ARIC Manuscript Proposal #4176

PC Reviewed: 7/14/26	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Arterial stiffness and 5-year change in biomarkers of cerebrovascular disease, Alzheimer's disease pathology, and neurodegeneration in late-life: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group (alphabetical):

Writing group members: Jennifer Deal, Timothy M. Hughes, Clifford Jack, Anna Kucharska-Newton, Pablo Martinez-Amezcua, Michelle Meyer, Thomas H. Mosley, James Pike, Sanaz Sedaghat, A. Richey Sharrett, Hirofumi Tanaka, B. Gwen Windham, 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: Analyses to start upon approval of proposal. Submit for publication within 6 months from proposal approval.

4. Rationale:

Arterial elasticity plays a vital role in dampening the arterial pressure waveform, thereby transforming central pulsatility into a steadier flow once it reaches the microvasculature[1-2,4]. Arterial stiffness refers to a loss of elasticity, primarily in the large arteries such as the aorta, mainly through an increase in collagen cross-linking and degradation of elastin fibers[1-2]. Arterial stiffening augments pressure wave propagation, making the arterial wave reach the aorta in the systolic phase of the cardiac cycle, instead of in diastole, thus increasing systolic blood pressure and pulse pressure[1,5].

Brain vulnerability to central hemodynamic alterations can be partially attributed to its low resistance and impedance, and the short distance between arterioles and arteries[2]. Arterial stiffness can lead to cerebral small vessel disease (SVD) and damage to white matter microstructure through parenchymal damage and cerebral hypoperfusion[1,3]. Imaging based markers that reflect SVD such as white matter hyperintensity volume (WMH), cerebral microbleeds, enlarged perivascular spaces, small subcortical infarcts, as well as disruptions to white matter microstructure, reflected in an increase in mean diffusivity (MD) and a decrease in fractional anisotropy (FA) have all been independently associated with increased arterial stiffness[1,4-6]. Though much less studied, a decrease in brain volume may be another consequence of arterial stiffness[1].

Central arterial stiffness has been consistently associated with a range of imaging markers reflecting SVD in cross-sectional studies[4]. However, besides their cross-sectional nature, many of these studies were limited by a lack of carotid-femoral pulse wave velocity (cfPWV)[7-15], the reference standard measure of arterial stiffness, small samples sizes, and having predominantly White populations.[16-17] Three longitudinal studies with inconsistent findings have been conducted to date. Rosano et al. evaluated the relationship between arterial stiffness and WMHs and gray matter volume in a population of 322 older adults (aged 79-89), finding higher baseline arterial stiffness measures to be associated with higher volumes of WMH and lower gray matter volumes at 9-years of follow-up[18]. In a cohort of 335 older adults (aged 66-80) from the Vanderbilt Memory and Aging Project higher aortic PWV at baseline was associated with a higher WMH volume, but not with gray matter volume, after 7-years of follow-up[19]. Another study of 1223 participants (aged 52-70) from the Framingham Offspring cohort found no association between a higher baseline cfPWV and change in WMH volume or cerebral brain volume over a 7-year follow-up20. These studies suffered from some of the same limitations found in the wider literature[4,21-23]. Moreover, except for the Framingham Offspring study, they did not have repeat imaging measures to assess for change in the brain outcomes. Finally, no longitudinal studies that we know of have studied the association between PWV and change in the white matter microstructure, as measured by diffusion tensor imaging (DTI).

Recent findings from the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) found a higher cfPWV to be cross-sectionally associated with a greater volume of WMHs, lacunar infarcts, microbleeds, and lower brain volumes in MRI scans[24] and greater amyloid-beta (Aβ) deposition and co-occurring Aβ deposition and high WMH in PET scans.[27] With this proposal, we aim to expand on those studies by evaluating changes in the imaging and plasma markers of SVD, neurodegeneration, white matter microstructure, and Alzheimer's disease (AD) pathology, as well as addressing some of the gaps in the current literature, such as small sample sizes, homogenous study populations, and use of measures of arterial stiffness other than the "reference standard" assessment of cfPWV. We also plan to examine associations between novel components of pulse wave velocity (PWV), including structural PWV and load-dependent PWV,[28] with 5-year change in biomarkers to provide insight into the arterial stiffness mechanisms most closely associated with dementia pathology.

