1.a. Full Title: Additive Interactions and the Metabolic Syndrome

b. Abbreviated Title (Length 26 characters): Interactions in MetS

2. Writing Group:
Writing group members:
Matthew J. Gurka, PhD
Abhishek Vishnu, PhD
Dustin Long, PhD
Baqiyah Conway, PhD
David Couper, PhD
Mark DeBoer, MD, MSc, MCR

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

First author: Matthew Gurka
Address: PO Box 9190
        Morgantown, WV 26506-9190

        Phone: 304-293-6760       Fax: 304-293-2700
        E-mail: mgurka@hsc.wvu.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 generally defined as a cluster of cardiovascular risk factors, including obesity, high blood pressure, elevated triglycerides, low HDL, and elevated fasting glucose, that has been observed to be associated with future disease (diabetes, cardiovascular disease). MetS has been argued to be a stronger risk factor for future disease than the individual components that comprise it, but this assertion is hotly debated amongst clinicians and researchers alike. In addition, questions remain regarding whether such additive interactions are similar across racial/ethnic groups.

The notion of additive interactions/synergy is not a new concept and has been studied extensively in the epidemiology literature (Rothman, Greenland, and Lash 2008; VanderWeele 2009; VanderWeele and Knol 2014). Rather than the traditional statistical interaction, which is in fact a multiplicative interaction (for a logistic or survival model), and is a measure of effect measure modification, we are often interested in additive interactions on these scales, particularly in cohort studies such as ARIC. In other words, is the joint effect of two exposures, E1 and E2, greater than the combined independent effects of E1 and E2 on the risk of outcome O? Numerous indices to measure additive interactions have been proposed in numerous settings, including the Synergy Index, the Relative Excess Risk due to Interaction (RERI), and the Attributable Portion due to Interaction (AP) (Skrondal 2003).

This concept of synergy is the basis for MetS, in that it is assumed that having MetS is a greater risk factor of future disease than the combined independent effects of the components that make up MetS. Surprisingly, however, MetS and the potential additive interactions among its components has not been studied epidemiologically using the aforementioned indices, particularly in ARIC. While others have examined additive interactions in ARIC (Li and Chambless 2007; Zou 2008), to our knowledge MetS has not been studied in this manner in ARIC. McNeill et al. (2005) came close to what we are proposing using ARIC, in that it assessed the ability of MetS to predict risk of CVD above and beyond its components. They did this by including the components in a (proportional hazards) model, and then included MetS in the model to determine if it added to the prediction of CVD (it did not). However, we propose a more comprehensive examination of whether any of the individual MetS components interact with one another (and in what fashion), as there are numerous definitions of MetS. We hope we are able to elucidate if certain particular combinations interact – leading to refinement of the traditional straightforward definition that requires “3 or more” elevations, whether interactions differ by sex and race, and whether it is beneficial to utilize continuous risk factors rather than binary cut points. Golden et al. (2002) was an additional ARIC study that examined which groupings were predictive of excess carotid IMT. The authors did utilize the concept of additive interactions in predicting this continuous outcome. We hope to expand on this by examining additive interactions on a risk scale of a binary outcome while also examining differences between sex and race.
A comprehensive study of additive interactions will not only advance the study of interactions in general, a greater understanding of the value of MetS in predicting future disease will result from this study.

5. Main Hypothesis/Study Questions:

This methodological paper, targeted for a journal such as the American Journal of Epidemiology, will attempt to extend the literature on additive interactions by proposing extensions to interaction indices (SI, RERI) that allow for three-way or higher additive interactions. Current indices can be calculated (with appropriate inference) for pairwise interactions, and even three-way interactions (VanderWeele 2012). However, most current definitions of MetS require elevations of five or more of its components listed above. Therefore, a systematic exploration of measures of four-way and five-way interactions (and the ability to make inferences) is essential. After the methodology is developed, the following questions will be answered:

**Study Question 1:** How do the components of MetS interact in an additive way to predict future CVD and diabetes?

**Study Question 2:** How do the observed interactions vary by sex and race/ethnicity?

We have discovered important differences in MetS by sex and race/ethnicity, both in how the components correlate with each other and how MetS is associated cross-sectionally with surrogates of disease (Gurka et al. 2014). Therefore, any additive interactions observed related to Study Question 1 may vary by sex and race-ethnicity. To our knowledge, no one has studied the concept of effect measure modification, when the “effect” is the measure of additive interaction (e.g., RERI).

**Study Question 3:** Do estimates of additive interaction among MetS components differ depending on whether one treats the components as binary variables (“high” vs. “normal” values) or whether one examines them continuously?

The cut point values for elevated levels of MetS components have been debated and not well-justified, and are not race-specific. RERI’s can be computed for continuous exposures as well, thus it would be informative to know how the components interact when utilized as binary variables vs. continuous.

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).

To parallel other studies and to limit complications with respect to selection bias, loss-to-follow up, and other missing data, we will focus on incident CVD and diabetes by Visit 4
of ARIC, excluding individuals with either of these conditions at Visit 1. As this is primarily a methodological paper that will focus on extensions/novel uses of additive interaction indices, we will focus first on log-linear (binomial) models of risk of CVD and diabetes (separately) at Visit 4, focusing on MetS and its binary components (e.g., “high” waist circumference, “low” HDL, etc.) at Visit 1. Pairwise interactions of the 5 components will be assessed via traditional indices (RERI), with 10 RERI measures (and 95% CI’s) calculated. Systematically, three-way, four-way, and the five-way interactions will then be calculated once the equations are formulated. This analysis will help determine if and how MetS provides additional 10-year risk information (for CVD and diabetes) above and beyond its components. We will study how to statistically compare RERI measures between four sex and race groups (white males, white females, black males, black females). RERI values will also be computed for the MetS components as continuous variables, comparing to their binary RERI counterparts. Finally, extensions of this interaction study to proportional hazards models of time to CVD/diabetes (similar to Li and Chambless 2007) will be explored.

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? ___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”? ___ 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.cscn.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)?

- This study is the closest to what we propose, in that it assessed the ability of MetS to predict risk of CVD above and beyond its components. This study did this by including the components in a (proportional hazards) model, and then included MetS in the model to determine if it added to the prediction of CVD (it did not). However, we propose a more comprehensive examination of whether any of the individual MetS components interact with one another (and in what fashion), as there are numerous definitions of MetS. We hope we are able to elucidate if certain particular combinations interact – leading to refinement of the traditional straightforward definition that requires “3 or more” elevations, whether interactions differ by sex and race, and whether it is beneficial to utilize continuous risk factors rather than binary cut points.


- This is another ARIC study that examined which groupings were predictive of excess carotid IMT. The authors did utilize the concept of additive interactions in predicting this continuous outcome. We hope to expand on this by examining additive interactions on a risk scale of a binary outcome while also examining differences between sex and race.


- This study looked at the synergy of MetS and plasma fibrinogen on predicting future disease; we however want to look at the synergy of the MetS components themselves


- This study is very similar to what we wish to do with respect to methodology, but it did not focus on MetS whatsoever.


- This was a methodological study that used ARIC as an example application, focusing on a gene x environment interaction (not related to MetS)
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 (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.

References


