PAPERS AND SHORT REPORTS

High density lipoprotein cholesterol is not a major risk factor for ischaemic heart disease in British men

S J POCOCK, A G SHAPER, A N PHILLIPS, M WALKER, T P WHITEHEAD

Abstract

The concentration of high density lipoprotein cholesterol (HDL cholesterol) in serum was measured at initial examination in a large prospective study of men aged 40-59 drawn from general practices in 24 British towns. After an average follow up of 4·2 years 193 cases of major ischaemic heart disease had been registered in 7415 men in whom both HDL cholesterol and total cholesterol values had been measured.

The mean HDL cholesterol concentration was lower in the men with ischaemic heart disease ("cases") compared with other men, but the difference became small and non-significant after adjustment for age, body mass index, blood pressure, cigarette smoking, and concentration of non-HDL cholesterol. The higher mean concentration of non-HDL cholesterol in "cases" remained highly significant after adjustment for other factors. Men in the highest fifth of non-HDL cholesterol values had over three times the risk of major ischaemic heart disease compared with men in the lowest fifth. Multivariate analysis showed that non-HDL cholesterol was a more powerful predictor of risk than the HDL to total cholesterol ratio.

These British findings were compared with six other prospective studies. All the larger studies showed similar results, suggesting that HDL cholesterol is not a major risk factor in the aetiology of ischaemic heart disease.

Introduction

In recent years there has been considerable interest in the role of increased serum concentrations of high density lipoprotein cholesterol (HDL cholesterol) as a protective factor against ischaemic heart disease. The enthusiasm for this hypothesis was probably enhanced by a weariness with the serum total cholesterol hypothesis and by the increased concentrations of HDL cholesterol associated with physical activity, alcohol intake, and leanness. The HDL cholesterol hypothesis has provoked considerable fundamental research into the mechanism of lipid transport and engendered much interest in the various components of blood lipids. Though plausible biological mechanisms have been developed,[1] some workers argued that there is no sound biological basis for regarding HDL cholesterol as a protective factor.[2]

Important scientific evidence on HDL cholesterol is derived from large prospective studies of ischaemic heart disease. This paper presents the first such findings in a British population and makes comparison with prospective surveys in other countries.

Subjects and methods

The British Regional Heart Study examined 7735 men aged 40-59 years selected at random from the age and sex registers of general practices in 24 towns in England, Wales, and Scotland. The criteria for selecting the towns, general practices, and subjects, as well as methods of data collection, have been described.[3-6] In brief, the 24 towns were primarily taken from those with populations of 50 000-100 000. They covered the full range of cardiovascular disease mortality and included all regions. Each town's general practice was required to have a social class distribution representative of that town. The men were selected at random from age and sex registers, with no attempt to exclude those with cardiovascular problems. The response rate was 78%. Research nurses administered a questionnaire and examined each man.

SERUM LIPID MEASUREMENTS

Non-fasting blood samples were obtained between 0830 and 1830. Serum total cholesterol and HDL cholesterol concentrations were determined in the Wolfson Research Laboratories, Birmingham. Serum total cholesterol was measured by a modified Liebermann-Burchard method on a Technicon SMA 12/60 analyser. HDL cholesterol was measured after precipitation by magnesium/phosphotungstate, initially by the Liebermann-Burchard method (11 towns) and then by an enzymatic procedure (13 towns).[7] Both methods were used in one town and a small correction factor applied to measurements from the first 11 towns. The distributions and determinants of total cholesterol, HDL cholesterol, and triglycerides have been described.[6]

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FOLLOW UP PROCEDURES

All 7735 men who were examined between 1978 and 1980 are to be followed up for both morbidity and mortality for 8 years, and at the time of this report 99% of the men had been followed up. Full details of follow up procedures have been published.[4,5]

CASE DEFINITION FOR MAJOR ISCHAEMIC HEART DISEASE

The following definitions were used to determine whether any reported cardiovascular event during follow up was accepted as a case of major ischaemic heart disease.

Fatal cases—Any subject whose death certificate recorded ischaemic heart disease (ICD codes 410-414) as the underlying cause of death without contradiction by the medical history or postmortem finding was accepted as a "case." Sudden death certified as due to ischaemic heart disease, with no other apparent cause, was included.

