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Genetic and Environmental Correlations among Serum Lipids and Apolipoproteins in Elderly Twins Reared Together and Apart

Debra A. Heller,[1,2] Nancy L. Pedersen,[2,3] Ulf de Faire,[4] and Gerald E. McClearn[1,2]

[1]Program in Behavioral Health and [2]Center for Developmental and Health Genetics, College of Health and Human Development, The Pennsylvania State University, University Park; [3]Department of Epidemiology, Institute for Environmental Medicine, The Karolinska Institute, and [4]Division of Cardiovascular Medicine, Department of Medicine, Karolinska Hospital, Stockholm

Summary

Genetic and environmental correlations among five serum-lipid measures were examined in the Swedish Adoption/Twin Study of Aging. The sample included 302 twin pairs; 146 of these twin pairs were separated at an early age and were reared apart. The lipid measures examined include total cholesterol, HDL-cholesterol, triglycerides, and apolipoproteins A-I and B. Genetic and environmental correlations were evaluated for two different age groups, formed by dividing the sample at the median. The younger group included individuals 41.8–65.4 years of age at the midpoint of testing, although only 24 individuals were <50 years of age. The older group included all those >65.4 years of age, up to age 87 years of age. Substantial genetic correlations were found within each age group, although there is no evidence for a single genetic factor common to all five lipids. The comparison of twins reared together with twins reared apart allowed estimation of the effects of shared rearing environment; however, shared rearing environment only appears to be a significant mediator of the phenotypic correlation between apolipoprotein B and cholesterol in the older group. Examination of the genetic and environmental covariances suggests that the relative contributions of genetic factors are lower in the older group. Nonshared environmental factors are relatively more important mediators of phenotypic correlations among the serum lipids in individuals >65.4 years of age than they are for the younger group. Sex differences in the mediation of these serum lipids were not as clear.

Introduction

The multifactorial nature of coronary heart disease (CHD) is well established (Stamler 1973; Bierman 1985). Risk factors such as hyper- and dyslipidemia, hypertension, disturbed glucose tolerance, and obesity presumably interact in the progression of the underlying atherosclerotic disease processes (Rifai et al. 1988). Because of these interactions, the degree to which two or more risk factors are influenced by common factors (the same genes or, alternatively, the same environmental factors) is potentially important in evaluating CHD risk and treatment. The goal of this study was to evaluate the extent to which different serum lipids and apolipoproteins are influenced by the same genetic or environmental factors.

Many studies have demonstrated the importance of genetic factors in determining population variation for the levels of serum lipids and lipoproteins (for reviews, see Berg 1989; Hopkins and Williams 1989; Sing and Moll 1989). Some twin and family studies have also shown shared family environment to be important in determining familial similarity levels (Feinleib et al. 1977; Whitfield and Martin 1983).

We have recently reported results of univariate genetic analyses on serum lipids and apolipoproteins in the Swedish Adoption Twin Study of Aging (SATSA) (Heller et al. 1993). SATSA combines the power of both the twin and adoption methods, comparing MZ and DZ twins reared together and reared apart. In our previously reported univariate genetic analyses, age comparisons were made on the basis of a median division of the sample, which separated those ≤65.4 years of age from those >65.4 years of age. Estimates of heritability in the younger group ranged from .63 for total cholesterol to .78 for apolipoprotein B. In the older group, heritabilities were lower, ranging from .28 for serum triglycerides to .55 for HDL-cholesterol. For apolipoprotein B and triglycerides, our genetic analyses revealed an apparent reduced importance of genetic factors in twins >65.4 years of age, as compared with those ≤65.4 years of age (with, necessarily, a concomitant increase in the importance of environmental influences). By comparing twins reared together with twins reared apart, it was possible to demonstrate an important role of rearing environment in determining variation for total serum cholesterol. For HDL-cholesterol and triglycerides, however, parameter estimates of shared rearing environment were not significant, and variance for these measures could be ex-

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Address for correspondence and reprints: Dr. Debra A. Heller, Center for Developmental and Health Genetics, Amy Gardner House, The Pennsylvania State University, University Park, PA 16802.

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plained on the basis of genetic and nonshared environmental variance.

Here we report genetic and environmental correlations for these serum lipids and apolipoproteins. The extent to which common genetic and environmental factors affect levels of serum lipids and apolipoproteins is of great interest, for several reasons. First, derangement of more than one of the different lipid and apolipoprotein fractions occurs simultaneously in some of the familial syndromes. From a medical intervention standpoint, it is important to be aware of the independent and interactive risks associated with each of the different serum lipids or apolipoproteins. The degree to which these interrelationships are due to the pleiotropic effects of genes or to the common effects of environmental factors may affect the response to treatment. Striving for effective interventions, then, may require consideration of the shared causal networks among these risk factors.

In contrast to many published univariate genetic studies of serum lipids, relatively few studies have addressed the genetic and environmental correlations among serum lipids. Genetic and environmental correlations among serum cholesterol, lipoprotein fractions, and triglycerides have been reported from studies of twins reared together (Colletto et al. 1981) and from using family and pedigree data (McGue et al. 1983; Rao et al. 1983; Boehnke et al. 1986; Vogler et al. 1987). In these family studies, the role of shared rearing environment was assessed on the basis of familial similarity for an index of variables assumed to be environmentally influenced. A different approach is used in SATSA, by comparing twins reared together with twins reared apart, which allows a direct estimation of the importance of shared early environment in mediating correlations among serum lipids and apolipoproteins.

Age differences in the etiology of the interrelationships among the lipid fractions are also of interest. Our univariate analyses suggested significant age differences in the genetic and environmental factors affecting serum lipids. Results of several epidemiological studies also suggest that profiles of risk due to abnormal levels of serum lipids or apolipoproteins may differ among age groups (Kannel and Gordon 1978; Kreisberg and Kasim 1987; Castelli et al. 1989). A study of relationships among serum lipids and apolipoproteins, then, should address possible age differences in the etiology of these relationships. The SATSA design provides a unique opportunity to address age differences in the genetic and environmental correlations among serum lipids.

Subjects and Methods

Subject Sample

The SATSA sample of twins separated early in life and of matched twins reared together was identified through the Swedish Twin Registry, which includes almost 25,000 pairs of like-sexed twins born in Sweden during 1886–1958 (Cederlöf and Lorich 1978). The SATSA subregistry was formed in 1984 by contacting twin pairs identified in the Swedish Twin Registry as having been reared apart, along with matched pairs reared together. The identification and characterization of the SATSA sample has been described in detail elsewhere (Pedersen et al. 1984).

The data on genetic and environmental correlations reported here were obtained from the subset of 302 twin pairs who were given physical examinations during testing in 1986–88 (Pedersen et al. 1991). When divided into four groups based on zygosity and rearing status, the sample consists of 46 pairs of MZ twins reared apart (MZA), 67 pairs of MZ twins reared together (MZT), 100 pairs of DZ twins reared apart (DZA), and 89 pairs of DZ twins reared together (DZT).

For age-group comparisons, a median division maximized sample size for group comparisons. Sex comparisons were based on comparing the 118 pairs of male twins with the 184 pairs of female twins; no unlike-sex DZ twins are included in the SATSA sample. Power and sample-size considerations precluded the simultaneous breakdown of the sample by both age and sex.

Serum Lipids and Apolipoproteins

Serum levels of total cholesterol, HDL-cholesterol, apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and triglycerides were measured from fasting blood samples. The data-collection and testing procedures employed for these serum lipids and apolipoproteins have been described elsewhere (Heller et al. 1993). Because some of the distributions were positively skewed, scores for triglycerides and the two apolipoprotein measures were log-transformed.

Analyses

The genetic analyses conducted in this study include comparisons of phenotypic and cross-twin correlations, by rearing and zygosity groups, as well as maximum-likelihood multivariate-model fitting of variance-covariance matrices by using LISREL 7 (Jöreskog and Sörbom 1989). For analyses controlling for sex, linear regression was used to first remove sex effects within age group, and the residuals were then used for subsequent genetic analyses. On the basis of our univariate findings, we chose to examine broad age differences by comparing younger versus older twins. However, because twins share the same age, it is also important to control for age effects even within the major age groups. In our analyses, age was included as a covariate in all structural equation models, according to the procedure of Neale and Martin (1989). Including age within the structural equation models not only provides the advantage of testing age effects directly, but also allows

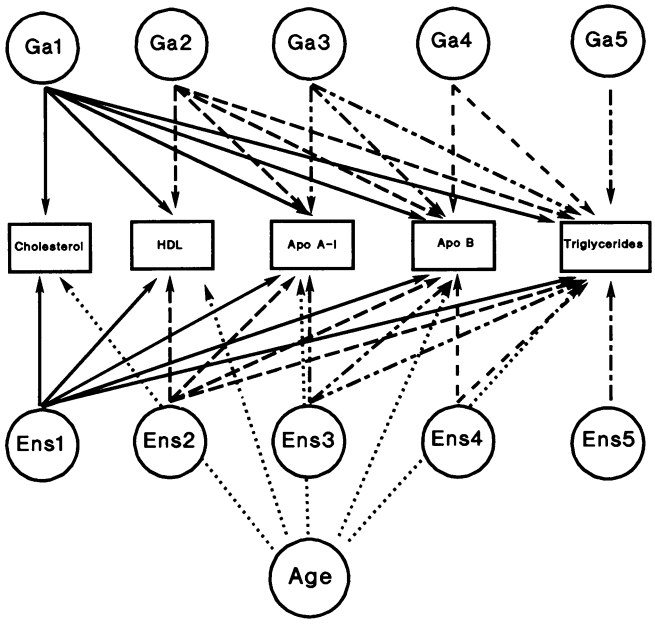

Figure 1 Path diagram depicting Cholesky decomposition for additive genetic (Ga1–Ga5) and nonshared environmental (Ens1–En5) influences on five lipid measures, for a single member of a twin pair. The model includes five latent variables for each type of influence. Genetic latent variables between co-twins are correlated depending on zygosity (e.g., additive genetic variance is correlated 1.0 between MZ twins and .50 between DZ twins). Nonshared or unique environmental latent variables Ens1–Ens5 are uncorrelated between twins, while shared-rearing environmental factors (not shown for simplicity) are, by definition, correlated 1.0 in twins reared together and 0 in twins reared apart.

estimation of genetic and environmental effects while controlling for continuous age effects.

The Multivariate Model

The primary goal of our multivariate genetic analysis was to decompose the phenotypic covariance matrix of serum lipids (C_P) into its genetic and environmental components, as follows:

$$C_P = C_G + C_{ES} + C_{ENS}, \quad (1)$$

where C_G, C_{ES}, and C_{ENS} are the genetic and shared-rearing and nonshared environmental covariance matrices, respectively.

The procedure for estimating C_G, C_{ES}, and C_{ENS} takes advantage of the Cholesky (or triangular) decomposition, in which a matrix is factored as the product of a triangular matrix and its transpose. For an explanation of the Cholesky decomposition and how it is applied to multivariate genetic analyses of twin data, see the work of Neale and Cardon (1992).

The Cholesky representation of the latent genetic and nonshared environmental factors affecting serum lipids in one twin is illustrated in figure 1. Considering the genetic factors, note that the first factor (Ga1) influences all of the observed variables and that a second factor (Ga2) influences all but one of the variables, a third factor (Ga3), influences all but two of the observed variables, and so forth. The last factor, Ga5, has a single path to the fifth observed variable, serum triglycerides in this case. Environmental influences are similarly represented in the Cholesky model, with five latent shared-rearing environmental (not shown in fig. 1) and five nonshared environmental factors.

The correlation between twins, for each latent genetic factor (i.e., Ga1 for twin A and twin B; Ga2 for twin A and twin B, etc.) is dependent on the coefficient of genetic relationship: 1.0 for MZ twins and .5 for DZ twins, under the assumption of additive genetic variance. Similarly, the correlation between twins, for each type of latent shared-rearing environmental factor, depends on their rearing status, defined to be 1.0 for twins reared together and 0 for twins reared apart. By definition, nonshared environmental factors are not correlated in twins but, rather, are unique to individuals.

Applying the Cholesky factorization to the four twin variance-covariance matrices (for MZA, MZT, DZA, and DZT) simultaneously in a LISREL model yields summary parameter estimates for three triangular matrices of genetic, shared-rearing environmental, and nonshared environmental path coefficients (see Neale and Cardon 1992). Multiplying each of these three triangular matrices by its transpose then yields C_G, C_{ES}, and C_{ENS}. As for any covariance, the genetic and environmental covariances can then be converted to their corresponding genetic and environmental correlations, through division by the square root of the multiplied genetic or environmental variances, i.e.,

$$\text{genetic correlation } x, y = \frac{\text{genetic covariance } x, y}{\sqrt{(\text{genetic variance}_x \times \text{genetic variance}_y}}.$$

For any pair of serum lipids, the genetic and environmental covariances can also expressed as fractions of the phenotypic correlation. This provides an indication of the relative contribution of each type of genetic or environmental influence in determining the phenotypic correlation between two traits.

For each sex and age group in this study, the five-variable Cholesky model was fitted to the phenotypic covariance matrix of serum lipids. The inclusion of genetic and shared-rearing and nonshared environmental parameters was dictated by the univariate results reported elsewhere (Heller et al. 1993). For example, the shared-rearing environmental correlation was only modeled for pairs of variables where shared rearing environment was a significant source of twin similarity for both measures. As a result, the shared-rearing environmental correlation was modeled

Table 1

Phenotypic Correlations for Serum Lipids and Apolipoproteins, by Age Group and Sex

A. By Age Group (Younger above Diagonal, Older below Diagonal)

	Cholesterol	HDL	apo A-I[a]	apo B[a]	Triglycerides[a]
Cholesterol	1.00 (. . .)	.05 (279)	.25 (291)	.78 (291)	.38 (290)
HDL	.15 (275)	1.00 (. . .)	.75 (280)	−.26 (280)	−.48 (280)
apo A-I[a]	.21 (293)	.72 (276)	1.00 (. . .)	−.05 (293)	−.32 (291)
apo B[a]	.76 (293)	−.18 (276)	.02 (298)	1.00 (. . .)	.49 (291)
Triglycerides[a]	.34 (293)	−.46 (276)	−.24 (294)	.49 (294)	1.00 (. . .)

B. By Sex (Women above Diagonal; Men below Diagonal)

	Cholesterol	HDL	apo A-I[a]	apo B[a]	Triglycerides[a]
Cholesterol	1.00 (. . .)	.11 (323)	.22 (344)	.75 (343)	.36 (339)
HDL	.02 (224)	1.00 (. . .)	.72 (329)	−.21 (327)	−.50 (325)
apo A-I[a]	.20 (233)	.78 (223)	1.00 (. . .)	−.03 (349)	−.31 (345)
apo B[a]	.81 (233)	−.26 (223)	−.03 (236)	1.00 (. . .)	.46 (342)
Triglycerides[a]	.38 (222)	−.46 (212)	−.29 (221)	.52 (221)	1.00 (. . .)

NOTE.—Data are Pearson correlations (data in parentheses are sample sizes) and were first residualized for sex and age in years (within age group).
[a] Data were log-transformed (see text).

only in the older group and for women, for associations among cholesterol, apo A-I, and apo B. For each age group, a series of models were tested, in which groups of parameters were dropped and changes in χ^2 were evaluated, in order to attain the most parsimonious solution. In order to evaluate the significance of age-group differences, models were also tested in which parameter estimates were constrained to be equal across age group. The goodness-of-fit indices of these models were then compared with those from models allowing estimates to differ by age group. Similarly, sex differences were also examined by comparing results for men and women and by testing models in which parameter estimates were constrained to be equal across sex.

Results

Serum Lipids and Apolipoproteins

Overall, cholesterol levels were 139.0–413.0 mg/dl, with a mean of 262.7. The mean HDL-cholesterol level was 57.0 mg/dl; the apo A-I level 140.0 mg/dl; the apo B level, 110.0 mg/dl; and the triglyceride level, 144.0 mg/dl. The mean levels and distributions of the serum lipids in the present sample, as well as their associations with age and sex, have been detailed elsewhere (Heller et al. 1993).

Phenotypic Correlation

The phenotypic correlations among the sex-residualized serum lipids are shown, in table 1, for the age groups and sexes separately. The phenotypic correlations are similar for each age group, with positive correlations among cholesterol, apo B, and triglycerides. Although the age groups appeared to differ in the correlation between total cholesterol and HDL-cholesterol (+.05 vs. +.15), this difference was not significant at an alpha level of .05 (Edwards 1976). Similarly, men and women differed, but not significantly, for the correlation between total cholesterol and HDL-cholesterol. For all groups, negative correlations are observed for HDL-cholesterol and apo A-I with apo B and triglycerides.

Genetic and Environmental Correlations

The genetic model illustrated in figure 1 and described above was applied to each age group. The resulting parameter estimates (path coefficients) are listed, in the accompanying Appendix, for the two age groups. After standardization to a common metric, separate from the within-group age effects, the three matrices of path coefficients (genetic and shared-rearing and nonshared environmental matrices) were multiplied by their transposes, yielding matrices of genetic and environmental variances and covariances (tables 2 and 3). The corresponding genetic and environmental correlations are displayed, in table 4, for the two age groups and sexes separately.

