Does genetic variation in the Δ^6-desaturase promoter modify the association between α-linolenic acid and the prevalence of metabolic syndrome?[1–3]

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ABSTRACT

Background: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with protection against components of the metabolic syndrome, but the role of α-linolenic acid (ALA), the metabolic precursor of EPA and DHA, has not been studied. The Δ^6-desaturase enzyme converts ALA into EPA and DHA, and genetic variation in the Δ^6-desaturase gene (*FADS2*) may affect this conversion.

Objectives: We hypothesize that high ALA is associated with a lower prevalence of the metabolic syndrome and that genetic variation in *FADS*2 modifies this association.

Design: We studied 1815 Costa Rican adults. Adipose tissue ALA was used as a biomarker of intake, and metabolic syndrome was identified with the definition from the National Cholesterol Education Program, Adult Treatment Panel III. Prevalence ratios (PRs) and 95% CIs were estimated from binomial regression models, and the likelihood ratio was used to test for effect modification.

Results: High concentrations of adipose tissue ALA were associated with lower PRs of the metabolic syndrome compared with low ALA (0.81; 95% CI: 0.66, 1.00, for the comparison between the highest and the lowest quintiles; *P* for trend < 0.02). Higher concentrations of adipose tissue ALA were associated with a lower PR among homozygote (0.67; 95% CI: 0.53, 0.86) and heterozygote (0.84; 95% CI: 0.72, 0.99) carriers of the *FADS2* T allele, but not among homozygote carriers of the deletion variant allele (0.99; 95% CI: 0.78, 1.27; *P* for interaction: 0.08).

Conclusions: Elevated ALA concentrations in adipose tissue are associated with lower prevalence of the metabolic syndrome. A lack of association among homozygote carriers of the *FADS2* deletion allele suggests that this association may be due in part to the conversion of ALA into EPA.   *Am J Clin Nutr* 2009;89:920–5.

INTRODUCTION

The prevalence of the metabolic syndrome has been increasing worldwide (1). In the United States the prevalence for the period 1999–2002 was 34.5% (2). Several Latin American countries are experiencing an increasing prevalence of metabolic syndrome that is becoming closer to that in the United States. For example, the overall prevalence of metabolic syndrome in a representative sample of 11,550 adults aged 25–64 y living in major cities from Venezuela, Colombia, Argentina, Peru, Mexico, Ecuador, and Chile was 20% (range: 14–27%) (3). The collection of metabolic risk factors that define the metabolic syndrome include obesity, high blood pressure and plasma triglyceride concentrations, low HDL cholesterol, and impaired fasting glucose among others. Although diet can affect the individual components of metabolic syndrome, few studies have evaluated the role of fatty acids on the metabolic syndrome (4, 5). Intake of long-chain n−3 (omega-3) fatty acids improves certain components of the metabolic syndrome (6–12). However, increasing intake of long-chain n−3 fatty acids may not be achieved, given the growing concern about the sustainability of the world's fisheries (13), and there is a need to find other strategies to address n−3 fatty acid deficiencies worldwide (14). α-Linolenic acid (ALA; 18:3n−3) may be a sustainable alternative to achieve a higher intake of n−3 fatty acids. ALA, an essential fatty acid found predominantly in some vegetable oils such as soybean, canola, and flaxseed oil, has been associated with lower fasting glucose (15), but the role of this essential fatty acid on metabolic syndrome is unknown (15, 16).

ALA could exert its potentially protective metabolic effects directly or through conversion to eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3), which were shown to reduce plasma triglycerides (6–8) and blood pressure (9–11). A high intake of vegetable oils rich in ALA elevates plasma lipid fractions and neutrophil phospholipids concentrations of EPA to an amount comparable to that of a diet supplemented with fish oil when the background intakes of linoleic acid, EPA, and DHA are low (linoleic acid: 3.3% ± 0.8% of total energy, maximum twice per week of non–fatty fish meals) (17). The conversion of ALA into EPA is mediated by the rate-limiting enzyme Δ^6-desaturase (18). The presence of a variant T to deletion (T-del) in the promoter of the Δ^6-desaturase gene (*FADS2*) leads to reduced EPA concentrations in

plasma and adipose tissue (19), suggesting that this variant decreases enzyme activity and therefore conversion from ALA. The presence of the *FADS2* T-del variant is also associated with higher plasma triglyceride concentrations (19).

