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# Physical Activity Modifies the Effect of *LPL, LIPC* and *CETP* polymorphisms on HDL-C Levels and the Risk of Myocardial Infarction in Caucasian Women

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## Abstract

**Background—**Recent genome-wide association studies have identified common variants associated with high-density lipoprotein cholesterol (HDL-C). Whether these associations are modified by physical activity, which increases HDL-C levels and reduces the risk of cardiovascular disease (CVD), is uncertain.

**Methods and Results—**In a prospective cohort study of 22,939 apparently healthy Caucasian US women, we selected 58 single nucleotide polymorphisms (SNPs) in 9 genes that demonstrated genome-wide association ($P<5\times10^{-8}$) with HDL-C levels and sought evidence of effect modification according to levels of physical activity (PA). PA modified the effects on HDL-C of 7 SNPs at 3 loci, and the strongest evidence of effect was observed for rs10096633 at *LPL*, rs1800588 at *LIPC* and rs1532624 at *CETP* (each P-interaction <0.05). The per-minor-allele increase in HDL-C for rs1800588 at *LIPC* and rs1532624 at *CETP* was greater in active than inactive women, whereas the reverse was observed for rs10096633 at *LPL*. Minor-allele carrier status at the *LPL* SNP was associated with a reduced risk of MI in active (Hazard Ratio [HR] 0.42, 95% Confidence Interval [CI] 0.23–0.76) but not amongst inactive women (HR 1.10, 95% CI 0.83–1.44; P-interaction=0.007). By contrast, carrier status at the *CETP* SNP was associated with a reduced risk of MI regardless of activity level (HR 0.72, 95% CI 0.57–0.92; P-interaction=0.71). No association between *LIPC* SNP carrier status and MI risk was noted

**Conclusions—**The effects of common variants in the *LPL, LIPC* and *CETP* genes on HDL-C levels are modified by PA. For a common variant in *LPL*, the impact on MI varied by activity level, while the effects of a common variant in *CETP* on MI risk did not.

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**Keywords**

genomic studies; HDL cholesterol; myocardial infarction; exercise

## Introduction

Prospective cohort studies demonstrate a strong inverse relationship between high density lipoprotein cholesterol (HDL-C) and risk of cardiovascular disease.[1] HDL-C levels are highly heritable and recent genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in at least 9 genes that alter HDL-C levels.2¯6 While some studies have demonstrated an association between SNPs associated with HDL-C levels and the risk of future cardiovascular events, others have not.6¯12

Environmental factors also contribute to the variation observed in HDL-C levels. Physical activity is associated with higher levels of HDL-C in several epidemiologic studies,[13–15] and variation in the *CETP*, *LIPC*, *APOA1*, *LIPG*, *APOE* and *LPL* genes have been reported to contribute to inter-individual variability in the HDL-C response to exercise.16¯23 The extent to which regular physical activity modifies the effect of recently discovered SNPs on HDL-C levels, or their effect on risk of myocardial infarction (MI) has not been well studied, particularly among women.

We sought to determine whether associations between common SNPs and HDL-C levels are modified by physical activity in a large cohort of healthy US Caucasian women. Additionally, to examine the clinical implications of our findings, we investigated whether favorable genotypes at significant loci are associated with lowered risk of MI, and if this risk is modified by level of physical activity.

## Methods

### Study participants

Participants were from the Women's Genome Health Study (WGHS), a prospective genetic evaluation of women in the Women's Heath Study (WHS).[24] Study participants in the WHS were female health professionals aged 45 years and older at the time of enrollment who were free of any major chronic disease including cancer and cardiovascular diseased (CVD) at study entry (1992–95). Information on baseline variables including race/ethnicity, demographic characteristics, medical history, medications, and dietary and lifestyle facts were reported on questionnaires. The WGHS includes 23,294 Caucasian women who consented to ongoing analyses using genetic data and for whom we have baseline plasma and DNA. We used all 23,294 women in our initial SNP screening step, and then restricted our sample to the 22,939 women for whom we also had information on physical activity and HDL-C. The study was approved by the institutional review board of the Brigham and Women's Hospital (Boston, Massachusetts).

### Genotyping and SNP Selection

DNA samples were genotyped with the Infinium II technology from Illumina (Human HAP300 panel) as previously described.[24] All samples were required to have successful genotyping using the BeadStudio v. 3.3 software (Illumina, San Diego, CA) for at least 98% of the SNPs. SNPs with call rates <90% and with a minor allele frequency <1% in Caucasians were removed from the analysis. SNPs were evaluated for deviation from Hardy-Weinberg equilibrium using an exact method and were excluded when the P-value was lower than $10^{-6}$. After quality control, a total of 339,596 SNPs were left for the

analysis. Genotyping success at SNPs used for our analysis ranged from 97% at rs1532624 to >99.99% at rs10096633 and rs1800588.

### Physical activity

At baseline, each participant was asked to report her approximate average time per week during the previous year spent on 8 groups of recreational activities (walking/hiking, jogging, running, bicycling, aerobic exercise/dance, lap swimming, tennis/squash/racquetball, and lower-intensity exercise) and the number of flights of stairs climbed on a questionnaire previously shown to be both valid and reliable.[25, 26] A metabolic equivalent (MET) score was assigned to each activity based on the energy cost of that activity and the energy expended on each activity was then estimated by multiplying its MET score with hours/week, and summed across all activities (MET-hours/week). The United States Government recommends at least 150 minutes per week of moderate-intensity aerobic activity (e.g., brisk walking), the equivalent of ≥ 7.5 MET-hrs per week.[27]

### Lipid Assessment

EDTA blood samples were obtained at the time of enrollment in the WHS and stored in vapor-phase liquid nitrogen (−170°C). Study participants had baseline blood samples assayed for HDL-C, ApoA1 and triglyceride (TG) levels in a core laboratory certified by the National Heart Lung and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program and had low coefficients of variance.[4] Among the 21,806 women for whom we have information on fasting status, 16562 (76%) were fasting for at least 8 hours prior to blood collection.

### Ascertainment of Cardiovascular Events

Criteria for endpoint assessment have been reported previously.[28] All study participants were followed for myocardial infarction through February 2008. An end-points committee of physicians reviewed medical records for all participants reporting myocardial infarction. Events were confirmed if symptoms met World Health Organization Criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiographic criteria. Only confirmed end-points were included in this analysis.

### Statistical Analysis

We identified the common SNPs in 9 previously described genes[3, 6] influencing HDL-C levels at a genome-wide level of statistical significance ($P<5\times10^{-8}$) in the 23,294 women for whom we have genotype information by performing linear regression in PLINK. In total 58 SNPs achieved genome wide significance for HDL-C (Supplementary Table 1). All 58 SNPs were screened for statistically significant evidence of effect modification by physical activity across the median in our cohort (8.8 MET-hours/week), using the unadjusted quantitative trait interaction procedure available in PLINK.[29] An *a priori* threshold of $P<0.05$ was used to select SNPs for further analysis. A sensitivity analysis using physical activity adjusted HDL-C levels identified 5 additional SNPs, two of which were in a tenth gene (*LCAT*) that was not identified in the primary analysis but which has been identified previously as a determinant of HDL-C.[6] These 5 SNPs were also tested for evidence of effect modification.

After restricting the sample to those with complete information for HDL-C and MET-hours of physical activity (N=22,939), characteristics of the study population were computed across the physical activity median in our cohort (8.8 MET-hours/week), and compared using two-sided t-tests for continuous variables and $\chi^2$ tests for categorical variables. We performed a multivariable linear regression analyses for each significant SNP, assuming an

additive model of inheritance, to test the association with HDL-C levels after adjustment for age, BMI, alcohol intake, hypertension, diabetes, and hormone use status. We calculated the effect estimates and mean levels of HDL-C for each genotype at each selected SNP, stratified by median activity levels. Tests for interaction were performed using multivariable linear regression models that included the above covariates, number of copies of the minor allele at each SNP (0, 1, or 2), physical activity below (0) and above (1) the median, and an interaction term (SNP*physical activity). We tested the significant SNPs for evidence of effect modification of ApoA1 levels, the major apolipoprotein on the HDL-C molecule, in similarly adjusted models. As a sensitivity analysis, we used a P-value threshold of 0.0056, which represents a P-value threshold of 0.05 corrected for the 9 genes tested for evidence of interaction.

