Genetic and Environmental Determinants of Serum Lipids and Lipoproteins in French Canadian Families

Louis Pérusse, Jean-Pierre Després, Angelo Tremblay, Claude Leblanc, Jean Talbot, Claude Allard, and Claude Bouchard

The contribution of genetic and environmental factors in serum triglycerides (TG), total cholesterol (CHOL), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and HDL-C/CHOL ratio were studied in 1630 subjects from 375 families of French descent by using a path analysis procedure. Familial correlations were computed in several pairs of biological relatives and relatives by adoption after adjustment for age and gender effects and after further adjustment for physical fitness, level of habitual physical activity, total body fat and fat distribution, diet, smoking, and alcohol consumption. The model of path analysis allowed the separation of transmissible variance (t²) into genetic (h²) and cultural (p²) components of inheritance. Under the most parsimonious solution and after adjustment for age, gender, and concomitants, the transmissible variance was entirely accounted for by genetic factors (t² = h²), with h² estimates of 0.52, 0.55, 0.60, 0.62, and 0.63 for TG, CHOL, LDL-C, HDL-C, and HDL-C/CHOL, respectively. These estimates were similar to those obtained after adjustment for age and gender effects only. The contribution of nontransmissible environmental factors ranged from 0.48 for TG to 0.37 for HDL-C/CHOL ratio. These results suggest that both genetic and environmental factors contribute to the variation in blood lipids and lipoproteins in this population and that nongenetic influences are not associated with cultural factors transmitted across generations. (Arteriosclerosis 9:308–318, May/June 1989)

Coronary heart disease (CHD) is a major cause of death in industrialized societies. To better understand the etiology of this disease, several studies have addressed the issue of the relative contribution of genetic and environmental influences in the major risk factors of CHD. Among the risk factors of CHD, blood lipids and lipoproteins have been extensively studied because of their predominant role in the development of atherosclerosis.

Several family 2–8 and twin 7–24 studies have assessed the role of heredity in blood lipid and lipoprotein variation. In most studies, as reviewed recently by Namboodiri et al., 9 significant correlations were observed in first-degree relatives (but not in spouses) for plasma lipid and lipoprotein levels, which suggests a stronger influence of genes than shared environment in the determination of these phenotypes. However, reported heritability estimates computed from twin data alone have been very heterogeneous, ranging from 0.3422 to 0.9226 for cholesterol. Other methods of analysis such as variance components analysis 22,26–27 and path analysis 26–37 have also been used to determine genetic and environmental influences on blood lipids. Although estimates of heritability obtained from path analysis are more homogeneous than those obtained from twin data alone, there is still considerable variation among studies, as shown by genetic effects ranging from 0.1929 to 0.8032 for triglycerides (TG), from 0.4235 to 0.7032 for total cholesterol (CHOL), from 0.4025 to 0.6333 for low density lipoprotein cholesterol (LDL-C), and from 0.3624 to 0.5226 for high density lipoprotein cholesterol (HDL-C).

Most of the studies published thus far have failed to provide adequate controls for environmental factors known to affect blood lipids and lipoproteins, which could partly explain the discrepancies observed among studies. In the present study, several relevant environmental and lifestyle variables such as level of habitual physical activity and physical fitness, total body fat and fat distribution, diet, smoking, and alcohol consumption were measured. The effects of these concomitants on serum TG, CHOL, LDL-C, HDL-C, and the HDL-C/CHOL ratio adjusted for age and gender were determined by regression analysis. Familial correlations adjusted for age and gender effects, as well as for age, gender, and the concomitants, were used to determine genetic and environmental sources of variation in lipids and lipoproteins by a path analysis procedure.

Methods

Population

The population of this study consisted of 1630 subjects from 375 families of French descent recruited through the...
media to participate in a research program designed to study the genetic influences on many biological attributes. These families included a total of 903 children and 727 parents with a mean age (±SD) of 14.6±3.3 and 43.2±5.2 years, respectively. All these subjects were volunteers and gave their written consent to participate in this study, which was approved by the Medical Ethics Committee of Laval University. At the time of their visit to the laboratory, these subjects were examined by a physician, and those retained for this study were free from metabolic and cardiovascular disorders. From this sample, the following pairs of biological relatives and relatives by adoption were formed: spouses (maximum number of pairs = 348), parent-offspring (1222), biological siblings (363), dizygotic (DZ) twins (61), monozygotic (MZ) twins (62), first-degree cousins (90), uncle/aunt-nephew/niece (86), sibs by adoption (110), and foster parent-adopted child (309).

