EPIDEMIOLOGY

Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men

The Caerphilly and Speedwell Collaborative Heart Disease Studies

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Abstract

Objective—To assess the roles of plasma triglyceride and high density lipoprotein (HDL) cholesterol concentrations in predicting ischaemic heart disease.

Design—Two prospective cohort studies with common core protocols.

Setting and participants—Both cohorts are 100% samples of middle aged men. In Caerphilly the 2512 men were living within a defined area. In Speedwell the 2348 men were registered with local general practitioners.

Main outcome measures—Fasting blood samples were taken at initial examination and plasma lipid concentrations were measured. Major ischaemic heart disease events were assessed from hospital notes, death certificates, and electrocardiograms.

Results—At first follow up, after an average of 5.1 years in Caerphilly and 3.2 years in Speedwell, 251 major ischaemic heart disease events had occurred. Men with triglyceride concentrations in the top 20% of the distribution had a relative odds value for ischaemic heart disease of 2.3 (95% confidence interval (95% CI) 1.3 to 4.1) compared with men in the bottom 20%, after adjusting for both plasma total and HDL cholesterol, and non-lipid risk factors. Men in the lowest 20% of the distribution of HDL cholesterol concentration had a relative odds value of 1.7 (95% CI 1.0 to 2.8) compared with the top 20%, after adjustment was made for total cholesterol and triglyceride concentrations, and non-lipid risk factors. These relations were not caused by β blockers, which were being taken by 5% of the men.

Conclusions—Plasma triglyceride concentration predicts major ischaemic events after allowance is made for total

and HDL cholesterol concentrations and other risk factors. In these populations, triglyceride is a more important predictor than total cholesterol concentration.

Many studies have shown that total cholesterol concentration is an important predictor of the development of ischaemic heart disease.¹⁻³ Interest in the role of high density lipoprotein (HDL) cholesterol in the aetiology of ischaemic heart disease was stimulated in 1975 by Miller and Miller.⁴ Since then, numerous epidemiological studies have shown that low concentrations of HDL cholesterol are independently associated with an increased risk of ischaemic heart disease.⁵ The first British study, however, to report on this association concluded that HDL cholesterol was not a major risk factor.⁶ A later report, based on a larger number of events and with a different method of analysis, revised that view and concluded that HDL cholesterol was important, but less so than total cholesterol concentration.⁷

Raised concentrations of total triglyceride are associated with an increased risk of ischaemic heart disease. Most studies suggest that, in men, triglyceride is not an independent risk factor and that its relation with ischaemic heart disease is explained by the association of both with other factors, particularly total cholesterol and HDL cholesterol.^{7,8} This, however, has not been a universal finding and the role of triglyceride is still uncertain.⁹ Understanding of this role is complicated by the fact that in some studies triglycerides were measured after the subjects had fasted overnight, whereas in others the subjects had not.

The Caerphilly and Speedwell studies recruited their joint population of 4860 middle age men between 1979 and 1983.¹⁰ Lipids were measured on fasting blood samples. In this report, the relations of

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triglyceride, HDL cholesterol, and total cholesterol concentration to the incidence of ischaemic heart disease are described.

Methods

STUDY POPULATIONS

In Caerphilly, a 100% sample of men was selected from within a defined area. They were aged between 45 and 59 when first examined. A total of 2512 men were seen—89% of the 2818 found to be eligible. In Speedwell, a 100% sample of men was selected from the age sex registers of 16 general practitioners working from two neighbouring health centres. The men were aged 45 to 59 when chosen, immediately before the study began. They were aged between 45 and 63 when first examined. A total of 2348 men were seen—92% of those eligible. The combined cohort thus numbers 4860 men.

