Published in final edited form as:

Nutr Metab Cardiovasc Dis. 2012 May ; 22(5): 449–455. doi:10.1016/j.numecd.2010.09.003.

Perilipin polymorphism interacts with saturated fat and carbohydrates to modulate insulin resistance^{1,2}

Caren E. Smith³, Donna K. Arnett⁴, Dolores Corella⁵, Michael Y. Tsai⁶, Chao-Qiang Lai³, Laurence D. Parnell³, Yu-Chi Lee³, and José M. Ordovás³

³Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA

⁴Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama

⁵Genetic and Molecular Epidemiology Unit, School of Medicine, University of Valencia, Valencia, Spain

⁶Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

Abstract

Macronutrient intakes and genetic variants have been shown to interact to alter the risk of insulin resistance, but replication of gene-nutrient interactions across independent populations may be difficult to achieve. Saturated fat and carbohydrate were previously shown to interact with genotype for insulin resistance for a variant of perilipin (*PLIN*), the major adipocyte-associated protein and a regulator of adipocyte metabolism. We investigated the same interaction for *PLIN* 11482G>A (rs894160) on insulin resistance in US men (n=462) and women (n=508) (mean $\pm$ SD, 49 $\pm$ 16 years). In multivariate linear regression models, we found a significant ($P<0.05$) interaction between the ratio of saturated fat to carbohydrate intake as a continuous variable and *PLIN* 11482G>A for HOMA-IR (homeostasis model assessment of insulin resistance) in women. For carriers of the minor allele but not for non-carriers, as the ratio of saturated fat to carbohydrate intake increased, predicted HOMA-IR increased significantly ($P=0.002$). By dichotomizing the ratio of saturated fat to carbohydrate intake into high and low, we found significant interaction terms for insulin and HOMA-IR ($P<0.05$). When the ratio of saturated fat to carbohydrate was high, insulin and HOMA-IR were higher in minor allele carriers ($P=0.004$ and $P=0.003$, respectively), but did not differ when the ratio was low. Similar patterns or trends were observed when saturated fat and carbohydrate were dichotomized into high and low as individual macronutrients. Replication of the previously reported interaction between macronutrient intakes and *PLIN* genotype for insulin resistance reinforces the potential usefulness of applying genotype information in the dietary management of insulin resistance.

¹Supported by the National Institutes of Health, National Institute on Aging, Grant Number 5P01AG023394-02 and NIH/NHLBI grant number HL54776 and NIH/NIDDK DK075030 and contracts 53-K06-5-10 and 58-1950-9-001 from the U.S. Department of Agriculture Research Service. C. E. Smith is supported by T32 DK007651-19.

²Author disclosures: C. E. Smith, D. K. Arnett, D. Corella, M. Y. Tsai, C. Q. Lai, L. D. Parnell, Y. C. Lee, J. M. Ordovás, have no conflicts of interest.

Correspondence to José M. Ordovás, PhD, Nutrition and Genomics Laboratory Jean Mayer USDA HNRCA at Tufts University, 711 Washington St., Boston, MA 02111-1524. jose.ordovas@tufts.edu.

Statement of Authors' Contributions to Manuscript: CES analyzed the data and drafted the manuscript, DKA, MYT, JMO and DC designed the research project, CQL and LDP provided computer informatics and technical support, and YCL performed the genotyping.

Introduction

The prevalence of insulin resistance is growing globally in conjunction with increased obesity prevalence (1) and a sedentary lifestyle (2), but glucose metabolism may also be modified by dietary macronutrients. The role of fat quantity and specific types of fatty acids (eg, saturated, monounsaturated (MUFA), omega-3) in modulating glucose metabolism has been extensively explored, often in the context of obesity and metabolic syndrome (3-7). However, high fat meals have been shown to alter insulin concentration and insulin sensitivity even in healthy individuals with normal glucose and lipid metabolism (4,7). Saturated fat, whether supplied through the diet (6) or as a component of lipid infusion (8) may be particularly detrimental to glucose metabolism, at least in overweight individuals (9).

While the evidence for a role of saturated fat in glucose metabolism is strong, results are not conclusive. In some studies, polyunsaturated and omega-3 fatty acids (10) or MUFA appear to play a larger role (3,4). These inconsistencies may be related to macronutrient substitutions and displacement among various fatty acid types. Alternatively, genetic variation in regulators of lipid metabolism is another potential source of variability in sensitivity of glucose metabolism to particular fatty acids.

One such metabolic regulator is perilipin, the most abundant protein surrounding the triglyceride droplet in adipocytes, where it regulates adipocyte metabolism and lipolysis (11). Perilipin interacts with hormone sensitive lipase to facilitate lipolysis of triglyceride, but also acts as barrier to inhibit triglyceride hydrolysis by preventing lipase access (12,13). One particular common variant, *PLIN* 11482G>A, has been extensively investigated and has been associated with altered adipocyte perilipin content, altered lipolysis rates and differences in plasma free fatty acid concentrations following weight loss (11,14). Although established primarily as a modifier of obesity risk (15-17), the same *PLIN* single nucleotide polymorphism (SNP) 11482G>A was also shown to modulate susceptibility to insulin resistance (18). Specifically, the relationship between the 11482G>A variant and insulin resistance was observed in the context of high saturated fat/low carbohydrate intake, suggesting that *PLIN* genotype could be a potential source of variability in the response of glucose metabolism to dietary macronutrients.

While evidence relating *PLIN* variants to obesity has accumulated from studies in several independent populations, relationships between *PLIN*, macronutrient intake and insulin resistance have been reported in a single, although large and multi-ethnic, study of Asians in Singapore. As a result of highly variable environmental factors and variable genetic backgrounds among global populations, genetic associations and gene-diet interactions can be difficult to replicate, although repeatability is considered critical to establishing scientific credibility. Therefore, in the current study, we examined associations between *PLIN* 11482G>A and insulin resistance, and potential interactions with saturated fat and carbohydrate intake in a White population living in the US.

Methods

Study Design and Subjects

Study subjects were recruited from the ongoing National Heart Lung and Blood Institute Family Heart Study (19) to participate in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study. The GOLDN study was designed to evaluate genetic factors that modulate dietary and fenofibrate responses, and its methods have been previously described (20). Study sites were located in Minnesota and Utah and the predominantly White subjects were genetically similar. Study protocol approval was obtained from the Human Studies

Committee of Institutional Review Board at the University of Minnesota, University of Utah, and Tufts Medical Center. All participants provided written informed consent. Questionnaires were used to collect demographic, lifestyle, medical history, medication and dietary data. Individuals taking insulin but not other anti-glycemic medications were excluded from the study.

Laboratory methods

Laboratory methods have been previously described in detail (20). Insulin resistance (fasting glucose $\times$ fasting insulin/22.5) was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) method.

Dietary intake

Dietary intake was estimated by use of the Diet History Questionnaire, a food frequency questionnaire that consists of 124 food items and includes both portion size and dietary supplement questions. The food list and nutrient database used with the Diet History Questionnaire are based on national dietary data [USDA 1994–96 Continuing Survey of Food Intakes by Individuals, available from the USDA Food Surveys Research]. Subjects with daily energy intake outside the range of 800–5500 kcal in men and 600–4800 kcal in women were excluded from analysis.

Genetic analysis

Genomic DNA was isolated from peripheral blood lymphocytes by standard methods. Perilipin SNP 11482G>A (rs894160) was genotyped using the ABI TaqMan SNP genotyping system 7900HT (Applied Biosystems, Foster City, California).

Statistical Analyses

All continuous variables were examined for normal distribution. Plasma glucose, plasma insulin and HOMA-IR were logarithmically transformed to improve normality. The relationship between *PLIN* genotype, dietary intakes and biochemical measures was evaluated by analysis of variance techniques. We used the generalized estimating equation approach with exchangeable correlation structure implemented in the SAS GENMOD procedure to adjust for familial relationships. Interactions between dietary macronutrient (saturated fat and carbohydrate) and the polymorphism were tested in a multivariate interaction model with control for potential confounders including age, alcohol, smoking, anti-glycemic medications, and waist circumference. Intakes of saturated fat, carbohydrate and the ratio between the two macronutrients were expressed as percentages of total energy intake and were included in analyses as categorical variables. To construct categorical variables, intakes were classified into two groups according to the median intake of the population. Saturated fat intake was also assessed according to tertiles of intake. The ratio of saturated fat to carbohydrate intake, each as percent of total energy intake, was evaluated as a continuous variable by computing predicted values for each subject from the adjusted regression model and plotting those predicted values against saturated fat: carbohydrate ratio depending on the *PLIN* genotype. Genotype effects were analyzed in the entire population and also separately in men and women. SAS (Version 9.1 for Windows) was used to analyze data. A *P* value of 0.05 was considered statistically significant.

Results

Demographic, biochemical, anthropometric, dietary and genotypic data are presented for men and women (Table 1). Saturated fat intake was strongly positively correlated with MUFA intake and negatively correlated with carbohydrate intake. Minor allele frequency

for *PLIN* 11482G>A was 0.29. Genotype frequency in unrelated subjects did not deviate from Hardy-Weinberg equilibrium expectations. No significant associations between glucose-related measures (glucose, insulin, or HOMA-IR) or BMI were observed for *PLIN* SNP 11482G>A (Table 2). Interactions between dietary intakes and *PLIN* 11482G>A were examined by dichotomizing macronutrients according to the median population intakes and evaluating their associations with measures of glucose metabolism and BMI (Table 3). A dominant genetic model was observed and homozygotes (TT) and heterozygotes (CT) of the minor allele (T) for *PLIN* were combined and compared to homozygous major subjects (CC) to increase statistical power. Dietary interactions were evaluated in the entire population and separately by gender. Multivariate adjustments for potential confounders included age, waist circumference, gender, smoking, alcohol, family relationships and anti-glycemic medications. We did not find significant interactions between *PLIN* and glucose-related measures or BMI in the population as a whole or in men. Results reported below pertain to *PLIN* 11482G>A evaluated only in women.

Saturated fat and carbohydrates were each dichotomized based on median intake of percent of daily energy into high levels (≥11.5 for saturated fat and ≥50.5 for carbohydrate) and low levels (<11.5 for saturated fat and <50.5 for carbohydrate). A tendency for significant interaction between carbohydrate and *PLIN* genotype was obtained for insulin ($P=0.084$) (Table 3). Insulin and HOMA-IR were higher in minor allele carriers ($P=0.021$ and $P=0.041$, respectively) with low carbohydrate intake, but did not differ when carbohydrate intake was high. Glucose and BMI did not differ by genotype under conditions of low or high carbohydrate intake.

Interaction terms for dichotomized saturated fat and genotype did not reach significance, however when tertiles of saturated fat were evaluated for interaction with genotype, significant interaction terms were obtained for insulin ($P=0.006$) and for HOMA-IR ($P=0.007$; data not shown). When saturated fat was dichotomized according to the population median intake for women (11.5), insulin and HOMA-IR were higher in minor allele carriers ($P=0.027$ and $P=0.036$, respectively) with high saturated fat intake, but did not differ when saturated fat was low. Glucose and BMI did not differ by genotype under conditions of low or high saturated fat.

We next examined interactions between genotype and the ratio of saturated fat to carbohydrate intake, dichotomized into high and low based on the population median ratio of 0.23. Significant interaction terms for the ratio were obtained for insulin ($P=0.025$) and HOMA-IR ($P=0.031$). When differences associated with genotype were examined at low (<0.23) or high (≥0.23) levels of the ratio of saturated fat to carbohydrate, insulin and HOMA-IR were higher in minor allele carriers ($P=0.004$ and $P=0.003$, respectively) with a high ratio, but did not differ when the ratio was low. As for individual macronutrients, glucose and BMI did not differ by genotype under conditions of low or high ratio of saturated fat to carbohydrate.

We also examined interactions between the ratio of saturated fat to carbohydrate intake as a continuous variable and *PLIN* 11482G>A on HOMA-IR. Predicted values for HOMA-IR are plotted against the ratio for carriers and non-carriers of the minor allele for *PLIN* 11482G>A in Figure 1. A significant interaction term between genotype and the ratio was obtained ($P=0.042$). For carriers of the minor allele but not for non-carriers, as the ratio of saturated fat to carbohydrate intake increased, predicted HOMA-IR increased significantly ($P=0.002$).

Discussion

We have replicated a significant interaction between *PLIN* 11482G>A polymorphism and dietary intake of saturated fat and carbohydrate, which was most apparent when these macronutrients were considered as a ratio. In the current study, responses to saturated fat and carbohydrate for *PLIN* minor allele carriers were in opposite directions such that higher saturated fat intake was associated with higher insulin resistance, and lower carbohydrate was associated with higher insulin resistance. These associations between a *PLIN* polymorphism and insulin resistance were not apparent when the population was considered in its entirety, independently of macronutrient intake, and were observed only in women.

Our results are consistent with those obtained from a previous study of *PLIN* in Chinese, Malay, and Asian Indian women living in Singapore, (18) but several differences are evident. Interactions in the previous study (n=2198) are stronger than in the current study (n=508), which is probably due to the greater statistical power of that study. The previous study evaluated a recessive genetic model, in which carriers of two copies of the minor allele were compared to the other two genotypes. MAF for the Singapore groups ranged from 0.34 to 0.45, which is higher than the 0.29 observed in the current population. The greater MAF combined with the greater number of subjects in the Singapore study ensured that a sufficient number of homozygous minor subjects were available for comparison to the other genotypes. Differences in the Singapore and US diets may have also influenced the nutrient thresholds at which genotype-associated differences were seen. For example, the previous study used tertiles rather than dichotomized groups for reporting interactions for individual macronutrients. However, the threshold for the highest tertile of saturated fat in the Asian population (11.8%) is very close to the median value used to define low and high intakes in the US GOLDN population (11.5%). Differences were larger for carbohydrate in which the upper limit for the lowest tertile in Asians (56.3%) is greater than the dichotomized (median) carbohydrate intake in the GOLDN women (50.4%). These differences between the populations illustrate a few of the complexities inherent in attempting gene-diet interaction replications. Variations in genetic background and linkage disequilibrium patterns between different ethnic and racial groups may further alter gene-nutrient relationships.

In addition to the Singapore study in which saturated fat and carbohydrate appeared to interact with *PLIN* 11482G>A, two other studies have presented evidence of carbohydrate modulation of *PLIN* 11482G>A genotype associated differences. Variation at the *PLIN* 11482G>A locus modulated weight loss in an energy-restricted and low carbohydrate (40% of total energy) intervention, in which *PLIN* 11482G>A minor allele carriers were resistant to weight loss compared to non-carriers (17). In another population composed predominantly of women (664 women in a total of 920 subjects), complex carbohydrate differentially modified obesity measures, depending on *PLIN* 11482G>A genotype (21). In that study, carriers of the minor allele consuming a high intake of complex carbohydrate were less likely to be obese than minor allele carriers consuming low complex carbohydrate intake. Taken together, these studies demonstrated that lower carbohydrate intake and/or higher saturated fat intake were associated with adverse metabolic consequences in those individuals carrying the minor *PLIN* allele for the 11482G>A SNP. Our results are also consistent with previous studies in that we observed the gene-nutrient interaction only in women. For example, Qi et. al. reported a gene-gender interaction with *PLIN* 11482G>A in whites in which obesity risk was limited to women (15).

The established relationships between *PLIN* genotype and obesity (15-17), and obesity and insulin resistance led us to question whether nutrient modulation of *PLIN*-associated obesity might mediate the effects of *PLIN* genotype on insulin resistance observed in the current

study. We did not observe a relationship between *PLIN* and BMI, with or without macronutrient interaction, suggesting that obesity is not the primary mediator of *PLIN*-associated insulin resistance in this population. However, in a previous study evaluating central obesity and diabetes risk, the *PLIN* 11482G>A minor allele was associated with increased risk of diabetes only in non-centrally obese individuals, implying that *PLIN* association with increased diabetes risk is modulated by central obesity (22). The high prevalence of central obesity in women in the current study (61%) may have increased the likelihood of detecting a relationship between *PLIN* genotype and insulin resistance.

We are limited in our ability to elucidate mechanisms for the observed effects, or to ascertain which nutrient (saturated fat or carbohydrate) may be of greater importance in modulating insulin resistance. Displacement of one nutrient by another is likely, as suggested by the strong inverse relationship between saturated fat and carbohydrate intakes. Relationships to other fatty acids, including MUFA, which are the greatest source of fats in our population (12.9%), are also unclear. Recent interventions suggest that MUFA intake may be protective for glucose metabolism. For example, a weight loss diet high in MUFA improved glucose metabolism more effectively than a low fat diet, an effect unrelated to the degree of weight regain associated with a given diet (23). Results from a study of post-prandial metabolism confirm the deleterious effects of saturated fatty acids on glucose metabolism, but demonstrate improved glucose metabolism in association with intake of MUFA (4). The strong correlation between MUFA and saturated fatty acids in the current study precludes the possibility of evaluating MUFA independently of saturated fatty acids.

Although we cannot effectively evaluate MUFA apart from saturated fatty acids, *in vitro* studies using adipocyte and myotubes have demonstrated inhibition of insulin signaling by long chain saturated fatty acids, which supports a role for saturated fatty acids in mediating insulin resistance (24,25). Another group demonstrated that incubation of skeletal muscle cells with the monounsaturated fatty acid oleate in addition to the 16-carbon saturated fatty acid palmitate prevented the insulin resistance related to impaired insulin signaling typically associated with saturated fatty acids (26). Saturated fatty acids may also interact functionally with perilipin protein. Incubation of adipocytes with palmitate induced the release of perilipin from adipocytes, reduced lipolysis, and interfered with the translocation of hormone-sensitive lipase and perilipin to and from the lipid droplet (27,28). Translation from these cell-based studies to physiologic regulation in the whole organism is not yet possible, but these observations do support potential mechanistic links between saturated fat, perilipin function, and insulin resistance.

In summary, we have replicated a gene-nutrient interaction for *PLIN* 11482 G>A and the ratio of saturated fat: carbohydrate intake on insulin resistance in an independent population of White women living in the US Midwest. Similar results were previously demonstrated in Chinese, Malay and Asian Indian women living in Singapore, in spite of differences in diet, genetic background and prevalence of obesity between these populations. The reproducibility of these results increases the plausibility that perilipin is a mediator of the relationship between nutrients and insulin resistance, and reinforces the potential usefulness of applying genotype information to create targeted nutritional advice.

Literature Cited

1. Nguyen NT, Magno CP, Lane KT, Hinojosa MW, Lane JS. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. *J Am Coll Surg*. 2008; 207(6):928–34. [PubMed: 19183541]
2. Pan Y, Pratt CA. Metabolic syndrome and its association with diet and physical activity in US adolescents. *J Am Diet Assoc*. 2008; 108(2):276–86. [PubMed: 18237576]

