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Common Genetic and Environmental Effects on Lipid Phenotypes: The HERITAGE Family Study

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Key Words
Lipids · Lipoproteins · Pleiotropic effect · Genetics · Exercise · Risk factors · Coronary heart disease

Abstract
Objective: Despite the well known genetic component influencing plasma lipid-lipoprotein levels and the observed correlations among these traits, little is known about pleiotropic heritable determinants among them. Our aim is to investigate pair-wise polygenic and environmental correlations among lipid-lipoprotein levels at baseline and in response to regular exercise in Whites and Blacks. ***Methods:*** Common pair-wise genetic and environmental correlations among levels of total cholesterol (TC), LDL-C, ApoB, HDL-C (also HDL_2-C and HDL_3-C), triglycerides (TG, HDL-TG and LDL-TG) and ApoA-1 were investigated at baseline and again after a 20-week endurance exercise program using a variance-components-decomposition. ***Results:*** With a few exceptions, all lipid phenotypes were heritable at baseline and for training responses in Blacks and Whites. Strong to high genetic and environmental correlations ($0.4 < \rho_g < 0.7$) were observed for the majority of the baseline pair-wise traits. For training responses, many of the same patterns were noted, although fewer genetic correlations were significant as compared to the baseline results. ***Conclusions:*** Results suggest that the observed phenotypic correlations among many of these traits may be due to in part to pleiotropic genes, in particular between LDL-C and ApoB and between TG and HDL-C. This shared genetic architecture should be considered in follow-up gene finding studies.

Introduction

It is well documented that dyslipidemia is an important risk factor for coronary heart disease (CHD). High plasma levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C) and reduced levels of high density lipoprotein-cholesterol (HDL-C) are associated with an increased risk of CHD [1]. Apolipoprotein B (ApoB) is the primary surface component of LDL particles and is also strongly associated with an in-

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creased risk of CHD [2]. HDL particles induce the removal of cholesterol from cells. Apolipoprotein A-1 (ApoA-1) is the primary protein in HDL; it activates the mobilization of cholesterol ester stores in macrophages, leading to the reduction of the cholesterol content. There are two interrelated subfractions of HDL-C, the HDL_2-C and HDL_3-C, in which HDL_3-C assimilates lipids and is converted to HDL_2-C. Although the risk of CHD increases with reduced levels of either subfraction [3], it is more prominent with diminished levels of HDL_2-C [4]. While TG subfractions (HDL-TG and LDL-TG) are scarcely described in the literature, some studies have shown that these phenotypes may be clinically important. For example, TG enriched HDL predisposes HDL particles to clear ApoA-I more rapidly, leading to a lowering of HDL-cholesterol levels in hypertriglyceridemia [5, 6]. The increased TG and decreased HDL levels are associated with the presence of atherogenic small, dense LDL-cholesterol [7]. The LDL-TG/apoB ratio, which measures the TG content per LDL particle, was also found to be negatively related to LDL particle size [8].

Regular physical exercise improves the lipid profile, particularly by increasing plasma HDL-C levels [9, 10], and it is recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines to reduce the risk for CHD [1]. The exercise training program in the HERITAGE study resulted in significant mean increases in HDL-C that is primarily due to an increase in HDL_2-C and in ApoA-1, but had no effect on LDL-C, TC and TG mean levels [11, 12]. It was also shown to improve the low HDL-C levels in the presence of elevated TG and abdominal obesity [13]. Heritability estimates of the fasting lipids and lipoproteins account for about 25% to 80% of phenotypic variance in normolipemic individuals at baseline [14] and about 25 to 65% of the responses to exercise training [15] in the HERITAGE study. Since that the levels of these traits are correlated phenotypically, the question this study address is whether these genetic determinants are shared across the lipids and lipoproteins.

