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Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study

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Abstract

Objective To investigate risk factors, such as heavy alcohol consumption, that might explain any increased risk of haemorrhagic stroke associated with low blood cholesterol.

Design Prospective cohort study.

Setting Korea.

Participants 787 442 civil servants (661 700 men, 125 742 women) aged 30-64.

Main outcome measures Cardiovascular risk factors were assessed at biennial health check. Data on morbidity and mortality were ascertained from 1990 to 2001 using hospital admissions and mortality surveillance systems.

Results 6328 cases of ischaemic stroke (6021 men, 307 women), 3947 cases of haemorrhagic stroke (3748 men, 199 women), 3170 cases of undefined stroke (2902 men, 268 women), and 4417 cases of myocardial infarction (4305 men, 112 women) occurred. Ischaemic stroke and myocardial infarction were strongly and positively associated with blood cholesterol (hazard ratio per 1 mmol/l cholesterol 1.20 (95% confidence interval 1.16 to 1.24) and 1.48 (1.43 to 1.53), respectively). Haemorrhagic stroke showed an inverse association in fully adjusted models (0.91, 0.87 to 0.95). This inverse association was confined to participants with hypertension. When stratified by concentration of γ glutamyl transferase (GGT), an indicator of alcohol consumption, the association was not seen in participants with low concentrations of GGT, and it was independent of hypertension in those with high concentrations of GGT (>80 U/l).

Conclusions High alcohol consumption may underlie the association between low blood cholesterol and increased risk of haemorrhagic stroke.

Introduction

The role of blood cholesterol as a cause of stroke remains uncertain.¹⁻³ The lack of an association between all types of stroke and concentrations of cholesterol may mask a positive association with ischaemic stroke and an inverse association with haemorrhagic stroke. The inverse association between serum cholesterol and haemorrhagic stroke may be

specific to men with hypertension; this has led to speculation that heavy alcohol consumption underlies hypertension, hypocholesterolaemia, and increased risk of haemorrhagic stroke.⁴

This uncertainty causes concern that treatment to lower cholesterol might increase the risk of haemorrhagic stroke.⁵ A recent review of randomised trials found no influence of such treatment on haemorrhagic stroke.⁶ However, only 204 cases were used to estimate the risk of haemorrhagic stroke, and confidence intervals were wide. We aimed to resolve this uncertainty by investigating the association of blood cholesterol with stroke subtype in a large cohort of Korean civil servants.

Methods

Participants and study measures

Participants were Korean male and female public servants aged 30-64, who had a health check provided by the Korean national health system between 1986 and 1990. In total, 902 222 people were examined. We excluded people who changed job or had a myocardial infarction or stroke between 1986 and 1990, and people who lack data on blood cholesterol, leaving a study population of 787 442 (661 700 men, 125 742 women). Extra information on risk factors was obtained from the biennial multiphasic health examination and a self administered questionnaire. We excluded values obtained after a cardiovascular event and used mean values between 1986 and 1996 for measures that were repeated.

We classified participants into six groups according to cholesterol concentrations (table 1). See bmj.com for categories used for other risk factors.

Alcohol consumption was categorised as <30 , 30-104, 105-209, 210-419, or ≥ 420 g/week. We also measured γ glutamyl transferase (GGT) as a proxy of alcohol intake (Spearman's correlation coefficient 0.40 between self reported alcohol consumption and GGT values; $P < 0.0001$). Because participants (especially heavy drinkers) may under-report alcohol consumption, we stratified the analyses by each measure.

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Table 1 Associations between cardiovascular risk factors and cholesterol concentrations. Korean national health system study, 1986-2001. Values are mean (SD) unless stated otherwise

