Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen city heart study

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Abstract

***Objective*—To estimate the influence of plasma total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease.**

***Design*—The Copenhagen city heart study is a prospective observational survey with two cardiovascular examinations at five year intervals. Non-fasting plasma lipids were measured in participants once at each examination, along with other variables. The Cox regression model was used to establish the effect of the factors recorded on cerebrovascular events of mostly, but not exclusively, ischaemic origin.**

***Subjects*—19 698 women and men at least 20 years old, randomly selected after age stratification from an area of central Copenhagen.**

***Main outcome measures*—Initial cases of stroke and transient ischaemic attack recorded from hospital records and death certificates from 1976 through 1988.**

***Results*—660 non-haemorrhagic and 33 haemorrhagic events were recorded. Total cholesterol was positively associated with risk of non-haemorrhagic events, but only for levels > 8 mmol/l, corresponding to the upper 5% of the distribution in the study population. For lower plasma cholesterol values the relative risk remained nearly constant. Plasma triglyceride concentration was significantly, positively associated with risk of non-haemorrhagic events. The relative risk corresponding to an increase of 1 mmol/l was 1·12 (95% confidence interval 1·07 to 1·16). There was a negative, log linear association between high density lipoprotein cholesterol and risk of non-haemorrhagic events (0·53 (0·34 to 0·83)). There was no indication that the effects of plasma lipids were different in women and men.**

***Conclusions*—The pattern of the association between plasma cholesterol and risk of ischaemic cerebrovascular disease was not log linear, and the increased risk was confined to the upper 5% of the cholesterol distribution. Further studies should concentrate on the association between plasma cholesterol and verified haemorrhagic stroke.**

See editorial by Garber and Avins

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Introduction

The association between total cholesterol concentration and risk of cerebrovascular disease has been investigated in several prospective and case-control studies. A recently published overview, based on 10 prospective studies, examining the relation between plasma total cholesterol and subsequent stroke found a significant association between plasma cholesterol > 5·7 mmol/l and risk of cerebrovascular disease.[1] The effect of lipid fractions was reported in only one prospective study, the Framingham study,[2] and the results were not uniform and several case-control studies found a negative association between high density lipoprotein cholesterol and cerebrovascular disease. We report the results of the analysis of the effect of plasma total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations on risk of cerebrovascular disease obtained from the Copenhagen city heart study. The statistical validity of this study relies on the use of a multivariate regression model with a methodical choice of confounders and, wherever relevant, a comparison of results from two follow up periods of six years.

Methods

The study population and sampling procedures have been described elsewhere.[3-5] Briefly, 19 698 persons were chosen randomly, but after age stratification, from an area of Copenhagen with approximately 90 000 inhabitants aged 20 or more years. They were all white and mainly from the lower or middle classes. They were invited to two cardiovascular examinations at five year intervals, in 1976-8 and 1981-3. The number of participants at the first examination was 14 223 and at the second, 12 411. At each of the two examinations data on several potential cardiovascular risk factors were recorded. The procedure and the complete questionnaire have been described elsewhere.[4] Non-fasting blood samples were obtained once from each participant at each examination. The laboratory measurement of plasma total cholesterol, triglyceride, and high density lipoprotein cholesterol concentrations is described elsewhere.[4]

The outcome measure was the first clinical evidence of stroke and transient ischaemic attacks. The methods of case ascertainment are detailed elsewhere.[6] Briefly, cases were identified through the history taken at the two cardiovascular examinations supplemented by neurological assessment; the national patient register; and the national health service register of deaths. The Danish national patient register provides information on all hospital admissions in Denmark, including patient and hospital unit identification, admission and discharge dates, and six-digit codes corresponding to all diagnoses at discharge. For those coded as 430-438 on the World Health Organisation's *International Classification of Diseases* (8th revision), hospital discharge letters were retrieved to identify participants who had had a cerebrovascular event.

