ARIC Manuscript Proposal #1933

PC Reviewed: 4/17/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Association between Serum Uric Acid, Diabetes Risk, and Diabetes Duration

b. Abbreviated Title (Length 26 characters): Serum Uric Acid, Diabetes

2. Writing Group:

Writing group members: Stephen P. Juraschek, Mara McAdams-DeMarco, Janet Maynard, Edgar R. Miller, Allan C. Gelber, Jim Pankow, JH Young, Josef Coresh, Elizabeth Selvin, others welcome

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

F**irst author**:

Address: Stephen P. Juraschek, BA
19 N. Ann Street
Baltimore, MD 21231

Phone: (781) 608-8413 Fax: None
E-mail: spj@jhmi.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: Elizabeth Selvin

Address: Welch Center for Prevention, Epidemiology, & Clinical Research
Johns Hopkins University
2024 E. Monument, Suite 2-600
Baltimore, MD 21205
Tel: 410-614-3752
Fax: 410-955-0476
lselvin@jhsph.edu

3. Timeline: Data analysis to begin after approval of this manuscript proposal. First draft should be available August, 2012.

4. Rationale:

The prevalence of diabetes mellitus is increasing in the US[1] and around the world.[2] While diabetes is defined by a state of chronically elevated glucose, the pathophysiology precipitating persistent hyperglycemia remains unclear. Previous studies have found associations between byproducts of glycolysis and subsequent diabetes,[3,4] suggesting that intracellular impairments to metabolism may lead to disruptions in extracellular glucose homeostasis. However, much remains unknown regarding the pathophysiology underlying the development of persistent hyperglycemic states.

Hyperuricemia is a well-described phenomenon associated with the metabolic syndrome.[5–7] Early studies in patients with von Gierke's disease, a type I glycogen storage disorder, established that excess intracellular, glycolytic precursors like glucose-6-phosphate contribute to hyperuricemia.[8] Similarly, epidemiologic studies have shown that fructose, a low-glycemic index sugar metabolized exclusively within liver cells, is associated with elevations in uric acid as well.[9–13] Together these studies suggest that uric acid is a marker for increased intracellular glycolysis, excess glycolytic substrates, and potentially dysfunctional metabolic pathways preceding detectable changes in intravascular glucose concentrations.

A number of prospective epidemiologic studies have shown that elevations in uric acid precede subsequent diagnoses of diabetes.[14–21] Similarly, studies have shown that uric acid is positively associated with 1-hour post-load plasma glucose.[22] Elevations in uric acid are believed to be caused by a combination of impaired glycolysis, diversion of metabolites to the hexose-monophosphate pathway, and inhibition of urate excretion by lactate or insulin resistance.[8,21,23] A potential causal association between uric acid and diabetes remains controversial, however. Recent genetic evidence suggests that genes associated with elevations in uric acid are not associated with diabetes.[24] Furthermore, many cross-sectional and prospective studies have shown an inverse association between diabetes and uric acid.[21,25–30] It is hypothesized that there is a threshold effect, such that excess elevations in fasting glucose among persons with diagnosed diabetes induce urinary excretion of uric acid, which accounts for the reduction in serum uric acid.[31–33] This suggests that the degree of impairment in glucose metabolism may differentially impact circulating levels of uric acid in the blood. However, few studies have utilized repeat measurements of uric acid and glucose to investigate the complex associations between dysglycemic states and serum uric acid.[21]

A better understanding of the relationship between uric acid and diabetes could improve the diagnosis and management of diabetes in a number of clinically relevant ways. First, increased knowledge of the intracellular precursors to glycemia could help to identify subgroups of the population at high risk for diabetes. Second, it could help elucidate pathways and metabolites that could serve as potential therapeutic targets. Finally, knowledge of the effect of diagnosed diabetes on serum uric acid could clarify the effects persistent hyperglycemia on uric acid over time and how diabetes can alter serum concentrations of a metabolite associated with cardiovascular and rheumatologic disease.

The ARIC Study is an ideal setting to examine the relationship between uric acid and prevalent and incident diabetes and pre-diabetic states. The proposed project will leverage repeat measurements of serum uric acid and glucose, long duration of follow-up,

and high number of incident diabetes cases (there were 1,526 incident cases of diabetes by visit 4 and >1,000 cases of incident self-reported diabetes ascertained during the annual telephone calls to participants after visit 4) in this diverse community-based cohort. Uric acid was measured at visits 1 and 4 in ARIC, allowing us to comprehensively examine changes in uric acid before and after the development of diabetes and pre-diabetic states among those persons without diabetes at visit 1.

