ARIC Manuscript Proposal #4150

PC Reviewed: 11/8/22 **Status: _____** **Priority: 2**
SC Reviewed: ___/___/___ **Status: _____** **Priority: ____**

1.a. Full Title: The Relationship Between Stroke Subtype with Post-Stroke Cognitive Trajectories, and Effect of Vascular Risk Factors, Sex, and Race on These Relationships – ARIC, CHS, FOS, and REGARDS (STROKE COG)

b. Abbreviated Title (Length 26 characters): STROKE COG Aim 2

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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: Manuscript preparation will be ongoing; expected draft completion on 04/28/2023.

4. Rationale:
Incident stroke is associated with an acute decline in cognitive function and also accelerated and persistent **cognitive** decline over years.[1] Stroke survivors are up to 50 times more likely than stroke-free adults to develop dementia.[2] It is plausible that treating vascular risk factors (VRFs) might prevent post-stroke cognitive decline and dementia in some stroke subtypes but not others. Most strokes are ischemic (85-90%), fewer are intracerebral hemorrhages (ICH, 10%) and subarachnoid hemorrhages (3%). Ischemic strokes can be classified as cardioembolic (~20%), large-artery atherosclerotic (~15%), lacunar/small vessel (~25%), cryptogenic (~30-40%), and other determined etiology (<5%).[3] The relationship between stroke subtype and post-stroke cognitive decline and dementia is unclear, but some have found greater risk for hemorrhagic, left hemisphere, and cardioembolic strokes.[4,5] One observational study suggested that VRF lowering might reduce post-stroke AD/ADRD risk in non-cardioembolic (atherosclerotic) ischemic strokes but not hemorrhagic or cardioembolic ischemic strokes.[6] Most current research is underpowered to meaningfully assess the impact of stroke subtypes, VRFs, and VRF treatment on post-stroke cognitive decline and dementia. Sex and race differences in post-stroke cognitive decline and dementia risk are also unclear.

Knowing the impact of stroke subtype and vascular risk factor (VRF) levels on post-stroke dementia risk will improve our understanding of vascular biology and suggest potential interventions and at-risk groups to target. This is important because trials have shown that intensive VRF lowering does not always lead to better outcomes and might cause harm, particularly in stroke survivors. We will leverage a pooled cohort using individual participant data from four well-characterized, American prospective cohorts—Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), and REasons for Geographic And Racial Differences in Stroke (REGARDS)—with expert-adjudicated incident strokes, stroke subtyping, and repeated objective measures of VRFs and cognition before and after stroke to determine the relationships between stroke subtype and post-stroke cognitive decline and dementia risk. We will also explore how sex and race affect these relationships.

5. Main Hypothesis/Study Questions:
Aim 2 of our study proposes to clarify the relationships between stroke subtype and post-stroke cognitive trajectories, and explore how VRFs, sex, and race affect these relationships.
Hypothesis: Post-stroke BP, glucose, and lipid levels partially explain the relationships between all stroke subtypes and post-stroke cognitive trajectories.

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).

Data [variables to be used, sample inclusions/exclusions]

Study Population: We will identify all participants who have incident stroke between the 1st and 2nd in-home visit. Inclusion criteria are:

- Black or White race
- ≥18 years of age at cohort baseline
- ≥1 cognitive assessment before incident stroke
- ≥1 cognitive assessment after incident stroke
- ≥1 systolic BP assessment before incident stroke
- ≥1 systolic BP assessment after incident stroke and before/at last post-stroke cognitive assessment

Exclusion Criteria: History of dementia before incident stroke.

Dependent Variables

- **Post-Stroke Cognitive Function:** The primary outcome will be the harmonized **global cognitive performance (GCP)** measure. Secondary outcomes will be the harmonized **memory** measure and the harmonized **executive function (EF)** measure. Each cognitive measure has been collected longitudinally and will be treated as a continuous variable.
- **Incident Dementia:** Additional secondary outcomes will be a) time to incident dementia. REGARDS measures incident cognitive impairment[7] and is developing an approach for classifying incident dementia but these data are not available yet (08/2022) for this manuscript. We will explore dementia types (e.g., AD, vascular dementia) as numbers and data allow.

