ARIC Manuscript Proposal #2189

PC Reviewed: 8/13/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Gout in older adults: Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Gout in older adults

2. Writing Group:

Writing group members: Bridget Burke, Andrew Law, Alan Baer, Josef Coresh, and Mara McAdams DeMarco. Others are welcome

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

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3. Timeline: Data analysis to start after approval of this manuscript proposal, first draft available by October, 2013

4. Rationale: Gout is the most common form of inflammatory arthritis and disproportionately affects adults over the age of 65 (1). There are an estimated 4.7 million older adults with gout in the US (2) and the prevalence is growing faster (1, 3) for older than younger adults (4).

There is increasing awareness that the risk factors, clinical presentation, and progression of gout differs for older adults (5). The sex-differences in the prevalence of gout that are observed in younger adults are less evident as the incidence in women rises with age. Additionally, the clinical presentation differs for older adults. Only 50% of older adults with incident gout experience an acute monoarticular attack in a lower limb joint as compared to 80-90% of younger adults (5). Furthermore, the progression of gout is quicker in older adults; older adults with gout may be at risk of developing early tophaceous gout without a history of prior acute arthritis (7).

To address the growing public health burden and distinct clinical aspects of gout in older adults, epidemiology studies must address important knowledge gaps in this field. These knowledge gaps include: 1) the incidence of gout in subgroups of older adults (women and African Americans) and 2) the ability of traditional and novel risk factors to predict gout incidence in older adults.

Prospective gout studies may not be generalizable to older adults because they only included white males and health care professionals of all ages (8-11) or were limited in geographic and racial diversity (12). Prospective population-based cohorts of older adults, of diverse demographic compositions like the Atherosclerosis Risk In Communities are needed to address the knowledge gaps.

5. Main Hypothesis/Study Questions:

Aim 1: To quantify the incidence and prevalence of gout among older adults by sex, race, and socioeconomic status (SES). ***Hypothesis***: The age-related increase in gout incidence and prevalence differ for women and African-Americans.

Aim 2: To identify risk factors in middle and older age that predict gout onset in older age. ***Hypothesis****:* Traditional and novel risk factors are predictive of incident gout in older adults.

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).

Population: For this study, we will restrict our analyses to those participants who self-report gout status at visit 4, or AFU. Additionally, we will limit the population to those who were white or African American, and were not missing any baseline or V4 predictors of gout.

Study design: Longitudinal cohort

Exposure: We will identify which clinical risk factors are associated with incidence of gout in older adults. We will consider baseline (1989) age, sex, race, blood pressure, alcohol intake (grams/week), diabetes, CHD, CHF, diuretic use, dietary factors, socioeconomic status, income, cigarette smoking, and body mass index as potential risk factors. Additionally, we will use serum creatinine, measured using a modified kinetic

Jaffé reaction, to calculate the estimated glomerular filtration rate (GFR) by using the CKD-Epi equation. Potentially, we will use eGFR in categories such as less than 60 mg/dL, 60-90 mg/dL, and greater than 90 mg/dL. In women, menopausal status (self-reported for women as pre-, peri-, or post-menopausal), and hormone replacement therapy (ever vs. never) will also be considered as potential predictors. We will consider these risk factors at baseline to represent middle-age risk factors and those at visit 4 to be older age risk factors.

Urate levels will also be considered a risk factor. Serum urate concentrations were measured with the uricase method at visits 1, 2, and will be measured at visit 5 in mg/dL. Plasma urate was measured at visit 4.

Additionally, we will consider novel risk factors including inflammation, and novel kidney markers such as cystatin C**,** beta-trace protein, BNP, troponin, and beta-2 microglobulin.

Outcome: At ARIC visits 4 and the most recent annual follow-up, participants are asked, "Has a doctor **ever** told you that you had gout?" Participants who answered, "Yes," to the gout query then reported the age of gout diagnosis.

All participants who respond affirmatively to the self-report of gout will be considered prevalent gout cases. If a participant self-reported gout onset after the age of 64, then they will be defined as having incident gout in older age.

Data analysis Aim 1:

First, we will establish the prevalence of physician-diagnosed gout at age 65, 70, 75, 80 and 85. We will then calculate the incidence rate of physician-diagnosed gout for adults aged ≥65 (in person-years) and use Poisson Regression and/or Negative Binomial Regression to compare the incidence rates of gout in older adults by sex, and race, after adjusting for potential confounders. All models will be selected based on AIC model fit.

We will conduct sensitivity analyses to better understand the prevalence and incidence of gout based on alternative gout definitions (gout with hyperuricemia, treated gout, and hospitalized gout). We will additionally define gout as 1) the self-report of a physician-diagnosis of gout with a history of hyperuricemia (serum/plasma urate>7.0 mg/dL), 2) the self-report of a physician-diagnosis of gout with the use of a gout medication (colchicine, probenicid, allopurinol, or febuxostat), or 3) the self-report of a physician-diagnosis of gout with hospital discharge summary containing an ICD-9 code (274.0, 274.1, 274.8, or 274.9) for gout. Finally, we will define gout as the meeting of any of the three definitions. Then, we will estimate the prevalence and incidence of gout based on each definition.

Data analysis Aim 2:

We will use survival analysis to identify traditional and novel risk factors of incident gout after the age of 65. We will use age as the time scale and discrete ties.

We will explore the relationship of urate levels (in middle age and older adulthood) as potential risk factors for incident gout. Furthermore, we will explore the role of changes in urate level (over 3 years and 9 years during middle age) in predicting incident gout in older adults.

We will adjust for baseline traditional risk factors to represent risk factors during middle age. Then in a separate model, we will adjust for visit 4 characteristics to represent risk factors during older age. Finally, we will adjust for time-varying characteristics to represent the change in risk factors associated with aging. Additionally, we will explore sex and race as potential effect modifiers. We will use AIC/BIC (maximum likelihood) based model selection to determine the best fitting model. We will repeat this process for novel risk factors.

Limitations: The main limitation of this study is that gout is self-reported. Therefore, we will explore various definitions of gout using drug and discharge data.

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"?
____ 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)?

2162: Trajectories in uric acid levels over 25 years
1473: Prevalence and risk factors for gout in women.
1876: Risk factors for hyperuricemia

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* 2012.27**)**

___ 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.