1.a. Full Title: Association between Arterial Stiffness and Pressure Pulsatility with Depressive Symptoms: A Cross-Sectional Study of The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): cfPWV and Depression

2. Writing Group:
   Writing group members: Jingkai Wei, Kenneth Butler, Mariana Lazo, Benjamin Capistrant, Priya Palta

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JW___ [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 9 months from proposal approval.

4. Rationale:
Depression and depressive symptoms are present in approximately 15% of community-dwelling older adults (1). Depressive symptoms can be categorized into somatic (e.g. sleep) and cognitive (e.g. sadness) depressive symptoms (2). Depression is a predictor for adverse health outcomes. Among older adults, depression is associated with risk of dementia, coronary heart disease, stroke, cancer and suicide (3). Considering the significant burden of depression among older adults and its associated poor health outcomes, it is important to identify relevant risk factors that may be intervened upon to prevent depression and depressive symptoms.

There are established risk factors of depression, including poor social support (4), sleep apnea (5), alcohol abuse (6), smoking (7), etc. Arterial stiffness and pulsatility may be two additional risk factors of depression. Arterial stiffness increases pulsatility, which damages
microvascular circulation and results in vasoreactivity and a higher risk of cerebral small vessel
disease (CSVD). CSVD has been shown to impair frontal and subcortical structures, which are
related to mood regulation, a key feature of depression (8, 9). Carotid-femoral pulse wave
velocity (cfPWV) is the gold standard measure of central arterial stiffness (10), and is widely
used in epidemiologic research (11-13). A recently published cross-sectional study showed that
higher arterial stiffness, measured with cfPWV, was associated with higher depressive symptoms
using the 15-item geriatric depression scale [GDS-15]. Moreover, the association was accounted
for by volumes of white matter hyperintensities and subcortical infarcts, manifestations of CSVD
(14). Pulsatility is the difference in the systolic and diastolic velocities in the circulation of the
blood. It is an essential property of the cardiovascular system because of its involvement in
preserving tissue perfusion. Pulsatility is increased with higher cfPWV, and therefore we
hypothesize that it may be similarly associated with depressive symptoms (15). Measures of
pulsatility include central pulse pressure (cPP) and central systolic blood pressure (cSBP) (16).
These measures have not been examined in relation to depression or depressive symptoms.

In addition, existing literature suggests that depressive symptom subtypes (e.g. somatic vs.
cognitive) carry different risks with respect to cardiovascular outcomes (17, 18). Specifically,
somatic (e.g. sleep) depressive symptoms, are reported to be more predictive of cardiovascular
outcomes compared to cognitive (e.g. sadness) depressive symptoms (19). The associations
between arterial stiffness and depressive symptom subtypes have not been explored in prior
studies.

To extend results from prior studies, we aim to examine the association between arterial
stiffness and measures of pulsatility with depressive symptoms within the informative setting of
the Atherosclerosis Risk in Communities (ARIC) Study cohort. Furthermore, we will examine if
the associations differ across subtypes of depressive symptoms (somatic vs. cognitive).

5. Main Hypothesis/Study Questions:
Study aim 1: We aim to examine the cross-sectional association between measures of arterial
stiffness and pulsatility (e.g. cfPWV, cPP and cSBP) with depressive symptoms.

Hypothesis 1: A higher central arterial stiffness (measured with cfPWV) and pulsatility
(measured with cPP and cSBP) are associated with (a) higher depressive symptoms and
(b) higher odds of clinically significant depressive symptoms (CES-D ≥9).

Study aim 2: We aim to examine whether the associations between central arterial stiffness and
pressure pulsatility with depressive symptoms differs across subtypes of depressive symptoms
(somatic vs. cognitive).

Hypothesis 2: A higher central arterial stiffness and pressure pulsatility is more strongly
associated with somatic depressive symptoms than cognitive depressive symptoms.

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 study of arterial stiffness measured at visit 5 with depressive
symptoms measured at visit 5.
Exclusions: participants with BMI ≥ 40 kg/m² and participants with major arrhythmias (based on ECG data for MN code 8-1-3, 8-3-1 or 8-3-2). Participants missing information on cfPWV or the depression measure (Centers for Epidemiologic Studies-Depression (CES-D)) will be excluded.

Exposures (visit 5):
cfPWV, cPP, cSBP: measured using the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan)

Outcome (visit 5): Depressive symptoms as measured by the 11-item Centers for Epidemiologic Studies-Depression (CES-D) Scale, which includes information on general depressive symptoms, as well as subtypes of depressive symptoms, including, (1) somatic depressive symptoms and (2) cognitive depressive symptoms (20). 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’, 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 9 points (21). In a secondary analysis, the CES-D will be analyzed continuously as somatic and cognitive depressive symptoms defined as follows:

(a) Somatic depressive symptoms include appetite, effort, sleep, fatigue (22), ranging from 0 to 8 points

(b) Cognitive depressive symptoms include depressed, happiness, loneliness, unfriendliness, enjoying, sadness, dislike, ranging from 0 to 14 points.

Covariates (visit 5):
Age, sex, race, smoking status, body mass index, hypertension (systolic BP≥140 mm Hg, diastolic BP≥90 mm Hg, current use of antihypertensive medications), heart rate, history of CVD (including CHD and stroke, according to medical records), diabetes (fasting glucose level ≥126 mg per 100 ml (7.0 mmol/l⁻¹), or non-fasting glucose level ≥200 mg per 100 ml (11.1 mmol/l⁻¹), or history of or treatment for diabetes), physical activity (total minutes/week of activity, measured with the Baecke physical activity questionnaire)

Statistical Analysis

Exploratory analyses: Upper 25th percentiles was chosen to define elevated level for cfPWV, cPP and cSBP will be created. Analysis on characteristics of participants at visit 5 will be conducted using T-test or chi-square test according to cutoffs of cfPWV, cPP and cSBP, respectively. If the CES-D scores are observed to be non-normally distributed, the scores will be log-transformed.

Hypothesis 1: A higher central arterial stiffness (measured with cfPWV) and pulsatility (measured with cPP and cSBP) are associated with higher depressive symptoms/depression (measured with 11-item CES-D) and clinically significant depressive symptoms (CES-D score≥9).
Linear regression models will be used to examine the association between continuous measurements of both arterial stiffness and pulsatility measures with the continuous CES-D depressive symptoms score.

Logistic regression models will also be used to test the hypothesis that a greater level of both pulse wave velocity and pulsatility are associated with higher odds of clinically significant depressive symptoms (CES-D score ≥ 9).

Covariates measured at visit 5: age, sex, race, smoking status, body mass index, hypertension, heart rate, prevalent CVD, diabetes, physical activity.

Hypothesis 2: Central arterial stiffness and pressure pulsatility are associated with a higher level of somatic depressive symptoms compared to cognitive depressive symptoms. Linear regression models will be conducted to examine the associations between measurements of both arterial stiffness and pulsatility with (1) total somatic (range: 0-8) and (2) total cognitive depressive symptoms (range: 0-14), as continuous variables. Covariates measured at visit 5: age, sex, race, smoking status, body mass index, hypertension, heart rate, prevalent CVD, diabetes and physical activity.

Methodological limitations: The cross-sectional design of this study precludes causal inferences about arterial stiffness/pulsatility and depression/depressive symptoms. Furthermore, it is difficult to measure other factors that may potentially account for depressive symptoms, including occupation, dietary intake of fruit and vegetables, etc. Prevalence of white matter hyperintensities and subcortical infarcts may in part explain the association between arterial stiffness/pulsatility and depressive symptoms; however, this may not be examined due to the cross-sectional design of this study at the visit 5 examination of ARIC. The short version of CES-D may not be the optimal tool for measuring depressive symptoms, since the reduced items from the original CES-D questionnaire may not predict well depressive symptoms within the population.

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 list 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)?

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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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.
REFERENCES