Effect of Apolipoprotein E Genotype and Saturated Fat Intake on Plasma Lipids and Myocardial Infarction in the Central Valley of Costa Rica

YADONG YANG,[1,2] EDWARD RUIZ-NARVAEZ,[1] PETER KRAFT,[3] AND HANNIA CAMPOS[1,4]

Abstract We assessed the effect of *APOE* polymorphisms −491 A/T, C112R (*APOE*4*), and R158C (*APOE*2*) and saturated fat intake on plasma lipid levels and risk of myocardial infarction (MI) in 1,927 case subjects and 1,927 population-based control subjects matched for age, sex, and residence, all living in the Central Valley of Costa Rica. A significant gene-diet interaction ($p = 0.0157$) was observed. High saturated fat intake was associated with a 49% increased risk of MI (OR = 1.49; 95% CI, 1.16–1.92) among wild-type subjects. In contrast, high saturated fat intake was associated with a 2.2-fold increased risk of MI among carriers of *APOE*2* (OR = 3.17; 95% CI, 1.58–6.36) and with a 1.6-fold increase among carriers of the −491T and *APOE*4* variants together (OR = 2.59; 95% CI, 1.38–4.87). Consistently, a high fat diet elicited a greater response in LDL cholesterol among carriers of *APOE*2* (+17%) and *APOE*4* (+14%) compared to noncarriers (+6%). The frequency of *APOE* variants was similar in case and control subjects, although *APOE*4* homozygotes were at increased risk of MI compared to noncarriers (OR = 2.26; 95% CI, 1.03–4.98). This study supports the hypothesis that the *APOE*2* and *APOE*4* variants increase susceptibility to MI in the presence of high saturated fat and could explain inconsistent findings on the effects of these variants on MI in various populations.

Apolipoprotein E (apoE) is a ligand for the low-density lipoprotein (LDL) receptor and the LDL receptor-related protein (LRP) (Mahley and Rall 2000). Through these receptors apoE mediates the uptake of chylomicron remnants into the liver and the uptake of circulating very low density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particles into peripheral tissues and cells (Mahley and Rall 2000).

About 30 naturally occurring single nucleotide polymorphisms (SNPs) have been found in the *APOE* gene, located at chromosome 19q13.2 in a span of about

[1]Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115.
[2]Program for Population Genetics, Department of Environmental Health, Harvard School of Public Health, Boston, MA.
[3]Departments of Epidemiology and Biostatistics, Harvard School of Public Health, Boston, MA.
[4]Centro Centroamericano de Población, Universidad de Costa Rica, San Pedro, Costa Rica.

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3.6 kb (Oikawa et al. 1997; Laws et al. 2003; Eichner et al. 2002). Some of the variant forms found in *APOE* result in apoE deficiency and have been observed in association with various diseases, including lipoprotein glomerulopathy, Alzheimer disease, and cardiovascular disease (Oikawa et al. 1997; Laws et al. 2003; Eichner et al. 2002). Three variants, −491 A/T, −427 C/T, and −219 G/T, have been found in the promoter of *APOE*, of which −491 A/T and −219 G/T lead to altered transcriptional activity (Artiga et al. 1998). An A to T base substitution at nucleotide −491 causes decreased promoter activity, whereas a T to G substitution at nucleotide −219 increases promoter activity (Artiga et al. 1998). In addition, the −491 A to T substitution is associated with decreased apoE levels in both plasma and the brain (Roks et al. 2002; Laws et al. 2002). Studies have also shown an association between the −219 G to T substitution and coronary heart disease (CHD) (Viitanen et al. 2001; Lambert et al. 2000).

