

ARIC Manuscript Proposal #2464

PC Reviewed: 11/11/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: A Multi-Ethnic Study of Gene-Lifestyle Interactions in Cardiovascular Traits: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Gene-Lifestyle Interaction

2. Writing Group:

Writing group members: ARIC writing group members include the individuals involved in generation and analysis of the 1000 Genomes data (alphabetical): Dan Arking, Eric Boerwinkle, Megan Grove, and Alanna Morrison. Additional collaborators include members of the CHARGE Gene-Lifestyle Working Group

I, the senior author, confirm that all the coauthors have given their approval for this manuscript proposal. ACM [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:

Completion of analyses and draft manuscript(s) beginning in late 2014.

4. Rationale:

Cardiovascular disease (CVD) and management of its risk factors such as blood pressure (BP) and plasma lipids continue to be a major public health problem. Therefore, understanding the genetic basis of these traits and how the environment modulates genetic effects in influencing these traits is important because it may provide important clues for interventions. It is increasingly recognized that the near-exclusive focus on main effects of common variants (which generally have small effects) has become a barrier to the identification of additional genes (with larger effects) underlying these disease traits. These discovery efforts need more sophisticated approaches such as gene-environment interactions. The analyses proposed by the CHARGE Consortium Gene-Lifestyle Working Group represent a well-powered large consortium-level effort for systematically evaluating gene-lifestyle interactions using very large sample sizes.

ARIC study participation in this gene-by-lifestyle analysis effort will primarily utilize 1000 Genomes imputed data for ARIC Whites and Blacks. The main cardiovascular traits of interest are blood pressure and plasma lipid levels. The goal of the proposed research is to leverage existing data in >25 large multi-ethnic cohorts to discover additional genetic loci for cardiovascular traits by modeling gene-lifestyle interactions.

5. Main Hypothesis/Study Questions:

The table below describes the primary proposed projects for this multi-ethnic study of gene-lifestyle interactions in cardiovascular traits.

The general hypotheses are:

1. To identify novel genetic loci for cardiovascular traits that may not have been detected previously when interaction was not considered.
2. To characterize gene-by-lifestyle interactions in known cardiovascular trait loci.
3. To integrate results across race-ethnic groups by carrying out meta-analysis as well as trans-ethnic meta-analysis for understanding the race-ethnicity context of the interactions and for possibly identifying additional novel loci.

Proposed analyses include:

Primary outcome	Lifestyle Factor	Project Lead	Other Project Leads
Blood pressure	Smoking	Yun Ju Sung	DC Rao
Smoking	N/A	Emily Olfson	Laura Bierut
Lipids	Smoking	Amy Bentley	Adrienne Cupples
Lipids	Alcohol	Alanna Morrison	Megan Grove, Michael Brown Eric Boerwinkle
Blood pressure	Education	Jacob Basson	DC Rao
Blood pressure	Alcohol	Ingrid Borecki	Llilda Barata
Lipids	Education	Jeannette Simino	DC Rao
Lipids	Physical activity	Tamuno Alfred	Ruth Loos
Blood pressure	Physical activity	Stella Aslibekyan	Donna Arnett
Blood pressure	Psychosocial	Myriam Fornage	

Additional gene-lifestyle projects may result from this collaborative effort.

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).

1000 Genomes Project Data

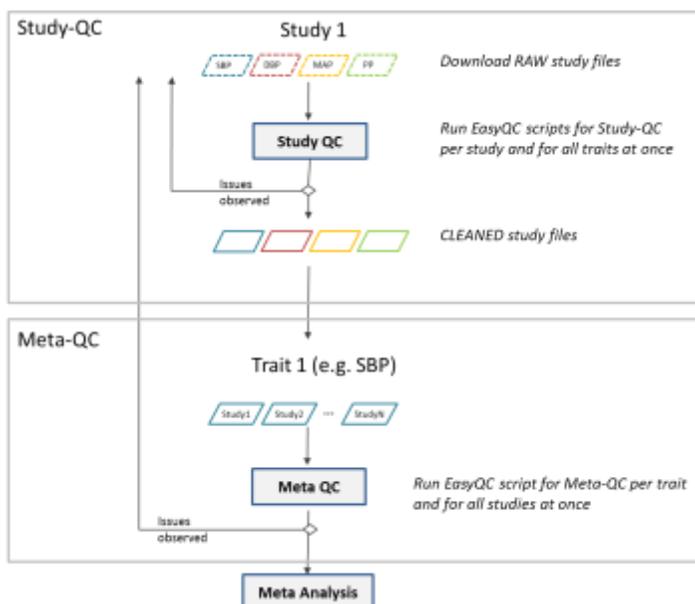
This study will utilize imputed SNPs based on data from the 1000 Genomes Project (1000G). Imputation was performed in two steps : (1) Pre-phasing with ShapeIt (v1.r532) and (2) Imputation with IMPUTE2. After frequency and genotyping pruning in Whites, there were 711,589 SNPs in the final set used for the imputation (682,749 autosomal SNPs). In Blacks, there were 806,416 SNPs in the final set used for the imputation (773,317 autosomal SNPs). Final imputations were done with IMPUTE2 using the reference panel :1,000 Genomes haplotypes -- Phase I integrated variant set release (v3) in NCBI build 37 (hg19) in chunks of size 5 Mb. All 1092 individuals were used for the imputation from the reference panel.

Analyses

For each project, we will typically consider 3 models for each trait/lifestyle variable combination. Model 1 will be applied to the entire sample, while Model 2 will be run for the total sample and separately by lifestyle variable strata. Model 3 will be run with all data to obtain an E adjusted effect of a SNP. Thus, for each trait/lifestyle variable combination, analysts will perform 5 analyses: one fitting Model 1 to all data (E=0 and E=1 combined); one fitting Model 2 to all data (i.e., all subjects that have data on the environmental exposure of interest); one fitting Model 2 to the E=1 subgroup; one fitting Model 2 to the E=0 subgroup; and one fitting Model 3 to all data. Analyses are performed using ProbABEL.

Meta-analysis

Quality control at the study level and meta-analysis level using EasyQC (**Figure**).



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

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?

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?

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"?

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.csc.unc.edu/ARIC/search.php>

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 manuscript proposals for the evaluation of 1000G data in relation to the specified gene-lifestyle interactions.

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

Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* _____)

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.csc.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.

Agree

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.csc.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.

Agree

13. References