Relation of parental history of early myocardial infarction to the level of apoprotein B in men

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ABSTRACT The relations between parental history of early myocardial infarction and plasma lipids and apoproteins have been examined in a population of 4045 middle-aged (20 to 60 years old) working men at the initial examination of the Paris Prospective Study 2. Subjects with a history of myocardial infarction, angina pectoris, or peripheral arterial disease or those treated with hypolipidemic drugs were excluded from the analysis. The numbers of subjects with a paternal or maternal history of early myocardial infarction were 123 and 30, respectively. After adjustment for age, cigarette consumption, alcohol consumption, and body mass index, subjects with parental history of myocardial infarction had higher levels of total cholesterol (p < .01), low-density lipoprotein (LDL) cholesterol (p < .01), and apoprotein B (APOB) (p < .0001) and a lower level of high-density lipoprotein (HDL) cholesterol (p < .05) than subjects with no parental history of myocardial infarction. On the other hand, apoprotein A1 (APOA1) and triglyceride levels were not different between the two groups. The ratios of HDL/total cholesterol and APOA1/APOB were also lower in presence of parental myocardial infarction (p < .001 and p < .01, respectively). When a discriminant analysis was performed, only APOB level was related to parental myocardial infarction. The results for paternal and maternal history were very similar and were grouped for the analysis. We conclude that part of the known relationship between parental history of myocardial infarction and coronary heart disease could be mediated by an increased APOB level.


SEVERAL STUDIES have shown that a parental history of coronary heart disease (CHD) is predictive of CHD in male adults. Adjustment for classic risk factors (age, blood pressure, plasma cholesterol, cigarette consumption, diabetes) usually reduces slightly the strength of this relationship but fails to remove it completely. As a consequence, it is necessary to look for other factors (see ref. 5 for an in-depth review). In particular, since plasma lipoprotein abnormalities appear to be the essential characteristics predisposing to atherosclerosis, it is of interest to investigate the relationship between parental history of CHD and the level of plasma lipids and apoproteins. Several case-control studies have suggested that plasma apoproteins A1 (APOA1) and B (APOB) are more strongly associated with CHD than the lipoprotein cholesterol subfractions. However, it is impossible to infer from these results that apoproteins are more relevant than the lipoprotein fractions of cholesterol in determining the risk of CHD, since this particular pattern of lipoprotein abnormalities could be consecutive to the atherosclerotic process (or to the changes in lifestyle accompanying it) and might not precede it. Prospective investigations are clearly needed to solve this issue. However, family data, especially when they are obtained from whole populations to avoid the selection biases potentially occurring in case-control studies, may help to elucidate the nature of these relationships. Freedman et al. have recently reported results from the Bogalusa Heart Study indicating that the mean level of APOA1 was significantly reduced in children with a parental history of myocardial infarction whereas the mean level of APOB was not affected. In this analysis of the baseline data of the Paris Prospective Study 2 (PPS2), our purpose is to explore the interrelationships be-

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tween parental history of early myocardial infarction, lipids, and APOA1 and APOB, and more specifically to determine whether APOA1 and APOB are more strongly related to parental history than high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol.

**Methods**

The PPS2 is an investigation on cardiovascular risk factors begun in 1982. The initial screening phase ended in December 1985 and the follow-up of the 4547 subjects (20 to 60 years old) who entered the study is presently under way. The study population is composed of male employees of large public organizations in Paris who were volunteers for a cardiovascular screening. Each subject was interviewed by a technician and had to answer a series of questionnaires on smoking habits, alcohol consumption, and a questionnaire on parental history of cardiovascular disease. The latter questionnaire was principally aimed at evaluating the parental history of myocardial infarction, which is more reliable than the history of angina pectoris, peripheral arterial disease, stroke, or hypertension. When a disease was reported, the interviewer had to ask for its circumstances and consequences to obtain a reasonable confidence in the reported history. The age of first occurrence of the disease also was noted. There was no other source of information concerning the parental history than this questionnaire. The subjects were then examined by a doctor and had their clinical history noted. All subjects having a clinical history of myocardial infarction, angina pectoris, or peripheral artery disease and all those taking hypolipidemic drugs were not included in the analysis (n = 150). Body mass index (BMI) was expressed as weight on height squared (kg/m²).