3. Due A, Larsen TM, Hermansen K, Stender S, Holst JJ, Toubro S, Martinussen T, Astrup A. Comparison of the effects on insulin resistance and glucose tolerance of 6-mo high-monounsaturated-fat, low-fat, and control diets. *Am J Clin Nutr.* 2008; 87(4):855–62. [PubMed: 18400707]
4. Lopez S, Bermudez B, Pacheco YM, Villar J, Abia R, Muriana FJ. Distinctive postprandial modulation of beta cell function and insulin sensitivity by dietary fats: monounsaturated compared with saturated fatty acids. *Am J Clin Nutr.* 2008; 88(3):638–44. [PubMed: 18779278]
5. Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, Quignard-Boulangé A, Vidal H, Slama G, et al. Treatment for 2 mo with n–3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. *Am J Clin Nutr.* 2007; 86:1670–1679. [PubMed: 18065585]
6. Lovejoy JC, Champagne CM, Smith SR, DeLany JP, Bray GA, Lefevre M, Denkins YM, Rood JC. Relationship of dietary fat and serum cholesterol ester and phospholipid fatty acids to markers of insulin resistance in men and women with a range of glucose tolerance. *Metabolism.* 2001; 50(1): 86–92. [PubMed: 11172480]
7. Mayer EJ, Newman B, Quesenberry CP Jr, Selby JV. Usual dietary fat intake and insulin concentrations in healthy women twins. *Diabetes Care.* 1993; 16(11):1459–69. [PubMed: 8299435]
8. Stefan N, Wahl HG, Fritsche A, Haring H, Stumvoll M. Effect of the pattern of elevated free fatty acids on insulin sensitivity and insulin secretion in healthy humans. *Horm Metab Res.* 2001; 33(7): 432–8. [PubMed: 11507682]
9. Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J, Bray GA. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care.* 2002; 25(8):1283–8. [PubMed: 12145222]
10. Warensjo E, Sundstrom J, Lind L, Vessby B. Factor analysis of fatty acids in serum lipids as a measure of dietary fat quality in relation to the metabolic syndrome in men. *Am J Clin Nutr.* 2006; 84(2):442–8. [PubMed: 16895896]
11. Mottagui-Tabar S, Ryden M, Lofgren P, Faulds G, Hoffstedt J, Brookes AJ, Andersson I, Arner P. Evidence for an important role of perilipin in the regulation of human adipocyte lipolysis. *Diabetologia.* 2003; 46(6):789–97. [PubMed: 12802495]
12. Brasaemle DL, Rubin B, Harten IA, Gruia-Gray J, Kimmel AR, Londos C. Perilipin A increases triacylglycerol storage by decreasing the rate of triacylglycerol hydrolysis. *J Biol Chem.* 2000; 275(49):38486–93. [PubMed: 10948207]
13. Miyoshi H, Souza SC, Zhang HH, Strissel KJ, Christoffolete MA, Kovsan J, Rudich A, Kraemer FB, Bianco AC, et al. Perilipin promotes hormone-sensitive lipase-mediated adipocyte lipolysis via phosphorylation-dependent and -independent mechanisms. *J Biol Chem.* 2006; 281(23): 15837–44. [PubMed: 16595669]
14. Jang Y, Kim OY, Lee JH, Koh SJ, Chae JS, Kim JY, Park S, Cho H, Lee JE, Ordovas JM. Genetic variation at the perilipin locus is associated with changes in serum free fatty acids and abdominal fat following mild weight loss. *Int J Obes (Lond).* 2006; 30(11):1601–8. [PubMed: 16585946]
15. Qi L, Corella D, Sorli JV, Portoles O, Shen H, Coltell O, Godoy D, Greenberg AS, Ordovas JM. Genetic variation at the perilipin (PLIN) locus is associated with obesity-related phenotypes in White women. *Clin Genet.* 2004; 66(4):299–310. [PubMed: 15355432]
16. Qi L, Tai ES, Tan CE, Shen H, Chew SK, Greenberg AS, Corella D, Ordovas JM. Intragenic linkage disequilibrium structure of the human perilipin gene (PLIN) and haplotype association with increased obesity risk in a multiethnic Asian population. *J Mol Med.* 2005; 83(6):448–56. [PubMed: 15770500]
17. Corella D, Qi L, Sorli JV, Godoy D, Portoles O, Coltell O, Greenberg AS, Ordovas JM. Obese subjects carrying the 11482G>A polymorphism at the perilipin locus are resistant to weight loss after dietary energy restriction. *J Clin Endocrinol Metab.* 2005; 90(9):5121–6. [PubMed: 15985482]
18. Corella D, Qi L, Tai ES, Deurenberg-Yap M, Tan CE, Chew SK, Ordovas JM. Perilipin gene variation determines higher susceptibility to insulin resistance in Asian women when consuming a high-saturated fat, low-carbohydrate diet. *Diabetes Care.* 2006; 29(6):1313–9. [PubMed: 16732014]

19. Higgins M, Province M, Heiss G, Eckfeldt J, Ellison RC, Folsom AR, Rao DC, Sprafka JM, Williams R. NHLBI Family Heart Study: objectives and design. *Am J Epidemiol.* 1996; 143(12): 1219–28. [PubMed: 8651220]
20. Corella D, Arnett DK, Tsai MY, Kabagambe EK, Peacock JM, Hixson JE, Straka RJ, Province M, Lai CQ, et al. The -256T>C polymorphism in the apolipoprotein A-II gene promoter is associated with body mass index and food intake in the genetics of lipid lowering drugs and diet network study. *Clin Chem.* 2007; 53(6):1144–52. [PubMed: 17446329]
21. Smith CE, Tucker KL, Yiannakouris N, Garcia-Bailo B, Mattei J, Lai CQ, Parnell LD, Ordovas JM. Perilipin polymorphism interacts with dietary carbohydrates to modulate anthropometric traits in Hispanics of Caribbean origin. *J Nutr.* 2008; 138(10):1852–8. [PubMed: 18806092]
22. Qi L, Zhang C, Greenberg A, Hu FB. Common variations in perilipin gene, central obesity, and risk of type 2 diabetes in US women. *Obesity.* 2008; 16(5):1061–5. [PubMed: 18356850]
23. Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: a 6-mo randomized, controlled trial. *Am J Clin Nutr.* 2008; 88(5):1232–41. [PubMed: 18996857]
24. Chavez JA, Holland WL, Bar J, Sandhoff K, Summers SA. Acid ceramidase overexpression prevents the inhibitory effects of saturated fatty acids on insulin signaling. *J Biol Chem.* 2005; 280(20):20148–53. [PubMed: 15774472]
25. Chavez JA, Knotts TA, Wang LP, Li G, Dobrowsky RT, Florant GL, Summers SA. A role for ceramide, but not diacylglycerol, in the antagonism of insulin signal transduction by saturated fatty acids. *J Biol Chem.* 2003; 278(12):10297–303. [PubMed: 12525490]
26. Coll T, Eyre E, Rodriguez-Calvo R, Palomer X, Sanchez RM, Merlos M, Laguna JC, Vazquez-Carrera M. Oleate reverses palmitate-induced insulin resistance and inflammation in skeletal muscle cells. *J Biol Chem.* 2008; 283(17):11107–16. [PubMed: 18281277]
27. Muller G, Jung C, Straub J, Wied S, Kramer W. Induced release of membrane vesicles from rat adipocytes containing glycosylphosphatidylinositol-anchored microdomain and lipid droplet signalling proteins. *Cell Signal.* 2009; 21(2):324–38. [PubMed: 19010410]
28. Muller G, Wied S, Over S, Frick W. Inhibition of lipolysis by palmitate, H₂O₂ and the sulfonylurea drug, glimepiride, in rat adipocytes depends on cAMP degradation by lipid droplets. *Biochemistry.* 2008; 47(5):1259–73. [PubMed: 18186616]

Abbreviations used

GOLDN	Genetics of Lipid Lowering Drugs and Diet Network
HOMA-IR	homeostasis model assessment of insulin resistance
MAF	minor allele frequency
MUFA	monounsaturated fatty acids
PLIN	perilipin
SNP	single nucleotide polymorphism

Figure 1.

Predicted values of HOMA-IR (natural log) by *PLIN* 11482G>A genotype (CC, n=254; CT +TT, n=254), plotted against saturated fat to carbohydrate ratio as a continuous variable. Predicted values for HOMA-IR (natural log) were calculated from the regression model after adjustment for age, waist, smoking, alcohol, family relationships, hormone replacement therapy and anti-glycemic medications. *P* value for interaction indicates the statistical significance of the interaction term for the ratio of saturated fat to carbohydrate ratio and *PLIN* genotype in the adjusted regression model. *P* values for CC and CT+TT indicate the statistical significance of the regression coefficients in the adjusted regression model.

Table 1Demographic, biochemical, anthropometric, dietary and genotype data.¹

	Men (n=462)	Women (n=508)
Age, years (range)	49 (17-88)	48(17-92)
Body mass index, kg/m ²	28.6 ± 4.9	28.0 ± 6.2
BMI≥30 kg/m ² (%)	176(38)	197(39)
Central obesity (%)	212(46)	311(61)
Plasma glucose, mmol/L	5.86 ± 1.15	5.43 ± 0.88
Plasma insulin, pmol/L	98.62 ± 59.03	92.37 ± 54.87
HOMA-IR ²	3.8 ± 2.8	3.3 ± 2.4
Anti-glycemic medication, n (%)	27(5.8)	27(5.3)
HDL cholesterol, mmol/L	1.08 ± 0.26	1.35 ± 0.36
Triglyceride, mmol/L	1.74 ± 1.62	1.41 ± 0.93
Current smokers, n (%)	39(8.4)	42 (8.3)
Current drinkers, n (%)	256(55.4)	291(57.3)
Total fat intake, %	36.1 ± 6.6	34.9 ± 6.7
Saturated fat intake, %	12.2 ± 2.7	11.6 ± 2.7
MUFA intake, %	13.7 ± 2.7	12.9 ± 2.8
Saturated fat: MUFA ³ correlation, R ² (P)	0.66(<0.0001)	0.65(<0.0001)
Carbohydrate, %	47.4 ± 8.5	50.4 ± 8.1
Saturated fat: carbohydrate correlation, R ² (P)	- 0.52(<0.0001)	- 0.67(<0.0001)
Energy intake, kcal/d	2366.7 ± 938.7	1742.8 ± 650.6
<i>PLIN</i> 11482G>A, n (%)		
CC	246(53)	254(50)
CT	165(36)	211(41.5)
TT	51(11)	43(8.5)

