1.a. Full Title: Socioeconomic Status and the Incidence of Heart Failure with Preserved versus Reduced Ejection Fraction: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): SES in HFpEF vs. HFrEF

2. Writing Group:
   Writing group members: Alvin Chandra, Brian L. Claggett, Stephen Y. Wang, Scott D. Solomon, others are welcomed

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.
4. **Rationale:**
Socioeconomic status (SES), as measured by total family income and education, have been inversely associated with cardiovascular disease (CVD).\(^1\)\(^2\) In particular, it has been shown to be a powerful predictor of incident coronary heart disease (CHD) and adverse CHD outcomes.\(^2\) Additionally, lower total family income has been associated with higher atrial fibrillation (AF) risk; lower education level was also associated with AF risk, though only in women.\(^3\)

Several large cohort studies, including ARIC, have examined the relationship between SES and heart failure (HF).\(^4\)\(^5\)\(^6\)\(^7\)\(^8\) Lower SES was consistently associated with higher incidence of HF. Individuals in lower SES category had an increase in adjusted risk of developing HF up to 50\%.\(^4\) HF hospital readmission rate is also significantly higher in those with lower SES. It has been estimated that SES inequality in HF result in nearly 24,000 additional deaths annually.\(^9\)

Most studies that have described the impact of SES on HF either consisted of patients with HF with reduced ejection fraction (HFrEF) or did not distinguish ejection fraction.\(^4\) Little is known regarding the impact of SES on patients with HF with preserved ejection fraction (HFpEF). One French cohort study reported that poor social conditions adversely affect survival in HFpEF patients.\(^10\) Even less is known regarding how the impact of SES differs on patients with HFpEF compared to patients with HFrEF. Yet, nearly half of those with HF have preserved ejection fraction.\(^11\) Alarming, the global burden of HFpEF is projected increase over time with HFpEF hospitalizations steadily rising, while HFrEF is declining.\(^12\)\(^13\)\(^14\) HFpEF also differs from HFrEF, not only in pathophysiology and treatment options, but also in associated risk factors.\(^15\) Compared to HFrEF, patients with HFpEF are more likely to be women, to be older, and to have multiple comorbidities.\(^16\)

Thus, in this analysis of the ARIC Study, we aim to assess and compare the associations of SES, as measured by total family income and education, with HFpEF and HFrEF within the ARIC cohort populations. Additionally, we will aim to characterize, in those free of HF, the association of SES with cardiac structure and function, as measured by echocardiography in ARIC visit 5, as abnormalities on cardiac structure and function may lead to HF in their later years.

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

**Study Aims:**
1) To evaluate the association of SES, as measured by total family income and education separately, with adjudicated cases of HFpEF and HFrEF in the ARIC cohort population
2) To evaluate the association of SES, as measured by total family income and education separately, with cardiac structure and function as measured by echocardiography among participants who remained free of HF at visit 5

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: The analysis evaluating the association of SES status, as measured by total family income and education separately, and incidence of HFpEF and HFrEF within the ARIC cohort will be a prospective analysis. It will assess the relationship of SES category at visit 4 with incident HF occurring from 2005 onwards, which was the start of ARIC HF adjudication. The analysis evaluating the association of SES with cardiac structure and function among participants who remained free of HF at visit 5 within the ARIC cohort will be a prospective analysis.

Exposures:
- Visit 4 household income categorized as: under $25,000, $25,000 - $49,999, $50,000 - $99,999, and above $100,000.
- Visit 1 education level categorized as: some high school or less, high school graduate/vocational school, college/some college, and graduate/professional school

Outcomes:
- The outcomes of the longitudinal analysis of SES status and HF will be incident HF, defined as the 1st adjudicated HF hospitalization or death related to HF beginning in 2005 until the most recent follow-up available. HF cases will be divided into HFpEF and HFrEF using the definition of LVEF ≥ 50% and <50% respectively.
- The outcomes of the analysis of SES and cardiac structure/function will be echocardiographic variables (visit 5) of LV structure (LV end-diastolic and end-systolic volumes and dimensions, wall thickness, and mass), LV diastolic function (E wave, A wave, TDI E’, LAVi), LV systolic function (LVEF, global longitudinal strain, and circumferential strain), and RV function (TDI tricuspid annular S’).

Exclusions: We will exclude all participants with known HF prior to the beginning of HF adjudication in 2005 and those with missing data on household income and education level. For the echo analysis, we will additionally exclude participants with incident HF prior to visit 5 and those with missing echo data.

Potential covariates: age, race, gender, body mass index, diabetes, hypertension, blood pressure, use of antihypertensive medications, hyperlipidemia, use of statin, HDL, LDL, triglyceride, family history of HF, alcohol intake, eGFR

Analytical approach: Continuously distributed data that are normally distributed will be displayed as mean ± standard deviation. Continuously distributed data that are not normally distributed will be displayed as median and interquartile range. Categorical data will be reported as percentages and frequencies. We will perform univariable comparisons of characteristics across total family income and education categories separately using 1-way ANOVA for continuous variables and chi-squared test for categorical variables.

For longitudinal analysis of SES status and HF, we will use Poisson regression models to calculate crude and adjusted incidence rates for HFpEF and HFrEF that are associated with total family income and education categories. We will use Cox regression models to estimate hazard ratios and 95% confidence intervals for incident HFpEF and HFrEF as associated with total family income and education categories. Regression models will then be adjusted for confounding variables as detailed in potential covariates.
For analysis of SES status and cardiac structure/HF in participants who remained free of HF, associations between total family income/education categories and cardiac variables will be evaluated using multivariable linear regression and logistic regression analysis adjusting for significant potential covariates. P <0.05 will be considered significant.

**Limitations:** A limitation of observational study will be the inability to make conclusions on causality. Income and education are both self-reported variables, which may result in inaccuracies. In evaluating visit 5 patients for the echo study, there is a potential survival bias as they may represent a healthier population.

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/mantrack/maintain/search/dtSearch.html](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)?
#1463 Socioeconomic Status (SES) and Case-Fatality among Participants with Incident Heart Failure
#1324 Neighborhood and Individual Socioeconomic Status and Heart Failure Rehospitalization: ARIC Cohort
#1160 Life Course Socioeconomic Exposures and Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study

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 https://www2.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://publicaccess.nih.gov/submit_process_journals.htm shows you which journals
     automatically upload articles to PubMed central.

References:


