ARIC Manuscript Proposal #1747

PC Reviewed: 2/8/11 Status: A Priority: 2

SC Reviewed: _____ Status: _____ Priority: ____

1.a. **Full Title**: Anemia and the risk of gout in the Atherosclerosis Risk in the Communities Study (ARIC)

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

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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3. **Timeline**: Data analysis to start after approval of this manuscript proposal, first draft available by March, 2011

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.[1] This growing disease burden warrants optimal understanding and quantification of gout risk factors. There are many well-recognized chronic conditions that are associated with gout: obesity, hypertension and chronic renal failure.[2] In clinical care, gout patients are often noted to be anemic. The relationship between anemia and gout may reflect the presence of other chronic medical conditions, or may reflect a novel risk factor for gout. No studies, to date, have tested the association of anemia and gout.

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 association of anemia with the development of incident gout.**
Specific Aim 2: **Test whether there is an interaction between anemia and serum urate, which increases the risk of developing gout.**

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 aims 1 and 2, we will restrict our analyses to those participants who self-reported gout at visit 4 and were free of gout before visit 1. Additionally, we will limit the population to those who were white or African American, and were not missing any covariates.

Study design: Prospective cohort design with the outcome (gout) ascertained at visit 4. Both aims will utilize the longitudinal cohort aspect of this data for the development of gout.

Data analysis:

Exposure: We will define anemia as baseline hemoglobin less than or equal to 12 g/dL in women and 13.5 g/dL in men, as has previously been defined in ARIC.[4] Serum urate concentrations were measured with the uricase method at visit 1 and 2. The reliability coefficient of serum urate was 0.91 and the coefficient of variation was 7.2% in a sample of 40 individuals with repeated measures taken at least a week apart.[5] Under aim 2, we will test for an interaction of baseline anemia and baseline serum urate.

Outcome: At ARIC visit 4, participants were 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. The outcome of interest is incident gout based on self-reported onset after visit 1. Our previous research suggests that self-report of a physician diagnosis of gout is a sensitive and reliable measure of gout.[6]

Potential confounders: We will consider baseline (1989) age, sex, race, blood pressure, alcohol intake (grams/week), diabetes and body mass index as potential confounders. 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.[7] Potentially, we will use eGFR in categories such as less than 60 mg/dL, 60-90 mg/dL, and greater than 90 mg/dL. Additionally, as a secondary analysis, we will limit the study population to those who have a baseline eGFR greater than or equal to 60 mg/dL by the CKD-EPI equation.

Analysis: First, we will compare the mean and prevalence of the covariates by baseline anemia status. The mean of continuous variables in those with baseline anemia will be compared to the mean of those without anemia 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 gout by anemia. We will use age as the time-scale. We will adjust for confounders of the association of anemia and gout including sex, race, BMI, ethanol, categorical estimated glomerular filtration rate, and hypertension. Next we will assess whether there is an interaction between baseline serum urate level and anemia on the risk of incident gout. We will add categorical visit 1 serum urate level to the adjusted Cox Proportional Hazard. We will use serum

urate <5 mg/dL as the comparator. We will stratify by anemia at baseline and test for an interaction with serum urate.

***Limitations**:* Gout was only ascertained at visit 4. Therefore, our sample size is limited to those participants who attended visit 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)?
There are no proposals to study anemia and gout.
#**952**: Anemia and kidney dysfunction as predictors of cardiovascular disease. We have defined anemia with the same definition as it appears in the published manuscript from this proposal.

#**863**: The risk of left ventricular hypertrophy associated with moderate kidney dysfunction and anemia among African Americans

#**954**: Electrocardiographic left ventricular growth associated with anemia and moderate kidney dysfunction

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)* 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.

Works cited:

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
2. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742-8.
3. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 2006;8 Suppl 1:S2.
4. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2006;151:492-500.
5. Eckfeldt JH, Chambless LE, Shen YL. Short-term, within-person variability in clinical chemistry test results. Experience from the Atherosclerosis Risk in Communities Study. Arch Pathol Lab Med 1994;118:496-500.
6. McAdams MA, Maynard JW, Baer AN, et al. Reliability and validity of the self-report of physician-diagnosed gout in the Campaign Against Cancer and Heart Disease (CLUE II) and Atherosclerosis Risk in the Community (ARIC) Cohorts. ePublished ahead of print in the Journal of Rheumatology 2010.

7. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.