The socioeconomic status of the families was assessed using the Blishen and McRoberts Index. This index, based on the 1971 census data, used income and level of education to rank approximately 480 occupations. The socioeconomic status associated with these occupations ranged from 18.3 to 75.3, and the average rating for the population of this study is 54.1±0.7, which is comparable to the general French Canadian population.

### Serum Lipid and Lipoprotein Determinations

Blood samples were obtained in the morning (about 8:00 AM) after a 12-hour overnight fast. Samples were collected in Vacutainer tubes (Becton Dickinson Labware, Lincoln Park, NJ) without anticoagulants and after clotting; serum was separated by centrifugation at 1500 g for 20 minutes. CHOL was determined with the commercial kit CHOD-PAP from Boehringer (Mannheim, West Germany), and the A-GENT kit of Abbott Laboratories (South Pasadena, CA) was used to measure TG. HDL-C was determined with the same method as for CHOL after separation of HDL from LDL and very low density lipoprotein (VLDL) fractions. LDL-C was estimated by using the Friedewald formula. Measurements of serum lipids with these procedures were found to be reliable.

### Environmental Variables

Several variables reflecting the familial environment, such as relative body weight, body fat distribution, physical fitness, cigarette smoking, alcohol consumption, diet, and level of habitual physical activity were considered in the analyses. Socioeconomic status was not found to be associated with any of the lipid or lipoprotein variables and, therefore, was not considered in the analyses. The body mass index (weight in kg/height in m²) was measured as an indicator of heaviness. Subcutaneous fat was determined by the sum of six skinfolds (biceps, triceps, medial calf, suprailiac, abdominal, and subscapular). The abdominal skinfold was used to estimate abdominal fat accumulation because it has been shown that this skinfold displays the highest association with serum TG and HDL-C levels in this population. The ratio of trunk (sum of subscapular, suprailiac, and abdominal skinfolds) to extremity (sum of biceps, triceps, and calf skinfolds) skinfolds was used as an indicator of body fat distribution.

### Statistical Procedures

Serum lipid data were first adjusted for age and gender by a multiple regression equation \[ Y = \text{age} + \text{gender} + (\text{age} \times \text{gender}) + E \] applied separately in parents and children. Residual scores of age and sex were obtained by subtracting the scores predicted by the regression equation from the original ones. A stepwise multiple regression procedure was used to assess the contribution of environmental and lifestyle factors on age- and sex-adjusted lipid values. However, because of the problem of multicollinearity among the independent variables (concomitants), we used a particular model of the SAS stepwise multiple regression procedure called the “maximum R² improvement technique.” This technique compares all possible combinations of independent variables at each step of the regression and, therefore, identifies the best one-variable model, the best two-variable model, and so forth. A statistic called the Cp statistic was used to choose the model that provided the best prediction. For a model with p independent variables, it has been recommended that the best model is the one in which Cp first approaches p. Residual scores of age, gender, and environmental variables retained by the stepwise regression were computed and normalized by taking the inverse normal transformation of the ranked residuals; these normalized phenotypic scores were used in the analysis. Correlations in the different pairs of relatives were computed and used in the model of path analysis described below.

### Path Analysis

The path analysis BETA model described by Cloninger et al. was used to determine the contribution of genetic factors in serum lipid and lipoprotein variation. The model assumes that a quantitative trait P can be partitioned as: \[ P = A + B + E \] where A and B denote additive genetic factors and cultural factors transmitted from parent to offspring, respectively, and E represents all other environmental factors that are not transmitted between generations. Transmission of cultural factors (cultural inheritance) may be learned or acquired when parents teach their children certain customs and preferences about diet, social environment, and other activities. Nontransmitted environmental factors (E) may be correlated within a generation because of shared environmental influences at
Results

Descriptive statistics of serum lipids and lipoproteins of parents and children are presented in Tables 1 and 2, respectively. The results obtained in parents indicate a more favorable lipid profile in adult women than in adult men; men had higher levels of TG, CHOL, and LDL-C and lower levels of HDL-C and HDL-C/CHOL than women (p<0.01). The results in children indicate that girls have slightly higher concentrations of CHOL (p<0.01) and LDL-C (p<0.05) than boys, but the differences observed for TG, HDL-C, and the ratio HDL-C/CHOL were not significant.

