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Lipoprotein lipase variants interact with polyunsaturated fatty acids for obesity traits in women: Replication in two populations

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Abstract

Background and aims—Lipoprotein lipase (*LPL*) is a candidate gene for obesity based on its role in triglyceride hydrolysis and the partitioning of fatty acids towards storage or oxidation. Whether dietary fatty acids modify *LPL* associated obesity risk is unknown.

Methods and results—We examined five single nucleotide polymorphisms (SNPs) (rs320, rs2083637, rs17411031, rs13702, rs2197089) for potential interaction with dietary fatty acids for obesity traits in 1171 participants (333 men and 838 women, aged 45–75 y) of the Boston Puerto Rican Health Study (BPRHS). In women, SNP rs320 interacted with dietary polyunsaturated fatty acids (PUFA) for body mass index (BMI) ($P = 0.002$) and waist circumference (WC) ($P = 0.001$) respectively. Higher intake of PUFA was associated with lower BMI and WC in homozygotes of the major allele (TT) ($P = 0.01$ and 0.005) but not in minor allele carriers (TG and GG). These interactions were replicated in an independent population, African American women of the Atherosclerosis Risk in Communities (ARIC) study ($n = 1334$).

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Conflicts of interest The authors have no competing interests.

Appendix A. Supplementary data Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.numecd.2014.07.003>.

Conclusion—Dietary PUFA modulated the association of *LPL* rs320 with obesity traits in two independent populations. These interactions may be relevant to the dietary management of obesity, particularly in women.

Keywords

Gene-diet interaction; Lipoprotein lipase; Polyunsaturated fatty acids; Obesity

Introduction

Obesity in the US has reached an overall prevalence of nearly 34% [1], with greater prevalence in some ethnic minorities [2], which might be related to differences in genetic background and behavioral factors [3–5]. The investigation of genetic variants for obesity in conjunction with behavioral factors, especially diet, may benefit development of more specific strategies to ameliorate susceptibility to weight gain.

Lipoprotein lipase (*LPL*) is a candidate gene for obesity, based on its encoded function to absorb fatty acids across tissues [6,7]. *LPL* contributes to fat storage in adipocytes [8], regulation of thermogenesis in skeletal muscle [9]. However, in spite of *LPL*'s demonstrated role in obesity, relevant association studies with *LPL* single nucleotide polymorphism (SNP) have inconsistent findings and show sex-specific differences [10,11].

One hypothesis that may account for the inconsistency is that unexamined factors may modulate *LPL*-associated obesity risk. Dietary fat type (e.g., saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA)) have been evaluated for obesity risk independently of genotype for decades [4]. However, it remains to be explored whether intakes of different fatty acids alter obesity-related traits in the context of *LPL* genotype.

Therefore, we aimed to determine whether dietary fatty acids interact with *LPL* variants for obesity traits in a population of multiple ancestries, stratified by sex. We also aimed to replicate our findings in an independent population.

Methods

Study populations

Discovery population: The Boston Puerto Rican Health Study (BPRHS)—In the BPRHS, there were 1171 participants of Puerto Rican origin, aged 45–75 years, living in the Greater Boston, MA metropolitan area, after excluding those with missing data and implausible energy intake, defined as <2512 kJ (600 kcal) per day or >20093 kJ (4800 kcal) per day. Details for the study have been described previously [12]. Fasting blood were collected for biochemical and genetic analyses. Anthropometric methods were consistent with techniques used by the National Health and Nutrition Examination Surveys. The study protocol was approved by the Institutional Review Board at Tufts Medical Center and Tufts University Health Sciences Campus. Informed consent was received by all participants or their representatives.

Replication population: Atherosclerosis Risk in Communities Study (ARIC)—

Participants of replication study in ARIC included 2186 African American (AA) and 8689 European American (EA), considering the multiple ancestry nature of the BPRHS. ARIC was a multi-center study with participants aged 44–66 years from Forsyth County, North Carolina; Jackson, Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland [13]. Individuals with implausible energy intakes, defined as in the BPRHS, were excluded from analysis. Body weight was measured using a calibrated scale with subjects in scrub suits without shoes and height was measured using a ruler. Waist circumference (WC) at the umbilicus was measured using a tape measure. Fasting blood was collected from an antecubital vein into a vacuum tube with ethylenediamine tetraacetic acid. Triglycerides and high-density lipoprotein (HDL) were assayed using enzymatic methods and dextran-magnesium precipitation respectively [14]. This study was approved by the Institutional Review Board at each field center, and the University of North Carolina at Chapel Hill. Informed consent was received by all participants or their representatives.

SNP selection, genotyping and linkage disequilibrium (LD) analysis

Four lipids related SNPs (rs2083637, rs17411031, rs13702, and rs2197089) [15–17], and rs320 (common name as *HindIII*) with inconsistent associations with obesity [10,11] were selected as discovery panel tested in BPRHS. Genotyping in BPRHS was performed using the ABI TaqMan SNP genotyping system 7900HT (Applied Biosystems, Foster City, CA). Hardy–Weinberg equilibrium (HWE) was evaluated by Chi-square tests. LD and haplotype was analyzed by HaploView4.2 [18] according to 1000 Genomes Project. Genotypes of replication SNP rs327 in ARIC was imputed by MACH (v1.0.16) [19] with HapMap r22 reference populations, Utah residents with Northern and Western European Ancestry (CEU) and Yoruba in Ibadan, Nigeria (YRI) based on the genome-wide SNP data obtained by the Affymetrix 6.0 chip (Affymetrix, Santa Clara, CA).

Dietary assessment

The BPRHS used a semi-quantitative food frequency questionnaire (FFQ) [20]. The ARIC study used a modified 66-item interviewer-administered FFQ [21]. Dietary fatty acids intake was expressed as a percentage of total energy intake.

Population ancestry admixture

The population admixture of participants in the BPRHS was estimated with reference to three ancestral populations including Native American (15%), Southern European (57%), and West African (27%), and the major principal component estimated by EIGENSTRAT was adjusted in the analysis [22]. The first 10 principal components, estimated using Eigensoft, represent admixture for ARIC EAs. Percentage of European ancestry for ARIC AAs was estimated based on the reference population of CEU using 1350 ancestry informative markers by ANCESTRYMAP [23].

Statistical analysis

Analysis of covariance and general linear models were applied to test genetic associations and interactions between SNPs and different types of dietary fat intake (SFA, MUFA and

PUFA) to modulate body mass index (BMI) and WC, assuming an additive genetic model and adjusting age, admixture, smoking, drinking, total fat intake (interaction test), total energy intake, antilipemic medication, diabetes status, hormone replacement therapy (in women), physical activity, and education. Dietary fat intake was analyzed as both continuous and categorical variables, dichotomized by the population median, for validation. Log transformation was performed when necessary. Data were analyzed using SAS 9.2 (SAS Institute, Inc. Cary, NC). A two-tailed P -value of <0.02 was considered statistically significant, adjusting for three multiple tests introduced by three SNPs reaching HWE. Successful replication was considered when the analysis with the same additive model and covariates resulted in the significant interactions in the same direction across different populations. Inverse-variance weighted fixed-effects meta-analyses were conducted using METAL (University of Michigan; www.sph.umich.edu/csg/abecasis/metal/) to summarize the interactions across populations.

Bioinformatics analysis

Sequences surrounding the candidate SNP with significant interactions were screened via NUBIScan [24], a software evaluated peroxisome proliferator-activated receptors response elements (PPREs), for which fatty acids (especially PUFAs) are the primary ligand.

Results

Population characteristics

Demographic data, anthropometrics, lipids, nutrient intakes, disease status and medication use for both the BPRHS and ARIC are presented by sex (Table 1). Women in the BPRHS and in ARIC AAs were characterized for obesity status, using the cutoff of BMI ≥ 30 kg/m² for obesity and cutoff of WC ≥ 88 cm in women for abdominal obesity. Dietary PUFA contributed 8.5% of energy intake in the BPRHS and 5% in ARIC, and it was similar for men and women within each cohort.

Discovery in BPRHS

Minor allele frequencies (MAF) were greater than 0.25 (Table 2). Rs2083637 and rs17411031 deviated from HWE ($P = 0.03$ and $P = 0.02$) and thus were excluded in the following analysis.

Rs320, rs13702, and rs2197089 were not associated with BMI and WC (Supplementary Table 1). Both categorical PUFA (Supplementary Table 2) and continuous PUFA (Fig. 1) showed significant interaction with rs320 for BMI ($P = 0.02$ and $P = 0.002$, respectively) and WC ($P = 0.02$ and $P = 0.001$, respectively). In homozygotes of the major allele (TT), higher PUFA intake associated with lower BMI ($P = 0.01$) and smaller WC ($P = 0.005$) (Fig. 1). However, in carriers of minor allele (TG and GG), there were no associations ($P > 0.1$) (Fig. 1). Significance and interaction pattern were similar for N6- and N3-PUFA (Supplementary Table 2). Results remained the same after excluding women ($n = 22$) using hormone replacement (Data not shown). No significant interactions were observed in men (Fig. 1 and Supplementary Table 2), for SFA or MUFA, or with rs13702 or rs2197089 (data not shown). Data reported below apply to the single SNP rs320.