Non-fatal cases—Any reported myocardial infarction which included at least two of the following manifestations was accepted: (*a*) infarction preceded by severe, prolonged chest pain; (*b*) electrocardiographic evidence of myocardial infarction; (*c*) cardiac enzyme changes.

Men with evidence of pre-existing ischaemic heart disease at initial screening were included and contributed to both the "cases" and the comparison group of other men.

STATISTICAL METHODS

As is usual in prospective studies of coronary heart disease the simultaneous contributions of HDL cholesterol and other factors to the risk of major ischaemic heart disease were analysed by a multiple logistic model. Specifically, the adjusted relative odds shown in figure 1 were obtained by using such models with each factor in turn fitted in five intervals—that is, with four dummy variables—while other factors were fitted as continuous measurements. More complex analyses which allowed for the town's differing follow up times made a negligible difference.

Results

Serum total cholesterol and HDL cholesterol concentrations were measured for 7415 men (96%). After an average of 4·2 years of follow up 193 of these men had become cases of major ischaemic heart disease. Table I compares these 193 "cases" with the 7222 other men for their mean concentrations of total cholesterol, HDL cholesterol, and non-HDL cholesterol—that is, total cholesterol minus HDL cholesterol—and the HDL cholesterol to total cholesterol ratio. The mean total cholesterol concentration was significantly higher in the cases, and the difference between cases and other men was even more pronounced for non-HDL cholesterol. Conversely, the mean HDL cholesterol value was significantly lower in the cases, as was the HDL cholesterol to total cholesterol ratio.

It is important to examine the interrelations between these blood lipids. Since HDL cholesterol concentration was not correlated with total cholesterol concentration ($r=-0·04$) it follows that HDL cholesterol and non-HDL cholesterol were negatively correlated ($r=-0·28$). HDL cholesterol is only a small part of total cholesterol, so there was a very strong association between total cholesterol and non-HDL cholesterol ($r=0·97$). Furthermore, the HDL cholesterol to total cholesterol ratio showed strong correlations with both HDL cholesterol ($r=0·81$) and non-HDL cholesterol ($r=-0·75$).

TABLE I—*Mean concentrations of serum total cholesterol, HDL cholesterol, non-HDL cholesterol, and HDL cholesterol to total cholesterol ratio for men with major ischaemic heart disease (cases) and other men*

	Cases (n=193)		Other men (n=7222)		
	Mean	SD	Mean	SD	*t* Value
Total cholesterol (mmol/l)	6·792	1·169	6·284	1·039	6·0
HDL cholesterol (mmol/l)	1·079	0·272	1·148	0·265	−3·5
Non-HDL cholesterol (mmol/l)	5·713	1·195	5·136	1·081	6·6
HDL: total cholesterol ratio	0·164	0·053	0·188	0·055	−6·2

Conversion: SI to traditional units—Cholesterol and HDL cholesterol: 1 mmol/l≈38·6 mg/100 ml.

The univariate findings shown in table I take no account of these interrelations or of relations with other risk factors. Therefore, analysis of covariance was used to determine the mean differences between cases and other men for HDL cholesterol and non-HDL cholesterol after adjustment for associations with one another and with age, blood pressure, body mass index, and cigarette smoking (table II). The mean difference in HDL cholesterol between cases and other men was reduced from −0·069 to −0·023 mmol/l (−2·7 to −0·9 mg/100 ml) and was no longer statistically significant. The mean difference for non-HDL cholesterol was also reduced but remained highly significant. The main reasons for a diminished difference in HDL cholesterol after adjustment were the lower concentrations of HDL cholesterol in cigarette smokers[6] and the negative association between HDL cholesterol and non-HDL cholesterol.

TABLE II—*Differences in mean concentrations of HDL cholesterol and non-HDL cholesterol between men with major ischaemic heart disease (cases) and other men, both unadjusted and after adjustment for one another and for age, blood pressure, body mass index, and cigarette smoking. Results expressed in mmol/l*

	Unadjusted	Adjusted ± 95% confidence limits
HDL cholesterol	−0·069	−0·023 ±0·036
Non-HDL cholesterol	+0·577	+0·429 ±0·148

Conversion: SI to traditional units—Cholesterol and HDL cholesterol: 1 mmol/l≈38·6 mg/100 ml.

