Fibrinogen and lipid concentrations as risk factors for transient ischaemic attacks and minor ischaemic strokes

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Abstract

Objective—**To determine whether fibrinogen and lipid concentrations are risk factors for ischaemic stroke.**

Design—**Case-control study with a population based comparison within the overall study.**

Setting—**Oxfordshire community stroke project and a neurology clinic.**

Subjects—**105 patients who had a transient ischaemic attack or minor ischaemic stroke and 352 randomly chosen controls matched for age and sex from the same general practitioners as the incident cases. 52 controls were ineligible or refused interview. 104 cases and 241 controls gave blood samples for analysis.**

Main outcome measures—**Response to structured questionnaire, height, weight, blood pressure, and serum concentrations of fibrinogen and lipids.**

Results—**Adjusted for other variables, odds ratios of ischaemic stroke were 1·78 (95% confidence interval 0·91 to 3·48; p=0·009) for fibrinogen concentrations >3·6 g/l; 1·73 (0·90 to 3·29; p=0·009) for total cholesterol concentrations >6·0 mmol/l; 1·34 (0·69 to 2·61; p>0·4) for low density lipoprotein cholesterol concentrations >3·5 mmol/l; and 0·32 (0·15 to 0·69; p=0·002) for high density lipoprotein cholesterol concentration >1·2 mmol/l. Similar results emerged comparing only community derived cases with transient ischaemic attacks and controls. The effects of fibrinogen, total cholesterol, and high density lipoprotein cholesterol were significant in a test of trend after adjusting for all other variables in the study (χ^2=4·14, p<0·05; χ^2=4·31, p<0·05, and χ^2=12·15, p>0·001, respectively). History of ischaemic heart disease and hypertension were the only other variables that showed significance, though both lost significance after adjustment (2·06, p=0·08 and 1·53, p=0·2, respectively).**

Conclusions—**Fibrinogen and lipids are important risk factors for ischaemic stroke. The pattern of changes mirrors that found in ischaemic heart disease.**

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Introduction

Many risk factors have been associated with stroke. Case-control and cohort studies have established age, blood pressure, heart disease, atrial fibrillation, transient ischaemic attack, peripheral vascular disease, diabetes mellitus, smoking, cervical arterial bruit, and male sex as risk factors.[1,2] A recent prospective study suggested that fibrinogen may be a more powerful predictor of stroke than is blood pressure,[3] although the study adjusted only for blood pressure, total cholesterol, and smoking habits and not for other variables that may also be confounders, such as social class.[4]

The precise relation between lipids, lipoproteins, and stroke is not clear. The study of metabolic variables in a case-control study is complicated by changes that occur after stroke: fibrinogen concentrations clearly rise[5] and total cholesterol concentrations fall.[6] We therefore conducted a case-control study to investigate the relation of fibrinogen and lipoproteins with stroke. We studied transient ischaemic attacks as a surrogate model for ischaemic stroke because such attacks are less likely to affect these metabolic variables. We also looked at minor ischaemic stroke. Our underlying assumption was that although transient ischaemic attack, minor ischaemic stroke, and major ischaemic stroke are clinically different, they arise from the same underlying arterial disease. We also conducted a case-control comparison of subjects with transient ischaemic attack and controls recruited through their general practitioners, to avoid any bias of hospital referral.

Patients and methods

We studied all patients over the age of 20 who were referred to a neurology clinic or reported to the Oxfordshire community stroke project[7] with a transient ischaemic attack or minor ischaemic stroke. The diagnosis was confirmed by one of us (CW), soon after the attacks, and all patients were studied within one year after notification of the episode.

We defined a transient ischaemic attack as an acute loss of focal, cerebral, or ocular function with symptoms lasting less than 24 hours that, after investigation, was assumed to be due to embolic or thrombotic vascular disease. A minor ischaemic stroke was defined as an acute loss of focal cerebral function with symptoms lasting longer than 24 hours but less than seven days that, after investigation, was assumed to be due to embolic or thrombotic vascular disease. We excluded patients with focal epilepsy, migraine, structural brain lesions (such as tumours), local disease of the eye (such as glaucoma), potential structural cardiac source for emboli (such as mitral valve disease), and general medical disorders such as myeloma. Patients who presented with transient ischaemic attack preceded by stroke and those who presented with minor ischaemic stroke preceded by major stroke were also excluded. Computed tomography was used to exclude intracranial haemorrhage in all patients with minor ischaemic strokes and, less importantly, 74% of those with transient ischaemic attacks.

The study was designed to detect a 0·4 g/l difference in fibrinogen concentration between the groups,[3] with over 95% power at the 5% level of significance and a ratio of one case to two controls. This power required 101 cases (the approximate number capable of being recruited within two years) and 202 controls. Given an expected 60% response rate among controls asked for blood samples, we asked 105 cases to participate and selected 352 controls. Although we had originally

intended to recruit twice as many cases as controls, recruitment of controls was increased to maintain statistical power when early case incidence and control compliance were lower than expected.

Control subjects were selected randomly from the age and sex registers of local general practitioners, stratified to give roughly equal proportions in five year age groups and sex to the series, which we predicted from the age and sex distribution of patients with transient ischaemic attack who had been recruited to the Oxfordshire community stroke project. Because of this the age distribution of controls differed slightly from that of cases. In particular, five people in the control group but no cases were aged under 40. The lipid concentrations in these five controls did not differ substantially from those in the other controls, so they were retained in the study. Age was adjusted for in multivariate analyses (see below).

Consenting cases and controls were seen at home; cases were visited at least four weeks after the attack. Cases and controls were asked about social class, history of vascular disease (ischaemic heart disease, hypertension, diabetes mellitus), history of cigarette smoking, alcohol consumption in past few months, and snoring habits. Blood pressure was recorded with a random zero sphygmomanometer; Korotkoff phase V was used to define diastolic pressure. Height and weight were also measured. Non-fasting blood samples were taken without venestasis during the visit, and the plasma was stored at −28°C.

Clottable fibrinogen concentration was estimated by a modification of the method of Ellis and Stransky[8] and total cholesterol concentration by the enzymatic method of Siedel *et al.*[9] High density lipoprotein cholesterol concentration was measured in the supernatant obtained after precipitating low density lipoprotein cholesterol and very low density lipoprotein cholesterol.[10] Low density lipoprotein cholesterol and high density lipoprotein cholesterol concentrations were measured in the supernatant obtained after precipitating very low density lipoprotein cholesterol,[11] and the concentration of low density lipoprotein cholesterol was calculated by deducting the value obtained when measuring only high density lipoprotein estimation. Packed cell volume was measured routinely on one Coulter counter. All assays were performed blinded.

STATISTICAL ANALYSIS

We used the statistical analysis system for all analyses.[12] All significance levels relate to two tailed probabilities. The Student's *t* test was used to compare group means. Odds ratios were used as a close approximation to relative risk. We calculated unadjusted odds ratios assuming an unmatched design using the (rounded) median values of the control group to dichotomise the variables. The odds ratio and significance after adjusting for possible confounding variables were calculated by unconditional multiple logistic regression.[13] Variables were analysed as dichotomous variables and as ordinal variables with four quarters to test the linear trend. Data on patients in the study who had been recruited from the Oxfordshire community stroke project with transient ischaemic attack and on all controls were analysed separately, providing a pure community based case-control study of patients whose symptoms had resolved within hours that was free of hospital referral bias.

The aetiological fraction (excess risk or population attributable risk), defined as the proportion of all cases of stroke in the target population attributable to high lipid or fibrinogen concentrations was calculated by standard formulas.[13] The exposure category was assigned by using concentrations above the median values for the control group. Provided that the association between the disease and the variable is causal, it can be interpreted as the proportion of transient ischaemic attacks or minor ischaemic strokes in the target population that would not have occurred had all subjects had values below the median.

Results

Among the 105 cases, 49 subjects with transient ischaemic attacks and 14 with minor ischaemic strokes had been recruited from the community and 41 with transient ischaemic attack and 1 with minor ischaemic stroke had been recruited from a neurology clinic. Blood samples were available from all but one of the cases (in a subject with a transient ischaemic attack recruited from hospital). Three hundred and fifty two controls were selected for the study from general practitioners' lists (excluding those who had died or moved away but remained on the general practitioners' registers). Ten were excluded because they had had a stroke, leaving 342 eligible controls. Forty two refused interview or were vetted as unsuitable by the responsible general practitioner, usually because of ill health or psychological factors. This left 300 consenting controls, 241 of whom provided blood samples, although all assays could not be performed for each control because of breakages and inadequate plasma volumes. The mean (SD) ages were 67·7 (10·8) years for cases and 67·6 (11·1) years for controls, and there were 68 (65%) and 161 (67%) men among cases and controls, respectively. The mean (SD) age of the controls who did not provide blood was 70·3 (10·7); 42 of these controls were men.

