Unraveling Ancestry-Based Gene-Diet Interactions Driving Health Disparities in Inflammation, Cardiovascular Disease, and Diabetes

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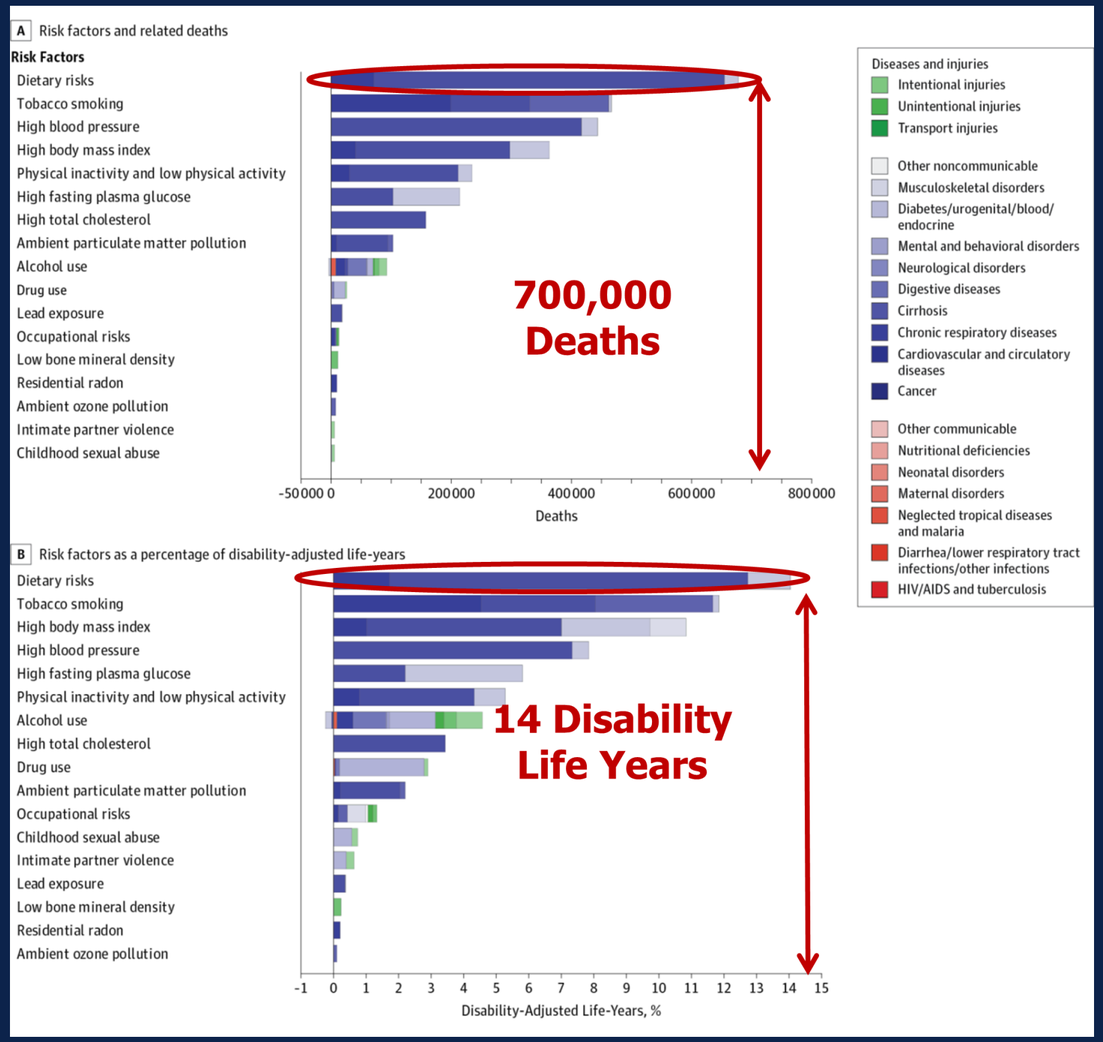
17 Leading Modifiable Risk Factors…Diet is #1



JAMA. 310(6):591-608, 2013

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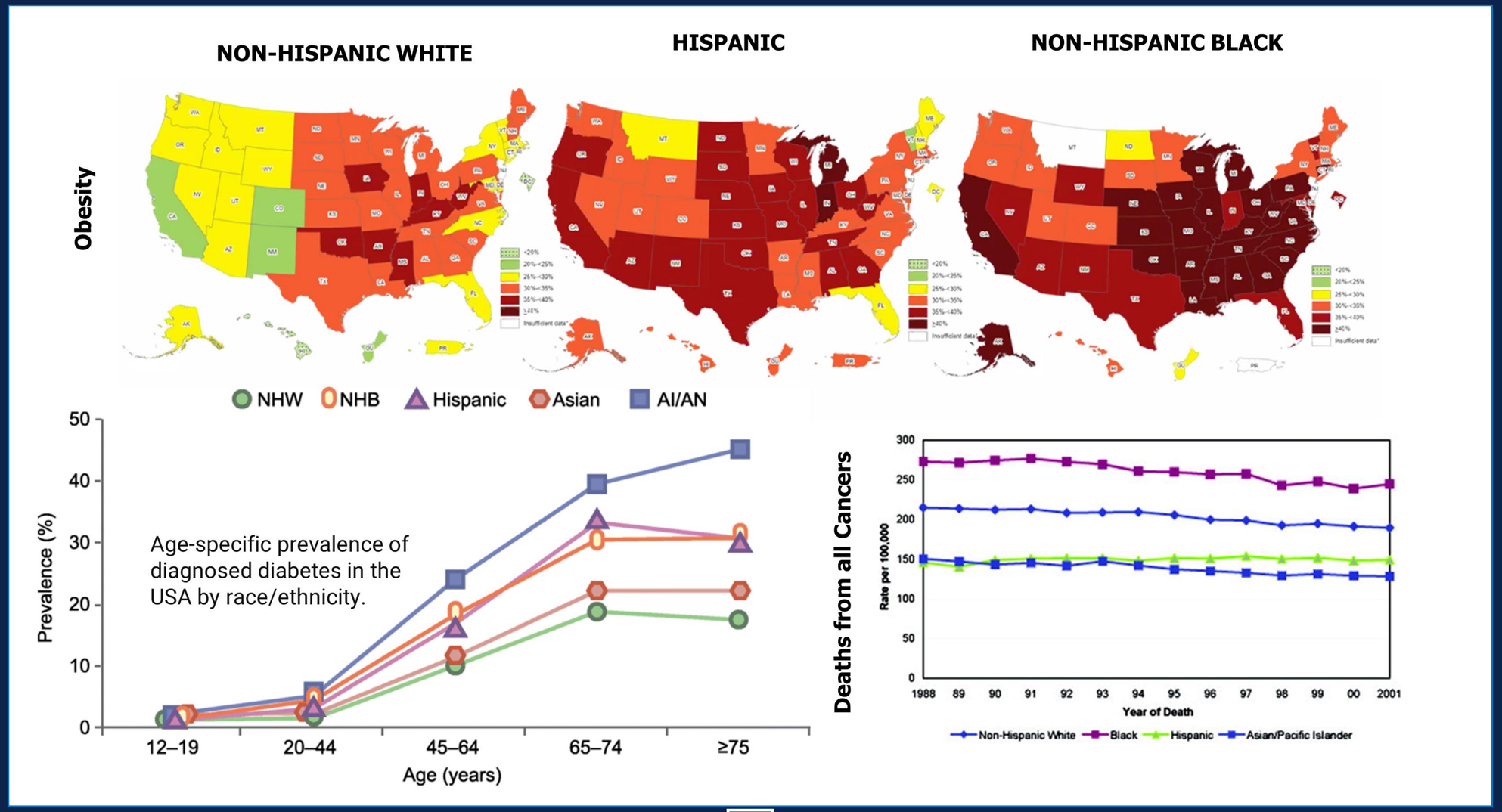
Certain Populations Are Much More Negatively Impacted Than Others



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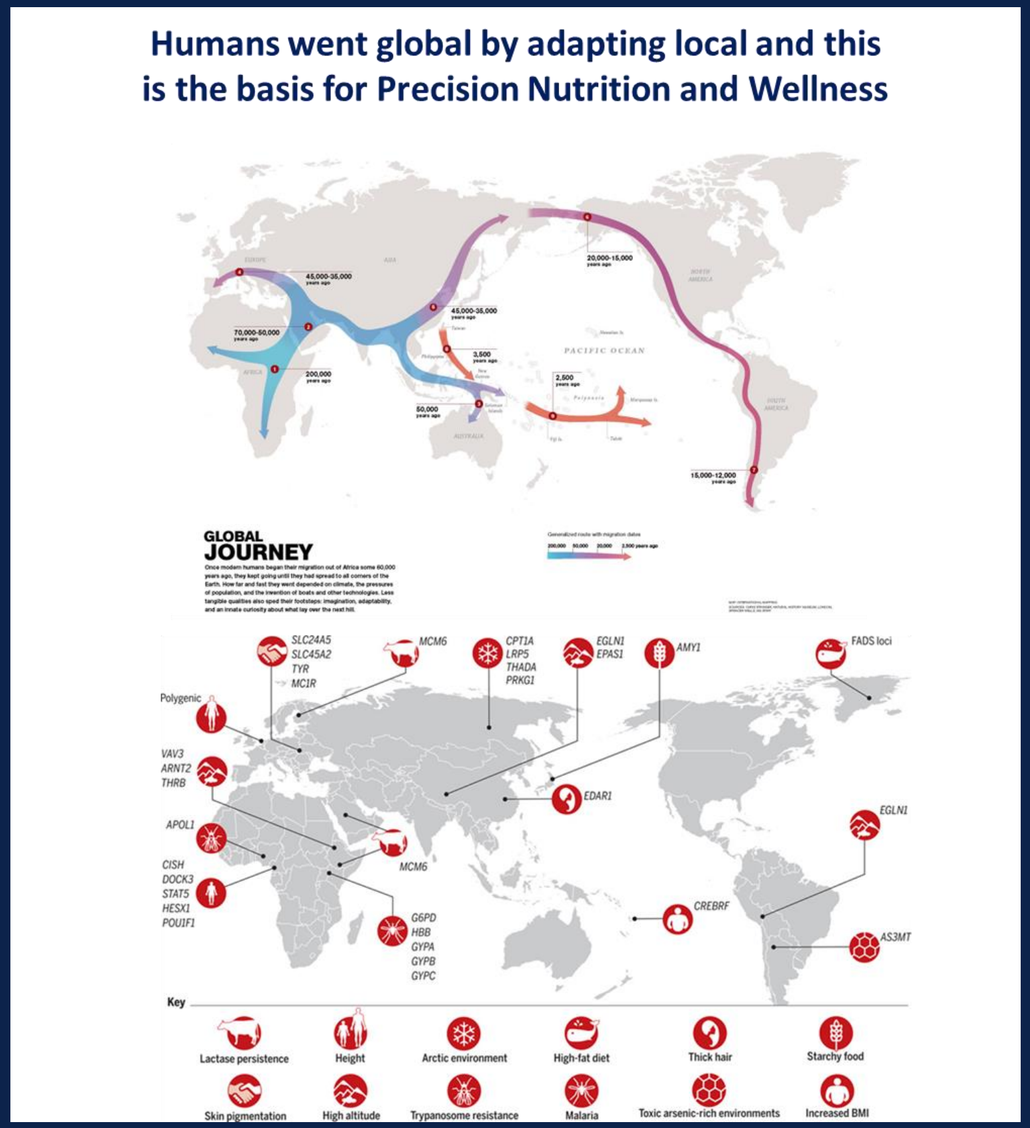
"Nothing in Biology Makes Sense Except in the Light of Evolution"
Theodosius Dobzhansky- First Principle



For Polyunsaturated Fatty Acids

Modern humans have undergone intense selective pressure over the past 300,000 years to optimize their capacity to obtain and use polyunsaturated fatty acids (PUFA) or PUFA metabolites for: 1) innate immunity (oxilipins); 2) energy, appetite & mood homeostasis (endocannabinoids) and 3) brain development/functions (HUFAs; ARA, EPA and DHA).

Nutritional transitions in PUFA ingestion (dramatic increase in omega-6 PUFA-based cooking oils and processed foods) emerging over the past 75 years make evolutionary discordance and mal-adaptations a likely outcome of our current nutritional and genetic environment.

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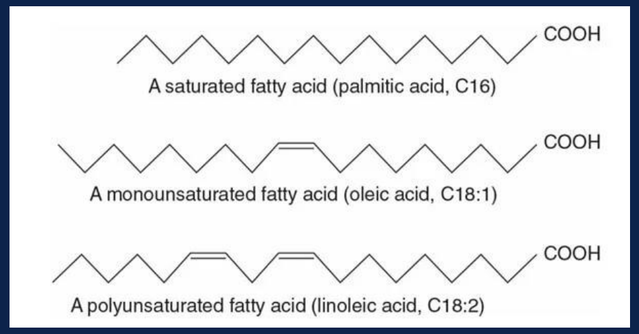
Fatty Acid Classification and PUFA to HUFA Metabolic Pathways

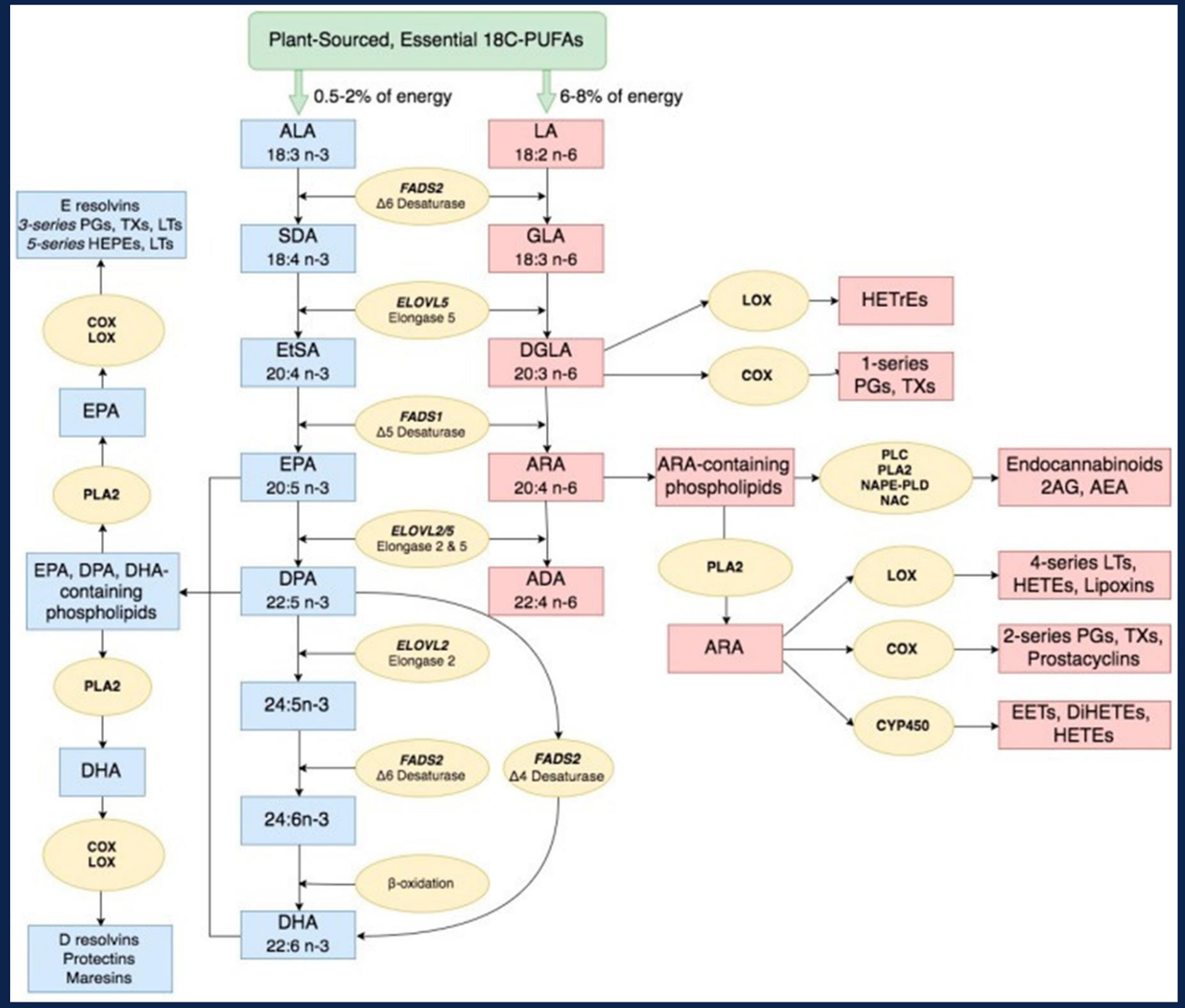


SFA: No double bonds → structure and energy

MUFA: One double bond → metabolic stability and cardioprotection

PUFA: Multiple double bonds → essential nutrients and HUFA precursors

HUFA: Long-chain PUFAs → master regulators of inflammation and signaling



Chilton et al., Nutrients. 2017;9(11):1165.

