Family Resemblance for Plasma Lipids and Lipoprotein Concentrations in Blacks

Cincinnati Lipid Research Clinic Family Study

Peter M. Laskarzewski, Charles J. Glueck, and Dabeeru C. Rao

Our specific aim in this study was to assess the family resemblance for lipids and lipoproteins in blacks randomly selected from the Princeton School District’s Family Study cohort, and compare the family resemblance of lipids and lipoproteins between the blacks and whites from the same cohort. There were 160 white and 59 black nuclear families ascertained through randomly selected family study probands. Familial correlations were estimated by the method of maximum likelihood. Father-child and sib-sib correlations were of larger magnitude in whites than blacks for each lipid and lipoprotein, with the exception of high density lipoprotein cholesterol, where the correlations in blacks were higher than in whites. Estimates of genetic heritability were larger in whites than in blacks for each lipid and lipoprotein, with the exception of high density lipoprotein cholesterol. Whereas environment has a substantial effect on high density lipoprotein cholesterol levels in both blacks and whites, there may be a greater genetic effect accounting for higher levels of high density lipoprotein cholesterol in blacks. This is highlighted in our current study by the consistent observation in blacks of increased measures of within-family resemblance for high density lipoprotein alone, of all lipids and lipoproteins.

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Despite having more hypertension, and possibly more severe clinical ramifications of high blood pressure, mortality from ischemic coronary heart disease (CHD) for black males is, in some studies, either less than or no greater than that for white males, although it is greater in black women than in white women, and greater in black women than in black men. Hypertension is both more prevalent and more severe in adult blacks, and obesity is pandemic in black women. The prevalence of familial associations of hyperlipoproteinemia is as high or higher in blacks than in whites. Low socioeconomic status is also a separate CHD risk factor, and remains characteristic of a majority of American blacks, on an average.

Since there are more CHD risk factors among blacks, it is important to raise the question of why CHD mortality and morbidity are not much higher among American blacks. One proposed “protective” factor, the consistently higher high density lipoprotein cholesterol (HDLC) levels in blacks, may play a leading role in protecting blacks from CHD, since there is a strong inverse association of HDLC and CHD. Hence, it may be of practical importance to discern whether there is a difference between black and white families in the degree of within-family association of lipids and lipoproteins that can be ascribed to genetic or to environmental factors. In the Princeton School District Lipid Research Clinic’s (LRC) Family Study, for parents and their pediatric offspring sharing a common environment,
and in parents and adult offspring, black father-child and mother-child correlations for HDLC were about twice as high as those for white parent-offspring pairs. Moreover, in pediatric sibling pairs, sib-sib correlations for HDLC were 0.542 for 21 black sibships containing 55 subjects and 0.359 for 73 white sibships containing 210 subjects. These observations suggest that the within-family aggregation of HDLC in blacks may be stronger than in whites, for unknown reasons.

Within the Princeton School District Study, we have also documented differing "environmental" within-family associations for blacks as compared to whites, relative to nutrient intake. When we examined the proportion of variation of children's nutrient intake accounted for by parental nutrient intake, we found that a large amount of variation explained in blacks was higher than that in whites for carbohydrate, saturated fat, and calories, variables which may well affect HDLC levels.

Our specific aim in this study was to assess the family resemblance for lipids and lipoproteins in blacks randomly selected from the Princeton School District's Family Study cohort, and to compare the family resemblance of lipids and lipoproteins between the blacks and whites from the same cohort.

