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Variability in the Response of HDL Cholesterol to Exercise Training in the HERITAGE Family Study

Abstract

In the HERITAGE Family Study, 675 sedentary, healthy, white and black men and women, aged 17 to 65 years, performed 20 weeks of supervised cycle ergometer exercise at the same relative intensity and weekly volume. As a group, subjects had normal mean baseline lipid levels for North Americans with the exception of below average high density lipoprotein cholesterol (HDL-C) levels. A significant mean increase in plasma HDL-C of 3.6% was observed; however, there was marked variability in responsiveness to training, ranging from a mean 9.3% decrease in Quartile 1 of HDL-C response to a mean 18% increase in Quartile 4 ($P < 0.0001$ by ANOVA). Parallel changes in HDL_2-C and HDL_3-C, apolipoprotein A-I levels, and lipoprotein lipase activity were noted across quartiles. The change in HDL-C across quartiles was inversely related to baseline HDL-C ($p < 0.0001$) and to changes with training in plasma triglycerides ($p = 0.0007$). No significant differences in HDL-C response were observed across quartiles by sex, race, age, or increase in $\dot{V}O_2$max with training; however, weak positive associations were observed with age-adjusted education level and with reduction in abdominal fat and increase in $\dot{V}O_2$max at the ventilatory threshold following training. Multivariate regression analysis including baseline variables and training responses only accounted for 15.5% of the variability in the HDL-C response to training. Thus, marked variability was found in the HDL-C response to the same endurance exercise training stimulus with only a modest amount of the response predictable by identified nongenetic factors.

Key words
Blood lipids · HDL · exercise training · HERITAGE Family Study

Introduction

Based primarily on the results of observational studies, a consensus exists that plasma high density lipoprotein (HDL) has antiatherogenic properties with its concentration inversely related to risk of coronary heart disease (CHD) [23,26]. A consensus also exists that an endurance exercise–induced increase in plasma levels of HDL cholesterol is one of the multiple mechanisms by which physical activity can reduce risk of CHD [24,35]. This conclusion is based on the results of both observational and exercise training studies over the past three decades. Wood et al. [44] first reported in 1979 that men and women runners had higher HDL cholesterol (and lower triglyceride) levels than age-matched sedentary controls. Following this report numerous

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other cross–sectional studies confirmed this observation in men and women of all ages performing a wide variety of aerobic activities [11]. Although it appears from these observational studies that a "dose-response relationship" exists between HDL cholesterol (primarily due to a higher level of the HDL_2 fraction) and both the volume of aerobic activities and level of maximal oxygen uptake ($\dot{V}O_2max$), confounding variables probably played important roles in these associations [11,35]. These might include genetic differences contributing to self-selection of activity levels and reduced body fat, (especially in the intra-abdominal region) in the more active individuals. Further, endurance exercise training studies performed during the past two decades have yielded inconsistent plasma lipid responses [11,20,35,38]. The study investigators reported either an increase in plasma HDL cholesterol (primarily in the HDL_2 fraction) and a reduction in triglycerides, consistent with the findings from cross-sectional studies, or no changes in lipids, and sometimes even a reduction in HDL cholesterol levels, generally associated with a concomitant cholesterol–lowering diet [20,36]. Such variability in responsiveness to training is understandable considering the multiple potential confounding variables, which can affect plasma lipid levels and their populations, in the design of the exercise training program, and in the physiologic responses to training, and in multiple behavioral factors affecting blood lipids [11,29,35]. Biological contributors to this variability include genetic factors and study participants' ethnic/racial origin, age, sex, hormonal status and menstrual periodicity, body weight and composition, and relative fitness levels. The subject's baseline lipid levels and day-to-day and seasonal fluctuations in blood lipids also may contribute significantly to reported outcome of studies. Differences in the study design and exercise training programs also undoubtedly contributed to the reported variability in responsiveness. These include adequacy of sample size relative to the expected magnitude and heterogeneity of the lipid effects, the type, volume, and intensity of exercise, duration of training, adherence to the program, and the associated changes with training in body weight, body composition, plasma volume, and $\dot{V}O_2max$. Fluctuations in behavioural characteristics, which may alter levels of blood lipids during the course of a training study include physical activity habits aside from the prescribed exercise, dietary habits, and the use of tobacco products, alcoholic beverages, hormonal replacement drugs and other medications. Analytical factors potentially affecting results include the number of blood samples before and after training, the timing of the blood drawings relative to the last meal and to the last exercise session, the body position during blood drawing, internal and external laboratory quality control of the lipid assays, and whether adjustments were made for plasma volume changes with training. In the HERITAGE Family Study (HERITAGE), we attempted to control many of these potential confounding environmental factors during a standardized and supervised endurance exercise training program, involving a large biracial group of men and women in a broad age range. Initial results of the blood lipid changes have recently been reported [21]. We wish to report here in more detail the observed variability in plasma HDL cholesterol response to exercise training in this study population, despite our attempts to minimize potential confounding factors, and to attempt to identify possible contributors to this variability.

