ARIC Manuscript Proposal # 3122

PC Reviewed: 2/13/18  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Sex Differences in The Interrelationship Among Obesity, Diabetes and Subclinical Myocardial Damage: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Sex, Obesity, DM & hs-cTnT

2. Writing Group: Rachit M. Vakil; Lucia Kwak; Roberta Florido; John W. McEvoy; Vijay Nambi; Erin D. Michos; Rita Kalyani; Roger S. Blumenthal; Christie M. Ballantyne; Josef Coresh; Elizabeth Selvin; Chiadi E. Ndumele; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___RV___ [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 major public health challenge, which threatens to impede gains in cardiovascular risk reduction achieved over the last several decades.\(^1\) Obesity (defined as body-mass index $\geq 30$ kg/m\(^2\)) is often complicated by diabetes, a condition associated with additional cardiovascular disease risk.\(^2-3\) However, many individuals with obesity do not develop diabetes, and a substantial number of diabetes cases occur among individuals with normal weight (BMI 18.5-25 kg/m\(^2\)) and overweight (BMI 25-30 kg/m\(^2\)).\(^4,5\) Both obesity and diabetes are potent independent risk factors for incident heart failure (HF).\(^6-10\) While the pathogenesis underlying these risk associations is not entirely clear, prior studies have demonstrated independent associations of both obesity\(^11\) and diabetes\(^12\) with subclinical myocardial damage as reflected by high sensitivity cardiac troponin-T (hs-cTnT), with hs-cTnT in turn being associated with markedly increased future HF risk. Because obesity and diabetes frequently co-exist in many individuals, it is important to understand not only their independent risk associations, but also the combined effects of these factors on myocardial damage and HF risk.

Prior studies suggest sex differences in the relationship between obesity and diabetes as well as in their combined associations with myocardial abnormalities. At a given level of excess weight, men are more likely to develop diabetes, and to do so at a younger age than women.\(^13\) Some studies suggest a predilection towards ventricular dilatation in men with diabetes, compared to a predominance of concentric hypertrophy among women with diabetes.\(^14,15\) A recent study further demonstrated a positive association between BMI and HF risk among men with diabetes, but a J-shaped association between BMI and HF risk among women with diabetes.\(^16\)

There is a need for further understanding of the joint effects of obesity and diabetes on HF risk, and an elucidation of any sex differences in these associations. Further insights may be gleaned by examining the combined associations of obesity and diabetes with rates of subclinical myocardial damage. Prior studies have also demonstrated gender differences in hs-cTnT levels.\(^17\) We propose to assess sex differences in the inter-relationship among obesity, diabetes and hs-cTnT among participants in the Atherosclerosis Risk in Communities (ARIC) Study. With extensive demographic and risk factor characterization, including thorough assessments of obesity and diabetes status, as well as existing hs-cTnT measurements, ARIC is an ideal setting for examining this question.

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

**Aims:**

1) To assess whether there are sex differences in the association between obesity and diabetes.

2) To assess whether there are sex differences in the combined associations of diabetes and obesity with hs-cTnT.
3) To assess the association between hs-cTnT and incident heart failure risk within cross-categories of diabetes and obesity status, and to assess for differences by sex.

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:** This study will have cross-sectional and prospective components. In the cross-sectional component, we will evaluate the associations of obesity with diabetes, and the combined associations of obesity and diabetes with hs-cTnT levels, with assessments for interactions by sex for each of these risk associations. In the prospective component, we will assess the associations of hs-cTnT levels with incident heart failure within cross-categories of obesity and diabetes status. Data from ARIC Visit 2 (1990-1992) will be used for cross-sectional analyses, and Visit 2 will also be the baseline for the prospective analyses.

**Exposures:** For cross-sectional analyses, the principal exposures will be body-mass index (BMI) and diabetes status, both assessed at Visit 2. BMI will be modeled continuously (e.g., per 5 kg/m² higher BMI), as BMI categories (normal weight [18.5-25 kg/m²], overweight [25-30 kg/m²], obese [30-35 kg/m²], and severely obese [>35 kg/m²]) and dichotomized (obese vs non-obese). Diabetes will be defined as present vs absent (using criteria of fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, self-reported physician diagnosis or taking diabetes medication) and categories of diabetes severity will be created based on prior diagnosis of diabetes and hemoglobin A1c level (A1c < 5.7, 5.7-6.4 or ≥6.5 with or without a prior diagnosis of diabetes). Self-reported sex will be evaluated as an effect modifier.

**Outcomes:** The primary outcomes for the cross-sectional analyses will be measurable hs-cTnT (>3 ng/L, the detection threshold for the assay) and “elevated” hs-cTnT (>14 ng/L, the 90th percentile of hs-cTnT in the ARIC cohort and a cut-point used in several prior analyses), measured at Visit 2. The primary outcomes for the prospective analyses will be incident HF occurring after Visit 2 through December 31, 2014 (or most current follow-up available).

**Exclusions:** Given the focus on subclinical myocardial damage, we will exclude participants with known HF or CHD prior to Visit 2 (self-reported HF or CHD at Visit 1 or HF events or adjudicated CHD events or silent MI at or prior to Visit 4). We will also exclude participants with BMI < 18.5 kg/m², those missing covariates of interest at baseline and the small number of participants not of black or white race.

**Covariates:** Age, sex, race, smoking status, alcohol use, systolic blood pressure, anti-HTN medication use, LDL-cholesterol, HDL-cholesterol, triglycerides, estimated GFR and NT-proBNP (all measured at Visit 2).
Main Analyses:

1) We will compare participant characteristics between those with and without obesity, with stratification by sex. We will also compare participant characteristics between those with and without prevalent diabetes, with stratification by sex. Continuous variables will be compared using t-tests and categorical variables using the chi-squared test.

2) All regression models will be adjusted for the covariates listed above.

3) We will construct multivariate logistic regression models to assess the association between higher BMI and diabetes (using prevalent obesity and then BMI categories), with tests for a statistical interaction with sex.

4) We will assess the proportions of individuals with measurable and elevated hs-cTnT within cross-categories of obesity and diabetes status, with stratification by sex.

5) We will perform logistic regression analyses examining the joint association of prevalent obesity and prevalent diabetes with measurable and elevated hs-cTnT. We will test for interactions between obesity and diabetes prevalence on hs-cTnT levels in analyses stratified by sex. Given the high prevalence of measureable hs-cTnT, in sensitivity analyses, we will perform additional analyses using relative risk regression to estimate prevalence ratios rather than odds ratios for the outcome of measureable hs-cTnT.

6) We will perform logistic regression analyses examining cross-tabulations of BMI categories (normal weight, overweight, obese and severely obese) and diabetes categories (no diabetes, prediabetes, diabetes) on the outcomes of measurable and elevated hs-cTnT. We will test for interactions between obesity and diabetes categories on hs-cTnT levels in analyses stratified by sex.

7) We will assess the continuous association of higher BMI (per 5 units higher and in cubic spline models) with measurable and elevated hs-cTnT among those with and without diabetes, in analyses stratified by sex. We will also assess the continuous association of higher hemoglobin A1c (per 1 unit higher and in cubic spline models) with measurable and elevated hs-cTnT among those with and without obesity, in analyses stratified by sex.

8) We will assess the association of elevated hs-cTnT with incident HF risk in cross-categories of prevalent obesity and diabetes, with tests for interaction by sex.

Secondary Analyses:

- We will perform secondary analyses using waist circumference and waist-to-hip ratio (categorized into quartiles) as alternative measures of adiposity.

Limitations:

- There is the likelihood for some residual confounding in our efforts to assess the above risk associations
- Some survival bias will be introduced by only including Visit 2 participants without CHD or HF by that time point
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)?


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.