- 19 Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. *N Engl J Med* 1977;297:405-9.
- 20 Kagan A, Yano K, Rhoads GG, McGee DL. Alcohol and cardiovascular disease: the Hawaiian experience. *Circulation* 1981;64(suppl 3):27-31.
- 21 Kozarevic D, McGee D, Vojvodic N, Racic Z, Dawber T, Gordon T, et al. Frequency of alcohol consumption and morbidity and mortality: the Yugoslavia cardiovascular disease study. *Lancet* 1980;ii:613-6.
- 22 Salonen JT, Puska P, Nissinen A. Intake of spirits and beer and risk of myocardial infarction and death—a longitudinal study in eastern Finland. *Journal of Chronic Diseases* 1983;36(7):533-43.
- 23 Kittner SJ, Garcia PM, Costas RJ, Cruz VM, Abbott RD, Havlik RJ. Alcohol and coronary heart disease in Puerto Rico. *Am J Epidemiol* 1983;117(5):538-50.
- 24 Friedman LA, Kimball AW. Coronary heart disease mortality and alcohol consumption in Framingham. *Am J Epidemiol* 1986;124(3):481-9.
- 25 Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med* 1988;319:267-73.
- 26 Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 1991;338:464-8.
- 27 Farchi G, Fidanza F, Mariotti S, Menotti A. Alcohol and mortality in the Italian rural cohorts of the seven countries study. *Int J Epidemiol* 1992;21:74-81.
- 28 Klatsky AL, Armstrong MA. Alcoholic beverage choice and risk of coronary artery disease mortality: do red wine drinkers fare best? *Am J Cardiol* 1993;71:467-9.
- 29 Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol* 1990;66:1237-42.
- 30 Klatsky AL, Armstrong MA, Friedman GD. Relations of alcoholic beverage use to subsequent coronary artery disease hospitalization. *Am J Cardiol* 1986;58:710-4.
- 31 Gronbaek M, Deis A, Sorensen TIA, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine, beer, or spirits. *BMJ* 1995;310:1165-9.
- 32 Barnard MJ, Linter SPK. Wine and coronary heart disease. *Lancet* 1992;340:313-4.
- 33 Segall JJ. Wine and coronary heart disease. *Lancet* 1992;340:313.
- 34 Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987;317:1303-9.
- 35 Manson JE, Tosteson H, Ridker PM, Satterfield S, O'Connor HP. The primary prevention of myocardial infarction. *N Engl J Med* 1992;326:1406-16.
- 36 Dunbabin DW, Sandercock PA. Preventing stroke by the modification of risk factors. *Stroke* 1990;21(12 suppl):IV36-9.
- 37 Rothman KJ. *Modern epidemiology*. Boston, MA: Little Brown, 1986.
- 38 Giovannucci E, Stampfer MJ, Colditz GA, Manson J, Rosner B, Longnecker M, et al. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. *Am J Epidemiol* 1993;137:502-11.
- 39 Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* 1991;133:810-7.
- 40 Klatsky AL, Armstrong MA, Kipp H. Correlates of alcoholic beverage preference: traits of persons who choose wine, liquor or beer. *British Journal of Addiction* 1990;85:1279-89.
- 41 Barboriak JJ, Barboriak DP, Anderson AJ, Hoffman RG. Drinking patterns and preferences among heart patients. *Currents in Alcoholism* 1981;8(293):293-9.
- 42 Ducimetiere P, Guize L, Marciniak A, Milon H, Richard J, Rufat P. Arteriographically documented coronary artery disease and alcohol consumption in French men. The CORALI study. *Eur Heart J* 1993;14(6):727-33.
- 43 Hulley SB, Gordon S. Alcohol and high density lipoprotein cholesterol. Causal inference from diverse study designs. *Circulation* 1981;64:57-63.
- 44 Thornton J, Symes C, Heaton K. Moderate alcohol intake reduces bile cholesterol saturation and raises HDL cholesterol. *Lancet* 1983;iii:819-22.
- 45 Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373-81.
- 46 Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rosner B, Van Denburgh M, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993;329:1829-34.
- 47 Langer RD, Criqui MH, Reed DM. Lipoproteins and blood pressure as biological pathways for effect of moderate alcohol consumption on coronary heart disease. *Circulation* 1992;85(3):910-5.
- 48 Criqui MH, Cowan LD, Tyroler HA, Bangdiwala S, Heiss G, Wallace RB, et al. Lipoproteins as mediators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality: results from the lipid research clinics follow-up study. *Am J Epidemiol* 1987;126(4):629-37.
- 49 Suh I, Shaten BJ, Cutler JA, Kuller LH. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group [see comments]. *Ann Intern Med* 1992;116:881-7.
- 50 Renaud SC, Beswick AD, Fehily AM, Sharp DS, Elwood PC. Alcohol and platelet aggregation: the Caerphilly prospective heart disease study. *Am J Clin Nutr* 1992;55:1012-7.
- 51 Ridker PM, Vaughan DE, Stampfer MJ, Glynn RJ, Hennekens CH. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA* 1994;272:929-33.
- 52 Kluft C, Veenstra J, Schaafsma G, Pikaar NA. Regular moderate wine consumption for five weeks increases plasma activity of the plasminogen activator inhibitor-1 (PAI-1) in healthy young volunteers. *Fibrinolysis* 1990;4(suppl 2):69-70.
- 53 Stampfer MJ, Rimm EB, Walsh DC. Commentary: alcohol, the heart, and public policy. *Am J Public Health* 1993;83:801-4.
- 54 Siemann EH, Creasy LL. Concentration of the phytoalexin resveratrol in wine. *American Journal of Enology and Viticulture* 1992;43:49-52.
- 55 Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. *Lancet* 1993;341:1103-4.
- 56 Maxwell S, Cruickshank A, Thorpe G. Red wine and antioxidant activity in serum. *Lancet* 1994;344:193-4.
- 57 Fitzpatrick DF, Hirschfield SL, Coffey RG. Endothelium-dependent vasorelaxing activity of wine and other grape products. *Am J Physiol* 1993;265:H774-8.

(Accepted 18 December 1995)

Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow up in the Copenhagen male study

Hans Ole Hein, Poul Suadicani, Finn Gyntelberg

See editorial and p 731

Abstract

Objectives—To investigate the interplay between use of alcohol, concentration of low density lipoprotein cholesterol, and risk of ischaemic heart disease.

Design—Prospective study with controlling for several relevant confounders, including concentrations of other lipid fractions.

Setting—Copenhagen male study, Denmark.

Subjects—2826 men aged 53–74 years without overt ischaemic heart disease.

Main outcome measure—Incidence of ischaemic heart disease during a six year follow up period.

Results—172 men (6.1%) had a first ischaemic heart disease event. There was an overall inverse association between alcohol intake and risk of ischaemic heart disease. The association was highly dependent on concentration of low density lipoprotein cholesterol. In men with a high concentration (≥ 5.25 mmol/l) cumulative incidence rates of ischaemic heart disease were 16.4% for abstainers, 8.7% for those who drank 1–21 beverages a week, and 4.4% for those who drank 22 or more beverages a week. With abstainers as reference and after adjust-

ment for confounders, corresponding relative risks (95% confidence interval) were 0.4 (0.2 to 1.0; $P < 0.05$) and 0.2 (0.1 to 0.8; $P < 0.01$). In men with a concentration < 3.63 mmol/l use of alcohol was not associated with risk. The attributable risk (95% confidence interval) of ischaemic heart disease among men with concentrations ≥ 3.63 mmol/l who abstained from drinking alcohol was 43% (10% to 64%).

Conclusions—In middle aged and elderly men the inverse association between alcohol consumption and risk of ischaemic heart disease is highly dependent on the concentration of low density lipoprotein cholesterol. These results support the suggestion that use of alcohol may in part explain the French paradox.

Introduction

Several epidemiological studies have shown an inverse association between alcohol consumption and risk of ischaemic heart disease, the association often being described as J or U shaped.¹

Epidemiological studies have shown a positive cor-

Copenhagen Male Study, Epidemiological Research Unit, 7122 Rigshospitalet, State University Hospital, DK-2200 Copenhagen N, Denmark
Hans Ole Hein, associate professor
Poul Suadicani, senior researcher
Finn Gyntelberg, professor

Correspondence to: Dr Hein.

BMJ 1996;312:736–41

relation between the serum concentration of low density lipoprotein cholesterol and risk of ischaemic heart disease.² A high intake of saturated fat is associated with an increase in concentration of low density lipoprotein cholesterol and subsequently an increased risk of ischaemic heart disease. Despite a high intake of saturated fat, in some parts of France the incidence of ischaemic heart disease is quite low, with a rate comparable with that in Japan. This apparent discrepancy between a risky lifestyle and a low risk of ischaemic heart disease has been named the French paradox. The suggestion of a French paradox is based on ecological studies.³⁻⁵

The low incidence of ischaemic heart disease in France might be the result of regular consumption of alcohol.³⁻⁵ A comparative ecological study of 21 developed, relatively affluent countries, showed that France had the highest consumption of wine and total alcohol per capita.⁵ The high fat and alcohol consumption and the low risk of ischaemic heart disease indicate the existence of an interaction between the concentration of low density lipoprotein cholesterol, alcohol consumption, and risk of ischaemic heart disease. To our knowledge, this issue has not previously been studied prospectively.

We investigated this interplay in a cohort of Danish men. As recently reviewed by Criqui and Ringel,⁶ in Denmark the average intake of dietary fat is higher than that in France, and also the average consumption of alcohol is quite high but lower than that in France. We took into account the type of beverage consumed, other lipid fractions particularly high density lipoprotein cholesterol, and several other potentially confounding factors.

Subjects and methods

The Copenhagen male study was set up in 1970 as a prospective cardiovascular study.^{6,7} The men came from 14 large work places in Copenhagen.⁶ All employed men (6125) aged 40 to 59 years (mean 48 years) were invited—from the managing director to the porter. A total of 5249 men participated (87%).

In 1971-2 the cohort was re-examined; the participation rate was 90.5%. Information was acquired about average daily use of alcohol during the preceding year. At that time alcohol consumption was reported in five categories: <1, 1-2, 3-5, 6-10, and >10 beverages a day. Thus, from these categories it was not possible to identify abstainers. The 1971-2 data were used to estimate changes in alcohol habits over time.

In 1985-6 a new baseline was established for the study and has been used in this report. All survivors from the 1970 study were traced by means of the Danish central population register. Between June 1985 and June 1986 all 4505 survivors (except 34 emigrants) from the original cohort were invited to take part in the current study. In total 3387 (75%) men participated and gave informed consent; their mean (range) age was 63 (53-74) years. Each subject was interviewed by a physician (HOH) about a previously completed questionnaire and examined, with height, weight, and blood pressure being measured and an electrocardiogram being recorded. A venous blood sample was taken after the subject had fasted for at least 12 hours for measurements of serum lipid concentrations, Lewis phenotypes, and serum cotinine concentration.

