

Common Variants in Lipid Metabolism–Related Genes Associate with Fat Mass Changes in Response to Dietary Monounsaturated Fatty Acids in Adults with Abdominal Obesity

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ABSTRACT

Background: Different fatty acids (FAs) can vary in their obesogenic effect, and genetic makeup can contribute to fat deposition in response to dietary FA composition. However, the antiobesogenic effects of the interactions between dietary MUFAs and genetics have scarcely been tested in intervention studies.

Objective: We evaluated the overall (primary outcome) and genetically modulated (secondary outcome) response in body weight and fat mass to different levels of MUFA consumption.

Methods: In the Canola Oil Multicenter Intervention Trial II, a randomized, crossover, isocaloric, controlled-feeding multicenter trial, 44 men and 71 women with a mean age of 44 y and an increased waist circumference (men ~108 cm and women ~102 cm) consumed each of 3 oils for 6 wk, separated by four 12-wk washout periods. Oils included 2 high-MUFA oils—conventional canola and high-oleic canola (<7% SFAs, >65% MUFAs)—and 1 low-MUFA/high-SFA oil blend (40.2% SFAs, 22.0% MUFAs). Body fat was measured using DXA. Five candidate single-nucleotide polymorphisms (SNPs) were genotyped using qualitative PCR. Data were analyzed using a repeated measures mixed model.

Results: No significant differences were observed in adiposity measures following the consumption of either high-MUFA diet compared with the low-MUFA/high-SFA treatment. However, when stratified by genotype, 3 SNPs within lipoprotein lipase (*LPL*), adiponectin, and apoE genes influenced, separately, fat mass changes in response to treatment ($n = 101$). Mainly, the *LPL* rs13702-CC genotype was associated with lower visceral fat (high-MUFA: -216.2 ± 58.6 g; low-MUFA: 17.2 ± 81.1 g; $P = 0.017$) and android fat mass (high-MUFA: -267.3 ± 76.4 g; low-MUFA: -21.7 ± 102.2 g; $P = 0.037$) following average consumption of the 2 high-MUFA diets.

Conclusions: Common variants in *LPL*, adiponectin, and apoE genes modulated body fat mass response to dietary MUFAs in an isocaloric diet in adults with abdominal obesity. These findings might eventually help in developing personalized dietary recommendations for weight control. The trial was registered at [clinicaltrials.gov](https://www.clinicaltrials.gov) as NCT02029833 (<https://www.clinicaltrials.gov/ct2/show/NCT02029833?cond=NCT02029833&rank=1>). *J Nutr* 2019;149:1749–1756.

Keywords: dietary fatty acids, fat quality, genotype, gene–nutrient interaction, fatness, adiposity

Introduction

The composition of dietary fatty acids (FAs) has been recognized as a determinant of fat deposition and distribution (1–5). FAs can vary in their obesity-inducing effects by influencing energy expenditure, fat oxidation, and thermogenesis, and/or

modulating appetite sensation (6–8). Increasing evidence has demonstrated that dietary MUFAs increase fat oxidation, diet-induced thermogenesis (8–10), and resting energy expenditure (11), and promote weight loss (12, 13) compared with SFAs. Our recent controlled feeding study showed that 2 test diets high in MUFAs—canola oil and a high-oleic

canola oil—significantly reduced android fat mass compared with a high-PUFA flaxseed/safflower oil in participants with abdominal obesity (1). These favorable effects might be attributed partly to interactions between FAs and genetic polymorphisms.

The genetic contribution to obesity is well recognized, and heritability of obesity is estimated to be 40–70% (14, 15). The responses of individuals with obesity to weight-gain prevention and reduction strategies can also vary broadly based on their genetic makeup (16). Therefore, examining gene–

nutrient interactions assists in estimating the role of qualitative intake of FAs on the onset/progression of obesity in a genotype-specific manner.

Evidence from controlled trials and observational studies suggests a contribution of the interactions between genetic polymorphisms and dietary FAs in modulating adiposity via several mechanisms. For instance, the consumption of a higher proportion of MUFAs (17–19) and PUFAs (20, 21) relative to SFAs was found to be associated with lower body weight in peroxisome proliferator activated receptor γ (*PPARG*) rs1801282-G allele carriers in different ethnic populations. Additionally, a meta-analysis of 14 studies in US and European Caucasians revealed a direct association between SFA consumption and BMI, as well as waist-to-hip ratio, in the rs2306692-TT genotype carriers of low-density lipoprotein receptor-related protein 1 (22).

Although current research provides emerging evidence for gene–MUFA interactions (17–19, 23–25), numerous polymorphisms in lipid metabolism–related genes have yet to be investigated. Moreover, to investigate fat deposition and distribution, surrogate biomarkers have been often used, potentially masking outcomes. This study aimed to assess associations of common genetic variants and changes of total and regional fat mass following 6-wk controlled isocaloric dietary interventions with different concentrations of dietary MUFAs. To meet our objective, we used whole-body DXA scanning, which provides a reliable identification of fat distribution and discrimination between different fat depots.

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Supplemental Tables 1–4 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/jn/>.

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Abbreviations used: ADIPOQ, adiponectin; COMIT, Canola Oil Multicenter Intervention Trial; FA, fatty acid; HOCO, high-oleic canola oil; LPL, lipoprotein lipase; RCFFN, Richardson Centre for Functional Foods and Nutraceuticals; RCO, regular canola oil; ROI, region of interest; SCAT, subcutaneous adipose tissue; SNP, single nucleotide polymorphism; TG, triglyceride; UTR, untranslated region; VAT, visceral adipose tissue.

Methods

Study design and population

This study of gene–nutrient interactions was conducted within the framework of the Canola Oil Multicenter Intervention Trial (COMIT) II. COMIT II was a randomized, controlled, double-blind, crossover study designed to evaluate the response of body composition to 3 oils with different MUFA concentrations, including regular canola oil (RCO), high-oleic acid canola oil (HOCO), and a low-MUFA/high-SFA oil blend. This trial was conducted from 2014 to 2016 at 3 sites in Canada and 1 site in the United States: the Richardson Centre for Functional Foods and Nutraceuticals (RCFFN) at the University of Manitoba in Winnipeg; the Canadian Centre for Agri-Food Research in Health and Medicine at St Boniface Hospital Albrechtsen Research Centre in Winnipeg; the Institute of Nutrition and Functional Foods at Laval University in Quebec City; and the Departments of Nutritional Sciences and Biobehavioral Health at The Pennsylvania State University in University Park. The protocol was reviewed and approved by institutional ethics boards across the participating clinical sites. The trial was registered at clinicaltrials.gov as NCT02029833.

Participants aged 20–65 y were included if they had abdominal obesity according to the International Diabetes Federation cutoff point for waist circumference (94 cm in men and 80 cm in women) in addition to at least 1 of the following metabolic syndrome criteria: fasting concentrations of blood glucose ≥ 5.6 mmol/L, triglycerides (TGs) ≥ 1.7 mmol/L, and HDL-cholesterol < 1 mmol/L (men) or < 1.3 mmol/L (women); and blood pressure ≥ 130 mmHg (systolic) and/or ≥ 85 mmHg (diastolic). Individuals were excluded if they had unstable thyroid disease, kidney disease, diabetes mellitus, or liver disease. Current smokers, individuals consuming more than 14 alcoholic beverages per week, individuals taking medication known to affect lipid metabolism for at least the last 3 mo, or individuals who were unwilling to stop taking any supplement at least 2 wk before the study were not permitted to participate. Written informed consent was obtained from all participants upon enrollment. Participants were randomly assigned to 1 of 6 treatment sequences using a random number generator at randomization.com.

Study diets

This study consisted of 3 treatment periods during which the participants consumed a controlled isocaloric, full-feeding diet with a fixed macronutrient composition of 35% fat, 50% carbohydrate, and 15% protein of total energy, as well as ~ 208 mg/3000 kcal/d cholesterol and ~ 38 g/3000 kcal/d fiber. The macronutrient composition of the 3 experimental diets has been previously reported (26). Menus for the 3 phases were identical except for the type of treatment oil provided. Treatment phases extended for 6 wk and were separated by 6-wk washout periods (ranged from 4 to 12 wk for a few participants). During the washout periods, participants were instructed to consume their habitual diets. Participants were asked to maintain their usual level of physical activity throughout the entire study. Physical activity changes were monitored by a weekly checklist.

The treatment oils, which comprised 20% of total energy, were incorporated into a smoothie beverage and were divided equally into 2 portions consumed at breakfast and supper. Treatment oils included: 1) RCO (Canola Harvest Canola Oil; Richardson International), which provided 6.6% SFAs, 65.3% MUFAs, 19.6% n-6 PUFAs, 8.5% n-3 PUFAs α -linolenic acid; 2) HOCO (Canola Harvest Canola Oil; Richardson International), which provided 6.7% SFAs, 75.9% MUFAs, 14.8% n-6 PUFAs, 2.6% n-3 PUFAs α -linolenic acid; and 3) a low-MUFA/high-SFA oil blend that provided 40.2% SFAs, 22.0% MUFAs, 29.6% n-6 PUFAs, 8.2% n-3 PUFAs α -linolenic acid. The low-MUFA/high-SFA oil blend was prepared using commercially available ghee/butter oil (36.0%, Verka), safflower oil (34.9%, eSutras), coconut oil (16.0%, eSutras), and flaxseed oil (13.1%, Shape Foods). Study food and treatment shakes were prepared based on a 7-d rotating menu cycle in the metabolic kitchen of the participating sites. Compliance was assessed by smoothie consumption where the participants were required to consume $\geq 90\%$ of the smoothies provided at each phase.

Participants signed a daily checklist to verify consumption of smoothies. To maximize compliance rate, participants were required to consume 1 smoothie at breakfast under the supervision of a clinical coordinator for 5 d/wk. During weekdays, participants were provided the rest of their meals and a second smoothie in a food cooler bag for consumption off-site. Weekend meals and treatment shakes were delivered to the participants' residences or handed out to them, upon their request, at the clinical site on Fridays.

Measurement of fat mass

DXA scans were performed by a trained operator using Lunar Prodigy Advance DXA (GE Healthcare) with the default configurations. A DXA scan was performed for all participants at the initiation and termination of each dietary phase. Participants were asked to remove any metal items and heavy clothes before scanning. Regions of interests (ROIs) were manually adjusted using enCORE 2012 software (version 14.10.022) according to the manufacturer's instructions. Fat mass was analyzed as total fat mass, as well as 4 different districts including trunk, legs, android, and gynoid fat masses. The android and gynoid ROIs were identified as per the manufacturer's instructions. The android region has been defined as a portion of the abdomen that starts at the pelvis cut line and extends upward to include 20% of the distance between the pelvis and neck cut lines, with the outer arms' cuts as the lateral boundaries. The gynoid region has been defined as a portion of the legs with upper boundary below the pelvis cut line by 1.5 times the height of the android region, extending downward to twice the height of the android ROI, with the outer legs' cuts as the lateral boundaries. Further, visceral adipose tissue (VAT) was assessed by the CoreScan feature in enCORE 2012 software (version 14.10.022), and used to calculate the subcutaneous adipose tissue (SCAT) by subtracting VAT mass from android fat mass (27). VAT measurement using the CoreScan has been validated using computed tomography scanning (28). Criteria used to identify the anatomical ROIs were identical across all sites.

Genotyping

Twelve-hour fasting blood samples were collected and processed at the beginning of the trial, then stored at -80°C until being shipped to the RCFFN for analysis. Genomic DNA was extracted from the buffy coat samples of the first day of the first phase using a Qiagen DNeasy Blood and Tissue Kit according to the manufacturer's instructions (Qiagen Sciences, Inc.). A Thermo Scientific NanoDrop 2000 microvolume spectrophotometer was used to assess the concentration and purity of the extracted DNA (Thermo-Fisher Scientific, Inc.). TaqMan GTXpress Master Mix with allele-specific probes (Applied Biosystems, Life Technologies Inc) was used for genotyping of the single-nucleotide polymorphisms (SNPs) of interest. Amplification and detection of DNA were conducted with the 7500 Fast Real-Time PCR System (Applied Biosystems, Life Technologies Inc). Data were acquired by software StepOne 2.1 (Applied Biosystems, Life Technologies Inc). Polymorphisms located in lipogenesis/adipogenesis-related genes were selected for their various roles in obesity development, where each SNP chosen was either a functional SNP, had a minor allele frequency ≥ 5 , and/or had been previously reported for gene–nutrient interactions. This study assessed possible gene–diet interactions in a total of 5 candidate variants (Supplemental Table 1), within 3 genes, namely adiponectin (*ADIPOQ*), apoE (*APOE*), and lipoprotein lipase (*LPL*). The role of *LPL* as the rate-limiting enzyme that catalyzes the hydrolysis of TGs underscores *LPL* as a candidate gene for obesity. The functional *LPL* rs13702 and rs3200218 are located in the 3' untranslated region (UTR) region and they are involved in translational regulation (29, 30). *LPL* rs13702-C allele is suggested to disrupt the microRNA recognition elements seed site and abolish the microRNA-410-mediated repression of mRNA at the *LPL* 3' UTR, therefore increasing the activity of *LPL* (31). Despite the master role of *LPL* in regulating the supply of FAs to adipose tissue, the effects of possible interactions between *LPL* polymorphism and dietary FA interactions on obesity have been scarcely studied. *ADIPOQ* rs266729 ($-11,377$ C/G) is located in the promoter region and has

been shown to alter the circulating adiponectin concentration as well as the risk of obesity and insulin resistance (24, 32). Lastly, *APOE4* isoform has been associated with abnormal lipid metabolism and increased risk for several health problems including obesity (33–35).

Statistical analyses and sample size

The primary aim of the COMIT II trial was to evaluate the effect of MUFA consumption on body composition, mainly VAT. Therefore, the sample size was calculated to detect a 55-g change in android fat mass using the variance parameter in android fat mass from our previous controlled trial (1). A total sample size of 140 was required to account for a dropout rate of 20%.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc.) based on a per protocol approach. Normality was assessed using the Shapiro–Wilk test and the skewness values. Nonnormally distributed variables were log-transformed before analysis. The results are expressed as least-squares means \pm SEMs unless otherwise specified, and statistical significance was set at $P < 0.05$. Multiple comparison was assessed using the Tukey–Kramer test. Changes in fat mass and body weight represent the difference over 6 wk between end point and baseline of each dietary phase. PROC MIXED (SAS Institute, Inc.) with repeated-measures procedure was used to assess the effect of the 3 dietary treatments on changes in body fat and body weight. Treatment, sex, age, and genotype were used as fixed effects, with participants as a repeated factor. Random effects were treatment sequence, clinical site, and participants. Prespecified potential confounders such as ethnicity, baseline body composition, baseline fasting concentrations of glucose, homeostatic model of insulin resistance, and cholesterol were investigated in all models. The Hardy–Weinberg equilibrium was assessed with a chi-square test.

For diet–gene interaction analysis, due to the considerable not exactly similar comparable concentrations of MUFAs in the 2 canola treatments compared with the low-MUFA/high-SFA treatment, the statistical analysis of diet-by-SNP interaction was conducted to compare the combined effect of the 2 high-MUFA diets (HOCO + RCO, averaged) with the low-MUFA/high-SFA diet on changes in body fat and body weight. This decision was also based on our inability to detect statistical differences between HOCO and RCO in body composition in the overall population in our previous trial (COMIT I) (1), and based on the predefined hypothesis that the small variation in the concentration of MUFAs between the 2 high-MUFA treatments will not significantly influence the effect of genes on obesity. Although our sample size was lower than the longitudinal, survey-based diet–gene interaction studies, the controlled, full-feeding, crossover design of this study reduced the need for a larger sample size because it eliminated a wide range of confounders associated with the former designs. However, we consider this analysis an exploratory study to identify SNPs that might influence the body fat response to dietary fat type.

Each individual SNP was assessed separately using the aforementioned statistical model. All SNPs were analyzed in the additive model. Dominant and recessive models were analyzed only when the simple effect of heterozygous-by-MUFAs (in addition, to 1 homozygotes-by-MUFAs) showed a significant interaction. Only 4 *APOE* isoforms (encoded by rs429358 and rs7412) were obtained, and were analyzed and presented as non-*E4* ($\epsilon 2/\epsilon 3$ and $\epsilon 3/\epsilon 3$ genotypes) and *E4* ($\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ genotypes).

Results

A total of 124 participants completed the counterbalanced trial and all of the required DXA scans. Three participants were excluded due to a high fasting blood glucose concentration (>7 mmol/L) and 6 participants were excluded due to large changes in body weight (weight change from baseline to endpoint $>5\%$) at any dietary period (Supplemental Figure 1).

Therefore, 115 participants (71 women and 44 men) were included in the analysis of the effect of dietary MUFAs on changes in body composition, as the primary outcome of the COMIT II trial. No significant differences were observed in changes in body weight or fat mass following the consumption of any of the 3 treatments (Supplemental Table 2).

The assessment of gene-by-diet interactions, the secondary outcome of the COMIT II trial, included 101 participants, because 14 participants did not consent for genetic analyses. Baseline characteristics are displayed in Table 1. Hardy–Weinberg equilibrium was not achieved for the *ADIPOQ* rs266729 and *APOE*. The effects of gene–diet interactions on changes in body weight, total fat mass, and selected regional fat mass were tested (Supplemental Tables 3 and 4). Diet was found to interact with common variants in *LPL*, *ADIPOQ*, and *APOE* to modify changes in body fatness in an isocaloric diet (Figures 1–3), as detailed below.

The *LPL* rs13702-CC genotype (Figure 1) was found to be associated with lower VAT and android fat mass following high-MUFA consumption compared with the low-MUFA diet. Likewise, carriers of the *LPL* rs13702-CC genotype showed trends toward less total fat mass and body weight following high-MUFA consumption compared with low-MUFA intake.

The consumption of high-MUFA diets protected the *ADIPOQ* rs266729-GG homozygotes from the increase in SCAT that was observed following consumption of the low-MUFA diet (Figure 2A). Further, in response to the low-MUFA diet, the carriers of *ADIPOQ* rs266729-GG homozygotes showed higher SCAT and android fat mass compared with C allele carriers (Figure 2). Lastly, *E4* carriers had greater reductions in total fat mass following consumption of the low-MUFA diet compared with high-MUFA diets (Figure 3).

Discussion

Results of the current study indicate that changes in total and compartmental fat mass and body weight in response to dietary fat substitutions are modified by common variants within lipid metabolism–related genes. Minor allele homozygotes of either *LPL* or *ADIPOQ* had lower body fat indices following consumption of high-MUFA diets compared with a low-MUFA diet, whereas *APOE4* carriers had lower body fat indices upon the consumption of a low-MUFA diet compared with a high-MUFA intake. These results highlight the genetic contribution to the responsiveness of body fatness to dietary MUFAs and could explain our inability to detect significant effects of MUFA consumption on body weight and fat mass compared with the low-MUFA/high-SFA diet in spite of the existing evidence (12, 13). Identifying the contribution of genetic architecture to the body’s response to dietary modifications can direct the pathway toward the era of personalized nutrition. From our dietary intervention trial, we cannot conclude on the exact mechanisms of the observed phenomena and we need to refer to future biochemical studies. However, some existing knowledge might help to illuminate the biochemistry underlying the present findings.

LPL is the rate-limiting enzyme that catalyzes the hydrolysis of TGs in the core of TG-rich lipoprotein constituents as well as facilitating the uptake of FAs by adipocytes (36, 37). These functions highlight *LPL* as a candidate gene for obesity. Ma et al. (38) reported no influence of the SNP *LPL* rs13702 under different dietary FA interventions on BMI or waist

TABLE 1 Characteristics of participants at the baseline of dietary intervention¹

Characteristic ²	Total (n = 101)	Female (n = 60)	Male (n = 41)
Age, y	43.3 ± 1.29	45.7 ± 1.64 ^a	39.9 ± 1.98 ^b
Ethnicity, n			
Caucasian	74	45	29
African	4	3	1
Asian	8	4	4
Hispanic	3	1	2
Others	12	7	5
Waist circumference, cm	104 ± 1.30	101 ± 1.60 ^a	108 ± 1.90 ^b
Systolic BP, mmHg	119 ± 1.30	118 ± 1.70	120 ± 2.00
Diastolic BP, mmHg	78.1 ± 1.08	77.5 ± 1.41	79.0 ± 1.70
Total cholesterol, mmol/L	5.19 ± 0.09	5.21 ± 0.12	5.15 ± 0.14
TGs, mmol/L	1.55 ± 0.07	1.46 ± 0.09	1.67 ± 0.11
HDL-cholesterol, mmol/L	1.35 ± 0.04	1.46 ± 0.04 ^a	1.20 ± 0.05 ^b
LDL-cholesterol, mmol/L	3.13 ± 0.08	3.09 ± 0.10	3.19 ± 0.12
Glucose, mmol/L	5.22 ± 0.04	5.21 ± 0.06	5.23 ± 0.07
Insulin, pmol/L	98.7 ± 6.10	94.3 ± 7.92	105.0 ± 9.58
VAT mass, g	1334 ± 84.0	1056 ± 99.0 ^a	1741 ± 120 ^b
SCAT mass, g	2213 ± 90.0	2293 ± 117	2097 ± 141
Legs fat mass, g	12,645 ± 430	13,790 ± 531 ^a	10,969 ± 642 ^b
Trunk fat mass, g	19,472 ± 721	18,584 ± 930	20,772 ± 1124
Android fat mass, g	3548 ± 145	3349 ± 187	3838 ± 226
Gynoid fat mass, g	6002 ± 206	6334 ± 264	5516 ± 319
Total fat mass, g	36,282 ± 1119	36,565 ± 1459	35,869 ± 1765
Body weight, kg	89.8 ± 1.88	83.0 ± 2.21 ^a	99.6 ± 2.67 ^b
BMI, kg/m ²	31.1 ± 0.53	31.0 ± 0.69	31.3 ± 0.84

¹Values are means ± SEMs unless otherwise specified. PROC MIXED (SAS Institute, Inc.) procedure was used to assess sex differences, $P < 0.05$ was considered significant. PROC MEANS (SAS Institute, Inc.) was used to determine the mean characteristics of the overall population. Labeled means within the same row without a common letter indicate sex-based statistical difference. BP, blood pressure; SCAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue.

²Lipid profiles and glucose concentrations were determined using Cobas enzymatic reagents on Roche/Hitachi c 501e automated clinical chemistry analyzers using serum samples. Serum insulin concentrations were measured with the Roche/Hitachi Cobas e immunoassay analyzer and electrochemiluminescence immunoassay kits.

circumference in 2 independent populations. The C allele in the functional *LPL* rs13702 is suggested to increase the hydrolytic activity of *LPL* (30, 31); however, to our knowledge, no interactions between *LPL* polymorphisms and dietary FAs to modulate regional fat masses have been reported. The consistent decrease of 4 distinct regions of fat mass in *LPL* rs13702-CC homozygotes following the high-MUFA diets (Δ high-MUFA compared with low-MUFA greater than -200 g per site) in an isocaloric condition provides validity to this interaction. Given the previously proposed *LPL* rs13702-C allele-induced elevation in *LPL* activity, MUFA-rich diets might, therefore, protect the *LPL* rs13702-CC carriers from an increment in fat mass by the activation of obesity-opposing pathways, such as increasing the activity of hormone-sensitive lipase (39) or elevating the ratio of skeletal muscle to adipose tissue *LPL* activity (40), which would reduce the propensity for fat deposition.

The *ADIPOQ* gene encodes the peptide hormone adiponectin, which modulates a number of metabolic processes including lipid oxidation in muscle and liver (41). The *ADIPOQ* rs266729-G allele has been identified as a risk factor for obesity in several studies (32, 42), and has been associated with a lower risk for obesity following the consumption of a higher percentage of energy derived from fat (43). The present study shows, despite the controlled isocaloric diet, that compared with the low-MUFA diet a higher MUFA intake significantly reduced SCAT in the android region (Δ high-MUFA compared

with low-MUFA approximately -160 g) among the *ADIPOQ* rs266729-GG homozygotes. However, the C-allele carriers had greater benefits following low-MUFA consumption (Δ low-MUFA compared with high-MUFA approximately -160 g and -190 g in SCAT and android fat mass, respectively) compared with high-MUFA intake. This finding constitutes further refinement of existing obesity associations, specifically because a previous study found no effect of dietary MUFAs on the association between the *ADIPOQ* rs266729 and obesity (24). However, we did not assess depot-specific concentrations of adiponectin or its receptors, leaving the validation of the underlying mechanism to future studies.

The *APOE* gene encodes apoE, which mediates the catabolism of the TG-rich lipoprotein particles in an isoform-dependent manner (44, 45). The *E4/E4* genotype has been associated with abnormal lipid metabolism and increased risk for several health problems including obesity (33–35, 46–49) and has previously shown responsiveness to dietary interventions (45, 46, 50). Mice carrying the human non-*E4* allele were heavier when fed low- and high-fat diets compared with *E4/E4* mice (51). The same study found that FA mobilization was lower in non-*E4* than in *E4/E4* mice, whereas *E4* mice overexpressed proteins involved in FA oxidation in skeletal muscle. Our results add another dimension to the evidence that *APOE* isoforms differentially influence fat mass, through demonstrating that the concentration of dietary MUFAs modulated fat loss in *E4* carriers (Δ low-

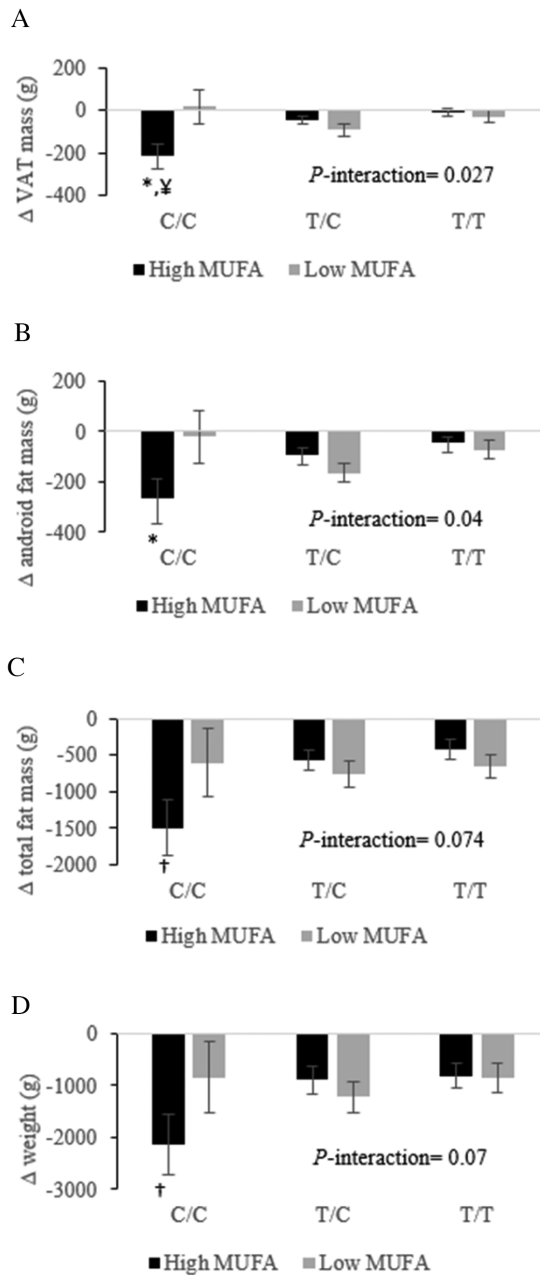


FIGURE 1 *LPL* rs13702 genotypes determine the effect of high- compared with low-MUFA consumption on 6-wk changes in VAT mass (A), android fat (B), total fat mass (C), and body weight (D) in adults with abdominal obesity. Changes were calculated by subtracting the baseline value of the selected fat mass from its corresponding 6-wk end-point value. Total participants = 101: $n = 50$ *LPL* rs13702-TT, $n = 45$ *LPL* rs13702-CT, and $n = 6$ *LPL* rs13702-CC. Values are least-squares means \pm SEMs. PROC MIXED (SAS Institute, Inc.) with repeated-measures procedure was used to assess the effect of gene-MUFA interactions on fat mass changes, using participants' identification code as a repeated factor. $P < 0.05$ was considered significant. *Statistical significance in the response of a specific fat mass to different concentrations of dietary MUFAs within the same genotype. †Trend toward statistical significance ($0.06 > P > 0.05$) in the response of a specific fat mass to different concentrations of dietary MUFAs within the same genotype. ‡Statistically significant ($P = 0.017$) greater reduction in VAT mass following high-MUFA consumption in CC carriers compared with TT carriers of *LPL* rs13702. *LPL*, lipoprotein lipase gene; VAT, visceral adipose tissue.

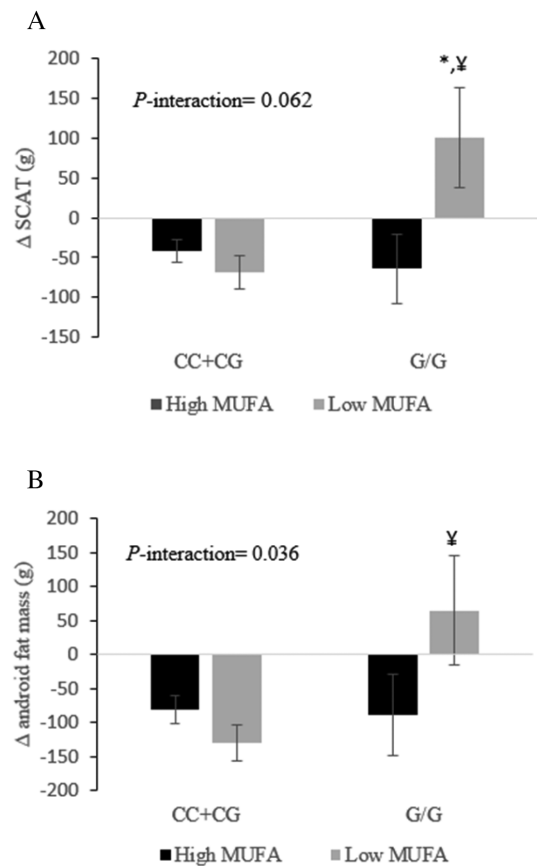


FIGURE 2 *ADIPOQ* rs266729 genotypes determine the effect of high- compared with low-MUFA consumption on 6-wk changes in SCAT (A) and android fat mass (B) in adults with abdominal obesity. Changes were calculated by subtracting the baseline value of the selected fat mass from its corresponding 6-wk end-point value. Total participants = 101: $n = 91$ *ADIPOQ* rs266729-CC + CG and $n = 10$ *ADIPOQ* rs266729-GG. Values are least-squares means \pm SEMs. PROC MIXED (SAS Institute, Inc.) with repeated-measures procedure was used to assess the effect of gene-MUFA interactions on fat mass changes, using participants' identification code as a repeated factor. $P < 0.05$ was considered significant. *Statistical significance in the response of a specific fat mass to different concentrations of dietary MUFAs within the same genotype. ‡Statistical significance of the greater reduction in SCAT mass and android fat mass following low-MUFA consumption in C carriers ($P = 0.012$ and 0.022 , respectively) compared with GG carriers of *ADIPOQ* rs266729. Recessive model (CC + CG compared with GG) was analyzed because the simple effect of heterozygous-by-MUFA showed a significant interaction on ≥ 1 compartmental fat masses. *ADIPOQ*, adiponectin gene; SCAT, subcutaneous adipose tissue.

MUFA compared with high-MUFA approximately -360 g) in an isocaloric condition. The *E4/E4* genotype was found to be associated with increased basal mitochondrial uncoupling and FA oxidation in mice (52), and this mechanism might be modulated by the quantity of dietary MUFAs, especially given that dietary MUFAs could increase fat oxidation and thermogenesis (8).

Assessing adiposity using DXA scanning provided a comprehensive assessment of the effect of these SNPs on total and regional adiposity. Another strength of this study was the crossover design with a controlled, isocaloric dietary intervention, which eliminated a range of confounders that might be

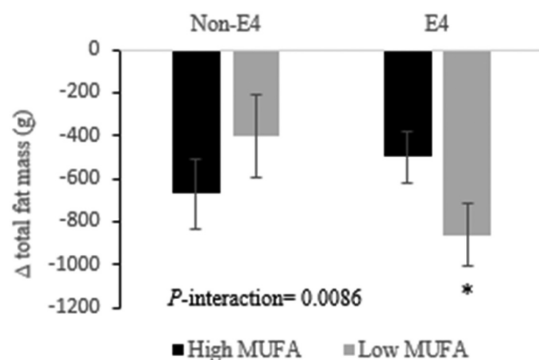


FIGURE 3 *APOE* genotypes determine the effect of high- compared with low-MUFA consumption on 6-wk changes in total fat mass in adults with abdominal obesity. Changes were calculated by subtracting the baseline value of the total fat mass from its corresponding 6-wk end-point value. Total participants = 101: $n = 35$ non-*E4* and $n = 66$ *E4*. Values are least-squares means \pm SEMs. PROC MIXED (SAS Institute, Inc.) with repeated-measures procedure was used to assess the effect of gene–MUFA interactions on fat mass changes, using participants’ identification code as a repeated factor. $P < 0.05$ was considered significant. *Statistical significance in the response of a specific fat mass to different concentrations of dietary MUFAs within the same genotype. *APOE*, apoE gene.

inherent with free-living and/or parallel study designs. However, an important limitation of the current study was that we did not apply stringent control for multiple testing, which could lead to a potential overstatement of our findings. Thus, large-scale studies are highly encouraged to evaluate these associations between the quality of dietary fat and polymorphisms within lipid metabolism-related genes. Additionally, Kien et al. (11) reported an attractive effect of dietary MUFA in which a high-MUFA consumption elevated physical activity levels compared with a high-SFA intake. The fact that participants of this study were instructed to maintain the same level of physical activity throughout the trial, and the lack of objective evaluation of physical activity, could have hindered the effect of different dietary FAs on physical activity; and consequently adiposity. The mixed ethnicity of this study population could also be perceived as a limitation, but might also provide generalizability of the current findings.

In summary, we report the contribution of common variants in *LPL*, *ADIPOQ*, and *APOE* genes to changes in body fatness in response to dietary MUFAs. These changes in body fat were observed regardless of the controlled isocaloric scenario. Although the observed changes in total and compartmental fat mass in response to gene–diet interactions were small over 6 wk, their statistical significance might indicate a potentially substantial clinical effect in weight reduction/maintenance regimens over prolonged periods.

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the study; and all authors: critically reviewed and read and approved the final manuscript.

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