Table I shows the mean values and differences between patients who had transient ischaemic attack or minor ischaemic stroke and the controls for fibrinogen, total cholesterol, low density lipoprotein, and high density lipoprotein cholesterol concentrations. Table II gives the odds ratios and 95% confidence intervals when these continuous variables were dichotomised at the arbitrary level of the rounded median of the control group and adjusted odds ratios after multivariate adjustment for all other possible confounding variables assessed. Fibrinogen, total cholesterol, and low density lipoprotein cholesterol concentrations were significantly higher in cases than in controls; high density lipo-

TABLE I—*Comparison of mean (SD) lipid and fibrinogen concentrations in all subjects recruited to study and in cases recruited from community with transient ischaemic attack*

	Cases		Controls		Difference in means (95% confidence interval)	p Value
	No of subjects	Mean (SD) value	No of subjects	Mean (SD) value		
All subjects:						
Fibrinogen (g/l)	103	4·08 (1·16)	232	3·65 (1·09)	0·43 (0·16 to 0·70)	0·001
Total cholesterol (mmol/l)	99	6·83 (1·31)	234	6·22 (1·27)	0·61 (0·30 to 0·92)	<0·0001
Low density lipoprotein cholesterol (mmol/l)	99	4·03 (1·13)	232	3·68 (1·08)	0·35 (0·09 to 0·61)	0·007
High density lipoprotein cholesterol (mmol/l)	99	1·15 (0·38)	233	1·30 (0·42)	−0·15 (−0·24 to −0·06)	0·002
Community derived subjects:						
Fibrinogen (g/l)	47	4·24 (1·21)	232	3·65 (1·09)	0·59 (0·21 to 0·96)	0·001
Total cholesterol (mmol/l)	45	6·91 (1·33)	234	6·22 (1·27)	0·69 (0·30 to 1·14)	0·001
Low density lipoprotein cholesterol (mmol/l)	45	4·09 (1·21)	232	3·68 (1·08)	0·41 (0·03 to 0·79)	0·02
High density lipoprotein cholesterol (mmol/l)	45	1·15 (0·41)	233	1·30 (0·42)	−0·14 (−0·27 to 0·01)	0·05

TABLE II—*Odds ratios for transient ischaemic attack and minor ischaemic stroke associated with fibrinogen and lipid concentrations*

	Median value of controls (rounded)	No (%) of cases		No (%) of controls		Unadjusted odds ratio (95% confidence interval)	p Value	Adjusted odds ratio* (95% confidence interval)	p Value	Aetiological fraction† (95% confidence interval)
		Above median in controls	Below median in controls	Above median	Below median					
Fibrinogen (g/l)	3·6	68 (66)	35 (34)	114 (49)	118 (51)	2·01 (1·25 to 3·25)	0·004	1·78 (0·91 to 3·48)	0·09	0·28 (0·0 to 0·55)
Total cholesterol (mmol/l)	6·0	67 (68)	32 (32)	118 (50)	116 (50)	2·06 (1·26 to 3·37)	0·001	1·73 (0·90 to 3·29)	0·09	0·27 (0·0 to 0·54)
Low density lipoprotein cholesterol (mmol/l)	3·5	67 (68)	32 (32)	118 (51)	114 (49)	2·02 (1·24 to 3·30)	0·005	1·34 (0·69 to 2·61)	>0·4	0·15 (0·0 to 0·46)
High density lipoprotein cholesterol (mmol/l)	1·2	34 (34)	65 (66)	124 (53)	108 (47)	0·46 (0·28 to 0·74)	0·002	0·32 (0·15 to 0·69)	0·002	0·52 (0·42 to 0·74)

*Simultaneous adjustment for age, sex, social class, history of hypertension, ischaemic heart disease, diabetes mellitus, systolic blood pressure, cigarette smoking, alcohol consumption, snoring, body mass index, packed cell volume, and variably, fibrinogen, total cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol concentrations.
†Calculated from the adjusted odds ratios.

