1.a. Full Title: Correlates of Gout and Its Association with Kidney Function: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): gout and kidney function

2. Writing Group:
   Writing group members: Anna Kottgen, Brad Astor, Alain Bertoni, Michael Flessner, Aaron Folsom, Caroline Fox, Josef Coresh

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

First author: Anna Kottgen, MD, MPH
Address: Welch Center for Prevention, Epidemiology & Clinical Research
2024 E Monument St, Suite 2-600
Baltimore, MD 21287
Phone: (410) 245 6897  Fax: (410) 955 0476
E-mail: akottgen@jhsph.edu

Corresponding/senior author (must be an ARIC investigator for the proposal but can be different in the published paper; correspondence will be sent to both the first author & the corresponding author): Josef Coresh, MD, PhD
Address: as above
Phone: (410) 955 0495  Fax: (410) 955 0476
E-mail: coresh@jhu.edu

3. Timeline: Data analysis to start after approval of the manuscript proposal, first draft available by September 2008

4. Rationale:
   The prevalence of gout over the last decade is increasing especially among elderly individuals,¹ and gouty arthritis accounts for about approximately 4 million outpatient
visits per year. It is therefore important to characterize risk factors for gout among middle-aged and elderly individuals in the general population. Serum uric acid levels are positively related with incident gout, and hyperuricemia can trigger gout attacks in susceptible individuals. Approximately 20-60% of patients with gout also have mild or moderate renal dysfunction, and chronic kidney disease (CKD) was associated with gout in the UK GPRD Study and in the Health Professionals Follow-up Study. The higher prevalence of gout in individuals with CKD could be explained by hyperuricemia as a consequence of reduced renal function and subsequent development of gout. CKD, and especially stage III CKD (estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73m²) is a highly prevalent condition in middle-aged and elderly US individuals. Alternatively, the high prevalence of CKD in individuals with gout could be due to the association of both conditions with common risk factors, specifically the metabolic syndrome. It is therefore of interest to 1) explore risk factors for gout, and specifically the association of kidney function and gout, in a US population-based study sample, and 2) to examine the role of serum uric acid levels in this association. Prior studies can be extended investigating risk factors for gout, and especially the relationship of kidney function and gout among both men and women, in African American as well as Caucasian study participants.

5. Main Hypothesis/Study Questions:

Primary study questions:
1. What are the correlates of gout in this biracial, population-based study sample?
2. Is there an association of eGFR at baseline and gout?
3. Can such an association be explained by hyperuricemia, and does adjustment for uric acid levels at visit 1 abolish any putative association?

Secondary study question:
4. Is there an association of the metabolic syndrome at baseline and gout?
5. How do correlates of gout differ among black and white ARIC participants, and can these differences account for the race-differences observed in gout prevalence?

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:
1. Gout at visit 4 will be examined cross-sectionally as a function of independent variables at visit 4 (estimated GFR, age, sex, race, hypertension, body mass index, thiazide diuretics)
2. Gout at visit 4 will be examined as a function of eGFR and other independent variables at study visit 1
**Inclusions/Exclusion:** Individuals missing eGFR or uric acid (visit 4 for cross-sectional analyses and visit 1 for prospective analyses) will be excluded, as will be those reporting race other than “black” or “white”. In secondary analyses, individuals reporting the intake of medications that influence serum uric acid levels (such as thiazides, allopurinol, and uricosuric medications) will be excluded.

**Outcome:** The primary outcome is reporting ever having been told you have gout at visit 4 (n=703 cases; 483 white and 220 black individuals). Additionally, gout will be evaluated by combining the cases detected on the questionnaire at ARIC visit 4 and cases detected by having had a hospitalization with a gout code (ICD 9 codes 274, 274.8, 274.9). We hypothesize the questionnaire will have relatively high sensitivity and relatively low specificity while the hospitalizations will have very high specificity and relatively low sensitivity. The combined definition should therefore increase sensitivity for cases who may have died or were lost to follow-up before visit 4, a potentially important group for the prospective analyses. Agreement between the two methods of case detection will be calculated and compared to literature on this topic.7, 8 For the prospective analyses, follow-up will be ended at visit 4 since the sensitivity of hospitalization data is low compared to the questionnaire.

**Other variables of interest:** Visit 1, 2, and 4 age, gender, study center, systolic and diastolic blood pressure, antihypertensive medication incl. use of thiazide diuretics, diabetes mellitus, smoking, triglycerides, HDL cholesterol, BMI, waist circumference, alcohol intake, insulin levels, serum creatinine, eGFR, and visit 4 albuminuria.

**Data analysis:**

**Primary analyses:** Cross-sectionally, the distribution of characteristics in the study population by outcome (gout status) as well as by categorical eGFR at visits 1 and 4 (≥90, 60-89, <60 ml/min/1.73m²) will be computed using t-tests, chi-square tests and ANOVA as applicable. Logistic regression will be used to examine the association of covariates with gout, specifically eGFR, age, sex, race, BMI, waist circumference, hypertension treatment, systolic blood pressure, and alcohol consumption, as well as further covariates found to be significantly associated with both eGFR and gout in the exploratory analyses. Multivariable-adjusted regression models will be evaluated before and after including uric acid levels at baseline into the model. We will test for interactions with sex and race since both are important risk factors.

Prospective analyses will be conducted using a logistic regression of gout (present vs. absent) among visit 4 participants who were free of gout at visit 1 (by self report at visit 4 as well as in response to the question of age of gout onset). Risk factors will be those measured at baseline (visit 1 estimated GFR, age, sex, race, BMI, waist and other metabolic syndrome components, hypertension treatment, and alcohol consumption). Estimated GFR will be calculated using the 4-variable MDRD Study equation9 and modeled as in previous work in ARIC examining the association of eGFR and heart failure10 (categorical as well as continuously with linear splines). Reported age of gout onset (available in visit attendees only) will then be examined as an adjustment variable as well as used as a stratification variable for early vs. late onset (divided at the median reported age of onset. The hospitalization data will be used to check (a) how many of the individuals who came to the visit and had a previous gout hospitalization did not report having gout, and (b) how many individuals who did not attend visit 4 had a gout...
hospitalization. We expect (a) to be small while being less certain about (b), the reason for evaluating a combination of self-report and hospitalization as an alternative outcome.

**Secondary analyses:** In sensitivity analyses, the different definitions of the outcome will be evaluated in order to investigate how associations vary by using self-report of gout only vs. self-report as well as hospitalizations. Differences between results should provide insight into how the different sensitivities of self-report and hospitalizations influence the observed association with risk factors. In secondary analyses, the effect of antihypertensive and uricosuric medications will be examined by first stratifying on medication intake, and then excluding individuals reporting medication intake from analyses. Further, reported age at the first time cases were told they had gout will be examined as a function of covariates.

**Limitations:** Cross-sectional design, gout only available at ARIC visit 4. Diagnostic suspicion bias, as individuals with CKD may be more likely to be tested for elevated uric acid levels.

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 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”?
   ____ 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](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)?
   1.  #759 - Serum uric acid and risk of stroke: the ARIC study; published
   2.  #1077r - Uric Acid and Hypertension; published
   3.  #1229 - Uric Acid & Metabolic Syndrome
4. #1311 - Serum uric acid, lung function and chronic obstructive pulmonary disease in adults
5. #525 1. Elevated uric acid as a risk factor for coronary heart disease: the ARIC study; published
6. #313 1. 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?  
   ___ X__ Yes  ____ No

11.b. If yes, is the proposal
   ___   A. primarily the result of an ancillary study (list number* __________)
   X__   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* albuminuria, AS#_2002.02_)

*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.
References


