1.a. Full Title: Serum uric acid, lung function and chronic obstructive pulmonary disease in adults: the Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Haidong Kan, Kathryn M. Rose, Eric Whitsel, Honglei Chen, Stephanie J. London

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. H.K. [please confirm with your initials electronically or in writing]

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3. Timeline: A first manuscript should be available for circulation to the ARIC investigators before June 1, 2008

4. Rationale:

   Increased serum uric acid has been associated with a range of adverse cardiovascular endpoints including myocardial infarction, stroke, hypertension and cardiovascular mortality\textsuperscript{1-4}. Uric acid is also elevated in association with a number of cardiovascular risk factors including obesity, glucose intolerance and hyperlipidemia\textsuperscript{5}. However, there is controversy regarding the meaning of this association. Prospective data suggests a role of
Uric acid in the development of disease states independently of other factors. Although the mechanisms underlying these associations are unclear, uric acid is a major endogenous antioxidant, accounting for 60% of the free-radical scavenging activity in human blood. Uric acid in the lung, which comes from circulating uric acid, appears to be involved in the response to oxidative stressors such as ozone and nitrogen dioxide.

There is a modest literature suggesting that uric acid may protect premature infants exposed to oxidative stress resulting from oxygen administration from the respiratory distress syndrome. However, there are very few data on uric acid in relation to the respiratory health of adults. In a recent study of 59 patients with chronic obstructive pulmonary disease (COPD), higher serum uric acid level and the ratio of uric acid to creatinine were associated with reduced lung function. In another small study, mean uric acid levels were higher in 24 COPD patients compared with 12 healthy controls. In a study (presented only as an abstract) of 110 patients with COPD, significant correlations were found between hypoxemia and uric acid levels and between COPD severity and uric acid levels. However, no published study exists on the association between serum uric acid and lung function in a general population sample.

We recently reported that higher intake of dietary fiber was inversely related to pulmonary function in ARIC. This association persisted after adjustment for intake of antioxidant micronutrients (vitamins C and E). One potential mechanism by which fiber may influence lung function is through modulation of oxidative stress and inflammation. This mechanism may also underlie our recent finding in ARIC that subjects living in closer proximity to busy traffic have lower function. Based on the importance of smoking as a risk factor, oxidative stress is presumed to be important in the etiology of COPD and impaired lung function. However, there is a paucity of data linking oxidative stress with lung function. A finding of an inverse association between serum uric acid and pulmonary function would provide some support for the role of oxidative stress in reduced lung function.

The pulmonary and serum uric acid data at visits 1 and 2, along with extensive data on potential confounders including medication use, provide us a unique opportunity in ARIC to investigate the relation between serum uric acid, lung function and COPD in adults.

5. Main Hypothesis/Study Questions:

Subjects with higher serum uric acid have reduced lung function and higher prevalence of COPD, after adjustment for a wide range of potential confounders available in ARIC.

Data analysis:

The main measurements of lung function for this analysis will be FEV1, FVC and the FEV1/FVC ratio. We will define our COPD outcomes as we have done in our analysis on fiber and lung function and has been done in another recent ARIC paper on COPD. COPD will be defined using GOLD criteria applied to the pre-bronchodilator values available in ARIC (FEV1/FVC ratio <0.7 and FEV1 < 80% predicted). Chronic bronchitis will be defined by persistent cough and production of phlegm on most days for at least three consecutive months of the year for two or more years.
Our primary analysis will be a cross-sectional analysis of the association between uric acid, lung function and COPD at visit 1. Although we have two measures of pulmonary function at both visits 1 and 2, they are only three years apart which is probably insufficient to detect longitudinal effects of uric acid. Nevertheless, we will perform supplementary longitudinal analysis.

We will explore the associations of serum uric acid with lung function using linear regression model and with COPD using logistic regression model. In the regression models, we will examine a number of potential confounding factors, including socio-demographic factors (gender, center, race, age, occupation and education), BMI, height, square of height, detailed parameterization of active smoking history, environmental tobacco smoke exposure, air pollution (traffic), medication use (corticosteroids, probenecid, sulfinpyrazone, colchicine, allopurinol, diuretics, salicylates, salicylates, nicotinic acid derivatives, cytotoxics and cyclosporine), medical history (non-skin cancers, hemolytic anemias, and severe psoriasis), dietary factors (fiber, vitamins C and E, omega-3 fatty acid, cured meats, alcohol, and dairy), glucose, triglycerides, cholesterol, fibrinogen, WBC counts, and measures of renal function (BUN and creatinine). In addition to treating conditions and medications that may influence uric acid levels as confounders, we will conduct analyses with and without excluding these subjects.

6. Data (variables, time window, source, inclusions/exclusions):
Visits 1-2: pulmonary function measures (FEV1 and FVC and their ratio), respiratory symptoms (cough, phlegm, wheeze, breathlessness), gender, center, race, age, BMI, occupations, education, height and square of height, smoking, exposure to environmental tobacco smoke, traffic exposure, medication use, medical history, dietary assessment including both dietary questionnaires and supplement data, serum levels of uric acid and creatinine, glucose, triglycerides, cholesterol, fibrinogen, and WBC counts.

Participants with gout and stage 4 or 5 chronic kidney disease will be excluded from the current analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript?  __X__ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER02 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?  __X__ Yes  ____ No
(This file ICTDER02 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 ICTDER02 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)?

# 450, 760, 782, 860, 861, 907

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

___ A. primarily the result of an ancillary study (list number*AS#2003.03)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ________________

Note – original ancillary study proposal expansion to include cardiovascular endpoints was approved by the Steering Committee at the meeting on April 14, 2004.

*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.

References:


