1.a. Full Title: The Association between Cystatin C and Cognitive Function: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Cystatin C and cognition

2. Writing Group:
   Writing group members: Priscilla Auguste B.A.; Rebecca F Gottesman M.D., PhD; Thomas Mosley; Alvaro Alonso M.D., PhD, M.P.H.; Elizabeth Selvin PhD, M.P.H.; Brad Astor M.D., PhD; Josef Coresh M.D., PhD, others welcome

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

First author: Priscilla Auguste
Address: Department of Epidemiology
         Johns Hopkins Bloomberg School of Public Health
         Welch Center for Prevention, Epidemiology, and Clinical Research
         2024 E Monument Street, 2-600
         Phone: (410) 614-6462
         Fax: (410) 955-0476
         E-mail: pauguste@jhsph.edu

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).
Name: Josef Coresh MD PhD
Address: Department of Epidemiology
         Johns Hopkins Bloomberg School of Public Health
         Welch Center for Prevention, Epidemiology, and Clinical Research
         2024 E Monument Street, 2-600
         Phone: (410) 955-0495
         Fax: (410) 955-0476
         E-mail: coresh@jhu.edu

3. Timeline: Data to be used in this proposal are currently available. Analyses and manuscript preparation will be performed over the next year.

4. Rationale:
   Chronic kidney disease (CKD) and cognitive decline are strongly associated with older age and both have a substantial microvascular disease etiology. Presently, 13% of individuals in the
US are living with CKD (1) and previous studies have demonstrated a high prevalence of cognitive impairment at varying levels of the disease spectrum (2), (3).

Currently there is limited research on a potential independent association of CKD with cognitive impairment. Of the seven studies examining this relationship, four cross-sectional and three prospective, six have placed emphasis on serum creatinine and estimated GFR (eGFR), and only one has examined cystatin C as a measure of kidney function (2;4-9). The availability of both serum creatinine as well as cystatin C measurements at visit 4 of the ARIC study provides an opportunity to compare the association using both measures, with an emphasis on cystatin C, over the course of 8 years of follow-up. The ARIC cohort also provides an opportunity to examine this relationship in a mixed group of both white and black participants.

Considering that cognitive impairment is a risk factor for dementia, a disease for which treatment is still under study, measures need to be taken in order to prevent or slow the transition to this latter non-reversible state (10). If shown that impaired kidney function is a risk factor, or a biomarker, for cognitive impairment, this may help to identify a high risk group for clinical dementia and as well as potentially suggest new targets for treatment.

5. Main Hypothesis/Study Questions:

Impaired kidney function as measured by quartiles of cystatin C at baseline (visit 4), will be associated with a greater change in cognitive function from baseline (visit 4) to the ARIC Carotid MRI visit (5-10 years later) independent of other factors.

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).

Inclusions: ARIC cohort participants with Cystatin C measured at visit 4, and data on cognitive function from visit 4 and the Carotid MRI study.

Exclusions: Individuals with history of stroke or TIA prior to baseline (visit 4) and persons taking medications that are highly likely to affect cognitive function under the assumption that these individuals may be too cognitively impaired to show progression via the cognitive function tests. Individuals at baseline below the 5th percentile of cognitive function for age, sex, and race will also be excluded as well as individuals missing data on covariates of interest.

Predictors: Baseline (visit 4) Cystatin C (mg/L) in quartiles, categories of GFR (<60, 60-75, 76-90, 90+) estimated from cystatin C, and cystatin C modeled continuously. Estimated GFR will be calculated from the equation published by Stevens et al after calibration of serum Cystatin C to the Cleveland Research Lab. (11)

Outcome: Change in cognitive function over follow-up (Visit 4 to Carotid MRI) in each of the following 3 cognitive function tests: Delayed Word Recall, Digit Symbol Subset of the Wechsler Adult Intelligence Scale-Revised, and the Controlled Oral Word Association (Word Fluency) test.

Other Variables of Interest (All measured at baseline: visit 4):
Sociodemographics: age, gender, race, education (# of grades completed), income, access to healthcare (insurance status), study site
Physical Information: BMI, systolic and diastolic blood pressures
Lifestyle: smoking, alcohol consumption
CVD Risk Factors: hypertension, diabetes status, CVD History (myocardial infarction and heart failure)
Cognitive impairment indicators: ICD codes for TIA, stroke, or non-vascular dementia related hospitalization
Medications of interest: hypertension meds, anti-depressants, CNS meds
Other: Apolipoprotein E genotype, C-reactive protein

Statistical Analysis:

The primary analysis will use a multiple linear regression. The dependent variable will be the change in cognitive function with a separate model for each of the three tests. The main independent variable will be Cystatin C (quartiles, categories of estimated GFR, and continuous). In addition to p-values for a test of significance of each coefficient, p-values will also be used to test for trend across quartile and eGFR category of Cystatin C. Cognitive impairment indicators will be used to access the decline in cognitive function over follow-up that is likely to not only be independent of the association under study, but also to affect performance on cognitive function tests. Stratified analysis will be used to assess for interaction via these indicators. All other covariates mentioned will be adjusted for in a stepwise fashion:

Model 1: age, gender, race, study site
Model 2: Model 1 plus income, access to healthcare, education, anti-depressant medications, Apolipoprotein E genotype
Model 3: Model 2 plus hypertension, diabetes
Model 4: Model 3 plus history of CVD, smoking, alcohol, BMI, CRP

Due to the nature of the stratified sampling design used in the Carotid MRI study (n=2066), all analyses will be weighted inversely to the probability of sampling to allow generalization to the ARIC population (n=15,792). We will use the sampling weights provided by the coordinating center.

We will also compare the strength of the association seen with Cystatin C to that seen using serum creatinine, the more traditional marker of low kidney function.

Secondary analyses will exclude individuals with a CESD score ≥ 16 at the ARIC Carotid MRI visit to analyze the impact of depression.

Limitations:
Use of a single baseline measure of Cystatin C may lead to misclassification of individuals who change to a different quartile later on. However, the misclassification will likely be non-differential.
Residual confounding is an inherent limitation of any observational study such as this one. In particular, depression, an important potential confounder of the association is measured at the Carotid MRI visit but not at visit 4. The only earlier pertinent information is whether participants are currently taking anti-depressants and the vital exhaustion measured at visit 3.
Other limitations to consider that will likely result in non-differential misclassification are the imperfect sensitivity and specificity of estimated GFR equations, and the cognitive function tests.

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?  _ X _ Yes  __ No  
(This file ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  
_ 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.csec.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)?

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* ARIC-CKD (2006.16), ARIC-Carotid MRI (2006.04C)
___  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.csec.unc.edu/aric/forms/

12. 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.
Reference List


