

**ARIC Manuscript Proposal # 1641**

**PC Reviewed:** 4/13/10  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Genome-wide association study of incident coronary heart disease in African Americans

**b. Abbreviated Title (Length 26 characters):** GWAS of incident CHD in A-A

**2. Writing Group:**

Writing group members: Maja Barbalic, Gerardo Heiss, Eric Boerwinkle, David Couper, and Tom Mosley.

Other ARIC authors will be invited as well as participants from other cohorts included in the study

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

Genotyping is complete. Data analysis will begin immediately.

**4. Rationale:**

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in the United States and elsewhere. Although family studies have determined a clear role of genetic variation in determining an individual's risk of CHD, the identification of genetic factors have been more challenging. Recent genome-wide association analyses led to the identification of putative loci associated with CHD, but only one of them (chromosome 9p21.3) has been consistently replicated. However, all mentioned GWA studies were limited to the populations of European ancestry, and up to date no GWAS in African Americans has been conducted. CHD is the leading cause of morbidity and mortality in African-Americans, and there is obvious clustering of CHD risk factors, such as hypertension and diabetes, in this under-studied population. The availability of incident CHD data over 20 years of follow-up in African-Americans makes ARIC a unique study to address this issue. Hence, we propose a genome wide association analysis of incident coronary heart disease in ARIC African Americans.

**5. Main Hypothesis/Study Questions:** To investigate the association of genome-wide genetic variation with incident coronary heart disease in African-American adults

**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).**

The association of genome-wide single nucleotide polymorphisms with incident CHD will be tested by additive a hazard model (1df) with age and sex as covariates. To account for population substructure, we will include principal components in the model that were calculated for ARIC African-Americans using EIGENSTRAT (<http://genepath.med.harvard.edu/~reich/Software.htm>). As secondary analyses, we will test the same association after adding the established CHD risk factors in the model as covariates. Additional secondary analyses will investigate the effect of those loci identified in studies of European ancestry on CHD risk in African-Americans. We will seek to replicate our top findings in studies of CHD in African-Americans. To avoid dismissal of true positives, we define less stringent significance level ( $p < 10^{-5}$ ) as a threshold for selecting top findings that will be carried forward for replication. At this time, our replication studies will be mostly limited to prevalent disease, because that is all that is available. In addition, we are in discussion with WHI regarding their participation as a replication sample.

*Exposure:* Genetic variants from Affymetrix 6.0 chip

*Outcome:* Incident coronary heart disease

*Exclusions:* Those without consent for genetic research

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 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  
 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

8.c. If yes, is the author aware that the participants with RES\_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?  
 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)? The CARE primary paper is limited to prevalent disease.

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\* 2007.02, CARE, genotyping in African Americans \_\_\_\_\_)

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/>

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. Agreed.**