

HDL Cholesterol and Mortality in Finnish Men With Special Reference to Alcohol Intake

Mikko Paunio, MD, PhD; Olli P. Heinonen, MD, DrSc; Jarmo Virtamo, MD, PhD;
Michael J. Klag, MD, MPH; Vesa Manninen, MD, PhD;
Demetrius Albanes, MD; George W. Comstock, MD, DrPH

Background There is substantial evidence that a low serum level of HDL cholesterol (HDL) is a risk factor for coronary deaths. However, data on older people are scarce, and previous studies have not examined this association in relation to alcohol intake.

Methods and Results Coronary mortality, all-cause mortality, and mortality due to alcohol and violence were related to HDL levels among 7052 male smokers 50 to 69 years old in south and west Finland enrolled from 1984 to 1988 in the ATBC (AT, alpha-tocopherol; BC, beta-carotene) Study placebo group. During the average follow-up period of 4.7 years, 620 men died; 222 of these deaths were from coronary heart disease and 82 from causes related to alcohol and violence. HDL levels were inversely associated with coronary mortality, irrespective of age, whereas high total cholesterol was positively associated with coronary mortality among the younger men, 50 to 59 years of age, but not among the older

men, 60 to 69 years old. Correction for temporal variation in HDL measurement indicated a 43% stronger inverse association between HDL and coronary mortality compared with that based only on a single value. The inverse association of HDL and coronary mortality was less marked at higher levels of alcohol intake. All-cause and alcohol- and violence-related mortality were positively associated with HDL among the younger men. All-cause mortality showed a U-shaped dose response among men ≥ 60 years old.

Conclusions Previous studies may have underestimated the beneficial effect of high HDL because of regression-dilution bias and the confounding effect of heavy alcohol intake. This study supports the view that, particularly among older men, lipoprotein fractions may be more appropriate for screening than total cholesterol. (*Circulation*. 1994;90:2909-2918.)

Key Words • cholesterol • risk factors • mortality • alcohol

There is considerable evidence that low levels of HDL cholesterol (HDL) increase the risk of fatal coronary events.¹⁻¹¹ Most of the data available on coronary disease risk factors, however, are from middle-aged populations. Information on coronary heart disease risk factors for the elderly is urgently needed because, in industrialized countries, there has been a shift of coronary morbidity toward older age groups.¹²⁻¹⁴

The ATBC (AT, alpha-tocopherol; BC, beta-carotene) study is a randomized clinical trial of the efficacy of α -tocopherol and β -carotene supplementation in the primary prevention of lung cancer in cigarette smokers. This study is being conducted in south and west Finland. Because information on lipid profiles, other cardiovascular disease risk factors, and alcohol consumption was collected at baseline, this study offers the opportunity to study the relation of HDL to mortality, taking into

account alcohol intake in male smokers who were 50 to 69 years old at the start of the study.

Methods

Participants

To be eligible, the ATBC study participants had to be male, 50 to 69 years old, smoking five or more cigarettes a day at entry, residing within the study area in south and west Finland, and willing to participate and to give written informed consent. Potential participants were excluded for the following reasons: proven malignancy other than nonmelanoma skin cancer or carcinoma in situ; unstable angina pectoris; chronic renal insufficiency; cirrhosis of the liver; chronic alcoholism; anticoagulant therapy; or use of vitamin E (>20 mg/d), vitamin A ($>20,000$ IU/d), or β -carotene (>6 mg/d) supplements. Persons on medications (eg, anticoagulants) that would have interacted harmfully with experimental treatments were excluded. At the baseline visit before randomization, nurses excluded persons with conditions limiting long-term participation, eg, alcoholism associated with a psychiatric disorder or physical disability.

The total sampling frame of the trial was approximately 290,000 men, who were first sent a questionnaire asking about smoking habits and willingness to participate. Men smoking at least five cigarettes per day and willing to participate were invited by mail to visit their local field center for evaluation and if they were eligible and willing, for randomization into the trial. A total of 29,246 men were randomly allocated to one of four treatment groups. This report is based on participants of the placebo group. Of the 7,318 men in the group, serum HDL measurements at baseline were available on 7,052. The 266 placebo group participants who accidentally lacked serum HDL information were excluded from further analysis; the late exclusions for cancer study were included.^{15,16}

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From the University of Helsinki, Department of Public Health (M.P., O.P.H.); The Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology (M.P., G.W.C.); the National Public Health Institute of Finland (J.V.); Welch Center for Prevention, Epidemiology and Clinical Research, The Johns Hopkins Health Institutions (M.J.K.); the University of Helsinki, First Department of Medicine (V.M.); and the Cancer Prevention Studies Branch, DCPC, National Cancer Institute (D.A.).

Correspondence to Mikko Paunio, MD, PhD, University of Helsinki, Department of Public Health, Haartmaninkatu 3, 00014 (Helsingin yliopisto), Helsinki, Finland.

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TABLE 1. Contributed Person-Years and Their Proportions of Coronary Risk Factor and HDL Cholesterol Categories in Two Age Groups of the Placebo Group of the ATBC Study

Risk Factor	Person-Years		Proportion, %	
	59-59 y	60-69 y	50-59 y	60-69 y
Alcohol consumption				
Nondrinkers	1855	1446	8.4	13.3
Light drinkers	14 009	6964	63.1	64.0
Moderate drinkers	4256	1423	19.2	13.3
Heavy drinkers	728	258	3.3	2.3
Unknown	1345	785	6.1	7.2
Body mass index, kg/m²				
<20.0	667	491	3.0	4.5
20.0-24	7635	4184	34.5	38.5
25.0-29	10 276	4735	46.3	43.5
≥30	3615	1466	16.2	13.5
Education				
Low	6402	4224	28.2	38.8
Medium	14 870	6282	67.0	57.8
High	921	371	4.1	3.4
Physical activity at leisure time				
Sedentary	9472	4535	42.7	41.7
Active	12 722	6341	57.3	58.3
Smoking habit				
Light	2930	2268	13.4	20.9
Moderate	10 799	6049	48.8	55.6
Heavy	8464	2559	37.8	23.5
Systolic blood pressure, mm Hg				
<140	11 598	4276	52.3	39.3
140-159	7477	3889	33.7	35.8
>160	3119	2712	14.1	24.9
Total cholesterol, mmol/L				
<6.15	10 642	5532	48.0	50.9
≥6.15	11 551	5344	52.0	49.1
HDL cholesterol, mmol/L				
<0.84	2076	1073	9.4	9.9
0.84-0.90	1604	784	7.2	7.2
0.91-1.15	7832	3942	35.3	36.2
1.16-1.61	8425	3973	38.0	36.5
>1.61	2256	1103	10.2	10.1

Recruitment and Follow-up Period

Recruitment to the study took place from September 1984 through June 1988. The cohort was followed for mortality to the end of 1991. The mean follow-up period was 4.7 years, with a range of 0.1 to 7.2 years. There were no losses to follow-up.

Lipid Measurements

At the baseline visit, before noon after a fast of at least 12 hours, a blood sample was drawn into Venoject VT-100PZ vacuum tubes (Terumo Europe NV). Blood samples were stored at +4°C and then centrifuged at 3000 rpm for 10

minutes. Serum was stored in 1.5-mL borosilicate glass vials (Fiolax-Glass Clear, Münnertstädter Glas Waren Fabrik) at -70°C. Serum specimens were transported to the National Public Health Institute and analyzed centrally for total and HDL cholesterol.

Serum total and HDL cholesterol were determined enzymatically (CHOD-PAP method, Boehringer Mannheim).¹⁷ HDLC was measured after precipitation of very-low-density lipoprotein (VLDL) and LDL with dextran sulfate magnesium chloride.¹⁸ Due to a batch change in the dextran sulfate magnesium reagent, a systematic difference in HDLC measurements occurred for 3456 specimens analyzed after May 22,

1987. The mean of these values was 4% lower than before the change in reagent; these samples were standardized to the mean \pm SD of the 3596 values analyzed before the batch change in the reagent.

Other Measurements

At the same baseline visit when blood was drawn, data on general background characteristics and on medical and smoking histories were collected by questionnaire. Height, weight, blood pressure, and heart rate were measured.¹⁵ A detailed dietary history questionnaire including data on alcohol consumption was given to the men to be filled in at home.¹⁹ Two weeks later, this questionnaire was returned and reviewed. Alcohol intake was recorded as weekly consumption of beer, wine, and hard liquor during the previous year. This was later transformed to pure alcohol consumption in grams per day. All procedures in the field centers were carried out by registered nurses with standardized instructions and training.

