ARIC Manuscript Proposal # 1680

PC Reviewed: 8/10/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Longitudinal patterns and determinants of metabolic subtypes of obese, overweight and normal weight individuals

b. Abbreviated Title (Length 26 characters): Metabolically healthy obesity

2. Writing Group:
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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:

Analyses will begin once the manuscript proposal is approved.

4. Rationale:

The epidemic level of obesity in the United States is well documented with approximately two-thirds of the adult population considered overweight or obese [1]. Excess adipose tissue is a well-established risk factor for heart disease, diabetes and several types of cancer [2, 3] which is believed to be due to its effects on dyslipidemia, insulin sensitivity and chronic systemic inflammation [4]. However, a subset of overweight and obese individuals exists who have relatively normal metabolic profiles [5]. These individuals, who represent over 30% of obese [body mass index (BMI) >=30 kg/m^2] and over 50% of overweight (BMI >=25 kg/m^2 and <30 kg/m^2) adults, have a relatively normal blood pressure and lipid profile, and exhibit a high degree of insulin sensitivity and glucose control [6]. This favorable metabolic profile may convey a risk of chronic disease similar to healthy, normal-weight individuals [7, 8]. Conversely, approximately 24% of normal-weight U.S. adults (BMI < 25.0 kg/m^2) are considered metabolically abnormal, placing them at elevated risk for chronic diseases that are typically associated with elevated BMI.

Fat patterning [9] and duration of obesity [10] have been shown to be associated with some of the metabolic subtypes, yet detailed data on sociodemographic and lifestyle factors associated with these subtypes is lacking. The singular study to examine these issues uses data from the 1999-2004 National Health and Nutrition Examination Surveys [6]. Wildman and colleagues report that among overweight and obese adults, the metabolically healthy phenotype was more common in younger adults, moderate alcohol drinkers, non-Hispanic blacks and those with higher levels of physical activity. The authors also found that normal-weight individuals were more likely to be metabolically abnormal if they were of older age and male gender, and less likely if they were moderately physically active. While this report has yielded important insights, additional work is needed to not only confirm these findings but also to identify additional sociodemographic and lifestyle factors related to these phenotypes. In particular, the association between dietary factors and metabolic subtypes of obesity remains blatantly unaddressed [7]. Previous work suggests that a Western dietary pattern, characterized by high intakes of refined grain products, fried foods and processed meat, is positively associated with development of the metabolic syndrome regardless of initial body size [11]. However, the association of other dietary characteristics with metabolic syndrome, including macronutrient intake, remains unclear, especially among individuals of varying body size.

The most pressing, yet completely unaddressed question regarding the metabolic subtypes of obesity is regarding their longitudinal patterns [12]. To date no study has evaluated the stability of the metabolically healthy phenotype, thus we know little about the critical question of what predicts the stability of the phenotype or the transition from metabolically-healthy obese to metabolically-unhealthy obese over time. For some obese individuals, the metabolically healthy condition may represent a transition to the higher risk unhealthy phenotype, while others may maintain the more favorable metabolic profile indefinitely. Characterization of this pattern, including identification of lifestyle and sociodemographic factors will highlight significant areas relevant for public health and clinical interventions.

In the proposed study we seek to examine factors associated with metabolic subtypes of obesity at baseline in a cross-sectional analysis, and additionally describe the longitudinal pattern of the metabolically healthy subgroups among overweight and obese individuals.

5. Main Hypothesis/Study Questions:

Aim 1: What is the prevalence of the body size-metabolic phenotypes [metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight (MHOW), metabolically unhealthy overweight (MUOW), metabolically healthy obese (MHOb), metabolically unhealthy obese (MUOb)] at the ARIC baseline visit?

What are the associations between these phenotypes with sociodemographic factors and lifestyle behaviors, including dietary behaviors and physical activity levels? Do these associations with the metabolically healthy phenotypes differ between obese/overweight and normal weight individuals?

Aim 2: What proportion of those who are metabolically healthy at the baseline visit (MHNW, MHOW, MHOb) eventually transition to metabolically unhealthy phenotypes (MUNW, MUOW, MUOb) across the follow-up? What are the associations between sociodemographic factors and lifestyle behaviors with this transition, including dietary behaviors and physical activity levels? Do the magnitude of these associations vary according to body size category?

