A Case-Control Study of Lipoprotein Particles in Two Populations at Contrasting Risk for Coronary Heart Disease

The ECTIM Study


The incidence of coronary heart disease (CHD) in middle-aged men is more than three times higher in Northern Ireland than in France. The ECTIM study, which is based on WHO MONICA centers in Belfast (Northern Ireland), Strasbourg (eastern France), Toulouse (southwestern France), and Lille (northern France), has been established to investigate this striking difference. Male patients aged 25–64 years with myocardial infarction (MI) and control subjects sampled from the general population were recruited in the four centers. Hypolipidemic drug treatment was much more frequent in France than in Belfast. “Hypercholesterolemia” defined by the presence of hypolipidemic drug treatment or a low density lipoprotein cholesterol level >200 mg/dl was more frequent in cases than in controls in both countries but was similar in both control groups. An in-depth study of lipid variables, including measurements of cholesterol fractions, triglycerides, apolipoproteins (apo), and lipoprotein particles (Lp), was performed in nonhypercholesterolemic subjects. In Northern Ireland and France, patients in comparison with controls had lower levels of high density lipoprotein cholesterol, apo A-I, apo A-II, Lp A-I, and Lp A-II: A-I and higher levels of Lp E:B and Lp(a): B. The levels of triglycerides, very low density lipoprotein cholesterol, apo B, and Lp C-III:B were higher in cases than in controls in both countries.

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A high-risk profile, characterized by a low Lp A-I level and by high levels of Lp E:B and Lp(a): B, was thus more frequent in the population of Northern Ireland. Further studies are needed to determine the contribution of environmental and genetic factors to this risk profile and to investigate its predictive value within populations.

Key Words • lipoproteins • apolipoproteins • lipoprotein particles • case-control studies • geographical differences in coronary heart disease risk

To investigate the large international differences in the trends in coronary heart disease (CHD) incidence and mortality and to study their relation to risk factor levels over time, the World Health Organization established the MONICA Project (Multinational MONItoring of trends and determinants in CArdiovascular disease). The project’s framework is ideally suited for the conduct of studies by groups of centers. ECTIM (Etude Cas-Témoins sur l’Infarctus du Myocarde) is a case-control study of myocardial infarction (MI) that was set up to investigate the large differences in CHD incidence and mortality between the French centers of Strasbourg, Toulouse, and Lille and the Northern Irish center in Belfast. Northern Ireland mortality and incidence rates for CHD are more than three times as great as those in France (in 1984–1986, the standardized mortality rates in men aged 25–64 years were 348, 105, 102, and 78 per 100,000 in Belfast, Lille, Strasbourg, and Toulouse, respectively). Differences in conventional risk factors (total cholesterol, blood pressure, and cigarette smoking) do not explain this striking contrast in incidence.

An investigation of lipid variables was performed in the ECTIM Study. Particular emphasis was placed on the study of lipoprotein particles. These particles are characterized by their content of apolipoproteins and constitute separate metabolic pools. Twenty years ago, Alaupovic proposed that plasma lipoproteins consist of a mixture of such particles. This concept has led to the develop-
ment of immunoassays, in which the use of a combination of polyclonal and monoclonal antibodies allows the discrimination of several types of particles that could differ in their atherogenic properties. The results presented here relate to the findings on lipids, lipoproteins, apolipoproteins, and lipoprotein particles. Because the MONICA data show that the incidence of CHD among the French centers is similar and that the mean lipid levels are homogeneous in France in the ECTIM Study, the data from the three French centers were pooled in this analysis and compared with the data for Northern Ireland.

Methods

Study Populations and Sampling of Cases and Controls

In ECTIM, the populations studied were those covered by the MONICA registers: Belfast and its surroundings in Northern Ireland; Strasbourg and the region of Bas-Rhin in northeastern France; Toulouse and the region of Haute-Garonne in southwestern France; and Lille and its suburbs in northern France. Men aged 25–64 years were eligible for inclusion in the study; they had to be residents of the region, and their parents and grandparents had to have been born in Europe (for the French centers) or the historical entity of Ulster (Northern Ireland).

