

ARIC Manuscript Proposal # 1785

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SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Interactions between genetic variants and dietary PUFAs for plasma phospholipid n-3 fatty acids

b. Abbreviated Title (Length 26 characters): dietary PUFA x SNP for plasma FA

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __CES__ [please confirm with your initials electronically or in writing]

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Data sharing deadline June 15

4. Rationale:

EPA and DHA are established dietary factors in the reduction of CVD mortality and morbidity (Lee, 2009; Mozaffarian, 2008; Mozaffarian, 2006; Albert, 1998; Siscovik, 1995), but achieving adequate dietary intakes from fish sources may be challenging. Fish intake varies among US populations (Chung, 2008). For example, Hispanic Americans consume less fish than European Americans or African Americans (Anderson, 2010; Fitten, 2008), and the types of fish consumed also differ across populations (Nahab, 2011). Alpha linolenic acid (ALA) consumption may provide an alternative or complementary strategy to fish for increasing tissue long chain PUFA, but ALA conversion to EPA is also highly variable, ranging from 0.2% to 8% (Burdge, 2004). Sources of variability for ALA conversion to long chain fatty acids include age, gender and intakes and/or ratios of other fatty acids, particularly linoleic acid (Wien, 2010; Goyens, 2006; Burdge, 2006).

Genetic factors are an additional source of variability in determining tissue concentrations of long-chain PUFA. Genetic modulators of plasma EPA, DPA and DHA that have been replicated across populations may act by altering metabolic capacity for ALA conversion to long-chain PUFA (Tanaka, 2009; Baylin, 2007; Schaeffer, 2006). In the CHARGE GWAS for plasma n-3 fatty acids, plasma phospholipid ALA interacted with *FADS2* genotype for plasma EPA, suggesting that interindividual variability in plasma long-chain PUFA may depend on both desaturase variants and ALA availability (unpublished data). Minor allele frequencies (MAF) of selected highly significant SNPs based on the CHARGE GWAS results appear to differ by ethnic group. For example, MAF for *FADS1* SNP rs174548 was 0.20 in African Americans, 0.29 in European Americans, and 0.52 in Hispanic Americans. For *ELOVL2* rs3734398, another highly significant SNP for long-chain PUFA, MAF was 0.42 in European Americans, 0.25 in African Americans and 0.92 in Chinese Americans.

Ethnically-based variability in allelic frequency of loci associated with plasma EPA and DHA suggests that population subgroups may require different PUFA intakes in order to achieve optimal tissue concentrations and cardio-protective benefits. Genetic susceptibility to lower plasma EPA or DHA may be either further exacerbated or, alternatively, ameliorated by dietary factors. Evaluation of the relationships between diet and genotype for plasma long-chain PUFA, may inform optimal dietary approaches with important implications for public health, and which are unexplored in majority and minority populations.

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5. Main Hypothesis/Study Questions:

The proposed project will evaluate interactions between selected dietary fatty acids and SNPs demonstrated to modulate plasma n-3 PUFA (ALA, EPA, DPA and DHA). We hypothesize that plasma fatty acids will be related to dietary intakes, but also that dietary fatty acids will interact with genetic variants which encode proteins that metabolize fatty acids. For example, we hypothesize that plasma ALA will reflect ALA intake, but that genes encoding enzymes which metabolize ALA (such as *FADS1*, fatty acid desaturase 1) will modify this association. These relationships are likely to be similar in principle for the longer-chain n-3 (EPA, DPA and DHA), but individual fatty acids which compete for the same enzyme (ALA and linoleic acid) may interact differentially with specific variants.

The analysis will begin in Whites. Other ethnic populations (European Americans, Hispanic Americans, African Americans, and Chinese Americans) will be evaluated following analysis of GWAS data in these groups for plasma n-3 outcomes.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

STUDY POPULATION:

MN Sample: Participants (n=3,793) with fatty acid data and genomic data.

EXCLUSIONS:

Individuals whose dietary data failed QC (e.g., extreme energy intake reporters)
Individuals taking EPA+DHA supplements

ENVIRONMENTAL EXPOSURES: (Associations and Interactors)

Alpha linolenic acid (ALA, g/day)
Linoleic acid (LA, g/day)
Polyunsaturated fatty acids (PUFA, g/day)
EPA+DHA (g/day)

For interaction testing, intake of each fatty acid (ALA, LA, PUFA and EPA+DHA), will be modeled as a categorical variable (dichotomized into high and low based on population median intake) and also as a continuous variable. For association testing, only continuous evaluations are needed.

****Categorical definitions for each fatty acids:** Low is defined as < population median intake and high is defined as \geq population median intake. Please code low as 0 and high as 1 for evaluation of fatty acids as categorical variables.

GENETIC EXPOSURE:

SNPs PROPOSED FOR ANALYSIS

No.	CLOSEST GENE	SNP	chromosome	Associated outcome
1	C11orf10	rs174538	11	ALA,EPA,DHA
2	ELOVL2	rs3734398	6	ALA,EPA,DPA,DHA
3	ELOVL2	rs3798713	6	EPA,DHA
4	PDXDC1	rs4985167	16	ALA
5	GCKR	rs780094	2	ALA,EPA,DPA,DHA
6	AGPAT3	rs7435	21	DPA
7	FADS1	rs174548	11	ALA,EPA,DPA,DHA

OUTCOMES:

Plasma ALA, EPA, DPA, DHA

ASSOCIATIONS (MAIN EFFECTS) TESTING:

A regression coefficient ($\beta \pm SE$) for the main effects term for fatty acids will be calculated in each cohort and values meta-analyzed for each ethnic group. Associations will be tested continuously.

MODEL COVARIATES FOR ASSOCIATIONS (MAIN EFFECTS OF FATTY ACIDS)

Model 1: sex, age (continuous years), total energy intake (continuous kcal), cohort-specific population substructure variables (this could include field center and also principal components-based variables reflecting population sub-structure)

INTERACTION TESTING:

A regression coefficient ($\beta \pm SE$) for the interaction term for dietary fatty acids*SNP will be calculated in each cohort and values meta-analyzed for each ethnic group. Initial phase is limited to whites, and will be extended to other ethnic groups as these data become available. Interactions will be tested continuously and categorically.

MODEL COVARIATES FOR INTERACTIONS (SNP*FATTY ACIDS)

Model 1: sex, age (continuous years), total energy intake (continuous kcal), cohort-specific population substructure variables as needed (this could include field center and also principal-components-based variables reflecting population sub-structure as needed)

We will also consider adding ALA as an additional covariate when examining the outcome of plasma n-3.

7.a. Will the data be used for non-CVD analysis in this manuscript?

Plasma phospholipid n-3 fatty acid levels are the phenotype of interest

- b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?** **Yes**

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? **Yes**

- 8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?** **Yes**

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. **Yes**

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#1600 **Lemaitre:** Genome-wide Association Study of Plasma Phospholipid Fatty Acids within the CHARGE Consortium

#890 **Wang:** Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: The Atherosclerosis Risk in Communities (ARIC) Study

#890B **Yamagishi:** Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults: The Atherosclerosis Risk in Communities (ARIC) Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

Yes GWAS via STAMPEDE & GENEVA, #2006.03

11.b. If yes—is the proposal a primarily the result of an ancillary study

ARIC is one of several cohort studies contributing data to the CHARGE-initiated meta-analysis. Since this work is a product of CHARGE which utilizes GWA data, ancillaries related to STAMPEDE & GENVA are also acknowledged (AS2006.03).

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

The lead author is aware of, and will comply with, this stipulation.

References

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