We created three separate genotype scores, one for each SNP (rs10096633 in LPL, rs1800588 in LIPG, and rs1532624 in CETP). At each SNP, we used a dominant model to categorize women into two groups: those who were homozygous for the major allele and those who were carriers of a minor allele. At rs10096633, rs1800588, and rs1532624, women homozygous for the major allele had lower HDL-C levels than women carrying at least one copy of the minor allele, and thus were defined as having a “deleterious” genotype. Minor allele carrier status was defined as “beneficial” for each of these three SNPs on the assumption that any impact on MI risk would be consistent with the observed effect on HDL-C. We used multivariable Cox proportional hazard models, adjusting for age, BMI, blood pressure (Framingham categories), history of diabetes, smoking, and total cholesterol, to estimate the hazard ratio (HR) of incident MI in the entire cohort associated with each genotype score. Next, we performed a stratified analysis, according to genotype score, to estimate the HR of incident MI associated with increased level physical activity, using inactive women (≤8.8MET-hrs/week, the median in our cohort) as the reference group.

All analyses were carried out using SAS/Genetics 9.1 package (SAS Institute Inc, Cary, NC) and PLINK.[29]

## Results

Women who reported physical activity levels above the median of 8.8 MET-hours/wk had, on average, a lower baseline body mass index (BMI), lower TG levels, higher levels of HDL-C and ApoA1, and a lower prevalence of self-reported diabetes and hypertension (Table 1). Post menopausal hormone use and moderate alcohol use was also more common amongst more active women.

The SNPs associated with HDL-C levels at a genome-wide level of statistical significance and their unadjusted P-values for interaction with the median level of physical activity (8.8 MET-hrs/week) are displayed in Supplementary Table 1, sorted by chromosomal position. Evidence of effect modification was observed for 8 SNPs in 4 genes, including 2 SNPs at *LPL* (8q21), 3 at *LIPC* (15q22), 2 at *CETP* (16q13), and 1 at *LIPG* (18q45). The SNPs with the smallest interaction P-value at each locus were rs10096633 (*LPL*; P-interaction=0.006), rs1800588 (*LIPC*; P-interaction=0.01), rs1532624 (*CETP*; P-interaction=0.008) and rs4939883 (*LIPG*; P-interaction=0.03). The absolute difference (SE) in HDL-C level per copy of each significant allele ranged from 1.098 (0.193) for rs4939883 in *LIPG* (minor allele frequency (MAF) = 0.17) to 3.067 (0.146) for rs1532624 in *CETP* (MAF = 0.43). We did not observe evidence of effect modification for other SNPs with similar MAF and effect sizes (Supplementary Table 1). None of the 5 SNPs identified in a sensitivity analysis using physical activity adjusted HDL-C met the pre-specified criteria for evidence of effect modification (Supplementary Table 2).

Mean (±SD) HDL-C by genotype and increase in HDL-C per copy of the minor alleles at significant SNPs within the *LPL, LIPC, CETP* and *LIPG* genes in all women and in women stratified by median levels of physical activity are displayed in Table 2. As shown, we observed a smaller per-allele increase in HDL-C for rs10096633 at *LPL* among active women (1.0 mg/dL per copy) than among inactive women (2.1 mg/dL per copy, P-interaction=0.004). By contrast, for rs1532624 at *CETP* and rs1800588 at *LIPC*, we observed a larger increase in HDL-C levels per copy of the minor allele in active women than in inactive women (P-interaction= 0.04 and 0.02, respectively). While our initial test for interaction suggested that the effect of rs4939883 at *LIPG* on HDL-C levels was modified by physical activity, this effect was no longer statistically significant in the fully adjusted model. Similar results were seen for the SNPs in *LPL*, *LIPC*, and *CETP* when using an alternative physical activity cutpoint (Supplementary Table 3). The distribution of HDL-C levels stratified by genotype and physical activity level are presented in the Supplementary Figure. The proportion of variance in HDL-C explained by the physical activity-genotype interaction was 0.03% for rs10096633 in *LPL*, 0.01% for rs1800588 in *LIPC*, and 0.03% for rs1532624 in *CETP*. By comparison, adding each of SNP individually to adjusted models explained an additional 0.27% (rs10096633), 0.58% (rs1800588), or 1.99% (rs1532624) of the variance in HDL-C. In sensitivity analyses using a P-value threshold corrected for the number of genes analyzed (P<0.0056), evidence of interaction remained statistically significant only for rs10096633 in *LPL*. When we restricted our analysis to women who had been fasting for at least 8 hours at the time of blood collection our observations did not differ substantially.

