ARIC Manuscript Proposal # 1064

1.a. Full Title: APOE Genotype and Progression of Common Carotid Atherosclerosis: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): APOE and IMT Progression

2. Writing Group:
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3. Timeline: November 2004-August 2005

4. Rationale:
   Vascular disease is the number one cause of morbidity and mortality in the United States and most industrialized nations1. Established risk factors for coronary vascular disease include age, physical inactivity, hypertension, diabetes, smoking, dyslipidemia, and obesity2. In the search to reduce incident events, increase the identification of those at risk, and better understand the etiology of cardiovascular disease; researchers have focused on preclinical markers of disease. Carotid intra-media thickness (IMT), assessed by ultrasound, is an important preclinical marker of cardiovascular disease, and is predictive of both heart disease and stroke3,4,5. Chambless et al showed that in ARIC the progression of IMT was associated with baseline diabetes, current smoking, high density lipoprotein cholesterol, pulse pressure, white-blood cell count, and fibrinogen.
Additionally, they reported that progression of IMT was also associated with changes in low density lipoprotein cholesterol, triglycerides, diabetes status, and hypertension status\(^6\).

Chambless et al were not able to look at apolipoprotein E (APOE) and its relation to IMT since genotyping had not been completed for the entire cohort. APOE genotype is a risk factor for coronary disease. Recently Song et al performed a meta-analysis of 48 studies and reported that, compared to those with ε3/ε3 genotype, those with the ε4 allele were 1.42 [95% CI, 1.26 to 1.61] times as likely to develop CHD\(^7\). Many researchers have examined the relation between APOE and the preclinical atherosclerosis marker carotid IMT. However, the reported relation of APOE to IMT has been inconsistent. A previous ARIC study looked at APOE and IMT in a cross-sectional subsample of the cohort and found a positive relation between ε2 and carotid artery atherosclerotic disease\(^8\). A recent meta-analysis showed that there was no association between APOE and IMT in women, while men with the APOE ε2 allele had thinner carotid IMT than did the ε3/ε3 reference group\(^9\). However, no studies have been able to examine the relation in terms of progression of IMT.

The entire ARIC cohort has been genotyped, and it is a natural extension of previous work to examine an established risk factor for CVD in relation to preclinical disease. This analysis would be superior to other reports due to the longitudinal nature and the size of the ARIC cohort. Previous reports have shown that the APOE genotypes are distributed differently in African-Americans and whites\(^10\), and this study will be able to report outcomes for African-Americans and whites separately.

References

5. **Main Hypothesis/Study Questions:** Intra-media thickness progresses faster in those with the APOE ε4 gene compared to ε3, while ε2 progresses slower. We will also explore the effect of gender and race on this relation.

6. **Data (variables, time window, source, inclusions/exclusions):**
   
   Inclusions: ARIC cohort.
   
   Exclusions: No ultrasound information, no APOE information, no genetic use consent.
   
   Dependent variables: IMT progression.
   
   Independent variables: APOE genotype.
   
   Other Covariates: Age, sex, race, blood pressure, anti-hypertensive medications, anthropometrics, diabetes, physical activity, smoking status, alcohol use, medications (lipid, hypertensive), prior CHD, fibrinogen, and blood lipids.

   **Analysis Plan:** The coordinating center will conduct a longitudinal cohort analysis examining IMT and APOE genotype controlled for other known risk factors. The independent and dependent variables are listed above. Categorical variables will be analyzed using their natural categories (ex: male and female for gender) and continuous variables will be analyzed as both continuous (blood pressure measure) and discrete (blood pressure divided into quartiles, etc). We will describe APOE as three categories: E2 (ε2/ε2, ε2/ε3), E3 (ε3/ε3) and E4 (ε4/ε3, ε4/ε4). We plan to exclude those with the 2/4 genotype, and expect that this will likely have little impact on the results given the rarity of this genotype. We will compare IMT progression among these categories, using the E3 group as the referent. We plan on using SAS PROC MIXED to obtain associations between progression and genotype. The association between change in IMT and APOE will be modeled with side-specific differences between follow-up and baseline IMT measurements as a function of APOE. We anticipate including confounders such as age, center, blood pressure, diabetes, etc. in our model, both at baseline and time-dependent where available and appropriate. Chambliss' previous work adjusted for baseline IMT and reported that it contributed little to the analysis, so we will not be adjusting for baseline IMT now. We will be able to report outcomes by race and gender.

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  __X__ Yes  ____ No

b. **If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 ICTDER02 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)? ARIC Manuscript #’s 104A, 243A

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