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Associations between HDL-cholesterol and polymorphisms in hepatic lipase and lipoprotein lipase genes are modified by dietary fat intake in African American and White Adults ^{1,2,3}

Jennifer A. Nettleton, Lyn M. Steffen, Christie M. Ballantyne, Eric Boerwinkle, and Aaron R. Folsom

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis (JAN, LMS, ARF); Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center and Baylor College of Medicine, Houston (CMB); Human Genetics Center, University of Texas-Houston Health Science Center, Houston (EB)

Abstract

Polymorphisms in genes involved in HDL-cholesterol (HDL-C) metabolism influence plasma HDL-C concentrations. We examined whether dietary fat intake modified relations between HDL-C and polymorphisms in hepatic lipase (*LIPC*-514C→T), cholesteryl ester transfer protein (*CETP* TaqIB), and lipoprotein lipase (*LPL* S447X) genes. Diet (food frequency questionnaire), plasma lipids, and *LIPC*, *CETP*, and *LPL* genotypes were assessed in ~12,000 White and African American adults. In both races and all genotypes studied, minor allele homozygotes had highest HDL-C concentrations compared to the other genotypes ($P < 0.001$). However, main effects were modified by usual dietary fat intake. In African Americans—women somewhat more strongly than men—*LIPC* *TT* homozygotes with fat intake $\geq 33.2\%$ of energy had ~3–4 mg/dL higher HDL-C concentrations than *CC* and *CT* genotypes. In contrast, when fat intake was $< 33.2\%$ of energy, *TT* homozygotes had HDL-C concentrations ~3.5 mg/dL greater than those with the *CC* genotype but not different from those with the *CT* genotype ($P_{\text{interaction}} = 0.013$). In Whites, *LPL* *GG* homozygotes had greatest HDL-C at lower total, saturated, and monounsaturated fat intakes but lowest HDL-C at higher intakes of these fats ($P_{\text{interaction}} \leq 0.002$). Dietary fat did not modify associations between *CETP* and HDL-C. In conclusion, these data show that plasma HDL-C differs according to *LIPC*, *LPL*, and *CETP* genotypes. In the case of *LIPC* and *LPL*, data suggest dietary fat modifies these relations.

Keywords

Hepatic lipase; lipoprotein lipase; cholesteryl ester transfer protein; dietary fat; HDL-C

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²Authors have no conflicts of interest to disclose.

³Reprints not available. Address correspondence to Dr. Folsom, University of Minnesota, Division of Epidemiology and Community Health, School of Public Health, 1300 South 2nd Street, Suite 300, Minneapolis, MN 55454. E-mail: folsom@epi.umn.edu.

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INTRODUCTION

Low plasma HDL-cholesterol (HDL-C) is associated with increased cardiovascular disease risk. Diet, in addition to various other factors, such as gender, menopausal status, hormone therapy, body size, exercise, and alcohol intake, can influence HDL-C concentrations. Dietary macronutrient composition, specifically the balance among carbohydrate, protein, and fat, as well as the particular fatty acid composition of the diet, affects HDL-C concentrations. Variation in genes involved in HDL-C synthesis and metabolism influences HDL-C concentration, and the interplay between genetics and environmental factors, such as diet, may be of key importance in determining HDL-C levels.

Hepatic lipase hydrolyzes triglycerides and phospholipids, is involved in lipoprotein uptake, and therefore, plays an important role in HDL-C metabolism (1-3). Hepatic lipase deficiency results in increased HDL-C concentrations (4), and polymorphisms in the hepatic lipase gene (*LIPC*) influence HDL-C concentrations (1). Persons with the -514C→T polymorphism in *LIPC* show reduced hepatic lipase activity and greater HDL-C concentrations (3,5,6). Observational studies have shown that this association is modified by dietary fat intake, although the nature of this interaction has varied among studies (7-9). While two of the three studies found that persons with the *TT* genotype had greater HDL-C concentrations only when fat intake was <30% total energy (7,8), the third study conducted in a cohort of diabetic men (9) found the -514C→T polymorphism to be associated with greater HDL-C concentrations only when fat intake was >32% of total energy. Important differences in the population sizes, genetic composition, and background diets of the populations studied may be partly responsible for these discordant results.

