

ARIC Manuscript Proposal #2341

PC Reviewed: 4/8/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

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

b. Abbreviated Title (Length 26 characters): Gout and physical function

2. Writing Group:

Writing group members: Bridget Burke, Andrew Law, Beverly Gwen Windham, 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]

First author: Mara McAdams DeMarco, PhD

Address: 2024 E. Monument St, Suite B-319, Baltimore, MD 21287

Phone: (410) 614-3822

Fax:

E-mail: mmcadams@jhsph.edu

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).

Name: **Josef Coresh, MD PhD**

Address: Welch Center for Prevention, Epidemiology & Clinical Research
2024 E. Monument St., Suite 2-600
Baltimore, MD 21287

Phone: (410) 245-0495

Fax:

E-mail: coresh@jhu.edu

3. Timeline: Data analysis to start after approval of this manuscript proposal, first draft available by June, 2014

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).

The clinical progression of gout contains 4 consecutive steps: asymptomatic hyperuricemia, acute attacks, intercritical period, and chronic tophaceous gout. Older adults with gout are at higher risk of developing early tophaceous gout without a prior history of acute arthritis than younger adults (5).

The consequences of gout for adults of all ages are vast and understudied for older adults. This inflammatory arthritis is characterized by severe joint pain, and leads to joint damage if untreated (6). Gout accounts for almost 4 million outpatient visits yearly (3, 7), and substantial economic burden (8-10) for patients of all ages. Patients with gout experience poor quality of life as well as physical and functional impairment that lead to decreased work productivity (1, 11-14). Case studies suggest that untreated gout leads to functional decline (15) and physical dysfunction among patients with gout often occurs in older age. Although the consequences of gout have only been studied in adults of all ages, the consequences of gout are thought to be worse in older age, yet there is a paucity of data to support this claim.

To address the growing public health burden and distinct clinical aspects of gout in older adults, we will examine physical function (short physical performance battery (SPPB) and grip strength) in older adults with gout. We will also test whether older adults with gout are more likely to have physical dysfunction compared to older adults without gout. SPPB will be a measure of lower extremity function and grip strength a measure of upper body function.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize physical function as measured by SPPB and grip strength in older adults with gout.

Aim 2: To test whether older adults with gout are more likely to have worse physical function as measured by SPPB and grip strength than older adults without 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 this study, we will restrict our analyses to those participants who self-report gout status at visit 4, or AFU and had a measure of SPPB and grip strength at visit 5.

Study design: Cross-sectional analysis.

Gout: 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.

Physical function: Lower extremity function is measured at Visit 5 using the Short Physical Performance Battery (SPPB), a performance-based assessment developed by Guralnik et al (16). The SPPB score consists of 3 measured batteries; 1) chair stand, 2) standing balance, and 3) gait speed and will be measured as was previously described (16). The SPPB score range from 0 to 12; a lower score is indicative of poor lower extremity dysfunction (16). We will empirically determine the threshold for lower extremity dysfunction as measured by poor performance on SPPB in this population-based cohort.

Grip Strength is measured at Visit 5. Grip strength will be ascertained in the participants' preferred or best hand using a dynamometer. We will consider any participant who is unable to complete the grip strength assessment as having low grip strength and will exclude participants with recent surgery on both hands. We will empirically determine the threshold for low grip strength.

Potential predictors: We will adjust for risk factors for gout and potential confounders (age, sex, race/cite and other confounders). We will consider adjusting for the following factors as potential confounders: hypertension (>140/90 mm Hg or use of an anti-hypertensive treatment), measured systolic and diastolic blood pressure, body mass index (BMI, kg/m²), beer intake (grams/week), liquor intake (grams/week), diuretic use, eGFR (estimated by using the CKD-Epi equation (17)), diabetes, coronary heart disease, congestive heart failure, anemia, smoking status, and dietary factors. 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.

Statistical methods: We will test whether older adults with gout are at higher risk of poor physical function as measured by lower extremity function and grip strength. Prevalent gout will be the main exposure of interest in this aim.

Using adjusted modified Poisson Regression will test whether prevalent physician-diagnosed gout is associated with lower extremity dysfunction and low grip strength separately. We will also explore any physical dysfunction by combining lower extremity dysfunction and low grip strength. We assume that the prevalence of low physical function is not rare and thus logistic regression will overestimate the relative risk, whereas modified Poisson regression directly estimates the relative risk (18). If we observe an association of gout and poor physical function, we will test whether duration of gout (based on age of gout onset) and treatment of gout are confounders. We will consider all 2-way interactions with sex, race, and OA.

Limitations: The main limitation of this study is that gout is self-reported. Therefore, we will explore various definitions of gout using gout-specific drugs 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 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
 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>
 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)?

2189: Gout in older adults
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? Yes _____ No

11.b. If yes, is the proposal
 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.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.

References:

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58(1):26-35.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis and rheumatism* 2011;63(10):3136-3141.
3. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med* 2012;125(7):679-687 e671.
4. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J Rheumatol* 2004;31(8):1582-1587.
5. Wernick R, Winkler C, Campbell S. Tophi as the initial manifestation of gout. Report of six cases and review of the literature. *Arch Intern Med* 1992;152(4):873-876.
6. Sundy JS, Hershfield MS. Uricase and other novel agents for the management of patients with treatment-failure gout. *Curr Rheumatol Rep* 2007;9(3):258-264.
7. Krishnan E, Lienesch D, Kwok CK. Gout in ambulatory care settings in the United States. *J Rheumatol* 2008;35(3):498-501.
8. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin* 2009;25(7):1711-1719.
9. Halpern R, Fuldeore MJ, Mody RR, Patel PA, Mikuls TR. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. *J Clin Rheumatol* 2009;15(1):3-7.
10. Garg R, Sayles HR, Yu F, Michaud K, Singh J, Saag KG et al. Gout-related healthcare utilization in U.S. emergency departments, 2006 through 2008. *Arthritis care & research* 2012.
11. Roddy E, Zhang W, Doherty M. Is gout associated with reduced quality of life? A case-control study. *Rheumatology (Oxford)* 2007;46(9):1441-1444.
12. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann Rheum Dis* 2008;67(9):1310-1316.
13. Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep* 2009;11(2):154-160.
14. Dibonaventura MD, Andrews LM, Yadao AM, Kahler KH. The effect of gout on health-related quality of life, work productivity, resource use and clinical outcomes among patients with hypertension. *Expert review of pharmacoeconomics & outcomes research* 2012;12(6):821-829.
15. Bolzetta F, Veronese N, Manzato E, Sergi G. Tophaceous gout in the elderly: a clinical case review. *Clin Rheumatol* 2012;31(7):1127-1132.
16. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49(2):M85-94.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604-612.
18. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159(7):702-706.