Two variants, C112R and R158C, which together determine the *APOE* genotype, are of particular importance because of their strong effects on plasma lipids (Ballantyne et al. 2000), their presence in all studied populations, and their significant influence on CHD (Ewbank 2002). Results from meta-analyses suggest that the *APOE*4* variant but not the *APOE*2* variant confers increased CHD risk (Wilson et al. 1996; Song et al. 2004). However, results from various studies are inconsistent, even within similar ethnic groups. Some of these inconsistencies can be attributed to differences in dietary intake among populations. For example, the studies that show an association between the *APOE*4* variant and risk of CHD have mostly been conducted in developed countries where intake of saturated fat is high (Wilson et al. 1996; Song et al. 2004). Intervention studies show that the *APOE*4* variant allele modulates the effect of saturated fat on plasma LDL cholesterol (Ordovas and Mooser 2002). However, none of the studies have examined whether this differential effect of *APOE* genetic variation on plasma lipid levels is also associated with differential effects on the risk of myocardial infarction (MI) in the general population. In addition, no data on this topic are available from Latin American countries (Song et al. 2004).

Because of the important role of diet in the risk of MI, studies evaluating genetic effects must be inclusive with regard to variation in dietary exposures and ethnic groups.

We conducted a case-control study of 1,927 MI case subjects of a first acute MI and 1,927 age-, sex-, and residence-matched control subjects, all living in the Central Valley of Costa Rica. This study was designed to examine whether the *APOE* variants −491 A/T, C112R, and R158C are associated with risk of MI and whether they modulate the well-established association between saturated fat intake and risk of MI.

Materials and Methods

Study Population and Data Collection. The catchment area consists of the 34 counties that compose the Central Valley of Costa Rica. Residents in this area

derive from a relatively small number of founders, and the expansion of the population occurred by reproduction rather than by immigration (Melendez 1982). From the 100–300 founding individuals who settled in the Central Valley in 1569, the population grew to almost 5,000 in the early 19th century and to more than 100,000 by the second half of the 19th century (Melendez 1982). Because the Central Valley is isolated politically and geographically from the rest of the country (Molina-Jiménez 1991), most current residents of this region (about 3 million individuals) are descended from these early residents (Tinoco 1977). Using 11 classical markers, Morera et al. (2003) estimated that this population derives mostly from the admixture of Spanish settlers (65%), indigenous Amerindians (28%), and West Africans (7%).

All MI case subjects and population-based control subjects were ascertained between 1994 and 2004. Eligible case subjects were men and women who were diagnosed as survivors of a first acute MI by two independent cardiologists at any of the six recruiting hospitals in the catchment area. MI was determined according to the World Health Organization criteria for MI, which required typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the ECG (Tunstall-Pedoe et al. 1994). One free-living control subject for each case, matched for age (±5 years), sex, and area of residence (county), was randomly selected using the information available at the National Census and Statistics Center of Costa Rica. Participation was 97% for case subjects and 88% for control subjects. All subjects gave informed consent on documents approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica.

Trained personnel visited all study participants at their homes for data collection. Sociodemographic characteristics, smoking status, socioeconomic status, and medical history data were collected during an interview using a questionnaire with close-ended questions. Anthropometric measurements and biological specimens were collected in the morning after an overnight fast. Blood samples (20 ml) were drawn in tubes containing 0.1% EDTA. The samples were immediately stored at 4°C, and within 24 hours they were centrifuged at 2,500 rpm for 20 min at 4°C to isolate and aliquot plasma and white blood cells. DNA was extracted using the Qiagen QIAamp DNA Blood Kit (Qiagen Inc., Valencia, California).

Genotyping. We originally selected the SNPs −491 A/T, −219 G/T, C112R (*APOE*4*), and R158C (*APOE*2*) for genotyping, because of their potential effect on apoE function. We also selected a neutral SNP, rs769450, in intron 2 for its relatively high allele frequency. We discontinued further genotyping of −219 G/T because it had a low variant allele frequency in this population. We also discontinued the genotyping of rs769450 because its variant allele frequencies were similar between the first 972 cases and the 1,020 control subjects genotyped. The allele frequencies were 1.8% versus 2.0% for −219 G/T and 30.9% versus 31.4% for rs769450 in case and control subjects, respectively.

