ARIC Manuscript Proposal #2404

1.a. Full Title: Obesity and incidence of components of the Metabolic Syndrome among healthy individuals

b. Abbreviated Title (Length 26 characters): Obesity and metabolic health

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

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3. Timeline:

Analyses will begin once the manuscript proposal is approved.
4. **Rationale:**
The subgroup of metabolically healthy overweight and obese subjects are currently poorly understood and thus of great interest to researchers and clinicians. Greater levels of adipose tissue has been linked to several chronic diseases such as coronary heart disease, type 2 diabetes, and several cancers. However, despite these associations, there is a subgroup of obese and overweight individuals who have a seemingly normal metabolic profile, referred to as the metabolically healthy obese (MHO) or metabolically healthy overweight (MHOW) (2, 3). These individuals, who represent over 30% of obese [body mass index (BMI) \( \geq 30 \text{ kg/m}^2 \)] and over 50% of overweight (BMI \( \geq 25 \text{ kg/m}^2 \) and \(< 30 \text{ kg/m}^2 \)) adults, have normal blood pressure and lipid profiles, and exhibit a high degree of insulin sensitivity and glucose control. This favorable metabolic profile may convey a risk of chronic disease similar to healthy, normal-weight (BMI < 25.0 kg/m2) individuals. Conversely, there is a significant portion of the normal weight population who are metabolically unhealthy, with an increased risk of chronic diseases, despite having a BMI level thought to be consistent with good health.

Although previous work has shown a strong relationship between body size and incidence of frank metabolic syndrome, there has been little work on the association between body size and incidence of the individual components, and most of the few studies reported have been limited to Asian populations. Most notably, a study by Chang and colleagues, using data from the 2002-2009 Prospective Cohort Study of Korean men aged 30 to 59 years old, examined the association between body size and incidence of each risk factor of metabolic syndrome (hyperglycemia, insulin sensitivity, hypertension, low HDL, hypertriglyceridemia, fatty liver) as well as a composite diagnosis of metabolic syndrome. All participants with any cardiometabolic risk factor (excluding abdominal obesity) or any serious medical concerns were excluded from this analysis. The authors found a 68% increased risk of developing any metabolic abnormality in the metabolically healthy obese at baseline when compared to their metabolically healthy normal weight counterparts. We know of no study that has compared the incidence of the individual components in obese and normal weight males and females of other racial and ethnic backgrounds who were initially free of all risk factors.

Other studies have considered either a composite definition of metabolic syndrome or a more limited set of metabolic abnormalities, mostly focused on diabetes. In the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia cohort (TwSHHH) Hwang and colleagues investigated the prevalence of the metabolically healthy obese subtype and its association with hypertension, diabetes, and a diagnosis of metabolic syndrome using a modified American Heart Association definition for Asians (diagnosis of at least three of the following component risk factors (1) waist circumference \( \geq 90 \text{ cm} \) for men and \( \geq 80 \text{ cm} \) for women; (2) triglycerides \( \geq 1.7 \text{ mmol} \text{ l} \); (3) HDL-C \( < 1.0 \text{ mmol} \text{ l} \) for men and \( < 1.3 \text{ mmol} \text{ l} \) for women; (4) systolic BP \( \geq 85 \text{ mmHG} \) or current use of antihypertensive drugs; and (5) fasting plasma glucose \( \geq 5.6 \text{ mmol} \text{ l} \) or current use of anti-hyperglycemic agents) During an average of 5.4 years of follow-up, metabolically healthy obese I (BMI of 25-26.9 kg/m^2; cutpoints suggested for Asian populations) participants at baseline had an almost nine fold increase in risk of being diagnosed with metabolic syndrome, almost 3 fold increase in developing hypertension, and a fivefold increase risk in developing type 2 diabetes mellitus as compared to metabolically healthy normal weight participants. Similarly, metabolically
healthy obese II (BMI of ≥27 kg/m²; Asian cutpoint) had an approximately twenty-four fold increase in risk of being diagnosed with metabolic syndrome, a fourfold increase risk of developing hypertension, and an eleven fold increase in risk of developing type 2 diabetes mellitus. Additionally, Soriguer and colleagues (10) investigated incidence of diabetes in a Spanish cohort of men and women. Participants were followed up at 6 and 11 years. They found that the metabolically healthy obese at baseline (BMI ≥ 30 kg/m², HOMA-IR < 90th percentile, triglycerides < 150 mg/dL, and fasting glucose < 110 mg/dL) had a two fold increase in the odds of developing type 2 diabetes at the 6 year follow-up and four fold increase in odds of developing type 2 diabetes at the 11 year follow-up when compared to metabolically healthy normal weight participants. In our previous study in the ARIC population,(7) we investigated the incidence and correlates of a diagnosis of frank metabolic syndrome (defined by the ATP III criteria) among normal weight, overweight, and obese subgroups who did not meet the formal criteria for metabolic syndrome (e.g. <=2 of the components). We reported a positive association between incidence of metabolic syndrome and BMI, with greater body size associated with a stronger effect. These studies illustrate that the metabolically healthy overweight and obese phenotypes may not be favorable conditions.

