ARIC Manuscript Proposal # 3102

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

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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]

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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” and the so-called “metabolically healthy obese” 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. Thus, given adiposity’s influence on disease etiology, using more specific markers of adiposity instead of BMI may more accurately identify individuals at high risk of morbidity and mortality.

Some researchers have considered measures of body composition in relation to mortality, but these have been in small, older, and racially homogeneous samples. Authors of a study in 921 Swedish adults ≥ 65 years of age who were being evaluated for osteoporosis reported an inverse association between mortality and lean mass in men and women, and a U-shaped association between fat mass and mortality among men. Using data from the Women’s Health Initiative, Bea and colleagues observed that total body fat was positively, and lean body mass negatively associated with mortality among postmenopausal women 50-59 years of age, but not among older women. Notably, the authors report a wide range of BMI values within quantiles of body fat, underscoring the limitations of BMI to uniformly reflect specific aspects of body composition. However, this study was limited to postmenopausal women, and the authors noted that they were underpowered to examine racial heterogeneity. The largest study to date, by Calling and colleagues, included 26,942 subjects from the Swedish Malmö Diet and Cancer Study. These authors reported an increasing rate of CVD-related death with greater percent body fat, but did not consider all-cause mortality.

Studies of adiposity and incident CVD and CHD outcomes have been similarly limited. In the Malmö Diet and Cancer Study, Calling et al observed that body fat was related to increased rate of coronary events in both men and women, with the association more pronounced among the former. An analysis in the Framingham Heart Study reported an increase in the risk of cardiovascular disease with greater levels of visceral adipose tissue.

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. 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 factors repeatedly assessed, including anthropometric measurements that can be used to estimate body composition, as well as the outcomes of overall mortality and cardiovascular disease outcomes.

5. **Main Hypothesis/Study Questions:**
We propose to use estimates of body composition (fat mass index and fat-free mass index) using recently developed equations to examine the relationship between body composition and mortality and incident CVD among participants of the Atherosclerosis Risk in Communities (ARIC) study. Overall and race-specific associations between body fat and mortality and incident CVD will be estimated and formally compared. The Aims of the proposed study are:

**Aim 1:** Determine and compare the relationship between body composition (percent body fat and percent lean mass) and all-cause mortality among African-American and white men and women.

- **Hypothesis 1.1:** Greater body fat will be associated with increased risk of death, while greater lean mass will be associated with decreased risk of death.
- **Hypothesis 1.2:** The size of these associations will differ between African-American and White men and women.

**Aim 2:** Determine and compare the relationship between body composition and CHD and CVD among African-American and white men and women.

- **Hypothesis 2.1:** Greater body fat will be associated with increased risk of heart disease, and greater lean body mass will be associated with decreased risk of heart disease.
- **Hypothesis 2.2:** 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**

Aims 1 and 2 will be addressed in a prospective cohort study design and will employ data from the four ARIC visits, along with mortality and CVD event data.

**Inclusion/Exclusion Criteria:** Our primary exclusion criteria for Aim 2 will be prevalent CHD or stroke at visit 1. For all Aims 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.

**Outcomes.** Outcomes for these analyses will include overall mortality (Aim 1) and CVD and fatal or nonfatal CHD events, or ischemic stroke (Aim 2) through the end of the most recently available follow-up period. Time under observation for the survival analyses will be time from study enrollment to time of event or censoring.

**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. We will calculate these measures using the body fat prediction equations recently developed by Stevens et al. These equations were generated using NHANES data to provide accurate race- and sex-specific estimates of percent body fat 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:

- \(\text{FM} = \% \text{BF} \times \text{measured total body weight in kg} = \text{kg fat mass, and}\\
- \(\text{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} = \text{FM/height}^2 = \text{kg fat mass/height}^2, \text{and}\\
- \(\text{FFMI} = \text{FFM/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, dietary factors [e.g. macronutrient distribution (percentage of total caloric intake by carbohydrate, fat and protein), total caloric intake, fiber intake], 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 package\(^ {22}\) with proportional hazards models fit using the survival\(^ {23}\) package.

Analyses for **Aims 1 and 2** will commence with data quality checks where we will examine distributions of each identified covariate with descriptive statistics (means and standard deviations for continuous variables; counts and proportions for categorical variables). For overall mortality, we will describe time to death nonparametrically with Kaplan-Meier failure curves and quantiles of event times (e.g., median time to death).

We will estimate hazard ratios (HR) and 95% confidence intervals (CI) for the body composition-mortality (**Aim 1**) and -CVD event (**Aim 2**) associations with Cox proportional hazards models.\(^ {24}\) A minimally sufficient set of confounders for each aim will be identified using a directed acyclic graph (DAG),\(^ {25}\) considering the additional covariates described above. The proportionality assumption for all models will be assessed through graphical (log-log survival plots) and model-based methods (covariate-by-time interactions), and time-stratified effects will be reported where appropriate. We will examine possible nonlinear relationships between body composition and mortality using spline coding of the exposures in the regression models,\(^ {26-28}\) comparing nested models with a likelihood ratio test to identify the most parsimonious expression.\(^ {27}\)
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.csc.c.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:

    #1456: Measures of obesity in predicting different CVD outcomes by race and sex in the ARIC study
    This study examined the risk of incident CHD and stroke, SCD and any CVD event in relation to anthropometric measures. Our analysis will include specific estimates of body composition which is a key distinguishing factor, in addition to the additional follow-up and overall mortality outcome.

    # 2385: The relative associations of obesity with subtypes of cardiovascular disease: the Atherosclerosis Risk in Communities (ARIC) Study.
This study examined the relationship between BMI and incident CHD, fatal CHD, HF, stroke and overall mortality considering BMI and waist circumference. The authors did not consider a measure of body fat such as we propose here.

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.cscce.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.cscce.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