Genotyping was carried out using a variation of the allele-specific assay. In

brief, DNA fragments were obtained using PCR primers designed according to the vicinity sequence of a genetic variant, with the reverse primers containing an artificially introduced sequence that was identical across all variants. The genetic variants were genotyped in three different multiplex reactions, with allele-specific forward primers and a universal reverse primer labeled with a fluorescent dye (FAM, HEX, or TET) to provide genotyping signal. Allele-specific assay products were separated by capillary electrophoresis with the ABI Prism 310 genetic analyzer (Applied Biosystems, Perkin-Elmer, Foster City, California) and analyzed using the Genotyper software. The two alleles of each variant were distinguished by size and fluorescent label. Genotype proportions were in Hardy-Weinberg equilibrium for the three variants −491 A/T, C112R (*APOE*4*), and R158C (*APOE*2*) included in the study.

Statistical and Genetic Analysis. All data were analyzed using the Statistical Analysis Software 9.1 (SAS Institute Inc., Cary, North Carolina). A total of 3,854 subjects (1,927 cases-control pairs) had complete questionnaire and genotype data for variants −491 A/T, C112R, and R158C. Differences in health characteristics and potential confounders were assessed using McNemar's test for categorical variables and a paired t test for continuous variables if normally distributed. If not normally distributed, the Wilcoxon signed-rank test was used. Least-square means and 95% confidence intervals from generalized linear models adjusted for age, sex, body mass index, and physical activity were used to report the relationship between plasma lipid levels, saturated fat intake, and *APOE* genotype. For this analysis homozygote and heterozygote carriers of the variant allele were combined into one group and saturated fat intake was divided into tertiles. Data are shown for the highest and lowest tertiles of saturated fat intake, labeled as high saturated fat and low saturated fat. These analyses were conducted in control subjects because lipid levels are likely to change after a MI in case subjects. Those subjects who reported use of medication known to affect lipid levels ($n = 130$) were excluded from analyses of lipid comparisons. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from multiple conditional logistic regression models. Likelihood ratio tests were used to test for interactions.

Results

The general characteristics of and *APOE* genotype distribution for case subjects of MI and control subjects are shown in Table 1. The variant allele frequencies for case and control subjects, respectively, were 0.211 and 0.191 for −491T, 0.098 and 0.094 for *APOE*4*, and 0.041 and 0.038 for *APOE*2*. No significant differences in allele or genotype frequencies were observed between case and control subjects.

Table 2 shows the average daily macronutrient intake in case and control subjects. Case subjects had higher total fat and saturated fat intake and lower polyunsaturated fat intake ($p < 0.01$). Intake of cholesterol, protein, and energy

Table 1. General Characteristics of Myocardial Infarction Case and Control Subjects

Characteristic	*Control Subjects (n = 1,927)*		*Case Subjects (n = 1,927)*	
Age	58 ± 11		58 ± 11	
Living in rural areas (%)	26		26	
Women (%)	27		27	
Diabetes (%)	14		24[a]	
Hypertension (%)	29		38[a]	
Hypercholesterolemia (%)	27		30	
Current smokers (%)	21		40[a]	
Body mass index (kg/m^2)	26.4 ± 4.3		25.9 ± 3.9[a]	
Waist-to-hip ratio	0.95 ± 0.07		0.97 ± 0.07[a]	
Physical activity [metabolic equivalent tasks (METS)]	1.56 ± 0.70		1.52 ± 0.71[a]	
Monthly income (US$)	571 ± 432		500 ± 396[a]	
Total cholesterol (mg/dl)	207 ± 42		187 ± 42[a]	
HDL cholesterol (mg/dl)	41 ± 9		37 ± 8[a]	
LDL cholesterol (mg/dl)	122 ± 39		106 ± 38[a]	
Total triglycerides (mg/dl)	220 ± 131		231 ± 121[a]	
APOE Genotype	*n*	*%*	*n*	*%*
−491 A/T				
1–1	1,260	65.4	1,193	61.9
1–2	598	31.0	653	33.9
2–2	69	3.6	81	4.2
C112R (*APOE*4*)				
1–1	1,576	81.8	1,573	81.6
1–2	338	17.5	331	17.2
2–2	13	0.7	23	1.2
R158C (*APOE*2*)				
1–1	1,785	92.6	1,774	92.1
1–2	138	7.2	148	7.7
2–2	4	0.2	5	0.3

a. $p < 0.01$ compared to control subjects. Lipid levels among case subjects were measured after the MI so they are likely to be affected by the use of medications.

