1.a. Full Title: Hyperuricemia, gout and cardiovascular outcomes

b. Abbreviated Title (Length 26 characters): HU, gout and CVD

2. Writing Group:
   Writing group members: Sara B. Seidelmann, Brian Claggett, Joe Coresh, Adrienne Tin, Scott D. Solomon, Daniel H. Solomon others welcome

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing the analysis and associated manuscript(s) within 1 year of data availability.

4. Rationale:
The ARIC cohort has collected relevant information on gout since its inception. Urate was measured in serum at Visits 1, 2, 4 and 5. At Visits 1, 2 and 4, the uricase method was used and standardized across all labs and all visits. At Visit 5, urate was measured using the enzymatic colorimetric method, as this is a more accurate measure for persons of older age; to ensure comparability of urate measures across all visits, urate levels were re-calibrated to Visit 5 based on re-running 200 frozen samples from each visit. Re-calibrated values will be used for all analyses in this research proposal.

We would like to pursue analyses examining differences in CV risk between ARIC participants with known hyperuricemia (≥6.8mg/dl), HU, with or without gout. Most people with HU do not develop gout and it is not understood why. But, we believe that risk factors for developing gout may be similar to risk factors for developing cardiovascular disease, CVD, events. These risk factors may relate to the sensitivity of innate immune cells for crystals, such as cholesterol and monosodium urate. People with high sensitivity for crystals may be more likely to develop gout and CVD events.

Thus, we would like to study persons with HU in ARIC to see whether the subset with gout are at an increased risk for CVD events.

5. **Main Hypothesis/Study Questions:**

Among the ARIC cohort with HU, gout will increase the risk for CVD events.

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 will identify participants in ARIC with a serum urate ≥ 6.8mg/dl. The value of 6.8mg/dl represents the phase change in vitro when urate comes out of solution and crystallizes. While there is inter-individual variation in the value for serum urate crystallization, ≥6.8mg/dl is used by most clinical laboratories as the solubility threshold for HU. The exposure of interest is prevalent or incident gout. In ARIC, participants are considered to have gout if they responded affirmatively to the query: “Has a doctor ever told you that you had gout?” administered at ARIC Visits 4. The age of gout onset is derived from the subsequent question: “How old were you when you were first told that you had gout?” Previous research indicates that self-report of a physician diagnosis of gout is both a reliable (3-year reliability kappa of 0.73) and sensitive (sensitivity of 84%) measure of gout.

Visit 4 will serve as baseline. Subjects with a serum urate ≥ 6.8mg/dl and/or on uric acid lowering medications prior to or at V4 will be classified as HU. Thus, the ARIC population with HU will form the eligible cohort who will be followed forward in time from V4. They will be censored at the first of any of the following: report of incident CVD event (outcome), death, loss to follow-up, or end of follow-up.
CVD events of interest include death, heart failure, myocardial infarction, ischemic stroke and atrial fibrillation. These have all been defined using standard methods and have been adjudicated within ARIC.

Covariates will include clinical, demographic, and anthropometric risk factors for CVD. These include age, sex, race, baseline and change in BMI, history of diabetes, history of CKD, baseline and change in serum creatinine, use of statins, use of beta-blockers, use of low-dose aspirin, use of anti-diabetic drugs, hyperlipidemia, and tobacco use.

We will first describe the baseline characteristics of the ARIC cohort with HU with and without prevalent gout. The rates of CVD events during follow-up will be described. The relationship between history of gout and CVD events will be described using Cox proportional hazards regression models. Initial models will only include age and gender. Then, all known CVD risk factors will be added. Finally, other variables will be tested and left in the model if p-values < 0.1.

Secondary analysis will include a more detailed, time varying approach to address our hypothesis. The ARIC population with HU will form the eligible cohort who will be followed forward in time from their first visit with HU (index date). Baseline for those with gout will be defined as the ARIC visit closest to their self-reported diagnosis of gout. If gout had been diagnosed prior to the start of ARIC, then V1 will be chose as baseline. The rates of CVD events during follow-up will be described. The relationship between the prevalent (prior to Visit 1) and incident gout (subsequent to V1) and CVD events will be described using Cox proportional hazards regression models.

Limitations of these analyses include:
- Immortal time bias: participants need to survive long enough to report on gout at visit 4
- Inaccurate gout diagnosis (misclassification bias)
- Residual confounding from unmeasured and poorly measured covariates

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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?  ____ 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”?  ____ 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.csc.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* _2017.21___)

___     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.csc.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.csc.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, approved manuscripts using 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 _x___ No.