**Methods**

The Cincinnati Lipid Research Clinic (LRC) Princeton School District Family Study (1976–1978) was part of the National Heart, Lung, and Blood Institute's multicenter collaborative program designed to assess the familial aggregation of lipid and lipoprotein levels. Briefly, the Princeton School District Population Study was a two-stage epidemiological survey of lipids, lipoproteins, and other coronary heart disease risk factors in a biracial population of school children in grades 1–12 and their parents. Following the first two visits of the Prevalence Study, a subgroup of probands was selected from this larger prevalence population for the family study. All first-degree relatives and spouses of selected probands were contacted; sociodemographic data, fasting plasma lipids and lipoproteins, and clinical chemistry measurements were obtained. Probands for the family study included both randomly selected subjects and hyperlipidemic subjects. This article deals with 160 white and 59 black nuclear probands were contacted; sociodemographic data, fasting plasma lipids and lipoproteins, and clinical chemistry measurements were obtained. Probands for the family study included both randomly selected subjects and hyperlipidemic subjects. This article deals with 160 white and 59 black nuclear bands studied included spouses, children, parents, and sibs. A few three-generation families were split into the component nuclear families, avoiding duplications wherever possible. Relatives of the probands studied included spouses, children, parents, and sibs. A very few adopted relatives and a small number of half-sibs were also studied, but due to the small sample sizes, the data on adopted relatives and half-sibs are not analyzed here. More details of the population studied can be found in the work of Morrison et al.

### Statistical Methods

**Data Transformations**

For whites and blacks separately, each lipid and lipoprotein was adjusted for the effects of age, sex, and the use of oral contraceptives, if the effect was significant, using multiple regression methods. Age and sex effects were expressed in terms of a cubic polynomial (Table 1). The adjusted lipid or lipoprotein was standardized and normalized.

**Familial Correlations**

Four familial correlations were considered: spouse-spouse, mother-child, father-child, and sib-sib. The familial correlations were estimated by the method of maximum likelihood, which also provides estimates of sample sizes. This method has been implemented in PATHMIX, a computer program written in FORTRAN for Harris computers.

### Method of Analysis

The statistical method of analysis utilized the distributional properties of Fisher's z transformation. The observed phenotypic correlation, above, was first converted into its z transform:

$$z_r = \frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right)$$

which asymptotically follows a normal distribution with mean:

$$z_r = \frac{1}{2} \ln \left( \frac{1 + \rho}{1 - \rho} \right)$$

and approximate variance 1/n, where ρ is the corresponding expected correlation. Under a purely additive polygenic model, with h² denoting the polygenic fraction of variance explained:

<table>
<thead>
<tr>
<th>Variable</th>
<th>CH</th>
<th>TG</th>
<th>HDLC</th>
<th>LDL</th>
<th>VLDLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-1.83</td>
<td>0.74</td>
<td>--</td>
<td>-8.52</td>
<td>0.67</td>
</tr>
<tr>
<td>Age²</td>
<td>4.49</td>
<td>--</td>
<td>-5.54</td>
<td>19.74</td>
<td>--</td>
</tr>
<tr>
<td>Age³</td>
<td>-2.28</td>
<td>--</td>
<td>5.37</td>
<td>-11.47</td>
<td>--</td>
</tr>
<tr>
<td>Sex</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.04</td>
<td>--</td>
</tr>
<tr>
<td>Age × sex</td>
<td>--</td>
<td>--</td>
<td>-2.83</td>
<td>8.04</td>
<td>-0.28</td>
</tr>
<tr>
<td>Age² × sex</td>
<td>--</td>
<td>-0.25</td>
<td>10.22</td>
<td>-15.94</td>
<td>--</td>
</tr>
<tr>
<td>Age³ × sex</td>
<td>--</td>
<td>--</td>
<td>-7.44</td>
<td>9.09</td>
<td>--</td>
</tr>
<tr>
<td>Contraceptive use</td>
<td>--</td>
<td>0.23</td>
<td>--</td>
<td>--</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Squared multiple correlation (R²)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.24</td>
<td>0.33</td>
</tr>
<tr>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

CH = plasma cholesterol; TG = triglyceride; HDLC = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; VLDLC = very low density lipoprotein cholesterol.
heritability, all the expected correlations are given by $h^2/2$ except for the marital correlation which is zero. Therefore, assuming all four observed correlations to be independent, which is an approximation, we take the overall log likelihood (approximately) as

$$\ln L = -\chi^2/2 + \text{constant},$$

where

$$\chi^2 = \sum_{i=1}^{4} n_i \left( z_i - \bar{z} \right)^2.$$  \hspace{1cm} (3)

