ARIC Manuscript Proposal # 3153

1.a. Full Title: Arterial stiffness and pressure pulsatility, white matter integrity and late-life depression: The ARIC-NCS study

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

2. Writing Group:
   Writing group members: Thomas Mosley, Clifford Jack, Priya Palta, Melinda C. Power, 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: If approved by the ARIC Publication Committee, the proposed work will be submitted as part of the lead author’s doctoral research. Hence the greater than usual scope of work. Similarly, the time line will exceed that of a narrowly focused manuscript proposal.

4. Rationale:
   Late-life depression and its relationship with cerebral vessel disease
   Late-life depression (LLD), defined as a major depressive episode taking place in older adulthood (60 year or older) is a significant public health issue, with a prevalence between 8-16% among community-dwelling older adults.\(^1\) Compared to depression in young adults, the prevalence of LLD is lower but with more severe outcomes, including higher risk of mortality\(^2\), suicide,\(^3\) physical disability\(^4\) and poor quality of life.\(^5\)
Being a syndrome with different etiologies, LLD can be categorized into early-onset depression (with first episode of depression observed in childhood, adolescence or young adulthood) and late-onset depression (with a first episode of depression observed around 60 years of age or older).\textsuperscript{6} Vascular depression is categorized as a subtype of depression, which originates from the recently proposed hypothesis of vascular depression.\textsuperscript{7} According to the vascular depression hypothesis, cerebrovascular disease is likely to contribute to the development of LLD.\textsuperscript{8} Typically, vascular depression occurs in the presence of white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI), a manifestation of cerebral small vessel disease (CSVD). CSVD impairs frontal and subcortical structures, which are related to mood regulation, a key feature of depression.\textsuperscript{8,9} Epidemiologic studies have found that CSVD,\textsuperscript{10,11} particularly manifested as WMH, is associated with higher levels of depressive symptoms.\textsuperscript{7,12-14}

**Arterial stiffness and pulsatility**

Arterial stiffness increases pulsatility, which damages microvascular circulation, resulting in poor vasoreactivity and cerebral hypoperfusion that manifests as CSVD.\textsuperscript{15} Population-based studies have shown that higher levels of arterial stiffness are associated with cerebral small vessel disease. Carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard measure of aortic stiffness when estimated by pulse wave velocity.\textsuperscript{16}

Pulsatility is an essential property of the cardiovascular system because of its involvement in preserving tissue perfusion. Elevated arterial pulsatility has shown to influence microstructural white matter.\textsuperscript{17} Therefore, we hypothesize that higher arterial pulsatility may be associated with higher levels of depressive symptoms.\textsuperscript{18} Measures of pulsatility, such as central pulse pressure (cPP),\textsuperscript{19} have not been examined however in relation to depression or depressive symptoms in longitudinal population-based studies.

**Arterial stiffness and late-life depression**

Only a few studies have examined the association between arterial stiffness and depressive symptoms among older adults. Conflicting results have been reported on the association between arterial stiffness and late-life depression. Onete et al.\textsuperscript{20} found that greater cfPWV is associated with major depressive disorder and depressive symptoms among middle-aged men and women (≥60 years), but not among older adults (>60 years) in a sample of 2,757 participants of the Maastricht Study. Van Sloten et al.\textsuperscript{21} found in 2,058 old participants (mean age 79.6 years) in the AGES-Reykjavik Study that greater PWV is associated with more depressive symptoms, and this association is partly accounted for by white matter hyperintensity volume and subcortical infarcts. Tiemeier et al.\textsuperscript{22} found in 3,704 older adults (≥60 years) of the Rotterdam Study that those with increased arterial stiffness measured as aortic PWV were more likely to have depressive symptoms. Paranthaman et al.\textsuperscript{23} found in a small sample (n=46) that depressed subjects have a higher PWV. However, these findings are based on cross-sectional designs, and thus susceptible to bias, and conceivably also reverse causality. A prospective study on arterial stiffness and pressure pulsatility with incident depression and repeat measures of depressive symptoms will help to elucidate these associations.

Moreover, the cross-sectional AGES-Reykjavik Study reported that WMH and subcortical infarcts mediate the association observed between arterial stiffness and depressive symptoms among older adults.\textsuperscript{21} However, the researchers only partially accounted for the association
between arterial stiffness and depressive symptoms, which suggests a direct association between arterial stiffness and depressive symptoms. It is thus desirable to examine whether arterial stiffness predicts incident depression and changes in depressive symptoms among older adults, independent of CSVD.