Genetic variation in other genes involved in HDL-C metabolism, such as cholesterol ester transfer protein (*CETP*) (10-12) and lipoprotein lipase (*LPL*) (13-16), also partly explain phenotypic HDL-C variation. A single nucleotide polymorphism in intron 1 of the *CETP* gene (*TaqIB*) is associated with differences HDL-C concentrations, with minor (*A*) allele homozygotes having highest HDL-C concentrations, and observational studies suggest environmental factors may influence the strength of this relation (17-19). The *LPL* polymorphism S447X results in a two-amino acid truncation of the *LPL* protein (20), and in addition to effects on triglyceride (TG) concentrations (16), individuals with this deletion have greater HDL-C concentrations than their genetic counterparts (14-16). To date, no large scale epidemiological investigations have published data regarding interactions between dietary fat and *CETP* or *LPL* genotypes in determining HDL-C levels.

Our primary hypotheses were that specific polymorphisms in *LIPC*, *CETP*, and *LPL* genes would be associated with HDL-C concentrations, consistent with previous reports where homozygous minor allele genotypes (*LIPC TT*, *CETP TaqIB AA*, and *LPL S447X GG*) would be associated with highest HDL-C concentrations. We further hypothesized that these associations would be modified by total dietary fat and/or saturated, monounsaturated, and polyunsaturated fat. Finally, given previously reported interactions between genotype and BMI (9,17,18), smoking status (17), and physical activity (21), we also investigated whether these factors modified genotype-HDL-C associations.

METHODS

Subjects

In 1987, the Atherosclerosis Risk in Communities (ARIC) study recruited a cohort of men and women, aged 45-64, from four communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; Northwest Minneapolis suburbs, Minnesota; Washington County, Maryland) (22). All protocols were approved by the institutional review boards at each

center. After providing informed consent, 15,792 participants were enrolled in the study, including 8,710 women and 7,082 men. Only African Americans were recruited from the center in Jackson, Mississippi, whereas mostly whites were recruited from the remaining three centers. The current investigation excluded participants who were neither African American nor White ($n = 48$), who were African American in two centers ($n = 55$, due to small numbers), who had a history of coronary atherosclerotic disease ($n = 766$) or stroke ($n = 284$), who were taking cholesterol-lowering medications ($n = 448$), who were not typed for the genotype of interest ($n = 680$ for *LIPC*, 938 for *CETP*, and 881 for *LPL*), or who fasted <8 hours ($n = 521$) (numbers not mutually exclusive). We further excluded 1,297 participants with type II diabetes and 264 participants who provided insufficient dietary data (>10 missing items on food frequency questionnaire) or had extreme energy intakes (kcal intake <600 or >4,200 for men or <500 or >3,600 for women; approximate lower and upper 1 percentiles of the energy-intake distribution). Our final sample for the study of the *LIPC* polymorphism was 11,806 (8,897 Whites/2,909 African Americans), for the *CETP* polymorphism 11,559 (8,764 Whites/2,795 African Americans), and for the *LPL* polymorphism 11,645 (8,968 Whites/2,677 African Americans).

Diet Assessment

At the baseline examination, participants completed a 66-item, interviewer-administered, semiquantitative food frequency questionnaire (FFQ). The questionnaire was modified from the 61-item FFQ designed and validated by Willett et al. (23). Participants were asked to report the frequency of consumption of each food/beverage on the basis of 9 categories, ranging from never or <1 time/mo to ≥ 6 times/d. Standard serving sizes were given as a reference for intake estimation. Interviewers obtained additional information, including the type of fat usually used in frying and in baking (butter, margarine, vegetable oil, vegetable shortening, lard), as well as the brand name of the breakfast cereal usually consumed (open-ended response). Intakes of each wine, beer, liquor were queried separately.

Genotyping

Genotyping of *LIPC* -514C→T (*rs1800588*), *CETP* TaqIB (*rs708272*), *LPL* S447X (*rs328*) polymorphisms were carried out by the TaqMAN assay following PCR amplification of the target sequences. Primers and probes for the assays are available from the authors upon request.

Plasma HDL-cholesterol and other relevant variables

Analytical methods used to determine total cholesterol, LDL-C, TG, HDL-C, HDL₃, apoB, and apoA-I have been previously described in detail (24). Cholesterol and TG were measured by enzymatic procedures (25,26), with reagents from Boehringer Mannheim Biochemical (analysis adapted for use in Cobas-Bio Analyzer, Roche). Cholesterol was measured in total HDL-C and HDL₃ (27,28), and HDL₂ was calculated from the difference (HDL-C - HDL₃). LDL-C was calculated with the Friedewald equation (29). ApoA-I was determined by a modified radioimmunoassay (30,31). ApoB was determined by radioimmunoassay (32), with minor modifications.

For measurement of plasma cholesterol, TG, and HDL-C, plasma pools from the US Centers for Disease Control and Prevention (CDC) were used as internal quality controls, following Lipid Research Clinics' protocols (33). External control consisted of successful participation in the CDC's Lipid Standardization Program. Laboratory-prepared in-house pools were used as quality controls for HDL-C, HDL₃-C, apoA-I, and apoB. Coefficients of variation for total cholesterol, LDL-C, TG, HDL-C, HDL₃, apoB, and apoA-I were 5%, 10%, 7%, 5%, 12%, 16%, and 14%, respectively. A study of intraindividual variability within the ARIC population showed that short-term repeatability of these lipids was also high (reliability coefficients ≥ 0.85) (34).

Statistical Analysis

All analyses were conducted according to genotype for each *LIPC*, *CETP*, and *LPL* in Whites and African Americans separately. Analysis of variance was used to calculate participant characteristics by *LIPC* genotype (*CC*, *CT*, *TT*), *CETP* TaqIB genotype (*GG*, *AG*, *AA*), and *LPL* S447X genotype (*CC*, *CG*, *GG*). Observed genotype frequencies were compared with expected genotype frequencies under Hardy-Weinberg equilibrium with the χ^2 test. Due to deviance from normality, TG concentrations were analyzed on the natural log scale and back-transformed to the geometric mean for presentation. General linear model regression (SAS Proc GLM) was used to assess the relation between genotype and concentrations of total cholesterol, LDL-C, HDL-C, HDL₂, HDL₃, (ln)TG, apo A-I, and apo B. In addition to unadjusted analyses, we also ran analyses adjusted for age (y), gender, education (<high school degree, high school degree or high school + vocational training, high school + ≥ 1 year of college), body mass index (<25.0, 25.0-29.9, >30.0 kg/m²), physical activity (Baecke score (35)), smoking (two variables, status: current, former, never and cigarette years), alcohol intake (non-drinker, 1-14 drinks/wk, 15-21 drinks/wk, ≥ 21 drinks/wk), energy intake (kcal/d), and use of medications that may have secondary effects on cholesterol concentrations (current vs. never user).

To assess the significance and nature of interactions between genotype and dietary fat for HDL-C, cross-product terms were added to an energy-adjusted (kcal/d) and fully-adjusted model (listed above). In all analyses, dietary fat was represented in the following ways: g/d (continuous), percent of total energy (continuous), and percent of total energy dichotomized according to the median value for each fat type (33.2 % energy/day from total fat; 12.0% energy/day from saturated fat; 12.8% energy/day from monounsaturated fat; 4.9% energy/day from polyunsaturated fat). However, because the results from the dichotomized analyses were largely mirrored by the results from the continuous analyses, we present only the continuous, percent of energy intake representations. We also tested for 3-way interactions among gender, genotype, and dietary fat intake in each analysis. In the event the 3-way interaction was significant, we present gender specific results within race. Because of its important metabolic relation to HDL-C, similar analyses were also conducted for (ln)TG. Because of potential confounding by carbohydrate intake, we made adjustments for carbohydrate (g/d or as percent energy) but found no attenuation nor change in the nature of the interactions. Adjustment of each dietary fat subclass for the other two types of fat (e.g., SF adjusted for MUFA and PUFA) also had no impact on results. Therefore, results from these models are not presented nor discussed further.

RESULTS

Characteristics and dietary intakes of participants genotyped for at least one of the three studied polymorphisms are given in Table 1 ($n = 12,297$). Minor allele frequencies in Whites for the three polymorphic genes studied were 0.21, 0.44, and 0.10 for *LIPC*, *CETP*, and *LPL*, respectively (Table 2). In African Americans frequencies of these same alleles were 0.53, 0.27, and 0.07 for *LIPC*, *CETP*, and *LPL*, respectively, although in the case of *LIPC*, the *T* allele was the more common allele. In Whites, *LPL* was in Hardy-Weinberg equilibrium, but *LIPC* ($P = 0.030$) and *CETP* were not ($P = 0.012$). In African Americans, all three genes were in Hardy-Weinberg equilibrium ($P = 0.38-0.67$). Because of the lack of Hardy-Weinberg equilibrium in two cases, the study's blind duplicate data were scrutinized ($n = 824$ pairs). The percent agreement for *LIPC*, *CETP*, and *LPL* was 96%, 95%, and 98%, respectively.

In most cases, participant characteristics and dietary intakes did not differ with respect to *LIPC*, *CETP*, or *LPL* genotype (exceptions noted in the following). Only use of medications that may have secondary effects on cholesterol concentrations (beta-blockers, calcium blockers, alpha-blockers, or diuretics) showed marginally significant differences among

LIPC genotypes in both Whites ($P = 0.053$) and African Americans ($P = 0.041$). Gender, education, and medication use (as above) differed among *LPL* genotypes in African Americans ($P \leq 0.05$ for all), but not in Whites. Results from fully-adjusted models, or from simplified models including the confounders discussed above, were not materially different from results of unadjusted models; therefore, for simplicity when presenting the relation between genotype and lipids, only unadjusted comparisons are given.

All three of the studied genetic polymorphisms were significantly related to HDL-C concentrations in both Whites and African Americans (Table 2). In general, differences in HDL-C among the various genotypes were paralleled by differences in both HDL₂ and HDL₃ subfractions and apo A-I (data not shown). For the *LIPC* polymorphism, the *TT* genotype was associated with ~2-4 mg/dL higher HDL-C concentrations compared to the *CC* or *CT* genotypes (Table 2, upper rows). Concentrations of TC, LDL-C, and TG did not differ among the three *LIPC* genotypes in either race group. Similarly, the *CETP* *AA* genotype was associated with greatest HDL-C in Whites and African Americans, lowest TG concentrations in Whites but not African Americans, and lowest LDL-C in African Americans but not Whites (Table 2, middle rows). Lastly, both African Americans and Whites homozygous for the minor *LPL* allele (*G*) had ~4-12 mg/dL greater HDL-C and ~6-17 mg/dL lower TG concentrations than their *CC* or *GC* counterparts. (Table 2, bottom rows).

LIPC

In Whites the relation between *LIPC* genotype and HDL-C was not modified by dietary fat intake, regardless of demographic and lifestyle variable adjustment (P for interaction 0.19-0.91, data not shown). In African Americans women, when percent total fat intake was low, HDL-C concentrations of *CC* genotypes were approximately 5 mg/dL lower than *CT* and *TT* genotypes; however, when percent total fat intake was high, HDL-C concentrations were similar between *CC* and *TT* homozygotes and ~3.5 mg/dL lower in *CT* heterozygotes (Figure 1A). Specifically, there were positive associations between percent of energy intake from total fat and HDL-C in *TT* and *CC* homozygotes, whereas in *CT* heterozygotes there appeared to be no association between dietary fat and HDL-C. In African American men, HDL-C concentrations of *TT* homozygotes were 4-5 mg/dL higher than other genotypes only when dietary fat intake was high (Figure 1B, P for interaction among gender, %energy from total fat, and *LIPC* genotype = 0.015). Interactions between *LIPC* genotype and other dietary fat classes (saturated fat, monounsaturated fat, and polyunsaturated fat) were not statistically significant in either African American men and women or White men and women (data not shown).

When analyzed for TG, we observed no interactions between *LIPC* genotype and percent energy from total dietary fat, MUFA, or PUFA in either race group ($P \geq 0.10$ for all, data not shown). However, there were significant interactions between *LIPC* genotype and percent energy from saturated fat in African Americans ($P = 0.042$) (Figure 2A). When percent energy intake from saturated fat was low, TG concentrations were approximately 5 mg/dL lower in *CT* than in *CC* or *TT* genotypes. However, when percent energy intake from saturated fat was high, TG concentrations were 5-8 mg/dL lower in *CC* than in *CT* and *TT* genotypes. The interaction was marginally significant in Whites ($P = 0.12$), but the nature of the interaction differed (Figure 2B). When percent energy intake from saturated fat was low, *TT* genotypes had highest TG concentrations and *CC* genotypes had lowest TG concentrations, but when percent energy intake from saturated fat intake was high, there were not differences among genotypes. These interactions did not differ by gender in either race (P for 3-way interaction = 0.21 – 0.27).

CETP

We observed no significant interactions between dietary fat and *CETP* genotype for either HDL-C or TG in either Whites or African Americans, regardless of the manner in which dietary fat was modeled (as percent energy dichotomized or continuous or as g/d continuous).

LPL

In Whites, but not African Americans, there was an interaction between genotype and dietary fat for HDL-C when dietary fat was modeled as a continuous variable (g/d) ($P = 0.002$, and a suggested interaction when dietary fat was modeled continuously as percent energy ($P = 0.13$). The interaction was also significant for SF (g/d) and MUFA (g/d and % of energy) ($P = <0.001 - 0.032$) and marginally significant for percent of energy from SF ($P = 0.13$). Specifically, HDL-C was positively associated with dietary fat intake in *CC* homozygotes and *CG* heterozygotes but inversely associated with dietary fat in *GG* homozygotes. Thus, HDL-C of the *GG* homozygotes was highest among the three genotypes when fat intake was low but lowest when fat intake was high. For consistency with our previous presentation, we present the data according to percent of energy from total fat (Figure 3). Although the P values for the 3-way interactions (gender $\times$ dietary fat $\times$ LPL genotype) ranged from 0.027–0.089 for the 3 dietary fat types studied, when we stratified the dietary fat $\times$ LPL genotype analysis by gender, conclusions were essentially uniform in both gender groups. Therefore, for simplicity we presented only the data from models with genders combined (Figure 3). For TG there were no interactions between *LPL* genotype and dietary fat intake (total, SF, MUFA, or PUFA) in either Whites or African Americans.

DISCUSSION

In both White and African American men and women from the ARIC study, there were differences in HDL-C among *LIPC* (-514 C $\rightarrow$ T), *CETP* (TaqIB, G+279A/*In1*), and *LPL* (S447X) genotypes. TG concentrations also differed by *LPL* genotype. In both ethnic groups, minor allele homozygotes had greater HDL-C, and in the case of *LPL*, also lower TG concentrations than their counterparts, a profile generally associated with reduced risk of CVD. These data add to a body of literature supporting the relation between these genetic polymorphisms and HDL-C in predominantly white participants (3,5,6,10-16,36) and provide additional data to the smaller pool of studies conducted in African Americans (37-41).

Diet is undoubtedly important in determining concentrations of both HDL-C and TG, and the effect of diet on CVD risk factors may differ on the basis of genotype (42). Previous studies have evaluated the presence of interactions between *LIPC* genotype and dietary fat for HDL-C (7-9). However, to our knowledge, no studies have evaluated such nutrient-gene interactions relative to *LPL* or *CETP* genotypes. The results of the current investigation suggested significant interactions between dietary fat and *LIPC* genotype for HDL-C and TG and between dietary fat and *LPL* genotype for HDL-C. There were no corresponding interactions between dietary fat and the particular *CETP* polymorphism studied.

Our results regarding *LIPC**dietary fat interactions for HDL-C are not consistent with previous observational studies of similar intent (7-9). Tai et al. (8) and Ordovas et al. (7) found that HDL-C was highest in *TT* homozygotes only when percent energy from fat was low (7,8), but Zhang et al. found the opposite to be true of male *T* allele carriers with diabetes (9). In our study, HDL-C concentrations of African American *TT* homozygotes were highest when percent of energy intake from total fat was high. This was slightly stronger in women than men. Thus, we noted important differences between *T* allele carriers and *T* allele homozygotes in the nature of the interaction with dietary fat, as have others (7,8). However, our finding that the effect of dietary fat on HDL-C in *LIPC* heterozygotes was unique from both *TT* and *CC* homozygotes is

counterintuitive, given the expectation of either an intermediate association in heterozygotes or, as reported by others (7,8), an association in heterozygotes that parallels that of *CC* homozygotes. Although our results are somewhat similar to those of Zhang et al. who found that *TT* homozygotes had highest HDL-C only when dietary fat intake was above the population median, comparison with their study is difficult since they combined *TT* and *CT* genotypes due to small numbers (9).

Comparison among previous studies and ours is further complicated by differences in the race and gender compositions of study populations. The Ordoas study was conducted in predominantly White men and women; the Tai study was conducted men and women of Chinese, Malay, or Asian Indian descent; the Zhang study was conducted in predominantly White men with type II diabetes; and our analyses were conducted in White men and women and African American men and women. In our study, the interaction between dietary fat intake and *LIPC* genotype for HDL-C was present in African Americans but not Whites and differed by gender. In the study by Tai et al. the interaction between *TT* genotype and dietary fat existed only in the Asian Indian participants but not other ethnicities studied (8). Racial differences in gene expression or ethnic differences in dietary intake may be partly responsible for these discordant findings. For example, the *LIPC* 514C→T polymorphism may be in strong linkage disequilibrium with another polymorphism in African Americans but not in Whites, therefore, serving only as a marker of another causal polymorphism (41). Ethnic differences in dietary patterns and food selection may also complicate interpretation since it is likely that food sources of fats and other nutrients differ between men and women and between Whites and African Americans, providing an additional set of potential confounders (43,44).

The findings of the Zhang study (9) raise the interesting possibility that the relation between *LIPC* polymorphisms and HDL-C depends not only on dietary fat but a combination of dietary fat and diabetes status. However, when we conducted supplementary analyses in only diabetic participants, we found no relations between *LIPC* genotype and HDL-C nor interactions between dietary fat and *LIPC* genotype for HDL-C. It is possible this was simply due to inadequate power in the smaller group of ARIC diabetics ($n = 489$ African Americans and 691 Whites), though our numbers are similar to that studied by Zhang et al. ($n = 752$).

Taken together, the results of previous studies, and those of the current study, do not definitively delineate the interaction between *LIPC* genotype and dietary fat. They do, however, lend support to the hypothesis that there may indeed be some unique differences among *LIPC* genotypes in their HDL-C response to dietary fat intake. It is likely that other environmental and genetic factors may muddy these observational investigations that dietary trials could disentangle.

In both Whites and African Americans, we also observed a significant interaction between *LIPC* genotype and saturated fat for TG. Of the previous observational studies conducting similar investigations for TG (7,8), only one found an interaction (8), and again results were opposite of those of the current study. Whereas Tai et al. found that percent energy from total dietary fat was positively associated with TG concentrations in only *TT* homozygotes (8), we observed opposite trends for saturated fat (with subtle differences in the nature of the interaction in each race group). Although our results are in contrast to this previous report, they are consistent with the predicted effect of fat (regardless of fatty acid type) on TG concentration (45) and are internally consistent with the interaction observed for HDL-C in African Americans. While the interaction for TG was observed only with saturated fat and not total fat or other fat classes, we cannot necessarily conclude the association is restricted to only saturated fat. It is also possible that results reflect more accurate assessment of dietary saturated fat intake than of intake of other fatty acid classes (46).

To some extent, *LPL* is involved in lipid metabolism under fasting conditions, but its key role is in postprandial lipid metabolism (47). Effects on postprandial lipemia may be one mechanism by which *LPL* S447X affects TG and HDL-C concentrations (48,49). Differences in dietary composition, namely fat, may also alter postprandial response, thus interacting with the effects of *LPL* S447X. We noted significant interactions between *LPL* and dietary fat for only HDL-C and not for TG. It is possible that the absence of interaction between *LPL* and dietary fat for TG was due to the lower plasma TG indicative of the fasting condition studied here.

Limitations of our study should be addressed. First, given the multiple hypotheses tested, it is possible that interactions deemed statistically significant were actually chance findings. Second, our study used a 66-item FFQ to assess diet. Dietary fat intake assessed by a more comprehensive questionnaire, as was used in the other studies of similar intent (7-9), may have yielded results different from those we report here. Third, carbohydrate is equally important in determining one's lipid profile, especially in the case of TG and HDL-C (45). The high degree of correlation between carbohydrate and dietary fat intake make it difficult to fully adjust for its potentially confounding effects. In the current study, adjustment for carbohydrate intake in multivariable models had nominal effects; however, carbohydrate and total fat showed a correlation of -0.68 (adjusted for total energy). Finally, neither *CETP* nor *LIPC* were in Hardy-Weinberg equilibrium in Whites, although the allele frequencies were similar to those reported in other Caucasian populations (10,19,50), and the blind duplicate data were consistent. Nevertheless, it is possible that our findings were biased by the greater number of wild type and minor allele homozygotes than expected for these two genes (51).

In summary, the findings of the current study bolster those of previous studies showing differences in HDL-C according to *LIPC*, *LPL* S447X, and *CETP* TaqIB genotypes. Nevertheless, defining causal interactive effects of nutrients and genes on complex phenotypes, such as lipids, will be a challenge for some time to come (52). Clinical studies are needed to best define these effects.

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Figure 1.

Interaction between LIPC genotype and percent energy from total dietary fat for HDL-C in (A) African American women and (B) African American men from the Atherosclerosis Risk in Communities Study (ARIC). P for interaction among gender, dietary fat, and LIPC genotype = 0.015. P for interaction between dietary fat and LIPC genotype in African American women = 0.12; in African American men $P = 0.20$. Analysis adjusted for study center (Forsyth County, NC; Jackson, MS; Washington county, MD; western Minneapolis suburbs, MN), age (y), gender, and education level (<high school degree, high school degree or high school + vocational training, high school + ≥ 1 year of college), smoking (status: current, former, never smoker and cigarettes/y), alcohol consumption (non-drinker, 1-14 drinks/wk, 15-21 drinks/wk, +21 drinks/wk), body mass index (<25.0, 25.0-29.9, >30.0 kg/m²), physical activity level

(Baecke score), and medication/supplements that may secondarily affect cholesterol (current users vs. non-user). Figures derived by taking mean HDL-C of each LIPC genotype and calculating expected change in HDL-C according to 1-and 2-SD changes in % of energy from total fat. For example, for CC individuals, mean HDL-C was 58.3 mg/dL. If the regression coefficient for the relation between % of energy from total fat and HDL-C (+0.358) is multiplied by the SD for % of energy from total fat intake (6.3 %), the result is 60.6 mg/dL. The same procedure was followed for a 2-SD increase, and for 1-and 2-SD decreases in % energy from total fat.

A.

B.

Figure 2.

