Serum Uric Acid Is Associated with Carotid Plaques: The National Heart, Lung, and Blood Institute Family Heart Study

TUHINA NEOGI, R. CURTIS ELLISON, STEVEN HUNT, ROBERT TERKELTAUB, DAVID T. FELSON, and YUQING ZHANG

ABSTRACT. ***Objective.*** To examine the association of serum uric acid (SUA) with a marker of preclinical cardiovascular disease (CVD), carotid atherosclerotic plaques (PLQ), where early evidence of risk may be evident, focusing on individuals without CV risk factors.

Methods. The National Heart, Lung, and Blood Institute Family Heart Study is a multicenter study designed to assess risk factors for heart disease. PLQ were assessed with carotid ultrasound. We conducted sex-specific logistic regression to assess the association of SUA with presence of PLQ, including analyses among persons without risk factors related to both CVD and hyperuricemia.

Results. In total, 4866 participants had both SUA and carotid ultrasound assessed (54% women, mean age 52 yrs, mean body mass index 27.6). The association of SUA with PLQ increased with increasing SUA levels, demonstrating a dose-response relation for men [OR 1.0, 1.29, 1.61, 1.75, for SUA categories < 5 (reference), 5 to < 6, 6 to < 6.8, ≥ 6.8 mg/dl, respectively; p = 0.002]. Similar associations were found in men without CV risk factors. We found no relation of SUA with PLQ in women.

Conclusion. In this large study, SUA was associated with carotid atherosclerotic plaques in men. Results were similar in the absence of CV risk factors. These results suggest that SUA may have a pathophysiologic role in atherosclerosis in men. (First Release Nov 15 2008; J Rheumatol 2009;36: 378–84; doi:10.3899/jrheum.080646)

Key Indexing Terms:
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From the Section of Clinical Epidemiology Research and Training Unit and Section of Preventive Medicine and Epidemiology, Boston University School of Medicine, Boston, Massachusetts; University of Utah, Salt Lake City, Utah; and Veterans Affairs Medical Center, University of California at San Diego, San Diego, California, USA.

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T. Neogi, MD, FRCPC, Assistant Professor of Medicine, Department of Medicine, Section of Clinical Epidemiology Research and Training Unit; R.C. Ellison, MD, Professor of Medicine, Department of Medicine, Section of Preventive Medicine, Boston University School of Medicine; S. Hunt, PhD, Professor of Medicine, Cardiology Division, University of Utah; R. Terkeltaub, MD, Professor of Medicine, Department of Medicine, Division of Rheumatology, VA Medical Center, University of California at San Diego; D.T. Felson, MD, MPH, Professor of Medicine; Y. Zhang, DSc, Professor of Medicine, Department of Medicine, Section of Clinical Epidemiology Research and Training Unit, Boston University School of Medicine.

Address reprint requests to Dr. T. Neogi, Clinical Epidemiology Unit, Boston University School of Medicine, 650 Albany Street, Suite X-200, Boston, MA 02118. Email: tneogi@bu.edu

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Studies examining the relation of hyperuricemia with cardiovascular disease (CVD) have had conflicting results. While many have found an independent association of higher serum uric acid (SUA) concentrations with increased risk of adverse cardiovascular outcomes[1-7], others have not[8-10]. Biological mechanisms linking hyperuricemia to CVD risk exist, but direct effects of uric acid on the vasculature remain controversial[11,12]. Moreover, some have argued that the positive association between SUA and CVD may be due to the concurrent cardiovascular comorbidities seen in many persons with hyperuricemia, including diabetes, dyslipidemia, hypertension, and obesity[13-15].

Clarifying the relation of SUA to CVD risk has clinical implications and public health importance. First, there has been a secular increase in the incidence and prevalence of gout and hyperuricemia[16,17]. Second, asymptomatic hyperuricemia is presently not an indication for urate-lowering therapy. If hyperuricemia is indeed an independent risk factor for CVD, it might motivate a change in traditional treatment recommendations.

Noninvasive assessment of preclinical lesions in contrast to adverse clinical events such as myocardial infarction may provide insight into potential pathophysiologic mechanisms

of risk factors. Further, such studies are less likely to suffer from low event rates and resultant low power compared to studies utilizing clinical endpoints. Advances in imaging technology have enabled the evaluation of markers of preclinical atherosclerotic disease, such as carotid plaques, which have been associated with prevalent and incident CVD[18]. Carotid plaques as measured by ultrasound may be a result of atherosclerosis causing intimal expansion, and/or a result of vascular hypertrophy and remodeling causing an increased thickness in the media[19].

