ARIC Manuscript Proposal #2104r

PC Reviewed: 10/09/2018  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Association of Serum Uric Acid and Cognitive Function and Dementia: The Atherosclerotic Risk In Communities Study

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

2. Writing Group: Writing group members: Aniqa Alam, Aozhou Wu, Melinda C. Power, Nancy West, Alvaro Alonso, others welcome

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

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3. Timeline:
Analysis is to be started immediately. Expected manuscript to be drafted over the next 6 months.
4. Rationale:

Cognitive impairment and dementia (CID) are public health issues that will increase in importance as the population of the United States ages. Prevalence estimates suggest that 22% of persons over age 70 have some form of non-dementia cognitive impairment and 13% over the age of 70 have a form of dementia. Serum uric acid (SUA) is involved in different mechanisms with potential competing effects on the risk of CID. On the one hand, SUA induces lowered nitric oxide levels in renal endothelium, leading to activation of the renin-angiotension system to promote hypertension. Kang 2005 demonstrates the ability of uric acid to promote vascular smooth muscle cell proliferation and atherosclerotic activity. These and other cardiovascular events are associated with CID.

On the other hand, serum uric acid is a serum anti-oxidant, and markers for oxidative damage are associated with dementia, suggesting that serum uric acid could reduce the risk of dementia. However, under some circumstances SUA can have pro-oxidant activity that damage the vascular endothelium. These competing properties make the overall association with cognitive impairment unclear.

A number of cross-sectional studies have reached conflicting results for the association between SUA and CID. Only one large (n=4618) prospective observational study has been conducted, which found a negative association between SUA at baseline and incidence of dementia and severity of non-dementia cognitive decline in the Rotterdam Study. Other prospective studies which replicated this finding were small, had short follow-up, and examined specific clinical subpopulations.

Evidence also suggests sex-based effect modification in SUA and cognitive decline. Higher baseline SUA has been shown to be protective against executive dysfunction in middle aged-men and visuospatial decline in older men, whereas SUA in older women was associated with increasingly poor working memory, but showed no relationship with visuospatial abilities or global cognitive functioning.

Finally, uric acid is associated with inflammation. However, few studies included markers of inflammation/use of anti-inflammatory drugs as covariates in their examination of the SUA/CID association.

Characterizing the association between serum uric acid and cognitive decline may have implications for identification of at-risk individuals, prophylaxis, and treatment. It may also yield insights into the relative contributions of the multiple mechanisms that act on risk of CID.

5. Main Hypothesis/Study:

Questions: We propose to examine the association between baseline serum uric acid and the risk of cognitive decline and dementia among the ARIC study participants. Our hypotheses:

1. Lower levels of serum uric acid at baseline will be associated with an increased risk of incident dementia in the follow-up through visit 6.
2. Lower baseline serum uric acid levels will be associated with faster cognitive decline in at least one cognitive domain among participants with baseline cognitive assessment at visit 2.
3. The associations will not differ by race.
4. Lower levels of serum uric acid will be associated with cognitive decline in men, but not with women.

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).

We intend to include all ARIC study participants who attended visit 2, excluding on:
- Refused consent to use data for genetic research
- History of coronary artery disease, heart failure, or stroke
- Prevalent dementia (based on incident dementia between baseline and visit 2)
- Individuals with an eGFR of less than 15 mL/min/1.73m2 (indicating severe kidney disease).

Variables
We will obtain the following variables for analysis, taken at visit 2:
- Age at baseline
- Sex
- Race-center
- Education
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Antihypertensive/diuretic medication
- estimated globular filtration rate (eGFR)
- Total Cholesterol
- HDL Cholesterol
- Diabetes mellitus
- Ever Smoked
- BMI
- WHR
- APOE e4 genotype
- Western and Prudent diet scores
- Serum Uric Acid level
- Serum Uric Acid level, in quartiles
- High sensitivity C-reactive protein as a marker of inflammation

Outcomes:
- Cognitive test scores measured between visit 2 and 6 (individual test z-scores from the DWRT, DSST, and WRT and global factor scores through V6)
Incident dementia and hospitalization through 2016 in individuals who attended visit 2 (defined by level 3 diagnosis of dementia by the ARIC-NCS committee)

**Statistical Analysis:**
We will study the association between serum uric acid and incident dementia (as defined by level 3 diagnosis) using Cox proportional hazards models, while using generalized estimating equations to study the association between serum uric acid and differences in cognitive function between visits 2 and 5.

Below, we provide a summary of the tables to be included in the manuscript:

Table I: Baseline Characteristics of study population

Table II: Hazard ratios (cox proportional hazards model) of dementia hospitalization by serum uric acid quartiles.
   Model 1: Cox proportional hazards model adjusted for age, gender, education, and race-center.
   Model 2: Cox proportional hazards model adjusted for age, gender, race-center, education level (six categories), ever smoking (dichotomous), systolic blood pressure (continuous), diastolic blood pressure (continuous), waist to hip ratio (continuous), total and HDL cholesterol (both continuous), diabetes mellitus (dichotomous), APOE e4 genotype (dichotomous), eGFR (continuous), antihypertensive diuretic use (3 levels), and C-reactive protein (continuous).

Table III: For each cognitive test: Differences in cognitive function by serum uric acid quartiles.
   Model 1: GEE model adjusted for age, gender, and race-center, time, and interactions of covariates with time.
   Model 2: GEE model adjusted for age, gender, race-center, education level (three categories), ever smoking (dichotomous), systolic blood pressure (continuous), waist to hip ratio (continuous), total and HDL cholesterol (both continuous), diabetes mellitus (dichotomous), APOE e4 genotype (dichotomous), eGFR (continuous), antihypertensive diuretic use (3 levels), C-reactive protein (continuous), time, and interactions of covariates with time.

We will conduct sensitivity analyses to evaluate the impact of losses to follow-up on the estimates of cognitive change.

For each table, we will stratify on race-center, gender, and eGFR (dichotomous) to assess effect modification.

**Limitations:**
This study will not differentiate between the types of dementia. We also may not be able to adjust for informative censoring due to losses to follow-up.

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?  __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

10. 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)?

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-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 be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csec.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: