ARIC Manuscript Proposal # 831
Revised

PC Reviewed: 09/10/03	**Status: A**	**Priority: 2**
SC Reviewed: 09/11/03	**Status: A**	**Priority: 2**

1.a. Full Title:
Associations of new definitions of the metabolic syndrome with cardiovascular disease and atherosclerosis

b. Abbreviated Title (Length 26 characters):
Metabolic syndrome & CVD

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 1999 and will begin immediately following approval of the proposed manuscript.

4. Rationale:

In 1988, Reavan[1] suggested that insulin resistance may underlie a number of disorders including hypertension, dyslipidemia (especially low HDL and/or and high triglycerides), and impaired glucose tolerance that are related to cardiovascular disease. The terms "syndrome X", "insulin resistance syndrome", "multiple metabolic syndrome", and "metabolic syndrome" have been used to describe the presence of these related disorders. Estimates of the prevalence of the metabolic syndrome, its individual components, and associations with prevalent CHD have been studied within a number of population-based cohorts.[2,3] Several studies using either cluster analysis or factor analysis have demonstrated that among diabetics and non-diabetics, various clusters of components related to the metabolic syndrome predict coronary heart disease and stroke.[4, 5, 6, 7]

However, 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[8] 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[9] (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]. Various methods for the indirect assessment of insulin resistance have been proposed, including fasting insulin[10], HOMA index[11], Bennett index[12], insulin to glucose ratio[13], and a combination of fasting insulin and fasting glucose.[12]

Given the use of different definitions, it is not surprising that the reported prevalence of the metabolic syndrome and association with prevalent coronary heart disease varies widely across studies. Using a definition of co-occuring hypertension, diabetes (FPG >=140 mg/dl), and dyslipidemia, previous studies[14,15] have reported the presence of a metabolic syndrome among ARIC cohort members in approximately 3% of participants at baseline. Rantala and colleagues[16] used ten different published definitions of a metabolic syndrome on randomly sampled populations of 1,200 hypertensives and controls and found that the prevalence of the metabolic syndrome ranged from 0.8 to 33.5% depending on the definition applied. In contrast, investigators with the Botnia Study[3], a prospective cohort of approximately 4,500 subjects aged 35-70 years of age in Finland and Sweden, applied the WHO definition for the metabolic syndrome. They found that the syndrome was present in 12%, 53%, and 81% of individuals with normal glucose tolerance, IFG/IGT, and diabetes, respectively. In their analysis, the presence of the metabolic syndrome was associated with a three-fold increase in the risk of prevalent CHD. Further, this risk was greater than the risk associated with any of the individual elements of the syndrome. 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, the National Cholesterol Education Program (NCEP) of the National Institutes of Health (NIH) proposed its own definition 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); *central obesity* (waist circumference > 102 cm in men, > 88 cm in women); and *impaired fasting glucose* (>= 110 mg/dl).

A review of the published literature on insulin resistance and the metabolic syndrome found few studies that assessed the association between these consensus-based definitions of the metabolic syndrome and atherosclerosis or cardiovascular disease outcomes
Our preliminary analysis indicates that approximately 25% of ARIC participants at baseline meet the NCEP criteria for the metabolic syndrome. Knowledge of the prevalence of the syndrome as a whole, as well as the different combinations of individual components, will provide an opportunity for comparison of the NCEP definition to other previously proposed definitions such as the one recommended by WHO. In cross-sectional analyses, we will also assess the magnitude of association between the presence of the syndrome and history of CHD. We will also examine the association between the metabolic syndrome and intimal-medial wall thickness (IMT) of the carotid arteries, a well-established marker of

generalized atherosclerosis. It is likely that the NCEP and/or WHO definitions will be adopted by other investigators, thus reporting cross-sectional analyses of the link between the metabolic syndrome and CHD within the ARIC cohort will allow for future comparisons across other population-based cohorts. Finally, we will assess the magnitude of association between the metabolic syndrome and incident coronary heart disease and ischemic stroke events using both NCEP and WHO definitions. 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.

5. Main Hypothesis/Study Questions:

Using the NCEP and WHO definitions, we will estimate the association between metabolic syndrome and incident cardiovascular outcomes (CHD and ischemic stroke) and subclinical CHD among the ARIC cohort using both cross-sectional and prospective methods. Although albuminuria is a suggested component of the WHO definition, it will not be included in our analyses because urine samples were not collected at the baseline visit. However, we will explore the utility of using fasting insulin or a combination of fasting insulin and fasting triglycerides as the insulin resistance component when estimating the risk of incident and subclinical CHD associated with the metabolic syndrome.

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 at baseline but without prior CHD or stroke, there have been 879 cases of incident CHD (i.e., MI, fatal CHD, silent MI, or cardiac procedure) and 216 cases of ischemic stroke.

Cross-sectional Analysis

The main objectives of the proposed study are to:

1. Describe and compare the prevalence of the metabolic syndrome as a whole and its individual components, by age, race, sex, and LDL-C categories 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.)
2. Describe the prevalence of different combinations of the individual components of the syndrome and determine the relative frequency of different combinations using definitions proposed by NCEP and WHO.
3. Assess the magnitude of association between the syndrome and history of CHD using definitions proposed by NCEP and WHO.
4. Assess the magnitude of association between the syndrome and subclinical CHD (e.g intima-medial wall thickness) using definitions proposed by NCEP and WHO.

Prospective Analysis

5. Estimate the relative risk of incident CHD (CHD death, nonfatal MI, silent MI, or cardiac procedure), and incident ischemic stroke among ARIC cohort

members with the metabolic syndrome compared to those without, controlling for relevant confounders (e.g., age, gender, ethnicity, social/lifestyle variables)

6. Estimate variations in risk (relative and absolute) by gender and ethnicity, and by level of LDL-C.
7. 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.

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

The study population will be taken from baseline data from the ARIC cohort. Individuals with the following conditions will be excluded:

- Bloodwork obtained after < 12 hours fasting (n=776)
- African-American participants not residing in Forsyth or Jacksonville centers (n=48)
- Race other than African American or White (n=43)

Additional exclusions will be required for the prospective analyses, including,

- Individuals with prevalent CHD, stroke, TIA, or missing values for these variables at baseline (n=1,446)
  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, triglycercides, waist-to-hip ratio, waist circumference, and BMI). Established derived variables within ARIC for prevalent CHD, 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 __X__ 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)?

Specifically, I have reviewed manuscript proposal numbers 635, 786, 784, 545, 289a and 808 for potential overlap and believe there to be none. In addition, I have consulted with the primary authors of proposals #545 (Bruce Duncan) and #635 (Sherita Golden) and they have agreed to serve on the writing group of this proposed manuscript.

11. 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.

References

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