Heritability of Longitudinal Measures of Body Mass Index and Lipid and Lipoprotein Levels in Aging Twins

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Body-mass index (BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels are known to be highly heritable. We evaluated the genetic and environmental relationships of these measures over time in an analysis of twin pairs. Monozygotic (235 pairs) and dizygotic (260 pairs) male twins were participants in the National Heart Lung and Blood Institute Veteran Twin Study, and were followed with three clinical exams from mean age 48 years to mean age 63 years. Structural equation modeling (SEM) with adjustment for *APOE* genotype (a significant contributor to TC and LDL-C) was used to assess longitudinal patterns of heritability. Results indicated a contribution of genetic factors to BMI, TC, LDL-C, HLD-C, and TG. Modest increases over time were observed in the heritability of BMI (from 0.48 to 0.61), TC (from 0.46 to 0.57), LDL-C (from 0.49 to 0.64), and HDL-C (from 0.50 to 0.62), but this trend was not present for TG. There was a corresponding decrease in shared environmental influences over time for these traits, although shared environment was a significant contributor only for HDL-C. Moreover, we observed that genetic influences for all measures were significantly correlated over time, and we found no evidence of age-specific genetic effects. In summary, longitudinal analyses of twin data indicate that genetic factors do not account for a significant proportion of the variation in age-related changes of BMI or lipid and lipoprotein levels.

Genetic factors are known to play an important role in determining the variability of predictors of complex traits, such as body mass index (BMI; body weight in kg divided by height in m^2) and lipid and lipoprotein levels (Garrison et al., 1979; Hunt et al., 1989; Knoblauch et al., 1997; Rice et al., 1993; Rice et al., 2002; Shearman et al., 2000). However, these factors change with age; in males, BMI generally increases up to age 70 years (Droyvold et al., 2006) and levels of total plasma cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) increase with age until the age of 60 years and then decline (Alvarez et al., 1984; Hershcopf et al., 1982; National Institutes of Health, 1982). Longitudinal data on lipids indicate that part of this later decline is not explained by changes in environmental covariates (Hershcopf et al., 1982; Newschaffer et al., 1992).

The classical twin study design provides a means to assess the relative influence of genetic and non-genetic factors in trait variation by comparing similarity of monozygotic (MZ) twin pairs to dizygotic (DZ) twin pairs. Structural equation modeling (SEM) of twin data can shed additional light on the pleiotropic action of genes and/or common environmental influences across traits or over timepoints (Fabsitz et al., 1992; Snieder et al., 1999; Williams & Wijesiri, 1993). Beekman et al. (2002) discussed the extent to which genetic control of lipid and lipoprotein levels varied with age in a cross-sectional multi-center study of twins of several ages. They found evidence for age effects on lipid levels; however, longitudinal data were not assessed (Beekman et al., 2002). Longitudinal analyses of female twins have provided evidence for a genetic influence on age-related changes in BMI (Austin et al., 1997) and lipoprotein levels (Friedlander et al., 1997). Increased understanding of changes in heritability (h^2) of these traits with age will inform gene identification efforts.

To determine whether the genetic proportion of variability in these traits changed with age, we assessed h^2 of BMI, TC, LDL-C, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels, in men who were longitudinally followed from mean age 48 to mean age 63 years as part of the National Heart, Lung, and Blood Institute (NHLBI) Veteran Twin Study. We

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applied SEM in a comprehensive longitudinal analysis to determine whether genetic factors appreciably control change in lipid and lipoprotein levels with age. Because the apolipoprotein E (*APOE*) genotype is a significant predictor of lipid and lipoprotein levels (Sing & Davignon, 1985), whose effects can change with age (Jarvik et al., 1994; Jarvik et al., 1997), we also modeled the influence of *APOE* genotype on trait means. Previously, h^2 of BMI, TC, LDL, HDL, and TG at mean age 48 was estimated to be 0.78, 0.43, 0.57, 0.46 and 0.56 in these data, respectively (Fabsitz et al., 1992; Feinleib et al., 1977). However, these earlier reports did not consider simultaneous longitudinal models, or the influence of *APOE* genotype (Williams & Wijesiri, 1993). The current analysis offers a unique opportunity to more precisely quantify the magnitude of genetic effects on the change in BMI and lipid levels over time.

