ARIC Manuscript Proposal # 3339

PC Reviewed: 2/12/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Association of Blood Pressure over the Life Course and Late-life Cognition in Blacks, Hispanics and Whites: ARIC, CARDIA, CHS, FHS, MESA, and NOMAS (BP COG)

b. Abbreviated Title (Length 26 characters): BP 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. _DAL_ **[please confirm with your initials electronically or in writing]**

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3. Timeline: We plan to submit an abstract for submission to the European Stroke Organization Conference (May 22-24, 2019, Milan, Italy), with a submission deadline of January 23, 2019. Manuscript preparation will be ongoing, with an expected draft completion date of 7/1/2019.

4. Rationale: Cognitive impairment and dementia (CID) disproportionately affect Blacks and Hispanics in the United States (US). Older Blacks are 2 times more likely and older Hispanics are 1.5 times more likely than older Whites to have CID, including Alzheimer's disease and Alzheimer's disease-related dementias (ADRDs). Among patients with dementia, Blacks and Hispanics have costs that are 30-45% higher than Whites with dementia. Vascular risk factors contribute to risk of CID, including Alzheimer's disease and ADRDs, and these risk factors are modifiable. Vascular risk factor interventions are likely to reduce racial/ethnic disparities in CID. Yet, potentially effective strategies to reduce disparities and prevent CID can't be studied because key information for the design of trials of vascular health interventions is lacking.

High BP, particularly in mid-life, increases the risk for CID and ADRDs. High BP is a common vascular risk factor and a leading contributor to racial/ethnic disparities in health. Blacks tend to

have an earlier age of onset, a longer duration, and a greater severity of high BP than Whites. Not only are Blacks and Hispanics more likely to have worse BP control than Whites, but they are also more likely to have detrimental brain effects from high BP. For example, the impact of high BP levels on stroke risk is 3-fold greater for Blacks than for Whites. Blacks' and Hispanics' greater vascular disease burden contributes to their greater white matter hyperintensity volume, a marker of cerebral small vessel disease, compared to Whites. While it is clear that lowering BP to optimal levels (<120/80) reduces cardiovascular disease (CVD) events in adults with high CVD risk, this group in the US is relatively small. It is unclear whether lowering BP to optimal levels also reduces CVD in the larger group of adults at lower CVD risk (e.g., Blacks age 55 with systolic BP 130-139 mmHg). And, it is unclear whether lowering BP reduces CID. Our group has shown that treating to target BP goals is not the best way to improve outcomes or narrow disparities. More harm can be prevented using "benefit-based tailored treatment" strategies where treatment is guided by a patient's risk and benefit of treatment instead. Though most studies enroll middle-aged and older adults, evidence is growing that the effect of high BP on cognition begins in young adulthood. Preliminary work by us shows that racial/ethnic disparities in BP control also begin in young adulthood. This highlights the need to study the effect of BP on cognitive decline from young adulthood to late-life and to include Blacks and Hispanics.

To determine the associations between BP levels and use of antihypertensive medication from young adulthood to late-life and CID risk, we will pool data from 6 longitudinal population-based cohorts: 1) the Atherosclerosis Risk in Communities study (ARIC), 2) the Coronary Artery Risk Development in Young Adults study (CARDIA), 3) the Cardiovascular Health study (CHS), 4) the Framingham Offspring Study (FOS), 5) the Multi-Ethnic Study of Atherosclerosis (MESA), and 6) the Northern Manhattan Study (NOMAS).

5. Main Hypothesis/Study Questions: Does Blacks' and Hispanics' worse BP control starting in young adulthood contribute to their greater risk of CID compared to Whites?

Hypothesis 1: Black-White and Hispanic-White differences in CID risk are partially explained by Blacks' and Hispanics' worse BP control and higher BP levels over the life course.

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).

