1.a. Full Title:
Prediction of subclinical atherosclerosis, incident CHD, and all-cause mortality using recently published definitions of the metabolic syndrome

b. Abbreviated Title (Length 26 characters):
Met. syndrome & CHD risk

2. Writing Group (list individual with lead responsibility first):
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3. Timeline: Analyses will use currently available ARIC cohort data files through 1998 and will begin immediately following approval of the proposed manuscript.

4. Rationale:
In 1988, Reaven suggested that insulin resistance may underlie a number of disorders including hypertension, dyslipidemia (especially low HDL and/or high triglycerides), and impaired glucose tolerance that are related to cardiovascular disease. The terms “syndrome X”, “insulin resistance syndrome”, “multiple metabolic syndrome”, and most recently “metabolic syndrome” have been used to describe the presence of these related disorders. Although a great deal of epidemiological and clinical research has been conducted to study the deleterious effects of type 2 diabetes and impaired glucose tolerance (IGT) on the risk of cardiovascular disease, much less research has been conducted to assess the effect of the presence of the metabolic syndrome and risk of CHD-related morbidity and mortality.

In addition, research has been hindered by the lack of a consistent, widely-accepted definition for which components constitute the presence of the syndrome as well as the appropriate cut-off levels for individual components. A review of the literature on metabolic syndrome by Liese and colleagues in 1998 identified the use of at least 11 different definitions for the syndrome. They reported that most published definitions included measures of glucose metabolism or insulin resistance, blood pressure, triglycerides,
and at least one measure of lipoprotein cholesterol (HDL or LDL) while a few definitions also included obesity or abdominal adiposity. Less common elements included uric acid; albumin; plasminogen activating inhibiting factor; lipolytic enzymes; small, dense LDL; free fatty acids; and factor VII.

In 1998, the World Health Organization\(^3\) (WHO) proposed their own definition for the metabolic syndrome that requires (1) impaired glucose regulation (diabetes, impaired glucose tolerance [IGT], or impaired fasting glycemia [IFG]) and/or (2) insulin resistance with two or more of the following components: hypertension, dyslipidemia, obesity/central obesity, or albuminuria. This definition was characterized by the report’s authors as, “…a working definition to be improved upon in due course [pg. 32]. Applying this definition, investigators with the Botnia Study\(^4\), a prospective cohort of approximately 4,500 subjects aged 35-70 years of age in Finland and Sweden, found that the syndrome was present in 12%, 53%, and 81% of individuals with normal glucose tolerance, IFG/IGT, and diabetes, respectively. During the median 6.9 years of follow-up, the relative risk of cardiovascular mortality was 80% higher among all subjects with the metabolic syndrome compared to those without.

In May 2001, National Cholesterol Education Program\(^5\) (NCEP) of the National Institutes of Health (NIH) proposed its own definitions for the metabolic syndrome based on the presence of three of the following five conditions: hypertension (systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mHg); high triglycerides (≥ 150mg/dl); low HDL (< 40 mg/dl in men, <50 mg/dl in women); obesity (waist circumference > 102 cm in men, > 88 cm in women); and impaired fasting glucose (≥ 110 mg/dl). Our review of the literature did not identify any studies using the NCEP definition to estimate the risk of coronary heart disease or all-cause mortality among population-based cohorts.

A further complication in the effort to produce a working definition for the metabolic syndrome is that the methodology or rational used to select cutpoints for the individual components is not well documented.\(^3,5\) Specifically, it is not clear whether correlations among components were considered when the NCEP and WHO definitions were derived. Depending on the statistical techniques chosen to estimate such cutpoints, significant collinearity among the individual components could result in the estimation of different cutpoints than those that would have been estimated if the confounding resulting from such collinearity had been taken into account.

A prospective analysis of the ability of the NCEP and WHO definition to predict incident and subclinical CHD within the same population will provide important information regarding the management and treatment decisions for individuals with the syndrome. Further, very few studies have looked at the effect of varying the specific cut-points of individual components of the syndrome and whether this significantly improves the prediction of coronary heart disease and overall mortality.