We observed similar associations between the above SNPs and ApoA1 levels (Table 3). As seen with HDL-C, the observed per-allele increase in ApoA1 for rs10096633 at *LPL* was greater among inactive women (interaction<0.001). Copies of the minor allele at rs1532624 *(CETP)* and rs1800588 (*LIPC*) were associated with a greater increases in ApoA1 levels amongst active women, compared to inactive women (P-interaction=0.02 and 0.09, respectively).

Higher HDL-C levels were observed among women with the beneficial as compared with deleterious genotype at rs10096633 in *LPL* (55.08 vs. 53.33mg/dL, P<0.0001), rs1800588 at *LIPC* (55.17 vs. 52.87mg/dL, P<0.0001), and rs1532624 at *CETP* (54.99 vs. 51.26 mg/dL, P<0.0001). However, only women who carried at least one copy of the minor allele at *CETP* had a reduced risk of MI (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.57–0.92; P=0.009) after adjusting for age, body mass index, diabetes, blood pressure, current smoking, and total cholesterol. Women with a beneficial genotype at rs10096633 (*LPL*) or rs1800588 (*LIPC*) were not at reduced risk of MI (*LPL*-HR 0.81, 95% CI 0.61–1.09, P=0.16; *LIPC*-HR 1.11, 95% CI 0.87–1.41, P=0.39).

The fully adjusted risks of MI for each of the four categories of genotype score and activity level are presented in Figure 1. As shown in Figure 1A, compared to inactive women with a deleterious genotype at *LPL*, active carriers of at least one copy of the minor allele at rs10096633 were at reduced risk of MI (HR 0.51, 95% CI 0.30–0.86; P=0.01). By contrast, inactive women with the beneficial genotype at *LPL* were not at reduced risk of MI (HR 1.13, 95% CI 0.79–1.61; P=0.50; P-interaction = 0.007). The effect of physical activity on MI risk did not appear to be modified by genotype score at rs1800588 (*LIPC*) (P-interaction = 0.71, Figure 1B). Finally, the reduction in risk associated with a beneficial genotype at rs1532624 at *CETP* appeared to be similar in active and inactive women, regardless of physical activity level (P-interaction = 0.71, Figure 1C).

## Discussion

In this study of 22,939 healthy U.S. Caucasian women, we report that the effects of SNPs at *LPL*, *LIPC* and *CETP* on HDL-C levels are modified by physical activity. In our study, the per-allele increase in HDL-C for rs1800588 at *LIPC* and rs1532624 at *CETP* was greater among active women, while the per-allele increase in HDL-C per copy of the minor allele of rs10096633 at *LPL* was larger among inactive women. Although minor allele carrier status at each of these loci was associated with higher levels of HDL-C, the associated reduction in risk of MI differed by SNP and by activity level. Minor allele carrier status at *LPL* was related to a 50% risk-reduction in MI only amongst active participants, and while carrier status at *LIPC* did not appear to afford protection from risk of MI, the carrier status at *CETP* was associated with approximately a 30% risk reduction in MI, regardless of activity levels.

We believe these data are of interest for several reasons. First, using a different study design and analytic approach than previous work in the field, we offer further evidence of the established role of *LPL*, *LIPC*, and *CETP* in modulating the response of HDL-C and ApoA1 to physical activity. Prior work has recognized that exercise-induced changes in lipid phenotypes, such as an increase in HDL-C, are related to decreases in plasma levels and activity of CETP,[30, 31] increases in LPL activity in both plasma and skeletal muscle,[20, 32, 33] and to decreases in post-heparin plasma LIPC activity.[34] Several studies have shown that genetic variation within *CETP* can modulate alterations in HDL-C due to exercise, possibly via a differential response of CETP activity or mass to exercise.[12, 18, 19, 35] Other studies have reported that physical activity modifies the effect of two common genetic polymorphisms in LPL on HDL-C.[20, 36] Finally, while common variation in LIPC is known to affect enzyme activity,[37] evidence that physical activity modifies the effects of genetic variation in *LIPC* on plasma LIPC activity and lipid phenotypes is inconsistent.[21, 34, 38] While our findings also implicate LPL, LIPC, and CETP as important mediators of the response in HDL-C to physical activity, we extend those findings to women, who were absent from many the prior studies.[20, 35, 38] We also measured leisure-time physical activity, which may be less likely to cause substantial charges in lipid metabolism and HDL-C levels than prescribed diet and exercise interventions, which were used in much of the previous work in this area.[18, 19, 21, 34]