During the study period, all male patients surviving an MI defined by MONICA criteria (category I) were eligible for the study. The patients were drawn from the MONICA registers, and further epidemiological data and blood samples were obtained at least 3 months and at most 9 months after the event.

Controls were obtained from the electoral rolls in France and from the lists of general practitioners held by the Central Services Agency in Northern Ireland. Stratification by age was employed to approximately match the age distribution of the controls with that of cases.

Informed consent was obtained from the subjects and their family doctors. Among the eligible control subjects, 40% in Belfast, 54% in Strasbourg, 49% in Toulouse, and 47% in Lille refused to participate, did not respond, or could not be traced.

The subjects were examined in clinics or, if necessary, at home by specially trained staff. A set of questionnaires was completed, which included details of personal history (including presence of CHD in controls), drug intake, cigarette smoking, and alcohol consumption (at the time of the MI).

Lipid, Lipoprotein, and Apolipoprotein Analyses

A blood sample of 20 ml was obtained and placed in tubes containing Na$_2$EDTA after the subjects had fasted for at least 10 hours, kept at room temperature, and centrifuged within 4 hours. After addition of preservative (final concentrations: EDTA, 0.27 mmol/l; e-aminocaproic acid, 0.9 mmol/l; chloramphenicol, 0.6 mmol/l; and glutathione, 0.3 mmol/l), the plasma was stored at 4°C for no longer than 6 days and sent at 4°C to the laboratory in Lille where all lipid measurements were performed immediately.

Plasma total cholesterol and triglycerides were measured by enzymatic methods (Boehringer Mannheim, FRG) adapted to a Hitachi 705 analyzer. Cholesterol was measured in the very low density lipoprotein (VLDL) fraction separated by ultracentrifugation and in the high density lipoprotein (HDL)–containing supernatant after sodium phosphotungstate/magnesium chloride precipitation (Boehringer Mannheim). Low density lipoprotein (LDL) cholesterol was estimated by subtraction. Apolipoproteins (apos) A-I and B were quantified by immunonephelometry (Behringwerke, Marburg, FRG). Apo A-II was measured by immunoenzymometric assay. Particles, defined by their apolipoprotein composition and containing apo A-II and A-I (Lp A-II:A-I), apo E and B (Lp E:B), apo C-III and B (Lp C-III:B), and apo(a) and B (Lp[a]:B) were measured by two-site immunoenzymatic assays as described elsewhere. Particles containing apo A-I but free of apo A-II (Lp A-I) were quantified by differential electroimmunoassay on ready-to-use plates.

The intra-assay and interassay coefficients of variation were 2.5% and 4%, respectively, for Lp A-I, 6% and 10% for Lp A-II:A-I, 3% and 8% for Lp E:B, 3% and 5% for Lp C-III:B, and 5% and 10% for Lp[a]:B.

Statistical Analysis

The results were analyzed using SAS statistical software (SAS Institute Inc., Cary, N.C.). The means were compared by analysis of variance with two grouping factors: case-control status (two levels) and population (two levels). Interactions between the two grouping factors and the dependent variables (the lipid measurements) were also tested to assess the homogeneity of the associations. Adjustment on covariates (age, body mass index, etc.) was performed by analysis of covariance. Because a large number of comparisons were made, a difference was considered significant if the probability value was <0.01. The lipid variables differing most significantly and independently between groups were identified by stepwise logistic regression analysis (a probability value of 0.01 was chosen for retaining a variable in the model). The standardized logistic regression coefficients given in the tables were obtained by dividing the regression coefficient estimates by the ratio of the standard deviation of the underlying distribution to the sample standard deviation of the explanatory variable.

Results

A total of 1,140 cases and controls are included in this analysis: 200 cases and 181 controls from Northern Ireland and 298 cases and 461 controls from France. Controls with CHD were excluded.