The purpose of this study was to *1*) examine whether increased ALA is associated with a lower prevalence of the metabolic syndrome and *2*) test whether this association is modified by the *FADS2* T-del variant. We hypothesized that the potentially protective association between ALA and the metabolic syndrome is attenuated among carriers of the deletion allele. ALA in adipose tissue, an excellent biomarker of intake available from all study participants, was used to assess diet.

SUBJECTS AND METHODS

Study population

The participants included in this study are control subjects ($n = 1815$) of a population-based case-control study of heart disease performed in Costa Rica from 1994 to 2004 (20, 21). The control subjects were selected by matching the case survivors of a first acute myocardial infarction for age (± 5 y), sex, and area of residence (county) according to the information available at the National Census and Statistics Bureau of Costa Rica. The participation rate for controls was 88%. This study was approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica. All subjects provided written informed consent.

Data collection

Trained personnel visited all study participants at their homes for collecting data, biological specimens, and anthropometric measurements. A general questionnaire was used to collect socio-demographic characteristics, medical history, and lifestyle habits. Dietary intake was collected with the use a food-frequency questionnaire that was developed and validated specifically to assess fatty acid intake among the Costa Rican population (22). Biological samples were always collected in the morning after an overnight fast. Subcutaneous adipose biopsies were collected from the upper buttock, with a 16-gauge needle, using a modified version of the method described by Beynen and Katan (23). Blood samples (20 mL) were drawn during the same visit in tubes containing 0.1% EDTA, after a 12–14-h fast. Tubes of blood were immediately stored at 4°C and protected from light. Within 36 h, they were centrifuged at 2500 rpm for 20 min at 4°C to isolate and divide the plasma and white blood cells into aliquots. Blood samples were sealed and stored under N_2, at -80°C until analysis in our laboratory.

Fatty acid analysis

Fatty acids from adipose tissue and plasma were quantified by gas-liquid chromatography (24, 25). Peak retention times and area percentages of total fatty acids were identified with the use of known standards (NuCheck Prep, Elysium, MN) and were analyzed with the ChemStation A.08.03 software (Agilent Technologies, Santa Clara, CA). Twelve duplicate samples, indistinguishable from others, were analyzed throughout the study for quality-control purposes. CVs were 3.87% for ALA and 14.2% for EPA. We have previously shown that adipose tissue ALA is a good biomarker of ALA intake (24, 25).

Single nucleotide polymorphism selection and genotyping

Of the 2 single nucleotide polymorphisms (SNPs) reported in the public databases in the core promoter region, the rs3834458 [T/$-$] polymorphism was selected because of its high frequency and its proximity to potential regulatory regions, such as binding sites for sterol regulatory element binding protein-1c (26) and peroxisome proliferator-activated receptor-α (27), which regulate the transcription of Δ^6-desaturase (28). An $\approx$1000-bp fragment containing regulatory regions in the promoter of the *FADS2* gene was resequenced in 96 subjects, but no novel SNPs were observed at this site among the Costa Ricans, as described previously (19). Genotyping was performed with the use of a variation of the allele-specific assay as previously described (19).

