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# APOE Genotype Affects Black-White Responses of High-Density Lipoprotein Cholesterol Subspecies to Aerobic Exercise Training

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## Abstract

**Objectives—**To determine whether ethnicity interacts with the APO E genotype to influence conventionally-measured high density lipoprotein cholesterol (HDL-C) subfraction levels and Nuclear Magnetic Resonance measured ($HDL_{NMR}$-C) particle size at baseline, after training, and changes with training.

**Methods—**After a 6-week dietary stabilization period, men and postmenopausal women 50-75 yrs old underwent baseline testing (NMR lipid, $VO_2$max, body composition, and genotyping assessments). Tests were repeated after completing 24 wks of endurance exercise-training.

**Results—**At baseline, APO E2/3 Blacks had significantly larger particle size ($P$<0.001) and higher total $HDL_{NMR}$-C particle concentration ($P$=0.006) than Whites. After 6 months of endurance exercise-training, APO E2/3 Blacks maintained a significantly larger $HDL_{NMR}$-C particle size ($P$<0.001), and particle concentration of the large $HDL_{NMR}$-C than APO E2/3 Whites ($P$<0.001). In multivariate ANOVAs adjusted for demographic and environmental confounding factors, and training-induced changes in lean body mass and intra-abdominal fat; the model explained ~33 percent of the observed variability in training-induced improvements in $HDL_{NMR}$-C particle size ($P$=0.002), with APO E2/3 Blacks having a greater increase in training-induced changes in $HDL_{NMR}$-C particle size. In a separate but similarly adjusted model for conventionally-measured $HDL_2$-C, the model explained, ~49 percent of the observed variability in training-induced changes in $HDL_2$-C.

**Conclusion—**Ethnicity interacted with the E2/3 genotype at the APO E gene locus to influence higher baseline, after training, and greater exercise training-induced improvements in the advantageous HDL-C subfractions in Blacks than in Whites. APO E2/3 Blacks may benefit more from aerobic-fitness to reduce CVD risk.

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**Keywords**

Cholesterol; Genetics; Ethnicity; Exercise

## Introduction

Concentrations of high density lipoprotein cholesterol (HDL-C) and its protective subfractions are inversely related to coronary artery disease (CAD) and cardiovascular disease (CVD) mortality.(1,2) This inverse relationship of HDL-C to CVD risk is strong, graded and independent of other plasma lipoprotein lipid levels and non-lipid risk factors.(3) Despite these strong relationships, there are substantial differences in plasma HDL-C levels across different ethnic groups. In fact, higher HDL-C levels have been consistently demonstrated in Blacks compared to Whites in most population as well as intervention studies.(4,5) Subsequent studies that focused on potential environmental explanations for these differences were unable to readily account for the differences in HDL-C in Whites versus Blacks.(6)

HDL-C particles are heterogeneous with respect to particle diameter, density, composition, and functional properties.(7,8,9) A more complete assessment of HDL-C particle sizes and concentrations is now possible using Nuclear Magnetic Resonance Spectroscopy (NMR). Substantial evidence indicates that these newer NMR measures of plasma HDL-C particle size and concentration provide a more precise estimate of CVD risk.(10,11)

Exercise training can reduce CVD risk by improving plasma lipoprotein-lipid profiles.(12, 13,14,15) Some recent evidence indicates that the training benefits also extend to NMR measures of HDL-C.(16,17) However, numerous studies have shown highly variable responses to standardized exercise training in terms of plasma lipoprotein lipid levels, suggesting that genetic heterogeneity may influence these training adaptations.(18,19) Independent evidence indicates that ethnicity contributes significantly to inter-individual differences in baseline and exercise training-induced changes in HDL-C.(12,18,20) This observation is supported by the presence of higher HDL-C in Blacks despite lower levels of habitual physical activity than Whites.(4,21) It is, however, unknown whether such ethnicity-related differences operate through, or interact with, genetic factors to amplify the effects of physical activity on plasma lipoprotein lipids.