TABLE III—*Effect of fibrinogen and lipids on risk of transient ischaemic attack and minor ischaemic stroke according to quarters of concentration*

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio* (95% confidence interval)	χ^2 for linear trend after adjustment* (p value)
Fibrinogen (g/l):			
3·0-	1·09 (0·51 to 2·33)	1·10 (0·39 to 2·96)	4·14 (0·05)
3·6-	1·66 (0·80 to 3·41)	1·37 (0·50 to 3·80)	
≥4·3	2·52 (1·27 to 4·99)	2·23 (0·85 to 5·84)	
Total cholesterol (mmol/l):			
5·4-	2·03 (0·91 to 4·57)	2·35 (0·77 to 7·26)	4·31 (<0·05)
6·0-	2·11 (0·95 to 4·69)	2·39 (0·67 to 8·62)	
≥6·9	4·02 (1·88 to 8·57)	5·06 (1·42 to 18·01)	
Low density lipoprotein cholesterol (mmol/l):			
3·0-	1·55 (0·72 to 3·35)	1·29 (0·46 to 3·66)	2·03 (0·2)
3·5-	2·18 (1·05 to 4·50)	1·22 (0·41 to 3·53)	
≥4·4	2·48 (1·20 to 5·12)	2·03 (0·77 to 5·28)	
High density lipoprotein cholesterol (mmol/l):			
1·0-	0·60 (0·32 to 1·10)	0·31 (0·14 to 0·75)	12·15 (<0·001)
1·2-	0·39 (0·19 to 0·77)	0·19 (0·07 to 0·52)	
≥1·5	0·43 (0·22 to 0·84)	0·22 (0·08 to 0·59)	

*Simultaneous adjustment for all other variables in the study.

protein cholesterol concentration was significantly lower in cases. Dichotomising these variables at the median value for controls gave significant unadjusted odds ratios in each case. After adjusting for possible confounders the odds ratios became non-significant except that for high density lipoprotein (p=0·002). The excess risk (aetiological fraction) attributable to the adjusted risk factors was 26% for fibrinogen, 27% for total cholesterol, 14% for low density lipoprotein cholesterol, and 52% for high density lipoprotein cholesterol.

Table III presents unadjusted and adjusted odds ratios for the quarters of the variables; quarters 2, 3 and 4 are compared with quarter 1 for each variable. We applied a test for linear trend on these quarters after adjusting for all other variables assessed in the study to examine dose-response relations. There were significant linear trends, after simultaneous adjustment for all other variables in the study, for fibrinogen, total cholesterol, and high density lipoprotein cholesterol concentrations. Low density lipoprotein cholesterol concentration was not significant after adjustment, though there seemed to be steady increases in both the unadjusted and adjusted odds ratios for increasing quarters.

Subset analysis of those cases recruited from the community with transient ischaemic attack and of controls showed results comparable with those obtained in the overall analysis (Table I). The mean differences in the variables were similar and, though confidence intervals were wider, the significance of the mean differences was little changed except for that for high density lipoprotein cholesterol. High density lipoprotein cholesterol concentration was lower in the cases than in the controls by a degree almost identical with that in the main analysis, but the difference was only just significant (p=0·05).

Table IV summarises the results for other variables assessed in the study. A history of ischaemic heart disease and a history of hypertension were significant in univariate analysis. Packed cell volume dichotomised at 0·45 was also significant, but the difference in means between cases and controls was small (0·6%) and not significant when compared with Student's *t* test (p=0·2, 95% confidence interval −0·4% to 1·6%). Body mass index was not a significant risk factor.

Discussion

We found higher concentrations of fibrinogen and total cholesterol and lower concentrations of high density lipoprotein cholesterol to be independent

TABLE IV—*Comparison of possible confounding factors for ischaemic stroke in cases and controls*

	No (%) of cases	No (%) of controls	Odds ratio (95% confidence interval)	p Value	Adjusted odds ratio (95% confidence interval)	p Value*
Ischaemic heart disease:						
No	71 (68)	252 (85)				
Yes	34 (32)	42 (15)	2·87 (1·68 to 4·65)	<0·0001	2·06 (0·96 to 4·43)	0·08
History of hypertension:						
No	51 (49)	206 (71)				
Yes	54 (51)	85 (29)	2·57 (1·63 to 4·03)	<0·0001	1·53 (0·80 to 2·91)	0·2
History of diabetes mellitus:						
No	100 (95)	277 (94)				
Yes	5 (5)	18 (6)	0·77 (0·28 to 2·12)	0·6	0·31 (0·07 to 1·28)	0·1
Snoring:						
No	30 (33)	101 (37)				
Yes	60 (67)	170 (63)	1·19 (0·72 to 1·97)	0·5	0·68 (0·36 to 1·24)	0·2
Cigarette smoking:						
Never smoked	26 (25)	94 (32)				
Current or ex-smoker	79 (75)	202 (68)	1·41 (0·85 to 2·34)	0·2	1·27 (0·57 to 2·88)	0·5
Alcohol consumption:						
Current non-drinker	14 (13)	31 (10)				
Current drinker	91 (87)	265 (90)	0·76 (0·39 to 1·49)	0·5	0·87 (0·36 to 2·07)	0·8
Body mass index:						
≤2·5	37 (36)	98 (44)				
>2·5	65 (64)	125 (56)	1·38 (0·85 to 2·33)	0·23	0·84 (0·42 to 1·68)	0·6
Packed cell volume (%):						
≤45	78 (76)	205 (87)				
>45	24 (24)	31 (13)	2·03 (1·13 to 3·66)	0·024	1·70 (0·74 to 3·87)	0·2
Blood pressure (mm Hg):						
≤160/90	47 (44)	129 (54)				
>160/90	58 (55)	108 (46)	1·47 (0·93 to 2·34)	0·1	0·85 (0·44 to 1·61)	0·6