Methods

The specific aims, study design, data and standardized training exercise protocol in each of the four clinical centers of the HERITAGE Family Study have been described in detail elsewhere [16]. In summary, the participants were measured in a sedentary state and after 20 weeks of endurance exercise training. The criteria for participation in the HERITAGE Family Study included age between 17 and 65 years, being healthy but sedentary for at least the previous 6 months, body mass index under 40 kg/m^2, and systolic/diastolic blood pressure less than 159/99 mm Hg. Individuals with confirmed or possible CHD, hypertension, chronic or recurrent respiratory problems, and uncontrolled endocrine and metabolic disorders, including diabetes and use of lipid-lowering drugs, were excluded from the study. Each subject was exercise-trained under supervision on a cycle ergometer three times a week for 20 weeks using a standardized training protocol. The intensity and duration of the training program were adjusted every 2 weeks beginning at a heart rate (HR) corresponding to 55% of their baseline maximal oxygen uptake (VO_{2max}) for 30 min per session, and increasing gradually to a training HR that was associated with 75% of the subject's VO_{2max} for 50 min during the last 6 weeks. The power output of the cycle ergometer was adjusted automatically to maintain the desired HR of the subject at all times during all training sessions.

Family structures included both parents and at least 2 offspring, but some black family units were smaller. The HERITAGE data consist of 529 subjects from 99 White families and 326 Black subjects from 101 families. However, samples included here were comprised of 520 Whites and 315 Blacks having lipid-lipoprotein at baseline and 468 Whites and 222 Blacks for response to training. The study was approved by the Institutional Review Board at each center and written informed consent was obtained from each subject.

All lipid phenotypes were obtained in the morning after a 12-hour fast. The lipid measurements, data adjustment procedure and statistical analysis are described in detail elsewhere [9, 11, 12, 15]. Blood was drawn twice at baseline at least 24 hours apart and twice at 24 and 72 h after the last training session. Blood samples were taken from post-menopausal women at any time of the month, but for the remaining women blood was drawn during the early follicular stage. TC and TG concentrations were determined in plasma (total) and in lipoproteins (HDL-TG and LDL-TG) by enzymatic methods using a Technicon RA-500 Analyzer (Bayer Corporation Inc, Tarrytown, NY). The apoA-I and apoB concentrations were measured in the infranatant by the rocket-immunoelectrophoretic method of Laurel [17]. HDL-C fraction was obtained after precipitation of LDL in the infranatant by the heparin-manganese chloride method [18]. Selective precipitation was used to isolate HDL_2 and HDL_3 subfractions using dextran sulfate [19]. Extensive quality control procedures ensured the validity and reproducibility of the lipid-lipoprotein measurements [20]. Daily variation was characterized by high intraclass correlations (from 0.79 for HDL_3-C to 0.95 for ApoB and TC), and the coefficient of variation was between 4.2% (ApoA-1) and 21.8% (TG). The laboratory measurement error was low, with repeated-measure and split-sample intraclass correlations that range from 0.93 (HDL_3-C) to 0.99 (TC, TG, HDL-C, LDL-C, ApoB) and coefficient of variations that range from 0.7 to 10%.

The two baseline values were averaged, as were the two post training values. The training response was computed as the difference between post-training and baseline values. Post training values were corrected for plasma volume changes due to exercise [11]. Data adjustments were carried out separately within sex, race and age groups (Whites: <30, 30–50, ≥ 50 years old; Blacks: <35, ≥ 35 years old). A stepwise multiple regression procedure was used, and only terms that were significant at the 5% level were retained. During model development, individuals with extreme scores (>4 standard deviations from the mean (mean ± SD)) were temporarily set aside so that they would not unduly influence the regressions. Each