Prevalence of Hypolipidemic Drug Treatment

In Northern Ireland the prevalence of hypolipidemic drug treatment was 5.0% in cases and 0.5% in controls whereas in France the percentages were 24.8% and 6.3% in cases and controls, respectively. The difference between cases and controls was highly significant in both countries, and the prevalence of hypolipidemic treatment was much higher in France than in Northern Ireland in cases as well as controls.
Analyses for Subjects Not Treated With Hypolipidemic Drugs

Hypolipidemic drugs and repeated in nonhypercholesterolemic subjects, as defined above, to check the consistency of the results.

Table 1. Age, Body Mass Index, Cigarette Smoking, and Alcohol Consumption in Different Groups of ECTIM Study (Subjects Treated With Hypolipidemic Drugs Excluded)

<table>
<thead>
<tr>
<th>Northern Ireland</th>
<th>France</th>
<th>Tests of differences* (F values and significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n=190)</td>
<td>Controls (n=180)</td>
<td>Cases (n=224)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54.4 (7.9)</td>
<td>54.1 (7.8)</td>
<td>54.0 (8.3)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.3 (3.6)</td>
<td>25.8 (3.6)</td>
<td>26.7 (3.5)</td>
</tr>
<tr>
<td><strong>Cigarettes/day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.1 (20.4)</td>
<td>5.2 (10.6)</td>
<td>8.8 (13.7)</td>
</tr>
<tr>
<td><strong>Alcohol (g/day)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.0 (50.0)</td>
<td>35.7 (48.5)</td>
<td>32.6 (33.0)</td>
</tr>
</tbody>
</table>

Values are mean and (SD). ECTIM, Etude Cas-Témoins sur l'Infarctus du Myocarde.

*Two-way analysis of variance. NS, not significant; †p<0.01; §p<0.001; ¤p<0.0001.

Prevalence of Hypercholesterolemia

The general characteristics of the subjects are shown in Table 1. The mean age was approximately the same in the four groups. The mean body mass index was similar in France and Northern Ireland, and no difference existed between cases and controls. The mean number of cigarettes smoked was much higher in cases than in controls. In Northern Ireland, cases smoked three times as many cigarettes as controls before their MI (p<0.0001); in France the difference was less striking. The mean alcohol consumption appeared slightly greater in the French controls than in the other groups.

The mean values of the lipid variables measured in the ECTIM study are shown in Table 2. The mean levels of HDL cholesterol, apo A-I, apo A-II, Lp A-I, and Lp A-II: A-I were much lower in cases than in controls in both populations. The largest difference concerned apo A-I; however, the mean levels of this apolipoprotein were similar in Northern Ireland and France. On the other hand, the mean levels of Lp A-I differed between cases and controls and were lower in Northern Ireland than in France in both controls and cases.

The levels of VLDL cholesterol, triglycerides, apo B, and Lp C-III:B were higher in cases in Northern Ireland and 224 cases and 432 controls in France were not on hypolipidemic treatment.

Table 2. Lipid Parameters in Different Groups of ECTIM Study (Subjects Treated With Hypolipidemic Drugs Excluded)

