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Title: Dietary fat modulation of hepatic lipase variant -514 C/T for lipids: a crossover randomized dietary intervention trial in Caribbean Hispanics

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Abstract

Background and Aims-The hepatic lipase (*LIPC*) locus is a well-established determinant of high-density lipoprotein cholesterol (HDL-C) concentrations, an association that is modified by dietary fat in observational studies. Dietary interventions are lacking. **Methods and Results**: We investigated dietary modulation of *LIPC* rs1800588 (-514 C/T) for lipids and glucose using a randomized cross-over design comparing a high-fat Western diet and a low-fat traditional Hispanic diet in individuals of Caribbean Hispanics descent (n=42; 4 weeks/phase). No significant gene-diet interactions were observed for HDL-C. However, differences in dietary response according to *LIPC* genotype were observed. In major allele carriers (CC/CT), HDL-C (mmol/L) was higher following the Western diet compared to the Hispanic diet: (Phase 1 (Western:1.3±0.03; Hispanic:1.1±0.04; P=0.0004). Phase 2 (Western:1.4±0.03; Hispanic:1.2±0.03; P=0.0003). In contrast, HDL-C in TT individuals did not differ by diet. Only major allele carriers benefited from the higher fat diet for HDL-C. Secondarily, we explored dietary fat quality and rs1800588 for HDL-C and triglycerides (TG) in a Boston Puerto Rican Health Study (BPRHS) subset matched for diabetes and obesity status (subset n=384). In the BPRHS, saturated fat was unfavorably associated with HDL-C and TG in rs1800588 TT carriers. **Conclusion**: *LIPC* rs1800588 appears to modify plasma lipids in the context of dietary fat. This new evidence of genetic modulation of dietary responses may inform optimal and personalized dietary fat advice, and reinforces the importance of studying genetic markers in diet and cardio-metabolic health.

Introduction

While consensus has been achieved on many of the defining characteristics of healthy diets, debate about the optimal macronutrient composition (e.g., fat vs. carbohydrates) for cardiovascular health persists (29,34). Although lower fat diets were recommended through 2000 (12), these recommendations shifted to moderate fat, lower in carbohydrate diets, particularly refined carbohydrate, thereafter (14). Higher fat diets, particularly higher in unsaturated fat, are thought to be cardio-protective, in part, because they result in higher high-density lipoprotein cholesterol (HDL-C) and lower triglyceride (TG) concentrations (2). However, considerable inter-individual variability in response to dietary fat and carbohydrate exists, and assessments of gene-diet interactions have identified variants in regulators of lipoprotein metabolism that contribute to differential responses (4).

One such regulator is hepatic lipase, which hydrolyzes triglycerides and phospholipids and provides a ligand-binding function for the uptake of lipoproteins and lipoprotein lipids (22). Therefore, hepatic lipase (*LIPC)* is a plausible candidate locus for plasma HDL-C and TG concentrations (27, 33). The nucleotide substitution that creates the *LIPC* -514 C/T promoter variant (rs1800588) has been shown to decrease hepatic lipase activity. Hepatic lipase activity is a major determinant of HDL-C concentration, such that higher lipase activity contributes to lower HDL-C (3) concentrations. The LIPC -514 C/T variant's association with lower hepatic lipase activity provides a functional basis for its association with higher HDL-C concentrations (8). However, the variant's inconsistent associations with plasma HDL-C and TG concentrations (19, 25, 32) suggested that other factors, including diet, might modulate its association with lipids.

Gene-diet interaction analyses support the premise that total dietary fat and types of fat (monounsaturated (MUFA), polyunsaturated (PUFA) and saturated (SFA)) modify *LIPC* -514 C/T associations with HDL-C concentration (19, 25). While higher fat intake is usually associated with higher HDL-C concentration when genotype is not considered, *LIPC -514* C/T modified this association, such that higher total fat (19, 25) and higher SFA (19) were associated with lower HDL-C concentration in minor allele T carriers. Furthermore, recognition of the coupling between lipid and glucose metabolism, led to investigation of the potential role of *LIPC* -514 C/T in glycemic outcomes (6, 30).

While observational studies can generate hypotheses, interventions provide a higher level of evidence. To rigorously investigate the hypothesis that dietary fat intake modifies *LIPC* -514 C/T associations with HDL-C concentration, we conducted a cross-over, randomized intervention using two diets, a high-fat Western diet and a low-fat traditional Hispanic diet, in Caribbean Hispanics. Secondarily, given the absence of studies for diet and *LIPC* -514 C/T in Caribbean Hispanics, we explored interactions between dietary fat and genotype for lipids in the Boston Puerto Rican Health Study (BPRHS).

