Family Aggregation of High Density Lipoprotein Cholesterol

Collaborative Lipid Research Clinics Program Family Study

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High density lipoprotein cholesterol data on a population-based random sample of 858 white and 72 black probands and their 3935 white and 205 black relatives were collected from nine North American clinics using a common protocol and standardized methodology. Familial associations were examined within clinics for whites and pooled across clinics for blacks. The influence of covariates and varying family size on correlations was examined using several sets of transformed and adjusted values and a variety of weighting schemes.

Parent-offspring and sibling correlations were significant in most cases, but spouse correlations were not, suggesting a stronger influence of shared genes than shared environment on high density lipoprotein cholesterol. Adjustment for covariates tended to weaken the correlations, but the effect of variable family size was imperceptible. Although pairs involving pediatric offspring or siblings tended to show higher correlation than their adult counterparts, the differences were not significant. All correlations except father-daughter and brother-brother were homogeneous across clinics in whites. There was no asymmetry in parent-child correlations by the sex of the offspring, but the pooled mother-child correlation was significantly higher than father-child values, suggesting a possible maternal influence on high density lipoprotein cholesterol. No heterogeneity in correlations in high density lipoprotein cholesterol was detected between blacks and whites except for mother-son pairs.

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Habits such as consumption of sucrose, starch, and alcohol. Racial differences also have been documented, with blacks — especially black males — manifesting higher levels than whites.12

Strong similarities in HDL-C levels in family members have been reported,13,14 suggesting that family studies may contribute information concerning the degree to which HDL-C levels are under genetic control. Comparisons of sibling correlations from adult and pediatric sibship and of parent-offspring correlation where the offspring are adults vs children can assist in separating genetic and environmental influences insofar as adult siblings and offspring no longer share a common household environment. Recently a number of investigators have addressed some of these issues,15-16 but these HDL-C studies14,15 have been conducted predominantly in white populations. There are few biracial familial studies.

The present report describes the association of HDL-C among first-degree relatives and spouses in families of randomly selected white and black probands who participated in the Collaborative Family Study phase of the LRC Population Studies, conducted in nine North American clinics during the period, 1976–1978. We estimated familial correlations of HDL-C using several different covariate adjustments, weighting schemes, and trimming procedures to assess the influence of concomitant variables and varying family size. Parent-offspring and sibling correlations were estimated conditional on the sex of the pair and tested for any sex-influenced asymmetry in aggregation. Correlations were computed by clinic and comparisons made across clinics and racial groups.

The present analysis of assessing familial aggregation should be viewed as an important and necessary prelude toward more complex genetic-epidemiologic analyses, namely, segregation and path analysis. Such analyses are aimed both at testing specific hypotheses like single major factor inheritance, and (using an analysis of variance or path analysis framework) at partitioning the population variance into genetic, cultural, and environmental components. These methods frequently require specific modeling assumptions, such as sex-symmetric transmission, which should be examined before formulating and testing specific hypotheses about the mode of inheritance. The present report seeks to describe the basic pattern of familial aggregation and its fluctuations with the effects of factors such as age, sex, socioeconomic status (SES), seasonality, body mass, and variable family size. The findings are compared with those of other studies.

Methods

The LRC Population Studies, which began in 1971, were epidemiological surveys conducted by 10 North American clinics from diverse base popu-

*Nine clinics participated in the Family Study.

lations to ensure wide ethnic, geographic, and socioeconomic variation.

Protocol

At the initial survey (Visit 1 or V1), plasma cholesterol and triglycerides were measured and basic demographic and medication information was obtained. A 15% random sample of V1 participants, all "hyperlipidemics" as defined by age-sex specific cut-off points, and participants on lipid-lowering medication were recalled for a second visit (V2). Information collected at this visit included data on lipids and lipoproteins, blood pressure, anthropometric measures, electrocardiographic tests, medication, and cardiovascular history. The selection of probands for the third phase — the Family Study (FS) — from those who participated in V1 and V2 was designed to ensure adequate representation of rare lipoprotein phenotypes as well as a 2% random sample of the original V1 population, and a hyperlipidemic component. A total of 2405 probands was selected. Relatives designated as eligible for participation were spouses and biologically or socially defined first-degree relatives (parents, step-parents, full or half-siblings, and offspring (biological, adopted, or step)). The overall response rates for the Family Study were high: 89% for probands and 75% for the relatives. In this report, only probands selected as the 2% random sample and their spouses and biological relatives are considered.

