ARIC Manuscript Proposal #4063

PC Reviewed: 6/14/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Orthostatic blood pressure variability, subclinical brain vascular disease, and the risk of dementia

b. Abbreviated Title (Length 26 characters):
Orthostatic BP and dementia

2. Writing Group:
(tentative)Yuan Ma, Yiwen Zhang, Josef Coresh, Anand Viswanathan, Kevin Sullivan, Keenan Walker, Chelsea Liu, Lewis Lipsitz, Elizabeth Selvin, Rebecca Gottesman, Deborah Blacker, Albert Hofman, B. Gwen Windham, Stephen Juraschek, others welcome.

Note: this manuscript proposal is part of an approved ancillary study in ARIC (K99, PI: Ma)

I, the first author, confirm that all the co-authors have given their approval for this manuscript proposal. YM **[please confirm with your initials electronically or in writing]**

First author: Yuan Ma, MBBS, PhD
Address: 677 Huntington Avenue
Kresge 906
Boston, MA 02115

Phone: 617-432-6049 Fax: NA
E-mail: yuanma@hsph.harvard.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: Yuan Ma, MBBS, PhD
Address: 677 Huntington Avenue
Kresge 906
Boston, MA 02115

Phone: 617-432-6049 Fax: NA
E-mail: yuanma@hsph.harvard.edu

3. Timeline:

May-June 2022: Analyses plan
July-August 2022: Statistical analyses
September-October 2022: Manuscript writing and edits
November 2022- December 2022: Manuscript submission to peer-review journals

4. Rationale:

Orthostatic blood pressure (BP) assessment is an important tool for assessing autonomic dysfunction and potentially impaired baroreflex sensitivity in older adults. Orthostatic hypotension is frequently observed in older adults, especially individuals with frailty and hypertension.[1] Many, though not all, epidemiological studies have linked orthostatic hypotension to increased risk of cardiovascular events, syncope, falls, and death.[1,2] It has been reported in several prospective cohort studies that orthostatic hypotension was also associated with cognitive decline and a higher risk of dementia.[3-8]

Increasing evidence, however, suggests that focusing only on the dichotomized component of orthostatic hypotension may not sufficiently capture the important clinical relevance of the highly dynamic BP regulatory processes during the first few minutes of postural change. Specifically, during the first 30s to 60s following postural change, there would be an abrupt decrease in BP due to reduced ventricular filling and cardiac output.[9] During this initial phase of orthostatic BP response, individuals with intact cerebral autoregulation are generally able to maintain stable cerebral blood flow, irrespective of such abrupt decreases in BP[10], whereas individuals with autoregulatory dysfunction, especially older adults and individuals with hypertension, might be susceptible to disturbed cerebral perfusion.[11,12] From approximately 60s onwards after the postural change, this transient decrease in BP would activate baroreflex-mediated compensatory sympathetic activities, decrease parasympathetic activities and invoke other compensatory mechanisms to restore cardiac output and BP. During this subsequent compensatory phase, a lack of these compensatory mechanisms, for example in the presence of autonomic dysfunction, may fail to restore BP level (e.g., manifested as orthostatic hypotension) whereas the hyperreactivity of certain compensatory mechanisms may also lead to increased BP (e.g., manifested as orthostatic hypertension).[1,13] Taken together, BP responses during the few minutes upon standing, although short, are likely to invoke different regulatory mechanisms across multiple stages. The changes in BP measured at different time points may reflect different underlying physiological responses and thus their association with disease outcomes may also differ by the timing of the orthostatic BP assessment.

Indeed, it has been reported in previous studies that the first measurement (~30 seconds within standing) of orthostatic BP change within 1 minute upon standing has the strongest association with dizziness and higher risk of fracture, fall, syncope, and mortality.[14,15] It remains undetermined whether the association of orthostatic BP change with the risk of dementia differs by the timing of orthostatic BP assessment. Moreover, orthostatic hypertension has been suggested to be an independent risk predictor for cardiovascular disease, stroke, and renal events[16-20], but the relationship between orthostatic hypertension and the risk of dementia is undetermined. Prior evidence has linked orthostatic BP change to subclinical brain vascular diseases, but it remains unclear to what extent the association between orthostatic BP change and dementia may be explained by subclinical brain vascular injury.

References:

1. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic Hypotension: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1294-309.
2. Juraschek SP, Taylor AA, Wright JT, et al. Orthostatic Hypotension, Cardiovascular Outcomes, and Adverse Events. Hypertension 2020.
3. Wolters FJ, Mattace-Raso FU, Koudstaal PJ, Hofman A, Ikram MA, Heart Brain Connection Collaborative Research G. Orthostatic Hypotension and the Long-Term Risk of Dementia: A Population-Based Study. PLoS Med 2016;13:e1002143.
4. Cremer A, Soumare A, Berr C, et al. Orthostatic Hypotension and Risk of Incident Dementia: Results From a 12-Year Follow-Up of the Three-City Study Cohort. Hypertension 2017;70:44-9.

5. Elmstahl S, Widerstrom E. Orthostatic intolerance predicts mild cognitive impairment: incidence of mild cognitive impairment and dementia from the Swedish general population cohort Good Aging in Skane. Clin Interv Aging 2014;9:1993-2002.
6. Hayakawa T, McGarrigle CA, Coen RF, et al. Orthostatic Blood Pressure Behavior in People with Mild Cognitive Impairment Predicts Conversion to Dementia. J Am Geriatr Soc 2015;63:1868-73.
7. Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic hypotension and cognitive function: the Atherosclerosis Risk in Communities Study. Neuroepidemiology 2010;34:1-7.
8. Rawlings AM, Juraschek SP, Heiss G, et al. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. Neurology 2018;91:e759-e68.
9. Shibao C, Lipsitz LA, Biaggioni I. Evaluation and treatment of orthostatic hypotension. Journal of the American Society of Hypertension 2013;7:317-24.
10. Novak V, Novak P, Spies JM, Low PA. Autoregulation of Cerebral Blood Flow in Orthostatic Hypotension. Stroke 1998;29:104-11.
11. Strandgaard S, Olesen J, Skinhøj E, Lassen NA. Autoregulation of Brain Circulation in Severe Arterial Hypertension. Br Med J 1973;1:507-10.
12. Naritomi H. Effects of Advancing Age on Regional Cerebral Blood Flow. Arch Neurol 1979;36:410.
13. Jordan J, Ricci F, Hoffmann F, Hamrefors V, Fedorowski A. Orthostatic Hypertension: Critical Appraisal of an Overlooked Condition. Hypertension 2020;75:1151-8.
14. Juraschek SP, Daya N, Rawlings AM, et al. Association of History of Dizziness and Long-term Adverse Outcomes With Early vs Later Orthostatic Hypotension Assessment Times in Middle-aged Adults. JAMA Internal Medicine 2017;177:1316.
15. Gangavati A, Hajjar I, Quach L, et al. Hypertension, Orthostatic Hypotension, and the Risk of Falls in a Community-Dwelling Elderly Population: The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study. J Am Geriatr Soc 2011;59:383-9.
16. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM. Postural Changes in Blood Pressure and Incidence of Ischemic Stroke Subtypes. Hypertension 2011;57:167-73.
17. Palatini P, Mos L, Saladini F, Rattazzi M. Blood Pressure Hyperreactivity to Standing: a Predictor of Adverse Outcome in Young Hypertensive Patients. Hypertension 2022;79:984-92.
18. Jordan J, Ricci F, Hoffmann F, Hamrefors V, Fedorowski A. Orthostatic Hypertension. Hypertension 2020;75:1151-8.
19. Kario K, Eguchi K, Hoshide S, et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol 2002;40:133-41.
20. Rahman M, Pradhan N, Chen Z, et al. Orthostatic Hypertension and Intensive Blood Pressure Control; Post-Hoc Analyses of SPRINT. Hypertension 2021;77:49-58.

5. Main Hypothesis/Study Questions:

We hypothesize that increased orthostatic BP variability, including both large decreases and increases in BP, at different time points after the postural change, may be associated with increased risk of dementia and the association may vary with time of postural change. The putative association between orthostatic BP change and dementia may be partly explained by the presence of subclinical brain vascular injury.

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
Inclusion criteria: participants free of major neurological diseases (including dementia, stroke and Parkinson's disease) at baseline with available data on orthostatic BP assessment at visit 1. In our primary analyses, we will only include participants who completed at least 4 out of 5 orthostatic BP measurements at visit 1.

Primary exposure measure: supine to standing BP change at five time points during baseline assessment as both continuous variables and categorical variables (cut-off points for orthostatic changes in SBP as categorical variables: <-20, -20 to -10, -10 to 10, 10-20 and >20 mmHg; cut-off points for orthostatic changes in DBP as categorical variables: <-10, -10 to -5, -5 to 5, 5-10 and >10 mmHg). We will assess orthostatic changes in SBP and DBP separately.

