1. **Full Title:** Pulse Wave Velocity and Late-Life Cognitive Change and Incident MCI and Dementia among Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study

2. **Abbreviated Title (Length 26 characters):** Pulse wave velocity and change in cognition/incident MCI/dementia

2. **Writing Group:**
   Writing group members: Priya Palta, Michelle Meyer, Jingkai Wei, Hirofumi Tanaka, David Knopman, Anna Kucharska-Newton, A. Richey Sharrett, Timothy Hughes, Kunihiro Matsushita, Thomas H. Mosley, 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)

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3. **Timeline:** Analyses to start upon approval of proposal. Submit for publication within 6 months from proposal approval.

4. **Rationale:**
   Vascular aging is associated with stiffening of the aorta and arterial segment-specific loss of arterial elasticity.\(^1\) 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 pulsatile stress forward into the cerebral micro-circulation,\(^5\) which can increase susceptibility to microvascular damage and remodeling in the brain, therefore resulting in impaired cognition.\(^6\) More specifically, central arterial stiffening is associated with hypertrophic remodeling of cerebral arterioles and in turn results in cerebral hypoperfusion and consequent cognitive dysfunction. Central arterial stiffening, measured by pulse wave velocity (PWV), is therefore 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.

Most studies to date of arterial stiffness/pressure pulsatility and brain-related outcomes have been cross-sectional precluding inferences of temporality. However, a recent meta-analysis\(^2\) cited 15 longitudinal studies (only 4 of which used the referent standard measure of carotid-femoral PWV (cfPWV)\(^{8-11}\) that have specifically examined the associations between arterial stiffness and cognitive decline and cognitive impairment. Although arterial stiffness and pressure pulsatility have been related to cognitive dysfunction and impairment, there is considerable heterogeneity across studies, mostly attributable to the varied tests of cognitive function and analytic approaches used. Of the longitudinal studies, three found an association between higher levels of arterial stiffness and greater decline in global cognitive function.\(^{8,10,11}\) Few studies have reported data on domain-specific cognitive function, addressing only a decline in the memory domain at higher levels of arterial stiffness.\(^{10}\) Longitudinal studies of pressure pulsatility with cognitive outcomes were more common (n=13), but all measured brachial pulse pressure and none included a measure of central pressure pulsatility. Lastly, the lack of adjustment for clinically relevant covariates, such as blood pressure or ApoE4, and homogeneous (mostly White) study samples limits the reported findings.

To address the limitations of prior longitudinal studies we propose to test the hypothesis that a higher level of arterial stiffness and central pressure pulsatility, as measured by carotid-femoral pulse wave velocity and central pulse pressure respectively, are associated with greater decline in domain-specific cognitive function, higher incident dementia, and greater progression from mild cognitive impairment (MCI) to dementia. ARIC provides the exceptional opportunity to contribute to the existing literature by examining this association in a well-characterized biracial cohort with longitudinal assessments of multidimensional cognition, adjudicated MCI and dementia outcomes, and use of the referent standard measure of central arterial stiffness.

5. **Main Hypothesis/Study Questions:**

**Aim 1:** To test the hypothesis that higher levels of arterial stiffness/pressure pulsatility measured in older adulthood (Visit 5) and greater change in arterial stiffness/pulsatility are associated with a greater decline in global and domain-specific cognition.

**Aim 2:** To test the hypothesis that higher levels of arterial stiffness/pressure pulsatility in older adulthood (Visit 5) and greater change in arterial stiffness/pulsatility are associated with a higher incidence of mild cognitive impairment.

**Aim 3:** To test the hypothesis that higher levels of arterial stiffness/pressure pulsatility in older adulthood (Visit 5) and greater change in arterial stiffness/pulsatility are associated with a higher incidence of dementia.

**Aim 3b:** To test the hypothesis that higher levels of arterial stiffness/pressure pulsatility are associated with a greater progression of MCI to dementia over ~ 5 years.

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 (baseline=Visit 5) and change in cognition from visit 5 to visit 6, and incident MCI or dementia.

**Exclusions:** We will exclude participants who did not attend visit 5 or who did not have a measure of cognitive status (normal, MCI, or dementia) or cognitive performance data. Participants with missing information on PWV, body mass index (BMI) \(\geq 40\) 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 \(\geq 5\) 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 will also be excluded.

For incident MCI/dementia analyses we will exclude prevalent MCI/dementia cases at visit 5.

**Exposure(s):**

(1) **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 examine the other two segment-specific measures of PWV (femoral-ankle PWV (faPWV), and brachial-ankle PWV (baPWV)): although these are not direct measures of central artery stiffness, they are reported by other studies. Our primary analysis will use PWV measured at visit 5. We will also consider change/progression in PWV from visit 5 to visit 6.

(2) **Pressure pulsatility measured by central pulse pressure**
Carotid artery systolic blood pressure is also measured by oscillometry using the VP-1000 plus system. Sitting brachial diastolic pressure is used to approximate central diastolic pressure based on the observation that peripheral and central diastolic pressures are closely correlated. Central pulse pressure will be estimated as central SBP-brachial DBP.

