ARIC Manuscript Proposal #2228

PC Reviewed: 9/10/13 **Status: A** **Priority: 2**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1a. Full Title: The relationship between cardiac structure and function and obesity assessed by body composition contrasted with anthropomorphic measures

b. Abbreviated Title (Length 26 characters): **Obesity and echo**

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

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3. Timeline:
Analysis will begin immediately following proposal approval and availability of the visit 5 data, with the aim of completing analyses and submitting an abstract to the AHA EPI/NPAM meeting (October 14 deadline). The subsequent aim will be to complete a manuscript within 6 months of full data availability.

4. Rationale:

The prevalence of overweight and obesity has grown over the past several decades; according to data from NHANES 2007-2010, 68% of US adults have a body mass index (BMI) that falls into the range of overweight or obese.[1] Along with the nationwide rise in BMI, there have been concomitant increases in the traditional cardiovascular risk factors of hypertension, dyslipidemia, and type 2 diabetes mellitus which together threaten to erase the gains in life-years made as a result of smoking cessation efforts.[1] Although the mechanisms remain to be elucidated, a growing body of evidence demonstrates many detrimental effects of obesity on hemodynamics and cardiac structure and function, including increased blood volume and wall stress, as well as adverse remodeling.[2] While obesity has been associated with increases in all-cause mortality,[1] there also exists an obesity paradox whereby obese individuals have better outcomes in congestive heart failure (CHF), peripheral vascular disease (PVD), and coronary artery disease (CAD) compared to those with a normal BMI.[3-6] However, a major criticism of the obesity paradox is that BMI is an inadequate estimate of body composition and may not accurately identify obese persons compared to a more objective measure such as fat-free mass.[7]

While most studies of the effects of obesity on cardiovascular outcomes used the anthropomorphic measures of BMI or waist circumference, newer techniques to evaluate body composition and determine fat mass versus lean body mass may help to elucidate the relationship between excess body fat and abnormalities of cardiac structure and function. Therefore, we propose to analyze variations in body composition and traditional anthropomorphic measures by sex and age in relation to cardiac structure and function in the elderly, biracial ARIC cohort.

5. Main Hypothesis/Study Questions:

We hypothesize that abnormalities in the components of body composition, including percent body fat, lean mass index (LMI), fat mass index (FMI), as well as the anthropomorphic measurements of body mass index (BMI), waist circumference, and waist to hip ratio are related to abnormalities of cardiac structure including increased left ventricular mass and remodeling, as well as decreased systolic and diastolic function assessed by conventional and novel echo techniques. We further hypothesize that age, gender, race/ethnicity, blood pressure, and diabetes mellitus modify these relationships. Thus, our specific study aims are:

1. To examine the cross-sectional relationships between traditional anthropomorphic measurements and body composition components with variations in cardiac structure and function.
2. To examine the cross-sectional correlates of body composition and anthropomorphic measurements, including associations with socio-demographic and clinical characteristics.

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 and Inclusion/Exclusion Criteria*:*

This will be a cross-sectional study of ARIC cohort participants who underwent echocardiography during Visit 5 (2011-2013). The study sample will include all participants who were free from cardiovascular disease at the time of the examination, underwent anthropometry, and had echocardiographic images of acceptable quality for analysis. Those with missing body composition, anthropometry values, or data regarding risk factors for CVD will also be excluded.

Exposure variables:

1. Body Composition: Percent body fat, lean mass index [lean mass (in kilograms) divided by height (in meters) squared], and fat mass index [fat mass (in kilograms) divided by height (in meters) squared] will be analyzed as continuous variables using restricted cubic splines, and in quartiles. Additionally, body fat percentage will be assessed as a binary variable for obese or not according to the established cut-offs of 25% (men) and 35% (women).[8-10]
2. Anthropomorphic Measurements:
   a. Body-mass index [defined as body weight (in kilograms) divided by height (in meters) squared] will be categorized into five predefined categories as follows: underweight (BMI≤18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obese (BMI 30-39.9 kg/m^2), and extremely obese (BMI

$\geq$40 kg/m^2). BMI will also be assessed in a continuous association using restricted cubic splines.

b. Waist circumference and waist to hip ratio will be assessed as continuous variables using restricted cubic splines. Abdominal obesity will also be categorized as a binary variable (waist circumference >102 cm in men or >88 cm in women).

Outcome variables:

The primary analysis will be to assess the impact of variations in body composition and anthropomorphic measures on the following parameters of cardiac structure and function:

1. Left ventricular (LV) dimensions, volumes, and ejection fraction
2. Global LV systolic strain (longitudinal, circumferential, radial)
3. LV diastolic function
4. Left atrial size
5. Right ventricular dimensions, volumes, and ejection fraction

Covariates of Interest:

Clinical characteristics, lab values, and echocardiographic cardiac structure and function will be compared between groups. Variables of particular interest include: age, sex, field site, CVD risk factors such as hypertension, dyslipidemia, diabetes mellitus and dysglycemia, COPD and asthma, alcohol use, smoking status, physical activity levels, heart rate, blood pressure indices, height, weight, body surface area, fasting glucose, HbA1c, lipids, BNP, hsTnT, CRP, and pulmonary function tests. Echocardiographic variables to be evaluated include those related to cardiac structure: left and right ventricular size, LV wall thickness, LV mass, LV geometry, left atrial size and volumes, aortic root dimension, valvular disease, and regional wall motion abnormalities. Parameters of cardiac function, including LV ejection fraction, right ventricular fractional area change, Doppler mitral inflow E and A wave peak velocities, E/A ratio, deceleration time, tissue Doppler systolic and diastolic indices at both the mitral and tricuspid annulus, as well as LV myocardial mechanics from speckle tracking imaging will be assessed. Noninvasive hemodynamic parameters including stroke volume, cardiac output, LV filling pressures, pulmonary vascular resistance, and pulmonary artery pressures will also be analyzed.

Statistical Analysis:

Descriptive statistics of the study sample will be presented overall and by weight category as well as by quantiles of BMI, waist circumference, percent body fat, and fat mass index. Unadjusted mean body weight, fat%, lean body mass, fat mass, BMI, waist circumference, and waist to hip ratio values will be stratified by sex and graphically displayed as a function of age (age quantiles will be determined based on the size of the study sample and relevant subgroups). Continuous normally distributed data will be displayed as mean and standard deviation values; continuous non-normally distributed data will be displayed as median and interquartile range values. Categorical data will be reported as percent frequencies. Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared between groups via Wilcoxon rank sum test or nonparametric trend tests as appropriate.

Univariable and multivariable linear regression analysis will be used to examine the cross-sectional associations of each body composition/ body mass component and echocardiographic characteristics at visit 5. Adjustments for age and sex as well as key socio-demographic and clinical characteristics will be performed. For significant correlates, we will test for effect modification by age, sex, and race/ethnicity. A two-sided p-value of <0.05 will be considered statistically significant.

Limitations:

A limitation of this study is the cross-sectional design, which precludes the ability make any inferences regarding causality. Another limitation is the use of impedance measurement, rather than dual-energy X-ray absorptiometry (DXA) or hydrodensitometry to determine body composition. Impedance is known to underestimate body fat, however there are validated formulas to estimate body fat appropriately from bioimpedance.[11]

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

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)?

MS # 1589 Ethnic differences in body composition given the same body mass index level
MS # 2025 Obesity and Subclinical Myocardial Injury: the Atherosclerosis Risk in Communities (ARIC) Study

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

___ 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.

References:

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