Risk factors	No of participants available	Serum cholesterol concentration (mmol/l)					
		≤3.36 (n=8319)	3.36-4.13 (n=105 293)	4.14-5.16 (n=415 744)	5.17-6.20 (n=217 158)	6.21-6.97 (n=32 945)	≥6.98 (n=7983)
Age (years)	787 442	40.1 (9.3)	39.9 (8.5)	41.8 (8.6)	43.8 (8.7)	45.4 (8.8)	46.1 (8.9)
Systolic blood pressure (mm Hg)	787 418	119.5 (13.4)	119.8 (12.5)	122.4 (12.8)	125.6 (13.7)	128.5 (14.7)	130.7 (16.0)
Diastolic blood pressure (mm Hg)	787 414	77.8 (9.3)	78.1 (8.5)	79.9 (8.6)	82.1 (8.9)	84.0 (9.4)	85.3 (10.1)
Body mass index	744 873	21.7 (2.2)	22.2 (2.3)	22.9 (2.4)	23.7 (2.4)	24.2 (2.4)	24.3 (2.4)
Glucose ≥7 mmol/l (%)	787 431	3.3	2.1	2.8	5.1	8.9	14.9
γ glutamyl transferase (U/l)*	500 419	36.2 (68.5)	33.9 (55.0)	38.8 (53.3)	48.0 (59.8)	59.2 (72.3)	76.8 (99.7)
γ glutamyl transferase >80 U/l*, n (%)	500 419	286 (7.8)	4 491 (6.9)	23 663 (8.7)	18 072 (13.1)	3 641 (19.1)	1082 (26.6)
≥20 cigarettes a day, n (%)	744 413	552 (8.7)	9 511 (9.8)	46 566 (11.8)	29 581 (14.2)	5 014 (16.3)	1258 (17.7)
No alcohol, n (%)	722 662	3643 (62.4)	52 523 (56.3)	198 096 (51.4)	97 533 (48.2)	14 137 (47.9)	3221 (48.2)
Alcohol <30 g/week, n (%)	722 662	3868 (66.3)	56 388 (60.4)	213 967 (55.6)	105 916 (52.4)	15 234 (51.6)	3422 (51.2)
Alcohol ≥210 g/week, n (%)	722 662	798 (13.7)	14 101 (15.1)	66 798 (17.3)	38 697 (19.1)	5 757 (19.5)	1450 (21.7)
Regular exercise, n (%)	742 973	932 (14.7)	15 489 (16.0)	69 324 (17.6)	39 345 (19.0)	5 800 (18.9)	1325 (18.7)
Lowest income group, n (%)	787 442	4430 (53.3)	38 469 (36.5)	123 498 (29.7)	57 240 (26.4)	9 052 (27.5)	2518 (31.5)

*Excluding participants positive for hepatitis B or of unknown status.

All risk factors were significantly different across concentrations of serum cholesterol (P<0.001) by χ^2 test, Mantel-Haenszel χ^2 test, and ANOVA.

Follow-up of mortality and morbidity from stroke

All myocardial infarctions, non-fatal strokes, and fatal strokes occurring between 1 August 1990 and 31 July 2001 were included. See bmj.com for ICD codes. Transient ischaemic attacks and subarachnoid haemorrhages were excluded. We ascertained fatal cases from the Korean national statistical office and the death benefit record of the Korean national health system. Morbidity was ascertained from hospital admissions.

Analytical methods

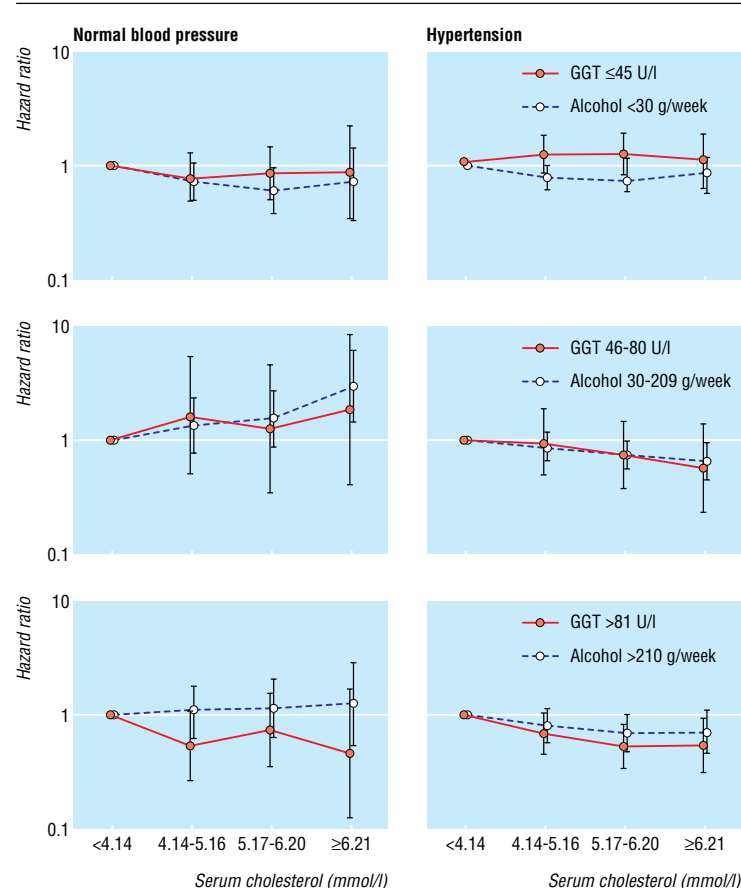
Follow-up began in August 1990, and the participants were censored at the date of admission or death attributable to stroke or myocardial infarction or other causes of death, or at 31 July 2001 if no censoring event occurred. We used Cox proportional hazards regression analysis to assess hazard ratios for myocardial infarction and subtypes of stroke according to concentrations of serum cholesterol. We used regression models for myocardial infarction, all stroke, ischaemic stroke, and haemorrhagic stroke, initially adjusting for age and sex and then for all covariates. To identify any effect of pre-existing occult disease, we repeated analyses after excluding events in the first five years of follow-up. We also stratified by presence or absence of hypertension and by both blood pressure and blood GGT concentrations (as a proxy for alcohol consumption) to evaluate the association between cholesterol and haemorrhagic stroke. We excluded 213 921 participants who had no GGT value or were positive or not tested for hepatitis B.

