ARIC Manuscript Proposal #3508

1.a. Full Title:
Mediation of the Association Between Midlife Blood Pressure and Late-life Dementia and Cognitive Decline.

b. Abbreviated Title (Length 26 characters): Mediation of BP & Cognition

2. Writing Group:
Writing group members: (Alphabetically)
Erin Bennett, M. Maria Glymour, Kan Z. Gianattiso, Rebecca Gottesman, Melinda C. Power (last), Keke Schuler (first), others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KS___ [please confirm with your initials electronically or in writing]

First author:  Keke Schuler
Address:  Department of Epidemiology and Biostatistics
Milken Institute School of Public Health
George Washington University
950 New Hampshire Ave, NW
Washington, DC 20052
Phone: (202)994-1329
E-mail: kschuler@gwu.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:  Melinda C. Power
Address:  Department of Epidemiology and Biostatistics
Milken Institute School of Public Health
George Washington University
950 New Hampshire Ave, NW
Washington, DC 20052
Phone: (202)994-7778
E-mail: power@gwu.edu

3. Timeline:
We plan on finishing data analyses and have this manuscript ready for submission within one year upon this approval.

4. **Rationale:**

Midlife elevated blood pressure and hypertension are associated with late-life dementia and cognitive decline, even in the absence of diagnosed stroke.\(^1\)\(^-\)\(^5\) Prior findings from the Atherosclerosis Risk in Communities (ARIC) study have shown that hypertension or elevated blood pressure in middle age was associated with increased risk of dementia,\(^3\)\(^,\)\(^6\) accelerated cognitive decline,\(^7\)\(^-\)\(^9\) and hospitalization with dementia through late life.\(^10\) Moreover, uncontrolled hypertension in midlife was significantly associated with greater cognitive decline in midlife.\(^11\)

It is likely that elevated midlife blood pressure contributes to increased risk of cognitive decline and dementia in the absence of stroke through multiple mechanisms. Prior studies have examined the association between elevated blood pressure and potential pathologic intermediates. For example, elevated blood pressure has been linked to multiple measures of small vessel disease (e.g. \(^12\)\(^-\)\(^20\)) and brain atrophy (e.g. \(^21\)\(^-\)\(^27\)). Other studies generally suggest that those with higher burden of small vessel disease have increased risk poor or declining cognition (e.g. \(^28\)\(^-\)\(^44\)), and that brain atrophy mediates the relationship between small vessel disease and cognition.\(^45\) Elevated blood pressure has also been linked to increased amyloid deposition in many,\(^46\)\(^,\)\(^47\) but not all\(^48\) prior studies, and greater brain amyloid burden has been linked to evidence of greater brain atrophy or worse or declining cognition\(^49\)\(^-\)\(^52\). These prior studies suggest two mechanistic pathways by which elevated midlife blood pressure may influence late life cognition, one involving amyloid and one involving small vessel disease. In addition, these pathways themselves may be inter-related, given demonstrated associations between amyloid and small vessel disease provide evidence of dependence.\(^53\)\(^,\)\(^54\)

To our knowledge, the relative contribution of each pathologic pathway, whether these known pathologies can fully account for the association between midlife elevated blood pressure and late-life cognition, and the extent to which these proposed pathologic pathways interrelate has not been comprehensively investigated. Thus, our objective was to simultaneously test the significance and inter-relationship of multiple measures of pathologies thought to mediate the effect of elevated midlife blood pressure on deficits in late life cognition in the absence of stroke or silent cortical infarct, using longitudinal data from the Atherosclerosis Risk in Communities (ARIC) Study.

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

Research question:
To what extent do MRI markers of subclinical cerebrovascular disease, brain volume, and amyloid simultaneously mediate the effects of blood pressure on dementia and cognitive decline, in the absence of stroke or silent cortical infarct.

Hypotheses:
MRI makers of subclinical cerebrovascular disease, brain volume, and amyloid fully mediate the effect of elevated midlife blood pressure on dementia and cognitive decline. The majority of the impact of elevated blood pressure on late-life cognition and dementia is mediated by impact on small vessel disease.

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:
Longitudinal study design with visit 1 as an analytic baseline.

Inclusion/Exclusion criteria:
Inclusion criteria require completion of stage 3 brain MRI at Visit 5/ARIC-NCS and available outcome data for the analysis of interest.
Exclusion criteria include multiple sclerosis, brain tumor, or surgery/radiation to the head, confirmed stroke through visit 6, presence of cortical infarcts at visit 5, non-black/non-white race, white in MS, black in MN or MD.

Confounders:
Socio-demographic information (age, race-center, sex, and education) and diabetes status established at Visit 1.

Exposures:
We will use systolic and diastolic BP at visit 1 and visit 2 to create a measure of midlife blood pressure. Systolic and diastolic BPs are both continuous variables and the mean between the second and third measures for each visit will be used for subsequent calculation. To create the systolic BP exposure variable, an average systolic BP between visit 1 and visit 2 is created for each participant. The similar calculation is used to create diastolic BP exposure variable.

Mediators:
We will use V5 MRI- and PET- based measures indicative of brain pathology. These include indicators of small vessel disease (i.e., white matter hyperintensities, lacunes, subcortical microbleeds, white matter mean diffusivity, white matter fractional anisotrophy), brain atrophy, (ie. Brain volumes), and amyloid (i.e. SUVR).

We will consider WMH volumes as a continuous variable. Both WMH and brain volumes will be normalized by intracranial volume. Lacunes subcortical microbleeds will be defined as absent (0) or present (1). Following the descriptions in Power et al. (2017), a weighted average overall measure will be created for FA and MD for use in analyses. For amyloid, we will primarily use a global cortical measure of amyloid.

Outcomes:
Main outcomes in the analyses include cognitive factor scores at visit 6 and prevalent dementia at visit 6. The cognitive factor scores include three cognitive domains: memory, execute
function, and language. We will examine each domain separately in the analyses. To maximize sample size we will use level 3 dementia diagnoses; level 1 diagnoses will be considered in sensitivity analyses.

Covariates and weighting:
A set of covariates is included in all analyses and they are based on data collected at visit 1, including age (years), sex (male and female), education (basic, intermediate, and advanced), race-center (MN-white, MD-white, MS-black, NC-black, NC-white), and diabetes (yes/no).

Analytic plan:
For the mediation analyses, we will begin by using structural equation modeling to simultaneously estimate whether the association between blood pressure and cognitive decline is mediated by WMH, lacunes, and subcortical microbleeds, WM FA, WM MD, and brain volume. Figure 1 below represents the conceptual model of the mediation analyses including MRI markers of subclinical cerebrovascular disease and total brain volume. Figure 2 represents the conceptual model expanded to include amyloid. The same mediation model will be used for each outcome.

We will explore the appropriateness of using a latent variable to summarize multiple markers of small vessel disease and check the model fit. If the model shows adequate model fit, we will proceed with the latent variable, instead of observed variables. Because binary variables are presented in each model, models will be estimated with weighted least square mean and variance adjusted method. Given amyloid information was only collected in a subsample, only these available cases will be included when examining the pathways involve amyloid. Analyzing potential multiple pathways simultaneously with amyloid would help clarify the contribution of amyloid in associations between high blood pressure and dementia and cognitive decline, but is considered a secondary analysis given the small available sample. Importantly, including amyloid in pathways of MRI markers of subclinical cerebrovascular disease and total brain volume would allow us to assess how amyloid is associated with other mediators and identify potential sequential mediation effects.

We will conduct several sensitivity analyses. We will consider analyses after using multiple imputation to handle missing blood pressure and covariates data to understand the impacts of missing data. We will also conduct weighted analyses to understand the impacts of selection process by which only participants who completed visit 5 MRI were selected in current analyses.
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”? __X__ 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/mantrack/maintain/search/dtSearch.html

__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)?

**Manuscript proposals examining brain abnormalities and dementia (last name of first author for each manuscript is listed by the end in the parenthesis):**
Manuscript Proposal #314: Cerebral Abnormalities Identified on Magnetic Resonance Imaging and Cognitive Functioning: The ARIC Study (Mosley)
Manuscript Proposal #1119r: MRI predictors of global and domain specific cognitive function at 10 years follow-up: the ARIC MRI Study (Coker)
Manuscript Proposal #2288: Associations of Brain Imaging with Cognitive Change over 20 years (Knopman)
Manuscript Proposal #2586: Neural correlates of prior domain-specific cognitive decline: a voxel-based morphometry study (Schneider)
Manuscript Proposal #3054: Brain Structural MRI Abnormalities Predict Dementia, MCI and Cognitive Decline in an Older Population (Wu)
Manuscript Proposal #3075: Association between white matter microstructural integrity and cognitive decline, MCI, and incident dementia (Power)

**Manuscript proposals examining vascular health and dementia (last name of first author for each manuscript is listed by the end in the parenthesis):**
Manuscript Proposal #388: Association of cognitive function with hypertension, its treatment and control - The ARIC Study (Liao)
Manuscript Proposal #734: Blood pressure over time and changes in cognitive function (de Moraes)
Manuscript Proposal #1365: Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study (Alonso)
Manuscript Proposal #3163: Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the ARIC cohort (Hodis)
Manuscript Proposal #2120: Prevalence of Mild Cognitive Impairment and Dementia and Their Relationship to Diabetes and Hypertension in ARIC (Knopman)
Manuscript Proposal #2120C: Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC (Gottesman)
Manuscript Proposal #2175: Midlife blood pressure and 20-year cognitive change: The ARICNeurocognitive Study (Gottesman)
Manuscript Proposal #3051: The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study (Walker)
Manuscript Proposal #2597: Pulse Wave Velocity and Neurocognitive Outcomes in a Community-Dwelling Sample of Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study (Palta)
Manuscript Proposal #3041: Preventing dementia: The case of elevated blood pressure in older persons - What to treat with? (Launer)
Manuscript Proposal #3365: Impact of vascular factors on the trends in dementia incidence (Kim)

Manuscript proposals examining vascular health and brain abnormalities (last name of first author for each manuscript is listed by the end in the parenthesis):
Manuscript Proposal #1553: Associations between vascular risk factors and longitudinal changes in ventricular size: a 14 year longitudinal study (Knopman)
Manuscript Proposal #2351: Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI (Power)
Manuscript Proposal #2384: Cardiac and Brain Structure and Function Associations: The ARIC Study (Gottesman)
Manuscript Proposal #2551: Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS study (Power)
Manuscript Proposal #3119: Vascular risk factors, brain amyloid deposition, and cognitive decline: The ARIC-PET Study (Gottesman)

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* ___2017.01_______)
   ____ 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 https://www2.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.