Logistic regression may also be used to study the simultaneous influence of several variables on risk of ischaemic heart disease. Table III shows logistic coefficients for HDL cholesterol and non-HDL cholesterol in a logistic regression that also included age, blood pressure, body mass index, and cigarette smoking. HDL cholesterol showed no significant association with risk of major ischaemic heart disease ($p=0·21$), while non-HDL cholesterol was highly significant ($p<0·0001$).

TABLE III—*Effects of HDL cholesterol and non-HDL cholesterol on risk of major ischaemic heart disease in multiple logistic model which also included age, blood pressure, body mass index, and cigarette smoking*

	Logistic coefficient	Standardised relative odds	p Value
HDL cholesterol	−0·406	0·90	0·21
Non-HDL cholesterol	0·378	1·50	<0·0001

Since total cholesterol and non-HDL cholesterol were strongly correlated there was only a small gain in prediction of ischaemic heart disease events by using non-HDL cholesterol instead of total cholesterol. The standardised relative odds for non-HDL cholesterol and total cholesterol were 1·53 and 1·48, respectively, after adjustment for other risk factors (but not for HDL cholesterol, since it was non-significant (table III)).

The standardised relative odds shown in table III illustrate the importance of non-HDL cholesterol compared with HDL cholesterol. The standardised relative odds, defined as the change in odds (approximate risk) of major ischaemic heart disease for a one standard deviation increase in the variable, were 0·90 for HDL cholesterol and 1·50 for non-HDL cholesterol. Hence a one standard deviation increase in HDL cholesterol had an estimated (non-significant) 10% decrease in risk, whereas a one standard deviation increase in non-HDL cholesterol had an estimated 50% increase in risk.

Figure 1 shows how specific concentrations of HDL cholesterol and non-HDL cholesterol related to risk of major ischaemic heart disease. For HDL cholesterol men are ranked in order of concentration and divided into five groups of equal size and the number of cases of major ischaemic heart disease determined for each fifth. The odds of major ischaemic heart disease for each fifth are expressed relative to the highest fifth. These relative odds are also shown after adjustment for other risk factors, including non-HDL cholesterol. Similar calculations were performed for non-HDL cholesterol, total cholesterol, and the HDL cholesterol to total cholesterol ratio. For non-HDL cholesterol and total cholesterol the odds are expressed relative to the lowest fifth of the distribution, adjustment having been made for HDL cholesterol and the other non-lipid factors mentioned above. For the HDL cholesterol to total cholesterol ratio adjusted odds take account of non-lipid factors only—namely, age, blood pressure, body mass index, and cigarette smoking.

For HDL cholesterol the unadjusted relative odds (fig 1) showed a doubling of risk in the lowest fifth (<0·93 mmol/l (35·9 mg/100 ml)) compared with the highest fifth of men (≥1·33 mmol/l (51·4 mg/100 ml)).

After adjustment for other risk factors, including non-HDL cholesterol, however, there was no clear evidence of a decreasing risk of ischaemic heart disease for higher concentrations of HDL cholesterol. Indeed, men with intermediate values had a slightly lower adjusted risk of ischaemic heart disease compared with men in the highest fifth.

For non-HDL cholesterol and total cholesterol there were definite and continuous increases in risk of ischaemic heart disease from the lowest to the highest fifth of values. These risk gradients were only slightly reduced after adjustment for other risk factors—that is, age, blood pressure, body mass index, cigarette smoking, and HDL cholesterol. Since HDL cholesterol had no significant risk association, not surprisingly its subtraction from total cholesterol disclosed a slightly increased risk gradient for non-HDL cholesterol. Thus men in the highest fifth of non-HDL cholesterol values had over three times the risk of men in the lowest fifth.