Methods

Protocol

The study design and methods used in HERITAGE were previously described in detail [3].

In brief, sedentary members of about 200 two-generation white and black families were exercise-trained under supervision for 20 weeks at 4 participating clinical centers. In the project reported here, blood lipid levels were compared before and after training and the variability in response of HDL cholesterol to training was assessed.

The study protocol was approved by the Institutional Review Boards protecting human subjects in research projects at each of the 4 participating clinical centers, and written informed consent was obtained from each subject. Participants received an incremental $1000 honorarium for successful completion of the study.

Subjects

White participants were members of two-generation nuclear families, consisting of both natural parents under 65 years of age and at least 2 offspring aged 17 to 40 years. The black participants were of similar ages, but were generally enrolled in smaller family units. Race was determined by self-classification by the participants. Data are presented from 675 (217 black and 468 white) participants, who had complete lipid data sets before and after training. To be eligible for participation in HERITAGE, participants were required to be in good health, but sedentary for at least the previous 6 months, to pass a physician-administered physical examination, and to have no significant electrocardiographic abnormalities on a maximal exercise test. Exclusion criteria included treated or untreated hyperlipidemia and moderate or severe hypertension, diabetes mellitus requiring medication, or a body mass index (BMI) exceeding 40 kg/m^2 with the exception of an occasional heavier individual receiving special medical clearance. Subjects' peak education level attained was classified in HERITAGE from 1 to 5 with 1 = < 6 grades; 2 = elementary school completion; 3 = high school completion; 4 = some college; and 5 = at least one college degree.

Clinical procedures

Following health screening, participants completed a battery of health-habit questionnaires assessing smoking and alcohol consumption habits, medication use, and menstrual history, the ARIC-Baecke Physical Activity Questionnaire [1,18], the Willett Food Frequency Questionnaire [40], and the Minnesota Eating Pattern Assessment Tool (EPAT) [28] which measures high and low dietary fat sources. The EPAT and ARIC-Baecke questionnaires were repeated during weeks 10 and 20 of exercise training.

Participants were counseled at baseline and the midpoint of the training program (10 weeks) not to alter their usual health habits. This included advice to continue their usual eating patterns, physical activity habits outside the study, alcohol and tobacco use, and oral contraceptive or hormonal replacement therapy. Mean alcohol intake in g/day was calculated from the usual amounts of alcohol contained in reported daily servings of beer, wine, mixed drinks, and other beverages. Good adherence to this advise was generally reported, including no significant group

mean changes from baseline in dietary and outside physical activity habits on the EPAT and ARIC-Baecke questionnaires.

In addition to anthropometric measurements and the BMI, hydrostatic weighing was used to determine body density, fat-free mass, and percent body fat [2] with adjustments made for residual lung volume by the oxygen-dilution method [42] at three of the clinical centers and by the helium-dilution method at the fourth center [22]. Subcutaneous, deep (i.e. visceral), and total abdominal fat areas were assessed by quantitative computed axial tomography (CT scans) obtained between the fourth and fifth lumbar vertebrae as previously described [3].

Maximal cycle ergometer exercise tests were performed twice on separate days (at least 48 hours apart) before training and twice after completion of training for determination of maximal oxygen uptake ($\dot{V}O_2$max), as previously described [3,4]. In brief, testing was performed on SensorMedics 800S cycle ergometers (Yorba Linda, CA) connected to a SensorMedics 2900 Metabolic Measurement Cart. Criteria for attaining $\dot{V}O_2$max were a respiratory exchange ratio greater than 1.1, a plateau in $\dot{V}O_2$ (change of $< 100\ ml \times min^{-1}$ during the last three 20-second intervals of the test), and a heart rate within 10 bpm of the predicted maximal heart rate for the participant's age.

All HERITAGE subjects achieved $\dot{V}O_2$max by one or more of these criteria on at least one of the two maximal exercise tests both before and after training. The average $\dot{V}O_2$max for each pair of tests was used as the $\dot{V}O_2$max level if the values were within 5% of each other. If they differed by more than 5%, the higher of the two values was used. Oxygen uptake at the ventilatory threshold [$\dot{V}O_2$at VT) also was determined retrospectively, using a combination of 3 previously validated methods [14]. Adequate $\dot{V}O_2$ at VT data were obtainable in 339 subjects (131 parents and 228 offspring) or 50.2% of the study participants. Another measure of submaximal endurance used in this study was the mean heart rate attained at a 50 W work output during the pair of maximal exercise tests.

Exercise training program

Participants trained under supervision on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA) at the 4 clinical centers, all using the same standardized exercise protocol [3,21]. In brief, participants exercised 3 times per week for 20 weeks, progressing from an initial duration of 30 to 50 minutes per session for the last 6 weeks of training. Similarly, exercise intensity was progressively increased from the heart rate associated with 55% $\dot{V}O_2$max during baseline testing to that associated with 75% $\dot{V}O_2$max. During training sessions, the power output of the cycle ergometer was automatically adjusted for each subject to the desired heart rate response during exercise via a built-in computerized control device. The estimated mean energy expenditure per subject during each training session over the 20 weeks period was about 328 kcal (1372 kJ) per session or 984 kcal (4116 kJ) per week.

Blood lipid and insulin determinations

Blood samples were obtained from an antecubital vein into vacutainer tubes containing EDTA in the morning after a 12–hour fast with participants in a semirecumbent position, twice at baseline and 24 and 72 hours after the last exercise training session. For eumenorrheic women, all samples were obtained in the early follicular phase of the menstrual cycle at baseline and 24 hours following training, at which time minimal lipid and lipoprotein variation is reported to occur [29]. Plasma samples from the 3 U.S. HERITAGE clinical centers were shipped refrigerated with ice packs to the HERITAGE Lipid Core Laboratory at the CHUL Research Center in Quebec, Canada, for determination of plasma lipids, lipoproteins, lipase activities, and specific apolipoproteins. This laboratory is a participant in several lipid laboratory certification programs. Cholesterol and triglyceride levels were determined in plasma and lipoproteins by enzymatic methods using a Technicon RA-500 analyzer (Bayer, Tarrytown, NY). Plasma VLDL was isolated by ultracentrifugation [17]. The HDL fraction was obtained after precipitation of low density lipoprotein (LDL) in the infranatant by the heparin–manganese chloride method [5]. Selective precipitation was used to isolate HDL-fractions using dextran sulfate [15].

The apo A-I level was measured in the infranatant fraction by the rocket-immunoelectrophoretic method of Laurel [19] with measurements calibrated against reference standards provided by the Centers for Disease Control and Prevention (Atlanta, GA). Plasma postheparin LPL and HL activities (PHLA) were measured once per subject, before and after training, following a 12 hour overnight fast, and 10 minutes after intravenous administration of heparin (60 IU per kg of body weight) [9,10,34]. PHLA were assayed by a modification of the method of Nilsson-Ehle and Ekman [25], and are expressed as nmoles of oleic acid released per ml of plasma per minute.

Plasma was obtained for insulin assays after an overnight fast at baseline and following training prior to initiating an intravenous glucose tolerance test [3]. Plasma insulin concentrations were assayed at the HERITAGE Central Laboratory using a radioimmunoassay with polyethylene glycol separation [8].

Extensive quality control procedures were implemented to ensure high quality lipid and other study data [10,13]. These include repeat lipid assays in 5% of all samples and analyses of split specimens prepared at each clinical center. Results from plasma specimens containing chylomicrons were discarded for analyses in this study as being suggestive of non-fasting status.

Data analysis

All HERITAGE data were analyzed at the Washington University (St. Louis) Data Coordinating Center using the SAS statistical package (version 6.1, SAS Institute, Cary, NC). Data are expressed in this manuscript as the mean ± standard deviation (SD). Paired *t* tests were used to determine significant differences between mean data obtained before and after training. ANOVA and Tukey's HSD test [39] were implemented to determine the influence of gender, generation (parents vs. offspring), and race (black vs. white) on the magnitude of change in each study variable. The percent change in plasma HDL cholesterol levels with training was further analyzed by quartiles of response for the total group and by gender, generation and race subgroups. Analysis of variance and Duncan's Multiple Range Test were used to determine significant changes across quartiles. Paired *t* tests were also used to compare values of potential confounding lipid and nonlipid variables between Quartiles 4 vs. Quartile 1 of percent HDL cholesterol change. Statistical significance was established at a p-level less than 0.05.

Pearson product–movement correlation coefficients were performed to determine the strength of the univariate associations between the group's mean HDL cholesterol response to exercise training and subject characteristics, body mass, body composition, physical fitness, and blood lipid variables and fasting plasma insulin levels, at baseline and following training.

Stepwise multiple linear regression analysis was also performed to determine the percentage of the nongenetic variability in HDL cholesterol response to training that could be explained by baseline variables and training-induced changes. For the multivariate regression analyses, only variables that were significant at the 0.05 level of significance were retained.

Results

Baseline characteristics

Baseline characteristics of the study population by gender are shown in Table **1**. The mean ages of the younger generation ("offspring") and older generation ("parents") were 26.5 and 51.5 years, respectively. Mean BMI and body composition measurements indicate that as a group they were overweight. As previously reported [21], dietary assessments at baseline revealed a mean dietary lipid intake for the group which was below average for North Americans and close to levels recommended by the United States National Cholesterol Education Program for Adults [23]. No significant change in mean dietary lipids intake was noted during training based on responses to the EPAT questionnaire [21].