Results

Of the 787 442 participants (661 700 men and 125 742 women), 6328 (6021 men and 307 women) had an ischaemic stroke, 3947 (3748 men and 199 women) a haemorrhagic stroke, 3170 (2902 men, 268 women) an undefined stroke, and 4417 (4305 men and 112 women) a myocardial infarction. Table 1 shows the distribution of risk factors according to serum cholesterol group.

When we looked at the associations between serum cholesterol and stroke subtypes and myocardial infarction, all strokes showed a trend of increasing risk with higher cholesterol concentration (hazard ratio for

highest versus lowest groups, age and sex adjusted 2.55, 95% confidence interval 2.04 to 3.20), but this was greatly attenuated when adjusted for other covariates (1.13, 0.87 to 1.48). See bmj.com. Examining the associations with ischaemic stroke showed a strong, linear association with serum cholesterol (age and sex adjusted 4.54, 3.07 to 6.70). Full adjustment for covariates attenuated the association with ischaemic stroke but did not completely remove this association (1.67,



Fully adjusted risk for haemorrhagic stroke after participants who were seropositive for hepatitis B were excluded. Korean national health system study, 1986-2001. GGT=γ glutamyl transferase

Table 2 Risk of stroke and myocardial infarction in Korean national health system study, 1986-2001. Values are fully adjusted hazard ratios (95% confidence interval)

γ glutamyl transferase (U/l)	Stroke		Myocardial infarction (n=1430)
	Ischaemic (n=2067)	Haemorrhagic (n=1066)	
≤45	1.00	1.00	1.00
46-80	1.14 (1.02 to 1.27)	1.11 (0.94 to 1.32)	0.85 (0.75 to 0.98)
≥81	1.11 (0.99 to 1.25)	2.02 (1.74 to 2.34)	0.67 (0.57 to 0.79)

Ischaemic stroke ICD I63, I67.8; haemorrhagic stroke ICD I61; myocardial infarction ICD I21-I24.

1.07 to 2.61). The association with haemorrhagic stroke was non-linear, with weak evidence of an increased risk in both the lowest and the highest serum cholesterol groups. The fully adjusted hazard ratios of ischaemic stroke and myocardial infarction for each 1 mmol/l increase in serum cholesterol were 1.20 (1.16 to 1.24) and 1.48 (1.43 to 1.53). Full adjustment for covariates completely attenuated the increased risk in the highest cholesterol group.

The pattern was similar when we excluded events during the first five years of follow-up. Stratifying by presence or absence of hypertension showed that the inverse association with cholesterol was confined to people with hypertension. In such participants, the hazard ratio for haemorrhagic stroke was 0.89 (0.84 to 0.94) for each 1 mmol/l increase in serum cholesterol. Participants without hypertension showed no evidence of increased risk of haemorrhagic stroke, but confidence intervals were wide.

GGT was positively associated with haemorrhagic stroke (table 2) and inversely associated with myocardial infarction, indicating a protective effect of alcohol. When stratified by GGT concentrations (low (≤ 45 U/l), intermediate (46-80 U/l) and high (≥ 81 U/l)), the inverse association was confined to participants in the intermediate and high groups and was seen only in hypertensive participants (figure). When the analysis was stratified by self reported alcohol consumption (< 30 , 30-209, ≥ 210 g/week), the pattern was similar but the results were less clear than when stratified by GGT. The results were the same when we excluded 1% of the highest values for cholesterol and alcohol consumption.

What is already known on this topic

Low blood cholesterol may increase the risk of haemorrhagic stroke, raising concern that treatments that lower blood cholesterol may be harmful

Heavy alcohol consumption raises blood pressure, impairs liver function, and has anticoagulant effects and may underlie any association between low blood cholesterol and increased risk of haemorrhagic stroke

What this study adds

Increased risk of haemorrhagic stroke is confined to people with low concentrations of blood cholesterol and markers of high alcohol consumption

Lowering cholesterol is unlikely to increase the risk of haemorrhagic stroke, even in a population with a high incidence of haemorrhagic stroke

Discussion

Our study included almost 4000 cases of haemorrhagic stroke, investigated a wide range of covariates including socioeconomic factors, and explored risk of haemorrhagic stroke at low concentrations of cholesterol. We found an association between haemorrhagic stroke and low serum cholesterol only in participants with hypertension, suggesting that hypertension may modify the effects of low cholesterol. We believe our results are robust, given the specificity of the result, agreement with the randomised evidence, and adjustment for a wide range of covariates.