<table>
<thead>
<tr>
<th>Northern Ireland</th>
<th>France</th>
<th>Tests of differences* (F values and significance)</th>
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</thead>
<tbody>
<tr>
<td>Cases (n=190)</td>
<td>Controls (n=180)</td>
<td>Cases (n=224)</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>241.8 (40.4)</td>
<td>235.4 (42.2)</td>
</tr>
<tr>
<td>HDL</td>
<td>42.0 (12.8)</td>
<td>51.3 (14.8)</td>
</tr>
<tr>
<td>VLDL</td>
<td>34.5 (14.5)</td>
<td>27.5 (15.9)</td>
</tr>
<tr>
<td>LDL</td>
<td>164.7 (37.1)</td>
<td>156.5 (39.0)</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>159.5 (87.1)</td>
<td>159.0 (88.9)</td>
<td>159.4 (77.0)</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>124.0 (20.2)</td>
<td>145.8 (26.2)</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>31.5 (7.6)</td>
<td>34.9 (8.2)</td>
</tr>
<tr>
<td>Apo B</td>
<td>146.5 (30.2)</td>
<td>131.7 (32.2)</td>
</tr>
<tr>
<td>Lp A-I</td>
<td>38.4 (9.4)</td>
<td>44.2 (11.8)</td>
</tr>
<tr>
<td>Lp A-II:A-I</td>
<td>75.2 (17.7)</td>
<td>80.2 (18.2)</td>
</tr>
<tr>
<td>Lp C-III:B</td>
<td>23.4 (15.5)</td>
<td>17.8 (15.9)</td>
</tr>
<tr>
<td>Lp E:B</td>
<td>56.0 (28.9)</td>
<td>48.2 (32.5)</td>
</tr>
<tr>
<td>Lp(a):B</td>
<td>20.6 (25.1)</td>
<td>14.2 (20.6)</td>
</tr>
</tbody>
</table>

Values are mean and (SD) and are in milligrams per 100 milliliters. HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; Lp, lipoprotein; ECTIM, Etude Cas-Témoins sur l'Infarctus du Myocarde.

*Two-way analysis of covariance: NS, not significant; †p<0.01; §p<0.001; ¤p<0.0001. The tests were adjusted for age, body mass index, cigarette smoking, and alcohol consumption.
Analyses for Normocholesterolemic Subjects

One hundred fifty-seven cases and 153 controls in Northern Ireland and 203 cases and 392 controls in France were not treated with hypolipidemic drugs and had an LDL cholesterol level ≤ 200 mg/dl.

When the analyses were limited to these subjects (Table 5), the differences between the groups were very similar to those reported in Table 2, in which only subjects treated with hypolipidemic drugs were excluded. As shown in Tables 3 and 4 (lower half), the results of the logistic regression analyses performed before and after exclusion of subjects with LDL cholesterol levels ≥ 200 mg/dl were very similar.

Discussion

Different approaches were used in Belfast and France to select controls. In Belfast the general practitioner lists include virtually everyone (97-98%). The only exceptions are those rare individuals who rely solely on private medicine. In France the electoral rolls include almost every adult French citizen. In both cases foreigners were not included because it was required that the subjects had to have been born in the region where they were sampled. In the first MONICA survey, the response rates were 70% and 57% in Belfast and France, respectively, and the mean cholesterol levels in men aged 35–64 were identical in both countries: 233 mg/dl.

The differences between controls in Northern Ireland and France (Table 4, upper half) are of particular interest because they are not biased by the presence of disease and thus probably more accurately reflect the actual differences between the Northern Irish and French populations. Both HDL cholesterol and Lp A-I differed strongly and independently between the two control groups. The adjusted level of HDL cholesterol was higher and the adjusted level of Lp A-I lower in Northern Ireland than in France. The adjusted levels of Lp E:B and Lp(a):B were both higher in Northern Ireland than in France.

Analyses for Normocholesterolemic Subjects

One hundred fifty-seven cases and 153 controls in Northern Ireland and 203 cases and 392 controls in France were not treated with hypolipidemic drugs and had an LDL cholesterol level < 200 mg/dl.

The differences between the groups were very similar to those reported in Table 2, in which only subjects treated with hypolipidemic drugs were excluded. As shown in Tables 3 and 4 (lower half), the results of the logistic regression analyses performed before and after exclusion of subjects with LDL cholesterol levels ≥ 200 mg/dl were very similar.