5. Main Hypothesis/Study Questions:

Using the NCEP and WHO definitions, we will estimate the risk of incident and subclinical CHD as well as all-cause mortality associated with the metabolic syndrome among the ARIC cohort. (Note: the WHO definition will not include albuminuria as one of the components of the metabolic syndrome because urine samples were not collected at the baseline visit.) Our preliminary analysis indicates that approximately 25% (n=3,484) of the eligible ARIC cohort meets the NCEP definition of the metabolic
syndrome at the baseline visit (see section 6 for a more detailed description of the eligible study population). Among the group of ARIC cohort members with metabolic syndrome, there have been 421 cases of incident CHD (i.e., MI, fatal CHD, silent MI, or cardiac procedure).

The main objectives of the proposed study are to:

1. Estimate the relative risk of incident CHD (CHD death, nonfatal MI, silent MI, or cardiac procedure), subclinical CHD, and all-cause mortality among ARIC cohort members with the metabolic syndrome compared to those without, controlling for relevant confounders (e.g., age, gender, ethnicity, social/lifestyle variables).

2. Estimate variations in risk (relative and absolute) by gender and ethnicity, and by level of LDL-C.

3. Explore whether a decision tree algorithm (recursive partitioning that accounts for significant collinearity among components) has utility in improving the prediction of the various outcomes by the presence of the metabolic syndrome.

4. Explore whether the cutpoints for the individual components outlined by NCEP and WHO are the most clinically useful in terms of predicting incident and subclinical CHD.

5. Determine if longitudinal changes (e.g., absolute or percent change) within individuals between visit 1 and visit two improve the prediction of CHD risk compared to measures taken at only one point in time. (Note: fasting insulin, a component of the WHO definition of metabolic syndrome, was not collected at visit 2 and thus the longitudinal analysis is limited to components comprising the NCEP definition.)

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

Data from visit 1, visit 2, and incident event files will be used. Individuals with the following conditions will be excluded:

- Bloodwork obtained < 12 hours after fasting (n=776)
- African-American participants not residing in Forsyth or Jacksonville centers (n=48)
- Race other than African American or White (n=43)
- Individuals with prevalent CHD, stroke, TIA, or missing values for these variables at baseline (n=1,446)
- Individuals with incident CHD (fatal CHD, MI, silent MI, and cardiac procedures) occurring between visit 1 and visit 2 will be excluded from longitudinal analyses that involve changes in the components of the metabolic syndrome and prediction of incident CHD and all-cause mortality. Our preliminary analysis indicates that 149 incident CHD events occurred between visit 1 and visit 2 among the proposed study population and thus would be excluded in longitudinal analyses. Applying this exclusion leaves 351 incident events among the 3,414 ARIC cohort members with NCEP-defined metabolic syndrome at visit 1.

Variables will include demographic indicators as well as those corresponding to individual components of the metabolic syndrome (e.g., systolic blood pressure,
diastolic blood pressure, fasting insulin, fasting glucose, high-density lipoprotein (HDL), small-dense LDL, triglycerides, waist-to-hip ratio, waist circumference, and BMI). Established derived variables within ARIC for incident CHD, intima-media wall thickness, and all-cause mortality will also be used.

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 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?  N/A  ____ 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  __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 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 list under the Study Members Area of the web site at: [http://bios.unc.edu/units/csc/ARIC/study/studymem.html](http://bios.unc.edu/units/csc/ARIC/study/studymem.html)

____X____ Yes  _______ No

Specifically, I have reviewed manuscript proposal numbers 786, 784, 545, 289a, and 808 for potential overlap and believe there to be none. In addition, I have consulted with the main author of proposal #545 (Bruce Duncan) and he has agreed to serve on the writing group of this proposed manuscript.

References