*Simultaneous adjustment for all variables in the study.

risk factors for transient ischaemic attack or minor ischaemic stroke. Although significance was lost after multivariate adjustment with the main variable treated as a dichotomous variable (with the exception of high density lipoprotein cholesterol), the variable retained significance in the more sensitive test for linear trend. This last test is more appropriate as fibrinogen and the lipid fractions have a log-linear relation with odds of disease. Age, sex, social class, history of hypertension, diabetes mellitus, ischaemic heart disease, cigarette smoking, alcohol, snoring, systolic blood pressure, body mass index, and packed cell volume cannot account for the observed associations. An association between low density lipoprotein cholesterol and transient ischaemic attack or minor stroke was also detected but became non-significant after adjustment.

We believe that transient ischaemic attack is a valid surrogate model for ischaemic stroke as the Oxfordshire community stroke project[1] and other studies have found no significant differences in the means or prevalence of almost all the risk factors examined[7,14-16] and as prognoses for transient ischaemic attack and non-disabling ischaemic stroke are remarkably similar.[17] Our comparison of people with transient ischaemic attack with controls recruited from the community rather than hospital means that all cases from a well defined source population were included. This subset analysis also had the advantages of standard and reliable criteria for the diagnosis of cases with rapid and expert assessment soon after notification; controls arising from the same population as the cases; and identical evaluation of both cases and controls in the same setting without recourse to proxy respondents and minimal loss of cases. The results of this subgroup analysis were remarkably similar to those of the overall analysis, indicating that including minor ischaemic strokes and hospital cases did not introduce serious bias.

Our study is in overall agreement with the results of the two small case-control studies relating fibrinogen to transient ischaemic attack.[18,19] One of the studies, however, used a control group that excluded subjects with any history of cardiovascular disease[18] and in the other the age distributions of the cases and of the controls were different.[19] Furthermore, no adjustment was made for confounding. The control subjects selected for the study that were thought unsuitable by their general practitioners were probably more ill than were those we studied. They were also more likely to have non-vascular disease, especially cancer. Cancer is known to increase fibrinogen concentrations,[19] thus bias from this source of non-response cannot be discounted. As the age match between cases and controls was so close despite the fact that age was not matched individually serious bias probably did not occur because of controls' refusal to participate.

The significant dose-response relation with fibrinogen, after adjustment for confounders, supports the existence of a true positive association. Though difficult to completely disprove, little evidence exists to support the notion that fibrinogen concentration increases after a transient ischaemic attack or minor ischaemic stroke.[20] Moreover, the differences in mean fibrinogen concentrations between cases and controls in this study and the first prospective study to identify fibrinogen as a risk factor for stroke[3] were similar: 0·43 g/l (this study) and 0·40 g/l[3] respectively. The Framingham study[21] found a significant association between increasing fibrinogen concentration and risk of stroke in men but not in women. In our study, however, although female controls had significantly higher fibrinogen concentrations than did male controls, there was no significant difference in the odds ratios for fibrinogen between men and women ($p>0·1$).

Our results for total cholesterol are supported by a prospective study that found total cholesterol concentration to be significantly higher, but only univariately, in those developing transient ischaemic attack than in controls.[22] The only other aetiological study of lipids and transient ischaemic attack found that total cholesterol concentrations were no higher in cases than in age and sex matched controls.[23] Though our results disagree with those of most prospective studies of stroke,[24-32] they agree with the findings of large multiple risk factor intervention trial, which found a positive association between serum cholesterol concentration and death from non-haemorrhagic stroke.[33] Our study also agrees with a recent meta-analysis of 10 prospective studies examining total cholesterol and stroke. (Qizilbash *et al* International Epidemiological Association, 12th international meeting, Los Angeles, 1990).