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: Aim 1 will employ a cross-sectional study design including only data at the baseline visit. Aim 2 will be a prospective cohort study and will employ all data from baseline and the three follow-up visits among those individuals who are overweight or obese and metabolically healthy at the baseline visit and who maintain the same body size category through all 4 visits.

Inclusion/Exclusion Criteria: For both aims we will exclude those subjects with implausible total energy intake, and missing dietary, physical activity, or other covariate data. 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.

For aim 2, only those subjects who fall into the MHOW and MHOb categories at the baseline visit, and maintain the same body size categorization throughout follow-up will be included, as the purpose is to ascertain the stability of the metabolically healthy phenotype in this sub-population.

Outcome variable: Metabolic health-body size subtypes defined according to cross-classification of the 3 standard BMI categories (normal weight: < 25 kg/m^2, overweight: 25-29.9 kg/m^2, obese: $>= 30$ kg/m^2) and presence or absence of metabolic syndrome as defined by National Cholesterol Program's Adult Treatment Panel III (ATP III) guidelines [13] (3 or more of the following risk factors: (1) abdominal obesity, men: >40 in, women: >35 in; (2) elevated

triglycerides: >=150 mg/dL; (3) low HDL cholesterol, men: <40 mg/dL, women: <50 mg/dL; (4) elevated blood pressure: >=130/>=85 mm Hg; (5) elevated fasting glucose: >=110 mg/dL).

Covariates: Covariates for both aims of this analysis 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 carried forward from the previous visit (e.g. diet at visit 2 will reflect visit 1, while diet at visit 4 will reflect visit 3).

Statistical Analysis: We will calculate unadjusted (association with each covariate individually) and multivariate adjusted models (all covariates included simultaneously). Test for trend for ordinal variables will be calculated utilizing the uncategorized variable, where appropriate. To determine if the associations between the covariates of interest and prevalent (Aim 1) or incident (Aim 2) metabolic syndrome are similar between normal weight and overweight/obese subjects we will compare the associations between these groups using the likelihood ratio test for multiplicative interaction. Should the sample size allow, effect modification by race/ethnicity and gender will also be assessed using the likelihood ratio test with a significance level of 0.10.

Aim 1: 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. Logistic regression will be utilized to calculate prevalence odds ratios and 95% confidence intervals examining the association between the covariates in the analysis and prevalence of each of the 6 body size-metabolic subtypes.

Aim 2: As the data is measured at 4 time points and the development of metabolic syndrome could occur between assessments, interval censored proportional hazards regression [14] will be employed to estimate the association between the covariates and incident metabolic syndrome among those obese or overweight throughout the follow-up. Covariates that are repeatedly assessed (e.g. dietary variables) will be treated as time-varying covariates in this analysis.

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

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)?

MS # 961: Natural History of the Metabolic Syndrome as defined by the National Cholesterol Education Program, Third Adult Treatment Panel Report (NCEP ATP III) ***[This proposal is noted as withdrawn on the ARIC website]***

The aims of this proposal were to describe the patterns of metabolic syndrome over time and determine the stability of the metabolic syndrome classifications within individuals with respect to individual components of the metabolic syndrome (lipids, blood pressure, insulin, etc...). In contrast, our analysis focuses specifically on the transition between the metabolically healthy to the metabolically unhealthy phenotype among obese and overweight individuals with a comparison to those normal-weight individuals who develop metabolic syndrome. Additionally, we will examine lifestyle factors associated with this transition, which was not a goal of MS#961.

MS #1173: Dietary intake and the development of the metabolic syndrome: The ARIC Study.

This study focused on the association between dietary patterns (derived by principal components analysis), food groups and incident metabolic syndrome among all subjects. Our analysis of incident metabolic syndrome will include dietary factors not considered in manuscript #1173 (e.g. macronutrient intake, fiber intake, glycemic index and glycemic load) and will focus on the transition between metabolically healthy to metabolically unhealthy obesity. We will also report associations with other sociodemographic and lifestyle factors that may affect the development of metabolic syndrome among overweight and obese individuals.

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/

12. 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.

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