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]

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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  _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?  
__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.cscce.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)?

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?  
__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.
References: