ARIC Manuscript Proposal #2597

PC Reviewed: 8/11/15	**Status: 2**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Pulse Wave Velocity and Neurocognitive Outcomes in a Community-Dwelling Sample of Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Pulse wave velocity and neurocognition

2. Writing Group:

Writing group members: Priya Palta, Michelle Meyer, Jingkai Wei, Hirofumi Tanaka, Jennifer Deal, Clifford Jack, David Knopman, Jacqueline Wright (invited), Michael Griswold, Thomas H. Mosley, Gerardo Heiss, others welcome

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

First author: Priya Palta
Address: University of North Carolina at Chapel Hill
137 E. Franklin Street, Suite 306
Chapel Hill, NC 27514
Phone: (352) 219-4108
E-mail: priya_palta@unc.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: Gerardo Heiss
Address: University of North Carolina-Chapel Hill
137 E. Franklin Street, Suite 306
Chapel Hill, NC 27514
919-966-1967
E-mail: gerardo_heiss@unc.edu

3. Timeline: Analyses to start upon approval of proposal. Submit for an abstract to AHA EPI/Lifestyle meeting due October 14th, 2015. Submit for publication within 9 months from proposal approval.

4. Rationale:

Vascular aging is associated with stiffening of the aorta and arterial segment-specific loss of arterial elasticity due to the replacement of elastin with collagen[1]. Several cardiovascular disease risk factors are associated with accelerated vascular aging, including elevated blood pressure[2], diabetes mellitus and blood glucose levels[3], and high adiposity[4]. Age associated central arterial stiffening results in increased pulsatility,[5] which can profoundly affect the blood-brain barrier resulting in hypoperfusion and increased susceptibility to microvascular damage and remodeling in the brain, therefore resulting in impaired cognition[6]. Central arterial stiffening is thus a plausible vascular contributor to cognitive aging and provides insights into previously observed associations between hypertension and risk of cognitive decline and dementia in the elderly.

A recent meta-analysis[5] cited 13 cross-sectional and 2 longitudinal studies that have examined the associations between arterial stiffness and brain magnetic resonance imaging (MRI) measures (e.g. white matter hyperintensities (WMH) and infarcts). A total of 15 cross-sectional studies and 7 longitudinal studies have quantified the associations between arterial stiffness and cognition. All but one of the cross-sectional studies and one of the longitudinal studies observed increased arterial stiffness to be associated with lower cognitive function and predictive of cognitive decline, respectively. Several methodological limitations should be noted in these prior studies. Many of the studies used different equipment and/or methods to measure arterial stiffness, with unknown implications. Brachial-ankle pulse wave velocity (baPWV), an estimated measure not recommended for use in older adults[7], was most often used in these studies. Although correlated with central (aortic) stiffness, baPWV is an indirect measure of the arterial stiffness not likely to impact the microvasculature of the brain. The Mini-Mental State Examination state (MMSE) was the most frequently cited measure of cognition in these studies; however, the MMSE is a screening test for dementia and is not sensitive to capture different aspects of cognition. Lastly, the lack of adjustment for clinically relevant covariates, such as ApoE4 and depression, limits the reported findings.

We propose to the test the hypothesis that higher central arterial stiffness, as measured by carotid-femoral pulse wave velocity, is associated with lower cognitive function, infarcts and WMH on brain MRI, and increased odds of mild cognitive impairment (MCI) and dementia. ARIC provides the unique opportunity to contribute to the existing literature by examining this association in a well-characterized biracial cohort with longitudinal assessments of multidimensional cognition, extensive brain MRI measures, and segment-specific measures of PWV.

5. Main Hypothesis/Study Questions:

Aim 1: To test the hypothesis that arterial stiffness measured in older adulthood is associated with a greater decline in domain-specific cognition measured from mid- to late-life.

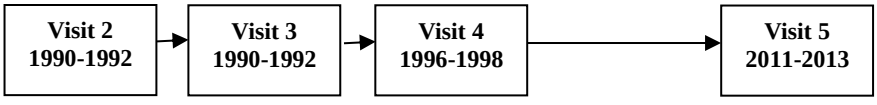
> **Aim 1.1:** Characterize the cross-sectional relationship of arterial stiffness with domain-specific cognitive function in a cohort of African-American and Caucasian older adults.

