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# Genetic variation in fatty acid elongases is not associated with intermediate cardiovascular phenotypes or myocardial infarction

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## Abstract

**BACKGROUND/OBJECTIVES—**Elongases 2, 4 and 5, encoded by genes *ELOVL2, ELOVL4* and *ELOVL5*, have a key role in the biosynthesis of very long chain polyunsaturated fatty acids (PUFAs). To date, few studies have investigated the associations between elongase polymorphisms and cardiovascular health. We investigated whether *ELOVL* polymorphisms are associated with adipose tissue fatty acids, serum lipids, inflammation and ultimately with nonfatal myocardial infarction (MI) in a Costa Rican population.

**SUBJECTS/METHODS—**MI cases ($n$ = 1650) were matched to population-based controls ($n$ = 1650) on age, sex and area of residence. Generalized linear and multiple conditional logistic regression models were used to assess the associations between seven common *ELOVL* polymorphisms and cardiometabolic outcomes. Analyses were replicated in The Nurses' Health Study ($n$ = 1200) and The Health Professionals Follow-Up Study ($n$ = 1295).

**RESULTS—**Variation in *ELOVL2, ELOVL4* and *ELOVL5* was not associated with adipose tissue fatty acids, intermediate cardiovascular risk factors or MI. In the Costa Rica study, the number of the minor allele copies at rs2294867, located in the *ELOVL5* gene, was associated with an increase in total and LDL cholesterol (adjusted $P$-values = 0.001 and <0.0001 respectively). Additionally, the number of the minor allele copies at rs761179, also located in the *ELOVL5* gene, was significantly associated with an increase in total cholesterol (adjusted $P$-value = 0.04). However, the observed associations were not replicated in independent populations.

**CONCLUSION—**Common genetic variants in elongases are not associated with adipose tissue fatty acids, serum lipids, biomarkers of systemic inflammation, or the risk of MI.



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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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### Keywords

fatty acid elongases; inflammation; cholesterol; triglycerides; myocardial infarction; Costa Rica

## INTRODUCTION

Elongases of very long chain fatty acids 2, 4 and 5, encoded by genes *ELOVL2, ELOVL4* and *ELOVL5*, respectively, have a key role in the biosynthetic pathway of polyunsaturated fatty acids (PUFAs).[1,2] As numerous epidemiological and laboratory studies have demonstrated associations between PUFA metabolism and the risk of several complex diseases, it is likely that genetic variants in the *ELOVL* family that alter expression or efficiency of elongases have implications for chronic disease development.[3]

Because the *ELOVL* genes were cloned only recently, the evidence for their role in human disease pathogenesis is extremely limited. A genome-wide association study demonstrated associations of single nucleotide polymorphisms (SNPs) in the *ELOVL2* gene with plasma and erythrocyte concentrations of several n-3 and n-6 very long-chain PUFAs in a cohort of US residents of European descent.[4] These associations were subsequently replicated in a meta-analysis of five genome-wide studies of total 8866 participants of European ancestry.[5] Finally, a candidate gene study conducted in the Chinese Han population reported a null association between variation in rs3756963 (*ELOVL2*) and the risk of coronary artery disease, although there was suggestive evidence of association between the outcome and the combined genotype of rs3756963 and rs174556 in the *FADS1* gene.[6]

Associations between other elongase genes and chronic disease outcomes are even less investigated. A genome-wide scan identified *ELOVL5* as a susceptibility gene for normal tension glaucoma,[7] whereas other reports linked changes in expression of elongase 5 to increased risk of depressive disorders.[8,9] Additionally, a variant in *ELOVL5* that has been linked to lower enzymatic activity has been shown to modulate the relation between breastfeeding and cognition in children.[10]

The mechanisms underlying the observed associations between elongases and disease risk are unclear but probably involve changes in conversion of precursor fatty acids, namely alpha-linolenic and linoleic, into very long-chain fatty acids.[4-10] We hypothesize that polymorphisms in *ELOVL2, ELOVL4* and *ELOVL5* genes that affect enzyme expression or efficiency are associated with changes in very long-chain PUFA biosynthesis, and therefore with changes in intermediate cardiovascular risk factors and ultimately in the risk of nonfatal myocardial infarction (MI). Furthermore, our study aims to evaluate whether elongase polymorphisms modify the established associations of dietary precursor PUFAs with cardiovascular outcomes in a population characterized by comparatively low intake of long-chain n-3 fatty acids.

## SUBJECTS AND METHODS

### Study populations

The population of the Costa Rica Study, described in detail in prior publications, included 4548 unrelated Hispanics who resided in the Central Valley of Costa Rica between 1994 and 2004.[11-13] Cases of first nonfatal acute MI were ascertained by two independent cardiologists and deemed eligible if they met the World Health Organization criteria, survived hospitalization, were under 75 years of age on the day of their first MI, and able to answer the questionnaire.[14] Cases were matched by 5-year age group, sex and area of residence to population controls, identified randomly using data from the National Census

and Statistics Bureau of Costa Rica. All cases and controls received home visits, during which trained study workers collected lifestyle and medical history data, anthropometric measurements and biological specimens. Participation was 98% for cases and 88% for controls. The study population is appropriate for investigating genetic markers of disease due to its origin in a small number of founders and low rates of migration.[15]

The original sample size was 2274 cases and 2274 controls. Participants missing information on outcomes, exposure or covariates were excluded from the analysis. Excluded participants did not differ ($P>0.05$) from the included participants for demographic (age, sex and area of residence), dietary (linoleic acid (LA) and alpha-linolenic acid (ALA)) or genetic covariates (individual ancestral proportions), reducing the possibility of bias due to the complete case approach. All participants provided written informed consent. The study was approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica.