¹Values are expressed as mean ± SD, n% or correlation coefficient (P value).²HOMA-IR (homeostasis model assessment of insulin resistance was calculated as (fasting glucose × fasting insulin/22.5).³MUFA=monounsaturated fatty acids.

Table 2Associations of *PLIN* 11482G>A genotype and metabolic outcomes in GOLDN women.¹

	CC (n=254)	CT+TT (n=254)	P value
Plasma glucose (mmol/L) ²	6.11 ± 0.06	6.13 ± 0.06	0.814
Plasma insulin (pmol/L) ²	78.92 ± 7.29	83.31 ± 7.33	0.100
HOMA-IR ^{2,3}	3.09 ± 1.06	3.27 ± 1.06	0.123
BMI (kg/m ²) ⁴	29.97 ± 0.95	30.75 ± 0.91	0.146

¹Values are means ± SEM²Adjusted for age, waist circumference, smoking, alcohol, hormones, family relationships, anti-glycemic medication³HOMA-IR (homeostasis model assessment of insulin resistance was calculated as (fasting glucose × fasting insulin/22.5)⁴Adjusted for age, smoking, alcohol, hormones, family relationships, anti-glycemic medication

Table 3

Nutrient interactions with *PLIN1* 1482 G>A for metabolic measures in GOLDN women¹

% Saturated fat intake	CC (n=254)	CT+TT (n=254)	P value	P interaction
<11.5	6.13 ± 0.06	6.14 ± 0.06	0.947	0.660
11.5	6.11 ± 0.06	6.14 ± 0.06	0.693	
<11.5	74.06 ± 7.33	76.82 ± 7.39	0.439	0.260
11.5	86.84 ± 7.51	95.69 ± 7.55	0.027	
<11.5	2.91 ± 1.07	3.02 ± 1.08	0.462	0.246
11.5	3.40 ± 1.08	3.76 ± 1.09	0.036	
<11.5	29.21 ± 1.00	29.99 ± 0.92	0.294	0.905
11.5	31.44 ± 1.58	32.29 ± 1.62	0.290	
% Carbohydrate intake				
<50.5	6.30 ± 0.06	6.29 ± 0.06	0.922	0.904
50.5	5.90 ± 0.06	5.93 ± 0.06	0.611	
<50.5	77.43 ± 7.39	85.96 ± 7.39	0.021	0.084
50.5	81.07 ± 7.46	81.89 ± 7.55	0.835	
<50.5	3.13 ± 1.07	3.46 ± 1.07	0.041	0.137
50.5	3.07 ± 1.09	3.12 ± 1.10	0.764	
<50.5	30.44 ± 1.33	31.55 ± 1.33	0.173	0.526
50.5	29.61 ± 1.17	30.08 ± 1.15	0.480	
Ratio saturated fat:CHO				
<0.23	5.98 ± 0.06	5.96 ± 0.06	0.878	0.686
0.23	6.25 ± 0.06	6.30 ± 0.06	0.520	
<0.23	77.17 ± 7.35	76.47 ± 7.43	0.851	0.025
0.23	81.22 ± 7.50	93.14 ± 7.51	0.003	
<0.23	2.95 ± 1.07	2.93 ± 1.09	0.854	0.031
0.23	3.25 ± 1.08	3.76 ± 1.08	0.004	
<0.23	29.70 ± 1.18	30.20 ± 1.13	0.509	0.483
0.23	30.63 ± 1.35	31.80 ± 1.37	0.176	

¹ Values are means $\pm$ SEM.

² Adjusted for age, waist, smoking, alcohol, family relationships, hormones, anti-glycemic medication

³ HOMA-IR (homeostasis model assessment of insulin resistance was calculated as (fasting glucose $\times$ fasting insulin/22.5)

⁴ Adjusted for age, smoking, alcohol, family relationships, hormones, anti-glycemic medication