ARIC Manuscript Proposal #2441

PC Reviewed: 9/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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

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

2. Writing Group: Roberta Florido, Chiadi E. Ndumele; Jennifer Schrack; Mariana Lazo; Vijay Nambi; Roger S. Blumenthal; Aaron Folsom; Josef Coresh; Christie M. Ballantyne; Elizabeth Selvin; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RF__ **[please confirm with your initials electronically or in writing] (still pending approval from Drs. Schrack, Nambi and Ballantyne).**

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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 an important risk factor for development of heart failure, but the pathways underlying this relationship remain poorly understood (1,2). Multiple studies have confirmed the association of obesity and heart failure (HF) independent of traditional risk factors such as hypertension and diabetes (3-8), indicating that non-traditional pathways would play an important role in this relationship. An increasing body of evidence suggests independent effects of obesity on the myocardium (9,10). A recent analysis demonstrated an independent association between obesity and subclinical myocardial injury, as evidenced by a high-sensitivity assay for cardiac troponin T (hs-cTnT) (11). Additionally, the presence of both obesity and high hs-cTnT was associated with a markedly increased risk of incident HF.

An important factor that appears to modify the relationship between obesity and HF is physical activity. Physical activity has long been appreciated as an important component of cardiovascular risk reduction (12,13). Data suggests that among overweight and obese individuals, higher levels of physical activity confer a protective effect against the development of HF (14,15). The exact mechanisms by which physical activity reduces the risk of HF associated with obesity are presently unclear, although limited evidence suggests an association between physical activity and hs-cTnT (16). It is currently unknown whether physical activity levels influence the relationship of obesity with measures of myocardial injury.

In this analysis of the Atherosclerosis Risk in Communities (ARIC) Study, we will evaluate whether physical activity modifies the relationship of obesity with myocardial injury. We hypothesize that overweight and obese individuals with low physical activity have higher levels of myocardial injury than those with high physical activity, which portend a higher risk of incident HF. We anticipate this analysis will provide additional insight into the interrelationships among obesity, physical activity and incident heart failure.

5. Main Hypothesis/Study Questions:

Aims:

1) To determine whether physical activity levels are independently associated with hs-cTnT levels
2) To assess whether physical activity modifies the association between obesity and elevated hs-cTnT
3) To assess whether hs-cTnT levels identify individuals within obesity/physical activity categories that are at highest risk of incident HF and 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 will evaluate the prospective associations and inter-relationship of physical activity and obesity with hs-cTnT levels. In primary analysis, we will assess these relationships using physical activity and anthropometric measurements from ARIC Visit 1, and hs-cTnT measurements from ARIC Visit 2.

Exposures: The primary exposures will be physical activity and body-mass index (BMI, height in kilograms divided by meters squared):

- Physical activity level, measured through a modified Baecke physical activity questionnaire at Visit 1, will be evaluated as an exposure (relationship with hs-cTnT) and potential effect modifier (interaction with obesity on the outcome of high hs-cTnT). As has been done in prior ARIC analyses, we will convert the Baecke sports indices into "minutes per week" of moderate or vigorous exercise. Moderate and vigorous exercise will be defined according to the metabolic equivalent of task (MET) based on the Compendium of Physical Activities. We will then categorize physical activity according to the AHA guidelines as "recommended" (≥150 min/wk of moderate intensity or ≥75 min/wk of vigorous intensity or ≥150 min/wk of moderate + vigorous intensity), "low" (1–149 min/wk of moderate intensity or 1–74 min/wk of vigorous intensity or 1–149 min/wk moderate + vigorous intensity), or "poor" (0 min/wk of moderate or vigorous exercise). We will also model physical activity as quartiles of work, leisure, sports, and total physical activity scores. In secondary analyses that assess change in hs-cTnT from V2 to V4 (see below), we will also incorporate assessments of physical activity from V3.
- BMI will be 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). For our primary analyses we will use Visit 1 BMI measurements to evaluate potential effect modification by physical activity of the relationship between obesity and hs-cTnT. We will also use waist circumference and waist-to-hip ratio as alternative measures of adiposity.

Outcomes: The primary outcome will be hs-cTnT levels at Visit 2, categorized as measurable (>3 ng/L) and elevated (>14 ng/L). Additional outcomes will be incident HF (defined as a HF-related hospitalization or death) and total mortality occurring after Visit 2.

In secondary analyses, we will additionally evaluate change in hs-cTnT from Visit 2 to Visit 4. We will model change in hs-cTnT in two ways: 1) categorized as a >50% increase in hs-cTnT, a > 50% decrease in hs-cTnT, or ≤ 50% change in hs-cTnT from Visit 2 to Visit 4; 2) modeled as the progression from non-elevated (<14 ng/L) to elevated (>14 ng/L) from Visit 2 to Visit 4.

Exclusions: We will exclude participants missing data on physical activity, BMI and hs-cTnT. We will exclude the small number of participants at baseline who are not black or white. We will also exclude participants with known CVD prior to Visit 2 (self-reported CVD or adjudicated CVD events at or prior to Visit 2).

