1.a. Full Title: Active and Passive Smoking, N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) and high sensitivity troponin T levels: The ARIC Study.

b. Abbreviated Title (Length 26 characters): Smoking, NT-proBNP and hsTroponin-T

2. Writing Group:
Writing group members: Wilson Nadruz Junior, Alexandra Gonçalves, Brian Claggett, Gabriela Querejeta Roca, Amil Shah, Susan Cheng, Gerardo Heiss, Scott D. Solomon, others welcome

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

First author: Wilson Nadruz Junior
Address: Brigham and Women’s Hospital
Cardiovascular Division
75 Francis Street, PBB-1 North
Boston, MA 02115
Phone: 617-971-7867 Fax: 617-582-6027
E-mail: wilsonnadruz@gmail.com or wnadrujunior@partners.org

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Scott D. Solomon
Address: Brigham and Women’s Hospital
Cardiovascular Division
75 Francis Street
Boston, MA 02115

Phone: 857-307-1960 Fax: 857-307-1944
E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:
Heart failure (HF) is a disorder afflicting 5 million Americans, with over 80% of HF hospitalizations occurring in elderly people. If current trends continue, 6 million of Americans aged >65 years will have HF by 2030. NT-pro brain natriuretic peptide (NT-proBNP) and high sensitivity troponin T (hsTroponin-T) levels provide important information regarding the pathogenesis of HF and are soluble risk markers for HF. NT-proBNP increases in response to hemodynamic stress — that is, when the ventricles are dilated, hypertrophic, or subject to increased wall tension, while hsTroponin-T increases as a consequence of myocardial injury. It is widely accepted that higher NT-proBNP and hsTroponin-T levels are associated with an increased risk of mortality and worse cardiovascular outcomes.

Cigarette smoking has been associated with incident HF, even after adjustment for coronary heart disease. Some reports have also suggested that smoking might exert effects on cardiac structure and function. For instance, population-base studies showed that smoking was related to worse LV function and higher LV mass in individuals without overt coronary heart disease. The mechanisms by which smoking could lead to cardiac dysfunction are not established but may include neurohormonal changes, oxidative stress, inflammation and hemodynamic overload. Cross-sectional studies showed that current smoking is associated with higher NT-proBNP and hsTroponin-T levels in general populations. Nevertheless, the relationship between environmental tobacco smoke (ETS) and NT-proBNP and hsTroponin-T levels has not been established yet. In addition, there is currently no information available regarding to what extent active and passive smoking determine temporal changes of these biomarkers over time.

5. Main Hypothesis/Study Questions:

1) Current smoking and exposure to ETS will be associated with higher NT-proBNP levels and hsTroponin-T levels and there will be a dose-response relationship between these biomarkers and pack-years of active smoking at Visit 4.

2) Current smoking and exposure to ETS at Visit 4 will be associated with higher increases in NT-proBNP and hsTroponin-T levels from Visit 4 to 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 and Inclusion/Exclusion Criteria:

To evaluate the first hypothesis, we will perform a cross-sectional analysis between smoking status (never, former and current smoking and exposure to ETS), pack-years of active smoking, NT-proBNP and hsTroponin-T levels at Visit 4. For the analysis, those with heart failure, coronary heart disease, chronic obstructive pulmonary disease, who were neither White nor African American and with missing smoking, NT-proBNP and troponin data at Visit 4 will be excluded.

For the second hypothesis, we will evaluate the relationship between smoking status (never, former and current smoking and exposure to ETS), pack-years of active smoking and the
variation in NT-proBNP and hsTroponin-T levels between Visit 5 and 4. For the analysis, those with coronary heart disease, chronic obstructive pulmonary disease, who were neither White nor African American and with missing smoking, NT-proBNP and troponin data at Visit 4 and 5 and those with heart failure at Visit 4 will be excluded.

Variables to be evaluated

Exposures variables:

1. Categorize participants into 6 groups based on Smoking status at Visit 4:
   a. Current smokers exposed to ETS*
   b. Current smokers not exposed to ETS
   c. Former smokers exposed to ETS
   d. Former smokers not exposed to ETS
   e. Never smokers exposed to ETS
   f. Never smokers not exposed to ETS

*Exposure to ETS was assessed using the following question: "During the past year, about how many hours per week, on average, were you in close contact with people when they were smoking?". Subjects will be classified as exposed to ETS if they reported being in close contact with smokers for more than 1 hour per week.15

2. Quantify smoking intensity and duration measured as a continuous variable (pack-years) using self-reported data collected from Visit 1 to Visit 4.

Outcome variables:

1. NT-proBNP and hsTroponin-T levels at Visit 4.

2. Differences in NT-proBNP and hsTroponin-T levels between Visit 5 and Visit 4.

Potential covariates:
Demographic characteristics (age, race, sex, body mass index, socioeconomic status), cardiovascular risk factors (diabetes, arterial hypertension, dislipidemia, family history of heart failure, alcohol consumption), blood pressure, use of antihypertensive medications or statins, plasma lipid levels (i.e. HDL and LDL cholesterol, apolipoprotein AI and B, triglycerides), creatinine clearance and C-reactive Protein levels.

Analytical approach:
Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Wilcoxon rank sum test, t test, Kruskall-Wallis
test and 1-way ANOVA followed by Bonferroni test as appropriate. Associations of smoking status / pack-years of smoking and cardiac biomarkers variables will be evaluated using linear regression and ordinal logistic regression analyses adjusting for the significant covariates. NT-proBNP will be modeled continuously using log transformed values, while hsTroponin-T will be modeled as an ordinal categorical variable using five categories. The relationship between pack-years of smoking and cardiac variables will be assessed in the whole sample as well as in current and former smokers. To evaluate the risk of survival bias at Visit 5, we will also assess the relationship between smoking status at Visit 4 and incident cases of coronary heart disease, stroke, heart failure and mortality between Visit 4 and Visit 5. P values<0.05 will be considered significant.

Limitations:
A limitation of the cross-sectional design will be the inability to make conclusions about causality. Conversely, smoking status and intensity and duration of smoking are self-reported variables, which may result in recall bias.

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 ICTDER03 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

  ____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)?

Relationship between pulmonary airflow obstruction, cardiac structure and function, and heart failure risk in a biracial elderly cohort: The ARIC study. #2117
Development of a quantitative model for the relative risk of cardiovascular disease by pack-years of cigarette smoking and assessment of modification of the strength of association by smoking rate and other host characteristics in the Atherosclerosis Risk in Communities Study. #1965

The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD # 1757

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.cscu.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:
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the