Table 2. Average Daily Dietary Intake in Case and Control Subjects

Component	*Control Subjects (n = 1,927)*	*Case Subjects (n = 1,927)*
Total energy (kcal)	2,450 ± 759	2,706 ± 938[a]
Protein (% energy)	12.9 ± 2.1	13.2 ± 2.2[a]
Carbohydrate (% energy)	55.5 ± 7.2	54.4 ± 7.5[a]
Total fat (% energy)	31.8 ± 5.8	32.3 ± 5.9[a]
Saturated fat (% energy)	10.4 ± 2.6	11.1 ± 2.9[a]
Monounsaturated fat (% energy)	11.8 ± 3.8	11.9 ± 3.5
Polyunsaturated fat (% energy)	6.2 ± 2.0	6.0 ± 2.0[a]
Trans fat (% energy)	1.2 ± 0.6	1.2 ± 0.6
Cholesterol (mg/1,000 kcal)	117 ± 52	126 ± 58[a]
Fiber (g/1,000 kcal)	10.0 ± 2.5	9.5 ± 2.4

a. $p < 0.01$ compared to control subjects.

Table 3. Odds Ratio and 95% Confidence Intervals for Risk of Myocardial Infarction[a]

APOE Polymorphism	*Genotype*	*Odds Ratio*	*95% Confidence Interval*
−491 A/T	1–1	1.00 (Reference)	
	1–2	1.09	0.93–1.29
	2–2	1.02	0.69–1.52
C112R (*APOE*4*)	1–1	1.00 (Reference)	
	1–2	1.04	0.84–1.27
	2–2	2.26	1.03–4.98
R158C (*APOE*2*)	1–1	1.00 (Reference)	
	1–2	1.07	0.79–1.44
	2–2	0.82	0.18–3.68

a. Adjusted for waist-to-hip ratio, cigarette smoking, income, and physical activity. $N = 3{,}854$.

was also higher in case subjects than in control subjects. Carbohydrate and fiber intake were lower in case subjects than in control subjects ($p < 0.05$).

The odds ratios and 95% confidence intervals for MI by *APOE* genotype are shown in Table 3. Homozygote carriers of the *APOE*4* allele were at increased risk of MI compared to noncarriers (OR = 2.26; 95% CI, 1.03–4.98). In contrast, no association with MI was observed for heterozygous *APOE*4* carriers or carriers of the *APOE*2* or −491T alleles.

Table 4 shows the plasma lipid levels by *APOE* genotype and saturated fat intake. As expected, carriers of the *APOE*2* allele had significantly ($p = 0.0001$) lower LDL cholesterol levels than noncarriers, whereas carriers of the *APOE*4* allele had significantly ($p = 0.0005$) higher plasma triglyceride levels than noncarriers, regardless of the amount of saturated fat in the diet. Compared to noncarriers, carriers of the *APOE*4* allele also had higher high-density lipoprotein (HDL) cholesterol levels ($p = 0.06$), whereas lower HDL cholesterol levels were observed among carriers of the *APOE*2* allele ($p = 0.06$). Overall, high saturated fat intake was associated with 6–9% higher LDL cholesterol levels among the wild-type groups ($p < 0.05$) and with 4% higher levels among carriers of the −491T allele. In contrast, carriers of the *APOE*4* and *APOE*2* alleles had 14% and 17% higher LDL cholesterol levels, respectively, on the high saturated fat diet compared to the low saturated fat diet ($p < 0.05$), although the interactions were not statistically significant (p for interaction = 0.51 for both). The high saturated fat diet was associated with lower plasma triglyceride levels (6–11%) among the wild-type groups and among carriers of the −491T and *APOE*4* alleles ($p < 0.05$). Interestingly, carriers of the *APOE*2* allele had 8% higher triglyceride levels in the high saturated fat group compared to the low saturated fat group, but the interaction was not statistically significant ($p = 0.37$). No association with HDL cholesterol levels was found for −491 A/T or *APOE*4*. In contrast, a significant interaction was found for HDL cholesterol, *APOE*2*, and saturated fat intake, where only carriers of the *APOE*2* allele had higher HDL cholesterol levels on the high saturated fat diet.

