ARIC Manuscript Proposal #1993

PC Reviewed: 9/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide Association of Ideal Cardiovascular Health

b. Abbreviated Title (Length 26 characters): GWAS of ideal CV health

2. Writing Group: The writing group represents multiple CHARGE co-authors and additional ARIC co-authors are welcome.

Allen, Norrina Bai; Hwang, Shih-Jen; Fornage, Myriam; Rasmussen-Torvik, Laura; Morrison, Alanna C; Lloyd-Jones, Donald; O'Donnell, Christopher

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

F**irst author**: Norrina Bai Allen, PhD
Address: 680 N Lake Shore Drive, Suite 1400; Chicago IL 60611

Phone: (312) 908-1723
E-mail: norrina-allen@northwestern.edu

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: Alanna C. Morrison, PhD
Address: 1200 Herman Pressler, Suite 453E; Houston TX 77030

Phone: (713) 500-9913 Fax: (713) 500-0900
E-mail: alanna.c.morrison@uth.tmc.edu

3. Timeline:
GWAS analyses will be completed upon approval and provided to Dr. Allen for meta-analyses with other CHARGE cohorts. The manuscript will be circulated to co-authors by late 2012.

4. Rationale:
Nearly half of all Americans will experience cardiovascular disease within their lifetime. Among participants of Framingham, the lifetime risk for cardiovascular disease has been found to be as high as 51% among men and 39% among women aged 50 years.[1] However, for individuals with optimal levels of cardiovascular risk factors, ideal CV health, the risk for CVD drops dramatically to 5-8%.[1] It remains unclear what genetic,

behavioral and/or environmental factors are associated with ideal cardiovascular health. Although only about 8% of the population is in ideal CV health,[2] understanding how these individuals achieve ideal CV health represents an important public health goal whose findings could help reduce the future burden of CVD.

Numerous studies have examined the genetic determinants of individual cardiovascular risk factors including blood pressure, lipid levels, glucose levels and BMI which have heritabilities ranging from 15-40%,[3-7] 40-60%,[4, 5, 8-20] 18-30%[20-22] and 25-60%,[3, 19, 20, 23, 24] respectively. In a recent study of the Framingham Heart Study there was evidence for significant, though modest, heritability of ideal CV health. Based upon these heritability findings, a GWAS in Framingham identified several potential SNPs of interest which are important to pursue in additional cohorts, such as CARDIA and ARIC.

5. Main Hypothesis/Study Questions:
The primary goal is to examine the genetic determinants of ideal CVD health during middle-age among White individuals participating in the ARIC study

Study Questions:

1. Evaluate whether there are there SNPs associated with clinical and behavioral determinants of ideal CV health
2. Are these results replicated in other participating cohorts? And if so, can a meta-analysis further confirm our specific findings measured in our ARIC cohort?

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).

Overview: To test our hypotheses and study questions, we will utilize ARIC data from the first four study visits. Imputed SNPs will be used in a GWAS involving logistic regression to measure any association between SNPs and two definitions of ideal cardiovascular health.

Exclusion Criteria: Individuals that are non-white or non-black will be excluded, as well as those that were not aged 50 ±5 years at any of the first four study visits. Also, subjects with prior MI or heart failure will be excluded as well. Any individual missing any variable or covariate used in the models will be excluded. Primary consideration is for white participants in this analysis, given the accessibility of imputed GWAS data and principal components of ancestry.

Inclusion Criteria: Individuals that are aged 50 ±5 years at any of the first four ARIC study visits. Data used to create response variables will be those measured at the first ARIC visit that the individual becomes eligible in terms of age (most individuals will meet this criteria age the first visit, and therefore, most of the individuals will be represented by data at this first visit).

Response/Dependent Variables: In this study, two definitions of ideal cardiovascular health will be studied.

1. Clinically ideal CV health: Serum cholesterol, use of lipid lowering drugs, systolic and diastolic blood pressure, use of antihypertensive drugs, fasting or casual glucose, use of anti-diabetic mediation. For classification of being in ideal CV health, one has to have serum cholesterol levels less than 200 mg/dl without lipid-lowering drug treatment; SBP/DBP of <120/<80 without antihypertensive drug treatment; and not be diabetic (fasting glucose < 126 mg/dL, casual glucose <201 mg/dL and no reported use of any anti-diabetic medications).

   Specific ARIC variables to use: LIPA01, LIPB01A, CHOLMDCODE01, CHOLMDCODE21, SBPA21 SBP22,HYPTMDCODE01, SBPB21, SBPB22, HYPTMDCODE21, FAST0802, GLUCOS01, INS, DMD, FAST0823, CHMB07, INS2, DMD2

2. Clinically and behaviorally ideal CV health: Same clinical variables as above, in addition to current smoking status and body mass index. To be in ideal CV health using this definition, individuals had to have serum cholesterol levels less than 200 mg/dl (<5.16 mmol/l) without lipid-lowering drug treatment; SBP/DBP of 120/80 or lower without antihypertensive drug treatment; not be a current smoker; have a BMI < 25 kg/m^2 and not be diabetic (fasting glucose < 126 mg/dL, casual glucose <201 mg/dL and no reported use of any anti-diabetic medications).

   Specific ARIC variables to use: LIPA01, LIPB01A, CHOLMDCODE01, CHOLMDCODE21, SBPA21 SBP22,HYPTMDCODE01, SBPB21, SBPB22, HYPTMDCODE21, FAST0802, GLUCOS01, INS, DMD, FAST0823, CHMB07, INS2, DMD2, CURSMK01, CURSMK21, BMI01, BMI21

Covariates: Age, sex, ARIC study site, principal components of ancestry.

Analysis:
Logistic regression will be used to conduct a genome-wide association analysis to measure association between ideal CV health and any potential SNP of interest. The genome-wide level of significance threshold will be set at one false positive per 2.5 million tests ($P < 5 \times 10^{-7}$)

This analysis utilizes imputed SNPs genotypes. Imputation results are summarized as an allele dosage, which was defined as the expected number of copies of the minor allele at each SNP. The ProbABEL software will be used for association analyses, to obtain beta coefficients and standard errors, along with R-squared-hat measures to measure imputation quality. Results for all SNPs will be reported as well as all results for any autosomal SNPs that have an rs number. This data will be generated and loaded into a comma separated document, so as to facilitate a meta-analysis of study findings.

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 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? _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)?

There are no obvious related active manuscript proposals for GWAS of ideal cardiovascular health.

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
___ A. primarily the result of an ancillary study (2006.03 and 2007.02**)**
___ 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.

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