ARIC Manuscript Proposal #2454

PC Reviewed: 10/14/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of metabolic syndrome and insulin resistance with pulse wave velocity: the ARIC Study

b. Abbreviated Title (Length 26 characters): Insulin resistance and pulse wave velocity

2. Writing Group:

Writing group members: Anna Poon, Michelle Snyder, Liz Selvin, David Couper, Laura Loehr, Hirofumi Tanaka, Gerardo Heiss, others welcome

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

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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).

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3. Timeline: Analysis to start once approval is obtained. We plan to complete the manuscript within eight months from approval of the proposal.

4. Rationale: Metabolic syndrome is associated with increased risk of cardiovascular disease [1, 2] and diabetes [3]. The metabolic syndrome is characterized by a clustering of risk factors, including raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity. The presence of three or more of these risk factors constitutes a clinical presentation of this condition [4, 5].

Pulse wave velocity is a valid and reliable measure of arterial stiffness and has been shown to predict cardiovascular morbidity and mortality [6, 7]. Indeed, prior studies have shown an association of metabolic syndrome with higher peripheral pulse wave velocity measurements [8-13]. These studies, however, were limited to clinical settings, homogeneous populations, and did not evaluate differences by either gender or race (subgroups with known differences in cardiovascular risk). Moreover, none of these studies evaluated multiple (i.e. different) indices of insulin resistance, which may mediate the association of metabolic syndrome with arterial stiffness. From a practical standpoint, we are interested in this question because the metabolic syndrome presents multiple targets (individual components) for intervention.

The goal of our analysis will be to examine the association of central and peripheral arterial stiffness measured by carotid-femoral pulse wave velocity, brachial-ankle pulse wave velocity, and femoral-ankle pulse wave velocity with the metabolic syndrome and insulin resistance indices in older adults.

5. Main Hypothesis/Study Questions:

Aim 1: To examine the association of the metabolic syndrome with carotid-femoral (cfPWV), brachial-ankle (baPWV), and femoral-ankle (faPWV) pulse wave velocity at ARIC Visit 5 (2011-2013). Our hypotheses include the following:

1. Hypothesis #1: Metabolic syndrome is positively associated with arterial stiffness. Average cfPWV, baPWV, and faPWV will be higher in persons with metabolic syndrome as compared to persons without metabolic syndrome.

2. Hypothesis #2: The association of metabolic syndrome with arterial stiffness is additive. The individual components of the metabolic syndrome will be positively associated with each pulse wave velocity measurement. Moreover, average cfPWV, baPWV, and faPWV will be higher in persons with a higher number of risk factors for the metabolic syndrome as compared to persons with a lower number of risk factors for the metabolic syndrome.

3. Hypothesis #3: Sex and race will modify the association of metabolic syndrome with arterial stiffness. The association of metabolic syndrome and cfPWV, baPWV, and faPWV (i.e. the difference in average cfPWV, baPWV, and faPWV between persons with and without metabolic syndrome) will be greater in females than males, and greater in African Americans than Caucasians.

Aim 2: To examine the association of the insulin resistance indices (as estimated by fasting insulin, the homeostatic model assessment (HOMA), McAuley's Index, and the triglycerides and glucose (TyG) index.) with carotid-femoral (cfPWV), brachial-ankle (baPWV), and femoral-ankle (faPWV) pulse wave velocity at ARIC Visit 5 (2011-2013). Our hypotheses include the following:

4. Hypothesis #1: Estimated insulin resistance is positively associated with arterial stiffness. Higher average cfPWV, baPWV, and faPWV will be associated with higher average levels of each insulin resistance index.

5. Hypothesis #2: Sex and race will modify the association of insulin resistance with arterial stiffness. The association of insulin resistance indices and cfPWV, baPWV, and faPWV will be greater in females than males, and greater in African Americans than Caucasians.

Aim 3: To prospectively track metabolic syndrome presentation at ARIC Visit 1 (1987-1989), Visit 2 (1990-1992), Visit 3 (1993-1995), Visit 4 (1996-1998), and Visit 5 (2011-2013).

6. Hypothesis #1: Once present, the metabolic syndrome designation (the presence of three out of five metabolic syndrome risk factors) will remain stable over time. Metabolic syndrome components (specifically, the presence of abdominal obesity, reduced HDL cholesterol levels, and elevated blood pressure) will rank comparably (or "track") over time, as compared to the preceding visit.

7. Hypothesis #2: Time-in-metabolic syndrome over the course of follow-up is (independently) associated with cfPWV, baPWV, and faPWV.

8. Hypothesis #3: The longitudinal association of the metabolic syndrome with PWV at Visit 5 reflects the intensity of exposure (number of metabolic risk factors / follow-up time on an additive scale) more so than the duration of the exposure (length of exposure normalized for intensity).

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).

Study design:

Aims 1 and 2: Cross-sectional. The study population will include ARIC participants with pulse wave velocity measurements at ARIC Visit 5 (2011-2013).

Aim 3: Prospective. The study population will include ARIC participants with measurements for waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose at ARIC Visits1 (1987-1989), Visit 2 (1990-1992), Visit 3 (1993-1995), Visit 4 (1996-1998), and Visit 5 (2011-2013).

Exclusions: Participants with missing values for the following variables will be excluded from the analysis: cfPWV, baPWV, faPWV, components of the metabolic syndrome and insulin resistance indices (gender, waist-circumference measurements, triglycerides, high-density lipoprotein cholesterol, systolic/diastolic blood pressure, fasting glucose, and fasting insulin) and other covariates of interest (including age and race). Participants with diabetes will be excluded from this analysis.

Additional exclusions for pulse wave velocity were made due to data quality concerns: (1) BMI $\geq$40 kg/m^2, (2) evidence of a major arrhythmia on a 12-lead ECG; (3) self-reported aortic revascularization surgery; (4) aortic aneurysm; (5) aortic stenosis and aortic regurgitation; and (6) pulse wave velocity values greater than 3 standard deviations away from the mean.

Exposure: *Metabolic syndrome.* The metabolic syndrome will be analyzed as a binary variable (yes or no) and indicator variable (indicators will be defined by the number of present risk factors: 0, 1, 2, 3, 4, and 5). This analysis will use the definition for metabolic syndrome set by the American Heart Association/National Heart, Lung, and Blood Institute [4]; central obesity will be based on waist circumference cut-points set by the International Diabetes Federation [14].

Components of the metabolic syndrome	Categorical cut points
Elevated waist circumference	102 cm in males 88 cm in females
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
Reduced HDL-C	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure	SBP ≥130 mm/Hg and/or DBP≥85 mmHg or antihypertensive drug treatment
Elevated fasting glucose	≥100 mg/dL

Insulin resistance. Insulin resistance indices will be analyzed continuously. Four insulin resistance indices will be examined [15-17]; each of the latter three measures have correlated well with or have been validated against the euglycemic clamp test, the gold standard for characterizing insulin resistance.

Insulin resistance indices	Definition
Fasting insulin	μU/mL
HOMA-IR	Fasting glucose (mg/dL) x fasting insulin (uU/mL) / 405
McAuley's Index (Mffm/I)	exp[2.63 – 0.28ln(insulin) – 0.31ln(TG)]
Triglycerides and glucose (TyG) index	[ln(fasting TG) (mg/dL) x fasting glucose (mg/dL) / 2]

Outcome: Pulse wave velocity will be analyzed continuously. Values for cfPWV, baPWV, and faPWV were measured using the Colin VP-1000 Plus system (Omron Co.,

Ltd., Komaki, Japan). The path length was calculated using the following: distance traveled (cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm)).

Statistical analysis:

(a) Aim 1, Hypothesis 1: Summary statistics for cfPWV, baPWV, and faPWV will be examined by metabolic syndrome diagnosis (yes or no) at baseline (visit 1). Multivariable regression will be used to estimate the association of metabolic syndrome with cfPWV, baPWV, and faPWV (estimated coefficients and 95% confidence intervals will describe the difference in cfPWV, baPWV, and faPWV between persons with and without diagnosed metabolic syndrome). We will examine unadjusted associations (model 1) and associations adjusted for age, race, and gender (model 2).

(b) Aim 1, Hypothesis 2: Summary statistics for cfPWV, baPWV, and faPWV will be examined stratified by the presence of 0, 1, 2, 3, 4, and 5 risk factors for metabolic syndrome. Multivariable regression will be used to estimate the association of the presence of each additional risk factor for metabolic syndrome with cfPWV, baPWV, and faPWV (estimated coefficients and 95% confidence intervals will describe the difference in cfPWV, baPWV, and faPWV between persons with 1, 2, 3, 4, and 5 risk factors, as compared to 0 risk factors; the referent group of 0 risk factors may change). We will examine unadjusted associations (model 1) and associations adjusted for age, race, and gender (model 2).

(c) Aim 1, Hypothesis 3: The analyses for aim 1 (hypotheses 1 and 2) will be repeated stratified by sex (model 3) and race (model 4). Formal tests for interaction will be included.

(d) Aim 2, Hypothesis 1: Scatter plots will be used to examine the unadjusted association of insulin resistance indices with cfPWV, baPWV, and faPWV; insulin resistance indices will be analyzed to reflect either linear or non-linear associations with pulse wave velocity measurements. Multivariable regression will be used to estimate the association of insulin resistance indices with cfPWV, baPWV, and faPWV. We will examine unadjusted associations (model 1) and associations adjusted for age, race, and gender (model 2).

(e) Aim 2, Hypothesis 2: The analyses for aim 2 (hypothesis 1) will be repeated stratified by sex (model 3) and race (model 4). Formal tests for interaction will be included.

(f) Aim 3, Hypothesis 1 - 4: Metabolic syndrome diagnosis (the presence of three out of five metabolic syndrome risk factors) will be tracked for Visits 1, 2, 3, 4, and 5. Components of the metabolic syndrome will be tracked for Visits 1, 2, 3, 4, and 5.

(g) Inverse probability weighting will be used to account for participant attrition.

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

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

_____ 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)?

- "The association of diabetes, impaired glucose tolerance, and chronic hyperglycemia with pulse wave velocity: the ARIC study." (First author: Laura Ross Loehr)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ 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.

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