1.a. Full Title: The association of socioeconomic status with elevation of N-terminal pro-B-type natriuretic peptide and subsequent risk of cardiovascular disease and mortality.

b. Abbreviated Title (Length 26 characters): SES and NT-proBNP

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

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3. Timeline:
   Since data for this project are already available, we anticipate to complete the project in approximately 6 months.
4. **Rationale:**
The association between socioeconomic status (SES) and clinical cardiovascular disease (CVD) is well established.\(^1\)\(^-\)\(^4\) However, the mechanism by which low SES leads to CVD is not completely understood. One of the potential mechanisms by which low SES is linked to CVD is suggested to be atherosclerotic in nature, potentially due to psychological stress associated with low SES.\(^5\) To examine this mechanism, a number of studies investigated the association of SES with carotid intima-media thickness and coronary artery calcification. These studies did not observe a consistent association between SES and these measures of subclinical atherosclerosis,\(^6\)\(^-\)\(^9\) suggesting that other mechanisms may also be important contributor to SES-CVD relationship.

NT-proBNP is a biomarker indicating cardiac overload or dysfunction and is used for diagnosing heart failure in clinical practice.\(^10\) Moreover, NT-proBNP has been shown to predict incident heart failure in the general population,\(^11\) suggesting its property as a marker of subclinical cardiac overload.

To explore a pathway in the association between SES and CVD via NT-proBNP, cardiac overload or dysfunction, first, we aim to examine the association of SES with NT-proBNP. Second, we aim to examine the association of NT-proBNP with CVD (i.e. with coronary heart disease, heart failure and stroke individually), and cardiovascular mortality. Finally, we aim to estimate the contribution of NT-proBNP in the association between SES and subsequent risk of coronary heart disease, heart failure and stroke, and cardiovascular mortality.

5. **Main Hypothesis/Study Questions:**
Study question 1: Whether, if at all, low SES is associated (Cross-sectionally and prospectively) with increased level of NT-proBNP among persons with no history of clinical cardiovascular disease at baseline (visit 2)?
Study question 2: Whether, if at all, NT-proBNP is associated (prospectively) with CVD (i.e. with coronary heart disease, heart failure and stroke individually) and CVD mortality?
Study question 3: Does, if at all, NT-proBNP contribute to the SES related differences in the incidence of coronary heart disease, heart failure and stroke, and CVD related mortality?

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:** We intend to use, both, cross-sectional and prospective data to explore those study questions.

**Inclusion/exclusion:** Participants with measured NT-proBNP, no history of cardiovascular disease at baseline, no missing information on SES measures (household income, educational attainment and health insurance status) and no missing information on covariates of interest (i.e. Total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, diabetes, estimated glomerular filtration rate, electrocardiogram-based left ventricular
hypertrophy, body mass index, physical activity index (sport), alcohol use, tobacco use at visit 2 (1990-1992) will be included.

**Exposure: SES**

SES will be defined using educational attainment, household income and health insurance status of participants.

**Outcome(s):**

1) Levels of NT-proBNP (at visit 2 for cross-sectional analysis and at visits 4 for longitudinal analysis)

2) Incident coronary heart disease

3) Incident stroke

4) Incident heart failure

5) Cardiovascular mortality

**Summary of data analysis:**

First, using regression analysis, cross-sectional associations of SES measures (household income, educational attainment and health insurance status) with NT-proBNP will be examined. Linear regression will be used when using NT-proBNP as a continuous variable and poisson regression when using NT-proBNP as a categorical variable 1) elevated ≥400 pg/ml and non-elevated <400 pg/ml12 2) quintiles of NT-proBNP.

For prospective association between SES and NT-proBNP: 1) using linear regression we will examine the associations between SES at baseline (visit 2) and the mean change in NT-proBNP over 6 years (calculated as visit 4 NT-proBNP level minus visit 2 NT-proBNP); 2) using multinomial logistic regression, among persons with non-elevated NT-proBNP, we will evaluate the association of SES at visit 2 (baseline) with incident elevated NT-proBNP assessed, 6-years later, at visit 4. We use multinomial logistic regression because risk of incident elevated NT-proBNP level would be different in individuals developing CVD (i.e. coronary disease, stroke and heart failure) compared to those not developing CVD. The multinomial regression approach, will allow us to model intervening cardiovascular events and deaths between visit 2 and visit 4 as possibilities separate from incident and no incident elevation in NT-proBNP. In a sensitivity analysis, we will examine association between SES and elevated NT-proBNP after excluding people with incident CVD between visit 2 and visit 4.

Survival analyses of the association of SES and NT-proBNP with coronary heart disease, stroke, heart failure, and mortality will be conducted using Cox proportional hazard models with follow-up through December 31, 2012 or most recent data available. Subsequently, to evaluate the contribution of NT-proBNP to the SES related differences in the incidence of CVD (i.e. coronary heart disease, heart failure and stroke) and CVD related mortality, we will estimate the percentage reduction in the regression coefficient of the association between SES and aforementioned outcomes after inclusion of NT-proBNP to the base model (adjusted for demographics and cardiovascular disease risk factors), using the formula: 100 × (βModel 1 − βModel 1 + risk factor)/(βModel 1). A 95% confidence interval (CI) will be calculated around the percentage attenuation using bootstrap method with 1000 re-samplings. If the 95% CI did not include 0, the amount of
attenuation will be considered to be significant. Statistical tests were 2-sided and a p-value of less than 0.05 will be considered statistically significant.

For historical reasons African-Americans have poor educational attainment and less economic opportunities and consequently, disproportionately high number of African-Americans belong to low SES. Moreover, levels of NT-proBNP might vary by race. Therefore, we will test the interaction between SES and race, and will stratify these analyses by race.

Anticipated methodologic limitations or challenges
SES is a multidimensional construct and one individual measure of SES might not be able to capture entire socioeconomic circumstances of an individual. To overcome this, we will assess the association of NT-proBNP with a number of SES measures, including household income, educational attainment and health insurance status.

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.cscce.unc.edu/ARIC/search.php](http://www.cscce.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)?

MP#2307 Socioeconomic status and incidence of subclinical myocardial damage
MP #2463 Active and Passive Smoking, N-Terminal pro-Brain Natriuretic Peptide (NTproBNP) and high sensitivity troponin T levels: The ARIC Study

MP #2334 Troponin T and N-terminal pro-B-type Natriuretic Peptide and Cognitive Decline and Dementia in the ARIC study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes  ____ No
ARIC Ancillary Study #2008.10: Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort (Ballantyne)
ARIC Ancillary Study #2009.16: Short-term Markers of Glycemia and Long-term Outcomes (Selvin)

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (list number* #2008.10, #2009.16)
____ 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.
References:


