ARIC Manuscript Proposal # 1081r

PC Reviewed: _09/20/05_   Status: _A__   Priority: __2_
SC Reviewed: _09/21/05_   Status: _A___   Priority: _2__

1.a. Full Title:
Concordance and Discordance between the National Cholesterol Education Program Adult Treatment Panel III (NCEP) criteria of the Metabolic Syndrome and the recently announced International Diabetes Federation (IDF) revised criteria in CHS and ARIC

b. Abbreviated Title (Length 26 characters):
NCEP vs IDF for MetS

2. Writing Group (list individual with lead responsibility first):
Annie McNeill, Wayne Rosamond, Cynthia Girman, Sherita Hill Golden, Ronit Katz (CHS), Sharon Jackson (CHS), Peter Savage (NIH-CHS), and other interested ARIC investigators

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3. Timeline: Analyses will begin immediately upon approval by the Publications and Steering committees.

4. Rationale:
In 2001, the National Cholesterol Education Program (NCEP), Third Adult Treatment Panel Report (ATP III)¹ proposed a definition of the metabolic syndrome to facilitate the use of uniform criteria in epidemiologic studies and as a tool to aid in the clinical evaluation of individuals at risk for coronary heart disease.

Since then, published studies using this definition have shown that individuals with the metabolic syndrome are at increased risk of developing diabetes²,³ and cardiovascular disease⁴,⁵ although no association between this condition and incident CHD was observed in the Strong Heart Study of Native Americans.⁶ Using data from the ARIC cohort, investigators have shown a significant association between the NCEP criteria and CHD and stroke, as well as with IMT.⁵⁻⁶ A separate analysis of the CHS cohort showed a significant, but somewhat weaker association.⁷

However, before and since the NCEP criteria were published, numerous definitions have been proposed and applied in epidemiological research, including those proposed by the World
In April 2005, the International Diabetes Federation (IDF) proposed a “worldwide definition of the metabolic syndrome,” presumably as a consensus definition between European and American experts. This revised definition is similar to NCEP but requires the waist circumference, plus two other components, as opposed to three of five components in the NCEP criteria. The consensus statement also indicated that the metabolic syndrome should be used to identify individuals at risk for CHD and type II diabetes.

Unlike the ATP III criteria, the IDF definition proposes lower cut points for the large waist component for Caucasians and African-Americans (94 vs 80 cm for men and women vs. 102 and 88 cm for ATP III) as well as specifying a different set of lower threshold values for Asian populations. It is likely that this consensus definition will replace the previous WHO definitions of the metabolic syndrome as several members of the IDF Consensus group also serve on the WHO Expert Committee for the Diagnosis of Diabetes. In addition, chairmen of both the IDF Consensus Group and the ATP III Report specifically have requested that comparative analyses of both the IDF and ATP III definitions of the MetS be conducted to assist their efforts to further refine and “harmonize” the two definitions.

For example, it is unclear however, how the different ATP III and IDF criteria agree, and whether the patients identified by one but not the other criteria are also at increased cardiovascular risk. In addition, the association of the newly proposed criteria with long-term cardiovascular outcomes has not been established to date. Whether the association with long-term outcomes is strengthened or attenuated by requiring the waist circumference will likely depend on the risk associated with those without obesity who meet NCEP criteria.

Finally, the newly proposed cut point of 100 mg/dl to define impaired fasting glucose (IFG) is part of the revised IDF definition. Possible attenuation of the association between the metabolic syndrome and cardiovascular or diabetes outcomes due to the lowering of the threshold for this component has not been sufficiently examined.

The Atherosclerosis Risk in Communities (ARIC) Study provides the opportunity to explore the concordance and discordance between the NCEP and IDF criteria, and to assess how the criteria compare in terms of strength of the association with cardiovascular outcomes.

The authors of this proposal are also submitting a similar manuscript request to address this research question in the elderly Cardiovascular Health Study cohort. If accepted, our plan would be to present results from separate analyses of both populations in the same publication. Such a publication would be advantageous in several respects. It would apply the same methodologic approach and provide information on the level of concordance between the two definitions in terms of the prevalence and magnitude of associations between incident CVD and diabetes in both middle and older age populations.

5. Main Hypothesis/Study Questions:

The purpose of this manuscript is to assess the concordance and discordance between the NCEP and the new IDF criteria for metabolic syndrome, and to assess the prospective association between ATP and IDF criteria and incident CVD and incident diabetes.

Study Questions
1. How well do the NCEP and IDF criteria agree in identifying subjects with metabolic syndrome?
2. Are there specific clinical characteristics (besides waist) that differ between the concordant and discordant patients? What are the estimated CVD incident rates for the discordant and concordant metabolic syndrome subjects?
3. Are there meaningful differences in the association with incident CVD, between the NCEP and IDF criteria?
4. Are there meaningful differences in the association with incident diabetes, between the NCEP and IDF criteria?
5. Do differences in the magnitude of association between the 2 definitions with CVD or diabetes differ between men and women or between African American and Caucasian subjects?

The agreement between the NCEP and proposed IDF criteria will be examined by gender (and race) using kappa statistics (with 95% confidence intervals). Because the dichotomization of the components agree except for requiring waist and the fasting plasma glucose threshold, further analyses will be conducted to explore how characteristics of patients who are discordant differ on these components. Since the majority of subjects in the ARIC cohort met the waist circumference criteria (particularly women), it is anticipated that the primary differences between criteria will be in men, especially African-American men, who exhibit lower levels of central obesity relative to African American women or Caucasian subjects.

Cox proportional hazards regression will be used to assess the strength of the association between a combined CVD, adjusting for age, center and potential confounders. Such models will be fit separately for each gender. Modification of the association between MetS and CVD by race/ethnicity will be explored. Estimates of the area under the ROC curve in crude and adjusted analyses will be used to assess the association of the criteria with CVD. Similar analyses will be conducted to assess the strength of the association between the 2 definitions of MetS and cumulative incidence of diabetes using logistic regression.

6. Data (variables, time window, source, inclusions/exclusions):
The study population will be taken from baseline data from the ARIC cohort. Incident CHD and stroke event files will be used to create a combined CVD outcome and time-to-event variables. Data from visits 2, 3, and 4 will be used to ascertain cumulative incidence of new onset diabetes from baseline.

Individuals with the following conditions will be excluded:
- Bloodwork obtained after < 8 hours fasting at the baseline visit.
- Race other than African American or White or Black participants not residing in Forsyth or Jackson centers. Race
- Missing data on any component of the metabolic syndrome
- Prevalent or missing CHD at the baseline visit
- Prevalent diabetes at the baseline visit (for analyses with incident diabetes as the outcome)

Variables will include those corresponding to individual components of the metabolic syndrome (e.g., systolic blood pressure, diastolic blood pressure, fasting glucose, high-density lipoprotein (HDL), triglycerides, waist circumference), and possible confounders, including established CVD risk factors, demographics, health behaviors (smoking, alcohol consumption, physical activity), and family history indicators.

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?  ____ 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 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)?


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.

The lead author agrees to this timeline.
References