Table 4. Plasma Lipid Levels by *APOE* Genotype and Saturated Fat Intake Among Control Subjects[a]

	Low Saturated Fat		*High Saturated Fat*		*Main Effects*		
Genotype	*Mean*	*95% CI*	*Mean*	*95% CI*	*Gene*	*Diet*	*Interaction*
LDL cholesterol (mg/dl)							
−491 A/T							
1–1	111	107–116	121	117–126			
1–2 + 2–2	114	108–121	118	111–125	0.74	0.04	0.54
C112R (*APOE*4*)							
1–1	113	109–117	120	116–124			
1–2 + 2–2	109	102–116	124	114–134	0.77	0.01	0.51
R158C (*APOE*2*)							
1–1	114	110–118	121	117–125			
1–2 + 2–2	92	81–103	109	94–125	0.0001	0.05	0.51
Total triglycerides (mg/dl)							
−491 A/T							
1–1	197	189–206	184	175–193			
1–2 + 2–2	194	182–207	181	168–194	0.74	0.06	0.31
C112R (*APOE*4*)							
1–1	192	184–200	181	173–189			
1–2 + 2–2	217	199–236	195	177–214	0.0005	0.06	0.79
R158C (*APOE*2*)							
1–1	197	189–204	182	174–190			
1–2 + 2–2	191	168–218	206	175–243	0.44	0.88	0.37
HDL cholesterol (mg/dl)							
−491 A/T							
1–1	39	39–40	40	39–41			
1–2 + 2–2	40	39–41	40	39–41	0.69	0.73	0.4
C112R (*APOE*4*)							
1–1	39	39–40	40	39–40			
1–2 + 2–2	41	39–42	41	40–43	0.06	0.74	0.57
R158C (*APOE*2*)							
1–1	40	39–41	40	40–41			
1–2 + 2–2	36	34–38	39	37–42	0.06	0.01	0.02

a. Values are adjusted for age, sex, body mass index, smoking, and physical activity. Lipids are presented for the lowest (< 9.3%) and the highest (> 11.8%) tertiles of saturated fat intake. The lowest and highest tertiles are labeled low saturated fat and high saturated fat, respectively. Subjects taking medications known to affect lipids were excluded from the analyses ($n = 130$). Total n used in the analysis = 1,797; for −491 A/T, 1–1 = 1,174 and 1–2 + 2–2 = 623; for C112R (*APOE*4*), 1–1 = 1,486 and 1–1 + 1–2 = 311; and for R158C (*APOE*2*), 1–1 = 1,675 and 1–1 + 1–2 = 122.

In sum, a high fat diet elicited a greater response in LDL cholesterol among carriers of the *APOE*2* and *APOE*4* alleles compared to noncarriers. Furthermore, carriers of the *APOE*2* allele had higher rather than lower plasma triglyceride levels on the high fat diet compared to the low fat diet. An association with higher HDL cholesterol levels on the high fat diet was observed only among carriers of the *APOE*2* allele.

Figure 1 shows the odds ratio for risk of MI associated with high saturated fat intake by *APOE* genotype using noncarriers (those who are noncarriers of any of the three variants) in the low saturated fat group as reference. A significant interaction between *APOE* genotype, saturated fat intake, and risk of MI was observed ($p = 0.0157$). High saturated fat intake was associated with a 49% increased risk of MI (OR = 1.49; 95% CI, 1.16–1.92) among noncarriers, which represented most of the population. High saturated fat intake was also associated with increased risk of MI to a similar extent among carriers of the −491T variant allele (OR = 1.84; 95% CI, 1.38–2.48) and among carriers of the *APOE*4* allele (OR = 1.49; 95% CI, 0.99–2.22). In contrast, high saturated fat intake was associated with a 2.2-fold increased risk of MI among carriers of the *APOE*2* allele (OR = 3.17; 95% CI, 1.58–6.36). Similar, although less striking results were observed when carriers of the *APOE*2* allele were also carriers of the −491T allele (OR = 2.19; 95% CI, 0.97–4.91). Interestingly, the presence of the −491T and *APOE*4* variants together was associated with a 110% increase in MI risk compared to when only *APOE*4* was present (OR = 2.59; 95% CI, 1.38–4.87).