One of the most important gene loci known to influence HDL-C metabolism is the Apolipoprotein (APO) E gene. APO E affects the hepatic binding, uptake, and catabolism of several classes of lipoproteins associated with HDL-C and its subfractions.(22,23) Mature HDL-C particles are partly cleared from plasma by binding to specific APO E receptors on hepatocytes, and by exchanging apoproteins and lipids with other lipoproteins in the tissue. (24) Whereas, the E4 allele of the APO E gene associates with lower HDL-C levels, the E2 and E3 alleles result in higher plasma HDL-C subfractions, making the APO E gene variants an important modifier of HDL-C subfractions.(20) However, it is not known whether ethnicity-specific APO E gene-exercise training interactions result in differences between Whites and Blacks in these newer NMR-measured HDL-C ($HDL_{NMR}$-C) subfractions.

Given a generally higher HDL-C in Blacks than in Whites, the graded relationship of APO E with HDL-C, and the known influence of exercise training on lipoprotein lipid levels, we hypothesized that APO E genotype would have a significant ethnicity-related influence on levels of HDL-C subfractions, and $HDL_{NMR}$-C particle size and concentration at baseline, after training, and on training-induced changes.

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## Methods

Sedentary White and Black men and women aged 50 to 75 yr were screened via telephone to ascertain interest, suitability and ability to participate in an exercise training intervention. The Institutional Review Boards at the University of Maryland College Park and Howard University approved the study protocol, and written informed consent was obtained during each participant's first laboratory visit. Eligible volunteers were non-diabetic, normotensive or hypertensive with blood pressure (BP) controlled with medication (systolic BP <160, diastolic BP <90 mmHg), non-smokers, body mass index (BMI) < 37 $kg/m^2$, not undergoing regular aerobic exercise, and no prior history of CVD. All women were postmenopausal and maintained the same hormone replacement therapy (HRT), either on or not on HRT, throughout the study.

During the participant's first laboratory visit, medical histories were reviewed to ensure subjects met the inclusion criteria, and BMI<37 was ascertained. Participants had blood chemistries and fasting plasma glucose levels determined, and underwent a standard oral glucose tolerance test. Those with fasting glucose >126 mg/dl or 2-hr glucose >200 mg/dl were excluded. Participants had to have ≥1 National Cholesterol Education Program lipid abnormality (25) as this study was part of a larger trial assessing training-induced plasma lipoprotein-lipid changes. Maximal treadmill exercise tests were performed; participants whose exercise test was terminated due to CVD signs or symptoms or showed other evidence of CVD were excluded.

Participants then completed 6 wks of instruction on the principles of an American Heart Association (AHA) Step 1 diet (<30% calories from fat; ~55% from carbohydrates; ~15% from protein; cholesterol intake <300 mg/d).(26) Participants completed 7-day food records, adhered to the diet for >3 wks prior to baseline testing, and maintained adherence to this diet throughout the study. A registered dietician analyzed all food records (Computrition Inc. Chatsworth, CA). Participants completed food records during the exercise training intervention, and met with the dietician every 2-3 weeks to ensure adherence to the diet.

In the morning after a 12-hour fast, venous blood samples were drawn for analyses of major plasma lipid concentrations and lipoprotein particle size. All baseline blood samples were drawn at the end of the 6-week dietary stabilization period, and at least 4 days following any exercise test. Plasma was isolated from blood samples by centrifugation at 3,000 × g for 15 minutes at 4°C in the presence of 0.01% EDTA, and frozen at -70°C until analyzed. To determine conventional plasma lipoprotein lipids levels, the averages of fasted samples drawn on two separate occasions were used. HDL-C was measured after precipitation with dextran sulfate.(27) $HDL_2$-C and $HDL_3$-C were separated using a second high-molecular weight dextran sulfate precipitation with $HDL_3$-C measured and $HDL_2$-C calculated.(28) Because each lipoprotein in plasma within a given diameter range emits a distinctive lipid NMR signal, the intensity of which is proportional to its bulk lipid mass concentration, these signals were used to determine $HDL_{NMR}$-C particle size and subfraction concentrations, using the second of the 2 samples pooled for conventionally measured HDL-C.(29,30) The HDL-C subfractions were determined as follows: large $HDL_{NMR}$-C (10 to 13 nm, similar to HDL-$C_{2b}$); intermediate $HDL_{NMR}$-C (8.2 to 10 nm, similar to HDL-$C_{2a}$ and HDL-$C_{3a}$); and small $HDL_{NMR}$-C (7.3 to 8.2 nm, similar to HDL-$C_{3b}$ and HDL-$C_{3c}$). A “particle size index,” describing the mass-weighted average size of particles within each lipoprotein class, was calculated by weighing each subclass concentration by a numerical size designation (1 to 3) with larger values representing larger particle subclasses. Close agreement has previously been demonstrated between NMR and chemically determined HDL-C (r=0.93).(31) HDL-C subclass distributions determined by NMR have also been shown to be closely related to conventionally-measured HDL-C subfractions.(31) Body composition was assessed by dual-energy- X-ray absorptiometry (DPX-L; Lunar Corp, Madison, WI), and subcutaneous and intra-abdominal