Methods

Study Subjects

Study subjects were participants in the NHLBI Veteran Twin Study, a cohort composed of Caucasian male twin pairs born between 1917 and 1927 who served in the United States military (Feinleib et al., 1977; Selby et al., 1991). There were 505 MZ pairs initially solicited; of these, 253 pairs participated in initial clinical examinations between 1969 and 1973, 179 pairs returned for a second examination between 1980 and 1981, and 138 pairs returned for a third examination between 1986 and 1987. Of the original 253 MZ pairs examined, 38 individuals from 36 pairs died between the first and third examinations (Selby et al., 1991). There were 560 DZ pairs originally solicited; of those, 260 participated in the first exam, 183 pairs returned for the second exam, and 129 pairs participated in the third exam. Of the 260 DZ pairs initially examined, 58 individuals in 55 pairs died prior to the third exam (Reed et al., 1993; Reed et al., 1991). Characteristics of participants and non-participants did not significantly differ for either zygosity at any examination (Reed et al., 1991). Based on genotype information, 13 twin pairs had zygosity reclassified during the course of the study, as described previously (Reed et al., 1993; Reed et al., 1991). Two additional MZ twin pairs were excluded here, because *APOE* genotyping revealed discordant genotypes. No exclusions were made for medical conditions or medications, which were considered to be part of the usual variance in lipid and lipoprotein levels.

Laboratory Methods

TC and TG (mg/dl) were measured enzymatically (Allain et al., 1974); LDL-C (mg/dl) was estimated (Friedewald et al., 1972) for individuals with measured TG (Sampson et al., 1975) less than 400 mg/dl (Warnick et al., 1990). Genotypes at the *APOE* ε2, ε3, and ε4 alleles were determined on all individuals with samples from the third exam, using the method described by Hixson and Vernier (1990). This included 124 MZ and 122 DZ pairs; 18 individuals with lipid levels at all three exams who did not have an *APOE* genotype available were assigned the ε3ε3 genotype, which is expected to be correct in 60% of individuals.

Statistical Methods

Descriptive statistics and within-pair intraclass correlations were calculated using SAS v. 9.0 (SAS Institute, Inc. Cary, NC). Because of the longitudinal nature of these data, SEM methods were applied, whereby we fit a genetic Cholesky decomposition to all available observed raw data on each measure (Cherny, 2005) using Mx (Neale et al., 2003). The model included an additive genetic component (A), a shared (common) environmental component (C), and a nonshared environmental component (E). Models allowed estimation of the proportion of variance attributable to A, C, and E for each trait, as well as estimation of the contribution of genes and environment to the correlations across exams. Longitudinal models were fitted to each of the five measures separately, yielding five independent sets of comparisons. Each full model (Model 1) included A, C, and E Cholesky decompositions (3 components × 6 decomposition parameters = 18 free parameters), regression weights at each age on each of the five *APOE* dummy-coded genotypes plus an intercept (3 age points × 6 *APOE* genotypes = 18), yielding a total of 36 free parameters. Nine nested models examined the influence of *APOE* genotypes on the traits at each age (Model 2 and Model 3), genetic components (A) and their covariance structure (Model 4, Model 5, and Model 6), shared environmental components (C) and their covariance structure (Model 7, Model 8, and Model 9), and nonshared environmental covariance structure (E) (Model 10). Components of each model were tested with a likelihood ratio χ^2 test.

Due to skewness, model fitting was done on natural-log (ln) transformed values for BMI, HDL-C, and TG. TC and LDL-C distributions were approximately normal, and therefore not transformed, although they were rescaled for convenience by dividing them by 100. Adjustments were not made for age or medication use, because only three participants used lipid-lowering medications, and the narrow age range (within 11 years) did not significantly predict variation in any trait. Adjustment of lipid and lipoprotein levels for *APOE* genotype (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, or ε4ε4) was performed by modeling residuals from a linear regression of each dependent variable on five dummy variables needed to uniquely code the six possible genotypes. As there was no evidence for mean differences across twins and zygosity for all measures, a common set of means were fitted to all individuals in the model. Twins were randomly ordered as the first and second co-twin.

Results

Descriptive statistics and within-pair intra-class correlations for BMI, TC, LDL-C, HDL-C, and TG using all available data (and therefore not correcting for *APOE* genotype) are provided in Table 1 and Figure 1,

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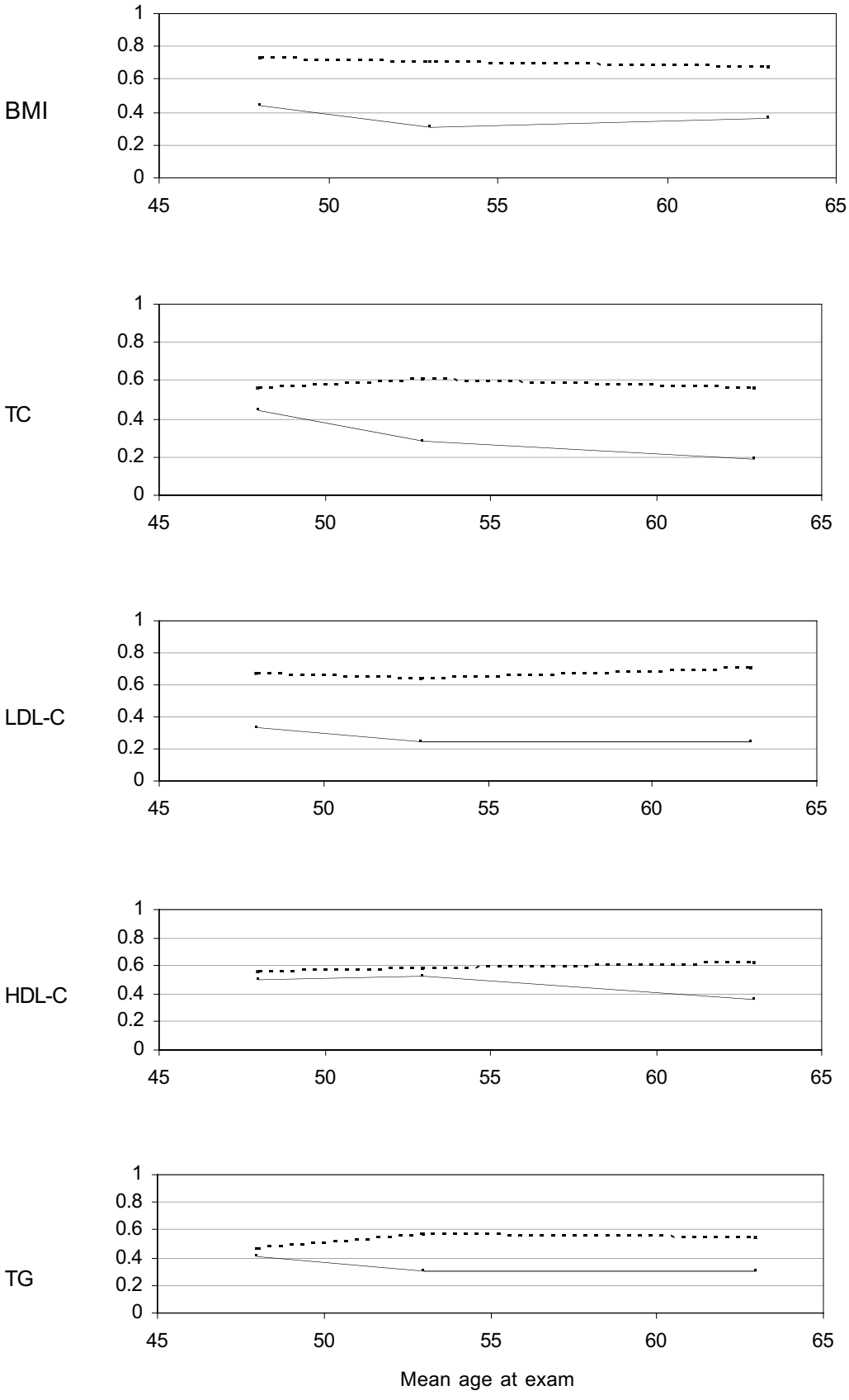

Figure 1

Within-pair intraclass correlations.

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Table 1

Descriptive statistics: Mean + *SD* (*N*)

	Zygosity	Exam 1	Exam 2	Exam 3
Age, years	MZ	47.8 ± 3.1 (505)	57.7 ± 3.1 (377)	63.2 ± 2.9 (305)
	DZ	47.9 ± 3.2 (520)	57.7 ± 3.1 (410)	63.1 ± 3.0 (312)
BMI, kg/m^2	MZ	25.7 ± 3.2 (505)	26.1 ± 3.2 (377)	26.4 ± 3.1 (305)
	DZ	25.8 ± 3.4 (520)	26.1 ± 3.8 (410)	26.8 ± 4.0 (312)
TC, mg/dl	MZ	221 ± 35 (503)	212 ± 34 (374)	221 ± 37 (285)
	DZ	220 ± 41 (516)	211 ± 37 (407)	221 ± 40 (295)
LDL-C, mg/dl	MZ	145 ± 33 (484)	136 ± 32 (366)	150 ± 35 (274)
	DZ	145 ± 37 (492)	135 ± 34 (393)	147 ± 35 (272)
HDL-C, mg/dl	MZ	44.5 ± 12.8 (498)	45.5 ± 11.9 (374)	44.8 ± 10.8 (285)
	DZ	46.3 ± 14.7 (511)	45.7 ± 13.6 (406)	46.6 ± 13.6 (295)
TG, mg/dl	MZ	135 ± 89 (502)	159 ± 85 (374)	140 ± 125 (285)
	DZ	131 ± 102 (511)	163 ± 111 (407)	155 ± 148 (295)

Note: BMI, body mass index; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides.

respectively. There were no apparent differences between MZ and DZ twin trait means (Table 1); however, values at each exam for each trait were more highly correlated among MZ twin pairs than DZ twin pairs, and DZ within-pair correlations decreased over time (Figure 1). This divergence in within-pair similarity between MZ and DZ twin pairs suggests that h^2 may increase over time for these traits.

SEM model fitting analyses were performed, allowing for examination of a full model and nine nested models for each trait, considering only those participants with *APOE* genotype assessed at the third exam; model comparisons shown in Table 2 provide broad tests of the variance components of each trait. For each trait, we tested whether a common set of *APOE* regression weights could be applied at each exam. We found that for all traits this was appropriate (Model 2 vs. Model 1, Table 2), and therefore assumed equal *APOE* weights in the base model for subsequent testing (Model 2). Our goal was to provide a fair test of the major components of each trait, rather than to identify the most parsimonious model. Next, we tested whether *APOE* had an influence on trait means at each exam (Model 3), and found that *APOE* had a significant influence only on TC ($p < .05$) and LDL-C ($p < .01$). *APOE* genotype accounted for 1.6% of the total variance of TC at Exams 1 and 2, and 0.5% at Exam 3. For LDL-C, *APOE* explained 2.4% of the total variance at Exam 1, but only 1.4% at Exams 2 and 3. *APOE* accounted for 1% of variance in TG at Exam 1, but less than 1% of the total variance in the other exams and traits. For consistency, we nonetheless retained the *APOE* parameters for all traits in subsequent model comparisons.

Table 3 provides the estimates of h^2 (the additive genetic contribution to trait variance), as well as the contributions of shared and nonshared environment, with adjustment for *APOE* genotype, obtained from fitting Model 2 to the data (h^2 estimates unadjusted for *APOE* were essentially identical). We first tested whether there was a genetic contribution to overall trait variance at the three exams; for each trait, the heritabilities presented in Table 3 were significant (Model 4). Estimates of h^2 are moderate (around .50) for each trait, with a slight trend towards an increase with time. Estimates of h^2 increased with age for BMI (from .48 to .61), TC (from .46 to .57), LDL-C (from .49 to .64), HDL-C (from .50 to .62), although this trend was not as apparent for TG. We found that genetic covariance across the three exams accounted for a significant component of the covariation of each trait across exams (Table 2, Models 5). Finally, we assessed whether there were genetic influences on the changes in each trait across exams by testing whether genetic correlations (correlations among genetic influences at each age) differed from 1.0 (Table 2, Models 6). That is, we tested whether the second and third Cholesky factors could be dropped, leaving only a single common factor. We found that for each trait, genetic influences were highly correlated across exams; pairwise correlations of the genetic components were greater than .75 for each trait (Table 4), and these estimates were not significantly different from 1.0 (Table 2, Models 6, all ps > .40). These results suggest that although h^2 increases modestly with age for BMI and lipid and lipo-protein levels, the age-related changes in each trait do not appear to be influenced by genetic factors, as evidenced by the genetic correlations not being significantly different from 1.0.