At the Family Study, blood was drawn after a fast of 12 hours or more to determine total cholesterol, triglycerides, and HDL-C. Demographic, socioeconomic, and cardiovascular history data were also collected. Use of the same protocol and standardized laboratory procedures17 at the nine clinics enhanced the reliability and comparability of lipid and lipoprotein determinations. A detailed description of the LRC population studies and the selection algorithm and data base for the Family Study are described more fully elsewhere.18-20 The distribution of probands and relatives by race and for whites by clinic in the randomly selected Family Study participants is given in Table 1.

Statistical Methods

Data Transformation and Covariate Adjustments

It is customary to adjust HDL-C for the effects of age, sex, gonadal hormone use, and other concomitant variables and to transform the data to achieve normality before performing statistical analyses of trends of familial aggregation. The HDL-C levels were logarithmically transformed to remove significant skewness, and several adjustment procedures were used on the transformed data, a detailed description of which is given elsewhere.21 To assess the impact of socioeconomic status, body mass, and similar factors on familial aggregation, we used several sets of adjusted values in the current analyses.
Table 1. Distribution of the Collaborative Family Study Random Sample Probands and Relatives by Race, and by Clinic In Whites

<table>
<thead>
<tr>
<th>Race</th>
<th>Clinic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>643</td>
<td></td>
</tr>
<tr>
<td>Relatives</td>
<td>4793</td>
<td></td>
</tr>
<tr>
<td>Whites (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>858</td>
<td></td>
</tr>
<tr>
<td>Relatives</td>
<td>3935</td>
<td></td>
</tr>
<tr>
<td>Blacks (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Relatives</td>
<td>205</td>
<td></td>
</tr>
</tbody>
</table>

These are:

1) Transformed HDL-C values were adjusted by regressing within each sex, gonadal hormone group on the following independent variables: clinic, age, age², age³, b, b², b³, c, c², and c³, where b = age if age < 15, 15 otherwise, and c = age if age > 45, 45 otherwise. The values were standardized within each sex, hormone group to mean zero and variance one. The portion of the total variance explained by this adjustment ranged from 5%-12% in the sex, hormone use groups. In order to minimize the effect of outliers, individuals with adjusted values which were outside ± 3.5 standard deviation units were eliminated from all correlation analyses. The residual value obtained from this piecewise cubic regression model will be referred to as R1.

2) The second adjustment procedure was intended to remove from the trait the effects of the additional environmental factors: socioeconomic status (SES, as measured by the education level of the head of the household) and seasonal effect (measured by the month during which blood was drawn). These were included in the regression model as independent variables along with those used for R1. Standardization and trimming were done as for R1. This model accounted for 6%-17% of the total variation of HDL-C among the sexes. This second residual value will be referred to as R2.

3) The third adjustment procedure was similar to that for R2, but with the anthropometric measures log (height) and log (weight) included as independent variables along with those for R2. This regression model explained 14%-20% of the total variation in HDL-C among the sexes. The standardization and trimming procedures were performed as before. This residual will be referred to as R3.

In addition to the above three adjustments, the data were examined for the effects of birth order and family size. These were found to have no significant effect on HDL-C values.

Familial Correlation Methods

Correlation analysis is a commonly used statistical technique for measuring and testing familial resemblance. In recent years, several investigators have examined the theoretical and empirical problems involved in estimating familial correlations under the complications of varying sibship size and nonindependence of pairs of relatives. A critical review of the existing methodology including maximum likelihood estimation of correlations and some alternate simpler approaches to the problem are given by Karlin et al.

Familial correlations are of two kinds: interclass correlations between parents and offspring, between spouses, or between opposite sex siblings; and intraclass correlations between same-sex siblings.

Interclass Correlations. Several methods exist for estimation of interclass correlations from familial data. The simplest and most widely used approach for parent-offspring correlations is to pair each child's value with the parent's value and compute the Pearson product moment correlations over all such pairs, often referred to as "pairwise estimator." However, the pairs within families are clearly not independent, because the parent's value is repeated for all children and also because of potential nonzero correlation for the trait among the children within a sibship. Moreover, this procedure gives undue emphasis to large sibships. To avoid these problems, other procedures including maximum likelihood estimators have been suggested, but there are disadvantages to these methods as well.

Simulation studies to investigate the relative performance of these estimators have shown that when the true correlation is small to moderate, the pairwise method is the preferred estimator. To assess the influence of variable sibship size on correlations, Karlin et al. proposed the use of weighted Pearson estimators, with several schemes for weighting the relative pairs. With weights \( w_i = 1 \) (equal weight to
pairs), an estimator WP equal to the pairwise estimator is obtained, while with $w_i = 1/k_i$, $k_i$ being the number of pairs in the $i^{th}$ family, an estimator WF giving equal weight to families is obtained. The latter reduces the effect of large families on the total correlation. Estimators for brother-sister and spouse pair correlations are defined similarly.

Following the methodology outlined above, in the present analyses we computed sex-specific parent-offspring, brother-sister, and spouse correlations using both weighting schemes for each of the adjusted values $R_1$, $R_2$, and $R_3$. Assuming the trait distribution is multivariate normal in families, Fisher's $Z$-transformation,\textsuperscript{26} given by

$$Z = Z(r) = 1/2 \log_e(1 + r)/(1 - r)$$  \hspace{1cm} (1)

where $r$ is the sample correlation coefficient, was used for hypothesis testing and confidence interval estimation. $Z$ is approximately normally distributed with mean $Z(p)$, where $p$ is the population correlation. When $r$ is derived from $N$ independent pairs of observations, the variance $Z$ is given by $(1/(N-3))$ (independent of $p$). With familial correlations, the observations are usually not independent, and the variance is therefore larger, corresponding to an $N$ somewhere between the number of pairs and the number of families. For parent-offspring correlations, we have estimated the appropriate degrees of freedom for each family as the "effective sibship size" $N_e$, which is computed as a function of both the sibship size $s$ and the estimated sibling correlation $r$ ($N_e = s/(1 + (s-1)r)$).\textsuperscript{23} For brother-sister correlations, the degrees of freedom per family is estimated as the product of the effective brothership size by the effective sibship size. In each case, this is summed across families to get the total degrees of freedom, $N$. It should be noted that use of the number of pairs for $N$ in the formula $(1/(N-3))$ for the variance of the $Z$-transformed correlation, results in underestimating the true probability of a Type I error (i.e., favors obtaining a significant result in the heterogeneity tests described below), whereas use of number of families for $N$ overstates the probability of Type I errors and biases against obtaining a significant result. Use of effective sibship size tends to bring a balance between these extremes in significance testing.

**Intraclass Correlations.** The most commonly used estimator for intraclass correlations is that derived from the analysis of variance (ANOVA). To assess the effects of varying sibship size, Karlin et al.\textsuperscript{15} have proposed three weighted Pearson correlations: the equal pair weight and equal family weight estimators WP and WF, defined as above; and an equal individual weight estimator WI, in which each pair is given a weight equal to the reciprocal of the number of pairs in which an individual appears. Of these estimators, WP emphasizes the contributions of large families the most, WF emphasizes large families the least, and WI lies in between WP and WF in its emphasis on large families. Recent simulation experiments (P. Green, unpublished observations) suggest that WI is preferred when the true correlation is between 0.1 and 0.5, the range found in our sample.

To examine the effect of family size on estimates of correlations, the present analyses used all three weighting schemes to compute brother-brother and sister-sister correlations. As with interclass correlations, hypothesis testing of pooled correlations was performed using $Z$-transformed values. For intraclass correlations $r$ computed from $N_e$ independent sibships of fixed size $s$, Fisher's $Z$ is defined by

$$Z = Z(r) = 1/2 \log_e((1 + (s-1)r)/(1 - r))$$  \hspace{1cm} (2)

where $Z$ has mean $Z(p)$ and variance $s/2(s - 1)(N_e - 2)$. In our sample sibship, the sizes vary, and we have approximated the $Z$-transform and variance estimate by using for $s$ the mean sibship size. The "effective degrees of freedom" $N$ is then $2(s - 1)(N_e - 2)/s$.