The replication study populations consisted of NHS (The Nurses' Health Study) and HPFS (The Health Professionals Follow-Up Study) participants. Detailed descriptions of the study cohorts have been published previously.[16,17] Information on design, covariate ascertainment and analysis of the replication cohorts can be found in Supplementary Information.

## Measurements of fatty acids, inflammatory biomarkers and lipids

Dietary intake of fatty acids in the Costa Rica Study was ascertained using a semiquantitative food frequency questionnaire, developed and validated in the study population.[18] The questionnaire collected information on intake of 135 food items and 20 supplements, types of fat used in cooking and frying, intake of fried foods both at home and away and meat consumption practices. Additionally, the selection of the type of fat/oil used for cooking, frying and baking at home was confirmed by the interviewer by visual examination of the containers during the home visit. Fatty acid composition of all commonly consumed foods and oils was assessed in the same laboratory using the same standards and instruments for peak identification that were used to measure fatty acids in tissues.[19] Nutrient intake was estimated from questionnaire data (frequency of intake nutrient content/portion) using our Costa Rican fatty acid composition table and the United States Department of Agriculture food composition tables at the Channing laboratory for other nutrients.[19] The estimates regarding oil consumption from the questionnaire were complemented by asking each participant about their recipes for staple dishes and incorporating that information into the questionnaire data.[19]

The following fatty acids were measured in adipose tissue: 18:3n-3 (ALA), 18:2n-6 (LA), 18:3n-6 (GLA (gamma-linolenic acid)), 20:3n-3 (ETA (eicosatrienoic acid)), 20:2n-6 (EDA (eicosadienoic acid)), 20:3n-6 (DGA (dihomo-gamma-linolenic acid)), 20:4n-6 (AA (arachidonic acid)), 20:5n-3 (eicosapentaenoic acid (EPA)), 22:6n-3 (docosahexaenoic acid (DHA)), 22:4n-6 (ADA (adrenic acid)). All biological samples were collected following an overnight fast. Subcutaneous adipose biopsies, collected following an overnight fast, were performed with a 16-gauge needle using a modification of the method proposed by Beynen and Katan.[20] Fatty acids from adipose tissue were quantified by gas-liquid chromatography. Peak retention times and area percentages of total fatty acids were identified with the use of known standards (NuCheck Prep) and were analyzed with the ChemStation A.08.03 software (Agilent Technologies, Santa Clara, CA, USA).[21] Serum lipids were analyzed using enzymatic reagents (Boehringer-Mannheim, Mannheim, Germany) and CRP (C-reactive protein) levels were assessed using immunoturbidometry on Roche Modular P chemistry autoanalyzer (Hoffman La Roche, Basel, Switzerland).[22]

### SNP selection

In all, 31 SNPs were identified in the *ELOVL2, ELOVL4* and *ELOVL5* genes using information from the HapMap Project (www.hapmap.org) and the National Center of Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/). To increase efficiency, 10 of 31 SNPs were selected as the 'tagging' SNPs using linkage disequilibrium block information obtained from HaploView (version 4.2; Massachusetts Institute of Technology/ Harvard Broad Institute, Cambridge, MA, USA). SNPs were removed from the analysis if the frequency of the minor allele in the discovery cohort was under 10%, leaving eight polymorphisms: rs2295601 (*ELOVL2*), rs10498676 (*ELOVL2*), rs3734397 (*ELOVL2*), rs17239120 (*ELOVL4*), rs17544464 (*ELOVL5*), rs2115564 (*ELOVL5*), rs2294867 (*ELOVL5*) and rs761179 (*ELOVL5*).

### Genotyping

Genotyping was performed using the SNPlex Genotyping System (Applied Biosystems, Foster City, CA, USA). Genotyping was attempted on 4082 individuals (90% of the total study population); of those, call rates ranged from 82% (for rs17544464) to 94% (for rs17239120). Ancestry was estimated using a set of 39 informative markers with allele frequencies from Amerindian, European, and West African samples and expected variance of individual ancestry proportions was calculated using a maximum likelihood approach with high precision.[23] For participants missing genotype data, imputation was performed using MACH software (version 1.0, Ann Arbor, MI, USA) with HapMap CEU phased II data (release 21) as the reference panel. $R$-squared values for imputation ranged from 0.84 (rs761179) to 0.94 (rs2294867).

### Statistical analysis

Data were analyzed using the SAS software package (version 9.2; SAS Institute Inc., Cary, NC, USA). To assess the significance of differences in general characteristics and potential confounders, we used paired $t$-tests for continuous variables, McNemar's tests for categorical variables and Fisher's exact test for minor allele frequencies. The ALLELE procedure was used to test for deviations from Hardy-Weinberg equilibrium among controls. Of all SNPs, only rs2295601 was found to be in violation of the Hardy-Weinberg equilibrium and removed from all subsequent analyses.

Linear regression models, adjusted for dietary and demographic covariates, were fit among controls to evaluate the association between the *ELOVL* SNPs and the adipose tissue concentrations of very long chain PUFAs as well as plasma concentrations of hsCRP, VCAM-1 and serum lipids. Log-transformations were carried out for non-normally distributed variables (GLA, hsCRP and triglycerides) and geometric means were reported. The intermediate risk factors models were adjusted for age, sex, residence area, and ancestry, whereas the PUFA models were additionally adjusted for dietary intake of all 11 fatty acids: ALA, LA, GLA, EDA, ETA, DGA, AA, EPA, DPA (docosapentaenoic acid), DHA, ADA. The relation between *ELOVL* SNPs and the MI outcome was modeled using conditional logistic regression, adjusted for age, sex, residence area (by matching) and ancestry. A Bonferroni correction was implemented to adjust for multiple testing. Finally, departures from additivity were considered for SNPs rs2294867 and rs761179, and the precursor fatty acids (ALA and LA). For the outcomes that showed a statistically significant relationship with both fatty acids and SNPs (total and LDL cholesterol), interaction terms were added to the linear regression models, which were further adjusted for dietary and demographic confounders. Homogeneity across genotypes was assessed using partial $F$-tests.

## RESULTS

The general characteristics of the three populations are summarized by case/control status in Table 1. None of the selected SNPs differed significantly in minor allele frequency by disease status. Cases were more likely to report MI risk factors, specifically smoking and history of chronic disease, although controls in the Costa Rica Study had a higher average body mass index (possibly due to reverse causality). Additionally, cases in the Costa Rica Study had significantly lower adipose tissue concentrations of ALA and LA. Ancestral admixture proportions in the Costa Rican population did not vary by case-control status in the discovery cohort and were estimated at 58% European, 38% Amerindian and 4% West African.

In multivariate-adjusted models, none of the adipose tissue PUFAs were significantly associated with the number of minor allele copies in 7 *ELOVL* cluster SNPs (Table 2). Similarly, serum inflammatory markers (VCAM-1 and hsCRP), HDL cholesterol and triglycerides did not vary significantly by *ELOVL* genotypes (Supplementary Information). However, LDL and total cholesterol showed linear increases as the number of copies of the C allele in rs2294867 (*ELOVL5*) increased (*P*-values = <0.0001 and 0.0002 respectively, or <0.0001 and 0.001 after adjustment for multiple comparisons due to seven independent tests) in the Costa Rican population (Table 3). Similar trends were observed for rs761179, also in *ELOVL5*, although after adjustment for multiple comparisons due to seven independent tests only the increase in total cholesterol remained statistically significant (*P*-value = 0.04). These associations were not replicated in the NHS or the HPFS cohorts (Table 3).

The risk of first nonfatal myocardial infarction was not significantly associated with genetic variation in elongases, with the exception of rs17544464 in the Costa Rica Study (Table 4). However, that association is likely to be falsely positive, as it was not replicated in other cohorts and did not remain statistically significant upon adjustment for multiple testing. Additive interactions between the precursor fatty acids (ALA and LA) and SNPs rs2294867 and rs761179 were evaluated for the LDL and total cholesterol outcomes in the Costa Rica Study. We observed a borderline statistically significant ($P = 0.05$) interaction between rs2294867 and dietary intake of LA in the models with LDL cholesterol as the outcome (data not shown).

## DISCUSSION

Findings from our study demonstrated null associations of *ELOVL* polymorphisms with adipose tissue PUFAs, selected markers of systemic inflammation, serum lipids and nonfatal MI. The null fatty acid findings from our study contrast with the genome-wide scan conducted by Tanaka *et al.*,[4] which reported a suggestive association between an *ELOVL2* polymorphism (rs953413), increased plasma EPA in an Italian population and increased plasma DPA as well as decreased DHA in a cohort of Americans of European ancestry. Our results also diverge from those reported by the meta-analysis of genome-wide studies from the CHARGE consortium, which found statistically significant associations between minor alleles in *ELOVL2* SNPs, increased plasma EPA and DPA, and decreased DHA in participants of European descent.[5] One explanation for the discrepancy between our findings and previously published studies may lie in the measurement of fatty acids. While the Costa Rica Study ascertained fatty acids in adipose tissue, Tanaka *et al.* used red blood cells and the CHARGE consortium study measured PUFAs in plasma phospholipids. It is possible that the effect of elongase variation on the PUFA pathway is short-term and as such cannot be observed from adipose tissue samples, which, unlike plasma or erythrocyte samples, reflect habitual rather than recent dietary intake and fatty acid metabolism.

The robust associations between two *ELOVL5* polymorphisms and LDL cholesterol as well as total cholesterol observed in the Costa Rica Study were not replicated in either NHS or HPFS cohorts. The reasons underlying the failure to replicate are unclear but could indicate baseline differences between the discovery and replication populations in both genetic and environmental characteristics, or that the observed associations with serum cholesterol levels in the discovery cohort are false positives. For instance, whereas allele frequencies at the *ELOVL* loci were similar across cohorts, the prevalence of some environmental risk factors (that is, smoking or diagnosis of diabetes) was strikingly higher in the Costa Rica Study. Additionally, approximately a quarter of the Costa Rican population use palm oil and are thus likely to have lower intake of both long- and short-chain n-3 PUFAs than in both US cohorts.[11] As the efficiency and expression of enzymes such as desaturases and elongases are substrate-dependent, it is possible that the association between elongase variation and serum cholesterol levels is more pronounced at lower PUFA intake levels. Finally, although we have controlled for admixture in the Costa Rica Study using principal components, the observed associations could be due to residual confounding by population substructure. Interestingly, Lemaitre *et al.*[5] also reported inconsistency of associations with Hispanic samples, where the C allele of rs3734398 (*ELOVL2*) was associated with higher DPA and lower DHA but not EPA. Although lack of statistical power remains a plausible explanation for this discrepancy, it is also possible that there exist racial and/or ethnic differences in elongase activity.[5] As the first report on elongase polymorphisms in a Hispanic population, our study bridges an important research gap and helps elucidate the role of ancestry in PUFA metabolism.