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fat were quantified at L4-L5 using a standardized computed tomography scan protocol.(32) $VO_2max$ was measured using a graded treadmill protocol.(16) Genomic DNA was extracted from peripheral lymphocytes using standard methods.(33) Subjects were typed at the APO E locus as previously described.(34)

Participants then underwent 3 supervised exercise training sessions/wk for 6 months. Initial sessions consisted of 20 min of exercise at 50% $VO_2max$ and progressed until 40 min of exercise at 70% $VO_2max$ was completed during each session.(16,35) Exercise consisted of treadmill walking/jogging, stair-stepping, and cycle and rowing ergometry. Participants added a lower intensity unsupervised 45-60 min walk on the weekend after 12 wks of training. After exercise training, body composition, $VO_2max$, and plasma lipoprotein lipid assessments were repeated as prior to training. The blood samples for plasma lipoprotein-lipid levels were drawn 24 to 36 hours after each subject's last exercise training sessions. Participants' dietary compliance was confirmed prior to final testing.

Statistical analyses were performed using the SAS statistical software system (SAS, Cary, NC) (25). Given the general biological gradient of the APO E genotypes (E2/2, E2/3, E3/3, E2/4, E3/4 and E4/4)(36,20) and relatively small sample size, E2/2, E2/3 and E3/3 were combined and designated as the E2/E3 group, whereas, E4 hetero- or homozygotes were designated as the E4 genotype group. Because there is insufficient information on the biologic gradient of E2/4, 2 volunteers having this genotype were excluded from these analyses. In the initial bivariate analysis, we used t-tests to compare E2/3 Vs E4 in the entire sample, and to determine ethnicity-related differences in baseline and after training HDL-C measurements within each genotype group. Multivariate ANOVA (General Linear Model approach) was used to evaluate the relationship of ethnicity and APO E with training-induced changes in HDL-C. At baseline, complete data were available on 170 subjects (Whites=133; Blacks=37). For the after training bivariate models, 149 subjects (Whites=120; Blacks=29) had complete data. Because of the confirmed significant relationship of ethnicity with training-induced changes in HDL subfraction ($P<0.05$) in the entire group, and the interaction of APO E gene with ethnicity ($P=0.045$) in our preliminary analyses, separate analyses comparing levels of HDL-C and $HDL_{NMR}$-C particle size and subfraction concentrations in White vs. Blacks were conducted for each genotype group. Initial models testing the influence of ethnicity on HDL-C within each APO E genotype group were first adjusted for the baseline values of the dependent variable, while the second models were further adjusted for age and gender. Because of the significant differences in intra-abdominal fat between Blacks and Whites at baseline, the final models included adjustment for training-related changes in lean body mass (LBM) and intra-abdominal fat. Separate analytic models for training-induced changes in HDL-C and $HDL_{NMR}$-C subfractions were constructed. For ethnicity comparisons, all full models testing differences in training-induced changes in $HDL_{NMR}$-C and conventional HDL-C subfractions were adjusted for corresponding baseline values of the dependent variables, age, gender and training-induced changes in LBM and intra-abdominal fat. Statistical significance was accepted at $P\leq0.05$.

## Results

Whites and Blacks in the APO E2/3 genotype group had similar baseline characteristics (Table 1) with respect to body composition and cardiovascular (CV) fitness. However, APO E2/3 Blacks had significantly less intra-abdominal fat than Whites. No differences in body composition or CV fitness were evident between APO E4 Whites and Blacks. In the initial t-test analysis, women on HRT weighed slightly more and had higher lean body mass at baseline, but were similar in all other characteristics compared to those not on HRT.