The data in Tables 1 and 2 reveal that there is considerable variation in serum lipids depending on the age and gender of the subjects. As indicated in Table 3, these effects accounted for 9% to 26% of the variation in lipids and lipoproteins of parents, whereas the corresponding values for children (Table 4) ranged from 4% to 14%. These tables also present the standardized partial regression coefficients of the concomitants retained from the stepwise regression procedure as the best predictors of the age- and gender-adjusted lipid values. The percentage of variance in serum lipids and lipoproteins accounted for by the concomitants ranged from 1% to 16% in parents and from 2% to 5% in children. The variable that was found the most consistently associated with age- and gender-adjusted lipids and lipoproteins in both parents and children was abdominal fat.

The residual scores of age and gender, as well as residual scores of age, gender, and concomitants, computed and normalized as described in the Methods section, were used as phenotypes for the analyses. The differences between means and variances of foster and
Table 3. Effects of Age and Gender ($R^2 \times 100$) on Serum Lipids and Lipoproteins and Standardized Partial Regression Coefficients for Concomitants Affecting Age- and Gender-adjusted Lipid Values in Parents

<table>
<thead>
<tr>
<th>Concomitant variable</th>
<th>TG</th>
<th>CHOL</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>HDL-C/CHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of age* and gender</td>
<td>13%†</td>
<td>9%‡</td>
<td>19%‡</td>
<td>19%‡</td>
<td>26%‡</td>
</tr>
<tr>
<td>Activity level</td>
<td>-0.29‡</td>
<td>0.10†</td>
<td>-0.15†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working capacity</td>
<td>0.12†</td>
<td>0.22‡</td>
<td>-0.18‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.14†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>0.13†</td>
<td>0.12†</td>
<td>0.22‡</td>
<td>-0.18‡</td>
<td></td>
</tr>
<tr>
<td>Abdominal fat</td>
<td>0.14†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk/extremity fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total caloric intake</td>
<td>0.12‡</td>
<td>0.09‡</td>
<td>0.11‡</td>
<td>-0.11‡</td>
<td></td>
</tr>
<tr>
<td>Percent fat intake</td>
<td>0.22‡</td>
<td>0.20‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.14†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent alcohol intake</td>
<td>0.12‡</td>
<td>0.11‡</td>
<td>-0.12‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Computed from the regression $Y=age+gender+(age \times gender)+age^2$.  †$p<0.01$, ‡$p<0.0001$.  §Percentage of variance accounted for by the concomitants that were found as the best predictors of age- and gender-adjusted lipid values by stepwise multiple regression (see Methods for details). Only the significant coefficients are presented.  Abbreviations are explained in the legend for Table 2.

Table 4. Effects of Age and Gender ($R^2 \times 100$) on Serum Lipids and Lipoproteins and Standardized Partial Regression Coefficients for Concomitants Affecting Age- and Gender-adjusted Lipid Values in Children

<table>
<thead>
<tr>
<th>Concomitant variable</th>
<th>TG</th>
<th>CHOL</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>HDL-C/CHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of age* and gender</td>
<td>6%§</td>
<td>8%§</td>
<td>4%§</td>
<td>14%§</td>
<td>5%§</td>
</tr>
<tr>
<td>Activity level</td>
<td>-0.07†</td>
<td>0.10†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working capacity</td>
<td>0.10†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>-0.23‡</td>
<td>-0.27‡</td>
<td>0.19†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal fat</td>
<td>0.13‡</td>
<td>0.32‡</td>
<td>0.43§</td>
<td>-0.11‡</td>
<td>-0.32§</td>
</tr>
<tr>
<td>Trunk/extremity fat</td>
<td>-0.10‡</td>
<td>-0.12‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total caloric intake</td>
<td>0.12‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent fat intake</td>
<td>-0.11‡</td>
<td>0.08†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent alcohol intake</td>
<td>-0.09†</td>
<td>0.09†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.11‡</td>
<td>0.09†</td>
<td>-0.06‡</td>
<td>-0.10‡</td>
<td></td>
</tr>
<tr>
<td>$R^2 \times 100$</td>
<td>5%§</td>
<td>2%‡</td>
<td>5%§</td>
<td>3%§</td>
<td>4%§</td>
</tr>
</tbody>
</table>

*Computed from the regression $Y=age+gender+(age \times gender)+age^2$.  †$p<0.05$, ‡$p<0.01$, §$p<0.0001$.  §Percentage of variance accounted for by the concomitants that were found as the best predictors of age- and gender-adjusted lipid values by stepwise multiple regression (see Methods for details). Only the significant coefficients are presented.  Abbreviations are explained in the legend for Table 2.