The residual $\chi^2$ after estimating the parameter ($h$) follows a $\chi^2$ distribution with 3 degrees of freedom. Therefore, by minimizing $\chi^2$ we can estimate $h^2$ and use the residual $\chi^2$ for testing the goodness of fit. The standard error of $h^2$ is routinely calculated by PATHMIX by numerically differentiating $\ln L$ or $\chi^2$.

To test for heterogeneity between races, the following test statistic is used:

$$\chi^2 = \sum_{i=1}^{2} \frac{2}{2} n \left( \bar{z}_i \right)^2,$$  \hspace{1cm} (4)

where

$$\bar{z} = \sum_{i=1}^{2} \frac{2}{n_i} \bar{z}_i.$$  \hspace{1cm} (5)

### Results

Table 1 displays the standardized partial regression coefficients for the variables included in the regressions separately for each lipid and lipoprotein for blacks. Gender or some function of gender had substantial effects on all lipid and lipoprotein levels with the exception of cholesterol. Age or a function of age significantly altered all lipid and lipoprotein values, while contraceptive use significantly altered only triglyceride and VLDLC values. Age, gender, their interactions, and contraceptive use explained 24% of the variation of plasma cholesterol, 33% of triglyceride, 16% of HDLC, 18% of LDLC, and 29% of VLDLC in blacks.

The maximum likelihood estimates of the four phenotypic correlations and their sample sizes for each lipid and lipoprotein by race are shown in Table 2. In blacks, the marital correlation is of a larger magnitude than in whites, and is often negative. Only for HDLC is the marital correlation positive in blacks, while in whites the marital correlation for HDLC, LDLC, and VLDLC is positive. The father-child and sib-sib correlations are larger in whites than in blacks for each lipid and lipoprotein, with the exception of HDLC, where the correlations in blacks are higher than in whites. Mother-child correlations in blacks are higher than mother-child correlations in whites for all lipids and lipoproteins with the exception of HDLC, where the relationship is reversed.

Table 3 displays the chi-square values which test the heterogeneity of correlations between races for each lipid and lipoprotein. Significant heterogeneity occurs only for the father-child correlations for cholesterol and LDLC. Heterogeneity of the familial correlations in sum is achieved only for total cholesterol; however, such a test is only approximate since the different $\chi^2$ values are not all independent of one another. Only two of the 20 correlations are significantly heterogenous, perhaps due to reduced power because of small sample sizes.

Statistics on the goodness of fit for the simple polygenic model with only one parameter, genetic heritability ($h^2$), are given in Table 4 for each variable by race. Also, the estimates of the phenotypic correlations for each race were also pooled for each variable and the simple polygenic model was fit. The goodness-of-fit statistics for the simple polygenic model and the estimates of heritability obtained from this model using the pooled phenotypic correlations are also given in Table 4. For blacks, whites, and the pooled correlations, the simple polygenic model fits well except for cholesterol in blacks. Estimates of $h^2$ are larger in whites than in blacks for all lipids and

### Table 2. Maximum-Likelihood Estimates of Familial Correlations (r) and Their Sample Sizes (n) for Lipids and Lipoproteins for Blacks and Whites