Metabolic syndrome

As detailed in the third report of the Adult Treatment Panel (29), subjects having ≥ 3 of the following criteria were defined as having the metabolic syndrome: abdominal circumference >102 cm in men or >88 cm in women, hypertriglyceridemia [serum triacylglycerols ≥ 1.69 mmol/L (150 mg/dL)], low HDL cholesterol [serum HDL cholesterol < 1.03 mmol/L (40 mg/dL) in men or < 1.28 mmol/L (50 mg/dL) in women], hypertension (blood pressure $> 130/85$ mm Hg), impaired fasting glucose [blood glucose ≥ 5.6 mmol/L (100 mg/dL)]. Subjects using antihypertensive or diabetic medication were considered to meet the criteria for hypertension or impaired fasting glucose, respectively. The fasting glucose cutoff was lowered to 100 mg/dL to reflect revised guidelines for impaired fasting glucose (29, 30).

Statistical analysis

All data were analyzed with the Statistical Analysis Systems software version 9.1 (SAS Institute Inc, Cary, NC). A total of 1956 subjects had information available on adipose tissue fatty acids. After deleting missing values, 1815 participants with complete data on adipose fatty acids, *FADS2* genotypes, and potential confounders were included in the final analysis evaluating the effect of *FADS2* genotypes on the relation of ALA and the risk of metabolic syndrome. Differences in the distribution of potential confounding variables, demographics, and components of the metabolic syndrome for subjects with and without the metabolic syndrome were calculated by performing *t* tests (for continuous, normally distributed variables) and the Wilcoxon's signed-rank test (for nonnormally distributed variables) and chi-square tests for categorical variables. Prevalence ratios (PRs) and 95% CIs were estimated from binomial regression models, given the high prevalence of metabolic syndrome and the components of the metabolic syndrome in this population. To test for trends across quintiles of ALA, the median intake of each quintile was set to each subject in the same quintile and treated as a continuous variable in regression analyses. The median was used to classify participants into low and high adipose tissue ALA groups. Likelihood ratio was used to test for interactions.

RESULTS

The general characteristics of the study population for metabolic syndrome status are shown in **Table 1**. A total of 656 subjects (36% of the sample) met the definition of the metabolic syndrome from the National Cholesterol Education Program

TABLE 1
General characteristics of the Costa Rican population by metabolic syndrome status ($n = 1815$)[1]

	Metabolic syndrome[2]		
	No ($n = 1159$)	Yes ($n = 656$)	P[3]
General characteristics			
Age (y)	57 ± 12[4]	61 ± 10	<0.0001
Sex (% of female)	19	40	<0.0001
Residence (% of rural)	41	36	0.052
Current smoker (% of ≥1 cigarettes/d)	25	14	<0.0001
Income (US$/mo)[5]	583 ± 430	574 ± 416	0.84
Physical activity (METs)	1.60 ± 0.71	1.46 ± 0.53	0.0008
BMI (kg/m²)[5]	25.0 ± 3.4	28.9 ± 4.4	<0.0001
Dietary variables			
Total calories (kcal)	2487 ± 742	2343 ± 762	<0.0001
Carbohydrates (% of energy)	55.3 ± 7.6	55.4 ± 6.9	0.95
Protein (% of energy)	12.8 ± 2.1	13.3 ± 2.2	0.0001
Total fat (% of energy)	31.9 ± 6.1	31.8 ± 5.3	0.59
Saturated fat (% of energy)	10.4 ± 2.7	10.4 ± 2.7	0.71
Monounsaturated fat (% of energy)	11.9 ± 4.1	11.6 ± 3.3	0.74
Polyunsaturated fat (% of energy)	6.2 ± 2.0	6.4 ± 2.1	0.13
trans Fat (% of energy)	1.3 ± 0.6	1.3 ± 0.6	0.64
Linoleic acid (% of energy)	6.22 ± 2.16	6.42 ± 2.24	0.12
EPA (% of energy)	0.04 ± 0.04	0.04 ± 0.04	0.10
DHA (% of energy)	0.07 ± 0.06	0.07 ± 0.06	0.98
Fish intake (g/d)[6]	16.8 ± 14.4	17.1 ± 15.2	0.99
Alcohol intake (g/d)	6.6 ± 15.2	4.8 ± 11.7	0.003
Fatty acids in adipose tissue (g/100 g total fatty acids)			
α-Linolenic acid (18:3n−3)	0.68 ± 0.21	0.62 ± 0.20	<0.0001
Linoleic acid (18:2n−6)	15.8 ± 3.9	15.3 ± 3.7	0.03
Arachidonic acid (20:4 n−6)[5]	0.44 ± 0.13	0.52 ± 0.13	<0.0001
Total *trans* fatty acids	3.7 ± 1.1	3.5 ± 1.0	<0.0001
Genotype frequency (%)			0.53
TT	27	25	—
T/−	49	52	—
−/−	24	23	—