Interaction between LIPC genotype and percent energy from saturated fat for TG in (A) African Americans and (B) Whites from the Atherosclerosis Risk in Communities Study (ARIC). Analysis adjusted for study center (Forsyth County, NC; Jackson, MS; Washington county, MD; western Minneapolis suburbs, MN), age (y), gender, and education level (<high school degree, high school degree or high school + vocational training, high school + ≥ 1 year of college), smoking (status: current, former, never smoker and cigarettes/y), alcohol consumption (non-drinker, 1-14 drinks/wk, 15-21 drinks/wk, ≥ 21 drinks/wk), body mass index (<25.0, 25.0-29.9, ≥ 30.0 kg/m²), physical activity level (Baecke score), and medication/supplements that may secondarily affect cholesterol (current users vs. non-user). *P* for

interaction = 0.042 in African Americans and = 0.12 in Whites. Figures were derived by taking geometric mean TG of each LIPC genotype and calculating expected change in TG according to 1- and 2-SD changes in %energy from saturated fat.

Figure 3.

Analysis adjusted for study center (Forsyth County, NC; Jackson, MS; Washington county, MD; western Minneapolis suburbs, MN), age (y), gender, and education level (<high school degree, high school degree or high school + vocational training, high school + ≥ 1 year of college), smoking (status: current, former, never smoker and cigarettes/y), alcohol consumption (non-drinker, 1-14 drinks/wk, 15-21 drinks/wk, ≥ 21 drinks/wk), body mass index (<25.0, 25.0-29.9, ≥ 30.0 kg/m²), physical activity level (Baecke score), and medication/supplements that may secondarily affect cholesterol (current users vs. non-user). Figures derived by taking mean HDL-C of each LPL genotype and calculating expected change in HDL-C according to 1- and 2-SD changes in percent of energy intake from total dietary fat.

Table 1

Demographic and lifestyle characteristics and nutrient intakes of White and African American men and women from the Atherosclerosis Risk in Communities (ARIC) study ¹

(N)	White Participants		African American Participants	
	Men(4,171)	Women(5,132)	Men(1,117)	Women(1,877)
Demographic and lifestyle characteristics				
Age	54.4 ± 0.1	53.7 ± 0.08	53.6 ± 0.2	52.8 ± 0.13
Education (% >high school degree)	84.0 ± 0.6	85.2 ± 0.5	57.7 ± 1.2	63.2 ± 0.9
Physical activity (% in quintile 5 of Baecke score ³)	30.1 ± 0.7	18.6 ± 0.5	13.1 ± 1.3	8.4 ± 0.8
Body mass index	27.2 ± 0.06	26.2 ± 0.08	27.2 ± 0.12	30.3 ± 0.13
Alcoholic drinks per week	7.7 ± 0.2	3.1 ± 0.1	11.2 ± 0.5	4.1 ± 2.5
Smoking (% current)	24.1 ± 0.7	24.7 ± 0.6	38.1 ± 1.3	25.2 ± 1.0
Hypertension medication (% current users)	15.5 ± 0.6	16.2 ± 0.6	30.1 ± 1.2	39.1 ± 0.9
Systolic blood pressure (mm Hg)	119.4 ± 0.3	116.1 ± 0.3	129.2 ± 0.5	126.6 ± 0.4
Dietary intake ⁴				
Energy intake (kcal/d)	1816 ± 10	1522 ± 12	1786 ± 20	1499 ± 8
Protein (% energy)	16.8 ± 0.1	18.4 ± 0.1	16.8 ± 0.1	18.3 ± 0.1
Carbohydrate (% energy)	47.3 ± 0.01	49.4 ± 0.1	48.7 ± 0.3	50.8 ± 0.2
Total fat (% energy)	33.8 ± 0.1	32.9 ± 0.1	32.0 ± 0.2	32.0 ± 0.2
Saturated fat (% energy)	12.5 ± 0.04	12.1 ± 0.04	11.4 ± 0.09	11.4 ± 0.07
Monounsaturated fat (% energy)	13.1 ± 0.04	12.4 ± 0.04	12.7 ± 0.08	12.4 ± 0.07
Polyunsaturated fat (% energy)	5.1 ± 0.02	5.1 ± 0.02	4.7 ± 0.04	4.9 ± 0.03
Cholesterol (mg/d)	272 ± 2	221 ± 1	316 ± 3	247 ± 2
Fiber (g/d)	17.5 ± 0.1	17.3 ± 0.1	16.3 ± 0.2	15.9 ± 0.1

¹ Data are based on 12,297 participants who were genotyped for at least one of the three polymorphisms studied.

² Values are unadjusted means (or percentages) ± SEM.