**White matter integrity as a potential mediator**

The reported associations between clinical features of cerebral small vessel disease (e.g., lacunar infarct, chronic hypoperfusion) and conventional MRI measures have not been consistent, perhaps reflecting an inability to characterize microstructural properties related to WMH. Novel methods, including diffusion tensor imaging (DTI), uses a tensor model to measure both the rate and directionality of the diffusion distribution of water molecules in tissue. Tractography can be used to spatially characterize white matter diffusion abnormalities along the pathway of a specific tract, with high sensitivity for detecting cerebral damage. 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. Therefore, DTI is expected to provide a better measure of white matter integrity than a conventional MRI.

Studies using DTI have shown associations of reduced anisotropy in the dorsolateral prefrontal cortex and uncinate fasciculus with late-life depression. Prior data also suggests that arterial stiffness is associated with loss of white matter integrity measured with DTI Therefore, white matter integrity may mediate the association between arterial stiffness and pressure pulsatility with late-life depression.

Drawing on the large and well-characterized cohort of ARIC-NCS, we propose to examine the association of arterial stiffness (measured with cPWV) and pressure pulsatility (cPP) with 5-year risk of depression and 5-year change in depressive symptoms among a community-dwelling sample of older adults. We also propose to examine whether DTI predicts 5-year risk of depression and 5-year change in depressive symptoms among older adults, and the degree to which white matter integrity measured by DTI mediates the association between arterial stiffness and pressure pulsatility with depression.

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

Figure 1. Conceptual framework of aortic stiffness and pulsatility, white matter integrity and late-life depression
Aim 1. Examine the association of baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults. 

Hypothesis: Higher baseline aortic stiffness and pressure pulsatility will be associated with greater 5-year risk of late-onset depression and greater 5-year increase in depressive symptoms among older adults.

Aim 2. Examine the associations between baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with white matter integrity among older adults. 

Hypothesis: Higher baseline aortic stiffness and higher baseline pressure pulsatility will be associated with lower white matter integrity.

Aim 3. Examine the associations between white matter integrity (Visit 5) with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults. 

Hypothesis: Higher white matter integrity is associated with lower 5-year increase in severity of depressive symptoms and 5-year risk of late-onset depression among older adults.

Aim 4. Examine whether the hypothesized associations between baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults are mediated by white matter integrity.

Aim 4.1. Examine whether the associations between baseline aortic stiffness and pressure pulsatility with 5-year change in severity of depressive symptoms among older adults are mediated by white matter integrity.

Aim 4.2. Examine whether the associations between baseline aortic stiffness and pressure pulsatility with 5-year risk of late-onset depression among older adults are mediated by white matter integrity.

Hypothesis: Associations between each of baseline aortic stiffness and pressure pulsatility with depression among older adults are partly accounted for by white matter integrity.

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 study using cfPWV and cPP at visit 5 as exposures. Incidence of depression at visit 6 is defined by a CES-D score ≥8 at visit 6 and CES-D score <8 at visit 5. The outcome of 5-year change of depressive symptoms is defined as the change of the CES-D score between visit 5 and visit 6.

The following will be exclusions for the primary analyses: Prior history of stroke, missing DTI, missing arterial stiffness/pressure pulsatility at visit 5, or missing CES-D score at visit 5 and/or
visit 6. 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, 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.\(^{30}\) 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.\(^{31,32}\) 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.\(^{33}\)

**Outcomes (visit 5 and visit 6):** Depressive symptoms as measured by the 11-item Centers for Epidemiologic Studies-Depression (CES-D) Scale, with a higher score indicating for more severe depressive symptoms. Specifically, the CES-D has 11 items, including questions on appetite, effort, sleep, fatigue, feeling depressed, happiness, loneliness, unfriendliness, enjoyment, sadness, and dislike. Responses to questions are scored on a range from 0 to 2 points, with 0 points indicating ‘hardly ever or never’, 1 point as ‘some of the time’, and 2 points as ‘much or most of the time’. The CES-D score will be analyzed both continuously and categorically. The conventionally accepted score cut off for the CES-D-11 for clinically significant depressive symptoms is 8 points or greater?

**Mediator (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.\(^{34}\) 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, hypertension, diabetes, total cholesterol, physical activity and ApoE4.

