ARIC Manuscript Proposal #2025

PC Reviewed: 10/9/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Obesity and Subclinical Myocardial Injury: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity and hs-cTnT

2. Writing Group: Chiadi E. Ndumele; Vijay Nambi; Mariana Lazo; Roger S. Blumenthal; Ron C. Hoogeveen; Elizabeth Selvin; Christie M. Ballantyne; 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:

Excess adiposity is an established risk factor for cardiovascular disease (CVD)(1), and recent data suggests that the obesity epidemic threatens to reverse advances in the cardiovascular health of the U.S. population that have been achieved over the last several decades(2). Overweight (body-mass index [BMI] 25 – 29.9 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) have been associated with measures of subclinical cardiovascular disease, such as coronary artery calcification(3) and asymptomatic left ventricular dysfunction(4), as well as with an increased incidence of cardiovascular events(5). The mechanisms underlying the association between obesity and CVD are incompletely understood. While obesity is associated with the development of several cardiovascular risk factors, such as diabetes, hypertension and dyslipidemia, previous studies suggest significant associations between obesity and CVD independent of these established risk factors(6).

A novel measure that may improve our understanding of the relationship between obesity and CVD is a newly developed high-sensitivity assay for cardiac troponin T. Troponin is the preferred biomarker for detecting myocardial injury among individuals with acute coronary syndromes(7). Recently, high-sensitivity assays have been developed that are able to detect cardiac troponin T levels far below the thresholds of conventional assays. Previous studies within ARIC and other cohorts demonstrate that a significant proportion of asymptomatic adults have detectable troponin levels using these high-sensitivity assays (hs-cTnT), and that elevated hs-cTnT levels are associated with an increased risk of cardiovascular events and mortality(8-10).

Given the associations of obesity with imaging measures of subclinical cardiovascular disease, it is plausible that excess weight may be associated with elevated levels of hs-cTnT. However, there is presently limited data regarding the association between obesity and troponin measured with this novel high-sensitivity assay, and regarding whether obese individuals with elevated hs-cTnT are at increased risk of cardiovascular events compared to obese individuals without detectable levels. In this analysis of the Atherosclerosis Risk in Communities (ARIC) study, we propose to examine the association of BMI with levels of hs-cTnT among asymptomatic adults without known cardiovascular disease, and to assess the prognostic implications of elevated hs-cTnT among obese individuals.

5. Main Hypothesis/Study Questions:

Aims:

1) To determine whether obesity is associated with an increased likelihood of detectable and elevated hs-cTnT, and to assess the extent to which any association is explained by traditional cardiovascular risk factors
2) To assess whether obese individuals with elevated levels of hs-cTnT are at an increased risk of incident cardiovascular events compared with obese individuals without detectable hs-cTnT

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 will evaluate the cross-sectional associations of increasing BMI categories with levels of hs-cTnT, and assess the prospective associations of hs-cTnT levels with incident CVD among individuals within the same BMI category. Data from ARIC Visit 4 (1996-1999) will be used for cross-sectional analyses, and Visit 4 will also be the baseline for prospective analyses.

Exposures: For cross-sectional analyses, the exposure will be body-mass index (height in kilograms divided by meters squared), categorized into the following BMI categories: normal (BMI 18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese (30-34.9 kg/m^2) and severely obese (>35 kg/m^2). We will also assess the continuous association between BMI and hs-cTnT using restricted cubic splines. For prospective analyses, the exposures will be BMI categories and levels of hs-cTnT.

Outcomes: The primary outcomes for the cross sectional analyses will be detectable hs-cTnT (>0.003 ng/ml, the detection threshold for the assay) and "high" hs-cTnT (>0.014 ng/ml, the 90^{th} percentile of hs-cTnT in the ARIC cohort). The primary outcomes for the prospective analyses will be incident CHD (defined as fatal CHD, definite or probable nonfatal myocardial infarction, angioplasty, or coronary artery bypass graft surgery), and incident CHF occurring after Visit 4 through January 1, 2009 (or most current follow-up available). Secondary outcomes will be cardiovascular and all-cause mortality.

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

Covariates: Age, sex, race, 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.

Main Analyses: Logistic regression analyses will be used to examine the association of BMI with detectable and elevated hs-cTnT, and Cox regression analyses will be used to evaluate the association of elevated hs-cTnT, among participants within each BMI category, with incident CVD.

1) We will perform univariate comparisons of obese individuals with and without detectable hs-cTnT with regards to demographics and cardiovascular risk factors
2) Using logistic regression, we will estimate the odds of detectable hs-cTnT associated with each BMI category, using individuals with a normal BMI (18.5-24.9 kg/m^2) as the reference group. Each BMI category will be assigned a dummy

variable to assess its association with detectable hs-cTnT relative to the reference group. Stepwise regression will be used to assess associations after adjustment for demographics, smoking status and traditional risk factors.

3) Logistic regression will also be used to estimate the odds of elevated hs-cTnT associated with each BMI category, using normal BMI as the reference group, before and after adjustment for the covariates of interest.
4) Logistic regression will also be used to determine the cross-sectional associations of metabolically benign and metabolically abnormal obesity with detectable and elevated levels of hs-cTnT. Metabolically benign obesity will be defined as having obesity (BMI $\geq$ 30 kg/m^2) with 0-1 of the following metabolic risk factors (fasting hyperglycemia [$\geq$ 100 mg/dL], hyperinsulinemia [HOMA-IR >90th percentile of the ARIC population], low HDL [<40 mg/dL for men or <50 mg/dL for women], hypertriglyceridemia [$\geq$ 150 mg/dL], hypertension [SBP $\geq$ 130 mmHg, DBP $\geq$ 85 mmHg, prior physician diagnosis of hypertension or anti-hypertensive medication use] or elevated hs-CRP [>3 mg/L]); metabolically abnormal obesity will be defined as having obesity with $\geq$ 2 metabolic risk factors. Similar analyses will be performed for individuals in the overweight BMI category (BMI 25-29.9 kg/m^2). This analysis may be used as the basis for an additional manuscript.
5) Restricted cubic splines will be used to assess the continuous association between BMI and hs-cTnT. Individuals with levels of hs-cTnT below the threshold of the assay will be assigned a value of 0.0015 ng/ml, as has been done in previous analyses.
6) Within each BMI category, we will estimate hazard ratios and their 95% CIs for the association of high hs-cTnT with incident cardiovascular events and mortality, with the reference group being individuals within each BMI category without detectable hs-cTnT.

Secondary Analyses:

- We will also assess the association of abdominal obesity, assessed by waist circumference, with levels of hs-cTnT
- Separate regression analyses will be performed to assess the prospective association between obesity at Visit 1 and detectable/elevated hs-cTnT levels at Visit 4

Limitations:

- There is the likelihood for some residual confounding in our efforts to assess the "independent" association between obesity and hs-cTnT

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)?

ARIC Manuscript Proposal # 1734: Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T

(The primary author for manuscript proposal #1734, Dr. Nambi, is a co-author on this proposal)

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

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8. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;**304**(22):2503-2512.

9. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;**304**(22):2494-2502.

10. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;**123**(13):1367-1376.