When necessary, all hospital records and additional information from the patient's general practitioner, family, or nursing home were collected. Death certificates were retrieved from the national health service register of deaths in all cases in which cerebrovascular disease was registered as either the underlying cause or the contributing cause of death. Whenever

TABLE I—*Relative risks of non-haemorrhagic events and corresponding proportions of study population and cerebrovascular cases with different ranges of plasma cholesterol values at first examination*

Plasma cholesterol (mmol/l)	No (%) of study population	6 Year follow up: No (%) of cases	6 Year follow up: Relative risk (95% confidence interval)	12 Year follow up: No (%) of cases	12 Year follow up: Relative risk* (95% confidence interval)
<5	1983 (15·7)	48 (14·9)	1·00	94 (14·7)	1·00
5-6	4042 (32·0)	93 (28·7)	0·80 (0·87 to 1·79)	183 (28·7)	0·86 (0·66 to 1·12)
6-7	3688 (29·2)	96 (29·6)	0·80 (0·87 to 1·79)	189 (29·6)	0·85 (0·66 to 1·11)
7-8	1857 (14·7)	50 (15·4)	0·78 (0·84 to 1·95)	105 (16·5)	0·88 (0·72 to 1·19)
8-9	631 (5·0)	17 (5·2)	0·71 (0·79 to 2·51)	44 (6·9)	0·99 (0·68 to 1·45)
>9	429 (3·4)	20 (6·2)	1·38 (0·79 to 2·41)	13 (3·6)	1·43 (0·89 to 2·32)

*Relative to plasma total cholesterol <5 mmol/l, based on 12 year follow up. Adjusted for age, sex, length of school education, combination of household income and marital status, cigarette smoking, consumption of >10 g alcohol/day, body mass index, systolic blood pressure, diabetes, and triglycerides.

TABLE II—*Relative risk of non-haemorrhagic events and corresponding proportions of study population and cerebrovascular cases (n=279) with different ranges of plasma cholesterol values at second examination*

Plasma cholesterol (mmol/l)	No (%) of study population (n=11 358)	No (%) of cases (n=279)	Relative risk* (95% confidence interval)
<5	2396 (21·1)	48 (17·1)	1·00
5-6	3919 (34·5)	95 (34·1)	1·07 (0·65 to 1·34)
6-7	3123 (27·5)	70 (25·1)	0·95 (0·65 to 1·39)
7-8	1352 (11·9)	39 (14·0)	1·19 (0·76 to 1·84)
8-9	420 (3·7)	18 (6·5)	1·88 (1·07 to 3·29)
>9	148 (1·3)	9 (3·2)	2·39 (1·14 to 5·00)

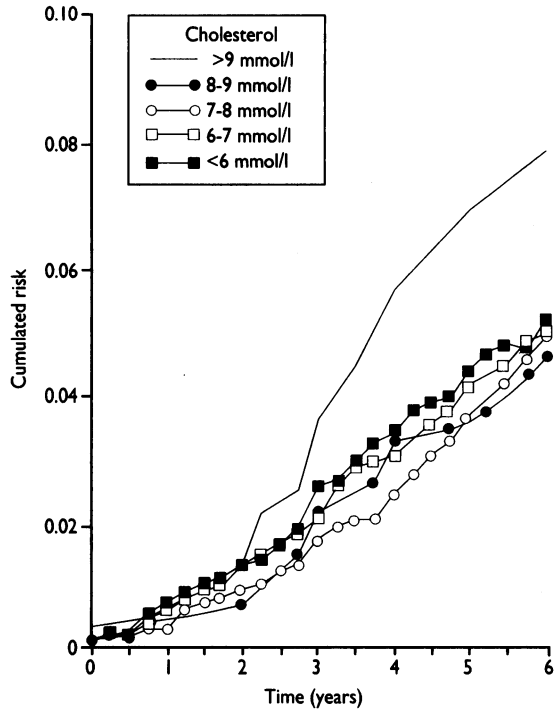
*Relative to plasma total cholesterol <5 mmol/l, based on six year follow up. Adjusted for age, sex, length of school education, combination of household income and marital status, cigarette smoking, consumption of >10 g alcohol per day, body mass index, systolic blood pressure, diabetes, and high density lipoprotein cholesterol.

possible, these certificates were supplemented by information from other sources, as mentioned above.

