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Lipoprotein receptor-related protein 1 variants and dietary fatty acids: meta-analysis of European origin and African American studies

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Abstract

OBJECTIVE—Low-density lipoprotein-related receptor protein 1 (LRP1) is a multi-functional endocytic receptor and signaling molecule that is expressed in adipose and the hypothalamus. Evidence for a role of LRP1 in adiposity is accumulating from animal and *in vitro* models, but data from human studies are limited. The study objectives were to evaluate (i) relationships between *LRP1* genotype and anthropometric traits, and (ii) whether these relationships were modified by dietary fatty acids.

DESIGN AND METHODS—We conducted race/ethnic-specific meta-analyses using data from 14 studies of US and European whites and 4 of African Americans to evaluate associations of dietary fatty acids and *LRP1* genotypes with body mass index (BMI), waist circumference and hip circumference, as well as interactions between dietary fatty acids and *LRP1* genotypes. Seven single-nucleotide polymorphisms (SNPs) of *LRP1* were evaluated in whites (*N* up to 42 000) and twelve SNPs in African Americans (*N* up to 5800).

RESULTS—After adjustment for age, sex and population substructure if relevant, for each one unit greater intake of percentage of energy from saturated fat (SFA), BMI was 0.104 kg m⁻² greater, waist was 0.305 cm larger and hip was 0.168 cm larger (all *P* < 0.0001). Other fatty acids were not associated with outcomes. The association of SFA with outcomes varied by genotype at rs2306692 (genotyped in four studies of whites), where the magnitude of the association of SFA intake with each outcome was greater per additional copy of the T allele: 0.107 kg m⁻² greater for BMI (interaction *P* = 0.0001), 0.267 cm for waist (interaction *P* = 0.001) and 0.21 cm for hip (interaction *P* = 0.001). No other significant interactions were observed.

CONCLUSION—Dietary SFA and *LRP1* genotype may interactively influence anthropometric traits. Further exploration of this, and other diet x genotype interactions, may improve understanding of interindividual variability in the relationships of dietary factors with anthropometric traits.

Keywords

low-density lipoprotein receptor-related protein 1; SNPs; saturated fatty acids; gene–diet interactions

INTRODUCTION

Obesity prevalence continues to increase globally,^{1,2} but a proportion of individuals experience less weight gain in spite of apparently similar environments. Characterizing the extent to which genetic and environmental factors, for example, diet, interact to influence weight gain may help to clarify the relevant mechanisms. In spite of the potential value of such research, well-designed investigations of gene–diet interactions are relatively few. Given the likely small magnitude of such interactions and the relatively high degree of measurement error inherent in the characterization of dietary intake, sample sizes needed to detect statistically significant interactions are much larger than most single population studies provide.^{3,4} Combining studies through meta-analysis increases sample size to address this challenge, but meta-analysis using published data is handicapped by heterogeneous definitions of exposures, inconsistent statistical methods and publication bias.⁵ Alternatively, a collaborative, multi-study approach where contributing studies centrally design analytic plans and consequently supply comparable genetic and phenotypic data may provide sufficient power and data consistency to detect gene–environment interactions,^{6–9} and avoid the potential bias of relying on published data alone. In summary, key features of the planned multi-study approach that may improve reliability compared with traditional meta-analytic approaches include: (1) meta-analysis of data from studies of similar design and purpose, (2) application of similar statistical and genetic models across studies and (3) standardization of exposures (for example, dietary data) to the fullest extent possible.

Planned multi-study approaches may be particularly useful when applied to complex, longstanding questions, such as the relationship between macronutrient intake (for example, fats, carbohydrates, proteins) and body weight. Despite decades of study, the role of dietary composition in body weight continues to be debated and has been extensively reviewed.^{10–12} In one meta-analysis, low-fat diets were associated with greater weight loss,¹³ and fat intake has been associated with greater energy consumption across a range of typical fat intakes.¹⁴ In other studies, including clinical trials in which energy intake was similar across groups, proportions of dietary macronutrients were unrelated to weight loss.^{15,16} Specific foods, rather than macronutrients, were shown in one study to be linked to body weight changes.¹⁷ However, genetic variation may also account, in part, for the conflicting data, as indicated by recent interaction studies in which dietary fat intake modulated the relationship between genetic loci and body weight.^{18–20}

An emerging new obesity candidate gene that may respond to dietary fat is that of the endocytic receptor, low-density lipoprotein receptor-related protein 1, encoded by *LRP1*. Most of the evidence for a role of *LRP1* in obesity comes from *in vitro* and animal knockout models^{21–24} but two human studies were recently published. One study reported the association of *LRP1* rs715948 genotype with body mass index (BMI) in US whites²⁵ and a second documented an interaction between *LRP1* rs1799986 and diet, in which saturated fat intake modulated anthropometric traits in US Puerto Ricans.²⁶ Notably, each of these previous studies was limited to a single population. Although data supporting a role of *LRP1* variants in obesity are accumulating, investigations that include interaction analyses in additional populations are warranted.

Therefore, the objective of the current study was to evaluate relationships of selected *LRP1* genotypes and dietary fatty acids, and also their interactions, for the outcome of anthropometric traits. We performed separate analyses in 14 independent US or European studies (*N* up to 42 000 whites) and four US studies (*N* up to 5800 African Americans).

MATERIALS AND METHODS

Subjects

We evaluated (i) main associations of each genetic variant and dietary fatty acids for anthropometric traits and (ii) interactions between dietary fatty acids and genetic variants for anthropometric traits were performed in 14 studies (Table 1, Supplementary Table 1). In four of the US cohorts, data for African American individuals were also available. Only participants with dietary or genetic data that met study-specific quality control standards were included in the analyses (Supplementary Tables 2 and 3). Informed consent for study participation and consent to use genetic data were provided by all participants whose data were analyzed, and study protocols were reviewed by institutional review boards for each study.

Dietary assessment and estimation of fatty acids intake as a percentage of total energy

Previous studies investigating gene–fatty acids interactions have most frequently analyzed saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs).^{18–20,27,28} In addition, animal and cell models have provided evidence that *LRPI* may be responsive to these fatty acids.^{29–31} Estimations of SFA and PUFA intakes were derived from food frequency questionnaires in all studies (Supplementary Table 2) using the reported frequency and portion sizes and corresponding macronutrient compositions of relevant foods, as provided in region-specific reference databases. Fatty acid intake was characterized as percentage of total energy intake, calculated as $100 \times ((\text{grams of fatty acid} \times 9) / \text{total energy})$. Fatty acid intakes were evaluated continuously and dichotomously (divided into high and low based on study-specific median intakes) to evaluate dose–response and threshold effects, respectively.

Anthropometric traits

Analyses were performed for BMI, waist circumference and hip circumference. Waist circumference has been associated with adverse metabolic consequences in ethnically diverse individuals³² and hip circumference has been shown to be protective.³³ Study-specific methods for measuring height and weight (to calculate BMI in kg m^{-2}), and waist and hip circumference are described for each study (Supplementary Table 4).

SNP selection and genotyping

LRPI genotype data were downloaded separately for CEU (individuals of Western and Northern European origin) and YRI (Yoruba in Nigeria) from HapMap phase 2. For each racial group, genotype data were imported into Haploview,³⁴ minimum allele frequency threshold was set to 0.05 and pair-wise tagging was applied with an r^2 threshold of 0.2 to obtain independent single-nucleotide polymorphisms (SNPs). Seven tag SNPs were selected for CEU and twelve tag SNPs for YRI for evaluation. Methods for genotyping including genome-wide chip technology, quality control and imputation methods are described for each cohort (Supplementary Table 3).

Statistical analyses by each study

Each study performed linear regression analysis to generate regression coefficients () and standard errors for (1) associations of *LRPI* genotype with anthropometric traits, (2) associations between continuously evaluated fatty acid intake (SFA and PUFA) and anthropometric traits (3) interactions between *LRPI* genotype and dietary fatty acids with respect to anthropometric traits.

Genotype associations models used an additive genetic model with adjustment for age (continuous), sex, field center and cohort-specific principal components (as needed to

account for population substructure and/or family structure). Associations between fatty acids and anthropometric traits (without inclusion of genotypes or interaction terms in the model) were evaluated using three hierarchical models: (model 1) age (years, continuous), gender, population substructure variables; (model 2) model 1+total daily energy intake (kcal/day, continuous; and (model 3) model 2+smoking status (categorical), physical activity (continuous, based on study-specific metric), alcohol intake (continuous), education (based on study-specific metric). Study-specific covariate definitions are presented in Supplementary Table 5.

Fatty acids–SNP interactions were evaluated using cross-product terms using the likelihood ratio test with an additive genetic model. Thus, the interaction regression coefficient represents the difference in the magnitude of the fatty acid association (per each +1 percent of total energy) with anthropometric outcomes (BMI, waist or hip) per copy of the effect allele.

Meta-analysis

Meta-analysis was performed using an inverse variance-weighted, fixed effects approach. For SNP associations and for SNP $\times$ fatty acids interaction meta-analysis, METAL software was used (<http://umich.edu/csg/abecasis/Metal/>). For fatty acids associations, *R* software was used.³⁵ Within each ethnic group, all available studies were meta-analyzed in order to maximize statistical power. Bonferroni correction based on the number of SNPs and the two types of nutrients tested (SFA and PUFA) was applied to establish a significance level with correction for multiple testing. Seven SNPs were evaluated in whites ($\alpha=0.05/7 \times 2=0.004$) and twelve SNPs in African Americans ($\alpha=0.05/12 \times 2=0.002$).

RESULTS

Participant characteristics and study descriptions are provided for each group (Table 1, Supplementary Table 1). SFA intake ranged from 9.4% of total energy (in Health Aging and Body Composition study (white participants)) to 14.4% (Rotterdam Study). PUFA intake ranged from 3.4% (InCHIANTI) to 8.7% (Health ABC, white participants). Allele frequencies and chromosomal positions for each SNP are shown for each study for whites and African Americans (Supplementary Table 6). Results described below are derived from meta-analysis of all cohorts in which genotype data were available with the number of studies for each SNP/trait combination provided in the table.

Associations of SFAs and PUFA intake with anthropometrics

Percentage of energy from SFA was associated with higher BMI and waist and hip circumference in whites adjusted for age, gender and population substructure variables (Table 2). Similar results were obtained with additional adjustment for lifestyle factors, including physical activity, smoking, alcohol, education level and total energy intake (Table 2). For each one percentage greater intake of energy from SFA, BMI was 0.104 kg m^{-2} greater, waist circumference was 0.305 cm larger and hip circumference was 0.168 cm larger (all $P<0.0001$). In African Americans, associations of SFA intake with BMI and hip circumference were similar to those observed in whites (Table 2). No associations between fatty acids and waist circumference were observed in African Americans.

Associations of LRP1 SNPs with anthropometrics

With adjustment for age, sex, and study-specific population substructure measures, none of the *LRP1* SNPs were associated with BMI, waist circumference, or hip circumference in whites. In African Americans, BMI was 0.726 kg m^{-2} lower ($P=0.017$) and hip was 3.404 cm lower ($P=0.015$) per copy of the A allele for *LRP1* rs1800141 (Table 3).

Interactions between LRP1 SNPs and SFA intake for anthropometrics

Of the seven variants tested for interaction in whites, only *LRP1* rs2306692 showed statistically significant evidence of interaction with SFA intake (Table 4; genotyped in only four white cohorts, $N \sim 13,000$). For each one percentage greater intake of energy from SFA, BMI was 0.107 kg m^{-2} greater (interaction $P=0.0001$), waist circumference was 0.267 cm larger (interaction $p=0.001$) and hip circumference was 0.21 cm larger (interaction $P=0.001$) per one additional copy of the effect allele (T). In other words, the magnitude of the association between SFA intake and these anthropometric traits was greater in the presence of the T allele compared with the absence of the T allele. Results were similar when SFA was modeled dichotomously using sample-specific median cut points (Supplementary Table 7). We did not observe corresponding statistically significant interactions between SFA and rs2306692 in African Americans (Table 3; genotyped in four cohorts, $N \sim 13,000$). The remaining SNP–SFA interactions tested in African Americans were also not statistically significant (Table 3).

Interactions between LRP1 SNPs and PUFA intake for anthropometrics

Interactions between *LRP1* SNPs and PUFA were evaluated continuously (Table 5) and dichotomously (Supplementary Table 8); none were statistically significant in either race/ethnic group.

DISCUSSION

We observed an interaction between an *LRP1* variant and saturated fat intake for anthropometric traits in whites using a meta-analytic approach that incorporated data from multiple populations. Specifically, the magnitude of the association between SFA and anthropometric traits was greater per each additional copy of the T allele for *LRP1* rs2306692. Although the differences in the slope of these associations were modest (BMI was 0.107 kg m^{-2} greater, waist circumference was 0.267 cm greater, and hip circumference was 0.21 cm greater), and the SNP available in a relatively small sample, these data provide preliminary evidence that dietary factors and genetic factors at this locus may interactively influence body size. Although in this instance we have described the 'interaction' in terms of genetic modulation of a dietary association, these findings could alternatively be interpreted as dietary modulation of an association between genetic variants and body size.

The majority of existing literature on the role of *LRP1* in adiposity is based on animal and *in vitro* models. A large-scale ($n \sim 123,000$ with follow-up in $\sim 126,000$) meta-analysis of genome-wide association studies did not identify statistically significant associations between the *LRP1* SNPs evaluated in our report and BMI, but interactions with dietary factors were not analyzed in that meta-analysis.³⁶ A single observational study in adults did report an association between *LRP1* rs715948 and BMI in a white population,²⁵ but this association was not replicated in our larger meta-analysis. Similarly, we did not replicate an interaction between SFA and a second *LRP1* variant (rs1799986) that was observed in a separate study of Boston Puerto Ricans.²⁶ Neither of these two previous single population studies analyzed rs2306692, the variant that showed statistically significant interaction with SFA intake for anthropometric traits in our meta-analysis of data from four studies. Inconsistencies in genetic association studies are common, and may be attributed to undetected environmental interactions, differences in confounding variables or false-positive results obtained in single populations. Differences in linkage disequilibrium across ethnic groups may also contribute to variable results. In the current study, SNPs were intentionally selected to minimize linkage disequilibrium ($r^2 < 0.2$) within each of the two ethnic groups, but these patterns may differ in groups with other ancestries.

Mechanisms for the observed interaction between rs2306692 and SFA can be hypothesized, but not directly evaluated in the current study. *LRP1* is expressed in many tissues, including adipose and the hypothalamus,²⁴ and both sites have been implicated in obesity. Previous studies with animal models demonstrated a role for LRP1 in adipogenesis, obesity and fat storage, with adipose-specific knockout conferring resistance to obesity.^{21–23} In contrast, hypothalamic-specific knockout of *LRP1* resulted in greater food consumption compared with controls, and an obese phenotype accompanied by insulin resistance.²⁴ Of potential relevance to eating behavior is LRP1's regulation of leptin, in that LRP1 binding to leptin is required for activation of Stat3 (signal transduction-activated transcript-3), a transcription factor whose knockout also promotes appetite and weight gain.^{24,37} Interestingly, SFA have been reported to modulate the relationship between genotype and adiposity for *STAT3*, as we report here for *LRP1*, in that high SFA intake was linked to obesity in carriers of *STAT3* variants.¹⁸ Moreover, additional genes encoding the hypothalamically expressed *FTO* and the postulated satiety signal apolipoprotein A-II (*APOA2*)^{19,38} also appear to be modulated by SFA. At both *FTO* and *APOA2* loci, the presence of variant alleles in individuals consuming high SFA is associated with greater body weight compared with individuals without the variants. We therefore postulate a hypothetical model in which high SFA intake promotes obesity via disruption of hypothalamic signaling pathways that regulate satiety and intake, for which genetic variants of *LRP1*, *STAT3*, *FTO*, *APOA2* and others as yet unidentified interact biologically with SFA to shape the pattern of disruption.

The primary goal of the current study was investigation of gene–nutrient interactions, but we also examined fatty acids and anthropometric traits without evaluation of genotype. Intakes of SFA, but not PUFA, were associated with greater BMI, waist circumference and hip circumference. Although we adjusted by major lifestyle factors, including physical activity, smoking, alcohol and education, we did not evaluate the role of other potential confounders related to food choices (for example, dietary fiber, fruits and vegetables, socioeconomic factors) and food sources of SFA. In animal models, SFA intake is associated with hypothalamic activation of Toll-like receptor signaling and impaired anorexigenic signaling that are hypothesized to contribute to obesity *via* increased energy intake.³⁹ However, in people, specific foods (including red meat and processed meats, sugar-sweetened beverages, potato chips), rather than specific nutrients, were shown to be associated with weight gain over time.¹⁷ Greater SFA intake may represent a marker for correlated dietary and behavioral factors that promote greater body size.

Our study is strengthened by its centrally designed analysis plan of primary data, large sample size and examination of multiple SNPs across the *LRP1* locus; however, our findings do not provide evidence of SNP functionality. In addition, genotypes for *LRP1* rs2306692 were measured in only 4 of the 14 white populations, and its availability in a comparatively small number of subjects ($n \sim 13\,000$) is an important limitation. The absence of interaction in African Americans provides evidence against *LRP1* rs2306692 being causal, as a functional SNP would be likely to demonstrate similar relationships cross-ethnically. Instead, rs2306692 could be a marker for a functional SNP, and the marker could differ across ethnic groups. Future studies testing the reliability of our findings could also utilize sequencing data to identify less common, and potentially functional, *LRP1* variants to which rs2306692 is linked.

In summary, from a meta-analysis of data from four US and European cohort studies, we observed an interaction between *LRP1* genotype and SFA intake for anthropometric traits. *LRP1* rs2306692 may represent a marker for greater sensitivity to SFA or to correlated lifestyle behaviors, leading to greater probability of higher body weight in the context of a diet high in saturated fats, such as the Western diet. Confirmation of these findings in the context of an interventional study that targets SFA intake and considers *LRP1* genotype is

needed to confirm that these relationships are valid in the context of dietary change. In spite of the importance of extending interaction analyses beyond a single population, replications and meta-analyses of interactions are relatively rare. This study represents one of a small, but growing, number of studies that apply centrally planned, collaborative methods to improve the reliability of genetic findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant characteristics by study

	<i>N</i>	<i>Age, years</i>	<i>Gender, % women</i>	<i>BMI, kg m⁻²</i>	<i>Waist, cm</i>	<i>Hip, cm</i>	<i>Total fat, % energy</i>	<i>Saturated fat, % energy</i>	<i>Polyunsaturated fat, % energy</i>
<i>European descent</i>									
Atherosclerosis Risk in Communities (ARIC) Study (USA)	9189	54.3 ± 5.7	52.8	27.0 ± 4.8	99.9 ± 13.9	106.4 ± 10.8	33.2 ± 6.8	12.2 ± 3.1	5.1 ± 1.5
Cardiovascular Health Study (CHS) (USA)	3222	72.3 ± 5.4	60.8	26.3 ± 4.5	93.1 ± 12.8	101.5 ± 9.6	32.3 ± 6.0	10.34 ± 2.2	7.4 ± 2.2
European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk (UK)	2353	45.0 ± 7.3	53.2	26.4 ± 3.9	88.4 ± 12.3	103.2 ± 7.9	32.3 ± 5.7	12.3 ± 3.2	6.2 ± 2.0
Family Heart Study (FamHS) (USA)	2980	52.9 ± 13.8	52.9	27.7 ± 5.5	97.7 ± 15.2	105.8 ± 11.2	30.5 ± 7.5	11.2 ± 3.2	4.5 ± 1.4
Fenland (UK)	1071	59.3 ± 9.0	56.1	27.0 ± 4.9	92.0 ± 13.5	104.1 ± 9.8	33.3 ± 5.9	12.3 ± 3.2	6.5 ± 1.8
Framingham Heart Study (FHS) (USA)	6374	46.8 ± 11.7	53.7	27.1 ± 5.2	92.7 ± 5.2	102.9 ± 9.6	28.4 ± 6.1	11.0 ± 3.0	5.8 ± 1.6
Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) (USA)	1120	48.5 ± 16.4	52.1	28.3 ± 5.6	96.6 ± 16.6	107.4 ± 11.6	35.5 ± 6.7	11.9 ± 2.7	7.6 ± 2.1
Health, Aging and Body Composition Study (Health ABC) (USA)	1499	74.8 ± 2.9	48	26.4 ± 4.1	98.8 ± 11.9	NA	32.9 ± 7.6	9.4 ± 2.5	8.7 ± 2.8
Health Professionals Follow-up Study (HPFS) (USA)	2326	55.5 ± 8.5	0	26.3 ± 3.7	97.7 ± 10.3	102.9 ± 8.4	32.8 ± 6.4	11.3 ± 2.8	6.1 ± 1.6
Invecchiare in Chianti (InCHIANTI) (Italy)	1100	67.6 ± 15.0	55.3	27.2 ± 4.2	91.4 ± 11.1	100.6 ± 8.8	31.0 ± 5.1	10.4 ± 2.2	3.4 ± 0.7
Multi-Ethnic Study of Atherosclerosis (MESA) (USA)	2289	62.6 ± 10.3	51.6	27.8 ± 5.1	98.0 ± 14.3	106.2 ± 10.5	33.4 ± 7.2	11.0 ± 3.3	7.0 ± 2.0
Nurses Health Study (USA)	3065	53.2 ± 6.8	100	27.2 ± 5.7	83.4 ± 13.2	104.2 ± 11.5	33.2 ± 5.6	11.8 ± 2.5	6.3 ± 1.6
Rotterdam Study (ROT) (The Netherlands)	4576	67.6 ± 7.7	58.6	26.3 ± 3.6	90.1 ± 11.0	99.8 ± 7.6	36.3 ± 6.1	14.4 ± 3.2	6.9 ± 1.1
Young Finns Study (YFS) (Finland)	1762	37.8 ± 5.0	56	26.0 ± 4.8	88.5 ± 13.5	99.8 ± 8.9	32.8 ± 4.8	11.8 ± 2.4	5.3 ± 1.1
<i>African Americans</i>									
Atherosclerosis Risk in	3078	53.4 ± 5.8	62	29.6 ± 6	102.8 ± 15.6	110.4 ± 13.7	32.1 ± 6.4	11.4 ± 2.7	4.8 ± 1.3

	<i>N</i>	<i>Age, years</i>	<i>Gender, % women</i>	<i>BMI, kg m⁻²</i>	<i>Waist, cm</i>	<i>Hip, cm</i>	<i>Total fat, % energy</i>	<i>Saturated fat, % energy</i>	<i>Polyunsaturated fat, % energy</i>
Communities (ARIC) Study									
Cardiovascular Health Study (CHS)	584	74 ± 5.3	63.4	28.1 ± 5.3	95.1 ± 12.6	101.7 ± 10	29.9 ± 6.5	10 ± 2.7	6 ± 1.9
Health, Aging and Body Composition Study (Health ABC)	869	74.4 ± 2.9	59	28.6 ± 5.5	100.5 ± 14	NA	34.2 ± 7.2	9.8 ± 2.4	9.3 ± 3.8
Multi-Ethnic Study of Atherosclerosis (MESA)	1313	62.2 ± 10	53.5	30 ± 5.7	101 ± 14.3	109.5 ± 11.9	34.5 ± 7.1	10.6 ± 2.9	7.6 ± 2.2

Abbreviations: BMI, body mass index; NA, not available.