Aim 2: To test the hypothesis that arterial stiffness is cross-sectionally associated with white matter hyperintensities (WMH) and infarcts on the brain MRI.

Aim 3: To test the hypothesis that arterial stiffness is cross-sectionally associated with higher odds of (a) mild cognitive impairment and (b) dementia.

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: Prospective cohort design of arterial stiffness measured in older adulthood (Visit 5) and change in cognition from visits 2 to 5.



PWV data:			n=5,683
Neurocognition data:			
- DWRT, DSST, WFT	n=5,525	n=5,164	n=5,264
- Full neuro battery			n=5,683
- Brain MRI			n=1,845

Exclusions: Participants with missing information on PWV, body mass index (BMI) ≥40 kg/m^2, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2), Minnesota code 8-1-2 with evidence of biased PWV waveforms, aortic aneurysms, abdominal aorta ≥5 cm, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, moderate or greater aortic regurgitation; participants self-identified as Asian; and African American participants from the Minnesota and Maryland sites

Exposure(s):

Arterial stiffness measured by pulse wave velocity
PWV was measured by the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan) and the path length 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. We are primarily interested in carotid-femoral PWV (cfPWV), but may explore the other two segment-specific measures of PWV (femoral-ankle PWV (faPWV), and brachial-ankle PWV (baPWV)) in secondary analyses.

Pulse pressure amplification
Considering the hypothesized link between arterial stiffness and cognition to be pulsatile vascular stress, we will consider the following specific measures (and other derived) variables to provide further mechanistic insight: carotid pulse pressure and augmentation index.

Outcomes- Neurocognitive outcomes

Aim 1.1. Cognition measured at visits 2, 4 and 5 (longitudinal)
Three cognitive tests were administered by trained interviewers using a standardized protocol at visits 2, 4 and 5: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), and the Word Fluency Test (WFT). The *DWRT is a test of immediate verbal memory* where participants are asked to learn a 10-word list and then must recall as many words as possible after a 5-minute delay.[8] The score is based on the total number of correctly recalled words. The *DSST is a test of executive function and psychomotor speed* where participants are asked to relate numbers to symbols using a key.[9] With a maximum score of 93, the participant's score is the number of correct symbol-number matches within 90 seconds. The *WFT is a test of language and executive function*.[10] Participants are asked to generate as many words as possible beginning with the letter, "F," "A," and "S" within one minute. The participant's score is the total number of correctly generated words from the three letters. To facilitate relative comparisons across these tests, the raw test scores will be standardized to accommodate differences in scales. For each cognitive test at a visit, *z* scores will be calculated based on the means and standard deviations at baseline (visit 2). The global cognition *z* score will be calculated by averaging the *z* scores across the three tests.

Aim 1.2. Cognition measured at visit 5 (cross-sectional)
The following tests were included in the comprehensive neuropsychological battery administered at ARIC visit 5:

- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word fluency test (WFT)
- Logical Memory I and II
- Trail Making Test, Part A
- Trail Making Test, Part B
- Boston Naming Test

- Animal Naming
- Digit Span Backwards
- Incidental Learning

Tests will be examined individually and within domains. To facilitate relative comparisons across these tests, the raw test scores will be standardized to accommodate differences in scales. For each cognitive test at a visit, *z* scores will be calculated based on the means and standard deviations. Domain scores will be estimated by averaging the *z* scores for tests within a particular domain and then standardizing the averaged score using the mean and standard deviation. This ensures that each domain score is standardized to a mean=0 and standard deviation=1.

Aim 2. Brain MRI measures (measured at visit 5)
Brain MRIs were obtained from a 3D-1.5T MRI scan at visit 5/ARIC-NCS (2011-2013).[11] We will include imaging features that have been previously related to PWV in the literature, namely white matter brain atrophy, hyperintensities, cerebral microbleeds, lacunar infarcts, silent subcortical infarcts, brain volumes, white matter hyperintensity volumes, gray and white matter volumes, in addition to an AD-signature region variable created for the ARIC MRI data.

