1. **Full Title:** Establishing Temporality Amongst Correlated Cardiometabolic Variables: Atherosclerosis Risk in Communities Study

   b. **Abbreviated Title (Length 26 characters):** SEM of metabolic variables

2. **Writing Group:**
   Writing group members: Dhananjay Vaidya, Mariana Lazo, J. Hunter Young, Josef Coresh; others welcome

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

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3. **Timeline:** We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal.

4. **Rationale:**
When two biomarkers are associated with each other in a cross-sectional study, it is well known that this association does not imply causation. An example of this is the mutual correlation of measures of obesity and fasting glucose. More generally, in the cluster of metabolic abnormalities known as the “metabolic syndrome”, do some of the subclinical abnormalities occur temporally earlier and other abnormalities temporally later? Temporality is a factor in distinguishing causes from effects, and targeting temporally prior abnormalities with interventions is likely to be more effective in preventing the correlated downstream outcomes of morbid obesity and Type 2 diabetes.

In longitudinal studies, we have multiple measures of the metabolic variables fasting glucose, waist circumference, systolic blood pressure, HDL-cholesterol levels, triglyceride levels. These are continuous variables with unimodal distributions with no biological threshold for abnormality. Although thresholds have been proposed for clinical
use, dichotomous analysis of incidence would miss the information from the continuous variables changing in the subthreshold and suprathreshold ranges. Studies have described the multiple cross sectional correlations, and correlation of delta-variables (change) in longitudinal, however, there are no studies that assess temporality of the changes. If successful, structural equation modeling will further our capacity to identify causal mechanisms in epidemiologic studies. We propose to use structural equation modeling to estimate the temporality of the changes in different variables.

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References:

5. Main Hypothesis/Study Questions:
Study question: To characterize the temporality of five cardiometabolic variables (waist circumference, systolic blood pressure, fasting glucose, HDL-cholesterol and triglycerides) from ARI visit 1 (baseline) to visit 2 (followup).
Hypothesis: Larger waist circumference is temporally prior to quantitatively abnormal levels of other cardiometabolic variables, namely fasting glucose, systolic blood pressure, HDL-cholesterol levels and triglyceride levels, in structural equation modeling adjusting for cross sectional and longitudinal correlations.

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).
The proposed structural equation model is shown in the figure below:

Here $X_1$ to $X_5$ are the 5 metabolic variables. For clarity, endogenous “error” variables and correlations between error variables are not shown. For the purpose of description a
single pair of measures \((X_1, X_2)\), and the associated variables at baseline and follow-up are highlighted, though all possible pairs are included within the model. Inherent temporality of the two visits allows single-headed arrows to be drawn between baseline measures going towards follow-up measures. Cross-sectional correlations are bidirectional. The temporal relationship of the correlations between and \(X_1\) and \(X_2\) are assessed by statistically comparing the magnitudes of the two unidirectional correlations \(r_{1,2}\) and \(r_{2,1}\), which are adjusted for all cross sectional correlations. If the magnitude of \(r_{1,2}\) is greater than that of \(r_{2,1}\), the level of variable \(X_1\) is temporally prior to the level of \(X_2\); and vice versa. If the magnitudes of \(r_{1,2}\) and \(r_{2,1}\) are comparable, then the two variables are changing in parallel with each other with neither variable being temporally prior to the other.

**Data required:**
Fasting glucose, waist circumference, systolic blood pressure, HDL-cholesterol, triglyceride levels from ARIC visit 1 and visit 2 will be used in the above schema. Only persons with non-missing data for both visits will be included. Persons with use of antihypertensive medication or antidiabetic medication during either visit will be excluded.
Covariates include baseline age, sex and race.

**Multicohort Study Related Note (Pooled/metaanalysis):** This is planned to be a pooled multi-cohort study. The analysis proposal is to be submitted to four different cohort studies: ARIC, MESA, CARDIA and Johns Hopkins GeneSTAR. The first author (Vaidya) is a co-investigator in all four studies and will have access to person-level data. In pooled models, a variable coding “study” will be added as a covariate. If any individual study publication committees do not permit pooling of individual level data, we will perform study-specific analysis and then perform metaanalysis of the SEM coefficients.

### 7.a. Will the data be used for non-CVD analysis in this manuscript?  
___ 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?  
___ 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 ___ 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 N/A
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.csc.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)?

None

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

___ A. primarily the result of an ancillary study (list number* ______)

___ 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.