ARIC Manuscript Proposal #4266

PC Reviewed: 6/13/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Proteomics of Social Adversity and its Role in Mediating Cardiovascular Events

b. Abbreviated Title (Length 26 characters): Social Proteomics and CHD/Stroke

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:

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

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3. Timeline:

This is a proposal for proteomics replication/validation. The analyses have been completed in CHS. Replication/validation analyses in ARIC will be performed by Dr Shah's group at BWH. We expect to have a draft of the manuscript circulated within 3-6 months.

4. Rationale:

There is a well-established link between social gradient and health. The Whitehall studies of the 1970's were among the first to describe a link between social class, assessed by job classification, and chronic disease outcomes.[1] In the past 50 years, there have been an abundance of studies linking educational attainment, income, and race/ethnicity with cardiovascular health outcomes.[2] Yet the mechanisms mediating these associations is only partially understood. Although tangible resources such as access to healthcare, healthy food, and physical activity resources contribute to health disparities, the association between social gradient and health outcomes remains after controlling for these factors. [2]

The allostatic load theory hypothesizes that chronic stress exposure can result in low-grade systematic inflammation, which contributes to immunoaging and chronic disease.[3] Evidence points towards a mediating role for allostatic load in the relationship between education and coronary heart disease.[4] Literature has demonstrated an association between income, education, race, and job class with inflammatory and thrombotic markers including C-reactive protein, fibrinogen, and interleukin-6, all known risk factors for cardiovascular outcomes. Whether other biologic pathways are involved is not known.[5-7]

In this study, we use the availability of high-dimensional proteomics assays as a discovery tool to evaluate pathophysiologic mediators of social adversity. We use low educational attainment, low-income, and blue-collar occupation as measures of this construct in CHS which will serve as a discovery cohort. We will evaluate the proteomic signatures of a factor encompassing these measures in order to develop hypotheses regarding the biologic pathways which mediate health inequities. We will explore differences by race, as we hypothesize that there may be differences in the effects of social adversity among Black participants due to differential social treatment including structural and individual level racism. We will then quantify the extent to which these proteomic pathways mediate the relationship between social adversity and cardiovascular outcomes. We will use ARIC as a validation cohort to validate 1) the top proteomic associations with the adversity factor, and 2) the mediation for cardiovascular outcomes.

5. Main Hypothesis/Study Questions:

Aim 1: To examine the association of a factor encompassing sociodemographic markers of adversity with the proteome.

Hypothesis: A factor encompassing sociodemographic markers of adversity will display a protein signature, as demonstrated by multiple significantly associated proteins.

Aim 2: To examine the contribution of proteins identified in Aim 1 as mediators of the relationship between social adversity and cardiovascular outcomes.

Hypothesis: One or more proteins identified in Aim 1 will mediate the relationship between social adversity and CHD and stroke.

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).

Exposure variables*:*
A factor encompassing education, income, and occupation derived using exploratory factor analysis with maximum likelihood, calculated in a pooled Black/White sample. We will also explore inclusion of area deprivation index (ADI) as Dr. Shah has used this approach in previous work.

Outcome variables:
Log_2-transformed and standardized values of SOMAscan proteins that meet significance threshold in White participants in CHS

Incident coronary heart disease (myocardial infarction and angina) and stroke

Covariates: Covariates in the primary model will include study site, age, sex, and eGFR. We adjust for eGFR since kidney filtration is related to protein concentration.

Secondary adjustment variables which could be confounders or mediators of the relationship between the proteome and cardiovascular outcomes include: BMI, smoking, alcohol use, physical activity, systolic and diastolic blood pressure, fasting glucose, eGFR, LDL and HDL cholesterol, blood pressure lowering medications, glucose lowering medications.

Analytic Plan:
There will be two sets of analyses for validation. All analyses will be stratified by race (Black vs. White/other racial groups).

Primary analyses will evaluate associations of the exposure with single log-normalized and standardized protein levels, adjusted for study site, age, sex and eGFR in race-stratified models. We will validate in ARIC the proteins that reached the p-value threshold of 1.0*10-5 (0.05 divided by 4985) for significance in White participants in CHS (*note: CHS has a larger sample of White participants than Black participants)*.

We will then conduct causal mediation analysis to evaluate the mediating effects of the proteins that met the significance threshold described above in the associations of each measure of social adversity with coronary heart disease and stroke, as separate outcomes.[10,11] Candidate proteins will be the subset of those proteins that were significantly associated with the adversity factor *and* significantly mediate the relationship between the factor and coronary heart disease and/or stroke in White participants in CHS. Causal mediation methods allow for an interaction between the exposure and mediator of interest, which will be included if the p-value for interaction <0.1. We will adjust for site, age, sex and eGFR in primary analyses, and adjust for secondary adjustment variables in a secondary set of analyses. We will use a Bonferroni-corrected p-value threshold.

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)?
MP #4163 "Proteomic markers linking social determinants of health and heart failure risk in a biracial community-based cohort: the ARIC study" (ARIC author: Amil Shah)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal
_x_ A. primarily the result of an ancillary study (list number* __2017.27__)
___ 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.