ARIC Manuscript Proposal #4339

PC Reviewed: 10/10/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: **Association of stroke incidence and severity with changes in cognitive function and dementia in participants in the STROKE COG pooled cohort**

b. Abbreviated Title (Length 26 characters): **Stroke and cognitive function**

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SK **[please confirm with your initials electronically or in writing]**

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3. Timeline: Final draft of the paper to be ready for ARIC review about 12 months after all the required data are available for analysis.

4. Rationale:
Cognitive impairment and dementia subsequent to stroke are common[1]. Studies have reported 15%-70% prevalence of cognitive impairment and dementia in stroke survivors[2-7] and about 25% incident dementia during the first year after stroke[8]. The association between incident stroke and cognitive

decline has been addressed in previous studies, but not in the pooled STROKE COG data which includes 4 US cohorts: Atherosclerosis Risk in Communities Study (ARIC)[9], Cardiovascular Health Study (CHS)[10], Framingham Offspring Study (FOS)[11], and Reasons for Geographic And Racial Differences in Stroke Study (REGARDS)[12], and incorporating stroke severity data available in ARIC, FOS and REGARDS. Dr. Levine's paper on this topic, published in 2015, was based on the REGARDS data only, which included 515 participants who survived incident stroke[13]. Another paper published in 2019 used data from the English Longitudinal Study of Ageing (ELSA). The ELSA is a large longitudinal cohort study; however, it used self-reported data on doctor-diagnosed incident stroke and limited tests for measurement of cognitive function[14]. In the proposed study, the analysis of the association between incident stroke and cognitive decline will be strengthened by using more years of data with a higher number of adjudicated incident strokes and more comprehensive evaluation of cognitive function available in the harmonized cohorts, and by including the available data on stroke severity to study post-stroke dementia incidence in STROKE COG.
Severity of stroke is the most important predictor of short- and long-term outcome[15]. Functional outcome after stroke is related not only to the size and location of the stroke, but also to the individual's age and sex[16], the presence of comorbidities[17,18], vascular risk factors prevalent at time of stroke incidence[19] and the etiology of the stroke[20]. These factors have also been linked to changes in cognitive function and dementia[21,22]. However, it is unclear whether the linkage between vascular risk factors and changes in cognitive function is related to their long-term effect on the cognitive function (before the stroke) or to their effect on stroke severity, which directly affects post-stroke cognition. A recent study reported independent associated between strokes of higher severity and lower Mini-Mental State Examination (MMSE) scores[23]. Moreover, stroke severity had a mediating effect in the association of hypertension and education level with post-stroke cognitive function. However, potential mediation and moderation effects of cardiovascular risk factors in the association between stroke severity and post-stroke cognitive function were not assessed. In addition, the study had certain limitations, e.g. cognitive function was assessed only once and using MMSE (which is less sensitive for detecting executive function or other specific areas of cognitive declines after vascular brain injury), the associations were not studied after controlling for pre-stroke cognitive trajectories, and longitudinal measurements of vascular risk factors before and after stroke were not available. We aim to address the limitations of previous studies in our proposed analysis of possible effects of vascular risk factors on the association of stroke incidence and severity with post-stroke cognitive decline and incident dementia, measured using harmonized cognitive measures based on batteries of cognitive tests.

The National Institute of Health Stroke Scale (NIHSS) is the most widely used scale for the assessment of stroke severity and is recognized as the "gold standard" for stroke severity rating in clinical trials[24]. The NIHSS score on admission strongly predicts functional outcome and mortality after stroke[25]. The likelihood of excellent functional outcome steeply declines with any increase in NIHSS score: one additional point on the NIHSS has been reported to decrease the likelihood of excellent outcomes at 7 days by 24% and at 3 months by 17%, after adjusting for age, race, gender, and history of a previous stroke[25].

Risk of dementia significantly differs by stroke severity. In the Oxford Vascular Study, dementia rates 1-year after stroke were higher in participants with severe stroke (NIHSS>10) compared to those with minor stroke[8]. Cognitive impairment after stroke is common in patients with low NIHSS scores, despite their successful recovery in physical function[26-28].

