ARIC Manuscript Proposal #3793

PC Reviewed: 3/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Associations between Blood Pressure, Race/Ethnicity, and Incident Stroke Type: A Pooled Cohort Analysis of ARIC, CARDIA, CHS, MESA, FOS, NOMAS

b. Abbreviated Title (Length 26 characters):

Blood Pressure, Race/Ethnicity, and Incident Stroke Type

2. Writing Group:

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

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3. Timeline:

Manuscript Proposal Submissions:	February-March 2021 (CARDIA, CHS, MESA, FOS, NOMAS)
Manuscript Development:	March 2021- June 2021
Expected Manuscript Completion:	June 30, 2021

4. Rationale:

Historically, the stroke literature has focused primarily on the differences in the distribution of the burden of stroke risk among four demographic categories: age, sex/gender, socioeconomic factors, and racial/ethnic groups.[1] Major stroke types are classified based on their underlying pathological disease pathways and mechanisms. The three major stroke types are ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Each type has

different management strategies, risks, and outcomes.[2] Stroke incidence has been associated with higher baseline values of systolic blood pressure (SBP) before the stroke event among different racial/ethnic groups.[3,4] Previous research has shown cumulative mean SBP measures (e.g. means of SBP levels measured from consecutive examinations) can have additional predictive value and improve model performance compared with single SBP measures.[5] In earlier research, diastolic blood pressure (DBP) was considered the primary driver of adverse cardiac outcomes in adults with hypertension.[6] A paradigm shift occurred when observational cohorts, including The Framingham Heart Study, demonstrated the importance of systolic blood pressure (SBP), leading to SBP becoming the focus of modern risk assessment and treatment.[6] SBP has been recognized as a stronger predictor of blood pressure (BP) related outcomes than diastolic BP.[7] Both SBP and DBP are considered inextricably linked and should be included when exploring the relationship between adults with hypertension and vascular health outcomes. The emphasis on stroke incidence by major stroke type has been concentrated in examining age and sex-dependent differences in modifiable risk factors, management, and prognosis.[8]

Some studies have also explored the relationships between race/ethnicity, BP, and stroke type. Howard et al. found racial differences in the impact of elevated SBP on stroke risk among Black and White participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.[9] However, the Howard study pooled ischemic and hemorrhagic strokes together. Similarly, Sacco and colleagues found an association between key stroke risk factors, including elevated BP on stroke risks between Blacks, Caribbean Hispanics, and Whites in the Northern Manhattan Study (NOMAS) for first-time ischemic stroke.[10] It is still unknown whether the relationship between cumulative mean systolic BP and stroke types differs by racial/ethnic group. The objective of our study is to fill the gap in the current literature by clarifying the relationship between cumulative mean SBP and first incident stroke among three major stroke types (IS, ICH and SAH), and explore how race/ethnicity affects these relationships. Our study will improve upon Howard and colleagues' previous analysis by examining time-varying cumulative mean SBP, including broader age ranges, and including Hispanics.

Our study will include data collected across the United States to widen the generalizability of our findings by using data from a pooled cohort.[7] Two advantages of a pooled cohort analysis include the increased study power and the ability to examine risks across large samples of individuals with heterogeneous exposures.[11] This analysis further permits a full examination of effect modification within the data.[11] An existing pooled cohort of six population cohort studies including Black, Hispanic and White individuals (ages 5-95 at cohort baseline) with repeated objective measures of BP will be leveraged and used to examine the association between cumulative mean SBP, race/ethnicity, and incidence of major stroke types.

5. Main Hypothesis/Study Questions:

Main Study Questions:

1. What is the association between cumulative mean SBP and incident stroke type [IS, ICH, SAH]?

2. Does race/ethnicity modify the association between cumulative mean SBP on incident stroke type [IS, ICH, SAH]?

Hypothesis:

1. Race/ethnicity modifies the association between cumulative mean SBP and incident stroke type.
2. The magnitude of the association between cumulative mean SBP and stroke incidence (total and for each stroke type) is greater in Blacks than in Hispanics.

