March 4, 2015

Subject: New MS Proposal “Race and Sex Differences in the Progression of Metabolic Syndrome Severity”

Dear ARIC Publications Committee members:

We enthusiastically submit a proposal to prepare a new ARIC manuscript titled “Race and Sex Differences in the Progression of Metabolic Syndrome Severity.” In this study, we plan to examine the trend of metabolic syndrome (MetS) severity as well as MetS prevalence in the ARIC study, and compare the trend by race and sex. We will calculate MetS severity using a severity calculator that we have recently developed (Cardiovasc Diabetol., 2012, 11; Metabolism, 2014; 63(2)). This manuscript is supported from the ARIC Ancillary study #2013.18. Please also find an ARIC manuscript proposal form attached to this letter.

Abhishek Vishnu is our post-doctoral fellow, and would lead the analysis and preparation of this manuscript. Abhishek has recently completed his PhD training in cardiovascular epidemiology from the University of Pittsburgh where he examined subclinical atherosclerosis between US and East Asia. He has previously completed medical training from a reputed medical school in India. Dr David Couper, PhD has accepted to serve as the designated ARIC investigator for this study.

Thank you for considering our proposal, and please do not hesitate to contact us with any questions you may have.

Sincerely,

Matthew J. Gurka, PhD
Associate Professor and Founding Chair
Department of Biostatistics
West Virginia University Health Sciences Center

Mark D. DeBoer, M.D., MSc., MCR
Associate Professor of Pediatrics
Division of Pediatric Endocrinology
University of Virginia School of Medicine
ARIC Manuscript Proposal #2513

PC Reviewed: 3/10/15  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1. a. Full Title: Race and Sex Differences in the Progression of Metabolic Syndrome Severity: The ARIC study
   
   b. Abbreviated Title (Length 26 characters):
   
   MetS Severity and Progression

2. Writing Group:
   Writing group members:
   
   • Abhishek Vishnu
   • Mark D. DeBoer
   • Matthew J. Gurka
   • Baqiyyah Conway
   • David Couper
   
   For the ARIC Study Group

1 Department of Biostatistics, School of Public Health, West Virginia University
2 School of Medicine, University of Virginia
3 Department of Epidemiology, School of Public Health, West Virginia University
4 Collaborative Studies Coordinating Center, Gillings School of Public Health, University of North Carolina

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AV_ [please confirm with your initials electronically or in writing]

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         E-mail: avishnu@hsc.wvu.edu
3. **Timeline:** The following timeline starts from the date of approval of the MS proposal.

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis and background review of the literature</td>
<td>Preparing first draft of the manuscript</td>
<td>Comments from co-authors</td>
<td>Addressing co-author comments and submission to ARIC P&amp;P committee</td>
<td></td>
</tr>
</tbody>
</table>

4. **Rationale:**

Metabolic syndrome (MetS) is a cluster of metabolic and cardiovascular risk factor derangements and is associated with future diabetes and cardiovascular disease. The prevalence of MetS increases during the middle-age (40-60 years)\(^1\) before plateauing in the 60s. However, the trend of MetS prevalence in the ARIC cohort is not reported.

Current MetS definition uses criteria that is based on cut-offs assigned to the various metabolic parameters (e.g. triglycerides $<$ or $\geq$ 150 mg/dl). Since this classification uses the same set of criteria for all sex-, race- categories, it is possible that this definition does not have similar level of validity for one or more of these categories, given the inherent differences among races with respect to these metabolic parameters.\(^2,3\) For example, African-Americans (AAs) have lower triglyceride and higher HDL-cholesterol levels than Whites in spite of a higher risk of a future CVD.\(^3,5\) Further, the traditional MetS definition potentially loses information about those individuals who have values closer to the cut-offs. We have developed a continuous z-score which assigns different weights to individual metabolic components in sex-, race- categories, and thus, potentially accounts for the sex-, race-differences in the levels of these parameters.\(^6,7\)
The prevalence of MetS is known to increase with age, with a consistently increasing trend seen between 40-60 years of age among US adults in the NHANES. However, it is not clear how the prevalence changes with increasing age in a closed population-based cohort followed over time. Although it is possible that the change in prevalence in a closed cohort would mimic the change seen with increasing age across a cross-section of the population, examining MetS prevalence in a cohort requires several additional considerations:

Birth-Cohort Effect: It is possible that the individuals who were born closer in time would follow similar trend e.g. individuals between 40-49 years of age at baseline would have a similar trend which is different from the trend followed by individuals who are 50-59 years of age at baseline. Assuming this population is similar to the general US population, younger-at-baseline individuals would be exposed to detrimental effects of obesity for a longer duration than older participants.

Period effect: Certain events in time are known to have strong influences over disease pattern in a population. We will examine any abrupt changes in the trend at any particular time-point in the study. In the ARIC population, it is possible that the recommendations made by NCEP ATP III in 2002 for controlling high blood cholesterol would be an important landmark in the follow-up of this cohort. Another possible landmark to be considered for women participants is the reporting of increased CVD risk with hormone-replacement therapy from the WHI in 2002.

Both of the epidemiological effects discussed above may be linked to the use of medications over time. It is possible that individuals who were younger at baseline got exposed to lipid-lowering medications at an earlier age (due to period effect) than those who were older to begin with. Additional consideration is the increasing prevalence of obesity in the US. We will take all these epidemiological concepts into consideration while performing the analyses.

5. Main Hypothesis/Study Questions:

A. For Traditional MetS definition:
   i) MetS prevalence increases over time in the ARIC cohort.
   ii) The trend in MetS in the ARIC cohort differs by sex and race.

B. For MetS z-score:
   i) MetS severity in the ARIC cohort increases over time.
   ii) Presence of cohort effect (age at baseline) and period effect (e.g. medication use) influences the trend in MetS severity in this cohort

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 methodological limitations or challenges if present).
We will use an epidemiological approach to study our hypotheses - trends in the traditional MetS as well as MetS severity score would be examined over time in the ARIC study.

1) Trend of individual MetS components will be examined in the ARIC cohort (as defined in MetS criteria as well as a continuous variable). Sex and Race differences in the trend will be assessed. Attention will be given to the use of medications for any metabolic derangements, including anti-hypertensives, anti-lipidemic agents, and hypoglycemic agents.

2) Trend in traditionally defined MetS will be assessed in the overall population as well as by sex and race.

Traditional MetS will be calculated as established by ATP III:

<table>
<thead>
<tr>
<th>ATP III Criteria (presence of 3 or more of the following criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
</tr>
<tr>
<td>&gt;88 cm (Females)</td>
</tr>
<tr>
<td>&gt;102 cm (Males)</td>
</tr>
<tr>
<td>Triglyceride</td>
</tr>
<tr>
<td>≥150 mg/dl, OR use of lipid-lowering meds</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
</tr>
<tr>
<td>&lt;50 mg/dl (Females)</td>
</tr>
<tr>
<td>&lt;40 mg/dl (Males), OR use of lipid-lowering meds</td>
</tr>
<tr>
<td>Fasting glucose</td>
</tr>
<tr>
<td>&gt;100 mg/dl, OR use of diabetes meds</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Systolic ≥ 130 mmHg, OR Diastolic ≥ 85 mmHg, OR use of BP-lowering meds</td>
</tr>
</tbody>
</table>

3) Trend in MetS severity assessed as weighted z-score in the overall population as well as by sex and race. Sex-, race- specific MetS severity score will be calculated using the sex- and race-weighted formula derived from the adult US population in NHANES 1999-2010. (Appendix)

4) Influence of birth cohort effect and period effect on MetS trend (presence as well as severity) will be assessed by -

   i) comparing MetS trend overtime between baseline age-groups i.e. 45-50 years, 50-55 years, 55-60 years and 60-65 years.
   ii) by stratifying the analysis into visit 1- visit 4 and visit 4 – visit 5 , then examining the trend between visit 4 and visit 5 to assess the effect of increasing use of medications between visit 4 and visit 5.
5) Given the significant time-difference between visit 4 and visit 5, a considerable number of participants were lost to follow-up between these visits. Thus, we will compare the characteristics of those who participated at visit 5 with those who were lost to follow-up between visit 4 and visit 5. It is possible that as compared to participants who were lost-to-follow-up between visit 4 and visit 5, participants who followed-up at visit 5 during 2011-13 were in-general younger and healthier at baseline.

**Statistical Analysis Plan:**

Baseline descriptive characteristics of the study population will be examined by sex and race. Differences between the groups will be assessed using descriptive statistics i.e. t-tests, chi-square tests and non-parametric tests, as appropriate. MetS presence will be evaluated using the criteria described in table 1 and MetS severity will be calculated using the sex- race- specific formulae as in the appendix A. Similarly MetS prevalence, MetS score and MetS severity will be calculated over the follow-up visits.

