1.a. Full Title: Uric Acid and the Risk of Kidney Function Decline in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Uric Acid and Kidney Function Decline

2. Writing Group: Judit Gordon, MD; Michelle M. Estrella, MD, MHS; Anna Kottgen, MD; Brad C. Astor, PhD, MHS; and Bernard G. Jaar, MD, MPH, and others are welcome to participate.

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

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3. Timeline:
After manuscript approval, plan for first draft August 2010
If approved, would like to present Abstract at ASN November 2010

4. Rationale:
Hyperuricemia is highly prevalent in patients with chronic kidney disease (CKD), but it is unclear whether hyperuricemia contributes to the development of CKD or is merely a consequence of CKD. Hyperuricemia is independently associated with cardiovascular disease (CVD), which shares pathogenic mechanisms with CKD. Studies with a clear independent association between hyperuricemia and incident kidney disease,
however, are lacking. Shah and colleagues recently reviewed multiple large trials that consistently showed an association between elevated uric acid levels and varying forms of cardiovascular disease (1). There is also emerging evidence that hyperuricemia is associated with metabolic syndrome and insulin resistance (2). Among 28,745 Chinese patients undergoing a general health examination, hyperuricemia was weakly associated with CKD and strongly associated with metabolic syndrome (3). The strong correlation that exists between uric acid and renal disease risk factors and comorbidities such as cardiovascular disease, insulin resistance, and obesity seen in epidemiological studies, render clearly identifying a causal relationship between hyperuricemia and CKD challenging (1,4,5).

Although there is emerging evidence suggesting an association between hyperuricemia and renal disease, the data have yielded conflicting results. The conflicting results likely stem from the differing study populations and study designs. In a community-based Taiwanese medical screening program of 31,331 adults over age 40, eGFR negatively correlated with serum uric acid levels, but only in patients with CKD Stage 3. (6). In 840 participants in the Modification of Diet in Renal Disease (MDRD) Study with stages 3 to 4 CKD, hyperuricemia was not an independent risk factor for kidney failure, but was for all-cause and CVD mortality (5). In contrast, in a Southeast Asian study of 5546 participants, hyperuricemia was independently associated with incident CKD (7). In a study of participants in a mass screening of 48,177 Japanese individuals, higher levels of serum acid in both men and women were associated with increased risk of end stage renal disease (8). In a study of 307 renal transplant patients at an American University Transplant center, hyperuricemia at 6 months was associated with higher incidence of new cardiovascular events and chronic allograft nephropathy at a mean follow-up of 4 years (9). A study comprised of a more racially diverse population and with observations prior to the onset of CKD will help elucidate the relationship between hyperuricemia and incident CKD.

We propose a longitudinal analysis among participants without CKD at baseline in ARIC to examine whether hyperuricemia is associated with development of incident CKD and end-stage renal disease (ESRD) independent of established risk factors for kidney disease.

5. **Main Hypothesis/Study Questions:**
To determine whether hyperuricemia is independently associated with incident CKD and ESRD among participants in ARIC.

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).**

The study population will include all ARIC Study participants (n = 15026, after exclusions) who do not meet the following exclusion criteria (all at Visit 1):
1. Prevalent CKD (defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m², n = 457)
2. Missing serum creatinine (n = 150)
3. Missing values for diabetes or hypertension (n = 118)
4. Missing lipid profile (n = 69)
5. Race other than African American or White (n = 47)

Outcome assessment:
Incident CKD will be defined as an eGFR <60 ml/min/ 1.73 m² at Visit 2 or Visit 4, or death or hospitalization with CKD based on ICD9 codes. A sensitivity analysis in which incident CKD will be defined as an increase in serum creatinine of 0.4 mg/dl or greater will also be performed.

ESRD cases will be assessed by surveillance of hospital records coding for dialysis related events or record for transplantation.

Other Measurements:
Prevalent diabetes will be defined as fasting glucose level > 126 mg/dL or non-fasting glucose level > 200 mg/dL or a history of diabetes treatment.
Prevalent hypertension will be defined by the mean of the last two of three measurements taken during clinic visits or use of antihypertensive medications.
Prevalent myocardial infarction (MI) will be defined as the presence of electrocardiogram changes consistent with a previous MI seen at visits or self-reported physician diagnosis.
Prevalent hypercholesterolemia will be defined by fasting lipid measurements, and calculated LDL (those with triglycerides > 400 mg/dL will be assigned a mean LDL value).
Smoking and alcohol use history will be assessed by participant self-report of tobacco or alcohol use, respectively.

Study Design:
The distributions of serum uric acid levels and levels of relevant covariates will be examined. Variables with skewed distributions will be log-transformed as necessary. Serum uric acid levels and covariates will be compared by outcome status using t-tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables, as appropriate. Serum uric acid will be categorized into sex-specific quartiles for analysis. We will compare demographic and health characteristics of CKD and ESRD cases with noncases using chi-square and t tests.

Survival analyses will be performed to determine time to CKD or ESRD from the date of enrollment through December 31, 2007. Kaplan-Meier survival estimates will be calculated for each serum uric acid quartile and compared by log-rank tests. Proportional hazards regression will be used to estimate adjusted and unadjusted hazard ratios and 95% confidence intervals (CI). The multivariate adjusted models will include age, sex, systolic and diastolic blood pressure, diabetes status, hypertension medication use, prevalent MI, smoking, alcohol use, HLD, LDL, and estimated GFR.

Limitations:
Albuminuria was only included in visit 4. Therefore, we cannot exclude participants that have Stage 1 or 2 CKD (based on albuminuria) at Visit 1. Use of ICD9 codes to determine CKD at the time of death or hospitalization may lead to misclassifications. Sensitivity analyses will be utilized to assess whether the observed associations differ by incident CKD definitions.

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 ___X__ 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? ____ 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”? N/A

____ 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)?
#1344 - Correlates of Gout and Its Association with Kidney Function: the Atherosclerosis Risk in Communities Study
#759 - Serum uric acid and risk of stroke: the ARIC study; published
#1077r - Uric Acid and Hypertension; published
#1229 - Uric Acid & Metabolic Syndrome
#1311 - Serum uric acid, lung function and chronic obstructive pulmonary disease in adults
#525 - Elevated uric acid as a risk factor for coronary heart disease: the ARIC study; published
#313 - Association between serum uric acid and asymptomatic carotid atherosclerosis: the ARIC study; published
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____X No

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

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


