1.a. Full Title: Genome-wide association study of monounsaturated fatty acids in Chinese and Caucasian cohorts: CHARGE Consortium Fatty Acid Working Group

b. Abbreviated Title (Length 26 characters): GWAS of MUFA

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JZ___ [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).
   Name: Lyn M. Steffen
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3. **Timeline:** 1 year (October 2012 to September 2013)

4. **Rationale:**
Levels of plasma phospholipids or erythrocyte monounsaturated fatty acids (MUFAs) are observed to be related to risk of type 2 diabetes (1-2), while dietary intake of MUFAs is inversely associated with risk of metabolic disorders including cardiovascular disease (3-4), diabetes (5), and related traits (6). Circulating MUFAs are determined by dietary intake and metabolism. Several studies have indicated that MUFAs are affected by elongase and stearoyl-CoA desaturase (SCD) (7-8). Besides, increased expressions of Using a genome wide approach, we will identify common genetic variants that are associated with plasma phospholipid fatty acid levels of n-6 fatty acids, including linolenic (LA; 18:2,n6), gamma linolenic (GLA; 18:3,n6), dihomo-gamma-linolenic (DGLA; 20:3,n6), arachidonic (AA; 20:4,n6) acids, adrenic acid (22:4,n6), and others. delta-6 desaturase (D6D) and delta-5 desaturase (D5D) genes are also induced by intake of high MUFAs (9) and striking differences in lifestyles like diet could modify effects of genetic variants on fatty acids (10). Furthermore, Chinese are different from Europeans both in genetic background and dietary intake of MUFAs (9). However, whether genes could determine levels of plasma phospholipid or erythrocyte MUFAs are still not well-understood, as well as variances of effect sizes between Chinese and Caucasians. Therefore, it is of interest to identify the genetic loci of MUFAs in genome-wide association studies (GWAS) among Chinese and Caucasians.

The GWAS of two MUFAs (16:1n-7 and 18:1n-9) in Caucasians have been already done in the CHARGE Fatty Acid Consortium as part of a separate proposal led by Jason Wu (paper submitted). Here we proposed to do the GWAS in Whites of 18:1n-7, 16:1n-9, 20:1n-9, 22:1n-9 and 24:1n-9, and the GWAS of all MUFAs in Chinese.

5. **Main Hypothesis/Study Questions:**
Using a genome wide approach, we will identify common genetic variants that are associated with plasma phospholipid fatty acid levels of MUFA.

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).**

**Exclusions:** those with missing fatty acids, non-White race, no genetic consent, extreme outliers for the fatty acids of interest

**Among Chinese** with genome-wide genotypes available, plasma phospholipids or erythrocyte MUFAs 16:1n-7, 18:1n-7, 16:1n-9, 18:1n-9, 20:1n-9, 22:1n-9 and 24:1n-9 are available for individuals from NHAPC (n = 2,865), 16:1n-7, 18:1n-9, 20:1n-9, 24:1n-9 are available for individuals from MESA (n=646).
Among Caucasians with genome-wide genotypes available, we will examine plasma phospholipids or erythrocyte MUFAs 18:1n-7, 16:1n-9, 20:1n-9, 22:1n-9 and 24:1n-9 if available in the cohorts in the CHARGE Fatty Acid Consortium ARIC (n= 3793), MESA = 704); CARDIA (1100+), others.

1. Outcomes:
   % fatty acids in plasma phospholipids or erythrocytes for the following MUFA’s:

   Among Caucasians and Chinese:
   a) 18:1n-7 (not available in ARIC)
   b) 16:1n-9 (not available in ARIC)
   c) 20:1n-9  
   d) 22:1n-9  
   e) 24:1n-9

2. Inclusion/exclusion criteria for participants:
   Inclusion: participants with Chinese ancestry only when analyzed in Chinese, participants with European ancestry only when analyzed in Caucasians.

3. Statistical analysis in each study
   a) Genotypes: Imputed alleles should be oriented the forward strand of the NCBI Build 36 human genome reference sequence. (Please use the HapMap data set for the forward strand, not the dbSNP strand).
   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 across cohorts (for Chinese and Caucasians separately):
   a) Fixed Effects 
   b) Significance threshold: p< 5x10^-8
   c) Final QC step (e.g. filtering MAF at 1% and 0.3 imputation quality) at meta-analysis stage

5. Look-up of top hits from GWAS in Chinese and Caucasians
   a) Genomic regions identified through CHARGE GWAS of MUFAs in Chinese and Caucasians will be selected for loop-up each other
   b) Use the HapMap to define regions of linkage disequilibrium surrounding top SNPs for each MUFA outcome
   c) Report the top SNP for each trait and genomic region, presenting results for each ethnic group separately
6. **Look-up of top hits across ethnic groups**
   a) Look-up top 100 SNPs from GWAS of MUFAs (including 16:1n-7, 18:1n-7, 16:1n-9, 18:1n-9, 20:1n-9, 22:1n-9 and 24:1n-9) in Chinese in GWAS of MUFA in Caucasians
   b) Look-up top 100 SNPs from GWAS of MUFAs in Caucasians in GWAS of MUFAs in Chinese

7. **Examining LD structure of key genomic regions**
   Measurement of LD will be computed within NHAPC for the following:
   a. Genomic regions
      i. All genomic regions reported through prior CHARGE meta-analysis of Caucasians for association with MUFAs
      ii. Any novel genomic regions displaying associations with MUFAs in the current analysis
   For each interested genomic region, we will examine and compare LD between NHAPC Chinese and HapMap-CUE samples.

7.a. Will the data be used for non-CVD analysis in this manuscript?  _____ Yes  _X__ 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?  _____ Yes  _____ No
      (This file ICTDER 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?  _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 list under the Study Members Area of the web site at: [http://www.cscce.unc.edu/ARIC/search.php](http://www.cscce.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)?
#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

#1600: Genome-wide Association Study of Plasma Phospholipid Fatty Acids within the CHARGE Consortium. Lead author: Rozenn Lemaitre

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

11.b. If yes, is the proposal

 _X_  A. primarily the result of an ancillary study (list number)* GWAS via STAMPEDE & GENEVA, #2006.03

 ___  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. OK

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.

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