ARIC Manuscript Proposal #3771

PC Reviewed: 2/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Individual Socioeconomic Status, Inflammation, and Arterial Stiffness in African Americans and Whites: The ARIC Cohort

b. Abbreviated Title (Length 26 characters): SES and Arterial Stiffness

2. Writing Group:

Writing group members: Telisa Spikes, RN, PhD, Tené T. Lewis, PhD, Aniqa Bushra Alam, MPH, Anna Kucharska-Newton, PhD, & Alvaro Alonso, MD, PhD, others welcome

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

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3. Timeline: 4-months

4. Rationale:

Despite decreases in the mortality rates from cardiovascular disease (CVD) in recent decades, important disparities exist that are patterned by race and socioeconomic status (SES). African Americans (AAs) or Blacks (referred hereafter as African Americans) regardless of SES, as well as individuals of lower SES, experience premature deterioration in health and higher CVD mortality rates than Whites and those of higher SES.[1,2] Additionally, Black race and lower SES have also been associated with greater systemic inflammation that further heightens the risk for target organ damage and CVD morbidity and mortality.[3-5]

Racial and socioeconomic disparities are also evident in markers of subclinical CVD, including arterial stiffness (AS).[6-11] Arterial stiffness, measured by pulse wave velocity (PWV), is acknowledged as an independent predictor of future cardiovascular (CV) events and all-cause mortality that extends beyond traditional CV risk factors.[6,12] Arterial stiffness among middle age and older adults has been extensively characterized with earlier studies largely reporting that AAs have greater AS compared to Whites;[7-9] however, some of these studies have found inter-racial variations in the magnitude of the association between SES and AS. An analysis of the ARIC cohort data suggests that the association of education with measures of AS (beta stiffness index and pulsatile arterial diameter change derived from brachial blood pressure and from echo-tracked systolic and diastolic carotid arterial diameters) differs by race: AAs with a high school or greater education had greater common carotid AS than AAs with less than a high school education, while no association was found among Whites.[8] In subsequent analysis in ARIC examining correlates of segmental PWV measured during visit 5, central femoral PWV was found to be higher in AAs than Whites.[9] Lastly, an analysis examining distributions of subclinical disease in a socioeconomically diverse cohort of adults 30-64 years found differences in AS by race, sex, and income, with high SES AAs having faster PWVs than both low SES AAs and Whites.[10]

Differences in the association of SES with CVD and CVD risk factors have been described in other settings.[13-16] These differences are postulated to be due to the divergent economic and social context of AAs relative to Whites--education, employment, income, wealth--and psychosocial stressors (discrimination, racism) derived from social adversity.[4,17-20] Consequently, chronic and cumulative exposure to these adversities have been associated with immune dysregulation and increased inflammatory biomarkers, which have also been associated with CVD and CVD mortality,[12,21] thus resulting in unfavorable health outcomes among socioeconomically disadvantaged relative to advantaged populations.[2,22] A paucity of studies have examined the associations of race, SES, and inflammation with subclinical CVD. Further, little is known regarding the effect that SES has on inflammatory burden and AS, or the potential mediating role that inflammation has on racial differences in AS, especially among middle age adults, a group where disparities in death from heart disease is especially pronounced between AAs and Whites.[23] Gaining a better understanding of the effect that SES may have on CVD risk may enhance efforts centered on preventative clinical measures in high risk groups.

This proposal seeks to extend prior investigations into the association of SES with AS by further examining and characterizing the association of individual SES with PWV an AS measure across race groups. In addition, this proposal will further examine whether inflammation (characterized by levels of circulating high-sensitivity C-reactive protein [hsCRP]) mediates the association between individual SES (education, income) and AS in a biracial cohort of middle age adults. We take advantage of a large study population with extensive characterization of CV risk factors and available PWV measurements.

5. Main Hypothesis/Study Questions:

RQ1: Is the association of individual socioeconomic status (education / income), and AS modified by race?
H1: We hypothesize that the association of SES with PWV will be stronger in AAs than in whites, irrespective of individual SES.
RQ2: Does chronic inflammation (hsCRP) mediate the association of individual SES with AS and explain racial differences in this association?
H2: hsCRP partly mediates the association of individual SES with AS; also, the association of hsCRP with individual SES and AS will be more robust in AAs than Whites and that difference partly explains the moderating effect of race on the SES-AS association.

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).

- **Design**: Cross-sectional study

Inclusion: ARIC participants attending visit 5, without CHD, HF, or stroke, with available PWV and hsCRP measurements. **Exclusion:** Prevalent CHD, heart failure, or stroke; We will exclude participants with missing information on PWV, body mass index (BMI) ≥40kg/m^2, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2), Minnesota code 8-1-2 with evidence of biased PWV waveforms, aortic aneurysms, abdominal aorta ≥5cm, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, moderate or greater aortic regurgitation, and missing covariates of interest (BMI, systolic blood pressure (SBP), heart rate, and smoking). Participants who self-identified as Asian and African American participants from Minnesota and Maryland sites will also be excluded due to small numbers.[9]

- **Variables of interest**:
  - Main exposure: education and income
  - Secondary exposure**:** race, hsCRP
  - Covariates: age, sex, center, BMI, smoking, alcohol use, diabetes, total cholesterol, HDL, systolic and diastolic blood pressure, lipid lowering and BP meds.
  - Outcome: cfPWV (considered the gold standard measure of arterial stiffness).[24]
- **Summary of data analysis:**

  Aim 1

  We will examine the association of individual SES (education, income) with cfPWV overall and separately by race using multivariable linear regression and will test race interactions with the Wald test. Models will adjust for age, sex, and potential confounders.

  Aim 2

  We will evaluate whether hsCRP mediates the associations of SES with AS using multivariable linear regression and comparing results from models with and without hsCRP. Specifically, we will evaluate the association of individual

SES with cfPWV adjusting for confounders of the association between these two variables. Next, we will run a separate model adjusting for hsCRP as well as potential confounders of the hsCRP and cfPWV association. Determination of the mediating effect of hsCRP will be done comparing coefficients for SES from the models with and without hsCRP adjustment. Models will be run in the entire sample and by race. In addition to adjusting for age, sex and center, these models will also adjust for potential confounders of the association between hsCRP and AS, such as BMI, smoking, and alcohol use.

Because of the overlap between race and center in ARIC, we will perform a secondary analysis restricted to Forsyth County participants.

Limitations

In this cross-sectional analysis it will not be possible to disentangle directionality of the associations, and therefore we will be careful in the interpretation of results. Also, information on individual SES is limited to education and income, and other aspects of social disadvantage are not evaluated. Finally, there is a perfect correlation between race and geographic area in ARIC, which will impede separating the effects of race and geographic area.

Nonetheless, the uniqueness of the ARIC data, including the size of the study and measurements of hsCRP and AS make it an ideal setting to explore this idea. Results from this analysis will serve as supporting data for future studies in other settings not afflicted by these limitations.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit"? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)?**
    - **a.** Diez-Roux A, Nieto FJ, Tyroler HA, Crum LD, Szklo M. Social Inequalities and Atherosclerosis The Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology.* 1995;141(10):960-972.
    - b. Din-Dzietham R, Couper D, Evans G, Arnett DK, Jones D. Arterial Stiffness Is Greater in African Americans Than in Whites. *American Journal of Hypertension.* 2004;17(304-313).
    - c. Meyer ML, Tanaka H, Plata P, et al. Correlates of Segmental Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study. American Journal of Hypertension. 2016; 29:114-122

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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