Discussion

Different approaches were used in Belfast and France to select controls. In Belfast the general practitioner lists include virtually everyone (97–98%). The only exceptions are those rare individuals who rely solely on private medicine. In France the electoral rolls include almost every adult French citizen. In both cases foreigners were not included because it was required that the subjects had to have been born in the region where they were sampled. In the first MONICA survey, the response rates were 70% and 57% in Belfast and France, respectively, and the mean cholesterol levels in men aged 35–64 were identical in both countries: 233 mg/dl. A value that is very close to those observed in the ECTIM Study: 231 and 235 mg/dl in Belfast and France, respectively, and the mean cholesterol levels in men aged 35–64 were identical in both countries: 233 mg/dl.

The differences between controls in Northern Ireland and France (Table 4, upper half) are of particular interest because they are not biased by the presence of disease and thus probably more accurately reflect the actual differences between the Northern Irish and French populations. Both HDL cholesterol and Lp A-I differed strongly and independently between the two control groups. The adjusted level of HDL cholesterol was higher and the adjusted level of Lp A-I lower in Northern Ireland than in France. The adjusted levels of Lp E:B and Lp(a):B were both higher in Northern Ireland than in France.

Analyses for Normocholesterolemic Subjects
Ireland and France, which has been confirmed by other sources, could not be avoided as a possible source of bias within the framework of a case–control study. In this article we tried to overcome this difficulty by performing the analyses in selected groups of subjects, in particular in subjects not treated with hypolipidemic drugs and in “nonhypercholesteremic” subjects. The “hypercholesteremic” group included all subjects treated with hypolipidemic drugs and all subjects with an LDL cholesterol level >200 mg/dl. This definition of hypercholesterolemia is, of course, not standard; in particular, although the threshold for LDL cholesterol may appear high, a rather high threshold was necessary because only one measurement of LDL cholesterol was made. We also used a lower level (180 mg/dl) to assess the robustness of the results, and we found that the associations were practically unchanged. With this definition, the prevalence of hypercholesterolemia in controls was identical in France and Northern Ireland (15.5% and 15.6%, respectively) but was higher in cases in France than in Northern Ireland (32.6% and 22%, respectively). The comparisons of prevalence of hypercholesterolemia involving the French cases may be biased, as doctors in France tend to treat MI patients at lower levels of LDL cholesterol than patients with no coronary complications. However, this bias is probably small because in the nonhypercholesteremic group, the mean levels of LDL cholesterol were similar in all groups. As a consequence, all differences or lack of differences in nonhypercholesteremic subjects reported in the tables concern groups of subjects with similar mean levels of LDL cholesterol and are not likely to be influenced by the differences in treatment prevalence between cases and controls and between Northern Ireland and France.

The results of case–control studies that focus on biological factors may be biased not only by the presence of hypolipidemic drug treatments but also by other drug treatments and the numerous dietary and lifestyle modifications occurring after MI. We tried to reduce this bias by delaying biological measurements for 3–9 months after MI and recording all treatments received by the patients to allow for potential adjustment. In fact, no adjustment except for hypolipidemic treatment was necessary, as all adjustments that we performed, using a broad pharmacological classification, did not modify the results.

In this study a lipid variable would be a candidate for a role in the development of CHD if its level was different between cases and controls within each population and also between control populations. Furthermore, the differences in case–control and population comparisons should be consistent. Among the variables that we measured, three fulfill these criteria: Lp A-I, Lp E:B, and Lp(a):B. As discussed above, among controls the prevalence of hypercholesterolemia is identical in Northern Ireland and France; this confirms the first MONICA population survey findings, which showed that the mean level of total cholesterol was similar in Belfast and the three French centers. This suggests that the differences in incidence of CHD in the two populations studied are unlikely to be explained by differences in LDL cholesterol levels. However, despite similar levels of LDL cholesterol and even after exclusion of hypercholesterolemic subjects, higher mean levels of triglycerides, VLDL cholesterol, apo B, and Lp All:A-I were observed in cases than in controls in Northern Ireland. In multivariate analysis, only the difference in apo B level remained significant. Elevated levels of triglycerides or apo B have frequently been observed in patients with