Total weekly alcohol consumption was calculated from questionnaire items about average alcohol consumption on weekdays and at weekends. Intakes of beer, wine, and spirits were recorded separately. One drink corresponded to 10-12 g ethanol. The men classed themselves as having never smoked, as having smoked, or as current smokers. Current tobacco smoking was calculated from information about the

number of cigarettes, cheroots, cigars, or the weight of pipe tobacco smoked daily. One cigarette was taken as equivalent to 1 g tobacco, one cheroot as 3 g, and one cigar as 4 g. As previously estimated from serum cotinine concentrations, the validity of tobacco reporting was high.⁸ The men also classed themselves as being physically active for four or more hours a week or for less than four hours a week. According to a system by Svalastoga,⁹ later adjusted, the men's social class was given as one of five social groups on the basis of education and job profile. The classes ranged from class I (self employed subjects with at least 21 employees, white collar workers with at least 51 subordinates, and men with an academic degree) to class V (unskilled blue collar workers such as unskilled labourers, mechanics, and drivers).

Concentrations of serum lipids, high density lipoprotein cholesterol, and triglycerides were determined by using standardised methods.¹⁰⁻¹³ Low density lipoprotein cholesterol was calculated from the above.¹⁴ Lewis typing was carried out on erythrocytes by using a saline haemagglutination technique in test tubes with monoclonal a and b antibodies (Seraclone, Biotest, Dreieich, Germany).¹⁵ One drop of antibody was mixed with one drop of 5% erythrocyte suspension and read macroscopically.

An electrocardiogram was recorded while the subject was supine and at rest with a three channel Mingograph-34 from 12 standard leads. The traces were coded according to the Minnesota code.¹⁶ Blood pressure was measured in the right arm with the subject seated by using a manometer developed by the London School of Hygiene and Tropical Medicine.¹⁷ Hypertension was defined as the subject receiving antihypertensive treatment or having a systolic blood pressure ≥ 150 mm Hg and a diastolic blood pressure ≥ 100 mm Hg. Body mass index (weight(kg)/(height (m)²)) was calculated. Chronic bronchitis was defined from a slightly modified version of the British Medical Research Council questionnaire on respiratory symptoms as cough and phlegm lasting three months or more for at least two years.¹⁸ Self reported history of cancer was accepted if verified by the Danish cancer registry. The men reported whether they took medicine regularly, their self assessed state of health, and whether they had non-insulin dependent diabetes mellitus.

We excluded from the prospective study men who at baseline had a history of acute myocardial infarction, angina, or stroke or who had intermittent claudication. We checked the hospital records of all those who reported admission to hospital because of acute myocardial infarction before the start of the study. The diagnosis was accepted if at least two of the following symptoms or signs were recorded: retrosternal pain lasting more than 20 minutes, typical serial electrocardiographic changes in more than two electrocardiograms, acute increase in activities of relevant serum enzyme concentrations (alanine aminotransferase, lactate dehydrogenase, or creatinine phosphokinase MB). Angina was assessed according to information from the questionnaire¹⁶ and confirmed by a physician. Intermittent claudication was established from the questionnaire,¹⁶ and stroke was verified by a doctor. A total of 342 men (10.1%) were excluded because of cardiovascular diseases or symptoms and 219 men (6.5%) because of missing data or conflicting answers. Overall, 2826 men were eligible for the incidence study.

In 1993 a register follow up was carried out on morbidity and mortality between 1985-6 and 31 December 1991. All men who had taken part in the 1985-6 study were traced from registers. Information on hospital admissions and death certificate diagnoses within the follow up period were obtained. We used

the diagnoses from registers. Accepted diagnoses for ischaemic heart disease were codes 410-414 (*International Classification of Diseases*, 8th revision). Correlating data on alcohol consumption and concentrations of serum lipids was done by regression analyses with adjustment for age. The age adjusted Pearson correlation coefficients are given, and χ^2 or non-parametric Mann-Whitney tests have been used for testing possible differences in the distribution of characteristics of abstainers and alcohol users.

To estimate which cardiovascular risk factors separated cases of ischaemic heart disease from non-cases and those who died from all causes from survivors forward stepwise logistic regression analyses were applied by using the maximum likelihood ratio method. Logistic regression analyses were performed with interaction terms for the concentrations of high and low density lipoprotein cholesterol (as continuous variables) and alcohol consumption (also continuous) to examine whether interactive effects significantly improved the model fit provided by main effects of the

single variables.¹⁹ For transparency, logistic regression analyses were performed stratified by three concentrations of low density lipoprotein cholesterol. To test for a possible dose-effect relation between alcohol consumption and risk of ischaemic heart disease, alcohol consumption was included as a three group categorical variable in the stratified analyses, and adjustments were made for main effects of potentially confounding factors. All basic analyses and the logistic regression analyses were performed with the SPSSPC+ statistical software, version 3.1.^{20,21} For all analyses a P value of ≤ 0.05 was taken as significant.

The study was approved by the ethics committee for medical research in the county of Copenhagen.

Results

The age adjusted correlation coefficients at baseline between alcohol consumption reported in beverages a week and serum concentrations of fasting lipid fractions (low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides) were -0.03, 0.20, and 0.05, respectively, in agreement with the Framingham study.²

The men were classed as three groups according to alcohol consumption: 298 abstainers, 1681 moderate drinkers (1-21 beverages a week), and 847 who consumed 22 beverages a week or more. The overall alcohol consumption median (2.5 and 97.5 centiles) was 15.0 (0 and 53.5) beverages/week. The median consumption in each group was 0 (0 and 0), 12 (4.5 and 21.5), and 31.5 (22.5 and 67.0), respectively. Among drinkers the alcohol consumption was 16.0 (4.5 and 54.0).

In the stratified analyses the men were classed as three groups according to their concentrations of low and high density lipoprotein cholesterol and triglycerides: the lowest fifth, the three middle fifths, and the highest fifth of the lipid fraction in question. The median concentration of low density lipoprotein cholesterol in mmol/l in each part of the distribution was: 3.22 (1.99 and 3.60), 4.41 (3.66 and 5.18), and 5.77 (5.26 and 7.51), respectively. The corresponding figures for high density lipoprotein cholesterol were 0.96 (0.69 and 1.07), 1.32 (1.09 and 1.61), and 1.81 (1.64 and 2.58), respectively, and for triglycerides were 0.81 (0.57 and 0.93), 1.31 (0.95 and 1.88), and 2.44 (1.95 and 7.36), respectively.

During the follow up period 172 men (6.1%) had a first ischaemic event; 42 were fatal. A total of 268 men (9.5%) died from all causes. Among 342 men excluded because of cardiovascular diseases, 96 (28%) died; 67 (70%) of cardiovascular disease (ICD-8 codes 390-458).

Table 1 presents characteristics of abstainers and alcohol users. Alcohol abstainers had significantly lower concentrations of high density lipoprotein cholesterol than had alcohol users. A much larger proportion of abstainers had a low alcohol consumption (<1 beverage a day) 15 years earlier as compared with alcohol users: 87% v 53%. With respect to health factors, a larger proportion of abstainers had a history of non-insulin dependent diabetes and cancer. A larger proportion of abstainers used medicine on a regular basis—that is, daily or weekly. Abstainers were on average three years older than alcohol users ($P < 0.001$). The electrocardiographic characteristics presented are those which were significantly associated with risk of ischaemic heart disease during the six year follow up (analysis not shown). Electrocardiographic changes were equally prevalent among abstainers and alcohol users.

Table 2 illustrates the crude association between low density lipoprotein cholesterol and risk of ischaemic heart disease during the six year follow up period

Table 1—Various characteristics of non-drinkers and alcohol users. Values are medians (2.5 and 97.5 centiles) or numbers (percentages) of subjects

Characteristic	Non-drinkers (n=298)	Alcohol users (n=2528)
Serum lipids (mmol/l)		
Low density lipoprotein cholesterol	4.52 (2.40 and 6.78)	4.40 (2.57 and 6.60)
High density lipoprotein cholesterol	1.20 (0.76 and 1.98)	1.33 (0.81 and 2.22)***
Triglycerides	1.37 (0.68 and 3.84)	1.31 (0.67 and 3.80)
Lifestyle factors		
Alcohol use reported in 1972 as <1 beverage/day during 1971	259 (87)	1340 (53)***
Tobacco (g/day)	1.5 (0 and 30)	5.0 (0 and 35)
Physical activity (<4 h/week)	143 (48)	1188 (47)
Clinical/paraclinical factors		
Body mass index (kg/m ²)	25.5 (19.7 and 33.9)	25.4 (20.0 and 33.0)
Systolic blood pressure (mm Hg)	119 (93 and 158)	120 (94 and 158)
Diastolic blood pressure (mm Hg)	70 (51 and 98)	72 (52 and 95)
Hypertension	34 (11)	288 (11.4)
Lewis phenotype Le(a-b-)	22 (7)	245 (10)
Health factors		
Non-insulin dependent diabetes	11 (4)	43 (2)
Bronchitis	47 (16)	354 (14)
History of cancer	32 (11)	163 (7)*
Regular use of medicine	110 (37)	784 (31)*
Self assessed good health	152 (51)	1441 (57)
Angina according to Rose questionnaire not verified by doctor	6 (2)	40 (2)
Intermittent claudication according to Rose questionnaire not verified by doctor	3 (1)	28 (1)
Electrocardiographic changes:		
High amplitude R	13 (4)	116 (5)
ST depression	17 (6)	111 (4)
T wave abnormalities	26 (9)	202 (8.0)
Other characteristics:		
Low social class	143 (48)	1277 (51)
Age (years)	64.5 (55.5 and 73.0)	61.5 (55.5 and 73.5)***

* $P < 0.05$; *** $P < 0.001$ —Mann-Whitney test or χ^2 analysis.

Table 2—Incidence of ischaemic heart disease over six years according to alcohol use and serum lipid concentration. Values are numbers (percentages) of subjects

Serum lipid concentration (mmol/l)	No of alcoholic beverages drunk a week		
	0 (n=298)	1-21 (n=1681)	≥ 22 (n=847)
Low density lipoprotein cholesterol:			
≤ 3.62	3/58 (5.2)	7/301 (2.3)	12/199 (6.0)
3.63-5.24	17/185 (9.2)	65/1031 (6.3)	23/488 (4.7)
≥ 5.25	9/55 (16.4)	29/349 (8.3)	7/160 (4.4)
High density lipoprotein cholesterol:			
≤ 1.07	12/91 (13.2)	33/375 (8.8)	6/116 (5.2)
1.08-1.63	15/178 (8.4)	56/1014 (5.5)	24/498 (4.8)
≥ 1.64	2/29 (6.9)	12/292 (4.1)	12/233 (5.2)

Table 3—Characteristics of men who had first ischaemic heart disease event during six year follow up and in others.* Values are medians (2.5 and 97.5 centiles) or numbers (percentages) of subjects

Characteristic	Ischaemic heart disease event (n=172)	No event (n=2654)	P value†
Hypertension	34 (20)	287 (4)	0.01
Low density lipoprotein cholesterol (mmol/l)	4.69 (2.70 and 6.61)	4.40 (2.51 and 6.62)	<0.001
Age (years)	63.5 (55.5 and 74.2)	62.5 (55.5 and 73.5)	0.02
Tobacco (g/day)	7.5 (0 and 44.7)	4.0 (0 and 32)	0.01
High density lipoprotein cholesterol (mmol/l)	1.22 (0.77 and 2.21)	1.33 (0.81 and 2.19)	0.002
Systolic blood pressure (mm Hg)	125 (94 and 165.2)	120 (93 and 158)	0.01
Alcohol×low density lipoprotein cholesterol‡		-0.08	0.002
Alcohol×high density lipoprotein cholesterol‡		0.06	0.01
Bronchitis	34 (20)	366 (14)	0.05

*Variables not significant after adjustment were triglyceride concentration, number of alcoholic beverages a week, physical activity, body mass index, diastolic blood pressure, non-insulin dependent diabetes, history of cancer, regular use of medicine, self assessed good health, symptoms of angina and intermittent claudication not verified by a doctor, Lewis phenotypes (Le(a-b-) v rest), and social class. †P value shows probability outcome after forward stepwise multiple logistic regression analysis with maximum likelihood ratio method. Variables are presented by order of entry into model. A priori probability to enter model was $P < 0.05$.

‡Interaction term between weekly alcohol consumption and lipid fraction. Values are partial regression coefficients.

Table 4—Relative risks (95% confidence intervals) of ischaemic heart disease during six years according to concentration of low density lipoprotein cholesterol and alcohol consumption. In analyses alcohol abstention group is regarded as reference category

Low density lipoprotein concentration (mmol/l)	Alcoholic beverages/week			P value†
	0 (n=298)	1-21 (n=1681)	≥ 22 (n=847)	
<3.62	1 (n=58)	0.5 (0.1 to 2.2) (n=301)	1.1 (0.3 to 4.3) (n=199)	0.32
3.63-5.24	1 (n=185)	0.8 (0.5 to 1.5) (n=1031)	0.7 (0.3 to 1.3) (n=488)	0.28
≥ 5.25	1 (n=55)	0.4 (0.2 to 1.0)* (n=349)	0.2 (0.1 to 0.8)** (n=160)	0.01

†P value represents probability outcome of test for trend in logistic model after adjustment for factors significantly associated with risk of ischaemic heart disease in table 3 (except low density lipoprotein cholesterol and interaction terms).

* $P < 0.05$; ** $P < 0.01$.

according to alcohol drinking. There was a strong inverse association between alcohol consumption and risk of ischaemic heart disease in men in the highest fifth of low density lipoprotein cholesterol concentration. Cumulative incidence rates were 16.4% for abstainers, 8.7% for those who drank 1-21 beverages a week, and 4.4% for those who drank 22 or more. In the large intermediate group there was a similar trend, though with a less steep slope. In men with low concentrations of low density lipoprotein cholesterol there was no inverse gradient.

Table 2 also shows the crude relation between high density lipoprotein cholesterol and risk of ischaemic heart disease during the six year follow up period according to alcohol intake. Abstainers had a high risk of ischaemic heart disease if they also had low concentrations of high density lipoprotein cholesterol (1.07 mmol/l or less) compared with men with higher concentrations (> 1.64 mmol/l). The inverse relation between alcohol consumption and risk was strong in men with low concentrations. In the large intermediate group there was a similar trend, though with a less steep slope. In men with high concentrations there was no inverse gradient.

Overall there was an increased risk of ischaemic heart disease with increasing concentration of triglycerides. There was no interaction between use of alcohol, concentration of triglycerides, and risk of ischaemic heart disease. For all three groups of triglyceride concentration alcohol abstainers had the

highest risk of ischaemic heart disease (not shown).

Table 3 gives the results of a multivariate forward stepwise logistic regression analysis that includes interaction terms between low density lipoprotein cholesterol, high density lipoprotein cholesterol, and alcohol consumption. The strongest predictive factors for ischaemic heart disease after multivariable adjustment were hypertension ($P = 0.01$), low density lipoprotein cholesterol concentration ($P < 0.001$), age ($P = 0.02$), tobacco use ($P = 0.01$), high density lipoprotein cholesterol concentration ($P = 0.002$), systolic blood pressure ($P = 0.01$), the interaction term alcohol×low density lipoprotein cholesterol ($P = 0.002$), the interaction term alcohol×high density lipoprotein cholesterol ($P = 0.01$), and bronchitis ($P = 0.05$).

Table 4 shows the relative risk of ischaemic heart disease for different concentrations of low density lipoprotein cholesterol according to alcohol consumption. In the analyses adjustments were made for potential confounders including other lipid fractions. The strongest inverse dose-effect association was found between use of alcohol and risk of ischaemic heart disease in men whose concentration of low density lipoprotein cholesterol was in the highest fifth. Compared with abstainers, men who drank 22 or more alcoholic beverages a week had a relative risk (95% confidence interval) of 0.2 (0.1 to 0.8; $P < 0.01$); and for 1-21 alcoholic beverages a week the relative risk was 0.4 (0.2 to 1.0; $P < 0.05$). Statistically, there was no difference in the incidence of ischaemic heart disease between the groups, neither in bivariate nor multivariate analyses that took into account potential confounders (not shown). In the three middle fifths of the distribution of low density lipoprotein cholesterol concentration (3.63-5.24 mmol/l) the inverse association with ischaemic heart disease was less pronounced and not significant. Corresponding analyses on middle groups of high density lipoprotein cholesterol gave less conspicuous results between use of alcohol and risk of ischaemic heart disease (not shown). However, men with concentrations in the lowest fifth who were also abstainers had a threefold increased risk of ischaemic heart disease compared with men who drank 22 or more beverages a week ($P < 0.05$).

The attributable risk of ischaemic heart disease among men with concentrations of low density lipoprotein cholesterol ≥ 3.63 mmol/l who also abstained from alcohol was 43% (10% to 64%). We examined which kind of beverage—beer, wine, or strong spirits—had the strongest relation with ischaemic heart disease among men with concentrations of low density lipoprotein cholesterol ≥ 3.63 mmol/l. Adjusted for age, the strongest inverse associations were found for strong spirits (partial regression coefficient -0.06, $P < 0.01$) and wine (partial regression coefficient -0.04, $P < 0.05$). The partial regression coefficient for beer drinking was -0.02 ($P = 0.34$). This agrees with the results of Rimm *et al*, who found that the use of strong spirits seemed to be more strongly associated than the use of wine with an increased risk of ischaemic heart disease.¹

Table 5 gives the results of a logistic regression analysis with all cause mortality as the outcome variable, including the same potential confounders as in table 2. Factors that significantly separated those who died from the others after multivariable adjustment were history of cancer, age, regular use of medicine, bronchitis, social class, use of tobacco, and concentration of high density lipoprotein cholesterol. There was no difference in weekly alcohol consumption between those who died and survivors: medians (2.5 and 97.5 centiles) were 15.0 (0 and 53.5) and 15.0 (0 and 53.5) beverages a week, respectively.

Table 5—Characteristics of men who died from all causes and of others.* Values presented are medians (2.5 and 97.5 centiles) or numbers (percentages) of subjects

Characteristic	All causes (n=268)	Others (n=2558)	P value†
History of cancer	60 (22)	135 (5)	<0.001
Age (years)	65.5 (55.5 and 74.5)	61.5 (55.5 and 73.5)	<0.001
Regular use of medicine	127 (40)	767 (30)	<0.001
Bronchitis	71 (27)	330 (13)	<0.001
Low social class	161 (60)	1259 (49)	<0.01
Tobacco (g/day)	9.0 (0 and 40)	3.0 (0 and 33)	0.05
High density lipoprotein cholesterol (mmol/l)	1.33 (0.82 and 2.47)	1.32 (0.80 and 2.15)	0.02

*Variables not significant after multivariable adjustment were low density lipoprotein cholesterol, triglyceride concentration, number of alcoholic beverages a week, physical activity, body mass index, systolic and diastolic blood pressure, non-insulin dependent diabetes, hypertension, self assessed good health, symptoms of angina and intermittent claudication not verified by a doctor, Lewis phenotypes (Le(a-b-) v rest), and interaction terms (alcohol×low density lipoprotein cholesterol and alcohol×high density lipoprotein cholesterol).

†P value shows probability outcome after forward stepwise multiple logistic regression analysis with maximum likelihood ratio method. Variables are presented by order of entry into model. A priori probability to enter model was $P < 0.05$.

For men in the highest fifth of concentration of low density lipoprotein cholesterol the all cause mortality was independent of use of alcohol, with cumulative incidences of 10.9%, 10.3%, and 8.8%, respectively; incidences adjusted for age were 8.9%, 10.3%, and 9.6%. Overall, abstainers had a slightly higher mortality compared with moderate and heavy drinkers; incidences adjusted for age were 11.1%, 9.3%, and 9.5%, respectively; these differences were not significant, neither in tests for trend nor heterogeneity.

Discussion

This study of 2826 middle aged and elderly men who were free from overt cardiovascular disease showed a strong interaction between use of alcohol, concentration of low density lipoprotein cholesterol, and risk of ischaemic heart disease. The inverse association between alcohol consumption and risk of ischaemic heart disease depended highly on the concentration of low density lipoprotein cholesterol. Among men with a high concentration of low density lipoprotein cholesterol a substantial number of ischaemic heart disease events could be ascribed to abstinence.

POTENTIAL BIAS

Were the results plausible or the result of bias? Abstainers were characterised by a disadvantageous risk factor profile. There was a significantly higher proportion of men with non-insulin dependent diabetes, and they had lower concentrations of high density lipoprotein cholesterol—both well known risk factors for ischaemic heart disease. Also they were older, had a higher prevalence of cancer, and used more medicine (table 1). These and other potentially confounding risk factors were included in the multivariate analyses where appropriate. Differences in risk factors in alcohol users and abstainers did not explain our findings.

Shaper *et al* suggested that the observed relation between use of alcohol and death from ischaemic heart disease in prospective studies is due to a large proportion of "sick quitters" among abstainers.^{22,23} We had a small group (n=35) of potentially sick quitters—that is, men who at the 1971-2 investigation reported drinking alcohol and in 1985-6 were non-drinkers. There were four cases of ischaemic heart disease in the six year follow up period in this group against an expected 2.1. Exclusion of these 35 men had no influence on our results (not shown).

In a previous paper we discussed the importance of validity of data and reporting bias.²⁴ Imprecision in the reporting of alcohol consumption and lack of precision

with respect to diagnosis of ischaemic heart disease would tend only to weaken real associations. Could the finding of a significant interaction between use of alcohol, concentration of low density lipoprotein cholesterol, and risk of ischaemic heart disease be an artefact caused by selection? This seems unlikely as we have adjusted for a large number of major potential confounders. In summary, major sources of bias—an adverse risk factor profile among abstainers, a particularly high risk of ischaemic heart disease among sick quitters, reporting bias, and bias due to selection—seem to be unlikely explanations.

