ARIC Manuscript Proposal #3672

PC Reviewed: 7/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Stroke Incidence and Severity as Risk Factors for Dementia and MCI in the Atherosclerosis Risk in Communities (ARIC) Cohort Study

b. Abbreviated Title (Length 26 characters): Stroke incidence, stroke severity and Dementia/MCI

2. Writing Group:

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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 in 3-6 months. Submission of an abstract to the International Stroke Conference (August 2020 deadline) planned.

4. Rationale: Reliable estimates for the risk of dementia and MCI after stroke are required to inform clinicians, researchers and policymakers. The study of potential effects of clinical characteristics of stroke, among them severity of stroke, on the association between stroke and cognitive function is crucial and will become even more important with the expected global increase in the proportion of older populations. Data from the population-based Faenza Community Aging Study showed increased risk of dementia and cognitive impairment/no

dementia (CIND) in participants with stroke. Moreover, these associations were stronger in individuals 61-74 years than 75+ years old[1]. Cognitive impairments affect up to one-third of stroke survivors[2] and pooled estimates of stroke-associated dementia show that about 25% of stroke patients develop incident dementia during the first year after stroke[3]. The association between stroke severity and dementia after stroke has been studied in the population-based Oxford Vascular Study (OxVasc). The 1-year standardized morbidity ratio for incident dementia was 47.3 (95% CI 35.9-61.2) for severe stroke (NIHSS score >10), 5.8 (4.4-7.5) for minor stroke (NIHSS score <3), and 3.5 (2.5-4.8) for transient ischemic attack, compared with the UK age-matched and sex-matched population. Substantial variation in the risk of dementia after stroke by age and stroke severity was observed: the 5-year cumulative incidence of dementia ranged from 0% for patients <65 years old diagnosed with TIA to over 80% in patients ≥75 years old diagnosed with a major recurrent stroke[3]. Gender, level of cognitive function before stroke, acute interventions at time of stroke, hemoglobin level and APOE ε4 status, as well as imaging characteristics of the stroke itself and evidence of microvascular brain disease, are additional factors that have been associated with risk of cognitive impairments or dementia after stroke[4].
Assessment of cognitive function in stroke survivors is challenging. First, consideration of the time frame of development of dementia post-stroke must be considered, as early changes may not represent true dementia. Secondly, aphasia, neglect and some level of global cognitive dysfunction might be present after stroke; therefore, comprehensive cognitive neurological assessment is recommended [4]. Such an assessment is conducted in ARIC-NCS since 2011-2013 (visit 5). The extensive neuro-cognitive evaluation includes three ARIC cognitive instruments that have been administered since ARIC visit 2 (Delayed Word Recall Test, Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale -Revised, and the Word Fluency Test); a comprehensive neuropsychology test battery, Logical Memory Immediate and Delayed recall, and Incidental Learning from the Wechsler Memory Scale-III, Trail-making Test parts A and B, WAIS-R Digits Span Backward, Boston naming test, Animal naming fluency and the Mini-Mental State Examination (MMSE). The comprehensive evaluation in ARIC is an important advantage over other cohort studies. For example, in OxVasc, cognitive function was assessed with MMSE and Montreal Cognitive Assessment, or diagnosed based on medical records. Also, the algorithm used in ARIC-NCS to standardize and describe the diagnoses of cognitively normal, MCI, or dementia[5] allows for evaluation of progression from normal cognitive function to MCI and to dementia. The study of rate of progression is essential based on previous findings suggesting that stroke survivors may progress faster from MCI to dementia[1] and MCI is a significant predictor of dementia in stroke survivors[6].
ARIC includes broad data on prevalence and treatment of midlife risk factors; therefore studying possible long-term effects of risk factors on the association between stroke and cognitive decline will be possible, as will be the ability to study an independent effect of stroke on dementia (independent of underlying shared risk factors). Data on stroke severity were not prospectively collected in ARIC. In December 2018, we initiated a large project aimed at retrospectively collecting data on severity in stroke events occurring among ARIC participants. Stroke hospitalization blinded charts of all incident and recurrent events adjudicated in ARIC as definite or probable ischemic or hemorrhagic (intracerebral hemorrhage- ICH and subarachnoid hemorrhage- SAH) stroke were reviewed and data on stroke severity were abstracted using an algorithm valid for retrospective assessment of the National Institute of Health Stroke Scale (NIHSS) score across the entire scale spectrum[7, 8]. Using all the data available in ARIC on stroke incidence, severity, cognitive function and risk factors, we aim to assess the risk of dementia and MCI after incident stroke, and study differences in risks by severity of stroke, assessing potential effects of midlife risk factors.