### TABLE 5. Mean Values of Lipid Parameters in Different Groups of the ECTIM Study: “Noncholesterolemic” Subjects*

<table>
<thead>
<tr>
<th></th>
<th>Northern Ireland</th>
<th>France</th>
<th>Tests of differences†</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=157)</td>
<td>Controls (n=153)</td>
<td>Cases (n=203)</td>
<td>Controls (n=392)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>230.2 (32.4)</td>
<td>224.3 (33.5)</td>
<td>214.6 (32.4)</td>
<td>222.5 (33.2)</td>
</tr>
<tr>
<td>HDL</td>
<td>41.8 (12.6)</td>
<td>52.2 (14.9)</td>
<td>43.0 (10.0)</td>
<td>52.6 (15.6)</td>
</tr>
<tr>
<td>VLDL</td>
<td>34.2 (14.8)</td>
<td>26.6 (16.4)</td>
<td>25.4 (15.6)</td>
<td>25.0 (15.9)</td>
</tr>
<tr>
<td>LDL</td>
<td>153.5 (29.2)</td>
<td>145.6 (29.5)</td>
<td>146.3 (26.5)</td>
<td>145.0 (30.0)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>196.8 (88.2)</td>
<td>150.3 (84.8)</td>
<td>151.3 (70.5)</td>
<td>149.5 (81.6)</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>123.3 (20.2)</td>
<td>145.8 (26.5)</td>
<td>126.9 (20.5)</td>
<td>148.7 (27.2)</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>31.5 (7.5)</td>
<td>34.6 (8.1)</td>
<td>29.9 (7.7)</td>
<td>35.5 (8.5)</td>
</tr>
<tr>
<td>Apo B</td>
<td>139.9 (26.9)</td>
<td>124.2 (27.7)</td>
<td>124.4 (23.7)</td>
<td>123.1 (27.8)</td>
</tr>
<tr>
<td>Lp A-I</td>
<td>38.2 (9.3)</td>
<td>44.5 (12.2)</td>
<td>43.1 (10.4)</td>
<td>50.5 (14.4)</td>
</tr>
<tr>
<td>Lp A-II:A-I</td>
<td>75.2 (17.9)</td>
<td>79.2 (16.2)</td>
<td>70.9 (16.1)</td>
<td>82.2 (18.6)</td>
</tr>
<tr>
<td>Lp C-III:B</td>
<td>22.6 (15.3)</td>
<td>16.8 (16.1)</td>
<td>16.5 (12.8)</td>
<td>15.5 (12.8)</td>
</tr>
<tr>
<td>Lp E:B</td>
<td>53.8 (27.1)</td>
<td>46.3 (32.6)</td>
<td>43.0 (24.6)</td>
<td>38.0 (24.1)</td>
</tr>
<tr>
<td>Lp(a):B</td>
<td>16.3 (20.0)</td>
<td>12.5 (19.6)</td>
<td>15.1 (19.9)</td>
<td>8.3 (14.4)</td>
</tr>
</tbody>
</table>

Values are mean and (SD) and are in milligrams per 100 milliliters.
ECTIM, Etude Cas-Témoins sur l'Infarctus du Myocarde; HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; Lp, lipoprotein.

**“Normocholesterolemic” subjects had an LDL cholesterol level <200 mg/100 ml and were not treated with hypolipidemic drugs.
†Two-way analysis of covariance: NS, not significant; *p<0.01, §p<0.001, |p<0.0001. The tests were adjusted for age, body mass index, cigarette smoking, and alcohol consumption.**
women have a higher mean level of this particle than atherosclerosis has not always been observed.21 Northern Ireland than in France. It must be noted, apo(a) is associated with apo B, thus excluding any A-II: A-I particles are subspecies of HDL and may have coronary atherosclerosis have a lower mean level of Lp cholesterol efflux from cells is mediated by Lp A-I and not different between control groups. Lp E:B and Lp C-III:B are heterogeneous particles: Lp E:B contains apo E and apo B (and possibly apo C-III and other apolipoproteins) whereas Lp C-III:B contains apo C-III and apo B (and possibly apo E and other apolipoproteins). As a consequence, Lp E:B and Lp C-III:B both include Lp E:C-III:B, which unfortunately cannot be reliably measured at the present time. Normally, because of the presence of apo E, Lp E:B should be rapidly cleared from the circulation. An increased level of this particle could be the consequence of reduced linking of apo E to the apo B/E receptor. Apo B alone or associated with C-III is probably not involved, as its level does not differ between the control groups. The atherogenic potential of high Lp E:B levels with no parallel increase in LDL cholesterol is presently unknown and warrants further investigation.