Some workers have favoured the HDL cholesterol to total cholesterol ratio.[8] As shown in figure 1, the ratio had a similar (but inverse) risk gradient to that for non-HDL cholesterol. In a logistic model incorporating both non-HDL cholesterol and the ratio, however, the former remained a highly significant predictor of risk (p=0·0007) while the latter did not (p=0·19). Thus the apparent importance of the ratio was probably due to the non-HDL component of its denominator and does not indicate any meaningful role for HDL cholesterol.

The analyses so far have included all men screened, including those with indications of pre-existing ischaemic heart disease as determined by electrocardiogram, chest pain questionnaire, or the men's recall of doctors' diagnoses.[9,10] Excluding men with pre-existing ischaemic heart disease leaves a sample of 5872 men (79%) with no pre-existing ischaemic heart disease, of whom 102 had a subsequent major ischaemic heart disease event. Table IV shows the difference between these new cases of major ischaemic heart disease and other men without pre-existing ischaemic heart disease for mean HDL cholesterol and mean non-HDL cholesterol, both unadjusted and after adjustment for other risk factors. After allowance for other factors there was no evidence of a lower mean HDL cholesterol concentration in new cases of ischaemic heart disease compared with other men without pre-existing ischaemic heart disease. The mean non-HDL cholesterol value, however, remained noticeably raised in new cases compared with other men without pre-existing disease. For men with pre-existing ischaemic heart disease similar results were obtained for HDL cholesterol (table IV). Non-HDL cholesterol remained a significant predictor of subsequent major ischaemic heart disease events, even in men with pre-existing ischaemic heart disease, though this was less pronounced than in men without pre-existing disease.

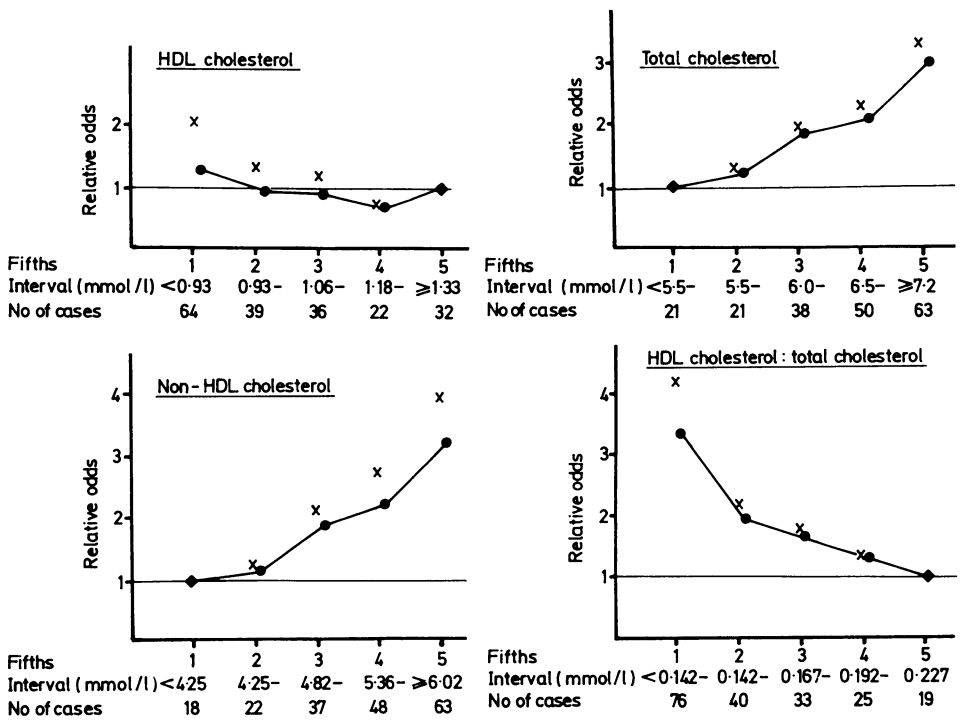

FIG 1—Relative odds for HDL cholesterol, non-HDL cholesterol, total cholesterol, and HDL cholesterol to total cholesterol ratio (by fifths of ranked distribution). (◆=Base group. ×=Unadjusted. ●=Adjusted for other risk factors.)

Conversion: SI to traditional units—Cholesterol and HDL cholesterol: 1 mmol/l≈38·6 mg/100 ml.

TABLE IV—*Effects of HDL cholesterol and non-HDL cholesterol on risk of major ischaemic heart disease in men with and without pre-existing ischaemic heart disease. Results expressed as differences in mean values between cases and controls (mmol/l)*

	Unadjusted	Adjusted ±95% confidence limits	Standardised relative odds
Men without pre-existing ischaemic heart disease (102 cases, 5770 other men)			
HDL cholesterol	−0·047	−0·002 ±0·049	0·98
Non-HDL cholesterol	+0·605	+0·473 ±0·202	1·55
Men with pre-existing ischaemic heart disease (91 cases, 1452 other men)			
HDL cholesterol	−0·081	−0·041 ±0·054	0·82
Non-HDL cholesterol	+0·469	+0·338 ±0·223	1·37

Conversion: SI to traditional units—Cholesterol and HDL cholesterol: 1 mmol/l≈38·6 mg/100 ml.

OVERVIEW OF OTHER PROSPECTIVE STUDIES OF HDL CHOLESTEROL

We have identified seven prospective studies (including our own) which have related HDL cholesterol values to risk of coronary heart disease. Two (in Finland[11] and Minnesota[12]) were cohort studies of deaths from ischaemic heart disease, while three other cohort studies (in Framingham,[13] Israel,[8] and Great Britain) and two prospective case-control studies (in Oslo[14] and Tromsø[15]) related HDL cholesterol to major ischaemic heart disease events, both fatal and non-fatal.

All these studies found a lower mean HDL cholesterol concentration in cases of major ischaemic heart disease. This was statistically significant in the five studies which included fatal and non-fatal events but not in the two mortality studies. A more meaningful overall assessment, however, is achieved by plotting for each study the difference in mean HDL cholesterol values for "cases" versus other men and its 95% confidence limits (fig 2). The Tromsø study showed a much greater difference than any other study. It should be noted that this was a small case-control study (17 cases versus 31 controls) with HDL cholesterol values determined from frozen samples. The six other studies showed considerable agreement, with differences in mean HDL cholesterol values (cases versus other men) ranging from −0·038 mmol/l (−1·5 mg/100 ml) in Finland to −0·085 mmol/l (−3·3 mg/100 ml) in Minnesota and all confidence intervals overlapping. The three largest studies in Framingham (138 cases), Israel (157 cases), and Great Britain (193 cases) provided more reliable estimates, as indicated by narrower confidence intervals.

For the British Regional Heart Study figure 2 also shows the difference in

mean HDL cholesterol values after adjustment for other risk factors (obtained from table II). The confidence interval included zero difference, indicating no evidence of an independent contribution of HDL cholesterol to risk of ischaemic heart disease in British men. It would have been appropriate to repeat this adjustment for the other studies, but such information was not available to us. Nevertheless, it seems likely that the observed differences in other major cohort studies would also become smaller and less significant if adjusted in this way.

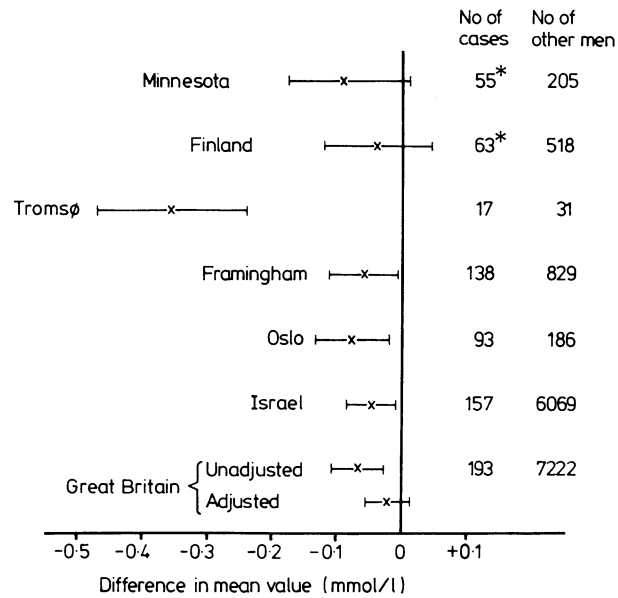

FIG 2—Differences in mean HDL cholesterol concentrations between men with ischaemic heart disease (cases) and other men in seven prospective studies. Crosses and bars are observed differences in mean HDL cholesterol values and 95% confidence limits.
*Fatal cases only.
Conversion: SI to traditional units—HDL cholesterol: 1 mmol/l≈38·6 mg/10 ml.

Discussion

Information from prospective observational studies of large cohorts is of critical importance in testing the hypothesis that raised concentrations of HDL cholesterol may protect against ischaemic heart disease. Cross sectional studies of prevalent ischaemic heart disease and retrospective case-control studies are not considered here since they provide much weaker evidence of aetiological relations. This prospective study showed no significant independent relation between HDL cholesterol concentrations and major ischaemic heart disease events and questions whether HDL cholesterol is of any importance for ischaemic heart disease in British middle aged men.

We have reported a similar conclusion for serum triglycerides[4]—that is, mean serum triglyceride concentrations tend to be higher in cases of major ischaemic heart disease compared with other men, but this difference becomes non-significant after taking account of other risk factors.

Interest in HDL cholesterol increased when Miller and Miller hypothesised that HDL values were inversely related to ischaemic heart disease,[1] and it was further stimulated by results from prospective studies in Tromsø[15] and Framingham.[13] The Tromsø study found a much greater difference between HDL cholesterol concentrations in cases and controls than all other studies. It was the smallest study, making multivariate analysis less reliable. Use of frozen material reduces HDL cholesterol concentrations but the effect on comparisons is uncertain. Perhaps the Tromsø study is different from all others because of a general "publication bias," whereby early small studies in any new topic tend to exaggerate unwittingly the magnitude of a relation.

The Framingham study also reported a negative association between HDL cholesterol concentrations and the risk of ischaemic heart disease, and some of the strongest statements regarding the importance of HDL cholesterol have arisen from its findings. The study was unusual in the selection of subjects for measurement of HDL cholesterol. The original Framingham cohort was recruited in 1949-50 when aged 30-59. During 1969-71 the group of survivors (then aged 49-82) were screened for HDL cholesterol, and those still free of ischaemic heart disease after 20 years of surveillance were followed up for a further four years.

More recent Framingham data on eight years of follow up with an increased number of cases of ischaemic heart disease have been made available to us. The difference in mean HDL cholesterol concentration between cases of major ischaemic heart disease and other men had narrowed (fig 2), so that univariate findings in the Framingham study showed close agreement with the British Regional Heart Study. Adjustment for other risk factors such as low density lipoprotein cholesterol and smoking may diminish the contribution of HDL cholesterol to risk of ischaemic heart disease, but such analyses on eight years of data are not yet available.

The Oslo study included a prospective comparison of cases of ischaemic heart disease and controls aged 40-49 using frozen material stored for five to six years. This produced a 35% reduction in HDL cholesterol concentration compared with fresh serum. A control group matched for smoking, total cholesterol concentrations, triglyceride values, age, and time of sampling showed HDL cholesterol concentrations not significantly different from those in the cases. A further control group, matched for age and time of sampling only, showed higher HDL cholesterol concentrations than in the cases of ischaemic heart disease ($p<0·05$). The main purpose of the study was to examine the role of HDL cholesterol in younger subjects and no comparison of total cholesterol and HDL cholesterol was made.

The Israeli study concerns a large cohort of middle aged men observed since 1963. The first major report showed that HDL cholesterol was somewhat less powerful an indicator of risk of ischaemic heart disease than total cholesterol.[16] The next report showed HDL cholesterol as an independent indicator of risk in men aged 50 or more.[8] A further paper found that mortality from ischaemic heart disease increased with concentrations of total cholesterol, but the inverse relation of mortality to HDL cholesterol emerged as dominant.[17] The latest publication confirmed a continuous inverse association of HDL cholesterol concentration with mortality from ischaemic heart disease.[18] For total cholesterol mortality from ischaemic heart disease remained fairly constant up to 5·6 mmol/l (216 mg/100 ml) and rose appreciably only in the highest quintile (≥6·2 mmol/l; ≥239 mg/100 ml).