Substantial genetic correlations are apparent within each sex and age group. The highest genetic correlations are between cholesterol and apo B (.76–.85) and, not surprisingly, between HDL-cholesterol and apo A-I (.75–.86). Substantial negative genetic correlations are apparent between HDL-cholesterol and triglycerides. Visual inspec-

Table 2

Genetic and Environmental Variance-Covariance Matrices, by Age Group

A. Additive Genetic

	Younger Group					Older Group				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.745					.367				
HDL	.004	.732				.075	.497			
apo A-I	.109	.557	.665			.139	.343	.400		
apo B	.592	−.199	−.114	.808		.364	−.191	−.026	.509	
Triglycerides	.371	−.354	−.282	.427	.728	.215	−.175	−.064	.342	.329

B. Shared Environmental[a]

	Younger Group					Older Group				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.044					.218				
HDL	...	...				...	...			
apo A-I	...	...	...			−.038	...	.062		
apo B	...	...	...	...		.118	...	−.085	.137	
Triglycerides	...	...	...	...	...	.000	...	...	...	...

C. Nonshared Environmental

	Younger Group					Older Group				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.211					.416				
HDL	.073	.268				.051	.503			
apo A-I	.147	.196	.335			.076	.366	.538		
apo B	.151	−.028	.044	.192		.253	.000	.110	.353	
Triglycerides	.006	−.119	−.059	.049	.272	.102	−.302	−.160	.120	.671

NOTE.—Each matrix (additive genetic, shared environmental, and nonshared environmental) is obtained by multiplying the respective triangular matrix of restandardized LISREL estimates by its transpose. Genetic and environmental variances (e.g., heritability) are on the diagonal; the off-diagonal elements are the genetic and environmental covariances.

[a] Some shared environmental variances and covariances were not estimable, because these parameters were not included in the multivariate model (see text).

tion suggests an age-group difference in genetic correlation for HDL-cholesterol with total cholesterol, where the genetic correlation for those ≤65.4 years of age is near 0, while those >65.4 years of age show a genetic correlation of .18.

On the basis of the results of univariate models, shared-rearing environmental correlations were modeled only for the older group, for apo B with cholesterol (.68) and for apo B with apo A-I (−.91), and for apo A-I with cholesterol (−.33). In contrast with the model specifications for shared rearing environment, the nonshared environmental correlation was included as a parameter in all models. This correlation represents environmental influence specific to individuals (i.e., not shared by co-twins) that affects the correlation between two traits. Consistently across sex and age groups, nonshared environmental correlations were highest for apo B with cholesterol (.60–.84).

Tests of Alternative Models

Table 5 summarizes information regarding the fit of several alternative models tested for each sex and age group, by evaluating changes, in χ^2, between full and nested models. Models that hypothesized a single common genetic factor were rejected for both age groups (table 5). Alternatively, models that tested the hypothesis of no common genetic factors were also rejected for both age groups and sexes.

In order to evaluate the significance of sex and age-group differences, models were also tested that constrained parameter estimates to be equal across groups (for

Table 3

Genetic and Environmental Variance-Covariance Matrices, by Sex

A. Additive Genetic

	Women					Men				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.520					.532				
HDL	.126	.607				−.110	.640			
apo A-I	.205	.448	.583			−.089	.525	.586		
apo B	.492	−.162	−.014	.648		.403	−.202	−.214	.527	
Triglycerides ...	.226	−.228	−.180	.351	.576	.333	−.202	−.243	.356	.476

B. Shared Environmental[a]

	Women					Men				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.237					.030				
HDL	...	...				...	...			
apo A-I	...	...	...			...	...	...		
apo B	.109	...	...	.156		...	...	...	...	
Triglycerides ...	...	...	...	...	...	...	...	...	...	...

C. Nonshared Environmental

	Women					Men				
	Cholesterol	HDL	apo A-I	apo B	Triglycerides	Cholesterol	HDL	apo A-I	apo B	Triglycerides
Cholesterol	.243					.437				
HDL	.000	.393				.151	.360			
apo A-I	.016	.272	.417			.280	.248	.414		
apo B	.131	−.037	−.009	.196		.383	−.013	.187	.473	
Triglycerides ...	.103	−.209	−.141	.080	.424	.043	−.223	−.047	.153	.524

NOTE.—Each matrix (additive genetic, shared environmental, and nonshared environmental) is obtained by multiplying the respective triangular matrix of restandardized LISREL estimates by its transpose. Genetic and environmental variances (e.g., heritability) are on the diagonal; the off-diagonal elements are the genetic and environmental covariances.

[a] Some shared environmental variances and covariances were not estimable, because these parameters were not included in the multivariate model (see text).

further details, see Neale and Cardon 1992). As table 5 shows, constrained models fit significantly less well than did free models, for both age and sex comparisons. In univariate models of these serum lipid measures, constrained models could be fitted for men and women, for several measures, by using correlations, rather than covariances, because of sex differences in overall variance (Heller et al. 1993). However, in the multivariate models reported here, models that constrained either all or just genetic-parameter estimates to be equal across the sexes fit significantly less well than did free models. Similarly, genetic parameters could not be constrained to be equal in those ≤65.4 years of age and those >65.4 years of age, a result similar to that found in univariate models for these measures.

Partitioning of Phenotypic Correlations

Although the genetic and environmental correlations provide useful information about the degree of overlap in the spheres of influence of the underlying genetic and environmental factors, it is also informative to consider the partitioning of the phenotypic correlations into their genetic and environmental components. As indicated by formula (1), the individual genetic and environmental covariances obtained in C_G, C_{ES}, and C_{ENS} can also be expressed as proportions of the phenotypic covariance. Figure 2 illustrates the partitioning of the phenotypic correlations estimated by the multivariate model, showing the relative contributions of the genetic and environmental components.

Table 4

Genetic and Environmental Correlations, by Age Group and Sex

A. By Age Group (Younger above Diagonal, Older below Diagonal)

	Cholesterol	HDL	apo A-I	apo B	Triglycerides
			Additive Genetic		
Cholesterol	1.000	.006	.154	.763	.504
HDL	.176	1.000	.797	−.259	−.484
apo A-I	.363	.769	1.000	−.155	−.405
apo B	.842	−.380	−.059	1.000	.557
Triglycerides	.618	−.432	−.177	.834	1.000
			Shared Environmental		
Cholesterol	1.000	...	...	...	...
HDL	...	1.000	...	...	...
apo A-I	−.330	...	1.000	...	...
apo B	.680	...	−.916	1.000	...
Triglycerides	...	...	...	...	1.000
			Nonshared Environmental		
Cholesterol	1.000	.309	.553	.750	.023
HDL	.112	1.000	.653	−.125	−.442
apo A-I	.160	.703	1.000	.173	−.196
apo B	.661	.001	.251	1.000	.216
Triglycerides	.194	−.521	−.266	.246	1.000

B. By Sex (Women above Diagonal, Men below Diagonal)

	Cholesterol	HDL	apo A-I	apo B	Triglycerides
			Additive Genetic		
Cholesterol	1.000	.225	.372	.847	.412
HDL	−.189	1.000	.753	−.259	−.487
apo A-I	−.159	.857	1.000	−.023	−.311
apo B	.761	−.348	−.386	1.000	.574
Triglycerides	.661	−.367	−.460	.711	1.000
			Shared Environmental		
Cholesterol	1.000	...	...	.568	...
HDL	...	1.000	...	...	...
apo A-I	...	...	1.000	...	...
apo B	...	...	...	1.000	...
Triglycerides	...	...	...	...	1.000
			Nonshared Environmental		
Cholesterol	1.000	.000	.050	.601	.319
HDL	.380	1.000	.672	−.135	−.512
apo A-I	.658	.642	1.000	−.030	−.336
apo B	.843	−.031	.422	1.000	.279
Triglycerides	.090	−.512	−.101	.308	1.000

It is clear that genetic and nonshared environmental factors are both important in mediating the phenotypic relationships among serum lipids (fig. 2). Some generalizations regarding the pattern of results are worth noting.

The left-hand panel of figure 2 illustrates the mediation of correlations in the two age groups. Although the magnitudes of the total phenotypic correlations are similar across the two age groups, the contributions of the genetic and environmental components differ between the age groups, for some of the relationships examined. Overall, a trend of lesser genetic mediation of phenotypic correlations is apparent in the older group. For the correlation

Table 5

Comparative Fits of Full and Reduced Models, by Age Group and Sex

A. Comparisons by Age Group		
Model	Younger Group	Older Group
Model 1:		
Full model	χ^2 = 331.32, 227 df	χ^2 = 338.89, 222 df
Model 2:		
No common genetic factors	χ^2 = 409.58, 237 df	χ^2 = 381.09, 232 df
χ^2 Difference from model 1	$\Delta\chi^2$ = 78.3, 10 df; reject model 2	$\Delta\chi^2$ = 42.2, 10 df; reject model 2
Model 3:		
All genetic factors are common	χ^2 = 450.97, 237 df	χ^2 = 360.51, 232 df
χ^2 Difference from model 1	$\Delta\chi^2$ = 119.7, 10 df, $P < .001$; reject model 3	$\Delta\chi^2$ = 21.62, 10 df, $P < .025$; reject model 3
	Groups Combined	
Model 4:		
Genetic parameters constrained to be equal across age groups	χ^2 = 719.31, 461 df	
χ^2 Different from model 1	$\Delta\chi^2$ = 49.1, 12 df, $P < .001$; reject model 4	

B. Comparisons by Sex		
Model	Female	Male
Model 1:		
Full model	χ^2 = 297.14, 225 df	χ^2 = 278.06, 227 df
Model 2:		
No common genetic factors	χ^2 = 369.56, 235 df	χ^2 = 331.85, 237 df
χ^2 Difference from model 1	$\Delta\chi^2$ = 72.42, 10 df, $P < .001$; reject model 2	$\Delta\chi^2$ = 53.79, 10 df, $P <$ 0.001; reject model 2
Model 3:		
All genetic factors are common	χ^2 = 360.51, 232 df	χ^2 = 338.92, 237 df
χ^2 Difference from model 1	$\Delta\chi^2$ = 72.37, 10 df, $P < .001$; reject model 3	$\Delta\chi^2$ = 60.86, 10 df, $P < .001$; reject model 3
	Groups Combined	
Model 4:		
Genetic parameters constrained to be equal across sex	χ^2 = 696.09, 464 df	
χ^2 Difference from model 1	$\Delta\chi^2$ = 120.89, 12 df, $P < .001$; reject model 4[a]	

[a] Men and women differed in overall variance, which contributed to the lack of fit in the constrained model. Models using correlations provided better fit for sex comparisons, although constrained models still fit significantly less well than did free models (χ^2 difference for constrained correlational model=25.04, 7 df).

between cholesterol and apo B, shared rearing environment contributes significantly (about a third) to the phenotypic correlation in the older group.

The right-hand panel of figure 2 shows the genetic and environmental contributions to the phenotypic correlations in men and women. Shared-rearing environmental factors contribute modestly to the correlation between apo B and cholesterol in women but not in men. Other than this, however, no clear pattern of sex differences in the mediation of these correlations is apparent.

Discussion

Phenotypic Correlations

The goal of this study was to explore the common genetic and environmental factors influencing phenotypic associations among serum lipids and apolipoproteins. It is important to consider that some of the phenotypic correlations can be explained in part by the natural physiological correlations existing among these serum lipids and apolipoproteins. The pattern of pheno-

typic correlations observed is consistent with what is known about the metabolic relationships existing among these lipid measures. The homogeneity of these phenotypic correlations can be contrasted with the heterogeneity of the genetic and environmental components that was found in this study. This heterogeneity will be discussed further below.

Metabolism of Lipids and Apolipoproteins

Although we modeled all 10 possible correlations among these five serum lipids, some of these relationships are metabolically—and, therefore, statistically—dependent. For example, HDL-cholesterol reflects part of the total cholesterol, and apo A-I is the major protein component found in HDL-cholesterol. Similarly, positive correlations between apo B and triglycerides are expected, because most of the triglycerides in a fasting state are carried within very-low-density lipoproteins (VLDL), of which apo B is a component. Positive phenotypic and genetic correlations are expected for measures linked by such metabolic relationships. Although the remaining correlations are not related to one another by direct causation, they may nevertheless reflect certain aspects of endogenous lipid transport and metabolism.

The positive associations (+.34 to +.38) observed for cholesterol with triglycerides are consistent with the results of other studies (Connor et al. 1982; Boehnke et al. 1986). The presence of both triglyceride and cholesterol (55% and 20%, respectively) within VLDL would be expected to contribute to a positive association between these two lipids. More important, high levels of VLDL being synthesized and converted to LDL would explain this association, because VLDL carries most of the triglycerides (in the fasting state) while LDL carries ~70% of the total cholesterol.

The strongly negative phenotypic correlations (~−.50) for HDL-cholesterol with triglycerides indicate an inverse relationship between HDL-cholesterol and VLDL levels. The similar negative correlations (~−.30) for apo A-I with triglycerides reflect the presence of apo A-I as a major component of HDL. Although HDL-cholesterol and VLDL have no simple precursor-product relationship, a negative correlation between VLDL triglyceride and HDL-cholesterol could be due to free cholesterol, phospholipids, and apolipoproteins being transferred to HDL during degradation of VLDL (Nikkilä et al. 1978). The conjunction of low levels of HDL-cholesterol and high levels of VLDL, which is often seen in diabetics and obese subjects, may reflect disturbances in lipoprotein lipase activity, with delayed degradation of triglyceride-rich VLDL particles and reductions in HDL-cholesterol (Nestel and Fidge 1981), although most HDL-cholesterol lipid is picked up from cellular cholesterol. Since apo B is present in both VLDL and LDL, the negative association of HDL-cholesterol with apo B may reflect HDL's inverse association with either VLDL or LDL.

Genetic Correlations

Substantial genetic correlations were found for each of the four pairs of lipids and apolipoproteins, for each age group. The high genetic correlations seen for cholesterol with triglycerides suggest an extensive overlap of genes affecting these traits. The negative genetic correlations observed for HDL-cholesterol with triglycerides, apo A-I with triglycerides, and HDL-cholesterol with apo B indicate that genes associated with higher levels of one lipid within a pair are associated with lower levels of the other lipid measure. It is interesting that, although genetic variance for these measures is lower in the older group, the genetic correlations are higher. These differences may reflect changes with age that occur in the genetic architecture; they may also reflect cohort differences.

No other genetic studies to date have reported genetic correlations between HDL-cholesterol and apo B. The phenotypic correlations between HDL-cholesterol and apo B may reflect the association of HDL-cholesterol with either VLDL or LDL. Colletto et al. (1981) found a positive genetic correlation of .22 for HDL-cholesterol with LDL. Vogler et al. (1987) found no genetic correlation between HDL and LDL. McGue et al. (1983) detected a modest negative genetic correlation (−.13) between the two lipoproteins but found that family environment could entirely explain the phenotypic association.

Our estimates of the genetic correlation between cholesterol and triglycerides are similar to those reported by Boehnke et al. (1986) but are higher than those found in other studies (Colletto et al. 1981; Rao et al. 1983). Similarly, the strongly negative genetic correlation (−.52) of HDL-cholesterol with triglycerides, which we found in the younger group, is substantially higher than those reported elsewhere (Colletto et al. 1981; McGue et al. 1983; Vogler et al. 1987). One potential explanation for our higher estimates of genetic correlations may be the power of studying twins reared apart. In family studies, shared family environment is estimated indirectly by using indices that include variables such as obesity and hematocrit (Rao et al. 1983). It is likely that some of these index variables are under substantial genetic influence. By studying twins reared apart, it may be possible to better separate genetic factors from environmental effects. It is also possible that the study of elderly twins may yield genetic estimates that are less confounded with environmental factors, because many twins have been apart for substantial portions of their lives.

The genetic correlation has been defined as the extent to which two variables or traits are influenced by the same