Relevance to cohort-approved ancillary study:

Aims 2 and 3 of the approved study proposal for NIH/NINDS-funded BP COG R01 involve simulation modeling of the association between BP and incident dementia and CVD events by race/ethnicity. We will examine inclusion of estimates of the association between BP and risk of CVD events from both RCTs and also the BP COG pooled cohort study. The simulation model will be used to inform the design of RCTs including pragmatic trials of less selected patients. The knowledge gap is that it is not known whether the incidence of different stroke types is differentially affected by elevated SBP and how these associations vary by race/ethnicity. The proposed paper will address these knowledge gaps, enable the BP COG simulation model and its results to be improved, and also provide useful information for researchers and policymakers who work with simulation models. The simulation model in BP COG R01 Aims 2 and 3 will be used to inform trials and policies.

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 stroke incidence: 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), and Northern Manhattan Study (NOMAS) for years 1971 to 2017. We will require all cohort participants to have ≥1 measurement of SBP before the first incidence of stroke. We will exclude participants reporting a baseline history of stroke or incident stroke before first BP measurement.

Outcomes:

The primary outcome will be time to first incident stroke. Secondary outcomes will be time to first incident IS, time to first incident ICH, and time to first incident SAH.

Main independent variables:

The primary independent variables will be cumulative mean SBP and diastolic BP (DBP). We will summarize SBP and DBP as the time-dependent cumulative mean (i.e. running average) of all BPs before outcome measurement.

Covariates:
Covariates will be measured before incident stroke. Covariates are factors that could influence BP, stroke incidence and stroke type. Covariates are age (continuous), race (White, Black), Hispanic ethnicity (CHS, MESA, NOMAS only) cohort (ARIC, CARDIA, CHS, MESA, FOS, NOMAS), education (eighth grade or less, grades 9-11, completed high school, some college but no degree, college graduate or more), current cigarette smoking, any physical activity, body mass index, waist circumference, history of atrial fibrillation, fasting glucose, LDL cholesterol, alcohol use, depressive symptoms, anticoagulant use and anti-hypertensive medication use. We have harmonized covariates across cohorts by choosing common response categories for categorical variables and converting measurements to common units for continuous variables. **Note:** We cannot include other socioeconomic factors (e.g., literacy, quality of education, occupation, and childhood socioeconomic status) because they are unavailable for all cohorts at or before the first incidence of stroke.

Statistical Analysis:
We will summarize participant characteristics of the pooled cohort study population and each cohort study population, including the outcomes and independent variables. A multivariable-adjusted Cox proportional hazard model will be used to estimate the association between time-varying cumulative mean BP and time to incident stroke (overall and by stroke type)- Research Question #1. To assess race/ethnic differences in associations between cumulative mean BP and time to incident stroke, we will add race/ethnicity *cumulative mean BP interaction terms to the model to test whether the association between cumulative mean BP and time to incident stroke (overall and by stroke type) differs by race/ethnicity- Research Question #2. Kaplan-Meier methods and log rank tests will also estimate the cumulative incidence of first stroke type by race/ethnic group.[12,13] These methods support the comparison of survival distributions, leading to the subsequent investigation of the relationship between cumulative mean SBP and time to incident stroke (overall and by stroke type) using the Cox proportional hazard regression model. The proportional-hazards assumption for each covariate will be tested using the scaled Schoenfeld residuals.[14] A log normal parametric model will be used as a parametric test to observe the model fit and assess prognostic factors that may contribute to the primary progress of disease.[11] The models will include a time dependent covariate for cumulative mean SBP, race/ethnicity, as well as covariates above. 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 BP. Possible interactions between cumulative mean SBP and race/ethnicity and other explanatory variables, such as age and gender, will be investigated by constructing interaction terms in the Cox model. [12]

The use of Cox regression (with time-dependent covariates) in this analysis is valid under the assumption that there are no competing risks and censored times are independent of event times. We will consider taking into account competing risk defined as an event that either hinders the observation of the event of interest or modifies the chance that this event occurs. Statistical significance for all analyses will be set as $P < 0.05$ (2-sided). All analyses will be performed using STATA 16.

References:

1. Cruz-Flores, S., Rabinstein, A., Biller, J., Elkind, M. S., Griffith, P., Gorelick, P. B., Howard, G., Leira, E.C., Morgenstern, L.B., Ovbiagele, B. & Peterson, E. (2011). Racial-ethnic disparities in stroke care: the American experience: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 42*(7), 2091-2116.