Israeli men have considerably lower concentrations of serum total cholesterol than their British counterparts—for example, their 80th percentile of 6·2 mmol/l is the median value in British men. The Multiple Risk Factor Intervention Trial showed a curvilinear relation between total cholesterol concentration and mortality rates from ischaemic heart disease with a much steeper gradient of risk at higher concentrations of total cholesterol.[19] Not surprisingly, therefore, the Israeli data showed total cholesterol to be less important. Also the determinants of HDL cholesterol were likely to be different in these two populations. Alcohol consumption produced noticeable increases in HDL cholesterol concentrations in British men,[6] whereas Israeli men consume much less alcohol. Possibly the fractions of HDL cholesterol raised by alcohol are not relevant to the risk of ischaemic heart disease and higher HDL cholesterol concentrations associated with leanness, exercise, and non-smoking may be more specific to the problem. It is relevant to note that preliminary findings in the British Regional Heart Study showed no consistent association between alcohol intake and major ischaemic heart disease events.[20]

The earlier Israeli data relating to both fatal and non-fatal ischaemic heart disease events show some agreement with British data. The Israeli workers have often preferred to express findings in terms of the HDL cholesterol to total cholesterol ratio, which may be open to misinterpretation. The ratio may be rewritten as 1/(1+[non-HDL cholesterol/HDL cholesterol]). Even if HDL cholesterol were irrelevant, this ratio would still show a relation to risk of ischaemic heart disease, since non-HDL cholesterol is

positively related to risk and there is a negative association between HDL cholesterol and non-HDL cholesterol. Thus the real test of whether such a ratio has any independent predictive ability is to fit a logistic model relating risk of ischaemic heart disease to both non-HDL cholesterol and the HDL cholesterol to total cholesterol ratio. In our data the ratio then made no significant contribution to risk of major ischaemic heart disease.

Conclusion

Despite the extent of current opinion about the protective effect of HDL cholesterol on ischaemic heart disease, there appears to be reasonable doubt regarding the strength and validity of this association. Data from the British Regional Heart Study have not shown HDL cholesterol to be an independent risk factor for ischaemic heart disease. It is possible that HDL cholesterol has a greater role in other communities with lower concentrations of total cholesterol and taking different diets.[21] The prospective studies reviewed in this paper are consistent in finding lower HDL cholesterol concentrations in men developing major ischaemic heart disease events. The difference, however, appears to be small and is reduced after appropriate adjustment for other risk factors. While HDL cholesterol will continue to be a focus of considerable interest and concern—particularly regarding its role in the removal of cholesterol from peripheral tissues—it does not appear to be a risk factor of importance to the present generation of middle aged British men.

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Children intoxicated by alcohol in Nottingham and Glasgow, 1973-84

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Abstract

The circumstances of ingestion, clinical course, and long term sequelae were examined retrospectively in 143 children (108 boys, 35 girls) admitted with acute alcohol intoxication in Glasgow and Nottingham over the 12 years 1973-84. Fifty three of the children were aged less than 7 years and 90 were aged 7-14. Twelve of the children were hypoglycaemic on arrival at hospital. Trauma related to intoxication occurred in 14 cases, and nine boys became drunk under duress, which in four cases was associated with sexual abuse.

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Introduction

Each year roughly 1000 children aged under 15 are admitted to hospital in England and Wales suffering from acute alcohol intoxication (Department of Health and Social Security, personal communication). Despite the relative frequency of such cases there have been few reports on the problem,[1] most studies having highlighted occasional dramatic complications.[2] The aim of our study was to assess the origins and overall medical importance of such incidents by systematically examining the circumstances of ingestion, the clinical course, and long term sequelae in all children with alcohol intoxication admitted to two paediatric centres in Britain, the Royal Hospital for Sick Children, Glasgow, and the children's department of University Hospital, Nottingham.

Patients and methods

The children's department at University Hospital, Nottingham, provides a primary paediatric referral service for 184 000 children aged under 15 in the city of Nottingham and the surrounding rural areas. In Glasgow the Royal Hospital of Sick Children provides a similar acute service for about 200 000 children. Teenagers in Nottingham who require acute medical care may be