Physical fitness and body composition changes

Detailed descriptions have been published on the effects of the HERITAGE exercise training program on $\dot{V}O_2$max [32] and body composition [43]. Among those participants reported here with satisfactory lipid data, mean increases were observed in $\dot{V}O_2$max ($ml \times min^{-1}$) of 18.6 ± 9.5 % and 15.1 ± 7.6 % in women and men, respectively, following 20 weeks of training with no significant differences in responses between the sexes. Associated small, but statistically significant ($p < 0.05$), reductions were observed in mean body mass of 0.18 ± 2.4 kg for the women and 0.42 ± 2.2 kg for the men. The associated mean reductions in total fat mass by underwater weighing and in total, subcutaneous, and deep abdominal fat areas by CT scan were significantly greater in the men as compared to the women participants. Such sex differences in body composition responsiveness to exercise training have previously been reported [12, 21].

Plasma lipids

Mean baseline plasma lipid and lipoproteins levels and PHLA are presented in Table **2**. We previously reported baseline plasma lipid levels separately for the male and female participants [21] and found that the mean values for both sexes were in the normolipidemic range for North Americans with the exception of HDL cholesterol [23]. The mean baseline concentration of HDL cholesterol for the women of 44.3 ± 10.2 $mg \times dl^{-1}$ (1.14 ± 0.25 $mmol \times l^{-1}$) and for the men of 37.1 ± 0.7 mg (0.96 ± 0.25 $mmol \times l^{-1}$) were both in the 25th percentile for North Americans.

Table **1** Baseline characteristics of the study population by sex (Mean ± Standard Deviation)

Variable	*Men (n = 299)*	*Women (n = 376)*
Age (years)	35.6 ± 14.1	34.4 ± 13.2
Body Mass (kg)	84.6 ± 16.1	69.3 ± 16.1
BMI ($kg \times min^{-1}$)	26.9 ± 4.9	26.2 ± 5.6
$\dot{V}O_2$max ($ml \times kg^{-1} \times min^{-1}$)	35.1 ± 6.9	25.5 ± 3.6
$\dot{V}O_2$max ($ml \times min^{-1}$)	2 068.8 ± 351.0	1 857.6 ± 367.7
Cigarette Smokers (%)	12.5 ± 3.3	14.8 ± 3.6
Alcohol Intake ($g \times day^{-1}$)	7.2 ± 12.1	3.2 ± 5.9

Table **2** Baseline lipid levels and lipase activities

A. Baseline plasma and lipoprotein concentrations (Mean ± Standard Deviation)

Variable (n = 675)	Concentration ($mg \times dl^{-1} \pm SD$)*
Total Cholesterol	171.0 ± 36.1
LDL Cholesterol	114.4 ± 31.5
VLDL Cholesterol	15.5 ± 12.6
HDL Cholesterol	41.1 ± 10.6
HDL_2 Cholesterol	13.9 ± 7.6
HDL_3 Cholesterol	27.2 ± 5.2
Triglyceride	110.1 ± 63.2
Apo A-I	117.5 ± 16.7
Ratio Total to HDL Cholesterol	4.4 ± 1.3

B. Baseline post-heparin plasma lipase activities

Type of Lipase	Activity ($nmol \times min^{-1} \times l^{-1} \pm SD$)
Lipoprotein Lipase	651.5 ± 32.2
Hepatic Lipase	190 ± 74.0

* To convert $mg \times dl^{-1}$ to $mmol \times l^{-1}$ divide cholesterol values by 38.7 and triglycerides by 88.54

As previously reported [21], 20 weeks of training resulted in a significant group mean increase in HDL cholesterol ($p < 0.001$) with small associated decreases in total triglycerides and VLDL triglycerides ($p < 0.01$). No significant changes from baseline were observed following training for the other lipid and lipoprotein parameters nor in the total cholesterol to HDL cholesterol ratio. The mean increase in HDL cholesterol for the entire group (n = 675) was 1.4 $mg \times dl^{-1}$ (0.36 $mmol \times l^{-1}$) or 3.6 ± 11.1 % with no significant difference in response observed by sex, generation, or race, although there was a trend for a greater increase in the offspring as compared to the parents ($p < 0.07$). The increase in HDL cholesterol primarily involved the HDL_2 fraction, but HDL_3 cholesterol also showed a small increase with training ($p < 0.001$). As would be expected from the HDL changes, there was an associated increase in apo A-I ($p < 0.002$). PHLA also were significantly altered by training. The mean increase in LPL activity was 18.3 % for the men and 6.6 % for the women ($p < 0.02$), while HL activity was significantly reduced following training, 6.9 % in men and 5. 1 % in women ($p < 0.05$).

Fig. **1** dramatically demonstrates the marked variability in percent change in plasma HDL cholesterol by quartiles of responsiveness for the entire group (n = 675). This ranged from a mean increase of 6.9 mg × dl^{-1} (0.18 mmol × l^{-1}) or 18 % above the baseline level in Quartile 4 to a reduction in Quartile 1 of 4.2 mg × dl^{-1} (0. 11 mmol × l^{-1}) or 9.3 % below the baseline levels.