Variables/measurements from the ARIC main study database to be analyzed:

DEPENDENT VARIABLES	VARIABLE NAME/DESCRIPTION
Cognitive Variables	**Cognitive test results from visits 2, 3 (subset), 4, and full cognitive batteries from visits 5 and 6. Also, adjudicated MCI/dementia status from visits 5 and 6.**

INDEPENDENT VARIABLES	VARIABLE NAME/DESCRIPTION
Systolic blood pressure	**SBP measurements from each visit**
Diastolic blood pressure	**DBP measurements from each visit**
Hypertension treatment	**Hypertension treatment status from all available visits**
Sociodemographics	
Age	**AGE**
Sex	**GENDER**
Race	**RACEGRP**
Education	**ELEVEL01, ELEVEL01**
Marital status	AFUcomp40a_D
Income	HOM62
Occupation	Occupation data from all available visits
Insurance status	Insurance status from all available visits
Vascular risk factors	
Cigarette smoking	Smoking status from all available visits
Waist circumference	WC measurements from each visit
Diabetes	Diabetes status from all available visits
Diabetes treatment	Diabetes treatment from all available visits
Exercise/physical activity	PA measurements from each visit
Alcohol use	Alcohol use measurements from each visit
Hyperlipidemia	Lipid measurements from each visit
Hyperlipidemia treatment	Hyperlipidemia treatment from all available visits
Atrial fibrillation	AF measurements from each visit
BMI	BMI measurements from each visit
Fasting glucose	Fasting glucose from all available visits
Hemoglobin A1c	HbA1c from visits 5 and 6
Other clinical factors	
Depression	Depression measures from each visit
Health Status	Health status from all available visits
Kidney function (Estimated GFR)	GFR measurements from all available visits
Physician-adjudicated stroke	
History of MI	History of MI from all available visits
Genetic factors	
ApoE	

Note: Bold variables will be included (forced) in the model based on a priori knowledge.

Study population: We will identify all cohort participants who have BP measurement at baseline, 1 or more follow-up BP measurement after baseline, and an initial measurement of each cognitive outcome. We will exclude participants who meet ≥1 criterion: 1) those with CID at baseline per the parent study; and 2) those reporting a baseline history of stroke.

We will pool and harmonize data across the 6 NIH-funded cohort studies after completing a thorough review of data measurement and data collection time points for variables representing demographics, socioeconomic status, blood pressure measures, cognitive function measures, baseline clinical factors, and incident events.

Harmonization of cognitive measures across cohorts: To make inferences about cognitive domains instead of individual cognitive tests, and to resolve the challenge of different cognitive tests administered across different studies, we will harmonize available cognitive tests across studies into 3 factors representing global cognitive performance, executive function, and memory using statistically appropriate confirmatory factor analysis. Models to produce these factors are equivalent to graded-response item response theory models.[1] Details are available in published work by Co-I Gross[2], which documented clinically relevant cut-points for cognitive impairment. We will externally scale the cognitive factors to the nationally representative Aging, Demographics, And Memory Study of the Health and Retirement Study. Briefly, item response theory uses probabilistic models to relate test responses to a cognitive factor. Both item response theory and standard scoring methods apply weights to individual tests in a summary score. In standard sum scoring, weights are assigned a priori by the test developer, often without data. Item response theory takes an empirical approach to test scoring. Tests successfully mastered by large proportions of a sample provide more information in the easy range of the ability spectrum. Performing poorly on such a test implies more impairment than a harder test. The key to harmonization is to have common tests across datasets to anchor the metric.

Statistical Analysis for Specific Aim 1:

Phase 1. Summary Statistics: In Phase 1, we will summarize the characteristics of each study population, including the outcome and independent variables (race/ethnicity, systolic BP and diastolic BP), and perform bivariate analysis. We will check the interpersonal correlation of cognitive tests across items and across years.

