ARIC Manuscript Proposal #3680

PC Reviewed: 8/11/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of CKD Markers with Signs of Neurodegeneration and Small Vascular Disease on Brain MRI

b. Abbreviated Title (Length 26 characters): CKD and Brain MRI Signs

2. Writing Group:

Writing group members:

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

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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 to be used in this study are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Dementia and cognitive decline are a growing public health problem in older adults leading to reduced quality of life, caregiver burden and increased healthcare costs [1]. The development of cognitive impairment or dementia is accompanied with certain structural brain changes, which can be made visible by imaging techniques, such as magnetic resonance imaging (MRI) [2]. MRI potentially also increases the accuracy of the clinical diagnosis of different dementia subtypes, such as Alzheimer's disease or vascular dementia [3]. Brain atrophy, as a measure of total neuron loss in the brain, relates to cognitive decline. In certain brain regions, such as hippocampus, it may indicate pathological damages related to specific neurodegenerative diseases, like Alzheimer's disease (AD) [4]. Further pathologies detectable by MRI, such as white matter hyperintensities (WMH), infarcts (primarily affecting the lacunes), and micro-hemorrhages are more likely to be markers of brain small vessel disease. WMH and infarcts have been shown to be associated with cognitive decline, while the evidence on micro-hemorrhages is inconsistent [4-9] .

Recent cross-sectional studies have shown patients with chronic kidney disease (CKD) to have an increased risk of dementia and cognitive impairment, with more advanced stages of chronic kidney disease (CKD) exhibiting a stronger cognitive decline [10-12]. However, studies conducted in the past and involving MRI imaging focused generally on estimated glomerular filtration rate (eGFR) and albuminuria as predictors [13, 14]. So far, there is insufficient evidence on the association of novel biomarkers of kidney disease with structural brain abnormalities as well as a detailed comparison of affected brain regions and type of damage. Such insights could provide valuable information on the pathophysiology of cognitive decline and dementia in patients suffering from CKD.

5. Main Hypothesis/Study Questions:

Study Aim:

Assess whether measures of kidney disease, such as eGFR, based on creatinine, Cystatin C or Beta-2 Microglobulin) and albuminuria are associated with structural abnormalities in the brain visible on MRI imaging at Visit 5. Such abnormalities could either be measures of cerebral small vessel disease (infarctions, increased white matter hyperintensity volume, micro-hemorrhages), measures of neurodegeneration (brain atrophy / reduced brain volume either globally or limited to certain regions of interest (ROI), such as AD signature regions) or signs of impaired microstructural integrity visible on diffusion tensor imaging (DTI) parameters, such as higher mean diffusivity (MD) and fractional anisotropy (FA).

Hypotheses:

1. Lower levels of eGFR and higher levels of albuminuria are associated with higher levels of cerebral small vessel disease (infarctions, increased white matter hyperintensity volume, micro-hemorrhages) visible in MRI imaging.
2. Lower levels of eGFR and higher levels of albuminuria are associated with higher levels of general neurodegeneration (brain atrophy / reduced brain volume) visible in MRI imaging.
3. Lower levels of eGFR and higher levels of albuminuria are associated with impaired microstructural integrity (higher mean diffusivity, lower fractional anisotropy) visible in diffusion tensor imaging.
4. In older people, markers of low eGFR which are unrelated to muscle mass (Cystatin C and Beta-2 Microglobulin) will lead to stronger associations with structural brain abnormalities than eGFR based on creatinine. Since eGFRcr often overestimates kidney function in older people, markers unrelated to muscle mass will also identify a larger number of individuals classified as having increased risk (e.g. eGFR<60).

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:

We will utilize a cross-sectional study design at Visit 5 assessing the association of kidney disease measures with brain structure abnormalities using MRI.

Study population:

Inclusion criteria:

All ARIC participants who had a brain structure MRI scan at Visit 5 with valid measurements of eGFR (based on creatinine, Cystatin C and Microglobulin), albuminuria.

Exclusion criteria:

- Race – The small number of individuals that are neither white nor African-American as well as African-Americans at Minnesota and Washington County will be excluded.
- Missing key covariate information (e.g. education)
- Prevalent severe disease at or before Visit 5: Dementia, stroke or end-stage renal disease (ESRD).

Exposure:

Measures of kidney disease:

- eGFR (linear scale, spline knot at 60). The CKD-EPI equations will be used to estimate eGFR from serum creatinine, Cystatin C and Beta-2 Microglobulin
- Albuminuria will be quantified as the albumin to creatinine ratio (UACR) in mg/g modeled on the log scale.

Outcomes:

Brain structure abnormalities measured on MRI imagining, including:

- Subclinical infarcts:
  - Existence of cortical, subcortical, and lacunar infarcts. (Binary variable).
  - Frequency of cortical, subcortical, and lacunar infarcts. (Categorical variable).
- Micro-hemorrhages:
  - Existence of micro-hemorrhages (Binary variable).
  - Frequency of micro-hemorrhages (Categorical variable).
- White matter hyperintensity volume: total volume of the area with WMH, adjusted for intracranial volume (Continuous variable).
- Microstructural integrity (mean diffusivity, fractional anisotropy) visible in diffusion tensor imaging
- Total gray-matter volume adjusted for intracranial volume (Continuous variable).
- ROI volumes: total gray-matter volume for AD signature regions (lateral temporal, lateral parietal, medial parietal, hippocampus and olfactory region), medial temporal lobe, and parts of frontal lobe (lateral frontal and medial frontal), analyzed as continuous variables

Covariates:

Age, sex, race, education level, smoking status (current, former, never), alcohol consumption (current, former, never), body mass index (BMI), apolipoprotein E4 genotype, total cholesterol, hypertension status, diabetes status, history of heart failure and stroke.

Statistical Analysis Plan:

We will use linear and logistic regression to model the associations of kidney disease measures with brain structure abnormalities visible using MRI imaging at Visit 5. We will use forward stepwise model selection starting with a basic demographic model adjusted for age, sex, education and apolipoprotein E4 genotype with later addition of further covariates listed above.

Limitations:

- By excluding prevalent dementia, stroke and ESRD cases we select on participants with an overall healthier condition.
- Brain structure MRI imaging was measured at Visit 5. With one-time measurement, it is impossible to assess brain atrophy. Instead, we will use the relative size of brain cortical volume among the study population as a surrogate measurement for atrophy.

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/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)?

To our knowledge, there are no ARIC proposal specifically focusing on measures of CKD and brain structural MRI abnormalities. Related ARIC proposals are:

- #3054: Brain Structural MRI Abnormalities Predict Dementia, MCI and Cognitive Decline in an Older Population [lead: A. Wu]
- #2120B: Mid-life vascular risk factors for Mild Cognitive Impairment in the ARIC NCS Study [lead: D. Knopman].
- #2120C: Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC [lead: R. Gottesman].
- #2606: Biomarkers of hyperglycemia, 20-year cognitive decline, and dementia risk: the Atherosclerosis Risk in Communities Study [lead: A. Rawlings]
- #2630: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes [lead: A. Lee].

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* #2008.06 (ARIC-NCS))

___ 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.

References:

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10. Elias, M.F., et al., *Chronic kidney disease, creatinine and cognitive functioning.* Nephrol Dial Transplant, 2009. **24**(8): p. 2446-52.
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14. Cho, E.B., et al., *Albuminuria, Cerebrovascular Disease and Cortical Atrophy: among Cognitively Normal Elderly Individuals.* Sci Rep, 2016. **6**: p. 20692.