Independent Variables of Primary Interest are measured after stroke.

- **Primary IVs:** Stroke type (hemorrhagic vs ischemic), ischemic stroke subtype (cardioembolic, large artery atherosclerosis, small vessel disease, cryptogenic, other determined etiology).
- **Secondary IVs:** Post-stroke systolic blood pressure (SBP, mmHg), post-stroke fasting glucose (mg/dL), post-stroke low-density lipoprotein cholesterol (LDL-C, mg/dL).

Covariates are measured closest to or before, but not after, the first post-stroke cognitive assessment except where specified:

We will follow a pre-specified **conceptual model by Levine et al**[5] to account for the potential confounders of the relationship between stroke type and post-stroke cognitive decline. **Demographics** include age, sex, race, and cohort study. **Socioeconomic status** will be measured by years of education and household income. **VRFs** include pre-stroke SBP, pre-stroke fasting glucose, pre-stroke LDL cholesterol, current cigarette smoking, waist circumference, body mass index, physical activity, alcohol drinks per week, history of myocardial infarction, history of atrial fibrillation, history of diabetes, diabetes status at first post-stroke cognition and glomerular filtration rate. We will summarize pre-stroke SBP, DBP, glucose, LDL, and other VRFs measured by continuous variables as cumulative means of all values before the first

measurement of post-stroke cognition. **Medication use** will include anti-hypertensive, diabetes, and lipid-lowering medication based on evidence of medication bottles and self-report from exams. Pre-stroke cognition will be measured using the harmonized GC, EF, and memory scores. Pre-stroke arithmetic means of all measurements before incident stroke will be used for SBP, glucose, LDL cholesterol, BMI, waist circumference, global cognition, executive function, and memory. **Post-stroke depressive symptoms** will be measured by the Center for Epidemiologic Studies Depression Scale and summarized as arithmetic means of scores. **The genetic factor** is the number of Apo lipoprotein E (APOE) E4 alleles. **Stroke location** is measured by hemisphere (right, left, both) and brain stem-cerebellum (right, left, both). **Stroke severity** is measured by the NIH Stroke Scale.[8,9] This ancillary study provided funding for REGARDS chart abstraction activities to obtain stroke location and severity for included incident stroke cases when these variables were not already available in the REGARDS dataset.

Brief Analysis Plan and Methods

Harmonization of Cognitive Measures Across Cohorts: To achieve Aim 1, we will harmonize cognitive and VRF measures across the cohorts based on previous studies.[10,11] 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 will co-calibrate 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. In a pre-statistical harmonization phase, we will identify all test items from all cognitive instruments across the cohorts and determined shared items between cohorts. Expert neuropsychologists (EMB, BJG) will assign 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 will compute factor scores from models for each domain using the regression-based method in Mplus version 8.1.[12,13] Cognitive outcomes will be set to a t-score metric (mean 50, standard deviation [SD] 10) at a participant's first cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 5 cohorts.

Statistical Analysis

In Phase 1, Wilcoxon rank sum and Chi-squared tests will be used to examine differences in participant characteristics by stroke subtype as appropriate. We will also examine the relationships between stroke type/severity and post-stroke BP, glucose, and lipid levels.

In Phase 2, we will test the Hypothesis for Aim 2, whether post-stroke BP, glucose, and lipid levels partially explain the relationships between all stroke subtypes and post-stroke cognitive trajectories (i.e., how much adding BP, glucose, and lipid levels alters the relationship between stroke type/severity and the cognitive outcomes), separately for each cognitive outcome (GCP, EF, memory). For each cognitive outcome, we will build a linear mixed-effects model using the pooled data from the cohorts.[14] When building a final model for each post-stroke cognition outcome measured longitudinally, we will consider models of the following form:

$$Y_{it} = \beta_0 + \beta_1 time_{it} + \beta_2 stroke\ type_i + \beta_3 stroke\ type_i * time_{it} + x'_{it}\beta + \alpha_i + \tau_i * time_{it} + \epsilon_{it}$$