<table>
<thead>
<tr>
<th>Relationship</th>
<th>CH</th>
<th></th>
<th>TG</th>
<th></th>
<th>HDLC</th>
<th></th>
<th>LDLC</th>
<th></th>
<th>VLDLC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>n</td>
<td>r</td>
<td>n</td>
<td>r</td>
<td>n</td>
<td>r</td>
<td>n</td>
<td>r</td>
<td>n</td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse-spouse</td>
<td>-0.19</td>
<td>27</td>
<td>-0.04</td>
<td>18</td>
<td>0.34</td>
<td>21</td>
<td>-0.11</td>
<td>27</td>
<td>-0.23</td>
<td>17</td>
</tr>
<tr>
<td>Father-child</td>
<td>-0.13</td>
<td>42</td>
<td>0.11</td>
<td>40</td>
<td>0.40</td>
<td>22</td>
<td>0.05</td>
<td>45</td>
<td>0.10</td>
<td>29</td>
</tr>
<tr>
<td>Mother-child</td>
<td>0.38</td>
<td>85</td>
<td>0.07</td>
<td>58</td>
<td>0.28</td>
<td>34</td>
<td>0.44</td>
<td>80</td>
<td>0.12</td>
<td>74</td>
</tr>
<tr>
<td>Sib-sib</td>
<td>0.15</td>
<td>96</td>
<td>0.12</td>
<td>102</td>
<td>0.47</td>
<td>56</td>
<td>0.21</td>
<td>76</td>
<td>0.12</td>
<td>85</td>
</tr>
<tr>
<td>Whites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse-spouse</td>
<td>-0.02</td>
<td>88</td>
<td>-0.03</td>
<td>98</td>
<td>0.04</td>
<td>89</td>
<td>0.00</td>
<td>94</td>
<td>0.08</td>
<td>88</td>
</tr>
<tr>
<td>Father-child</td>
<td>0.36</td>
<td>146</td>
<td>0.20</td>
<td>137</td>
<td>0.20</td>
<td>136</td>
<td>0.38</td>
<td>136</td>
<td>0.28</td>
<td>117</td>
</tr>
<tr>
<td>Mother-child</td>
<td>0.25</td>
<td>135</td>
<td>0.05</td>
<td>175</td>
<td>0.32</td>
<td>201</td>
<td>0.27</td>
<td>151</td>
<td>0.11</td>
<td>170</td>
</tr>
<tr>
<td>Sib-sib</td>
<td>0.38</td>
<td>176</td>
<td>0.20</td>
<td>170</td>
<td>0.34</td>
<td>163</td>
<td>0.39</td>
<td>171</td>
<td>0.27</td>
<td>194</td>
</tr>
</tbody>
</table>

CH = plasma cholesterol; TG = triglyceride; HDLC = high density lipoprotein cholesterol; LDLC = low density lipoprotein cholesterol; VLDLC = very low density lipoprotein cholesterol.
Table 3. Chi-Squared (χ²) Values to Test for Heterogeneity Between Races for Each Familial Correlation for Each Lipid and Lipoprotein

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spouse-spouse</th>
<th>Father-child</th>
<th>Mother-child</th>
<th>Sib-sib</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH</td>
<td>0.60</td>
<td>9.05‡</td>
<td>1.10</td>
<td>3.83*</td>
<td>14.58‡</td>
</tr>
<tr>
<td>TG</td>
<td>0.00</td>
<td>0.28</td>
<td>0.02</td>
<td>0.40</td>
<td>0.70</td>
</tr>
<tr>
<td>HDLC</td>
<td>1.64</td>
<td>0.83</td>
<td>0.05</td>
<td>0.97</td>
<td>3.49</td>
</tr>
<tr>
<td>LDLC</td>
<td>0.24</td>
<td>4.56†</td>
<td>1.89</td>
<td>2.22</td>
<td>8.91*</td>
</tr>
<tr>
<td>VLDLC</td>
<td>1.35</td>
<td>0.78</td>
<td>0.00</td>
<td>1.35</td>
<td>3.48</td>
</tr>
</tbody>
</table>

The χ² for each correlation for each variable has 1 df. Total χ² has 4 df (the four correlations for each variable within each race are assumed to be independent, again only a rough approximation). See Table 1 for abbreviations.

- ‡p < 0.10.
- †p < 0.05.
- ‡‡p < 0.01.

