another advantage is the high number of both stroke and CHD events in APCSC, due to stroke being relatively common in many parts of Asia, unlike Australia and other Western countries. Furthermore, the proportion of strokes that are haemorrhagic is relatively higher in Asia than in Western countries. Previous publications from APCSC have shown that: TC is positively associated with CHD and ischaemic stroke, but inversely associated with haemorrhagic stroke; similarly, have an independent positive association with CHD and ischaemic stroke, with no evidence of an effect on haemorrhagic stroke; a range of lipid variables, including ratios of subfractions, each have a positive (inverse for HDL cholesterol) association with fatal CHD and cardiovascular disease, with better prediction for TG, HDL cholesterol, TC/HDL cholesterol, and TG/HDL cholesterol compared with TC alone. No data from APCSC have yet been published to show associations between HDL cholesterol and stroke or CHD events. This paper aims to fill these gaps.

Methods

Details of APCSC, including study identification, data collection, and event verification, are described elsewhere. Briefly, APCSC is an overview of pre-existing cohort studies in the Asia-Pacific region which had at least 5000 person-years of follow-up. Studies were excluded from APCSC if enrolment was dependent upon having a particular condition or risk factor.

Twenty-five studies in APCSC recorded HDL cholesterol at baseline. Serum lipid measurements were obtained after fasting in...
\text{…} 93\% of participants. Since these studies were initiated over a long period of time (1966–1994), the methods and instruments used varied. Information regarding the method of cholesterol analysis was available for about 70\% of all participants; among these, 96\% of assays used enzymatic methods. The method of HDL cholesterol assay was reported by 23 studies: ten used an enzymatic method, 12 used ultracentrifugation, and one used electrophoresis.

Deaths, and their causes, were ascertained using monitoring, re-surveying, record linkage, or a combination of these. Deaths, ascribed solely to their underlying cause, were classified (after re-coding, where necessary) according to the ninth revision of the International Classification of Diseases. The codes for CHD were 410–414; for ischaemic stroke were 433.0–434.9; and for haemorrhagic stroke were 431.0–432.9. Ten of the 25 studies also recorded non-fatal cardiovascular events. Most studies used only routine sources of event notification. However, none of the 25 studies had additional verification processes; in these studies, 515 (85\%) of 606 cases of stroke were subtyped using imaging, lumbar puncture, or autopsy.

Associations between both HDL cholesterol and TC/HDL cholesterol and both stroke and CHD were obtained from Cox regression models, stratified by sex and study,\textsuperscript{20} with adjustment for age. As sensitivity analyses, on smaller samples where data were available, extra adjustments were made for systolic blood pressure (SBP) and smoking status; and for both these and additionally drinking status and body mass index (BMI). We derived hazard ratios (HRs) for HDL cholesterol and TC/HDL cholesterol in three equal groups (their thirds), with 95\% confidence intervals (CIs) obtained from floating absolute risks,\textsuperscript{20} and as continuous variables, obtaining the HR for a standard deviation (SD) increase. Heterogeneity in the HRs between individual studies was tested using Cochrane's Q statistic.\textsuperscript{20}

Table 1

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HDL, HDL cholesterol; TC, total cholesterol; FUP, follow-up (years).

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Results

HDL cholesterol, at baseline, was recorded for 79 694 (46\% female; 70\% from Asia) of the 600 443 participants in APCSC (Table 1). Mean HDL cholesterol was the same...
(1.35 mmol/L), to two decimal places, in Asia and Australia, but TC HDL cholesterol was significantly higher ($P < 0.001$) in Australia (4.51 mmol/L) than Asia (4.09 mmol/L).

Over a median follow-up of 6.8 years, there were 644 fatal coronary and 470 fatal stroke events recorded (Table 2). Of the half of fatal strokes subtyped into ischaemic or haemorrhagic, 69% were haemorrhagic. Non-fatal CHD events were recorded in six centres, yielding 127 non-fatal events, and stroke in 10 centres, yielding 375 events.

**Associations of high-density lipoprotein cholesterol with coronary heart disease and stroke**

HDL cholesterol was inversely associated with all CHD events, showing a significant dose-response effect across its thirds (Figure 1A). The HR (95% CI), comparing the lowest with the highest third, was 1.81 (1.63–2.01). When fatal CHD events alone were analysed, the HR was 1.75 (1.54–1.98). The HR for all CHD events, for a 1 SD lower level of HDL cholesterol (0.4 mmol/L) was 1.39 (1.22–1.57). The corresponding result for fatal CHD events only was 1.45 (1.26–1.66). Adjustments for potential confounding factors, in addition to age, had no important effects. Extra adjustment for SBP and smoking, on a subset of 79,694 subjects, reduced the HR for all CHD events, for a 1 SD reduction in HDL cholesterol, by 0.9%; further adjustment for alcohol drinking and BMI, on a subset of size 66,682, caused an overall reduction of 4%.