**Heterogeneity Tests**

Heterogeneity across clinic, race, sex, and age groups was tested by computing $Z$-transformed correlations for each group and applying the following procedure:

- Under the hypothesis that $p$ normal variates ($Z_i, i = 1, 2, \ldots, p$) all have the same distribution mean, the test statistic
  $$\sum_{i=1}^{p} w_i (Z_i - \bar{Z})^2$$  \hspace{1cm} (2)

  where $\bar{Z} = \sum_{i=1}^{p} w_i Z_i/\sum w_i$, and $w_i, i = 1, 2, \ldots, p$ are the reciprocals of the respective variances of the $Z$'s, is distributed as $\chi^2_{p-1}$. If the statistic is nonsignificant, a pooled estimate $(\bar{r})$ of $p$ is computed from $\bar{Z}$.

**Results**

The distribution of probands and relatives by race and, for whites, by clinic is given in Table 1. For the black sample, small numbers within individual clinics necessitated pooling over all clinics. The detailed familial correlation estimates for different covariate adjustments ($R_1$, $R_2$, and $R_3$) and weighting schemes (WP, WI, and WF) for each of the nine clinics are deposited with NAPS. Here only the salient features of these data manipulations on familial correlations are reported.

**Effects of Covariate Adjustments and Weighting Schemes on Familial Correlations**

In general, covariate adjustments $R_2$ and $R_3$ gave progressively weaker familial correlations than with $R_1$. However, the significance level of correlations was not altered and therefore for all subsequent analyses we used $R_2$, the residual values of HDL-C adjusted for age, sex, hormone use, SES, clinic, and seasonal effects. The different weighting schemes
did not show any consistent trends in correlations. Hence, the widely used weighting method WP was used for hypothesis testing with effective degrees of freedom computed as described earlier for interclass and WI for intraclass correlations.

Age Trends in Familial Correlations

To examine whether familial resemblance differs among age categories of relatives, we classified parent-offspring pairs by age of the offspring as adult (age > 18) or pediatric (age ≤ 18). Sibling pairs were similarly classified as adult (both sibs aged > 18) or pediatric (both sibs aged ≤ 18). Pairs of siblings, where the members belonged to different age strata, were omitted from these analyses. As some clinics had only a few relatives in the pediatric age range, a sample size requirement was imposed; only those clinics with at least 20 pairs of each relation type for interclass correlations and at least 10 families and 20 same-sex siblings for intraclass correlations were included in these analyses. The black sample size was too small to permit such age stratification and hence these analyses were carried out only in whites. Within the pediatric and adult groups, tests for clinic heterogeneity were performed and pooled correlations for all clinics for each age group were computed. The results are given in Table 2. The heterogeneity of correlations among clinics was negligible; only one adult father-daughter correlation, out of 14 tests, was significant at the 5% level, a finding which may well be attributable to chance alone. The pooled correlations for the pediatric and adult groups show a generally consistent trend of higher correlation for the pediatric group, especially among the sibling types. Tests of heterogeneity of those pooled correlations among the two age groups, however, were not significant.

Familial Correlations among Clinics and Tests of Heterogeneity in Whites

The clinic-specific familial correlations for whites are graphically summarized in Figure 1. The spread of the clinic specific values in comparison to the pooled correlation and its 95% confidence interval is also illustrated for each relation type. A summary of the significant familial correlations for HDL-C by clinic for whites and pooled over clinics for blacks is given in Table 3. The spouse correlations were invariably nonsignificant, suggesting that sharing of marital environment did not contribute to any familial aggregation for HDL-C. The parent-offspring correlations in whites were significant in the vast majority of clinics with the mother-offspring resemblance somewhat more pronounced than that of father-offspring. Among the blacks, most parent-child correlations were nonsignificant. The sibling correlations were mostly significant in both blacks and whites. The magnitude of the correlation was not very different between parent-offspring and sibling pairs.

### Table 2. Temporal Trends in Familial Correlations for HDL-C and Tests of Heterogeneity Among Clinics Within Age Groups and Between Age Groups in Whites

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age group</th>
<th>N</th>
<th>Pooled correlation</th>
<th>Test between clinics within age group</th>
<th>Test between age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>χ²</td>
<td>df</td>
</tr>
<tr>
<td>Father-son</td>
<td>1</td>
<td>201</td>
<td>0.300</td>
<td>3.29</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>440</td>
<td>0.159</td>
<td>6.02</td>
<td>8</td>
</tr>
<tr>
<td>Father-daughter</td>
<td>1</td>
<td>163</td>
<td>0.149</td>
<td>3.35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>393</td>
<td>0.165</td>
<td>15.32*</td>
<td>7</td>
</tr>
<tr>
<td>Mother-son</td>
<td>1</td>
<td>252</td>
<td>0.297</td>
<td>2.94</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>570</td>
<td>0.296</td>
<td>7.63</td>
<td>8</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>1</td>
<td>213</td>
<td>0.281</td>
<td>2.86</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>598</td>
<td>0.244</td>
<td>9.72</td>
<td>8</td>
</tr>
<tr>
<td>Brother-sister</td>
<td>1</td>
<td>126</td>
<td>0.325</td>
<td>0.09</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>940</td>
<td>0.227</td>
<td>9.90</td>
<td>8</td>
</tr>
<tr>
<td>Brother-brother</td>
<td>1</td>
<td>89</td>
<td>0.398</td>
<td>3.08</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>407</td>
<td>0.260</td>
<td>14.23</td>
<td>8</td>
</tr>
<tr>
<td>Sister-sister</td>
<td>1</td>
<td>68</td>
<td>0.432</td>
<td>3.05</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>418</td>
<td>0.224</td>
<td>6.84</td>
<td>8</td>
</tr>
</tbody>
</table>

**Age group:** 1 indicates the Pediatric Group: for parent-offspring pairs, offspring age ≤ 18 years; for sib pairs, both sibs ≤ 18 years; 2 indicates Adult Group: offspring or both siblings > 18 years.

Since some clinics had only a few relatives in the younger age groups, only those where there were at least 10 families and 20 individuals for sibs and at least 20 parent-offspring pairs of each type were included in these analyses.

*p ≤ 0.05.
Figure 1. Clinic-specific familial correlations for HDL-C in whites using R2 adjustment and WP and Wl as weighting schemes for inter- and intra-class correlations, respectively. Correlation estimate pooled over clinics (horizontal line) and 95% confidence intervals (stippled area) are also overlaid on the figure. Relative pairs are: F-S = Father-Son; F-D = Father-Daughter; M-S = Mother-Son; M-D = Mother-Daughter; Sp-Sp = Spouses, B-SI = Brother-Sister; B-B = Brother-Brother; and SI-SI = Sister-Sister. For clinic mnemonic, see Table 1.

Table 3. Summary of Significant Familial Correlations by Clinics and Relationship

<table>
<thead>
<tr>
<th>Race</th>
<th>Clinic</th>
<th>Spouse</th>
<th>Father</th>
<th>Mother</th>
<th>Brother</th>
<th>Sister</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Son</td>
<td>Daughter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Son</td>
<td>Daughter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sister</td>
<td>Brother</td>
<td>Sister</td>
</tr>
</tbody>
</table>

Whites
- CN
- IA
- JH
- OK
- LJ
- MN
- SE
- ST
- TR

Blacks
- CN
- IA
- JH
- OK
- LJ
- MN
- SE
- ST
- TR

*p ≤ 0.05.
Analysis is based on R2 with weights WP or Wl for inter- and intraclass correlations, respectively.
Because clinic differences in correlations among whites are of interest, heterogeneity tests among clinics were performed for each relation type and the results are given in Table 4. Of the eight sets of relative pairs tested, two were significant at the 5% level: father-daughter and brother-brother. The clinic-specific correlations for the former type ranged from 0.005 to 0.446 and for the latter from 0.011 to 0.427 (see Figure 1). Since none of the tests was significant at the 1% level, pooled estimates of the familial correlations were computed along with 95% confidence intervals and these are also given in Table 4. The pooled estimates of correlations are used for testing heterogeneity of correlations among the sexes and also among the two racial groups.

