ARIC Manuscript Proposal #2999

PC Reviewed: 06/06/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Arterial stiffness, pressure pulsatility, and white matter integrity assessed by diffusion tensor imaging. The ARIC-NCS study

b. Abbreviated Title (Length 26 characters): **PWV and DTI**

2. Writing Group:

Writing group members (in alphabetical order): Rebecca Gottesman, Gerardo Heiss, Clifford Jack, Thomas Mosley, Priya Palta, Melinda C. Power, Robert Reid, Denise Reyes, Richey Sharrett, Hirofumi Tanaka (invited), Keenan Walker, Jingkai Wei, others welcome

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

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3. Timeline: Finish statistical analysis and manuscript writing within 12 months from approval of the manuscript proposal.

4. Rationale:

Cerebral small vessel disease (CSVD), a set of pathological processes of various etiologies that affect cerebral small arteries, arterioles, venules, and capillaries, is associated with dementia.[1] Structural and functional neuroimaging techniques, including magnetic resonance imaging (MRI), are key in the study of cerebral small vessels and other attributes of brain structure and function.[2] White matter hyperintensities (WMH), have been found to be associated with decreased cognitive performance, particularly executive function.[3] However, reported correlations between clinical features of CSVD (e.g., lacunar infarct, chronic hypoperfusion) and

conventional MRI measures have not been consistent, perhaps reflecting the inability to characterize microstructural properties related to WMH with a conventional MRI.[4]

Diffusion tensor imaging (DTI) uses a tensor model to measure both the rate and directionality of the diffusion distribution of water molecules in tissue.[5] Tractography can be used to spatially characterize white matter diffusion abnormalities along the pathway of a specific tract, with high sensitivity in detecting cerebral damage.[2] Mean diffusivity (MD) represents the average rate of diffusion independent of the directionality, and fractional anisotropy (FA) indicates the fraction of the tensor that can be assigned to anisotropic diffusion. Higher MD and lower FA are thought to be independently related to white matter tract integrity. DTI is expected therefore to provide a better measure of white matter integrity than conventional MRI.

Increased arterial stiffness, a marker of arterial wall remodeling, is associated with cognitive decline and dementia.[6] Central arterial stiffness and pressure pulsatility, in addition to previously studied risk factors, such as HbA1c, hypertension, total- and LDL-cholesterol,[7] are associated with CSVD and WMH[8-11]. Increased central arterial stiffness may lead to insufficient flow wave dampening and transmission of excessive pulsatile energy into the microvascular bed, particularly in low impendence organs such as the brain.[12] The associations between arterial stiffness and pressure pulsatility (measured with central pulse pressure (cPP)) have been reported by studies using conventional MRI data,[9,13-15] while only a few studies have examined associations of white matter outcomes measured with DTI. The Framingham Heart Study Third-Generation cohort showed that higher carotid-femoral pulse wave velocity was associated with lower FAs. [16,17] Tarumi et al.[18] showed that higher cfPWV is independently associated with lower FA. Sala et al. [19] indicated that increased aortic arch pulse wave velocity (PWV) was associated with decreased white matter FA among patients with hypertension. Tjeerdema et al. [20] showed that aortic stiffness is independently associated with reduced white matter integrity in patients with type 1 diabetes. However, several of these studies were based on individuals with chronic conditions and homogeneous study populations (i.e., mostly white participants). Additionally, previous studies reported that African Americans have higher arterial stiffness and pulsatility,[21,22] as well as higher prevalence of white matter disease[23], but no studies to date have examined the associations between arterial stiffness and white matter integrity in a biracial sample of older adults. Moreover, no study has examined the potential joint association of arterial stiffness and pulsatility in the association with white matter integrity.

Drawing on the large and well-characterized cohort of Whites and Blacks in ARIC-NCS, we propose to examine the association of central arterial stiffness and pulsatility with white matter integrity, measured by DTI, among a community-dwelling sample of older adults.

5. Main Hypothesis/Study Questions:

Aim 1: Examine the association of aortic arterial stiffness (i.e. carotid femoral pulse wave velocity [cfPWV]) with white matter integrity (measured with DTI) among older adults.

Aim 1.1. Examine the association of cfPWV with FA measured with DTI among older adults.

Aim 1.2. Examine the association of cfPWV with MD measured with DTI among older adults.

We hypothesize that a higher cfPWV is associated with greater MD and lower FA measured with DTI among older adults.

Aim 2: Examine the association of pressure pulsatility (i.e. central pulse pressure [cPP]) with white matter integrity measured with DTI among older adults.

Aim 2.1. Examine the association of cPP with FA measured with DTI among older adults.

Aim 2.2. Examine the association of cPP with MD measured with DTI among older adults.

We hypothesize that higher cPP are associated with greater MD and lower FA measured with DTI among older adults.

Aim 3: Examine the interaction of aortic arterial stiffness and pulsatility with white matter integrity measured with DTI among older adults.

Aim 3.1. Examine the joint association of cfPWV and cPP with FA measured with DTI among older adults.