The mean levels of several components of HDL, i.e., apo A-I, apo A-II, Lp A-I, and Lp A-II: A-I, are lower in cases than controls. The large difference in the apo A-I level between cases and controls is particularly striking and confirms the results of several studies, which suggest that apo A-I levels might be more strongly associated with CHD than are HDL cholesterol levels.17,18 However, among these variables only Lp A-I strongly differs between the populations, a lower mean level of this particle being observed in Northern Ireland than in France in controls as well as in cases. Also, the results of the multivariate analysis suggest that the Lp A-I to HDL cholesterol ratio might be particularly important because controls in France have a higher mean adjusted level of Lp A-I and a lower mean adjusted level of HDL cholesterol than controls in Northern Ireland. HDL particles, which are relatively rich in apo A-I and poor in apo A-II, might thus be particularly protective. Lp A-I and Lp A-II: A-I particles are subspecies of HDL and may have different biological functions. It has recently been demonstrated in cultures of mouse adipocytes that the cholesterol efflux from cells is mediated by Lp A-I and not Lp A-II: A-I.19 It has also been shown that patients with coronary atherosclerosis have a lower mean level of Lp A-I than those without coronary lesions20 and that women have a higher mean level of this particle than men.22 The low level of Lp A-I in the Belfast group could thus partly explain the higher risk of CHD observed in Northern Ireland than in France. It must be noted, however, that a lower level of Lp A-I in coronary atherosclerosis has not always been observed.21 Lp(a): B specifically measures the particles in which apo(a) is associated with apo B, thus excluding any cross-reactivity with plasminogen.11 A higher level of Lp(a) in patients with CHD than in controls has been demonstrated in numerous epidemiological studies22; this association has been confirmed in the ECTIM Study. The mechanism of the association is still unclear, and the metabolic role, if any, of this particle is unknown.23 Utermann et al24-25 have demonstrated that the circulating level of Lp(a) is largely determined by a genetic size polymorphism of apo(a), which is probably the consequence of a variable number of kringles IV repeats.23 The possible role of Lp(a) in the familial aggregation of CHD has been suggested by previous studies.26,27 The higher level of Lp(a): B in cases than controls in the two populations of the ECTIM Study and the high level of Lp(a) in Northern Ireland controls compared with French controls would therefore be compatible with the observed differences in the incidence of CHD between Northern Ireland and France and suggests that these differences could be partly genetic. However, caution should be exercised in attempting to extrapolate interpopulation differences to the individual level.28 In the case of Lp(a), high mean levels have been observed in low-risk populations, such as the Sudanese23 and Congolese.29

Many factors may differ between the Northern Irish and French populations that are in no way causally related to the risk of CHD. Such ecological bias28 may generate associations that may erroneously be considered causal. The plausibility of a causal association is increased, however, when the association is also shown to be present at the individual level and the factors investigated are biologically related to the development of the disease. The postulated high-risk profile observed in Northern Ireland, characterized by a low Lp A-I level and by high levels of Lp E: B and Lp(a): B but normal LDL and HDL cholesterol levels, is biologically plausible and might be potentially atherogenic. If its relation with the risk of CHD were causal, it could explain part of the large excess of CHD observed in Northern Ireland compared with France. In our opinion, the problem is of sufficient importance to justify a prospective study aimed at determining the predictive value of this profile.

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