One of the main limitations of the previous studies is that they have been restricted to heterogeneous Asian and European cohorts with relatively small sample size. To the best of our knowledge the impact of BMI on the incidence of the individual components of metabolic syndrome (in healthy individuals free of all those abnormalities: (1) elevated triglycerides: >=150 mg/dL; (2) low HDL cholesterol, men: <40 mg/dL, women: <50 mg/dL; (3) elevated blood pressure: >=130/>=85 mm Hg; (4) elevated fasting glucose: >=110 mg/dL) has gone unaddressed in a large population-based US cohort. Another significant limitation of the previous works is the inconsistent definitions of the metabolically healthy phenotypes, making comparisons across studies difficult. Some analyses defined metabolic health as the absence of all components of metabolic syndrome, excluding abdominal obesity, some variant of the National Cholesterol Program’s Adult Treatment Panel III (ATP III) guidelines for assessing metabolic syndrome, or use selected biochemical markers (HOMA, fasting insulin, plasma lipids, uric acid, c-reactive protein) (2, 11). These differences in measurements account for different estimated prevalences of this sub-population within each study and different limitations. Limitations due to lack of uniformity in definitions of metabolic health include small number of events due to strict cut-off criteria of components of metabolic syndrome and phenotypes and lack of comparison studies for the proposed inclusion/exclusion criteria. Finally, although previous work has established that the metabolically healthy obese condition does not necessarily convey a favorable longitudinal pattern of risk factors, we have limited knowledge of which components of metabolic syndrome emerge first among these individuals. Knowledge of which condition(s) that the metabolically healthy obese are most likely to face will inform clinical practice and public health interventions aimed at reducing disease burden in this high-risk population.

In the proposed study using data from the ARIC cohort, we seek to refine our previous work by understanding which components of metabolic syndrome are most common in a population free from all such abnormalities (excluding waist circumference) and whether these differ by body size subgroups. This will be the first study to examine
this in a racially diverse US population of men and women. Additionally, by limiting our definition of “metabolically healthy” to those free from all metabolic abnormalities we will provide a clearer understanding of the effect of adiposity on incident cardiovascular disease risk factors.

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

   **Aim 1:** Among metabolically healthy individuals (i.e. those free from all components of MetSyn, excluding elevated waist circumference) what is the incidence of each metabolic abnormality in the obese (BMI >=30) and overweight (25<=BMI<30), relative to those of normal weight (18.5<=BMI<25)?

   a) Elevated triglycerides: >=150 mg/dL
   b) Elevated blood pressure: >=130/>=85 mm Hg
   c) Low HDL cholesterol, men: <40 mg/dL, women: <50 mg/dL: >=110 mg/dL
   d) Elevated fasting glucose: >=110 mg/dL

   **Aim 2:** Is there effect modification of the BMI association due to select variables (sex, age, weight change) during the 3 year follow-up?

