ARIC Manuscript Proposal #2352

PC Reviewed: 4/8/14     Status: A     Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Weight History, Subclinical Myocardial Injury and Incident HF: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Weight history, hs-cTnT and HF

2. Writing Group: Chiadi E. Ndumele; Laura K. Cobb; Mariana Lazo; Natalie Bello; Amil Shah; Vijay Nambi; Scott Solomon; Roger S. Blumenthal; Christie M. Ballantyne; Elizabeth Selvin; Josef Coresh; others welcome

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.
4. **Rationale:**

Obesity is a potent risk factor for heart failure, but the mechanisms underlying this relationship remain poorly understood (1). Animal models suggest that myocardial injury may play a role in the progression to clinical heart failure (HF) among individuals with obesity (2-5). We have previously demonstrated a graded, independent association between BMI and subclinical myocardial injury, as indexed by levels of a novel high-sensitivity assay for cardiac troponin T (hs-cTnT), among ARIC participants without clinical cardiovascular disease (6). Additionally, those individuals with obesity and high hs-cTnT levels were at markedly increased risk for incident HF compared to normal weight individuals with undetectable hs-cTnT (6).

Weight history may be more informative than a single anthropometric measurement for characterizing the risk of heart failure associated with excess adiposity. For example, prior studies have found that the duration of morbid obesity is strongly associated with the degree of ventricular dysfunction and the likelihood of HF (7-8). However, it is presently unknown which weight history metrics (e.g., duration of obesity vs. average BMI over time vs. absolute change in BMI) have the strongest association with the likelihood of future HF. Additionally, the relationship between weight history and subclinical myocardial injury has not yet been explored.

In this analysis of the Atherosclerosis Risk in Communities (ARIC) study, we will compare different approaches to characterizing weight history by constructing different models of weight history and evaluating their relative associations with elevated hs-cTnT and incident HF. In doing so, this analysis will allow us to evaluate which weight history metrics have the strongest associations with the development of myocardial injury and incident HF.

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

**Aims:**

1) To compare the relative strengths of association between different weight history metrics and the development of subclinical myocardial injury

2) To compare the relative strengths of association between different weight history metrics and the development of incident HF

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: Prospective cohort analysis (baseline for follow-up = Visit 4) evaluating the relationship between weight history from ARIC Visit 1 to Visit 4 and the presence of elevated hs-cTnT at ARIC Visit 4 and incident HF after Visit 4. We will perform univariate comparisons of weight history models, as well as multivariable comparisons with simultaneous inclusion of multiple weight history models.

Exposures: The exposure of interest will be weight history from ARIC Visit 1-4. Our primary weight metric will be body-mass index (height in kilograms divided by meters squared). We will also assess waist circumference (WC) as a secondary weight metric.

Outcomes: The outcomes of interest will be elevated hs-cTnT levels at ARIC Visit 4, and incident HF occurring after Visit 4. Hs-cTnT was measured from stored plasma samples at Visit 4 with the Elecsys Troponin T high-sensitivity assay using a sandwich immunoassay method (Roche Diagnostics). Elevated hs-cTnT will be defined as >14 ng/L, approximately the 90th percentile in the ARIC cohort and a threshold used in prior analyses. Incident HF will be defined as the first hospitalization or death related to HF, as identified by HF discharge codes (ICD-9 code 428 for hospitalizations and deaths early during follow-up and ICD-10 code I50 for later deaths). Incident HF events after 2004 were additionally adjudicated by a panel of experts.

Exclusions: We will exclude participants with known CVD, including HF, prior to Visit 4 (self-reported CVD or adjudicated CVD events at or prior to Visit 4), the small number of participants at Visit 4 who are not black or white, and those participants missing covariates of interest.

