ARIC Manuscript Proposal # 3243

PC Reviewed: 09/11/18   **Status:** _____   **Priority: 2**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Association of Kidney Disease Measures and Incident Dementia in the Community

  b. Abbreviated Title (Length 26 characters): Kidney Disease and Dementia

2. Writing Group:
    Writing group members:
Johannes B. Scheppach, MD, MPH; and (alphabetically) Josef Coresh, MD, PhD, MHS; Rebecca F. Gottesman, MD, PhD; Morgan E. Grams, MD, PhD; David S. Knopman, MD; Silvia Koton, PhD; Thomas H. Mosley, PhD; A. Richey Sharrett, MD, DrPH; Aozhou Wu, MHS; others welcome.

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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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, increased healthcare costs and premature mortality [1]. The identification of high-risk patient groups and quantifiable risk factors could allow for earlier recognition, more targeted surveillance and possibly earlier treatment or better control of the factors conveying risk.

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 CKD exhibiting a stronger cognitive decline [2-4]. Patients with diabetes mellitus, hypertension and other cardiovascular risk factors, which are common causes of CKD, are also at high risk of incident dementia [5-8].

However, the quantitative and longitudinal association between measures of CKD, such as estimated glomerular filtration rate (eGFR) and albuminuria, with incident dementia has not yet been assessed. It is also unclear, whether such an association is independent from already established risk factors, such as diabetes mellitus, hypertension or cardiovascular disease (CVD).

5.   Main Hypothesis/Study Questions:

Study Aims:
1. Assess the association of eGFR and albuminuria with incident dementia after visit 5.
2. Assess the association of eGFR and albuminuria with incident dementia after visit 4.
3. Assess the association of eGFR and albuminuria modeled as time dependent covariates (from visit 1 to visit 5) with incident dementia.
4. Explore the longitudinal association between eGFR and albuminuria and >25-year cognitive decline from visit 2 to visit 6.

Hypotheses:
1. Lower levels of eGFR and higher levels of albuminuria are independently associated with higher incidence of dementia and greater long-term cognitive decline.
2. In older people, markers of low eGFR which are unrelated to muscle mass (Cystatin C, Beta-Trace Protein and Beta-2 Microglobulin) will lead to stronger associations with dementia and cognitive decline 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 perform a survival analysis for incident dementia and longitudinal data analysis for cognitive decline. We will examine several baseline periods since the prevalence of CKD varies with age.

Study population:

Inclusion criteria:

All ARIC participants with valid measurements of eGFR and albuminuria. At risk populations will be defined separately at visit 2 and again at visit 5.

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 data for eGFR or albuminuria.
- Missing information on education and/or missing cognitive score at visit 2.
- Prevalent severe disease at baseline: Dementia, Stroke or 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. When additional filtration markers are available they will be used to provide complementary estimates of GFR (visit 2: Cystatin C, Beta-2 Microglobulin; visit 4: Cystatin C, Beta-Trace Protein, Beta-2 Microglobulin; visit 5: Cystatin C). Albuminuria will be quantified as the albumin to creatinine ratio (UACR) in mg/g modeled on the log scale (visits 4 and 5).

Outcome:

- Incident dementia: We will use the ARIC NCS dementia incidence files. Briefly, validated dementia events by committee review (level 1), or by dementia surveillance or hospitalization records or death certificates with a dementia ICD-9/10 code (level 3). We will consider dementia type information (2 categories: Alzheimer's alone or vascular (as first or secondary diagnosis) when available.
- Cognitive test score changes: We will follow the ARIC NCS recommended procedures and datasets for longitudinal data analysis and correction for informative losses. Briefly, cognitive test scores measured at visits 2, 4, 5 and 6 including: the delayed word recall test (DWRT), the digit symbol substitution test (DSST), and the word fluency test (WFT) and the 7 other tests used at exams 5 and 6. Standardized z-scores (standardizing to visit 2) will be used for each test. A For measuring decline between visits 2 and 5, a composite score will be calculated by summing the z-scores of the three tests and then standardized to the global scores at visit 2. Declines between visits 5 and 6 will be measured using

all 10 cognitive tests administered. Cognitive test score changes will be estimated using random effect models with correction for informative losses using multiple imputation by chained equations. We will use the same methods as described in ARIC MSP #2523: Imputing missing outcome data using multiple imputation by chained equations: simulation and validation in the ARIC study.