To clarify the role of the shared environment (C) among twin pairs on BMI and lipid and lipoprotein levels, models with and without these terms were also compared using SEM. Overall tests of shared environmental variance, with adjustment for *APOE* genotype (Table 2, Models 7), indicated that only HDL-C had a

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Table 2

Model comparisons

	Model		–2LL	*N* parameters	Comparison model	χ^2	*df*	*p*
BMI	1.	Full	-3414.699	36				
	2.	Equal *APOE* weights	–3400.186	26	1	14.513	10	> .15
	3.	Drop *APOE*	–3397.765	21	2	2.421	5	> .75
	4.	Drop all A	–3384.186	20	2	15.700	6	**< .02**
	5.	Drop A covariances	–3386.713	23	2	13.473	3	**< .005**
	6.	Drop A change	–3397.787	23	2	2.399	3	> .45
	7.	Drop all C	–3397.322	20	2	2.864	6	> .80
	8.	Drop C covariances	–3397.322	23	2	2.864	3	> .40
	9.	Drop C change	–3400.186	23	2	0.000	3	1.0
	10.	Drop E covariances	–3275.012	23	2	125.174	3	**< .001**
TC	1.	Full	1067.771	36				
	2.	Equal *APOE* weights	1073.225	26	1	5.454	10	> .85
	3.	Drop *APOE*	1084.342	21	2	11.117	5	**< .05**
	4.	Drop all A	1114.899	20	2	41.673	6	**< .001**
	5.	Drop A covariances	1106.778	23	2	33.553	3	**< .001**
	6.	Drop A change	1075.624	23	2	2.399	3	> .45
	7.	Drop all C	1077.915	20	2	4.689	6	> .55
	8.	Drop C covariances	1074.062	23	2	0.837	3	> .80
	9.	Drop C change	1073.225	23	2	0.000	3	1.0
	10.	Drop E covariances	1108.433	23	2	35.208	3	**< .001**
LDL-C	1.	Full	576.482	36				
	2.	Equal *APOE* weights	584.504	26	1	8.022	10	> .60
	3.	Drop *APOE*	600.192	21	2	15.688	5	**< .01**
	4.	Drop all A	636.316	20	2	51.811	6	**< .001**
	5.	Drop A covariances	629.206	23	2	44.702	3	**< .001**
	6.	Drop A change	587.232	23	2	2.728	3	> .40
	7.	Drop all C	590.178	20	2	5.673	6	> .45
	8.	Drop C covariances	585.278	23	2	0.774	3	> .85
	9.	Drop C change	584.504	23	2	0.000	3	1.0
	10.	Drop E covariances	607.824	23	2	23.320	3	**< .001**
HDL-C	1.	Full	-483.383	36				
	2.	Equal *APOE* weights	–472.687	26	1	10.696	10	> .35
	3.	Drop *APOE*	–471.000	21	2	1.687	5	> .85
	4.	Drop all A	–422.270	20	2	50.417	6	**< .001**
	5.	Drop A covariances	-432.305	23	2	40.382	3	**< .001**
	6.	Drop A change	–471.960	23	2	0.727	3	> .85
	7.	Drop all C	–459.200	20	2	13.488	6	**< .05**
	8.	Drop C covariances	–468.212	23	2	4.476	3	> .20
	9.	Drop C change	–468.866	23	2	3.821	3	> .25
	10.	Drop E covariances	–411.616	23	2	61.072	3	< .001
TG	1.	Full	2308.128	36				
	2.	Equal *APOE* weights	2321.778	26	1	13.650	10	> .15
	3.	Drop *APOE*	2329.227	21	2	7.449	5	> .15
	4.	Drop all A	2340.567	20	2	18.789	6	**< .005**
	5.	Drop A covariances	2334.902	23	2	13.124	3	**< .005**
	6.	Drop A change	2323.698	23	2	1.920	3	> .55
	7.	Drop all C	2325.443	20	2	3.665	6	> .70
	8.	Drop C covariances	2325.078	23	2	3.300	3	> .30
	9.	Drop C change	2321.778	23	2	0.000	3	1.0
	10.	Drop E covariances	2387.379	23	2	65.600	3	**< .001**

Note: Models considered traits across all three exams; *p* values represent influence of dropped variables using likelihood-ratio testing of nested to full models; BMI, body mass index (kg/m^2); TC, total cholesterol (mg/dl); LDL-C, low density lipoprotein cholesterol HDL-C (mg/dl), high density lipoprotein cholesterol (mg/dl); TG, triglycerides (mg/dl).

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Table 3

Variance Components Estimates

	Exam 1	Exam 2	Exam 3
BMI			
Genetic (A)	.48	.49	.61
Shared environment (C)	.14	.19	.04
Nonshared environment (E)	.38	.32	.35
Total cholesterol			
Genetic (A)	.46	.61	.57
Shared environment (C)	.18	.01	.00
Nonshared environment (E)	.36	.38	.43
LDL-C			
Genetic (A)	.49	.62	.64
Shared environment (C)	.18	.00	.02
Nonshared environment (E)	.33	.37	.34
HDL-C			
Genetic (A)	.50	.40	.62
Shared environment (C)	.20	.25	.05
Nonshared environment (E)	.30	.35	.33
TG			
Genetic (A)	.40	.51	.29
Shared environment (C)	.18	.09	.21
Nonshared environment (E)	.42	.40	.49

Note: Values (which sum to 1.0 at each exam) represent proportion of total variance, adjusted for *APOE* genotype, that is attributable to genetic, shared environmental, and nonshared environmental influences. BMI, body mass index (kg/m^2); TC, total cholesterol (mg/dl); LDL-C, low density lipoprotein cholesterol HDL-C (mg/dl), high density lipoprotein cholesterol (mg/dl); TG, triglycerides (mg/dl).

Table 4

Correlations Among Variance Components

	Exam 1: Exam 2	Exam 2: Exam 3	Exam 1: Exam 3
BMI			
Total	.84	.91	.81
Genetic (A)	.90	.95	.99
Shared environment (C)	1.00	1.00	1.00
Nonshared environment (E)	.70	.90	.55
Total cholesterol			
Total	.60	.67	.50
Genetic (A)	.87	.89	.89
Shared environment (C)	1.00	−1.00	−1.00
Nonshared environment (E)	.25	.37	.16
LDL-C			
Total	.61	.69	.51
Genetic (A)	.96	.90	.75
Shared environment (C)	1.00	1.00	1.00
Nonshared environment (E)	.20	.31	.12
HDL-C			
Total	.60	.77	.58
Genetic (A)	.94	.99	.88
Shared environment (C)	.55	.99	.40
Nonshared environment (E)	.19	.50	.14
TG			
Total	.68	.78	.65
Genetic (A)	.83	.99	.86
Shared environment (C)	1.00	1.00	1.00
Nonshared environment (E)	.42	.57	.35

Note: Correlations presented are adjusted for *APOE* genotype and obtained from the genetic, shared environmental, and nonshared environmental covariances divided by square root of the product of the heritabilities or shared and nonshared environmental variance components, respectively; BMI, body mass index (kg/m^2); TC, total cholesterol (mg/dl); LDL-C, low density lipoprotein cholesterol HDL-C (mg/dl), high density lipoprotein cholesterol (mg/dl); TG, triglycerides (mg/dl).

significant shared environmental component. However, when attempting to dissect this component of variance into whether it was shared across exams (Model 8) or specific to each exam (Model 9), neither test showed a significant effect. That is, while the overall shared environmental influence on HDL-C is significant, we can exclude those components of shared environment that account for correlations across age (Model 8) and those components which allow the shared environmental correlation to deviate from 1.0 (Model 9). Therefore, we cannot conclude whether those shared environmental influences are common across ages, unique to each age, or a combination of the two. For BMI, TC, LDL-C, and TG, however, no test of shared environment was significant, suggesting that environmental factors shared by members of a twin pair did not influence their similarity in these traits. This is readily apparent from the estimates presented in Table 3; the estimates of shared environmental components are either small or near zero for four of the measures, but equal .20 and .25 for HDL-C at Exams 1 and 2 respectively. Although we present shared environmental correlations in Table 4, none are significant, implying the true correlations among the very small, if any, shared environmental influences, could just as likely be 0 as 1.0.

The influence of a nonshared environment (E) considering *APOE* genotype was also assessed. In particular, we tested whether nonshared environment contributes significantly to exam to exam continuity (Table 2, Models 10). For each trait, the nonshared environment did contribute significantly to age to age stability ($p < .001$). We did not test whether the nonshared environmental correlations deviated from 1.0, because it makes little statistical sense and would result in a nonpositive definite expected covariance matrix. Because error variance is a major part of this component, it would also imply that all errors are perfectly correlated, which is not realistic.

