# ARIC Manuscript Proposal #2515

**1.a.  Full Title**:  **An Ethnicity-Specific MetS Severity Score to Assess Risk for Type 2 Diabetes and Cardiovascular Disease**

  **b. Abbreviated Title (Length 26 characters)**: **MetS Severity and Disease Risk**

**2.    Writing Group**:
    Writing group members:

Mark D. DeBoer (University of Virginia School of Medicine)
Matthew J. Gurka (West Virginia University School of Public Health)
Abhishek Vishnu (West Virginia University School of Public Health)
Baqiyyah Conway  (West Virginia University School of Public Health)
Solomon Musani (University of Mississippi Medical Center)
David Couper (University of North Carolina Gillings School of Public Health)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MDD__

F**irst author**: **Mark DeBoer, MD, MSc., MCR**
Address:      PO Box 800386
              University of Virginia
              Charlottesville, VA 22908

              Phone: 434-924-9833              Fax: 434-924-9181
              E-mail:  deboer@virginia.edu

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

    Name:    **David Couper, PhD**
    Address: Gillings School of Global Public Health
             University of North Carolina
             137 Franklin St, Ste 203
             Campus Box 8030
             Chapel Hill NC 27599-8030

             Phone:  919-962-3229          Fax:  919-962-3265
             E-mail:  david_couper@unc.edu

3. **Timeline**: Submission by Summer 2016

4. **Rationale**:

The metabolic syndrome (MetS) is a cluster of cardiovascular indices that increases risk for coronary heart disease (CHD), stroke and Type 2 diabetes (T2DM)—all highly prevalent diseases among African Americans. MetS classification is currently based on cut-off points for its various components. However, use of cut-offs misses classifying individuals with moderate elevations just below cut-off levels. Additionally, MetS criteria exhibit racial/ethnic differences in their association with disease.

*We have designed a sex- and race/ethnicity-specific continuous MetS severity score that takes into account how the individual components of MetS (elevated BP, low HDL, etc.) cluster and correlate differentially by sex and racial/ethnic group*. Based on these differences the score assigns different weights to each component by sex and race/ethnicity. An individual's score is calculated from standard clinical measures using equations specific to each sex and racial/ethnic group. This score has potential for clinical application for risk assessment. The score takes into account unique features of MetS seen in African Americans and expresses MetS severity such that it can be compared between individuals and followed over time within an individual. It must be emphasized that while MetS-related studies have been performed in ARIC previously, none have used an ethnicity-specific score to assess MetS severity, such as we propose, giving this manuscript proposal clear novelty.

We propose to use this MetS score to evaluate participants of both ARIC and the Jackson Heart Study, for improved power in our analysis. Our plan is three-fold. 1) We will assess baseline and longitudinal epidemiologic and lifestyle factors likely to affect MetS severity, 2) we will assess baseline MetS severity (using the MetS severity score) between individuals who do/do not progress to develop CHD, stroke, and T2DM, and 3) we will evaluate intra-individual changes in MetS severity leading to diagnosis of CVD-associated diseases. We will report our findings as guidance to clinicians regarding the use of MetS severity as an ominous indicator of future disease—with an ultimate goal of CVD prevention. The aim of the manuscript relates to baseline analysis of risk prediction for incident disease.

5. **Main Hypothesis/Study Questions**:

Increasing degree of severity of MetS at baseline (as measured over time by our score) and worsening of MetS severity over time will both be found to be a strong risk factors for future CHD, stroke and T2DM, and will be associated with worsening cardiovascular and T2DM risk markers over time.

**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).**
These analyses involve an epidemiological approach to assessing the ability of MetS (both using our severity score and ATP-III criteria when possible) to predict progression to disease diagnosis and progression of disease-related factors over time. As mentioned previously, we propose to

combine ARIC data with corresponding data from the Jackson Heart Study for improved power in these analyses.

Our approach will include both assessments of potentially relevant psychosocial factors and assessment of relationships between prevalent and future disease (CHD, stroke, any CVD, and T2DM) and MetS severity over time. Univariate cross-sectional associations at baseline between psychosocial predictors and MetS severity, as measured by the MetS score, will first be performed via linear regression. Linear mixed models will be used to examine the association between baseline predictors and MetS severity (separately). Such a modeling framework will allow for a cross-sectional analysis examining the association between these potential risk/protective factors and MetS severity at baseline, as well as their influence on MetS severity as it changes over the span of the study. These models will be used to account for within-subject correlations between the multiple MetS scores on each individual (at each of the primary exam periods). The hypothesis tests of interest will involve the fixed effects portion of the model, namely the baseline psychosocial predictors. Utilizing a continuous measure over time will allow for the simultaneous inclusion of all of the predictors listed above in the model without concerns over statistical power or reliability of estimates; such a strategy will account for any confounding influences of these predictors with each other. Covariates will be removed if they are not significant predictors of MetS severity over time by themselves ($p < 0.10$) and they do not confound the relationship with any other factors associated with MetS. In the latter case, a variable will be considered a confounder if its removal results in a difference of more than 10% of the parameter estimate of any other variables in the model. A backwards strategy for variable removal from a statistical and epidemiologic standpoint will be employed. The most parsimonious multivariable model that includes all the eligible confounders would be our main model. Interactions within these fixed effects will also be explored.

We will then use several approaches to estimate the strength of association between MetS and severity of MetS as measured by our MetS score and the outcomes (incident CHD, stroke, any CVD, and T2DM), depending on the type of variable (continuous or discrete) and the analytical approach (cross-sectional or longitudinal). For incident disease outcomes collected over the span of the study, we are primarily interested in time to those events occurring (incident CHD, stroke, T2DM) as a function of baseline MetS (using ATP-III and our MetS severity score). To that end, hazards ratios (HR) will be estimated from Cox proportional hazards (PH) models. Confounders would be selected based on standard criteria.

Inclusion criteria: participants with adequate data for all variables at baseline.
Exclusion criteria (for longitudinal analysis): baseline CVD and T2DM

Outcomes of interest: diagnosis of CHD, stroke, CVD, and T2DM.

Limitations: we recognize the problems with drop out over time and will utilize survival curves to analyze data, accounting for drop out over time.

**7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes   ____ 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? __ X __ Yes   ____ No**

(This file ICTDER 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"?  __X__  NA ____ 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)?**

McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care. 2005 Feb;28(2):385-90.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes    ____ No**

**11.b. If yes, is the proposal**
     **__X__ A. primarily the result of an ancillary study (list number* 2013.18)**
     **___    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/

**12a. 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.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research.  It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy.  Four files about the public access policy  from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under  Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.