Second, the magnitude of the per-allele effect of common polymorphisms on HDL-C levels varies according to level of physical activity. For example, the effect of variation at rs10096633 in *LPL* on HDL-C level is larger among sedentary than active women, while the effect of variation at rs1532624 in *CETP* on HDL-C levels is smaller among sedentary than active women. This differential modification provides a possible biological explanation for the wide variability in HDL-C response to exercise, and for the clinical observation that some individuals do not experience improvements in HDL-C level despite adopting an exercise regimen.[17]

Third, in contrast to rs1532624 at *CETP*, we report a lack of association between beneficial genotypes at rs10096633 in *LPL* and rs1800588 at *LIPC* and risk of incident MI. This is in spite of the fact that women with at least one copy of the minor allele at either locus had HDL-C levels that were, on average, 1.75–2.3 mg/dL higher than those with a deleterious genotype score at those loci. This lack of association, when viewed in the context of a strong association between *CETP* genotype and MI risk in our cohort[7] and others[12] highlights the understanding that increases in HDL-C levels due to variation in key lipid metabolism genes do not necessarily lead to the expected reduction in vascular risk.[9, 10, 39, 40] Our observation that regular physical activity reduces MI risk among women with a beneficial *LPL* genotype, but not among those with a deleterious genotype, raises the additional possibility that the effects of lifestyle choices on cardiovascular events may vary by genotype. While one other

study has reported evidence that physical activity alters the vascular risk conferred by the −480C>T mutation in *LIPC*, this report is the first of which we are aware that the effects of physical activity may differ according to variation within *LPL*.[10] The biological mechanism by which physical activity might reduce the risk of MI among female carriers but not among non-carriers of the minor allele at rs10096633 is unclear. The identity and biological action of the true causal variant are unknown (it is unlikely to be rs10096633), as are the mechanisms by which it might alter LPL levels and/or function, HDL-C levels and/or function, and downstream vascular risk. While it is certainly possible that altered *LPL* catalyzes important functional changes in HDL-C that then affect MI risk, the design of the WHS prevents us from being able to tease out whether functional changes in HDL-C or another biologic process is the cause of the observed differences in MI risk.

## Strengths and Limitations

Strengths of the present study include its large sample size and the careful collection of physical activity data at the time of blood sampling. However, a number of limitations need to be considered. First, our analytic approach selected only those SNPs related to HDL-C levels at a Bonferroni-corrected genome wide level of significance ($P<5\times10^{-8}$). This approach would not detect genes that had opposite per-allele effects in the two strata of physical activity, although the biological plausibility of such an interaction with a continuous exposure such as physical activity is uncertain. Second, while our sample size is large, our power to detect statistically significant interactions is dependent upon allele effect size and minor allele frequency. Third, physical activity, weight, height, diabetes and hypertension were assessed by self-report. Imprecise reporting of the variables may have occurred; however, any misclassification of this kind would be expected to bias the results towards the null since reports were prospective and predated the occurrence of MI. Lastly, our study only includes Caucasians and may not be generalizable to other groups.

We believe that the evidence of effect modification reported here is real, in part because the 3 reported loci have been implicated in prior reports of effect modification. In conjunction with findings from previously published work, these findings support the hypothesis that genetic determinants of key steps in HDL-C metabolism, involving the *LPL*, *LIPC*, and *CETP* genes, are differentially modified by physical activity. Finally, our data raise the possibility that the effects of common variants in these genes on MI risk may also be modified by activity level.

## Conclusion

In summary, we report evidence that the effects of common polymorphisms in the *LPL*, *LIPC*, and *CETP* genes on HDL-C levels are modified by physical activity. We observed greater per-minor-allele increases in HDL-C for rs1800588 in *LIPC* and rs1532624 in *CETP* among active than inactive women, and smaller per-allele increases in HDL-C for rs10096633 at *LPL* among active than inactive women. Minor allele carrier status at *LPL* was related to risk-reduction in MI only amongst active participants, whereas carrier status at *CETP* was associated with reductions in risk of MI, regardless of activity status. Minor allele carrier status at *LIPC* did not appear to associate with MI risk. Common variation within these genes appears to influence the response of HDL-C to physical activity. The protection from MI afforded by higher plasma levels of HDL-C may depend both on absolute levels and variation in the genetic determinants of those levels.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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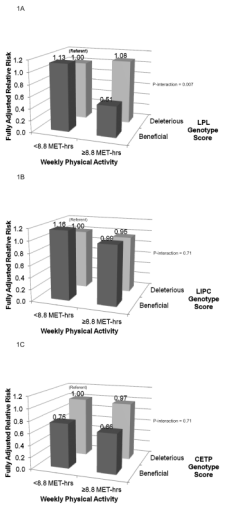


**Figure 1.**

Risk of incident myocardial infarction according to categories of leisure-time physical activity level and genotype score at the *LPL* (1A), *LIPC* (1B), and *CETP* (1C) loci. Women with at least one copy of the minor allele at each locus were defined as having a beneficial genotype at that locus, while those homozygous for the major allele were defined as having a deleterious genotype at that locus. Compared to those with a deleterious genotype score, high-density lipoprotein cholesterol levels among those with a beneficial genotype score at *LPL* (rs10096633) were 1.75 mg/dl higher, at *LIPC* (rs1800588) were 2.3 mg/dL higher, and at *CETP* (rs1800588) were 3.73 mg/dL higher (Each P<0.0001).

## Table 1

Characteristics of Study Participants According to Physical Activity Levels

| | **≤8.8MET-hours/week N=11,446** | **> 8.8MET-hours/week N=11,493** |
|---|---|---|
| Age, y | 52.0 (48.0–58.0) | 52.0 (48.0–59.0) |
| BMI, kg/m$^2$ | 25.7 (22.9–29.6) | 24.1 (21.9–27.0) |
| Cholesterol treatment, % | 3.2 | 3.2 |
| Diabetes, % | 3.0 | 2.1 |
| Hypertension, % | 27.1 | 22.0 |
| Metabolic syndrome, % | 28.4 | 17.8 |
| Paternal history of MI, % | 13.2 | 12.7 |
| Post-menopausal hormone use, % | 42.2 | 45.5 |
| Alcohol consumption, % | | |
| Rarely | 48.2 | 38.4 |
| 1–3 drinks/mo | 13.4 | 13.2 |
| 1–6 drinks/wk | 28.8 | 36.7 |
| ≥ drinks/d | 9.7 | 11.8 |
| TG, mg/dL | 127.0 (88.0–184.0) | 114.0 (79.0–167.0) |
| HDL-C, mg/dL | 50.1 (41.9–60.4) | 53.7 (44.7–63.9) |
| ApoA1, mg/dL | 146.8 (130.5–165.4) | 151.6 (134.7–170.4) |

Values shown for continuous variables are median (IQR).

HDL denotes high-density cholesterol, ApoA1 denotes Apolipoprotein A1 and TG denotes Triglycerides.

**Table 2**

Mean HDL-C (mg/dl) Levels per copy of the Minor Allele at Significant SNPs in the Entire Cohort and Across Median levels of Physical Activity

