ARIC Manuscript Proposal #1876

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. **Full Title**: Predictors of incident hyperuricemia in the Atherosclerosis Risk in the Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Hyperuricemia risk factors

2. **Writing Group**:

Writing group members: Mara McAdams DeMarco, Janet Maynard, Alan Baer, and Josef Coresh. 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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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. **Timeline**: Data analysis to start after approval of this manuscript proposal, first draft available by January 2012

4. **Rationale**:

The prevalence of gout is increasing in the United States; in 2005, the estimated prevalence in the US was 3 million cases, which has increased from 2.1 million in 1995 (Lawrence, 2008). Hyperuricemia is a necessary but not sufficient cause of gout. One study has identified predictors of incident hyperuricemia in Japanese men (Nakanishi, 2001). No studies, to date, have identified risk factors for incident hyperuricemia in domestic subgroups such as women and African-Americans. Serum urate levels are also associated with incident CVD mortality independent of kidney function (Neri, 2011). Although, previous research has identified serum urate as influential on the development of chronic conditions such as hypertension, it is unclear how these chronic conditions impact the onset of hyperuricemia in older patients who are free of hyperuricemia.

We strive to fill the knowledge gap in this investigative area using the existing and valuable research infrastructure of a long-term prospective cohort: Atherosclerosis Risk in the Communities Study (ARIC). We will test our hypotheses with the following specific aims:

Specific Aim 1: **Estimate the incidence of hyperuricemia in ARIC over 3 years and 9 years.**
Specific Aim 2: **Identify risk factors for incident hyperuricemia 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).

Population: For this study, we will restrict our analyses to those participants who were not hyperuricemic at visit 1. Additionally, we will limit the population to those who were white or African American, and were not missing any covariates. Finally, we will exclude those who are taking a urate lowering medication at baseline.
Study design: Prospective cohort design with the outcome (incident gout) ascertained at visit 2 and 4. Both aims will utilize the longitudinal cohort aspect of this data for the development of gout.

Data analysis:

Exposure: We will identify which clinical risk factors are associated with incident gout over 3-years and over 9-years. We will consider baseline (1989) age, sex, race, blood pressure, alcohol intake (grams/week), diabetes 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 (Levey, 2009). Potentially, we will use eGFR in categories such as less than 60 mg/dL, 60-90 mg/dL, and greater than 90 mg/dL. Furthermore, we will examine the relationship of disease markers such as triglycerides, total cholesterol, measured blood pressure, hemoglobin A1c, white blood cell count, blood urea nitrogen and hemoglobin levels.

Outcome: The outcome of interest is incident hyperuricemia at visit 2 and visit 4. We will consider hyperuricemia to be a measured serum urate level ≥7 mg/dL. Patients who initiate a serum urate lowering drug after baseline will be considered to have hyperuricemia.

Analysis: We will estimate the cumulative incidence of hyperuricemia over 3-years and over 9-years. Furthermore, we will estimate the incidence of hyperuricemia by sex and race.

Next, we will compare the mean and prevalence of the covariates by incidence of hyperuricemia. The mean of continuous variables in those with incident hyperurcemia will be compared to the mean of those hyperuricemia using a *t*-test and the prevalence of categorical factors by chi-squared tests.

Using a Cox Proportional Hazards model, we will estimate the hazard rate ratio (HR) of incident hyperuricemia by clinical risk factors. We will use age as the time-scale. Patients who develop hyperuricemia by visit 2 will not contribute person-time after this visit. All participants without hyperuricemia will contribute person-time until there last visit. We will test for interactions with sex and race by clinical risk factors.

Limitations*:* Participants had serum urate level measured only at visits 1, 2 and 4.

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.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)?

The majority of proposals that propose to study serum urate levels focus on serum urate as a risk factor for other chronic conditions. There are no proposals to study clinical risk factors for hyperuricemia. The most similar proposals are listed below.
1364: Sweetened beverage consumption and development of chronic kidney disease, hyperuricemia and albuminuria.
1473: Prevalence and risk factors for gout in women.

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* 2009.09 __)

__ 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.