ARIC Manuscript Proposal # 3643

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: **Association Between Acute Kidney Injury and Dementia**

1b. Abbreviated Title (Length 26 characters): **AKI and Dementia**

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ST__

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Data analysis will begin once the manuscript proposal is approved. The manuscript is expected to be completed within 6 months.

4. Rationale:

Acute kidney injury (AKI) is a common kidney complication that has been shown to cause other end-organ damage in animal models. Several pathways have been identified that may explain this phenomenon, including inflammatory response, apoptosis, oxidative stress, differential molecular expression, and leukocyte trafficking. AKI is also thought to lead to

impairment of brain function, though the exact mechanisms that lead to this outcome are still unclear. Studies have found that uremia may be associated with significant biochemical changes in the brain, specifically in calcium concentrations and water levels. Additionally, studies have examined how neurotransmitters may play a role. In animal models, bilateral renal ischemia reperfusion injury was associated with a decrease in dopamine turnover, as well as a decrease in motor activity. The study of animal models also demonstrated that renal ischemia may increase levels of cytokines in the brain. [i]

Previous studies have shown that in the long term, AKI may be associated with the risk of developing dementia, even in those who have undergone complete renal recovery. One Taiwanese study published in 2017 studied 689 patients with fully recovered AKI and 2756 control adults followed in routine clinical care and found that patients with a history of AKI had a two-fold higher risk of developing dementia. [iii] Another study published in 2019 used propensity score matching to compare the risk of dementia in 1041 fully recovered AKI patients with 1041 control patients in a clinical database, demonstrating a three-fold higher risk of dementia among patients with a history of AKI. [ii]

The Atherosclerosis Risk in Communities study provides a unique opportunity to expand upon these results with the carefully collected parameters of kidney function, availability of APOE genotype, active follow-up for AKI, and rigorous assessment of cognitive function and dementia development. Approximately 20% of the study population are African American, a subset of the general population that has not been adequately studied. The goal of this study is to evaluate the association between interval AKI and risk of developing dementia over 20 years (visit 4 in 1996-7 to visit 6 in 2017) of follow-up using data collected from the ARIC cohort. We predict that AKI will be associated with an increased risk of incident dementia.

5. Main Hypothesis/Study Questions:

AKI will be associated with higher long-term risk of developing dementia.

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: Prospective study of the ARIC cohort

Inclusion criteria: Patients without a history of dementia, end-stage renal disease (ESRD), or previous stroke at visit 4

Outcomes: Incident dementia was measured by a cognitive battery test at visit 4. An in-person cognitive assessment at visits 5 and 6. For those who were unable to attend, a telephonic instrument of cognitive status-modified (TICS-m) was offered. For those who were unable to be evaluated in person and unable to undergo the telephone interview, an informant interview was completed if dementia was suspected or could not be ruled out or if

ICD-9 dementia discharge code was administered at any point since the start of the cohort study. [v] In sensitivity analyses, we will also evaluate other markers of cognitive impairment.

Predictor: Incident AKI, as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 584.5 to 584.9 or 10th Revision, Clinical Modification (ICD-10-CM) codes N17.0 to 17.9 among discharge diagnoses [iv]

Other variables of interest: Age, sex, race, education level (less than high school, high school graduate or GED, beyond high school), smoking status, BMI, baseline eGFR, baseline urine albumin-to-creatinine ratio, cardiovascular disease, diabetes, hypertension, APOE genotype, C-reactive protein

Data analysis: 1) We will evaluate AKI as a time-varying exposure in the study population and compare baseline characteristics between those who develop AKI and those who do not using t-tests and chi-squared. 2) We will estimate the association between AKI and cognitive outcomes using multivariable Cox proportional hazards regression model. We will adjust the models for the baseline covariates listed in the above section. In secondary analysis, we will also explore propensity matching cases of AKI with participants without AKI and evaluating the comparative risk of dementia in this cohort. We will also explore associations after adjusting for the competing event of death using the methods of Fine and Gray.

Limitations: Observational study (unable to determine causality or mechanism), possibility of residual confounding variables

7a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes ___X_ No

7b. 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.)

8a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8b. 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/search.php

__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)?

3243: "Association of Kidney Disease Measures and Incident Dementia in the Community," Johannes Scheppach

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

11b. 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 http://www.cscc.unc.edu/aric/forms/

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript **____ Yes __X__ No**

i Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81:942–948.

ii Kendrick J, Holmen J, Srinivas T, You Z, Chonchol M, Jovanovich A. Acute Kidney Injury Is Associated With an Increased Risk of Dementia. *Kidney Int Rep*. 2019;4(10):1491–1493. Published 2019 Jul 27. doi:10.1016/j.ekir.2019.07.012

iii Kao CC, Wu CH, Lai CF, et al. Long-term risk of dementia following acute kidney injury: A population-based study. *Ci Ji Yi Xue Za Zhi*. 2017;29(4):201–207. doi:10.4103/tcmj.tcmj_40_17

iv Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol*. 2010;21(10):1757–1764. doi:10.1681/ASN.2010010128

v Knopman DS, Gottesman RF, Sharrett AR, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)*. 2016;2:1–11. doi:10.1016/j.dadm.2015.12.002