Serum high density lipoprotein cholesterol, alcohol, and coronary mortality in male smokers

Mikko Paunio, Jarmo Virtamo, Carl-Gustaf Gref, Olli P Heinonen

See editorial by White

Abstract

Objective—To determine whether the increase in mortality from coronary heart disease with high concentrations (>1.75 mmol/l) of high density lipoprotein cholesterol could be due to alcohol intake.

Design—Cohort study.

Setting—Placebo group of the α tocopherol, β carotene cancer prevention (ATBC) study of south western population in Finland.

Participants—7052 male smokers aged 50–69 years enrolled to the ATBC study in the 1980s.

Main outcome measures—The relative and absolute rates adjusted for risk factors for clinically or pathologically verified deaths from coronary heart disease for different concentrations of high density lipoprotein cholesterol with and without stratification for alcohol intake. Similar rates were also calculated for different alcohol consumption groups.

Results—During the average follow up period of 6.7 years 258 men died from verified coronary heart disease. Coronary death rate steadily decreased with increasing concentration of high density lipoprotein cholesterol until a high concentration. An increase in the rate was observed above 1.75 mmol/l. This increase occurred among those who reported alcohol intake. Mortality was associated with alcohol intake in a J shaped dose response, and those who reported consuming more than five drinks a day (heavy drinkers) had the highest death rate. Mortality was higher in heavy drinkers than in non-drinkers or light or moderate drinkers in all high density lipoprotein categories from 0.91 mmol/l upward.

Conclusions—Mortality from coronary heart disease increases at concentrations of high density lipoprotein cholesterol over 1.75 mmol/l. The mortality was highest among heavy drinkers, but an increase was found among light drinkers also.

Introduction

There is substantial evidence that low concentrations of serum high density lipoprotein cholesterol are associated with high mortality from coronary heart disease.^{1–12} Two recent studies in men, however, have also identified a clear increase in coronary mortality at high concentrations.^{11,12} Alcohol intake might underlie this phenomenon because heavy drinkers have increased concentrations.^{12–14}

The observation that moderate alcohol intake (fewer than five drinks a day) prevents myocardial infarction¹⁴ has recently received support from indirect evidence that high density lipoprotein cholesterol lies in the causal pathway.^{15–17} The interrelations between alcohol consumption, high density lipoprotein cholesterol concentrations, and coronary mortality, however, seem to be complex.^{12,14,18,19} Heavy drinking (more than five drinks or 60 g a day) has been associated with higher coronary mortality^{12,14,19} compared with moderate drinking, though this observation among heavy drinkers may have resulted from the misclassification of disorders such as cardiomyopathies, arrhythmias, and hypertensive heart disease as coronary heart disease.¹⁸

We examined whether alcohol intake explains the upward trend of coronary mortality at high concentra-

tions of high density lipoprotein cholesterol.^{11,12} The placebo group from the α tocopherol, β carotene cancer prevention (ATBC) study was especially suitable to study this as smoking and alcohol drinking are strongly positively associated.²⁰

Subjects and methods

POPULATION

The subjects were participants of the study, a randomised placebo controlled prevention trial to examine whether supplementation with α tocopherol and β carotene can reduce the incidence of lung and other cancers.²¹ The participants were male smokers aged 50–69 years residing in south western Finland. Exclusion criteria included a history of cancer, severe angina with exertion (Rose criteria, grade 2), cirrhosis of the liver, chronic alcoholism, use of anticoagulants, and supplementation with β carotene or vitamin A or vitamin E. The participants were enrolled in 1984–8, when they were randomly assigned to one of four supplementation regimens: α tocopherol 50 mg a day, β carotene 20 mg a day, both α tocopherol and β carotene, or placebo. The design, methods, and characteristics of participants have been published.^{12,22}

This study is based on the placebo group participants of the study. Of the 7318 men, 7052 had their concentrations of high density lipoprotein cholesterol determined at baseline.

EXAMINATION PROCEDURES

Serum high density lipoprotein cholesterol was determined enzymatically after precipitation of very low density and low density lipoprotein with dextran sulphate and magnesium chloride (CHOD-PAP method, Boehringer Mannheim).^{23,24} High density lipoprotein cholesterol cut off points were defined as 0.91 mmol/l, the internationally accepted lower limit for low concentration of high density lipoprotein cholesterol,¹⁰ and 1.16 mmol/l, the commonly used lower limit for ideal high density lipoprotein cholesterol concentration.¹⁰ The top and bottom tenths were defined by the following concentrations: upper (1.61 mmol/l) and lower (0.84 mmol/l). The top tenth was further divided at 1.75 mmol/l according to results from a Norwegian study which found an upturn of coronary mortality above this point and suggested that this might result from alcohol intake.¹¹

Dietary information, including data on alcohol consumption, were filled in by the men at home and reviewed during their visit.²⁵ Alcohol intake was recorded as daily, weekly, or monthly consumption of beer, wine, and hard liquor during the previous year. This was later converted to pure alcohol in g/day. Alcohol consumption was divided into four categories: non-drinkers, light drinkers (≤ 2 drinks a day), moderate drinkers (>2 –5 drinks a day), and heavy drinkers (>5 drinks a day). Self reported alcohol consumption was missing for 463 men. One drink is equal to 14 g pure alcohol, which corresponds to the alcohol content of one bottle (0.33 l) of strong Finnish beer.

FOLLOW UP

The mortality follow up continued until death or the end of 1993 with a mean of 6.7 years (range 0.1–9.3). The deaths were identified through Statistics Finland, which records all deaths of Finnish citizens. The underlying cause of death, on the basis of data on the death

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Table 1—Crude and adjusted* relative coronary mortality and proportion of person years contributed by heavy drinkers (5 drinks/day) in different categories of high density lipoprotein cholesterol

High density lipoprotein cholesterol (mmol/l)	Person years	% Person years contributed by heavy drinkers	Crude mortality/ 1000 person years	Crude relative mortality	Adjusted* relative mortality (95% confidence interval)
<0.84†	4 351	1.0	8.7	1.00	1.00
0.84-0.90	3 308	1.2	6.0	0.70	0.71 (0.41 to 1.22)
0.91-1.15	16 390	2.5	5.6	0.64	0.68 (0.46 to 1.00)
1.16-1.61	17 237	3.1	5.3	0.61	0.72 (0.49 to 1.07)
1.62-1.75	2 202	5.3	1.8	0.21	0.24 (0.08 to 0.80)
>1.75	2 645	7.6	4.9	0.56	0.68 (0.35 to 1.30)

*Adjusted for age, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, and serum total cholesterol.

†Reference category.

Table 2—Crude and adjusted* relative coronary mortality in different alcohol consumption categories

Drinking habit	Person years	Crude mortality/ 1000 person years	Crude relative mortality	Adjusted* relative mortality (95% confidence interval)
Non-drinkers	4 584	5.9	1.40	1.10 (0.66 to 1.80)
Light drinkers	29 185	5.4	1.29	1.13 (0.77 to 1.65)
Moderate drinkers†	7 880	4.2	1.00	1.00
Heavy drinkers	1 356	8.8	2.10	2.20 (1.13 to 4.28)

*Adjusted for age, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, and serum total cholesterol.

†Reference category.

certificate, was reviewed by a board certified internist. Death assessments were made without knowledge of the subject's treatment group or medical history or physical findings, including high density lipoprotein cholesterol and self reported alcohol intake. For this study only clinically or pathologically verified coronary deaths (*International Classification of Diseases*, 9th revision (ICD-9) codes 410-414) were accepted as end points—that is, those coronary deaths in which the data indicated admission to hospital with definite acute myocardial infarction (diagnostic findings on the electrocardiogram or specific enzymes, or both) in the 28 days before death or necropsy findings of acute myocardial infarction or atherosclerotic coronary heart disease with no other cause of death.

STATISTICAL ANALYSIS

Crude mortality, the number of deaths divided by person years of follow up, was assessed to examine the association of coronary deaths with high density lipoprotein cholesterol and alcohol consumption. Adjust-

ment for coronary risk factors (age, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, and serum total cholesterol) was done with Cox proportional hazards model.²⁶ Categorisation of these variables has been published.¹² Adjustment for systolic blood pressure or high density lipoprotein (for alcohol) was not performed as they have been shown to be part of the causal pathway.¹⁵⁻¹⁷ In a detailed stratified analysis non-drinkers with lowest concentrations of high density lipoprotein cholesterol were taken as the reference category. Cells with no deaths were omitted from this analysis. Thus 19 dummy variables were defined.

The proportionality assumption was checked by introducing time dependent (log time) high density lipoprotein cholesterol or alcohol dummy variables into the Cox model.²⁷

Results

Mortality from coronary heart disease decreased with increasing serum concentration of high density lipoprotein cholesterol except in the highest category (>1.75 mmol/l) (table 1). An upward trend of coronary mortality was observed in this highest category compared with that in the second highest category (1.62-1.75 mmol/l). The proportion of person years attributed to heavy alcohol drinkers steadily increased with increasing concentration of high density lipoprotein cholesterol (table 1).

There was a J shaped association of self reported alcohol intake and coronary deaths (table 2). Heavy drinkers had over twice the mortality due to coronary deaths compared with moderate drinkers (relative risk 2.2 (95% confidence interval 1.13 to 4.28)).

There were few non-drinkers in the two upper categories of concentration of high density lipoprotein cholesterol, and no coronary deaths occurred in these categories (table 3). An upturn in coronary mortality was seen in all groups of drinkers when the concentration of high density lipoprotein cholesterol exceeded 1.75 mmol/l. Heavy drinkers had an adjusted coronary death rate in all concentration categories above 0.90 mmol/l that was 1.5 to 5 times higher than in non-drinkers or light or moderate drinkers. The risk increment of coronary mortality within different strata of concentrations above 0.91 mmol/l after adjustment was especially apparent among heavy drinkers, but the same was true to a lesser extent among those who consumed less alcohol (table 3). This increment was primarily caused by age adjustment. Non-drinkers were older than those who tended to consume alcohol (table 3).

Discussion

The reversal of the decreasing trend in mortality from coronary heart disease with rising concentrations of high density lipoprotein cholesterol over 1.75 mmol/l

Table 3—Crude and adjusted* coronary mortality per 1000 person years across categories of alcohol consumption and concentrations of high density lipoprotein cholesterol

High density lipoprotein cholesterol (mmol/l)	Non-drinkers		Light drinkers		Moderate drinkers		Heavy drinkers	
	Rate (person years)	Adjusted rate (95% confidence interval)	Rate (person years)	Adjusted rate (95% confidence interval)	Rate (person years)	Adjusted rate (95% confidence interval)	Rate (person years)	Adjusted rate (95% confidence interval)
<0.84	9.7 (720)†	9.7	8.4 (2974)	10.0 (4.4 to 23.2)	2.6 (380)	3.9 (0.5 to 31.8)	0 (42)	NA‡
0.84-0.90	7.3 (545)	8.4 (2.4 to 29.1)	4.2 (2138)	5.3 (1.9 to 14.4)	5.4 (370)	6.8 (1.4 to 32.8)	0 (41)	NA‡
0.91-1.15	5.0 (1805)	6.2 (2.3 to 16.7)	5.3 (10 971)	6.8 (3.1 to 14.9)	3.9 (2296)	5.9 (2.1 to 15.9)	12.0 (415)	18.4 (5.8 to 58.6)
1.16-1.61	5.1 (1361)	6.6 (2.3 to 18.8)	5.5 (10 742)	7.9 (3.5 to 17.3)	4.7 (3407)	7.5 (3.1 to 18.1)	7.4 (540)	11.8 (3.4 to 40.5)
1.62-1.75	0 (81)	NA‡	1.8 (1108)	3.1 (0.7 to 15.2)	1.8 (554)	3.9 (0.4 to 35.5)	8.5 (117)	16.6 (2.0 to 135.6)
>1.75	0 (72)	NA‡	4.0 (1252)	5.9 (1.8 to 18.9)	4.6 (874)	8.0 (2.3 to 27.4)	9.9 (202)	17.6 (3.6 to 86.4)

*Adjusted for age, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, and serum total cholesterol.

†Reference category.

‡Not assessed.

confirms observations in other studies.^{11 12} The reversal trend in this study was seen among men who reported drinking alcohol.

There is a temptation to suggest that heavy drinking, which is associated with high coronary death rate and high concentrations of high density lipoprotein cholesterol,¹³ would explain the upturn in the rate above 1.75 mmol/l. We found that coronary mortality increased above 1.75 mmol/l even among light and moderate drinkers. An earlier report on this material¹² indicated that heavy drinkers are differentially misclassified, especially as moderate drinkers but also to some extent as light drinkers, and only two of 22 of those who died of alcohol related causes reported being heavy drinkers. This might explain why coronary mortality increases above 1.75 mmol/l even among light drinkers.

The upturn of coronary mortality at high concentrations may attenuate the overall inverse association between concentration and coronary mortality. The inverse association has been found to be stronger among women than men and among men with underlying cardiovascular disease compared with healthy men.^{9-11 28 29} These differences might ultimately be explained by alcohol intake because women and those men who have underlying cardiovascular disease drink less than healthy men.^{30 31} The high per capita alcohol consumption (14 litres) in Russia in the 1980s³² could explain why among healthy men there is even a slight positive association of coronary mortality and high density lipoprotein cholesterol concentration when no other factors are controlled.²⁸ A relatively weak inverse association of coronary mortality and high density lipoprotein cholesterol concentration, however, became evident also in this Russian cohort when men with underlying cardiovascular disease were included.²⁸ In the final report of the Russian cohort sudden coronary deaths and high density lipoprotein cholesterol concentration were associated in a U shaped fashion.³³

As we dealt only with clinically or pathologically verified coronary deaths the observed upward trend of coronary deaths among the drinkers probably does not result from misclassifying other cardiac diseases as coronary deaths. Obviously, some of the increased risk could be attributed to the fact that heavy drinkers had on average 10 mm Hg higher systolic blood pressure than non-drinkers (data not shown). The mechanisms of how alcohol intake otherwise enhances coronary mortality are not clear but may involve arrhythmias and increased blood clotting, especially after large intermittent doses of alcohol as it has been observed that bleeding time is shortened during a hangover.³⁴⁻³⁷ Also, after heavy drinking episodes men with normal coronary arteries seem to experience coronary thrombosis.³⁸ More steady light and moderate alcohol intakes, however, probably prevent blood clotting.³⁹⁻⁴² Binge drinking during weekends is common in Finland.⁴³

This study supports the findings that the inverse association between concentrations of high density lipoprotein cholesterol and mortality from coronary heart disease ceases above concentrations of 1.75 mmol/l. Mortality from coronary heart disease is highest among heavy drinkers above this concentration but an increase in mortality is found even among light drinkers.

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Conflict of interest: None.

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Key messages

- There is an inverse association between concentration of high density lipoprotein cholesterol and mortality from coronary heart disease except at high concentrations, when coronary mortality increases
- Heavy drinkers have increased coronary death rates and often have high concentrations of high density lipoprotein cholesterol
- Mortality from coronary heart disease increased at concentrations of high density lipoprotein cholesterol above 1.75 mmol/l, which was due to drinking alcohol but was not associated with the amount of alcohol intake
- Heavy drinkers (>5 drinks a day) had 1.5 to 5 times higher coronary mortality than non-drinkers or light or moderate drinkers at concentrations of 0.91 mmol/l upward

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Correction

Effect on lipoprotein profile of replacing butter with margarine in a low fat diet: randomised crossover study with hypercholesterolaemic subjects

Two errors occurred in table 4 of this paper by Alexandra Chisolm *et al* (13 April, pp 931-4). The mean percentage fatty acid composition of C20:4n-6 on the margarine diet should be 0.80 [not 0.08 as published], and C16:0 on the margarine diet needs to have an asterix to indicate it is significantly different from C16:0 on the butter diet. The authors would also like to express their thanks to Sarah Bethell and Steve Tiszavari for their excellent technical help.

Population mixing and the incidence of childhood leukaemias: retrospective comparison in rural areas of New Zealand

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In 1988 Kinlen hypothesised that childhood leukaemia occurs as a rare response to a common infection and that population influxes into rural areas with higher proportions of susceptible individuals favour epidemics of the infection and increases in the incidence of leukaemia.¹ Most ecological studies of childhood leukaemia in relation to this issue have supported the hypothesis.² Our study was conducted to test whether population influxes into rural areas of New Zealand were associated with increases in the incidence of childhood leukaemias.

Subjects, methods, and results

Forestry developments, including the building of a pulp and paper mill, occurred in the adjacent Rotorua, Matamata, and Whakatane areas of New Zealand's North Island in the 1950s. These developments led to population growth and the establishment of the new towns of Kawerau and Murupara. In this study boundaries were defined for the Rotorua, Matamata, and Whakatane areas (study areas) based on local government divisions. Care was taken to ensure that the areas remained as equivalent as possible over the years. The population of the combined study areas increased greatly at the time of the forestry developments compared with a smaller increase in the rest of New Zealand (fig 1). Similar increases occurred in each individual area (Rotorua, Matamata, and Whakatane).

Childhood leukaemia registrations for New Zealand residents (1949-83, ages 0-14) were obtained from the

National Cancer Registry. On the basis of the street address at diagnosis (or occasionally the domicile code) each child was classified as living in one of the study areas or in the rest of New Zealand. Quinquennial age specific incidence rates were calculated for childhood leukaemias in the study areas (combined) and in the rest of New Zealand. Age adjusted incidence rate ratios (Mantel-Haenszel method³) with 95% confidence intervals were also calculated. To assess differences among the trends in the age specific rates we used the likelihood ratio test for heterogeneity.³

Fig 1—Rate ratios for childhood leukaemia (ages 0-14, study areas versus the rest of New Zealand). Middle years of the time periods were census years, and population increases are average annual increases for all ages since previous census

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