ARIC Manuscript Proposal # 3101

1.a. Full Title: Body composition and incidence of components of the Metabolic Syndrome.

b. Abbreviated Title (Length 26 characters): Adiposity and MetSyn

2. Writing Group:
   Patrick T. Bradshaw, Ph.D.
   June Stevens, Ph.D.
   Jianwen Cai, Ph.D.
   Salim Virani, M.B.B.S., Ph.D.
   Other interested parties

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

First author:
Address: Patrick T. Bradshaw, Ph.D.
   School of Public Health
   Division of Epidemiology and Biostatistics
   University of California, Berkeley
   Berkeley, CA 94720

Phone: 510/664-7299       Fax: 510/643-5163
E-mail: pbradshaw@berkeley.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
   Name: June Stevens, Ph.D
   Address: University of North Carolina
   Department of Nutrition, CB #7461
   Chapel Hill, North Carolina 27599-7461

Phone: 919/966-7348       Fax: 919/966-7215
E-mail: june_stevens@unc.edu

3. Timeline: This work is a component of an R01 grant proposal that will be submitted in February of 2018. Dataset preparation and analysis will start immediately upon funding. If the R01 is not funded, we will seek other support for this work. We plan to complete the analysis and manuscript before the manuscript approval period expires.
4. **Rationale:**

Body mass index (BMI) is the most common marker of excess adiposity, however its inability to differentiate fat from lean mass creates ambiguity that has likely contributed to several apparently contradictory observations in the epidemiology literature, including the “obesity paradox”\(^1,2\) and the so-called “metabolically healthy obese”\(^3,4\) (MHO) phenotype. Importantly, adiposity and lean mass at a given BMI vary considerably, and these differences are pronounced with regard to race, with African-Americans possessing, on average, less fat mass and more lean mass compared to whites.\(^5\) Thus, given adiposity’s influence on disease etiology, using more specific markers of body composition instead of BMI may more accurately identify individuals at high risk of morbidity and mortality.

The metabolically healthy obese (MHO) phenotype refers to the observation that a sizable proportion of those with obesity possess cardiometabolic risk factors within normal ranges (blood pressure, triglycerides, HDL-cholesterol, fasting glucose, insulin sensitivity, and inflammation). Conversely, the metabolically unhealthy normal weight (MUN) refers to individuals at a healthy weight yet possess a cluster of cardiometabolic abnormalities more commonly seen among those who are overweight or obese. The MHO have been found to account for nearly 1/3 of U.S. adults with obesity and the MUN nearly 1/4 of those of normal weight.\(^6\) The existence of the MHO may imply that the factors believed to mediate the relationship between obesity and chronic disease risk may not follow from excess adiposity in some individuals. Additional support for the validity of this concept comes from the observation that the MHO appear to have risk of chronic disease that is intermediate between the healthy normal weight and unhealthy obese.\(^7,8\) However, previous work,\(^9,13\) including that by the authors here,\(^9,13\) has shown that the MHO are unlikely to remain “healthy.” These findings have precipitated a heated debate regarding the clinical and public health utility of this concept.\(^3,4\) Issues around the definition of the MHO have revolved around the lack of a consensus definition of metabolic health,\(^14\) but others have noted that the prevalence varies substantially if obesity is defined by BMI vs. percent body fat.\(^15,16\) One study noted that a MHO prevalence of 34.0% using a BMI-based obesity definition compared to 47.7% using percent body fat to define obesity.\(^15\) Differences in body composition are thought to drive metabolic health\(^17\) and thus a body fat-based classification may provide a more accurate definition of these obesity subtypes. To the best of our knowledge, there is little extant work considering the role of body composition on incidence of metabolic dysfunction among the MHO, and none in a prospectively followed, racially diverse sample such as ARIC.

Gold standards of body composition, such as dual-emission X-ray absorptiometry (DEXA), are logistically cumbersome and prohibitively expensive in large studies. A more feasible approach is to estimate body fat and lean tissue using prediction equations that include demographic and anthropometric variables. Recently, we developed a set of such equations that include complex mathematical forms and interactions to produce results that explain a high percentage of variance, have low bias across sex, race, and BMI categories, and are generalizable to the United States population.\(^18\) These equations have been validated in both internal and external data, but have yet to be used to examine associations between body composition and health risks.