Bias from non-response may have underestimated the mean difference found between cases and controls as some of the controls considered unsuitable for the study by their general practitioners could have had cancer, which may depress total cholesterol concentration.[34] Any bias from the fall in total cholesterol concentrations after an acute episode of transient ischaemic attack or minor ischaemic stroke and from dietary changes after the onset of these conditions (for example, reduced consumption of saturated fats) would also underestimate any observed difference.[6]

By studying transient ischaemic attack and minor ischaemic stroke we had an aetiologically more homogeneous case series than generally exists in prospective studies of stroke. This may explain why we found cholesterol to be a risk factor for transient ischaemic attack and minor ischaemic stroke, and by implication, for ischaemic stroke in general. The significant dose-response association further suggests that the relation is real.

Although low density lipoprotein cholesterol was strongly associated with transient ischaemic attack or minor ischaemic stroke in univariate analysis, after adjusting for confounders the association became non-significant. Case-control studies have found low density lipoprotein cholesterol concentrations to be univariately higher in transient ischaemic attack than in hospital controls matched for age and sex.[23] The Framingham study found low density lipoprotein cholesterol to be negatively associated with stroke in women ($p<0·05$) but not in men.[35] This suggests that the effect may be spurious, resulting from lack of statistical power in the subgroup analysis. The apparent dose-response relation supports this contention.

Our study concurs with the results of another case-control study of high density lipoprotein cholesterol and transient ischaemic attack.[23] In the Framingham study high density lipoprotein cholesterol was negatively associated with stroke in men, but a weak and non-significantly positive association emerged for women.[36] This contradictory result may have been due to chance analysis. Changes in high density lipoprotein cholesterol concentration after an acute episode of transient ischaemic attack, minor stroke, or major stroke have not been observed and thus are an unlikely source of bias.[6] Again, a significant dose-response relation suggests that our finding is real.

The actions of these risk factors in ischaemic stroke may be similar to those in ischaemic heart disease. The association with total cholesterol concentration probably reflects accelerated atherosclerosis from high low density lipoprotein cholesterol concentrations, and high density lipoprotein cholesterol may act as a reverse transporter of cholesterol from peripheral tissues to the liver.[36] Fibrinogen may be involved in atherosclerosis as it has been found in the intima of cerebral artery bifurcations[37] or it may enhance thrombus formation.[38]

The univariate significant results for the subsidiary variables—that is, ischaemic heart disease and a history of hypertension—agree with other data that suggest these variables are risk factors for transient ischaemic attack and ischaemic stroke.[39] That no difference emerged between cases and controls for blood pressure probably reflects greater medical surveillance and treatment of cases. Negative results for body mass index and packed cell volume also bear out other data.[2] Our results for diabetes mellitus and cigarette smoking are at odds with other evidence on these variables.[1,40] Alcohol was not a risk factor; although some studies have suggested it may be a risk factor, the evidence is unclear.[1] Snoring did not emerge as a risk factor, although one study has suggested an association with ischaemic stroke.[41]

In conclusion, we have identified fibrinogen, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol concentrations as risk factors for transient ischaemic attack and minor ischaemic stroke (though low density lipoprotein cholesterol was significant only univariately). By extrapolation, they may also be risk factors for ischaemic stroke. This pattern of results closely resembles that found in ischaemic heart disease.

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ONE HUNDRED YEARS AGO

We have the best authority for giving an absolute denial to the statement circulated this week alleging a continued failure of Mr. Gladstone's health since his late attack of influenza, and alleging a state of feebleness as the cause of his approaching visit to Biarritz and the Riviera. A precisely opposite state of things exists. Mr. Gladstone is, we are able to state, in an exceedingly, and indeed marvellously, vigorous state of health; and, far from being enfeebled, he is in a high state of physical vigour and mental activity, and in very high spirits. He did not suffer in the least from fatigue after his great oratorical effort at Newcastle, and was, indeed, fully authorised and approved by his physician, Sir Andrew Clark, in making another speech on the next day. There is not the slightest ground for any allegation of failing health; so much so, that it has not even been thought necessary that his physician should visit him at Hawarden prior to his undertaking his foreign journey. (*British Medical Journal* 1891;ii:1162)