**Biochemical methods.** Until July 1983, cholesterol was determined by an automatic procedure based on the Liebermann-Burchard reaction. After this date, an automatic enzymatic procedure was used (Technicon SMA system). Duplicate measurements of serum cholesterol were performed on a group of 200 subjects to assess the comparability of the two methods. The correlation between the two methods was .97, but a lower mean level (10 mg/dl) was observed with the enzymatic procedure. This discrepancy was taken into account in the statistical analysis. HDL cholesterol was measured after precipitation of very low–density lipoproteins (VLDL) and LDL cholesterol by a heparin–manganese reagent. An estimate of the LDL cholesterol level was computed with the following formula: LDL cholesterol = total cholesterol – (HDL cholesterol + 0.16 × triglycerides). According to the results of the Lipid Research Clinics study, this formula is more accurate than the classic Friedewald formula, in which the coefficient for triglycerides is 0.2 instead of 0.16, and it gives a good approximation of LDL cholesterol, even in hypertriglyceridemic subjects. The triglycerides were measured by an enzymatic procedure (Technicon SMA system). APOA1 and APOB were assayed simultaneously by immunoelectrodiffusion. The percentage of linoleic acid in the cholesterol esters was estimated by gas chromatography as described previously. A detailed description (in French) of the biochemical methods used for the measurement of lipoproteins and apoproteins and of their reproducibility is available from the authors upon request.

**Statistical analysis.** Since the method of measurement of cholesterol changed during the study, a two-period adjustment was performed for all the presented comparisons, even those that do not involve cholesterol; this was equivalent to a poststratification on a dichotomous variable defining the period. The adjustment on covariates and on period was performed in the following way: the multiple regression coefficients of each dependent variable on the different covariates and period were estimated separately in the groups with or without a parental history of myocardial infarction. Since the values of the regression coefficients in the two groups were not significantly different (at the .05 level) for any of the covariates or period, the multiple regression coefficients were estimated in the whole population and used to compute individual values, adjusted on each covariate. The means and standard deviations of these adjusted variables are given in the tables and are used in the comparisons of the subjects with or without a parental history of myocardial infarction. The programs BMDP1D, BMDP1V, and BMDP7M were used to perform this statistical analysis.

**Results**

After exclusion of the subjects with a personal history of myocardial infarction, angina pectoris, or peripheral arterial disease, those treated with hypolipidemic drugs, and those with missing data, 4045 subjects remained for the analysis. Among them, 305 reported a paternal and 94 a maternal history of myocardial infarction. When compared with subjects with no parental myocardial infarction, those with a paternal history of myocardial infarction had a slight elevation of APOB (98.2 vs 94.7 mg/dl; p < .05) and those with a maternal history of myocardial infarction had lower HDL cholesterol levels (54.6 vs 57.9 mg/dl; p < .01).

An age limit of 60 was chosen a priori to define early parental myocardial infarction; no other grouping was attempted. The numbers of subjects with early paternal or maternal myocardial infarction were 123 and 30, respectively. One subject whose parents both had an early myocardial infarction was arbitrarily classified with those having a paternal history. Late parental myocardial infarction (60 years or later) was unrelated to any of the variables studied; as a consequence, the subjects with such parental history were classified with those with no parental myocardial infarction.

The main characteristics of the study population are given in table 1 according to parental early myocardial infarction. The subjects with a paternal history of early myocardial infarction are significantly younger and have a lower mean alcohol consumption than those having no paternal myocardial infarction. The correlations between the characteristics of the subjects and the plasma lipids and apoproteins are shown in table 2. BMI is positively correlated with LDL cholesterol, triglycerides, and APOB and negatively correlated with HDL cholesterol and to a much lower extent with APOA1. The pattern of correlations of cigarette consumption with the lipid and apoprotein variables is identical to that of BMI but the coefficients are of
smaller magnitude. Alcohol consumption is positively correlated with all the variables but to a greater extent with HDL cholesterol and APOA1. Age is also moderately positively correlated with all the variables.

The comparisons of the levels of plasma lipids and apoproteins adjusted for BMI, cigarette consumption, alcohol consumption, and age according to parental history are given in Table 3. When compared with subjects with no parental history of early myocardial infarction, subjects with paternal history have higher levels of total cholesterol, LDL cholesterol, and APOB and a lower level of HDL cholesterol; those with a maternal history have a higher level of APOB. Since the associations are very similar in the presence of a paternal or maternal history, the pooled results concerning parental myocardial infarction are given in Table 3. The most important differences concern the level of APOB (p < .0001) and the ratio HDL/total cholesterol (p < .001); a higher level of LDL cholesterol is also noted in subjects with a parental history of early MI (p < .01), whereas no difference in the ratio LDL cholesterol/APOB is observed, suggesting that there is no clear disproportionate increase of APOB relative to LDL cholesterol in this group of subjects.

As shown in Table 4, the lipid and apoprotein levels are highly intercorrelated (consider in particular the correlation between APOB and LDL cholesterol). To identify independent associations between the different lipid variables and parental history, a stepwise discriminant analysis was performed with parental history of early myocardial infarction as the grouping variable and the lipoprotein cholesterol subfractions, apoproteins, and ratios given in Table 3 as potential discriminating variables. The results indicate that only APOB is a significant independent discriminant variable.

Since a major environmental factor affecting LDL cholesterol and APOB is the lipid composition of the diet, the percentage of linoleic acid in the fatty acids of plasma cholesterol esters (LA) was used as a marker of this composition to investigate a potential difference in the type of lipid intake in subjects with or without a parental history of early myocardial infarction. LA was measured in 3653 subjects, among whom 108 had a paternal history of myocardial infarction and 29 had a maternal history of myocardial infarction. The mean percentages of LA in the subjects with a parental history of early myocardial infarction (47.7 ± 6.1% SD) and in subjects with no such history (48.2 ± 5.6% SD) are not different, suggesting that the association between a parental history of early myocardial infarction and LDL cholesterol and APOB is not likely to be the consequence of a familial resemblance in the type of fat consumed.

**Discussion**

The associations demonstrated by the present analysis should be interpreted with the relative imprecision of the information on parental history kept in mind. The specificity of the responses concerning early parental history of myocardial infarction has not been evaluated in this work and it is likely that some false-negative and false-positive responses were reported; however, if the responses were not biased, the only
consequence of this imprecision would be a reduction in the strength of the observed relationships. Could some biases explain the results? We can hypothesize that subjects who suffered from a myocardial infarction or a related disease such as angina pectoris or peripheral arterial disease were more prone to report a positive parental history of myocardial infarction for two reasons: first because there is a familial aggregation for this disease, and second because these patients are more concerned and less likely to omit a parental antecedent. The exclusion from the analysis of the subjects who had a myocardial infarction, angina pectoris, or a peripheral arterial disease and of those treated with hypolipidemic drugs is likely to reduce this bias considerably. Delong et al. have recently proposed a formula to estimate LDL cholesterol from the measurements of total cholesterol, HDL cholesterol, and triglycerides that appears to be more accurate than the classic Friedewald formula, especially in hypertriglyceridemic subjects. When applied to our data, this formula leads to an estimate of LDL cholesterol that is slightly more strongly correlated with the covariates (BMI, cigarette consumption, alcohol consumption, and age) than the estimate obtained from Friedewald’s formula; however, the two estimates are similarly associated with parental history of myocardial infarction.

The results show that a parental history of early myocardial infarction is associated with a substantial increase of LDL cholesterol and APOB levels with no changes of APOA1 and triglyceride levels. The results of the discriminant analysis suggest that APOB is more strongly related with parental myocardial infarction than LDL cholesterol. Some authors have used the ratio LDL cholesterol/LDL APOB to look for a possible disproportionate increase of APOB relative to LDL cholesterol in some patients with coronary heart disease. In the Bogalusa study, the ratio LDL cholesterol/total APOB (an approximation of the above ratio) was decreased in children with a paternal history of

<table>
<thead>
<tr>
<th>Table 3</th>
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<tr>
<td>Parental history of early myocardial infarction related to plasma lipids and apoproteins in male adults</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parental early myocardial infarction</th>
<th>Father (n = 123)</th>
<th>Mother (n = 30)</th>
<th>Either (n = 153)</th>
<th>None (n = 3892)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>229.9 (37.3)^a</td>
<td>235.2 (47.4)</td>
<td>231.0 (39.3)^b</td>
<td>221.8 (38.8)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>123.8 (73.1)</td>
<td>147.3 (112.2)</td>
<td>128.4 (82.3)</td>
<td>123.6 (81.1)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>56.7 (10.0)</td>
<td>54.5 (12.9)</td>
<td>56.2 (10.6)^a</td>
<td>57.8 (12.4)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>153.5 (37.5)^b</td>
<td>157.1 (46.2)</td>
<td>154.2 (39.2)^b</td>
<td>144.3 (37.0)</td>
</tr>
<tr>
<td>Apo A1 (mg/dl)</td>
<td>159.2 (20.9)</td>
<td>155.6 (20.5)</td>
<td>158.5 (20.8)</td>
<td>156.4 (21.7)</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>101.9 (22.9)^c</td>
<td>107.2 (30.0)^a</td>
<td>103.0 (24.4)^b</td>
<td>94.7 (24.9)</td>
</tr>
<tr>
<td>HDL/total cholesterol</td>
<td>0.253 (0.058)^b</td>
<td>0.244 (0.079)</td>
<td>0.251 (0.062)^c</td>
<td>0.269 (0.074)</td>
</tr>
<tr>
<td>Apo B/Apo A1</td>
<td>0.653 (0.170)^a</td>
<td>0.711 (0.247)^a</td>
<td>0.665 (0.188)^b</td>
<td>0.615 (0.173)</td>
</tr>
<tr>
<td>LDL cholesterol/Apo B</td>
<td>1.53 (0.30)</td>
<td>1.50 (0.29)</td>
<td>1.53 (0.20)</td>
<td>1.56 (0.29)</td>
</tr>
</tbody>
</table>

Data expressed as means adjusted for period, age, BMI, alcohol consumption, and cigarette consumption, with standard deviations in parenthesis.

^a p < .05; ^b p < .01; ^c p < .001; ^d p < .0001. The reference group is the group without parental history.

<table>
<thead>
<tr>
<th>Table 4</th>
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<tr>
<td>Adjusted correlations between the plasma lipids and apoproteins in the whole population</td>
</tr>
</tbody>
</table>

<p>| Pearson correlation coefficients^a (n = 3521) |
| --- | --- | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>HDL cholesterol</th>
<th>LDL cholesterol</th>
<th>APOA1</th>
<th>APOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>.319</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>.026</td>
<td>-.331</td>
<td>1.0</td>
<td></td>
<td></td>
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<tr>
<td>LDL cholesterol</td>
<td>.926</td>
<td>.094</td>
<td>-.190</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>APOA1</td>
<td>.148</td>
<td>-.056</td>
<td>.581</td>
<td>-.018</td>
<td>1.0</td>
</tr>
<tr>
<td>APOB</td>
<td>.753</td>
<td>.270</td>
<td>-.224</td>
<td>.768</td>
<td>.122</td>
</tr>
</tbody>
</table>

^a Adjusted for period, age, BMI, alcohol consumption, and cigarette consumption. All coefficients larger than ± .032 are significant at the p < .05 level.
myocardial infarction. In our study, this ratio was not related with paternal or maternal myocardial infarction. Thus there is no evidence of a disproportionate increase of APOB relative to LDL cholesterol in patients with a parental history of myocardial infarction.

Parental history of myocardial infarction has already been shown to be associated with increased levels of lipids and apoproteins. Freedman et al. have recently reported results from the Bogalusa Heart Study showing an association between APOA1 and parental history of myocardial infarction in children, whereas there was no statistically significant association between parental history and APOB. Furthermore, the ratios APOB/APOA1 and APOB/LDL cholesterol were both raised in children with a paternal history of myocardial infarction. In their study, De Backer et al. have obtained very similar results; they have measured the levels of lipids and apoproteins in the offspring of patients who suffered a myocardial infarction before age 50 and found that, when compared with controls, they had a lower mean level of APOA1 and higher ratios (VLDL cholesterol + LDL cholesterol)/APOB and HDL cholesterol/APOA1. On the other hand, in the same study, in male offspring the mean levels of APOB, LDL cholesterol (estimated by the Friedewald formula), HDL cholesterol, and triglycerides did not differ significantly between the two groups. Kukita et al. have compared first-degree relatives of patients with angiographically defined coronary artery disease with control subjects and found that they had a lower level of APOA1 and HDL cholesterol and a higher level of APOB and triglycerides. In the study of Van Stiphout et al., a paternal history of severe atherosclerosis (estimated by coronary angiography) was associated in offspring with higher levels of APOB and of the ratio APOB/APOA1. LDL cholesterol was also raised in these children but not significantly, and the mean level of APOA1 was similar to that of controls.

There are some discrepancies among the studies. Some point to the more important role played by APOA1, whereas others, like the PPS2, point to the important role played by APOB. Nevertheless, all the results are concordant in showing a stronger association of CHD with apoprotein levels than with the lipoprotein cholesterol subfractions. This observation is in agreement with the results of many case-control studies involving patients with coronary atherosclerosis.

We cannot explain the lack of relationship between HDL cholesterol or APOA1 and parental history of early myocardial infarction in the PPS2. The population of the Bogalusa Heart Study is composed of children, as opposed to the adult men of our study. This factor could be of importance because there may be strong interactions between genetic and environmental factors that might only become apparent in adults and mask the effects of genetic mechanisms that would be more easily observed in children. Alcohol consumption is high in the population of the PPS2; its interaction with genetic factors is possible and it probably accounts for the higher mean levels of HDL cholesterol and APOA1 in this study when compared with other population-based studies in Northern Europe or the United States.

Familial aggregation of lipoprotein abnormalities and CHD is often exclusively attributed to genetic factors without any argument; yet the strong role of environmental variables (such as diet, cigarette smoking, contraceptive use, etc.) on lipid metabolism and the risk of CHD is well known, as is the obvious environmental similarity of subjects sharing or having shared the same environment. It is then essential to control for possible environmental confounders. Adjustment for BMI, cigarette consumption, and alcohol consumption was performed for this purpose and an index of the type of fat consumed in the diet (cholesterol esters linoleic acid) was compared in subjects with or without a parental history of myocardial infarction. This index does not take into account the quantity of fat consumed or the cholesterol intake, both of which could affect the level of serum cholesterol, but it is probably sufficiently accurate to discriminate groups according to their type of fat consumption. Since the association observed between parental history of myocardial infarction and APOB level was not affected by all these adjustments, the likelihood of an underlying genetic mechanism is strengthened. However, this does not exclude a permissive or modulator role of some environmental factors such as the type of fat consumed.

Conclusion. These results indicate that adult men with a parental history of early myocardial infarction have an increased level of APOB, which is most likely to increase their own CHD risk. It is important to elucidate the genetic mechanisms responsible for this increased level; compared with the LDL receptor abnormalities specific for familial hypercholesterolemia, they have a relatively small effect at the individual level, but their widespread distribution is likely to account for a significant part of the CHD in the population. Nevertheless, their interaction with environmental factors such as the quantity and type of fat consumed should be investigated carefully in the search for more specific interventions in high-risk subjects.
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