Discussion

We assessed the effect of the *APOE* polymorphisms −491 A/T, C112R (*APOE*4*), and R158C (*APOE*2*) and saturated fat intake on plasma lipid levels and risk of MI in the Central Valley of Costa Rica. Results show a significant interaction between *APOE* genotype, saturated fat intake, and risk of MI. High saturated fat intake was associated with a 49% increased risk of MI among noncarriers of any of the variant alleles, which represented most of the population. In contrast, a greater response was observed for carriers of the variant alleles. That is, high saturated fat intake was associated with a 2.2-fold increase in risk of MI among carriers of the *APOE*2* allele compared to noncarriers on the low saturated fat diet. Furthermore, a high saturated fat diet was associated with a 1.6-fold increase in MI risk in the presence of the −491T and *APOE*4* variants together. Consistent with this finding, a high fat diet was associated with a greater response in LDL cholesterol among carriers of the *APOE*2* (+17%) and *APOE*4* (+14%) alleles compared to noncarriers (+6%). No significant difference in the frequency of *APOE* variant alleles was found between case and control subjects, although homozygote carriers of the *APOE*4* allele were at increased risk of MI compared to noncarriers. The validity of these findings is supported by the relatively large sample size, ethnic homogeneity, availability of dietary information and plasma biomarkers, and a high participation of both case and control subjects.

This study supports the hypothesis that the *APOE*4* allele increases susceptibility to MI in the presence of the −491T variant and diets that are high in saturated fat and suggests that population differences in the observed effects of the *APOE*4* variants on the risk of MI can be explained by background genetic factors and diet. Results from two meta-analyses concluded that carriers of the *APOE*4* allele are at increased risk of CHD, although great variation exists be-

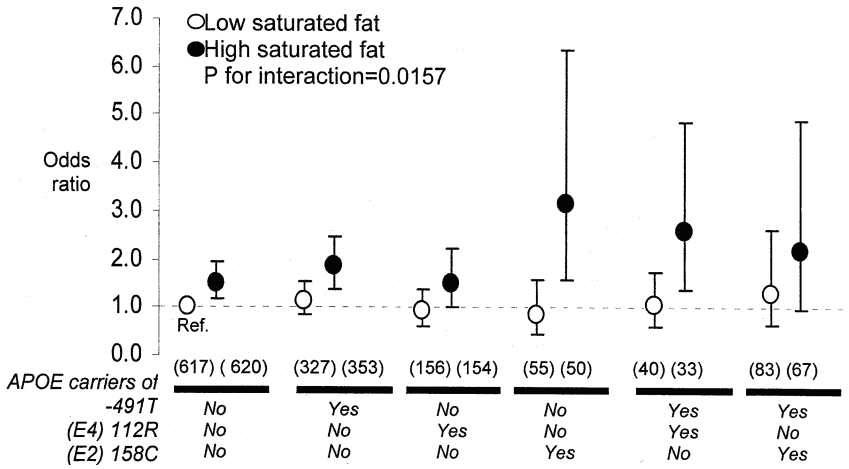

Figure 1. Odds ratio for myocardial infarction by *APOE* genotype and saturated fat intake. Data on saturated fat are shown for the lowest tertile (<9.3%) and the highest tertile (>11.8%) of saturated fat intake, labeled as low saturated fat (open circles) and high saturated fat (filled circles). The sample size for each group is shown in parentheses.

tween studies (Wilson et al. 1996; Song et al. 2004). Because most studies have been conducted in developed countries with higher intakes of saturated fat, it is not surprising that an overall positive association between the *APOE*4* allele and risk of CHD has been observed. Our data show that the *APOE*4* allele is not associated with increased susceptibility to MI in the absence of the −491T variant. Because the presence of the −491T allele is unknown for previous studies, differences in variation at this site could also explain some of the discrepant results. The observed association between *APOE*4*, saturated fat, and MI in this study is consistent with intervention studies showing that carriers of the *APOE*4* variant have a greater plasma LDL cholesterol response to diets high in saturated fat (Ordovas and Mooser 2002). In the current study we also observed that a diet high in saturated fat increased LDL cholesterol levels to a greater extent among carriers of the *APOE*4* allele compared to noncarriers.