There was no clear evidence of a dose-response relationship between HDL cholesterol and stroke (Figure 1B–D), although the point estimates by thirds increased consecutively for haemorrhagic stroke. The HR comparing the lowest with the highest third was 0.89 (0.70–1.12) for ischaemic stroke, 0.81 (0.62–1.07) for haemorrhagic stroke, 1.06 (0.87–1.28) for unclassified stroke, and 1.00 (0.87–1.14) for all stroke events. The HR for a 1 SD lower level of HDL cholesterol was 0.89 (0.74–1.07) for ischaemic stroke, 0.89 (0.74–1.07) for haemorrhagic stroke, 1.06 (0.94–1.20) for unclassified stroke, and 0.95 (0.86–1.06) for all stroke events. Similar results were found for analyses involving fatal events only. As with CHD, adjustments for potential confounding factors (in addition to age) had little effect. For example, the HR for a 1 SD reduction in HDL cholesterol for haemorrhagic stroke was reduced by 0.7% after further adjustment for SBP and smoking status and by 0.8% after adjustment for SBP, smoking, drinking, and BMI; for ischaemic stroke the corresponding percentages were 4.0 and 4.8%.

There was no evidence of significant heterogeneity ($P > 0.05$) between the individual studies in APCSC in the HRs.
for a 1 SD reduction in HDL cholesterol for CHD or any of the stroke subtypes.

Differences between subgroups in the associations of high-density lipoprotein cholesterol with coronary heart disease and stroke

After age adjustment, there were no significant differences ($P > 0.43$) between the regions or between the sexes in the continuous associations between HDL cholesterol and either all CHD or all stroke events (Figure 2). Similar concordance was found when HDL cholesterol was analysed in its thirds (data not shown). There was, however, evidence of an attenuation of the inverse relationship between HDL cholesterol and CHD with increasing age ($P = 0.02$). There was no statistical evidence ($P = 0.14$) of differences between age groups in the relationships of HDL cholesterol to all stroke events. However, as with CHD, there was a higher HR among those aged below 60 years compared with others. Indeed, the below 60 years subgroup was the only subgroup for stroke where the estimated HR for a 1 SD lower level of HDL cholesterol was above one, even if not significantly so (HR = 1.20, 95% CI: 0.93–1.54).

Associations of the total to high-density lipoprotein cholesterol ratio with coronary heart disease and stroke

The associations of TC/HDL cholesterol with CHD and stroke were essentially the inverse of those seen for HDL cholesterol in Figure 1. There was no evidence of a dose-response relationship between TC/HDL cholesterol and ischaemic ($P = 0.25$), haemorrhagic ($P = 0.22$), or unclassified stroke ($P = 0.42$), but a significant positive trend for CHD ($P < 0.0001$). Comparing the highest with the lowest third, the HRs (95% CIs) for fatal and non-fatal events combined, were 1.81 (1.63–2.01) for CHD, 1.21 (0.95–1.52) for ischaemic stroke, 0.77 (0.57–1.05) for haemorrhagic stroke, 1.06 (0.88–1.28) for unknown stroke, and 1.06 (0.92–1.21) for all strokes. Associated results for a 1 SD (1.63 units) higher level of TC/HDL cholesterol, after accounting for regression dilution, were 1.53 (1.41–1.67) for CHD, 1.14 (0.96–1.36) for ischaemic stroke, 0.73 (0.56–0.93) for haemorrhagic stroke, 1.11 (0.96–1.30) for unknown stroke, and 1.03 (0.93–1.15) for all strokes. The fatal-only analyses showed no important differences from these results. Similar results were found when analysing TC–HDL cholesterol (i.e. non-HDL cholesterol), and when stratifying HDL cholesterol.
analyses by thirds of TC. For example, for CHD, a 1 SD higher level of TC–HDL cholesterol was associated with an increase in risk of 48%, compared with 53% for TC/HDL cholesterol, while a 1 SD lower level of HDL cholesterol conferred 45, 51, and 39% excess risk in the three thirds of TC, listed in increasing order.