5. Main Hypothesis/Study Questions:

1. Stroke is associated with increased risk of dementia. This will be true for either ischemic or hemorrhagic (intracerebral hemorrhage, ICH) stroke, with stronger associations for ICH than ischemic stroke.
2. Among individuals with ischemic stroke, stroke severity by NIHSS category is positively associated with risk of dementia.
3. Stroke is associated with increased odds of MCI, with similar hypothesized associations by stroke type as in #1.
4. Among individuals with stroke, stroke severity by NIHSS category is associated with increased odds of MCI.
5. Examine if the associations are uniform across categories of sex, age, race, education, and APOE e4 status.

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 Design: Survival analysis of risk of dementia associated with stroke incidence as a time dependent variable. We will allow for multiple strokes. Participants with dementia diagnosis before stroke will be counted in the non-stroke group. Sensitivity analysis using a discrete-time logistic regression model with a complimentary log-log link will be performed to look for consistency, since in ARIC, Level 3 dementia diagnosis is determined in part by assessments conducted at clinic visits. Also as sensitivity analysis, stroke severity will be considered in separate models, quantified in the majority of strokes. Stroke severity will be stratified according to the NIHSS score as follows: minor stroke (NIHSS$\leq$5), including the majority of the strokes, mild to moderate stroke (NIHSS 6-10) and moderate to severe (NIHSS$\geq$11 and NIHSS$\geq$16) stroke. MCI risk will be analyzed similarly, but the need for visits to quantify MCI means the analysis will be logistic with grouped time incidence for MCI. We will use multinomial logistic regression for the analysis of MCI.

Exclusion Criteria: We will exclude ARIC participants with prevalent stroke at ARIC baseline (1987-1989), as well as participants with missing information on the main covariates in multivariable models.

Exclusion of cerebrovascular events other than ischemic stroke, ICH and SAH, as well as events with data not sufficient to categorize severity according to the previously defined categories, will be considered to avoid undue influence on the non-stroke group. They will be modeled as a separate exposure.

Definition of outcomes: Dementia and MCI defined according to ARIC criteria. In participants with stroke, dementia or MCI after stroke will be reported if diagnosed $\geq$1 year after incident stroke in order to exclude cases of acute changes in cognitive function after stroke.

Main covariates: Time from baseline to diagnosis of dementia with stroke incidence considered as a time dependent covariate. Models will be adjusted for baseline age, sex, race/center, APOE

ε4 status, education, and time-varying age at stroke, smoking, BMI, diabetes, systolic blood pressure, total cholesterol, anti-hypertensive medication and statin use. In sensitivity analyses, we can consider baseline cognition (measured at visit 2), and accordingly in this sensitivity analysis would consider other covariates at visit 2 instead.

Summary of data analysis:
Hypotheses 1&2 will be studied with Cox proportional hazards models. Follow-up time will be from baseline to first diagnosis of dementia, death, loss to follow-up, or administrative censoring on December 31st, 2018, whichever occurs first. Models will include the above covariates and in sensitivity analyses we will adjust for the competing risk of death. For hypothesis 1, risk of dementia will be assessed with incident stroke modeled as a time dependent covariate comparing time after stroke to time without a history of stroke. Ischemic stroke and intracerebral hemorrhage will be considered both together as well as in separate models. For hypothesis 2, we will tabulate risk among stroke individuals by severity categories: mild to moderate stroke (NIHSS 6-10) and moderate to severe stroke (using both definitions NIHSS≥11 and NIHSS≥6) compared with minor stroke (NIHSS≤5), and restrict our primary analysis to individuals with ischemic stroke. In a sensitivity analysis, we could also model stroke severity using an interaction term between stroke incidence (0/1 time dependent variable) and severity category (namely severity is only assigned to stroke cases). In the minority of cases where severity scores are unavailable, we could use multiple imputation.

Hypotheses 3&4 for MCI will be modeled similarly to hypothesis 1 & 2 for dementia with the main distinction that we will use logistic regression models for MCI as outcome. We will need to consider the censoring impact of dementia (and associated death or missed visits) in analyzing subsequent MCI as an outcome.

Stratified analyses will be conducted by age of stroke (< >75 years according to previous publications[1]) and 2 stroke severity categories (severe stroke vs. other). We will assess potential effect modification by age at time of stroke, race, sex and APOE ε4 status.

Anticipated challenges: Sub-group analyses might be limited due to power considerations. Informative censoring is a recurrent challenge in analyses of dementia and we will consider the approaches of MICE and IPAW discussed at ARIC NCS analysis calls. Individuals with stroke have shorter survival aggravating the informative censoring issues and hence we will quantify the association of stroke with both mortality and missed visits to understand this issue in detail. An important limitation in the analysis of MCI is that in ARIC, MCI was diagnosed only after visit 5.

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? _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)?

Data on stroke severity was not previously available, therefore there have not been proposals on this topic; however, papers on trends in stroke incidence and many papers on dementia/MCI have been published in the last years. We think that the following manuscripts can be considered related to this proposal:

1. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014;312(3):259-68.
2. Koton S. Sang Y, Schneider ALC, Rosamond WD, Gottesman RF, Coresh J. Stroke Incidence Decrease in Older US Adults: An Update from the Atherosclerosis Risk in Communities (ARIC) Cohort Study. *JAMA N*eurology. 2019; 77:109-113.
3. Gottesman RF, Albert M, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, Schneider ALC, Windham BG, Wruck LM, Knopman DS. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurology*. 2017.
4. Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, Schneider AL, Hengrui S, Alonso A, Coresh J, Albert MS, Mosley TH, Jr. Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk In Communities neurocognitive study (ARIC-NCS). *Alzheimer's & dementia*. 2016;2:1-11

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 ARIC-NCS ancillary

*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.

References:

1. De Ronchi D, Palmer K, Pioggiosi P, Atti AR, Berardi D, Ferrari B, Dalmonte E, Fratiglioni L. The combined effect of age, education, and stroke on dementia and cognitive impairment no dementia in the elderly. *Dementia and geriatric cognitive disorders*. 2007;24:266-273
2. Mijajlovic MD, Pavlovic A, Brainin M, Heiss WD, Quinn TJ, Ihle-Hansen HB, Hermann DM, Assayag EB, Richard E, Thiel A, Kliper E, Shin YI, Kim YH, Choi S, Jung S, Lee YB, Sinanovic O, Levine DA, Schlesinger I, Mead G, Milosevic V, Leys D, Hagberg G, Ursin MH, Teuschl Y, Prokopenko S, Mozheyko E, Bezdenezhnykh A, Matz K, Aleksic V, Muresanu D, Korczyn AD, Bornstein NM. Post-stroke dementia - a comprehensive review. *BMC medicine*. 2017;15:11
3. Pendlebury ST, Rothwell PM, Oxford Vascular S. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: Analysis of the population-based oxford vascular study. *The Lancet. Neurology*. 2019;18:248-258
4. Gottesman RF, Hillis AE. Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. *The Lancet. Neurology*. 2010;9:895-905
5. Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, Schneider AL, Hengrui S, Alonso A, Coresh J, Albert MS, Mosley TH, Jr. Mild cognitive impairment and dementia prevalence: The atherosclerosis risk in communities neurocognitive study (aric-ncs). *Alzheimer's & dementia*. 2016;2:1-11
6. Narasimhalu K, Ang S, De Silva DA, Wong MC, Chang HM, Chia KS, Auchus AP, Chen C. Severity of cind and mci predict incidence of dementia in an ischemic stroke cohort. *Neurology*. 2009;73:1866-1872
7. Lindsell CJ, Alwell K, Moomaw CJ, Kleindorfer DO, Woo D, Flaherty ML, Air EL, Schneider AT, Ewing I, Broderick JP, Tsevat J, Kissela BM. Validity of a retrospective national institutes of health stroke scale scoring methodology in patients with severe stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2005;14:281-283
8. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the nih stroke scale. *Stroke*. 2000;31:858-862