It is interesting to note that the presence of the −491T variant was required to detect the association with MI among *APOE*4* carriers. In general, in Western countries carriers of the *APOE*4* allele have higher plasma levels of LDL cholesterol and triglycerides compared to noncarriers (Mahley and Rall 2000; Ballantyne et al. 2000; Dallongeville et al. 1992). In our study we found higher plasma triglyceride levels among *APOE*4* allele carriers regardless of the intake of saturated fat. However, our data suggest that this lipid effect may not be sufficient per se to increase the risk of MI among *APOE*4* carriers. It has been shown that the −491T variant lowers *APOE* transcription and apoE levels in plasma (Artiga

et al. 1998; Roks et al. 2002). It is possible that the presence of high saturated fat and the −491T allele in addition to *APOE*4* leads to greater increases in LDL cholesterol levels and CHD risk because there is less apoE available for clearance of VLDL and IDL particles before they are converted to LDL.

It has long been known that the *APOE*2* variant causes lower LDL cholesterol levels in plasma, and consequently a number of studies have suggested that the presence of this allele is protective against MI (e.g., Song et al. 2004). We were not able to identify an overall protective effect of *APOE*2* on MI risk. In fact, our study showed that *APOE*2* conferred increased susceptibility to MI risk in the context of diets that are high in saturated fat. It is well established that the presence of the *APOE*2* allele leads to decreased binding affinity of apoE-containing particles to hepatic B/E receptors (Mahley and Rall 2000; Dallongeville et al. 1992; Davignon et al. 1999). This characteristic can result in an accumulation of atherogenic remnant triglyceride-rich lipoproteins and large VLDL cholesterol particles in plasma (Mahley and Rall 2000; Dallongeville et al. 1992; Davignon et al. 1999). It is possible that this potentially atherogenic effect of the *APOE*2* allele is magnified by saturated fat, offsetting the potential benefit of low levels of LDL cholesterol that characterize *APOE*2* carriers.

We also examined the promoter −219 G/T and rs769450 variants in a subset of 971 case subjects and 1,020 control subjects, but found similar allele frequencies between the case and control groups, suggesting no involvement of these two genetic variants in MI risk in this population. The promoter −219 G/T variant, which has been reported to be common and associated with a higher risk of MI in European populations (Viitanen et al. 2001; Lambert et al. 2000), is rare in the Costa Rican population. Given that Spanish ancestors were some of the recent founders of this population, the fate of the −219 G/T variant in the isolate of Costa Rica since colonization is of interest.

In sum, we found a significant interaction between *APOE* genotype, saturated fat intake, and risk of MI among residents of the Central Valley of Costa Rica. A diet high in saturated fat increased the risk of MI to a larger extent among carriers of the *APOE*4* allele in the presence of the −491T variant and among carriers of the *APOE*2* allele regardless of the −491 variant compared to noncarriers. This study supports the hypothesis that discrepant results in the observed effects of the *APOE*2* and *APOE*4* variants on the risk of MI can be explained by differences in saturated fat intake between the studied populations.

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Literature Cited

Artiga, M. J., M. J. Bullido, I. Sastre et al. 1998. Allelic polymorphisms in the transcriptional regulatory region of apolipoprotein E gene. *FEBS Lett.* 421(2):105–108.

Ballantyne, C. M., J. A. Herd, E. A. Stein et al. 2000. Apolipoprotein E genotypes and response of plasma lipids and progression-regression of coronary atherosclerosis to lipid-lowering drug therapy. *J. Am. Coll. Cardiol.* 36(5):1572–1578.