Table 4. Goodness of Fit χ² (3 df Each) Values and Estimates of Heritability (h²)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black k=1</th>
<th>1±SE</th>
<th>White k=1</th>
<th>1±SE</th>
<th>Pooled k=1</th>
<th>1±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH</td>
<td>9.15*</td>
<td>0.385±0.128</td>
<td>1.82</td>
<td>0.673±0.083</td>
<td>0.67</td>
<td>0.581±0.070</td>
</tr>
<tr>
<td>TG</td>
<td>0.14</td>
<td>0.209±0.140</td>
<td>2.83</td>
<td>0.292±0.089</td>
<td>2.52</td>
<td>0.269±0.075</td>
</tr>
<tr>
<td>HDLC</td>
<td>3.73</td>
<td>0.802±0.158</td>
<td>2.02</td>
<td>0.585±0.081</td>
<td>3.36</td>
<td>0.628±0.073</td>
</tr>
<tr>
<td>LDLC</td>
<td>6.01</td>
<td>0.540±0.130</td>
<td>1.73</td>
<td>0.695±0.082</td>
<td>0.21</td>
<td>0.649±0.069</td>
</tr>
<tr>
<td>VLDLC</td>
<td>0.92</td>
<td>0.238±0.143</td>
<td>3.46</td>
<td>0.431±0.087</td>
<td>2.28</td>
<td>0.377±0.074</td>
</tr>
</tbody>
</table>

- *p < 0.05.
- †This column merely presents "goodness of fit" of the polygenic model to the pooled correlations. It does not test for heterogeneity between races; such a test is reported in Table 3 on the correlations. See Table 1 for abbreviations.

Discussion

We are aware that family environment plays an important role for plasma lipids and lipoproteins, but to a much lesser extent than genetic factors, as judged from our experience with whites. We used a purely additive polygenic model here to investigate the race differences in a parsimonious way, since genetic and familial environmental effects are not resolvable in this type of data. In assessing family resemblance for randomly selected black and white kindreds from the Princeton School District's LRC Family Study Cohort, the most fundamental and consistent black-white difference was for the familial resemblance of HDLC. Father-child and sib-sib correlations were greater in whites than in blacks for each lipid and lipoprotein, except for HDLC, where the correlations in blacks were higher than in whites but not significantly different. Fitting the simple polygenic model comprised of genetic heritability (h²) yielded larger estimates of h² in whites than in blacks for all lipids and lipoproteins with the sole exception of HDLC, where the estimate of h² in blacks was 0.802 and in whites, 0.588.

Black girls, boys, and men have higher HDLC than do whites, which potentially "protects" them against augmented CHD, given the excess of certain CHD risk factors, particularly hypertension, among blacks. Conversely, adult black women do not have consistently significantly higher HDLC levels than adult white women. The loss of this protective HDLC difference in adult black women is likely due to their pandemic obesity.

Inasmuch as blacks smoke more, are more likely to have diabetes, and are more often treated with antihypertensives, these factors would tend to reduce black-white differences in HDLC. Moreover, black-white differences in alcohol intake and habitual and leisure time physical activity would, in aggregate, be unlikely to affect black-white differences in HDLC. Since (speculatively) blacks and whites share similar environmental determinants of HDLC, there may be a major genetic factor partly

lipoproteins except HDLC. In blacks, the genetic heritability ranges from 0.209 ± 0.140 for triglyceride, to 0.802 ± 0.158 for HDLC. In whites, the genetic heritability ranges from 0.292 ± 0.089 for triglyceride, to 0.695 ± 0.082 for LDLC.
accounting for higher HDLC levels in blacks.\textsuperscript{30, 35} This is highlighted in our current study by the consistent in-family resemblance for HDLC alone, of all lipids and lipoproteins. However, the tentative nature of this speculation prohibits any definitive conclusion.

References

5. Gillum RF. Pathophysiology of hypertension in blacks and whites. Hypertension 1979;1:468–475

Index Terms: genetic heritability • lipoproteins • blacks
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