Primary outcome: incident dementia cases identified throughout the follow-up period. To allow for statistically adequate analyses among all the participants with available orthostatic BP assessment, we will use dementia adjudication that combines surveillance and clinical visits (i.e., level 3 dementia diagnosis) for all participants.

Statistical analyses

Dynamic patterns of orthostatic BP changes and dizziness We will first describe the dynamic changes in BP upon standing at five individual time points at approximately 30, 50, 80, 100 and 120 seconds after standing, for all participants and then stratified by self-reported orthostatic dizziness, respectively. To determine the trajectory and rate of orthostatic BP changes within the first 2 minutes of standing, we will fit mixed models with piecewise cubic spline functions for orthostatic BP changes as continuous variables. The pattern of orthostatic BP change over time will be illustrated as Figure 1. The consideration of orthostatic dizziness in the analyses is to better inform the clinical relevance of a symptomatic measure with orthostatic BP assessment and the risk stratification of dementia. To deal with missing data in orthostatic BP assessment, especially the fifth (last) measurement, likelihood based random effects model will be used assuming data are missing at random. The characteristics of participants with and without missing data will also be compared to inform the potential mechanisms of missingness, including the comparison of orthostatic dizziness. Sensitivity analyses will be carried out to assess its impact on the findings.

Orthostatic BP changes and risk of dementia. In our primary analyses, we will assess the association of postural BP change measured with risk of dementia using Cox proportional-hazards models, where postural BP changes at the five individual time points will be analyzed in separate models. In our primary analyses, we will verify the proportional hazards assumption through visually inspecting the Schoenfeld residual plots. To control for potential confounding factors, we will adjust for age, sex and race in the initial model and in the final fully adjusted model (i.e., the primary model) we will further adjust for attained education, *APOE* 4 carrier status, body mass index, alcohol intake, smoking status, total cholesterol level, sitting systolic blood pressure, and history of diabetes and coronary heart disease at baseline. Since the primary exposure orthostatic BP change was only measured at visit 1, we will consider potential confounding variables collected at the same visit in our primary model to avoid adjustment of potential mediators at subsequent visits. To account for the potential confounding by time-varying covariates such as smoking, alcohol consumption and weight status at subsequent visits, we will conduct sensitivity analyses treating these variables as time-varying covariates. To provide causal relative risk estimates in the presence of the competing risk of death, we will use cause-specific hazard ratios.

In our secondary analyses, we will examine potential effect modification by age, sex, hypertension status, antihypertension medication use, *APOE* genotype, and length of follow-up (to assess the potential explanation of the association as reverse causation), and duration of standing through subgroup analyses stratified by these factors. To explore potential underlying mechanisms, we will further conduct the analyses stratified by arterial stiffness as measured by ankle-brachial index and the presence of atherosclerotic plaques in carotid arteries at visit 1. Since in typical orthostatic BP responses, a transient decrease in BP will be followed by increases in BP resulting from multiple compensatory mechanisms, we will assess whether the putative association of initial decreases in BP with the risk of dementia attenuates or disappears after additionally adjusting for subsequent compensatory increases in BP and whether this association attenuates with further adjustment for orthostatic dizziness. In our sensitivity analyses, we will further adjust for diastolic blood pressure and antihypertensive medication use in separate models.

Orthostatic BP change and presence of subclinical brain vascular disease. To further shed light on the underlying brain pathology that may link orthostatic BP changes to dementia, we will assess the association between orthostatic BP changes and imaging markers of brain vascular pathology, including both brain MRI markers and retinopathy assessed by fundus photography. For the analyses on the presence of retinopathy as a potential mediator, since this measurement is available for nearly all participants (~12,000), dementia diagnosis that combines surveillance and clinical visit data (level 3 dementia diagnosis) will be used. We will assess the severity of retinopathy as a categorical variable (none, mild, or moderate/severe). Although retinal assessment does not directly quantify brain vascular pathology, it has been considered as a surrogate of cerebrovascular pathology given that retinal microvasculature resembles brain microvasculature and it can be more conveniently assessed compared to brain MRI assessment. For the analyses on brain MRI structural measures among a subset of participants who underwent Brain MRI scan at visit 3 (approximately 2000 participants at visit 3 and nearly 2000 at visit 5), level 3