Table 2

Meta-analyzed associations between fatty acids and anthropometric traits in European descent and African Americans

	<i>N</i>	Regression ^a coefficients (95% CI) for BMI	<i>P</i> -value	<i>N</i>	Regression ^a coefficients (95% CI) for waist circumference)	<i>P</i> -value	<i>N</i>	Regression ^a coefficients (95% CI) for associations for hip circumference)	<i>P</i> -value
<i>European descent</i>									
<i>Saturated fatty acids</i>									
Model 1	42 884	0.104 (0.089, 0.118)	< 0.0001	40 368	0.305 (0.263, 0.346)	< 0.0001	34 709	0.168 (0.134, 0.202)	< 0.0001
Model 2	42 884	0.107 (0.093, 0.122)	< 0.0001	40 367	0.304 (0.262, 0.346)	< 0.0001	34 709	0.169 (0.134, 0.204)	< 0.0001
Model 3	39 173	0.088 (0.0727, 0.104)	< 0.0001	36 754	0.252 (0.208, 0.297)	< 0.0001	31 363	0.141 (0.104, 0.178)	< 0.0001
<i>Polyunsaturated fatty acids</i>									
Model 1	42 884	0.02 (−0.002, 0.041)	0.072	40 368	0.054 (−0.008, 0.115)	0.086	34 709	0.046 (−0.004, 0.096)	0.070
Model 2	42 884	0.023 (0.001, 0.044)	0.038	40 367	0.054 (−0.007, 0.116)	0.085	34 709	0.046 (−0.004, 0.096)	0.071
Model 3	39 173	0.006 (−0.015, 0.027)	0.598	36 754	0.051 (−0.009, 0.111)	0.094	31 363	0.02 (−0.029, 0.068)	0.426
<i>African Americans</i>									
<i>Saturated fatty acids</i>									
Model 1	5834	0.05 (−0.002, 0.102)	0.060	4791	−0.015 (−0.053, 0.024)	0.448	3673	0.148 (0.029, 0.266)	0.015
Model 2	5834	0.059 (0.006, 0.112)	0.03	4791	−0.008 (−0.047, 0.031)	0.696	3673	0.162 (0.041, 0.284)	0.009
Model 3	5767	0.057 (0.003, 0.111)	0.038	4736	0.126 (0.014, 0.239)	0.028	3628	0.236 (0.1, 0.372)	0.0007
<i>Polyunsaturated fatty acids</i>									
Model 1	5831	0.044 (−0.03, 0.118)	0.239	4788	−0.025 (−0.065, 0.014)	0.211	3670	0.075 (−0.073, 0.223)	0.322
Model 2	5831	0.046 (−0.028, 0.12)	0.222	4788	−0.021 (−0.059, 0.017)	0.285	3670	0.082 (−0.063, 0.227)	0.265
Model 3	5764	0.036 (−0.038, 0.11)	0.337	4733	0.012 (−0.093, 0.118)	0.818	3625	0.129 (−0.035, 0.292)	0.123

Abbreviations: BMI, body mass index; CI, confidence interval. Model 1: age, gender, population-specific substructure. Model 2: model 1 + total daily energy intake. Model 3: model 2 + smoking status, physical activity, alcohol intake, education.

^a Represents estimated difference in anthropometric trait per + 1-unit intake of fatty acid expressed as a percentage of total daily energy.

Table 3
Associations between *LRP1* SNPs and anthropometric traits in European descent and African American cohorts

SNP	Effect allele/other allele	Number of cohorts ^a	Regression coefficients for associations for BMI				Regression coefficients for associations for waist circumference				Regression coefficients for associations for hip circumference			
			N	b	s.e.m.	P-value	N	b	s.e.m.	P-value	N	b	s.e.m.	P-value
European descent														
rs17119494	A/G	14,14,13	42 569	-0.105	0.07	0.134	40 049	-0.159	0.1977	0.423	34 391	-0.133	0.162	0.414
rs715948	A/G	14,14,13	42 569	0.025	0.036	0.489	40 049	0.02	0.101	0.847	34 391	-0.012	0.082	0.880
rs1799986	T/C	14,14,13	42 569	-0.061	0.046	0.185	40 049	-0.13	0.13	0.317	34 391	-0.132	0.106	0.211
rs2306692	T/C	4,4,4	13 224	0.052	0.0873	0.552	12 176	-0.032	0.26	0.903	11 464	-0.038	0.206	0.855
rs10876966	C/T	12,12,11	39 145	-0.017	0.041	0.676	36 628	-0.046	0.118	0.694	30 967	-0.16	0.096	0.094
rs1800176	C/T	14,14,13	42 569	0.021	0.033	0.540	40 049	0.033	0.094	0.724	34 391	-0.04	0.077	0.604
rs12814239	C/T	14,14,13	42 569	-0.081	0.084	0.338	40 049	0.203	0.239	0.397	34 391	0.169	0.199	0.395
African Americans														
rs715948	A/G	4,4,3	5544	-0.124	0.141	0.380	4554	-0.343	0.413	0.406	3467	-0.499	0.397	0.209
rs1799986	T/C	4,4,3	5832	-0.177	0.206	0.391	4788	-0.641	0.605	0.289	3672	-0.463	0.586	0.430
rs2306692	T/C	4,4,3	5841	-0.041	0.118	0.731	4796	0.106	0.348	0.761	3680	-0.094	0.328	0.774
rs1800176	C/T	4,4,3	5809	-0.108	0.114	0.346	4774	-0.359	0.331	0.278	3657	-0.285	0.312	0.360
rs4759277	A/C	4,4,3	5843	0.055	0.106	0.603	4798	0.188	0.308	0.542	3680	0.193	0.288	0.503
rs7304504	A/G	2,2,2	3362	0.205	0.184	0.267	2375	1.121	0.58	0.053	2154	0.522	0.507	0.303
rs1800164	G/A	4,4,3	5544	-0.15	0.122	0.221	4554	-0.108	0.354	0.761	3467	-0.321	0.33	0.331
rs1800141	A/G	2,2,1	1453	-0.726	0.305	0.017	1073	-0.539	0.99	0.587	207	-3.404	1.397	0.015
rs1800159	A/G	4,4,3	5544	0.094	0.118	0.427	4554	0.183	0.344	0.594	3467	0.026	0.339	0.939
rs6581127	C/G	3,3,2	4960	0.242	0.234	0.301	4347	0.463	0.65	0.476	3260	0.667	0.653	0.307
rs34574998	C/T	2,2,1	1453	-0.1	0.317	0.753	1073	1.209	0.956	0.206	207	-0.615	1.545	0.691
rs6581124	A/G	1,1,1	584	0.566	0.420	0.178	207	-0.774	1.73	0.655	207	-0.625	1.321	0.636

Abbreviations: BMI, body mass index; CI, confidence interval; SNP, single-nucleotide polymorphism; SNP, single-nucleotide polymorphism.

^aNumber of cohorts indicates the count of populations in which BMI, waist and hip (in that order) were measured in genotyped individuals.

^b Represents estimated difference in anthropometric trait per copy of effect allele.

Table 4

Interactions between SFA evaluated continuously and *LRP1* SNPs for anthropometric traits in European descent and African American cohorts

SNP	Effect allele/other allele	Number of cohorts ^a	Regression coefficients for interactions between SFA (% energy) × SNP for BMI				Regression coefficients for interactions between SFA (% energy) × SNP for waist circumference				Regression coefficients for interactions between SFA (% energy) × SNP for hip circumference			
			N	b	s.e.m.	P-value	N	b	s.e.m.	P-value	N	b	s.e.m.	P-value
European ancestry														
rs17119494	A/G	14, 14, 13	42,569	0.008	0.023	0.726	40,049	0.0783	0.067	0.241	34,391	0.022	0.055	0.686
rs715948	A/G	14, 14, 13	42,569	−0.009	0.012	0.475	40,049	−0.0477	0.034	0.159	34,391	−0.021	0.028	0.439
rs1799986	T/C	14, 14, 13	42,569	0.013	0.015	0.400	40,049	0.0601	0.043	0.158	34,391	0.011	0.035	0.748
rs2306692	T/C	4, 4, 4	13,224	0.107	0.028	0.0001	12,176	0.267	0.082	0.001	11,464	0.21	0.066	0.001
rs10876966	C/T	12, 12, 11	39,145	0.0007	0.014	0.963	36,628	−0.0125	0.041	0.760	30,967	−0.033	0.033	0.314
rs1800176	C/T	14, 14, 13	42,569	0.015	0.011	0.191	40,049	0.0198	0.032	0.530	34,391	0.015	0.026	0.565
rs12814239	C/T	14, 14, 13	42,569	0.005	0.025	0.846	40,049	0.0374	0.07	0.595	34,391	0.03	0.059	0.610
African Americans														
rs715948	A/G	4, 3, 2	5544	0.081	0.051	0.114	4347	0.2663	0.161	0.098	3260	0.159	0.153	0.299
rs1799986	T/C	4, 3, 2	5832	0.046	0.074	0.538	4581	−0.0655	0.223	0.769	3465	0.266	0.205	0.195
rs2306692	T/C	4, 3, 2	5841	−0.04	0.043	0.360	4589	−0.0734	0.133	0.581	3473	−0.002	0.122	0.985
rs1800176	C/T	4, 3, 2	5809	−0.043	0.041	0.290	4567	−0.1082	0.124	0.382	3450	−0.203	0.115	0.078
rs4759277	A/C	4, 3, 2	5843	0.018	0.039	0.648	4591	−0.0113	0.118	0.923	3473	0.091	0.108	0.403
rs7304504	A/G	2, 1, 1	3362	0.034	0.069	0.620	2168	0.2580	0.223	0.247	1947	0.177	0.205	0.388
rs1800164	G/A	4, 3, 2	5544	−0.039	0.039	0.313	4347	−0.1162	0.115	0.311	3260	−0.09	0.106	0.397
rs1800141	A/G	2, 1, 0	1453	−0.089	0.117	0.445	866	0.2220	0.494	0.653	0			
rs1800159	A/G	4, 3, 2	5544	0.075	0.042	0.079	4347	0.2095	0.132	0.111	3260	0.235	0.127	0.065
rs6581127	C/G	3, 3, 2	4960	0.13	0.087	0.136	4347	0.2241	0.241	0.353	3260	0.147	0.232	0.526
rs34574998	C/T	2, 1, 0	1453	−0.259	0.119	0.029	866	−0.3490	0.474	0.462	0			
rs6581124	A/G	1, 0, 0	584	0.019	0.134	0.887	0				0			

Abbreviations: BMI, body mass index; CI, confidence interval; SFA, saturated fatty acid; SNP, single-nucleotide polymorphism.

^aNumber of cohorts indicates the count of populations in which BMI, waist and hip (in that order) were measured in genotyped individuals.

^bRepresents the difference in the magnitude of the fatty acids association (per + 1-unit intake of fatty acid expressed as a percentage of total daily energy) with anthropometric traits per copy of the effect allele.

Table 5

Interactions between PUFA evaluated continuously and *LRP1* SNPs for anthropometric traits in European descent and African American cohorts

SNP	Effect allele/other allele	Number of cohorts ^a	Regression coefficients for interactions between PUFA (% energy) × SNP for BMI			Regression coefficients for interactions between PUFA (% energy) × SNP for waist circumference			Regression coefficients for interactions between PUFA (% energy) × SNP for hip circumference					
			N	s.e.m.	P-value	N	b	s.e.m.	P-value	N	b	s.e.m.	P-value	
European ancestry														
rs17119494	A/G	14, 14, 13	42 569	0.061	0.035	0.077	40 049	0.214	0.099	0.031	34 391	0.118	0.082	0.149
rs715948	A/G	14, 14, 13	42 569	−0.012	0.018	0.481	40 049	−0.046	0.05	0.360	34 391	−0.045	0.041	0.275
rs1799986	T/C	14, 14, 13	42 569	0.04	0.023	0.079	40 049	0.031	0.064	0.626	34 391	0.006	0.052	0.908
rs2306692	T/C	4, 4, 4	13 224	−0.02	0.055	0.72	12 176	−0.165	0.163	0.31	11 464	−0.051	0.128	0.692
rs10876966	C/T	12, 11, 11	39 145	0.028	0.02	0.171	36 628	0.065	0.06	0.276	30 967	0.036	0.048	0.455
rs1800176	C/T	14, 14, 13	42 569	0.004	0.016	0.830	40 049	−0.032	0.047	0.498	34 391	0.007	0.038	0.864
rs12814239	C/T	14, 14, 13	42 569	0.023	0.04	0.558	40 049	0.153	0.111	0.169	34 391	0.038	0.095	0.691
African Americans														
rs715948	A/G	4, 3, 2	5544	0.055	0.071	0.439	4347	0.077	0.218	0.723	3260	−0.11	0.252	0.662
rs1799986	T/C	4, 3, 2	5832	−0.001	0.1	0.990	4581	0.418	0.311	0.178	3465	0.118	0.347	0.733
rs2306692	T/C	4, 3, 2	5841	−0.05	0.059	0.404	4589	−0.063	0.179	0.724	3473	−0.112	0.2	0.574
rs1800176	C/T	4, 3, 2	5809	0.061	0.060	0.308	4567	0.1	0.173	0.565	3450	0.074	0.192	0.700
rs4759277	A/C	4, 3, 2	5843	0.041	0.054	0.450	4591	0.090	0.161	0.577	3473	0.144	0.169	0.395
rs7304504	A/G	2, 1, 1	3362	−0.138	0.109	0.206	2168	−0.55	0.405	0.175	1947	−0.363	0.363	0.317
rs1800164	G/A	4, 3, 2	5544	0.02	0.057	0.728	4347	−0.140	0.168	0.403	3260	0.118	0.174	0.497
rs1800141	A/G	2, 1, 0	1453	−0.031	0.129	0.811	866	−0.086	0.436	0.844	0			
rs1800159	A/G	4, 3, 2	5544	0.036	0.059	0.541	4347	0.031	0.177	0.859	3260	−0.032	0.205	0.877
rs6581127	C/G	3, 3, 2	4960	0.037	0.118	0.751	4347	−0.054	0.314	0.864	3260	−0.25	0.362	0.490
rs34574998	C/T	2, 1, 0	1453	−0.008	0.126	0.948	866	−0.086	0.401	0.830	0			
rs6581124	A/G	1, 0, 0	584	−0.034	0.173	0.844	0				0			

Abbreviations: BMI, body mass index; CI, confidence interval; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acid; SNP, single-nucleotide polymorphism.

^aNumber of cohorts indicates the count of populations in which BMI, waist and hip (in that order) were measured in genotyped individuals.

^bRepresents the difference in the magnitude of the fatty acids association (per + 1-unit intake of fatty acid expressed as a percentage of total daily energy) with anthropometric traits per copy of the effect allele.