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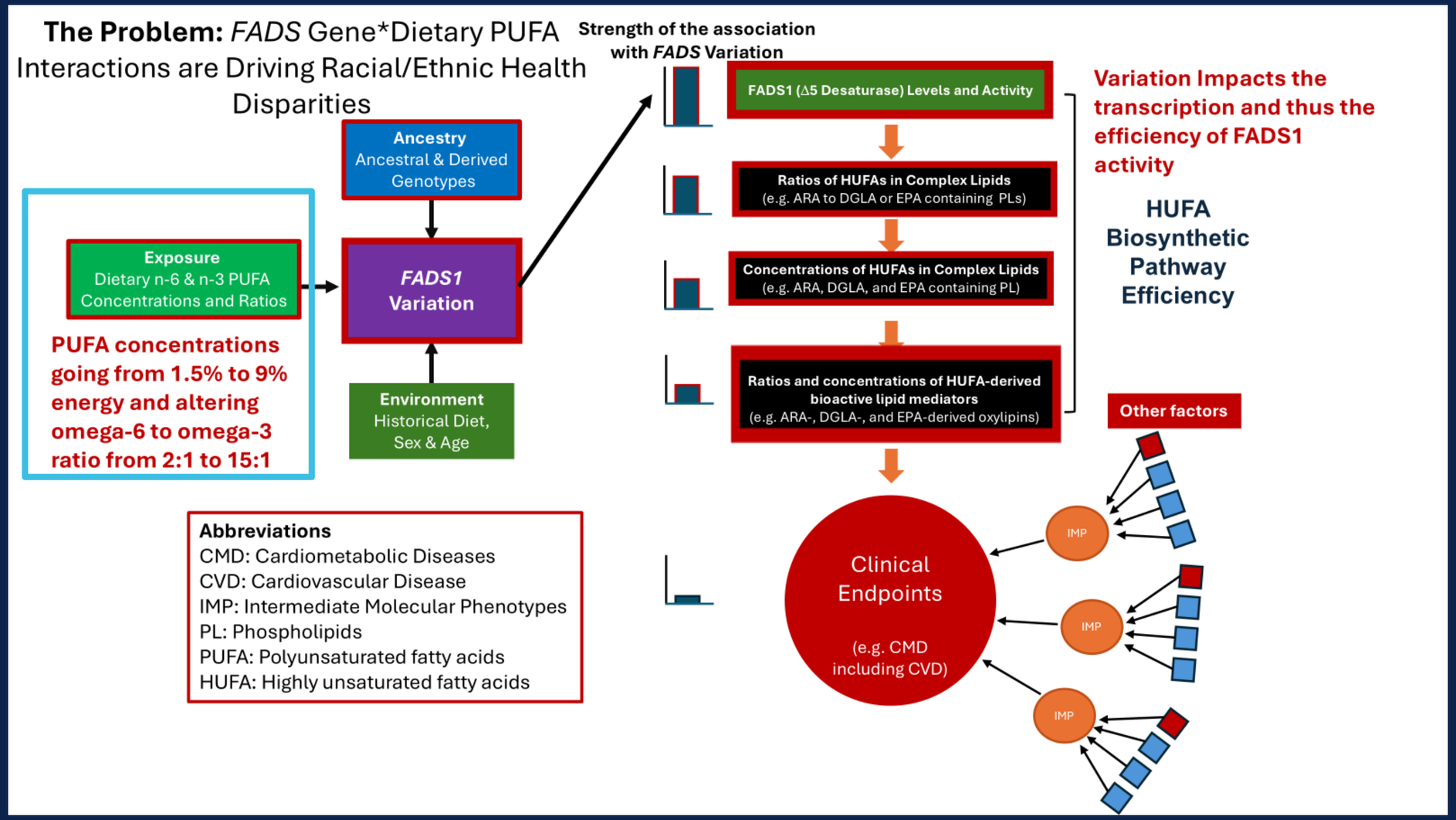
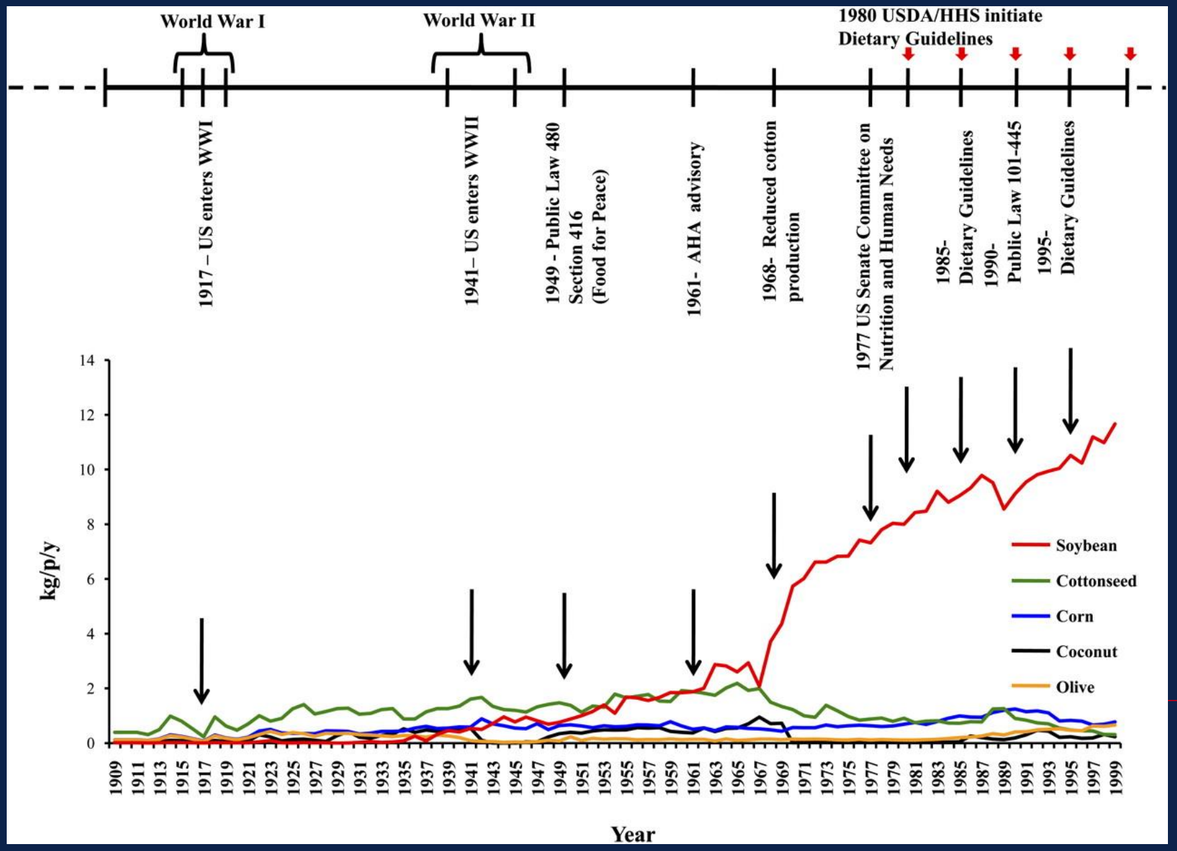
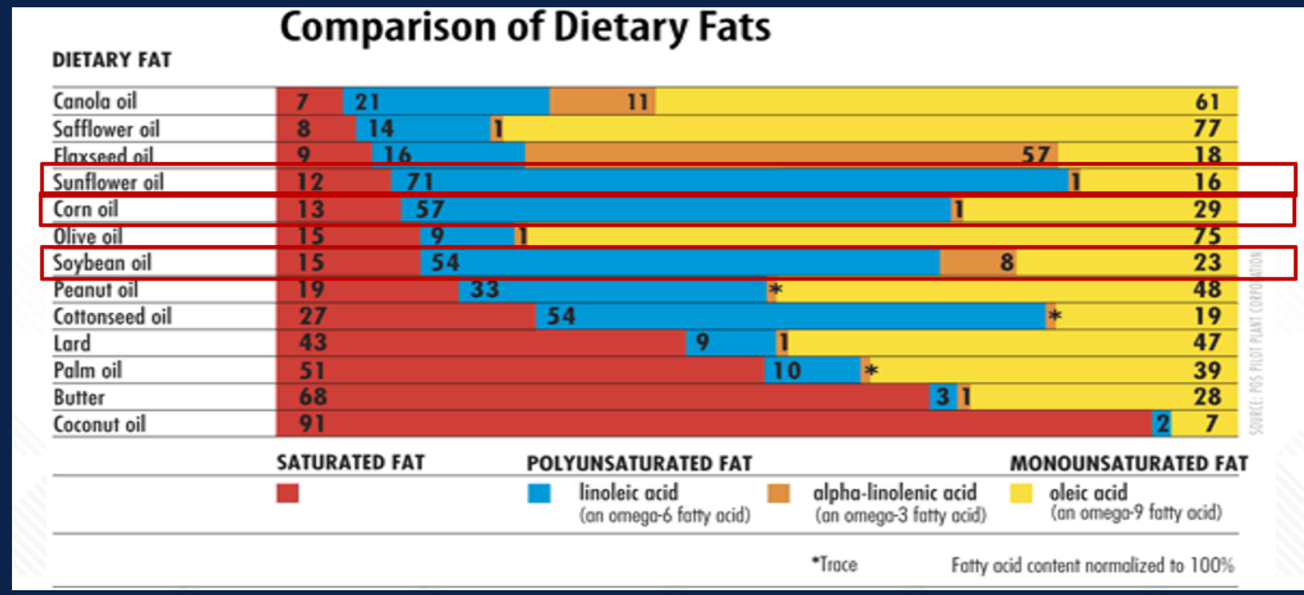
The Anatomy of a Potentially Harmful Gene-PUFA Interaction (Step 1, Exposure)



A Dramatic Increase in the Consumption of Vegetable Oils containing the Omega-6 PUFA, Linoleic Acid over the Past 60 Years





Blasbalg T L et al. Am J Clin Nutr 2011;93:950-962

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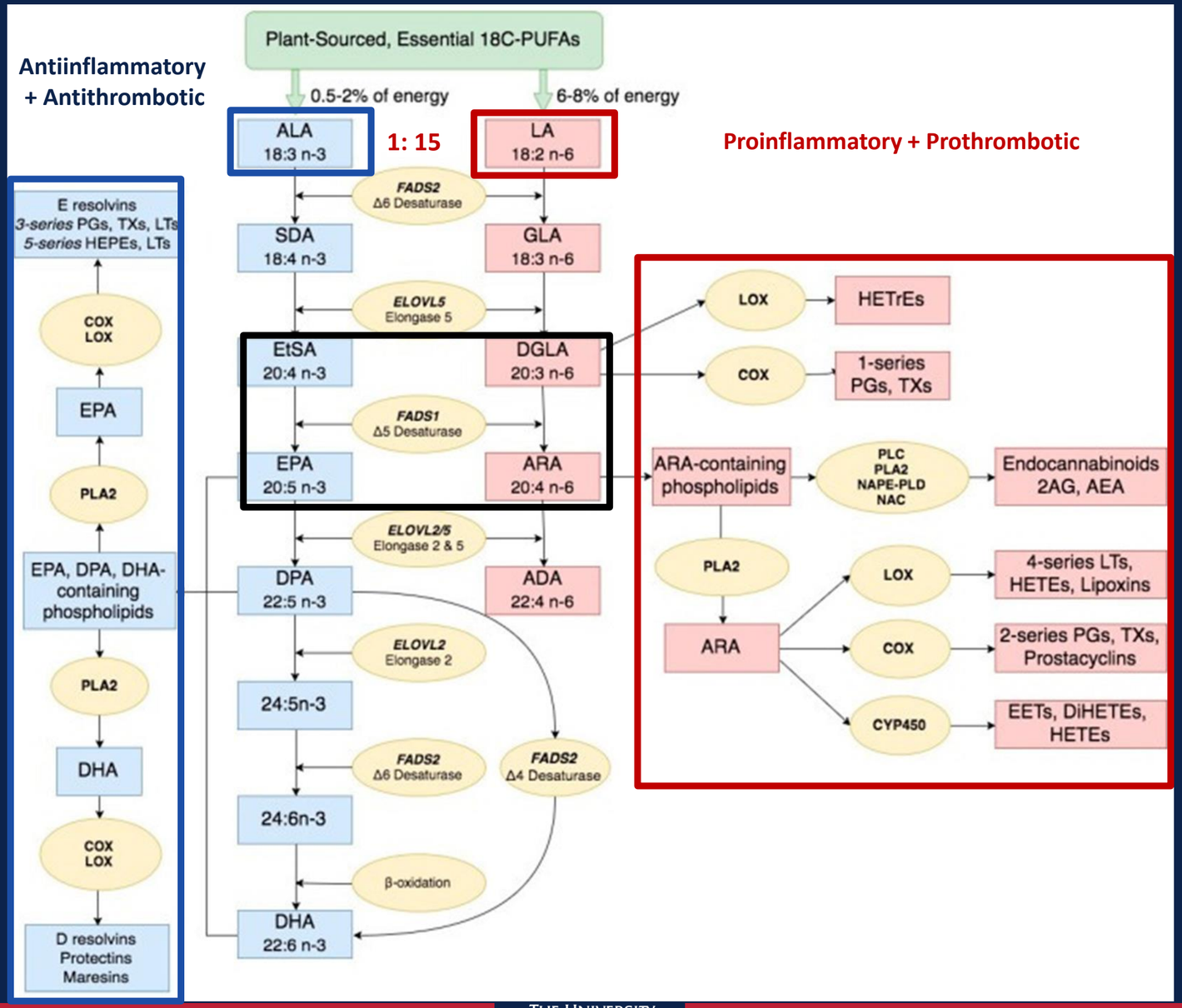
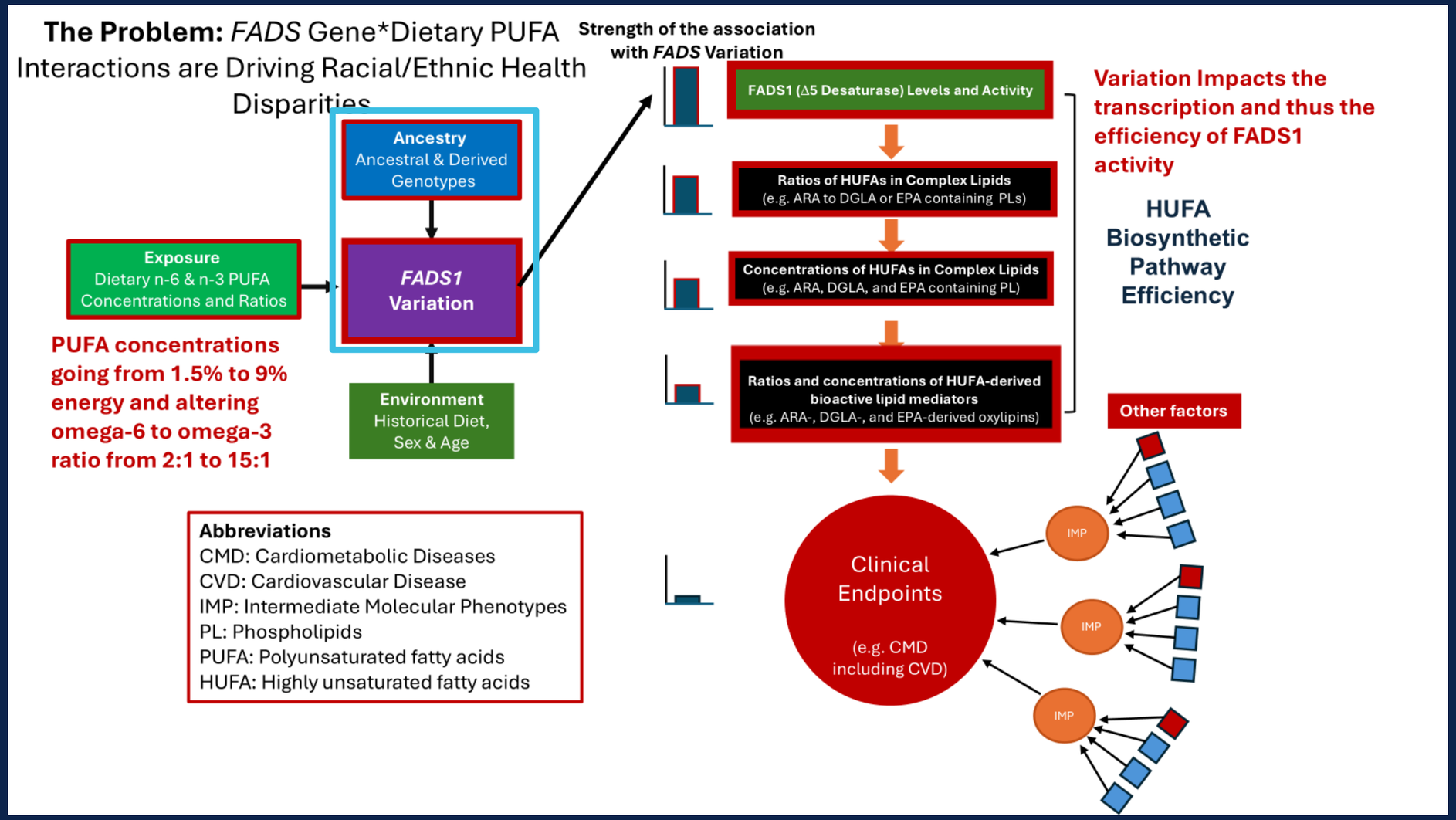
The Potential Impact of an Increase in Dietary PUFA Exposure to Omega-6 Fatty Acids

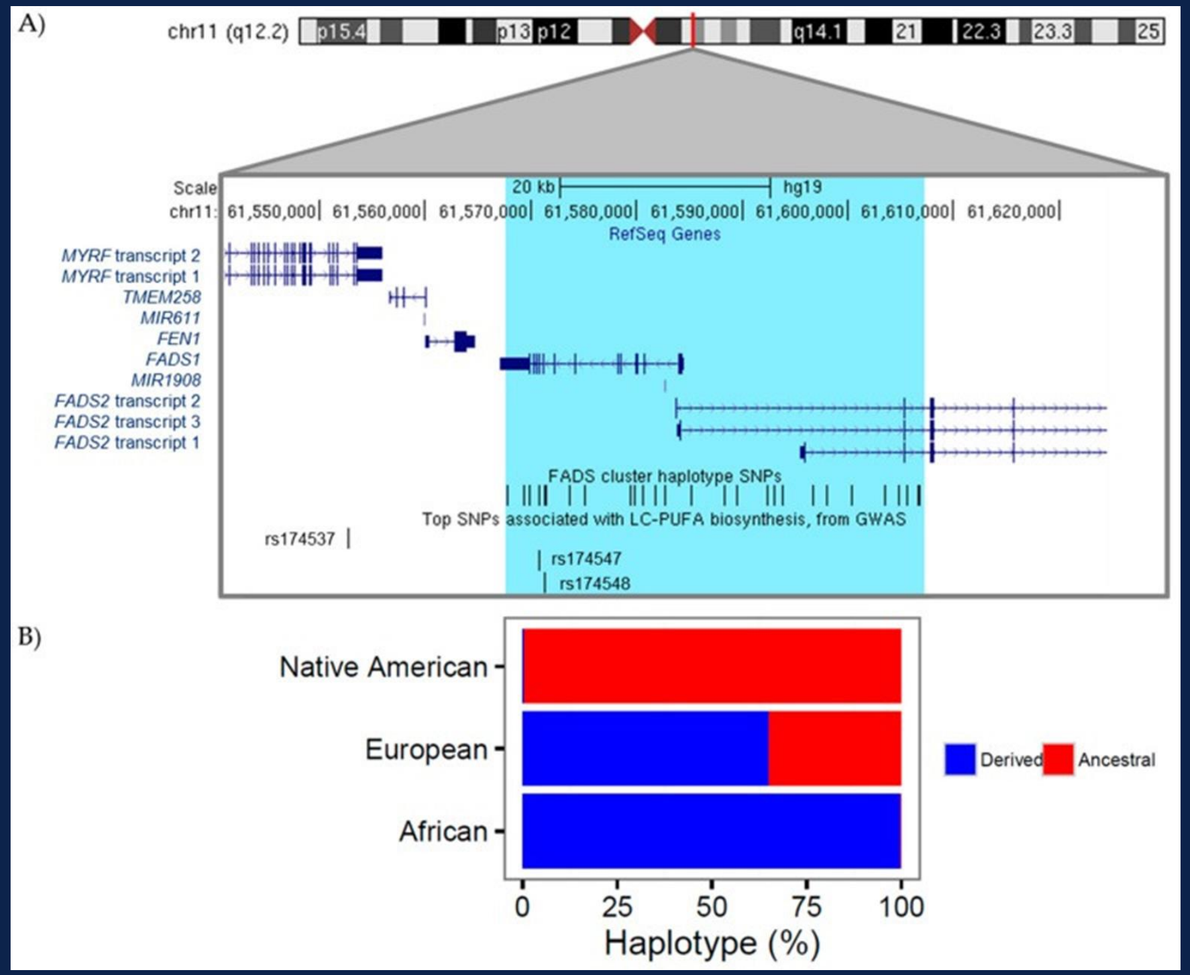


Nutrients. 2017;9(11):1165.

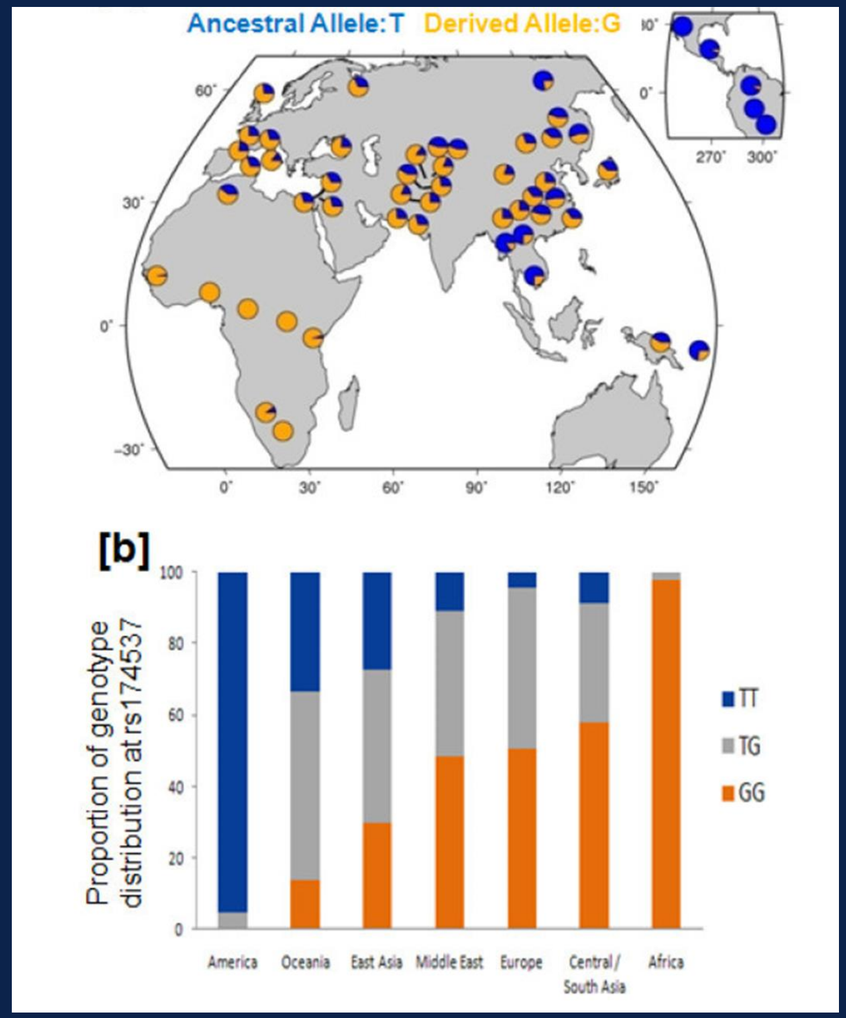
The Anatomy of a Potentially Harmful Gene-PUFA Interaction (Step 2, Ancestry-Driven Genetic Variation)



Genetic Variation in the *FADS* Cluster Impacting Omega-6 and Omega-3 HUFA Biosynthesis



Nutrients2017 Oct 25;9(11):1165. doi: 10.3390/nu9111165.



PLoS One. 2012;7(9):e44926. doi: 10.1371.

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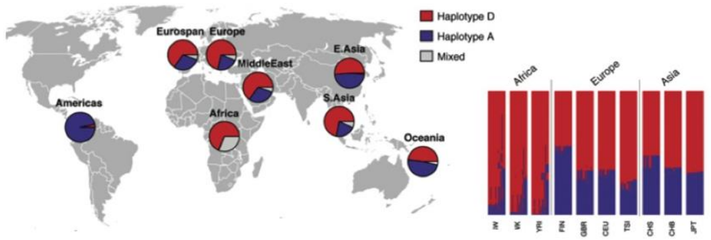
Why the Dramatic Ancestry Differences?
Evolution of the *FADS* Cluster Impacting Omega-6 and Omega-3 HUFA Biosynthesis

ARTICLE

Genetic Adaptation of Fatty-Acid Metabolism: A Human-Specific Haplotype Increasing the Biosynthesis of Long-Chain Omega-3 and Omega-6 Fatty Acids

Adam Ameur,[1] Stefan Enroth,[1] Åsa Johansson,[1] Ghazal Zaboli,[1] Wilmar Igl,[1] Anna C.V. Johansson,[1] Manuel A. Rivas,[2] Mark J. Daly,[2] Gerd Schmitz,[3] Andrew A. Hicks,[6] Thomas Meitinger,[9] Lars Feuk,[1] Cornelia van Duijn,[4] Ben Oostra,[5] Peter P. Pramstaller,[6,7,8] Igor Rudan,[10,11] Alan F. Wright,[12] James F. Wilson,[11] Harry Campbell,[11] and Ulf Gyllensten[1,*]

The American Journal of Human Genetics *90*, 809–820, May 4, 2012



September 2012 | Volume 7 | Issue 9 | e44926

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PLOS | ONE

Adaptive Evolution of the *FADS* Gene Cluster within Africa

Rasika A. Mathias[1,2*], Wenqing Fu[3], Joshua M. Akey[3], Hannah C. Ainsworth[4,5], Dara G. Torgerson[6], Ingo Ruczinski[7], Susan Sergeant[4,5], Kathleen C. Barnes[2], Floyd H. Chilton[5,8]

1 Division of General Internal Medicine, Department of Medicine, The Johns Hopkins University, Baltimore, Maryland, United States of America, **2** Division of Allergy and Clinical Immunology, Department of Medicine, The Johns Hopkins University, Baltimore, Maryland, United States of America, **3** Department of Genome Sciences, School of Medicine, University of Washington, Seattle, Washington, United States of America, **4** Department of Biochemistry, Wake Forest University Health Sciences, Winston-Salem, North Carolina, United States of America, **5** Wake Forest Center for Botanical Lipids and Inflammatory Disease Prevention, Wake Forest University Health Sciences, Winston-Salem, North Carolina, United States of America, **6** Department of Medicine, University of California San Francisco, San Francisco, California, United States of America, **7** Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, United States of America, **8** Department of Physiology/Pharmacology, Wake Forest University Health Sciences, Winston-Salem, North Carolina, United States of America

Abstract

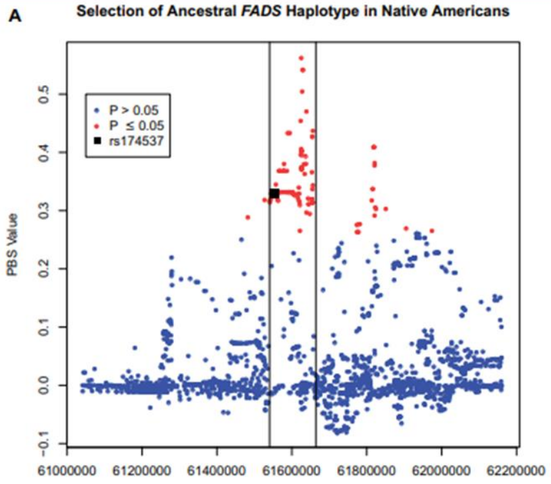
Long chain polyunsaturated fatty acids (LC-PUFAs) are essential for brain structure, development, and function, and adequate dietary quantities of LC-PUFAs are thought to have been necessary for both brain expansion and the increase in brain complexity observed during modern human evolution. Previous studies conducted in largely European populations suggest that humans have limited capacity to synthesize brain LC-PUFAs such as docosahexaenoic acid (DHA) from plant-based medium chain (MC) PUFAs due to limited desaturase activity. Population-based differences in LC-PUFA levels and their product-to-substrate ratios can, in part, be explained by polymorphisms in the fatty acid desaturase (*FADS*) gene cluster, which have been associated with increased conversion of MC-PUFAs to LC-PUFAs. Here, we show evidence that these high efficiency converter alleles in the *FADS* gene cluster were likely driven to near fixation in African populations by positive selection ~85 kya. We hypothesize that selection at *FADS* variants, which increase LC-PUFA synthesis from plant-based MC-PUFAs, played an important role in allowing African populations obligatorily tethered to marine sources for LC-PUFAs in isolated geographic regions, to rapidly expand throughout the African continent 60–80 kya.

Evolution of Hominin Polyunsaturated Fatty Acid Metabolism: From Africa to the New World

Daniel N. Harris[1,2,3,*], Ingo Ruczinski[4], Lisa R. Yanek[5], Lewis C. Becker[5], Diane M. Becker[5], Heinner Guio
Tao Cui[7], Floyd H. Chilton[8], Rasika A. Mathias[5], and Timothy D. O'Connor[1,2,3,*]

Abstract

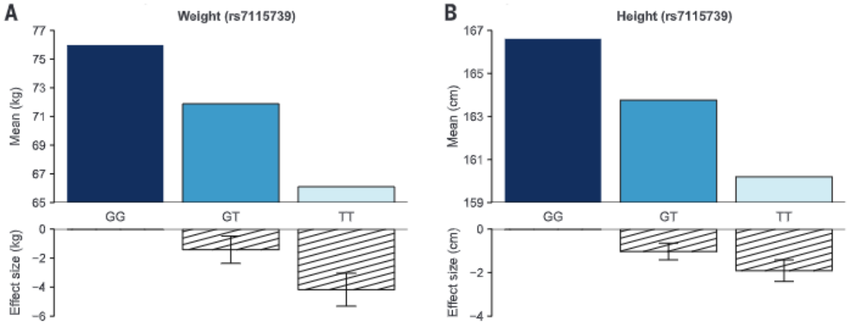
The metabolic conversion of dietary omega-3 and omega-6 18 carbon (18C) to long chain (>20 carbon) polyunsaturated fatty acids (LC-PUFAs) is vital for human life. The rate-limiting steps of this process are catalyzed by fatty acid desaturase (*FADS*) 1 and 2. Therefore, understanding the evolutionary history of the *FADS* genes is essential to our understanding of hominin evolution. The *FADS* genes have two haplogroups, ancestral and derived, with the derived haplogroup being associated with more efficient LC-PUFA biosynthesis than the ancestral haplogroup. In addition, there is a complex global distribution of these haplogroups that is suggestive of Neanderthal introgression. We confirm that Native American ancestry is nearly fixed for the ancestral haplogroup, and replicate a positive selection signal in Native Americans. This positive selection potentially continued after the founding of the Americas, although simulations suggest that the timing is dependent on the allele frequency of the ancestral Beringian population. We also find that the Neanderthal *FADS* haplotype is more closely related to the derived haplogroup and the Denisovan clusters closer to the ancestral haplogroup. Furthermore, the derived haplogroup has a time to the most recent common ancestor of 688,474 years before present. These results support an ancient polymorphism, as opposed to Neanderthal introgression, forming in the *FADS* region during the Pleistocene with possibly differential selection pressures on both haplogroups. The near fixation of the ancestral haplogroup in Native American ancestry calls for future studies to explore the potential health risk of associated low LC-PUFA levels in these populations.



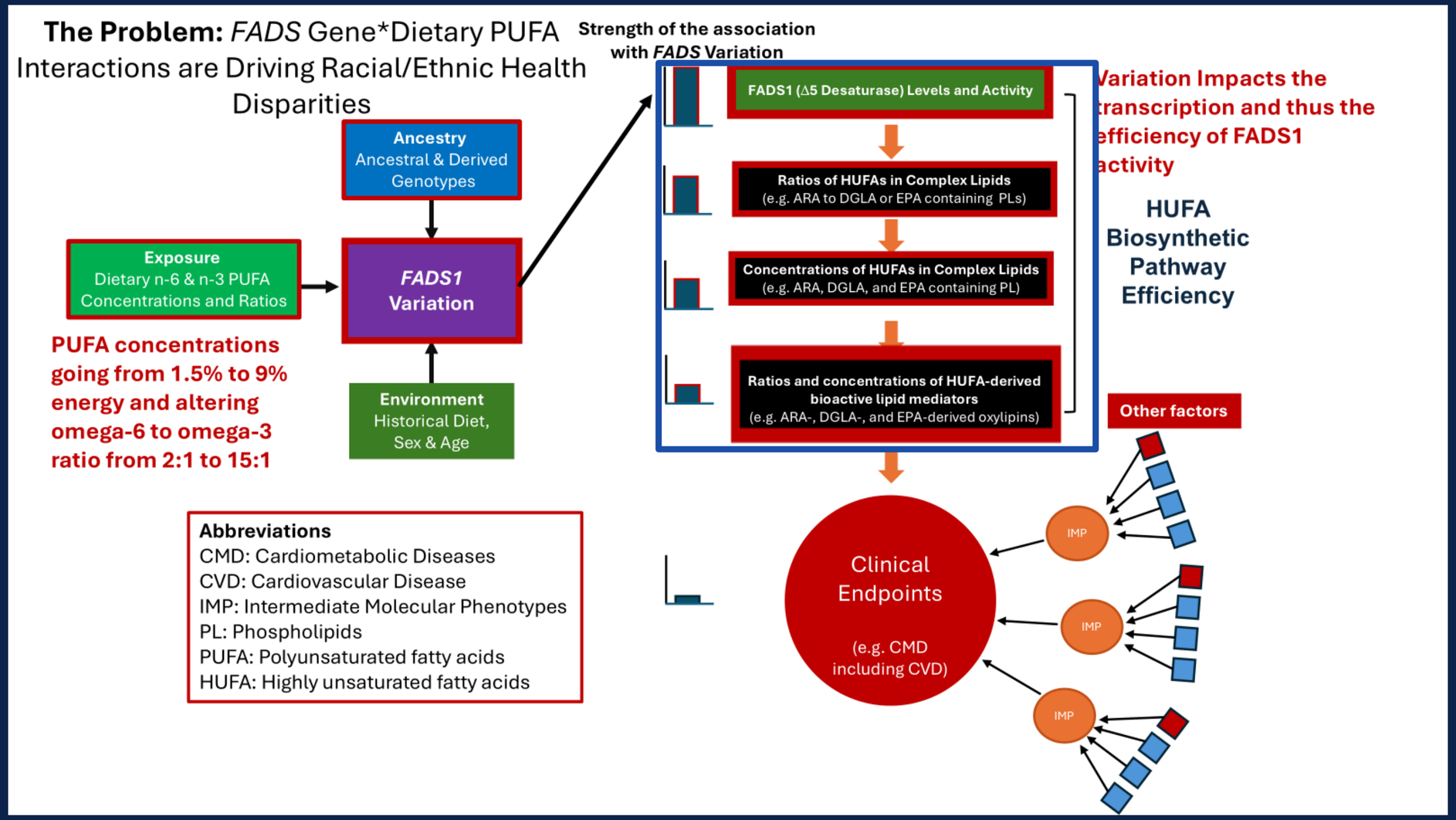
Greenlandic Inuit show genetic signatures of diet and climate adaptation

Science
Volume 349, Issue 6254
Sep 2015

Matteo Fumagalli,[1,2*] Ida Moltke,[3*] Niels Grarup,[4] Fernando Racimo,[2] Peter Bjerregaard,[5,6] Marit E. Jørgensen,[5,7] Thorfinn S. Korneliussen,[8] Pascale Gerbault,[1,9] Line Skotte,[3] Allan Linneberg,[10,11,12] Cramer Christensen,[13] Ivan Brandslund,[14,15] Torben Jørgensen,[10,16,17] Emilia Huerta-Sánchez,[18] Erik B. Schmidt,[17,19] Oluf Pedersen,[4] Torben Hansen,[4†] Anders Albrechtsen.[3†] Rasmus Nielsen[2,20†]



The Anatomy of a Potentially Harmful Gene-PUFA Interaction (Step 3, Impact Molecular Phenotype)



Impact of *FADS* Variation on n-6 PUFAs Levels and *FADS1* Enzymatic Efficiency between the AfAm and EuAm Populations

Mathias *et al. BMC Genetics* 2011, **12**:50
http://www.biomedcentral.com/1471-2156/12/50

BMC Genetics

RESEARCH ARTICLE Open Access

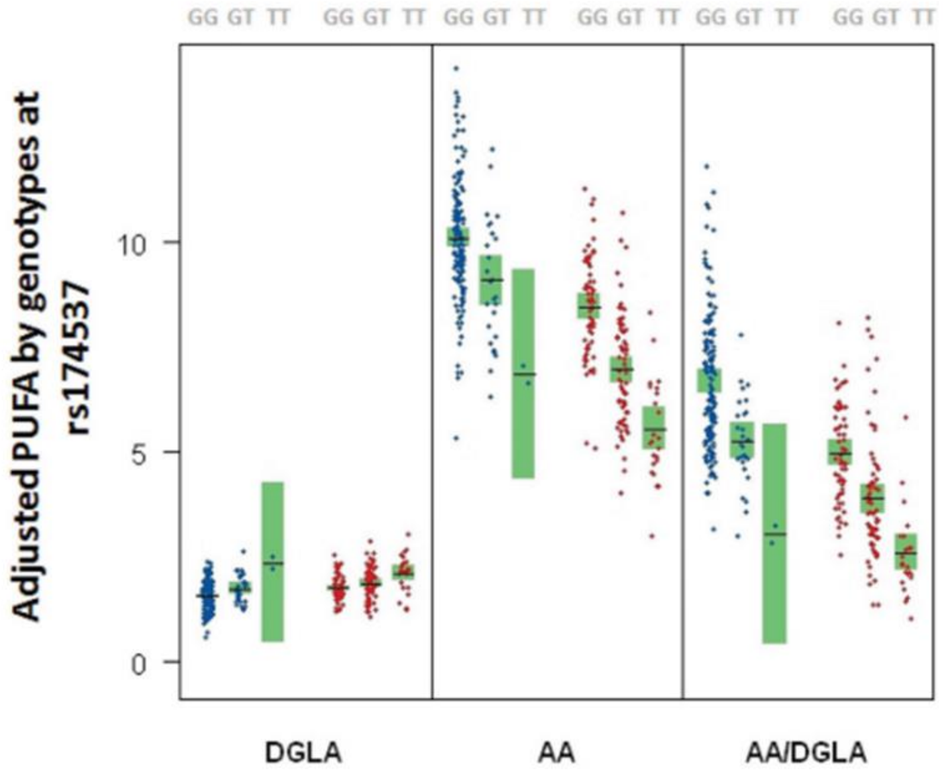
The impact of *FADS* genetic variants on ω6 polyunsaturated fatty acid metabolism in African Americans

Rasika A Mathias[1,2*], Susan Sergeant[3,4], Ingo Ruczinski[5], Dara G Torgerson[6], Christina E Hugenschmidt[7], Meghan Kubala[1], Dhananjay Vaidya[1], Bhoom Suktitipat[1], Julie T Ziegler[8], Priscilla Ivester[4,9], Douglas Case[8], Lisa R Yanek[1], Barry I Freedman[10], Megan E Rudock[11], Kathleen C Barnes[2], Carl D Langefeld[8], Lewis C Becker[1], Donald W Bowden[3,7,11], Diane M Becker[1] and Floyd H Chilton[4,9]

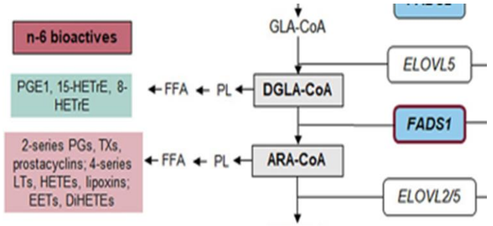
British Journal of Nutrition (2012), **107**, 547–555
doi:10.1017/S0007114511003230

Differences in arachidonic acid levels and fatty acid desaturase (*FADS*) gene variants in African Americans and European Americans with diabetes or the metabolic syndrome

Susan Sergeant[1,2], Christina E. Hugenschmidt[3], Megan E. Rudock[4], Julie T. Ziegler[5], Priscilla Ivester[1,6], Hannah C. Ainsworth[1,6], Dhananjay Vaidya[7], L. Douglas Case[5], Carl D. Langefeld[5], Barry I. Freedman[8], Donald W. Bowden[2,3,4], Rasika A. Mathias[7,9] and Floyd H. Chilton[1,6*]



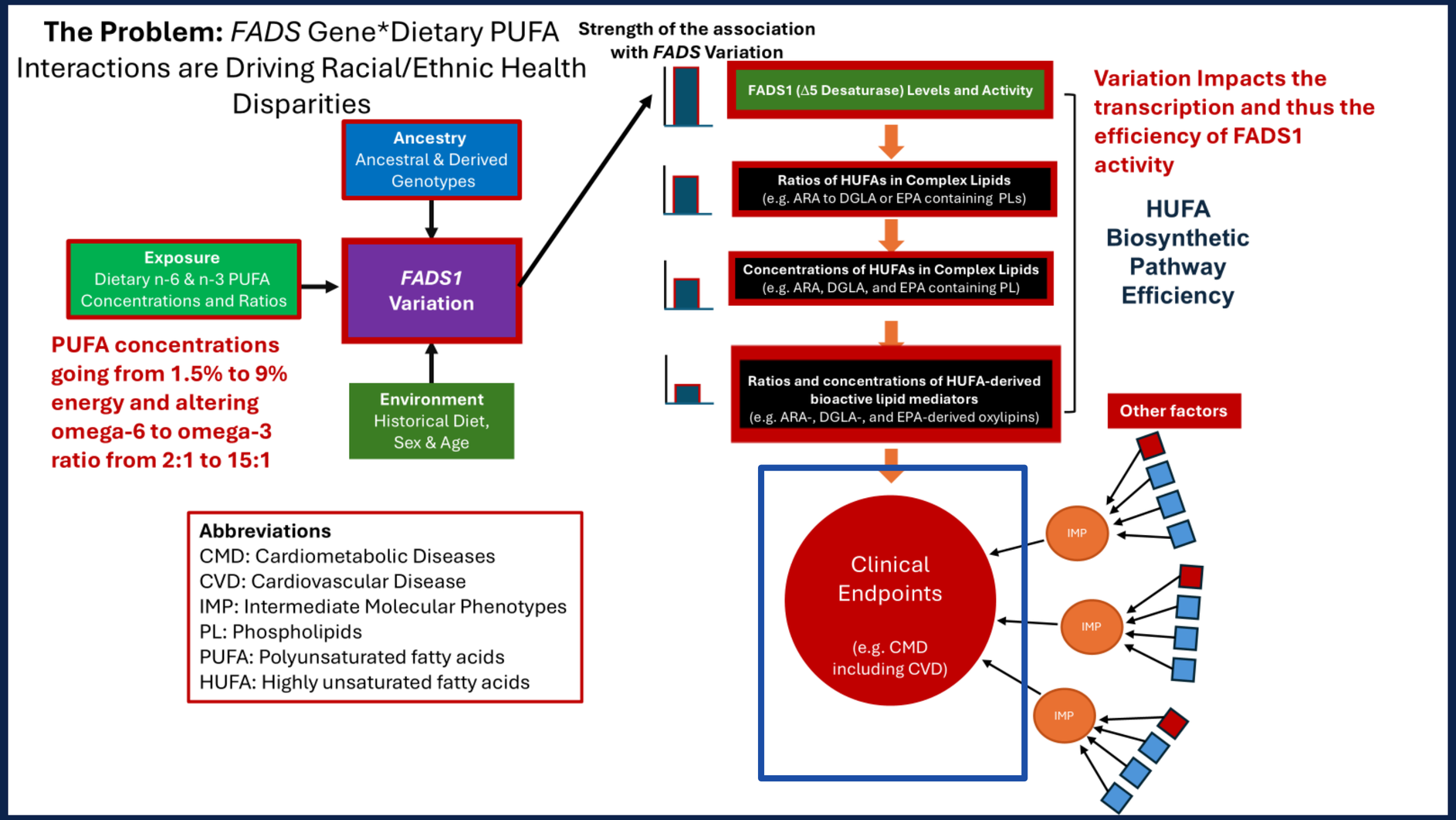
Derived allele at rs174537=G
Ancestral allele at rs174537=T



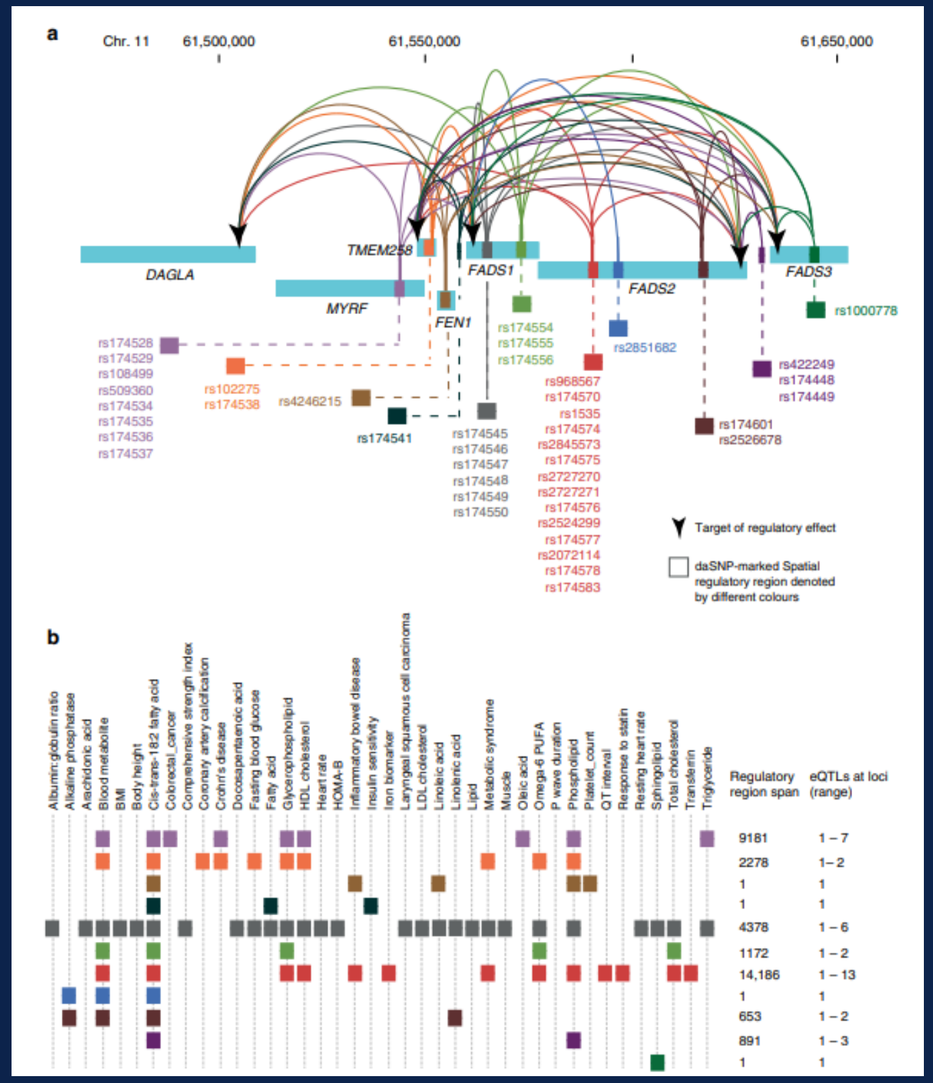
Four Major Points:

1) Genotypic Effects the Same between Races
2) Dramatic Frequency Differences
3) Still Unresolved Genetic Differences
4) Variability within Genotype

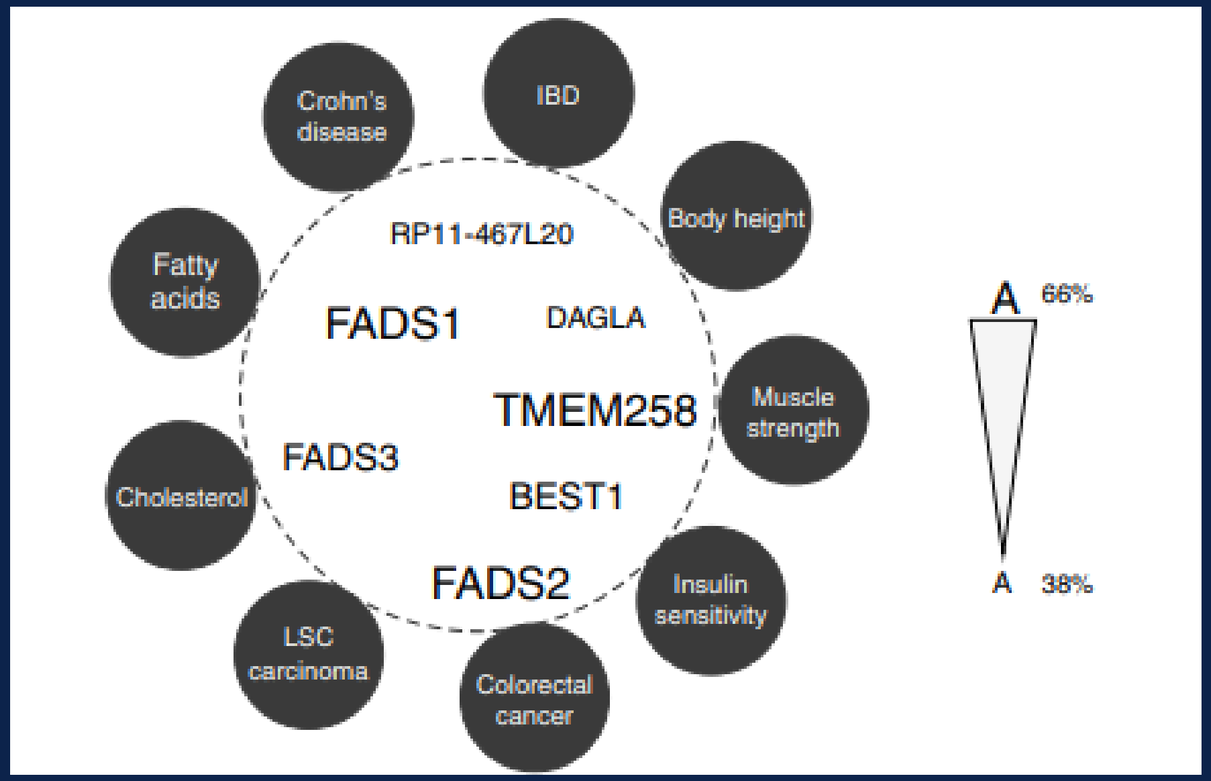
The Anatomy of a Potentially Harmful Gene-PUFA Interaction (Step 4, Impact Clinical Phenotypes)



How Important is this Portion of the Genome? Chromatin Interactions & Related EQTLs Revealed the *FADS* Cluster to be the Major Morbidity Region of the Entire Genome



Genetic Variation Associated with 100s Distinct Phenotypes



Nature Communications 9:5198, 2018

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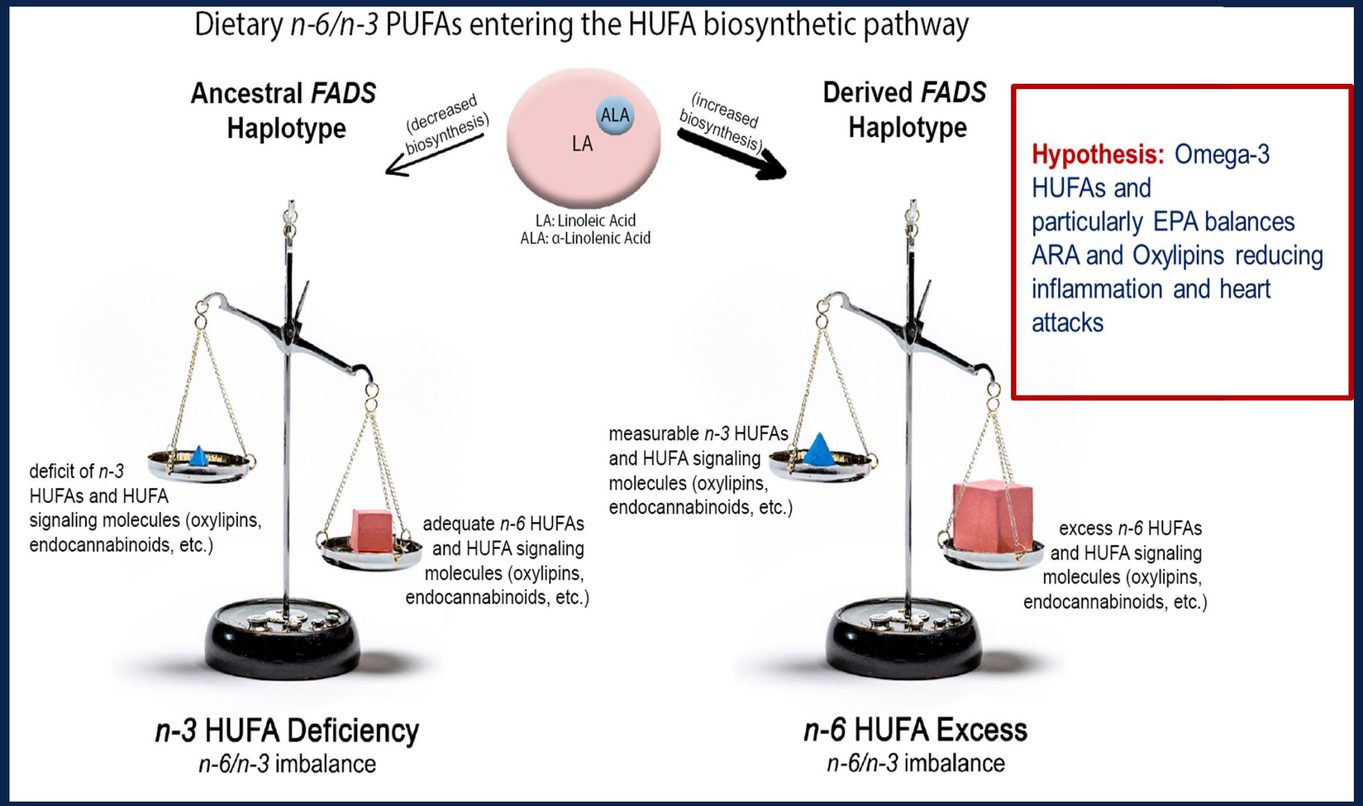
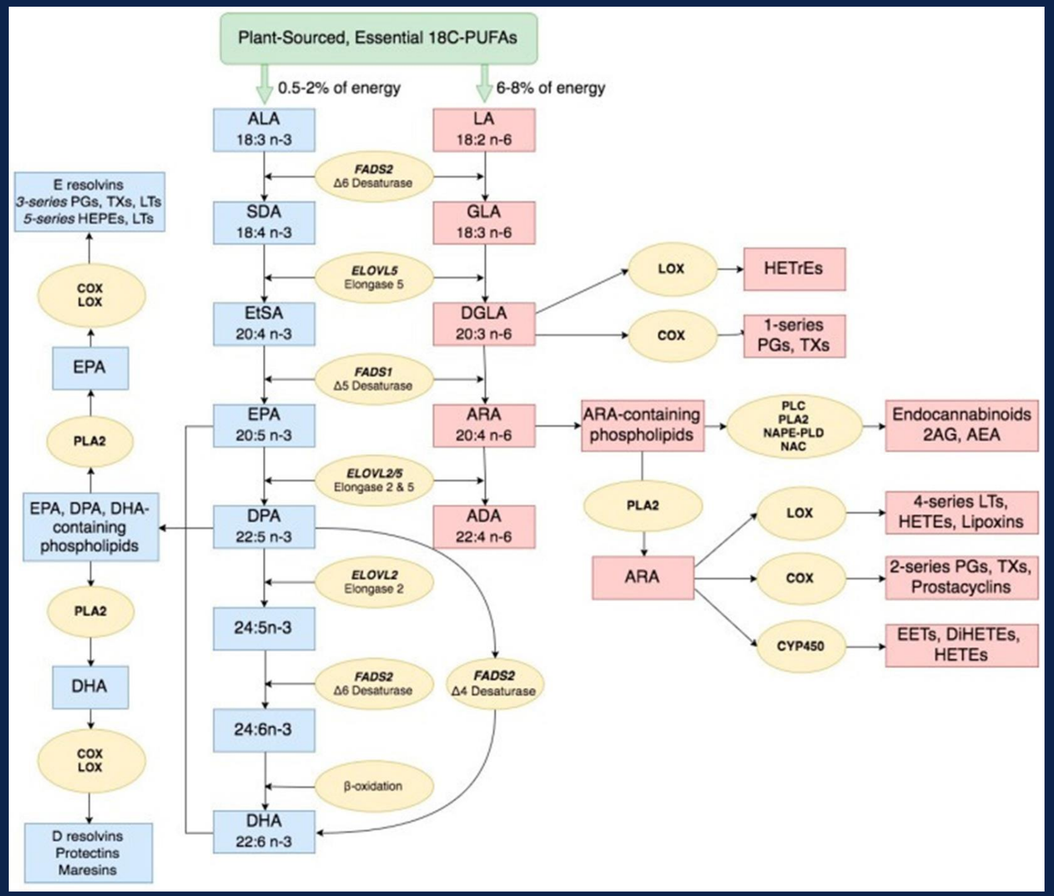
African-Ancestry Populations Make Much Higher Levels of Omega-6 Signaling Molecules (HUFAs) Whose Products Enhance Inflammation & Thrombosis

Key Tested Hypothesis: Omega-3 Supplementation Can Offset This and Show Clinical Efficacy particularly in AfAm





Chilton et al., Nutrients. 2017;9(11):1165.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

RESULTS

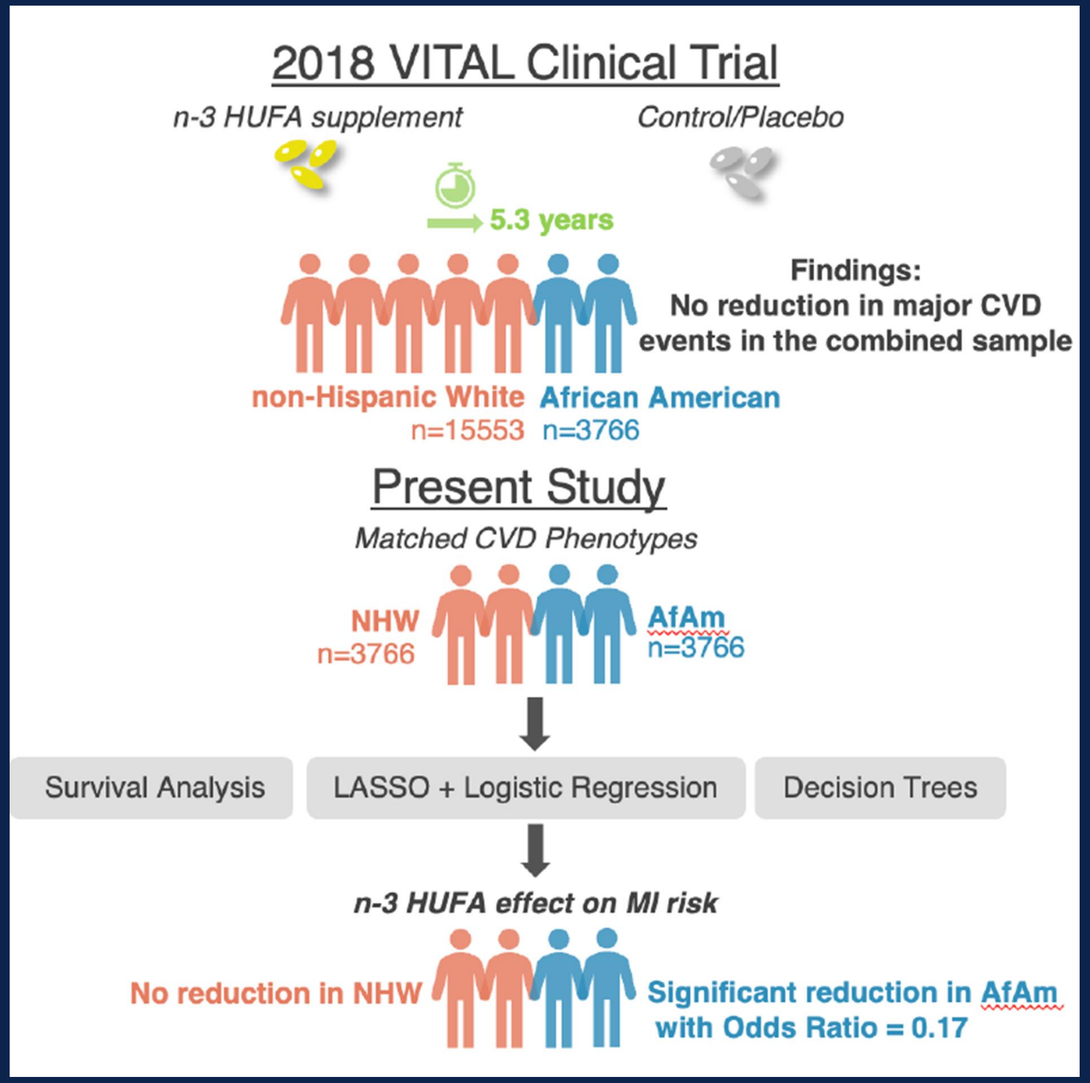
A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, a major cardiovascular event occurred in 386 participants in the n–3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n–3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

CONCLUSIONS

Supplementation with n–3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

Our Reanalysis of the VITAL Clinical Trial

Our Reanalysis of the VITAL Clinical Trial (Nutrients 6(17):2933, 2024)

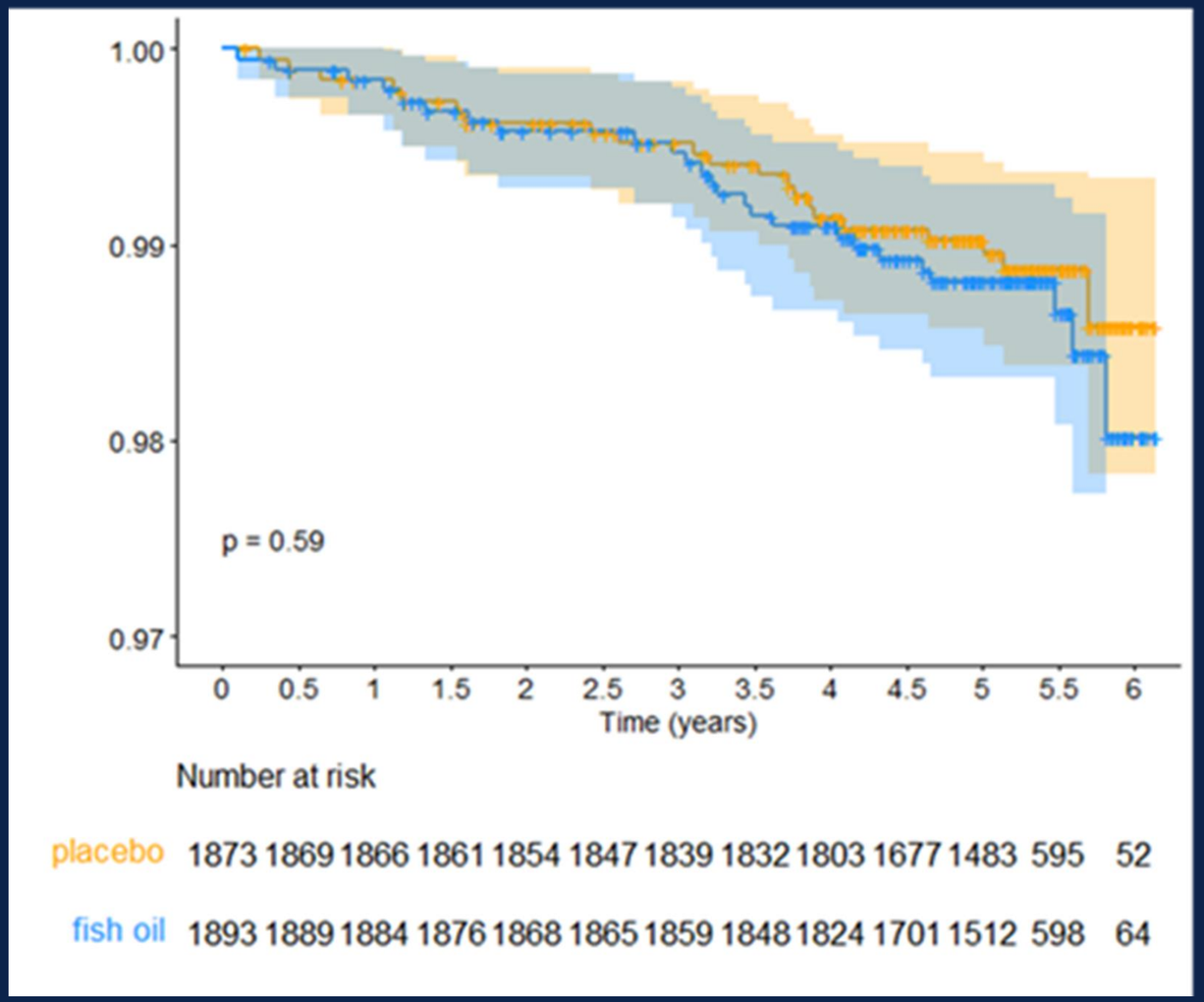


Utilization of Optimal Pair Matching Balanced the Potential Confounding Variables

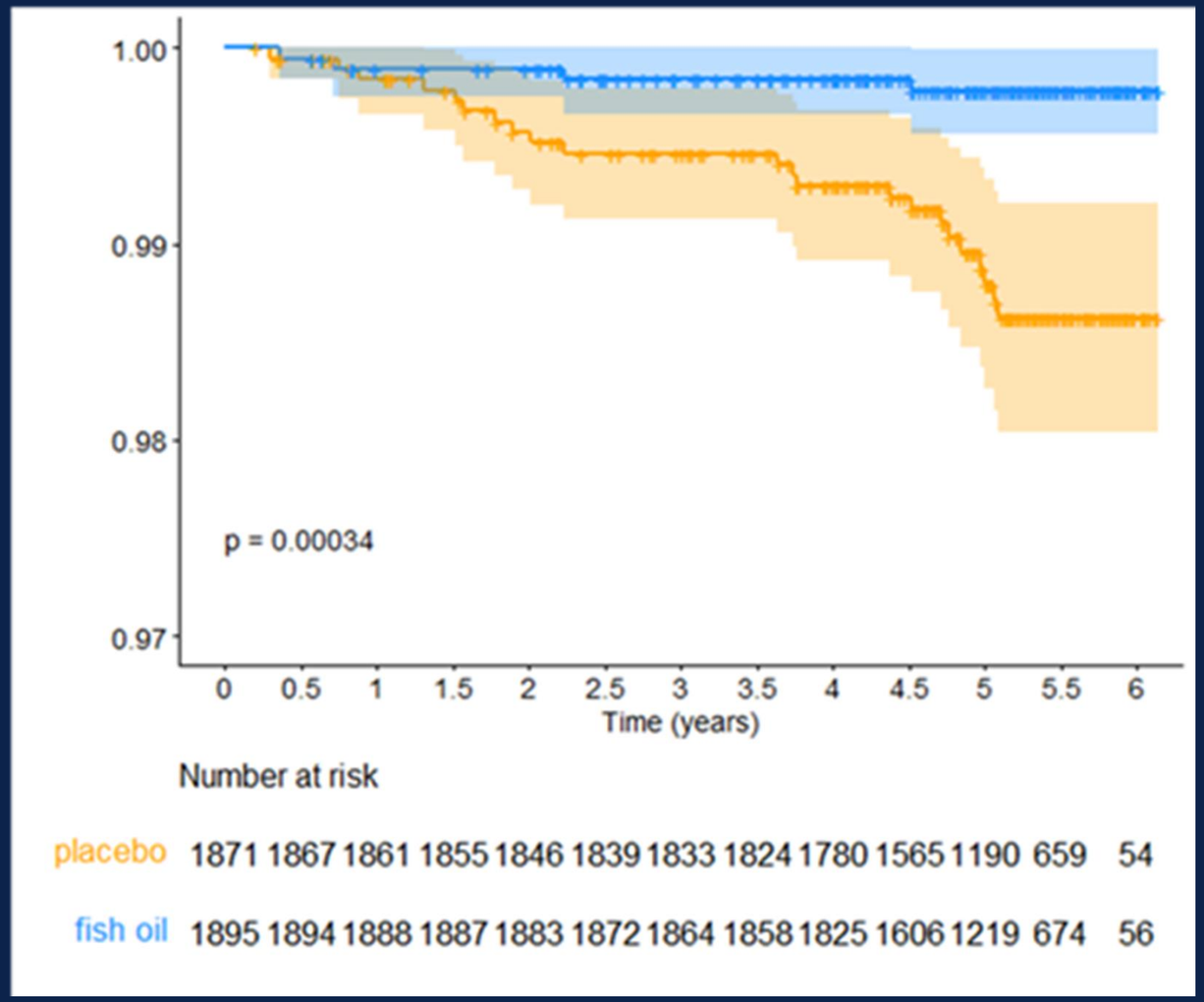
Characteristic		Total (N=7532)	Af Am (N=3766)	Eu Am (N=3766)
Age		62.8±6.3	62.4±6.6	63.1±5.9
Female		4587 (60.9)	2347 (62.3)	2240 (59.5)
BMI		30.3±6.6	30.6±6.5	29.9±6.1
Current smoking		979 (13.0)	528 (14.0)	451 (12.0)
Hypertension medication		4754 (63.1)	2446 (64.9)	2308 (61.3)
Cholesterol medication		2451 (32.5)	1200 (31.9)	1251 (33.2)
Diabetes		1617 (21.5)	871 (23.1)	746 (19.8)
Diabetes medication		1267 (16.8)	675 (17.9)	592 (15.7)
Parental history of MI		1161 (15.4)	591 (15.7)	570 (15.1)
Fish consumption (≥1.5/wk)		3750 (49.8)	1890 (50.2)	1860 (49.4)
Aspirin use		2885 (38.3)	1431 (38.0)	1454 (38.6)
Statin use		2279 (30.3)	1114 (29.6)	1165 (30.9)
Vitamin D supplements		2271 (30.2)	1096 (29.1)	1175 (31.2)
CVD risk factors	0	1661 (22.1)	778 (20.7)	883 (23.4)
	1	2634 (35.0)	1315 (34.9)	1319 (35.0)
	>1	3237 (43.0)	1673 (44.4)	1564 (41.5)

Kaplan-Meier Survival Curves for Myocardial Infarction in n-3 HUFA Treatment and Placebo Groups after Optimal Pair Matching

a



b



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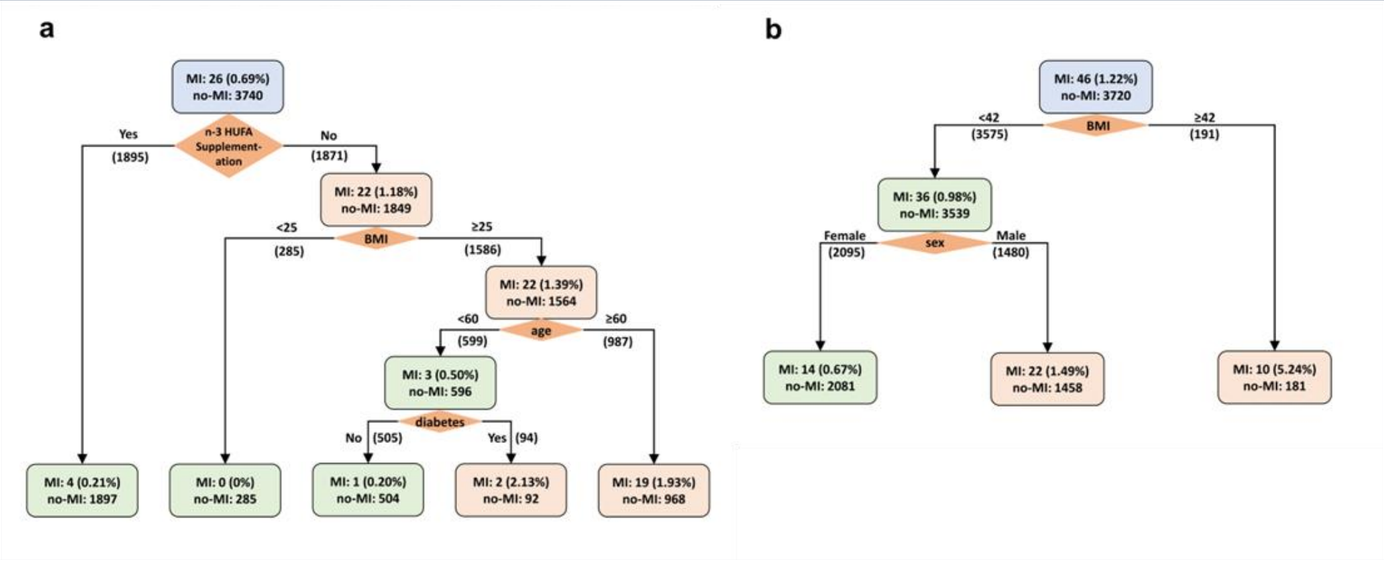
Machine Learning Weighted Decision Tree and Lasso Regression Analysis of Myocardial Infarction in Matched AfAm and EuAm Participants



Weighted Decision Tree

Variables	Estimate	OR	Non-parametric Bootstrap			Parametric Bootstrap		
			Std. Error	P-value	95% CI for OR	Std. Error	P-value	95% CI for OR
(Intercept)	-3.7599	0.0233	1.9965	0.0597	(0.0005, 1.1656)	1.8195	0.0388	(0.0007, 0.8239)
Female	-0.7184	0.4875	0.3501	0.0402	(0.2455, 0.9683)	0.3448	0.0372	(0.2480, 0.9583)
Age	0.0552	1.0568	0.0277	0.0463	(1.0009, 1.1157)	0.0251	0.0279	(1.0060, 1.1100)
BMI	0.0304	1.0309	0.0249	0.2221	(0.9818, 1.0824)	0.0234	0.1939	(0.9847, 1.0792)
Current Smoker	0.7167	2.0477	0.4155	0.0845	(0.9069, 4.6232)	0.4471	0.1089	(0.8525, 4.9186)
Diabetes	0.4599	1.5839	0.4255	0.2798	(0.6879, 3.6469)	0.3381	0.1738	(0.8165, 3.0728)
Fish consumption (1.5/wk)	-0.7424	0.4760	0.3755	0.0480	(0.2280, 0.9936)	0.3274	0.0234	(0.2505, 0.9042)
n-3 HUFA supplementation x Af Am	-1.7747	0.1695	0.6410	0.0056	(0.0483, 0.5955)*	0.6944	0.0106	(0.0435, 0.6613)*
n-3 HUFA supplementation x Eu Am	0.0000	1.0000	0.1508	1.0000	(0.7442, 1.3438)*	0.1566	1.0000	(0.7357, 1.3593)*

Logistic regression analysis with interaction terms between n-3 HUFA supplementation and other variables (including race), identified n-3 HUFA supplementation as the most significant predictor of MI incidence among AfAm participants with an OR of 0.17 and a CI of [0.048-0.59]

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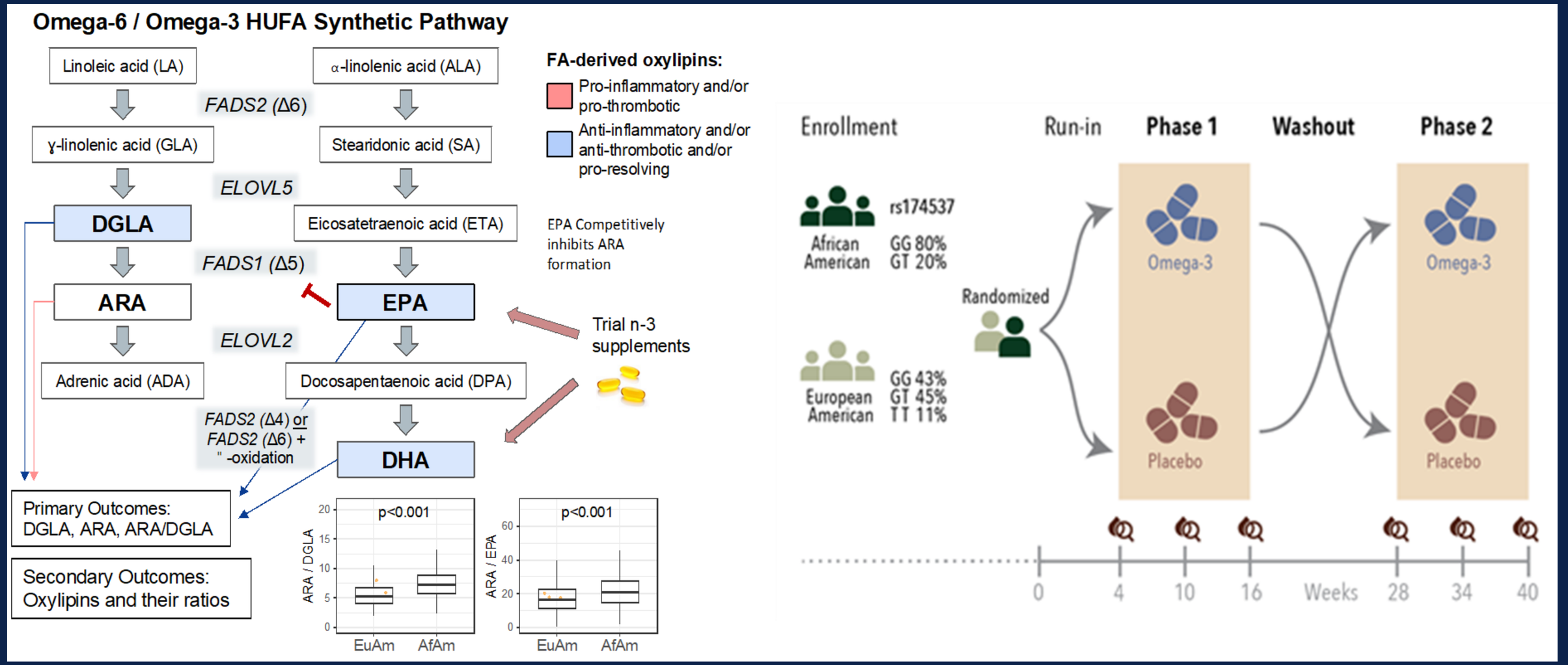
Our NIH-Funded Multicenter Clinical Trial (UA & Georgetown), Based on the Previous Analysis, "A Genotype-Stratified Mechanistic Trial of Omega-3 Fatty Acids and FADS Variants in Diet-Induced Inflammation"; R01 AT008621-08



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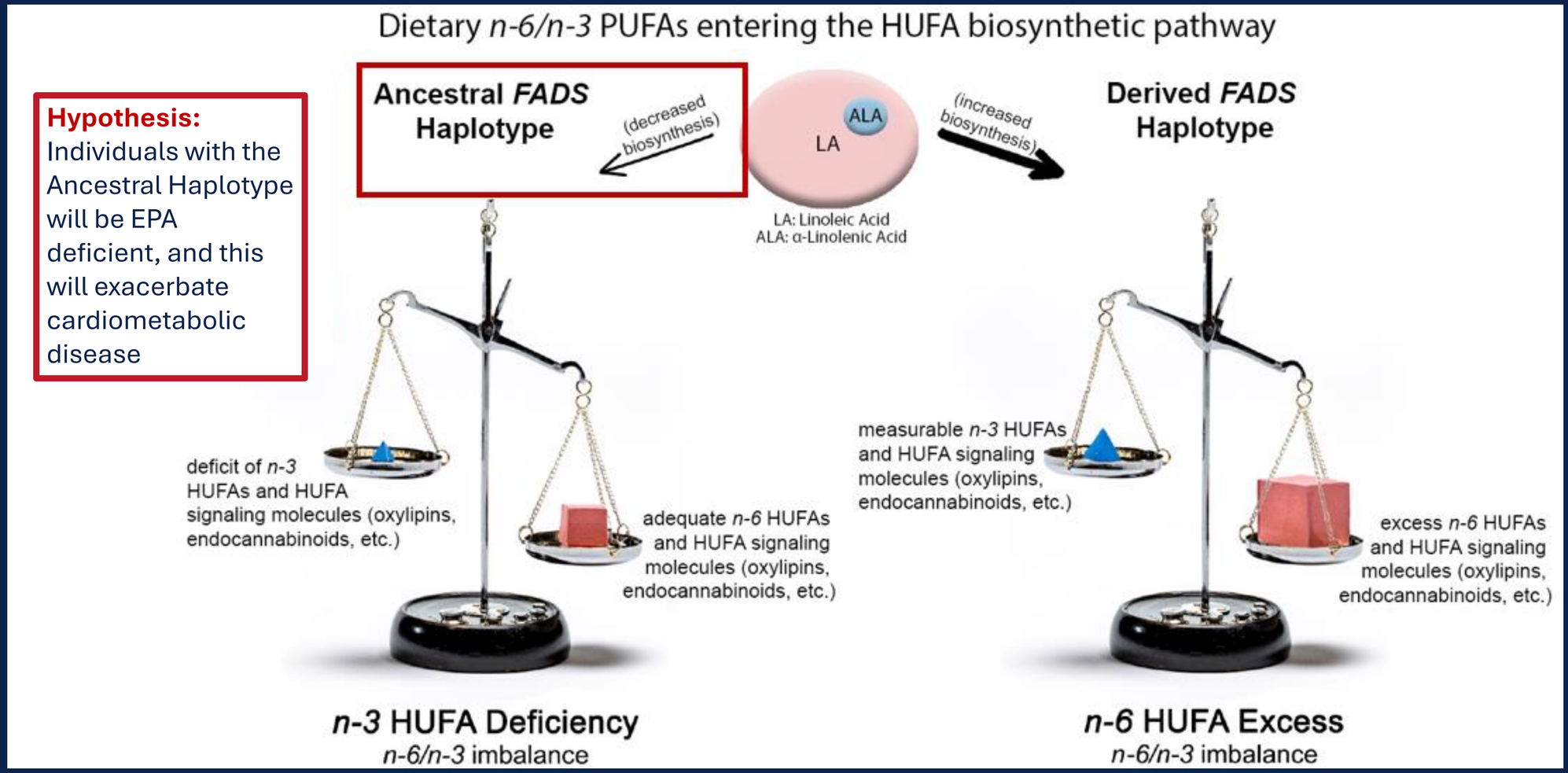
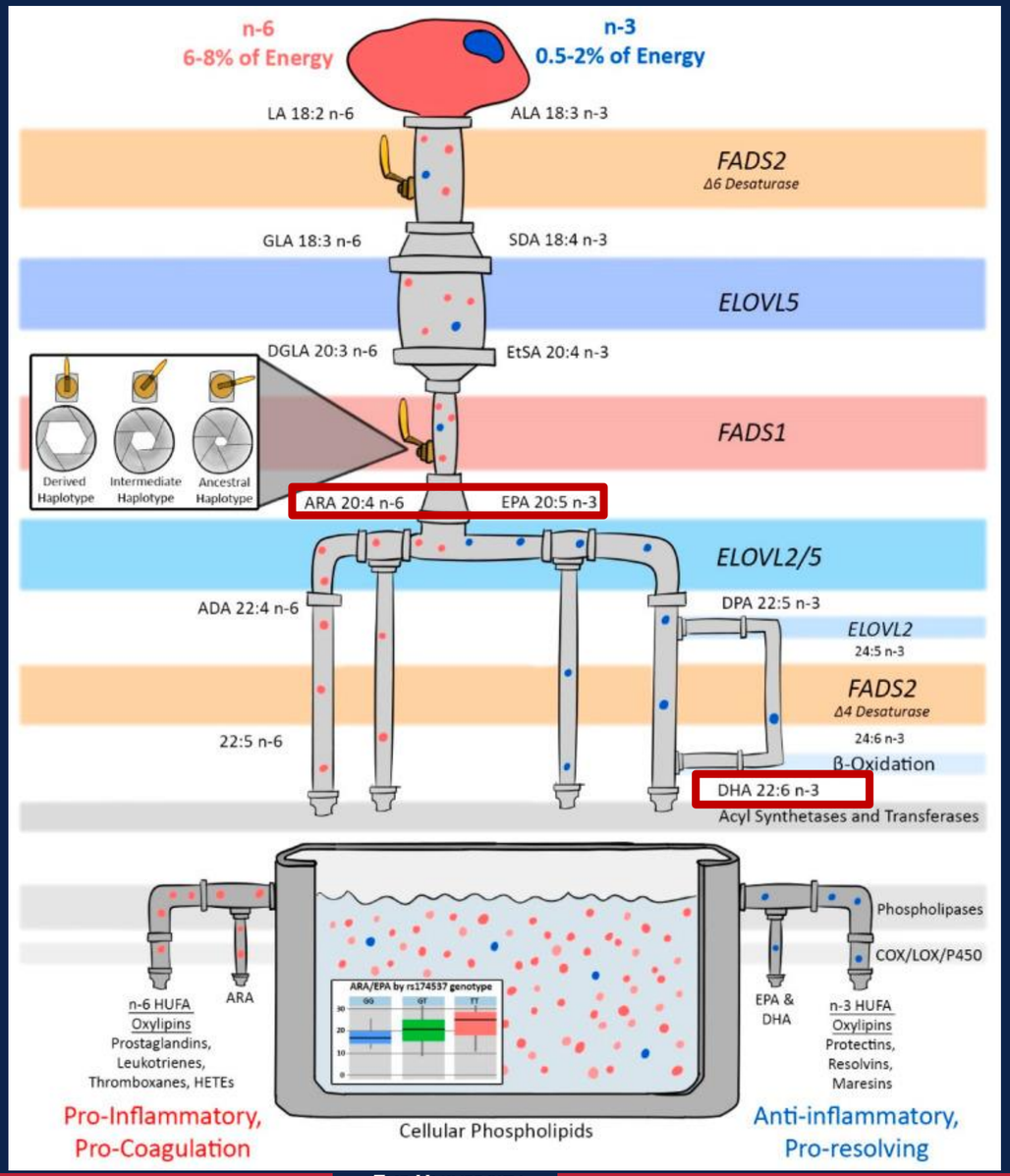
How about Indigenous American Ancestry (Ancestral Haplotype) Populations (>50% of Mexican Americans)?

Make Much Lower Levels of Omega-3 HUFAs

Hypothesis:
Individuals with the Ancestral Haplotype will be EPA deficient, and this will exacerbate cardiometabolic disease



The Conceptual Framework for a Gene-PUFA Interaction for Indigenous Ancestry Populations



Omega-3 Deficiency and Cardiometabolic Traits in Hispanic Populations

communications biology

ARTICLE

https://doi.org/10.1038/s42003-021-02431-4 OPEN

Impact of Amerind ancestry and FADS genetic variation on omega-3 deficiency and cardiometabolic traits in Hispanic populations

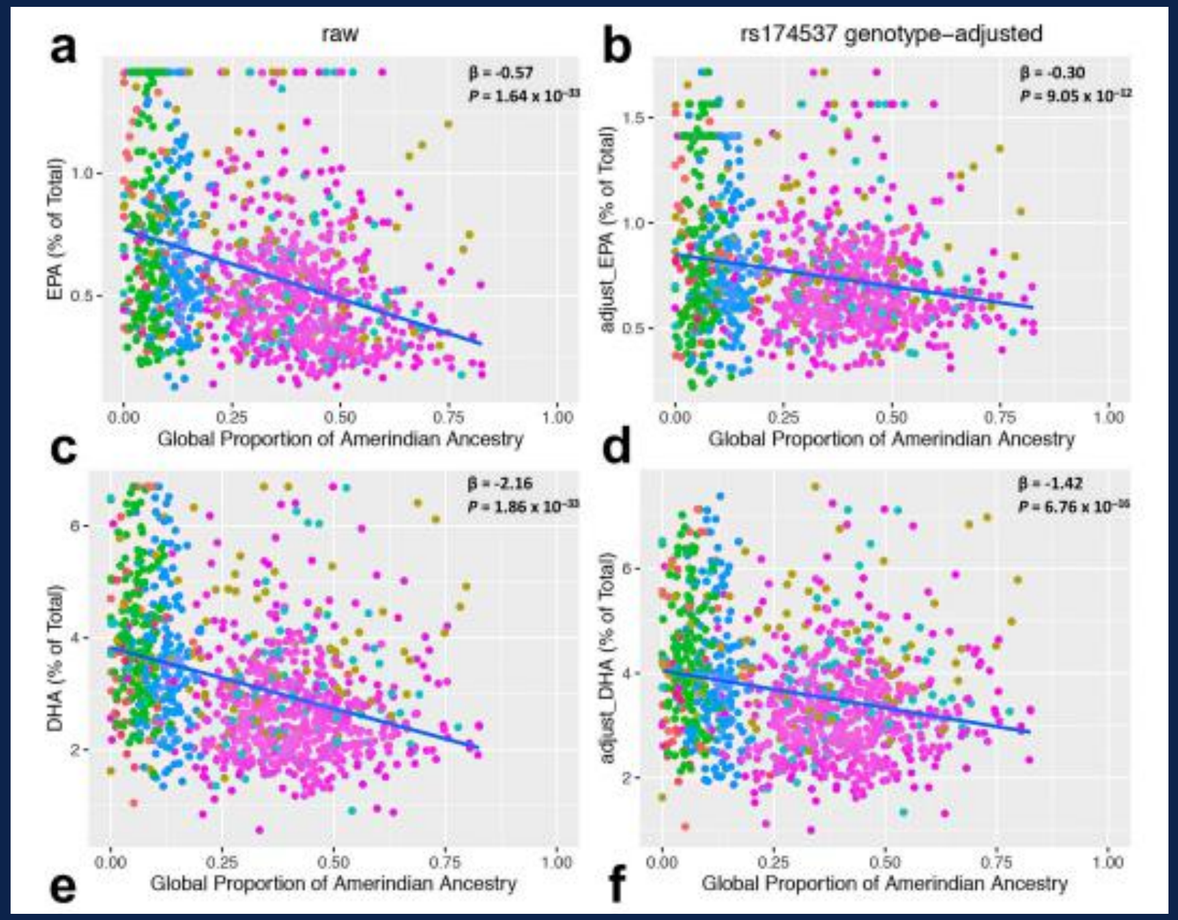
Chaojie Yang[1,2], Brian Hallmark[3], Jin Choul Chai[4], Timothy D. O'Connor[5], Lindsay M. Reynolds[6], Alexis C. Wood[7], Michael Seeds[8], Yii-Der Ida Chen[9], Lyn M. Steffen[10], Michael Y. Tsai[11], Robert C. Kaplan[4,12], Martha L. Daviglus[13], Lawrence J. Mandarino[14], Amanda M. Fretts[15], Rozenn N. Lemaitre[16], Dawn K. Coletta[14,17], Sarah A. Blomquist[18], Laurel M. Johnstone[19], Chandra Tontsch[18], Qibin Qi[4], Ingo Ruczinski[20], Stephen S. Rich[1], Rasika A. Mathias[21], Floyd H. Chilton[18,22] & Ani Manichaikul[1,22]✉

COMMUNICATIONS BIOLOGY | (2021)4:918 | https://doi.org/10.1038/s42003-021-02431-4 | www.nature.com/commsbio

Table 1 Participant characteristics for individuals of self-identified Hispanic origin from the MESA cohort.

Characteristics	Self-reported Hispanic country/region of origin						Total (N = 1102)
	Cuba (N = 45)	Dominican (N = 145)	Puerto Rico (N = 167)	South Amer. (N = 93)	Central Amer. (N = 80)	Mexico (N = 572)	
Sex (Female)	42.2%	53.1%	52.7%	54.8%	58.8%	48.3%	50.6%
Age (years)	69.8 (9.1)	58.8 (10.1)	59.3 (9.4)	62.9 (10.3)	58.7 (8.1)	61.8 (10.2)	61.2 (10.1)
Study Site: Columbia University	73.33%	99.31%	86.24%	60.22%	20%	0.54%	35.93%
Study Site: University of Minnesota	15.56%	0.69%	11.37%	15.05%	13.75%	38.98%	24.95%
Study Site: UCLA	11.11%	0	2.39%	24.73%	66.25%	60.48%	39.12%
Height (cm)	163.1 (9.7)	163.3 (9.4)	162.6 (9.3)	160.4 (8.9)	159.6 (9.2)	161.7 (9.5)	161.8 (9.4)
Weight (kg)	75.3 (13.9)	75.4 (14.3)	79.5 (17.4)	71.4 (12.3)	74.9 (15.3)	77.7 (15.8)	76.8 (15.6)
Waist-to-hip ratio	0.98 (0.06)	0.93 (0.08)	0.94 (0.08)	0.94 (0.07)	0.96 (0.06)	0.97 (0.07)	0.96 (0.07)
BMI (kg/m^2)	28.3 (5.3)	28.2 (4.6)	29.9 (5.7)	27.7 (4.1)	29.3 (5.2)	29.6 (5.2)	29.3 (5.1)
HDL-C (mg/dl)	49.8 (18.1)	47.2 (10.7)	49.7 (14.2)	50.8 (13.9)	48.0 (12.1)	45.9 (12.5)	47.4 (13.0)
LDL-C (mg/dl)	121.1 (26.1)	124.7 (35.5)	118.0 (33.3)	115.8 (29.6)	120.9 (38.3)	119.4 (32.8)	119.8 (33.2)
Triglycerides (mg/dl)	154.2 (100.4)	132.9 (69.9)	134.4 (72.1)	151.5 (168.8)	144.1 (75.5)	173.6 (113.4)	157.5 (107.6)
s-ICAM (ng/ml)	311.7 (71.8)	262.4 (88.2)	307.6(110.6)	276.4 (72.3)	286.6 (69.4)	298.7 (80.6)	293.2 (86.2)
E-Selectin (ng/ml)	64.05 (32.8)	54.15 (17.9)	63.65 (27.4)	57.96 (29.8)	62.74 (26.1)	67.07 (29.3)	63.06 (27.4)
Fish intake (servings/day)	0.19 (0.28)	0.21 (0.22)	0.21 (0.25)	0.20 (0.28)	0.22 (0.23)	0.15 (0.21)	0.18 (0.23)
EPA (% of total fatty acids)	0.90 (0.55)	0.87 (0.68)	0.76 (0.55)	0.72 (0.43)	0.58 (0.38)	0.52 (0.29)	0.64 (0.46)
DPA (% of total fatty acids)	0.98 (0.24)	0.95 (0.26)	0.90 (0.20)	0.89 (0.22)	0.83 (0.18)	0.84 (0.19)	0.88 (0.21)
DHA (% of total fatty acids)	3.71 (1.51)	4.15 (1.31)	3.58 (1.23)	3.76 (1.25)	3.24 (1.15)	2.69 (0.90)	3.19 (1.23)
ARA (% of total fatty acids)	12.18 (2.58)	12.84 (2.52)	12.00 (2.65)	10.53 (2.26)	11.04 (2.40)	10.64 (2.36)	11.22 (2.56)
Global Proportion of Amerind ancestry	0.06	0.06	0.12	0.33	0.39	0.41	0.30
Global Proportion of African ancestry	0.19	0.41	0.23	0.09	0.16	0.04	0.14
Global Proportion of European ancestry	0.75	0.53	0.65	0.58	0.45	0.55	0.56
rs174537 frequency* of effect allele T (versus G allele)	0.28	0.27	0.40	0.56	0.59	0.59	0.51

Phenotypic descriptive statistics are presented as percentages for dichotomous variables and mean (standard deviation) for continuous variables.
*For comparison, the rs174537 effect allele frequencies were 0.007, 0.328, and 0.858 in the 1000 Genomes AFR, EUR and AMR populations, respectively, where the allele frequency calculation was restricted to the cleaned set of samples that were included in the reference set for local ancestry analysis (see Supplementary Methods for details).



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Effect of Amerind Ancestry and *FADS* Genotype on Fasting Lipid and Anthropomorphic and Inflammatory Endpoints

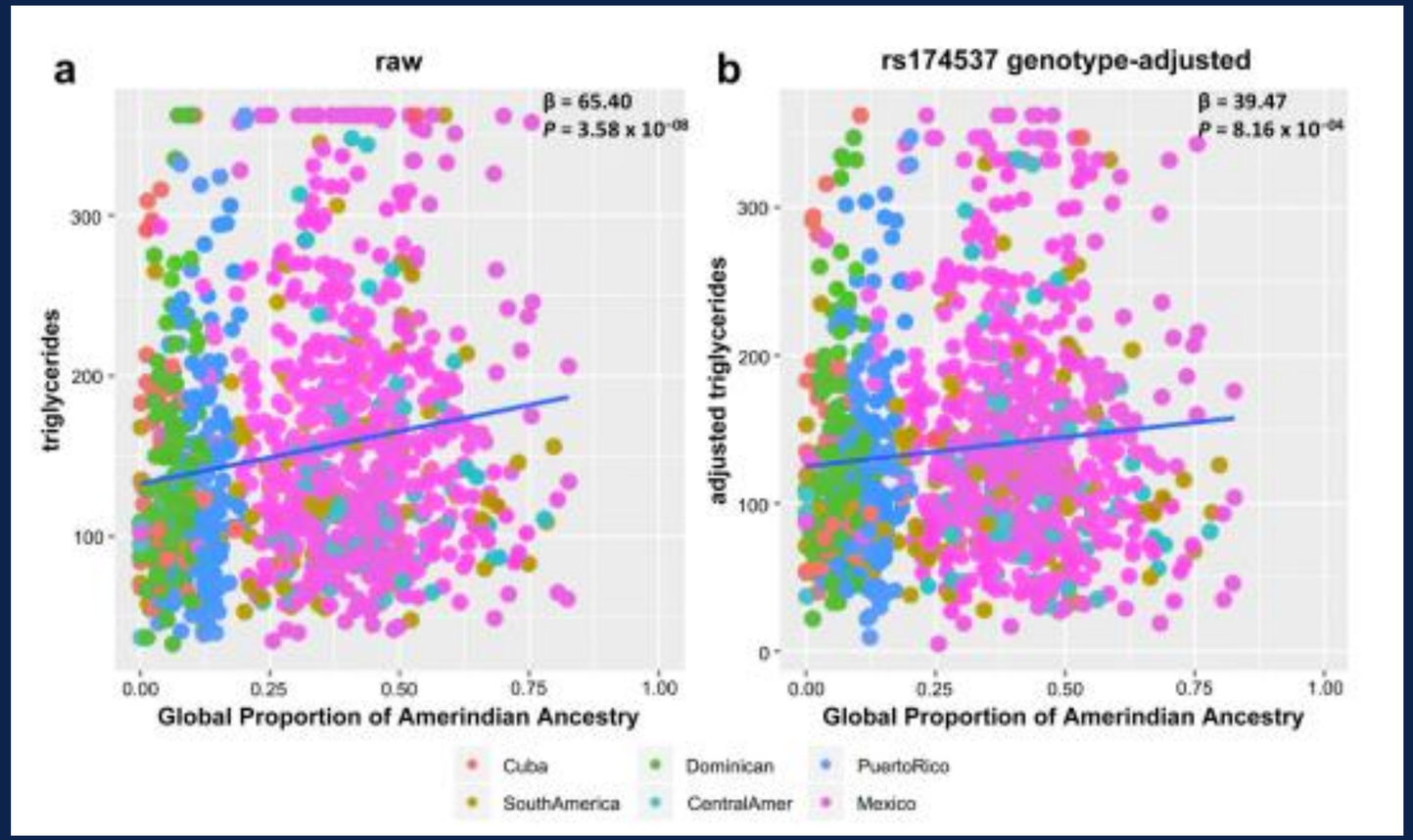

Table 2 Genotypic effects of rs174537 on fasting lipids, anthropometrics and inflammatory traits.

			Beta	*P* value
Fasting lipids	Triglycerides (mg/dL)	GT	21.27	0.0001
		TT	29.94	1.01×10^{-06}
	HDL-C (mg/dL)	GT	−1.30	0.141
		TT	−2.48	0.010
Anthropometrics	waist-hip ratio	GT	0.006	0.152
		TT	0.013	8.94×10^{-03}
	Height (cm)	GT	−1.36	0.002
		TT	−3.46	6.59×10^{-12}
	Weight (kg)	GT	−1.89	0.077
		TT	−3.12	7.48×10^{-03}
	BMI (kg/m^2)	GT	−0.25	0.50
		TT	−0.002	0.99
Inflammatory	s-ICAM (ng/mL)	GT	30.64	0.002
		TT	26.09	0.018
	E-Selectin (ng/mL)	GT	10.00	0.048
		TT	11.50	0.032

Regression analysis results for the effect of rs174537 genotype on fasting lipids, anthropometrics and inflammatory with adjustment for age and sex. For the effect sizes, the effects of GT and TT are in reference to GG. The sample size is 1102 (GG: 293; GT: 484; TT: 325) for waist-hip ratio; height; weight and BMI, 1101 (GG: 293;GT: 483;TT: 325) for triglycerides and HDL-C, 439 (GG: 112; GT: 194; TT: 133) for s-ICAM and 183 (GG: 48; GT: 76; TT: 59) for E-Selectin. *P*-values are calculated using two-sided *t* test for the regression coefficient.

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FADS Variation, Omega-3 Deficiency, and CMD Risk in the MxAm (AIR) Population

The influence of *FADS* genetic variation and omega-3 fatty acid deficiency on cardiometabolic disease risk in a Mexican American population

Sarah A. Blomquist[1], Jil H. Albrecht[1], Brian Hallmark[2,3], Yann C. Klimentidis[3,4], Luis A. Garcia[5,6], Lawrence J. Mandarino[5,6], Dawn K. Coletta[5,6,7] and Floyd H. Chilton[1,3,8,9]*

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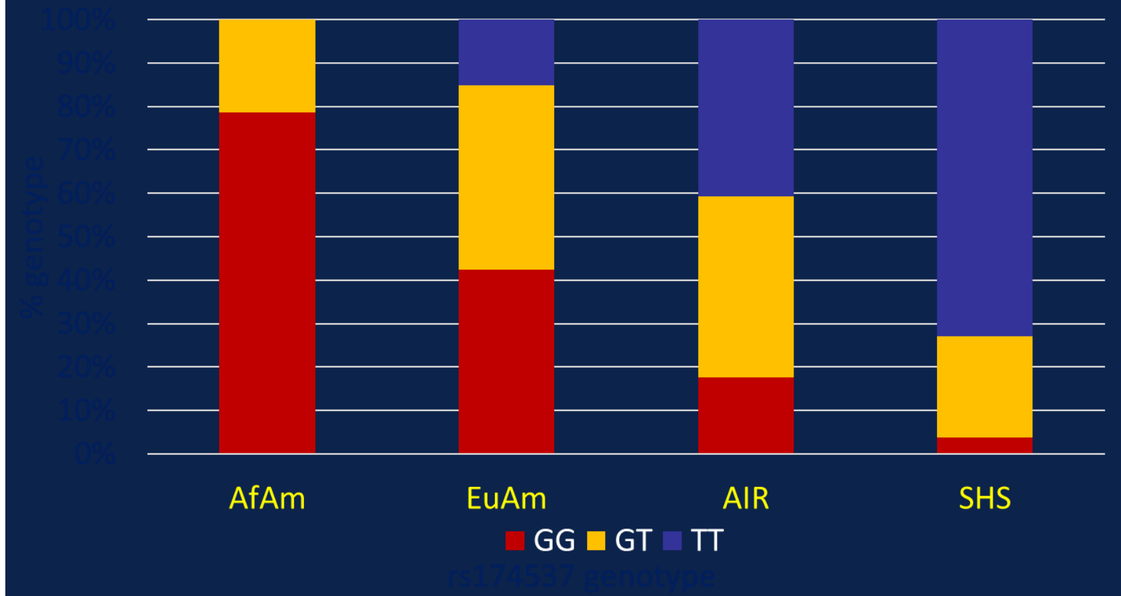
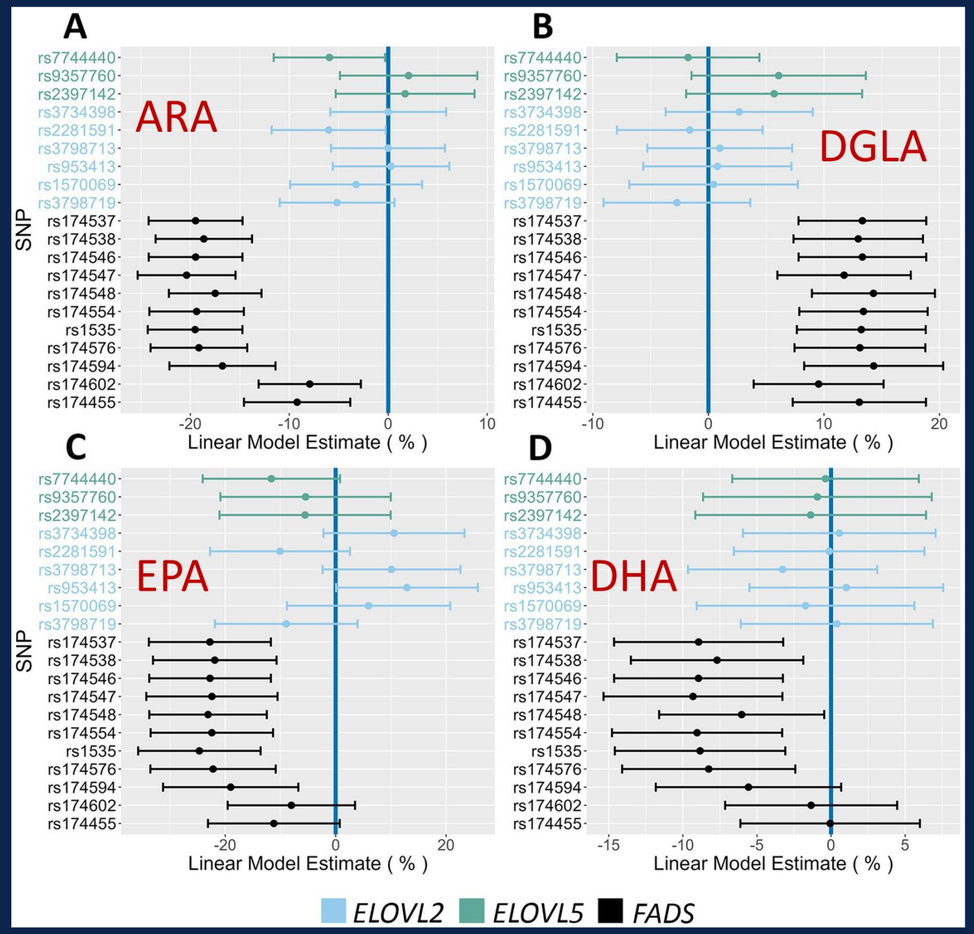


Derived
(efficient)

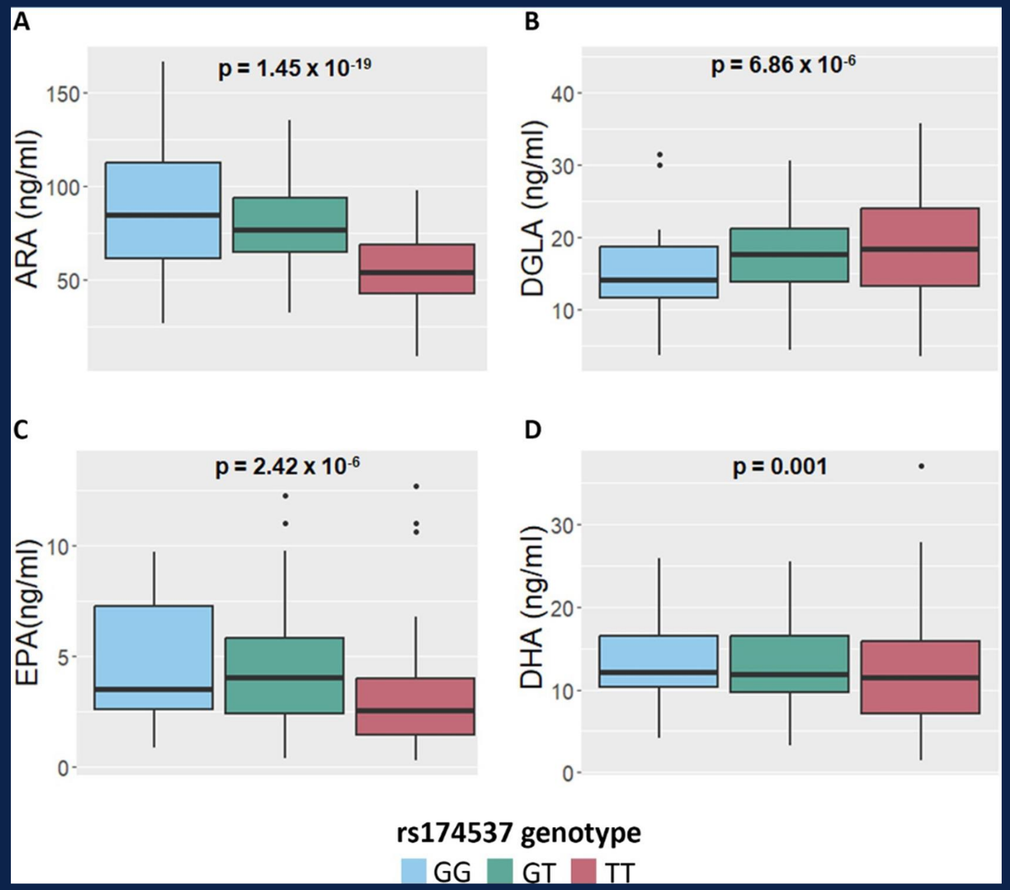
Ancestral
(inefficient)

Impact of *FADS* and *ELOVL* alleles on Omega-6 and Omega-3 HUFA Plasma Levels

Omega-6 HUFAs



Omega-3 HUFAs



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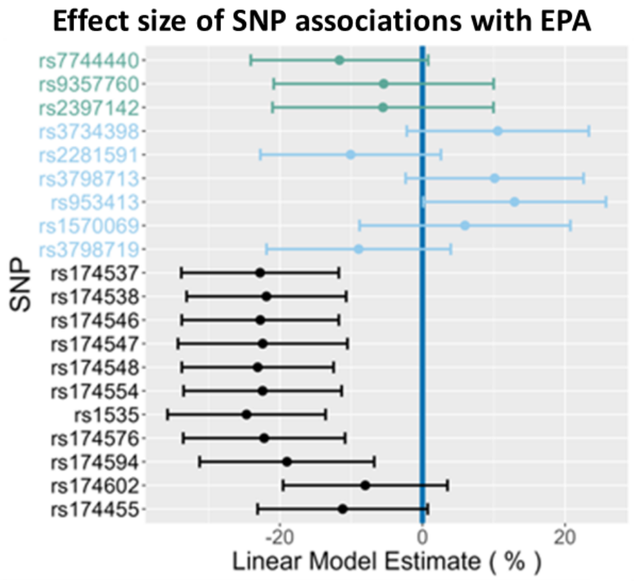
Comparison of Homozygous Genotypes at rs174455 for CMD Phenotypes

Phenotype	Homozygous major allele (GG)	Homozygous minor allele (AA)	Estimate	95% CI	*p*-value
2 Hr Glucose (mg/dL)	138.21	130.64	−0.59%	(−7.66, 7.00)	0.87
HOMA-IR	2.31	1.78	44.96%	(11.69, 88.13)	<0.01
Fasting Glucose (mg/dL)	94.77	93.67	−0.72%	(−3.37, 2.00)	0.59
Fasting Insulin (μIU/mL/mL)	9.35	7.21	43.26%	(10.97, 84.96)	<0.01
HDL (mg/dL)	42.79	46.3	−6.06%	(−12.51, 0.85)	0.08
Triglycerides (mg/dL)	144.18	108.74	33.03%	(15.76, 52.86)	<0.01
LDL (mg/dL)	107.49	100.53	3.64%	(−4.48, 12.46)	0.39
VLDL (mg/dL)	23.8	17.29	29.90%	(13.69, 48.43)	<0.01
Male fat mass (%)	20.85	18.9	−0.44%	(−13.34, 14.36)	0.94
Female fat mass (%)	27.21	25.35	−2.46%	(−7.22, 2.54)	0.33
Male hip circumference (cm)	106.7	106.66	0.62%	(−1.79, 3.09)	0.61
Female hip circumference (cm)	110.36	109.71	−0.61%	(−2.18, 1.00)	0.46
Male height (cm)	164.82	165.56	0.26%	(2.59, 3.20)	0.85
Female height (cm)	161.85	163.13	−0.31%	(−2.38, 1.79)	0.77
Male weight (kg)	81.68	80.9	7.05%	(−4.01, 19.38)	0.22
Female weight (kg)	77.29	83.82	−9.56%	(−17.38, −1.00)	0.03

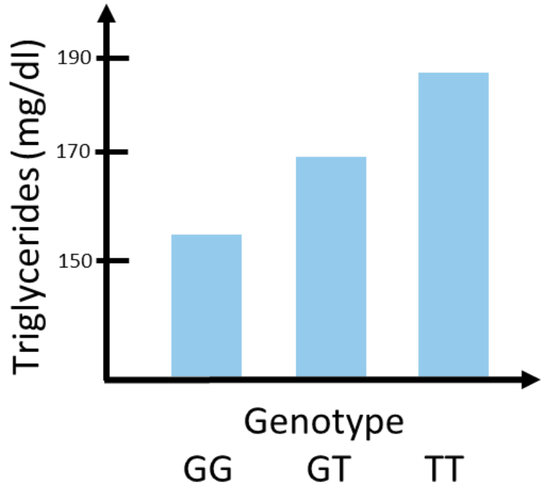
Impact of *FADS* Genetic Variation on EPA and Triglyceride Levels



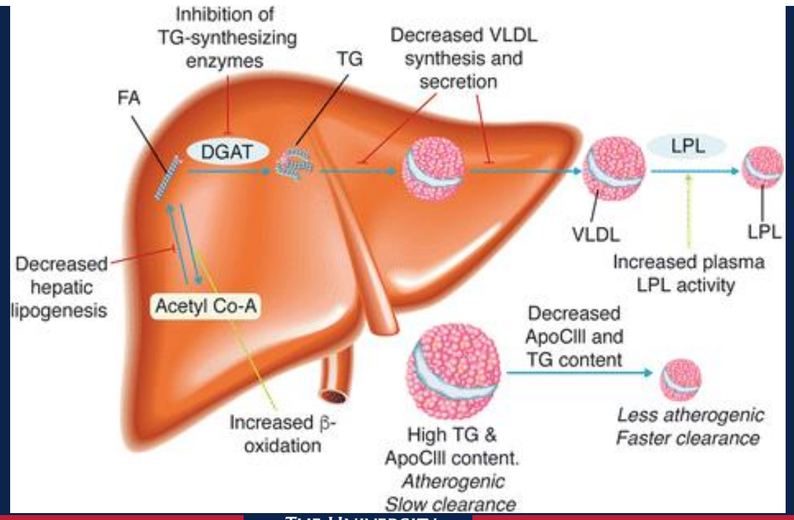
***Per ancestral allele, there is ~20% decrease in EPA**

*** With two ancestral alleles, there is ~40% decrease in EPA levels.**

(Omega-3 Deficiency Syndrome)

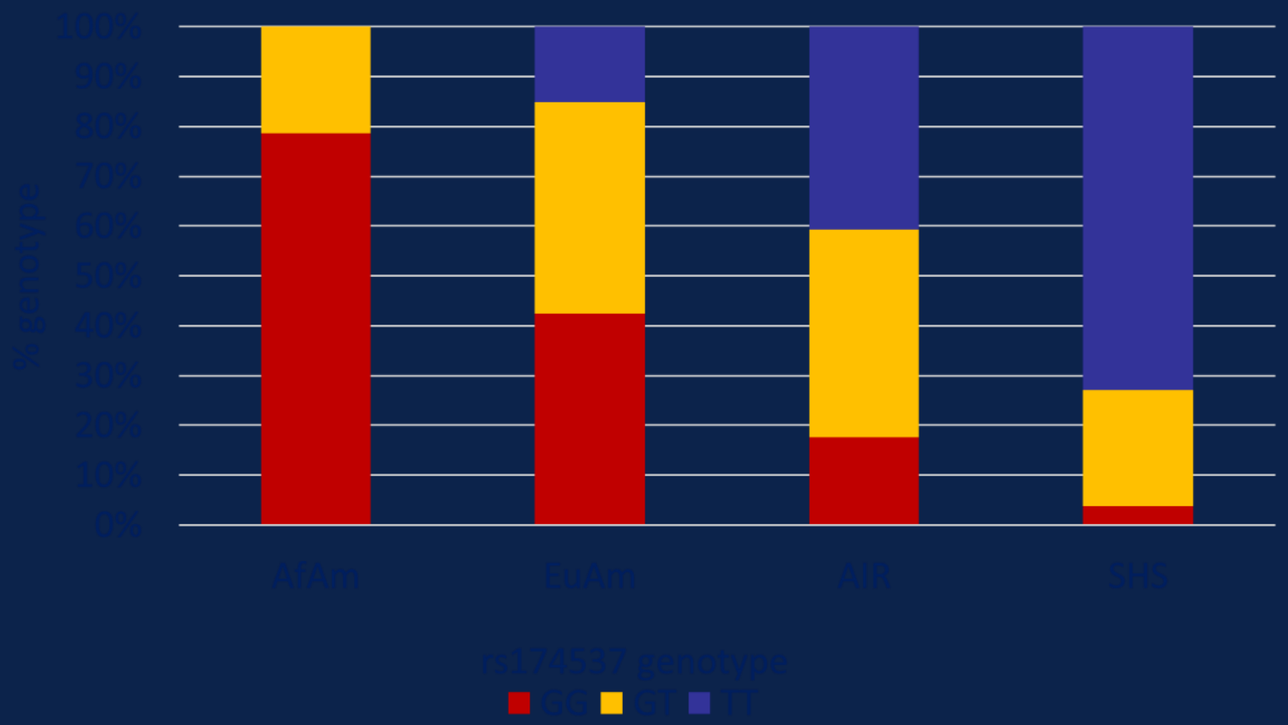


***Per ancestral allele, there is a 20mg/dL increase in triglycerides**



The clinical relevance of omega-3 fatty acids in the management of hypertriglyceridemia

The Strong Heart Study



In the early 1980s, a government task force identified a lack of data on cardiovascular disease (CVD)in American Indians, prompting the creation of the Strong Heart Study (SHS). The SHS began with three main components: tracking CVD mortality rates, conducting clinical exams of 4,500 tribal members, and ongoing surveillance of morbidity and mortality. Over time, the study expanded to include genetic research, launching the Strong Heart Family Study (SHFS) to explore hereditary risk factors, eventually including nearly 3,800 individuals from 94 families.

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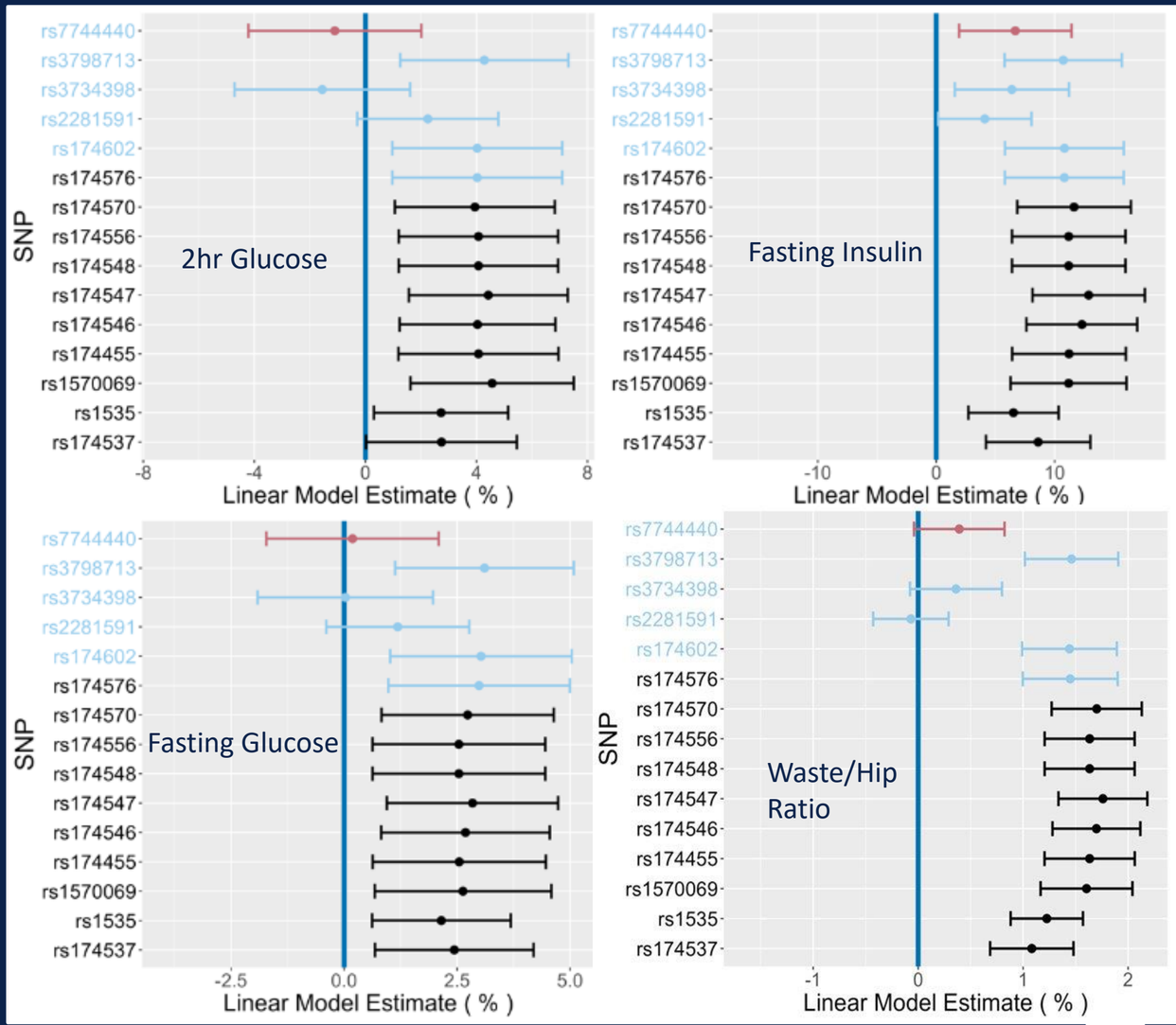
Impact of *FADS* Variation on Type 2 Diabetes Status in American Indians



Factor model (GG / GT / TT)					
T2D status	**rs174537GT**		**rs174537TT**		
--	OR	P-val	OR		P-val
Pre-T2D	1.98	0.03	2.33		0.007
T2D	2.01	0.01	3.25		0.00001

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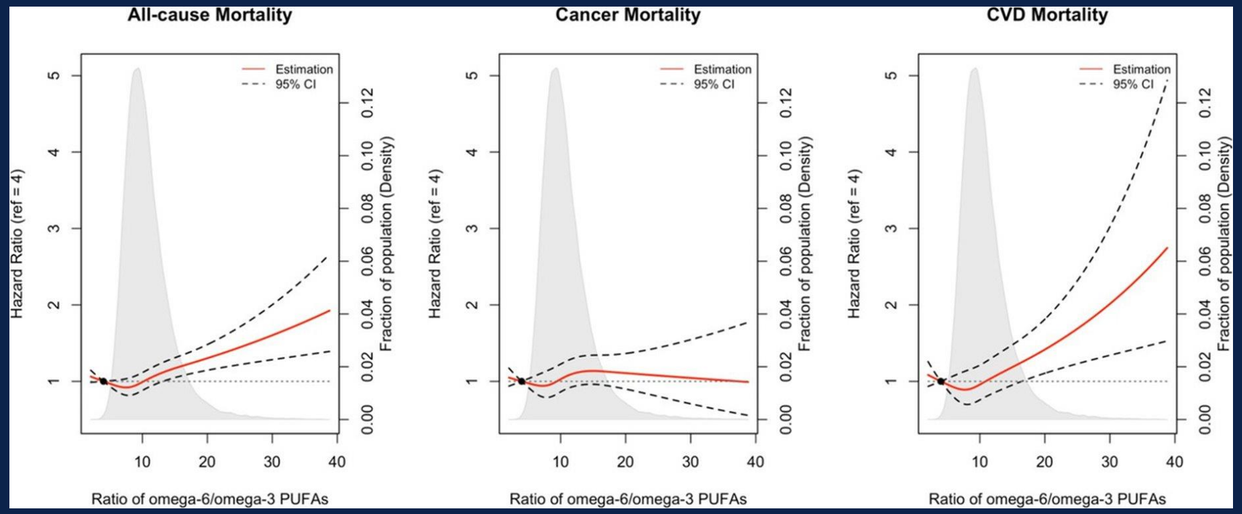
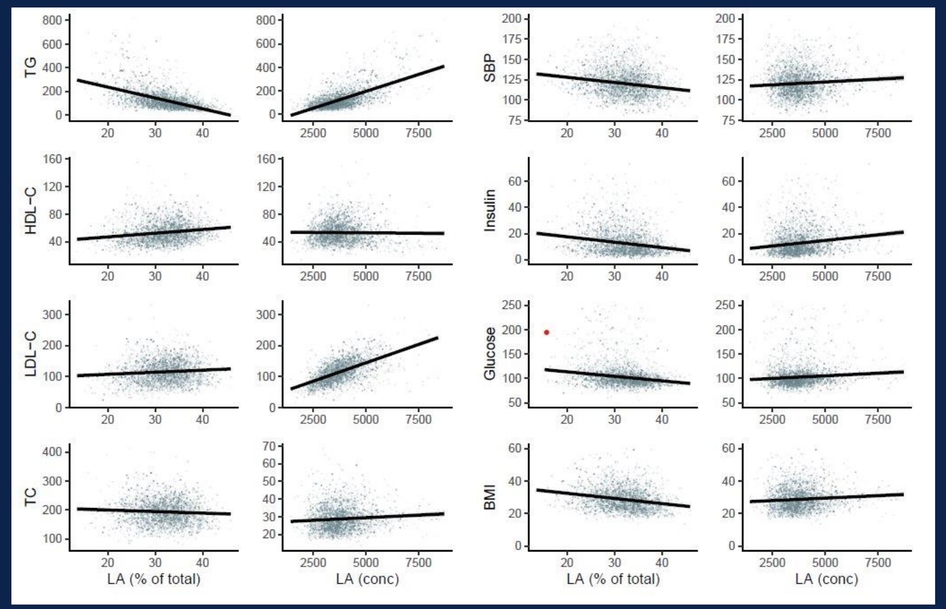
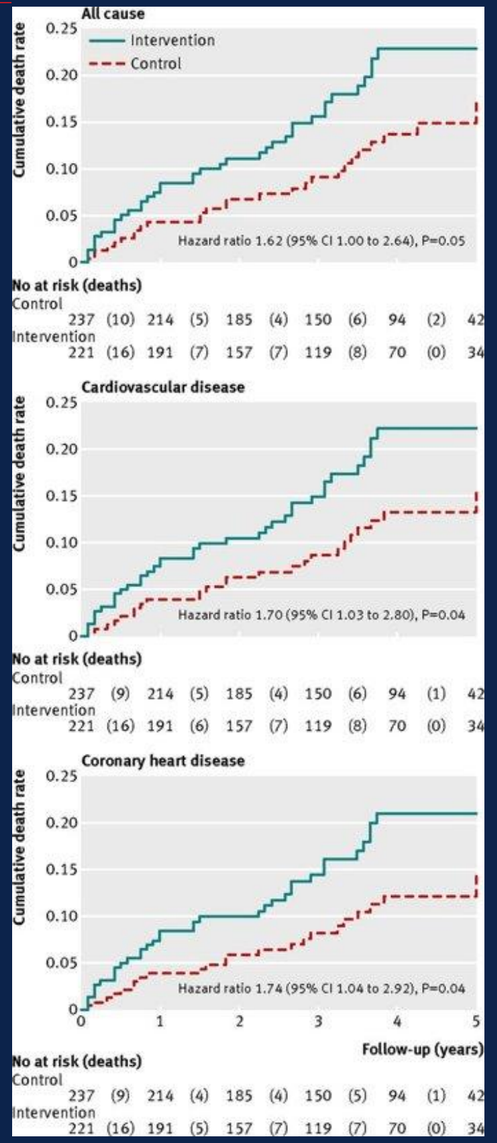
Our Deep Concerns for the AHA's PUFA Recommendations Continue to Grow



Zhang et al., eLife. 2024;12:RP90132.



Hallmark and Chilton Nutrients (submitted)



Ramsden et al. BMJ 2013;346:bmj.e8707

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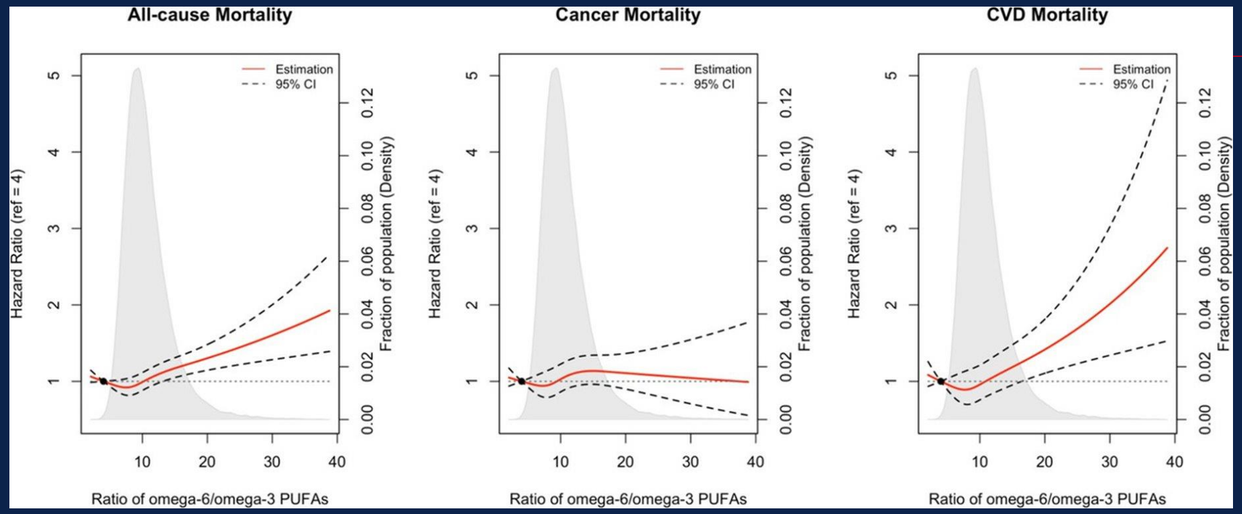
Our Deep Concerns for the AHA's PUFA Recommendations Continue to Grow



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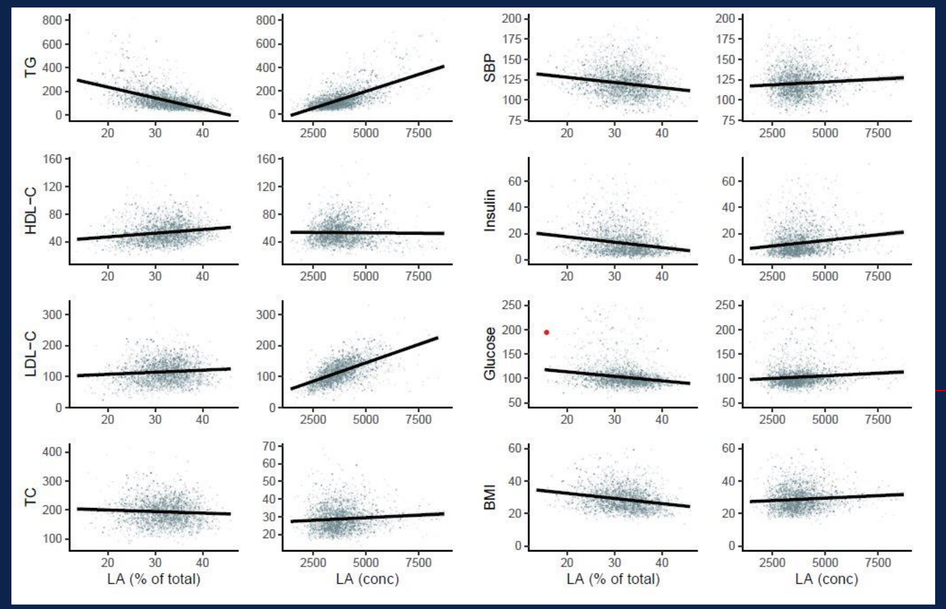
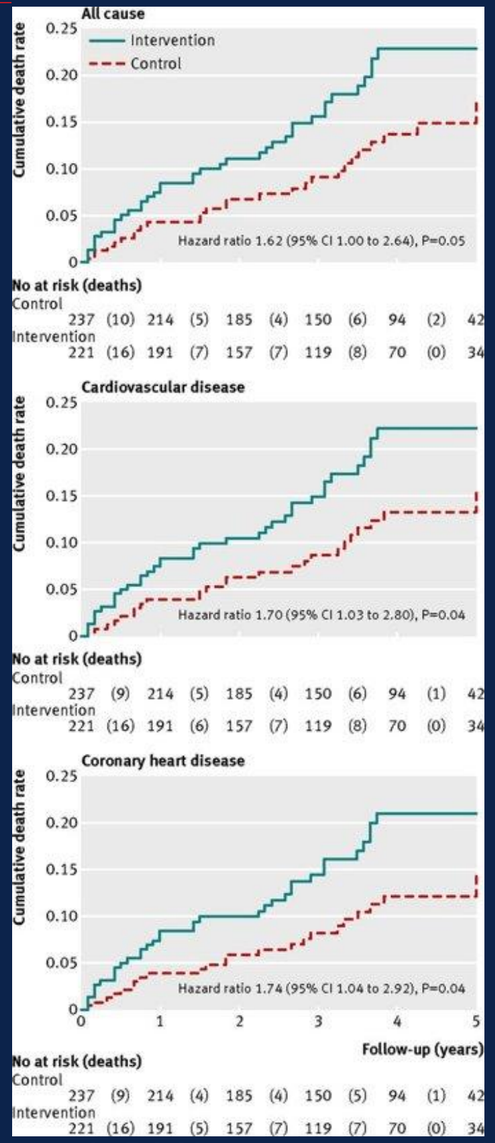


Hallmark and Chilton
JAMA Network



Ramsden et al. BMJ 2013;346:bmj.e8707

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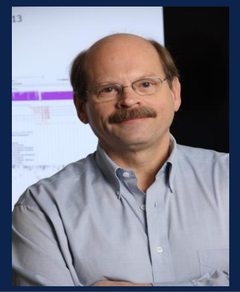

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