Table 1. Descriptive characteristics for unadjusted traits and covariates

Traits	Whites			Blacks		
	n	mean ± SD	range	n	mean ± SD	range
Baseline						
TG, mmol/l	520	1.37 ± 0.78	0.38 to 6.33	315	1.03 ± 0.60	0.36 to 4.62
HDL-TG, mmol/l	520	0.22 ± 0.06	0.11 to 0.51	314	0.22 ± 0.05	0.12 to 0.46
LDL-TG, mmol/l	520	0.26 ± 0.11	0.05 to 0.89	314	0.26 ± 0.12	0.06 to 0.92
LDL-C, mmol/l	520	2.99 ± 0.81	0.73 to 6.04	315	2.85 ± 0.77	1.25 to 5.18
ApoB, mmol/l	520	0.86 ± 0.24	0.21 to 1.56	314	0.80 ± 0.22	0.38 to 1.66
TC, mmol/l	520	4.48 ± 0.95	1.92 to 7.70	315	4.24 ± 0.88	2.30 to 6.99
HDL-C, mmol/l	520	1.04 ± 0.26	0.49 to 2.02	315	1.08 ± 0.30	0.56 to 3.55
HDL_2-C, mmol/l	520	0.35 ± 0.18	0.03 to 0.98	314	0.36 ± 0.22	0.06 to 2.00
HDL_3-C, mmol/l	520	0.69 ± 0.13	0.30 to 1.11	314	0.72 ± 0.15	0.39 to 1.55
ApoA-1, mmol/l	520	1.18 ± 0.17	0.68 to 1.91	314	1.15 ± 0.16	0.78 to 1.78
Training responses						
TG, mmol/l	468	–0.02 ± 0.42	–1.83 to 2.31	222	–0.04 ± 0.35	–1.68 to 1.41
HDL-TG, mmol/l	468	0.00 ± 0.04	–0.16 to 0.14	222	0.00 ± 0.05	–0.14 to 0.13
LDL-TG, mmol/l	468	0.01 ± 0.06	–0.22 to 0.25	222	0.01 ± 0.06	–0.20 to 0.25
LDL-C, mmol/l	468	–0.02 ± 0.37	–1.29 to 1.41	222	–0.01 ± 0.34	–0.79 to 1.49
ApoB, mmol/l	468	0.00 ± 0.11	–0.39 to 0.32	222	0.01 ± 0.10	–0.34 to 0.36
TC, mmol/l	468	0.01 ± 0.41	–1.36 to 1.58	222	0.01 ± 0.38	–1.09 to 1.73
HDL-C, mmol/l	468	0.04 ± 0.11	–0.33 to 0.54	222	0.03 ± 0.12	–0.46 to 0.43
HDL_2-C, mmol/l	468	0.02 ± 0.11	–0.48 to 0.54	222	0.04 ± 0.11	–0.25 to 0.48
HDL_3-C, mmol/l	468	0.01 ± 0.10	–0.23 to 0.37	222	–0.02 ± 0.10	–0.34 to 0.24
Covariates						
Age, years old	529	35.4 ± 14.5	17.0 to 65.2	326	32.9 ± 11.6	17.0 to 65.9
Hormonal use	529	30%		326	50%	

Note: To convert mmol/l to mg/dl, multiple triglyceride by 88.54.

The hormonal use is given in % and represents women taken contraceptives and/or hormone replacement therapy (0 = no, 1 = yes).

phenotype was adjusted for the effects of age (age, age^2, age^3) and hormonal use (contraceptives and hormone replacement therapy; 0 = no, 1 = yes). The residual variances were also examined by regressing the squared residuals from the mean age regression on another similar regression model in a stepwise manner and retaining significant terms. The final phenotypes for all subjects were computed using the best regression models with the residuals standardized to a mean of 0 and a SD of 1. The responses were adjusted for the similar covariates (age and hormonal use) in addition to the respective baseline levels.

Bivariate correlation analyses were employed using a variance components model as implemented in the computer program SOLAR version 2.1.2 [21]. A maximum likelihood variance components method was used to partition the phenotypic variance into 2 components, one due to additive familial effect (the so-called polygenic heritability; h^2) and another due to non-familial effects (the environmental component). In brief, the observed covariances between two subjects within a pedigree were compared to the expected values based on the product of their coefficient of relationship (twice the kinship coefficient). As lipid-lipoprotein phenotypes were previously adjusted for covariate effects (as described above), the heritabilities and phenotypic variances were estimated on these adjusted phenotypes. Heritability was tested using likelihood ratio test. The null hypothesis of no genetic effect ($h^2 = 0$) was compared with the alternative (estimating h^2). The difference in minus twice the log likelihoods (–2lnL) of the two hypotheses is asymptotically distributed as a χ^2 with one degree of freedom. The heritability estimates between Black and White families were compared using a heterogeneity likelihood ratio test. If the heritability estimates were not significantly different, the Black and White families were combined for greater power and precision in the estimation. The bivariate model partitioned the phenotypic correlation (ρ_p) between a given pair of quantitative traits into their additive genetic (ρ_g) and random environmental (ρ_e) correlations. Tests addressed whether the correlations were significantly different from zero ($\rho_I = 0$) and whether the correlations were unity ($\rho_I = 1$).

