ARIC Manuscript Proposal # 3051

PC Reviewed: 10/3/17   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study

 b. Abbreviated Title (Length 26 characters): Blood pressure and dementia
2. Writing Group:

Writing group members: Keenan Walker (first and corresponding author); Rebecca Gottesman (last author); Richey Sharrett; Andrea Schneider; Marilyn Albert; Alvaro Alonso; Karen Bandeen-Roche; Josef Coresh; Alden Gross; Beverly Gwen Windham; David Knopman; Melinda Power; Andreea Rawlings; Thomas Mosley

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

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3. Timeline: 6-9 months; manuscript submission spring 2018.

4. Rationale:
Given the dearth of available treatment options for Alzheimer's disease and other forms of dementia, there is an urgent need to identify risk factors that can be modified to delay, and potentially prevent, the onset of neurodegenerative disease. Hypertension, high blood pressure (BP), and in certain circumstances, low BP, have been associated with cognitive decline and dementia incidence in community-based studies, suggesting that BP may serve as a viable target for primary or secondary dementia prevention. Accumulating evidence, including reports from the Honolulu-Asia Aging Study[1–3] and the Atherosclerosis Risk in Communities (ARIC) Study[4,5], suggests that hypertension during midlife may serve as a stronger risk factor than late-life hypertension for cognitive decline and dementia. These findings are consistent with the idea that midlife hypertension may serve as a proxy for greater hypertension duration and chronicity, meaning prolonged exposure to the harmful effects of high BP[6,7]. While the effect of high BP during the 7th, 8th, and 9th decades of life on dementia incidence is less clear[8], emerging evidence suggests that the optimal BP ranges for older adults may depend on earlier BP patterns. For example, several studies have found that low, but not high, late-life BP is associated with cognitive impairment[9,10], particularly among individuals who were previously hypertensive[11,12]. However, few large studies have prospectively examined BP, cognition, and dementia incidence over the decades spanning middle to late adulthood, making it difficult to draw firm conclusions about the effects of hypertension chronicity and mid- to late-life BP changes on neurocognitive outcomes[11,13].

An improved understanding of the evolving relationship between BP levels, past hypertension, age, and neurocognitive functioning must be established before recommendations can be made with regard to BP targets for lowering the risk of cognitive decline and dementia in older adults. The ARIC Neurocognitive Study (NCS) has employed dementia surveillance methods that allow for the evaluation of dementia incidence as it relates to BP characteristics over nearly three decades spanning from middle to late life. Using this large, biracial community sample, the current study will examine the association of middle and late-life hypertension, hypertension duration, and hypertension treatment with late-life cognitive decline, mild cognitive impairment (MCI) risk, and incident dementia. We will also directly test the hypothesis that individuals with both midlife hypertension and low BP later in life are at an especially high risk for cognitive decline, MCI, and incident dementia. Given evidence for the moderating effect of race[14], *APOE* ε4 status[15,16], and diabetes[17] on the association between BP characteristics and cognitive decline, we will explore the potentially modifying role of each.

5. Main Hypothesis/Study Questions:
H1. Midlife (Visits 1 and 2) hypertension and prehypertension will be associated with greater late-life cognitive decline and an increased rate of conversion to MCI and dementia. These associations will be weaker when hypertension/prehypertension are measured at subsequent visits.

H2. High systolic and diastolic blood pressure during midlife (measured as continuous variables, in separate models) will be associated with greater late-life cognitive decline and an increased rate of conversion to MCI and dementia. These associations will be weaker when BP is measured at subsequent visits.

H3. Participants diagnosed with hypertension during or before midlife (before Visit 4) who then have hypotension or low BP during late-life (Visit 5) will demonstrate greater subsequent cognitive decline and an increased rate of conversion to MCI and dementia compared to participants with other blood pressure patterns.

H4. Compared to participants who were treated for hypertension, untreated participants will demonstrate greater cognitive decline and an increased rate of conversion to MCI and dementia.

H5. The associations in H1-H3 will be stronger among white participants, participants who are *APOE* ε4 positive, and participants diagnosed with diabetes.

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).

Inclusion criteria: We will include all participants who attended Visit 5 and all participants who have cognitive data available from the annual follow-up (AFU) between Visits 5 and 6.

Exclusion Criteria: We will exclude non-white and non-African-American participants and non-white participants in Washington Co. and Minnesota, participants with stroke prior to Visit 5, participants missing education, and participants missing information on Visit 5 cognitive status (i.e., normal/MCI/dementia classification and cognitive domain factor scores). Participants with interim incident strokes will be censored at the time of stroke in a secondary analysis.

Exposure variables: The following variables will be measured at Visits 1, 2, 3, 4 and 5, unless otherwise specified.

Hypertension (SBP≥140, DBP≥90, or antihypertensive medication use)
Pre-hypertension (SBP 120-139 or DBP 80-89 and not classified as hypertensive)

Normal (SBP<120 or DBP<80, no antihypertensive medications, and no hypotension)

Hypotension (SBP<90 and DBP<60)

Measured systolic BP (continuous)

Measured diastolic BP (continuous)

Longitudinal BP patterns: To examine whether a pattern of midlife hypertension and low late-life BP is associated with greater cognitive decline, dementia incidence, and MCI risk, participants with midlife hypertension will be grouped into one of the following categories (Table 1). Each group will be compared to the group of participants who maintain normal blood pressure.

Table 1. Blood pressure patterns of interest among participants who attended Visit 5

Pattern	Midlife (Visits 3 & 4)	Late-life (Visit 5)	*n*
Late-life hypotension [a]	Hypertension	Hypotension	484
Sustained hypertension [a]	Hypertension	Hypertension	1,722
Sustained normal BP [a, b]	Normal	Normal	1,572
Late-life SBP < 140	Hypertension	SBP < 140	1,114
Late-life SBP recommended	Hypertension	SBP < 120	412
Late-life SBP low recommended	Hypertension	SBP < 100	40
Late-life SBP hypotension	Hypertension	SBP < 90	13
Late-life DBP < 90	Hypertension	DBP < 90	1,706
Late-life DBP recommended	Hypertension	DBP < 80	1,538
Late-life DBP low recommended	Hypertension	DBP < 70	1,066
Late-life DBP hypotension	Hypertension	DBP < 60	483

[a] Pattern used for primary analysis
[b] Reference group
Note. DBP = diastolic blood pressure; SBP = systolic blood pressure

Cumulative hypertension exposure: We will also evaluate cumulative exposure to hypertension (ranging from 0 to 1, representing the proportion of time until visit 5 within ARIC when known to be hypertensive), as well as cumulative SBP and DBP, using previously described methods, such as a time-averaged measurement[18].

Outcome variables:

Dementia incidence: Dementia incidence between Visit 5 (2011-13) and Visit 6 (2015-2017) will be examined among participants who were classified as either cognitively normal or having MCI at Visit 5. Dementia incidence will be analyzed in two separate groups.

Persons examined at Visit 5. Dementia will be defined using both the information from the full Visit 6 examination with expert committee diagnosis and information captured in AFU interviews using the Six Item Screener (SIS) and the Ascertain Dementia 8-item Informant Questionnaire (AD8). Date of dementia onset will be captured using the SIS and AD8, and dementia diagnosis will be confirmed at Visit 6 in those who attend Visit 6. Participants who attended Visit 5, but not Visit 6, and have SIS and AD8 information available from the AFU will also be included.

Persons alive at Visit 5 who did not attend Visit 5. In order to evaluate potential selection effects of Visit 5 attendance, we will examine separately those participants who did not attend Visits 5, but have available SIS and AD8 data during this period. Their rate of probable dementia based on SIS and AD8 data will be compared with the similarly-defined probable dementia among Visit 5 attendees.

Dementia: Dementia will be defined at Visit 6 when three criteria are met: (1) FAQ > 5 or CDR sum of boxes > 3, (2) at least 2 domain scores worse than – 1.5 Z and (3) a decline since visit 5

on the serial full ARIC cognitive battery of >0.055 standard deviations/year (ARIC Visit 6 Manual 17).

Mild cognitive impairment (MCI): MCI will be defined at Visit 6 as at least one domain score worse than -1.5 Z, a CDR sum of boxes between >0.5 and ≤3, an FAQ ≤5, and a decline on the serial full ARIC cognitive battery since visit 5 of >0.055 standard deviations/year (ARIC Visit 6 Manual 17).

Cognitively normal: Participants will be categorized as cognitively normal if they have not been previously diagnosed with dementia, and all cognitive domains scores are better than -1.5 Z, or if there is an absence of decline in the full ARIC cognitive battery of >0.055 standard deviations/year (ARIC Visit 6 Manual 17).

Cognitive change: We will examine cognitive change from Visit 5 to Visit 6 in domains of memory, language, and processing speed and executive function. We will use a latent variable approach, described previously[19], for the measurement of cognitive domains.

The composition of each cognitive domain composite score is described below.

Memory Composite
Delayed Word Recall Test (DWRT)
Logical Memory I & II
Incidental Learning

Language Composite
Word Fluency Test (WFT)
Animal Naming
Boston Naming Test

Processing Speed/Executive Function Composite
Digit Symbol Substitution Test (DSST)
Digit Span Backwards
Trail Making Test-A
Trail Making Test-B

Covariates:
Covariates will include the following: linear and a quadratic term for baseline age, sex, race-center (Washington County white; Minneapolis white; Forsyth County white; Forsyth County African American; Jackson African American), education (less than high school; high school/GED/vocational school; or any college), cigarette smoking and alcohol use status (current; former; never), BMI (kg/m^2), total cholesterol, HDL, diabetes, coronary heart disease, late-life weight loss (based on PFX-Aging working group definition), self-reported health status, and *APOE* ε4 status. We will update time-varying covariates to match the exposure of interest, allowing for appropriate control for confounding.

