**ARIC Manuscript Proposal #2568**

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| **PC Reviewed: 6/9/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: **Socio-economic Status and Calibration of the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator**

**b. Abbreviated Title (Length 26 characters)**: **SES & ASCVD Risk Calibration**

**2. Writing Group**:

Writing group members: Kamal Henderson, Patricia Chang, Sally Stearns, Randi Foraker, David Goff, Anna Kucharska-Newton, Carla Sueta, David Couper and "Others welcome"

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


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**3. Timeline**:
Data Analysis: Summer of 2015
Manuscript Preparation: Fall and winter of 2015
Manuscript Submission: Winter and spring of 2016

**4. Rationale**:

In 2014, the American College of Cardiology (ACC) and American Heart Association (AHA) jointly published new guidelines on the assessment of cardiovascular risk.[1] Noted changes include assessing risk of both coronary heart disease and stroke, now termed atherosclerotic cardiovascular disease (ASCVD). Another major change is the development of the new race- and sex-specific Pooled Cohort Equations to predict 10-year risk of a first hard ASCVD event in individuals between ages 40-79 years of age. Factors assessed in the Pooled Cohort Equations include gender, age, race, total cholesterol levels, total HDL-cholesterol levels, systolic blood pressure, hypertension treatment, diabetes, and smoking status.

The new ASCVD risk calculator provides the clinician and patient with an approach to a quantitative assessment of ASCVD risk to be used to guide care and prevention measures. Based on current guidelines, a 10-year predicted risk for first ASCVD event $\geq 7.5\%$ is considered high-risk.[1] Being categorized as high-risk implies specific pharmacologic prevention therapy and lifestyle modification measures for prevention of ASCVD.[1,2] New guidelines on the treatment of blood cholesterol utilize the 10-year risk for ASCVD to guide intensity of statin therapy for primary prevention of ASCVD.[2]

Prior studies established an independent interaction between socioeconomic status and incidence of ASCVD.[3,4,5,6,7,8,9,10,11] Although social economic status (SES) may be assessed in various ways, lower SES status was associated with increased incidence of stroke and coronary heart disease. Studies have shown significant differences in outcomes when comparing lower SES groups to higher SES groups for both outcomes as well.[12,13,14,15]

Prior literature has also shown that traditional cardiovascular risk calculators such as the Framingham Risk calculator were not well calibrated at predicting coronary heart disease risk when controlling for socioeconomic factors.[17,18] The inability of prior coronary heart disease risk calculators to accurately predict cardiovascular risk accurately based on socioeconomic status led to the development of three risk models that are primarily used in the United Kingdom and Scotland.[19,20,21,22] These risk calculators used area-level socioeconomic factors due to the ease of using postal codes from treatment in clinical settings to assess patient neighborhood socioeconomic status. From our review of the literature, no studies have assessed the use of ASCVD risk calculators based on socioeconomic status using a United States longitudinal population cohort.

The Pooled Cohort Equations do not use socioeconomic status as a factor to assess ASCVD risk. If ASCVD risk varies by SES (e.g., lower SES individuals have higher risk), then individuals with lower area-level SES may not be assessed adequately

and may not receive proper preventive measures for ASCVD when compared with individuals with higher area-level SES. This study will assess the predictive performance of the new Pooled Cohort Equation risk calculator to predict 10-year risk for a first ASCVD event (coronary heart disease, stroke) for ARIC cohort members who reside in neighborhoods with varying levels of neighborhood deprivation. If the ASCVD risk predictions from the Pooled Cohort Equations are shown to vary significantly by socioeconomic status, then it may be necessary to re-calibrate the risk calculator to assess gradients in ASCVD risk by SES and improve risk predictions.

**5. Main Hypothesis/Study Questions**:

**Research Question:** What is the ability of the new atherosclerotic cardiovascular disease risk calculator (the Pooled Cohort Equations) to predict 10-year risk for a first ASCVD event across levels of neighborhood deprivation?

**Hypothesis:**
The Pooled Cohort Equations will be better calibrated (measured as predicted to observed ratio) and have greater discrimination (measured by sensitivity, specificity, and area under receiver operator curve) to predict the 10-year risk of ASCVD among individuals participating in the ARIC cohort when controlling for SES measures such as the individual level neighborhood deprivation index.

**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).**

**Study design:**
Prospective cohort study using the Atherosclerosis Risk in Communities Study (ARIC) cohort.

**Subjects:**
White and black participants of the ARIC study ages 45 to 64 years of age free of stroke and coronary heart disease at baseline (Visit 1) assessment will be included in the study. Participants with missing zip code information and racial data at their baseline assessment will be excluded.

**Outcomes:**
We are interested in the calibration and discrimination of the current Pooled Cohort Equations in predicting ASCVD risk among different area levels of social economic status. The primary outcome is the observed event rate of first validated coronary heart disease and stroke as a composite outcome. Coronary heart disease, myocardial infarction, fatal myocardial infarction, stroke and fatal stroke will also be analyzed separately to assess the effect each individual outcome has on the composite outcome.

**Analysis:**

The primary analysis will be the calibration and discrimination of the Pooled Cohort Equations to predict 10-year risk of first ASCVD event. The predicted to observed ratio for each SES group will be used to assess calibration. A Predicted 10-year ASCVD risk calculation will be performed for each included ARIC participant. The mean Pooled Cohort Equations predicted 10-year risk would be assessed for each SES group using both the Census Block measure and the ADI measure. The 10-year cardiovascular mortality rate will be estimated using Kaplan-Meier analysis for each SES group to assess the time to observed incident ASCVD event.

Area under the receiver-operating curve for Pooled Cohort Equations predicted 10-year risk will be assessed for each SES group (census block or ADI score). Thresholds will be assessed at <2.5%, 2.5%-5%, >5%-7.5% and >7.5%. These thresholds were chosen based on current guidelines for pharmacotherapy management of cholesterol management for primary prevention of ASCVD.[2] Calculated sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, likelihood ratio of a negative test for <2.5%, 2.5%-5%, >5%-7.5%, and >7.5% threshold of 10-year CVD event risk stratified by SES index will be performed to further assess discrimination.

The predictor variable being assessed is area-level socioeconomic status of participants' place of residence. Place of residence will be based on address at Visit 1; we will not adjust the analyses for participants who move out of their census block or zip code area, though we will do a sub-group analysis for people who do not move out of their area within 10 years. Two methods of assessing neighborhood SES will be utilized for comparison.

- One method will use the neighborhood SES index established for the ARIC cohort using census block-groups as proxies for neighborhoods.[4,16] The index uses six variables to assess neighborhood SES based on dimensions of wealth/income, education, and occupation. Neighborhood SES context of this index has been previously shown to be related to incidence of coronary heart disease.[4] Each participant will be given a neighborhood SES index score based on his or her registered address as previously done. Neighborhood SES index will be divided into race-specific tertiles and analysis stratified by race. The first (bottom) tertile will represent the lowest aggregate area level SES group and the third tertile will represent the highest aggregate area level SES group.

- Following prior work by Randi Foraker, we will also explore whether single measures such as median household income or percent below poverty work as wel as the SES index described above.

- We will also like to assess the role of neighborhood SES using a second method based on the Area Deprivation Index (ADI) established by Gopal Singh and colleagues.[6] The ADI can assess neighborhood SES at census tract, county, and nine-digit zip code level. The ADI uses 17 factors that assess sub-domains of

education, income and wealth, employment, housing, and transportation. Prior studies show that ADI neighborhood SES is related to cardiovascular disease mortality and 30-day re-hospitalization rates.[6,23] We believe that the ADI will provide an improved measure of SES over the census block measures because of its validated ability to assess neighborhood SES at three geographical levels and temporal stability in assessing SES gradients for cardiovascular disease outcomes. Prior 10-year risk calculators that factor in SES utilize postal zip code because it is easier to assess from patients in a clinical setting.[19,20,21,22] The ADI provides a measure of neighborhood SES at the 9-digit zip code level, and this could prove useful in creating a new10-year risk calculator that accounts for SES in addition to traditional cardiovascular risk factors.

To link the ADI to the ARIC cohort, we will need to link the ADI score based on the 9-digit zip code to each cohort member. We believe the best way to link this information would be to request a list of de-identified cohort residence latitude and longitude measures from the ARIC Study Coordinating Center. After receiving the de-identified data, we will identify the nine-digit zip codes reported at baseline assessment associated with the latitude/longitude measures, and then return the ADI value for each latitude/longitude measure with the ADI to the ARIC Study Coordinating Center. The ARIC Study Coordinating Center would then merge the ADI value to each cohort member and then give us a file of cohort IDs and ADI values. Although the process requires two steps on the part of the ARIC Study Coordinating Center, it would preserve the de-identification of cohort address.

The mean Pooled Cohort Equations predicted 10-year risk will be assessed for each SES group using both the Census Block measure and the ADI measure. Additionally, we could use the actual ADI value to control for SES, or we could use a categorical measure based on the ADI score (e.g., a three-category measure in which the first (bottom) tertile will represent the lowest aggregate area level SES group and the third tertile will represent the highest aggregate area level SES group).
As described above, our main focus will be to assess the predictive performance of the current Pooled Cohort Equations prediction model. Our analyses will be descriptive in the sense that we will focus on the effect of SES on overall risk prediction using the new prediction model. Also, the power of the study may be limited to the extent that the number of events occurring within 10 years may be limited; in this case, we may extend the follow-up beyond 10 years. Another important issue is that the risk prediction parameters from the Pooled Cohort Equations may differ from parameters for the same model estimated using the ARIC data. Therefore, as a sensitivity analysis we will re-estimate the Pooled Cohort Equations using the ARIC data to see the extent to which the risk prediction parameters and the risk score differ when we use the ARIC data for both predicted and observed risk. We will estimate this model both with and without the area-level SES measures to see the impact of including SES directly in the risk prediction equations. We will also consider using Net Reclassification Improvement or similar approaches to assess the extent to which adding the SES measures to the risk prediction models will reclassify individuals.[24]

**References:**


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**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?**
**____ Yes __x__ 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.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)?**

The lead author of this manuscript proposal has reviewed the list of ARIC Study manuscript proposals and has found no significant overlap with previous proposals. Potential manuscript proposal overlap and explanation of dealing with overlap is listed below:

1711a – (SES is not included in their analysis of different cardiovascular disease risk calculators.)

1646 – (This study analyzed calibration of the Framingham Risk Score on SES and other factors. We are assessing calibration of the new Pooled Cohort Equations by neighborhood SES group.)

454 – (Calculating 10-year risk of ASCVD is not included in their analysis of neighborhood SES and incidence of cardiovascular disease.)

455 – (Calculating 10-year risk of ASCVD is not included in their analysis of neighborhood SES and trends of cardiovascular risk factors in the ARIC cohort.)

1102 – (Dr. Foraker who was the lead author for this study and has been included in the writing group.)

**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.