Among whites, tests for sex differences for parent-child correlations were not significant between father-son and mother-daughter types. So pooled father-child and mother-child correlations were computed and tested for differences in correlation between these two parental classes. The father-child correlation was very low: -0.054 compared to 0.288 and interclass correlations for both races. The heterogeneity x² test was significant for only the mother-child over father-child correlation. Because this assumption is violated, the tests are biased downward, favoring false significant results. So, while there is no problem interpreting the nonsignificant results, as they will be even more nonsignificant when the bias is corrected, the significant result of higher mother-child over father-child correlation has to be viewed with caution as the two groups are not independent.

Heterogeneity in Correlations among Blacks and Whites

The pooled clinic correlations for HDL-C for blacks and whites were compared and the results are given in Table 5. As stated earlier, the sample size for blacks is much smaller than that of the whites. Table 5 gives the effective degrees of freedom and intra- and interclass correlations for both races. The heterogeneity x² test was significant for only the mother-son type ($\chi^2_{(1)} = 5.8, p < 0.02$). For blacks, this correlation was very low: -0.054 compared to 0.288 in whites.

Discussion

Because of the inverse association of HDL-C with CHD, evidence of familial aggregation of HDL-C levels is of great interest to clinicians and public health practitioners. The present study examines the aggregation of HDL-C among spouses and first-degree relatives in a biracial sample from nine Lipid Research Clinics. Although the clinic populations were diverse, the samples were population-based and the determination of HDL-C was done in all clinics under rigorously standardized laboratory conditions. This study design allows both examination of the familial aggregation pattern within each clinic and comparison of patterns across clinics and races to gain a broader perspective.
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Some features of the LRC populations are worth noting here. The V1 population, although well defined, was not a random sample of the general United States population. So information derived from subsequent samples like V2 and FS can be used only to make inferences about the V1 population. Two factors could make such inferences difficult for the FS. First, the FS relatives did not form part of the V1 population; only the probands did. This raises the possibility of nonrepresentativeness of the FS relatives to the V1 population. Second, differential response rates to subsequent visits within and among sample sites could also distort the representative nature of samples. Both these issues were examined and found to have little impact on the representativeness of the FS sample, the details of which are given elsewhere.20 The distribution of HDL-C in FS subjects was found to be very similar to the V2 random sample. The overall response rates were very high and although the rates ranged from 82%–97% for probands and 70%–89% for relatives among the clinics, the lipoprotein profile at V2 of the participants and nonparticipants at FS showed virtually no difference, assuring no distortion due to nonresponse.

As a simple descriptive procedure, adjusted values R1, R2, and R3 were used to examine any consistent effects of SES, seasonality, and body mass on familial aggregation without imposing complicated causal schemes and modelling assumptions of path analysis. For example, if the correlations decrease with progressive covariate adjustments, it can be argued that the covariates tended to inflate the original familial correlations. On the other hand, if the correlations increase, the adjustments may have, by removing the effects of confounders, helped to unmask real trends in familial association. Although the effects of different covariate adjustments on familial correlations in the present study were somewhat varied among clinics and relation types, in general, progressive adjustments tended to weaken the familial resemblance. However, the significance levels of the correlations remained unchanged, suggesting no appreciable influence of these factors on familial associations of HDL-C in this sample.

Estimation of correlations in families of variable sibship size has always been a problem. The best approach to estimate correlations from familial data is by using maximum likelihood methods, which take into consideration the nonindependence among pairs. However, that method imposes distributional assumptions of multivariate normality to familial data which may not always hold. Moreover, while for constant sibship size the estimation is straightforward, for varying sibship size, explicit maximum likelihood estimates are inaccessible and even numerical evaluation can at times be formidable.25 As an alternate simpler approach to this problem, different weighting schemes with fewer assumptions are suggested. The use of these weighting procedures is aimed at revealing effects of family size on correlations. If the two extremes, WP and WF, tend to give similar results, one may be fairly certain that family size has little impact on the correlations between relatives. In the present analyses, the weighting methods, however, did not have any consistent effects on familial correlations. Thus while it is important to examine the range of estimators using different approaches and to recognize their limitations for practical purposes, the commonly used pairwise estimator WP appears to be adequate for interclass correlations.

