ARIC Manuscript Proposal # 1854

PC Reviewed: 10/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association study of odd-numbered chain saturated fatty acids in plasma phospholipids: CHARGE Fatty Acid Consortium

b. Abbreviated Title (Length 26 characters): **GWAS of odd numbered fatty acids**

2. Writing Group members: Qi Sun, Lyn Steffen, Weihua Guan, Rozenn Lamaitre, David Siscovik, Bruce Psaty, Joshua Bis, Kenneth Rice, Barbara McKnight, Irena King, Jennifer Nettleton, Mike Tsai, Steve Rich, Ani Manichaikul, Myriam Fornage, Donna Arnett, Jason Wu, Dariush Mozaffarian, Frank Hu, Eric Rimm, and other CHARGE investigators participating in the fatty acid working group

Additional authors TBD (this is a multi-cohort effort—ARIC is one of several participating cohorts, *including other cohorts from the CHARGE Plasma Fatty Acids Working Group, tentative list: ARIC, CARDIA, CHS, InCHIANTI, GOLDN, MESA, Nurses' Health Study, Health Professionals' Followup Study)*

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __QS___ **[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:

6-9 months: individual center analysis; meta-analysis
6 months: writing the manuscript

4. Rationale:

Odd-numbered chain fatty acids (OCFAs) are primarily produced by bacteria and other lower organisms.[1] These fatty acids can be found in most animal tissues, although the levels are especially high in tissues of ruminant animals probably because ruminal microorganisms have particularly strong capacity of synthesizing OCFAs.[2] Because human body cannot produce OCFAs through *de novo* synthesis, levels of these fatty acids in human tissues are determined by their intake levels and post-absorption metabolism within human body. A moderate to strong correlation was found between levels of certain OCFAs (15:0 and 17:0) and dairy fat intake in human observational studies,[3-5] suggesting that at least some of OCFAs can be used as biomarkers of dairy fat consumption. However, it is unknown whether there are other factors, related to either diet or metabolism, that determine the levels of these fatty acids in human body.

5. Main Hypothesis/Study Questions:

In this analysis, we aim to shed light on the genetic determinants for the levels of OCFAs in plasma in a genome-wide association (GWA) analysis within the CHARGE Fatty Acid Consortium.

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).

1. Outcomes:

Levels of the following fatty acids in plasma phospholipids or erythrocytes:

a) 15:0 (if available)
b) 17:0 (if available)
c) Sum of 15:0 and 17:0 (if both fatty acids are non-missing)
d) 19:0 (available in the NHS and HPFS only)
e) 21:0 (available in the NHS and HPFS only)
f) 23:0 (available in the ARIC, NHS and HPFS only)

2. Inclusion/exclusion criteria for participants:

Inclusion: participants with European ancestry only.
Exclusion: Missing data of 15:0 AND 17:0.

3. **GWA analysis**
   a) Genotypes: Genotyped SNPs or imputed HapMap CEU SNPs (release r22).
   b) Chromosomes: All chromosomes excluding the sex-chromosomes
   c) Additive models using linear regression that takes into account uncertainty of imputation (i.e., dosage of imputed SNP alleles should be used). Robust variance estimators will be applied to derive standard errors and to calculate P values.
   d) Covariates: age (yr), gender, case-control status (if case-control study), study site (if applicable), population substructure (if needed, based on your judgment, please adjust principal components to correct for population stratification)
   e) Separate models for each fatty acid outcome.

4. **Meta-analysis:**
   a) Fixed-effects model
   b) Weighed by using the inverse of the corresponding standard errors
   c) Significance threshold: $P < 5\times10^{-8}$
   d) Final QC step at meta-analysis stage: effect sample size > 150.

References

1. Rezanka T, Sigler K. Odd-numbered very-long-chain fatty acids from the microbial, animal and plant kingdoms. *Prog Lipid Res* 2009; **48**(3-4)**:** 206-38
2. Wu Z, Palmquist DL. Synthesis and biohydrogenation of fatty acids by ruminal microorganisms in vitro. *J Dairy Sci* 1991; **74**(9)**:** 3035-46.
3. Wolk A, Furuheim M, Vessby B. Fatty acid composition of adipose tissue and serum lipids are valid biological markers of dairy fat intake in men. *J Nutr* 2001; **131**(3)**:** 828-33.
4. Wolk A, Vessby B, Ljung H, Barrefors P. Evaluation of a biological marker of dairy fat intake. *Am J Clin Nutr* 1998; **68**(2)**:** 291-5.
5. Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr* 2007; **86**(4)**:** 929-37.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No

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? _X___ Yes ____ No
(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? GWAS data __X__ Yes ____ No

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"?

__X__ Yes ____ No

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. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X____ Yes _____ No

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)?

Other GWAS fatty acid manuscripts are similar – except that different fatty acids have been examined.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

Aaron Folsom's analysis of Minnesota plasma for fatty acids.

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* no number listed)

Fatty acid data analyzed in Minnesota only

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.