Biological parents and unrelated biological sibs were tested for all the phenotypes. Whether data were adjusted for concomitants or not, no significant differences between means and variances were found between these groups of subjects (results not shown). Familial correlations of serum lipids and lipoproteins adjusted for age and gender and for age, gender, and concomitants were then computed. Because these two sets of correlations were similar, only the latter are presented in Table 5. The patterns of covariation indicate that relatives who share an increased fraction of their genes by descent tend to be more alike in their lipid profile, the monozygotic twins showing the highest correlations ($0.72 \leq r \leq 0.87$). The low correlations generally observed in spouses, sibs by adoption, and foster parent-adopted child suggest that the familial environment shared by individuals living together does not contribute greatly to the familial aggregation observed in lipids and lipoproteins. These data support the hypothesis of an important contribution of biological inheritance in blood lipids and lipoproteins.

To test this hypothesis and quantify the contribution of genetic factors, these correlations, as well as those obtained on lipid values adjusted only for age and gender effects (results not shown), were used in the BETA model.
Table 5. Interclass Correlations for Serum Lipid and Lipoprotein Values Adjusted for Age, Gender, and Concomitants

<table>
<thead>
<tr>
<th>Type of relative*</th>
<th>TG</th>
<th>CHOL</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>HDL-C/CHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster parent-adopted child (271-300)</td>
<td>-0.09</td>
<td>0.08</td>
<td>-0.03</td>
<td>0</td>
<td>-0.06</td>
</tr>
<tr>
<td>Sibs by adoption (104-108)</td>
<td>0.26†</td>
<td>0.13</td>
<td>0.10</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Spouses (264-345)</td>
<td>0.11</td>
<td>0.14†</td>
<td>0.11</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Uncle (aunt)-nephew (niece) (79-86)</td>
<td>0.23‡</td>
<td>0.09</td>
<td>0.06</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>First-degree cousins (88–92)</td>
<td>0.33‡</td>
<td>0.19</td>
<td>0.22‡</td>
<td>0.08</td>
<td>0.29‡</td>
</tr>
<tr>
<td>Parent-offspring (1031–1202)</td>
<td>0.25‡</td>
<td>0.29‡</td>
<td>0.28‡</td>
<td>0.29‡</td>
<td>0.29‡</td>
</tr>
<tr>
<td>Biological sibs (346–355)</td>
<td>0.25‡</td>
<td>0.36‡</td>
<td>0.36‡</td>
<td>0.41‡</td>
<td>0.38‡</td>
</tr>
<tr>
<td>Dizygotic twins (58–60)</td>
<td>0.39‡</td>
<td>0.40‡</td>
<td>0.41‡</td>
<td>0.19</td>
<td>0.37‡</td>
</tr>
<tr>
<td>Monozygotic twins (55–62)</td>
<td>0.72†</td>
<td>0.79‡</td>
<td>0.81‡</td>
<td>0.87‡</td>
<td>0.83‡</td>
</tr>
</tbody>
</table>

*Range in the number of pairs in parentheses.
†p<0.01, ‡p<0.05.
Abbreviations are explained in the legend for Table 2.

