ARIC Manuscript Proposal #2738

PC Reviewed: 4/12/16  Status: A  Priority: 2
SC Reviewed: ________  Status: _____  Priority: ____

1.a. Full Title:
Metabolically healthy obesity, cumulative exposure to obesity, and progression to incident metabolic syndrome: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Is MHO a transient state?

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MMC__ [please confirm with your initials electronically or in writing]

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3. **Timeline:** Analysis to begin immediately. The authors expect to submit an abstract based on this work to the American Heart Association Cardiovascular Epidemiology/Lifestyle Conference in October 2016, with manuscript submission to follow shortly.

4. **Rationale:**

   Increasing interest in discriminating between different levels of cardiometabolic risk has led to the concept of metabolically healthy obesity. While more and more research is conducted on this group, it remains unclear how to differentiate metabolically health obese from those who suffer from the comorbidities traditionally associated with obesity. While several studies have sought to determine whether metabolically healthy obese are really at lower risk for cardiovascular disease and mortality compared to other obese subgroups,\(^1\)\(^{-3}\) the question of whether this group is really “healthy” is increasingly pressing. The literature suggests that those with metabolically healthy obesity have intermediate levels of metabolic factors,\(^4\) and that metabolically healthy overweight is a risk for cardiovascular disease when follow up is longer than 15 years.\(^4\) Several studies have also indicated that the prevalence of metabolically healthy obesity declines with age.\(^4\)\(^{-6}\) To our knowledge, only one study provides evidence that metabolically healthy obesity is a temporally intermediate stage on the pathway to cardiometabolic disease,\(^4\) and only one study reports inconsistent results for the relationship of obesity severity and duration with cardiovascular risk in metabolically healthy obesity.\(^7\)

   Studies on the health risks of the duration of obesity indicate that increased exposure to obesity leads to increased cardiometabolic risks.\(^8\)\(^{-12}\) While these studies have investigated the health risks of the duration of obesity, almost none have discriminated between the risks from obesity duration and severity. This is particularly of interest with regards to metabolically healthy obesity, because severity may often act as a proxy for duration if few people go from normal weight to overweight to level III obesity in a short amount of time. The length and extent of this progression may have important implications for the metabolic health of individuals at different stages along this pathway to obesity and cardiometabolic dysfunction. The combination of obesity severity and duration forms a more comprehensive measurement of the cumulative exposure to obesity. Within this framework, we hypothesize that metabolically healthy obese will have a lower cumulative exposure to obesity (ie: either low severity and/or low duration of obesity) compared to those with both obesity and metabolic syndrome or its components. If true, this hypothesis will help explain why metabolically healthy obese are at intermediate risk for cardiometabolic outcomes between normal weight individuals and individuals in other obesity subgroups. This lower risk compared to regular obesity may only be temporary as metabolically healthy obese progress to worsening cardiometabolic function through additional exposure to obesity duration and severity.

   With anthropometry, metabolic syndrome, and cardiovascular risk factor measurements at every visit, the ARIC study provides an ideal cohort to investigate the temporal progression of obesity and cardiometabolic profile.

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

   To determine whether cumulative exposure to obesity explains the variation in cardiometabolic health known as metabolically healthy obesity.
**Hypothesis:** Longer duration of obesity combined with higher severity of obesity will be strongly associated with prevalent and incident metabolic syndrome and metabolic syndrome components in obesity. Intermittent obesity will be associated with intermediate risk for incident metabolic syndrome.

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).

We will include all ARIC participants with at least one visit documenting the presence of obesity (BMI>30 kg/m²).

**Exposure:** Cumulative exposure to obesity as the combination of obesity severity and duration, defined by BMI at each visit

- **Obesity duration:** We will define obesity duration as the cumulative time since visit of first measured obesity (BMI>30).
- **Obesity severity:** We will define obesity severity both continuously using BMI and categorically using the WHO BMI cut-points (Level I 30.0-34.9, Level II 35.0-39.9, and Level III 40.0+).

**Outcome:**

**Primary outcome:** Incident metabolic syndrome without waist circumference, defined as two or more of the following Adult Treatment Panel III criteria:
- Triglyceride level ≥150mg/dL
- HDL cholesterol <40mg/dL in men and <50mg/dL in women
- Systolic blood pressure ≥130mmHG or diastolic blood pressure ≥85mmHG or blood pressure medications
- Fasting glucose ≥110mg/dL or diagnosis of diabetes

**Secondary outcomes:** Prevalent metabolic syndrome. Incident dichotomous individual metabolic syndrome components including hypertension, low HDL, high triglycerides, and type 2 diabetes. Traditionally defined metabolic syndrome.

**Other Covariates:** Demographic factors such as sex, race/ethnicity, socioeconomic status, and age. Smoking and exercise. Medical conditions such as cancer, thyroid conditions, kidney disease, or other chronic disease. Medication use such as thiazolidinediones and hormone replacement therapy.

**Exclusions:** Participants with no measured obesity during ARIC follow up.

- **For primary outcome:** Metabolic syndrome at baseline.
- **For other outcomes:** Metabolic syndrome components of interest at baseline.

**Analysis plan:**

The main goal of this paper is to investigate the association between the cumulative exposure to obesity with cardiometabolic profile in order to better understand metabolically healthy obesity. We will describe the prevalence of metabolic syndrome in ARIC by categories of combined obesity severity and duration. We will
We will use repeated measures logistic regression (xtlogit in Stata) with time varying exposure to estimate the association of cumulative exposure to obesity with prevalent and incident metabolic syndrome, separately. Using a random effects model, we will assess whether there is significant individual heterogeneity in metabolic syndrome. We will run this analysis separately for each of the metabolic syndrome components as well. We will assess the association of obesity severity and duration separately and in concert and will test for an interaction between obesity duration and severity. We will also adjust for confounding by demographic and socioeconomic factors and will formally test for effect modification by sex, race/ethnicity, and age. If significant interaction is found, separate estimates will be reported. We will also test to see if intermittent obesity is associated with worse metabolic health profile in addition to continuous obesity duration. We will investigate these relationships with BMI as a continuous variable in addition to using the WHO categories.

Since there is not currently a standard definition of metabolic syndrome, we will determine whether these results are sensitive to using the traditional definition of metabolic syndrome that includes waist circumference. We will determine whether our results are robust to potential misclassification of obesity duration in two ways: 1. We will restrict the analysis to those with incident obesity and 2. We will conduct subgroup analysis to compare those with obesity at age 25 determined from self-reported weight at age 25 and those without obesity at age 25. We will conduct additional sensitivity analyses to determine whether results differ for subgroups with diagnosed comorbidities at baseline such as cancer, thyroid conditions, and kidney disease, or medication use such as thiazolidinediones or hormone replacement therapy.

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 ICTDER 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)?

The most related ARIC proposals are #1680, #2035, and #2404. #1680 assessed the prevalence of metabolically healthy obesity at baseline and investigated some of the socioeconomic and lifestyle determinants of metabolic syndrome in this group. #2035 determined the association between weight loss within BMI categories and cardiovascular risk factors for those with metabolically healthy obesity. #2404 focuses exclusively on those free from any component of the metabolic syndrome to determine whether BMI category is associated with metabolic syndrome components.

Our proposal explores obesity duration in addition to obesity severity to investigate how cumulative obesity exposure is associated with incident metabolic syndrome among those with metabolically healthy obesity. We will use a repeated measures model to include all ARIC participants with metabolically healthy obesity at any visit in order to make use of as much ARIC data as possible. Patrick Bradshaw, the first author on the two most related proposals (1680 and 2404) has agreed to participate in this new project and has approved the current proposal.

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.cscc.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ___X__ No.