Individual HERITAGE subject responses of HDL cholesterol to exercise training ranged from a 66 % increase to a 24 % reduction, as compared to baseline levels. We next examined the association of subject characteristics with the percent change in HDL cholesterol across quartiles. No significant differences were observed in the variability in response across quartiles by sex, generation, or race. However, a statistically significant association was observed across quartiles with increasing education level, a commonly used parameter of socioeconomic status (SES). The mean education level ranged from 3.6 ± 0.9 units in Quartile 1 to 3.9 ± 1.0 units in Quartile 4 ($p < 0.05$).

There were no significant differences observed by ANOVA between HDL cholesterol responsiveness to training across quartiles with baseline levels of the following variables: smoking, alcohol intake, dietary lipid intake by the baseline EPAT score and the Willett Questionnaire responses, BMI, percent body fat, abdominal CT scans for total, subcutaneous or deep fat areas. A significant ($p < 0.01$) inverse association was observed between HDL cholesterol response across quartiles and its baseline concentration. In Quartile 1, the mean baseline HDL cholesterol level was 43.6 mg × dl^{-1} (1.13 mmol × l^{-1}) as compared to 38.8 mg × dl^{-1} (1.00 mmol × l^{-1}) in Quartile 4. However, no significant associations were observed between HDL cholesterol response across quartiles and baseline levels of other assessed lipid-related parameters (i. e., total, LDL, and VLDL cholesterol, triglycerides and PHLA).

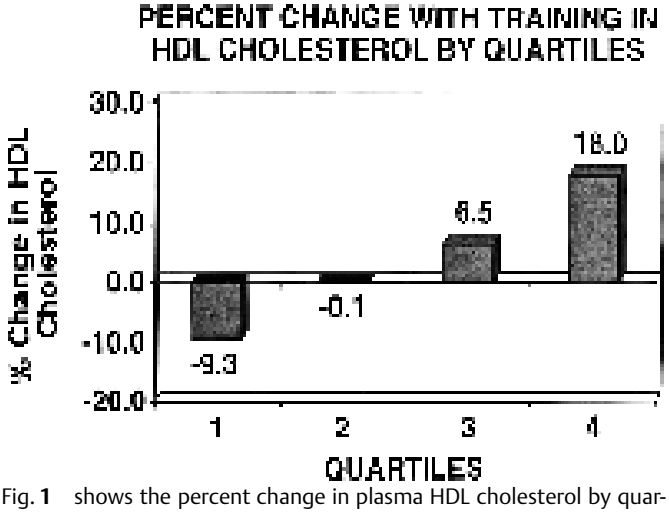

Fig. **1** shows the percent change in plasma HDL cholesterol by quartiles of response to 20 weeks of exercise training (n = 675).

Table **3** shows a comparison of the percent changes with exercise training in other lipid-related variables with the percent change in HDL cholesterol across quartiles. The percent changes in HDL_2 and HDL_3 cholesterol and apo A-I levels paralleled the HDL cholesterol response ($p < 0.0001$). A trend also was noted for an increase in LDL cholesterol across quartiles ($p < 0.07$). In addition, significant inverse associations were observed between changes in levels of triglyceride and VLDL cholesterol and VLDL triglyceride (data not shown), with percent change in HDL cholesterol ($p < 0.0001$). A positive relationship also was noted between percent change in LPL activity and the response in HDL cholesterol to training across quartiles ($p < 0.0001$). In contrast, the reduction in HL activity with training was not significantly different across quartiles.

Table **4** shows training-induced changes in body composition and physical fitness variables by quartiles of percent change in HDL cholesterol. No significant associations were noted between either percent loss of body mass or of fat mass with training and changes in HDL cholesterol across quartiles. However, the mean percent reductions of total and subcutaneous abdominal fat areas (but not the deep fat area) via CT scans paralleled the increase in HDL cholesterol across quartiles with p-values of 0.02 and 0.01, respectively.

The percent increase in $\dot{V}O_2max$ (ml × min^{-1}) with training was not significantly associated with the percent change in HDL cholesterol across quartiles nor was an association found between the change with training in heart rate at a 50 W power output on the cycle ergometer and percent change in HDL cholesterol across quartiles. However, there was a significant association observed between percent increase in $\dot{V}O_2$ at VT and the change in HDL cholesterol across quartiles ($p < 0.01$).