Cerebrovascular disease included cerebral infarction, intracerebral haemorrhage, and unspecified stroke; subarachnoid haemorrhage was excluded. The diagnosis of transient ischaemic attack was clinical. Haemorrhagic and non-haemorrhagic strokes could be distinguished (by computed tomography or brain autopsy) in 40% of cases; the remaining cases were classified as unspecified. We wished to consider haemorrhagic and ischaemic events separately. Very few events were verified as haemorrhagic so we focused on the remaining cerebrovascular events, which we presumed were mostly but not exclusively ischaemic in origin.

For statistical analysis we used Cox's regression model[3 7] and the BMDP statistical package. Variables were set up in a hierarchic system after we had established a hypothesis concerning the direction of influences among them.[3] Thus, in the Cox regression model that related the hazard of cerebrovascular event to plasma lipids, the following variables were included together with plasma cholesterol: age, sex, years of schooling, combination of household income and marital status, cigarette smoking, consumption of >10 g alcohol per day, body mass index, systolic blood pressure, antihypertensive treatment, and diabetes.[8 9]

The association between plasma cholesterol and risk of non-haemorrhagic event was investigated in the six year follow up periods after the first and the second examinations. The eligibility criteria were no previous cerebrovascular event; all the relevant variables recorded at the examination in question; and age 30 years or more at examination. The attributable risks were measured according to the method of Breslow and Day.[10]



Time course of strokes and transient ischaemic attacks during six years of follow up. Risk applies to a physically active, 60 year old man, body mass index 25, systolic blood pressure 150 mm Hg, not receiving antihypertensive drugs, no diabetes, triglyceride concentration 1 mmol/l, who has had seven years of schooling, is a smoker, married or cohabiting, has a low household income, and consumes 10 g alcohol/day

Results

Altogether 693 initial cases were identified: 206 cerebral infarctions, 33 intracerebral haemorrhages, 343 unspecified strokes, 105 transient ischaemic attacks, and six retinal artery occlusions—that is, 33 haemorrhagic strokes and 660 events that were presumed to be mostly ischaemic in origin.

RISK OF NON-HAEMORRHAGIC EVENTS

Plasma total cholesterol

Initially we analysed total cholesterol recorded at the baseline examination versus the risk of non-haemorrhagic event during six year follow up. A total of 12 630 people were eligible, and 324 cases were recorded. When total cholesterol was included directly in the model, which implicitly assumes an exponential change of the risk of cerebrovascular disease over the whole range of cholesterol values, no significant influence could be shown (relative risk 1·02; 95% confidence interval 0·90 to 1·14). With a more appropriate model, when the cholesterol values were divided into six intervals of 1 mmol/l, a distinct risk pattern emerged. Dividing cholesterol concentrations into six levels gave a better fit in the statistical model than when cholesterol was included as a continuous variable. As shown in table I the relative risk was unchanged and close to 1 for all the cholesterol levels <9 mmol/l, the reference value being <5 mmol/l. For values >9 mmol/l the relative risk was increased.

To investigate if the value of plasma cholesterol as a predictor of change in risk of cerebrovascular event with length of the observation period we repeated this analysis for the 12 year follow up from the first examination. The results of this analysis (table I) show an almost unchanged risk pattern as compared with the six year follow up. It indicates that the second half of the 12 year follow up period did not contribute further to the predictive value of plasma cholesterol as a risk factor for cerebrovascular disease. This was verified in the next model, where plasma cholesterol recorded at the first examination was related to the risk of non-haemorrhagic event in the six year observation period starting six years after the first examination. In this model the different cholesterol levels were associated with almost the same level of risk.

The figure shows the time course of the non-haemorrhagic events during the six year period following the first examination for five different cholesterol levels. It can be seen that the risk of cerebrovascular event was nearly constant with time, except for the first year and a half, when it was lower. Also, the cerebrovascular event risks in the five cholesterol strata were proportional, and the risks for strata 2 through 5 were nearly equal, and lower than in stratum 1, confirming the plateau pattern described above.

In the next model, total plasma cholesterol recorded

at the second examination was analysed as a potential risk factor for non-haemorrhagic events during a six year follow up. Among 11 358 eligible people, 279 initial events were recorded. Included as a continuous variable in the Cox regression model, plasma cholesterol was a significant risk factor for cerebrovascular disease (relative risk per mmol/l= 1·12; 1·01 to 1·16). However, when plasma cholesterol was grouped into six levels, which gave a statistically better model, the risk increased significantly only for levels >8 mmol/l. For cholesterol levels below 8 mmol/l the relative risk was almost constant and close to 1 (figure). An interaction between plasma cholesterol and age was revealed by a decreasing effect of cholesterol level >8 mmol/l with increasing age ($P<0·08$). The relative risk associated with cholesterol level >8 mmol/l was 8 at the age of 30 years but 1 at the age of 80 years. There was no significant interaction between plasma cholesterol and sex ($P<0·80$). Also, there was no significant interaction between plasma cholesterol and triglycerides ($P<0·70$) and between plasma cholesterol and high density lipoprotein cholesterol ($P<0·40$). Among subjects with plasma cholesterol >8 mmol/l, 27 non-haemorrhagic events were recorded during the second follow up.

The attributable risk of non-haemorrhagic events, corresponding to plasma cholesterol values >8 mmol/l and based on the second six year follow up, was 6·5% for men, 3·2% for women, and 4·5% overall, corresponding to 450 new cases per year in Denmark.

Plasma triglycerides

Plasma triglyceride level as a continuous variable was positively and significantly associated with risk of a non-haemorrhagic event in a Cox regression model based on six year follow up from the first examination (relative risk per 1 mmol/l increase in plasma triglycerides=1·12; 1·07 to 1·16). Grouping triglyceride values into six consecutive levels confirmed a systematic, exponential increase in relative risk, without any apparent plateau. The predictive value of triglyceride concentration was not improved when the analysis was carried out for a 12 year follow up period. There was no significant interaction between plasma triglycerides and age ($P<0·60$) or sex ($P<0·80$).

High density lipoprotein cholesterol

High density lipoprotein cholesterol included as a continuous variable was significantly, negatively associated with a risk of non-haemorrhagic events (relative risk 0·53; 0·34 to 0·83). This means that the decrement of relative risk per mmol/l of high density lipoprotein cholesterol was 47%. The increase of relative risk with decreasing high density lipoprotein cholesterol was also found when high density lipoprotein cholesterol was grouped into five levels. There was no significant interaction of high density lipoprotein cholesterol and sex ($P<0·60$) or age ($P<0·70$).

RISK OF HAEMORRHAGIC EVENTS

As we focused on cerebrovascular events that were presumed to be ischaemic, we will mention the data on the association of plasma cholesterol or triglyceride concentration and risk of haemorrhagic events only briefly. These data were based on 12 year follow up from the first examination and 33 cases.

The association was U shaped, with lowest relative risk (non-significant) corresponding to concentrations of 6-8 mmol/l rather than at the lowest concentrations of <4 mmol/l. Plasma triglycerides were measured only at the baseline examination. The association between plasma triglycerides and risk of haemorrhagic stroke was positive and log linear, the relative risk associated with an increase in triglyceride level by 1 mmol/l being 1·16 ($P<0·08$). High density lipoprotein cholesterol was measured systematically at the second examination only; therefore its effect on risk of ischaemic cerebrovascular disease was based on six years of follow up from the second examination and we were not able to control for high density lipoprotein cholesterol while analysing the effect of triglycerides.

Discussion

PLASMA CHOLESTEROL AND RISK OF CEREBROVASCULAR DISEASE

Several case-control studies have shown no significant association between plasma total cholesterol and risk of a cerebrovascular event.[11-18] The results of case-control studies, however, should be interpreted with caution, because plasma lipid concentrations are influenced by cerebrovascular disease, both in the acute stage[19 20] and long term because of poor nutrition or possible deliberate dietary changes. A prospective study of cerebrovascular atherosclerosis culminating in necropsy did not find a positive association between severity of this condition and plasma cholesterol concentrations over 7·8 mmol/l.[21] In some prospective studies stroke mortality was the end point. Some found no positive association[22-24] and others showed a positive association with non-haemorrhagic stroke[24-26] or a positive but non-significant assciation with total stroke mortality.[27]

Few prospective studies found a positive, significant association between plasma cholesterol and risk of cerebrovascular disease. The Honolulu heart programme, which included only men, found a positive but non-significant association between plasma cholesterol and cerebral infarction,[28] and the Framingham study found a significant, positive association with cerebral infarction, but only in men 50-59 years old and for cholesterol concentrations >6·24 mmol/l.[29] Later the Framingham study found no further effect of plasma cholesterol on stroke risk in men, but a non-significant negative association between plasma cholesterol and cerebral infarction in women.[23] A positive, significant association between total cholesterol and stroke risk in men was found in a prospective study from Oslo that used univariate analysis.[30] Most prospective studies showed no effect of total cholesterol on risk of cerebral infarction[31-33] or total stroke.[23 34 35]

The conflicting results emerging from these studies could be explained by too few cases or inadequate statistical models. A recent overview of 10 prospective studies of the association between plasma cholesterol concentrations >5·7 mmol/l and stroke risk found a pooled risk of 1·31, which was statistically significant.[1] Two of the 10 studies have been commented on above.[25 27]

Our results show that the association between plasma cholesterol and risk of non-haemorrhagic events is not log linear: only relatively high cholesterol concentrations are associated with significantly increased risk. This pattern was found previously[3] and has now been confirmed by two separate analyses, corresponding to consecutive six year follow up periods. This high risk group, corresponding to 5% of the study population, does not correspond to the subgroup with familial hypercholesterolaemia, the frequency of which in Denmark is only 0·5%. Nor is it a question of a combined metabolic disorder, as we controlled for the effect of blood pressure and diabetes. The cholesterol threshold we found might represent a level above which the reverse transport of cholesterol from tissues through high density lipoprotein might be incapacitated so that atherosclerotic vascular changes accelerate.

We are aware of the problem of regression dilution which might be attached to risk factor analysis based

Public health implications

- This study shows that the risk of ischaemic stroke is increased only with plasma cholesterol concentrations >8 mmol/l
- Trials of cholesterol lowering have not yet shown significant reduction of the risk of ischaemic stroke
- The association between very high total cholesterol and stroke does not in itself justify dietary advice for the normal population
- Trials of dietary modification should focus on triglyceride and high density lipoprotein cholesterol and evaluate the risk of ischaemic as well as haemorrhagic stroke

on single measurements.[36 37] Our analyses based on two six year follow ups showed the consistency of our results.

The incidence of non-haemorrhagic events attributable to plasma cholesterol concentrations >8 mmol/l was 4·5%. For Denmark, this corresponds to 450 new cases of cerebrovascular disease per year.[6] Our study did not show that the effect of plasma cholesterol varied between women and men, but it should be understood that at the same level of plasma cholesterol men have twice the risk of cerebrovascular disease as women, all other factors being equal.[8] The results of the Framingham study could suggest that the effect of cholesterol was different in women (negative association) and in men (positive association),[23] but neither association was significant and these results could be due to the inclusion of cholesterol as a continuous variable.

Published data suggest that the association between plasma cholesterol and haemorrhagic stroke may take various forms. We found a U shaped association between plasma cholesterol and risk of haemorrhagic stroke, but the analysis was based on very few cases. Several studies have reported a negative association between total plasma cholesterol and risk of haemorrhagic stroke, either significant,[28 32 33 38 39] or non-significant.[40] This negative association was also found with death from haemorrhagic stroke.[24-26] Gatchev *et al* found a J shaped association between plasma cholesterol and death from cerebral haemorrhage in men, but not in women.[41] In our study, the 33 verified cases of haemorrhagic stroke represent 5·6% of all strokes. In the literature haemorrhagic strokes represent about 10% of cases[42]; we have probably missed a few, which have been included among cases of unspecified stroke. Those relatively few cases are unlikely to influence our results for non-haemorrhagic events.

