**ARIC Manuscript Proposal # 1600**

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| **PC Reviewed: 1/12/10** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: *Genome-wide Association Study of Plasma Phospholipid Fatty Acids within the CHARGE Consortium*

**b. Abbreviated Title (Length 26 characters)**: *CHARGE fatty acid GWAS*

**2. Writing Group**:

Writing group members:


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The list of cohorts that will eventually participate is not yet complete, and other authors will join the list above. So far, we know the work will include CHS, ARIC, CARDIA.

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

*Cohort-specific data analyses: February 15, 2009*
*Meta-analysis: March 15, 2009*
*Manuscript drafting complete: May 15, 2009*

**4. Rationale**:

Fatty acids in phospholipids (plasma and cell membranes) originate from the diet (e.g. n-3 and trans fatty acids) or from endogenous metabolism. Phospholipid n-3 and trans-fatty acids are associated with sudden cardiac death, CHD incidence, CHD death and non-fatal myocardial infarction.[1-6] In ARIC, saturated plasma fatty acids were associated with increased risk of incident heart failure, and in women, long chain n-3 fatty acids were associated with lower heart failure risk [7]. In addition, others have observed an association of several membrane fatty acids from endogenous metabolism with risk of sudden cardiac death.[8]

While dietary intake clearly influence levels of plasma phosholipids, evidence from a family study suggests strong heritability of all erythrocyte fatty acids.[9] Recently a case-control genome wide association study (GWAS) reported association between polymorphism at the FADS gene cluster and several polyunsaturated phospholipid fatty acids. [10]

In collaboration with several other groups, we propose to participate in a collaborative effort to identify genetic predictors of fatty acid phenotypes by analyzing the ARIC data and integrating our results with the other participating cohorts through meta-analysis.

**5. Research Hypothesis:**

Using a genome wide approach, we can identify common genetic variants that are associated with plasma phospholipid fatty acid levels of n-3 fatty acids, trans-fatty acids and endogenous fatty acids.

**6. Design & Analysis**

Sample: Minnesota participants (n=4,009) with fatty acid data and genomic data

Exclusions: missing fatty acid components, non-White race, no genetic consent

Independent variables: genome-wide genetic information by imputation (build 36, MACH)

Dependent variables: plasma phospholipid fatty acid levels of n-3 fatty acids (DHA, EPA, and ALA), trans fatty acids (trans-18:1 isomers, trans-18:2 and trans-16:1), and endogenous fatty acids 16:0, 16:1n7 and 16:1n9

Covariates of interest: age and sex

*Brief analysis plan and methods*:

The analysis will be a linear regression of all 2.5 M SNPs against each phenotype of interest. The primary analysis will be adjusted for age, sex and study sites. Phospholipid fatty acids are expressed as percentages of total fatty acids. Genetic variants will be modeled additively.

Association results will be meta-analyzed across the other participating cohorts in the CHARGE consortium.[11] Imputation of genotypes to the HapMap will allow the comparison and integration of GWAS from multiple platforms. Significance thresholds for genotype-phenotype association p-values will be adjusted to account for multiple hypothesis testing ($p < 5 \times 10^{-8}$).

*Summary/conclusion*:

We propose to undertake a genome-wide study of plasma phospholipid levels using the ARIC cohort and integrate our results using meta-analysis with several other genomic studies (including CHS and CARDIA- *new participant in CHARGE consortium*) to identify novel genetic variants associated with phospholipid fatty acids. These findings may identify novel candidate genes and mechanisms regulating phospholipid fatty acids.

*References*

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

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

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

**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.*


1. *Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr. 2003;77:319-325.*
2. *Lemaitre RN, King IB, Mozaffarian D, Sotoodehnia N, Rea TD, Kuller LH, Tracy RP, Siscovick DS. Plasma phospholipid trans fatty acids, fatal ischemic heart disease, and sudden cardiac death in older adults: the cardiovascular health study. Circulation. 2006;114:209-215.*
3. *Lemaitre RN, King IB, Raghunathan TE, Pearce RM, Weinmann S, Knopp RH, Copass MK, Cobb LA, Siscovick DS. Cell membrane trans-fatty acids and the risk of primary cardiac arrest. Circulation. 2002;105:697-701.*
4. *Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, Cobb L, Copass M, Psaty B, R L, B R, M C, Knopp RH. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. Jama. 1995;274:1363-1367.*
5. *Lemaitre RN, King IB, Sotoodehnia N, Rea TD, Raghunathan TE, Rice KM, Lumley TS, Knopp RH, Cobb LA, Copass MK, Siscovick DS. Red blood cell membrane alpha-linolenic acid and the risk of sudden cardiac arrest. Metabolism. 2009;58:534-540.*
6. *Wang L, Folsom AR, Eckfeldt JH. Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Nutr Metab Cardiovasc Dis. 2003;13:256-266.*
7. *Yamagishi K, Nettleton JA, Folsom AR. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2008;156:965-974.*
8. *Lemaitre RN, King IB, Sotoodehnia N, Knopp RH, Mozaffarian D, McKnight B, Rea TD, Rice KM, Friedlander Y, Lumley TS, Raghunathan TE, Copass MK, Siscovick DS. Endogenous red blood cell membrane fatty acids and sudden cardiac arrest. Metabolism. 2009;in press.*
9. *Lemaitre RN, Siscovick DS, Berry EM, Kark JD, Friedlander Y. Familial aggregation of red blood cell membrane fatty acid composition: the Kibbutzim Family Study. Metabolism. 2008;57:662-668.*
10. *Tanaka T, Shen J, Abecasis GR, Kisialiou A, Ordovas JM, Guralnik JM, Singleton A, Bandinelli S, Cherubini A, Arnett D, Tsai MY, Ferrucci L. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. PLoS Genet. 2009;5:e1000338.*
11. *Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, Uitterlinden AG, Harris TB, Witteman JC, Boerwinkle E. Cohorts for Heart and Aging Research in Genomic Epidemiology*

*(CHARGE) Consortium: Design of Prospective Meta-Analyses of Genome-Wide Association Studies from 5 Cohorts. Circ Cardiovasc Genet. 2009;2:73-80.*