End Points

Vital status was verified through the Central Population Register, and death certificates obtained from Statistics Finland were reviewed for the underlying cause of death by a board-certified internist (J.V.). End points of interest in these analyses were deaths due to coronary disease (n=222), all causes (n=620), alcohol (n=23), and violence (n=59). Coronary deaths were validated according to the Helsinki Heart Study protocol.²⁰ This protocol also categorized deaths as either natural or violent. Alcohol- and violence-related deaths (n=82) were grouped together for most analyses. Alcohol-related deaths were defined as those due to alcoholic cirrhosis (n=11), alcohol intoxication (n=9), acute pancreatitis (n=2), and alcohol cardiomyopathy (n=1) as indicated by ICD-9 code.²¹ The cause of death was based on autopsy in 58% and on autopsy and/or hospital inpatient diagnosis in 90% of all deaths.

Statistical Methods

Cutoff points for continuous variables were selected according to the literature to promote comparability of results. Age was categorized into two groups: 50 to 59 and 60 to 69 years. Alcohol consumption was divided into 5 categories: (1) non-drinkers, (2) light drinkers (two or fewer drinks per day), (3) moderate drinkers (more than two up to five drinks per day), (4) heavy drinkers (more than five drinks per day), and (5) unknown. Two drinks were equivalent to 28 g pure alcohol, which corresponds to the alcohol content of two bottles of Finnish strong beer or about two drinks. In many analyses, the two highest alcohol consumption categories were grouped together (more than two drinks) to reduce variability. Results for alcohol consumption are presented for both age groups combined because the relative risks associated with alcohol consumption were similar in both age groups and because the follow-up time contributed by heavy drinkers among the elderly was small. Information on previous drinking habits was not registered. Body mass index was categorized according to Bray,²² ie, (1) <20, (2) 20 to 24, (3) 25 to 29, and (4) \geq 30 kg/m². Education was categorized as (1) low, defined as elementary school (\leq 7 years of compulsory education) and no vocational training; (2) medium, defined as vocational school or secondary school; and (3) high, defined as university or other higher education. Leisure-time physical activity was dichotomized as light or more strenuous exercise at least once a week (active) versus sedentary. Cigarette smoking habit was categorized as number of cigarettes smoked daily: (1) light smokers, 5 to 10; (2) moderate smokers, 11 to 20; and (3) heavy smokers, >20. Systolic blood pressure was categorized as (1) <140 mm Hg, (2) 140 to 159 mm Hg, and (3) \geq 160 mm Hg. Total cholesterol was dichotomized at the median value, 6.15 mmol/L. End-point analyses using deciles of total cholesterol yielded results similar to those treating cholesterol

as a dichotomous variable. HDLC cutoff points were defined as 0.91 mmol/L (35 mg/dL), the internationally accepted limit for low HDLC,²³ and 1.15 mmol/L (45 mg/dL), the commonly used lower limit for ideal HDLC level.⁹ To gain statistical power, mortality at the extremes in the lower (<0.84 mmol/L, or 32.5 mg/dL) and upper (>1.61 mmol/L, or 62.3 mg/dL) deciles of the HDLC distribution was also compared (omitting other deciles).

The Cox proportional-hazards model^{24,25} was used to model main effects of covariables after stratified univariate analysis. HDLC and other covariables were introduced into the model as categorical variables. Separate models were first constructed to adjust the effect of HDLC on coronary mortality for one covariate at a time. Cox regression and crude person-year analyses were performed for separate age and alcohol strata to illustrate interactions; age at baseline was introduced into the Cox model within each age stratum as a continuous variable. Time-dependent dummy variables of alcohol, total cholesterol, and HDLC were used to test the proportionality assumption of the Cox proportional-hazards model.²⁵ Confidence intervals (95%) of the estimates were calculated by

$$e^{b \pm 1.96 \times \text{SEE}}$$

where *b* is the point estimate from the Cox model and SEE its standard error. Confidence intervals (95%) for crude rates were calculated according to the Poisson distribution.²⁶

HDLC was also introduced into the Cox regression model as a continuous variable, and the results were expressed as a change in mortality for each 0.026 mmol/L (1 mg/dL) decrease in HDLC to facilitate comparisons with four American prospective studies.⁸ The results for HDLC as a continuous covariable are presented for both age groups combined because the relative risks of coronary mortality with decreasing HDLC were similar in both age strata. After residual analysis for the Cox model was performed, additional categorization was made according to the Norwegian study, which found an upward trend of coronary mortality above 1.75 mmol/L of HDLC.¹¹

Estimates of the association of HDLC with subsequent coronary death are attenuated by the variability in HDLC measurements, especially when relying on only a single baseline HDLC measurement. To address errors due to temporally extreme values, ie, regression-dilution bias, variability in HDLC was estimated from a second HDLC measurement performed 3 years after enrollment in 5528 men. Cox regression coefficients were corrected by use of a parametric procedure described by MacMahon et al.²⁷

Alcohol intake can raise HDLC,²⁸⁻³³ and heavy drinkers may underreport alcohol intake.^{34,35} Therefore, several analyses were undertaken to evaluate the role of alcohol consumption as a potential confounder. Alcohol intake is likely to be high among men who die of causes related to alcohol and violence regardless of self-reported alcohol consumption.³⁶⁻³⁹ The degree of association of HDLC with these deaths was thus determined. Mean HDLC levels were compared between alcohol consumption categories, and a *t* test, using the least significant difference method for detecting statistical differences, was performed.⁴⁰

Results

The average age of the cohort at baseline was 57.6 years. The 50- to 59-year-old age group consisted of 4660 men and the older age group, of 2392 men. The majority of men consumed some alcohol, most at a level of two or fewer drinks per day (Table 1). The older men, however, reported a lower alcohol intake than the younger men. There were few in either age group who were very lean, but the older men tended to be somewhat leaner than the middle-aged men. Most men had at least a secondary school education, but older men

TABLE 2. Crude and Adjusted Relative Mortality in Different HDL Cholesterol Categories in Two Age Groups of the Placebo Group of the ATBC Study, Holding the Highest HDL Cholesterol Decile as the Reference Category

Age Group, y	HDL Cholesterol, mmol/L	Coronary			Alcohol and Violence Related		
		Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted* Relative Mortality (95% CI)	Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted† Relative Mortality (95% CI)
50-59	<0.84	6.7	2.16	1.93 (0.74-5.02)	1.0	0.17	0.21 (0.05-0.99)
	0.84-0.90	6.2	2.00	1.72 (0.63-4.70)	1.9	0.33	0.40 (0.11-1.46)
	0.91-1.15	4.9	1.58	1.46 (0.63-3.37)	0.8	0.15	0.19 (0.07-0.48)
	1.16-1.61	4.5	1.45	1.45 (0.64-3.29)	3.1	0.53	0.64 (0.32-1.28)
	>1.61‡	3.1	1.00	1.00	5.8	1.00	1.00
60-69	<0.84	17.7	2.42	2.09 (0.87-5.04)	1.9	0.53	0.51 (0.09-2.86)
	0.84-0.90	11.5	1.57	1.37 (0.51-3.68)	2.6	0.72	0.68 (0.12-3.80)
	0.91-1.15	10.9	1.49	1.32 (0.60-2.90)	1.8	0.50	0.48 (0.13-1.67)
	1.16-1.61	9.1	1.25	1.18 (0.54-2.56)	4.0	1.11	1.06 (0.35-3.23)
	>1.61‡	7.3	1.00	1.00	3.6	1.00	1.00

*Adjusted for age, mean daily alcohol consumption, body mass index, education, physical activity in leisure time, number of cigarettes smoked daily, systolic blood pressure, and total cholesterol.

†Adjusted for age and mean daily alcohol consumption.

‡Reference category.

were less educated than younger men. Among both age groups, nearly 60% reported that they performed leisure-time exercise. Given the purpose of the trial, all of the men were smokers. Heavy smoking was more prevalent among the 50- to 59-year-old men than among the older men. Mean number of years the men had smoked was 35.9 (SD, 8.4 years), with a range of 1 to 60 years. Systolic blood pressure clearly increased with age. The average systolic blood pressure was 139.4 mm Hg in the younger age group and 145.6 mm Hg in the older. Conversely, levels of serum cholesterol were lower in the older age group. The distribution of HDLC values was similar in these two age groups. Coronary mortality rose progressively as HDLC levels decreased, with men in the lowest decile of HDLC in both age groups having twice the mortality of those in the highest decile (Table 2). Unlike HDLC, the relation between total cholesterol and coronary death was present only in the 50- to 59-year-old men (Table 3). Similar results were obtained when serum cholesterol was analyzed by decile or as a continuous variable (data not shown).