In the REGARDS study, the rate of the cognitive decline in global cognition and executive function, but not memory, after stroke was faster than that seen pre-stroke with evidence supporting differences in the trajectory of decline for the various cognitive function domains[13]. A recent study including individuals with minor stroke (admission NIHSS score 2.7 on average) who were assessed for cognitive function at 1, 6 and 12 months after stroke also showed unique trajectories for each cognitive domain. Although some degree of improvement in nearly all domains was observed between 1 and 6 months after stroke, the recovery after 6 months was less consistent, particularly in verbal memory. Notably, the NIHSS score continued to show association with cognitive function after 6 months[29]. Using the ARIC data, we have previously evaluated the association of ischemic stroke incidence, severity and recurrence with post-stroke dementia[30]. Increased risk of dementia was evident in ARIC participants with stroke compared to those without stroke, independent of prevalence of risk factors shared by both stroke and dementia. Furthermore, the risk of dementia increased with severity of stroke, as well as with the number of recurrent stroke events. Importantly, we observed larger increases in dementia risk in individuals with stroke at a younger age (below age 75) than that seen in those older at the time of stroke[30]. We now aim to assess associations of stroke incidence and severity with changes in cognitive function and dementia among participants in the STROKE COG cohort participants. The use of pooled individual-level data available in the cohorts participating in STROKE COG will allow for the assessment of the aforementioned associations in a large sample using harmonized cognitive data from different US cohort studies.

5. Main Hypothesis/Study Questions:
Study hypotheses:

1. Risk of cognitive decline increases from no stroke to minor stroke (NIHSS 0-5), to mild stroke (NIHSS 6-10) and to severe stroke (NIHSS≥11).
2. Risk of dementia increases from no stroke to minor stroke (NIHSS 0-5), to mild stroke (NIHSS 6-10) and to severe stroke (NIHSS≥11).
    - In the analysis for this hypothesis, we will also update and confirm results from a study using data on 1,378 ischemic strokes (1,155 incident) and 2,860 dementia cases identified in ARIC through December 31, 2019[30], expanding the analysis to all STROKE COG cohorts with data and examining cognitive decline as an outcome.
3. In exploratory analyses, we will investigate whether the associations between stroke and cognitive decline are moderated by underlying vascular risk factors, namely BP, cholesterol, diabetes/glucose levels and BMI.

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).

We will follow the general methods established in STROKE COG, including a similar paper (MP#4150) on the relationship of stroke subtype to cognitive decline, with this proposal extending the hypotheses to stroke severity as a primary focus.

Study Design*:* Cognitive factors harmonized across the cohorts in the STROKE COG pooled cohort will be used. The harmonized data includes the following cognitive domains: global cognition (global cognitive performance- GCP), memory (learning and delayed recall/recognition- Memory), and executive function (complex and/or speeded cognitive functions- EF).

Main exposure variables:

Stroke incidence: Participant's first definite stroke as reported in each cohort. ARIC and CHS have data also on probable strokes, therefore we will conduct secondary analysis looking at first definite/probable stroke as exposure in ARIC and CHS participants.

Stroke severity: We will use data on stroke severity collected in the 3 cohorts (ARIC, FOS, REGARDS) in the STROKE COG study using protocols similar to the Stroke Severity in ARIC study protocol[30,31]. De-identified hospital charts of events that were previously adjudicated at each cohort as stroke events were reviewed by physicians and data on all items in the NIHSS were evaluated according to an algorithm for retrospective collection of the NIHSS score that has been shown to be valid across the entire stroke severity spectrum[32,33]. To address potential non-linear scaling of stroke severity and for clinical utility, we will classify stroke severity according to the NIHSS score as follows: no stroke, minor stroke (NIHSS 0-5, including the majority of the strokes), mild to moderate stroke (NIHSS 6-10) and moderate to severe stroke (NIHSS≥11).

***Exclusion Criteria*:** We will exclude participants with missing information on the main covariates in multivariable models. Participants with prevalent stroke at study baseline will be excluded in sensitivity analyses. Participants with documented aphasia following stroke will be excluded if they cannot complete cognitive testing and this will be noted as a study limitation; we will report numbers of such participants. Participants with a dementia diagnosis before stroke will be excluded.

Definition of outcomes:

Cognitive function: Harmonized global cognitive performance (primary cognitive outcome for Aim 1) and harmonized memory and executive function (secondary outcomes) longitudinally measured and treated as continuous variables.

Dementia: As defined according to cohort-specific criteria. In participants with stroke, dementia after stroke will be reported if diagnosed ≥1 year after incident stroke in order to exclude cases of acute changes in cognitive function after stroke.

Main covariates:

Cohort and baseline age, sex, race/ethnicity, years of education, and time-varying, smoking, BMI, fasting glucose, systolic blood pressure, total cholesterol, anti-hypertensive medication and statin use. For BP, cholesterol, diabetes and BMI, available as time-varying, we will use data at baseline (most proximal to, but before, the incident stroke), as well as post-stroke. APOE4 status will be added as a covariate in sensitivity analysis because data on APOE4 are not available for all the participants. Stroke location and mean pre-stroke cognitive functioning will also be covariates if available at time of analysis. In cohort-specific sensitivity analyses, we will additionally adjust for race/center in ARIC.