Covariates: Age, sex, race, smoking status, alcohol use, systolic blood pressure, use of anti-hypertensive medications, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR (all measured at Visit 1).

Main Analyses: Logistic regression analyses will be used to examine the relationship between physical activity and hs-cTnT, and the interaction of obesity and physical activity on the outcome of hs-cTnT. Cox regression analyses will estimate the risk of HF and mortality associated with higher hs-cTnT within obesity/physical activity categories.

1) We will perform univariate comparisons of individuals across four obesity/physical activity categories with regards to demographics and cardiovascular risk factors: non-obese (BMI<30) and low/poor physical activity levels; non-obese and recommended physical activity levels; obese (BMI $\geq$ 30) and low/poor physical activity levels; and obese and recommended physical activity levels
2) We will assess the relationship of physical activity levels at V1 with hs-cTnT levels at V2 using logistic regression. We will perform stepwise regression to adjust for the covariates of interest as follows:
    a. Model 1: Adjusted for age
    b. Model 2: Adjusted for Model 1 + sex, race, smoking status and alcohol intake
    c. Model 3: Adjusted for Model 2 + systolic blood pressure, anti-hypertension medication use, fasting glucose, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR.
3) Restricted cubic splines will be used to assess the continuous association between physical activity levels and elevated hs-cTnT levels. In linear regression analyses examining hs-cTnT as a continuous variable, individuals with levels of hs-cTnT below the measurement limit of the assay will be assigned a value of 1.5 ng/L, as has been done in previous analyses.
4) We will perform stratified analyses to examine the combined relationship of obesity and physical activity levels at V1 on the outcome of hs-cTnT at V2, using successive levels of adjustment as described above. BMI will be categorized as described above. Physical activity levels within each BMI category will also be categorized as recommended or low/poor. We will formally assess for multiplicative interactions of physical activity levels and BMI category on the outcome of hs-cTnT.
5) We will perform Cox regression analyses to estimate the hazard ratios and associated 95% CIs for incident HF and all-cause mortality associated with higher hs-cTnT levels within obesity/physical activity categories. In initial analyses, we will use the same 4 obesity/physical activity categories from the univariate analyses above: non-obese and low/poor physical activity levels; non-obese and recommended physical activity levels; obese and low/poor physical activity levels; and obese and recommended physical activity levels
6) We will perform additional analyses using waist circumference and waist to hip ratio as secondary measures of adiposity. In examining the interrelationship between physical activity and these secondary anthropometric measures, we will

use the WHO's sex-specific cutpoints for waist circumference (>88 cm for women and > 102 cm for men) and waist to hip ratio (>0.85 for women and >0.90 for men)

7) We will perform analyses stratified by race, gender and age (≥ or < than 60 years), and assess their 3-way interactions with BMI and physical activity.

Secondary Analyses:

- We will additionally assess the inter-relationship of physical activity and obesity with another biomarker of subclinical myocardial disease, NT-proBNP (measured at Visits 2 and 4)
- We will also assess the interrelationship of obesity and physical activity with change in hs-cTnT from V2 to V4, using Poisson regression analyses to estimate the risk of incident elevated hs-cTnT at V4. For this complicated analysis, we will use methods from prior ARIC analyses of change in hs-cTnT (Selvin et al. Circulation. 2014 Aug 22. pii: CIRCULATIONAHA.114.010815. [Epub ahead of print]). In performing this change analysis, we will incorporate physical activity measures from both V1 and V3, (assessing both average physical activity levels over the 2 visits and changes in physical activity level from Visit 1 to 3).

Sensitivity Analyses:

- In secondary analyses examining physical activity at V1 and V3, we will additionally consider modeling change in weight from V1 to V3

Limitations:

- There is the likelihood for some residual confounding in our efforts to assess the "independent" association between physical activity and hs-cTnT levels
- There is the likelihood of some bias in the self-reporting of physical activity levels.
- We do not have concurrent physical activity and hs-cTnT data, and some participants may have had changes in activity levels from V1 to V2 that increase the likelihood of misclassification in assessing the relationship between physical activity and myocardial injury.

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)?

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 press at JACC: Heart Failure*

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 Apr 5;123(13):1367-76.

Agarwal SK, Avery CL, Ballantyne CM, Catellier D, Nambi V, Saunders J, Sharrett AR, Coresh J, Heiss G, Hoogeveen RC. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study. Clin Chem. 2011 Jun;57(6):891-7. doi: 10.1373/clinchem.2010.159350. Epub 2011 Apr 25. PMID: 21519038

Manuscript #2029: Obesity, physical activity and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

Manuscript #511 Physical activity and arterial stiffness

Manuscript #321: Physical Activity Patterns and the Risk of Stroke and All-Cause Mortality

Manuscript #1715: Physical activity and incidence of cardiovascular disease in African Americans

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* 2009.16 and 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.

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