Replication in ARIC

Rs327 was selected for replication in ARIC because of its close distance to rs320 (459 bp), the high imputation quality ($R^2 = 1$), and its strong LD with rs320 in CEU, African ancestry in the Southwest USA (ASW), and Mexican ancestry in Los Angeles (MXL) populations in the 1000 Genomes Project ($R^2 > 0.8$) (Fig. 2).

Interaction with continuous PUFA in AA women was significant for WC ($P = 0.01$) and approached significance for BMI ($P = 0.07$). Interactions were not significant in AA men or EAs (Fig. 2), and similar results were with categorical PUFA (Supplementary Fig. 1).

In a meta-analysis of the women from all three populations, rs320/rs327 showed significant interaction with continuous PUFA intake for both BMI ($P = 0.009$) and WC ($P = 0.003$) (Fig. 2). However, interaction P values were even lower when the meta-analysis included only two women population, BPRHS and ARIC AAs ($P = 0.001$ for BMI and $P = 4 \times 10^{-5}$ for WC). The betas for the interaction term were consistently negative in three populations. There were no interactions in men (Fig. 2). Analysis with categorical PUFA exhibited similar results (Supplementary Fig. 1).

Bioinformatics analysis

There was a PPRE approximately 14 kb downstream of rs320 (Fig. 3).

Discussion

In the current study, we identified and replicated significant interactions between dietary PUFA intake and *LPL* rs320 for obesity traits in women. In the homozygosity for the major allele (TT), increase in PUFA intake associated with lower BMI and WC. Our observed gene–diet interaction may have improved our ability to detect dietary effects that are apparent only under certain genotype.

Genetic modulation of dietary associations has been suggested by the studies for plasma lipids [25,26]. TT group showed greater improvement in plasma lipids with calorie restriction intervention [25]. Our group also found that TT genotype had a greater postprandial lipidemia response following an oral fat load [26]. These may suggest that T-carriers are more responsive to diet than G-carriers, which is consistent with our findings for PUFA intake. Considering the existence of the PPRE near rs320, we hypothesize that the apparently greater responsiveness of T allele to PUFA may involve the higher binding affinity to the transcription factor of this allele compared to G allele [27]. The anti-obesity effects of PUFA found are consistent with previous studies [28], which may be related to decreased adipocyte LPL activity [29], reduced triglyceride storage and less fat deposition.

Our sex-specific finding is consistent with previous study [7], and may be due to the sex-specific *LPL* response. *LPL* expression in muscle was 160% higher in women than men [6]. Our finding of null genetic association with obesity is consistent with a US study [11] not a French one [10], which may further support our hypothesis of gene–diet interaction due to potential differences in dietary pattern.

Limitations include the cross-sectional design and the absence of adipose LPL expression measurement. The variable ancestral admixtures and high prevalence of obesity in both minority populations (BPRHS and ARIC AAs) restricted our study from drawing conclusions about the relative contributions of genetic background, behavioral and socio-economic factors to the observed interactions. As our results are preliminary, additional studies are desirable.

In summary, we detected a significant interaction between *LPL* rs320 and dietary PUFA for obesity-related outcomes in women, and these findings were strengthened by replication in a second, independent population. Our observations may be relevant to the nutritional management of obesity in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

LPL	lipoprotein lipase
SNP	single nucleotide polymorphism
SFA	saturated fatty acids
MUFA	monounsaturated fatty acids
PUFA	polyunsaturated fatty acids
BPRHS	Boston Puerto Rican Health Study
ARIC	Atherosclerosis Risk in Communities Study
AA	African American
EA	European American

WC	waist circumference
HDL	high density lipoprotein
LD	linkage disequilibrium
HWE	Hardy–Weinberg Equilibrium
CEU	Utah residents with Northern and Western European Ancestry
YRI	Yoruba in Ibadan, Nigeria
FFQ	food frequency questionnaire
BMI	body mass index
PPRE	peroxisome proliferator-activated receptors response element
MAF	minor allele frequency
ASW	African ancestry in Southwest USA
MXL	Mexican ancestry in Los Angeles
LDL	low density lipoprotein
UTR	untranslated region
TSS	transcription start site