Dallongeville, J., S. Lussier-Cacan, and J. Davignon. 1992. Modulation of plasma triglyceride levels by apoE phenotype: A meta-analysis. *J. Lipid Res.* 33(4):447–454.

Davignon, J., J. S. Cohn, L. Mabile et al. 1999. Apolipoprotein E and atherosclerosis: Insight from animal and human studies. *Clin. Chim. Acta* 286(1–2):115–143.

Eichner, J. E., S. T. Dunn, G. Perveen et al. 2002. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *Am. J. Epidemiol.* 155(6):487–495.

Ewbank, D. C. 2002. Mortality differences by *APOE* genotype estimated from demographic synthesis. *Genet. Epidemiol.* 22(2):146–155.

Lambert, J. C., T. Brousseau, V. Defosse et al. 2000. Independent association of an *APOE* gene promoter polymorphism with increased risk of myocardial infarction and decreased APOE plasma concentrations—The ECTIM study. *Hum. Mol. Genet.* 9(1):57–61.

Laws, S. M., E. Hone, K. Taddei et al. 2002. Variation at the *APOE* −491 promoter locus is associated with altered brain levels of apolipoprotein E. *Mol. Psychiatr.* 7(8):886–890.

Laws, S. M., E. Hone, S. Gandy et al. 2003. Expanding the association between the *APOE* gene and the risk of Alzheimer's disease: Possible roles for *APOE* promoter polymorphisms and alterations in *APOE* transcription. *J. Neurochem.* 84(6):1215–1236.

Mahley, R. W., and S. C. Rall Jr. 2000. Apolipoprotein E: Far more than a lipid transport protein. *Annu. Rev. Genom. Hum. Genet.* 1:507–537.

Melendez, C. 1982. *Conquistadores y pobladores: Origenes historicos-sociales de los costarricenses.* San José, Costa Rica: Editorial Universidad Estatal a Distancia.

Molina-Jiménez, I. 1991. *Costa Rica 1800–1850: El legado colonial y la génesis del capitalismo.* San José, Costa Rica: Editorial de la Universidad de Costa Rica.

Morera, B., R. Barrantes, and R. Marin-Rojas. 2003. Gene admixture in the Costa Rican population. *Ann. Hum. Genet.* 67(pt. 1):71–80.

Oikawa, S., A. Matsunaga, T. Saito et al. 1997. Apolipoprotein E Sendai (arginine 145 <arrow-R> proline): A new variant associated with lipoprotein glomerulopathy. *J. Am. Soc. Nephrol.* 8(5):820–823.

Ordovas, J. M., and V. Mooser. 2002. The *APOE* locus and the pharmacogenetics of lipid response. *Curr. Opin. Lipidol.* 13(2):113–117.

Roks, G., M. Cruts, J. J. Houwing-Duistermaat et al. 2002. Effect of the *APOE* −491 A/T promoter polymorphism on apolipoprotein E levels and risk of Alzheimer disease: The Rotterdam Study. *Am. J. Med. Genet.* 114(5):570–573.

Song, Y., M. J. Stampfer, and S. Liu. 2004. Meta-analysis: Apolipoprotein E genotypes and risk for coronary heart disease. *Ann. Intern. Med.* 141(2):137–147.

Tinoco, L. D. 1977. *Población de Costa Rica y orígines de los costarricenses.* San José, Costa Rica: Editorial Costa Rica.

Tunstall-Pedoe, H., K. Kuulasmaa, P. Amouyel et al. 1994. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 90(1):583–612.

Viitanen, L., J. Pihlajamaki, R. Miettinen et al. 2001. Apolipoprotein E gene promoter (−219 G/T) polymorphism is associated with premature coronary heart disease. *J. Mol. Med.* 79(12):732–737.

Wilson, P. W., E. J. Schaefer, M. G. Larson et al. 1996. Apolipoprotein E alleles and risk of coronary disease: A meta-analysis. *Arterioscler. Thromb. Vasc. Biol.* 16(10):1250–1255.