5. Main Hypothesis/Study Questions:

Primary study questions:

1. Are serum uric acid concentrations measured at visit 1 associated with incident diabetes ascertained between visits 1&4 or after visit 4 (self-reported cases ascertained during the annual follow-up telephone calls) among individuals with a glucose <100 mg/dL and a glucose of 100-125mg/dL after controlling for potential confounders?

2. Is glycemic status at visit 4 (fasting glucose < 100mg/dL, fasting glucose of 100-125 mg/dL, diagnosed diabetes) associated with change in serum uric acid from visit 1 to visit 4?

3. Among persons with incident diabetes, is duration of diabetes (determined by the difference between visit 4 date and date of incident diabetes ascertainment) associated with change in serum uric acid from visit 1 to visit 4?

Secondary study questions:

1. Are the associations between uric acid and incident diabetes independent of fasting glucose and fasting insulin?

Hypotheses:

1. Uric acid as a marker of aberrant intracellular glycolysis will be associated with increased risk of incident diabetes even among individuals with a normal fasting glucose
2. Diabetes status will be associated with change in serum uric acid between visits 1 and visit 4. Specifically, persons with pre-diabetics will have a past increase in serum uric acid (relative to normoglycemic participants) and diagnosed diabetes will be associated with a past decrease in serum uric acid (relative to normoglycemic participants).
3. Duration of diabetes will be associated with reductions in serum uric acid, but this change will plateau as duration increases.

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).

Study Design: Prospective and cross-sectional analyses of data from the ARIC Study. See **Figure**.

Inclusion/Exclusion:

We will include all subjects with known diabetes case status and valid uric acid measurements at both visits 1 and 4. We will exclude individuals who were not fasting for at least 8 hours at the time of uric acid measurement, individuals who represent a rare study ethnic group (Indian or Asian), and those missing covariate information. In prospective analyses, individuals with an existing diabetes diagnosis at the baseline period (visit 1 for incident diabetes between visits 1-4 or visit 4 for incident diabetes ascertained via annual follow-up questionnaires) will be excluded. A sensitivity analysis will be performed excluding participants taking urate-lowering medications.

Exposure Assessment:

The following exposures will be assessed in this proposed study:

1. Uric acid assessed at visits 1 and 4 will be treated as a categorical variable (based on population quartiles). Uric acid was measured using the uricase-peroxidase enzymatic method with a reliability coefficient of 0.91 and the within-person variability was 7.2%.[34–36]
2. Visit 4 diabetes status will be classified as (1) normoglycemic with fasting glucose < 100mg/dL, (2) pre-diabetic with fasting glucose of 100-125 mg/dL, (3) diabetes incident case diagnosed by self-report between visit 1 and visit 4, and (4) diabetes prevalent case at visit 1.
3. Diabetes duration by visit 4: a continuous variable calculated as the date of visit 4 minus the date of incident diabetes diagnosis. This will also be evaluated as a categorical variable using quartiles.

Outcome:

The following outcomes will be examined in this proposed study:

1. Incident diabetes ascertained between visits 1 and 4 using the following criteria: a fasting glucose ≥ 126 mg/dL, a nonfasting glucose ≥ 200 mg/dL, use of a diabetes medication, or self-reported physician diagnosis. Time of diagnosis is estimated using a linear increase in glucose from the last diabetes-free visit.[37]
2. Incident diabetes ascertained between visit 4 and the most recent annual follow-up data files available from annual telephone calls to all participants. Incident diabetes will be based on self-report during annual telephone calls made to all ARIC participants between visit 4 and April 18th, 2011. Participants will be considered having diabetes on the date they responded "yes" to glucose-lowering medication use or the following questions: "Has a doctor ever said you have Diabetes or sugar in the blood?" (2006-February 7, 2008) or "Since we last

contacted you has a doctor said you have diabetes or sugar in the blood?" (February 7, 2008 – April 18th, 2011).

3. Change in uric acid defined as the difference in measurements between visit 1 and visit 4

Other Variables of Interest:

Covariates will include gender (male or female), age (continuous), race (black or white), field center, body mass index (continuous), hypertension history (average SBP>140, DBP>90, or medication use), eGFR-CKDEPI creatinine equation (continuous), fasting glucose (continuous), LDL cholesterol (continuous), HDL cholesterol (continuous), triglycerides (log10 transformed and continuous), education (dichotomous greater or less than high school), family history of diabetes (dichotomous), fasting insulin (continuous), smoking status (current, former, and never), alcohol status (current, former, and never), and diuretic use.

Survival Analysis (Primary):

Proportions and mean baseline characteristics of the study participants will be reported by uric acid quartiles. Uric acid quartiles will be utilized in Cox proportional hazard models to examine the risk of incident diabetes for each ascertainment period: visit 1 up through visit 4 and visit 4 up through April 18th, 2011 (annual follow-up questionnaire). Individuals, who do not develop diabetes will be censored on the date of their last questionnaire response. The cumulative incidence and incidence rates will be further explored with crude cumulative incidence estimates, incidence rate ratios, Kaplan-Meier curves, and various combinations of cubic and linear splines with knots at the medians of each uric acid quartile. Furthermore, effect modification of the association between uric acid and incident diabetes will be evaluated in strata of impaired fasting glucose status (100-126mg/dL) versus normal serum glucose (<100mg/dL).

Cross-sectional Analysis (Secondary):

Multivariable linear regression models will be used to examine the associations between (1) diabetes duration and visit 4 uric acid values, (2) between diabetes duration and change in uric acid values from visit 1 to visit 4, and (3) between visit 4 diabetes status (normoglycemic, prediabetic, incident diabetes, and prevalent diabetes prior to visit 4). These models will be adjusted for factors thought to be related to serum uric acid concentrations and diabetes, namely, age, gender, race, lipoproteins (HDLc and LDLc), triglycerides, body mass index, hypertension status, kidney function (estimated glomerular filtration rate), education attainment, smoking status, alcohol use, diuretic use, fasting glucose, and fasting insulin.

Limitations:

There are several limitations to this study design. The survival models rely on single uric acid measurements at visit 1 and visit 4. Furthermore, there is a difference in definition of diabetes after visit 4 in that utilization of self-reported diabetes misses the undiagnosed/mild cases of diabetes. The cross-sectional duration analysis is subject to survival bias in that a participant needed to live until visit 4 to be included in the analysis. Finally, as an observational study, residual confounding is always a concern.

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 _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.cscc.unc.edu/ARIC/search.php

_____ Yes _X_ 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)?

ARIC Publications on Uric Acid:

- MS# 759 - Serum Uric Acid and Risk of Ischemic Stroke: the Atherosclerosis Risk in Communities (ARIC) Study PMID: 16239005
- MS# 1077 - Serum Uric Acid Predicts Incident Hypertension in a Bi-Ethnic Cohort: The ARIC Study PMID: 17060502
- Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. PMID: 10813506
- Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. PMID: 22031222
- Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). PMID: 21855838

Aric Publications on Incident Diabetes:

- Strength of Association for Incident Diabetes Risk Factors According to Diabetes Case Definitions: The Atherosclerosis Risk in Communities Study. PMID: 22247044
- Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. PMID: 21367942
- Serum and dietary potassium and risk of incident type 2 diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) study. PMID: 20975023
- Performance of A1C for the classification and prediction of diabetes. PMID: 20855549
- Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. PMID: 20048267

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.

References:

1. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2006;29(6):1263–1268.
2. Choi YJ, Kim HC, Kim HM, et al. Prevalence and management of diabetes in Korean adults: Korea National Health and Nutrition Examination Surveys 1998-2005. *Diabetes Care*. 2009;32(11):2016–2020.
3. Crawford SO, Hoogeveen RC, Brancati FL, et al. Association of blood lactate with type 2 diabetes: the Atherosclerosis Risk in Communities Carotid MRI Study. *Int J Epidemiol*. 2010;39(6):1647–1655.
4. Ohlson LO, Larsson B, Björntorp P, et al. Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia*. 1988;31(11):798–805.

5. Kylin E. Studien. Hypertonie-Hyperglykamie-Hyperurikamiesyndrome. *Zentralblatt fur innere Medizin*. 1923;44.
6. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365(9468):1415–1428.
7. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am. J. Med.* 2007;120(5):442–447.
8. Howell RR. The interrelationship of glycogen storage disease and gout. *Arthritis Rheum.* 1965;8(5):780–785.
9. Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am. J. Physiol. Renal Physiol.* 2006;290(3):F625–631.
10. Stirpe F, Della Corte E, Bonetti E, et al. Fructose-induced hyperuricaemia. *Lancet*. 1970;2(7686):1310–1311.
11. Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet*. 1967;2(7515):528–531.
12. Emmerson BT. Effect of oral fructose on urate production. *Ann. Rheum. Dis.* 1974;33(3):276–280.
13. Fox IH, Kelley WN. Studies on the mechanism of fructose-induced hyperuricemia in man. *Metab. Clin. Exp.* 1972;21(8):713–721.
14. Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care*. 2009;32(9):1737–1742.
15. Bhole V, Choi JWJ, Kim SW, de Vera M, Choi H. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am. J. Med.* 2010;123(10):957–961.
16. Boyko EJ, de Courten M, Zimmet PZ, et al. Features of the metabolic syndrome predict higher risk of diabetes and impaired glucose tolerance: a prospective study in Mauritius. *Diabetes Care*. 2000;23(9):1242–1248.
17. Klein BEK, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care*. 2002;25(10):1790–1794.
18. Perticone F, Maio R, Tassone JE, et al. Interaction between uric acid and endothelial dysfunction predicts new onset of diabetes in hypertensive patients. *International Journal of Cardiology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22245480. Accessed February 8, 2012.
19. Viazzi F, Leoncini G, Vercelli M, Deferrari G, Pontremoli R. Serum uric acid levels predict new-onset type 2 diabetes in hospitalized patients with primary hypertension: the MAGIC study. *Diabetes Care*. 2011;34(1):126–128.
20. Wang T, Bi Y, Xu M, et al. Serum uric acid associates with the incidence of type 2 diabetes in a prospective cohort of middle-aged and elderly Chinese. *Endocrine*. 2011;40(1):109–116.
21. Herman JB, Goldbourt U. Uric acid and diabetes: observations in a population study. *Lancet*. 1982;2(8292):240–243.
22. Perticone F, Sciacqua A, Perticone M, et al. Serum uric acid and 1-h postload glucose in essential hypertension. *Diabetes Care*. 2012;35(1):153–157.
23. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA*. 1991;266(21):3008–3011.
24. Pfister R, Barnes D, Luben R, et al. No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia*. 2011;54(10):2561–2569.
25. Ryu S, Chang Y, Zhang Y, et al. A cohort study of hyperuricemia in middle-aged South Korean men. *Am. J. Epidemiol.* 2012;175(2):133–143.
26. Burchfiel CM, Hamman RF, Marshall JA, et al. Cardiovascular risk factors and impaired glucose tolerance: the San Luis Valley Diabetes Study. *Am. J. Epidemiol.* 1990;131(1):57–70.
27. Rodríguez G, Soriano LC, Choi HK. Impact of diabetes against the future risk of developing gout. *Ann. Rheum. Dis.* 2010;69(12):2090–2094.

28. Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q. Diabetes associated with a low serum uric acid level in a general Chinese population. *Diabetes Res. Clin. Pract.* 2007;76(1):68–74.
29. Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J*. 1986;62(733):1001–1006.
30. Yano K, Rhoads G, Kagan A. Epidemiology of serum uric acid among 8000 Japanese-American men in Hawaii. *J Chronic Dis*. 1977;30(3):171–184.
31. Greene HL, Wilson FA, Hefferan P, et al. ATP depletion, a possible role in the pathogenesis of hyperuricemia in glycogen storage disease type I. *J. Clin. Invest.* 1978;62(2):321–328.
32. Herman JB, Keynan A. Hyperglycemia and uric acid. *Isr. J. Med. Sci.* 1969;5(5):1048–1052.
33. Boner G, Rieselbach RE. The effect of glucose upon reabsorptive transport of urate by the kidney. *Adv. Exp. Med. Biol.* 1974;41:781–787.
34. Hozawa A, Folsom AR, Ibrahim H, et al. Serum uric acid and risk of ischemic stroke: the ARIC Study. *Atherosclerosis*. 2006;187(2):401–407.
35. Mellen PB, Bleyer AJ, Erlinger TP, et al. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. *Hypertension*. 2006;48(6):1037–1042.
36. Tamariz L, Agarwal S, Soliman EZ, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). *Am. J. Cardiol.* 2011;108(9):1272–1276.
37. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52(7):1799–1805.

Figure. Study Design