Aim 3.1. Examine the joint association of cfPWV and cPP with MD measured with DTI among older adults.

We hypothesize that cfPWV and cPP are jointly associated with greater MD and lower FA measured with DTI in an additive manner among older adults.

Aim 4: Estimate the race-specific association of cfPWV, cPP on MD and FA measured with DTI.

Aim 4.1. Examine the association of cfPWV and cPP independently, on FA measured with DTI among Whites and Blacks, respectively.

Aim 4.2. Examine the association of cfPWV and cPP independently on MD measured with DTI among Whites and Blacks, respectively.

Aim 4.3. Examine the joint association of cfPWV and cPP on FA measured with DTI among Whites and Blacks, respectively.

Aim 4.4. Examine the joint association of cfPWV and cPP with MD measured with DTI among Whites and Blacks, respectively.

We hypothesize that the associations of cfPWV and cPP with FA and MD among Blacks are further away from the null (i.e. smaller association for FA and larger association for MD), compared to Whites.

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: Cross-sectional analysis at Visit 5 of the association between arterial stiffness/pressure pulsatility and white matter integrity measured by DTI.

The following will be exclusions for the primary analyses: Prior history of stroke, missing DTI or arterial stiffness/pressure pulsatility data. Due to small numbers, race other than black or white, and black participants examined at MD or MN will be excluded. For optimal PWV data quality, the analyses will also exclude participants with evidence of a major arrhythmia on the 12-lead ECG (MN code 8-1-3, 8-3-1, 8-3-2), and participants with aortic aneurysm, aortic stenosis and aortic regurgitation.

Exposures (visit 5): cfPWV and cPP were measured using the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan). Carotid-femoral pulse wave velocity (cfPWV) is the gold standard measure of central arterial stiffness.[24] cfPWV was calculated using the following formula: path length

(cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm)). A minimum of two measurements were taken per participant and the last two usable measurements (i.e., non-zero values) were averaged. cSBP were measured in the supine position using an applanation tonometry sensor over the right common carotid artery using the automated Omron VP-1000 plus device (Omron Healthcare Co, Kyoto, Japan). A recorded carotid waveform was calibrated with simultaneously measured supine brachial mean arterial pressure (MAP) and diastolic blood pressure (DBP) using a cuff over the arm. The calibration assumes that MAP and DBP are largely constant between the brachial and carotid arteries.[25,26] cPP was defined as the difference between cSBP minus supine right brachial DBP, with the assumption that DBP values are largely uniform throughout the arterial tree.[27]

Outcomes (visit 5): DTI data was measured using 2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners. FA (ranges from 0.05 to 0.81) and MD (ranges from 0.0004 to 0.0019) were extracted for regions of interest (ROIs) using the ICBM DTI-81 Atlas.[28] ROIs include the following composite ones: tracts in the brainstem, commissural fiber, association fibers, projection fibers and a whole-brain composite measure. FA is normally distributed, and MD is right skewed.

Covariates (visit 5): age, sex, education, smoking, alcohol use, BMI, heart rate, APOE genotype, hypertension, diabetes, total cholesterol, WMH.

Effect measure modifiers: In addition to race, individuals carrying APOE4 allelic variant has shown reduction of FA and increase in MD in healthy adults compared to non-carriers,[29] which may be a potential moderator between arterial stiffness and pulsatility with white matter integrity.

Analysis plan:
For quantification of arterial stiffness and pressure pulsatility, cfPWV and cPP will be dichotomized at the upper 25th percentile to, indicate 'high' arterial stiffness and pulsatility. Analysis of participant characteristics at visit 5 will be conducted using T-test or chi-square test according to categories of cfPWV and cPP, respectively. We will examine the continuous distributions of FA or MD, and if observed to be non-normally distributed, the values will be log-transformed.

We will incorporate the ARIC-NCS MRI sampling weights in the analysis. Thus, weighted linear regression models will assess the relationship between each measure of arterial stiffness (cfPWV) and pressure pulsatility (cPP) with each DTI measure of white matter integrity (FA and MD). Due to their associations with both arterial stiffness/pressure pulsatility and cerebral small vessel disease, potential confounders include age, sex, education, smoking, heart rate, ApoE4 allele genotype, hypertension, diabetes, total cholesterol. We will further adjust for white matter hyperintensities (as measured by structural MRI), due to the strong correlation between WMH and FA and MD. We will examine potential interactions between cfPWV and cPP. In addition, we will examine potential effect measure modification by race and ApoE4 allele genotype.

Methodological limitations:

The cross-sectional design of this study precludes causal inferences about arterial stiffness/pulsatility and white matter integrity. Furthermore, participants of this study only include individuals ≥70 years of age, which constrains generalizability and can introduce selection bias.

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? ____ 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.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)?
#2551 Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS study

2866 The association of midlife and late-life inflammatory biomarkers with cerebral small vessel disease and white matter integrity in the elderly: The ARIC Study

#2597 Pulse Wave Velocity and Neurocognitive Outcomes in a Community-Dwelling Sample of Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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