**Outcome(s)**

(1) **Cognitive change from V5 to V6**— We will quantify the change in cognitive function from visit 5 to visit 6 in the domains of memory, language, executive function/processing speed and general cognitive performance. The following tests will be used for each cognitive domain:

- **Memory:** Logical Memory I & II, Incidental Learning, Delayed Word Recall Test (DWRT)
- **Language:** Animal Naming, Boston Naming Test, Word Fluency Test (WFT)
- **Executive Function/Processing Speed:** Trail Making Test—Part A, Trail Making Test—Part B, Digit Span Backwards, Digit Symbol Substitution Test (DSST)

Using data from these tests in a factor analysis, factor scores for general cognitive performance, executive functioning/processing speed, memory and language will be derived, as previously described. Change in specific domains will be determined on only participants evaluated at follow up visit(s); whereas change in global cognition may be estimated using both observed follow up scores and those derived from multiple imputation.

(2) **Dementia Incidence**—the following definitions for cognitively normal, mild cognitive impairment, and dementia were derived by the coordinating center:

*Cognitively Normal:* all cognitive domain scores are > -1.5 Z scores or the absence of decline in the full ARIC cognitive battery of >0.055 standard deviation units/year (Manual 17, ARIC Visit 6).

*Mild Cognitive Impairment:* performance ≤ -1.5 Z scores in at least one domain; a CDR sum of boxes between >0.5 and ≤ 3; an FAQ ≤ 5; and a decline in the full ARIC cognitive battery >0.055 standard deviation units/per year (Manual 17, ARIC Visit 6).
**Dementia:** the following 3 criteria must be met for level 1 dementia: (1) FAQ >5 or CDR sum of boxes >3; (2) at least 2 domain scores ≤ 1.5 Z scores; and (3) a decline since visit 5 on the full ARIC cognitive battery of >0.055 standard deviation units/per year (Manual 17, ARIC Visit 6). Levels 2a, 2b, 2c and 3 dementia are based on surveillance as defined by the Coordinating Center.

Dementia incidence will be separately quantified among participants who attended visit 5 and among participants who were alive at visit 5 but did not attend.

**Covariates:** All covariates were assessed at ARIC visit 5, except race-center (Minnesota Whites; Maryland Whites; North Carolina Whites; North Carolina Blacks; Mississippi Blacks), sex, and education (less than high school, high school or equivalent, and greater than high school), which were assessed at visit 1. Additional covariates to consider include age; mean arterial pressure; cigarette smoking status (never vs. ever); diabetes mellitus (defined as fasting glucose ≥126 mg/dL, self-reported history of diabetes mellitus diagnosis by a physician, or use of diabetes mellitus medication); heart rate; total physical activity (total metabolic (MET)-equivalent minutes/week); anti-hypertensive medication use; and apolipoprotein (APOE) ε4 genotype (0 or ≥ 1 allele).

**Analysis:** Arterial stiffness/pressure pulsatility will be analyzed continuously and 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:** Arterial stiffness/pressure pulsatility and change in cognitive function (v5-v6):
Among Visit 6 participants with a baseline measure of cognitive function (visit 5), quantify the change in late-life cognitive function by taking the difference (Cog_v6-Cog_v5/Δtime). This estimate will be standardized to the sample mean and standard deviation. Linear regression will be used to quantify the association of arterial stiffness/pressure pulsatility with late-life cognitive decline. Cognitive change will be examined separately in participants who are cognitively normal vs. mild cognitively impaired at visit 5.

**Aim 2 and Aim 3a:** Arterial stiffness/pressure pulsatility and incident MCI and Dementia
Among cognitively normal participants at visit 5 (n~4,800), we will conduct a survival analysis using Cox proportional hazards regression to estimate the incidence of MCI and dementia. We will also explore the 5-year incidence rates of MCI and dementia using a time to event analysis and assuming a Poisson distribution for the number of incident cases. Person-time will be determined from the date of the visit 5 examination (the first time dementia/MCI was adjudicated) to date of visit 6 follow-up. Using a Poisson regression model, we will calculate the incident rate ratios and incident rate differences of MCI and dementia across levels of arterial stiffness/pressure pulsatility.

**Aim 3b:** Arterial stiffness/pressure pulsatility and progression from MCI to Dementia
Among those with MCI at visit 5 (n=1,374), use logistic regression models to quantify the odds of dementia at visit 6.

For the above analyses, we will look at 3 sequential models:
(1) Unadjusted
(2) Adjusted for sociodemographic factors (i.e. age, sex, education, race-center, ApoE4)
(3) Adjust for sociodemographic and clinical characteristics (i.e. mean arterial pressure, ever smoking status, diabetes, physical activity, heart rate, body mass index, anti-hypertensive medication use)

We will test for effect modification by sex, race, and ApoE4.

As a subsidiary analysis, we will consider the role of ‘cognitive/brain reserve’ in protecting against cognitive decline in late-life by testing for effect modification by (a) education level and (2) standardized brain volume (as measured with MRI at the visit 5 exam).

We will also account for the competing risk of death without dementia in our time-to-event analyses.

**Attrition:** Attrition is of concern with almost 40% of ARIC cohort participants who were present for the visit 5 examination not examined at visit 6. Per recommendations from the NCS analysis working group, missing cognitive test scores at visit 6 will be imputed using multiple imputation by chained equations (MICE) models. We will also consider inverse probability of attrition weighting (IPAW) for the incident MCI and dementia analyses.

**Methodological limitations:** 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, estimated on the basis of cfPWV, on cognitive function.

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 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  ____ 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)?

Michelle Meyer (MS#3050): Change in Arterial Stiffness in Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study

Priya Palta (MS#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?     __X__ Yes    ____ No

11.b. If yes, is the proposal

___X___ A. primarily the result of an ancillary study (list number* 1998.02-Life course SES, social context, and CVD (SESCVD)

2015.23: Arterial stiffness, cerebral and renal small vessel disease

___ 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