Our proposed study will be the first to include a large, racially diverse sample of adult men and women with comprehensive risk factor assessment, including anthropometric measurements that can be used to estimate body composition, and repeatedly measured cardiometabolic outcomes.
5. Main Hypothesis/Study Questions:

The aim of the current study is to: determine and compare the relationship between body composition and development of cardiometabolic risk factors.

**Hypothesis 1:** Greater body fat will be positively associated, and greater lean mass will be inversely associated with risk of cardiometabolic abnormalities.

**Hypothesis 2:** The size of these associations will differ between African-American and White men and women.

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:** The study aim will be addressed in a prospective cohort design and will employ all data from the four ARIC visits among those who are metabolically healthy (free from all components of metabolic syndrome except waist circumference: (1) elevated triglycerides: \(\geq 150\) mg/dL; (2) low HDL cholesterol, men: \(<40\) mg/dL, women: \(<50\) mg/dL; (3) elevated blood pressure: \(\geq 130/\geq 85\) mm Hg; (4) elevated fasting glucose: \(\geq 110\) mg/dL) at the baseline visit.

**Inclusion/Exclusion Criteria:** Our primary exclusion criteria will be presence of any component of the metabolic syndrome (elevated triglycerides, low HDL cholesterol, elevated blood pressure or elevated fasting glucose as defined by National Cholesterol Program’s Adult Treatment Panel III (ATP III) guidelines\(^{19}\)) at visit 1. We will additionally exclude those subjects with missing covariates. If, upon undertaking the analysis, the proportion of missing data for these or other variables is concerning, then missing data methods, such as multiple imputation, will be employed.

**Outcome variables:** We will consider 4 outcomes separately: incident events for each of the components of the metabolic syndrome (as defined by National Cholesterol Program’s Adult Treatment Panel III (ATP III) guidelines [13]): (1) elevated triglycerides: \(\geq 150\) mg/dL; (2) low HDL cholesterol, men: \(<40\) mg/dL, women: \(<50\) mg/dL; (3) elevated blood pressure: \(\geq 130/\geq 85\) mm Hg; (4) elevated fasting glucose: \(\geq 110\) mg/dL) among those that are free of all metabolic abnormalities excluding abdominal obesity (men: \(>40\) in, women: \(>35\) in).

**Exposure.** The exposures in all analyses will be measures of body composition: fat mass index (FMI, kg of fat mass/height in cm\(^2\), and fat-free mass index (FFMI, kg of lean mass/height in cm\(^2\)); the sum of these measures equals BMI.\(^{20}\) We will calculate these measures using the body fat prediction equations recently developed by Stevens et al.\(^{18}\) These equations were generated using NHANES data to provide accurate race- and sex-specific estimates of percent body fat (% BF) assessed by dual-emission X-ray absorptiometry (DEXA) in U.S. adults and youth. The variables used in these equations were specifically selected to include those commonly collected in studies such as ARIC in order to facilitate future applications such as the analyses proposed herein.

Stevens et al. present results for 14 equations per gender\(^{18}\) (denoted by letters A-N) using different subsets of predictor variables with individual terms involving possible interactions or nonlinear transformations (e.g. the variable squared). The authors recommend the use of models A-M for research purposes based on their assessment of each model’s accuracy. The data
available at the 4 ARIC visits will allow estimation of % BF across all visits by equation L (requiring age, sex, race, height, weight, BMI, and waist circumference). Fat mass (FM) and fat-free mass (FFM) will be calculated by:

\[ FM = \% \text{BF} \times \text{measured total body weight in kg} = \text{kg fat mass, and} \]

\[ FFM = (1-\% \text{BF}) \times \text{measured total body weight in kg} = \text{kg lean mass} \]

with % BF estimated from equation L. Preliminary work using data from NHANES has shown that measures of concordance between these transformed measures of percent body fat and DEXA-based measurements is high, with R-squared >0.92 and RMSE <2.9 kg for some of these equations (unpublished data). These measures will then be used to estimate FMI and FFMI from:

\[ \text{FMI} = \frac{\text{FM}}{\text{height}^2} = \text{kg fat mass/height}^2, \text{and} \]

\[ \text{FFMI} = \frac{\text{FFM}}{\text{height}^2} = \text{kg lean mass/height}^2. \]

Because there are no established cutpoints for high FMI/low FFMI, for the analyses proposed here, FMI and FFMI will be treated continuously and dose-response relationships will be estimated. We will also consider categorizing these measures using cutpoints from previously published work in other outcomes.²¹