2. Krishnamurthi, R. V., Barker-Collo, S., Parag, V., Parmar, P., Witt, E., Jones, A., Mahon, S., Anderson, C.S.,Barber, P.A.& Feigin, V. L. (2018). Stroke Incidence by Major Pathological Type and Ischemic Subtypes in the Auckland Regional Community Stroke Studies: Changes Between 2002 and 2011. *Stroke, 49*(1), 3-10.

3. Levine, D. A., Galecki, A. T., Langa, K. M., Unverzagt, F. W., Kabeto, M. U., Giordani, B., & Wadley, V. G. (2015). Trajectory of Cognitive Decline after Incident Stroke. *JAMA, 314*(1), 41-51.

4. Fischer, U., Cooney, M. T., Bull, L. M., Silver, L. E., Chalmers, J., Anderson, C. S., Mehta, Z. & Rothwell, P. M. (2014). Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *The Lancet Neurology*, *13*(4), 374-384.

5. Pool, L. R., Ning, H., Wilkins, J., Lloyd-Jones, D. M., & Allen, N. B. (2018). Use of Long-term Cumulative Blood Pressure in Cardiovascular Risk Prediction Models. *JAMA Cardiology*, *3*(11), 1096-1100.

6. McEvoy, J. W., Chen, Y., Rawlings, A., Hoogeveen, R. C., Ballantyne, C. M., Blumenthal, R. S., Coresh, J & Selvin, E. (2016). Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. *Journal of the American College of Cardiology, 68*(16), 1713-1722.

7. Levine, D. A., Gross, A. L., Briceño, E. M., Tilton, N., Kabeto, M. U., Hingtgen, S. M., Giordani, B.J., Sussman, J.B., Hayward, R.A., Burke, J.F. & Elkind, M. S. (2020). Association Between Blood Pressure and Later-Life Cognition Among Black and White Individuals. *JAMA Neurology*. Published online April 13, 2020. DOI:10.1001/jamaneurol.2020.0568

8. Trimble, B., & Morgenstern, L. B. (2008). Stroke in minorities. *Neurologic Clinics, 26*(4), 1177-1190.

9. Howard, G., Lackland, D. T., Kleindorfer, D. O., Kissela, B. M., Moy, C. S., Judd, S. E., Safford, M.M., Cushman, M., Glasser, S.P & Howard, V. J. (2013). Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA Internal Medicine*, *173*(1), 46-51.

10. Sacco, R. L., Boden-Albala, B., Abel, G., Lin, I. F., Elkind, M., Hauser, W. A., Paik, M.C. & Shea, S. (2001). Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. *Stroke*, *32*(8), 1725-1731.

11. Friedenreich, C. M. (2002). Commentary: Improving pooled analyses in epidemiology. *International Journal of Epidemiology*, *31*(1), 86-87.

12. Wang, Y., Rudd, A. G., & Wolfe, C. D. (2013). Trends and survival between ethnic groups after stroke: the South London Stroke Register. *Stroke*, *44*(2), 380-387.

13. Habibi, D., Rafiei, M., Chehrei, A., Shayan, Z., & Tafaqodi, S. (2018). Comparison of Survival Models for Analyzing Prognostic Factors in Gastric Cancer Patients. *Asian Pacific Journal of Cancer Prevention: APJCP*, *19*(3), 749.

14. Fitzpatrick, A. L., Kuller, L. H., Lopez, O. L., Kawas, C. H., & Jagust, W. (2005). Survival following dementia onset: Alzheimer's disease and vascular dementia. *Journal of the Neurological Sciences*, *229*, 43-49.

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 _____ N

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)?

1. Muller CJ, Alonso A, Forster J, et al. "Stroke Incidence and Survival in American Indians, Blacks, and Whites: The Strong Heart Study and Atherosclerosis Risk in Communities Study." *J Am Heart Assoc*. 2019;8(12):e010229.

2. Koton S, Schneider ALC, Rosamond WD, et al. "Stroke incidence and mortality trends in US communities, 1987 to 2011." JAMA. 2014;312(3):259-68.

3. Rosamond WD, Folsom AR, Chambless LE, et al. "Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort." Stroke. 1999;30(4):736-43.

4. Koton S, Sang Y, Schneider ALC, Rosamond WD, Gottesman RF, Coresh J. "Trends in Stroke Incidence Rates in Older US Adults: An Update From the Atherosclerosis Risk in Communities (ARIC) Cohort Study." JAMA Neurol. 2020;77(1):109-113.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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.

This is understood.

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.

This is understood.