Impact of *FADS* and *ELOVL2/5* Genetic Variation on Fatty Acid and Cardiometabolic Endpoints in Mexican American Individuals

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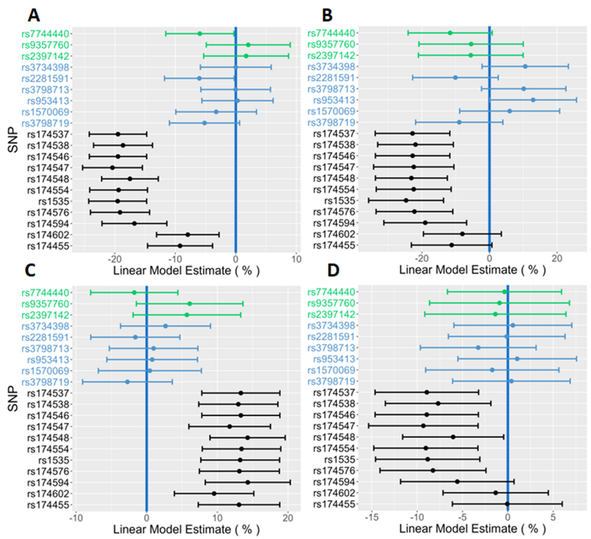
Objectives

- Hispanics are among those with the highest prevalence of obesity, diabetes, and cardiometabolic disease (CMD).
- Previous studies demonstrate fatty acid desaturase (*FADS*) variants within an ancestral haplotype are associated with a limited. capacity to synthesize highly unsaturated fatty acids (HUFAs), particularly n-3 HUFAs.
- These variants occur in high frequencies in Amerind (AI)-Ancestry populations, like Mexican Americans (MxAm).
- This study assesses whether *FADS* and other variants like elongases (*ELOVL2* and *ELOVL5*) in the HUFA biosynthetic pathway impact CMD risk in this population.

Methods

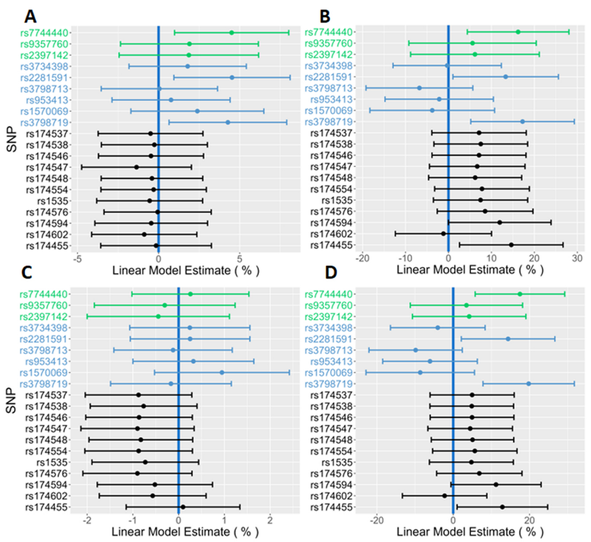
- Associations between genotypes and FA levels or CMD markers were tested using additive linear regression models (coded by 0, 1, 2, ancestral alleles). Covariate adjustments include age, sex, BMI, T2D status.
- Genotypes were determined from 20 single nucleotide polymorphisms in the *FADS1/2* and *ELOVL 2/5* gene regions.
- Levels of 37 fatty acids were measured by gas chromatography flame ionization detection.
- CMD markers included lipoproteins, weight, height, waist-hip ratio, adiponectin, AST/ALT, insulin, glucose, HbA1c, HOMA-IR, Matsuda and disposition indices.
- n=497 adult Latinos from the AIR cohort.

Figure 1: Primary Fatty Acid Associations



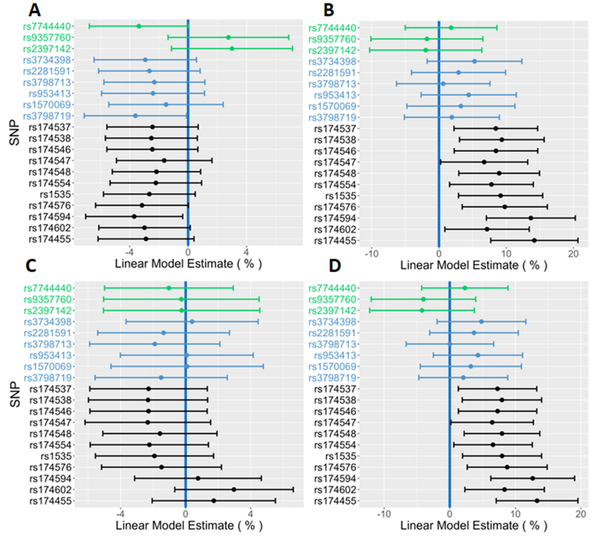
A) ARA, B) EPA, C) DGLA, D) DHA

Figure 2: Insulin Regulator Associations



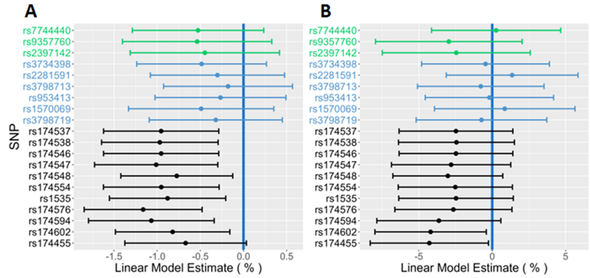
A) 2 Hr Glucose, B) HOMA-IR, C) Fasting Glucose, D) Fasting Insulin

Figure 3: Lipid Associations



A) HDL, B), TG, C) LDL, D) VLDL

Figure 4: Anthropometric Associations



A) Female Hip Circumference, B) Female Weight

Table 1: Comparision of Homozygous Genotypes

	FADS SNP	Homozygous Reference Allele (AI)	Homozygous Alternative Allele
Hip Circumference (cm)*	rs174576	107.63	110.19
Weight (kg)*	rs174602	77.68	84.79
Triglycerides (mg/dl)	rs174455	169.51	132.06
HDL (mg/dl)	rs174594	43.76	47.24
VLDL (mg/dl)	rs174455	25.12	19.84
Fasting Insulin (uIU/ml)	rs174455	10.40	8.27
HOMA-IR	rs174455	2.52	1.95

**all comparisons above are statistically significant ($p < .05$)
*females only

ELOVL2 SNPs *ELOVL5* SNPs *FADS* SNPs

Results

- *FADS* variants are significantly associated with primary n-6 and n-3 HUFA levels.
- HUFA levels are drastically reduced in AI-Ancestry, especially n-3 HUFAs, with ARA/EPA ~20:1 and ARA/DHA ~5:1, respectively.
- *FADS* and *ELOVL* variants are significantly associated with insulin regulator phenotypes, including HOMA-IR and fasting insulin where each *FADS* ancestral variant increases the parameter by 45% and 41%, respectively.
- *FADS* variants are significantly associated with TG and VLDL levels.
- *FADS* variants are significantly associated with hip circumference and weight in females.

Conclusions

- These results demonstrate significant associations between *FADS* (and some *ELOVL*) variants and primary HUFAs and CMD risk biomarkers.
- Higher numbers of *FADS* ancestral alleles relate to reduced HUFA levels (especially n-3).
- Higher numbers of *FADS* ancestral alleles. are associated with CMD risk biomarkers.
- ARA/EPA and ARA/DHA ratios may indicate reduced anti-inflammatory HUFA bioactives.
- These data suggest that genetically-induced alterations in HUFA levels and ratios may strongly impact CMD risk in MxAm populations, and that n-3 HUFA supplementation may be effective in MxAm populations.