**APOA2, Dietary Fat, and Body Mass Index**

**Replication of a Gene-Diet Interaction in 3 Independent Populations**

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**Background:** Nutrigenetics studies the role of genetic variation on interactions between diet and health, aiming to provide more personalized dietary advice. However, replication has been low. Our aim was to study interaction among a functional APOA2 polymorphism, food intake, and body mass index (BMI) in independent populations to replicate findings and to increase their evidence level.

**Methods:** Cross-sectional, follow-up (20 years), and case-control analyses were undertaken in 3 independent populations. We analyzed gene-diet interactions between the APOA2 −265T>C polymorphism and saturated fat intake on BMI and obesity in 3462 individuals from 3 populations in the United States: the Framingham Offspring Study (1454 whites), the Genetics of Lipid Lowering Drugs and Diet Network Study (1078 whites), and Boston–Puerto Rican Centers on Population Health and Health Disparities Study (930 Hispanics of Caribbean origin).

**Results:** Prevalence of the CC genotype in study participants ranged from 10.5% to 16.2%. We identified statistically significant interactions between the APOA2 −265T>C and saturated fat regarding BMI in all 3 populations. Thus, the magnitude of the difference in BMI between the individuals with the CC and TT + TC genotypes differed by saturated fat. A mean increase in BMI of 6.2% (range, 4.3%-7.9%; \( P = .01 \)) was observed between genotypes with high- (>22 g/d) but not with low-saturated fat intake in all studies. Likewise, the CC genotype was significantly associated with higher obesity prevalence in all populations only in the high-saturated fat stratum. Meta-analysis estimations of obesity for individuals with the CC genotype compared with the TT + TC genotype were an odds ratio of 1.84 (95% confidence interval, 1.38-2.47; \( P < .001 \)) in the high-saturated fat stratum, but no association was detected in the low-saturated fat stratum (odds ratio, 0.81; 95% confidence interval, 0.59-1.11; \( P = .18 \)).

**Conclusion:** For the first time to our knowledge, a gene-diet interaction influencing BMI and obesity has been strongly and consistently replicated in 3 independent populations.

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Genomics is revolutionizing biomedical research and providing great expectations with regard to disease prevention and treatment. The classic candidate gene approach and the newer genome-wide association studies have identified genetic variants that predispose patients to common diseases. If the current trends continue, most common disease-predisposition polymorphisms will soon be identified. Thus, a major remaining research challenge will be to characterize gene-environment interactions because these are essential for the translation of genomics into clinical medicine and improved public health. Diet is one of the most important environmental factors that interacts with the genome to modulate disease risk, and better understanding of these interactions has the potential to support disease prevention via modification of dietary recommendations. However, progress in this area has been slow because of the low evidence level achieved so far. Although studies reported enticing gene-diet interactions, their level of replication has been extremely low. Thus, a vast proportion of gene-diet interactions has not been replicated. Only a small number of interactions have been replicated twice, and, to the best of our knowledge, none has been replicated in 3 or more independent populations. This problem has plagued classic genotype-phenotype association studies and, currently, consistency

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is thought to be a crucial causal criterion of credibility of genome-wide association studies. Therefore, the National Cancer Institute—National Human Genome Research Institute Working Group on Replication in Genotype-Phenotype Associations supports replication as the most reliable approach to increase evidence level and subsequent clinical applications.

Consistent with these recommendations, our major aim was to conduct a replication study in nutrigenetics. For this purpose, we focused on our recently reported association between the functional −265T>C single nucleotide polymorphism (SNP) in the APOA2 gene promoter, food intake, and obesity risk in non-Hispanic white Americans. The second major high-density lipoprotein apolipoprotein, APOA2, is an enigmatic protein in search of a function. Although animal models have found that overexpression of APOA2 results in hypertriglyceridemia, obesity, and insulin resistance, its role in humans remains controversial. Therefore, our goals were (1) to analyze the association between the APOA2 −265T>C SNP and obesity-related variables in the Framingham Offspring Study, with a focus on gene-diet interactions with fat intake and (2) to study the replication of these gene-diet interactions in other American populations.

**METHODS**

We studied 3462 individuals from 3 independent populations. The populations are from the Framingham Offspring Study (FOS), the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study, and the Boston–Puerto Rican Centers on Population Health and Health Disparities (Boston–Puerto Rican) Study. All participants provided written informed consent.

**THE FRAMINGHAM OFFSPRING STUDY**

We included 1454 genetically unrelated non-Hispanic whites (716 men and 738 women), aged 26 to 80 years, who participated in the fifth-examination visit of the FOS and had complete data for the genetic, clinical, dietary, and anthropometric variables analyzed. These individuals were obtained from an FOS cohort that had yielded a standard previously plated set of unrelated DNA strands in which only 1 individual from each pedigree was randomly selected. The institutional review boards (IRBs) for human research at Boston University and Tufts University/New England Medical Center approved the protocol. Alcohol, tobacco smoking, diabetes mellitus status, and physical activity were defined previously. For longitudinal analysis, we included 1087 unrelated individuals (340 men and 547 women) who attended each of the first 5 examinations: examination 1, August 30, 1971, to September 3, 1975; examination 2, October 9, 1979, to October 27, 1983; examination 3, December 20, 1984, to September 30, 1987; examination 4, April 22, 1987, to September 11, 1991; and examination 5, January 23, 1991, to June 29, 1995. Anthropometric and demographic variables were measured at each cycle.

**THE GENETICS OF LIPOID-LOWERING DRUGS AND DIET NETWORK STUDY**

For the GOLDN Study, a total of 1200 adults of European ancestry were recruited from 2 National Heart, Lung, and Blood Institute Family Heart Study field centers (Minneapolis, Minnesota, and Salt Lake City, Utah), as previously reported. We included 1078 adults (514 men and 564 women) for whom data for all examined variables were complete. The protocol was approved by the institutional review boards at the University of Alabama, University of Minnesota, University of Utah, and Tufts University.

**THE BOSTON–PUERTO RICAN CENTERS ON POPULATION HEALTH AND HEALTH DISPARITIES STUDY**

Comprising approximately 1200 free-living ethnic Puerto Rican (Hispanics of Caribbean origin) individuals, aged 43 to 75 years, in the greater Boston, Massachusetts, area, the Boston–Puerto Rican Study is one of the National Institutes of Health–funded Centers on Population Health and Health Disparities. We analyzed the 930 (263 men and 667 women) individuals for whom we had complete data. The protocol was approved by the institutional review board at Tufts University. In these populations, individuals included did not differ from those excluded because of incomplete data with regard to the variables analyzed.

**ANTHROPOMETRIC, PHYSICAL ACTIVITY, AND BIOCHEMICAL DETERMINATIONS**

Anthropometric variables, such as height, weight, and waist circumference, were measured in all cohorts by standard techniques. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI of 30 or greater. Physical activity in the FOS was assessed with the physical activity index calculated at examination 4 from the number of hours each day spent sleeping, sedentary, performing slightly physical activities, moderately physical activities, or highly physical activities, weighted in accordance with the estimated oxygen consumption required. In the GOLDN Study, a nonvalidated questionnaire was used that contains questions with regard to the number of hours per day dedicated to different activities. In the Boston–Puerto Rican Study, a physical activity score based on the Paffenbarger questionnaire of the Harvard Alumni Activity Survey was estimated. Fasting glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol levels were measured by standard methods. For the FOS samples, plasma APOA1 and APOA2 concentrations were determined by means of turbidimetric immunonassays (Wako Chemicals USA Inc, Richmond, Virginia).

**DIETARY INTAKE**

Diet was measured by validated questionnaires in each specific population, the Willett semiquantitative food frequency questionnaire, administered at examination 5, in the FOS; the Diet History Questionnaire in the GOLDN Study, and a specially designed and validated food frequency questionnaire in the Boston–Puerto Rican Study. Nutrient data were derived from the Harvard University food composition database, the United States Department of Agriculture database, and the Minnesota Nutrient System.

**GENETIC ANALYSES**

We isolated DNA from blood by means of an examination kit (QiAmp DNA Blood Maxi Kit; Qiagen, Hilden, Germany). We performed the APOA2 −265T>C genotyping (rs5082) by means of a Taqman assay with allele-specific probes on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems Inc, Foster City, California). Quality control measures were ap-
plied. Genotype frequencies were consistent with Hardy-Weinberg equilibrium in all populations.

STATISTICAL ANALYSES

We used χ² tests to verify percentages. Normality of continuous variables was examined. Triglycerides were log transformed, and alcohol and polyunsaturated fatty acids were square root transformed. We applied analysis of variance and the t test to compare crude means. Because of the results obtained in the previous GOLDN Study,12 in which similar effects were found to compare crude means. Because of the results obtained in the previously described.12 In the Boston–Puerto Rican Study, fur-

tional adjustments for family relationships were undertaken as additional adjustments of basic models for physical activity were

lipid medication, and total energy intake (basic models). Ad-

ses for sex, age, tobacco smoking, alcohol consumption, diabetes,

sults. In addition to the unadjusted models, we adjusted analy-

saturated fat or high–saturated fat intake based on the FOS re-

formed, and alcohol and polyunsaturated fatty acids were square

ous variables was examined. Triglycerides were log trans-

the multivariate adjustments. Saturated fat intake was consid-

dition model and the plotting of these values against saturated

predicted values for each individual from the adjusted regres-

fat intake by the

−265T

were estimated in stratified analyses by genotype. Regression coefficients

−265T

C SNP for each

of the magnitude of the effect, the allele frequency, and the

considered statistically significant at P < .05. With consideration

odds ratio (OR) and the Boston–Puerto Rican Study. The Table gives the demographic, anthropometric, clinical, biochemical,

dietary, and lifestyle characteristics of participants in accordance with the APOA2 −265T>C SNP for each population. Prevalence of individuals with the CC genotype did not differ between the FOS (16.2%) and the GOLDN Study (15.3%). A statistically significant lower prevalence (10.5%) was found in the Boston–Puerto Rican Study. Demographic characteristics and physical activity did not differ significantly between CC and T allele carriers in any of the 3 populations (Table). Among white populations, prevalence of obesity was higher in the GOLDN Study cohort than in the FOS. Likewise, mean fat intake, mainly saturated fat, was higher in the GOLDN Study population than in the FOS. No significant assoco-

apoA2 and APOA1 were only determined in the FOS population. In this cohort, plasma APOA2 concentrations (eTable 1; http://www.

archinternmed.com) were significantly lower in individuals with the CC genotype, whereas no effects were observed for APOA1, a result that supports the function-

ality and specificity of this SNP.

we next examined in the FOS population our previously described association between the APOA2 SNP, food intake, and body weight. In the FOS, we also found that individuals with the CC genotype had higher energy intake than T allele carriers (P = .02) (Table). These results were consistent with our previous finding in the GOLDN Study, which showed that daily energy intake was approximately 200 kcal/d higher in individuals with the CC genotype than in T allele carriers (P = .005). However, the magnitude of the genotype effect was lower in FOS (approximately 100 kcal/d), and differences in total fat intake, satu-

fat, and monounsaturated fatty acids did not reach the statistical significance that they did in the GOLDN Study. This difference could be owing to the higher prevalence of obesity and total fat and saturated fat intake in the GOLDN Study population (Table). Therefore, we hypothesized that the APOA2 SNP would have a greater influence in determining food intake in individuals with obesity. Consistent with this notion, we found that individuals with obesity who have the CC genotype from the FOS had statistically
higher intakes of calories, total fat, saturated fat, monounsaturated fatty acids, protein, carbohydrates, and fructose than those who carry the T allele carriers (Table 2). The greater carbohydrate and fructose intake in individuals from the FOS with obesity who have the CC genotype compared with those from the GOLDN Study with those same characteristics could reflect a greater intake of fruit and cereal in the FOS participants to satisfy their greater appetite. Possibly this is the case for individuals from the FOS, despite their following a healthy diet, because they possess the CC genotype. Further adjustment for physical activity did not affect the statistical significance of results.

Moreover, in the FOS population as a whole, the CC genotype was not associated with higher BMI or obesity as previously observed in the GOLDN Study population (Table). In view of the different dietary fat intakes among these populations, we focused on gene–dietary fat interactions. We found a statistically significant interaction between total fat and the APOA2 SNP (P = .04). However, on analysis of the different fat types, the interaction was stronger and more significant for saturated fat, which indicates a more specific effect of this variable; therefore, we focused on saturated fat. When we considered saturated fat as continuous in the FOS population (Figure 1A), the individuals with the CC genotype exhibited a higher association (B = 0.108 kg/m²; P = .006) than carriers of the T allele (B = 0.033 kg/m²; P = .03) between saturated fat intake and BMI (P for interaction = .02). Thus, the impact of increased saturated fat intake with regard to BMI increase was most noticeable for individuals with the CC genotype, with the crossing point between the 2 regression lines at 22 g/d of saturated fat, which was approximately the population mean. We next assessed the relationship of the APOA2 SNP with BMI, stratified according to these levels of saturated fat (Figure 1B). We also detected a statistically significant interaction term (P = .01) between the APOA2 SNP and saturated fat intake as categorical. Among those within the lower saturated fat strata (<22 g/d), the APOA2 SNP was not significantly associated with BMI (P = .22). In contrast, the CC genotype was associated with greater BMI (approximately 4.3%, P = .02) in the higher–saturated fat strata. Further adjustment of this interaction for physical activity did not alter the statistical significance of results (P = .03). Furthermore, in the FOS population we examined whether the APOA2–saturated fat interaction is influenced by plasma APOA2 concentrations. Thus, the basic model was adjusted for APOA2, and we found...
that the significance of the interaction term remained practically unchanged ($P = .01$).

To verify the internal replication of this gene-diet interaction, we analyzed BMI data from 1087 individuals who attended FOS examinations 1 through 5 (20 years of follow-up). When the interaction with saturated fat was not considered, no differences in BMI were observed, depending on the APOA2 SNP at any examination (Figure 1C). However, if 2 strata of saturated fat intake were considered (with the assumption of a similar fat intake strata across the examinations), a statistically significant interaction between the APOA2 SNP and saturated fat ($P = .04$) with regard to BMI across the 20-year follow-up period was noted (Figure 1D). Thus, consistent with the results observed for examination 5, individuals with the CC genotype have a higher BMI than the other genotypes throughout the 20-year follow-up period only when they have a high–saturated fat consumption.
Because of the relevance and novelty of this gene-diet interaction, we examined its replication in the GOLDN Study. With consideration of the 2 categories of saturated fat (<22 g/d and ≥22 g/d) that we examined in the FOS, we consistently found the same statistically significant interaction whether considering the unadjusted model or the multivariate basic model (P = .01) (Figure 2A). Further adjustment of this basic model for family relationships (P = .04) or physical activity (P = .01) did not alter the statistical significance of results. Given that this GOLDN Study population consumes a higher–saturated fat diet, the APOA2 SNP was generally associated with higher BMI. However, this observation was not present in GOLDN Study participants with a low–saturated fat intake (P = .45). In contrast, the CC genotype was strongly associated with greater BMI in individuals with a high–saturated fat intake (approximately 6.4%, P = .002). Further internal replication of this interaction was obtained from separate analyses of the Minnesota-based and Utah-based study participants (Figure 2B and C).

Furthermore, we investigated the replication of this gene-diet interaction in an ethnically different population of Hispanics of Caribbean origin living in Boston. We consistently found a statistically significant interaction between the APOA2 SNP and saturated fat with regard to BMI (basic models) whether saturated fat was considered as continuous (P = .003) or categorical (P = .002) (Figure 3). After additional adjustment for physical activity, the interaction terms remained statistically significant (P = .004 and P = .001, respectively). These results were totally in accordance with our previous findings in whites. Thus, in the Boston–Puerto Rican study, when saturated fat intake was high, individuals with the CC genotype also had significantly higher BMI than carriers of the T allele (approximately 7.9%; P = .02). Moreover, further adjustment of basic models for admixture did not change the statistical significance of the interaction terms (P = .006 and P = .003 for continuous and categorical saturated fat variables, respectively).

With the consideration that in the Boston–Puerto Rican Study population prevalence of diabetes was high (42%), we analyzed whether the APOA2–saturated fat interaction was present in individuals with and without diabetes. The internal replication of this interaction was also obtained (P for interaction < .05 in each group: P = .04 for

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**Figure 2.** Interaction between the APOA2 –265T>G polymorphism and saturated fat intake with regard to body mass index (BMI) in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study. Means of BMI values in the entire GOLDN Study population (A), in GOLDN Study–Minnesota participants (n=558) (B), and in GOLDN Study–Utah participants (n=520) (C) were according to the APOA2 –265T>G polymorphism, in accordance with the strata of saturated fat intake (<22 g/d [low] and ≥22 g/d [high]). Estimated means were adjusted for sex, age (as continuous), tobacco smoking (as categorical), alcohol consumption (as categorical), diabetes mellitus status (as categorical), cholesterol medication (as categorical), and total energy intake (as continuous). The P-values for the interaction terms between saturated fat intake (as dichotomous) and the APOA2 polymorphism in each population were obtained in the hierarchical multivariate interaction model. In the stratified analysis by saturated fat intake levels, P-values for mean comparisons of BMI values between APOA2 genotypes were estimated after multivariate adjustment for the covariates indicated herein. Bars indicate SEMs.
individuals with and \( P = .01 \) for individuals without diabetes mellitus, results not shown).

Finally, we examined the APOA2–saturated fat interaction to determine obesity in the 3 populations independently and pooled in a meta-analysis (Figure 4). We found consistent gene-diet interactions across all 3 populations. The CC genotype was only associated with a higher prevalence of obesity in individuals in the high–saturated fat stratum. If saturated fat consumption was low, the CC genotype was not associated with obesity. In the meta-analysis, we observed no significant heterogeneity either for the high–saturated fat \( (I^2 = 0\%) \), or for the low–saturated fat stratum \( (P = .90) \) group. The overall association meta-analysis in the high–saturated fat group showed a statistically higher OR of obesity for CC homozygotes \( (OR, 1.84; 95\% CI, 1.38-2.47; P < .001) \), by means of the fixed-effect model. However, in the low–saturated fat group, no increased OR for obesity was found for CC homozygotes in comparison with carriers of the T allele \( (OR, 0.81; 95\% CI, 0.59-1.11; P = .18) \).

**COMMENT**

In 3 independent US populations, we have replicated a gene-diet interaction that influences body weight. This is the first time, to our knowledge, that such consistent replication is found in nutrigenetic studies. This novel and reliable interaction involves influence of the APOA2–265T>C SNP and saturated fat intake on BMI and obesity. When saturated fat intake is low, the APOA2–265T>C SNP does not affect BMI. However, when saturated fat intake is high, this SNP is strongly associated with BMI and obesity. Therefore, this APOA2–saturated fat interaction may clarify previous controversial associations reported for this promoter polymorphism.10,12,16,17 The APOA2 SNP can be considered as a thrifty genotype because, depending on the presence of an obesogenous (high–saturated fat diet) or restrictive (low–saturated fat diet) environment, the phenotypic expression is different. We have selected the cutoff point of 22 g/d to define the 2 saturated fat strata based on the results of the FOS and with consideration that this amount of fat represents 10% of daily energy intake in a standard 2000-kcal/d diet. This figure has been largely reported as the threshold between low–saturated fat and high–saturated fat diets.29 Moreover, we have demonstrated a linear dose effect in the interaction that contributes to its independence from a fixed cutoff level. Another strength of this study is the replication of the interaction, not only in white Americans but also in Hispanics of Caribbean origin living in Boston, with a lower C allele prevalence, which contributes to its external validity and reinforces the notion that individuals with the CC genotype are especially susceptible to the detrimental effect of high–saturated fat diets with
would contribute to the diversity and complexity of obe-
10% to 15% of the population (those with the CC geno-
dependent on the individual genotype. We demonstrate herein
alyzed diets of FOS participants at examinations 3 and 5,
the whole period. However, in previous work that ana-
replication within each population. Of note is the inter-
A, Logistic regression estimation in determination of obesity risk in each independent population was according to the saturated fat intake strata
22 g/d and
22 g/d). Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for each strata of saturated fat intake. Two separate
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analysis) than usually reported in relevant genetic studies.30 Our findings also demonstrated a good internal replication within each population. Of note is the inter-
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the assumption of a similar classification of participants into lower–saturated fat or higher–saturated fat strata for the whole period. However, in previous work that analyzed diets of FOS participants at examinations 3 and 5, we demonstrated stable patterns of consumption over time, specifically for intakes of saturated fat.31
On the other hand, the association between saturated fat intake and obesity risk is controversial and has been the subject of intense debate.32,33 One explanation may be the different response to saturated fat, depending on the individual genotype. We demonstrate herein that the effect of saturated fat on BMI and obesity is highly dependent on the APOA2 –265T>C genotype. Furthermore, although this gene-diet interaction only applies to 10% to 15% of the population (those with the CC genotype), other genes could have similar interactions, which would contribute to the diversity and complexity of obe-

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allele-specific binding of the transcription factor CCAAT/enhancer binding protein α (CEBPA), which has been involved in adipogenesis.37 Our results also suggest that APOA2 acts as a satiety signal, as described for APOA4 in other studies,38 giving the significant associations between the APOA2 –2657>C SNP and food intake in the FOS and GOLDN studies.12

In conclusion, we have consistently replicated a gene-diet interaction with regard to BMI and obesity in 3 US populations by which individuals with the APOA2 CC genotype seem more susceptible to increased BMI and obesity when they consume a high–saturated fat diet. Therefore, if no unmeasured confounders exist, and these results are replicated in subsequent trials, personalized nutritional recommendations in terms of specific reductions of saturated fat intake in individuals with the CC genotype may be a future nutrigenetics application.

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