ARIC Manuscript Proposal #3751

PC Reviewed: 12/8/20   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: The association of kidney function with brain amyloid deposition: The ARIC-PET Study

  b. Abbreviated Title: kidney and brain amyloid

2.   Writing Group:
Sanaz Sedaghat, Pamela Lutsey, Aaron Folsom, Timothy Hughes, Josef Coresh, Morgan E Grams, Thomas H Mosley, Rebecca F Gottesman, other interested investigators are welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. Sanaz Sedaghat

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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 to begin immediately after proposal approval and data access
Draft completion spring/Summer 2021
Send to coauthors summer 2021
Submission fall 2021

4.   Rationale:

Patients with kidney impairment exhibit multiple features of accelerated brain aging.[1] Chronic decline in kidney function is strongly related to brain atrophy, cerebral small and large vessels diseases[2] and elevated risk of all-cause dementia and Alzheimer's disease (AD).[3,4] Individuals at all stages of chronic kidney disease (CKD) have a higher risk of developing cognitive disorders and dementia.[1] The burden of cognitive impairment among individuals with CKD is high; as many as 20-50% of CKD patients have mild to moderate cognitive impairment or overt dementia.[1] Despite the compelling evidence that individuals with kidney dysfunction are at higher risk of cognitive impairment, mechanisms remain unknown. A role for shared cardiovascular risk factors, such as hypertension, diabetes and hyperlipidemia, has been implicated in this association.[5] However, multiple studies confirm that the elevated risk for cognitive impairment in relation to kidney function is independent of these factors,[6,7] suggesting that other mechanisms may be involved.

Kidneys are considered to be excretory organs and control levels of metabolites via regulating and filtering minerals from blood.[8] Several studies suggested kidneys as organs involved in clearance of Amyloid-β (Aβ).[8-11] A study including participants with kidney disorders detected soluble AB in human urine.[8] In a radiographic experiment, injected intracranial or intravenous I125-labelled Aβ was detected in the kidneys and urine.[11] Indeed, the serum Aβ levels and brain Aβ depositions were found to be significantly increased in CKD patients. Taken together, these findings suggest that the reduced kidney-mediated Aβ clearance may contribute to AD pathology in brain.[8,10,11] However, there is no evidence whether worse kidney function is associated with brain amyloid deposition measured using positron emission tomography (PET) in a population-based setting. We aim to investigate the association of kidney function measures with brain amyloid deposition in the cohort of The Atherosclerosis Risk in Communities (ARIC)-PET Amyloid Imaging Study. This research will contribute to our understanding of whether kidney impairment may contribute to amyloid accumulation leading to cognitive decline and dementia.

5.   Main Hypothesis/Study Questions:

In ARIC-PET participants, measures of kidney function– lower glomerular filtration rate and higher albuminuria– are associated with higher brain amyloid deposition. This will be true when kidney function is assessed both cross-sectionally and prior to the Aβ measurement.

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
Both cross-sectional at visit 5 and prospective components (visit 4 kidney function data and visit 5 brain amyloid deposition)

Inclusion/Exclusion
Participants with kidney function measures and PET scan data will be included.

Participants who were not black or white, and blacks from the Minnesota and Maryland sites will be excluded (due to low numbers).

Variables
Exposures: Estimated glomerular filtration rate [eGFR] (using serum creatinine, cystatin C and both) and urinary albumin-to-creatinine ratio [ACR] at visit 4 and visit 5. eGFR will be estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation. ACR (mg/g) will be estimated by dividing urine albumin by creatinine. Because urine ACR values are not normally distributed, we will use log base 2 transformed values to obtain values per 2-fold higher urine ACR. Both eGFR and ACR will be modeled continuously and categorized using clinical cutoff points (<60 ml/min/1.73 m^2, 60-90, and >90 for eGFR; <30 mg/g, 30-300 and >300 for ACR).

Outcome: Global cortical measure of amyloid, using florbetapir PET scans, at visit 5 and calculated as a weighted average of standardized update value ratios (SUVRs) in various regions of the brain. Due to the highly skewed florbetapir SUVR variable, we will use a dichotomous (SUVR>1.2) measure to define abnormal amyloid uptake, as in prior ARIC publications.

Potential effect modifiers: Race, sex, APOE-4 allele status

Confounders: Age, sex, race, ARIC field center, history of hypertension, diabetes mellitus and cardiovascular disorders, total cholesterol, smoking and alcohol consumption (at the time of kidney function assessment).

Data Analysis
We will use logistic regression models to evaluate the associations of kidney function markers (continuously and categorized) and brain amyloid deposition. We will examine three models:
(1) crude model,
(2) model 1 including age, sex, race*field center (5-level variable) and
(3) model 2 additionally adjusted for history of hypertension, diabetes mellitus and cardiovascular disorders, total cholesterol, smoking and alcohol consumption.

Cross-sectional analyses will use inverse probability weighting to account for selection into the visit 5 brain MRI study (given that PET participants were recruited from the brain MRI cohort). For models using kidney function at visit 4 and amyloid deposition at visit 5, inverse probability weighting will be used to account for attrition due to death, visit non-attendance, and selection into brain MRI study.

Models will be stratified by race, sex and APOE status (1 or 2 ε4 alleles versus no ε4 alleles), with test for interaction on a multiplicative scale.

Sensitivity analysis
We will perform series of sensitivity analysis to test the robustness of the results including excluding participants with history of cardiovascular disease, excluding participants with mild cognitive impairment (MCI), evaluating change in kidney function as the exposure, and using different florbetapir thresholds.

In addition, in a subset (n=2,588), we will examine whether kidney function markers are associated with plasma Aβ measured at visit 5 in individuals exhibiting impaired cognitive status.

Power calculation
With the sample size of 346, among them 50.9% considered as cases (SUVR>1.2), we have 90% power to detect odds ratio of 1.42.[12]

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

8.a. Will the DNA data be used in this manuscript? 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

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)?

MS#2466 (lead: Rebecca Gottesman) – The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype

MS#2511 (lead: Rebecca Gottesman) – Vascular risk factors and brain amyloid deposition: The ARIC-PET Study

MS#3680 (lead: Josef Coresh) – Association of CKD Markers with Signs of Neurodegeneration and Small Vascular Disease on Brain MRI

MS#1388 (lead: Josef Coresh) – Chronic Kidney Disease and Risk of Subclinical Brain Infarction: The Atherosclerosis Risk in Communities Study

MS#3243 (lead: Joseph Coresh) – Association of Kidney Disease Measures and Incident Dementia in the
Community

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

11.b. If yes, is the proposal
A. primarily the result of an ancillary study (list number* 2009.29)

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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