1.a. Full Title: The relationship of socioeconomic status with self-reported health status, subclinical myocardial damage and clinical cardiovascular disease outcomes among older adults in the ARIC study.

b. Abbreviated Title (Length 26 characters):

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

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3. Timeline:
Data for this project is readily available, thus we intend to conduct analysis and manuscript preparation in 6-7 months from approval.
4. **Rationale:**

Among American adults living with cardiovascular disease (CVD, 85.6 million), over half (43.7 million) are 60 years of age and older.\(^1\) Beyond traditional risk factors, such as diet and lifestyle, a substantial body of research has examined the role of socioeconomic status (SES) on CVD risk.\(^1\) Literature suggests that SES does not affect CVD directly, rather it can reflect an individuals’ health behavior choices,\(^1,2\) exposure to neighborhood environments,\(^3-5\) health system utilization,\(^6,7\) and exposure and coping with chronic stressors.\(^8,9\) Low SES (both area and individual-level) has been consistently associated with CVD risk factors\(^10\) and subsequent morbidity and mortality.\(^11,12\) Moreover, among older adults, low individual-level SES at old age can be a marker for a history of low SES throughout their lifespan and may reflect cumulative exposure to risk factors associated with SES such as hypertension.\(^13\)

More recent work has focused on SES as a risk factor for subclinical measures of CVD. For example, SES has been related to carotid intima-media thickness\(^14\) and coronary artery calcification\(^15\) — markers of subclinical measures of CVD. The highly sensitive cardiac troponin T (hs-cTnT) test is a novel tool that can detect subclinical myocardial damage in asymptomatic populations and identify individuals at high risk for future cardiovascular events.\(^16\) A 2011 ARIC study\(^16\) established that minute elevations in hs-cTnT are strongly associated with future risk of heart disease, heart failure, and all-cause mortality.\(^17,18\) A more recent ARIC investigation showed that people with low SES were more likely to have elevated hs-cTnT concentrations in midlife and these associations conferred risk of cardiovascular events and future elevations in hs-cTnT.\(^19\)

Assessment and improvement of health related quality of life (HRQOL) is a valuable measure of disease impact and treatment effects of CVD, particularly among older adults.\(^20\) HRQOL is a multidimensional construct that has been increasingly used as a patient-derived indicator assessing general health status related to physical, psychological, social and emotional functioning.\(^21,22\) A 2016 joint scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society systematically identified gaps in cardiovascular clinical care guidelines for older adults and concluded that while objective outcomes, such as CVD are common in late-life, relevant subjective domains, such as HRQOL have not been assessed adequately in populations of older adults. Moreover, limited research has examined how an individual’s HRQOL varies based on both clinical and subclinical CVD profile. Given the increasing survival from CVD, focusing on good HRQOL is of great importance.

Therefore, we aim to examine the association of SES, clinical and subclinical CVD as risk factors for poor HRQOL among older adults. The prospective follow-up of the ARIC cohort from mid- to late-life provides a unique opportunity to extend the existing research to a contemporary examination of this phenomenon in older age and could inform prevention efforts.
5. Main Hypothesis/Study Questions:

**Aim 1.** Examine the association between SES (individual and neighborhood SES) and HRQOL at Visit 5. These associations will be evaluated before and after adjustment for demographic and traditional CVD risk factors.

**H1:** Individuals with low as compared to high SES will have poorer HRQOL at old age (Visit 5).

**Aim 2.** Evaluate the association of SES with subclinical myocardial damage and cardiovascular disease prevalence at Visit 5.

**H2:** Low SES will be associated with elevated levels of hs-cTnT and clinical CVD prevalence (heart failure, stroke, and coronary heart disease) at old age.

**Aim 3.** Evaluate the extent to which the association of SES with poorer HRQOL is explained by the presence of subclinical and clinical CVD, recognizing the limitations of cross-sectional data.

**H3:** Markers of subclinical CVD as well as clinical CVD explain much of the lower HRQOL at older age and some of the SES related gradients.

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:** Cross-sectional analysis of HRQOL measured at ARIC visit 5 with risk factors measured concurrently (SES, hs-cTnT levels and cardiovascular disease prevalence) and in the past (history of CVD risk factors).

**Inclusion/Exclusion Criteria:** Participants will be excluded if they are missing information on: hs-cTnT, SES, CVD prevalence data or HRQOL at Visit 5. If the percentage of missing data is high (>10%) then analyses with multiple imputations for missing data will be conducted. Participants will also be excluded if they identify as non-White race in Minnesota.

**Outcomes:**

1) **HRQOL** Health-related quality of life will be measured using data from the SF-12 Questionnaire administered at Visit 5. HRQOL is the outcome for aims 1 and 3. The SF-12 is a questionnaire that assesses different domains (physical and mental) of health-related quality of life. This questionnaire assesses participants’ limitations due to pain, their energy level, and their ability to perform everyday tasks such as climbing stairs. We will use the Z-score transformations of the separate function (physical and mental) scales (e.g., SF12PFZ51 for physical functioning): higher scores indicate a better health status. The summary scales can range from 0 to 100 with the US population mean of 50 and the corresponding standard deviation of 10. We will analyze the score continuously. Sensitivity analyses can examine the individual domains separately.
2) *Hs-cTnT* measured at ARIC Visit 5 measured using a highly-sensitive novel assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, Indiana). Hs-cTnT is an outcome for aim 2. Given the advanced age of participants at visit 5, we will use similar cut points as a previous ARIC study to define age- and sex-specific 99th percentile reference values of elevated hs-cTnT for adults >65 years of age: >31 ng/l for men and >17 ng/l for women.\textsuperscript{23,24} We will also examine log hs-cTnT levels as a continuous measure.

2) *CVD* (heart failure, stroke, and coronary heart disease) will be obtained from visit 5 data and previous incidence. CVD is an outcome for aim 2. *Heart failure* is defined as prior hospitalization before visit 5, physician confirmed heart failure, reported hospitalization, self-report of heart failure, or treatment for heart failure (we thought NT-pro-BNP and echocardiogram data could be explored but merit their own paper). *Stroke* is defined as self-report of prior stroke or ascertained from ARIC surveillance data on the cohort. *Coronary heart disease* is defined as self-report of prior CHD or ascertained from ARIC surveillance on the cohort.

**Key exposures:**

1) *Neighborhood SES:* Similar to previous analyses,\textsuperscript{25} we will use neighborhood SES at Visit 5 defined as a z-score that sums six indicators of neighborhood characteristics at the census-tract level, based on the geocoded address at Visit 5 of each participant. The six indicators represent various dimensions of SES including income/wealth, education, and occupation at the census-tract level (see Table 1). A z-score will be estimated for each indicator by subtracting the overall mean and dividing by the standard deviation. The six indicators will be summed to create a summary score. We will then generate race-specific tertiles of high, medium or low neighborhood SES based on the race-specific z-score distribution; we can also examine continuous z-score. We will also consider visit 1-4 measures of neighborhood SES in secondary analyses as neighborhood SES has changed over time for participants.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Income/Wealth</td>
<td></td>
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<tr>
<td>Household income</td>
<td>log of median household income</td>
</tr>
<tr>
<td>Housing value</td>
<td>log median housing value</td>
</tr>
<tr>
<td>Household rental income</td>
<td>percent of household with interest or rental income</td>
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<tr>
<td>Education</td>
<td></td>
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<tr>
<td>High school education</td>
<td>proportion of adults &gt;25 years old with high school education</td>
</tr>
<tr>
<td>College education</td>
<td>proportion of adults &gt;25 years old with college education</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
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</tbody>
</table>
Professionally employed proportion of adults > 16 years old with executive, managerial or professional occupations.

2) *Individual-level SES:* Individual-level SES will be characterized using annual household income measured at visit 5 (variable: PHX1; we will also examine an analysis in which income is assessed at the closest visit to age 60 to standardize the age at measurement and examine variation across midlife) and lifetime educational level measured at visit 1 (education typically does not increase after midlife). We can conduct a sensitivity analysis for income using Medicaid insurance as a proxy for low income (variable= AQC3c). Individuals and families with low incomes and limited resources qualify for the Medicaid insurance program.

**Statistical Analysis:**
Linear regression models will be used to examine the adjusted association HRQOL with SES (aim 1). We will use Poisson regression with robust standard errors to model elevated versus non-elevated hs-cTnT levels and their adjusted association with SES (aim 2). We will similarly model the prevalence of CVD with SES. We will then return to modeling HRQOL in relation to SES with progressive adjustment for covariates and key risk factors (aim 3). The emphasis will be on examining the extent to which SES associations are explained by concurrent clinical and subclinical CVD, recognizing the limitations of cross-sectional data. Models with progressive degrees of adjustment will be implemented. Model 1 will be unadjusted. In Model 2, we will adjust for age, sex, race-center. In Model 3, we will further adjust for BMI, hypertension, diabetes, total cholesterol, HDL-c, alcohol consumption, physical activity, and smoking status. Model 4, will include all variables from Model 3 plus measures of SES. Model 5 will further adjust for markers of subclinical CVD and for measures of prevalent CVD. Further analysis will explore the role of the past history of CVD risk factors in explaining HRQOL at visit 5. Multilevel modeling will also be considered since we have individuals nested within census tracts.

**Limitations**
We will only have cross-sectional measures of our key exposures and outcomes; thereby limiting inferences to the health status of older adults and causality of association. In addition, it is reasonable to expect a selective mortality could be occurring in this sample, which may be related to death before visit 5 or attrition at visit 5 due to loss to follow-up (poor quality of life/too sick to attend visit). Selective mortality is less of a problem if one is making inferences to a similarly aged population. However, it will make cross-sectional associations differ from longitudinal associations. We will explore IPAW for non-response compared to living individuals at the time of visit 5 and in thinking about which individuals died before visit 5 by SES level.
References


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](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)?

- #2817 Fretz et al. Lifestyle-related health behaviors and six-year change in high sensitivity cardiac troponin T
- #2307 Fretz et al. Socioeconomic status and incidence of subclinical myocardial damage
- #2311 Palta et al. Individual and contextual socioeconomic profile and physical function in late life: the Atherosclerosis Risk in Communities (ARIC) Study
- #2383. Windham et al. Relationship of Life’s Simple 7 Score in Midlife to Late Life Physical Function
- #2465 Kucharska-Newton et al. Operationalizing frailty in the ARIC cohort
- # 2646 Rotter et al. Measuring Changes in SF-12 Status Over Time
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.cscunc.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.cscunc.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, approved manuscripts using 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.