1.a. Full Title: Blood Pressure Trajectory from Midlife to Late Life and Cognitive Change: The Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Blood Pressure Trajectory and Cognition

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

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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).

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3. Timeline:
June 2017: Submit proposal.
July-August 2017: Perform analysis.
September 2017-November 2017: Prepare manuscript.
December 2017: Send draft to co-authors and submit to journal

4. Rationale:
Evidence supporting a link between higher systolic blood pressure (SBP) levels in midlife and lower cognitive function in late life continues to accumulate.\textsuperscript{1-12} Conversely, association of SBP with cognition in later life has been inconsistent.\textsuperscript{1-3} BP tends to decrease the years before dementia diagnosis.\textsuperscript{9-12} BP tends to decline from midlife to later life because of comorbidities related to cognitive dysfunction (e.g., frailty and heart failure).\textsuperscript{6,7} Therefore, we hypothesized
that BP trajectories from midlife to later life would be more likely than midlife BP measured at a single time point to relate to cognitive change in later life. The determination may provide clinicians with a way to identify middle-aged and older adults at high risk for developing cognitive dysfunction in later life, and to intervene to prevent cognitive decline.

The Honolulu-Asia Aging Study (HAAS) that recruited 1,778 Japanese American men demonstrated that, those who developed dementia had increased SBP from midlife to late life, followed by a steeper decrease in later life, compared with those who did not develop dementia. Similar results were observed in Swedish women (n=1,462). However, cognitive function was assessed at a single time point in these studies. Therefore, it remains to be determined whether BP trajectories are only associated with cognitive function concurrently or whether it is also related to individual cognitive decline.

Using data from the Atherosclerosis Risk in Communities (ARIC) Study that enrolled middle-aged black and white individuals and measured clinic BP and cognitive function over multiple visits, we will characterize BP trajectories from midlife to later life and the association with cognitive decline.

5. Main Hypothesis/Study Questions:
Prior study in ARIC (Manuscript Proposal #2394) identified 3 SBP or DBP trajectory groups (Figure 1). We will employ a similar approach to identify the BP trajectory groups.

**H1.** The high-stable group in SBP (see Figure 1) will be associated with lower cognitive function at Visit 4 and greater cognitive decline from Visit 4 to Visit 5 compared with the moderate-increasing and low-increasing groups.

**H2.** The moderate-increasing group in SBP will be associated with lower cognitive function at Visit 4 and greater cognitive decline from Visit 4 to Visit 5 compared with the low-increasing group.

**H3:** The high-decreasing group in DBP (see Figure 2) will be associated with lower cognitive function at Visit 4 and greater cognitive decline from Visit 4 to Visit 5 compared with the moderate-decreasing and low-stable groups.

**H4:** The moderate-decreasing group in DBP will be associated with lower cognitive function at Visit 4 and greater cognitive decline from Visit 4 to Visit 5 compared with the low-stable group.
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).

**Design:**
Longitudinal data analysis.

**Inclusion criteria:**
Participants in the ARIC study with measures of BP from Visit 1 to Visit 4 and of cognitive function at Visit 4 and Visit 5.

**Outcomes:**
Cognitive function measures (the Delayed Word Recall Test [DWRT], the Digit Symbol Substitution Test [DSST], the Word Fluency Test [WFT]) at Visit 4 and Visit 5, related Z-scores and the global cognitive Z-score as previously defined in ARIC publications.

**Exposures:**
SBP and DBP trajectories from Visit 1 to Visit 4.

We will use latent class modeling, specifically group-based trajectory modeling, to identify participants with similar underlying patterns of trajectory in BP from the Visit 1 to Visit 4 examinations. The models will fit using STATA 13.1 traj program (equivalent to PROC TRAJ in SAS). Based on the Bayesian Information Criterion, we will select the number and shape of the trajectories that best represent distinct patterns of change in SBP and DBP, respectively. Model adequacy will be assessed by comparing posterior predicted probabilities of final group assignment and comparing odds ratios of final group classification (and 95% confidence intervals [CIs]). Trajectories will be labeled (see Figure 1 and Figure 2) by initial BP levels (low [<120mmHg SBP, <75mmHg DBP]; moderate [120-140mmHg SBP, 75-90mmHg DBP]; or high [≥140mmHg SBP, ≥90mmHg DBP]) and pattern of change in BP with age (increasing; decreasing; or stable).

**Covariates:**
Covariates will include sociodemographic characteristics (age, sex, race, education, apolipoprotein E ε4 alleles, and study site), clinical characteristics at Visit 4 (body mass index [BMI], current smoking, current drinking, prevalent diabetes, use of antihypertensive drugs, and prevalent stroke). These covariates will be selected *a priori* because they have known correlations with BP and are risk factors for cognitive dysfunction.

**Analysis:**
Associations of BP trajectories with cognitive change will be examined by linear mixed effects models using Stata version 14.0 (StataCorp; College Station, TX). We will verify the model assumptions of linearity, normality of residuals, homoscedasticity, and absence of collinearity. Reference will be defined as low-stable BP trajectory group. The BP trajectories, interval (Visit 4-Visit 5; 15 years), and the BP trajectories x interval will be modeled as fixed effects. The
intercept and interval will be allowed to vary between individuals and modeled as random effects.

To assess whether BP trajectories from Visit 1 to Visit 4 would be more likely than BP Visit 1 or Visit 4 to relate to cognitive change from Visit 4 to Visit 5, comparison of model fits across different models will be conducted. The likelihood ratio $\chi^2$, Akaike information criterion (AIC), and Bayes’ information criterion (BIC) estimates will be used to assess model fit.

In sensitivity analyses, analyses for heterogeneity of effect between BP trajectories and outcomes by sex, race, antihypertensive medication use, or apolipoprotein E ε4 allele will be performed, with inclusion of interaction terms. If the interaction is observed, stratified analyses will be conducted. To examine the effects of attrition on our findings, we will conduct sensitivity analyses as recommended by the ARIC analysis committee to account for missing data using inverse-probability-of-attrition (IPA) models. Statistical significance will be defined as $P<0.05$ on 2-sided tests.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes

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

(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? 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

Yes

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 Manuscript Proposal #2394, “Determinants of blood pressure trajectories from midlife to older age: the Atherosclerosis Risk in Communities (ARIC) Study”

ARIC Manuscript Proposal #2146, “Systolic blood pressure trajectories and incident cardiovascular disease”.
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

___ A. primarily the result of an ancillary study (list number* ______)
__X   B. primarily based on ARIC data with ancillary data playing a minor role
(usually control variables; list number(s)* ______2009.29______ __________)

*ancillary studies are listed by number at http://www.cscn.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.cscn.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, approved manuscripts using 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 _____ No.

References