[1] METs, metabolic equivalents; EPA, eicosapentaenoic acid (20:5n−3); DHA, docosahexaenoic acid (22:6n−3); TT, homozygous for the wild-type allele; T/−, heterozygous; −/−, homozygous for the variant allele.

[2] According to the Adult Treatment Panel III criteria of abdominal obesity: waist girth > 102 cm for men and >88 cm for women; hypertriglyceridemia: fasting triacylglycerols ≥ 150 mg/dL; low HDL cholesterol: HDL cholesterol < 40 mg/dL for men and <50 mg/dL for women; high blood pressure: blood pressure ≥ 130/85 mm Hg; high glucose: fasting blood glucose ≥ 100 mg/dL.

[3] Determined with *t* tests (for continuous, normally distributed variables), the Wilcoxon's signed-rank test (for non-normally distributed variables), and chi-square tests for categorical variables.

[4] Mean ± SD (all such values).

[5] Values were missing for income (130), BMI (15), and adipose tissue arachidonic acid (1).

[6] Adjusted for total energy intake by the residuals method.

third report of the Adult Treatment Panel. These subjects were older, more likely to be women, less likely to be smokers and to be physically active, and had a higher body mass index (in kg/m²) than did subjects without the metabolic syndrome. Subjects with the metabolic syndrome had significantly lower ALA (0.62% compared with 0.68% of total fatty acids) in adipose tissue. Protein intake and adipose tissue arachidonic acid were significantly higher among subjects with metabolic syndrome, whereas alcohol intake, adipose tissue linoleic acid, and *trans* fatty acids were lower. No significant differences were observed in the distribution of the *FADS2* genotype across subjects with and without the metabolic syndrome.

The proportion of each component of the metabolic syndrome and plasma lipid concentrations by metabolic syndrome status are shown in **Table 2**. When evaluating potential confounding factors across quintiles of ALA in adipose tissue, the proportion of

women and alcohol consumption decreased across ALA quintiles. However, adipose tissue concentrations of linoleic acid and *trans* fatty acids showed increasing trends across quintiles of ALA. Other variables did not show any clear trend.

The association between metabolic syndrome and components of the metabolic syndrome and adipose tissue ALA is shown in **Table 3**. When adjusted for age, sex, and area of residence in model 1, the PRs decreased across increasing quintiles of ALA with a value of 0.72 (95% CI: 0.59, 0.88) in the highest quintile of ALA (*P* for trend < 0.0001). After adjustment for other potential confounders, the association was attenuated, but a significant linear trend remained ($P = 0.02$). Further adjustments for other dietary variables (fiber and saturated fat intakes) and income did not change the results. The association between ALA and metabolic syndrome remained significant independent of the definition used. PRs by quintile of ALA with the use of the

TABLE 2
Components of the metabolic syndrome and plasma lipids by metabolic syndrome status ($n = 1815$)

	Metabolic syndrome[1]		
	No ($n = 1159$)	Yes ($n = 656$)	P^2
Individual components of the metabolic syndrome (%)			
Abdominal obesity	5	52	<0.0001
Hypertriglyceridemia	58	91	<0.0001
Low HDL cholesterol	51	85	<0.0001
High blood pressure	24	79	<0.0001
High fasting glucose	5	38	<0.0001
Plasma lipids (mg/dL)			
Total cholesterol[3]	210 ± 43[4]	204 ± 39	0.004
LDL cholesterol[3]	132 ± 36	121 ± 35	<0.0001
HDL cholesterol	42 ± 9	39 ± 8	<0.0001
Triacylglycerols	202 ± 129	246 ± 125	<0.0001

