ARIC Manuscript Proposal #3521

PC Reviewed: 12/10/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Blood Pressure over the Life Course and Later-life Cognition in Hispanics and Whites (BP-COG): A Pooled Cohort Analysis

b. Abbreviated Title (Length 26 characters): BP and cog decline in Hispanics and Whites

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 Organisation and World Stroke Organization joint conference (May 12-15, 2020, Vienna, Austria), with a submission deadline of January 15, 2020. Manuscript preparation will be ongoing, with an expected draft completion date of 7/1/2020.

4. Rationale: Cognitive impairment and dementia (CID) disproportionately affect Hispanics in the United States. 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, 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.

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. Not only are Hispanics more likely to have worse BP control than Whites, but they are also more likely to have detrimental brain effects from high BP. Hispanics' greater vascular disease burden contributes to their greater white matter hyperintensity volume, a marker of cerebral small vessel disease, compared to Whites. Whether higher BP levels in Hispanics explain Hispanic-White differences in CID risk is uncertain.

Leveraging six population-based cohorts of individuals aged 5 to 95 at cohort baseline with repeated objective measures of BP and cognition, we will conduct a pooled cohort study to determine the extent to which Hispanic-White differences in cognitive decline are explained by Hispanics' worse BP control and therefore higher BP levels over the life course. We hypothesize that Hispanic-White differences in BP control across the life course contribute to Hispanic-White disparities in cognitive decline.

5. Main Hypothesis/Study Questions:

Main study question: Does Hispanics' worse BP control starting in young adulthood contribute to their greater risk of CID compared to Whites?

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

Note: This paper represents the second planned Aim 1 analysis contrasting Hispanics and Whites. The first paper contrasted Blacks and Whites. Although some cohorts do not have Hispanics, all cohorts will provide estimates of cognitive change in Whites.

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 population: We will conduct a pooled cohort analysis using individual participant data from six well-characterized American prospective cohort studies with repeated measures of BP and cognition: Atherosclerosis Risk in Communities Study (ARIC), Coronary Artery Risk Development in Young Adults Study (CARDIA), Cardiovascular Health Study (CHS), Framingham Offspring Study (FOS), Multi-Ethnic Study of Atherosclerosis (MESA) study, and Northern Manhattan Study (NOMAS) for years 1971 to 2017. We will require participants to have ≥1 measurements of cognition and ≥1 measurement of BP at or before the first measurement of cognition. We will exclude participants reporting a baseline history of stroke and those with incident stroke or cohort-defined incident dementia at or before the first measurement of cognition.

Harmonization of cognitive measures across cohorts: To make inferences about cognitive domains instead of individual cognitive test items, and to resolve the challenge of different cognitive tests administered across the cohorts, we have co-calibrated available cognitive test items into factors representing global cognition (global cognitive performance), memory (learning and delayed recall/recognition), and executive function (complex and/or speeded cognitive functions) using item response theory (IRT) methods that leverage all available cognitive information in common across cohorts and test items unique to particular cohorts.[1] Cognitive outcomes will be set to a t-score metric (mean 50, standard deviation [SD] 10) at a participant's first post-stroke cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the six cohorts. Expert neuropsychologists (EMB, BJG) assigned each test item to a cognitive domain. In IRT, each test item is weighted based on its correlation with other items and empirically assigned a relative location along the latent trait (e.g., global cognition) corresponding to its estimated difficulty. We computed factor scores from models for each domain using the regression-based method in Mplus version 8.1. This approach has been described and used empirically with evidence that the factors have the same meaning across datasets, even with different cognitive tests.[2-4] Co-I Gross et al have shown empirically that this IRT approach produces cognitive scores that are more precise than those derived from a z-score approach that standardizes and averages test scores.[5]

Outcomes: The primary outcome will be change in global cognition. Secondary outcomes will be change in memory and executive function.

Independent variable: Each cohort study measured BP at in-person visits using standard protocols and equipment. We will summarize systolic BP (SBP) as the time-dependent cumulative mean (i.e., running average) of all BPs before each measurement of cognition. Long-term cumulative mean SBP has improved prediction of clinical outcomes compared with single BP measurements[6] or mean BP over discrete intervals (e.g., 1 year, 1 to 5 years) before outcome measurement.[7] We will use SBP because it tends to be a stronger predictor of BP-related outcomes than DBP.[7-9]

Covariates: Covariates will be factors that could influence systolic blood pressure (SBP) and cognition. We will use covariate values measured closest to, but not after, the first cognitive assessment. We will harmonize covariates across cohorts by choosing common response categories for categorical variables and converting measurements to common units for continuous variables. Demographics included age, sex, years of school, and cohort study. Vascular risk factors included alcohol use, cigarette smoking, body mass index, waist circumference, physical activity, fasting glucose, low-density lipoprotein (LDL) cholesterol, and history of atrial fibrillation. Language used for cognitive assessment (Spanish vs English) will be examined as a covariate.

Statistical Analysis: We will follow a pre-specified analysis plan. We will compare participant characteristics by ethnicity using a 2-sample t-test with equal variance, Wilcoxon Rank Sum test or $\chi 2$ test as appropriate. Linear mixed-effects models will measure changes in each continuous cognitive outcome over time by ethnicity.[10,11] The models will include covariates listed above, interaction terms for age at the time of first cognitive assessment*follow-up time, sex*follow-up time, and ethnicity*follow-up time, as well as subject-specific random effects for intercepts and

slopes. All continuous variables will be centered at the overall median, except cumulative mean SBP, which will be centered at 120 mmHg. Glucose, LDL cholesterol, and SBP values will be divided by 10 so that the parameter estimates reflect a 10-unit change in the variables. Time will be treated as a continuous measure defined as years since first measurement of each cognitive outcome.

For each outcome, all available cognitive observations will be used in the primary analysis except observations after the time of first cohort-adjudicated incident stroke during follow-up, because incident stroke alters the cognitive trajectory.[12] We will inspect residual plots to evaluate the assumptions of the linear mixed-effects models (e.g., linearity of relationships of interest and normality of residual errors). Based on the literature**,** we will examine whether race/ethnicity,[13] age,[14] or hypertension treatment[15] modify the effect of BP on cognition by introducing interaction terms into the models.

To estimate Hispanic-White differences in cognitive decline, Model A included a Hispanic ethnicity*follow-up time interaction term. To examine whether time-dependent cumulative mean SBP confounded the Hispanic-White differences in cognitive decline, Model B added SBP and an SBP*follow-up time interaction term to Model A. To investigate whether hypertension treatment confounded the Hispanic-White differences in cognitive decline, Model C added hypertension treatment and a hypertension treatment at first cognitive assessment*follow-up time interaction term to Model B. Statistical significance for all analyses will be set as $P < 0.05$ (2-sided), and all analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity Analyses: We plan to repeat analyses after including participants' cognitive observations after the time of incident stroke and also after adding kidney function (glomerular filtration rate, GFR[16]) and history of myocardial infarction because they may be on the causal pathway.

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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"? ____ 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.