Table **3** Percent change in lipid variables (± standard deviation) with training by quartile of HDL cholesterol response (n = 675)

	Percent Change (± SD) by Quartile (Q) of Change in HDL Cholesterol				
Lipid variables	Q^1	Q^2	Q^3	Q^4	p Value (ANOVA)
Total Cholesterol	–2.6 (8.5)	–0.01 (7.5)	1.3 (8.8)	4.4 (9.4)	0.0001
LDL Cholesterol	–1.0 (14.0)	–0.7 (10.9)	0.7 (14.0)	2.2 (12.2)	0.07
VLDL Cholesterol	19.0 (62.9)	3.6 (45.4)	–1.2 (37.4)	–4.6 (41.5)	0.0001
HDL Cholesterol	–9.3 (4.8)	0.1 (1.9)	6.5 (2.0)	18.0 (8.0)	0.0001
HDL_2 Cholesterol	–9.3 (27.1)	8.1 (31.1)	19.5 (34.1)	44.0 (49.8)	0.0001
HDL_3 Cholesterol	–6.1 (15.7)	–1.0 (12.3)	3.6 (12.5)	10.6 (13.0)	0.0001
Triglyceride	8.0 (31.6)	0.2 (27.3)	–1.8 (23.4)	–2.6 (24.9)	0.0001
Apo A-I	–2.2 (9.5)	–0.1 (7.7)	4.5 (9.1)	8.2 (10.0)	0.0001
LPL Activity	23.2 (68.7)	38.1 (96.0)	27.3 (93.2)	65.9 (143.9)	0.0001
HL Activity	–4.5 (23.8)	–0.3 (26.7)	–1.3 (27.9)	–4.2 (25.3)	0.77

Table **4** Percent change with training in body composition and fitness variables by quartile of percent change in HDL cholesterol with training

Variable	Percent Change by Quartile (Q) Q^1	Q^2	Q^3	Q^4	p Value (ANOVA)
Body Mass (kg)	0.02	–0.40	–0.26	–0.53	0.51
Fat Mass (kg)	–2.62	–2.95	–3.41	–4.20	0.62
Abdominal Fat Area (cm^2)					
Total	–1.80	–4.11	–3.96	–5.45	0.02
Subcutaneous	–0.68	–4.05	–3.96	–5.04	0.01
Deep	–3.37	–3.95	–3.49	–4.97	0.45
$\dot{V}O_2$max ($ml \times min^{-1}$)	16.6	18.6	17.7	17.7	0.31
$\dot{V}O_2$ at VT ($ml \times min^{-1}$)	27.9	30.5	34.2	36.0	0.01
HR at 50 W	–8.6	–8.5	–8.8	–9.1	0.34

Pearson product correlational analyses were used to assess associations between the mean percent change in HDL cholesterol with training and mean group measurements obtained at baseline and following exercise training. Table **5**A contains the independent baseline variable correlations which were found to be statistically significant ($p < 0.05$). Training-induced change in HDL cholesterol was unrelated by univariate analysis to sex, age, race, health habits (i.e. use of tobacco products, alcoholic beverages, and dietary lipid intake), baseline BMI, body composition variables, nor to baseline physical fitness variables (i.e. $\dot{V}O_2$max HR at 50 W, or $\dot{V}O_2$ at VT). A weak, but statistically significant, correlation was observed with peak education level ($r = 0.088$; $p < 0.022$), which persisted after adjustment for age, sex, and race.

Significant inverse associations were observed between the change in HDL cholesterol with training and baseline levels of HDL cholesterol ($r = -0.191$), its subfractions, and its apo A-I component. However, no significant associations were observed with the other assessed baseline lipid–related variables by univariate analysis. Table **5**B lists training–induced changes significantly associated with the observed changes in HDL cholesterol. Statistically significant, but weak, negative correlations were found with training–induced reductions in fat mass ($r = -0.108$) and total abdominal ($r = -0.120$) and subcutaneous abdominal fat areas by CT scans. Change in $\dot{V}O_2$ at VT was the only assessed endurance fitness parameters found to be significantly associated with the HDL cholesterol response to training ($r = 0.140$).

Percent change in HDL cholesterol was also directly related to changes in total cholesterol ($r = 0.296$), LDL cholesterol ($r = -0.087$) and LPL activity ($r = 0.145$), as well as would be expected, with changes in both major HDL subfractions and apo A-I level. In addition, significant inverse associations were evident with changes in VLDL cholesterol ($r = -0.188$) and triglycerides ($r = -0.154$). However, no significant correlations were found with mean training-induced changes in hepatic lipase activity and fasting insulin levels.

A number of stepwise multiple linear regression models were tested to select the best combination of independent variables to help explain the variance in HDL response to exercise training. The best stepwise regression model limited to baseline variables as predictors could only explain about 12% of the variance. This model included baseline HDL cholesterol, sex, alcohol consumption, lipoprotein lipase activity, peak education level, and percent body fat.