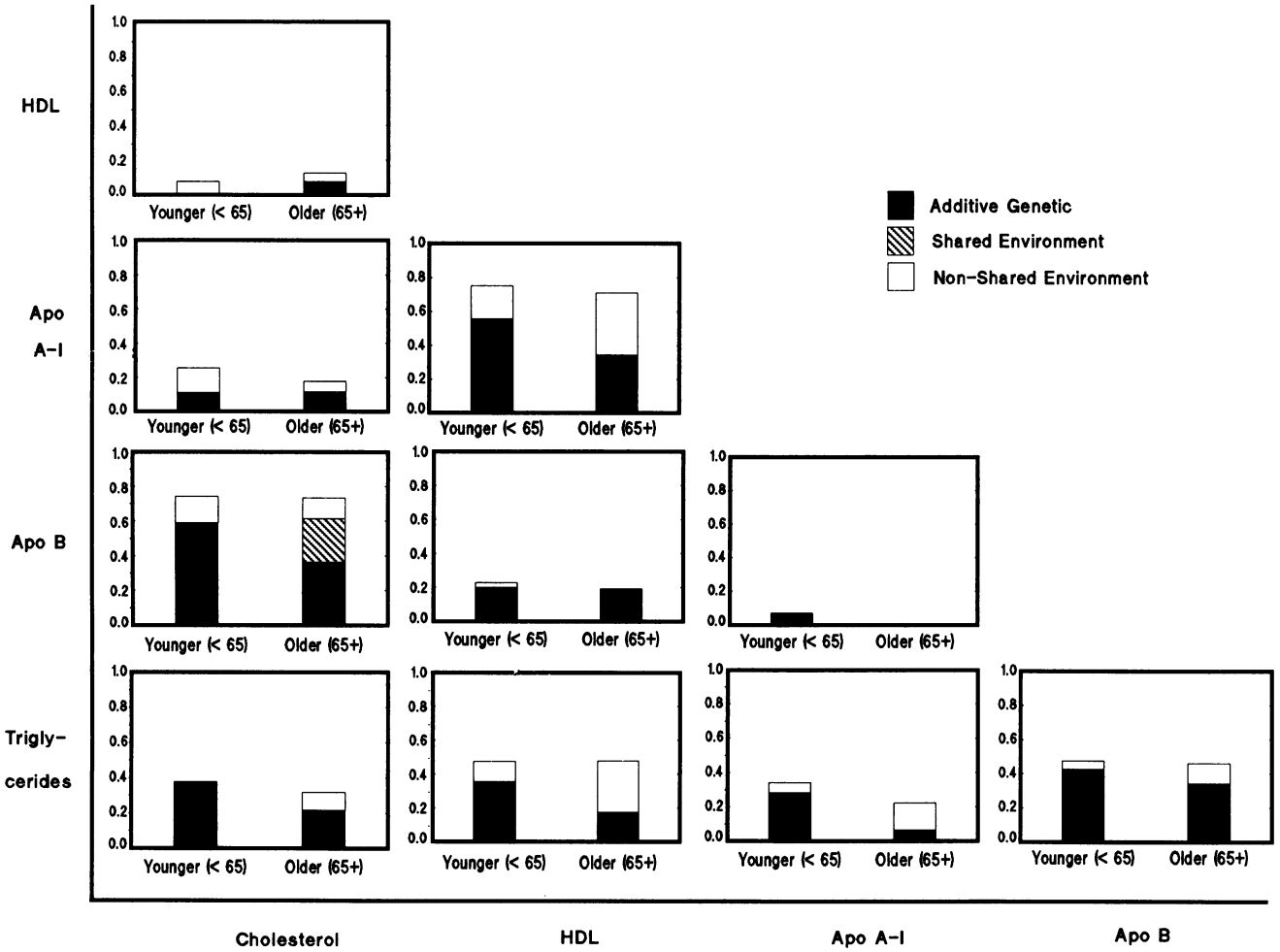

Figure 2 Components of phenotypic correlations, by age group (*above*) and sex (*facing page*), showing contributions of additive genetic covariance, shared-rearing environmental covariance, and nonshared environmental covariance.

genes, reflecting pleiotropy (Falconer 1981). More recently, Carey (1988) has differentiated *biological pleiotropy*, in which the same genes underlie different traits, from *statistical pleiotropy*, in which allelic effects on one trait predict allelic effects on another trait. According to Carey, Falconer's definition applies to statistical, rather than to biological, pleiotropy. In the present case, where common physiological pathways of lipid metabolism are involved, caution must be employed in interpreting the genetic correlations. Although our genetic correlations do suggest extensive overlap in the genetic factors influencing these serum lipids, it is impossible to make inferences regarding the percentage of shared loci from the genetic correlations obtained here.

Environmental Correlations

Environmental correlations, whether due to early rearing environment or due to experiences specific to individuals, reflect the degree to which two traits are influenced by the same environmental factors. Because our inclusion of parameters was based partly on our univariate findings, shared-rearing environmental correlations were modeled only for the older group, for cholesterol, apo A-I, and apo B. Our findings present no evidence for a single common shared-rearing environmental factor for these lipids.

In contrast to our finding of nonsignificant effects of shared rearing environment on correlations among these serum lipids, other studies have found substantial effects of family environment on relationships among these measures (McGue et al. 1983). As discussed above, the difference between the shared-rearing environmental index used in family studies and our parameter based on comparing twins reared together and apart may explain our contrasting results. For example, some family-environmental indices have used measures such as obesity or hematocrit, which themselves may contain substantial genetic vari-