We will assess the trend in MetS by plotting MetS prevalence and severity over time – using overall population, and after stratifying by race, sex and baseline age. Estimates at each visit and inferences regarding trends over time will be calculated using generalized linear mixed models that account for the correlation among observations from the same participant. These models will also be used for formal assessment of interactions between MetS over time and sex, race, and baseline age.

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 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?

NA

___ 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”?
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.csec.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.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

___ Yes  _X_ No

11.b. If yes, is the proposal  

_ X_ A. primarily the result of an ancillary study (list number* 2013.18)  

_ X_ 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.  

- I agree to this requirement (Abhishek Vishnu)

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.  

- I agree to this requirement (Abhishek Vishnu)

References


### Adolescent (Ages 12-19 Years)

<table>
<thead>
<tr>
<th>Group</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>$-4.9310 + 0.2804 \times \text{BMI Z-score} - 0.0257 \times \text{HDL} + 0.0189 \times \text{SBP} + 0.6240 \times \ln(\text{Tri}) + 0.0140 \times \text{Glu}$</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>$-4.7544 + 0.2401 \times \text{BMI Z-score} - 0.0284 \times \text{HDL} + 0.0134 \times \text{SBP} + 0.6773 \times \ln(\text{Tri}) + 0.0179 \times \text{Glu}$</td>
</tr>
<tr>
<td>Hispanic</td>
<td>$-3.2971 + 0.2930 \times \text{BMI Z-score} - 0.0315 \times \text{HDL} + 0.0109 \times \text{SBP} + 0.6137 \times \ln(\text{Tri}) + 0.0140 \times \text{Glu}$</td>
</tr>
</tbody>
</table>

| **Females**       |                                               |
| Non-Hispanic White| $-4.3757 + 0.4849 \times \text{BMI Z-score} - 0.0176 \times \text{HDL} + 0.0257 \times \text{SBP} + 0.3172 \times \ln(\text{Tri}) + 0.0083 \times \text{Glu}$ |
| Non-Hispanic Black| $-3.7145 + 0.5136 \times \text{BMI Z-score} - 0.0190 \times \text{HDL} + 0.0134 \times \text{SBP} + 0.4442 \times \ln(\text{Tri}) + 0.0108 \times \text{Glu}$ |
| Hispanic          | $-4.7637 + 0.3520 \times \text{BMI Z-score} - 0.0263 \times \text{HDL} + 0.0152 \times \text{SBP} + 0.6910 \times \ln(\text{Tri}) + 0.0133 \times \text{Glu}$ |

### Adult (Ages 20+ Years)

<table>
<thead>
<tr>
<th>Group</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>$-5.4559 + 0.0125 \times \text{WC} - 0.0251 \times \text{HDL} + 0.0047 \times \text{SBP} + 0.8244 \times \ln(\text{Tri}) + 0.0106 \times \text{Glu}$</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>$-6.3767 + 0.0232 \times \text{WC} - 0.0175 \times \text{HDL} + 0.0040 \times \text{SBP} + 0.5400 \times \ln(\text{Tri}) + 0.0203 \times \text{Glu}$</td>
</tr>
<tr>
<td>Hispanic</td>
<td>$-5.5541 + 0.0135 \times \text{WC} - 0.0278 \times \text{HDL} + 0.0054 \times \text{SBP} + 0.8340 \times \ln(\text{Tri}) + 0.0105 \times \text{Glu}$</td>
</tr>
</tbody>
</table>

| **Females**       |                                               |
| Non-Hispanic White| $-7.2591 + 0.0254 \times \text{WC} - 0.0120 \times \text{HDL} + 0.0075 \times \text{SBP} + 0.5800 \times \ln(\text{Tri}) + 0.0203 \times \text{Glu}$ |
| Non-Hispanic Black| $-7.1913 + 0.0304 \times \text{WC} - 0.0095 \times \text{HDL} + 0.0054 \times \text{SBP} + 0.4455 \times \ln(\text{Tri}) + 0.0225 \times \text{Glu}$ |
| Hispanic          | $-7.7641 + 0.0162 \times \text{WC} - 0.0157 \times \text{HDL} + 0.0084 \times \text{SBP} + 0.8872 \times \ln(\text{Tri}) + 0.0206 \times \text{Glu}$ |

### Abbreviations and Units:

- BMI z-score: Body mass index z-score (calculated from height and weight)
- WC: Waist circumference (cm)
- HDL: High-density lipoprotein (mg/dL)
- SBP: Systolic blood pressure (mm Hg)
- Tri: Triglycerides (mg/dL)
- Glu: Fasting blood glucose (mg/dL)