Aim 3. MCI and dementia as ascertained at visit 5

Covariates: For Aim 1.1, we will consider the following covariates measured at visit 2: age, sex, educational attainment, smoking, heart rate, prevalent CVD, diabetes, body mass index, blood pressure, anti-hypertensive medication use, depression, ApoE4.

For Aims 1.2, 2 and 3, time-varying covariates (smoking, heart rate, pulse pressure, prevalent CVD, diabetes, body mass index, blood pressure, anti-hypertensive medication use, depression) are measured at visit 5.

Analysis: Pulse wave velocity will be analyzed using distribution-based cut points and/or meaningful cut points published recently by the Arterial Stiffness' Collaboration group using data from eight European countries which provided reference values for cfPWV[12].

Aim 1.1: Using time on study, we will perform a longitudinal analysis using mixed effects models with a random intercept, a random slope for spline 1 and a random slope for spline 2.We will use an independence covariance matrix for the random effects. To account for the lapse in data collection in ARIC, a linear spline will be included at 6 years (visit 4) to estimate the change in cognition from (a) 0-6 years and (b) 6 years - end of study. An interaction term between categorical PWV and each time spline will be incorporated to estimate the change separately for years 0-6 and 6 years-end of study.

> **Aim 1.2:** Multivariable linear regression model will be used to estimate the cross-sectional associations of PWV with each cognitive test *z* score and cognitive domain score at visit 5.

Aim 2: A weighted multivariable linear regression model will be used to estimate the cross-sectional associations of PWV with WMH and infarcts on the brain MRI. We will perform a subsidiary mediation analysis to examine the extent to which the association between PWV and cognition is mediated by WMH and infarcts. Prior to doing a formal mediation analysis, we will first confirm whether both the exposure (PWV) and the outcome (cognitive function) are independently associated with the brain MRI measures. A test for mediation will be performed by including the brain MRI measures (e.g. WMH or infarcts) into the final model and assessing whether the estimates are attenuated after its inclusion. If the estimates are attenuated greater than 15%, as recommended in

published literature, then it suggests that these brain MRI measures may explain some of the variation in the association between the exposure (PWV) and the outcome (cognitive function). A formal mediation analysis will be used as was previously done in Knopman et al. 2015.[11]

Aim 3: Multivariable logistic regression analyses will be used to estimate the risk of MCI or dementia per unit increase in continuous measures of PWV and using distribution-based cut points for PWV measured at visit 5. Models will be weighted to account for sampling probability. Vascular etiologies have been attributed to diagnoses of MCI and dementia in the ARIC cohort (data unpublished, Knopman et al.). As a subsidiary analysis, we will examine the association between PWV and MCI/dementia among persons both with and without cerebrovascular features (e.g. history of stroke, infarcts on imaging, extensive WMH).

For the above analyses, we will examine effect modification by race, systolic blood pressure and ApoE4.

Attrition and selection biases are of concern when using ARIC data since healthier individuals would have the greatest influence on associations when analyses are restricted to visit 5. At the time of the visit 5 examination (2011-2013), 33% (n=5,275) of participants had died and 38% (n=3,979) of those alive did not attend the examination. We will use multiple imputation by chained equation (MICE)[13] methods to account for bias due to attrition in the longitudinal analysis in Aim 1.1. These methods utilize the following information to account for individuals that were not observed at visit 5: retrospective ascertainment of hospitalization with dementia codes, clinical dementia rating (CDR) scale conducted with proxies (~94% of cohort members have a proxy), and a comprehensive assessment of conditions associated with impaired cognition (e.g. functional abilities, CVD risk factors, etc.). For the visit 5 cross-sectional analyses (Aims 1.2, 2 and 3), we will use Heckman selection models to account for informative missingness for those participants who either died prior to visit 5 or were alive and did not attend visit 5.[14,15] The Heckman selection model is a type of joint model that allows for a two-stage estimation of submodels; Model 1: the probability of non-attendance at visit 5 due to either death or dropout, and Model 2: the exposure-outcome association accounting for the probability of non-attendance. We have previously identified several sociodemographic, clinical, and social risk factors associated with non-attendance to identify common predictors of both death and dropout. The following variables were identified as significant predictors of non-attendance: age, education, race-center, self-rated health, income, and functional status. In the first submodel, we will estimate the probability of not attending visit 5 using the above set of predictors. This estimated probability of non-attendance at visit 5 will then be included in the second submodel as an explanatory variable for the exposure-outcome associations described in Aims 1.2, 2 and 3). Similar Heckman-type selection models have been used and validated in other epidemiologic studies to account for selection biases.[16,17]