In summary, longitudinal analyses of male MZ and DZ twin data found an influence of *APOE* genotype on TC and LDL-C, of additive genetic factors on BMI, TC, LDL-C, HDL-C, and TG, and of shared environmental factors on HDL-C. We observed that h^2 of BMI, TC, LDL-C, and HDL-C increased with age, and that genetic factors are all correlated across age, but these factors do not account for a significant proportion of the variation in age-related changes of any of the traits observed.

Discussion

Our analysis of an aging male cohort suggests that the relative contribution of genetics to BMI tends to

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increase slightly with age, and that genetics does not play a significant role in the change of BMI with age. Fabsitz et al. previously assessed h^2 of trends in BMI (slope of each individual's regression curve) from military induction (mean age of 20 years) through exam three in the cohort considered here and estimated an h^2 of .70 (Fabsitz et al., 1994). Our present analysis assessed the genetic influences on the relative rankings of BMI and the continuity and change in those rankings over time, while the growth curve analysis of Fabsitz et al. addresses the genetic influences on differences among people in their rate of weight gain. A cross-sectional study of older male twins found higher h^2 for BMI among male twins aged 60 to 76 years than among male twins aged 46 to 59, suggesting increase of h^2 with age (Herskind, 1996). Our results show a similar trend, and further show an influence of *APOE*. Both Herskind (1996) and our current analysis found high BMI h^2, and little influence of shared environment overall.

Results also suggest that h^2 of lipids and lipoprotein levels (TC, LDL-C, HDL-C, and TG) increased with age from mean age 48 to 63 years; this appeared to mainly result from a decline in the correlations among DZ twins. This suggests that genetic determinants of TC, LDL-C, HDL-C, and TG at least remain as important, and likely become more important, as men enter the age group in which lipid-related disease plays an increasingly important role in health. Although atherosclerosis may begin in childhood and continues to progress with age, lipid levels in the seventh decade continue to be predictive of health (Metter et al., 1992). It is possible that the h^2 of these traits may be over-estimated at all ages due to increased environmental sharing in MZ versus DZ twins (Hunt et al., 1989; O'Connell et al., 1988); however, this effect would not lead to the trend of increasing heritability with age, unless the level of shared environmental change within this age range changes differentially for MZ and DZ twins, an unlikely scenario. Additionally, relative to genetic variance, the covariance due to shared environment in families was found to be small for lipids and lipoproteins in the present study, consistent with previous findings (Brenn, 1994; Hunt et al., 1989; Rice et al., 1991a; Rice et al., 1991b), and further suggesting that inflated heritability due to unequal environments is unlikely. In one study comparing twins reared together and apart, shared environment impacted covariance of TC, but not that of TG and HDL-C (Heller et al., 1993). Friedlander et al. (1997) estimated h^2 at .25 to .36 over a 10-year period in LDL-C and .23 to .58 for HDL-C in a longitudinal study of adult female twins (Friedlander et al., 1997). Nance et al. (1998) found evidence for changes in HDL h^2 among teenaged twins.

Genetic factors do not contribute to age-to-age change in any of the traits observed in the present study; however, the increases in h^2 with age reinforce the need to evaluate gene by age interactions carefully when evaluating loci which impact lipid level (Heijmans et al., 2005; Knoblauch et al., 1997). The finding that heritability of lipid levels appears highest later in life suggests the possibility of identifying the loci that influence lipid levels would be most productive when those levels are measured in older people.

The generalizability of these results may be limited because the sample was drawn from military recruits healthy enough for induction. Previous analyses of those completing all three exams suggest that their lipid and lipoprotein distributions are representative of the total NHLBI sample as well as that of the age-specific male population in the United States (Jarvik et al., 1994).

While many studies support significant h^2 of lipid and lipoprotein levels, and many of the genes which contribute to this h^2 have been described (for reviews, see Breslow, 2001; Comuzzie et al., 2001; Crook, 2002; Snieder et al., 1999; Talmud & Humphries, 2001); longitudinal studies such as this one are less susceptible than cross-sectional studies to group differences due to differential survival. Our study of aging men suggests that the influence of some genes on cardiovascular risk factors may vary with age. Behavioral factors clearly may also influence the effect of genetics on these factors (Greenfield et al., 2004; Williams et al., 2005). We conclude that genetic factors may become increasingly important determinants of BMI, TC, LDL-C, HDL-C, and TG as men age from their late forties to their early sixties, and that h^2 should not be thought of as a static measure throughout life.

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