



Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study

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Summary

Background Whether lipoproteins are better markers than lipids and lipoproteins for coronary heart disease is widely debated. Our aim was to compare the apolipoproteins and cholesterol as indices for risk of acute myocardial infarction.

Methods We did a large, standardised case-control study of acute myocardial infarction in 12 461 cases and 14 637 age-matched (plus or minus 5 years) and sex-matched controls in 52 countries. Non-fasting blood samples were available from 9345 cases and 12 120 controls. Concentrations of plasma lipids, lipoproteins, and apolipoproteins were measured, and cholesterol and apolipoprotein ratios were calculated. Odds ratios (OR) and 95% CI, and population-attributable risks (PARs) were calculated for each measure overall and for each ethnic group by comparison of the top four quintiles with the lowest quintile.

Findings The apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio had the highest PAR (54%) and the highest OR with each 1 SD difference (1.59, 95% CI 1.53–1.64). The PAR for ratio of LDL cholesterol/HDL cholesterol was 37%. PAR for total cholesterol/HDL cholesterol was 32%, which was substantially lower than that of the ApoB/ApoA1 ratio ($p < 0.0001$). These results were consistent in all ethnic groups, men and women, and for all ages.

Interpretation The non-fasting ApoB/ApoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and it should be introduced into worldwide clinical practice.

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Introduction

Coronary heart disease is now the major cause of death worldwide. The human and economic costs of premature vascular disease are not confined to developed countries. Developing countries already account for most of the cases of coronary heart disease and indeed in regions such as south Asia, clinical events seem to be arising at a younger age and involve women more frequently than in the rest of the world. The INTERHEART study^{1,2} showed that the same nine modifiable risk factors (smoking, exercise, fruit and vegetables, alcohol, hypertension, diabetes, abdominal obesity, psychosocial, high apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio) accounted for almost all the population-attributable risk (PAR) of myocardial infarction and that these same factors applied to all the major population groups in the world. Of these risk factors, the ApoB/ApoA1 ratio—an index of the proatherogenic and antiatherogenic lipoproteins in plasma—accounted for half the PAR.

Perhaps no issue in lipidology has been as contentious as whether ApoB and ApoA1 are better markers than are their cholesterol counterparts of risk of vascular disease.

All the major guideline groups previously recommended a cholesterol-based approach, effectively excluding apolipoproteins from routine clinical use. However, the American Diabetes Association and the American College of Cardiology³ have stated that ApoB is the test of choice to assess the adequacy of statin treatment and should therefore be introduced into routine clinical practice. Several studies^{4–8} have shown that ApoB is a better marker of risk than is LDL cholesterol.⁴ Non-HDL cholesterol is better than LDL cholesterol^{9,10} and, in some studies,¹¹ but not in others,^{10,12} is equal to ApoB. HDL must also be measured to estimate the full lipoprotein-related risk of vascular disease. However, the comparison of ApoA1 and HDL cholesterol concentrations has produced much more inconsistent results than has the comparison of ApoB and LDL cholesterol concentrations.

Ratios are particularly complex to compare because the final result might differ, dependent on the numerator and the denominator. For example in the Framingham Offspring Study¹³ the ratio of ApoB/ApoA1 and the traditional lipid ratios were equivalent but ApoB was a better risk factor than was total cholesterol, and

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See [Comment](#) page 185

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HDL cholesterol was a much better risk factor than was ApoA1. Most epidemiological studies comparing the ApoB/ApoA1 and total cholesterol/HDL cholesterol ratios were made on the basis of few events. In AMORIS (Apolipoprotein-related MOrtality RiSk),⁸ a large prospective epidemiological study, the ApoB/ApoA1 ratio was clearly better than any of the cholesterol ratios. However, the AMORIS study⁸ has been criticised because concentrations of LDL cholesterol and HDL cholesterol were not assessed by conventional methods.

We compared ApoB/ApoA1 with other cholesterol ratios as markers for the risk of acute myocardial infarction in all the major ethnic groups of the world.

Methods

Participants

The study enrolled 12 461 individuals with a first acute myocardial infarction and 14 637 age-matched (up to 5 years older or younger than the cases) and sex-matched controls from 262 centres in 52 countries in Asia, central, eastern, and western Europe, Middle East, Africa, North America, and South America, and Australia and New Zealand. All patients (irrespective of age) admitted to the coronary-care unit or equivalent cardiology ward within 24 h of initial symptoms were screened. Patients were eligible if they had characteristic symptoms together with electrocardiogram changes indicating a new acute myocardial infarction. The controls had no history of chest pain on exertion or known heart disease. The hospital-based controls (58%) were admitted to the same hospital as the matched cases without known cardiovascular disease. Controls (36%) from the community were attendants or relatives of a patient from a non-cardiac ward or an unrelated attendant of a cardiac patient. The WHO MONICA¹⁴ study provided 3% of the controls, and the remaining 3% were from an undocumented source.²

The study protocol was approved by the ethics committees in all participating centres and all participants provided informed written or verbal consent.

Procedures

Non-fasting blood samples were obtained from cases and controls, and the times since last meal and from onset of symptoms were recorded. We decided which lipid measurements were important before data were gathered. Although patients were screened up to 24 h from symptom onset, blood samples were obtained later than 24 h from 21% of cases because of delays in patient presentation in low-income countries. The blood samples were obtained at variable times after the last meal. Blood samples were available from 9345 cases and 12 120 controls (79%). ApoB and ApoA1 are unaffected by the non-fasting state; after a meal plasma concentrations of total cholesterol do not change and HDL cholesterol changes little, if at all. Blood samples were obtained and centrifuged within 2 h of admission, then separated and

	Controls (N=12 120)	Cases (N=9345)	Overall (N=21 465)
European	2443	1999	4442
Chinese	3032	2554	5586
South Asian	1946	1631	3577
Other Asian	1042	630	1672
Latin American	1580	910	2490
Arab/Persian	1442	1246	2688
Black African	286	119	405
Coloured African	296	214	510
Other ethnic group	53	42	95

Table 1: Blood samples available from study participants with myocardial infarction and controls by ethnic origin

	Cases (N=9345)	Controls (N=12 120)	p value
Total cholesterol (mmol/L)	5.13 (5.11–5.16)	5.00 (4.98–5.03)	<0.0001
HDL cholesterol (mmol/L)	0.98 (0.98–0.99)	1.02 (1.01–1.02)	<0.0001
Non-HDL cholesterol (mmol/L)	4.07 (4.04–4.09)	3.89 (3.87–3.91)	<0.0001
ApoA1 (mmol/L)	1.09 (1.09–1.10)	1.18 (1.17–1.18)	<0.0001
ApoB (mmol/L)	0.93 (0.93–0.94)	0.88 (0.87–0.88)	<0.0001
Total cholesterol/HDL cholesterol ratio	5.23 (5.19–5.26)	4.92 (4.89–4.95)	<0.0001
ApoB/ApoA1 ratio	0.86 (0.85–0.86)	0.75 (0.74–0.75)	<0.0001
Non-HDL cholesterol/HDL cholesterol ratio	4.15 (4.11–4.18)	3.83 (3.80–3.86)	<0.0001

Data are mean (95% CI) after adjustment for age and sex, unless otherwise indicated. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B100.

Table 2: Concentrations of lipids and their ratios in cases and controls

immediately frozen at -20°C or -70°C , dependent on the availability of specific freezers. Samples were periodically shipped in nitrogen vapour tanks for storage at -80°C in China or -160°C in liquid nitrogen in Hamilton, ON, Canada. All samples, other than those from China, were analysed in Hamilton. All reagents and kits used were supplied by Roche Diagnostics (Mannheim, Germany).

Concentrations of total cholesterol, HDL cholesterol, ApoA1, and ApoB were measured with the Roche Hitachi 917 analyser, and concentrations of non-HDL cholesterol were calculated as total cholesterol minus HDL cholesterol. Ratios of non-HDL cholesterol/HDL cholesterol are presented but are not plotted since they are identical to the ratios of total cholesterol/HDL cholesterol because they are linear transformations of each other. Cholesterol concentrations were measured with an enzymatic colourimetric method (CHOD-PAP) with cholesterol esterase, cholesterol oxidase, and 4-aminoantipyrine. Concentrations of HDL cholesterol were measured with a homogeneous enzymatic colourimetric assay (HDL-C plus, 2nd generation) that uses cholesterol esterase and cholesterol oxidase coupled with polyethylene glycol to the amino groups.

Concentrations of triglycerides (GPO-PAP) were measured for all individuals and those less than or equal to 4.5 mmol/L were used to calculate LDL cholesterol