dementia diagnosis will be used in the primary analyses to be consistent with the analyses described above in the overall study population. In a sensitivity analysis, we will also conduct the analysis using level 1 dementia adjudication (which requires in-person clinical visits at visit 5) to assess the robustness of the findings. For brain MRI assessment, potential mediators of interest include total brain tissue volume, hippocampus volume (as an important marker for Alzheimer's disease), and presumed markers of cerebral small vessel disease, including white matter hyperintensities (0-9 rating scale at visit 3 and volumetric measure at visit 5), silent infarcts (as a binary indicator of presence or absence), cerebral microbleeds (as a binary indicator of presence or absence, and also based on the presence of lobar and deep microbleeds given their potential different pathophysiology). Causal mediation analyses will be conducted to quantify to what extent the putative association of orthostatic BP changes with the risk of dementia may be mediated by the markers of brain vascular pathology as described above. There are several methodological limitations in conducting the causal mediation analyses. The first one is potential inadequate statistical power to examine the above brain MRI markers as potential mediators since these data are only available in approximately 2,000 participants. We will consider using a composite score of overall subclinical brain vascular burdens to examine the overall proportion of the putative association that could be mediated. Also, brain MRI markers were available at both visit 3 and visit 5, given the timing of MRI may affect the mediated effect and the measures are quantified slightly different (e.g., white matter hyperintensities using visual rating scale at visit 3 and automatic volumetric measure at visit 5), mediation analyses will be conducted for these two sets of brain MRI markers in different models. We will also consult with experts on causal mediation analyses to consider the option of multi-stage mediation analyses. Also given that neuroimaging markers were not available in all participants, we will also compare the characteristics of the participants included in and excluded from the mediation analyses to evaluate potential selection bias and inform the generalizability of our findings.

Other methodological considerations: There has been limited evidence on the clinical relevance of the timing of orthostatic BP assessment, largely because of the unavailability of orthostatic BP measures within the first minute in most studies. To test the robustness and generalizability of our findings, we will also consider replicating the analyses in the Rotterdam Study, another population-based cohort study that has a similar assessment of orthostatic BP change at five-time points after the postural change and standardized diagnosis of dementia, but have a slighter older study population.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes X **No**

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? x **Yes ____ No**

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? √ **Yes ____ No**

Note: only the *APOE* genotype data will be used in the analyses as a covariate and the related variables were distributed by the Coordinating Center.

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 website at: http://www.cscc.unc.edu/aricproposals/dtSearch.html

x Yes _____ No

Note: because this manuscript proposal will focus on analyzing the risk of dementia and subclinical vascular brain changes in relation to time pattern of orthostatic BP change at five individual time points, it does not overlap with prior two publications on dementia listed below. In addition, through close collaborations with Dr. Stephen Juraschek, who is the lead author of the ongoing manuscript proposal on orthostatic hypotension and adverse clinical outcomes, we have made sure there is no overlap in our proposed analyses.

- *Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic hypotension and cognitive function: the Atherosclerosis Risk in Communities Study. Neuroepidemiology 2010;34:1-7.*
- *Rawlings AM, Juraschek SP, Heiss G, et al. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. Neurology 2018;91:e759-e68.*

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)?

Orthostatic Hypotension and Risk of Falls in the Atherosclerosis Risk in Communities Study (ARIC) | Stephen P Juraschek
Hits_43 | Size_327k | 9/2/2015

Phenotypes of orthostatic hypotension and their association with adverse clinical outcomes in Middle-Aged Adults | Stephen P Juraschek
Hits_16 | Size_128k | 5/11/2022

Orthostatic Hypotension and Cognitive Function: the ARIC Study (MS1104) | Rose, K
Hits_15 | Size_55k | 5/23/2012

ARIC Manuscript Proposal #2829 PC Reviewed: 09/13/16 Status: Prio |
Hits_18 | Size_163k | 8/30/2016

MP: 2539: Yano Y,… Gottesman RF, Mosley TH et al. Long-term blood pressure level and variability from midlife to later life and subsequent cognitive change: the ARIC Neurocognitive study.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? √ Yes ____ No

11.b. If yes, is the proposal

√ A. primarily the result of an ancillary study (list number* 2020.17 and 2008.06)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

Note: This is an ancillary study that will use existing data that have been collected in the ARIC study and it does not involve new data collection.

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.