| | | | | Mean (SD) HDL-C per allele, copy mg/dl | | | | |
|---|---|---|---|---|---|---|---|---|
| **SNP** | **Chromosome, Gene** | | **N** | **0** | **1** | **2** | **β (SE)** | **P** |
| rs10096633 | 8p21, *LPL* | All women | 22,938 | 53.3 (15.0) | 55.0 (15.3) | 55.9 (15.2) | 1.6 (0.2) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,445 | 51.5 (14.4) | 53.9 (14.9) | 54.1 (14.6) | 2.1 (0.3) | <0.0001 |
| | | >8.8MET-hours/week | 11,493 | 55.2 (15.2) | 56.1 (15.6) | 57.7 (15.6) | 1.0 (0.3) | <0.001 |
| | | Test for interaction | | | | | | 0.004 |
| rs1800588 | 15q22, *LIPC* | All women | 22,936 | 52.9 (14.6) | 54.9 (15.5) | 56.9 (15.5) | 2.0 (0.2) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,445 | 51.3 (14.2) | 53.0 (15.1) | 54.4 (14.3) | 1.7 (0.2) | <0.0001 |
| | | >8.8MET-hours/week | 11,491 | 54.4 (14.9) | 56.8 (15.7) | 59.3 (16.3) | 2.3 (0.2) | <0.0001 |
| | | Test for interaction | | | | | | 0.04 |
| rs1532624 | 16q13, *CETP* | All women | 22,195 | 51.3 (14.2) | 54.1 (15.0) | 57.5 (15.7) | 3.0 (0.1) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,065 | 50.0 (14.1) | 52.2 (14.4) | 55.5 (15.2) | 2.7 (0.2) | <0.0001 |
| | | >8.8MET-hours/week | 11,130 | 52.6 (14.2) | 55.8 (15.4) | 59.4 (16.0) | 3.3 (0.2) | <0.0001 |
| | | Test for interaction | | | | | | 0.02 |
| rs4939883 | 18q45, *LIPG* | All women | 22,763 | 54.2 (15.2) | 53.0 (14.7) | 51.6 (14.6) | −1.2 (0.17) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,353 | 52.6 (14.8) | 51.0 (13.9) | 49.7 (14.0) | −1.4 (0.2) | <0.0001 |
| | | >8.8MET-hours/week | 11,410 | 55.7 (15.3) | 55.0 (15.1) | 53.7 (15.0) | −0.9 (0.2) | 0.0001 |
| | | Test for interaction | | | | | | 0.14 |

Values for HDL (high-density cholesterol) levels are mean (±SD).

**Table 3**

Mean ApoA1 (mg/dl) Levels per copy of the Minor Allele at Significant SNPs in the Entire Cohort and Across Median levels of Physical Activity

| | | | | Mean (SD) ApoA1 per allele, copy mg/dl | | | | |
|---|---|---|---|---|---|---|---|---|
| **SNP** | **Chromosome, Gene** | | **N** | **0** | **1** | **2** | **β (SE)** | **P** |
| rs10096633 | 8p21, *LPL* | All women | 22833 | 150.6 (25.5) | 152.4 (25.8) | 153.2 (25.5) | 1.77 (0.31) | <0.0001 |
| | | ≤8.8MET-hours/week | 11390 | 148.1 (25.1) | 151.1 (25.0) | 152.4 (26.2) | 2.92 (0.43) | <0.0001 |
| | | >8.8MET-hours/week | 11443 | 153.0 (25.7) | 153.7 (26.6) | 154.0 (24.9) | 0.64 (0.45) | 0.15 |
| | | Test for interaction | | | | | | 0.0003 |
| rs1800588 | 15q22, *LIPC* | All women | 22,831 | 149.3 (25.2) | 153.1 (26.0) | 158.2 (26.3) | 4.0 (0.3) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,390 | 147.4 (24.6) | 150.6 (25.7) | 154.8 (25.9) | 3.6 (0.4) | <0.0001 |
| | | >8.8MET-hours/week | 11,441 | 151.2 (25.6) | 155.7 (26.0) | 161.6 (26.1) | 4.5 (0.4) | <0.0001 |
| | | Test for interaction | | | | | | 0.09 |
| rs1532624 | 16q13, *CETP* | All women | 22,195 | 147.5 (25.0) | 151.6 (25.7) | 155.5 (25.9) | 4.0 (0.2) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,065 | 145.9 (24.5) | 149.3 (25.1) | 152.9 (25.6) | 3.4 (0.3) | <0.0001 |
| | | >8.8MET-hours/week | 11,130 | 149.2 (25.3) | 153.8 (26.0) | 158.1 (25.9) | 4.4 (0.3) | <0.001 |
| | | Test for interaction | | | | | | 0.02 |
| rs4939883 | 18q45, *LIPG* | All women | 22,809 | 151.8 (25.8) | 149.4 (25.0) | 146.6 (25.0) | −2.6 (0.3) | <0.0001 |
| | | ≤8.8MET-hours/week | 11,377 | 149.9 (25.4) | 146.8 (24.3) | 144.6 (24.1) | −2.7 (0.4) | <0.0001 |
| | | >8.8MET-hours/week | 11,432 | 153.9 (26.1) | 152.0 (25.5) | 148.8 (25.9) | −2.4 (0.4) | <0.0001 |
| | | Test for interaction | | | | | | 0.59 |

Values for ApoA1(Apolipoprotein A1) levels are mean (±SD).