Genetic variation in the elongase cluster was not associated with an increase in MI risk in any of the three cohorts. These findings are consistent with a recent small-scale candidate gene study in the Chinese Han population, which found no evidence of association between variation in rs3756963 (*ELOVL2*) and coronary artery disease.[6] However, because of the variety of physiological pathways relevant to PUFAs, the overall effect of elongase polymorphisms on MI risk is likely to involve a combination of mechanisms including but not limited to inflammation, changes in serum lipids and/or blood pressure, endothelial function, cardiac rhythm and thrombosis.[24,25] As a result, MI findings may be consistent across cohorts even when results involving a specific MI risk factor (high LDL- and total cholesterol) are not. Additionally, other reports suggest presence of epistatic interactions between *ELOVL2* and other genes involved in PUFA metabolism, namely *FADS1*, which encodes delta-5 desaturase and has been linked to cardiovascular outcomes.[6] Because of the complexity of the underlying biological pathways, further studies are necessary to comprehensively characterize the role of elongases in the etiology of heart disease.

To our knowledge, this is the first study to examine the relationship between elongase polymorphisms and intermediate cardiovascular disease risk factors including inflammation and serum lipids. In addition to the novelty of the question, the strengths of our study include its large size, high response rates, the representativeness of the sample of the Costa Rican population and extensive information on genetic and dietary covariates including biomarker measures. However, the results of this study should be interpreted in light of several important limitations. First, missing genotypes in the Costa Rica Study were imputed using the HapMap CEU population as referent, which may not be appropriate given considerable Amerindian and West African admixture in our cohort. Our sensitivity analyses (data not shown) demonstrated that excluding imputed samples did not affect the observed results, suggesting that any inaccuracies resulting from imputation were non-differential with regard to the outcomes and are thus unlikely to be a source of bias. Second, 5 out of 7 ELOVL SNPs were not directly genotyped in the replication cohorts and were also imputed using HapMap CEU data. However, the high quality of imputation, as indicated by the $r^2$ values exceeding 0.90, and the evidence of tight linkage disequilibrium in the *ELOVL*

cluster (data not shown) also reduce the possibility of biased findings. Finally, the observational nature of the three cohorts precludes from establishing any causal relations between the genetic and dietary exposures and the outcomes.

In conclusion, evidence from the Costa Rica Study as well as the NHS/HPFS cohorts does not support an association between variation in the elongase cluster, fatty acid metabolism and cardiovascular risk. Future studies are warranted to further explore the role of genetic variation in elongases in chronic disease etiology.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Table 1

General characteristics of the study populations

| *Variable* | *Costa Rica Study* | | *Nurses' Health Study* | | *Health Professionals Follow-Up Study* | |
|---|---|---|---|---|---|---|
| | *Cases (n = 1650)* | *Controls (n = 1650)* | *Cases (n = 403)* | *Controls (n = 797)* | *Cases (n = 435)* | *Controls (n = 860)* |
| Age, years | 58.4 ± 10.9 | 58.1 ± 11.1 | 60.2 ± 6.3 | 59.6 ± 6.5 | 64.5 ± 8.6 | 64.2 ± 8.6 |
| % Female | 26 | 26 | 100 | 100 | 0 | 0 |
| % History of hypertension | 39 | 30 | 50 | 27 | 37 | 29 |
| % History of hypercholesterolemia | 31 | 27 | 53 | 41 | 49 | 40 |
| % History of diabetes | 24 | 14 | 15 | 6 | 9 | 4 |
| % Current smokers | 39 | 22 | 27 | 25 | 10 | 9 |
| Body mass index, kg/m$^2$ | 25.9 ± 3.9 | 26.3 ± 4.3 | 26.6 ± 5.4 | 25.1 ± 4.3 | 26.0 ± 3.2 | 25.6 ± 3.3 |
| *Adipose tissue fatty acids, % total* | | | | | | |
| Alpha-linolenic | 0.62 ± 0.21 | 0.65 ± 0.21 | – | – | – | – |
| Linoleic | 15.1 ± 3.8 | 15.6 ± 3.8 | – | – | – | – |
| *Minor allele frequency, %* | | | | | | |
| rs10498676 (A/G) | 24 | 24 | 18 | 19 | 21 | 20 |
| rs3734397 (A/G) | 18 | 19 | 24 | 23 | 22 | 24 |
| rs17239120 (C/G) | 10 | 10 | 6 | 7 | 6 | 6 |
| rs17544464 (C/T) | 21 | 18 | 7 | 6 | 6 | 6 |
| rs2115564 (A/C) | 48 | 50 | 47 | 46 | 46 | 47 |
| rs2294867 (A/C) | 44 | 43 | 38 | 36 | 37 | 37 |
| rs761179 (C/T) | 25 | 26 | 37 | 34 | 36 | 34 |

## Table 2

Least square means[a] (+/– s.e.m.) of adipose fatty acids by genotype among controls in the Costa Rica Study (*n* = 1798 unless otherwise specified)

| | *Homozygous (major allele)* | *Heterozygous* | *Homozygous (minor allele)* | P-*value*[b] |
|---|---|---|---|---|
| *rs10498676 (ELOVL2)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.64 ± 0.02 | 0.43 |
| LA | 15.46 ± 0.10 | 15.66 ± 0.13 | 15.50 ± 0.30 | 0.34 |
| GLA (*n* = 1687) | 0.062 ± 0.0003 | 0.065 ± 0.002 | 0.063 ± 0.003 | 0.77 |
| EDA | 0.219 ± 0.002 | 0.222 ± 0.002 | 0.214 ± 0.005 | 0.96 |
| ETA | 0.0213 ± 0.0003 | 0.0210 ± 0.0004 | 0.0195 ± 0.0010 | 0.14 |
| DGA (*n* = 1771) | 0.318 ± 0.003 | 0.317 ± 0.004 | 0.296 ± 0.009 | 0.09 |
| AA (*n* = 1797) | 0.486 ± 0.005 | 0.486 ± 0.006 | 0.465 ± 0.013 | 0.32 |
| EPA | 0.042 ± 0.001 | 0.043 ± 0.001 | 0.043 ± 0.002 | 0.34 |
| DPA (*n* = 1797) | 0.187 ± 0.002 | 0.187 ± 0.002 | 0.179 ± 0.004 | 0.39 |
| DHA | 0.144 ± 0.002 | 0.146 ± 0.002 | 0.136 ± 0.005 | 0.63 |
| ADA | 0.206 ± 0.002 | 0.205 ± 0.003 | 0.195 ± 0.006 | 0.15 |
| *rs3734397 (ELOVL2)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.63 ± 0.02 | 0.39 |
| LA | 15.50 ± 0.10 | 15.58 ± 0.14 | 15.70 ± 0.39 | 0.49 |
| GLA (*n* = 1687) | 0.063 ± 0.001 | 0.063 ± 0.002 | 0.067 ± 0.005 | 0.74 |
| EDA | 0.219 ± 0.002 | 0.221 ± 0.003 | 0.219 ± 0.007 | 0.76 |
| ETA | 0.0208 ± 0.0003 | 0.0217 ± 0.0004 | 0.0208 ± 0.0013 | 0.23 |
| DGA (*n* = 1771) | 0.315 ± 0.003 | 0.321 ± 0.004 | 0.303 ± 0.012 | 0.76 |
| AA (*n* = 1797) | 0.484 ± 0.004 | 0.487 ± 0.006 | 0.484 ± 0.017 | 0.71 |
| EPA | 0.043 ± 0.001 | 0.042 ± 0.001 | 0.041 ± 0.003 | 0.34 |
| DPA (*n* = 1797) | 0.187 ± 0.002 | 0.185 ± 0.002 | 0.181 ± 0.006 | 0.18 |
| DHA | 0.143 ± 0.002 | 0.146 ± 0.002 | 0.147 ± 0.006 | 0.27 |
| ADA | 0.205 ± 0.002 | 0.205 ± 0.003 | 0.205 ± 0.008 | 0.95 |
| *rs17239120 (ELOVL4)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.66 ± 0.04 | 0.53 |
| LA | 15.52 ± 0.09 | 15.57 ± 0.17 | 16.32 ± 0.79 | 0.50 |
| GLA (*n* = 1687) | 0.064 ± 0.001 | 0.062 ± 0.002 | 0.059 ± 0.010 | 0.43 |
| EDA | 0.219 ± 0.002 | 0.222 ± 0.003 | 0.225 ± 0.015 | 0.31 |
| ETA | 0.0210 ± 0.0003 | 0.0212 ± 0.0006 | 0.0233 ± 0.0025 | 0.49 |
| DGA (*n* = 1771) | 0.317 ± 0.003 | 0.315 ± 0.005 | 0.305 ± 0.024 | 0.58 |
| AA (*n* = 1797) | 0.486 ± 0.004 | 0.483 ± 0.008 | 0.458 ± 0.035 | 0.48 |
| EPA | 0.042 ± 0.001 | 0.042 ± 0.001 | 0.042 ± 0.006 | 0.59 |
| DPA (*n* = 1797) | 0.187 ± 0.001 | 0.185 ± 0.003 | 0.182 ± 0.013 | 0.64 |
| DHA | 0.144 ± 0.001 | 0.145 ± 0.003 | 0.135 ± 0.013 | 0.93 |
| ADA | 0.205 ± 0.002 | 0.206 ± 0.004 | 0.203 ± 0.017 | 0.81 |
| *rs17544464 (ELOVL5)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.65 ± 0.02 | 0.30 |

| | *Homozygous (major allele)* | *Heterozygous* | *Homozygous (minor allele)* | P-*value*[b] |
|---|---|---|---|---|
| LA | 15.56 ± 0.10 | 15.44 ± 0.14 | 15.70 ± 0.35 | 0.79 |
| GLA (*n* = 1687) | 0.064 ± 0.001 | 0.063 ± 0.002 | 0.063 ± 0.004 | 0.69 |
| EDA | 0.220 ± 0.002 | 0.218 ± 0.003 | 0.225 ± 0.006 | 0.95 |
| ETA | 0.0211 ± 0.0003 | 0.0207 ± 0.0005 | 0.0233 ± 0.0011 | 0.52 |
| DGA (*n* = 1771) | 0.316 ± 0.003 | 0.317 ± 0.004 | 0.327 ± 0.011 | 0.41 |
| AA (*n* = 1797) | 0.486 ± 0.004 | 0.481 ± 0.006 | 0.487 ± 0.015 | 0.65 |
| EPA | 0.043 ± 0.001 | 0.042 ± 0.001 | 0.041 ± 0.003 | 0.40 |
| DPA (*n* = 1797) | 0.188 ± 0.002 | 0.182 ± 0.002 | 0.193 ± 0.006 | 0.27 |
| DHA | 0.145 ± 0.002 | 0.140 ± 0.002 | 0.149 ± 0.006 | 0.37 |
| ADA | 0.206 ± 0.002 | 0.203 ± 0.003 | 0.211 ± 0.007 | 0.87 |
| *rs2115564 (ELOVL5)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.63 ± 0.01 | 0.52 |
| LA | 15.46 ± 0.15 | 15.49 ± 0.11 | 15.68 ± 0.15 | 0.27 |
| GLA (*n* = 1687) | 0.063 ± 0.002 | 0.064 ± 0.001 | 0.064 ± 0.002 | 0.94 |
| EDA | 0.218 ± 0.003 | 0.220 ± 0.002 | 0.222 ± 0.003 | 0.41 |
| ETA | 0.0209 ± 0.0005 | 0.0211 ± 0.0003 | 0.0211 ± 0.0005 | 0.61 |
| DGA (*n* = 1771) | 0.316 ± 0.004 | 0.315 ± 0.003 | 0.320 ± 0.005 | 0.14 |
| AA (*n* = 1797) | 0.484 ± 0.007 | 0.483 ± 0.005 | 0.489 ± 0.007 | 0.59 |
| EPA | 0.043 ± 0.001 | 0.042 ± 0.001 | 0.043 ± 0.001 | 0.97 |
| DPA (*n* = 1797) | 0.187 ± 0.002 | 0.185 ± 0.002 | 0.188 ± 0.002 | 0.77 |
| DHA | 0.144 ± 0.002 | 0.144 ± 0.002 | 0.145 ± 0.002 | 0.95 |
| ADA | 0.203 ± 0.003 | 0.205 ± 0.002 | 0.206 ± 0.003 | 0.69 |
| *rs2294867 (ELOVL5)* | | | | |
| ALA | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.63 ± 0.01 | 0.46 |
| LA | 15.57 ± 0.13 | 15.51 ± 0.11 | 15.51 ± 0.17 | 0.73 |
| GLA (*n* = 1687) | 0.064 ± 0.002 | 0.064 ± 0.001 | 0.064 ± 0.002 | 0.38 |
| EDA | 0.223 ± 0.002 | 0.217 ± 0.002 | 0.221 ± 0.003 | 0.45 |
| ETA | 0.0212 ± 0.0004 | 0.0211 ± 0.0004 | 0.0207 ± 0.0005 | 0.51 |
| DGA (*n* = 1771) | 0.319 ± 0.004 | 0.316 ± 0.003 | 0.315 ± 0.005 | 0.50 |
| AA (*n* = 1797) | 0.489 ± 0.006 | 0.485 ± 0.005 | 0.476 ± 0.008 | 0.18 |
| EPA | 0.043 ± 0.001 | 0.042 ± 0.001 | 0.041 ± 0.001 | 0.36 |
| DPA (*n* = 1797) | 0.188 ± 0.002 | 0.186 ± 0.002 | 0.185 ± 0.003 | 0.34 |
| DHA | 0.146 ± 0.002 | 0.144 ± 0.002 | 0.142 ± 0.003 | 0.19 |
| ADA | 0.208 ± 0.003 | 0.205 ± 0.002 | 0.201 ± 0.004 | 0.11 |
| *rs761179 (ELOVL5)* | | | | |
| ALA | 0.64 ± 0.01 | 0.63 ± 0.01 | 0.60 ± 0.02 | 0.06 |
| LA | 15.61 ± 0.10 | 15.47 ± 0.12 | 15.23 ± 0.28 | 0.14 |
| GLA (*n* = 1687) | 0.064 ± 0.001 | 0.062 ± 0.001 | 0.064 ± 0.004 | 0.35 |
| EDA | 0.221 ± 0.002 | 0.218 ± 0.002 | 0.223 ± 0.005 | 0.61 |
| ETA | 0.0215 ± 0.0003 | 0.0207 ± 0.0004 | 0.0199 ± 0.0009 | 0.04 |
| DGA (*n* = 1771) | 0.318 ± 0.003 | 0.316 ± 0.004 | 0.306 ± 0.008 | 0.27 |
| AA (*n* = 1797) | 0.488 ± 0.005 | 0.482 ± 0.005 | 0.472 ± 0.013 | 0.19 |

| | *Homozygous (major allele)* | *Heterozygous* | *Homozygous (minor allele)* | P-*value*[b] |
|---|---|---|---|---|
| EPA | 0.043 ± 0.001 | 0.042 ± 0.001 | 0.041 ± 0.002 | 0.28 |
| DPA (*n* = 1797) | 0.187 ± 0.002 | 0.186 ± 0.002 | 0.183 ± 0.005 | 0.54 |
| DHA | 0.145 ± 0.002 | 0.143 ± 0.002 | 0.139 ± 0.005 | 0.16 |
| ADA | 0.207 ± 0.002 | 0.203 ± 0.003 | 0.200 ± 0.006 | 0.15 |

Abbreviations: AA, arachidonic acid; ADA, adrenic acid; ALA, alpha-linolenic acid; DGA, dihomo-gamma-linolenic acid; DHA, docosahexaenoic acid;DPA, docosapentaenoic acid; EDA, eicosadienoic acid; EPA, eicosapentaenoic acid; ETA, eicosatrienoic acid; GLA, gamma-linolenic acid; LA, linoleic acid; PUFA, polyunsaturated fatty acid.