	Total cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Non-HDL cholesterol (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoB/ApoA1	Total cholesterol/HDL cholesterol	Non-HDL cholesterol/HDL cholesterol
Men								
Overall	4.93 (4.91-4.95)	0.98 (0.97-0.99)	3.85 (3.83-3.88)	1.14 (1.14-1.15)	0.87 (0.87-0.88)	0.76 (0.76-0.77)	5.03 (4.99-5.06)	3.93 (3.89-3.97)
European	5.26 (5.20-5.32)	1.12 (1.10-1.14)	4.05 (4.00-4.11)	1.22 (1.21-1.24)	0.93 (0.92-0.94)	0.76 (0.75-0.77)	4.71 (4.63-4.79)	3.63 (3.55-3.71)
Chinese	4.72 (4.68-4.77)	1.05 (1.04-1.07)	3.59 (3.55-3.64)	1.19 (1.18-1.20)	0.79 (0.78-0.80)	0.66 (0.65-0.67)	4.47 (4.41-4.54)	3.41 (3.34-3.47)
South Asian	4.76 (4.71-4.81)	0.83 (0.82-0.85)	3.84 (3.79-3.90)	1.05 (1.04-1.06)	0.88 (0.87-0.90)	0.84 (0.83-0.85)	5.71 (5.61-5.81)	4.62 (4.52-4.72)
Other Asian	5.38 (5.29-5.46)	1.06 (1.04-1.08)	4.21 (4.13-4.30)	1.21 (1.19-1.23)	0.93 (0.91-0.95)	0.78 (0.76-0.79)	5.09 (4.97-5.21)	3.99 (3.87-4.12)
Latin American	4.88 (4.86-4.91)	0.90 (0.88-0.92)	3.94 (3.87-4.00)	1.09 (1.08-1.11)	0.91 (0.90-0.92)	0.83 (0.81-0.84)	5.48 (5.37-5.59)	4.39 (4.28-4.51)
Arab/Persian	4.91 (4.85-4.98)	0.90 (0.88-0.92)	3.92 (3.86-3.99)	1.08 (1.07-1.10)	0.89 (0.88-0.91)	0.83 (0.81-0.84)	5.47 (5.36-5.58)	4.37 (4.26-4.49)
Black African	4.10 (3.97-4.24)	1.05 (1.00-1.10)	2.95 (2.82-3.08)	1.10 (1.07-1.14)	0.70 (0.67-0.73)	0.64 (0.61-0.67)	3.90 (3.71-4.11)	2.81 (2.63-3.01)
Coloured African	4.94 (4.78-5.10)	1.01 (0.96-1.05)	3.80 (3.65-3.97)	1.12 (1.09-1.16)	0.87 (0.84-0.91)	0.79 (0.75-0.82)	4.95 (4.70-5.20)	3.74 (3.50-3.99)
Women								
Overall	5.25 (5.20-5.29)	1.14 (1.13-1.16)	4.01 (3.97-4.06)	1.28 (1.27-1.29)	0.90 (0.89-0.90)	0.70 (0.69-0.71)	4.60 (4.54-4.67)	3.52 (3.46-3.58)
European	5.59 (5.50-5.69)	1.27 (1.24-1.30)	4.22 (4.14-4.31)	1.33 (1.31-1.36)	0.95 (0.93-0.97)	0.71 (0.70-0.73)	4.40 (4.29-4.52)	3.33 (3.22-3.44)
Chinese	4.95 (4.88-5.03)	1.17 (1.14-1.19)	3.71 (3.64-3.78)	1.31 (1.29-1.33)	0.81 (0.79-0.82)	0.62 (0.60-0.63)	4.25 (4.15-4.35)	3.18 (3.08-3.28)
South Asian	4.99 (4.85-5.14)	0.93 (0.90-0.97)	3.94 (3.80-4.09)	1.17 (1.13-1.20)	0.90 (0.87-0.93)	0.77 (0.74-0.80)	5.35 (5.11-5.59)	4.20 (3.96-4.45)
Other Asian	5.74 (5.57-5.92)	1.19 (1.13-1.24)	4.46 (4.28-4.63)	1.34 (1.29-1.38)	0.97 (0.94-1.00)	0.73 (0.70-0.76)	4.84 (4.62-5.08)	3.79 (3.56-4.04)
Latin American	5.44 (5.31-5.57)	1.11 (1.08-1.15)	4.26 (4.13-4.39)	1.28 (1.25-1.31)	0.96 (0.93-0.99)	0.75 (0.73-0.78)	4.93 (4.75-5.11)	3.86 (3.68-4.04)
Arab/Persian	5.16 (5.02-5.32)	1.00 (0.96-1.05)	4.10 (3.95-4.25)	1.17 (1.14-1.21)	0.92 (0.89-0.95)	0.79 (0.76-0.82)	5.15 (4.92-5.39)	4.07 (3.83-4.32)
Black African	4.72 (4.52-4.93)	1.16 (1.09-1.23)	3.45 (3.26-3.65)	1.30 (1.24-1.35)	0.79 (0.75-0.83)	0.62 (0.58-0.66)	4.08 (3.81-4.37)	2.98 (2.73-3.26)
Coloured African	5.46 (5.23-5.70)	1.19 (1.12-1.26)	4.18 (3.95-4.41)	1.30 (1.24-1.35)	0.95 (0.90-1.00)	0.73 (0.69-0.78)	4.60 (4.31-4.92)	3.52 (3.23-3.84)
Men and women								
Overall	5.00 (4.98-5.03)	1.02 (1.01-1.02)	3.89 (3.87-3.91)	1.18 (1.17-1.18)	0.88 (0.87-0.88)	0.75 (0.74-0.75)	4.92 (4.89-4.95)	3.83 (3.80-3.86)
European	5.34 (5.29-5.39)	1.15 (1.14-1.17)	4.09 (4.04-4.14)	1.25 (1.24-1.26)	0.93 (0.92-0.94)	0.75 (0.74-0.76)	4.63 (4.57-4.70)	3.55 (3.48-3.61)
Chinese	4.77 (4.74-4.81)	1.08 (1.07-1.09)	3.62 (3.58-3.66)	1.22 (1.21-1.23)	0.79 (0.78-0.80)	0.65 (0.64-0.66)	4.42 (4.36-4.47)	3.35 (3.30-3.41)
South Asian	4.82 (4.77-4.87)	0.86 (0.85-0.87)	3.88 (3.83-3.93)	1.08 (1.07-1.09)	0.89 (0.88-0.90)	0.82 (0.81-0.84)	5.62 (5.53-5.71)	4.52 (4.43-4.62)
Other Asian	5.46 (5.39-5.54)	1.09 (1.07-1.11)	4.27 (4.19-4.34)	1.24 (1.22-1.26)	0.90 (0.89-0.91)	0.76 (0.75-0.78)	5.03 (4.92-5.14)	3.94 (3.83-4.05)
Latin American	5.04 (4.99-5.10)	0.95 (0.93-0.96)	4.01 (3.95-4.07)	1.14 (1.12-1.15)	0.92 (0.91-0.93)	0.81 (0.80-0.82)	5.34 (5.25-5.44)	4.26 (4.16-4.36)
Arab/Persian	4.98 (4.92-5.04)	0.93 (0.91-0.94)	3.96 (3.90-4.02)	1.11 (1.09-1.12)	0.90 (0.89-0.91)	0.82 (0.80-0.83)	5.39 (5.29-5.49)	4.30 (4.19-4.40)
Black African	4.28 (4.17-4.40)	1.07 (1.03-1.11)	3.10 (3.00-3.21)	1.17 (1.14-1.20)	0.73 (0.70-0.75)	0.64 (0.62-0.67)	4.00 (3.84-4.17)	2.90 (2.75-3.06)
Coloured African	5.08 (4.95-5.22)	1.05 (1.01-1.09)	3.91 (3.78-4.04)	1.24 (1.22-1.26)	0.90 (0.87-0.93)	0.77 (0.75-0.80)	4.86 (4.66-5.06)	3.69 (3.50-3.89)

Data are mean (95% CI) based on log transformed data and then back transformed to the original scale to reflect skewed distribution of some of the measures; CIs are not necessarily symmetric about the mean value. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B100.

Table 3: Mean concentrations of lipids, lipoproteins, apolipoproteins and their ratios in the control population of men and women by ethnic origin

concentrations with the Friedwald formula, and the concentrations were included in the ratios of LDL cholesterol/HDL cholesterol. Because of the reduced accuracy and possible limitations of calculation of LDL cholesterol in non-fasting individuals, the ratios of LDL cholesterol/HDL cholesterol are not reported here (for completeness they are included in the web-appendix).

Imprecision and medical decision limits were assessed according to the guidelines of the National Committee for Clinical Laboratory Standards manual EP5-T2. With the Roche Diagnostics (normal and increased) lipid controls and a human serum sample, the intra-assay imprecision (n=21) for the lipid, lipoprotein, and apolipoprotein measures was less than 1.5%. For the complete INTERHEART analysis, the inter-assay imprecision (n=500) was less than 3.0% for cholesterol and HDL cholesterol, and less than 4.0% for the apolipoproteins.

Apolipoprotein concentrations were measured with the Tina-quant ApoB and ApoA1 kits (version 2, with the IFCC SP3-07 reference standard and IFCC SP1-01 reference preparation), which are standardised methods for measurement of ApoB and ApoA1. The same measurement kits and a Roche Hitachi 911 analyser were used in Beijing, China. The two laboratories were further standardised with analysis of the same lot numbers of Precinorm and Precipath controls in every run. In all runs of patient sample analyses in China, two study patients and two reference pool samples were measured from samples that had been previously analysed in the central core laboratory in Canada.

Statistical analysis

Continuous variables were summarised with means or medians and were compared with ANOVA model-based tests. For comparison of means across subgroups, values were adjusted for age and sex with ANCOVA models.