BIOLOGICAL PLAUSIBILITY

The strong inverse dose-effect relation between use of alcohol and risk of ischaemic heart disease in men with a high concentration of low density lipoprotein cholesterol suggests a biological dependency. The results of some recent studies support this hypothesis. In a review article Folsom reported that use of alcohol was inversely correlated with fibrinogen in eight observational and intervention studies.²⁵ In a prospective study of 2116 healthy men Heinrich *et al* found that a low plasma fibrinogen concentration was associated with low coronary risk even when the concentration of low density lipoprotein cholesterol was raised.²⁶ Though no information about use of alcohol was presented, it is interesting that the results of Heinrich *et al* indicate that a high concentration of low density lipoprotein cholesterol is not necessarily associated with an increased risk of ischaemic heart disease.

Ridker *et al* found that among 631 apparently healthy male physicians there was a positive association between moderate use of alcohol and plasma concentrations of endogenous tissue type plasminogen activator antigen and that this association was independent of high density lipoprotein cholesterol concentration.²⁷ This suggested that changes in fibrinolytic potential may be an important mechanism whereby moderate alcohol consumption may decrease the risk of ischaemic heart disease. Hendriks *et al* showed that the postprandial fibrinolytic potential was increased after the intake of moderate amounts of alcohol.²⁸ In these studies different concentrations of low density lipoprotein cholesterol and alcohol consumption were not analysed.²⁶⁻²⁸ These studies indicate that in men with a high concentration of low density lipoprotein cholesterol use of alcohol may be associated with profound derangements in plasma fibrinogen and the fibrinolytic system.

Another more speculative biological mechanism of action could be an antiatherogenic effect of alcohol. Kiechl *et al* have shown that an inverse association exists between alcohol intake and atherosclerosis of the carotid arteries.²⁹ A similar association might exist between alcohol intake and atherosclerosis of coronary arteries.

Several studies³⁰⁻³⁴ have found a positive correlation between alcohol consumption and concentration of high density lipoprotein cholesterol and an inverse association between it and risk of ischaemic heart disease. These associations have made high density lipoprotein cholesterol an obvious relevant potential confounder, and studies on alcohol and risk of ischaemic heart disease have repeatedly focused on high density lipoprotein cholesterol or its subfractions. It has been suggested that at least some of the effect of alcohol on risk of ischaemic heart disease is due to the rise in high density lipoprotein cholesterol concentration induced by alcohol. When we adjusted for potential confounders, however, even among men with low concentrations of high density lipoprotein cholesterol (≤ 1.07 mmol/l) abstainers had a significantly higher risk of ischaemic heart disease compared with men who drank 22 or more alcoholic beverages a week,

Key messages

- An inverse association between alcohol consumption and risk of ischaemic heart disease is not a general phenomenon
- The low risk of ischaemic heart disease in men with a low concentration of serum low density lipoprotein cholesterol was not modified by use of alcohol
- The risk of ischaemic heart disease in men with a high concentration of serum low density lipoprotein cholesterol was strongly modified by use of alcohol: those who did not drink alcohol had five times the risk of ischaemic heart disease compared with those who consumed three alcoholic beverages or more a day
- The results support the hypothesis that the apparent discrepancy between a low risk of ischaemic heart disease and a high intake of fat, a phenomenon known as the French paradox, may partly be explained by consumption of alcohol
- In studies of the use of alcohol and risk of ischaemic heart disease, serum low density lipoprotein cholesterol should be regarded as a potentially strong effect modifier not as a potential confounder

indicating a protective effect of alcohol independent of concentration of high density lipoprotein cholesterol.

LOW DENSITY LIPOPROTEIN CHOLESTEROL: AN EFFECT MODIFIER

The above studies have also analysed the association between use of alcohol, serum lipids, and risk of ischaemic heart disease.³⁰⁻³⁴ Because of the weak correlation between concentration of low density lipoprotein cholesterol and use of alcohol found in most studies, low density lipoprotein cholesterol has correctly not been regarded as a relevant potential confounder. If included as a single term variable in multivariate analysis, low density lipoprotein cholesterol does not account for any effect of alcohol on risk. Our results show that analysis of stratified concentrations of low density lipoprotein cholesterol reveals the strong association between alcohol, low density lipoprotein cholesterol, and risk. Thus, in studies on use of alcohol and risk of ischaemic heart disease, low density lipoprotein cholesterol should be regarded as a potentially strong effect modifier, not as a confounder. It might be futile to compare results of different cohort studies on use of alcohol and risk of ischaemic heart disease or to perform meta-analyses without taking into consideration different concentrations of low density lipoprotein cholesterol.

Low density lipoprotein cholesterol concentration is partly determined by dietary habits. Our finding that a high concentration was not associated with an increased risk of ischaemic heart disease in men who drank three alcoholic beverages or more a day supports the suggestion that alcohol intake, at least in part, may be responsible for the unexpected low risk of ischaemic heart disease known as the French paradox.

Funding: Grants from King Christian X's Foundation, the Danish Medical Research Council, the Danish Heart Foundation, and the Else and Mogens Wedell-Wedellsborg Foundation.

Conflict of interest: None.