- We will consider all-cause mortality as competing risk in the secondary analysis for dementia incidence.

Covariates:

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

Statistical Analysis Plan:

Missing data imputation:

To account for informative drop-out and population attrition, we will impute the missing cognitive test results in visits 2, 4, 5 and 6 due to participants' loss to follow up as well as missing covariates listed above. We will use the same methods as described in ARIC MSP #2523: Imputing missing outcome data using multiple imputation by chained equations: simulation and validation in the ARIC study.

Analysis for aims 1,2 and 3:

We will perform a survival analysis using Cox regression to analyze the incidence of dementia using eGFR and albuminuria as predictors. 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. The covariates will be modeled both as fixed and time-dependent covariates.

Analysis for aim 4:

We will use measures of kidney disease (eGFR and albuminuria) as exposures and cognitive test scores recorded at visits 2, 4, 5 and 6 as outcomes to conduct a longitudinal analysis of cognitive decline. Cognitive test scores will be standardized to visit 2 measurements using the mean and standard deviation of the scores at visit 2. Kidney disease measures will be modeled as continuous variables (eGFR on the linear scale with a spline knot at 60 and UACR on the log scale. Random effect models will be used to accommodate the correlation between repeated cognitive test measures over time. To model the association with cognition change trajectories, both random intercept and random slope will be included. An independent correlation structure for the random effects will be assumed. The time-frame will be the time since visit 2, and cognitive test scores at visit 2, 4, 5 and 6 will be modeled as dependent variables. To allow the flexibility of cognitive changes, we will add linear splines with knots at visit 4 and 5. Interaction terms between exposure and time-spline will be included as the primary variables of interest. We will use forward

stepwise model selection starting with a basic demographic model adjusted for age and sex with later addition of further covariates listed above. Time-interaction terms, which contribute to the slope of cognitive change, will be included. Non-linearity will be checked for the exposure-outcome association and appropriate modeling approaches will be adopted to address the non-linear association if there is any.

Sensitivity Analysis:
- Interaction and Subgroup analysis:
  Interaction effects with cognitive slopes will be checked with the following covariates: gender, race, BMI, diabetes status, hypertension status at baseline and apolipoprotein E4 genotype. Subgroup analysis will be conducted in the subgroups of covariates that have significant modification effects on exposure-outcome association.
- Impact of stroke and CNS-altering medications used:
  To assess the robustness of the results, we will censor participants at the time point of clinical stroke and/or CNS-altering medications use after study baseline from the primary analytical population.
- Re-do the analysis using non-imputed data with inverse probability weighting to account for informative missingness and cohort attrition.

Limitations:
- Intervals between visits are not similar in length with higher losses due to mortality and attrition in the long interval between visit 4 and visit 5.
- Urine data are only available starting at visit 4.

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 incident dementia. Related ARIC proposals are:
   - #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].

   We will also utilize the imputation method developed in the proposal #2523: Imputing missing outcome data using multiple imputation by chained equations: simulation and validation in the ARIC study [lead: A. Rawlings].

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:
1. Fiest, K.M., et al., *The Prevalence and Incidence of Dementia: a Systematic Review and Meta-analysis.* Can J Neurol Sci, 2016. **43 Suppl 1**: p. S3-s50.
2. Elias, M.F., et al., *Chronic kidney disease, creatinine and cognitive functioning.* Nephrol Dial Transplant, 2009. **24**(8): p. 2446-52.
3. Kurella, M., et al., *Cognitive impairment in chronic kidney disease.* J Am Geriatr Soc, 2004. **52**(11): p. 1863-9.
4. Madan, P., et al., *Cognitive impairment in chronic kidney disease.* Nephrol Dial Transplant, 2007. **22**(2): p. 440-4.
5. Ott, A., et al., *Diabetes mellitus and the risk of dementia: The Rotterdam Study.* Neurology, 1999. **53**(9): p. 1937-42.
6. Leibson, C.L., et al., *Risk of dementia among persons with diabetes mellitus: a population-based cohort study.* Am J Epidemiol, 1997. **145**(4): p. 301-8.
7. Gottesman, R.F., et al., *Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort.* JAMA Neurol, 2017. **74**(10): p. 1246-1254.
8. Knopman, D.S., et al., *Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study.* Alzheimers Dement, 2018.