**Analysis plan:**

For quantification of arterial stiffness and pressure pulsatility, cfPWV (every 10m/s) and cPP (mmHg) will be analyzed in a continuous manner and categorized into quartiles based on distribution. 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. A difference in CES-D score between visit 5 and visit 6 will be calculated. We will examine the continuous distributions of the differences in CES-D scores, and if observed to be non-normally distributed, the values will be log-transformed.
For **Aim 1:** Multivariable log-linear models will be applied to assess the associations between cfPWV and cPP at visit 5 with 5-year risk of late-onset depression, respectively. Multivariable linear regression models will be applied to assess the associations between cfPWV and cPP with 5-year change of CES-D scores, respectively.

For **Aim 2:** Multivariable linear regression models will be applied between cfPWV and cPP with FA and MD.

For **Aim 3:** Multivariable linear regression models will be conducted between FA and MD with 5-year change of CES-D scores. Multivariable logistic regression models will be conducted between FA and MD with 5-year risk of late-onset depression.

For **Aim 4:** A formal mediation analysis will be applied to test potential mediations by FA and MD in the association between cfPWV and cPP with 5-year risk of late-onset depression and 5-year change in severity of depressive symptoms among older adults (with the assumption that cfPWV and cPP reduce white matter integrity, which then further results in 5-year changes in severity of depressive symptoms and higher 5-year risk of late-onset depression. The pathway of a postulated mediation process is shown in the following figure.

For the outcome of late-onset depression, the logistic regression model for the outcome is shown as follows, with an exposure-mediator interaction: $\text{logit}\{P(Y=1|A=a, M=m, C=c)\}=\theta_0+\theta_1a+\theta_2m+\theta_3am+\theta_4c$, where A stands for exposure (aortic stiffness), M stands for mediator (white matter integrity), Y stands for outcome (late-onset depression) and C stands for covariates. A linear regression model is fit for the model for the mediator: $E[M|A=a, C=c]=\beta_0+\beta_1a+\beta_2c$. The log-transformed risk ratio of the indirect effect (IE) (through the pathway of white matter integrity) is calculated as $\log(\text{RR}^{\text{IE}})\approx(\theta_2\beta_1+\theta_3\beta_1a)(a-a^*)$.

For the outcome of change in depressive symptoms, a linear regression model for the outcome is shown as follows, with an exposure-mediator interaction: $E\{P(Y=1|A=a, M=m, C=c)\}=\theta_0+\theta_1a+\theta_2m+\theta_3am+\theta_4c$, where A stands for exposure (aortic stiffness), M stands for mediator (white matter integrity), Y stands for outcome (change in depressive symptoms) and C stands for covariates. A linear regression model is fit for the model for the mediator: $E[M|A=a, C=c]=\beta_0+\beta_1a+\beta_2c$. The indirect effect (IE) (through the pathway of white matter integrity) is calculated as $\text{IE}=\theta_2\beta_1+\theta_3\beta_1a(a-a^*)$. 
All these models will be adjusted for age, sex, education, smoking, alcohol use, BMI, hypertension, diabetes, total cholesterol, physical activity and ApoE4.

Methodological limitations:
Participants of this study only included male or female ARIC cohort members alive ≥70 years, which may limit generalizability and is susceptible to selection bias. Inverse probability of censoring weighted estimation will be obtained through additional analysis. Also, the definition of depression using a cutoff of CES-D score ≥8 opens the possibility of misclassification bias. Sensitivity analysis will be conducted among participants with information of diagnosed depression and antidepressant use.

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

____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)?

ARIC MP#2837, by Wei et al. Association between Arterial Stiffness and Pressure Pulsatility with Depressive Symptoms: A Cross-Sectional Study of The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) (considered merged into the present manuscript proposal)

ARIC MP#2999, by Wei et al. Arterial stiffness, pressure pulsatility, and white matter integrity assessed by diffusion tensor imaging. The ARIC-NCS 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.cscie.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.cscie.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


Appendix. Detailed specific aims

Aim 1. Examine the association of baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults.

Aim 1.1. Examine the association of baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with 5-year risk of late-onset depression among older adults.

Aim 1.1.1. Examine the association of baseline aortic stiffness (cfPWV) with 5-year risk of late-onset depression (CES-D≥8 at visit 6 only) among older adults.