[a]Models adjusted for age, sex, residence, ancestry and dietary intake of the following PUFAs: ALA, LA, GLA, EDA, ETA, DGA, AA, EPA, DPA, DHA and ADA.

[b]Unadjusted for multiple comparisons.

## Table 3

Least square means[a] (+/– s.e.m.) of total and LDL-cholesterol by genotype among controls

| | *Homozygous (major allele)* | *Heterozygous* | *Homozygous (minor allele)* | P-*value*[b] |
|---|---|---|---|---|
| *rs10498676 (ELOVL2)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 210.07 ± 1.40 | 208.90 ± 1.71 | 210.07 ± 4.10 | 0.71 |
| NHS (*n* = 797) | 224.92 ± 1.76 | 227.60 ± 2.51 | 242.50 ± 8.18 | 0.09 |
| HPFS (*n* = 860) | 202.27 ± 1.53 | 202.09 ± 2.20 | 208.06 ± 6.01 | 0.63 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 129.45 ± 1.26 | 127.92 ± 1.54 | 127.71 ± 3.70 | 0.41 |
| NHS (*n* = 797) | 133.42 ± 1.65 | 136.80 ± 2.35 | 146.79 ± 7.65 | 0.14 |
| HPFS (*n* = 860) | 125.98 ± 1.33 | 125.55 ± 1.90 | 131.63 ± 5.21 | 0.54 |
| *rs3734397 (ELOVL2)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 210.00 ± 1.31 | 208.50 ± 1.87 | 212.58 ± 5.30 | 0.80 |
| NHS (*n* = 797) | 227.66 ± 1.85 | 224.62 ± 2.38 | 222.01 ± 6.46 | 0.48 |
| HPFS (*n* = 860) | 201.38 ± 1.60 | 204.74 ± 2.07 | 199.49 ± 5.04 | 0.37 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 128.90 ± 1.18 | 127.93 ± 1.70 | 134.03 ± 4.89 | 0.85 |
| NHS (*n* = 797) | 135.66 ± 1.73 | 133.90 ± 2.23 | 133.00 ± 6.04 | 0.78 |
| HPFS (*n* = 860) | 125.44 ± 1.39 | 127.51 ± 1.80 | 124.02 ± 4.37 | 0.59 |
| *rs17239120 (ELOVL4)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 209.61 ± 1.21 | 209.97 ± 2.39 | 205.32 ± 10.77 | 0.98 |
| NHS (*n* = 797) | 225.58 ± 1.53 | 229.54 ± 3.97 | 250.44 ± 15.16 | 0.18 |
| HPFS (*n* = 860) | 202.61 ± 1.31 | 201.59 ± 3.61 | 192.40 ± 20.81 | 0.86 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 128.39 ± 1.09 | 130.51 ± 2.14 | 130.30 ± 9.37 | 0.37 |
| NHS (*n* = 797) | 134.41 ± 1.43 | 137.31 ± 3.72 | 148.62 ± 14.19 | 0.48 |
| HPFS (*n* = 860) | 125.78 ± 1.14 | 128.42 ± 3.13 | 123.50 ± 18.04 | 0.72 |
| *rs17544464 (ELOVL5)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 209.54 ± 1.31 | 209.02 ± 1.91 | 215.33 ± 4.73 | 0.57 |
| NHS (*n* = 797) | 225.78 ± 1.51 | 230.36 ± 4.33 | 235.71 ± 28.40 | 0.58 |
| HPFS (*n* = 860) | 202.95 ± 1.31 | 198.75 ± 3.61 | 198.57 ± 25.47 | 0.54 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 128.90 ± 1.18 | 127.42 ± 1.72 | 136.63 ± 4.38 | 0.61 |
| NHS (*n* = 797) | 134.43 ± 1.41 | 138.41 ± 4.05 | 151.65 ± 26.54 | 0.53 |
| HPFS (*n* = 860) | 126.43 ± 1.13 | 123.24 ± 3.13 | 137.02 ± 22.08 | 0.56 |
| *rs2115564 (ELOVL5)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 207.62 ± 2.04 | 208.68 ± 1.47 | 213.661 ± 2.04 | 0.40 |