Methods

Study population and design

We conducted a crossover, randomized dietary intervention to evaluate interactions between *LIPC* -514 C/T, two diets of different fat content, and plasma lipids in Caribbean Hispanics living in the Boston, MA metropolitan area. Individuals aged 20 to 64 years with self-reported Caribbean Hispanic ancestry were recruited from January 2008-July 2011. Study exclusions included: diabetes (fasting glucose >140 mg/dL), other chronic disease, lipid-lowering or hypoglycemic medications, BMI >34 kg/m^2, excessive alcohol, smoking within 6 months, pregnancy/lactation, recent weight change, extreme physical activity, vegetarians/vegans and food allergies. The Tufts University Institutional Review Board (IRB) approved the protocol, and informed written consent was obtained. The principal investigator was blinded to the randomization scheme until study completion. The study is registered at ClinicalTrials.gov (identifier: NCT02938091).

Diet procedures

A Consolidated Standards of Reporting Trials (CONSORT) chart documents the flow of participants through the intervention processes including screening, enrollment, randomization, follow-up, washout, cross-over and analysis (Figure 1). The CONSORT chart was developed by the CONSORT group to improve and standardize the reporting of randomized controlled trials. (17).

Briefly, participants were randomized to one of two study diets for four weeks, followed by a 2-8-week break period before beginning the second diet for four weeks. A four-week diet period was chosen to enable stabilization of the lipoprotein endpoints, and to facilitate recruitment and

adherence. Participants were provided with a high-fat Western diet (39% fat) and a low-fat traditional Hispanic diet (20% fat) based on their random order assignment (**Table 1**). A registered dietitian calculated the estimated energy requirements to maintain each participant's body weight, with adjustments to keep weight stable. All foods and beverages were provided by the research kitchen with no other foods permitted. Participants were asked to eat all of the food provided.

All study visits were conducted at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA), by bilingual study coordinators and Metabolic Research Unit (MRU) staff. Each study phase consisted of 12 visits, usually requiring 1-3 hours/visit. Participants were required to eat at least three meals per week at the HNRCA. The remainder of the weekly food and beverages was pre-packaged for each participant.

Data collection

Venous blood was collected at four visits, including baseline, and in week 3 of each phase for an oral glucose tolerance test (OGTT). Individuals fasted for 12 hours before each blood draw, including for the OGTT determination. Anthropometrics were measured using standardized protocols. Diet was assessed using a food frequency questionnaire designed and validated for Caribbean Hispanics. Intervention compliance was maximized and monitored with ongoing interaction between participants and study coordinators.

Genotyping and biochemical analyses

DNA was isolated and purified for PCR analysis using the QIAamp Kit (Qiagen Inc. Chatsworth, CA), and *LIPC* rs1800588 genotyping was performed using the TaqMan assay (Perkin–Elmer). Fasting total cholesterol and TG concentrations were determined by automated enzymatic methods, and HDL-C was measured following precipitation of plasma very low density lipoprotein and low density lipoprotein (LDL) with dextran sulphate-Mg^{2+}. LDL-C was measured directly using LDL-Direct (Sigma Chemicals, Inc. St. Louis, Mo). Glucose was measured by a glucose oxidase enzymatic procedure (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY).

Boston Puerto Rican Health Study

To extend analyses to a larger Hispanic sample, we investigated interactions between dietary fat and *LIPC* rs1800588 for HDL-C and TG concentration in the BPRHS. The longitudinal cohort BPRHS examined health status in Puerto Ricans, and modification of cardio-metabolic biomarkers by nutritional status and genetic variation as previously described (11, 15, 16, 28). Participants were self-identified Puerto Ricans, aged 45-75 years, residing in metropolitan Boston, MA, and for whom genome-wide genotypes, dietary, lifestyle, medical, biochemical and socio-economic data were obtained. The BPRHS averages 57.2% European, 27.4% African, and 15.4% American Indian ancestry (13). The study was approved by the Tufts, Northeastern University and the University of Massachusetts-Lowell IRBs. Participants provided written informed consent.

Statistical analysis

Data were analyzed using SAS (SAS Institute Inc., Cary, NC). Categorical traits were compared using Pearson's chi-square test, except for sex for which Fisher's exact test was used. Continuous variables were compared using analysis of variance (ANOVA). Triglycerides were log-transformed to improve distribution. For the dietary intervention, initial linear mixed effects models included phase, dietary intervention, diet-phase interaction, *LIPC* rs1800588 genotype, diet-genotype interaction and a random subject effect. Because no carryover effect was detected between diet phases (P=0.89), the diet-phase interaction term was removed from subsequent analyses. We tested for SNP x sex interactions to determine whether sex-stratified analyses of the intervention data was statistically justified. The interaction term was not significant so intervention data were analyzed with both sexes combined. Potential confounders included age, sex, waist, and baseline lipid or pre-OGTT glucose concentration. Interaction analyses were conducted using generalized linear model regressions.

Analyses were conducted in a BPRHS subset with exclusions similar to those applied in the intervention (BMI≤34, without diabetes). We dichotomized dietary exposures for total fat, PUFA, MUFA and SFA (% total energy) into high and low according the median population intake, and evaluated interactions between diet and *LIPC* genotype for HDL-C, LDL-C, total cholesterol and TG. Models were adjusted for age, smoking status, alcohol, total energy, waist, physical activity and ancestry.

Results

Cross-over dietary intervention

Forty-two participants completed the trial, including one who was subsequently excluded due to unusually high HDL-C (124 mg/dL) concentration, leaving 41 in the analytic sample. A CONSORT chart documents the flow of participants through the intervention trial (Figure 1). Of 41 participants (aged: 20-64 y, 80% female) national origins included: Dominican (n=25), Puerto Rican (n=9), other Caribbean Hispanics and Central Americans (n=7).

The minor allele (T) frequency (MAF) was 40.2%. Nutrient profiles of the two diet interventions confirmed higher fat (total and all types) and lower carbohydrate in the Western diet (**Table 1**). Baseline cardio-metabolic traits measured prior to the dietary intervention did not differ across genotypes. HDL-C concentration was marginally higher with TT genotype (P=0.05; **Table 2**).

We first evaluated the effect of dietary interventions without considering genotype for HDL-C, TG, LDL-C, total cholesterol, and OGTT 2-hour glucose concentrations (**Table 3**). With all genotypes combined, consumption of the Western diet was associated with higher post-intervention HDL-C, LDL-C, and total cholesterol concentrations, compared to the Hispanic diet (Table 3**,** all $P \leq 0.02$). However, TG and OGTT 2-hour glucose concentration did not differ between diets.

We next evaluated gene-diet interactions, including analysis by dietary phase for HDL-C, LDL-C and total cholesterol (**Table 4).** Based on published data for HDL-C (16), we applied a recessive genetic model (CC/CT, n=33; vs. TT, n=8) to evaluate lipids. No significant interaction was observed between SNP and diet for HDL-C. However, dietary responses

differed by *LIPC* genotype. In major allele carriers (CC/CT), HDL-C was higher following the Western diet compared to the Hispanic diet: (Phase 1 (Western: 1.3 ±0.03; Hispanic: 1.1 ± 0.04; P=0.0004). Phase 2 (Western: 1.4.0±0.03; Hispanic: 1.2±0.03; P=0.0003). In contrast, HDL-C in TT carriers did not differ by diet. In summary, major allele carriers benefited from the higher fat diet for HDL-C, while minor allele carriers did not. For LDL and total cholesterol, no significant interactions were observed between SNP and diet, but several differences by genotype were observed. In major allele carriers (CC/CT) but not in minor allele carriers, the Western diet was associated with higher LDL-C in Phase 1 (Western: 2.9±0.13; Hispanic: 2.5±0.14; P=0.025) and with higher total cholesterol in Phase 1 (Western: 4.9±0.14; Hispanic: 4.2±0.14; P=0.001) and Phase 2 (Western: 5.0±0.13; Hispanic: 4.6±0.14; P=0.018). Finally, we evaluated gene-diet interactions for TG. No significant interactions or difference by genotype were observed by diet for TG (P>0.05; not shown).

We performed similar gene-diet interaction analyses for OGTT 2-hour glucose (**Table 5**). For OGTT 2-hour glucose, a dominant genetic model was used, based on published data for glycemic traits (27). We observed a marginally significant interaction for Phase 1 (P-interaction=0.07). In Phase 1, CC participants showed a lower glycemic response on the Hispanic diet (P=0.04), while minor allele carriers (CT/TT) showed no difference. In contrast, CT/TT participants showed a lower glycemic response on the Western diet in Phase 2 (P=0.008). The SNP-diet interaction for OGTT in Phase 2 was not significant.

Cross-sectional analysis of the BPRHS

Finally, to extend analyses to a larger Caribbean Hispanic population, we tested *LIPC* SNP-diet interactions for HDL-C in the BPRHS **(Table 6)**. The *LIPC* rs1800588 MAF was 0.31 and genotypes were consistent with Hardy-Weinberg equilibrium. We limited analyses to a subset matched to the intervention for BMI (≤ 34 kg/m^2) and without diabetes, and applied the same recessive genetic model. We dichotomized total dietary fat intake into high and low, based on the median intake (% total energy), and observed no significant interaction. We next evaluated a sex-total fat interaction and observed a significant interaction (P=0.036) for HDL-C. Due to the small number of men in the subset (10 with TT genotype, n=5 men in each fat intake group), subsequent SNP-diet interaction analyses for dichotomized total fat (31%), SFA (9%), PUFA (7%) and MUFA (11%) were conducted only in women (n=269; Table 6). Significant interactions for HDL-C were observed only for SFA (P-interaction: 0.036; Table 6). Minor allele carriers (TT) had higher HDL-C (P=0.038) with low SFA intake (1.5 ± 0.1 mmol/L) compared to high SFA intake (1.2 ± 0.1 mmol/L). No difference was observed for HDL-C in major allele carriers (CC/CT) by SFA intake. SNP-diet interactions were not observed for other types of fats.

In addition to HDL-C, we evaluated each type of fat (% total energy) in women without diabetes and BMI ≤34 for TG (Table 6). As for HDL-C, we observed a significant interaction term for SFA (P-interaction: 0.005), with CC/CT individuals showing higher TG (P=0.003) with low SFA intake (1.7 (95% CI: 1.5, 1.8) mmol/L) compared to high SFA intake (1.4 (95% CI: 1.1, 1.9) mmol/L). In TT carriers, high SFA was marginally associated with higher TG. Interactions between *LIPC* genotype and dichotomized intakes of other fats for TG were not significant.

Finally, we evaluated each type of fat (% total energy) in women without diabetes and BMI ≤34 for total cholesterol and LDL-C (Table 7). No statistically significant interactions were identified for either of these outcomes.

Discussion

Our investigation of dietary modulation of *LIPC* -514 C/T and cardio-metabolic traits in a dietary intervention showed differences in dietary responses that depended on genotype. Specifically, while minor allele homozygotes (TT) did not demonstrate a reduction in HDL-C in response to higher fat intake, neither did they show the significant increase observed in major allele carriers (CC+CT). We did not detect a statistically significant gene-diet interaction, but the benefits derived from greater fat intake were limited to specific *LIPC* genotypes.

Previous studies provide evidence that this locus responds to dietary fat, although the designs and specific findings of the studies vary, and the mechanisms are not well-understood. Two observational studies, the Framingham Heart Study and Singapore Indians, demonstrated interactions between dietary fat intake and the variant, such that high fat intake was associated with higher HDL-C in major allele carriers, but with lower HDL-C in minor allele carriers (19,25). Two interaction interventions confirmed this apparent sensitivity to dietary fat. One weight loss intervention showed that carriers of the minor (T) allele responded more to an intensive, lower fat (<30% energy) lifestyle intervention than to the usual care (9). In a second weight loss intervention that compared low-fat (20% total energy) and high-fat (40% total energy) diets, a difference in HDL-C by *LIPC* 514 C/T genotype was observed only in the low-fat group (31). In the current study, we expected that minor allele carriers would show lower HDL-C concentrations with the high fat (Western) diet intervention. While there was no

statistically significant gene-diet interaction, the high fat diet increased HDL-C concentrations in major allele carriers but not in minor allele homozygotes. Evaluations of LDL-C and total cholesterol were similar to HDL-C, in that the Western diet caused statistically significant changes (increases) in major allele carriers but not minor allele homozygotes. Observations for all three lipids are consistent with previous evidence that higher fat diets do not benefit *LIPC* minor allele carriers.

The lack of a significant SNP-diet interaction for HDL-C in the current intervention could be related to insufficient statistical power, and could also be related to obesity-related complications, especially insulin resistance. Insulin increases hepatic lipase activity, and greater lipase activity reduces HDL-C (10, 20, 26). *LIPC* -514 C/T is associated with lower lipase activity and higher HDL-C, and the variant also interferes with insulin regulation of the lipase (3, 10). The combination of genetically determined loss of insulin-responsiveness and obesity-related insulin resistance may obscure the detection of gene-diet interactions. Both a previous study (in which visceral obesity masked the association of *LIPC* 514 C/T with HDL-C)(24) and the current study support this hypothesis. Among intervention participants at baseline, the mean BMI in TT carriers approached obesity (BMI=29.3 kg/m^2) with waist circumference in the abdominally obese range (21). Obesity, which is often associated with lower HDL-C concentrations, may have prevented the genotype association with HDL-C from reaching statistical significance. Similarly, adiposity may have impaired the detection of SNP-diet interactions, by modulating HDL-C across all genotype categories.

Detection of SNP-diet interactions for OGTT could also have been obscured by insulin resistance. For OGTT, there was a marginally significant interaction between *LIPC* genotype

and diet only for Phase 1, in which the glucose concentration was higher with the Western diet compared to the Hispanic diet in CC individuals. There are several possible explanations for the lack of interaction in Phase 2. First, we had some evidence that participants were more compliant to the diet during Phase 1 than Phase 2, which would maximize differences between the diets, to improve interaction detection. Second, the baseline diet for most participants was probably closer to the Western diet than the Hispanic diet (data not shown). For those whose Phase 1 diet represented a shift from Western to Hispanic, genetically based-differences in response to diet may have been more detectable, and these differences could have driven the marginal interaction seen in Phase 1. By Phase 2, when individuals were shifting from one intervention diet to the other, reduced compliance could have reduced actual differences between the diets, impairing our ability to detect interactions. However, these explanations remain speculative, particularly since no carryover effect was detected between diet phases.

Findings from the current intervention study and the BPRHS differed to some extent, and these differences could be related to design and sample size. Specifically, in the BPRHS the interactions between dietary fat and the SNP for HDL-C were consistent with earlier interaction analyses in FHS and Singapore Indians. In all three populations, high fat intake was detrimental for HDL-C concentration in minor allele carriers. In the dietary intervention, the interaction term for SNP x dietary pattern did not reach significance, but the higher fat (Western) diet was beneficial for HDL-C only in major allele carriers. One possibility is that large populations are needed to detect statistically significant gene-diet interactions, to minimize the impact of heterogeneity in individual responses. In addition, the dietary patterns differed not only in total

fat, but also in fat composition (e.g., greater monounsaturated fatty acids in the Hispanic diet), which could also alter responses.

Intervention findings are strengthened by partial validation in the BPRHS, but limitations exist. Our confirmation of the *LIPC* SNP x diet interaction in the BPRHS and failure to reach interaction significance in the dietary intervention are likely related to insufficient statistical power in the intervention. The small number of TT individuals (n=8, all women) and few men (n=8) in the intervention precluded our ability to formally conduct sex-specific analyses, which is highly relevant to HDL-C. In addition, heterogeneity in the degree of insulin resistance among participants may have masked detection of gene-diet interactions. Although we excluded diabetes and severe obesity from both studies, the prevalence of metabolic syndrome rose between 2002 (the year of the Framingham *LIPC* study and 2011 (current intervention completion). This decline in US metabolic health, especially in susceptible ethnic minorities such as Hispanics, may impede the detection of gene-diet interactions (7,23).

In summary, findings from our gene-diet intervention supported but did not entirely confirm interaction patterns established in previous observational studies. Understanding of these inconsistencies is limited, but the differences are not surprising given the considerable variability in outcomes related to this locus. The current study illustrates the complexities and limitations of studying gene-diet interactions using different designs and at different historical time points. Future studies might be improved through more stringent control of variability in phenotypes that influence outcomes, and may require larger sample sizes. In spite of the challenges specific to *LIPC*, as well as those of gene-diet interactions overall, this study reinforces the need to

consider genotype in dietary trials. Moreover, these findings highlight the critical importance of considering ethnicity in studies related to genetics, diet and cardio-metabolic health.

AUTHOR CONTRIBUTIONS

Author contributions: JMO, KLT, AHL, JM: conception and design of research; MIVR and JFG: data collection; MIVR and CES: data analysis; CES and MIVR: drafted manuscript; JMO, KLT, AHL, MIVR, CES, BGB, JMO, JFG : edited and revised manuscript; BGB: performed genotyping

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Disclosures

The authors disclose no conflicts of interest.

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Figure Captions

Figure 1. A CONSORT chart documents the flow of participants through the intervention processes.

Table 1. Nutrient profiles of intervention diets

Nutrient	High-fat Western Diet	Low-fat Hispanic Diet
Total fat (% total energy)	39.3	20.4
SFA (% total energy)	14.4	5.5
MUFA (% total energy)	12.4	9.6
PUFA (% total energy)	9.6	3.7
SFA (% total fat)	36.6	27
MUFA (% total fat)	31.5	47
PUFA (% total fat)	24.4	18.1
Cholesterol (mg/1,000 kcal)	149	76.5
Protein (% total energy)	20.2	20.5
Carbohydrate (% total energy)	41.6	61.0
Added sugar (g/1,000 kcal)	6.7	24.6
Total fiber (g/1,000 kcal)	8.8	13.7
Soluble fiber (g/1,000 kcal)	2.7	3.3
Insoluble fiber (g/1,000 kcal)	6.0	10.3

Abbreviations: SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids

Table 2. Baseline characteristics by *LIPC -514 C/T* genotype[a,b]

	C/C (n = 16)	C/T (n = 17)	T/T (n = 8)	P
Age, y[c]	39.9 (10.4)	44.8 (11.2)	35.4 (13.5)	0.15
Female, n (%)[d]	12 (75%)	13 (76%)	8 (100%)	0.36
BMI, kg/m^2[e]	26.9 (3.2)	27.0 (3.3)	29.3 (3.4)	0.26
Waist circumference, cm	85.5 (7.6)	84.9 (7.8)	90.4 (8.2)	0.29
Total cholesterol, mmol/L [mg/dL][f]	4.7(0.8) [183 (33.6)]	4.7(0.8) [182 (34.2)]	5.4(0.8) [207 (36.2)]	0.26
LDL-C, mmol/L [mg/dL]	3 (0.8) [117 (28.4]	2.8 (0.8) [109 (28.9)]	3.2(0.8) [124 (30.5)]	0.51
HDL-C, mmol/L [mg/dL]	1.2(0.4) [46.7(9.6)]	1.3(0.4) [51.5 (9.9)]	1.5(0.3) [57.7 (10.2)]	0.05
TG, GM (95% CI), mmol/L [mg/dL]	1(0.7, 1.3) [85.8(66, 112)]	1(0.7,1.2) [84.9 (65.3,110)]	1.2(0.8,1.8) [106(71.3,159)]	0.62
Glucose, mmol/L [mg/dL]	5(0.4) [89.3 (8)]	4.8(0.4) [86.7(8)]	4.9(0.6) [88.9(9)]	0.64
Systolic blood pressure, mm Hg	119 (14)	116 (14.4)	115 (15.3)	0.74
Diastolic blood pressure, mm Hg	75.3 (7.6)	78.9 (7.8)	71.2 (8.2)	0.11

[a]Data are mean (SD) except where otherwise indicated

[b]Laboratory meausurements were made before the dietary intervention was begun

[c]Continuous variables were compared across LIPC genotypes using analysis of variance

[d]Proportion of females across LIPC genotypes was compared using Fisher's exact test

[e]BMI and waist circumference were adjusted for age and sex

[f] Lipids, glucose, and blood pressure measures were adjusted for age, sex, and baseline waist circumference

[g]Triglycerides were log-transformed to improve distribution

Abbreviations: BMI: body mass index; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides

Table 3. Main effects of diet on HDL-C, TG and 2-hour OGTT concentrations at end of intervention diets[a]

	High-fat Western Diet	Low-fat Traditional Hispanic Diet	P[f]
HDL-C[b], mmol/L [mg/dL]	1.34 (0.03) [51.8 (1.0)]	1.21 (0.03) [46.7 (1.0)]	<0.0001
TG[c], mmol/L [mg/dL]	0.95 (0.8, 1.11) [83.8 (71.1, 98.7)]	0.93 (0.79, 1.09) [82.2 (69.9, 96.7)]	0.76
LDL-C[d], mmol/L [mg/dL]	3.0 (0.09) [116 (3.5)]	2.7 (0.09) [103 (3.6)]	0.02
Total cholesterol[d], mmol/L [mg/dL]	4.9 (0.1) [188 (3.7)]	4.4 (0.09) [171 (3.6)]	0.0002
OGTT 2-hour glucose[e], mmol/L [mg/dL]	4.9 (0.2) [87.6 (3.6)]	5.0 (0.2) [90.1 (3.7)]	0.44

[a] Values are mean (SEM) except for TG which is geometric mean (95% CI).
[b] Mixed model regression was used to obtain mean HDL-C concentrations at end of intervention periods, adjusting for phase, age, sex, baseline HDL-C and waist circumference, and post-diet TG concentration.
[c] Mixed model regression was used to obtain geometric mean triglyceride concentrations at end of intervention periods, adjusting for phase, age, sex, baseline triglycerides and waist circumference, and post-diet HDL-C concentration.
[d] Mixed model regression was used to obtain mean LDL-C and total cholesterol concentrations at end of intervention periods, adjusting for phase, age, sex, baseline lipid concentration and waist circumference.
[e] Mixed model regression was used to obtain mean 2-hour OGTT glucose concentrations, adjusting for phase, age, sex, baseline waist circumference, and pre-load glucose.
[f] P-value for difference between diets
Abbreviations: HDL-C: high density lipoprotein lipase; TG: triglyceride; OGTT: oral glucose tolerance test

Table 4. Interaction between diet and *LIPC* for lipids[a] at end of intervention diets

	C/C + C/T (n = 33)	T/T (n = 8)	P-interaction
HDL-C			
Phase 1			0.203
Hispanic Diet	1.1 (0.04) [43.9 (1.4)]	1.3 (0.07) [50.0 (2.6)]	
Western Diet	1.3 (0.03) [51.1 (1.3)]	1.3 (0.1) [50.9 (3.9)]	
P-value	0.0004	0.848	
Phase 2			0.837
Hispanic Diet	1.2 (0.03) [47.5 (1.2)]	1.3 (0.09) [50.8 (3.4)]	
Western Diet	1.4 (0.03) [54.0 (1.3)]	1.5 (0.06) [56.5 (2.4)]	
P-value	0.0003	0.166	
LDL-C			
Phase 1			0.453
Hispanic Diet	2.5 (0.14) [95.8 (5.4)]	2.7 (0.26) [105 (9.9)]	
Western Diet	2.9 (0.13) [112 (5.0)]	3.5 (0.41) [137 (16.0)]	
P-value	0.025	0.099	
Phase 2			0.812
Hispanic Diet	2.8 (0.14) [109 (5.6)]	2.8 (0.14) [98.8 (18.2)]	
Western Diet	3.1 (0.16) [119 (6.0)]	3.1 (0.16) [103 (11.2)]	
P-value	0.198	0.823	
Total Cholesterol			
Phase 1			0.605
Hispanic Diet	4.2 (0.16) [161 (6.0)]	4.5 (0.28) [174 (11.0)]	
Western Diet	4.9 (0.14) [188 (5.6)]	5.5 (0.46) [212 (17.7)]	
P-value	0.001	0.064	
Phase 2			0.697
Hispanic Diet	4.6 (0.13) [176 (4.9)]	4.3 (0.39) [168 (15.2)]	
Western Diet	5.0 (0.14) [192 (5.2)]	4.6 (0.25) [177 (9.8)]	
P-value	0.018	0.597	

[a] Values are means (SEM) in mmol/L [mg/dL]. Adjusted for age, sex, baseline waist circumference, and baseline lipid concentration. HDL-C was also adjusted for post-diet triglyceride concentration.

Abbreviations: HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

Table 5. Interaction between diet and *LIPC* for 2-hour oral glucose tolerance test glucose concentration[a]

	C/C (n = 16)	C/T + T/T (n = 25)	P-interaction
Phase 1			0.071
Hispanic Diet	4.4 (0.3) [80.1 (5.2)]	5.0 (0.3) [89.2 (5.5)]	
Western Diet	5.5 (0.4) [99.2 (7.2)]	4.9 (0.3) [88.3 (4.9)]	
P-value	0.038	0.891	
Phase 2			0.308
Hispanic Diet	4.9 (0.4) [89.0 (7.9)]	5.3 (0.3) [96.2 (5.3)]	
Western Diet	4.5 (0.3) [80.4 (5.8)]	4.2 (0.4) [75.3 (6.6)]	
P-value	0.376	0.008	

[a]Values are mean (SEM) in mmol/L [mg/dL]. Adjusted for age, sex, baseline waist circumference, and pre-load glucose.

Table 6. Interaction between dietary fat and *LIPC* for HDL-C and TG in Boston Puerto Rican Health Study women[a]

	HDL-C, mmol/L [mg/dL]			TG, mmol/L [mg/dL]		
	C/C + C/T (n=241)	**T/T (n = 28)**	**P interaction**	**C/C + C/T (n=241)**	**T/T (n = 28)**	**P interaction**
Total Fat						
Low (< 31 % energy)	1.3(0.04) [50.7(1.4)]	1.4(0.1)[55.9 (4.4)]	0.532	1.6(1.4, 1.8) [141.1 (127.7, 155.8)]	1.8(1.2, 2.3) [149.3 (108.4, 205.6)]	0.523
High (≥ 31 %energy)	1.3(0.03)[49.8 (1.3)]	1.3(0.1) [51.4 (3.2)]		1.4(1.3, 1.6) [127.1 (115.3, 140.1)]	1.7(1.4, 2.2) [153.3 (121.9, 192.7)]	
P	0.605	0.406		0.097	0.902	
SFA						
Low (< 9 % energy)	1.3(0.04)[50.0 (1.4)]	1.5(0.1)[58.0 (3.5)]	0.036	1.7 (1.5-1.8) [147.6 (133.5, 163.1)]	1.4(1.3, 1.5) [127.8 (99.4, 164.4)]	0.005
High (≥ 9 % energy)	1.3(0.03)[50.7 (1.3)]	1.2(0.1)[47.4 (3.7)]		1.4(1.1,1.9) [121.8 (110.9, 133.8)]	2.1(2.6, 2.7) [183.1 (140.5, 238.7)]	
P	0.686	0.038		0.003	0.054	
PUFA						
Low (< 7 % energy)	1.3(0.03)[50.5 (1.3)]	1.4(0.1)[54.0 (4.3)]	0.858	1.5 (1.4, 1.7) [137.1 (124.4, 151)]	1.7(1.3, 2.4) [154.5 (111.6, 209.5)]	0.871
High (≥ 7 % energy)	1.3(0.04)[49.9 (1.4)]	1.4(0.1)[52.4 (3.2)]		1.5(1.3, 1.6) [130.1 (118.1, 143.9)]	1.7(1.4, 2.2) [151.6 (119.7, 191.0)]	
P	0.718	0.759		0.421	0.924	
MUFA						
Low (< 11 % energy)	1.3(0.03)[50.6 (1.3)]	1.4(0.1)[54.5 (4.2)]	0.782	1.6(1.4, 1.7) [140.6 (127.6, 154.8)]	1.8(1.3, 2.4) [126.5 (115.3, 213.2)]	0.812
High (≥ 11 % energy)	1.3(0.04)[49.8 (1.4)]	1.3(0.1)[52.1 (3.3)]		1.4(1.3, 1.6) [126.5 (114.3, 140)]	1.7(1.3, 2.1) [149.3 (118, 188.8)]	
P	0.645	0.653		0.098	0.752	