SURVEY METHODS AND FOLLOW UP PROCEDURE

The two studies had a common core protocol and common procedures as described elsewhere.¹⁰⁻¹² Briefly, when recruited, the men attended an afternoon or evening clinic at which a standard medical and smoking history was obtained; subjects answered the London School of Hygiene and Tropical Medicine chest pain questionnaire; height, weight, and blood pressure were measured; and a 12 lead electrocardiogram was recorded. The men returned, after an overnight fast, to an early morning clinic where a blood sample was taken with minimal venous stasis and anticoagulated with 1 mg/ml disodium ethylenediaminetetraacetate. Fasting samples were obtained from 4641 men. The minimal duration of the overnight fast was eight hours and the typical duration was 12 hours.

The results reported in this paper refer to the first follow up. In Caerphilly, this was at a nearly constant interval of (mean (SD)) 61 (5) months, whereas in Speedwell the mean follow up period was 38 (3) months. At follow up the chest pain questionnaire was answered again, and a second electrocardiogram recorded. The chest pain questionnaire was extended to include questions about stays in hospital for severe chest pain. The questionnaires, together with hospital activity analysis notifications of admissions coded as 410-414 (ischaemic heart disease) on the International Classification of Diseases (ICD), were used as the basis for a search of hospital notes for events which satisfied the World Health Organisation (WHO) criteria for definite acute myocardial infarction. For men who had died before the follow up, a copy of the death certificates was automatically received from the National Health Service Central Registry. From this information, three categories of events associated with ischaemic heart diseases were defined¹²: death from ischaemic heart disease (cause of death coded as ICD 410-414), clinical non-fatal myocardial infarction (an event satisfying the WHO criteria), and electrocardiographic myocardial infarction (appearance of major or moderate Q or QS waves, Minnesota codes 1-1-1 to 1-2-5

or 1-2-7 on the follow up electrocardiogram; when there were no Q or QS waves, Minnesota codes 1-1-any, 1-2-any, or 1-3-any on the recruitment electrocardiogram). All electrocardiograms were read by one of two highly experienced persons. The same persons read, independently, recruitment and follow up electrocardiograms for both studies.

LABORATORY METHODS

Because of the heavy workload separate laboratories had to be used for the lipid analyses for the two areas. Plasma samples were transported at 4°C by rail to the laboratories on the day of venepuncture. Cholesterol and triglyceride concentrations were measured with enzymatic procedures.¹³⁻¹⁴ The HDL fraction was isolated by precipitation of the low and very low density lipoproteins with sodium phosphotungstate and magnesium chloride (Caerphilly),¹⁵ or with heparin and manganese chloride (Speedwell).¹⁶

In both studies at least one in every 20 of the blood samples was sent to the laboratory as a split duplicate to assess reproducibility. This was similar in the two laboratories. Coefficients of variation were 7% (Caerphilly) and 10% (Speedwell) for total cholesterol, 14% and 15% for triglyceride, and 20% in both laboratories for HDL cholesterol.

Over the course of the recruitment phase, 91 of the Speedwell blood samples were split, one aliquot going to the Speedwell laboratory and the other to the Caerphilly laboratory. Mean differences in concentration between laboratories were 0.50 mmol/l for cholesterol, 0.01 mmol/l for HDL cholesterol, and 0.11 mmol/l for triglyceride. The Speedwell laboratory measured higher for cholesterol and HDL cholesterol and lower for triglyceride. These between laboratory differences were consistent from sample to sample and the variation between laboratories was indistinguishable from the variation when two aliquots were sent to the same laboratory. In all analyses the concentration of cholesterol, HDL cholesterol, and triglyceride were adjusted to that of the Speedwell laboratory using the mean differences cited.

STATISTICAL METHODS

Adjusted mean differences in lipids between various groups (tables 1, 2 and 5) were obtained by analysis of covariance with standard multiple linear regression techniques.

The rest of the analysis was performed by multiple logistic regression with the occurrence or not of a major ischaemic heart disease event as the dependent variable. Logistic regression takes no account of the duration of follow up. This is likely to be immaterial, however, as the duration of follow up was virtually constant within each area. Any model involving time would also face the problem that no time of event is available for electrocardiographically defined myocardial infarction. In the logistic regression analyses lipid concentrations were treated in two ways. Firstly, their distributions were divided into equal fifths, and the results presented as the odds of major ischaemic heart

Table 1 Mean (SD) concentrations* (mmol/l) of lipids and incidence of ischaemic heart disease (IHD): areas combined

Lipid	No major incident IHD (n = 4408)	Major incident IHD (n = 233)	Age and area standardised mean difference (95% CI)
Cholesterol	6.04 (1.17)	6.32 (1.38)	0.29 (0.13 to 0.44)
HDL cholesterol	1.12 (0.35)	1.04 (0.33)	-0.09 (-0.14 to -0.04)
Triglyceride	1.72 (1.16)	2.01 (1.12)	0.31 (0.16 to 0.46)

*Mean concentrations are area standardised. HDL, high density lipoprotein.

disease in each fifth relative to baseline fifth; 95% confidence intervals (95% CIs) for these relative odds were also estimated. The fifths were calculated within area, using each area's own quintiles. Secondly, the lipids were entered as continuous variables and the results presented as standardised relative odds, defined as the proportionate change in odds for a 1 SD change in the variable. Except for the essentially univariate analyses of tables 1 and 2, triglyceride concentration was transformed to natural logarithms.

Ischaemic heart disease at recruitment was assessed by the London School of Hygiene and Tropical Medicine chest pain questionnaire and the 12 lead electrocardiogram. Three categories of pre-existent disease—namely, angina, prolonged severe chest pain, and electrocardiographic ischaemia—were defined in a standard manner.¹⁷ Among the total cohort of 4860 men, 1171 (24%) had some evidence of ischaemic heart disease. Four hundred and ninety one (10%) had asymptomatic electrocardiographic ischaemia, and 261 (5%) had had at least one episode of severe chest pain lasting more than half an hour for which they had consulted a doctor who diagnosed ischaemia or, in a small number of cases, passed no opinion to the subject.¹⁸ This overall prevalence of ischaemic heart disease at recruitment of 24% is close to that found by the British Regional Heart Study.³

The men with evidence of ischaemic heart disease when first examined have not been excluded from the analysis. Reasons for this are given elsewhere.¹² Briefly, exclusion of such a large group, among whom roughly half the major events occur, does not seem satisfactory. The usual practice is to exclude a small group of subjects such as the 261 (5%) who had had an episode of prolonged severe chest pain that was considered by a doctor to be ischaemic in origin.³ It is then assumed, incorrectly, that the remaining subjects are free of disease. Instead we have chosen (as did the Regional Heart Study) to include all men but to adjust for the presence of pre-existent disease by including

standardised measures of angina, severe chest pain, and electrocardiographic ischaemia on entry to the study as three covariates in the logistic regression analyses. This is a conservative procedure that may underestimate the association between lipid concentrations and incidence of ischaemic heart disease. Deaths attributed to causes other than ischaemic heart disease were treated as events not associated with ischaemic heart disease.

In all analyses of the major lipid fractions the data from the two studies were combined. The difference in incidence between the areas due to the different durations of follow up was accommodated by including area as a two level factor in all analyses. This assumes that the relations between incidence of ischaemic heart disease and the major lipids in the two areas are parallel on the logit scale. The assumption was tested by adding interaction terms to the models. No significant interactions were found.

Results

INCIDENCE OF MAJOR ISCHAEMIC HEART DISEASE A total of 251 major ischaemic heart disease events occurred during follow up; 153 in Caerphilly and 98 in Speedwell. The average annual incidence was 1.2% in Caerphilly and 1.3% in Speedwell. The distribution of the three types of event was similar in the two areas; 50% were fatal, 39% were clinical non-fatal myocardial infarction, and 11% were electrocardiographically defined myocardial infarction.