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).**

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  ____ Yes  ____ 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.)

**Study Design:** Aims 1 and 2 will be addressed in a prospective cohort study design and will employ all data from baseline and the three follow-up visits among those individuals who are overweight or obese and metabolically healthy (free from all components of metabolic syndrome except waist circumference: (1) elevated triglycerides: >=150 mg/dL; (2) low HDL cholesterol, men: <40 mg/dL, women: <50 mg/dL; (3) elevated blood pressure: >=130/>=85 mm Hg; (4) elevated fasting glucose: >=110 mg/dL) at the baseline visit and allowing for changing BMI throughout the follow-up.

**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 (12)). 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).

**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:** Separately for each outcome, we will calculate unadjusted (association of each outcome with BMI) and multivariate adjusted models (BMI and all confounders included simultaneously). Test for trend for ordinal variables will be calculated utilizing the uncategorized variable, where appropriate. To determine if the associations between the body size and incident outcomes are similar between levels of effect modifiers (e.g. sex) we will include a multiplicative interaction term between the effect modifier and BMI and evaluate its statistical significance using the likelihood ratio test with a significance level of 0.05.

Descriptive statistics for all variables at the baseline visit will be calculated including means and standard deviations for continuous variables and frequencies for categorical variables.

As the outcome data are measured at 3 time points (visits 2, 3 and 4) and the development of metabolic syndrome could occur between assessments, interval censored proportional hazards regression (13) will be used to estimate the association between the covariates and incident outcomes throughout the follow-up. Covariates that are repeatedly assessed (e.g. BMI, weight change between visits) will be treated as time-varying covariates in this analysis. Briefly, as described in Hosmer and Lemeshow (13) we will construct a long-format dataset where each subject will have multiple records in the dataset, each record corresponding to an individual’s outcome and covariate data at each follow-up (up to and including when they experience the event of interest). A generalized linear model with a complementary log-log link function, and Bernoulli distribution for the outcome will be fit as a function of the covariates (including BMI) and indicator variables corresponding
to the period of measurement (accounting for the baseline hazard). The parameters from this model estimate the log-hazard ratios from a proportional hazards model in a discrete-time setting.(13) Assumptions of proportionality of the hazard ratios will be assessed through interaction of each covariate with the period (time) indicators.

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.cscu.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)?

   # 1085: Black/white differences in the relationship of the MetSyn components to insulin resistance
   Janice Williams, Annie McNeill, Sherita Golden Mercedes Carnethon, Viola Vaccarrino, Jerome Abramson

   The purpose of this study 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 in the metabolically healthy at study baseline.

   # 1173r: Dietary intake and the development of the metabolic syndrome: The ARIC study.
   Pamela L. Lutsey, Lyn M. Steffen, June Stevens, and other interested investigators

   This study investigated the association between dietary intake (food group and dietary intake) and the development of a composite diagnosis of metabolic syndrome. Our study is distinct in that we will examine the relationship between BMI and individual components of metabolic syndrome.

   # 1680: Longitudinal patterns and determinants of metabolic subtypes of obese,
overweight and normal weight individuals
Patrick Bradshaw, Keri Monda, June Stevens

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. We will add to this study by investigating the metabolic abnormalities that are acquired among a completely metabolically healthy (defined as 0 risk factors) population at baseline and whether metabolic abnormalities differ by BMI category.

#2035: Effect of 3-year weight loss on cardiometabolic risk factors in metabolically healthy obese individuals
Zhaohui Cui, Patrick Bradshaw, June Stevens

This study investigated the relationship between obesity phenotypes and weight loss with a focus on the MHO middle aged and cardiometabolic risk factors. In contrast, our study will focus on metabolically healthy phenotypes and the transition to metabolically unhealthy.

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.
References