³ Based on Baecke questionnaire (34), quantifying sport and exercise activity.

⁴ With the exception of energy intake, all dietary variables are adjusted for total energy intake (kcal/d).

Table 2

Race-stratified mean total cholesterol, LDL-C, HDL-C, and TG concentrations according to LIPC, CETP, and LPL polymorphisms in White and African American men and women from the Atherosclerosis Risk in Communities (ARIC) study.¹

Hepatic Lipase C/T								
Genotype Frequency	White Participants (N = 8,897)			p ⁵	African American Participants (N = 2,909)			
	CC 0.625	CT 0.326	TT 0.049		CC 0.219	CT 0.505	TT 0.276	p ⁵
Total cholesterol (mg/dL)	212.9 ± 0.5	213.9 ± 0.7	215.5 ± 1.9	0.28	211.9 ± 1.8	213.3 ± 1.2	214.7 ± 1.6	0.50
LDL-C (mg/dL)	136.6 ± 0.5	135.5 ± 0.7	133.8 ± 1.8	0.18	136.4 ± 1.7	136.5 ± 1.1	135.6 ± 1.5	0.89
HDL-C (mg/dL)	51.1 ± 0.22	53.3 ± 0.31	54.9 ± 0.81	<0.001	54.7 ± 0.72	56.3 ± 0.47	58.7 ± 0.63	<0.001
TTG (mg/dL)	112.0 (110.5, 113.4)	112.8 (110.8, 114.8)	117.3 (112.0, 122.8)	0.16	92.5 (89.2, 95.9)	93.2 (91.0, 95.4)	94.6 (91.7, 97.7)	0.61
Cholesteryl Ester Transfer Protein G/A								
Genotype Frequency	White Participants (N = 8,764)			p ⁵	African American Participants (N = 2,795)			
	GG 0.326	AG 0.478	AA 0.196		GG 0.534	AG 0.398	AA 0.068	p ⁵
Total cholesterol (mg/dL)	211.8 ± 0.7	213.8 ± 0.6	213.9 ± 1.0	0.069	213.8 ± 1.2	212.5 ± 1.4	215.4 ± 3.3	0.62
LDL-C (mg/dL)	136.6 ± 0.7	136.5 ± 0.6	134.1 ± 0.9	0.063	138.7 ± 1.1	134.0 ± 1.3	130.2 ± 3.2	0.003
HDL-C (mg/dL)	49.7 ± 0.3	52.0 ± 0.3	55.5 ± 0.4	<0.001	54.4 ± 0.5	58.2 ± 0.5	64.2 ± 1.3	<0.001
TTG (mg/dL)	113.6 (111.5, 115.6)	112.9 (111.3, 114.6)	109.5 (107.0, 112.1)	0.041	93.2 (91.1, 95.4)	93.6 (91.1, 96.2)	91.8 (86.0, 98.0)	0.86
Lipoprotein Lipase C/G								
Genotype Frequency	White Participants (N = 8,968)			p ⁵	African American Participants (N = 2,677)			
	CC 0.806	CG 0.185	GG 0.010		CC 0.873	CG 0.122	GG 0.005	p ⁵
Total cholesterol (mg/dL)	213.3 ± 0.5	212.7 ± 1.0	213.8 ± 4.3	0.81	213.1 ± 0.9	214.6 ± 2.5	223.0 ± 12.3	0.63
LDL-C (mg/dL)	136.2 ± 0.4	135.3 ± 0.9	136.8 ± 4.0	0.65	136.1 ± 0.9	136.8 ± 2.4	137.9 ± 11.9	0.96
HDL-C (mg/dL)	51.4 ± 0.2	54.2 ± 0.4	55.4 ± 1.8	<0.001	56.1 ± 0.4	59.2 ± 1.0	68.7 ± 4.9	<0.001
TTG (mg/dL)	114.7 (113.4, 116.0)	104.2 (101.8, 106.7)	97.9 (88.4, 108.5)	<0.001	94.6 (92.8, 96.3)	85.5 (81.4, 89.9)	78.0 (61.0, 99.7)	<0.001

¹ Unadjusted values presented as mean ± SEM, with the exception of TG values which were log-transformed and back-transformed to the geometric mean (95% confidence interval).

² T allele frequency = 0.212 and 0.529 in Whites and African Americans, respectively;

³ A allele frequency = 0.435 and 0.267 in Whites and African Americans, respectively;

⁴ G allele frequency = 0.102 and 0.066 in Whites and African Americans, respectively;

⁵ P for comparison among genotypes within each race group separately based on analysis of variance. P values for trend across genotype with genotype category treated as a continuous variable were nearly identical.