We propose the following aims to be evaluated using data from the 2011-2013, 2016-2019, and 2020-2024 examinations of the ongoing ARIC-NCS cohort[25].

5. Main Hypothesis/Study Questions:

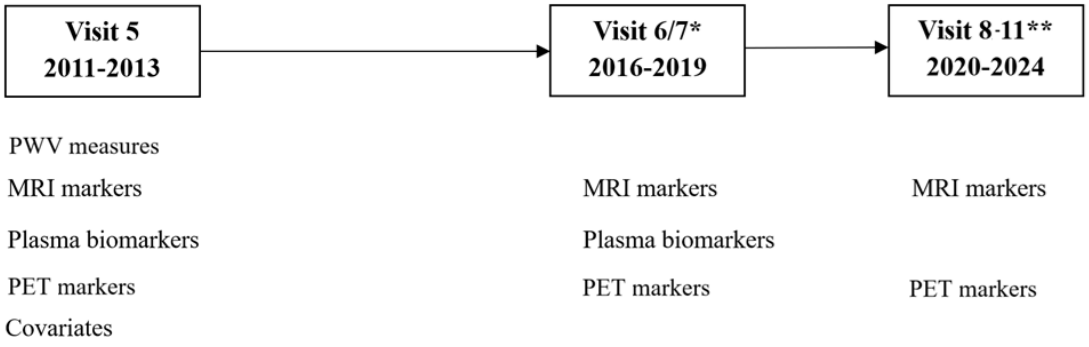
Primary aim: To study the association between baseline arterial stiffness (as measured by cfPWV, structural PWV, and load-dependent PWV) and 5-year change in the burden of cerebral small vessel disease (i.e., white matter hyperintensities, lacunar infarcts, and cerebral microbleeds) neurodegeneration (i.e., cortical thickness and total and region of interest (ROI) brain volumes) and white matter microstructural integrity (i.e., mean diffusivity and fractional anisotropy) in a community-based sample of older adults. We hypothesize that baseline PWV measures will be positively associated with an increased burden of cerebral small vessel disease (i.e., greater increase in WMH volume, lacunar infarcts, and cerebral microbleeds), neurodegeneration (i.e., greater decrease in brain volume and cortical thickness), and damage of white matter microstructural integrity (i.e., greater increase in mean diffusivity and greater decrease in fractional anisotropy) over up to 13 years of follow-up.

Secondary aim 1: To study the association between baseline arterial stiffness (as measured by cfPWV, structural PWV, and load-dependent PWV) and 5-year change in plasma biomarkers of AD pathology (i.e., the ratio of Aβ42 to Aβ40 [Aβ42:Aβ40], phosphorylated tau at threonine 181 [p-Tau181]), neurodegeneration (neurofilament light chain [NfL]), and neuroinflammation (glial fibrillary acidic protein [GFAP]) in a community-based sample of older adults. We hypothesize that baseline PWV measures will be positively associated with faster increases in the burden of AD pathology (i.e., greater decreases in Aβ42:Aβ40, greater increases in p-Tau181), neurodegeneration (i.e., greater increases in NfL), and neuroinflammation (i.e., greater increases in GFAP) over up to 8 years of follow-up.

Secondary aim 2: To study the association between baseline arterial stiffness (as measured by cfPWV, structural PWV, and load-dependent PWV) and 5-year change in PET markers of cerebral SVD (i.e., cerebral microbleeds, lacunes, whiter matter hyperintensities, cerebral SVD burden) and AD pathology (i.e., Aβ deposition) in a community-based sample of older adults. We hypothesize that baseline PWV measures will be positively associated with faster increases in the burden of cerebral SVD (i.e., greater increases in WMH, greater increases in cerebral SVD burden, greater increases in cerebral microbleeds, greater increases in lacunes) and AD pathology (i.e., faster increases in Aβ deposition) over up to 13 years of follow-up.

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



* MRI, PET, and plasma biomarkers were each measured at either Visit 6 or Visit 7, but not both.

** MRI and PET were each collected at one time between Visits 8 and 11.

Primary Aim:

- Exposures: Arterial stiffness (cfPWV, structural PWV, load-dependent PWV) measured at visit 5
- Outcome: Change in MR imaging markers from visit 5 to visit 6/7 and/or visit 8/11.

Arterial stiffness measured at visits 5 and MRI biomarkers measured at visits 5 & 6/7, and 8-11.

Secondary Aim 1:

- Exposure: Arterial stiffness (cfPWV, structural PWV, load-dependent PWV) measured at visit 5
- Outcome: Change in plasma biomarkers from visit 5 to visit 6/7.

Arterial stiffness measured at visit 5 and plasma biomarkers measured at visits 5 and 6/7.

Secondary Aim 2:

- Exposure: Arterial stiffness (cfPWV, structural PWV, load-dependent PWV) measured at visit 5
- Outcome: Change in PET from visit 5 to visit 6/7 and/or visit 8/11.

Arterial stiffness measured at visit 5 and PET biomarkers measured at visits 5 & 6/7, and 8-11.

Exclusions:

- Participants with arrhythmias, biased PWV waveforms, aortic aneurysms, history of aortic graft or aortic revascularization, aortic stenosis, moderate or greater aortic regurgitation.
- Participants with missing data on cfPWV.
- Participants who self-reported race other than Black or White due to small numbers.
- Primary aim: No baseline (visit 5) or follow-up (visit 6/7 OR visit 8-11) MRI
- Secondary aim 1: No baseline (visit 5) or follow-up (visit 6/7) plasma biomarker measurements
- Secondary aim 2: No baseline (visit 5) or follow-up (visit 6/7 OR visit 8-11) PET scan

Exposure(s) Assessment:

Arterial stiffness measured by cfPWV at visit 5. cfPWV was measured by the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan) and 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. cfPWV will be analyzed both continuously and using distribution-based quartiles. We will winsorize the values at the 1%- and 99%-tiles.

Structural PWV and load-dependent PWV will be derived[28] from cfPWV and the systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements obtained at the time of cfPWV measurement using an Omron VP-1000 Plus oscillometric automated sphygmomanometer (Omron Healthcare, Kyoto, Japan) while participants were supine.

Baseline PWV measures will be considered and analyzed both continuously (per 1 standard deviation), according to distribution-based quartiles, and as a binary categorization at the upper 25th percentile to determine high vs. non-high PWV measures.

Outcome(s) Assessment:

MRI: MRI scans were performed at visit 5 (2011-2013), visit 6 or 7 (2016-2019), and at one time between visits 8 and 11 (2020-2024). We will include imaging markers that have previously been described in the literature to be associated with arterial stiffness. Specifically, we will include white matter hyperintensity volumes, presence/absence of lacunar infarcts, presence/absence of cerebral microbleeds, measures of white matter microstructural integrity (mean diffusivity, fractional anisotropy), and markers of neurodegeneration, including cortical thickness and total brain volume. Brain MRI scans were obtained using 3 Tesla Siemens scanners, with a typical set of sequences, which included 3D volumetric Magnetization Prepared Gradient Echo (MPRAGE) and Fluid Attenuated Inversion Recovery (FLAIR) sequences[25]. Specifically, WMH burden was quantified by the algorithm developed at Mayo Clinic25. Lacunar infarcts included subcortical T2 fluid-attenuated inversion recovery lesions with central hypointensity > 3 mm and hyperintensity < 20 mm in the caudate and lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebellum, white matter, centrum semiovale, and corona radiata; cerebral microbleeds included lesions on gradient echo T2 weighted imaging sequences of <5 mm in diameter and were classified as lobal or subcortical[25]. Diffusion tensor imaging (DTI) for measures of white matter microstructural integrity were conducted with 2.7-mm slices for Skyra and Verio scanners, and 3-mm slices for Trio scanners[26]. Mean diffusivity (MD) comprises the average rate of diffusion independent of directionality, while white fractional anisotropy (FA) represents the fraction of the tension that can be assigned to anisotropic diffusion[26]. Higher mean diffusivity and lower fractional anisotropy are considered to be associated with worse white matter microstructural integrity[26]. Freesurfer software 5.3 was used to derive total and regional cortical volumes, and measures of cortical thickness[24].

