ARIC Manuscript Proposal #2733

PC Reviewed: 4/12/16     Status: A     Priority: 2
SC Reviewed: _________     Status: _____     Priority: ____

1.a. Full Title: Serum Uric Acid, Cognitive Decline and Dementia: Mendelian Randomization Analysis in The Atherosclerotic Risk In Communities Study

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

2. Writing Group:
   Writing group members: Yasuhiko Kubota, Josef Coresh, Anna Köttgen, B. Gwen Windham, Faye Norby, Weihong Tang, Alvaro Alonso

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

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3. Timeline:
Data analysis: 1-2 months from manuscript approval date.
First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:
   Serum uric acid (SUA) is associated with cognitive impairment and dementia (1-5). The direction of this association, however, remains controversial. Some studies have suggested an inverse association between SUA concentrations and cognitive impairment or dementia risk (1-3), while others have reported the opposite association (4, 5).
Three reasons could explain these conflicting results (6). First, many previous studies were not prospective but mainly case-control, which complicate the assessment of temporality. SUA concentrations may change over time according to cognitive decline as a consequence of changes in nutritional status and physical activity level. Second, SUA and cognitive outcomes could be confounded by several other related factors such as diet and medication. Previous studies might not have controlled adequately for these potential confounders. Lastly, some studies failed to differentiate vascular dementia and other dementia subtypes. SUA has a pro-inflammatory effect on vascular cells (7-9), leading to the progression of atherosclerosis. In fact, higher SUA concentrations have been associated with increased stroke risk. Through this mechanism, elevated SUA may increase the risk of vascular dementia. On the other hand, as SUA also has strong hydrophilic antioxidant properties, potential neuroprotective properties have been suggested that could be important in neurodegenerative diseases, such as Alzheimer disease dementia or dementias related to Parkinson disease (10). These potential competing effects of SUA on the risk of dementia might have made the association less clear.

In order to address these methodological problems, we sought to prospectively investigate the association of SUA with cognitive decline and dementia using a Mendelian randomization approach.

5. **Main Study Questions:**
Is there a causal association of SUA with cognitive function and dementia risk?

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).**

   **Design**
   Prospective cohort study with visit 2 as baseline

   **Inclusion/exclusion criteria**
   Inclusion criteria: all ARIC study participants who attended visit 2

   Exclusion criteria: -History of cardiovascular disease and dementia at visit 2  
   -Race other than black or white, and blacks in Minneapolis or Washington County centers  
   -Individuals with missing data on SUA, covariates, and cognitive test scores at visit 2  
   -For the genetic analysis, we will exclude participants who did not consent to use of their genetic data, were missing genetic data, and those of non-European ancestry

   **Main exposure:** SUA concentrations
Mean value of SUA at visit 1 and 2 if serum uric acid at visit 1 is available (otherwise, value of SUA at visit 2 only).

Covariates
Age, sex, race/ARIC field center, education, body mass index, waist hip ratio, systolic blood pressure, hypertension medication use, total cholesterol, HDL cholesterol, diabetes mellitus, estimated GFR, smoking status, pack-year of smoking, alcohol drinking and amount, physical activity, APOE e4 genotype, diuretic use, probenecid and allopurinol.

Instrumental variable
So far genome-wide association studies (GWASs) have identified 33 SNPs (11). We will create a genetic urate score (weighted) using these 33 SNPs.

Endpoints
1. Cognitive function change between 2 visits of visit 2, 4 or 5. Cognitive function tests are as follows:
   i. Delayed word recall test (DWRT)
   ii. Digit symbol substitution test (DSST)
   iii. Word Fluency Test (WFT)
   iv. Composite score derived from the DWRT, DSST, and WFT (“Global-Z”)

   We will perform analyses using z-scores that were generated by the ARIC coordinating center for each cognitive test (at visits 2, 4, and 5), standardized using the visit 2 mean and standard deviation. We will also perform analyses using a global Z-score, which is calculated as an average of the test z-scores and then standardized using the visit 2 global z mean and standard deviation.

2. Dementia
Dementia identified from visit 5 adjudication, informant interviews, hospital discharge diagnosis, and death certificates.

   In a subanalysis, we will examine the association between baseline SUA concentrations and dementia subtypes (nonvascular or vascular dementia) only among participants whose information on cognitive diagnosis was available at visit 5 (about 6,500 individuals).

Statistical analysis
Part I: Association of SUA level with cognitive decline and dementia

   We will use linear mixed models to estimate the relationship between SUA and cognitive decline. The models will be adjusted for baseline covariates, and will include interaction terms between time x SUA and time x covariates.

   Hazard ratios and their 95% confidence intervals for dementia will be calculated using Cox proportional hazard models in relation to SUA concentration with adjustment for covariates. Restricted cubic splines also will be created to study the shape of the SUA relation and used to determine the best approach to model SUA concentrations (continuous, categories, etc.).
For the subanalysis including dementia etiologic subtypes from visit 5 (Alzheimer-type, vascular), we will use multinomial logistic regression adjusting for attrition with inverse probability weighting or multiple imputation with chained equations (MICE, 12).

Part II: Association of a genetic risk score with SUA level
We will assess the association between a weighted genetic risk score and baseline SUA level using linear regression models with adjustment for covariates (age, sex).

Part III: Association of a genetic risk score with cognitive decline and dementia
We will use linear mixed models to estimate the relationship between a genetic risk score and cognitive decline. The models will be adjusted for covariates.

Hazard ratios and their 95% confidence intervals for dementia will be calculated using Cox proportional hazard models in relation to a genetic risk score with adjustment for covariates.

Part IV: Instrumental variable analyses
We will calculate instrumental variable estimates of genetically determined odds ratios by using the Wald-type estimator, which involves taking the ratio of the cognitive decline or dementia allele score log odds ratio to the exposure allele score coefficient and then exponentiating to express it as an odds ratio (13).

We anticipate that participants with cognitive decline are more likely not to return. Thus, we plan to account for this by using MICE methods.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ___ 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

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)?

Multiple ARIC papers on individual outcomes. For example:

#2104r: Association of serum uric acid and cognitive function and dementia: the ARIC study (Buhr)
#2120C: Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC
#2503: Menopause aging genes, cognition and frailty: The Atherosclerosis Risk in Communities Study
#2628: The Relationship of Central Adiposity and Cognitive Decline: The Atherosclerosis Neurocognitive Study
#2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study

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)

___ 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.
13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References: