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## RESEARCH REPORT

# Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe

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See end of article for  
authors' affiliations

Correspondence to:  
Dr M L Bots, Julius Centre  
for General Practice and  
Patient Oriented Research,  
room D01.335, University  
Medical Centre Utrecht,  
Heidelberglaan 100, 3584  
CX Utrecht, the  
Netherlands;  
M.L.Bots@jc.azu.nl

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**Background:** Controversy remains on the relation between serum lipids levels and stroke risk. This paper investigated the association of total and HDL cholesterol level to fatal and non-fatal, and haemorrhagic and ischaemic stroke in four European cohorts participating in EUROSTROKE.

**Methods:** EUROSTROKE is a collaborative project among ongoing European cohort studies on incidence and risk factors of stroke. EUROSTROKE is designed as a nested case-control study. For each stroke case, two controls were sampled. Strokes were classified according to MONICA criteria or reviewed by a panel of four neurologists. At present, data on stroke and risk factors were available from cohorts in Cardiff (84 cases), Kuopio (74 cases), Rotterdam (157 cases), and Novosibirsk (79 cases).

**Results:** Pooled analyses showed no significant association between total cholesterol and risk of stroke (odds ratio for increase of 1 mmol/l in cholesterol of 0.98 (95% CI 0.88 to 1.09)). Analyses for haemorrhagic stroke and cerebral infarction revealed odds ratios of 0.80 (95% CI 0.61 to 1.05) and 1.06 (95% CI 0.94 to 1.19), respectively. The association of HDL cholesterol to stroke was different in men compared with women. In men, there was a general trend towards a lower risk of stroke with an increase in HDL (odds ratio per 1 mmol/l increase in HDL cholesterol 0.68 (95% CI 0.40 to 1.16)). In women, however, an increase in HDL was associated with a significant increased risk of non-fatal stroke and of cerebral infarction (odds ratios of 2.46 (95% CI 0.1.20 to 5.04) and 2.52 (95% CI 1.15 to 5.50), respectively. The difference between men and women in the association of HDL with stroke seemed to differ mainly in smokers and never smokers, but not among ex smokers.

**Conclusion:** This analysis of the EUROSTROKE project could not disclose an association of total cholesterol with fatal, non-fatal, haemorrhagic or ischaemic stroke. HDL cholesterol however, seemed to be related to stroke differently in men than in women.

There is abundant evidence indicating that increased levels of total cholesterol and low levels of HDL cholesterol are strong and important risk factors for coronary atherosclerosis and symptomatic coronary heart disease. Furthermore, recent guidelines have emphasised the use of serum lipid measurements in the prevention of coronary heart disease.<sup>1</sup> The evidence on the association of cholesterol and stroke has been more controversial. Compared with coronary heart disease, stroke is a more heterogeneous disease and comprises at least three main types: subarachnoid haemorrhage, cerebral haemorrhage, and cerebral infarction. Each type of stroke may have a different aetiology, and thus may have different or even, partly competitive risk factors that cause the stroke to occur.<sup>2-5</sup> Therefore, the association between cholesterol and stroke may not be as straightforward as for coronary heart disease.

Prospective population-based studies have yielded equivocal results. Some have reported a direct association with total cholesterol and total stroke,<sup>6</sup> or cerebral infarction,<sup>7-10</sup> others showed little or no association with total stroke<sup>11</sup> or cerebral infarction.<sup>12-13</sup> Some demonstrated an inverse relation between total cholesterol and death from haemorrhagic stroke.<sup>8-14</sup> The only three available prospective population-based studies on the association between HDL cholesterol and risk of stroke showed a tendency towards a higher risk of cerebral infarction with a lower HDL level.<sup>15-16</sup>

We set out to evaluate the association between total and HDL cholesterol and fatal, non-fatal, haemorrhagic and ischaemic stroke using data from four European cohorts participating in EUROSTROKE.

## METHODS

The rationale and design of EUROSTROKE have been described in detail elsewhere.<sup>17</sup> In short, EUROSTROKE is a collaborative study among European research centres to investigate (1) the variation in incidence of fatal and non-fatal ischaemic and haemorrhagic stroke among populations in different European countries; (2) whether the observed differences in stroke incidence across countries can be explained by differences in prevalence of established cardiovascular risk factors; (3) the relative importance of smoking and some selected dietary factors (potassium intake, alcohol consumption), haemostatic disturbances (fibrinogen) and comorbidity (rheumatic heart disease, atrial fibrillation) compared with established risk factors as determinants of the occurrence of ischaemic and haemorrhagic stroke. The EUROSTROKE database is drawn from ongoing European population-based prospective follow up studies (cohorts) and is designed as a case-control study nested within these ongoing studies. For each stroke case, two controls were sampled. Controls were matched on day of baseline examination only. Apart from its objectives, the EUROSTROKE database allows for aetiological analyses looking into various risk factors for stroke. EUROSTROKE formally started on 1 January 1994. At present, data from four cohorts were available for analysis.

## Finland

The Finnish contribution to EUROSTROKE comes from the Kuopio Ischaemic Heart Disease Risk Factor study, which is a

population-based prospective cohort study comprised of an age stratified random sample of 2682 men aged 42, 48, 54 and 60 years. The baseline examination was performed between 1984 and 1989.<sup>18</sup> Fatal and non-fatal stroke cases were collected through the national mortality statistics and the FINMONICA stroke registries. Stroke was defined according to FINMONICA criteria and definitions.<sup>19</sup> Case ascertainment from the baseline examination to 1 January 1993 revealed 74 stroke cases. Controls subjects (n=148) were randomly drawn from the cohort that remained free from stroke during follow up.

### The Netherlands

The Dutch contribution to EUROSTROKE comes from the Rotterdam Study, which is a population-based prospective follow up study among 7983 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, the Netherlands.<sup>20</sup> Baseline data were collected from March 1990 to July 1993. In the Rotterdam Study, information on incident fatal and non-fatal events is obtained from the general practitioners (GPs) working in the study district of Ommoord as described earlier.<sup>21</sup> The GPs involved report all possible cases of stroke to the Rotterdam research centre. Events are presented in coded information following the International Classification of Primary Care (ICPC).<sup>22</sup> With respect to the vital status of the participants, information is obtained at regular intervals from the municipal authorities in Rotterdam and also death of a participant is reported as code A96 by GPs. When an event or death has been reported, additional information is obtained by interviewing the GP and scrutinising information from hospital discharge records in case of admittance or referral. All suspected cerebrovascular events reported by the GPs were submitted for review to the EUROSTROKE case review board. From baseline to December 1994, 192 stroke cases were identified and submitted for review and a total of 384 control subjects were drawn from the remainder of the cohort that remained free from stroke during follow up. A total of 157 events were classified as definite or probable strokes.

### Russia

The Russian contribution to EUROSTROKE comes from studies performed in the Otyabrsky, the Kirovsky and Leninsky districts of Novosibirsk, Siberia. The Novosibirsk cohort is based on three population-based surveys, which were conducted between 1984 and 1989 as part of the WHO MONICA project.<sup>23</sup> The Novosibirsk cohort comprises 9006 men and women aged 25 to 64 years. Stroke cases were collected through a specifically developed stroke registry, aiming to identify fatal and non-fatal hospitalised and non-hospitalised stroke patients.<sup>24,25</sup> Stroke events were defined according to MONICA criteria and definitions.<sup>26</sup> From baseline to December 1995, a total of 100 stroke cases had been identified and 200 control subjects were drawn from the database. Finally, 79 subjects proved to be true strokes.

### United Kingdom

The British contribution to EUROSTROKE comes from the Caerphilly Heart Disease study in Wales, United Kingdom, in which 2512 men, aged 45 to 59 years are participating.<sup>27</sup> Baseline examinations took place from 1979 to 1983. Follow up examinations were performed from 1984 to 1988 (phase II) and from 1989 to 1993 (phase III). Stroke events were registered through national mortality statistics, hospital discharge records, self report and family report. Of the registered events, additional information on signs and symptoms, on neuroimaging, necropsy and a copy of the discharge records were collected. When complete, stroke cases were submitted for review to the EUROSTROKE case review board as described earlier. On 1 December 1996, 100 stroke events

### Key points

- EUROSTROKE is based on population-based ongoing cohort studies.
- Total cholesterol is not associated with risk of stroke nor with cerebral infarction.
- Increased HDL cholesterol might be related to stroke in women, whereas in men an increased relation is not found.

had been submitted for review and 200 controls subjects had been drawn from the remaining cohort. Eighty four stroke cases were classified as definite/probable stroke by the EUROSTROKE review board.

### EUROSTROKE case review board

The review board comprised of four Dutch neurologists. Based on all information, including symptoms and signs obtained by interviewing the GP or, in case of hospital referral, hospital data, the neurologists classified the events as definite, probable and possible stroke. Events were classified by two neurologists. In case of disagreement a third neurologist was consulted, whose opinion was decisive for the final classification. The present analysis is restricted to definite and probable events, outcomes in which a stroke most probably did occur according to the neurologist's opinion. For the present analysis an incident stroke was considered to have occurred when (1) the event had led to a hospitalisation and the hospital discharge record indicated a diagnosis of a new stroke. The clinical diagnosis was based on signs and symptoms, and neuroimaging investigations during hospital stay (definite stroke); or (2) in case of no hospitalisation, signs and symptoms associated with the event obtained from the GP records and interview were highly suggestive of a stroke according to the neurologists (probable stroke) or (3) in case of out hospital death, when the GPs reported that the cause of death was a cerebrovascular accident and a cardiac cause was judged by the GP to be highly unlikely (probable stroke).

The event was classified into first and recurrent stroke and into subarachnoid haemorrhage, intracranial haemorrhage, intracerebral infarction, and unspecified (not documented). For the non-MONICA centres (the Netherlands, United Kingdom) ischaemic stroke was further classified into lacunar infarct; total anterior circulation infarct; partial anterior circulation infarct; posterior circulation infarct and unspecified infarct (undocumented). The classification was made following the guidelines described by Bamford and coworkers<sup>28</sup> and by the European Atrial Fibrillation Trial.<sup>29</sup>

### Cardiovascular risk factors

As EUROSTROKE is based on ongoing cohort studies, information on cardiovascular risk factors in each of the participating centres was already being collected before the EUROSTROKE project was established. Whenever possible, an exhaustive attempt was made to further harmonise the collected information to make comparison across studies possible. Nevertheless, baseline measurements could not be standardised beyond the attempts done in each individual study.

In each of the centres information on smoking, alcohol consumption, and medial history was obtained by questionnaire. The subject's smoking behaviour was categorised into current, former or never. Alcohol consumption was categorised into current drinkers and non-current drinkers (former and never). In addition, an estimate of grams of alcohol per day was obtained. Presence of diabetes mellitus was generally based on the question "Do you suffer from diabetes mellitus?". In the Rotterdam study diabetes mellitus was considered present when subjects used blood sugar lowering drugs, whereas in the Novosibirsk study presence of diabetes mellitus

**Table 1** General characteristics of the study population

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	Novosibirsk, RUS	All
Case/control	80/195	72/143	127/376	67/191	346/905
Age (y)	57.6 (5.9)	55.2 (4.1)	72.8 (10.1)	51.6 (9.1)	62.1 (12.2)
Female (%)	*	*	64.2	40.7	34.2
Systolic pressure (mm Hg)	146 (22)	132 (18)	144 (24)	144 (25)	143 (24)
Diastolic pressure (mm Hg)	86.4 (12.7)	88.7 (10.4)	74.2 (12.9)	93.1 (13.9)	83.6 (14.8)
Total cholesterol (mmol/l)	5.8 (1.2)	6.1 (1.2)	6.6 (1.3)	5.8 (1.3)	6.2 (1.3)
HDL cholesterol (mmol/l)	1.05 (0.33)	1.26 (0.28)	1.34 (0.37)	1.27 (0.38)	1.26 (0.36)
Current smoking (%)	46.1	27.9	23.0	34.1	31.2
Body mass index (kg/m <sup>2</sup> )	26.6 (3.6)	26.9 (3.4)	26.1 (3.6)	28.4 (5.4)	26.9 (4.1)
Diabetes mellitus (%)	4.4	6.5	8.8	NA†	6.6

Values are unadjusted proportions or means with standard deviations in parentheses of all subjects. \*Only men participated in the study; †NA=not assessed.

**Table 2** Stroke characteristics of the participating centres

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	Novosibirsk, RUS	Pooled
Total stroke	80	72	127	67	346
Fatal	22	14	33	17	86 (24.9)
Non-fatal	58	58	94	50	260 (75.1)
Haemorrhagic	10	15	12	10	47 (13.6)
Ischaemic	56	52	76	51	235 (67.9)
Unspecified	14	5	39	6	64 (18.5)

Values are absolute numbers with percentages in parentheses.

was not evaluated for the entire cohort. Information on a history of stroke was obtained by direct questioning at baseline "Did you ever suffer from a stroke?". A similar approach was taken for myocardial infarction. Presence of angina pectoris was based on either the cardiovascular Rose questionnaire or direct questioning.

In general, systolic and diastolic blood pressure were measured twice at one occasion in sitting position. In Cardiff, only one blood pressure measurement was performed. Height and weight were measured and body mass index (kg/m<sup>2</sup>) was calculated. In all four centres an electrocardiogram was made and the presence of a Q-wave myocardial infarction and left ventricular hypertrophy were assessed according to the Minnesota classification system, or in Rotterdam, by using the automated diagnostic classification system of the Modular Electrocardiogram Analysis System (MEANS).<sup>30–31</sup> Apart from Rotterdam, a fasting blood sample was taken for determination of serum lipids (total cholesterol, HDL cholesterol). Serum total cholesterol level was determined with an automatic analyser using enzymatic procedures in Rotterdam,<sup>32</sup> in Cardiff,<sup>33</sup> in Finland,<sup>34</sup> and Novosibirsk.<sup>35</sup>

### Data analysis

The analyses were first performed for each centre separately. To identify potential confounding variables, cardiovascular risk factors were related to stroke using logistic regression models and to cholesterol using linear regression models. Factors that were related to both stroke and cholesterol ( $p < 0.10$ ), and that were not assumed to be in the causal pathway of cholesterol leading to stroke were considered confounding variables. Systolic blood pressure, diastolic blood pressure, body mass index, current smoking, and diabetes mellitus were evaluated as potential confounders. Cholesterol level as predictor of stroke was studied as a continuous variable using logistic regression analysis. Initially adjustments were made for age, and subsequently for potential confounding cardiovascular risk factors.

An interaction term (cholesterol  $\times$  centre) was used to study whether the association between level of cholesterol and stroke differed across the four centres. Similarly, an interaction term (cholesterol  $\times$  sex) was used to evaluate whether the

association differed between men and women. Results are presented as odds ratios, with their corresponding 95% confidence intervals (95% CI).

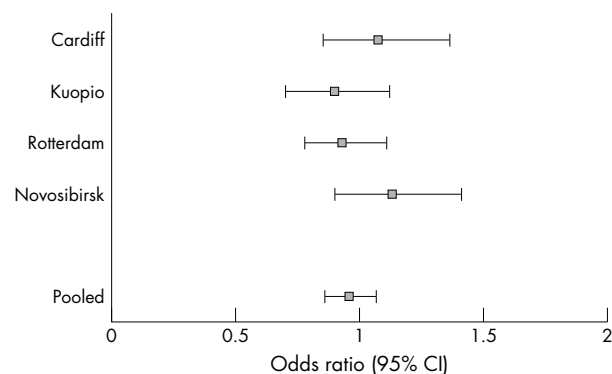
In the analyses in which information from all four centres was combined (pooled analyses) cholesterol was studied as a continuous variable and in quartiles based on the pooled cholesterol distribution. Logistic regression analysis was used (with three dummy variables) to evaluate the association between level of cholesterol and stroke. Adjustments were first made for age and subsequently for cardiovascular risk factors. Separate analyses were performed for total stroke, first ever stroke, fatal stroke (death within 28 days after onset), non-fatal stroke, and for haemorrhagic stroke and cerebral infarction.

Because it has been suggested that the association between total cholesterol and stroke may be present only at the extremes of the total cholesterol distribution,<sup>7</sup> we performed additional analyses in strata of total cholesterol ( $< 5.0$ ,  $5.0–5.9$ ,  $6.0–6.9$ ,  $7.0–7.9$ ,  $\geq 8.0$  mmol/l).

### RESULTS

General characteristics of the studied populations are given in table 1. Characteristics of the events are presented in table 2. Some 73% of the strokes were hospitalised, where of all strokes 55% had neuroimaging performed (CT/MRI). In the pooled analyses systolic blood pressure, diastolic blood pressure, current smoking, body mass index, and history of diabetes mellitus were positively, and significantly related to stroke. Body mass index showed a strong significant positive association with cholesterol level, whereas systolic blood pressure, body mass index, and diabetes mellitus were inversely related to HDL cholesterol and thus these factors were considered as confounders.

The statistical significance ( $p$  value) of interaction terms to evaluate whether the association between cholesterol and stroke differed across the four centres was 0.68 for total cholesterol and 0.13 for HDL cholesterol. The  $p$  value of the interaction term for sex was 0.19 for total cholesterol and 0.016 for HDL cholesterol. Therefore, the results for HDL cholesterol are presented for men and women separately. No interaction was found for diabetes or hypertension.

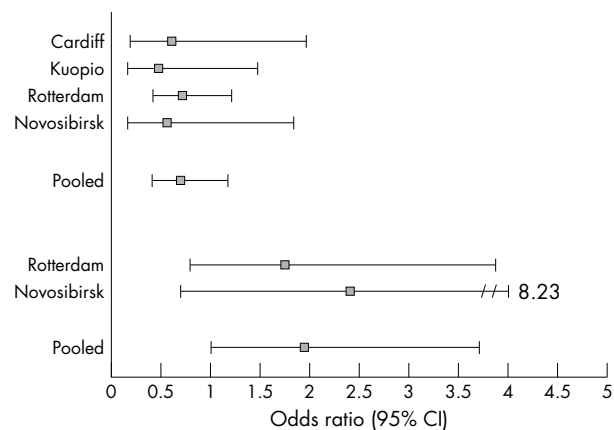


**Figure 1** Risk of stroke per increase of 1 mmol/l in total cholesterol, adjusted for age, sex, and body mass index, by centre.

The association of total cholesterol to stroke for each centre is given in figure 1. In all centres non-significant associations were seen without evidence for heterogeneity. The pooled analyses with total cholesterol level in quartiles are presented in table 3. Total cholesterol was not associated with an increased risk of any type stroke. There was a suggestion of a reduced risk of haemorrhagic stroke among those with total cholesterol levels in the upper quartile of the distribution relative to those at the lower quartile of the distribution. Subjects with cholesterol levels of 8.0 mmol/l or above were not at a significantly increased risk of total stroke nor of cerebral infarction relative to those with levels of 5 mmol/l or lower. Relative to subjects with total cholesterol levels below 5.0 mmol/l, the age, sex and body mass index adjusted risks of cerebral infarction were 0.88, 1.29, 1.26, and 0.93 for subjects with total cholesterol levels of 5.0–5.9, 6.0–6.9, 7.0–7.9 and  $\geq 8.0$  mmol/l.

In men, an increase in HDL cholesterol was associated with a non-significant reduced risk of stroke in all centres (fig 2). In the pooled analyses among men, HDL cholesterol was not significantly associated with an increased risk of stroke, fatal stroke, non-fatal stroke, and type of stroke although all point estimates suggest a reduced risk with increasing HDL levels (table 4). In women, a non-significant increased risk of stroke with increasing HDL levels was found in both the Rotterdam and Novosibirsk cohorts (fig 2). The pooled analyses with HDL cholesterol level in quartiles revealed significant increased risks of cerebral infarction and non-fatal stroke with increasing HDL levels (table 4).

When analyses were stratified by sex and smoking category (current, ex, never), it appeared that association of HDL and stroke were clearly different between men and women in the current and never smoking groups. The risk of stroke associated with an 1 mmol HDL increase in current smoking men (102 cases/189 controls) was 0.72 (0.35 to 1.51), for women (18 cases/41 controls) an odds ratio of 3.64 (0.92 to 14.4). For never smokers the odds ratio in men (112/317) was 0.50 (0.11 to 2.19) and for women (83/267) 1.47 (0.64 to 3.42).



**Figure 2** Risk of stroke per increase of 1 mmol/l in HDL cholesterol, adjusted for age, body mass index, systolic blood pressure, and diabetes mellitus, by centre (top for men, bottom for women).

## DISCUSSION

This analysis from the EUROSTROKE project does not support the presence of an association between total cholesterol and fatal, non-fatal, haemorrhagic and ischaemic stroke. HDL cholesterol, however, seemed to be related to stroke differently in men than in women.

Several aspects of this study should be considered. Firstly, EUROSTROKE is designed as a case-control study. The proportion of fatal cases across the centres differed from 19% in Kuopio to 28% in the other centres (table 2), the latter may be indicative for some underrepresentation of non-fatal cases. It is not likely that the completeness of non-fatal case ascertainment is differential across cholesterol levels, although this cannot be verified. Yet, if non-fatal cases have been selected at a higher level of the exposure of interest, this may bias a true positive association towards a stronger association, rather than blur a true positive association towards a null finding (present results). Secondly, as the number of haemorrhagic strokes is limited (n=47), these stroke type specific results should be interpreted with some caution. Strengths of this study are the fairly large number of well diagnosed and classified events for both men and women, presence of data on a large number of potential confounders, a wide age range, and risk factor assessment before the occurrence of the stroke event. In addition, we were able to distinguish between different subtypes of strokes and thus to evaluate the effect of lipids on ischaemic stroke.

Recently, the Prospective Studies Collaboration has reviewed the association between cholesterol and mortality from stroke using data obtained in 45 prospective population-based cohort studies.<sup>11</sup> The cause of death in the various studies varied from death certificates alone, or, in some studies with additional medical information and/or necropsy findings. A differentiation in type of stroke could not be made, nor

**Table 3** Total cholesterol and risk of stroke in quartiles of the cholesterol distribution

Stroke	First quartile		Second quartile		Third quartile		Fourth quartile*		Trend†
	Cases	1.0	Cases		Cases		Cases		
All	80	1.0	89	0.97 (0.68 to 1.41)	93	1.32 (0.91 to 1.90)	84	1.02 (0.70 to 1.49)	0.96 (0.86 to 1.07)
Fatal	25	1.0	24	0.73 (0.39 to 1.38)	19	0.78 (0.40 to 1.51)	18	0.60 (0.30 to 1.20)	0.82 (0.67 to 1.00)
Non-fatal	55	1.0	65	1.08 (0.71 to 1.62)	74	1.55 (1.02 to 2.34)	66	1.21 (0.79 to 1.85)	1.01 (0.90 to 1.13)
Haemorrhagic	14	1.0	12	0.80 (0.37 to 1.79)	17	1.28 (0.60 to 2.75)	4	0.29 (0.09 to 0.92)	0.78 (0.61 to 1.02)
Ischaemic	51	1.0	58	1.05 (0.68 to 1.61)	63	1.49 (0.98 to 2.30)	63	1.31 (0.85 to 2.02)	1.05 (0.93 to 1.18)
Ischaemic‡	66	1.0	77	1.02 (0.69 to 1.51)	76	1.33 (0.90 to 1.98)	79	1.17 (0.79 to 1.74)	0.99 (0.89 to 1.11)

Odds ratios with 95% CI relative to the first quartile of serum total cholesterol, adjusted for age, sex, and body mass index. Number of control subjects in the respective quartiles were 227, 248, 202 and 228. \*Cut off points 5.26, 6.10 and 6.91 mmol/l; †trends: odds ratio per 1 mmol/l increase in total cholesterol; ‡ischaemic stroke including unspecified stroke events.

**Table 4** HDL cholesterol and risk of stroke in quartiles of the distribution

Stroke	First quartile		Second quartile		Third quartile		Fourth quartile		Trend†
	Cases		Cases		Cases		Cases		
<b>Men*</b>									
All	77	1.0	47	0.79 (0.51 to 1.26)	63	0.98 (0.61 to 1.57)	28	0.71 (0.44 to 1.14)	0.71 (0.42 to 1.20)
Fatal	17	1.0	10	0.65 (0.27 to 1.54)	10	0.57 (0.21 to 1.51)	9	0.86 (0.37 to 1.95)	0.90 (0.33 to 2.41)
Non-fatal	10	1.0	37	0.82 (0.50 to 1.34)	53	1.10 (0.67 to 1.82)	19	0.65 (0.38 to 1.11)	0.66 (0.37 to 1.19)
Haemorrhagic	8	1.0	8	0.85 (0.29 to 2.47)	6	0.67 (0.19 to 2.37)	8	1.35 (0.51 to 3.57)	1.20 (0.40 to 3.63)
Ischaemic	56	1.0	34	0.79 (0.47 to 1.32)	50	1.16 (0.70 to 1.92)	16	0.56 (0.32 to 0.98)	0.65 (0.35 to 1.19)
Ischaemic‡	69	1.0	39	0.77 (0.48 to 1.24)	57	1.01 (0.62 to 1.64)	20	0.60 (0.36 to 1.00)	0.62 (0.35 to 1.12)
<b>Women*</b>									
All	17	1.0	13	0.62 (0.29 to 1.33)	26	1.15 (0.54 to 2.43)	49	1.27 (0.65 to 2.47)	1.93 (1.00 to 3.70)
Fatal	5	1.0	7	0.74 (0.18 to 2.96)	8	1.83 (0.53 to 6.33)	12	0.73 (0.21 to 2.59)	0.87 (0.22 to 3.27)
Non-fatal	12	1.0	6	0.62 (0.26 to 1.44)	18	0.99 (0.42 to 2.35)	37	1.49 (0.72 to 3.09)	2.46 (1.20 to 5.04)
Haemorrhagic	1	1.0	2	No cases	2	1.97 (0.38 to 10.1)	6	1.18 (0.24 to 5.85)	1.49 (0.26 to 8.67)
Ischaemic	9	1.0	6	0.74 (0.30 to 1.85)	18	1.21 (0.48 to 3.07)	29	1.63 (0.73 to 3.64)	2.52 (1.15 to 5.50)
Ischaemic‡	16	1.0	11	0.68 (0.31 to 1.50)	23	1.06 (0.47 to 2.37)	43	1.32 (0.66 to 2.64)	2.02 (1.02 to 4.01)

Odds ratios with 95% CI relative to the first quartile of HDL cholesterol, adjusted for age, body mass index, systolic blood pressure, current smoking and diabetes mellitus. The number of controls among men in the respective quartiles were 162, 103, 154, 91. The number of controls among women in the respective quartiles were 46, 33, 115, 121. \*Cut off points were 0.95, 1.16 and 1.37 mmol/l for men and; 1.12, 1.35 and 1.60 mmol/l for women; †trends: odds ratio per 1 mmol/l increase in HDL cholesterol; ‡ischaemic stroke including unspecified stroke events.

were analyses presented for men and women separately. Also HDL cholesterol was not measured in these surveys. In none of the participating studies a significant association between cholesterol and fatal stroke was observed: the odds ratio per 1.0 mmol/l in cholesterol increase varied between 0.80 and 1.40.<sup>11</sup> We confirm these findings and expand these results to non-fatal stroke and to cerebral infarction.

We could not disclose a direct positive association between cholesterol and stroke or cerebral infarction. Also, when a cut off point of 8.0 mmol/l was used, no association was found. Some studies have reported an inverse association between cholesterol and haemorrhagic stroke, in which the risk of haemorrhagic stroke was particularly increased in subjects with a cholesterol level below 4.0 mmol/l. We found an inverse association with haemorrhagic stroke, which, however, did not achieve statistical significance. Yet, those in the upper quartile of the total cholesterol distribution had a significantly lower risk of stroke compared with those in the lower quartile. In this study the number of haemorrhagic strokes among subjects with cholesterol levels below 4.0 mmol/l was too small to reliably evaluate the associations.

Several explanations have been given for the absence of an association between cholesterol and stroke. Firstly, in studies where only total stroke is considered, a positive association between increased cholesterol and cerebral infarction may be counterbalanced by the inverse association between low cholesterol and cerebral haemorrhage. This may be particularly relevant for fatal stroke because mortality from haemorrhage is generally higher than from cerebral infarction, which leads to a higher proportion of haemorrhagic stroke among the fatal cases. However, in our study no association was found with fatal and non-fatal stroke, nor with the type of stroke. Secondly, as stroke and coronary heart disease share risk factors, an attenuation of the association with cholesterol may be attributable to competing of coronary heart disease. Stroke typically occurs later in life than coronary heart disease, probably because of the time related development of atherosclerotic lesions first in the aorta, then in the coronary arteries and finally in the cerebral arteries. When in populations the incidence of coronary heart disease early in life is relatively higher than that of stroke, the association with stroke may be attenuated. Many people with increased cholesterol may die from coronary heart disease before a stroke can occur. This leaves subjects at risk of stroke with either moderately increased cholesterol levels or subjects with high cholesterol levels whose cardiovascular system for some reason is relatively resistant to high cholesterol. Thirdly, subjects who

survive a myocardial infarction, or who suffer from severe angina may undergo radical risk factor intervention to prevent further atherosclerotic events from occurring. This may further attenuate the association between cholesterol and stroke. Finally, it should be noted that the importance of one risk factor is relative to the presence of other potential factors contributing to the disease of interest. In industrialised societies, smoking, increased blood pressure, diabetes mellitus may reduce the relative importance of increased cholesterol as a risk factor for stroke. However, in our analyses the finding for total cholesterol and HDL cholesterol and stroke were not different in the full model compared with the age and sex adjusted model. In addition, this reasoning is exemplified in a published risk score to estimate an individual's risk of stroke within 10 years, in which serum lipids were not included.<sup>13</sup>

In an overview of results of trials on the efficacy of cholesterol lowering, a significant reduction in fatal or non-fatal stroke incidence with lipid lowering regimens compared with placebo treatment could not be demonstrated.<sup>36</sup> In a recent trial among 6595 men free from myocardial infarction at baseline and with increased cholesterol levels, in which cholesterol lowering was achieved through a newer lipid lowering drug (hydroxy-methylglutaryl-coenzyme A reductase inhibitor) a non-significant reduction of 11% in risk of fatal and non-fatal stroke was observed.<sup>37</sup> In the 4S trial among 4444 subjects with previous coronary heart disease and increased cholesterol levels, lipid lowering with a HMG-CoA reductase inhibitor resulted in a significant 30% reduction in cerebrovascular events (fatal and non-fatal stroke, and transient ischaemic attacks).<sup>38</sup> All these trials were not specifically designed to assess the efficacy of lipid lowering in the reduction of fatal and non-fatal stroke, in particular they did not have the appropriate sample size.<sup>39</sup> Their results support the view that the relation of cholesterol with stroke is not as strong as with coronary heart disease. The beneficial effect of cholesterol lowering on stroke in the two recent trials may be attributable to reduced progression (or regression) of atherosclerosis or, more probably, to the prevention of secondary effects of myocardial infarction—that is, embolic stroke or transient ischaemic attacks.

Few prospective population-based studies have examined the association between HDL cholesterol and stroke. Those available were of the same sample size as this study. In general the results from these studies showed a tendency towards a increased risk of cerebral infarction with lower levels of HDL cholesterol. In these studies a decrease of 0.26 mmol/l was associated with odds ratios between 1.08 and 1.18. In our

study such an analyses would show a non-significant odds ratio of 1.09 and therefore be compatible with these reports, at least for men. Surprisingly, a high HDL cholesterol in women conferred an increased risk of stroke in the present analysis, in particular among smokers and non-smokers. This finding has not been reported before and is in contrast with the available evidence relating high HDL levels to beneficial changes in carotid atherosclerosis and cardiovascular disease. Therefore, further studies are need to confirm this finding.

In conclusion, this analysis of the EUROSTROKE project could not disclose an association of total cholesterol with fatal, non-fatal, haemorrhagic or ischaemic stroke. HDL cholesterol however, seemed to be related to stroke differently in men than in women.

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## Authors' affiliations

**M L Bots, D E Grobbee**, Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, the Netherlands

**M L Bots, D E Grobbee**, Julius Centre for General Practice and Patient Oriented Research, University Medical Centre Utrecht, Utrecht, the Netherlands

**P C Elwood**, Centre for Applied Public Health Medicine, University of Wales College of Medicine, Cardiff, UK

**Y Nikitin**, Russian Academy of Medical Sciences Siberian Branch, Institute of Internal Medicine, Novosibirsk, Russia

**J T Salonen**, Research Institute of Public Health, University of Kuopio, Kuopio, Finland

**A Freire de Concalves**, Neurology, Hospitais da Universidade de Coimbra, Coimbra, Portugal

**D Inzitari**, Neurological and Psychiatric Sciences, University of Florence, Florence, Italy

**J Sivenius**, Department of Neurology, Kuopio University Hospital, Kuopio, Finland

**V Benetou**, Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece

**J Tuomilehto**, Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland

**P J Koudstaal**, Neurology, University Hospital Rotterdam Dijkzigt, Rotterdam, the Netherlands

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