[1] According to the Adult Treatment Panel III criteria of abdominal obesity: waist girth > 102 cm for men and >88 cm for women; hypertriglyceridemia: fasting triacylglycerols ≥ 150 mg/dL; low HDL cholesterol: HDL cholesterol < 40 mg/dL for men and <50 mg/dL for women; high blood pressure: blood pressure ≥ 130/85 mm Hg; high glucose: fasting blood glucose ≥ 100 mg/dL.

[2] Determined with *t* tests (for continuous, normally distributed variables), Wilcoxon's signed-rank test (for nonnormally distributed variables), and chi-square tests for categorical variables.

[3] Values were missing for total cholesterol (1) and LDL cholesterol (138).

[4] Mean ± SD (all such values).

International Diabetes Federation definition were 1.01 (95% CI: 0.89, 1.14), 0.91 (95% CI: 0.80, 1.04), 0.85 (95% CI: 0.73, 0.98), and 0.80 (0.67, 95% CI: 0.94) (*P* for trend: 0.001). About the components of the metabolic syndrome, ALA is mainly associated with decreased prevalence of increased waist circumference. ALA is also associated with decreased prevalence of high blood pressure in the model adjusted for age, sex, and area, but after adjusting for other potential confounders the *P* value became borderline significant. ALA is not associated with the other components of the metabolic syndrome (high triacylglycerols, low HDL, and impaired fasting glucose).

The PRs for the metabolic syndrome according to genotype and stratified by ALA concentration (low and high according to the median levels) are shown in **Figure 1**. Subjects with high

TABLE 3
Prevalence ratios and 95% CIs for the metabolic syndrome (MS) and each component of the MS by quintile (Q) of α-linolenic acid (ALA) in adipose tissue in Costa Rica ($n = 1815$)

	Q1	Q2	Q3	Q4	Q5	*P* for trend
Median adipose tissue ALA[1]	0.42	0.53	0.63	0.74	0.93	
MS/no MS (*n*)	161/202	149/214	129/234	116/247	101/262	
MS						
Model 1[2]	1.00	0.99 (0.85, 1.15)[3]	0.86 (0.73, 1.02)	0.80 (0.67, 0.96)	0.72 (0.59, 0.88)	<0.0001
Model 2[4]	1.00	1.01 (0.86, 1.17)	0.91 (0.76, 1.08)	0.86 (0.72, 1.04)	0.81 (0.66, 1.00)	0.02
Increased waist girth						
Model 1[2]	1.00	0.94 (0.75, 1.16)	0.90 (0.72, 1.13)	0.84 (0.66, 1.06)	0.56 (0.41, 0.76)	0.0002
Model 2[4]	1.00	0.99 (0.79, 1.23)	0.96 (0.76, 1.20)	0.95 (0.74, 1.21)	0.66 (0.48, 0.92)	0.0254
High triacylglycerols						
Model 1[2]	1.00	1.05 (0.96, 1.14)	0.93 (0.84, 1.02)	0.90 (0.82, 1.00)	0.94 (0.85, 1.03)	0.0215
Model 2[4]	1.00	1.05 (0.96, 1.15)	0.93 (0.84, 1.03)	0.93 (0.84, 1.03)	0.98 (0.89, 1.08)	0.21
Low HDL						
Model 1[2]	1.00	1.00 (0.91, 1.10)	0.96 (0.87, 1.06)	1.00 (0.91, 1.10)	1.03 (0.93, 1.14)	0.636
Model 2[4]	1.00	1.01 (0.91, 1.12)	0.97 (0.87, 1.08)	1.00 (0.90, 1.11)	1.02 (0.91, 1.14)	0.7099
High blood pressure						
Model 1[2]	1.00	0.95 (0.82, 1.09)	0.86 (0.74, 1.01)	0.88 (0.75, 1.02)	0.82 (0.70, 0.96)	0.0091
Model 2[4]	1.00	0.94 (0.82, 1.08)	0.87 (0.75, 1.01)	0.90 (0.77, 1.05)	0.86 (0.73, 1.01)	0.0623
Impaired fasting glucose						
Model 1[2]	1.00	0.99 (0.73, 1.34)	1.02 (0.76, 1.37)	0.83 (0.60, 1.15)	0.82 (0.59, 1.13)	0.1312
Model 2[4]	1.00	1.03 (0.76, 1.41)	1.06 (0.78, 1.45)	0.92 (0.66, 1.29)	0.93 (0.66, 1.32)	0.5261

[1] To test for trends across quintiles of ALA, the median intake of each quintile was set to each subject in the same quintile and treated as a continuous variable in regression analyses.

[2] Adjusted for age, sex, and area of residence.

[3] Prevalence ratio from binomial regression models; 95% CI in parentheses (all such values).

[4] As in model 1 with additional adjustment for smoking status, physical activity, adipose tissue *trans* fatty acids, and alcohol intake. Further adjustments did not change the results.

ALA adipose tissue had a lower PR of metabolic syndrome across all 3 genotypes than did subjects with low ALA concentrations. However, subjects who were wild type for the *FADS2* polymorphism had the lowest PR (0.67; 95% CI: 0.53, 0.86), followed by subjects heterozygous for the polymorphism (PR: 0.84; 95% CI: 0.72, 0.99), with subjects homozygous for the *FADS2* polymorphism having the highest PR (0.99; 95% CI: 0.78, 1.27; *P* for interaction: 0.08).

DISCUSSION

Consistent with our hypothesis, subjects with higher concentrations of adipose tissue ALA had lower PRs for metabolic syndrome than did subjects with low concentrations of adipose tissue ALA. Furthermore, a lack of association among homozygote carriers of the *FADS2* deletion allele suggests that this association may be due in part to the conversion of ALA into EPA.

Evidence about the direct effect of ALA on the metabolic syndrome is scarce (16). Significant correlations between ALA in plasma triacylglycerols and apolipoprotein B and LDL diameter were reported in a study performed among 97 white men with a mean age of 45.1 ± 7.2 y (31). ALA was associated negatively with apolipoprotein B and positively with LDL diameter. However, correlations with components of the metabolic syndrome (triacylglycerols, HDL cholesterol, blood pressure, body mass index, and insulin) were low and not significant, although in the expected direction it was positively related with HDL and LDL diameter and inversely related with the rest (31). The association between ALA and metabolic syndrome seen in the Costa Rican study may be due to the many protective properties of the metabolites of ALA, EPA and DHA. The ability of these long-chain n−3 fatty acids to lower plasma triacylglycerols is the best supported by the literature (32–34). Elevated plasma HDL-cholesterol concentrations were also observed along with high EPA and DHA consumption (32, 35). However, the effect of long-chain n−3 fatty acids on insulin sensitivity varies according to the metabolic characteristics of the population (36). Positive effects were found among subjects with hypertriglyceridemia (7) and subjects with hypertension (37), whereas results in subjects with diabetes are inconsistent, with studies showing negative (38) and positive (39) results. It has been suggested that the role of long-chain n−3 fatty acids on insulin sensitivity depends on inflammatory status (36). The hypotensive properties of long-chain n−3 fatty acids are also well established (11).