Covariates: Age, sex, race, center, smoking status, hypertension (prior physician diagnosis, use of anti-hypertensive medications, SBP>140 mmHg or DBP>90 mmHg), systolic blood pressure, fasting glucose, diabetes, LDL-, and HDL-cholesterol, triglycerides, alcohol intake and estimated GFR measured at Visit 1. We will additionally consider physical activity measurements performed at V1. We will model some variables as time-varying covariates (smoking status, diabetes mellitus, hypertension, LDL-C, and estimated GFR), using serial measurements from Visits 2 through 4.

Main Analyses:

We will create different models for weight history from ARIC Visit 1-4 and compare their association with myocardial injury (hs-cTnT) and incident HF.

1) We will model weight history in the following ways:
   - Average BMI from V1-4
   - Change in BMI category from V1-4
   - Absolute BMI Change from V1-4
   - Area under the curve for BMI from V1-4
   - Duration of Obesity
   - Trajectory of BMI (modeled using latent trajectories)
2) In cross-sectional analyses, we will construct separate logistic regression models to examine the relationship between different models of weight history from ARIC V1-4 and elevated hs-cTnT at ARIC V4. In regression models, we will perform sequential adjustment using the Models below:
- Model 1: Adjusted for age
- Model 2: Adjusted for Model 1 + sex, race-center and smoking status at V1
- Model 3: Adjusted for Model 2 + baseline (measured at V1) hypertension, systolic blood pressure, diabetes, LDL-, and HDL-cholesterol, triglycerides, alcohol intake, and estimated GFR.
- Model 4: Adjusted for Model 3 + time varying covariates (change in smoking status, diabetes mellitus, hypertension, LDL-C, and estimated GFR from V1 to V4).

3) In prospective analyses, we will construct separate Cox regression models to examine the relationship between different models of weight history from ARIC V1-4 and incident HF after V4, using successive levels of adjustment as described above.

4) For both cross sectional and prospective analyses, we will perform univariate comparisons of different weight history models using Akaike Information Criterion (AIC): -2logL + 2*(# of variables)

5) For both cross-sectional and prospective analyses, we will also perform multivariable comparisons assessing improvements in the likelihood ratio test (LRT) associated with the addition of different weight history models to a combined multivariable model

6) We will repeat all analyses stratified by race, gender and age. If significant differences are observed, we will test for interactions between these demographic variables and weight history models on the outcomes of interest.

7) We will perform sensitivity analyses using waist circumference as a secondary weight metric. We will also assess the relationship of self-reported weight at age 25 (and change in weight from age 25 to V4) with the outcomes of interest.

Secondary Analysis:
- In a sensitivity analysis, we will examine change in hs-cTnT from Visit 2 to Visit 4 as a secondary measure of subclinical myocardial injury (incident myocardial injury).

Sensitivity Analysis:
- In sensitivity analyses, we will also compare weight history models in analyses stratified by BMI category at Visit 1.
• We will also consider analyses excluding individuals who developed malignancies between Visits 1 and 4, because of the association between malignancy and unintentional weight loss.

Limitations:
• There is the likelihood for some residual confounding in our efforts to assess the independent associations of weight history with elevated hs-cTnT and incident HF
• By only including ARIC V4 participants free of CVD at V4, our analysis may be affected by bias due to the exclusion of individuals who developed CVD or died prior to V4. We will consider using inverse probability of attrition weighting (IPAW) to adjust for the impact of informative censoring on the results.
• ARIC participants range from 45-64 at the start of the cohort. If weight in young adulthood (or even childhood) is most important for predicting HF and myocardial damage, we may not be able to fully capture that in this analysis.

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?  __ No
   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)?

   ARIC Manuscript Proposal # 1734: Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T
Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR, Selvin E, Ballantyne CM, Nambi V. Obesity, Subclinical Myocardial Injury and Incident Heart Failure. In revision at JACC: HF


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* 2008.10)
 ___ 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/

12. 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.

Reference List


Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR, Selvin E, Ballantyne CM, Nambi V. Obesity, Subclinical Myocardial Injury and Incident Heart Failure. *In revision at JACC: HF*