Table **5** Significant pearson correlation coefficients (r) with percent change in plasma HDL cholesterol following exercise training (dependent variable)

Independent variables	r	p Value
A. Baseline		
Education (Highest Level)	0.088	0.022
HDL Cholesterol	–0.191	0.0001
LDL Cholesterol	–0.132	0.0006
HDL_2 Cholesterol	–0.132	0.0006
HDL_3 Cholesterol	–0.197	0.0001
Apo A-I	–0.160	0.0001
B. Following Training		
Δ Body Mass (kg)	–0.018	0.007
Δ Total Abdominal Fat Area (CT Scan)	–0.120	0.002
Δ Subcutaneous Abdominal Fat Area (CT Scan)	–0.121	0.002
Δ $\dot{V}O_2$ at VT	0.140	0.005
% Δ Total Cholesterol	0.296	0.0001
% Δ LDL Cholesterol	0.087	0.023
% Δ VLDL Cholesterol	–0.188	0.0001
% Δ HDL_2 Cholesterol	0.515	0.0001
% Δ HDL_3 Cholesterol	0.470	0.0001
% Δ Triglyceride	–0.154	0.0001
% Δ Apo A-I	0.414	0.0001
% Δ LPL	0.145	0.002

Table **6** Stepwise linear regression analysis dependent variable: percent change in HDL cholesterol with training

Step	Independent variable	Partial r^2	Model $100 \times r^2$ *
1.	% Change Triglyceride	0.088	8.8
2.	Baseline HDL Cholesterol	0.015	10.3
3.	Baseline LPL Activity	0.012	11.5
4.	Baseline Insulin	0.010	12.5
5.	Gender (1 = Male, 2 = Female)	0.009	13.4
6.	% Change LPL Activity	0.008	14.2
7.	Baseline % Body Fat	0.005	14.7
8.	Peak Education	0.005	15.2
9.	Alcohol (g/d)	0.003	15.5

* $100 \times r^2$ = percent of variance in change in HDL cholesterol explaining following addition of each step

Table **6** shows the best multilinear stepwise regression model containing a combination of both significant baseline variables and training–induced changes. Included in this table are the partial r^2 contribution of each variable entering the model and the percent of the variance explained following each entry step. It will be noted that the only independent training-induced changes accepted into the stepwise regression model were percent changes in triglyceride and LPL activity. Each of the 9 independent variables in the model explained less than 2% of the variance

and overall model explained only 15.5% of the nongenetic variance. The addition to the model of the change in apo A-I with training, which is not an independent variable since it is structurally related to HDL, increases the explained variance to 34.5%. $\dot{V}O_2$ at VT can also make a small additional contribution to the explained variance, but was not included in the model since adequate retrospective determination of this variable from exercise test results could only be obtained in half of the study subjects. Baseline variables which failed to be accepted into the stepwise regression models, included the following: age, race, cigarette smoking, dietary lipid intake, BMI, CT-scan abdominal fat areas, triglyceride, LDL cholesterol and HL activity. Training-induced changes in the following variables also were rejected from the model: body mass, fat mass, $\dot{V}O_2$max HR at 50 W, LDL cholesterol, and HL activity.

Discussion

The HERITAGE participants as a group, despite their pre–training sedentary lifestyles and overweight status, otherwise practiced relatively good health habits. These included a low prevalence of cigarette smokers and a below average consumption of alcoholic beverages and percent of daily energy from dietary lipids for North Americans. Their mean baseline blood lipid profile was normal with the exception of low plasma HDL cholesterol levels for both men and women. The low mean baseline HDL cholesterol levels undoubtedly reflect both genetic and environmental influences. Familial aggregation of baseline HDL cholesterol levels was previously demonstrated in the HERITAGE study population with the maximal heritability estimated at 83% [27]. Baseline environmental contributors to low mean baseline HDL cholesterol levels in HERITAGE subjects probably also included their sedentary life-styles (a recruitment requirement) and their relatively low dietary intake of fat, cholesterol, and alcohol [11,20,35].

The most important change noted in the participant's blood lipid profile with exercise training was a modest mean increase in plasma HDL cholesterol of 3.6% with no significant differences in response noted by sex, generation, or race [21]. A review of the literature reveals that only about half of published endurance exercise studies in men and less than half of the studies involving women observed significant increases in HDL cholesterol with an average increase of about 5% reported from meta-analyses of studies in which there were no concomitant dietary changes involving a total of over 2000 participants [20,38]. The increase in HDL cholesterol with training in this and most other studies primarily involved the HDL_2 fraction, and was generally accompanied by an increase in apo A-I and in LPL activity and a reduction in HL activity [11,20,21]. These findings suggest both an increased synthesis and reduced catabolism of HDL [11,21,37].

Potential factors which can contribute to the variability in the response of HDL cholesterol to exercise training were briefly reviewed earlier. Despite attempts to control many of the potential environmental, behavioral, and experimental variables that affect plasma lipid levels, considerable variability was still observed in the plasma HDL cholesterol response to 20 weeks of a standardized and supervised exercise training in this previously sedentary population. This variability was unrelated to generation or race of the participants. Sex differences was only a minimal contributor to the variability in responsiveness based on multivariate analysis.