MEN WITH COMPLETE DATA OR MISSING VALUES Among the 4641 men who provided a fasting blood sample there were 233 major ischaemic heart disease events. Information was missing on cholesterol concentrations for 79 men, HDL cholesterol concentrations for 119 men, and triglyceride concentrations for 115 men. Sixty four men had missing data for non-lipid risk factors (smoking, body mass index, blood pressure). The univariate analyses are based on all men who had a measurement for each lipid. The multivariate analyses are based on 4371 men with complete data.

UNIVARIATE ANALYSES Table 1 shows the mean concentrations of cholesterol, HDL cholesterol, and triglyceride for the men who had a major ischaemic event and for those who did not. The age and area adjusted mean difference and its 95% CI are also given. Total cholesterol and triglyceride concentrations were higher, by 0.29 and 0.31 mmol/l respectively, in men who had an event, and HDL cholesterol concentration was lower, by 0.09 mmol/l. All these differences are significant (p < 0.001). Table 2 shows that the age adjusted mean differences of each of these lipids were similar in the two areas. Only for HDL cholesterol concentration was there any appreciable difference between the areas: in Speedwell HDL cholesterol concentration was 0.13 mmol/l lower in men developing ischaemic heart disease, whereas in Caerphilly it was 0.06 mmol/l lower. This difference between the areas is not statistically significant.

Table 2 Mean differences in concentrations of lipids between men developing IHD and those not: areas analysed separately

Lipid	Age-standardised mean differences (95% CI) in lipids between men developing IHD and those not	
	Caerphilly	Speedwell
Cholesterol	0.28 (0.08 to 0.47)	0.30 (0.05 to 0.55)
HDL cholesterol	-0.06 (-0.12 to -0.01)	-0.13 (-0.21 to -0.05)
Triglyceride	0.29 (0.06 to 0.51)	0.35 (0.14 to 0.55)

Abbreviations as in table 1.

Table 3 Correlation coefficients between lipids

	Cholesterol	HDL cholesterol
HDL cholesterol:		
Caerphilly	0.03	—
Speedwell	0.04	—
Triglyceride:		
Caerphilly	0.36	−0.24
Speedwell	0.34	−0.28

Triglyceride concentration transformed to natural logarithms. Abbreviation as in table 1.

INTERRELATIONS BETWEEN LIPID MEASUREMENTS

Table 3 shows correlation coefficients between cholesterol, HDL cholesterol, and triglyceride concentrations. They are given separately for each area, and are similar in the two areas. Association between total cholesterol and HDL cholesterol was minimal, but triglyceride concentration was associated positively with cholesterol concentration and negatively with HDL cholesterol concentration.

RELATIONS WITH OTHER RISK FACTORS

Both cholesterol and HDL cholesterol concentrations showed little association with smoking, age, or blood pressure. Triglyceride concentration was higher by 0.14 mmol/l in smokers than in non-smokers, and showed a small positive association with diastolic blood pressure ($r = 0.16$ in Caerphilly and 0.11 in Speedwell). Body mass index showed a weak positive association with cholesterol concentration ($r = 0.04$ and 0.09), but stronger associations with HDL cholesterol ($r = -0.17$ and -0.23) and triglyceride concentrations ($r = 0.27$ and 0.26).

Men who had any evidence of pre-existent disease (angina, history of severe chest pain, or ischaemia on electrocardiogram) at recruitment, had higher cholesterol concentrations (by 0.14 mmol/l in both areas), lower HDL cholesterol concentrations (by 0.04 mmol/l in both areas) and higher concentrations of triglyceride (by 0.25 mmol/l in Caerphilly and by 0.19 mmol/l in Speedwell).