Methodological limitations: The cross-sectional design of aims 2 and 3 limits the inferences relating to causality in the observed associations between PWV and brain MRI measures and risk of MCI and dementia. Additionally, issues related to reverse causality will need to be addressed in the manuscript for the longitudinal aim 1.1. Some PWV measurements were not obtained on visit 5 participants due to technical issues, participant factors and scheduling conflicts. Height-based formulas used to estimate baPWV and faPWV were validated in Japanese populations limiting its applicability to other racial and/or ethnic groups; however, we are primarily interested in the impact of central aortic arterial stiffening on cognitive function.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

MS#2544 (lead: Timothy M. Hughes) – Arterial Stiffness and β-Amyloid Deposition in the ARIC-PET Study- This study will be looking at the relation between PWV and brain MRI measures, but only within the subsample of the ARIC-PET Study

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 (list number* 1998.02)

___ 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. Agreed

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

1. Zhang Y, Agnoletti D, Xu Y, Wang JG, Blacher J, Safar ME. Carotid-femoral pulse wave velocity in the elderly. *J Hypertens.* Aug 2014;32(8):1572-1576; discussion 1576.
2. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *Journal of the American College of Cardiology.* Apr 8 2008;51(14):1377-1383.
3. van Popele NM, Elizabeth Hak A, Mattace-Raso FU, et al. Impaired fasting glucose is associated with increased arterial stiffness in elderly people without diabetes mellitus: the Rotterdam Study. *J Am Geriatr Soc.* 2006;54(3):397-404.
4. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, et al. Adiposity, Obesity, and Arterial Aging: Longitudinal Study of Aortic Stiffness in the Whitehall II Cohort. *Hypertension.* Aug 2015;66(2):294-300.
5. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: a systematic review. *Ageing research reviews.* May 2014;15:16-27.
6. Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. *Journal of Alzheimer's disease : JAD.* 2014;42 Suppl 4:S401-410.
7. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European heart journal.* Nov 2006;27(21):2588-2605.
8. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Archives of neurology.* Feb 1989;46(2):141-145.
9. Wechsler. *Manual for the Wechsler Adult Intelligence Scale-Revised*. New York The Psychological Corporation 1981.
10. Lezak M, Howieson D, Loring D. *Neuropsychological Assessment* 4th ed. New York, NY: Oxford University Press, Inc; 2004.
11. Knopman DS, Griswold ME, Lirette ST, et al. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke; a journal of cerebral circulation.* Feb 2015;46(2):433-440.
12. Reference Values for Arterial Stiffness C. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *European heart journal.* Oct 2010;31(19):2338-2350.
13. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *International journal of methods in psychiatric research.* Mar 2011;20(1):40-49.
14. Heckman J. The common structure of statistical models of truncation, sample selection and limited dependent variables and a simpler estimator for such models. *Annals of Economic and Social Measurement.* 1976;5:475-492.
15. Heckman J. Sample selection bias as a specification error. *Econometrica.* 1979;47:153-161.
16. Barnighausen T, Bor J, Wandira-Kazibwe S, Canning D. Correcting HIV prevalence estimates for survey nonparticipation using Heckman-type selection models. *Epidemiology.* Jan 2011;22(1):27-35.
17. Clark SJ, Houle B. Validation, replication, and sensitivity testing of Heckman-type selection models to adjust estimates of HIV prevalence. *PloS one.* 2014;9(11):e112563.