Genetic factors undoubtedly contributed to this variability in responsiveness of HDL cholesterol to training. A familial clustering of HDL cholesterol response to exercise training was previously observed in HERITAGE with estimated maximal heritabilities of 29% and 26% observed in white and black participants, respectively [30]. The corresponding maximal heritability of the change in HDL's apo A-I levels with training was even higher, i.e. 89% and 33% for black and white participants, respectively. The influence of heredity on the plasma lipid and lipoprotein response to short-term exercise training was previously reported in male twins [7]. In a recent study involving a small group of men, it was suggested that the apolipoprotein E (apo E) genotype, inherited from each parent in a single Mendelian fashion, influenced the response of plasma HDL cholesterol to training [16]. This observation may have relevance to findings in this present study, and we are currently exploring the association of apo E genotypes in HERITAGE subjects to their plasma lipid responses. Another possible heritable factor contributing to HDL responsiveness to exercise is the relative proportion of type 1 red skeletal muscle fibers, which are known to have a high LPL activity [35].

In HERITAGE, the percent change in HDL cholesterol with training was inversely related to baseline HDL cholesterol levels, which is consistent with the findings of a recent meta-analysis [20]. However, this differs from the observations of Williams et al. [41] and Zmuda et al. [46], who found that men with low initial HDL cholesterol levels were less likely to increase HDL cholesterol levels through endurance exercise training. This issue deserves additional attention. The finding of an inverse association between the responses of plasma HDL cholesterol and triglyceride levels to training has previously been reported [11,16,21,29,36,37]. The coexistence in the present study of an increase in triglycerides and a reduction in HDL cholesterol in Quartile 1 of HDL cholesterol response suggests that participants represented in this subgroup may have reduced their dietary fat intake in favor of more carbohydrates, as often occurs in individuals initiating endurance exercise training; however, this could not be confirmed by repeated EPAT assessments. Other observed lipid–related predictors of the HDL cholesterol response across quartiles were the mean baseline LDL activity and its increase with training. The relationship of LPL activity to an increase in HDL cholesterol has been previously reported with exercise training in HERITAGE and other studies [9,10,21,37]. This finding also is consistent with the observed inverse triglyceride changes across quartiles of HDL cholesterol response, since LPL is involved with the lipolysis of triglycerides in VLDL (as well as chylomicrons). We previously reported small, but statistically significant, reductions following exercise training in body weight and total fat mass and in abdominal fat in HERITAGE [43]. However, only the reduction in total and subcutaneous abdominal fat areas by CT scan was significantly related across quartiles to HDL cholesterol response to training, although a trend also was noted for an increase in HDL cholesterol with reduction in total body and fat mass.

Controversy has existed in the literature on whether a loss of body weight and fat are primarily responsible for the increase in HDL cholesterol during exercise training. Wood et al. [45] in a one year randomized controlled trial involving overweight men failed to find an increase in HDL cholesterol with exercise training in the absence of weight loss. However, more recently Thompson et al. [37] also performed a one year exercise training study involving overweight men in which both body weight and the lipid content of the diet were held constant (via use of a metabolic kitchen). They demonstrated mean 10% increases in HDL cholesterol and apo A-I levels, despite a nonsignificant reduction in fat mass, consistent with an independent effect of exercise on HDL. This confirmed a similar observation in an earlier, short-term, supervised, endurance exercise study by Sopko et al. [33] in which body weight also was maintained and a metabolic kitchen was employed to control dietary lipid intake. It should be noted that obesity and excess abdominal fat are typical male characteristics associated with clustering of metabolic risk factors including dyslipidemias with elevated triglycerides and reduced HDL cholesterol levels, predisposing to cardiovascular disease and type 2 diabetes.

A limited number of other studies have evaluated the effects of exercise on abdominal fat content using a quantitative imaging technique similar to that used in the present study [31]. They also generally found that exercise with or without weight loss is associated with a reduction in abdominal fat in agreement with the findings in the present study. Also in agreement with the findings in the present study, Thompson et al. [37] failed to find an association between change with training in $\dot{V}O_2max$ (expressed either in $ml \times min^{-1}$ or in $ml \times kg^{-1} \times min^{-1}$) and change in HDL cholesterol. However, a significant association in the present study was noted between the training–induced change in $\dot{V}O_2$ at VT, a sensitive measure of improvement in submaximal exercise endurance and HDL cholesterol response.

An unexplained finding in this study was the weak, but statistically significant, association of peak education level to HDL responsiveness. Education level is a commonly-used surrogate indicator of SES, and low SES is associated with increased risk of CHD mortality [6]. Perhaps, reduced plasma HDL cholesterol in association with low SES contributes to this increased risk of CHD in population studies.

Stepwise linear multiple regression analyses including subject characteristics and habits and body weight and composition, physical fitness, and blood lipid–related variables, before and after training, accounted for only 15.5% of the variance in change in HDL cholesterol with training. Since maximal heritability explained only an additional 26% to 29% of the variance, a large percentage of the nongenetic contributors to the variance remains unexplained. Unreported changes in dietary lipid intake and/or in alcohol consumption may have contributed to some of the unexplained variance. We currently are investigating the possible relationship of exogenous sex hormone use in HERITAGE female participants to blood lipid responses and the possible contribution of apo E genotypes to variability in HDL cholesterol response to exercise.

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