Phase 2. Models: To test Hypothesis 1, whether there is a significant effect of race/ethnicity on the slope of cognition after adjusting for BP and other covariates, we will fit linear mixed-effects models to measure changes in cognitive function over time using pooled data from the cohorts.[3,4] The basic model is:

$$\begin{aligned}\mathbf{Cognition_{it}} = {} & \boldsymbol{\beta_0} + \boldsymbol{\beta_1 t_{it}} + \boldsymbol{\beta_2 race_i} + \boldsymbol{\beta_3 age_i} + \boldsymbol{\beta_4 SBP_{it}} + \boldsymbol{\beta_5 DBP_{it}} + \boldsymbol{\beta_6 race_i * SBP_{it}} \\ & + \boldsymbol{\beta_7 race_i * DBP_{it}} + \boldsymbol{\beta_8 race_i * t_{it}} + \boldsymbol{\beta_9 age_i * t_{it}} + \boldsymbol{\beta_{10} SBP_{it} * t_{it}} + \boldsymbol{\beta_{11} DBP_{it}} \\ & * \boldsymbol{t_{it}} + \boldsymbol{\alpha_i} + \boldsymbol{\tau_i * t_{it}} + \boldsymbol{\epsilon_{it}}\end{aligned}$$

$$\text{where } \boldsymbol{\epsilon_{it}} \sim \mathbf{N}(\mathbf{0}, \boldsymbol{\sigma_\epsilon^2}), \text{ random effects } \begin{bmatrix}\boldsymbol{\alpha_i} \\ \boldsymbol{\tau_i}\end{bmatrix} \sim \mathbf{N}(\mathbf{0}, \mathbf{D}) \text{ and } \mathbf{D} = \begin{bmatrix}\boldsymbol{\sigma_\alpha^2} & \mathbf{cov}(\boldsymbol{\alpha_i}, \boldsymbol{\tau_i}) \\ \mathbf{cov}(\boldsymbol{\alpha_i}, \boldsymbol{\tau_i}) & \boldsymbol{\sigma_\tau^2}\end{bmatrix}.$$

Subscripts i and t indicate individual and observation at time t, respectively. Time is expressed as the years from baseline BP measurement. The basic model includes race/ethnicity (categorical), systolic BP, diastolic BP, and time from baseline, each treated as continuous variables, along with their two-way interactions. We note that systolic BP and diastolic BP are

considered to be time-dependent covariates. The main effect of interest in terms of testing Hypothesis 1 is associated with race/ethnicity by time interaction, i.e. with the term $\beta_8 race_i * t_{it}$. The random intercepts α_i and slopes τ_i are included in the model to accommodate for correlation of cognitive measures within participants over time and to allow participant-specific rates of cognitive change. The D matrix defines variance-covariance for subject-specific random effects. They are normally distributed and independent between individuals. Also, random errors ϵ_{it} are all independent from each other.

Note that for simplicity, the basic model includes terms involving selected covariates only, such as race/ethnicity, age, and BP. Other covariates, such as cohort indicator, sex, and education will be considered in developing the final model for testing Hypothesis 1. Models will be developed for each of the continuous cognitive outcomes (global cognitive performance, executive function, and memory). Each cognitive outcome is set to missing (censored) at the time of first expert-adjudicated incident stroke, death, loss to follow-up, or the end of follow-up, whichever occurs first. Based on our aims and the literature, in addition to testing Hypothesis 1, we will examine whether race/ethnicity[5], age[6], or hypertension treatment[7] modify the effect of BP on cognition by introducing interaction terms into the models. A BP*cohort interaction term will test whether the BP-cognition relationship differs by cohort.

Secondary outcomes of dementia and MCI: To analyze time to event data, i.e., time to dementia, we will use a Cox proportional regression model or its extensions[8-10] to account for repeated events. We will validate our models in FOS. While we recognize that FOS includes only Whites, it is the only study that spans ages 18 to 90+. For secondary analyses, we will add APOE E4 with/without an APOE E4*BP interaction to models (fewer participants have APOE data). Given that each cohort performs brain MRI exams on a subset of participants, we will explore whether brain MRI correlates mediate the effect of BP on our harmonized cognitive outcomes.

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? __X__ 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/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)?
Co-author Rebecca Gottesman has published articles on BP and cognition using ARIC data. Co-author Alden Gross has published article on harmonization of cognitive measures using ARIC data.

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* 2008.06, ARIC-NCS, PI Coresh)

_ __ 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. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.