See Online for webappendix

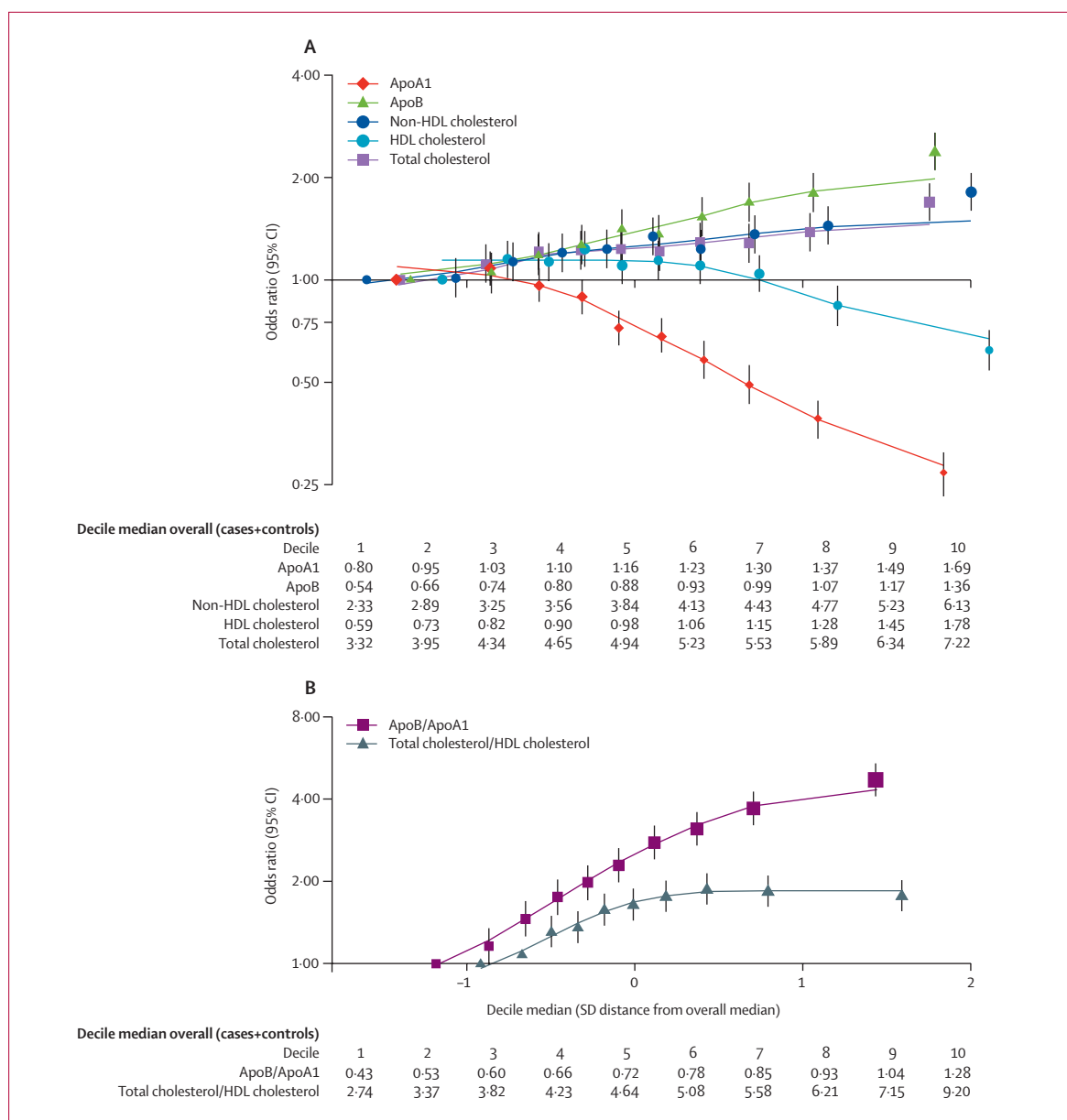


Figure 1: Risk of myocardial infarction for increasing decile medians (adjusted for age, sex, and region) of (A) lipids, lipoproteins, and apolipoproteins and (B) ratios of apolipoprotein B/apolipoprotein A1 and total cholesterol/HDL cholesterol

Note the doubling scale on the y axis for both figures. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B100.

Sex-specific quintile values from controls were used to classify continuous variables. Univariate associations were explored with frequency tables and Pearson's χ^2 tests for independent proportions. Unconditional logistic regression with adjustment for matching factors was used to control for confounding by other risk factors. Results from unconditional analyses were similar to those from the analyses of conditional and mixed-effect models (<5% variation). The results were consistent by use of the two types of controls and so the results are presented with the overall analysis.

Population-attributable risk (PAR) was adjusted for age, sex, smoking, and geographic region, and the 95% CIs were calculated for the top four quintiles (Q2–Q5) in controls versus the lowest quintile (Q1) for each lipid with a method based on unconditional logistic regression and Interactive Risk Attributable Program software (version 2.2).¹⁵ The PARs for the nine modifiable risk factors were reported extensively in the original INTERHEART report.²

The importance of various lipids as markers of acute myocardial infarction was assessed in several different

ways. First, we compared the odds ratios (ORs) across various categories (eg, quintiles or deciles); second, we estimated the OR for a 1 SD change in the measure (with both overall and subgroup specific SD); third, we compared the receiver-operator-characteristic (ROC) curves in relation to myocardial infarction for each measure. The overall SD for each measure was used in the standardised analyses of the lipids. We analysed the effect of the ratios of ApoB/ApoA1 and total cholesterol/HDL cholesterol and their joint effects. All statistical tests were two-sided. Statistical analyses were produced with the SAS system (version 9.1) and S-Plus (version 6.1). All our models are multivariate models including a wide range of combinations of lipid markers and the other risk factors we have studied. However, in general, we have adjusted for age, sex, smoking, and geographic region.

The subgroup analysis of time since first clinical symptoms was adjusted by fasting time because cases in each class of blood sample were referenced against matched controls; therefore to calculate the time from symptoms to when the sample was obtained in controls was not possible. We matched controls to the cases in each time-since-symptoms group for age and sex, and then assigned the controls to the same time group as their matched case.

Since lipid and apolipoprotein measurements were done at two centres, assessment of bias was accomplished with a linear transformation based on fitted regression models of Hamilton standard readings versus China standard readings for the range of the standards. The calculated slopes and intercepts were used to do the bias correction before any analysis was done:

$$\text{Hamilton ApoA1} = -0.0279 + 0.9341 \times \text{China ApoA1}$$

$$\text{Hamilton ApoB} = 0.0547 + 0.9067 \times \text{China ApoB}$$

$$\text{Hamilton total cholesterol} = 0.4448 + 0.9657 \times \text{China total cholesterol}$$

$$\text{Hamilton HDL cholesterol} = 0.0431 + 0.9981 \times \text{China HDL cholesterol}$$

For the analyses, we used single measurements of lipids, lipoproteins, and apolipoproteins concentrations. Because a single point estimate has more uncertainty (spread) than the mean of repeated measurements, it would be expected to produce an underestimation of ORs compared with the usual values (average of several values). The effect of regression-dilution bias was estimated in a subsample of INTERHEART controls (n=279) who had a repeat measurement and risk factor assessment after a median of 409 days. The adjustment multipliers were calculated by measurement of the difference between the fifth and first quintile means for each risk factor, for the initially measured value, and then for the estimated usual value. The ratio of single

measurement versus usual measurement gives an estimated slope adjustment factor. This approach allows for correction of the associations of lipids and other risk factors with prediction of myocardial infarction, providing an estimate of the increase of their predictive strengths based on the assumption that prevalence of the risk factor was constant.¹⁶

ROC curves were constructed, and area under the ROC curve (AUC) was a C statistic for the corresponding adjusted logistic regression models. The statistical comparison of AUCs in competing models used a nonparametric method.¹⁷

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Blood samples for analysis were available from patients (2209 women and 7136 men) and controls (2937 women and 9183 men) in different ethnic groups (table 1). Median ages of patients with myocardial infarction at presentation were 51 years in South Asians, 52 years in Arabs and Persians, 59 years in Latin Americans, 63 years in Chinese, and 62 years in Europeans. Patients had higher total cholesterol, non-HDL cholesterol, and ApoB concentrations, and lower HDL cholesterol and ApoA1 concentrations than did controls (table 2). No difference was reported in fasting times between cases (mean 7.1 h) and controls (7.15 h), with a median of 5 h for both.

ApoB/ApoA1, total cholesterol/HDL cholesterol, non-HDL cholesterol/HDL cholesterol ratios were designed to associate higher values with increased risk of acute myocardial infarction and lower values with reduced risk (table 3). Although some variation in the ethnic group ranking occurred, the highest values for the ratios were seen in south Asians, Arabs and Persians, and Latin Americans, for men and women, separately and combined. The lowest ratios were recorded in the Chinese and black-African populations (table 3). High ratios and lipid concentrations arose in the other-Asian group, which included Malays and Filipinos and both of these ethnic groups have higher lipid concentrations than do the Chinese and Japanese (Japanese included in other Asians). The Chinese and south Asians had very similar concentrations of total cholesterol but greatly different ratios arising from the lower HDL cholesterol and ApoA1 concentrations, along with the higher ApoB concentrations in the south Asians (table 3).

The highest concentrations of total cholesterol for men and women were noted in other Asians and Europeans (table 3). The ApoB concentrations showed a similar ethnic distribution pattern in men and women to that of

	Total cholesterol	HDL cholesterol	Non-HDL cholesterol	ApoA1	ApoB	Total cholesterol/ HDL cholesterol	ApoB/ApoA1
1 SD change	1.22	0.36	1.20	0.27	0.26	2.53	0.32
Overall	1.16 (1.13-1.19)	0.85 (0.83-0.88)	1.21 (1.17-1.24)	0.67 (0.65-0.70)	1.32 (1.28-1.36)	1.17 (1.13-1.20)	1.59 (1.52-1.64)
European	1.08 (1.02-1.15)	0.78 (0.73-0.83)	1.17 (1.10-1.24)	0.70 (0.66-0.75)	1.24 (1.16-1.32)	1.31 (1.21-1.42)	1.47 (1.37-1.59)
Chinese	1.16 (1.09-1.23)	0.83 (0.78-0.88)	1.24 (1.68-1.31)	0.67 (0.63-0.71)	1.28 (1.20-1.36)	1.34 (1.24-1.45)	1.77 (1.63-1.92)
South Asian	1.23 (1.14-1.31)	0.97 (0.90-1.05)	1.23 (1.15-1.31)	0.72 (0.66-0.78)	1.38 (1.29-1.48)	1.10 (1.04-1.17)	1.53 (1.42-1.64)
Other Asian	1.13 (1.03-1.25)	0.79 (0.72-0.87)	1.20 (1.09-1.32)	0.53 (0.47-0.59)	1.37 (1.23-1.52)	1.08 (0.99-1.17)	1.89 (1.67-2.14)
Latin American	1.05 (0.97-1.14)	1.03 (0.94-1.13)	1.04 (0.96-1.28)	0.67 (0.61-0.74)	1.18 (1.09-1.28)	0.97 (0.90-1.05)	1.27 (1.17-1.38)
Arab/Persian	1.24 (1.15-1.33)	0.95 (0.87-1.03)	1.25 (1.16-1.35)	0.69 (0.63-0.76)	1.37 (1.27-1.48)	1.17 (1.09-1.26)	1.71 (1.56-1.87)
Black African	1.05 (0.83-1.34)	0.69 (0.56-0.85)	1.25 (0.98-1.60)	0.67 (0.55-0.83)	1.58 (1.24-2.02)	1.69 (1.29-2.20)	1.59 (1.28-1.97)
Coloured African	1.25 (1.05-1.50)	0.75 (0.63-0.90)	1.34 (1.13-1.60)	0.63 (0.52-0.76)	1.49 (1.24-1.78)	1.43 (1.16-1.77)	1.98 (1.60-2.59)

Data are odds ratio (95% CI). ApoA1=apolipoprotein A1. ApoB=apolipoprotein B100.

Table 4: Change in risk for myocardial infarction with a 1 SD change in each of the lipid measures in each ethnic group

cholesterol concentrations; the lowest three concentrations of ApoB were noted in Chinese, black Africans, and south Asians. In each ethnic group, women had higher concentrations of total cholesterol than did men; however, women in all ethnic groups had higher mean HDL cholesterol concentrations. The lowest mean concentrations of HDL cholesterol and ApoA1 were noted in south Asians, Arabs and Persians, and South Americans and Mexicans (table 3).

Figure 1A shows the OR (95% CIs) for increasing decile medians of the lipids and apolipoproteins and the risk for myocardial infarction. In figure 1B, increases in the deciles showed a strong association with the presence of acute myocardial infarction, with the ApoB/ApoA1 ratio (previously reported²) showing the steepest increase. By contrast the association between total cholesterol/HDL cholesterol ratio and acute myocardial infarction is weaker.