- 1 Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Asherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary heart disease in men. *Lancet* 1991;338:464-8.
- 2 Castelli WP, Gordon T, Hjortland H, Kagan A, Doyle JT, Hames CG, et al. Alcohol and blood lipids: the cooperative lipoprotein phenotyping study. *Lancet* 1977;ii:153-5.
- 3 Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339:1523-6.
- 4 Tunstall-Pedoe H, Kuulasmaa K, Amooey P, Arveiler D, Rajakangas A-M, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90:583-612.
- 5 Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994;344:1719-23.
- 6 Gynelberg F. Physical fitness and coronary heart disease in male residents in Copenhagen aged 40-59. *Dan Med Bull* 1973;20:1-4.
- 7 Gynelberg F. One- and two-years incidence of myocardial infarction in Copenhagen males aged 40-59. *Dan Med Bull* 1975;22:81-4.
- 8 Suadicani P, Hein HO and Gynelberg F. Serum cotinine validated form of smoking does not account for social inequalities in risk of ischaemic heart disease: the Copenhagen Male Study—4 years' follow-up. *Int J Epidemiol* 1994;23:293-300.
- 9 Svalastoga K. *Prestige, class and mobility*. Copenhagen: Munksgaard, 1959.
- 10 Siedel J, Klose S, Ziegenhorn J, Wahlefeld AW. Improved reagent for the determination of serum cholesterol. *J Clin Chem Biochem* 1981;19:838-9.
- 11 Stahl F, Gruber W, Stinshoff K, Roschlau P. Eine praxis gerechte enzymatische Cholesterin-Bestimmung. *Med Lab* 1977;30:29-37.
- 12 Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *Lipid Res* 1970;11:583-95.
- 13 Lopes-Virella, MF. Cholesterol determination in high-density lipoproteins separated by three different methods. *Clin Chem* 1977;23:882-4.
- 14 Friedewald WT, Levy J, Friedrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-509.
- 15 Hein HO, Sørensen H, Suadicani P, Gynelberg F. The Lewis blood group—a new genetic marker of ischaemic heart disease. *J Intern Med* 1992;232:481-7.
- 16 Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular survey methods*. 2nd ed. Geneva: World Health Organisation, 1982.
- 17 Rose GA, Holland WW, Crowley EA. A sphygmomanometer for epidemiologists. *Lancet* 1964;i:296-300.
- 18 Medical Research Council's committee on the aetiology of chronic bronchitis. Standardised questionnaires on respiratory symptoms. *BMJ* 1960;iii:1665.
- 19 Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiological research. Principles and quantitative methods*. London: Lifetime Learning Publications, 1982.
- 20 Norusis M. *SPSS/PC + base manual*. Chicago, Illinois: SPSS, 1988.
- 21 Norusis M. *SPSS/PC + advanced statistics*. Chicago, Illinois: SPSS, 1988.
- 22 Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet* 1988;iii:1267-73.
- 23 Shaper AG. Alcohol and mortality: a review of prospective studies. *Br J Addiction* 1990;85:837-47.
- 24 Hein HO, Suadicani P, Sørensen H, Gynelberg F. Alcohol consumption, Lewis phenotypes, and risk of ischaemic heart disease. *Lancet* 1993;341:392-6.
- 25 Folsom AR. Epidemiology of fibrinogen. *Eur Heart J* 1995;16(suppl A):21-3.
- 26 Heinrich J, Balleisen L, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. *Arterioscler Thromb* 1994;14:54-9.
- 27 Ridker PM, Vaughan DE, Stampfer J, Glynn RJ, Hennekens CH. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA* 1994;272:929-33.
- 28 Hendriks HF, Veenstra J, Velthuis te Wierik EJ, Schaafsma G, Kluft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ* 1994;308:1003-6.
- 29 Kiechl S, Willeit J, Egger G, Oberhollenzer M, Aichner F. Alcohol consumption and carotid atherosclerosis: evidence of dose-dependent atherogenic and antiatherogenic effects. Results from Bruneck study. *Stroke* 1994;25:1593-8.
- 30 Castelli WP. Epidemiology of coronary heart disease: the Framingham Study. *Am J Med* 1984;76:2-12.
- 31 Yano K, Rhoads GG, Kagan A. Coffee, alcohol, and risk of coronary heart disease among Japanese men living in Hawaii. *N Engl J Med* 1977;297:405-9.
- 32 Criqui MH, Cowan LD, Tyroler HA, Bangdiwala S, Heiss G, Wallace RB, et al. Lipoproteins as mediators for the effect of alcohol consumption and cigarette smoking on cardiovascular mortality: results from the lipid research clinics follow-up study. *Am J Epidemiol* 1987;126:629-37.
- 33 Suh I, Shatan BJ, Cutler JA, Kuller LH. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol: the multiple risk factor intervention trial research group. *Ann Intern Med* 1992;116:881-7.
- 34 Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rosner B, VanDenburgh M. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993;329:1829-34.

(Accepted 9 January 1996)

ONE HUNDRED YEARS AGO

THE CIGARETTE.

The cigarette in modern life is as ubiquitous as the bacillus, and if we are to believe some who profess to speak with authority, it is as mischievous as the most truculent of those invisible enemies. Let us listen for instance to the preaching of Dr. George F. Shrady, a man of light—laryngoscopic and general—and leading in the medical profession of New York, editor of the *Medical Record* of

that city, and therefore, it must be presumed, accustomed to use words with an exact appreciation of their meaning:

To smoke a cigarette is to use tobacco in its very worst form. It will produce physical irritability and mental and moral strabismus. It attacks the physical organisation at four points—the stomach, the brain, the heart, and the lungs. It deadens the sensibility of the membranes with which the smoke comes in contact, destroys the appetite, and causes the sufferer to endure all the attendant evils which attach themselves to the results of over-stimulation.

(*BMJ* 1896;i:624.)