1.a. Full Title: Factors of the metabolic syndrome and incidence of coronary heart disease, stroke and type 2 diabetes

b. Abbreviated Title (Length 26 characters): MS factors and risk of CHD, stroke, and diabetes

2. Writing Group (list individual with lead responsibility first):

   Lead: Weihong Tang
   Address: Division of Epidemiology
            University of Minnesota
            1300 South Second Street, Suite 300
            Minneapolis, MN 55454
   Phone: (612) 626-9140 Fax: (612) 624-0315
   E-mail: tang0097@tc.umn.edu

   Writing group members: James Pankow, Sherita Hill Golden, Maria Inês Schmidt, Christie M. Ballantyne, Heejung Bang, a UNC representative, a Jackson center representative

3. Timeline: 12/03 – 07/04

4. Rationale:

   The metabolic syndrome (MS), also commonly termed the insulin resistance syndrome or syndrome X, describes the clustering of insulin resistance and metabolic cardiovascular disease risk factors including hyperinsulinemia, glucose intolerance, obesity, hypertension and dyslipidemia (1-4). In addition, hyperuricemia (5) and impaired fibrinolytic and procoagulant activities (6, 7) also commonly co-occur with the syndrome. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) recently proposed unifying and clinically applicable criteria to define the metabolic syndrome (8) as the presence of three or more of the following five abnormalities: abdominal obesity, high triglycerides, low HDL, hypertension, and fasting hyperglycemia. Based on this definition, nearly 1 in 4 men and women in US adults (NHANES III, 1988-1994) are affected (9, 10). Given the strong and elevated risk of type 2 diabetes (5-9-fold) and CVD morbidity and mortality (3-4 fold), the MS is emerging as clinical and public health concern of considerable magnitude (11, 12).

   Factor analysis modeling, a multivariate correlation method that is used to summarize interrelated variables with a smaller number of uncorrelated composite factors, was used by many studies to investigate the correlation architecture among MS-related risk variables in adults, children and elderly (13, 14). Factor analysis characterizes the underlying multivariate correlation structure of the MS and provides useful information on the underlying
pathophysiological pathway for the MS. Many studies identified a three- or four-factor model, where the major factor that accounted for the most variation in the data was strongly loaded by obesity and insulin variables (5, 7, 13, 15-19), glucose (7, 18, 19), dyslipidemia (5, 13, 16, 18, 19), and, more weakly, blood pressure. Studies that included novel risk factors such as uric acid, procoagulant, and/or fibrinolytic variables, revealed that uric acid (5) and PAI-1 (7) clustered with the factor exhibiting strong loading for obesity and insulin variables. Recently, Shen et al (20), based on findings from previous studies, proposed and confirmed a hierarchical four-factor model for MS. This model included a second-order factor reflecting the MS that unites four first-order factors reflecting obesity, insulin resistance, lipid and blood pressure. In summary, results from factor analyses suggested that multiple linked physiological pathways mediate the clustering of MS variables.

Prospective epidemiological studies of factors derived from factor analysis of MS-related variables can yield useful insights into relationships between various metabolic pathways and disease risk. While several studies have demonstrated that factors of the MS predict coronary heart disease (CHD) (12, 17, 18, 21) and stroke (18), none of the studies have evaluated the ability of different factors to predict incident CHD and stroke. Furthermore, there are fewer prospective data investigating the ability of various MS factors to predict incident type 2 diabetes. One such study conducted a factor analysis of traditional MS-related variables in Pima Indians (22). In this study, four MS-related factors, reflecting insulinemia, body size, lipidemia and blood pressure, were identified. The insulinemia factor was most strongly associated with risk of incidence type 2 diabetes, followed by the body size and lipidemia factors. The blood pressure factor was not a significant predictor. Furthermore, analysis of receiver operating characteristic (ROC) curves showed that the first three factors predicted diabetes similarly well, and significantly better than the blood pressure factor. It was noticed that the above-mentioned reports were based on Caucasian or Pima Indian populations, and there is no data available on MS factors and these outcomes in African Americans.

References:


5. Main Hypothesis/Study Questions:

The factors derived from factor analysis of MS-related variables are significantly associated with risk of incident CHD, stroke and type 2 diabetes, and the magnitude of associations will differ among various MS factors. These factors will also have different ability to predict each disease outcome as shown by the ROC analysis.

Study questions:
1. Conduct a factor analysis to identify the factor-loading pattern of MS-related variables (measured at visit 1) among the ARIC participants free of CHD, stroke or type 2 diabetes at baseline
2. Estimate the relative risk of incident CHD (CHD death, nonfatal MI, silent MI, or cardiac procedures), stroke, and type 2 diabetes associated with the MS factors among ARIC cohort members, controlling for relevant confounders (e.g. age, sex, ethnicity, and lifestyle variables)
3. Conduct ROC analyses to evaluate the ability of factor scores to predict each disease outcome

6. Data (variables, time window, source, inclusions/exclusions):

Inclusion/Exclusion: inclusion: all ARIC visit 1 participants free of CHD, stroke or type 2 diabetes; exclusion: 1) Bloodwork obtained after <12 hours fasting; 2) Race other than African Americans or Whites; 3) Individuals with missing values for prevalent CHD, stroke or type 2 diabetes at baseline
Primary variables included in the factor analysis (from visit 1): BMI, waist, WHR, HDL-c, triglycerides, fasting glucose and insulin, SBP, DBP, fibrinogen, white cell count, uric acid. These variables will be subjected to a maximum likelihood-based factor analysis model, and factor scores will be derived and used as independent variables for subsequent disease prediction analyses.

**Dependent Variables:** CHD and stroke incidence through 2000, diabetes incidence through visit 4.

**Possible Covariates (from visit 1):** age, gender, race, field center, hypertension, parental history of diabetes, medication use, LDL

**Analysis Plan:** Factor and prospective analyses. 1) We propose to conduct a maximum likelihood-based factor analysis of the above MS-related variables obtained at baseline. The analysis will first be conducted in African Americans and Whites separately, and if factor loading patterns are similar between the two groups, the final factor analysis will be repeated in a combined group to derive factor scores for each individual; 2) Proportional hazards regression models and ROC curves will be used to investigate the prediction of incident disease outcomes by the factor scores.

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 ICTDER02 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 ICTDER02 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  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

_____ 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)?

There are 47 ARIC proposals related to “metabolic syndrome” and 89 related to “insulin resistance”. I have reviewed all of them and found none of them include factor analysis approach. Among them, two proposals are most relevant to the topic I am proposing. These two are: #831 (Annie McNeill): Associations of new definitions of the metabolic syndrome with prevalent and incident coronary heart disease and IMT; #832 (Annie McNeill): Prediction of subclinical atherosclerosis, incident CHD, and all-cause mortality using recently published
definitions of the metabolic syndrome. These manuscripts study the association of the incident diseases with the WHO- and NCEP ATPIII-based metabolic syndrome and individual risk variables as well, and factor analysis will not be included. In addition, I have consulted with the lead author Annie McNeill to confirm that factor analysis is not part of their analysis plan. To avoid overlap with #831 and #832, I will not look at the associations between the disease outcomes and the metabolic syndrome defined by WHO and NCEP ATPIII, or the individual risk variables. I will cite #831 and #832 if it is necessary to discuss the data in the paper.