For the total study population, a 1 SD difference in ApoA1 was associated with a 33% reduction in the risk of myocardial infarction compared with only 15% reduction with a 1 SD difference in HDL cholesterol ($p<0.0001$; table 4). A 1 SD change in ApoB and ApoA1 concentrations seemed to be associated with the same magnitude of change in myocardial infarction risk (32% and 33%, respectively) but in opposite directions. For non-HDL cholesterol and total cholesterol, a 1 SD difference showed a weaker association with myocardial infarction than did ApoB ($p<0.0001$; table 4). Figure 2 shows the ratios of ApoB/ApoA1 for each ethnic group. The ApoB/ApoA1 ratio had a strong association with the risk of myocardial infarction, with a 1 SD difference associated with a substantially higher OR than that for a 1 SD difference in the total cholesterol/HDL cholesterol ratio ($p<0.0001$; figure 2).

A 1 SD difference in HDL cholesterol concentration was associated with a 19% reduction in risk of myocardial infarction in women (OR 0.81, 95% CI 0.76-0.85) and 12% in men (0.88, 0.85-0.91). However, ApoA1 concentrations were more strongly

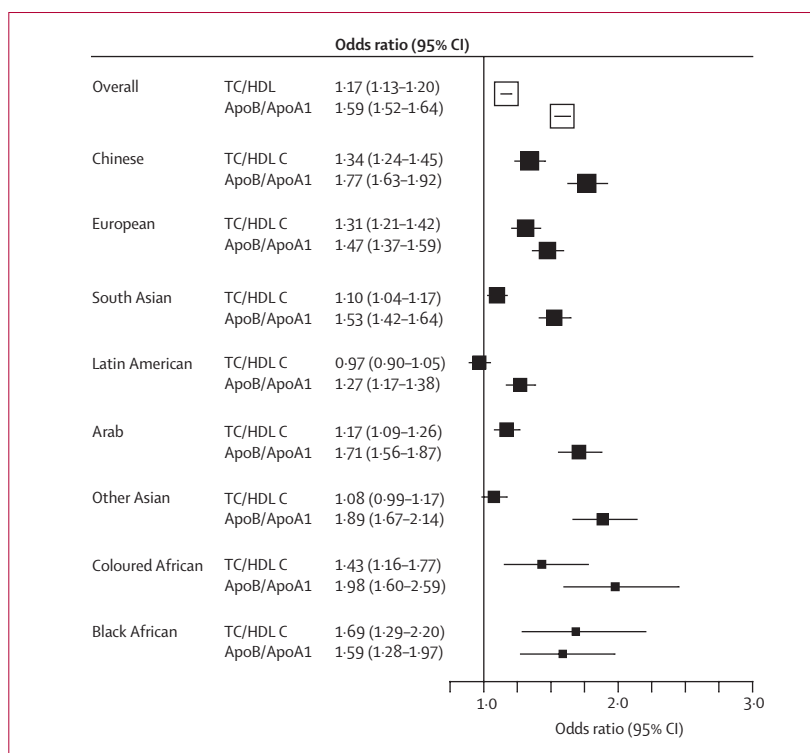


Figure 2: Change in risk (odds ratio, 95% CI) of myocardial infarction overall and within each ethnic group with a 1 SD change in each of the ratios

1 SD change for total cholesterol (TC)/HDL cholesterol (HDL C) ratio=2.53. 1 SD change for apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1)=0.32. Note that the increase in risk for a 1 SD increase in the ApoB/ApoA1 ratio is substantially greater than a similar increase in the TC/HDL C ratio overall and in almost all ethnic groups.

associated with a reduction in risk of myocardial infarction in women (31%, 0.69, 0.65-0.73) and men (33%, 0.67, 0.64-0.69) than were HDL cholesterol concentrations ($p<0.0001$). The ratios of ApoB/ApoA1 and total cholesterol/HDL cholesterol were more powerfully associated with acute myocardial infarction in women (1.76, 1.64-1.90 and 1.34, 1.25-1.44, respectively) than in men (1.54, 1.48-1.60 and 1.13, 1.09-1.17, respectively) for a 1 SD change ($p<0.0001$ for heterogeneity). However, the ratio of

	ApoA1	ApoB	ApoB/ApoA1	Total cholesterol/ HDL cholesterol
1 SD change	0.27	0.26	0.32	2.53
Age (years)				
<45	0.62 (0.57-0.67)	1.49 (1.39-1.59)	1.76 (1.63-1.89)	1.18 (1.11-1.25)
45-55	0.67 (0.63-0.71)	1.46 (1.38-1.54)	1.70 (1.59-1.81)	1.23 (1.16-1.30)
56-65	0.68 (0.69-0.72)	1.32 (1.24-1.34)	1.59 (1.49-1.70)	1.22 (1.14-1.30)
66-70	0.63 (0.57-0.68)	1.10 (1.01-1.19)	1.52 (1.37-1.69)	1.08 (0.98-1.18)
>70	0.77 (0.72-0.83)	1.06 (0.98-1.14)	1.24 (1.13-1.35)	0.98 (0.9-1.07)

Data are odds ratio (95% CI) for a 1 SD change. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B100.

Table 5: Prediction of risk by age with a 1 SD change in each lipid measure

	ApoB/ApoA1	Total cholesterol/ HDL cholesterol
Overall	54.0% (50.6-57.4)	31.9% (27.6-36.4)
Women	52.3% (46.1-52.3)	32.9% (25.8-40.9)
Men	54.1% (50.0-58.2)	30.7% (25.5-36.3)
European	42.5% (33.8-51.8)	29.7% (21.8-39.0)
Chinese	44.4% (39.0-49.9)	30.5% (24.0-38.0)
South Asian	65.2% (54.9-74.2)	32.3% (19.2-48.9)
Other Asian	67.8% (55.6-78.0)	38.7% (24.5-55.1)
Latin American	46.4% (31.9-61.5)	..
Arab/Persian	66.8% (56.3-75.9)	45.6% (32.7-59.2)
Black African	70.9% (54.0-83.4)	49.1% (30.9-67.6)
Coloured African	70.1% (51.3-83.9)	50.8% (31.4-70.0)

Data are population-attributable risk (95% CI). Apolipoprotein B100=ApoB. Apolipoprotein A1=ApoA.