The contribution of alcohol

GGT reflects alcohol consumption and might be a better measure than self reporting.⁷ Raised GGT concentrations were caused mainly by hepatitis infection, alcohol consumption, and body mass index, so we excluded hepatitis carriers and adjusted for body mass index. Our finding that GGT was positively associated with haemorrhagic stroke and inversely associated with myocardial infarction agrees with earlier studies and validates the use of GGT as a marker of alcohol intake, especially for heavy drinkers.⁸ Previous studies have shown that people with low cholesterol concentrations are more likely to be heavy drinkers.⁹ Hypertension and other effects of alcohol could explain the increased risk of haemorrhagic stroke.¹⁰ In our study, increased risk of haemorrhagic stroke in people with low concentrations of blood cholesterol (< 4.14 mmol/l) was restricted to those with high GGT values; this relation was less evident when alcohol consumption was measured by self report. The measures of blood pressure might not have been a true reflection of risk, as transient high blood pressure associated with binge drinking may have an important role in haemorrhagic stroke.⁸ At low concentrations of GGT, low serum cholesterol was not associated with a higher risk of haemorrhagic stroke. In effect, low blood cholesterol may act as a marker of the health damaging effects of alcohol, rather than be a cause of haemorrhagic stroke.

Limitations

All information was routinely collected, but assessments of the quality of cholesterol assays are high. Errors may have been made in assigning the subtype of stroke. However, a high rate of neuroimaging can be expected in our study.

The high ratios of stroke to myocardial infarction and haemorrhagic stroke to ischaemic stroke in our study are consistent with current data from Korea. Our use of an occupational cohort might result in healthy worker effects, although these should not influence associations between risk factors and outcomes. Heavy drinkers might have been excluded from the workforce, but this would have attenuated the observed associations.

Implications

Low blood cholesterol may not in itself increase risk of haemorrhagic stroke. Blood cholesterol values in the range likely to be achieved by treatment with statins are not associated with increased risk of haemorrhagic stroke. In countries with high rates of haemorrhagic

stroke, preventive strategies that include lowering blood cholesterol should not be tempered because of concerns about a possible increased risk of haemorrhagic stroke.

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Ethical approval: Internal review board of Samsung Medical Centre and Korea National Health Insurance Corporation.

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Smoking, obesity, and their co-occurrence in the United States: cross sectional analysis

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Abstract

Objectives To describe the prevalence of obesity, smoking, and both health risk factors together among adults in the United States.

Design Cross sectional analysis of a national health interview survey.

Setting United States.

Participants 29 305 adults (aged ≥ 18) in 2002.

Main outcome measures Prevalence of adults who are obese (body mass index ≥ 30), who smoke, and who are obese and smoke. Prevalence was stratified by age, sex, ethnic group, education, and income.

Results 23.5% of adults were obese, 22.7% smoked, and 4.7% smoked and were obese.

Conclusions Although the proportion of adults who smoke and are obese is relatively low, this subgroup is concentrated among lower socioeconomic groups.

Introduction

Obesity and cigarette smoking are primary risk factors for several chronic conditions and early death in a large number of people in the United States. The prevalence of smoking among adults is 22.5% (45.8 million people).¹ The proportion of obese adults is also high—about 31% of adults have a body mass index of 30 or more.² Although smoking and obesity are public health priorities in the US,³ the overlap between the two conditions has not been measured at population level. Because the presence of these two conditions together probably carries an increased risk to health, statistics on how these conditions overlap could help in the development of an effective policy for prevention and treatment.

Methods

We used data from the 2002 national health interview survey (NHIS) to conduct a cross sectional analysis of 29 305 adults (≥ 18 years) and estimate the proportion of adults in the US who smoke and are obese. Prevalence was stratified by various sociodemographic factors. Rubin's multiple imputation procedure was used to replace missing values of family income. We analysed all data with Stata software, version 8 and adjusted the results with sampling weights to derive population estimates from the survey sample.

Results

Nearly 41.5% of adults (81 million aged ≥ 18 years) in the US are obese or smoke, and about 4.7% (9 million) smoke and are obese (table). Overall, 5.3% of men and 4.2% of women smoke and are obese. This proportion is higher in African Americans (7.0%) than in other racial or ethnic groups. A greater proportion of people with lower income and education levels smoke and are obese. With the exception of the over 65 age group, in which the prevalence of both conditions is low (1.1%; probably because these risk factors are associated with early death), little variation occurs across age groups.

Discussion

Although the proportion of adults who smoke and are obese in the US is relatively low (4.7%), the total number is 9 million. Each condition carries an independent health risk, and the presence of both

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