MULTIVARIATE ANALYSIS

In the multivariate analysis the relation between incidence of ischaemic heart disease and each of the three major lipid fractions was assessed after adjustment for both the other

Table 4 Effect of successive adjustment for other risk factors on the standardised relative odds of developing major IHD in relation to total cholesterol, HDL cholesterol, and total triglyceride concentrations

Adjusted for	Standardised relative odds		
	Cholesterol	HDL cholesterol	Triglyceride
Age and area only	1.24**	1.37***	1.41***
All non-lipid risk factors:†	1.17*	1.26**	1.29***
+ Cholesterol	—	1.27**	1.25**
+ HDL cholesterol	1.18*	—	1.19*
+ Triglyceride	1.12	1.22*	—

*p < 0.05; **p < 0.01; ***p < 0.001. Standardised relative odds are the proportionate change in odds for a 1 SD increase in cholesterol and triglyceride, and a 1 SD decrease in HDL cholesterol. Triglyceride transformed to natural logarithms. †Successive adjustment for additional risk factors. Abbreviations as in table 1.

Relative odds of major ischaemic heart disease with different concentrations of cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride. ■, base group; ●, adjusted for age and area only; ▽, adjusted for age, area, smoking, diastolic blood pressure, body mass index, ischaemic heart disease at recruitment, and the two other major lipids.

two fractions and for the non-lipid risk factors, age, smoking, diastolic blood pressure, body mass index, and each of the three types of pre-existent disease.

The figure shows the relative odds of major ischaemic heart disease by “fifths” of the concentration of each lipid variable. Two sets of values are given; one with adjustment for age and area only, the other with adjustment for all non-lipid risk factors and both of the other two lipid fractions. Table 4 shows the standardised relative odds of major ischaemic heart disease with successive adjustment for other variables.

TOTAL CHOLESTEROL

The relative odds value for major ischaemic heart disease in the top 20% of the distribution of cholesterol concentration compared with the bottom 20% was 1.66 (95% CI, 1.10 to 2.52) when adjusted for age and area only. On adjusting for the non-lipid risk factors and for HDL cholesterol and triglyceride concentrations, the relative odds value fell to 1.30 (95% CI 0.82 to 2.06). A major factor in this decline was the adjustment for triglyceride concentration (table 4). The standardised relative odds value for ischaemic heart disease was 1.24 ($p < 0.01$) on adjustment for age and area only. Adjustment for the other non-lipid risk factors reduced this to 1.17 ($p < 0.05$). The main reason for the decline was the adjustment for pre-existent disease. Adjustment for HDL cholesterol concentration marginally increased the standardised odds value to 1.18, and the final adjustment for triglyceride concentration

caused a further reduction to 1.12. This value was not significantly different from 1.0. The mean difference in cholesterol concentration between men who developed ischaemic heart disease and those who did not declined from 0.26 mmol/l ($p < 0.01$) with adjustment for age and area only, to 0.22 mmol/l ($p < 0.05$) after adjustment for all non-lipid risk factors and HDL cholesterol concentration, and to 0.13 mmol/l (not significant) after the final adjustment for triglyceride concentration.

HDL CHOLESTEROL

The figure shows that relative odds of major ischaemic heart disease increased steadily as HDL cholesterol concentration decreased so that in the lowest 20% of the distribution the value was 2.32 (95% CI 1.46 to 3.67) after adjustment for age and area only, declining to 1.72 (95% CI 1.04 to 2.84) on adjustment for all risk factors. Table 4 shows that the standardised relative odds decreased correspondingly from 1.37 ($p < 0.001$) to 1.22 ($p < 0.05$). The mean difference in HDL cholesterol concentration between men who developed major ischaemic heart disease and those who did not was -0.10 mmol/l ($p < 0.001$) on adjustment for age and area only, decreasing to -0.06 mmol/l ($p < 0.05$) on adjustment for all other factors. The association between HDL cholesterol concentration and incidence of ischaemic heart disease was unchanged with adjustment for cholesterol concentration and declined slightly on further adjustment for triglyceride concentration (table 4). The fully adjusted standardised relative odds value of 1.22 was both significantly greater than 1.0 and higher than the non-significant value of 1.12 for total cholesterol concentration.