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Ethnicity was associated with differences in baseline $HDL_{NMR}$-C particle size and subfraction levels in the APO E2/3 group, with Blacks having a significantly larger particle size than Whites (*P*<0.001) (Table 2). E2/3 Blacks also had a significantly higher total $HDL_{NMR}$-C particle concentration than Whites (P=0.006). This higher total $HDL_{NMR}$-C particle concentration in E2/3 Blacks resulted from a higher large $HDL_{NMR}$-C particle concentration, which averaged approximately twice that of Whites, whereas both groups had similar medium and small $HDL_{NMR}$-C particle concentrations. The ethnic differences in $HDL_{NMR}$-C were also evident in the conventional measures of HDL-C, as demonstrated by a significantly higher HDL-C, $HDL_2$-C, and $HDL_3$-C levels in E2/3 Blacks than E2/3 Whites (*P*=0.002, *P*=0.012, and *P*=0.009, respectively), although $HDL_3$-C was also higher in E2/3 Blacks compared to E2/3 Whites (Table 3). APO E4 Blacks and Whites had comparable NMR and conventionally-measured HDL-C subfractions.

The slightly higher body weight and lean body mass observed at baseline in women taking HRT Vs those not on HRT remained unchanged after training. Six months of aerobic-exercise training resulted in favorable responses in both ethnic groups. Though Whites and Blacks in the E2/3 genotype group and E4 Blacks had decreases in intra-abdominal fat, E2/3 Whites still had a significantly higher intra-abdominal fat compared to E2/3 Blacks (*P*=0.003) (Table 1). E2/3 and E4 Blacks and Whites had comparable improvements in $VO_2$ max with CV fitness training, whereas, E2/3 Blacks maintained the significantly better $HDL_{NMR}$-C profile, with larger particle size (*P*<0.001), and higher particle concentration of large $HDL_{NMR}$-C than E2/3 Whites (*P*<0.001) (Table 2). Conversely, though Whites and Blacks in the E2/E3 genotype group were similar at baseline and had statistically non-significant within group decreases in training-related changes in medium $HDL_{NMR}$-C particle concentration, after training levels were significantly lower in E2/3 Blacks than Whites (*P*=0.022) (Table 2). When we examined the relationship between training-induced changes in HDL-C and APO E genotype, training-induced improvements in $HDL_{NMR}$-C particle size were greater in APO E2/E3 Blacks, with the increase being ~2.5 times that in the E2/3 Whites (0.26±0.06 nm vs. 0.10±0.03 nm; *P*=0.015) (Figure 1). However, E4 Blacks had the same training-induced increases in $HDL_{NMR}$-C particle size as E4 Whites. Blacks had slight decreases, while Whites had slight increases with training in levels of conventionally-measured HDL-C compared to baseline, yet HDL levels remained significantly higher in Blacks than Whites (Table 3). Black vs. White differences in after training levels of cardio-protective $HDL_2$-C followed the same general trends observed for large $HDL_{NMR}$-C particle size and concentration, with greater improvement with training in E2/3 Blacks than E2/3 Whites (*P*=0.046). Though Whites had slight increases and Blacks slight decreases in $HDL_3$-C levels, ethnicity did not affect training-related levels of the smaller and less protective $HDL_3$-C between the groups (Table 3). Within the APO E4 genotype group, there was no significant White vs. Black differences in the levels or the training-induced changes in either NMR or conventionally-measured HDL-C subfractions after 6 months of aerobic exercise training.

Initial multivariate analysis for the entire group confirmed our hypothesis of ethnicity-related differences in training-induced changes in HDL subfractions (*P* <0.05). Significant interaction of ethnicity with APO E in a separate model (*P*=0.045) indicates that this ethnicity-related difference differed between E2/E3 and E4. Subsequent multivariate analysis to determine the association of ethnicity with changes in $HDL_{NMR}$-C particle size within the APO E2/3 genotype group included ethnicity and baseline $HDL_{NMR}$-C levels. This model accounted for ~20 percent of the observed variability in training-induced improvements in HDL particle size (*P*<0.001). After adding age and gender to the model, the observed variability increased to ~27 percent (*P*<0.001). In order to control for additional environmental confounding factors, we also adjusted for the effect of training on LBM and intra-abdominal fat; this model explained ~33 percent of the observed variability in training-induced improvements in particle size (*P*=0.002), with E2/E3 Blacks having a disproportionately greater increase in training-induced

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changes in particle size in the complete model. The models for training-induced changes in $HDL_2$-C were generally similar to those observed for particle size, with the initial limited model contributing ~46 percent ($P$=0.011) to the observed variability. Further adjustment for age and gender did not change the explained variability (~47 percent; $P$=0.014). With additional adjustment for differences in body composition, the model contribution increased to ~49 percent ($P$=0.005) of the observed variability in training-induced changes in $HDL_2$-C. However, the gene and ethnicity effects of aerobic exercise training appear limited to $HDL_2$-C and large particle size, as Black vs. White differences in training-induced HDL-C changes were generally not significant in the limited model, or in the fully adjusted model.