Summary of data analysis:

Cognitive decline (random effects models): Linear mixed-effects models will be used to parameterize longitudinal change in cognitive function, adjusting for covariates. The difference in cognitive trajectory by stroke incidence and severity (no stroke, minor stroke [NIHSS 0-5], mild to moderate stroke [NIHSS 6-10] and moderate to severe stroke [NIHSS≥11]) will be parameterized by testing for interactions between a piece-wise linear spline at the date of stroke and stroke severity.

The models will include random effects for intercept and slopes as well as fixed effects for each cohort (sensitivity analyses will be stratified by cohort). We will consider models of the following form:

Aims 1 and 2. The timescale is time since starting the study:

$$Y_{it} = \alpha_i\ \beta 0 + \beta 1\ \text{time}_{it} + \beta 2\ \text{strk\_sev\_minor}_{it} + \beta 3\ \text{strk\_sev\_mild}_{it} + \beta 4\ \text{strk\_sev\_severe}_{it} + \beta 5\ \text{strk\_sev\_minor}_{it}*\text{time}_{it} + \beta 6\ \text{strk\_sev\_mild}_{it}*\text{time}_{it} + \beta 7\ \text{strk\_sev\_severe}_{it}*\text{time}_{it} + \beta 8\ \text{cohort}_i + \beta 9\ \text{cohort}_i*\text{time}_{it} + \sum^{m}_{k=10} \beta k*\text{covariates}_{mit} + \epsilon_{it}$$

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

Subscripts i and t represent individual i and observation at time t, respectively. The dependent variable Y_{it} is cognition (GCP, EF or Memory) or time to dementia. Follow-up time, $time_{it}$, is expressed as the years before or after incident stroke, where negative values indicate time before stroke in the case of incident strokes. Parameters of interest for testing the hypotheses are the $\beta 5 - \beta 7$ interaction terms of stroke severity with time. The group with no stroke are the reference group. We will examine the change in the stroke severity*time interaction term after adding time-varying risk factors and their interactions with time. Pursuant to Aim 2, we will examine three-way interactions (including component two-way interactions) between severity, time, and vascular risk factors (BP, cholesterol, diabetes, and BMI).

Term $\sum_{k=10}^{m}$ includes the covariates (see *Main covariates*) and their interactions with follow-up time. Models will include age*time, sex*time, and race*time interaction terms because there is evidence that the post-stroke cognitive slope differs by age and sex based on the results of ARIC MS#3903. 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. We will repeat analyses within cohort to assess heterogeneity of effects.

Dementia incidence: Risk of dementia will be studied with Cox proportional hazards models using pooled data as primary analysis and also stratified by cohort in a sensitivity analysis. Follow-up time will be from baseline to first diagnosis of dementia, death, loss to follow-up, or administrative censoring, whichever occurs first. Risk of dementia will be assessed **with stroke events occurrence and severity modeled as a time dependent covariate** comparing time after stroke to time without a history of stroke. In cases where NIH stroke severity scores are unavailable, they will be imputed using multilevel multiple imputation by chained equations.
In sensitivity analyses for aim 2 (dementia as an outcome), we will adjust for the competing risk of death by fitting Cox proportional hazards models with death coded as a censoring case.
We will also conduct a sensitivity analysis including individuals without stroke as a reference rate of cognitive decline. For these individuals, the incident stroke variables would stay 0 for all time.
In addition, we will look at trajectories of general and domain-specific cognitive performance to assess possible differences in trajectories.

Anticipated challenges and limitations:

- Information on stroke severity was not prospectively assessed, but determined based on data in the hospitalization records from admission. However, the information was collected by trained chart reviewers, experienced in evaluation of stroke patients. Severity was categorized based on all the data available in the hospitalization charts and following a validated algorithm for chart-based retrospective evaluation of stroke severity[32,33]and previously used in ARIC papers[20,30,31].
- Individuals with stroke have shorter survival than those without stroke and among stroke patients, those with larger and more severe strokes are less likely to survive and be evaluated for long-term outcomes. We will mention this limitation in the paper.
- General cognitive performance measure has more data points, and thus potentially more power, than memory or executive functioning factors.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X_ 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 _X__ No

8.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

__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#3672: Ischemic Stroke Incidence, Severity and Recurrence as Risk Factors for Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort Study
- MP#3800: Methods for stroke severity assessment by chart review in the ARIC study
- MP#4150: 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). Our proposed study is different from ARIC MP#4150 (Levine et al.) which aims to use stroke severity as a covariate.

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* 2017.22**)**

___ 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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