After adjustment for all covariables in Table 1, relative coronary mortality was 2.02 times (95% CI, 1.06 to 3.85) higher in the lowest decile of HDLC than the highest decile in both age groups combined. When coronary mortality at various HDLC categories was

compared with the highest HDLC decile, coronary mortality increased at lower levels of HDLC in a similar fashion in both age groups (Table 2). In general, the relative risks of coronary mortality were almost always lower after adjustment than the crude relative risks (Table 2). The relative risks of coronary mortality associated with categories of HDLC did not change meaningfully when analyses were stratified for all covariables in Table 1, including alcohol (data not shown), thus excluding meaningful interactions. When covariates were separately entered into the Cox regression model, body mass index and alcohol consumption had the greatest effect on the inverse association of HDLC with coronary mortality. Age adjustment had a negligible effect on the coefficients of different HDLC categories.

When HDLC was treated as a continuous variable, a similar association with coronary mortality was seen. After adjustment for all the covariables in Table 1, an increase in HDLC of 0.026 mmol/L (1 mg/dL) was associated with a 1.2% decrease in coronary mortality (Table 4). The estimate corrected for temporal high and low values (regression dilution bias) indicated a 43% steeper inverse association of HDLC with coronary mortality than the uncorrected estimate.

Residual analysis of the Cox regression revealed that the log-linear fit was poor. Plotted observations, at the

TABLE 2. Continued

All Causes		
Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted* Relative Mortality (95% CI)
11.5	0.65	0.75 (0.43-1.30)
13.1	0.74	0.87 (0.50-1.52)
11.7	0.66	0.76 (0.50-1.13)
13.5	0.76	0.87 (0.60-1.27)
17.8	1.00	1.00
49.4	1.56	1.46 (0.91-2.32)
34.4	1.08	1.03 (0.61-1.74)
27.1	0.85	0.84 (0.56-1.25)
28.9	0.91	0.91 (0.61-1.34)
31.7	1.00	1.00

*Adjusted for age, mean daily alcohol consumption, body mass index, education, physical activity in leisure time, number of cigarettes smoked daily, systolic blood pressure, and total cholesterol.

†Adjusted for age and mean daily alcohol consumption.

‡Reference category.

upper HDLC extreme, were found to be tightly clustered above the predicted line, whereas observations at lower HDLC levels were systematically distributed below it. Coronary mortality was 25% higher among men with an HDLC level >1.75 mmol/L compared with men in the 1.61 to 1.75 mmol/L range. This exception made the inverse relation weaker when estimated by a linear model.

In stratified analyses, when HDLC was introduced into the model as a continuous variable, the inverse association of HDLC and coronary mortality was markedly attenuated at higher levels of alcohol intake (Fig 1). This attenuation was due to a larger number of coronary deaths in men with very high HDLC levels at successively higher levels of alcohol intake.

In contrast to the findings for coronary mortality, the association of HDLC with total mortality varied by age (Table 2). There was a positive association between HDLC and all-cause mortality (univariate log-linear trend $P < .05$) among the 50- to 59-year-old men. Most of this association was due to a higher death rate among men in the highest decile of HDLC and was no longer statistically significant after adjustment (Table 2). Among the men 60 to 69 years of age, HDLC was related to all-cause mortality in a U-shaped fashion (Table 2). The lowest adjusted rate was in the group with HDLC levels between 0.91 and 1.15 mmol/L, 71% lower than the lowest HDLC category ($P < .01$).

HDLC was positively related to violence- and alcohol-related mortality in both age groups, but the association of HDLC with alcohol- and violence-related mortality was substantially stronger among the 50- to 59-year-old men (univariate log-linear trend $P < .0001$) compared with the older men (univariate log-linear trend $P < .17$) (Table 2). The proportion of violence- and alcohol-related deaths among all deaths was also greater among the 50- to 59-year-olds than the older men in each HDLC category, but especially in the highest HDLC decile (Fig 2). While these associations may be attributable to alcohol intake, they were only minimally attenuated after adjustment for self-reported alcohol consumption (Table 2). Alcohol-related mortality in both age groups was increased 4.03-fold (log-linear trend $P < .005$) by a 1 mmol/L increase of HDLC. Adjustment for alcohol intake attenuated this association to 2.80 (log-linear trend $P < .06$). This somewhat minor change in the relative risk of alcohol-related deaths associated with a 1 mmol/L increase in HDLC after adjustment for alcohol intake suggested substantial underreporting of alcohol intake. Consistent with this observation, only 2 of the 23 men who died of alcohol-related causes reported being heavy drinkers.

To examine whether the associations of HDLC with total mortality were due to confounding by alcohol use, the relation was examined in men who reported no

TABLE 3. Crude and Adjusted Relative Coronary Mortality in Two Total Cholesterol Categories in Two Age Groups of the Placebo Group of the ATBC Study, Holding Those Below Median (<6.15 mmol/L) as the Reference Category

Age, y	Total Cholesterol, mmol/L	Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted* Relative Mortality (95% CI)
50-59	<6.15†	2.6	1.00	...
	≥6.15	6.8	2.61	2.53 (1.68-3.99)
60-69	<6.15†	10.3	1.00	...
	≥6.15	10.8	1.05	1.09 (0.75-1.57)

*Adjusted for age, mean daily alcohol consumption, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, systolic blood pressure, and HDL cholesterol.

†Reference category.

TABLE 4. Crude and Adjusted Percentage Increases of Coronary Mortality per 1 mg/dL* Decrease of HDL Cholesterol in the Placebo Group of the ATBC Study and Corresponding Regression Dilution Bias-Corrected Estimates

Estimate	Point Estimate, %	95% CI, %
Crude estimate	1.6	0.5-2.8
Crude but regression dilution bias-corrected estimate	2.3	0.7-4.0
Adjusted†	1.2	0.0-2.5
Adjusted† and regression dilution bias-corrected estimate	1.7	0.0-3.6

*1 mg/dL HDLC=0.02586 mmol/L HDLC.

†Adjusted for age, mean daily alcohol consumption, body mass index, education, physical activity in leisure time, systolic blood pressure, number of cigarettes smoked daily, and total cholesterol.

alcohol intake. Among the nondrinkers, HDLC was inversely associated with all-cause mortality up to the highest HDLC decile (Fig 3). There were few nondrinkers in the highest HDLC decile, in which only 4 deaths occurred per 109 person-years, resulting in a high death rate (36.7/1000 person-years) with wide 95% confidence limits (14.3 to 94.4/1000 person-years). After adjustment for all the variables in Table 1 except alcohol, a 1 mmol/L increase in HDLC was associated with a 61% decrease in total mortality ($P<.3$) among the nondrinkers. The corresponding crude percentage, based on the same log-linear fit, was 69% ($P<.3$).

There was an increased risk of death from coronary disease at both extremes of alcohol intake (Table 5). After adjustment for all the variables in Table 1 except HDLC, heavy drinkers had 39% higher coronary mortality compared with moderate drinkers; nondrinkers and light drinkers also had higher coronary death rates compared with moderate drinkers. Heavy alcohol consumption was strongly and positively associated with increased alcohol- and violence-related mortality. Light

and moderate drinkers had the lowest all-cause mortality and heavy drinkers, the highest death rate.

Alcohol-related mortality in both age groups per 1000 person-years was 0.0 in nondrinkers, 0.5 in light drinkers, 1.6 in moderate drinkers, and 2.0 in heavy drinkers, suggesting that many heavy drinkers were misclassified as moderate drinkers but also to some extent as light drinkers. It is also possible that some men, especially those dying of liver cirrhosis, may have recently reduced their alcohol intake due to the target organ damage.

HDLC levels were strongly related to self-reported alcohol intake, and those reporting heavy alcohol intake had 20.5% higher mean HDLC compared with nondrinkers (Table 6).

Discussion

The completeness of the follow-up and the standardized assessments of coronary mortality are strengths of the present study. Absolute mortality differences between HDLC categories might not be readily generalizable to other populations, because this study population is a select subset of healthy, smoking, middle-aged and older men. The relative risks are more readily generalizable because such selection bias is likely to affect both numerators and denominators. However, the inverse association of HDLC with coronary mortality in the present study is somewhat less than that found in analyses from four American prospective studies.⁸ Heavy alcohol intake has been shown to be much more prevalent among smokers than nonsmokers in Finland.⁴¹ If heavy alcohol intake attenuates the inverse association of HDLC and coronary mortality, it could also explain why the inverse association in this study is weaker than in American cohorts.