## Discussion

In the present study, we showed that ethnicity interacted with the E2/3 genotype at the APO E gene locus to influence HDL-C indices at baseline and after training. Compared to Whites, Black APO E2/3 carriers had higher baseline and greater exercise-training induced improvements in the advantageous HDL-C subfractions, whereas E4 allele carriers did not demonstrate any evidence of Black-White differences in HDL-C at baseline or after 6 months of aerobic exercise training, or in the changes resulting from exercise training.

It is now recognized that HDL-C particles are heterogeneous with respect to particle diameter, density, composition, and functional properties.(7,8,9) Mature HDL-C particles are partly cleared from plasma by binding to specific apolipoprotein E (apoE) receptors on hepatocytes, and by exchanging apoproteins and lipids with other lipoproteins in the tissue.(24) Through the activation of lipoprotein lipase (LPL), HDL-C transfers apo E and apolipoprotein C-II (apoC-II) to both chylomicrons and to very low density lipoprotein (VLDL).(37) Mature HDL-C particles are designated as $HDL_3$, which after losing their cholesterol and gaining triacylglycerol, become the larger cardioprotective $HDL_2$-C particles.(38) Whereas small HDL-C particles are positively related to risk of CAD(9,39,40,41) the protective effect of HDL-C has been most consistently observed for large HDL-C particles.(9,42) Though the influence of the APO E gene on baseline $HDL_2$-C levels in relatively sedentary populations was previously reported,(43) ethnicity-related differences in the effect of APO E gene variants on $HDL_{NMR}$-C particle size and concentration, which are newer, more accurate and a direct measure of HDL-C, have not been described.

Heller and colleagues previously reported that more than 50 percent of the variation in HDL-C levels in humans is genetically determined, and that gene products which influence the amount and nature of lipids contained within HDL-C particles have important effects on the metabolism of HDL-C particles.(44) APOE gene is one of the most widely studied polymorphic variants known to affect lipid metabolism. Its three common alleles code for 3 isoforms of the apo E protein, i.e., ε2, ε3, and ε4.(36) Whereas apoliporotein ε4 preferentially associates with VLDL, apo ε2 and ε3 preferentially associate with HDL-C.(45) In large epidemiological studies, the hierarchy of the APO E phenotypes from the lowest to the highest cholesterol levels was E2/2, E2/3, E3/3, E2/4, E3/4 and E4/4.(36,46,20) This biological gradient of the APO E gene effect on lipid metabolism has important implications for CVD.

Though the exact mechanism by which exercise interacts with APO E genotype to increase large particle size HDL-C remains to be fully elucidated, studies in endurance athletes showed that aerobic fitness can increase HDL-C half-life by several days.(47) This fitness-induced prolongation of HDL-C half-life may allow for the modification of HDL-C particle distribution in the circulation, and APO E2/3 alleles may interact with the increased HDL-C survival caused by exercise to favorably alter HDL-C particle distribution. It is therefore relevant that APO E allele frequencies differ between Blacks and Whites with APO E2 frequency being ~27 to ~33 percent higher and E3 ~8 to ~21 percent lower in Blacks compared to Whites.(48,49,

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50) Trends for baseline and after training APO E genotypes' frequency distribution between Blacks and Whites, approximates generally reported estimates -- 12.8 percent vs 15.8 percent for E2/3; 57.9 percent vs 50 percent for E3/3; and 29.3 percent vs 34.2 percent for E4 heterozygotes. Notably, these differences may underscore some of the ethnicity-related variations in HDL-C levels. Though women on HRT weighed slightly more, and had higher lean body mass at baseline and after training compared to those not on HRT in the initial t-test, these differences did not explain our findings, since the final multiple regression analysis adjusted for body composition.