[a] Values are mean (SD) for HDL-C and geometric mean (95% CI) for TG. Limited to women without diabetes and BMI≤34. Models are adjusted for age, smoking, alcohol status, total energy, waist circumference, physical activity and ancestral admixture.

Abbreviations: HDL-C: high density lipoprotein ; TG: triglyceride; SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids

584 **Table 7. Interaction between dietary fat and LIPC for TC and LDL-C in Boston Puerto Rican Health Study Women[a]**
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	TC, mmol/L [mg/dL]			LDL, mmol/L [mg/dL]		
	C/C + C/T (n=241)	**T/T (n = 28)**	**P interaction**	**C/C + C/T (n=241)**	**T/T (n = 28)**	**P interaction**
Total Fat						
Low (< 31 % energy)	5.2 (0.1) [199.5(4.1)]	4.9 (0.3) [189.2 (13.2)]	0.563	3(0.09) [116.9 (3.5)]	2.6(0.3) [102.2 (11.1)]	0.857
High (≥ 31 %energy)	5.1 (0.1) [195.8 (4)]	5.1 (0.2) [195.3 (9.4)]		3.1(0.09) [119 (3.4)]	2.8(0.2) [107 (8.2)]	
P	0.482	0.706		0.642	0.731	
SFA						
Low (< 9 % energy)	5.2(0.1) [202.6 (4.2)]	4.9(0.3) [187.8 (10.5)]	0.195	3.1(0.1) [120.4 (3.6)]	2.6(0.2) [102 (8.9)]	0.403
High (≥ 9 % energy)	5(0.1) [193.1 (4)]	5.1(0.3) [199.1 (11.1)]		3(0.1) [115.7 (3.4)]	2.8(0.3) [109 (9.8)]	
P	0.079	0.456		0.316	0.594	
PUFA						
Low (< 7 % energy)	5.2(0.1) [202.5 (4)]	5.2(0.3) [202.9 (12.8)]	0.753	3.1(0.1) [121.3 (3.4)]	3(0.3) [116.6 (10.8)]	0.431
High (≥ 7 % energy)	5(0.1) [192.4 (4.1)]	4.9(0.2) [187.6 (9.5)]		3(0.1) [114.1 (3.5)]	2.5(0.2) [98.2 (8.3)]	
P	0.056	0.336		0.111	0.177	
MUFA						
Low (< 11 % energy)	5.2(0.1) [199.3 (4)]	4.8(0.3) [185 (12.5)]	0.307	3(0.1) [117.1 (3.4)]	2.5(0.3) [98.2 (10.6)]	0.478
High (≥ 11 % energy)	5.1(0.1) [195.6 (4.2)]	5.1(0.3) [198.2 (9.7)]		3.1(0.1) [118.7 (3.6)]	2.8(0.2) [109.8 (8.5)]	
P	0.485	0.401		0.737	0.388	

586 [a] Values are mean (SEM). Limited to women without diabetes and BMI≤34. Models are adjusted for age, smoking, alcohol status,
587 total energy, waist circumference, physical activity and ancestral admixture. Abbreviations: LDL-C: low density lipoprotein; TC: total
588 cholesterol ; SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids

Figure 1. CONSORT Flow Diagram