HDLC levels in this middle-aged and older male smoking population were inversely associated with coronary mortality even after adjustment for other cardiovascular disease risk factors. These results are in accordance with a large body of literature.¹⁻¹¹ Biological plausibility⁴² and the data from randomized clinical trials^{8,43-46} support the conclusion that the association

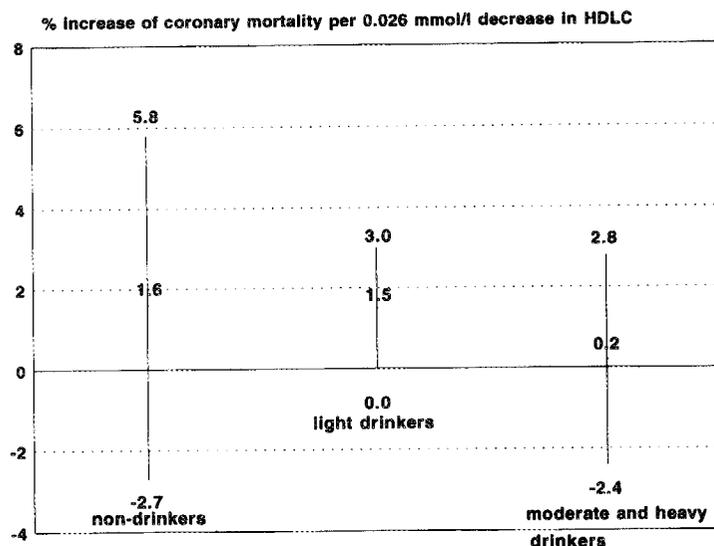


FIG 1. Graph showing adjusted percentage increases and their 95% CIs of coronary mortality per 0.026 mmol/L (1 mg/dL) decrease of HDL cholesterol (HDLC) in different alcohol consumption categories in the placebo group of the ATBC study. Percentage is adjusted for age, body mass index, education, physical activity in leisure time, number of cigarettes smoked daily, systolic blood pressure, and total cholesterol.

(*age, body mass index, education, physical activity at leisure time, number of cigarettes smoked daily, systolic blood pressure and total cholesterol)

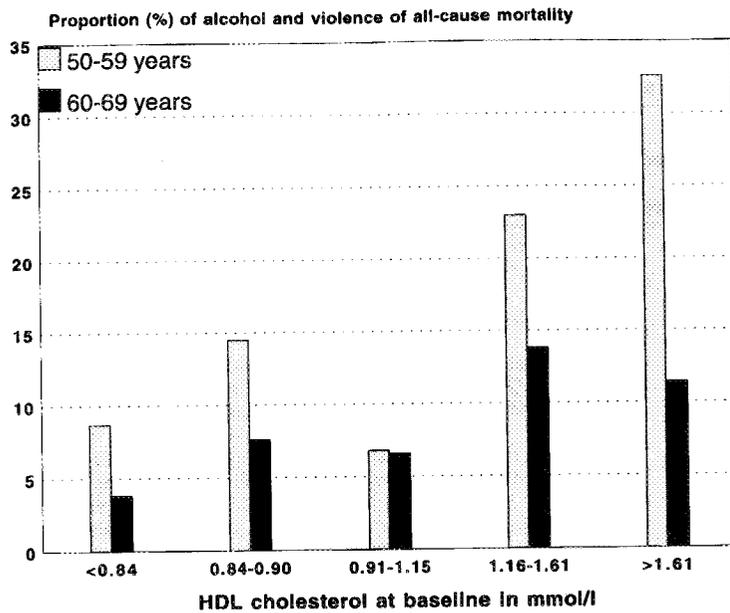


FIG 2. Bar graph showing proportion of alcohol- and violence-related mortality of all-cause mortality in different HDL cholesterol categories at baseline in two age groups in the placebo group of the ATBC study.

between HDLC and coronary mortality implies at least some degree of causality.²³

Correction for regression dilution bias increased the inverse association of HDLC and coronary mortality by 43%, even though this correction was based on only one additional HDLC measurement, attesting to the considerable variance of HDLC measurements.⁴⁷⁻⁵⁰ Thus, it is quite possible that previous studies^{1-11,51-55} based on only one baseline HDLC measurement have markedly underestimated the beneficial effect of high HDLC on coronary mortality.

All-cause mortality was positively associated with HDLC among 50- to 59-year-olds; among men ≥ 60 years, there was a U-shaped pattern. This is also consistent with previous studies.^{7,8,11,51,53,54} Alcohol- and violence-related mortality was strongly positively associated with HDLC among the 50- to 59-year-olds, similar to findings from a recent Norwegian study.¹¹ There was a less marked positive association among the 60- to 69-year-old men.