Table 2. Maximal heritability estimates for adjusted traits, at baseline and training response in Blacks and Whites

Traits	Whites, $h^2 \pm$ SE		Blacks, $h^2 \pm$ SE	
	baseline	training response	baseline	training response
TG	0.48 ± 0.07	0.22 ± 0.08	0.21 ± 0.13	0.32 ± 0.18
HDL-TG	0.45 ± 0.08	0.49 ± 0.07	0.46 ± 0.13	0.42 ± 0.19
LDL-TG	0.59 ± 0.07	0.26 ± 0.08	0.50 ± 0.13	0.59 ± 0.15
LDL-C	0.53 ± 0.07	0.31 ± 0.08	0.80 ± 0.09	0.14 ± 0.15*
ApoB	0.62 ± 0.07	0.18 ± 0.08	0.78 ± 0.09	0.48 ± 0.16
TC	0.67 ± 0.07	0.26 ± 0.08	0.70 ± 0.10	0.25 ± 0.17
HDL-C	0.58 ± 0.06	0.26 ± 0.08	0.63 ± 0.11	0.27 ± 0.15
HDL_2-C	0.56 ± 0.06	0.49 ± 0.07	0.63 ± 0.11	0.57 ± 0.14
HDL_3-C	0.43 ± 0.07	0.35 ± 0.07	0.39 ± 0.12	0.41 ± 0.14
ApoA-1	0.57 ± 0.07	0.36 ± 0.08	0.43 ± 0.12	0.21 ± 0.20*

h^2 = Maximal heritability (± standard error (SE), the % of phenotypic variance due to the additive familial effects.

* Non-significant ($p \geq 0.05$).

Results

Table 1 shows the descriptive statistics for the plasma levels of unadjusted lipid and lipoprotein phenotypes and covariates at baseline and their training responses in Whites and Blacks. Age was a significant predictor of baseline lipid and lipoprotein levels accounting for ~20% of the phenotypic variance. For training responses, the baseline level was the most consistent predictor accounting for ~10 to 40% of the variance.

The maximal heritabilities for adjusted plasma lipid and lipoprotein levels are reported in table 2. The heritabilities were significant ($p < 0.05$) for all traits at baseline and in response to exercise in both Black and White families, except for LDL-C and ApoA-1 training responses in Black families. For each lipid and lipoprotein trait, heterogeneity in the heritabilities between Black and White samples was tested at baseline as well as in response to training. As noted in table 2, larger intra-individual variations in lipid and lipoprotein levels (i.e., the standard errors (S.E.)) were found in Black than in White samples, which is probably due to the reduced sample size in Blacks. The heritabilities were homogeneous (not different, $p > 0.05$) between samples for each trait at baseline, with the exception of baseline LDL-C (results not shown). The general pattern of baseline results was for somewhat higher estimates for TC, LDL-C and ApoB (0.6 to 0.7 range) followed by HDL-Cs and ApoA-1 (0.5 to 0.6 range), with lower values for the TGs (0.4 to 0.5 range). The heritabilities for the training responses were generally lower than for baseline, and were less consistent across races. In fact the heritability was nearly twice as high in Blacks for LDL-TG and ApoB training responses. However, the heterogeneity tests suggested that these estimates were not significantly different for response traits (results not shown). Consequently, further bivariate analyses were undertaken on combined White and Black families for homogeneous traits (baseline and training response traits); while the heterogeneous baseline LDL-C was analyzed separately as well as in the combined sample.