Differences between subgroups in the associations of the total to high-density lipoprotein cholesterol ratio with coronary heart disease and stroke

Results of analyses of subgroups for increasing levels of TC/HDL cholesterol were very similar to those for decreasing levels of HDL cholesterol (Figure 2), particularly for CHD. Unlike for HDL cholesterol, there was a significant regional difference for the association between TC/HDL cholesterol and stroke ($P = 0.03$): Australian studies alone showed decreasing risk as the ratio increased, the HR for a 1 SD higher level of TC/HDL cholesterol being 0.82 (0.65–1.04) for Australia and 1.10 (0.98–1.24) for Asia. The corresponding HRs (with 95% CIs) for Australia were lower than those for Asia for all stroke subtypes: 0.87 (0.52–1.46) vs. 1.19 (0.99–1.43) for ischaemic stroke, 0.32 (0.14–0.70) vs. 0.81 (0.62–1.05) for haemorrhagic stroke, and 0.93 (0.71–1.11) vs. 1.22 (1.02–1.37) for unclassified stroke. The difference reached statistical significance only for haemorrhagic stroke ($P = 0.03$). The regional differences may be due to the lower age at which stroke was experienced in the Asian studies (Figure 2).

Discussion

In an individual participant data analysis of almost 80 000 subjects, we have shown that HDL cholesterol has a strong, most likely log linear, inverse relationship with CHD events. After taking account of age, an increase of 0.4 mmol/L (15.6 mg/dL) in the usual, long-term, level of HDL cholesterol is associated with a reduction in risk for CHD of 27% (95% CI: 17–36%). The reduction in risk for fatal CHD alone appears to be slightly higher. There is no evidence of a differential effect in Asia compared with the predominantly Caucasian population of Australia, nor between the sexes. However, the proportionate effect of higher levels of HDL cholesterol may be greater in younger people. The relationship of HDL cholesterol to CHD appears to be largely independent of other CVD risk factors. As TC decreases relative to HDL cholesterol, the risk of CHD seems to decrease at a somewhat faster rate than found when increasing HDL cholesterol, in terms of a standardized scale of measurement based on SDs. A 1 SD (1.63 units) reduction in the TC to HDL cholesterol ratio is estimated to result in a 35% (95% CI: 29–40%) reduction in the risk of a CHD event.

We found little evidence of a dose-response relationship between cholesterol and stroke, for any subtype. As with CHD, the association of HDL cholesterol with stroke seemed to be largely independent of SBP, smoking, drinking, and BMI, and was similar for fatal and combined fatal and non-fatal events, for men and women and for Asia and Australia. The results here contrast with most of the previous literature, which has reported an inverse relationship.
between HDL cholesterol and ischaemic stroke, ischaemic stroke plus transient ischaemic attacks, haemorrhagic stroke, and total stroke. One study reported an inverse relationship for non-fatal stroke, but not fatal stroke, and another found an inverse relationship for men, but a positive one for women. The Women’s Health Study found no significant association between HDL cholesterol and ischaemic stroke. The lack of association we, and the Women’s Health Study, found between HDL cholesterol and ischaemic stroke may be due to using an overall definition of ischaemic stroke. A case–control study in Belgium reported significant associations between HDL cholesterol and atherosclerotic (i.e. large vessel disease) but not with non-atherosclerotic (i.e. small vessel disease, cardioembolic, etc.) ischaemic stroke subtypes. Furthermore, a higher HDL cholesterol level was found to have more protection for atherosclerotic, when compared with other ischaemic stroke subtypes, in a population-based case–control study in Northern Manhattan. All these previous studies were based in populations where haemorrhagic stroke and small intracranial artery disease is relatively unusual, compared with APCSC.

We found evidence that higher values of TC/HDL cholesterol are associated with a decreased risk of haemorrhagic stroke. A 1.63 increase was associated with a decrease in risk of 27% (7–44%). The relationship between TC, HDL cholesterol, and ischaemic stroke may be due to using an overall definition of ischaemic stroke. A case–control study in Belgium reported significant associations between HDL cholesterol and atherosclerotic (i.e. large vessel disease) but not with non-atherosclerotic (i.e. small vessel disease, cardioembolic, etc.) ischaemic stroke subtypes. Furthermore, a higher HDL cholesterol level was found to have more protection for atherosclerotic, when compared with other ischaemic stroke subtypes, in a population-based case–control study in Northern Manhattan. All these previous studies were based in populations where haemorrhagic stroke and small intracranial artery disease is relatively unusual, compared with APCSC.