Aim 1.1.2. Examine the association of baseline pressure pulsatility (cPP) with 5-year risk of late-onset depression (CES-D≥8 at visit 6 only) among older adults.

Aim 1.2. Examine the association of baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with 5-year change in severity of depressive symptoms among older adults.

Aim 1.2.1. Examine the association of baseline aortic stiffness (cfPWV) and 5-year change in severity of depressive symptoms (differences in CES-D score between visit 6 and visit 5) among older adults.

Aim 1.2.2. Examine the association of baseline pressure pulsatility (cPP) and 5-year change in severity of depressive symptoms (differences in CES-D score between visit 6 and visit 5) among older adults.

We anticipate that (a) each of higher baseline cfPWV and cPP are associated with greater 5-year risk of late-onset depression among older adults, and (b) each of higher baseline cfPWV and cPP are associated with greater 5-year change in severity of depressive symptoms among older adults.

Aim 2. Examine the associations between baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with white matter integrity among older adults.

Aim 2.1. Examine the associations between baseline aortic stiffness and white matter integrity among older adults.

Aim 2.1.1. Examine the associations between baseline cfPWV and FA among older adults.

Aim 2.1.2. Examine the associations between baseline cfPWV and MD among older adults.

Aim 2.2. Examine the associations between baseline pressure pulsatility and white matter integrity among older adults.

Aim 2.2.1. Examine the associations between baseline cPP and FA among older adults.

Aim 2.2.2. Examine the associations between baseline cPP and MD among older adults.

We anticipate that (a) each of higher baseline cfPWV and cPP are associated with lower FA, and (b) each of higher baseline cfPWV and cPP are associated with greater MD.
Aim 3. Examine the associations between white matter integrity with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults.

Aim 3.1. Examine the associations between white matter integrity and CSVD and 5-year risk of late-onset depression among older adults.

Aim 3.1.1. Examine the association between FA with 5-year risk of late-onset depression among older adults.

Aim 3.1.2. Examine the association between MD with 5-year risk of late-onset depression among older adults.

Aim 3.2. Examine the associations between white matter integrity and CSVD and 5-year change in severity of depressive symptoms among older adults.

Aim 3.3.1. Examine the associations between FA with 5-year change in severity of depressive symptoms among older adults.

Aim 3.3.2. Examine the associations between MD with 5-year change in severity of depressive symptoms among older adults.

We anticipate that (a) each of lower FA and greater MD is associated with 5-year greater risk of late-onset depression among older adults; (b) each of lower FA and greater MD is associated with great 5-year increase in severity of depressive symptoms among older adults.

Aim 4. Examine whether the associations between baseline (Visit 5) (a) aortic stiffness and (b) pressure pulsatility with (a) the 5-year risk of late onset depression and (b) 5-year change in depressive symptoms among older adults are mediated by white matter integrity.

Aim 4.1. Examine whether the associations between baseline aortic stiffness and pressure pulsatility with 5-year change in severity of depressive symptoms among older adults are mediated by white matter integrity.

Aim 4.1.1. Examine whether the associations between cfPWV with 5-year change in severity of depressive symptoms among older adults are mediated by FA.

Aim 4.1.2. Examine whether the associations between cfPWV with 5-year change in severity of depressive symptoms among older adults are mediated by MD.

Aim 4.1.3. Examine whether the associations between cPP with 5-year change in severity of depressive symptoms among older adults are mediated by FA.

Aim 4.1.4. Examine whether the associations between cPP with 5-year change in severity of depressive symptoms among older adults are mediated by MD.

Aim 4.2. Examine whether the associations between baseline aortic stiffness and pressure pulsatility with 5-year risk of late-onset depression among older adults are mediated by white matter integrity.

Aim 4.2.1. Examine whether the associations between cfPWV with 5-year risk of late-onset depression among older adults are mediated by FA.
Aim 4.2.2. Examine whether the associations between cfPWV with 5-year risk of late-onset depression among older adults are mediated by MD.

Aim 4.2.3. Examine whether the associations between cPP with 5-year risk of late-onset depression among older adults are mediated by FA.

Aim 4.2.4. Examine whether the associations between cPP with 5-year risk of late-onset depression among older adults are mediated by MD.

We anticipate that the associations between baseline cfPWV and cPP with 5-year risk of late-onset depression and 5-year change in depressive symptoms among older adults were mediated by FA and MD.