Statistical analysis:

H1-H2: We will examine the association between mid- and late-life BP characteristics and time to dementia onset among participants who are cognitively normal or MCI at Visit 5. The earliest date of dementia classification based on the comprehensive neurocognitive assessment (2015-2017), the SIS or AD-8 administered as part of the AFU, or hospitalization discharge or death certificate code will be used to define dementia onset. To account for the lag in ascertainment, 6 months will be subtracted from the estimated dates of the dementia onset classified via informant interviews, hospitalization discharge, and death certificate codes. Participants without dementia diagnosis on any level will be censored at the date of their latest assessment up to January 1, 2018. Cox proportional hazard models will be used to examine the association of continuous and categorical BP characteristics with dementia incidence.

H1-H2: We will examine the association of mid- and late-life BP characteristics with Visit 6 MCI risk among the >4,500 participants who are cognitively normal at Visit 5. Binary logistic regression will be used to examine the association of continuous and categorical BP characteristics with MCI risk.

H1-H2: We will examine the association of continuous and categorical BP characteristics with cognitive change using multivariable linear regression. We will examine changes in global cognitive functioning, as well as domain-specific cognitive change using the comprehensive neuropsychological battery.

H3: We will examine whether a pattern of midlife hypertension followed by late-life hypotension is associated with time to dementia onset among participants who are cognitively normal or MCI at Visit 5 using Cox proportional hazard models. We will focus on the group with midlife (Visits 3 and 4) hypertension and late-life (Visit 5) hypotension for our primary analysis. Each group of interest will be compared to participants who had normal blood pressure across all visits (the referent group). Similarly, we will use logistic and linear regression to determine whether a pattern of midlife hypertension followed by late-life low BP is associated with greater MCI risk and late-life cognitive decline. We may additionally examine the association of other mid- to late-life BP patterns (defined in Table 1) with exposure variables in a secondary analysis.

H4: To evaluate the effect of antihypertensive medication on cognitive decline and rate of conversion to MCI and dementia, we will compare treated and untreated hypertensive participants on all outcome variables. Additionally, among participants with a pattern of midlife hypertension followed by late-life hypotension, we will examine whether neurocognitive outcomes differ based on late-life antihypertensive use (if sample size permits). Participants in treated and untreated groups will be matched based on propensity scores. Propensity scores for antihypertensive medication use will be generated using logistic regression equations that will account for demographic characteristics, physiological factors, and medical comorbidity.

We will use three regression models for the analyses described above. *Model 1* will covary for demographic factors (i.e., age, sex, race-center, education, and *APOE* ε4 status). Model 2 will covary for demographic factors, physiological and disease variables (i.e., BMI, total cholesterol, HDL, diabetes, and coronary heart disease), and vascular risk factors (i.e., cigarette smoking and alcohol use status). *Model 3* will covary for demographic factors, physiological and disease variables, vascular risk factors, weight loss and self-reported health status. Multiplicative

interaction terms will be used to evaluate effect modification by race (white/African American), *APOE* ε4 allele status (0/≥1), co-occurring diabetes (yes/no) (**H5**).

Sensitivity analyses for will be conducted using inverse probability of attrition weighting (IPAW) to determine the effect of sampling bias related to differential death and dropout on cognitive decline analyses. We will also consider using IPAW to examine the effect of study dropout before Visit 5 among participants who are alive at the time of Visit 5. A two-sided p value < .05 will be used as the cutoff for statistical significance. Analyses will be conducted using Stata Version 14 (StataCorp, College Station, Tex., USA).

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? __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 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/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)?
MP# 2511. Vascular risk factors and brain amyloid deposition: The ARIC-PET Study. Gottesman et al.

MP# 2120 a. Mid-life vascular risk factors for Mild Cognitive Impairment in the ARIC NCS Study. Knopman et al.

MP# 2120 b. Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC. Gottesman et al.

MP# 2120 c. Prevalence of Mild Cognitive Impairment and Dementia and Their Relationship to Diabetes and Hypertension in ARIC. Knopman et al.

MP# 2175. Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study. Gottesman et al.

MP# 2829. Associations of orthostatic hypotension and postural change in blood pressure with 20-year cognitive decline, incident dementia, and incident stroke: The Atherosclerosis Risk in Communities Study. Rawlings et al.

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* __2009.29__)**
 ___ **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, 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 __X__ No.

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4   Gottesman RF, Schneider ALC, Albert M, *et al.* Midlife Hypertension and 20-Year Cognitive Change. *JAMA Neurol* 2014; **21287**: 1–10.
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7   Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke* 1998; **29**: 2334–40.

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