We found evidence that higher values of TC/HDL cholesterol are associated with a decreased risk of haemorrhagic stroke. A 1.63 increase was associated with a decrease in risk of 27% (7–44%). The relationship between TC, HDL cholesterol, and haemorrhagic stroke remains controversial. While one cross-sectional study in Japan showed that low TC is an independent risk factor for haemorrhagic stroke in men, a case–control study in Korea found a positive association between TC and haemorrhagic stroke. While the Copenhagen Stroke Study found no statistically significant association, it is not inconsistent that TC and HDL cholesterol atherogenetic abnormalities found to be associated with CHD have no association with haemorrhagic stroke. There is also evidence that the association between atherosclerosis and intracranial aneurysm is weak. These analyses confirm that stroke subtypes should be considered separately when considering the effects of lipids. A meta-analysis of data from clinical trials also showed a protective effect of reducing TC for ischaemic, but not haemorrhagic stroke. Results for all stroke, such as those reported in the current analyses, will depend upon the distribution of stroke subtypes, and thus may be misleading when applied in other populations.

This study has the great advantages of having a large sample size and a wide range of HDL cholesterol and TC values. Its drawbacks include the lack of a common protocol between studies, which is partially offset by having common analyses using individual participant data. The differences, between studies and over time, in the methods used to measure lipids might have caused differences between the results for individual studies. Although there was no significant heterogeneity in the measures of association between HDL cholesterol and the risk of the events considered here, it is still possible that somewhat different estimates may have been obtained if modern assay methods had been used throughout. Outcome data were incomplete; only 10 of the 25 studies recorded non-fatal events, sometimes only strokes, although results for fatal outcomes only (which were complete) showed similar results to the composite outcome of fatal plus non-fatal events. Subtyping of stroke was also incomplete; only 51% of fatal and 68% of non-fatal strokes were able to be verified as ischaemic or haemorrhagic, due to lack of opportunity for verification at the times and places where the data were collected. For this reason, we have included results for unclassified stroke. These suggest that the reported HRs for both HDL cholesterol and TC/HDL cholesterol, for both subtypes of stroke, may be more extreme than would be the case if classification had been more complete. On the other hand, the decision to allocate subtypes only when objective confirmation was available means that there is less chance of classification error. Another potential source of bias arises from missing data, since only 13% of APCSC participants had HDL cholesterol measurements recorded. Most of this missingness was due to studies not including HDL cholesterol at all (19/44 studies in APCSC did not report HDL cholesterol). These 'missing studies' were distributed across the region; for example, 7/16 from mainland China, 5/12 from Japan, and 4/8 from Australia were missing. Furthermore, there were no systematic differences in missingness within studies for mean values of any of the other standard cardiovascular risk factors recorded or duration of follow-up. Nevertheless, if data were more complete it is possible that the estimates of the effect of HDL cholesterol may have been different in some unpredictable way.

In summary, this study shows clear evidence of an advantage of a higher HDL cholesterol with regard to the risk of CHD, and that lower levels of TC relative to HDL cholesterol are associated with decreased coronary risk. For haemorrhagic, but not ischaemic stroke, there is some evidence that decreasing the TC to HDL cholesterol ratio might have adverse effects. This finding may be important for cardiovascular risk assessment, but requires confirmation in other studies.

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Appendix: Members of the APCSC

Writing committee
References


Clinical vignette

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Impending paradoxical embolism

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A 52-year-old woman presented at the emergency department with deep vein thrombosis and pulmonary embolism (PE). Transthoracic echocardiography revealed right ventricular dysfunction and disclosed an echogenic serpentine mass in all four heart chambers, compatible with a thrombo-embolus crossing a patent foramen ovale (PFO) (Panels A and B). Impending paradoxical thrombo-embolism was confirmed with transoesophageal echocardiography (Panel C). The surgeon removed the 17 cm long intracardiac thrombus (Panel D) and the pulmonary emboli and closed the foramen ovale. Conventional anticoagulant therapy was initiated. Follow-up up to 1 year after surgery is uncomplicated.

An impending paradoxical embolus is an uncommon finding in patients with PE. Routine echocardiography in these patients would perhaps increase the incidence of finding a trapped thrombo-embolus in a PFO. Paradoxical embolism is clinically suspected in patients with cryptogenic stroke or peripheral arterial embolism and a PFO. A history of venous thrombo-embolism strengthens this clinical suspicion.

See online supplementary movie files available at European Heart Journal online.

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