Age trends in correlations were not statistically significant for HDL-C in this data, but the consistent pattern of higher correlation of the pediatric group compared with their adult counterparts speculatively reflects the influence of shared household environments on HDL-C levels in biological relatives. The spouse correlations were all consistently low and none were significantly different from zero. Information on the length of cohabitation of spouses was not available to examine any differential association of HDL-C with duration of marriage. However, as a crude measure, examination of correlation among spouses with adult vs pediatric children did not reveal any significant trends in association. This suggests that after age, sex, gonadal hormone use, and clinic adjustments, there is no significant familial resemblance in HDL-C among spouses, although they share life styles and environment. Correlations of blood relatives — parent-child, especially mother-child and siblings — were significant in most clinics.

Generally, the presence of dominance in genetic effects and/or environmental correlation among sibs results in higher sibling than parent-offspring correlations. The magnitude of the correlation estimates for parent-child and sibling types was very similar, suggesting no appreciable influence of such factors on the familial resemblance for HDL-C in this sample.

Heterogeneity tests indicated that, with the exception of father-daughter type, parent-offspring correlations are homogeneous across clinics. Tests for asymmetry among sexes showed the pooled mother-child correlation to be significantly higher than the pooled father-child correlation. This corroborates the findings from other studies summarized in Table 6 and could reflect more closely shared life styles between mother and children, influence of prenatal intrauterine environment on HDL-C levels, or perhaps the effects of maternal transmission (such as cytoplasmic inheritance). Significant sex-linked factors influencing HDL-C levels would result in higher father-daughter than father-son correlations. Absence of such asymmetry in father-child correlations in this sample argues against sex-linked transmission of HDL. Brother-brother, sister-sister, and brother-sister correlations were significantly different from zero in most clinics. However, there were clinic differences (X^2 = 15.8, p ≤ 0.05) in brother-brother correlations, with three clinics showing low correlations (see Figure 1). Some limitations of the LRC
Table 6. Summary of Familial Correlations of HDL-C from Other Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Relationship</th>
<th>No. of Pairs</th>
<th>Correlation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feinleib (1975)</td>
<td>MZ twins</td>
<td>249</td>
<td>0.686</td>
<td>Rared together</td>
</tr>
<tr>
<td>NIH Twin Study</td>
<td>Sibs</td>
<td>262</td>
<td>0.454</td>
<td>Rared together</td>
</tr>
<tr>
<td>Weinberg et al. (1976)</td>
<td>MZ twins</td>
<td>20</td>
<td>0.310</td>
<td>Rared together</td>
</tr>
<tr>
<td>Tromso Heart Study, Norway</td>
<td>Sibs</td>
<td>30</td>
<td>0.280</td>
<td>Rared together</td>
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<tr>
<td>Mjos et al. (1977)</td>
<td>Spouses</td>
<td>81</td>
<td>0.150</td>
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<tr>
<td>Ellefson et al. (1978)</td>
<td>Father-son</td>
<td>82</td>
<td>0.210</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Garrison et al. (1979)</td>
<td>Father-daughter</td>
<td>87</td>
<td>0.010</td>
<td>Adjusted</td>
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<tr>
<td>Shear et al. (1978)</td>
<td>Mother-son</td>
<td>109</td>
<td>0.360</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Shear et al. (1979)</td>
<td>Mother-daughter</td>
<td>126</td>
<td>0.320</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Rao et al. (1979)</td>
<td>Brother-sister</td>
<td>36</td>
<td>0.180</td>
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<tr>
<td>Shear et al. (1980)</td>
<td>Brother-brother</td>
<td>40</td>
<td>0.510</td>
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<tr>
<td>Sosenko et al. (1980)</td>
<td>Sister-sister</td>
<td>43</td>
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<tr>
<td>Ellefson et al. (1978)</td>
<td>Sib-sib</td>
<td>577</td>
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<tr>
<td>Shear et al. (1978)</td>
<td>Sib-sib</td>
<td>709*</td>
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<tr>
<td>Bogalusa Heart Study</td>
<td>Sib-sib</td>
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<td>0.054</td>
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<tr>
<td>Framingham Offspring Study</td>
<td>Spouses</td>
<td>1004</td>
<td>0.053</td>
<td>Age adjustment</td>
</tr>
<tr>
<td></td>
<td>Spouses</td>
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<td>-0.002</td>
<td>Other adjustment</td>
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<td>0.239</td>
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</tr>
<tr>
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<td>Sisters</td>
<td>283</td>
<td>0.268</td>
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<tr>
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<td>1405</td>
<td>0.219</td>
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<tr>
<td></td>
<td>Father-child</td>
<td>1436</td>
<td>0.187</td>
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<tr>
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<td>Midparent-son</td>
<td>73</td>
<td>0.460</td>
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<td>Midparent-daughter</td>
<td>66</td>
<td>0.400</td>
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<tr>
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<td>Midparent-child</td>
<td>139</td>
<td>0.360</td>
<td>No adjustment</td>
</tr>
<tr>
<td></td>
<td>Mother-child</td>
<td>139</td>
<td>0.320</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>Father-child</td>
<td>139</td>
<td>0.170</td>
<td>Adjusted</td>
</tr>
</tbody>
</table>