**Covariates:** Covariates to be included as potential confounders or effect modifiers include: age, sex, race-ethnicity, education level, menopausal status, hormone use, smoking status, alcohol use, leisure time physical activity, macronutrient distribution (percentage of total caloric intake by carbohydrate, fat and protein), total caloric intake, fiber intake, glycemic index and glycemic load, and family history of diabetes or cardiovascular disease. Values for variables measured less frequently than every visit (e.g. diet) will be averaged between visits (e.g. diet at visit 2 will reflect the mean from visit 1 and visit 3, while diet at visit 4 will be carried forward from visit 3).

**Statistical Analysis.**

All statistical analyses, including graphical representations of data, will be conducted using the R statistical software package²² with proportional hazards models fit using the survival²³ package. After data quality checks, descriptive statistics for the covariates, and nonparametric description of times to event will be presented using cumulative incidence curves.

Hazard ratios (HR) and 95% confidence intervals (CI) for the association of body composition with incidence of each metabolic outcome will be estimated using a Weibull model for interval-censored time-to-event data.²⁴ A minimal set of confounders of the body composition-metabolic outcome relationships will be identified using a directed acyclic graph (DAG).²⁵ Interval censored methods are appropriate because the outcomes for this analysis were assessed according to the ARIC visit schedule and thus the specific dates of onset are unknown and the length of the intervals between visits varies across individuals. For each of the four cardiometabolic outcomes (elevated triglycerides, low HDL cholesterol, high blood pressure, elevated glucose) and for the outcome of any one or more of the above, a dataset of multiple records per subject will be created (one observation per subject per ARIC visit, with a minimum of 1 and a maximum of 3 observations per subject) with a binary variable indicating if the outcome had occurred within the corresponding interval or not. Subjects will be right censored if they did not achieve the outcome by their last observed follow-up. For analyses of each individual metabolic factors, subjects will also be censored if they developed any of the other risk factors before the one under consideration as this would violate our definition of metabolically healthy for subsequent outcomes. The primary exposures, percent body fat and percent lean mass at the beginning of each interval, will be treated as time-varying covariates.
because their values are allowed to change at each follow-up visit. To assess the trend with respect to continuous body composition variables will use splines, comparing nested models using the likelihood ratio test.\(^6\)

To assess heterogeneity by race we will included product terms for body composition and race group (black, white) and report race-specific HRs. Models with the multiplicative interaction will be compared to models without the corresponding interaction terms using the likelihood ratio test with a significance level of 5%.

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](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)?

Because we are using novel measures of body composition that have not been considered previously, there is no significant overlap between this proposal and other ARIC manuscript proposals. The closest ones are:

**#2738: Metabolically healthy obesity, cumulative exposure to obesity, and progression to incident metabolic syndrome: The Atherosclerosis Risk in Communities Study.**

This study will examine whether cumulative exposure to obesity (based on BMI) explains the variation in cardiometabolic health. Our analysis considers measures of body composition instead of BMI.

**#2404: Obesity and incidence of components of the Metabolic Syndrome among healthy individuals**
This study (led by Drs. Bradshaw and Stevens) examined incidence of individual cardiometabolic abnormalities in relation to BMI category among those free from all components of metabolic syndrome (excluding waist circumference) at visit 1. The proposed manuscript will examine these relationships considering body composition (fat and muscle indices) instead of BMI, and will provide new insight into the relationship of specific aspects of body composition and metabolic outcomes.

# 1680: Longitudinal patterns and determinants of metabolic subtypes of obese, overweight and normal weight individuals

The aims of this study were to investigate the proportion of participants that were metabolically healthy (absence of a diagnosis of metabolic syndrome: 2 or fewer risk factors) normal weight, overweight, and obese at baseline that developed the composite diagnosis of metabolic syndrome during the study follow-up period. Our study will examine the incident of individual components in relation to body composition.

# 1085: Black/white differences in the relationship of the MetSyn components to insulin resistance

The purpose of this study (led by Drs. Bradshaw and Stevens) was to investigate the racial differences in the prevalence of metabolic abnormalities that are associated with the development of insulin resistance. Our study will also look at racial difference in the ARIC population but it will investigate the differences in the incidence of each metabolic abnormality according to body composition.

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.cscn.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.  

Noted.

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.cscn.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.  

Noted.
Bibliography