Table 6: Population-attributable risks for ratios of total cholesterol to HDL cholesterol and apolipoprotein B100/apolipoprotein A1

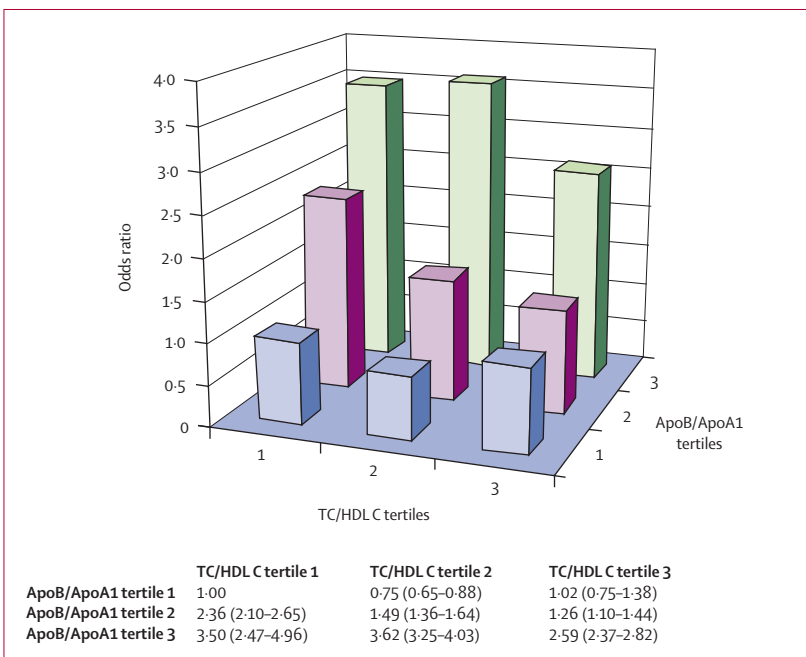


Figure 3: Odds ratio (95% CI) of myocardial infarction by tertiles for apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) and total cholesterol (TC)/HDL cholesterol (HDL C) ratios

ApoB/ApoA1 was the most powerful marker associated with acute myocardial infarction in both sexes.

ApoB was a more powerful marker of risk than was total cholesterol in all the ethnic groups (table 4). In each ethnic group, except black Africans, increase in ApoA1 concentration was associated with a greater reduction in the risk of myocardial infarction than was HDL cholesterol concentration. In all ethnic groups, again with the exception of black Africans, a 1 SD change in the ApoB/ApoA1 ratio was the most powerful indicator of an increase in the risk of myocardial infarction (figure 2). The number of black Africans in this study was small compared with the numbers of individuals in the other ethnic group and the CI of the estimates were wide and therefore did not contradict the overall pattern of the ratio ApoB/ApoA1 being the most powerful lipid marker of myocardial infarction.

ROC analysis (log transformed values) adjusted for age, sex, and region, showed that the AUC for the ApoB/ApoA1 ratio was 0.641, whereas that for total cholesterol/HDL cholesterol was 0.577. The AUC for the ratio of ApoB/ApoA1 was greater ($p < 0.0001$) than the AUCs for all the other cholesterol ratios.

The protective effect of ApoA1 is consistent in men and women at all ages with a modest, but significant reduction of the benefit in the oldest age group ($p = 0.004$ for trend; table 5). By contrast, the OR of ApoB decreased with age ($p < 0.0001$ for trend). Consequently, the OR for the ratio of ApoB/ApoA1, although remaining high at all ages, was reduced with age, ($p < 0.0001$ for trend). However, the effect of total cholesterol/HDL cholesterol ratios was much weaker than that noted with ratios of ApoB/ApoA1 in all age-groups (table 5).

The overall PAR (Q2-Q5 vs Q1) for the ratio of ApoB/ApoA1 was greater than that associated with the ratio of total cholesterol/HDL cholesterol (table 6). The overall PAR for total cholesterol was 16.2% (95% CI 11.8-21.8), non-HDL cholesterol 21.0% (16.6-26.2), HDL cholesterol 29.5% (25.0-34.3), ApoA1 53.3% (49.8-56.8), and ApoB 29.7% (25.4-34.3). The PAR for ApoB was 31.2% (22.5-41.5) in women and 29.3% (24.5-34.5) in men. By contrast, the PAR for ApoA1 in women was 41.5% (35.7-47.5) and was much higher in men at 57.6% (53.2-61.9). No difference in PAR for HDL cholesterol between women and men was noted (26.0% [19.6-33.7] and 29.5% [23.9-35.9], respectively). For comparison the PAR for smoking was 44.0% (41.6-46.5) in men and 15.7% (13.3-18.4) in women.² In younger individuals (men <50 years plus women <65 years) the PAR for the ratio of ApoB/ApoA1 was 66.2% (61.7-70.5) and in older individuals (men >50 years plus women >65 years) it was 45.3% (40.4-50.3).

Overall, blood samples were obtained from 7383/9345 (79%) of cases within 24 h of initial symptoms, and 5090/12120 (42%) of controls and 2897/9345 (31%) of cases reported that they each fasted for at least 8 h before

venepuncture. The webtable shows the effect of time since symptoms and time since last meal on the OR.

Medication before enrolment was very low; aspirin was the drug used most by both controls (1020 [8%]) and cases (2171 [18%]), whereas cholesterol-lowering drugs were used by 385 (3%) controls and 750 (6%) cases. In a separate analysis, exclusion of individuals on cholesterol-lowering drugs did not alter our results (data not shown).

Correction of the regression-dilution bias for a 1 SD change in each ratio showed that the association of the ratios of ApoB/ApoA1 and total cholesterol/HDL cholesterol with myocardial infarction was increased by 20·3% and 20·8%, respectively, increasing the OR to 1·75 and 1·33, respectively. When the overall PAR was corrected for regression-dilution bias, the PARs for the two ratios were 60·3% and 36·9%, respectively.

At every tertile of the total cholesterol/HDL cholesterol ratio, increasing ratios of ApoB/ApoA1 increased the risk of myocardial infarction. By contrast, in the second and third tertiles of ApoB/ApoA1, increases in the ratios of total cholesterol/HDL cholesterol were associated with a reduced risk of myocardial infarction (figure 3), suggesting an interaction between the apolipoproteins and lipoproteins.

Discussion

In all ethnic groups and both sexes, the ApoB/ApoA1 ratio was a better risk marker of myocardial infarction than was the ratio of total cholesterol/HDL cholesterol. Importantly, the C statistic derived from the ROC analysis confirmed this finding. Moreover, although the risk associated with the ApoB/ApoA1 ratio decreased with age, mainly because the risk associated with ApoB became less pronounced, the ApoB/ApoA1 ratio was more associated with risk at all ages than were any of the cholesterol ratios. Indeed, the PAR of ApoB/ApoA1 ratio was almost double that of the total cholesterol/HDL cholesterol ratio. Thus, in every comparison, the ApoB/ApoA1 ratio was substantially better than any of the cholesterol ratios—ie, total cholesterol/HDL cholesterol, non-HDL cholesterol/HDL cholesterol, and LDL cholesterol/HDL cholesterol (webappendix).

In the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study,¹⁸ the hazard ratio for the ApoB/ApoA1 ratio was significantly higher than that for the total cholesterol/HDL cholesterol ratio. Because the C statistics for the ratios of ApoB/ApoA1 and the total cholesterol/HDL cholesterol did not differ, the two ratios were interpreted as equivalent. However, to test the predictive power of closely correlated variables, studies must be large and include many events. EPIC-Norfolk¹⁸ was a case-control study with only 869 events. The Framingham Offspring Study Cohort,¹³ a prospective study, was even smaller with only 291 events and neither total cholesterol nor LDL cholesterol were significant predictors in men or women. In this Framingham study,¹³ neither the hazard ratio nor the C statistic was significantly

different between the ratios of total cholesterol/HDL cholesterol and ApoB/ApoA1. The study showed a key limitation of ratios—namely, that a ratio can mask important differences in the numerator or the denominator. In the Framingham Offspring Study,¹³ ApoB was a better risk marker of myocardial infarction than was total cholesterol or LDL cholesterol, whereas HDL cholesterol was more predictive than was ApoA1.

In our study, although the statistical power was reduced for each individual ethnic group compared with the total study population, the presence of 1672 to 5586 participants in each of the first six groups (ie, European, Chinese, south Asian, other Asian, Latin American, and Arab and Persian) with more than 800 cases of acute myocardial infarction within every major ethnic group (other than black or coloured Africans), is statistically sound. INTERHEART compared a very large number of cases to a very large number of controls, ensuring that real differences in predictive power would not be obscured by the close correlation that exists between cholesterol and apolipoproteins.

An important feature of our results is that ApoB was better than total cholesterol, LDL cholesterol (webappendix), and non-HDL cholesterol; and ApoA1 was better than HDL cholesterol in predicting myocardial infarction. Our results are consistent with the findings of the AMORIS⁸ cohort study of 69 030 men and 57 168 women followed-up for a mean of 98 months).¹⁹ The risk associated with a 1 SD change in the ratio of ApoB/ApoA1 in this INTERHEART study is nearly identical to that noted in the AMORIS study.⁸ The consistency of results in the largest studies with different designs in different populations reinforces the robustness of our findings. Our study, however, explored the association of lipids and apolipoproteins in all the major ethnic groups of the world. Evidence that the ApoB/ApoA1 ratio is better than the other ratios in our study is highly consistent and highly robust across virtually all the ethnic groups. The apolipoprotein ratios are consistently stronger than ratios of total cholesterol/HDL cholesterol even when the delay between the meal and the blood sampling is long, implying that even after a 12 h fast the apolipoproteins are better risk markers.

The pathophysiological basis for why the ApoB/ApoA1 ratio is better than the cholesterol ratios is not completely understood. Each atherogenic lipoprotein particle contains one molecule of ApoB; therefore, the number of plasma ApoB molecules equals the total number of atherogenic particles, of which LDL predominates. Small, dense, cholesterol-depleted LDL particles are common and, when present, LDL cholesterol underestimates the number of LDL particles.^{20,21} Unlike HDL cholesterol, ApoA1 has several physiological roles. ApoA1 guides reverse cholesterol transport, is an antioxidant and anti-inflammatory, and helps to produce nitric oxide.²¹ By contrast with ApoB, no simple association exists between

See Online for webtable

either HDL cholesterol or ApoA1 and HDL particle number. Moreover, the association between ApoA1, HDL cholesterol, and plasma triglycerides differs. In the controls in our study, as the median concentrations of triglycerides (webappendix) increased from the first to the tenth decile, the concentrations of HDL cholesterol progressively decreased, whereas, the median value of ApoA1 was unchanged. These data are consistent with those reported previously²² showing that increases in plasma triglycerides are associated with greater reductions in HDL cholesterol than in ApoA1. This discordance between HDL cholesterol and ApoA1 suggests that the effects of core lipid exchange between the cholesterol-rich HDL-2 and VLDL are more prominent than any associated changes in HDL clearance.

LDL-lowering treatment is a potent proven method to prevent cardiovascular events. ApoB was first suggested as an alternative target treatment by the Canadian Working Group.²³ The American Diabetes Association and the American College of Cardiology have just issued a joint Consensus Statement³ that ApoB should be the final test of the adequacy of any LDL cholesterol-lowering treatment.

The more accurately risk can be defined, the more cost effective primary prevention will be. The clinical measurement of apolipoproteins is standardised, simple, inexpensive, and can be done with samples obtained from non-fasting individuals. Our data provide broad and straightforward support that ApoB and ApoA1 should be introduced worldwide into clinical practice for the assessment of the risk of vascular disease.

Contributors

SY initiated the INTERHEART study, supervised its conduct and data analysis, reviewed and commented on all drafts of this paper. SO coordinated the worldwide study, and reviewed and commented on drafts. MJM had overall responsibility for all laboratory analyses and had primary responsibility for writing this report. SH did all data analyses and reviewed and commented on drafts. XW had responsibility for laboratory analyses, in China, and reviewed and commented on drafts. AS contributed extensively to the interpretive analysis of the data, and reviewed and commented on drafts. All other authors contributed greatly to the study in their respective countries and provided comments on drafts of the report. SY, SH, and MJM had full access to all data and they took responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest statement

We declare that we have no conflict of interest.

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