Plasma biomarkers: Plasma biomarkers of Aβ42, Aβ40, NfL, and GFAP were measured in stored plasma samples from visit 5 (2011-2013) and visit 6 (2016-2017) or 7 (2018-2019) using the Quanterix Simoa Neurology 4-Plex E assay. Plasma p-Tau181 was measured using a Quanterix Simoa singleplex assay.

PET: Florbetapir PET scans were performed at visit 5 (2011-2013), visit 6 or 7 (2016-2019), and at one time between visits 8 and 11 (2020-2024). Isotope was injected through a butterfly needle, with images acquired from 50 to 70 minutes for a 20-minute (4 x 5 minutes) uptake scan. The PET image analysis center at Johns Hopkins University (subsequently, at Washington University in St. Louis) reviewed images qualitatively for incidental findings and image quality; the center also quantified standardized uptake value ratios (SUVRs).

Covariates:

All covariates will be collected at baseline (Visit 5), and will include the following: sex, age, race-center, education, mean arterial pressure, antihypertensive medication use, cardiovascular disease, diabetes, smoking, body mass index (BMI). Analyses of volumetric imaging markers will additionally be adjusted for estimated total intracranial volume. Analyses of plasma

biomarkers will be additionally adjusted for time-varying estimated glomerular filtration rate (eGFR) and time-varying BMI.

Analysis:

Baseline cfPWV, structural PWV, and load-dependent PWV at visit 5 will serve as the main exposures of interest and will be expressed as both continuous variables (per 1 standard deviation) and categorically, based on distribution-based quartiles, with the lowest 25th percentile as the reference group. Binary categorizations of high vs. non-high PWV measures will be determined at the upper 25th percentile. Change (from visit 5 to visit 6/7 or visit 8-11) in MRI markers will serve as the primary outcome of interest. Change (from visit 5 to visit 6/7) in plasma biomarkers and change (from visit 6 to visit 6/7 or visit 8-11) in PET markers will serve as the secondary outcomes of interest.

We will conduct a longitudinal analysis using generalized estimation equations (GEEs) with robust standard errors and an unstructured correlation matrix. For continuous outcomes (WMH volume, brain volume, cortical thickness, MD and FA, all plasma biomarkers, all PET markers except Aβ positivity), we will estimate the mean change per 1 SD PWV unit and when modeled categorically, comparing change across quartiles, as well as comparing high vs. non-high PWV measures. For binary outcomes (cerebral microbleeds, lacunar infarcts, Aβ positivity defined using a standardized uptake value ratio [SUVR] cutoff of >1.2 [as used in prior ARIC-PET analyses]), we will estimate the odds following the same approach. We will also include an interaction term between PWV measures and time to calculate the rate of change. All analyses will include sampling weights to account for the selection for an MRI scan or plasma biomarker measurement.

Attrition is a significant concern with over 30+ years of follow-up from baseline in ARIC and since those participants that remain in the study at follow-up are generally healthier. To appropriately handle the bias due to attrition, we will limit the primary analysis to participants with two MRI scans (for visit 5 and visit 6/7 or visit 8-11) and the secondary analyses to participants with plasma biomarker measurements at two timepoints (visit 5 and visit 6/7) for plasma biomarker analyses or PET scans at two timepoints (for visit 5 and visit 6/7 or visit 8-11) for PET analyses. We will aim to explore any potential differences between participants who have repeat biomarker assessments and those who did not, and we will consider using inverse probability weighting to account for potential differences.

We will also utilize a series of model diagnostics to evaluate the primary model, including, but not limited to the following: the mean of the model residuals, by both levels of exposure, and across time/visits; scatterplots of model residuals against the predicted values of the model; and a q-q plot of models' residuals to evaluate for normality.

Potential Limitations: Selection bias is of significant concern, since remaining ARIC participants are healthier than the original cohort. Moreover, while the ARIC study includes both Black and

White participants, it does not include informative sample sizes of any other racial/ethnic groups, therefore limiting generalizability to other populations and geographic areas.

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

MP#4235 (lead: Priya Palta) – Predictors of change in blood-based biomarkers of Alzheimer's disease pathology and neurodegeneration measured from mid- to late-life and their associations with late-life measures of brain health in 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* 2015.23, 2020.27, 2009.29)

___ 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.

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