Alcohol meets the two necessary conditions to confound the association of HDLC and mortality: (1) In this and other studies,^{28-33,36,56} alcohol intake is positively related to HDLC, and (2) alcohol intake is a risk factor for nonnatural and alcohol-related deaths,³⁶⁻³⁹ cardiomyopathy,⁵⁶ cancer,^{36,56,57} stroke,^{35,36,56-58} and at high levels, also for coronary death.^{28,56,58-60} Despite its potential confounding effect, it appears that alcohol use has not received the attention it deserves in studies assessing the association of HDLC and mortality.

Absolute differences in coronary mortality between HDLC categories were more marked in the older men, which is in accordance with the literature,^{1,61,62} while the positive association of serum cholesterol with coronary mortality was less pronounced, as has also been noticed in most studies.⁶²⁻⁶⁹ Thus, interventions designed to increase HDLC may have a greater public health impact on coronary mortality than decreasing total cholesterol, especially among the elderly.

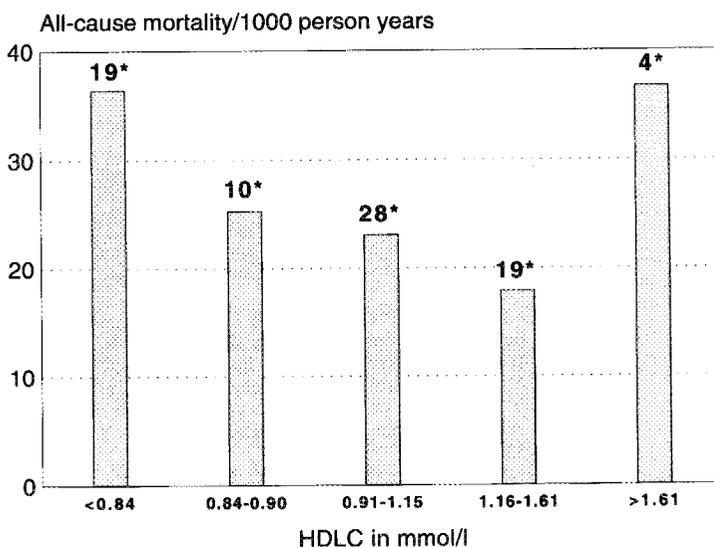


FIG 3. Bar graph showing all-cause mortality and number of deaths (*) in different HDL cholesterol (HDLC) categories among nondrinking men in the placebo group of the ATBC study.

*Number of deaths

TABLE 5. Crude and Adjusted Relative Mortality in Different Baseline Alcohol Consumption Categories of the Placebo Group of the ATBC Study, Holding the Moderate Drinkers as the Reference Category

Alcohol Intake	Coronary			Alcohol and Violence Related			All Causes		
	Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted* Relative Mortality (95% CI)	Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted Relative Mortality (95% CI)†	Crude Mortality per 1000 Person-Years	Crude Relative Mortality	Adjusted* Relative Mortality (95% CI)
Nondrinkers	9.4	1.92	1.72 (1.02-2.88)	2.1	0.88	0.74 (0.30-1.83)	24.2	1.43	1.26 (0.94-1.71)
Light drinkers	6.6	1.35	1.28 (0.85-1.93)	1.8	0.80	0.76 (0.42-1.37)	17.3	1.02	0.99 (0.79-1.24)
Moderate drinkers‡	4.9	1.00	1.00 (...)	2.4	1.00	...	16.9	1.00	1.00 (...)
Heavy drinkers	7.1	1.45	1.39 (0.61-3.19)	9.1	3.50	3.47 (1.52-7.92)	25.4	1.50	1.50 (0.90-2.17)

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

†Age adjusted.

‡Reference category.

TABLE 6. Mean HDL Cholesterol Levels and Their SDs in Different Alcohol Consumption Categories in the Placebo Group of the ATBC Study

Alcohol Consumption	No.	Mean*	SD
Nondrinkers	721	1.08	0.26
Light drinkers	4463	1.17	0.30
Moderate drinkers	1195	1.31	0.35
Heavy drinkers	210	1.36	0.37

*All planned comparisons (every alcohol consumption class against each other) with least significant difference method significant at $P < .05$ level.

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