In addition to possible ethnicity-specific gene variants in HDL-C metabolic pathways, other yet unknown ethnicity-related factor may interact with the APO E genotype to influence baseline levels of $HDL_{NMR}$-C particle size and concentration in a relatively sedentary population. Such factors may also have selective interaction with specific alleles of the APO E gene to effect higher, large $HDL_{NMR}$-C particle size and concentration in Blacks than Whites. Together, our observations support many epidemiological studies showing higher HDL-C subfraction levels in Blacks than Whites, suggesting that higher levels of $HDL_{NMR}$-C and subfraction in Blacks may be partly related to the differential APO E2/3 genotype effects in Blacks compared to Whites. Future studies must focus on the identification of biologic or environmental factors, and the evaluation of the interaction of such factors with APO E gene.

Training-induced levels of conventionally-measured $HDL_2$-C support the presence of higher levels of the large $HDL_{NMR}$-C particles in E2/3 Blacks compared to Whites. Though we are unaware of previous studies that examined the combined influence of APO E gene and ethnicity on training-induced changes in $HDL_{NMR}$-C subfractions, our observation of higher $HDL_2$-C in the APO E2/3 genotype group is in concordance with previous reports from Wood et al, who showed that exercise training-induced increases in plasma HDL-C levels appears to result largely from an increase in the less dense $HDL_2$ subfraction.(54) The greater training-induced changes in $HDL_2$-C levels in our study correlated with our NMR data in APO E2/3 genotype group, and are consistent with a previous report from Hagberg et al who showed that, E2 carrier overweight men were more responsive to training-induced changes in $HDL_2$-C than E3 and E4 allele carriers.(34)

The HERITAGE Family Study has reported the strongest supportive evidence for the interactive effects of ethnicity with genetics on plasma lipid lipoprotein responses to aerobic exercise training.(20) For example, Leon et al examined the effect of APO E genotype on lipid responses to a 20-week 3 days/week exercise-training intervention in a family-based cohort of Whites and Blacks from the HERITAGE study. Distinct race-based differences in exercise training lipid response by APO E genotype were observed.(20) Of all races and gender in the study, white women had the greatest APO E-related training-induced changes in conventionally measured HDL-C and subfraction, whereas black women showed significant differences in APO AI levels by APO E genotype. Although our study lacks the power to make gender-based comparisons between Blacks and Whites, we provide an important addition to the literature by using a newer and more accurate NMR method to quantify HDL-C particle size and concentration. Given the White-Black differences in baseline and after training $HDL_{NMR}$-C and subfractions within the APO E2/3 genotype group in the our study, we concur with Rice and colleagues(12 that the discrepancy in Black vs White differences in training-induced changes in plasma lipoprotein lipid, may indicate genetic heterogeneity in possible underlying pleiotropic genes affecting baseline phenotypic expression and exercise-training adaptation. Further, a significantly higher training-induced improvements in $HDL_{NMR}$-C particle size and $HDL_2$-C in Blacks than Whites even after accounting for the contribution of baseline values, suggests that our results were independent of baseline differences. This observation supports the likelihood that the APO E gene may interact with specific ethnicity-based environmental and/or biologic factors to differentially affects plasma lipoprotein-lipid

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responses to standardized aerobic exercise training. Importantly, given the cardioprotective effect of $HDL_{NMR}$-C and its subfractions, the identification of additional ethnicity-related factors interacting with environmental and/or biologic factors to affect $HDL_{NMR}$-C responses to standardized aerobic exercise training need further investigation.

One of the important limitations of this study is that it lacks the power to make gender comparisons within APO E genotype groups. Second, we are unable to draw had conclusions on black-white comparison in the E4 group, given the relatively small sample size of this group. In spite of this limitation, a major strength of this study was the use of a newer and more accurate NMR technique to show the APOE-race differences in response to aerobic exercise training. This is especially important, given the heterogeneity in HDL-C particle size response to aerobic exercise-training among subjects, suggesting that genotyping may be important to identify those who might benefit more from fitness adaptation to reduce CVD risk. Additionally, our study has the advantage of a 6-month standardized aerobic exercise training program, dietary stabilization on the AHA step I diet prior to training, monitoring of adherence to this diet, and an individually-tailored exercise intervention while preserving uniformity in training attendance and exercise volume. In conclusion, we provide new evidence that APO E2/3 Blacks have greater improvement in HDL-C particle size and concentration with exercise training than Whites, while maintained on a constant AHA step 1 low-fat diet. Given the relatively low level of physical activity in Blacks, this study provides new and clinically relevant information which can be useful in encouraging and targeting aerobic exercise-training to high CVD risk subjects with specific genotypes in populations at high CVD risk.

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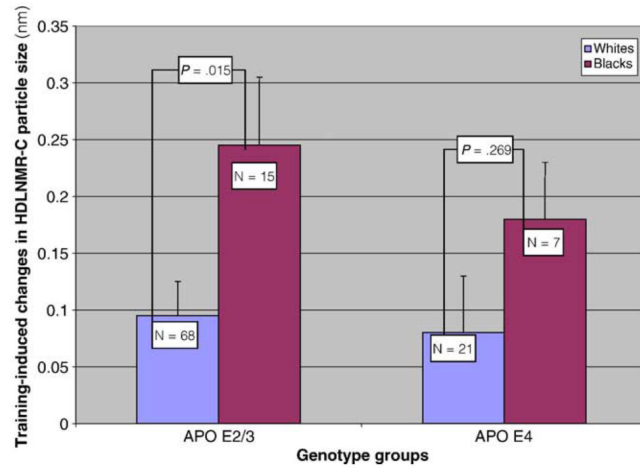


**Figure 1.**
White and Black comparison of training-induced changes in $HDL_{NMR}$-C particle size within APO E genotype.

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**Table 1**

Baseline and after training characteristics of the sample within each ethnicity and APO E genotype groups

| Parameter | | Baseline | | After Training | |
|---|---|---|---|---|---|
| | | Whites | Blacks | Whites | Blacks |
| **APO E2/E3** | | **(n=91-94)** | **(n=22-24)** | **(n=79-81)** | **(n=18)** |
| Age (yrs) | | 58.1±0.6 | 58.7±1.0 | 58.1±0.6 | 59.6±1.3 |
| Gender: | Men | 47% | 36% | 45% | 38% |
| | Women | 53% | 64% | 54% | 62% |
| Body weight (kg) | | 83.2±1.6 | 81.1±3.0 | 81.2±1.7† | 77.3±3.1† |
| Body mass index ($kg/m^2$) | | 28.7±0.5 | 28.8±0.9 | 27.8±0.4† | 27.5±1.0† |
| Lean body mass (kg) | | 49.0±12.6 | 47.7±23.4 | 49.8±14.0† | 47.2±24.3 |
| Total body fat (%) | | 36.4±0.9 | 36.2±2.1 | 34.9±0.9† | 34.8±2.8† |
| Subcutaneous fat ($cm^2$) | | 312.9±12.5 | 334.0±31 | 306.0±13 | 323.6±36† |
| Intra-abdominal fat ($cm^2$) | | 143.9±5.7 | 106.7±11* | 128.1±5† | 91.6±9* |
| $VO_2$max (ml/kg/min) | | 25.3±0.46 | 23.6±0.87 | 29.3±0.6† | 27.3±1.7† |
| **APOE 4** | | **(n=37-39)** | **(n=11-13)** | **(n=34-39)** | **(n=9-11)** |
| Age (yrs) | | 58.1±1.0 | 57.0±1.5 | 57.9±1.0 | 57.9±1.7 |
| Gender (%): | Men | 41% | 31% | 36% | 30% |
| | Women | 59% | 69% | 64% | 70% |
| Body weight (kg) | | 81.0±2.6 | 86.9±2.9 | 78.1±2.6 | 84.4±3.1† |
| Body mass index ($kg/m^2$) | | 28.5±0.8 | 30.3±0.9 | 27.5±0.8 | 29.7±1.0† |
| Lean body mass (kg) | | 46.7±1.7 | 49.4±3.2 | 47.1±1.7† | 49.5±4.5 |
| Total body fat (%) | | 37.0±1.6 | 39.6±2.7 | 35.0±1.7† | 37.8±3.8 |
| Subcutaneous fat ($cm^2$) | | 334.4±2.3 | 364.4±3.0 | 295.7±1.8 | 365.6±3.8 |
| Intra-abdominal fat ($cm^2$) | | 120.2±0.9 | 120.7±1.3 | 120.7±1.1 | 107.1±1.2† |
| $VO_2$max (ml/kg/min) | | 24.9±0.9 | 21.7±1.0 | 28.4±1.1† | 24.2±1.6† |

Note: Data are mean ± SE;

*indicates statistically significant difference between ethnic groups with the same genotype at $P < 0.05$;

†indicates statistically significant within ethnic and genotype groups change with training at $P < 0.05$. Ranges of sample size for each ethnicity and genotype groups are presented, because not all participants completed all measurements.

