ARIC Manuscript Proposal #2742

PC Reviewed: 4/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of a novel cardiovascular genetic risk score with atherosclerotic cardiovascular disease events and statin use in a population-based cohort: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): cGRS and ASCVD events in ARIC

2. Writing Group:

Writing group members: Jamie Jarmul,[1,2] Christy Avery,[3] David Couper,[4] Alanna Morrison,[5] Paul de Vries,[5] Kristen Hassmiller Lich,[1] Stephanie Wheeler,[1] Morris Weinberger,[1] Michael Pignone[2] and Mark Pletcher.[6]

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We welcome additional nominations/authorship suggestions.

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

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3. Timeline: Analysis will begin in mid-2016, upon approval. We aim to submit the manuscript for P&P review by late summer, 2016.

4. Rationale:

Prediction of cardiovascular disease (CVD) risk is important to aid clinical decision-making, such as whether or not to prescribe statins or aspirin. Risk prediction algorithms, such as the Pooled Cohort Equations or Framingham equations, rely on primarily on a set of traditional risk factors (age, sex, blood pressure, lipid levels and smoking). Many novel, independent CVD risk factors have been identified, but whether they merit inclusion in risk assessment and clinical decision-making algorithms remains controversial and the subject of much ongoing research.[1-5]

Another area of intense research is the use of cardiovascular genetic risk information in clinical decision-making.[6-11] Early papers looking at 21-SNP cardiovascular genetic risk scores reported statistically significant, but small magnitude, improvements in area under the curve, after incorporating traditional risk factors.[12-15] In 2015, Mega et al. published an analysis in Lancet in which they demonstrated a significant association between a 27-SNP cardiovascular genetic risk score (cGRS) and coronary heart disease (CHD) outcomes (nonfatal and fatal myocardial infarction), after adjusting for traditional cardiovascular risk factors.[16] Furthermore, Mega et al. reported that individuals with higher cGRS experience a greater absolute risk reduction from statin therapy compared to individuals with a low cGRS.

Despite Mega et al's intriguing results, we believe there are gaps that merit evaluation. First, Mega et al. used pooled data from several randomized clinical trials examining statin efficacy; as such, the association between the genetic risk score and CHD outcomes may not replicate across populations, particularly African Americans or in population-based settings.[17] Furthermore, Mega et al's analysis was limited by the relatively short follow-up period in the statin efficacy trials (maximum 5 years).

5. Main Hypothesis/Study Questions:

In this analysis, we propose to fill these gaps by attempting to replicate Mega et al.'s findings using ARIC cohort data. Specifically, we will evaluate: 1) if the association between Mega et al.'s 27-SNP cGRS and CHD incidence can be replicated in a community-based sample of Caucasian and African-American individuals through race/ethnic specific analyses 2) differences in association between the cGRS and 5-year CHD and 10-year CHD incidence by race/ethnicity; 3) differences in the association between the cGRS and individual CVD events (CHD, ischemic stroke) compared to pooled CVD events (i.e. CHD and ischemic stroke together) by race/ethnicity; 4) and evaluate modification of the cGRS-CHD association by restricting to statin users by race/ethnicity.[17]

Although our *a priori* belief is that the cGRS will perform poorly in African Americans given race/ethnic specific LD patterning and population-specific variants, among other factors, we believe it is important to demonstrate the expected lack of association between Mega et al's cGRS in African-Americans.[17] In particular, high-profile papers restricted to European ancestral populations propagate research disparities in non-European populations. It is therefore important to highlight instances where genetics and "personalized medicine" require expansion to other global populations.

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).

Data elements requested:

1. Visit 1 measured age, sex, race/ethnicity, systolic blood pressure, fasting status, total cholesterol, LDL cholesterol, HDL cholesterol, smoking history, current medications, derived stroke, CHD, diabetes, and heart failure variables, and GWAS data. Although we prefer to estimate a minimal model adjusting for age, sex, center, and ancestral principal components, we anticipate that reviewers will request results adjusted for the aforementioned CVD risk factors (i.e. a maximally adjusted model), which we consider as mediators.
2. Cohort surveillance variables: Incident CHD, incident stroke, incident CHF, all-cause and CHD mortality

Inclusion criteria: Individuals with visit 1 data who have consented to allow use of genetic data for research.

Exclusion criteria: Implemented when follow-up begins (see below): participants with congestive heart failure (HF) defined using the Gothenburg criteria or hospitalized HF, prevalent coronary heart disease (CHD), diabetes, or prevalent stroke. Prevalent diabetes, CHD, and stroke are classified using ARIC investigator definitions.

Operationalization of key variables:

Cardiovascular genetic risk score

We plan to operationalize "cardiovascular genetic risk" using the 27-SNP cGRS reported by Mega et al. in The *Lancet in* 2015. However, we appreciate that the development of cGRS is an open area of research and are prepared to evaluate other scores if/when they become available, such as recent work by Deghan et al.[20]

For the risk score developed by Mega et al., the cGRS will be calculated in each race/ethnicity using 1000 genomes imputed data as the sum of the dosage for each SNP in Table 1 weighted by the log of the odds ratio reported with the SNP in the table, as shown in Equation 2.[16]. The SNPs, risk alleles and associated odds ratios used in the cGRS were selected from a literature review of GWAS- CHD outcomes studies completed by Mega et al. We will exclude SNPs with poor imputation quality (oevar_imp <0.3) or with minor allele counts <10.

Equation 1

$$\text{Cardiovascular genetic risk score} = \sum_i \frac{1}{Odds\ Ratio_{SNPi}} (SNP_i\ dosage)$$

where i is the index of SNPs included in Table 1.

Table 1: Lead SNPs and ORs for CHD used to calculate the cardiovascular genetic risk score (cGRS)[16]

Gene	Lead SNP	Odds Ratio for coronary heart disease	Risk allele
1p13.3 (*SORT1*)	rs646776	1.19	T
1p32.3 (*PPAP2B*)	rs17114036	1.17	A
1p32.3 (*PCSK9*)	rs11206510	1.15	T
1q41 (*MIA3*)	rs17465637	1.14	C
2q33.1 (*WDR12*)	rs6725887	1.17	C
6p21.31 (*ANKS1A*)	rs17609940	1.07	G
6p24.1 (*PHACTR1*)	rs9349379	1.12	G
6q23.2 (*TCF21*)	rs12190287	1.08	C
6q25.3 (*LPA*)	rs3798220	1.47	C
6q25.3 (*LPA*)	rs10455872	1.70	G
7q32.3 (*ZC3HC1*)	rs11556924	1.09	C
9p21.3 (*CDKN2A*)	rs4977574	1.29	G
9q34.2 (*ABO*)	rs9411489	1.10	T
10q11.21 (*CXCL12*)	rs1746048	1.17	C
10q24.32 (*CYP17A1*)	rs12413409	1.12	G
11q23.3 (*APOA5*)	rs964184	1.13	G
12q2.4 (*HNF1A*)	rs2259816	1.08	T
12q24.12 (*SH2B3*)	rs3184504	1.13	T
13q3.4 (*COL4A1*)	rs4773144	1.07	G
14q32.2 (*HHPL1*)	rs2895811	1.07	C
15q25.1 (*ADAMTS7*)	rs3825807	1.08	T
17p11.2 (*RASD1*)	rs12936587	1.07	G
17p13.3 (*SMG6*)	rs216172	1.07	C
17q21.32 (*UBE2Z*)	rs46522	1.06	T
19p13.2 (*LDLR*)	rs1122608	1.15	G
21q22.11 (*KCNE2*)	rs9982601	1.20	T

Atherosclerotic cardiovascular disease (ASCVD) outcomes:

For all individuals at Visit 1, 1st event recorded within 10 years of baseline:

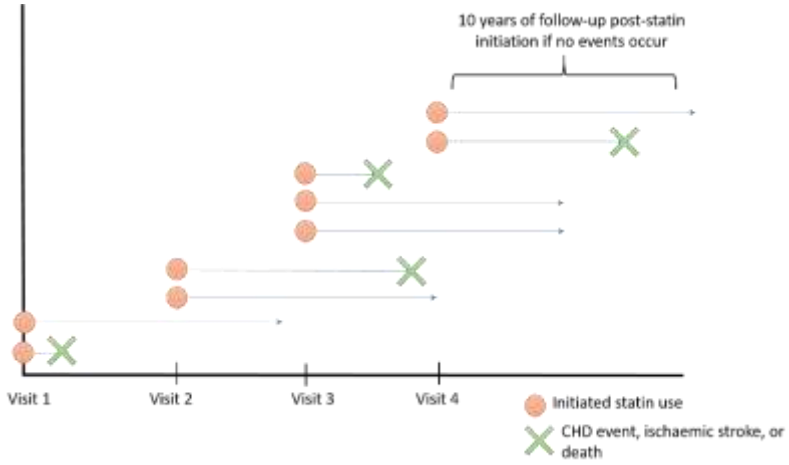
1. Definite or probable non-fatal MI ("incident CHD"; primary outcome of interest)
2. Definite or probable fatal MI ("incident CHD"; primary outcome of interest)
3. Definite or probable non-fatal ischemic stroke ("pooled ASCVD"; secondary outcome of interest)
4. Definite or probable fatal ischemic stroke ("pooled ASCVD"; secondary outcome of interest)
5. All-cause mortality
6. CHD-specific mortality*

* CHD-specific mortality is not adjudicated in ARIC; however, we will use define CHD-specific mortality by looking at the presence of CHD-related events and absence of ischaemic stroke events within a certain time frame of death.

Hypotheses 1-3: we will use a race/ethnic-specific Cox proportional hazard model to assess the risk of incident CHD and the pooled ASCVD outcomes for each quintile of "genetic risk," with the first quintile assigned as the reference group. We will also assess the risk for categories defined as low risk (quintile 1), intermediate risk (quintiles 2-4) and high risk (quintile 5) as performed by Mega, noting that power may require restricting to this approach. Follow-up will begin at baseline (i.e. visit 1). As described above, we will consider a minimally adjusted model (i.e. adjusting for age, sex, center, and ancestral principal components) as well as a maximally adjusted model extended to include smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, and anti-hypertension medication at baseline. Analyses will be performed restricting to 5-years and 10-years post-baseline, allowing us to estimate 5-year and 10-year CHD and ASCVD risk associated with the cGRS.

Hypothesis 4: Finally, we will evaluate the performance of the cGRS by race/ethnicity restricting to statin users. We restrict to statin users as opposed to using non-users as the referent group (i.e. fitting a statin*cGRS interaction) due to the uncertain ability of non-users to serve as the counterfactual for statin users. Here, follow-up begins as the first date at which new statin use is observed, therefore restricting to participants who were non-users at study baseline. Of note, statins were introduced to the market in 1987; we therefore expect that the majority of ARIC participants will be "new users".[18] For example, follow-up time for participants who were not statin users at visit 1, but reported statin use at visit 2 will be the participant's visit 2 date; we then will estimate 5-year and 10-year CHD and ASCVD risk from this point in time. We will also describe the percentage of ARIC participants that are statin users at each visit.

The beta estimate for the cGRS in this analysis will be interpreted as the effect of the cGRS on CHD or ASCVD incidence among statin users. We will model cGRS as quintiles, as well as by low, intermediate and high risk categories as described above, where low risk is defined as quintile 1, intermediate risk is defined as quintiles 2-4 and high risk is defined as quintile 5. Our previous work in the pharmacogenomics working group demonstrated that >1,000 white ARIC participants with GWAS data initiated statins between visits 2-4.[19]



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 lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

Per Christy Avery: The majority of approved ARIC manuscript proposals examining genetic risk scores for CHD and related outcomes were proposed five-eight years ago. We also have engaged ARIC colleagues were involved in these early proposals to ensure the least amount of overlap possible.

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)?

See above

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/

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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