A summary of the phenotypic, genetic and environmental correlations for pair-wise traits in the combined sample and in Whites and Blacks for baseline LDL-C are given in table 3. For combined sample, there are significant cross-trait familial effects for 17 of the 22 baseline pair-wise traits, ranging from strong ($\rho_g \geq 0.65$) to moderate ($\pm 0.21 \leq \rho_g < 0.65$). Only 5 of the baseline genetic correlations are not significantly different from zero.

In contrast, the training response genetic correlations are generally lower, not significantly different from zero for 14 of 22 pairwise traits, and not different from 1.0 for one pair (TC – LDL-C). These results likely arise from the low power to detect the modest correlations, perhaps owing in part to the modest sample sizes in both races. For the significant 6 pairs of responses, the results suggest there may be pleiotropic genes that underlie the covariation in responses.

Although the estimates assumed no Black-White differences, there were sample differences for 5 baseline LDL-C pairwise traits (table 3). It is interesting to note that the pairwise genetic correlations (baseline TC – LDL-C and LDL-C – ApoB) are similar in Blacks and Whites. The TG – LDL-C genetic correlation in the Black sample cannot be distinguished from one, while the other 2 genetic correlations, LDL-C – ApoA-1 and LDL-C – HDL-C, were not significant in either race.

Discussion

The heritabilities of plasma lipids and lipoproteins have been widely reported in studies presumably involving individuals with heterogeneous habitual activity level backgrounds [14, 22, 23]. In contrast, reports from the HERITAGE Family Study are based on individuals and families in which activity levels were controlled [11, 15]. Genetic and environmental pleiotropic

Table 3. Phenotypic (ρ_p), genetic (ρ_g) and environmental (ρ_e) correlations between pair-wise, for combined samples at baseline and training responses and baseline Whites and Blacks

Trait pairs	Combined sample					
	baseline			training responses		
	ρ_p	ρ_g	ρ_e	ρ_p	ρ_g	ρ_e
TG – LDL-C	0.31	0.40	0.22	0.06	–0.30*	0.18
TG – ApoB	0.57	0.65	0.52	0.33	0.23*	0.37
TG – LDL-TG	0.68	0.71	0.66	0.48	0.63	0.43
TG – HDL-TG	0.63	0.68	0.60	0.57	0.66	0.54
TG – TC	0.46	0.48	0.47	0.32	–0.18*	0.49
TG – HDL-C	–0.39	–0.40	–0.40	–0.18	–0.23*	–0.16
TG – HDL_2-C	–0.46	–0.50	–0.42	–0.10	–0.04*	–0.19
TG – HDL_3-C	–0.20	–0.19*	–0.20	–0.09	–0.37	0.04
TG – ApoA-1	0.04	0.03*	0.05	0.22	0.32*	0.18
TC – LDL-C	0.90	0.95	0.85	0.85	0.95†	0.82
TC – ApoB	0.87	0.89	0.83	‡		
TC – HDL-C	0.08	0.21	–0.16	0.28	0.59	0.17
TC – ApoA-1	0.30	0.29	0.33	0.35	0.22*	0.41
LDL-C – ApoB	0.87	0.92	0.79	0.65	0.33*	0.76
HDL-C – ApoA-1	0.69	0.74	0.64	0.44	0.28*	0.51
HDL_2-C – ApoA-1	0.44	0.58	0.27	0.22	0.41	0.09
HDL_3-C – ApoA-1	0.72	0.76	0.68	0.40	0.10*	0.57
HDL-C – HDL_2-C	0.81	0.88	0.70	0.56	0.70*	0.50
HDL-C – HDL_3-C	0.72	0.80	0.65	0.53	0.27*	0.66
LDL-C – ApoA-1	0.11	0.07*	0.16	0.20	0.13*	0.23
HDL-C – ApoB	–0.26	–0.17*	–0.41	0.00	0.06*	–0.02
LDL-C – HDL-C	–0.09	0.04*	–0.28	0.12	0.45	–0.01
	Baseline Whites			Baseline Blacks		
TG – LDL-C	0.30	0.38	0.22	0.31	0.51†	0.27
TC – LDL-C	0.91	0.94	0.87	0.91	0.96	0.80
LDL-C – ApoB	0.87	0.91	0.82	0.89	0.94	0.68
LDL-C – ApoA-1	0.14	0.17*	0.10	0.06	–0.11*	0.36
LDL-C – HDL-C	–0.07	0.14*	–0.34	–0.11	–0.15*	–0.02