*Number of sibships.

†Correlations are maximum likelihood estimates.

Data, like the lack of zygosity determination for twins and small sample sizes for half-siblings, adopted and step relatives, did not permit exploration of association of HDL-C levels among these special classes of relatives which would otherwise have provided more insights to the relative contributions of shared genes vs shared environment in the determination of this lipoprotein.

The pooled clinic correlations given in Table 5 can be compared with the correlations reported in the literature as summarized in Table 6. Pairwise estimators were used for parent-offspring correlations and the ANOVA method for sibling correlations except where indicated. The Framingham Offspring Study and the Honolulu Heart Study have the largest number of pairs compared with other studies. In the former, where adjustment for varying concomitant factors was reported, the results were similar to the LRC study in that the correlations were not altered to an appreciable degree, although there was a slight weakening trend in the association with adjustments. As in the present LRC study, spouse correlations were all close to zero, suggesting no strong influence of shared environment in familial aggregation, at least for adults. Parent-child and sibling correlations showed a wide range of variation, possibly due to their geographic and cultural diversity and also perhaps due to the method of analysis. But in most cases, as in the present study, the correlations range from 0.2 to 0.3 for siblings and 0.1 to 0.3 for parent-offspring pairs. The high correlation reported between monozygotic twins and the low correlation between spouses could reflect either a greater influence of shared genes than of shared environment in the determination of HDL-C, or that shared marital environment has a trivial effect compared with a shared childhood environment.

Tyroldo et al. reported racial differences in HDL-C levels which were more pronounced in males than in females. No racial heterogeneity in correlations was
observed in the present study except for mother-son pairs. In general, familial association of HDL-C was weak in blacks with none of the correlations significantly different from zero except for mother-daughter and sister-sister. This may be due to the small sample size available for the present study, but in the Bogalusa Study, Sneath et al. reported the sib correlation in 251 black sibships to be low also (0.04), compared with that in 709 white sibships (0.12). The apparent trend in the present black sample of higher correlation for pairs where both members are female (mother-daughter and sister-sister) needs further exploration.

In summary, correlations between relatives reported here and elsewhere point to virtually no resemblance in HDL-C levels among spouses, strong parent-offspring resemblance, especially between mother and children, and also strong sibling correlations. This finding of positive association between blood relatives from populations comprising diverse geographic and occupational groups in the collaborative LRC Family Study and in a number of other studies using varying methodologies suggests appreciable genetic influence in the determination of HDL-C.

We intend in subsequent papers to estimate the relative importance of genetic, cultural and random environmental factors governing HDL-C levels, using path analytic techniques to model the correlations among family members. The present report lays the groundwork for that task by establishing significant familial association for HDL-C in this sample and also by examining the assumptions of homogeneity of correlations across clinic, sex, age, and family size which underlie some path analysis models.

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Family Study Executive Committee

William Schull (Chairman), Trudy Bush, Gary Chase, Robert Elston, Marion Fisher, Kathe Kelly, Peter Kwiterovich, Richard Mowery, Kadamba Namboodiri, and Herman Tyrorler.

LRC Directors Committee


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Index Terms: familial correlations • HDL-cholesterol • genes • environment • biracial
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