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

Subscripts i and t represent individual and observation at time t, respectively. The dependent variable Y_{it} is post-stroke cognition (GCP, EF or Memory). Post-stroke follow-up time, $time_{it}$, is expressed as the years after incident stroke. The effect of interest for testing the hypothesis is associated with the $stroke\ type_{it} * time_{it}$ interaction term. We will examine the change in the stroke type*time interaction term after adding time-varying post-stroke SBP, fasting glucose and LDL-C and their interactions with time.

Vector $\boldsymbol{x}_{it}$, includes the following covariates and their interactions with follow-up time: pre-stroke mean SBP, LDL-C, and glucose levels, race, sex, sex$* time_{it}$, age, age$* time_{it}$, education, income, BMI, waist circumference, current smoking status, physical activity, alcohol use, MI history, atrial fibrillation history, eGFR, pre-stroke mean cognition (GCP, EF or Memory), and medication use (anti-hypertensive, diabetes and/or cholesterol-lowering), medication use$* t_{it}$, and cohort. Models will include age*time and sex*time interaction terms because we found evidence that the post-stroke cognitive slope differs by age and sex but not race based on the results of Aim 1. Random intercepts α_i and slopes τ_i are included to accommodate the correlation of cognitive measures within participants over time and to allow participant-specific rates of cognitive change. The $\boldsymbol{D}$ matrix defines variance-covariance for subject-specific random effects, which are assumed to be normally distributed. Random errors ϵ_{it} are independent from each other.

Sensitivity Analysis: Primary analyses will be repeated: **1)** using time-invariant cumulative mean of all post-stroke SBP, glucose and LDL cholesterol measurements; **2)** adding post-stroke depressive symptoms; **3)** adding number of ApoE4 alleles; and **4)** adding baseline history of diabetes and diabetes status at first post-stroke cognition.

Assessing Heterogeneity in Associations Across Cohorts: We will repeat analyses within each cohort. We will also add stroke subtype*cohort and stroke subtype*cohort interaction terms to the model to test whether the stroke subtype-cognitive slope relationship differs by cohort.

Assessing Influence of Stroke Location and Stroke Severity: We will repeat analyses adding stroke location and stroke severity to models within cohorts that have the data. We completed the chart abstraction of incident stroke cases in the REGARDS cohort to incorporate data on stroke severity and stroke location in the analyses in December 2021. Co-Is Ronald Lazar, PhD and Virginia Howard, PhD at the University of Alabama at Birmingham supervised the work. The REGARDS chart abstraction strategy is based on the ARIC[15] and FHS methods for collecting data on stroke severity and stroke location to ensure consistent measures across studies and the rigor and reproducibility of results. FHS and ARIC are the other two cohorts providing us with data for stroke severity and stroke location. We obtained the data on stroke features from FHS. We are working with ARIC investigator and STROKE COG collaborator Silvia Koton, PhD, to request the chart abstraction data on stroke features from ARIC after it has been completed and validated.

Summary/Conclusion

This study will advance the science of stroke, AD, and ADRDs to better address the challenges of developing VRF interventions to reduce post-stroke AD/ADRD in stroke survivors. By estimating the potential impact of optimal VRF control to reduce post-stroke AD/ADRD, this study will lead to better-informed clinical decision-making and population health policies for VRF treatment in all stroke survivors because the potential to add AD/ADRD risk reduction to the other clinical benefits of VRF lowering may persuade many patients, physicians, and health systems to intensify VRF treatment.

Incident Dementia: A secondary outcome will be time to incident dementia. REGARDS is developing an approach for classifying dementia and MCI, but these data are not available yet (08/2022) for this manuscript. An addendum to this manuscript proposal will be submitted when these data are available.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ☐ **Yes** ☒ **No**

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit?" ☐ **Yes** ☐ **No**
(The 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** ☒ **No**

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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
☒ **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)?

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

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 https://sites.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.

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