References

- [1]. Flegal KM, Carroll MD, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *J Am Med Assoc.* 2012; 307(5):491–7.
- [2]. Zhang H, Rodriguez-Monguió R. Racial disparities in the risk of developing obesity-related diseases: a cross-sectional study. *Ethn Dis.* 2012; 22(3):308–16. [PubMed: 22870574]
- [3]. Cheng CY, Reich D, Coresh J, Boerwinkle E, Patterson N, Li M, et al. Admixture mapping of obesity-related traits in African Americans: the Atherosclerosis Risk in Communities (ARIC) Study. *Obes (Silver Spring).* 2010; 18(3):563–72.
- [4]. Moussavi N, Gavino V, Receveur O. Could the quality of dietary fat, and not just its quantity, be related to risk of obesity? *Obes (Silver Spring).* 2008; 16(1):7–15.
- [5]. Kirby JB, Liang L, Chen HJ, Wang Y. Race, place, and obesity: the complex relationships among community racial/ethnic composition, individual race/ethnicity, and obesity in the United States. *Am J Public Health.* 2012; 102(8):1572–8. [PubMed: 22698012]
- [6]. Kiens B, Roepstorff C, Glatz JF, Bonen A, Schjerling P, Knudsen J, et al. Lipid-binding proteins and lipoprotein lipase activity in human skeletal muscle: influence of physical activity and gender. *J Appl Physiol.* 2004; 97(4):1209–18. [PubMed: 15155715]
- [7]. Corella D, Guillen M, Portoles O, Sorli JV, Alonso V, Folch J, et al. Gender specific associations of the Trp64Arg mutation in the beta3-adrenergic receptor gene with obesity-related phenotypes in a Mediterranean population: interaction with a common lipo-protein lipase gene variation. *J Intern Med.* 2001; 250(4):348–60. [PubMed: 11576322]
- [8]. Gonzales AM, Orlando RA. Role of adipocyte-derived lipoprotein lipase in adipocyte hypertrophy. *Nutr Metab (Lond).* 2007; 4:22. [PubMed: 17971230]
- [9]. Kusunoki M, Tsutsumi K, Iwata K, Yin W, Nakamura T, Ogawa H, et al. NO-1886 (ibrolipim), a lipoprotein lipase activator, increases the expression of uncoupling protein 3 in skeletal muscle and suppresses fat accumulation in high-fat diet-induced obesity in rats. *Metabolism.* 2005; 54(12):1587–92. [PubMed: 16311090]

- [10]. Jemaa R, Tuzet S, Portos C, Betoulle D, Apfelbaum M, Fumeron F. Lipoprotein lipase gene polymorphisms: associations with hypertriglyceridemia and body mass index in obese people. *Int J Obes Relat Metab Disord*. 1995; 19(4):270–4. [PubMed: 7627251]
- [11]. Nicklas BJ, Ferrell RE, Rogus EM, Berman DM, Ryan AS, Dennis KE, et al. Lipoprotein lipase gene variation is associated with adipose tissue lipoprotein lipase activity, and lipoprotein lipid and glucose concentrations in overweight postmenopausal women. *Hum Genet*. 2000; 106(4): 420–4. [PubMed: 10830909]
- [12]. Tucker KL, Mattei J, Noel SE, Collado BM, Mendez J, Nelson J, et al. The Boston Puerto Rican Health Study, a longitudinal cohort study on health disparities in Puerto Rican adults: challenges and opportunities. *BMC Public Health*. 2010; 10:107. [PubMed: 20193082]
- [13]. Monda KL, Ballantyne CM, North KE. Longitudinal impact of physical activity on lipid profiles in middle-aged adults: the Atherosclerosis Risk in Communities Study. *J Lipid Res*. 2009; 50(8): 1685–91. [PubMed: 19346332]
- [14]. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989; 129(4):687–702. [PubMed: 2646917]
- [15]. Aulchenko YS, Ripatti S, Lindqvist K, Boomsma D, Heid IM, Pramstaller PP, et al. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. *Nat Genet*. 2009; 41(1):47–55. [PubMed: 19060911]
- [16]. Wallace C, Newhouse SJ, Braund P, Zhang F, Tobin M, Falchi M, et al. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. *Am J Hum Genet*. 2008; 82(1):139–49. [PubMed: 18179892]
- [17]. Deo RC, Reich D, Tandon A, Akyzbekova E, Patterson N, Waliszewska A, et al. Genetic differences between the determinants of lipid profile phenotypes in African and European Americans: the Jackson Heart Study. *PLoS Genet*. 2009; 5(1):e1000342. [PubMed: 19148283]
- [18]. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005; 21(2):263–5. [PubMed: 15297300]
- [19]. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 34(8):816–834. [PubMed: 21058334]
- [20]. Tucker KL, Bianchi LA, Maras J, Bermudez OI. Adaptation of a food frequency questionnaire to assess diets of Puerto Rican and non-Hispanic adults. *Am J Epidemiol*. 1998; 148(5):507–18. [PubMed: 9737563]
- [21]. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr*. 1999; 69(2):243–9. [PubMed: 9989687]
- [22]. Lai CQ, Tucker KL, Choudhry S, Parnell LD, Mattei J, Garcia-Bailo B, et al. Population admixture associated with disease prevalence in the Boston Puerto Rican health study. *Hum Genet*. 2009; 125(2):199–209. [PubMed: 19107526]
- [23]. Patterson N, Hattangadi N, Lane B, Lohmueller KE, Hafler DA, Oksenberg JR, et al. Methods for high-density admixture mapping of disease genes. *Am J Hum Genet*. 2004; 74(5):979–1000. [PubMed: 15088269]
- [24]. Podvinec M, Kaufmann MR, Handschin C, Meyer UA. NUBIScan, an in silico approach for prediction of nuclear receptor response elements. *Mol Endocrinol*. 2002; 16(6):1269–79. [PubMed: 12040014]
- [25]. Jemaa R, Tuzet S, Betoulle D, Apfelbaum M, Fumeron F. Hind III polymorphism of the lipoprotein lipase gene and plasma lipid response to low calorie diet. *Int J Obes Relat Metab Disord*. 1997; 21(4):280–3. [PubMed: 9130024]
- [26]. Lopez-Miranda J, Cruz G, Gomez P, Marin C, Paz E, Perez-Martinez P, et al. The influence of lipoprotein lipase gene variation on postprandial lipoprotein metabolism. *J Clin Endocrinol Metab*. 2004; 89(9):4721–8. [PubMed: 15356086]
- [27]. Chen Q, Razzaqhi H, Demirci FY, Kamboh MI. Functional significance of lipoprotein lipase HindIII polymorphism associated with the risk of coronary artery disease. *Atherosclerosis*. 2008; 200(1):102–8. [PubMed: 18242618]

- [28]. Whigham LD, Watras AC, Schoeller DA. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. *Am J Clin Nutr.* 2007; 85(5):1203–11. [PubMed: 17490954]
- [29]. Baltzell JK, Wooten JT, Otto DA. Lipoprotein lipase in rats fed fish oil: apparent relationship to plasma insulin levels. *Lipids.* 1991; 26(4):289–94. [PubMed: 1865765]

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Figure 1. Discovery of continuous interaction between rs320 and dietary PUFA intake for obesity traits in the BPRHS, by sex

Predicted BMI (A for women, B for men) and WC (C for women, D for men) by rs320 genotype were plotted against continuous dietary PUFA adjusted for age, admixture, smoking, drinking, total energy intake, total fat intake, diabetes status, antilipemic medication, hormone replacement therapy in women, physical activity, and education. *P* values indicate the statistical significance of the adjusted interaction term and adjusted regression coefficients in the regression line corresponding to three genotype groups of rs320 (TT, TG, and GG).

Figure 2. Replication and meta-analysis of continuous interaction between rs320/rs327 and dietary PUFA intake for obesity traits by sex

LD correlation ($100 \times R^2$ value in diamond), haplotypes and corresponding frequencies of rs320 and replication SNP rs327 in 1000 Genomes CEU (A), ASW (B) and MXL (C) are presented. Forest plots of this continuous interactions modulating BMI (left) and WC (right) in women (D) and men (E) are presented. The estimates represent the difference in the magnitude of the PUFA association (per +1-unit intake of PUFA) with BMI or WC per copy of the T allele of rs320/rs327, adjusting for age, admixture, smoking, drinking, total energy intake, total fat intake, diabetes status, antilipemic medication, hormone replacement therapy in women, physical activity, and education. Filled square and horizontal line represent the estimate and 95% CI for each population, and the filled diamond represent the summary estimate and its 95% CI.

Figure 3. Genomic structure of *LPL* locus

The gene is transcribed as indicated by the large horizontal arrow. Exons are the larger rectangular black boxes.

Table 1Participant characteristics in the BPRHS and ARIC, by sex.^a

	Discovery		Replication			
	BPRHS		ARIC African American		ARIC European American	
	Men (n = 333)	Women (n = 838)	Men (n = 852)	Women (n = 1334)	Men (n = 4170)	Women (n = 4519)
General characteristics						
Age, year	57 (8)	58 (7)	53.92 (6)	53.2 (6)	54.66 (6)	53.9 (6)
Current smoker, <i>n</i>	111 (33%)	172 (21%)	310 (36%)	335 (25%)	1009 (24%)	1142 (25%)
Current drinker, <i>n</i>	158 (47%)	290 (35%)	423(50%)	280 (21%)	2961 (71%)	2818 (62%)
Anthropometric measures						
BMI, kg/m ²	29.6 (5.1)	32.9 (7.0)	28 (4.8)	30.7 (6.6)	27.4 (4.0)	26.5 (5.4)
WC, cm	102 (15)	102 (16)	98 (13)	100 (16)	100 (10)	93 (15)
Lipids						
Triglycerides, mmol/l	1.66 (1.77)	1.55 (1.63)	1.4 (1.25)	1.24 (0.74)	1.66 (1.13)	1.45 (0.93)
Total cholesterol, mmol/l	4.47 (1.14)	4.87 (1.05)	5.47 (1.11)	5.62 (1.16)	5.45 (0.99)	5.64 (1.1)
HDL cholesterol, mmol/l	1.03 (0.31)	1.21 (0.31)	1.29 (0.42)	1.5 (0.44)	1.11 (0.32)	1.49 (0.44)
LDL cholesterol, mmol/l	2.57 (0.91)	2.86 (0.89)	3.57 (1.06)	3.57 (1.13)	3.61 (0.91)	3.49 (1.02)
Dietary Intake						
Total energy, kcal/d	2483 (883)	2044 (875)	1732 (657)	1514 (569)	1799 (652)	1515 (522)
Carbohydrate, % total energy/d	48.9 (7.5)	51.5 (7.7)	48.5 (9.1)	50.5 (9.6)	47.3 (9.1)	49.5 (9.3)
Protein, % total energy/d	16.8 (2.9)	17.2 (3.5)	17.2 (3.9)	18.7 (4.5)	17.1 (3.7)	18.5 (4.2)
Total fat, % total energy/d	32.9 (5.7)	31.7 (5.5)	32.0 (6.3)	32.1 (6.5)	33.6 (6.8)	32.8 (6.8)
SFA, % total energy/d	10.1 (2.5)	9.6 (2.3)	11.4 (2.7)	11.4 (2.7)	12.4 (3.0)	12.1 (3.1)
MUFA, % total energy/d	11.4 (2.1)	11.0 (2.1)	12.6 (2.8)	12.5 (2.9)	13.0 (3.0)	12.4 (3.0)
PUFA, % total energy/d	8.6 (2.0)	8.5 (2.0)	4.7 (1.2)	4.9 (1.3)	5.1 (1.5)	5.1 (1.5)
Cholesterol, mg/d	377 (191)	283 (162)	312 (162)	250 (124)	269 (139)	223 (104)
Disease and medication						
Have diabetes, <i>n</i>	137 (41%)	331 (40%)	156 (18%)	256 (19%)	405 (10%)	334 (7%)
Take antilipemic medication, <i>n</i>	133 (40%)	343 (41%)	6 (1%)	7 (1%)	84 (2%)	87 (2%)
Take anti-depressants, <i>n</i>	84 (25%)	323 (39%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Take hormone replacement therapy in women, <i>n</i>	0 (0%)	22 (3%)	0 (0%)	211(16%)	0 (0%)	984 (22%)

^aData are means (standard deviation) or *n* (%).

Table 2Minor allele frequency (MAF) of *LPL* SNPs in the BPRHS.^a

		Men	Women	<i>P</i> ^b
rs320	MAF	0.29	0.27	0.08
	TT	154	418	
	TG	135	332	
	GG	22	50	
rs2083637	MAF	0.28	0.24	0.03
	AA	166	454	
	AG	131	334	
	GG	25	32	
rs17411031	MAF	0.28	0.24	0.02
	CC	162	446	
	CG	130	332	
	GG	24	31	
rs13702	MAF	0.36	0.35	0.7
	TT	125	334	
	TC	142	370	
	CC	41	93	
rs2197089	MAF	0.39	0.41	0.25
	AA	123	286	
	AG	149	390	
	GG	50	140	

^aData are *n*.^b*P*: *P* value for HWE testing.