TOTAL TRIGLYCERIDE

Figure 1 shows that the relative odds of major ischaemic heart disease rose as triglyceride concentration increased, to a value of 3.10 (95% CI 2.25–6.17) in the top 20% of the distribution. On adjustment for all other factors this decreased to 2.26 (95% CI 1.26 to 4.05). Table 4 shows that the standardised relative odds declined steadily with each successive adjustment from 1.41 ($p < 0.001$) with adjustment for age and area only to 1.19 ($p < 0.05$) with adjustment for all other factors. The mean difference in triglyceride concentration between men who developed ischaemic heart disease and those who did not showed the same pattern.

The decline both in standardised relative odds and mean differences with each successive

adjustment was steeper for triglyceride than for either cholesterol or HDL cholesterol concentration. The standardised relative odds value of 1.19 after adjustment for all other factors was, however, like that for HDL cholesterol concentration, both statistically significant ($p < 0.05$) and larger than the odds associated with total cholesterol concentration.

EFFECT OF PRE-EXISTENT DISEASE

Of the 251 major ischaemic heart disease events among the total cohort of 4860 men, 131 events occurred among the 1171 men with ischaemic disease at recruitment. The age and area adjusted relative odds value for a major event for men with pre-existing disease was 3.61 (95% CI 2.77 to 4.70) compared with men with no disease at recruitment. Men with pre-existent disease had higher concentrations of cholesterol and triglyceride and lower concentrations of HDL cholesterol at recruitment. In theory, associations between each of the three lipids and the incidence of ischaemic heart disease could arise simply as a consequence of pre-existent disease. The multivariate analysis, which includes an adjustment for the three types of pre-existent disease, shows that this is not the case, and table 5 confirms this. Mean differences in the three lipids between men who developed major ischaemic heart disease and those who did not are shown separately for men with and without pre-existent disease. For both HDL cholesterol and triglyceride concentrations the differences were larger for men with no evidence of disease at recruitment. All mean differences were significantly different ($p < 0.05$) from zero except those for total cholesterol for men without pre-existent disease which, however, did not differ significantly from the corresponding difference in men with pre-existent disease.

EFFECT OF β BLOCKADE

As one of the items in the medical history, the men were asked whether they had taken any prescribed medicines in the past seven days. The names of all medicines were recorded. Of the total cohort of 4860 men, 245 (5.0%) were taking β blockers. These had been prescribed for 148 (12.6%) of the 1171 men with pre-existent ischaemic heart disease, compared with 97 (2.6%) of the 3689 men without pre-existing disease. Thirty three major ischaemic heart disease events occurred among the 245 men taking β blockers, giving an incidence of 13.5%. This compares with 218 (4.7%) events among the 4615 men not taking β blockers. The higher incidence among the men taking β blockers reflects the fact that they are a selected, high risk group.

The men taking β blockers had substantially different lipid concentrations from those not taking the drug. Total cholesterol concentrations were higher by 5%, total triglyceride concentration was higher by about 30%, and HDL cholesterol concentration was lower by 10%. The effect of β blockade on the relations between lipids and incidence of disease was therefore examined.

There was no evidence that the difference in

Table 5 Mean differences in concentrations* of lipids between men with and without incident IHD according to IHD status at recruitment

	No pre-existent IHD† (n = 3350)	Any pre-existent IHD (n = 1021)
Cholesterol (mmol/l)(95% CI)	0.15 (−0.07 to 0.38)	0.29 (0.04 to 0.53)
HDL cholesterol (mmol/l) (95% CI)	−0.08 (−0.15 to −0.01)	−0.07 (−0.14 to 0.00)
Log triglyceride (mmol/l) (95% CI)	0.17 (0.07 to 0.26)	0.09 (0.00 to 0.19)

*Mean differences are adjusted for all non-lipid risk factors.
†Pre-existent IHD includes angina or history of severe chest pain from the chest pain questionnaire or evidence of ischaemia on electrocardiogram. Abbreviations as in table 1.

lipid concentrations between men who had a major incident and those who did not varied according to whether or not they were taking β blockers. Formally, interaction terms added to the multiple regression models of table 1 were not significant. Mean differences in lipid concentrations adjusted for age, area, and β blockade were 0.26 mmol/l, -0.08 mmol/l, and 0.27 mmol/l for total cholesterol, HDL cholesterol, and total triglyceride concentrations respectively. These were all slightly smaller than the corresponding differences shown in table 1.

The analysis given in table 4 was also repeated with additional adjustment for β blockade. The fully adjusted standardised relative odds values were unchanged for total cholesterol and triglyceride concentrations. For HDL cholesterol concentration the value was marginally reduced, from 1.22 to 1.21.

Discussion

The results from the Caerphilly and Speedwell studies confirm that concentrations of cholesterol, HDL cholesterol, and triglyceride are associated with the development of major ischaemic heart disease. Questions about their relative importance remain, however. The only other large prospective British study that has considered this in detail concluded that concentration of triglyceride was not an independent risk factor and that cholesterol was a more important risk factor than HDL cholesterol concentration.⁷ Our results suggest the opposite.

The Regional Heart Study found that triglyceride concentration did not predict incidence of ischaemic heart disease once other risk factors had been taken into account.⁷ This accords with other published views,^{8,19} but the evidence is not consistent. For example, Carlson *et al* found in the Stockholm Study that after allowing for age, blood pressure, and smoking, plasma triglyceride concentrations were more strongly predictive than was cholesterol.²⁰ This corresponds with our findings.

Some studies including ours were based on fasting triglyceride concentrations whereas others, such as the Regional Heart Study, measured non-fasting concentrations. Non-fasting samples contain higher and more variable concentrations of triglycerides than do fasting samples because of the presence of chylomicrons when not fasting. It is debatable whether fasting or non-fasting samples are more appropriate. One advantage of fasting samples is that all subjects are in the same metabolic state. On the other hand, subjects spend most of the day in the postprandial state. Unfortunately, it is impossible with a large free living cohort to draw a blood sample at a standard time after a typical meal, even if a typical meal for each subject could be defined.

Another aspect of this debate has recently been raised by Davey Smith and Phillips.^{21,22} It is well known that random errors in a putative risk factor result in underestimation of regression coefficients and hence of relative odds. Davey Smith and Phillips show that

when considering whether a risk factor is independently associated with a disease, after adjusting for a confounding variable with which it is highly correlated, the relative sizes of the random error in the estimation of the risk factor and the confounder may be very important. Such random error would include both measurement error and intraindividual variation. In particular, Davey Smith and Phillips suggest the possibility that differential random error could induce the common finding that the univariate association between triglyceride concentration and ischaemic heart disease largely disappears on adjustment for HDL cholesterol concentration whereas the association between HDL cholesterol concentration and ischaemic heart disease remains on adjustment for triglyceride concentration. This could explain the apparent inconsistency between the Regional Heart Study and our studies. The Regional Heart Study measured non-fasting triglycerides and our studies measured fasting concentrations. Thus the random error in the triglyceride concentration relative to that in the HDL cholesterol concentration is likely to be substantially smaller in our studies. It seems unlikely, however, that the general inconsistency between studies can be so explained because studies that claim no independent role for triglyceride include not only those based on non-fasting samples⁷ but also others based on fasting samples.^{8,19}

Early reports from the Framingham Study suggested that triglyceride is not an independent risk factor for men.²³ A more recent report found that it is a risk factor in men with low concentrations of HDL cholesterol.⁹ We found no evidence for such an interaction. Incidence of ischaemic heart disease increases with increasing triglyceride concentration at all concentrations of HDL cholesterol. For example, if the distributions of both variables are divided into thirds, then the unadjusted odds of ischaemic heart disease for men who are in the top third of the triglyceride distribution relative to those in the bottom third are 2.1, 2.0 and 3.1 respectively within the low, middle, and top thirds of the distribution of HDL cholesterol.

Initially, the Regional Heart Study reported that HDL cholesterol was not a major risk factor for the disease in British men.⁶ A later report revised that view and concluded that it was important,⁷ but less so than cholesterol, which was the most important single blood lipid risk factor in men. In our data, the standardised relative odds value for HDL cholesterol concentration after adjusting for age, blood pressure, smoking, body mass index, pre-existing disease, and total cholesterol was 1.27, compared with a value of 1.18 for total cholesterol concentration adjusted for the same non-lipid risk factors and HDL cholesterol concentration. The standardised relative odds value of 1.27 for HDL cholesterol concentration is similar to the figure of 1.30 found by the Regional Heart Study.⁷ The corresponding adjusted mean difference of -0.07 mmol/l between men who developed ischaemic heart disease and those who did not is also close to the

Regional Heart Study's value of -0.06 mmol/l. The review paper of four American prospective studies showed that after adjustment for a similar set of risk factors, a 1 mg/dl (0.026 mmol/l) decrease in HDL cholesterol concentration was associated with proportionate increases of 1.9% , 2.1% , and 2.3% in odds of a major ischaemic heart disease event in the Framingham Study, the Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics Coronary Primary Prevention Trial respectively.⁵ The corresponding figure for the Caerphilly and Speedwell Studies is 2.1% . Thus substantial agreement exists between these studies on the strength of the association between HDL cholesterol concentration and incidence of ischaemic heart disease.

The reason that the relative importance of HDL cholesterol and cholesterol concentrations is opposite to that found by the Regional Heart Study is because the association between cholesterol concentration and incidence of disease is less strong in our studies. The standardised relative odds value of 1.18 from table 4 compares with a value of 1.54 from the Regional Heart Study. Similarly, adjusted mean differences in total cholesterol concentrations between men who developed ischaemic heart disease and those who did not are about half the value of 0.46 mmol/l found by the Regional Heart Study.

β Blockers are known to affect the lipoprotein profile. Cruickshank concludes that triglyceride concentration is increased by $20\text{--}30\%$, and HDL cholesterol concentration is decreased by 10% , but that plasma total cholesterol concentration is unchanged.²⁴ In our study, the men taking β blockers had triglyceride and HDL cholesterol concentrations that differed by almost the same percentages. The number of men taking β blockers was small, 245 (5%) of the total cohort of 4860 men, but they were a highly selected group with a high incidence of major ischaemic events. The age and area adjusted relative odds value for a major incident event among men taking β blockers was 2.86 (95% CI 1.88 to 4.36) compared with men not taking the drugs.

Therefore it is possible that part of the association between, particularly, triglyceride concentrations and incidence of disease is an artefact, arising because a group at high risk is taking a drug that substantially inflates their triglyceride concentration. This is not the case, however. The increased triglyceride concentrations in men who go on to develop major disease are found both in those groups taking β blockers and in those not taking β blockers. Table 1 shows that in the cohort as a whole, the men who had a major event had triglyceride concentrations that were 0.31 mmol/l higher. Among men not taking β blockers, the corresponding increase in triglyceride concentration was 0.29 mmol/l. Again for triglyceride concentration, the standardised relative odds value for a major event is 1.19 after adjusting for all the non-lipid risk factors and both cholesterol (table 4). When this analysis is restricted to the men not on β blockers the standardised relative

odds value increases slightly to 1.21 .

Thus the association between triglyceride concentration and incidence of major ischaemic heart disease is independent of the role of β blockers. The fact that in this large cohort of men the association is stronger than that with plasma total cholesterol concentration calls for a re-evaluation of the role of triglyceride concentration in ischaemic heart disease.

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