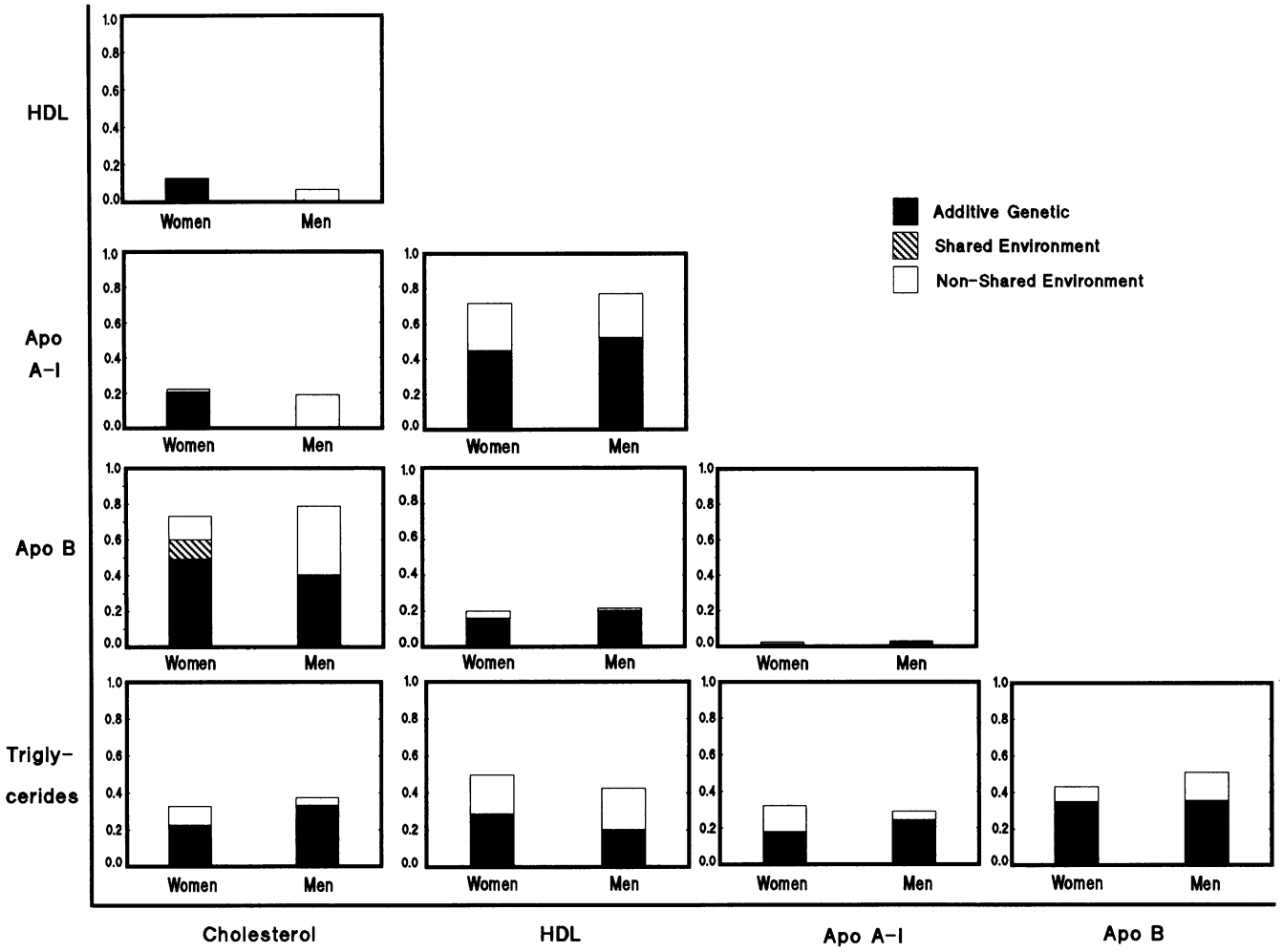

Figure 2 (continued)

ance. Such indices may lead to familial similarity being attributed to shared-rearing environmental, rather than to genetic, sources. Since our subjects are older than those reported in other studies, cohort differences may also be responsible.

The nonshared environmental correlation represents the overlap in environmental factors affecting two traits that are unique to individuals (i.e., not shared by co-twins). No clear patterns of age differences in the absolute magnitude of nonshared environmental correlation are apparent for these measures.

Both the genetic and environmental components combine together to yield phenotypic correlation. The relative importance of genetic and environmental influences in mediating phenotypic correlation is dependent on the univariate genetic and environmental components of variance, as well as on the absolute magnitude of the genetic and environmental correlations. The differences in sign that are apparent among genetic correlation, shared-rearing environmental correlation, and nonshared environmental correlation, for apo A-I and apo B, suggest that genetic and environmental sources of variation may affect apo A-I and apo B through different physiological mechanisms.

Age-Group and Sex Differences

The consistent phenotypic correlations across age groups suggest that there is age continuity in the physiological relationships among the serum lipids and apolipoproteins. However, it is apparent that the relative contributions of genetic factors are lower in the older group, as environmental correlations become more salient. This pattern is clearest for associations between HDL-cholesterol and triglycerides.

Models constraining equal parameters in the younger and older groups fit significantly worse than did models allowing different parameters across age groups, suggesting age differences. We also examined the genetic and environmental correlations by sex; however, as in the univari-

Appendix

Table A1

Parameter Estimates and Goodness-of-Fit Statistics Obtained from LISREL Models, by Age Group

	Age (years)	Additive Genetic					Shared Environmental					Nonshared Environmental				
		Ga1	Ga2	Ga3	Ga4	Ga5	Es1	Es2	Es3	Es4	Es5	Ens1	Ens2	Ens3	Ens4	Ens5
Younger group:[a]																
Age (years)	4.909															
Cholesterol	.162	1.041					.253					.554				
HDL	.027	.002	.353				...	...				.066	.203			
apo A-I	.011	.024	.124	.091			...	...	...			.061	.056	.073		
apo B	.042	.142	−.049	−.020	.108		...	...	...	...		.068	−.034	−.007	.049	
Triglycerides	.023	.211	−.204	−.068	.019	.290	...	...	...	...	...	.006	−.121	.012	.012	.225
Older group:[b]																
Age (years)	4.716															
Cholesterol	−.213	.757					.583					.806				
HDL	.014	.047	.263				.000	...				.030	.267			
apo A-I	.003	.039	.077	.064			−.014	...	.040			.020	.086	.088		
apo B	−.035	.124	−.079	.005	.005		.052	...	−.056	.0[c]		.081	−.009	.034	.085	
Triglycerides	−.017	.154	−.137	−.033	.140	.000	...	...	...	...	...	.069	−.194	.040	.024	.000

[a] $\chi^2 = 331.32, 227$ df, $P < .001$.
[b] $\chi^2 = 338.89, 223$ df, $P < .001$.
[c] Unidentified parameter (subsequently set to zero).

ate case, no clear pattern of sex differences emerged, although constrained models fit less well than did free models.

Conclusions

Substantial phenotypic, genetic, and environmental correlations exist among serum lipids and apolipoproteins. In this study of older twins reared together and apart, there is evidence for age differences in the importance of genetic factors mediating the phenotypic association among these lipid measures. Individuals >65.4 years of age show a relatively greater impact of environmental factors in the mediation of the phenotypic correlations, in comparison with younger individuals.

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