PLASMA TRIGLYCERIDES AND RISK OF CEREBROVASCULAR DISEASE

A strong log linear association between plasma triglycerides and non-haemorrhagic events is apparent from our study. If corrected for regression dilution this association would be even stronger,[43] but we had only one measurement available. This association might also be stronger if non-fasting measures had been used. Some studies did not find any association between plasma triglycerides and stroke risk[2 12 18 31]; some found a positive association with total stroke,[15] ischaemic stroke,[17] total stroke (but only in patients receiving antihypertensive treatment),[44] or cerebral infarction (but only in men aged 45-54).[45] In the last mentioned study plasma triglyceride concentration seemed to be a less good predictor of stroke than total cholesterol,[45] whereas in a Spanish case-control study the association between plasma triglycerides and stroke was stronger than between total cholesterol and stroke,[15] which is in agreement with our results. A recent study[46] showed that high postprandial concentrations of triglyceride were associated with atherosclerosis of extracranial carotid arteries.

HIGH DENSITY LIPOPROTEIN CHOLESTEROL AND CEREBROVASCULAR DISEASE

The association between high density lipoprotein cholesterol and risk of non-haemorrhagic events in our study agrees with several case-control studies that found a significant negative association with stroke risk[15 17 18 42 47 48]; a few have found no such association.[31] The only prospective study that reported a relation between high density lipoprotein cholesterol and stroke risk is the Framingham study, in which high density lipoprotein cholesterol had a non-significant protective effect overall in both women and men and on ischaemic stroke in men.[49] In our study, the second prospective study dealing with high density lipoprotein cholesterol and risk of cerebrovascular disease, the results differ from the Framingham study but agree with several of the case-control studies already mentioned. Although both our and the Framingham study based the analysis of high density lipoprotein cholesterol on a six year follow up, our study had more subjects and cases than did the Framingham study (11 342 *v* 2723 and 279 *v* 99).[49]

The negative association between high density lipoprotein cholesterol and coronary heart disease has also been shown in a large prospective study.[50] These findings are consistent with current conceptions of atherosclerosis,[51] that high density lipoprotein cholesterol is responsible for reverse transport of cholesterol from tissues for bile formation.

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Multicentre criterion based audit of the management of induced abortion in Scotland

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Abstract

***Objectives*—To assess and improve the quality of care provided to women undergoing induced abortion.**

***Design*—Two rounds of prospective, criterion based case note review audit.**

***Setting*—Ten NHS gynaecology units throughout Scotland.**

***Subjects*—2004 patient episodes of abortion care identified consecutively during two rounds of audit. The first round comprised 967 cases and the second round 1037.**

***Interventions*—Dissemination of results from the first round of audit and recommendations for change in the form of a written report and at postgraduate meetings in participating hospitals.**

***Main outcome measures*—Improvements in quality of care as assessed against 16 previously agreed criteria, both overall across the 10 study hospitals and within individual hospitals.**

***Results*—Overall, four significant improvements occurred: increased availability of early medical abortion, decreased utilisation of surgical abortion at very early gestation, increased use of mifepristone priming before second trimester medical abortion, and increased provision of follow up. At the individual hospital level 42 of 150 elements of care studied were "close to optimal" at the time of the first round of audit, rising to 54 at the second round (NS). A total of 31 significant improvements in individual elements of care occurred, but 11 significant deteriorations also occurred (at the $P < 0.05$ level).**

***Conclusions*—The prospective multicentre audit proved feasible and achieved the aims of any form of audit in terms of identifying deficiencies and variations in care. The audit results prompted objective review of local abortion services in participating hospitals. At least for some elements of care in some hospitals significant improvements were detectable.**

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Introduction

Induced abortion is one of the commonest components of the Scottish NHS gynaecological workload, accounting for around 11 000 procedures per year.[1] Abortion care was therefore considered to be a particularly appropriate topic for medical audit and was recently addressed by means of a criterion based approach in the gynaecology audit project in Scotland.[2]

Methods

A list of criteria for good quality care was agreed by a combination of objective review of contemporary medical publications, panel discussions, and postal survey of all consultant gynaecologists in Scotland (response rate 92%), as described.[3] The 16 criteria which were addressed in the multicentre audit are listed in the box.

Ten hospitals throughout Scotland representing 10 different health board areas and employing around half of all consultant gynaecologists in Scotland were included. During each of two audit periods an audit