Although the interaction between ALA and *FADS2* genotype was borderline significant, we found a clear positive trend in the PR for metabolic syndrome across genotype. Homozygote carriers of the wild-type *FADS2* allele had the lowest PR, followed by subjects heterozygous for the *FADS2* variant allele. No association between ALA and metabolic syndrome was found for homozygote carriers of the *FADS2* variant allele. We have previously shown that the *FADS2* variant allele is associated with lower concentrations of long-chain polyunsaturated fatty acids as well as with increased plasma triacylglycerols in a dose-response manner, suggesting a lower conversion of ALA into EPA and DHA (19). Thus, a higher prevalence of metabolic syndrome among those homozygous for this variant suggests that the potential protective properties of ALA may be due to its metabolism into long-chain n−3 fatty acids. The importance of this biosynthetic pathway emphasizes the role of EPA and DHA derived from dietary ALA among populations with low fish intake in attenuating the symptoms of the metabolic syndrome. Furthermore, the Δ^6-desaturase is shared by both the n−3 and n−6 metabolic pathways. A high ratio of dietary linoleic acid to ALA in the diet may decrease the efficacy of ALA regardless of the amount of its absolute consumption because the synthesis of ALA into EPA may be decreased in diets high in linoleic acid as a result of the competition for the Δ^6-desaturase (28). Adipose tissue linoleic acid, an excellent biomarker of long-term intake of linoleic acid (24, 25), is higher in US populations [18.5% in the Nurses' Health Study (40) and 20.5% in the Adventists Health Study (41)] than in Costa Rica (15.6%). This could explain why ALA may not be associated with metabolic syndrome in other populations with a higher intake of linoleic acid. Nevertheless, it is also possible that ALA exerts protective effects on its own.

Strengths of this study lie in the large sample size, the high participation rate, the representativeness of the sample of the Costa Rican population, and the use of adipose tissue to assess ALA intake. Adipose tissue samples were shown to be more valid in measuring long-term dietary intake than questionnaire-based methods (24, 25). As in all observational studies we cannot establish a causal relation, and results from our cross-sectional study should be confirmed with the use of a longitudinal design. Our results are not likely to be confounded by age, sex, area of residence, smoking, physical activity, and other dietary factors, but we cannot totally rule out residual confounding. Finally, it is possible that the T-del is in linkage disequilibrium with other functional SNPs in the *FADS2* gene, and further studies assessing more polymorphisms in this gene are warranted.

In conclusion, we found an association between high concentrations of adipose ALA and a decreased prevalence of the metabolic syndrome within a Costa Rican population with low fish intake. Furthermore, we established a novel relation between the *FADS2* variant, ALA, and metabolic syndrome, suggesting that genetic variation may play an important role along with diet in the development of the metabolic syndrome in this population.
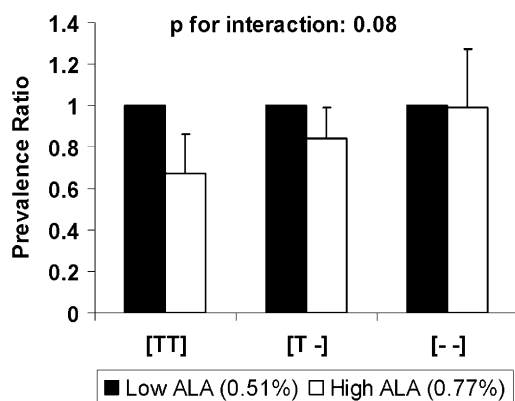

FIGURE 1. Prevalence ratios for metabolic syndrome by genotype and α-linolenic acid (ALA) concentration in Costa Rica (*n* = 1815). Values are prevalence ratios and 95% CIs from binomial regression models. Adjusted for age, sex, area of residence, smoking status, physical activity, adipose tissue *trans* fatty acids, and alcohol intake. Further adjustments did not appreciably alter the results. Likelihood ratio was used to test for interaction. TT, homozygous for the wild-type allele; T−, heterozygous; −−, homozygous for the variant allele.

Future studies will be of special importance in those populations in which the intake of ALA and long-chain n−3 fatty acids (EPA and DHA) from fish is low.

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