1.a. **Full Title**: Trajectories in uric acid levels over 25 years in Atherosclerosis Risk in Communities Study (ARIC)

b. **Abbreviated Title (Length 26 characters)**: Trajectories in uric acid

2. **Writing Group**: Writing group members: Mara McAdams DeMarco, Christina Parrinello, Andrew Law, 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 August, 2013
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. However, little is known about the trajectories of uric acid levels as adults age. Furthermore, it is unclear what risk factors are associated with trajectories in uric acid. One study has identified predictors of incident hyperuricemia in Japanese men (Nakanishi, 2001). No studies, to date, have identified risk factors for changes uric acid levels over time, especially 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 changes in uric acid levels over time in middle-aged adults.

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:

5. **Main Hypothesis/Study Questions:**

   **Specific Aim 1:** Estimate the trajectories of uric acid level in ARIC over 9 years and over 25 years.
   **Specific Aim 2:** Identify predictors for changes in uric acid level over time 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 have available measures of uric acid at visit 1, 2, 4, and 5. Additionally, we will limit the population to those who were white or African American, and were not missing any baseline predictors of uric acid trajectories. Finally, we will exclude those who are taking a urate lowering medication at any visit. As a sensitivity analysis, we will exclude those with gout self-reported at visit 4 or 5.

   **Study design:** Longitudinal cohort

   **Exposure:**

   We will identify which clinical risk factors are associated with trajectories of uric acid levels over 9-years and 25-years. We will consider baseline (1989) age, sex, race, blood pressure, alcohol intake (grams/week), diabetes, CHD, CHF, diuretic use, dietary factors, 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. Additionally, we will consider time-varying risk factors.

Data analysis: We will use longitudinal data analysis to assess trajectories of uric acid levels over 9 years and 25 years. We will plot the trajectories of using a spaghetti plot. Finally, we will use multilevel modeling (linear mixed model) to assess which baseline risk factors are associated with trajectories of in uric acid over 9-years and over 25-years. We will consider random slopes and random intercepts and identify the best fitting model. We will also account for clustering within ARIC center.

Limitations:
The main limitation of this study is that the analytic study population requires measured urate level at visits 1, 2, 4, and 5. Thus, there is the potential for survival bias. We will explore this potential bias and may need to use inverse probability weights to account for the differential loss to follow-up.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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)?
There are no studies of the trajectories of urate level in ARIC. The most related abstracts are:
1364: Sweetened beverage consumption and development of chronic kidney disease, hyperuricemia and albuminuria.
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* _______2009.09)
   ____ 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.