1.a. Full Title: Serum Uric Acid and development of the Metabolic Syndrome: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Uric Acid & Metabolic Syndrome

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

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3. **Timeline:**
Analysis – March 2007
Manuscript Preparation – April 2007
Manuscript Revision – May-June 2007
Manuscript Submission – July 2007

4. **Rationale:**
The cross-sectional association between serum uric acid (SUA) and components of the metabolic syndrome has been demonstrated in multiple studies\(^1,2\), including the ARIC cohort\(^3\). However, it is unclear whether this association represents a causal relationship or is merely an epiphenomenon, as hyperuricemia could be a reflection of hyperinsulinemia\(^4\) and/or early renal dysfunction.

Recent data from animal models suggest that elevated SUA may be in the causal pathway of the metabolic syndrome. In experimental models, hyperuricemia is associated with decreased expression of endothelial nitric oxide synthase\(^5\) and circulating nitric oxide\(^6\). This provides a link between SUA and endothelial dysfunction, an early pathogenic feature of the metabolic syndrome\(^7\). Furthermore, inhibition of uric acid production prevents the development of insulin resistant features (hyperinsulinemia, hypertension, hypertriglyceridemia, and weight gain) in fructose-fed rats, an animal model of the metabolic syndrome\(^8\).

Limited data in humans supports the hypothesis that serum uric acid may play a causal role in the pathogenesis of insulin resistance. Serum uric acid has been positively associated with weight gain\(^9\) and change in plasma insulin\(^10\) in longitudinal studies. In one previous report from the ARIC cohort, baseline serum uric acid was an independent predictor of subsequent hyperinsulinemia\(^11\). In a separate study, we found an independent association between baseline serum uric acid and incident hypertension\(^12\). We seek to build upon these observations by evaluating the longitudinal association between baseline serum uric acid and the development of the metabolic syndrome over nine years of follow-up in the ARIC cohort.

Reference List

5. Main Hypothesis/Study Questions:
Hypothesis: Uric acid predicts the development of the metabolic syndrome, independent of baseline levels of component measures.

Primary research questions:
- Do uric acid levels independently predict the metabolic syndrome in middle-aged men and women?

Secondary research questions:
- Is baseline serum uric acid independently associated with metabolic syndrome component severity at follow-up?

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).

Variables:
Visits 1,2,3,4: Age, ethnicity, gender, waist circumference, weight, HDL, triglycerides, fasting glucose, SBP, DBP, hypertension status, diabetes status, anti-hyperlipidemic medications, current smoking, alcohol intake

Visits 1,2: serum uric acid, serum creatinine

Visits 1,3: physical activity

Exclusions:
Participants will be excluded for the following prevalent conditions at baseline: metabolic syndrome, cardiovascular disease, diabetes mellitus, hypertension (BP ≥ 140/90 or antihypertensive medication use), use of lipid lowering medications, or estimated GFR < 60 mL/min/1.73 m².

Analysis plan:
The outcome of interest is the metabolic syndrome, defined by a modified ATP-III definition as meeting 3 or more of the following criteria:
Waist Circumference: Men - > 102 cm; Women - > 88 cm
Triglycerides: ≥ 150 mg/dL
HDL-C: Men - < 40 mg/dL; Women - < 50 mg/dL
Blood pressure: SBP ≥130 mmHg, DBP ≥ 85 mmHg, or antihypertensive medication use
Fasting glucose: ≥ 100 mg/dL or hypoglycemic medication use.

Onset of the metabolic syndrome will be estimated at the midpoint between the exam at which it was noted and the previous exam.

Cox proportional hazards analyses will be used to evaluate the association between baseline serum uric acid levels and incident metabolic syndrome through Exam 4, adjusting for baseline age, race, gender, ARIC field center, and baseline estimated glomerular filtration rate. These analyses will then be repeated using baseline components of the metabolic syndrome (waist circumference, fasting glucose, systolic blood pressure, diastolic blood pressure, triglycerides, and HDL-C). Additional models will evaluate these models including smoking, alcohol intake, and physical activity as time-dependent covariates. Any potential effect modification by race or gender will be evaluated using interaction terms, and additional analyses will be stratified as indicated by these interaction terms. Since uric acid and the measures that constitute the metabolic syndrome are subject to measurement error, sensitivity analyses will evaluate the same models using measures averaged from Exam 1 and Exam 2, with Exam 2 serving as the baseline exam.

One critique of the utility of the ‘metabolic syndrome’ is its dichotomization of a series of continuous parameters to generate a single ‘disease’ state, which fails to adequately represent the continuum of risk associated with this cluster of factors. To better represent the continuous nature of this process, we propose secondary analyses using the following metabolic syndrome components to generate a ‘metabolic score’: waist circumference, SBP, fasting glucose, and log(fasting triglyceride/HDL). Each metabolic score component will transformed to generate a standard normal distribution (where mean=0 and SD=1), and a summary score will be computed by the addition of the four standardized components. For subsequent measures in individuals taking hypoglycemic, lipid-lowering, or antihypertensive medications at follow-up, values will be imputed based on baseline measures, age, race, sex, and weight change from baseline. General linear mixed models will be used to evaluate the association between baseline SUA and repeated measures of follow-up metabolic score, adjusted for the baseline metabolic score as well as the covariates outlined above. As an alternative approach, principal components analyses will be used to derive one or more metabolic ‘factors’, which will be modeled as outcome measures in mixed models as described above. Analyses will be performed by Dr. Mellen, in consultation with the co-authors and under the guidance of Dr. Goff, using SAS 9.1 (Cary, NC).

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 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? ___ 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)?

   MS# 786 Carnethon, MR et al. Risk factors for progression to incident hyperinsulinemia
   This manuscript noted that uric acid predicted incident hyperinsulinemia. Dr. Carnethon has commented on the current proposal and has agreed to serve on the writing group.

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)* __________ __________)

*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.