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**Table 2**

$HDL_{NMR}$-C and its subfractions within each ethnicity and genotype group at baseline and after training

| | Baseline | | | After Training | | |
|---|---|---|---|---|---|---|
| | **Whites** | **Blacks** | **P Value** | **Whites** | **Blacks** | **P Value** |
| **APOE2/3 Group** | **(n=68)** | **(n=15)** | | **(n=68)** | **(n=15)** | |
| HDL-C mean particle size (nm) | 8.7±0.1 | 9.2±0.1 | <0.001 | 8.8±0.1 | 9.4±0.1 | <0.001 |
| HDL-C particle concentration (umol/L) | | | | | | |
| Total (umol/L) | 33.6±0.6 | 34.1±1.2 | 0.006 | 34.5±0.6 | 33.7±1.3 | 0.003 |
| Large size (umol/L) | 4.6±0.4 | 8.7±1.3 | <0.001 | 5.6±0.4 | 10.3±1.0 | <0.001 |
| Medium Size (umol/L) | 6.3±0.7 | 4.7±1.8 | 0.37 | 5.3±0.6 | 2.4±1.0 | 0.022 |
| Small Size (umol/L) | 22.7±0.7 | 20.7±1.8 | 0.80 | 23.7±0.7 | 21.0±1.5 | 0.251 |
| **APO E4 Group** | **(n=21)** | **(n=7)** | | **(n=21)** | **(n=7)** | |
| HDL-C mean particle size (nm) | 8.8±0.1 | 8.9±0.2 | 0.60 | 8.8±0.1 | 9.1±0.2 | 0.33 |
| HDL-C particle concentration (umol/L) | | | | | | |
| Total (umol/L) | 35.1±1.3 | 32.1±1.5 | 0.20 | 36.0±1.5 | 33.5±3.6 | 0.45 |
| Large size (umol/L) | 5.8±0.9 | 5.9±1.1 | 0.94 | 6.6±0.9 | 7.4±1.1 | 0.76 |
| Medium size (umol/L) | 7.3±1.3 | 2.7±1.2 | 0.06 | 7.5±1.1 | 3.9±1.3 | 0.08 |
| Small Size (umol/L) | 22.0±1.4 | 23.5±1.9 | 0.52 | 22.0±1.2 | 22.2±2.4 | 0.78 |

Data are means ± SE. *P* value are for the comparison of Whites Vs Blacks.

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**Table 3**

Conventionally measured HDL-C and its subfraction within each genotype group at baseline and after training

| | Baseline | | | After Training | | |
|---|---|---|---|---|---|---|
| | **Whites** | **Blacks** | **P Value** | **Whites** | **Blacks** | **P Value** |
| **APOE2/3 Group** | **(n=94)** | **(n=24-25)** | | **(n=81)** | **(n=16)** | |
| HDL-C (mg/dl) | 47.1±1.6 | 59.0±3.8 | 0.002 | 49.2±1.6 | 58.2±3.8 | 0.023 |
| $HDL_2$-C (mg/dl) | 5.8±1.2 | 12.4±2.5 | 0.012 | 6.2±0.9 | 13.9±3.5 | 0.046 |
| $HDL_3$-C (mg/dl) | 41.4±0.9 | 46.5±1.8 | 0.009 | 43.1±0.9 | 44.5±2.7 | 0.522 |
| **APO E4 Group** | **(n=39)** | **(n=13)** | | **(n=33)** | **(n=10)** | |
| HDL-C (mg/dl) | 49.0±2.4 | 47.9±4.1 | 0.814 | 52.2±2.6 | 48.9±3.7 | 0.524 |
| $HDL_2$-C (mg/dl) | 6.0±1.2 | 5.2±2.1 | 0.760 | 7.3±1.5 | 4.8±2.3 | 0.419 |
| $HDL_3$-C (mg/dl) | 43.1±1.6 | 42.5±2.2 | 0.839 | 45.2±1.8 | 43.8±1.9 | 0.685 |

Data are means ± SE. *P* value are for the comparison of White Vs Black.