| | *Homozygous (major allele)* | *Heterozygous* | *Homozygous (minor allele)* | P-*value*[b] |
|---|---|---|---|---|
| NHS (*n* = 797) | 223.99 ± 2.62 | 226.39 ± 2.04 | 229.22 ± 3.04 | 0.43 |
| HPFS (*n* = 860) | 204.12 ± 2.37 | 201.11 ± 1.69 | 203.74 ± 2.73 | 0.51 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 126.71 ± 1.85 | 127.47 ± 1.32 | 133.59 ± 1.85 | 0.29 |
| NHS (*n* = 797) | 132.97 ± 2.45 | 135.11 ± 1.91 | 137.05 ± 2.84 | 0.55 |
| HPFS (*n* = 860) | 125.22 ± 2.05 | 126.22 ± 1.47 | 126.89 ± 2.37 | 0.40 |
| *rs2294867 (ELOVL5)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 204.84 ± 1.79 | 210.83 ± 1.50 | 214.94 ± 2.31 | 0.0002 |
| NHS (*n* = 797) | 222.80 ± 2.22 | 229.71 ± 2.09 | 225.16 ± 3.97 | 0.07 |
| HPFS (*n* = 860) | 204.04 ± 1.97 | 201.33 ± 1.76 | 201.89 ± 3.53 | 0.58 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 124.85 ± 1.61 | 128.81 ± 1.35 | 135.60 ± 2.09 | < 0.0001 |
| NHS (*n* = 797) | 132.91 ± 2.08 | 136.86 ± 1.95 | 134.21 ± 3.71 | 0.37 |
| HPFS (*n* = 860) | 125.83 ± 1.71 | 126.77 ± 1.52 | 124.12 ± 3.06 | 0.73 |
| *rs761179 (ELOVL5)* | | | | |
| Total cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1788) | 207.49 ± 1.41 | 211.38 ± 1.67 | 217.37 ± 3.84 | 0.005 |
| NHS (*n* = 797) | 224.92 ± 2.15 | 226.74 ± 2.15 | 229.61 ± 4.04 | 0.57 |
| HPFS (*n* = 860) | 203.15 ± 1.89 | 201.40 ± 1.80 | 204.29 ± 3.74 | 0.70 |
| LDL cholesterol, mg/dl | | | | |
| Costa Rica Study (*n* = 1645) | 127.05 ± 1.28 | 129.86 ± 1.51 | 136.67 ± 3.47 | 0.008 |
| NHS (*n* = 797) | 134.49 ± 2.01 | 134.56 ± 2.01 | 137.57 ± 3.77 | 0.75 |
| HPFS (*n* = 860) | 125.34 ± 1.64 | 126.59 ± 1.56 | 126.79 ± 3.25 | 0.84 |

Abbreviations: HPFS, Health Professionals Follow-Up Study; LDL, low-density lipoprotein; NHS, Nurses' Health Study.

[a]Models fit to the Costa Rican data were adjusted for age, sex, residence, and ancestry. Models fit to the NHS and the HPFS data were adjusted for sex (by restriction) and age.

[b]Unadjusted for multiple comparisons.

## Table 4

The risk of nonfatal myocardial infarction by *ELOVL* polymorphism

| *SNP* | *OR (95% CI)* [a] | P-*value*[b] |
|---|---|---|
| *rs10498676 (ELOVL2)* | | |
| Costa Rica Study (*n* = 3300) | 1.01 (0.90, 1.13) | 0.88 |
| NHS (*n* = 1200) | 0.96 (0.76, 1.20) | 0.70 |
| HPFS (*n* = 1295) | 1.12 (0.92, 1.36) | 0.28 |
| *rs3734397 (ELOVL2)* | | |
| Costa Rica Study (*n* = 3300) | 0.98 (0.87, 1.11) | 0.77 |
| NHS (*n* = 1200) | 1.09 (0.88, 1.34) | 0.43 |
| HPFS (*n* = 1295) | 0.92 (0.76, 1.11) | 0.39 |
| *rs17239120 (ELOVL4)* | | |
| Costa Rica Study (*n* = 3300) | 0.95 (0.81, 1.11) | 0.51 |
| NHS (*n* = 1200) | 0.94 (0.66, 1.34) | 0.74 |
| HPFS (*n* = 1295) | 0.94 (0.66, 1.32) | 0.71 |
| *rs17544464 (ELOVL5)* | | |
| Costa Rica Study (*n* = 3300) | 0.87 (0.77, 0.98) | 0.02 |
| NHS (*n* = 1200) | 1.35 (0.94, 1.93) | 0.10 |
| HPFS (*n* = 1295) | 0.91 (0.63, 1.30) | 0.59 |
| *rs2115564 (ELOVL5)* | | |
| Costa Rica Study (*n* = 3300) | 0.91 (0.83, 1.01) | 0.07 |
| NHS (*n* = 1200) | 0.97 (0.82, 1.16) | 0.77 |
| HPFS (*n* = 1295) | 0.97 (0.82, 1.14) | 0.70 |
| *rs2294867 (ELOVL5)* | | |
| Costa Rica Study (*n* = 3300) | 0.94 (0.85, 1.03) | 0.20 |
| NHS (*n* = 1200) | 1.03 (0.86, 1.24) | 0.76 |
| HPFS (*n* = 1295) | 1.05 (0.89, 1.25) | 0.56 |
| *rs761179 (ELOVL5)* | | |
| Costa Rica Study (*n* = 3300) | 1.06 (0.94, 1.18) | 0.35 |
| NHS (*n* = 1200) | 0.96 (0.80, 1.15) | 0.66 |
| HPFS (*n* = 1295) | 1.07 (0.90, 1.27) | 0.45 |

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; OR, odds ratio.

[a] All odds ratios were estimated using additive models. Models fit to the Costa Rican data were adjusted for age/sex/residence (by matching) and ancestry. Models fit to the NHS and the HPFS data were adjusted for sex (by restriction) and age.

[b] Unadjusted for multiple comparisons.