Table 6. Parameter Estimates and \( \chi^2 \) Statistics Obtained from Fitting General BETA Model and Constrained Models to Serum Triglycerides

<table>
<thead>
<tr>
<th></th>
<th>( m )</th>
<th>( \beta )</th>
<th>( h )</th>
<th>( b )</th>
<th>( c )</th>
<th>( c_{o2} )</th>
<th>( c_{ba} )</th>
<th>Chi-square (df) goodness-of-fit</th>
<th>Chi-square (df) contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides adjusted for age and gender effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General model</td>
<td>.16 (.04)</td>
<td>.70*</td>
<td>.52 (.07)</td>
<td>.32 (.07)</td>
<td>.07 (.06)</td>
<td>.36 (.12)</td>
<td>.55 (.08)</td>
<td>23.40 (2)†</td>
<td></td>
</tr>
<tr>
<td>No genetic effect (h=0)</td>
<td>.16 (.04)</td>
<td>.70*</td>
<td>0</td>
<td>.52 (.02)</td>
<td>0</td>
<td>.29 (.10)</td>
<td>.62 (.06)</td>
<td>32.48 (3)†</td>
<td>9.08 (1)†</td>
</tr>
<tr>
<td>No cultural inheritance (( \beta=b=0 ))</td>
<td>.17 (.04)</td>
<td>0</td>
<td>.66 (.03)</td>
<td>0</td>
<td>.16 (.06)</td>
<td>.45 (.13)</td>
<td>.52 (.08)</td>
<td>26.41 (4)†</td>
<td>3.01 (2)</td>
</tr>
<tr>
<td>Most parsimonious (( \beta=b=c=0 ))</td>
<td>.17 (.04)</td>
<td>0</td>
<td>.69 (.02)</td>
<td>0</td>
<td>0</td>
<td>.44 (.09)</td>
<td>.49 (.09)</td>
<td>29.99 (5)†</td>
<td>6.53 (3)</td>
</tr>
<tr>
<td>Triglycerides adjusted for concomitants in addition to age and gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General model</td>
<td>.11 (.04)</td>
<td>.70*</td>
<td>.63 (.07)</td>
<td>.14 (.17)</td>
<td>.11 (.07)</td>
<td>.25 (.14)</td>
<td>.52 (.09)</td>
<td>14.99 (2)†</td>
<td></td>
</tr>
<tr>
<td>No genetic effect (h=0)</td>
<td>.10 (.04)</td>
<td>.70*</td>
<td>0</td>
<td>.50 (.03)</td>
<td>.00 (.05)</td>
<td>.18 (.11)</td>
<td>.63 (.06)</td>
<td>29.24 (3)†</td>
<td>14.25 (1)†</td>
</tr>
<tr>
<td>No cultural inheritance (( \beta=b=0 ))</td>
<td>.12 (.04)</td>
<td>0</td>
<td>.65 (.03)</td>
<td>0</td>
<td>.13 (.06)</td>
<td>.28 (.14)</td>
<td>.51 (.09)</td>
<td>15.08 (4)†</td>
<td>0.09 (2)</td>
</tr>
<tr>
<td>Most parsimonious (( m=b=c=c_{o2}=0 ))</td>
<td>0</td>
<td>0</td>
<td>.72 (.02)</td>
<td>0</td>
<td>0</td>
<td>.43 (.10)</td>
<td>21.39 (7)†</td>
<td>6.40 (5)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are SE.
*Fixed at the upper (or lower) limit permitted by the model. †p<0.01. ‡The most parsimonious solution is the one that fits the data with the fewest parameters.

of path analysis. The parameter estimates derived from the general model and from two constrained models are presented in Tables 6 to 10 for each lipid and lipoprotein variable. Except for TG (Table 6), the general model provided a good fit to the data for total cholesterol (Table 7), LDL-C (Table 8), HDL-C (Table 9), and HDL-C/CHOL ratio, whether data were adjusted for concomitants or not \((0.99<\chi^2<5.60)\). Specific hypotheses of no genetic effect \((h=0)\) and no cultural inheritance \((\beta=b=0)\) were tested by using the likelihood ratio tests. The \( \chi^2 \) values associated with these tests is presented in the last column of Tables 6 to 10 and reveals that the hypothesis of no genetic effect was rejected \((9.08<\chi^2<37.49; \ p<0.01)\), whereas the hypothesis of no cultural inheritance was accepted \((0<\chi^2<3.01; \ p>0.05)\) for all variables. These tables also present the parameter estimates obtained under the most parsimonious solution, which is the solution that could fit the data with the fewest parameters. When data adjusted for age, gender, and concomitants were considered, the results of the most parsimonious solutions indicated that a model including only two parameters \((h \text{ and } c_{ba})\) was sufficient to account for the variation in TG, LDL-C, HDL-C, and the HDL-C/CHOL ratio, while for CHOL, a three-parameters model \((m, h, \text{ and } c_{ba})\) was retained as the most parsimonious solution.