Note = Entries without footnote denote ($0 < \rho_g < 1$).
* $\rho_g = 0$ (not significant different from 0, $p \geq 0.05$).
† $\rho_g = \pm 1$ (not significant different from ± 1, $p \geq 0.05$).
‡ It does not converge.

effects among plasma levels of lipid and lipoprotein traits have not been widely reported [24], and no study has dealt with the issue in response to regular exercise. The highest phenotypic correlations were found among baseline TC, LDL-C and ApoB ($\rho_p \sim 0.9$), followed by correlations among HDL-C and subfractions and ApoA-1 ($0.4 < \rho_p < 0.8$), and TG and subfractions with the other lipoproteins ($0.3 < \rho_p < 0.7$). The lowest phenotypic correlations ($\rho_p < \pm 0.2$) were among baseline TG and HDL_3-C, TC – HDL-C, LDL-C – ApoA-1, LDL-C – ApoB, and LDL-C – HDL-C. For training responses, the phenotypic correlations were generally lower, and many of the genetic correlations were not significantly different from zero.

The present results at baseline show approximately similar phenotypic correlations for all bivariate traits recently described [24] in Hispanic and African American families. Strong and moderate genetic and environmental correlations were observed for LDL-C – ApoB (ρ_g and $\rho_e > 0.70$) and TG – HDL-C (ρ_g and $\rho_e \sim -0.40$) on both studies. However, the HERITAGE baseline genetic correlations are higher than those reported [24] for TG –

LDL-C (0.09 vs. 0.40) and TG – ApoB (0.38 vs. 0.65). The discrepancies between these studies could be attributed to various factors such as allele frequency differences across population stratifications, and/or gene-environmental interaction due to different habitual activity levels. Although the phenotypic correlations between HDL-C – ApoB (ρ_p = –0.25) and LDL-C – HDL-C (ρ_p = –0.09) are the same in both studies, they are not statistically significant in HERITAGE, that is likely due to the difference in the sample size.

Studies have reported that HDL_2-C has an inverse association with the risk of CHD [25, 26], and is the most variable subclass reflecting changes in HDL-C in type 2 diabetes mellitus [4]. Moreover, inverse correlations between the plasma HDL_2-C levels and severity of lesions (r = –0.72) and rate of lesion progression (r = –0.58) were described in the normotriglyceridemic patients who had survived a myocardial infarction [26]. We observed that the genetic correlation between baseline plasma levels of HDL_2-C – TG (–0.50) is somewhat stronger than that between HDL-C – TG (–0.40) in the combined sample, while the TG – HDL_3-C genetic correlation is not different from zero.

Epidemiological studies have shown that a decrease in HDL-C is independent of LDL-C at any level [10, 27, 28]. Our finding suggests no significant genetic correlation (ρ_g = 0) between HDL-C – LDL-C at baseline. However, a genetic correlation of 45% was found in response to regular exercise in the combined sample. Since training responses were adjusted for baseline values, the additive genetic correlation for the response to regular exercise presumably reflects a gene by environmental interaction effect.

In summary, our results show many additive genetic correlations reflecting concomitant variations in plasma lipid and lipoprotein levels. In reality these proportions could represent shared genetic or familial environmental or both factors, and more sophisticated methods are necessary to distinguish among them. However, the present results may contribute to understanding the genetic basis of lipid-lipoprotein that are involved in metabolic disorders and risk of CHD and may serve as guides for gene discovery mainly using pleiotropic statistical approach. Genetic correlations over 50% for many bivariate traits in the sedentary state were found. A similar pattern was observed for exercise-training response phenotypes although the magnitude of genetic correlations is lower. It is worth noting that the training responses were adjusted for baseline levels, thus suggesting that pleiotropic estimates are specific for the response to regular exercise, i.e. gene-environmental interaction. Consequently, much error or noise in the variance for training responses are observed as compared to baseline data.

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