From the most parsimonious solutions presented in Tables 6 to 10, the components of phenotypic variance were computed (see Equation 4). Because of the absence of cultural inheritance, we can see from Equation 4 that the transmissible variance was entirely accounted for by
genetic factors ($t^2=\text{h}^2$) and that $e^2=\text{h}^2+\varepsilon^2$. The fraction of phenotypic variance accounted for by genetic factors ($\text{h}^2$) or biological inheritance is shown in Figure 1 for data adjusted for age and gender and for data adjusted for age, gender, and concomitants. Estimates of heritability ranged from 52% for TG to 63% for the HDL-C/CHOL ratio after adjustment for age, gender, and concomitants (dashed bars). Therefore, the fraction of the phenotypic variance accounted for by nontransmissible environmental factors (1-$\text{h}^2$, where $t^2=\text{h}^2$) ranged from 48% (TG) to 37% (HDL-C/CHOL). The results also indicate that data adjusted only for age and gender effects tend to give lower estimates of heritability for TG, HDL-C, and HDL-C/CHOL ratio, while these estimates remained unchanged for CHOL and LDL-C.

### Discussion

This study was undertaken to quantify the contribution of genetic factors to serum lipid and lipoprotein variation in a French Canadian population after adjustment for several relevant concomitants by use of a path analysis.
strategy. The results obtained under the most parsimonious solutions revealed that the genetic component of inheritance accounted entirely for the transmission effect observed in every lipid and lipoprotein measurement, with heritability estimates ranging from 0.52 for serum TG to 0.63 for the HDL-C/CHOL ratio.

These estimates of heritability are in the range of those already reported in other studies that have used variance components analysis or path analysis to assess genetic and environmental sources of variation in blood lipids and lipoproteins. The adjustment for concomitants, in addition to age and gender, did not considerably change the estimates of heritability. The estimates remained about the same for CHOL and LDL-C, while they slightly increased for TG, HDL-C, and HDL-C/CHOL ratio. The rationale underlying the adjustment for concomitants in such analysis is that the familial aggregation observed in lipid and lipoprotein concentrations may be partly explained by shared environmental factors. In this context, adjusting for concomitants may be helpful in discriminating between genetic and cultural sources of variation. In the present study, we performed this adjustment on data already...
corrected for age and gender effects and found that estimates of heritability were not much altered. These results should not be interpreted as an indication that the concomitants for which we adjusted do not affect lipid data, but rather as an indication that a substantial fraction of the variation attributable to these concomitants was already accounted for by prior adjustment for age and gender effects. Indeed, significant effects of age and gender have already been reported for most of the concomitant variables measured in the population of this study. Furthermore, when unadjusted data were regressed on concomitants (results not shown), the percent of variation accounted for by the concomitants ranged from 2% to 25% in parents and from 3% to 9% in children.

A consistent finding in most of the studies published thus far is the small contribution of the cultural component of inheritance, which was found to account for about 10% or less of the phenotypic variation. However, unlike the results reported in other studies, the cultural component of inheritance was negligible in the present study, as the hypothesis of no cultural inheritance ($\beta = \beta = 0$) could not be rejected for any of the lipid measurements (see Tables 6 to 10). These data indicate that environmental factors affecting blood lipids and lipoproteins are not transmitted from parents to offspring. These nontransmissible environmental factors accounted for about 40% to 50% of the phenotypic variance. Therefore, despite the strong influence of heredity, the nongenetic factors are still important determinants of interindividual differences in blood lipids and lipoproteins.

Common familial environment and random environmental factors specific to each individual may contribute to this nontransmissible environmental component of phenotypic variation. However, the data obtained under the most parsimonious solutions revealed that shared environmental influences do not contribute significantly to the resemblance observed in regular sibs ($c = 0$) and in dizygotic twins ($c_{DZ} = 0$). This finding suggests that environmental factors shared by siblings (except MZ twins) living together have only limited impact on the serum lipid and lipoprotein variation of this population and that environmental factors specific to each individual and not common to siblings living together may be more important. This finding can also be interpreted as evidence that a component of the familial environment specific to the monozygotic twins may influence blood lipid and lipoprotein levels.

It is important to consider the contribution of environmental factors to variation in blood lipids and lipoproteins in the development of strategies aimed at the reduction of cardiovascular disease in populations, because modifications of the lipid profile may be achieved by appropriate manipulation of the environment. This is an important issue if we consider that the average serum cholesterol level of the adult population of this study is over 200 mg/dl and that the Canadian consensus conference on cholesterol recommended that public health programs directed at the reduction of cholesterol should consider a population mean of 190 mg/dl as the long-term goal. Several studies have already shown that variables like exercise, diet, body fat and fat distribution, and cigarette smoking were associated with variations in blood lipids, suggesting that changes in some characteristics of lifestyle may contribute to lower serum cholesterol levels in this French Canadian population and may, consequently, reduce the risk of coronary heart disease.

However, the presence of a significant component of biologic inheritance affecting blood lipids and lipoproteins is also an indication that genetic factors are involved in the development of coronary heart disease. Under the model of analysis used in this study, the genetic effect is assumed to be polygenic, i.e., caused by the contribution of several genes with small additive effects on the phenotype. Although single gene defects, like mutations in the LDL receptor gene causing familial hypercholesterolemia, may have a major effect on lipid and lipoprotein levels, the frequency of these genes is small and, therefore, they account for only a small fraction of individual differences in the population at large. The characterization of the genes involved in this polygenic variation has already been undertaken, and genetic polymorphisms for the apolipoprotein (apo) E and apo B genes, as well as for the apo A-I/C-III/A-IV gene cluster, have already been shown to be associated with some of the genetic variability in lipids and lipoproteins. This is particularly the case for CHOL, as polymorphisms at only three loci (apo A-IV, apo B, and apo E) were found to account for almost 50% of the genetic variation.

It is important to keep in mind that the relative contribution of genetic and environmental factors in determining blood lipids and lipoproteins may not be the same from one population to another. Indeed, each population has its own genetic background, which combines with a particular set of environmental factors at the time of measurement to determine the distribution of the major risk factors in the population. The particular genetic background of the French Canadians is of special interest for genetic studies, with the use of genealogic records, it has been estimated that this population evolved from about 10,000 founders who emigrated from France between the years 1608 and 1763 and that, until recently, little crossbreeding took place between French Canadians and other ethnic...
groups in Canada. This indicates the relative genetic homogeneity of the French Canadian population compared to other populations in which the genetics of blood lipids and lipoproteins have been studied. Another factor that must be considered when attempts are made to compare estimates of heritability between populations is the time dependence of these estimates. The cross-sectional nature of most of the genetic studies implies that the estimates of the components of the phenotypic variance are time dependent. Indeed, the genetic effect measured in a given phenotype may vary with age because of different sets of genes involved in the determination of this phenotype at different periods of life or simply because of differential responses to environmental agents with age or fluctuations in lifestyle and environmental conditions with time.

Another assumption of the model of path analysis that we used is that genetic and environmental factors combine additively to account for the phenotypic variance. It is important to keep in mind that this assumption of no genotype-environment interaction may not be valid for blood lipids and lipoproteins. Recent data from our laboratory have shown that changes induced in some blood lipid and lipoprotein variables after chronic overfeeding and exercise training were significantly associated with the genotypes of the individual, implying that there were genetically high responders and low responders to a given set of environmental conditions. As a matter of fact, this genotype-environment effect appears to be ubiquitous for traits associated with cardiovascular disease. The presence of this genotype-environment interaction suggests that there may be genes other than the structural genes responsible for the response of blood lipid and lipoprotein phenotypes to modifications in behaviors or in environmental conditions and that these genes may be involved in determining someone's risk of developing coronary heart disease.

In summary, the results of this study show that genetic factors account for about 50% to 60% of the variation in serum lipids and lipoproteins. The adjustment for several relevant concomitants, after prior adjustment for age and gender, did not change these estimates of genetic variance. No significant cultural inheritance was found, which suggests that environmental influences affecting blood lipids and lipoproteins are not transmitted from one generation to another. These results suggest that genetic factors and nonfamilial environmental influences are both major determinants of serum lipids and lipoproteins in this population.

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References

25. Sing CF, Orr JD. Analysis of genetic and environmental sources of variation in serum cholesterol in Tecumseh,

70. Robertson FW, Cumming AM. Effects of apoprotein E polymorphism on serum lipoprotein concentration. Arteriosclerosis 1985;5:283–292


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