While prior studies have examined the association of carotid atherosclerosis with various risk factors for cardiovascular morbidity and mortality, few have evaluated the relation of hyperuricemia to preclinical carotid atherosclerotic disease to date, with conflicting results[20-26]. Such conflicting results may in part be related to differences in analytic approaches and/or effectiveness of controlling for potential confounding.

Further, prior studies have not examined SUA's effects in individuals who are free from comorbidities, which themselves can both increase SUA and increase risk for preclinical CVD. If SUA were associated with preclinical CVD in persons without any such comorbidities, it would constitute stronger evidence for SUA's association with CVD than has been presented in previous studies.

We evaluated the association of SUA with carotid plaques in a large multicenter study, the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study, and further assessed these associations for the modifying and confounding effects of concomitant cardiovascular comorbidities using different analytic approaches.

MATERIALS AND METHODS

Study population. The NHLBI Family Heart Study is a multicenter study designed to assess genetic and nongenetic determinants of heart disease[27]. Participants were recruited between 1993 and 1995 from community-based cohorts at 4 sites: The Framingham Heart Study in Framingham, MA; the Atherosclerosis Risk in Communities (ARIC) cohorts in NC and MN; and the Utah Health Family Tree Study in Salt Lake City, UT. Between 2002 and 2004, a cohort of African Americans at University of Alabama at Birmingham from the Hypertension Genetic Epidemiology Network study was also included. All individuals had clinical examinations, questionnaires, blood collections, and imaging procedures that were measured at a centralized location. The parent study had institutional review board approval.

Measurement of variables. Outcome variable. Carotid plaques were assessed by experienced readers centrally using a high-resolution B-mode ultrasound according to the validated ARIC protocol[28], performed bilaterally on 3 segments: the common carotid artery, the bifurcation, and the internal carotid artery. The presence of an atherosclerotic plaque was determined as the presence of ≥ 2 of the following criteria: irregularity of surface, increased overall thickness, and echogenicity. For each subject, the total number of plaques was recorded. The interrater reliability (kappa) for the presence of any carotid plaques was 0.76. In the current analysis, a carotid plaque was defined as being present in an individual if any of the 3 arterial segments on either the right or the left was identified as having a plaque.

Exposure variable. SUA was measured in fasting blood collected and processed at the Family Heart Study field centers[27], and analyzed at the Family Heart Study Central Laboratory at the Fairview-University Medical Center in Minneapolis, MN, using the Vitros thin-film clinical analyzer (Ortho Clinical Diagnostics, Rochester, NY, USA) absorptiometry method[29].

Covariates. Information on age, education, smoking [never, former, current (including number per day)], alcohol intake (average number of drinks consumed per wk on average over the past 12 mo), and comorbidities (see below) was obtained at the clinic visit interview. Medication use was assessed by questionnaire and medication inventory. Anthropometric data were collected while the participants were wearing scrub suits, with body weight measured on a balance scale and height measured with a wall-mounted vertical ruler. Cholesterol (total, high and low-density lipoprotein, triglycerides), creatinine, and glucose were measured using standard assays after a 12-h fast at the central study laboratory. Persons were asked if they ever had evidence of coronary artery disease, defined as myocardial infarction, percutaneous angioplasty, or coronary artery bypass graft surgery, and stroke. Hypertension was defined as the average of the 2nd and 3rd measurements (of 3 measurements) of a systolic pressure ≥ 130 mm Hg, diastolic pressure ≥ 85 mm Hg, or use of antihypertensive medication (including diuretics). Diabetes/hyperglycemia was defined as having a fasting blood sugar ≥ 110 mg/dl or receiving dietary or pharmacologic therapy for physician-diagnosed diabetes. Renal insufficiency was defined as creatinine clearance ≤ 60 ml/min. Aspirin use was categorized as none, ≤ 325 mg/day, or > 325 mg/day. Smoking was categorized as never, former, < 20/day, or ≥ 20/day. Education was categorized as ≤ 11, 12, > 12 but ≤ 16 years, and > 16 years.

Statistical analysis. We divided SUA into 4 groups: < 5, 5 to < 6, 6 to < 6.8, ≥ 6.8 mg/dl. Individuals taking urate-lowering drugs were considered to be in the highest category of SUA. We used 6.8 mg/dl as one cutpoint, as it is the concentration that meets or exceeds the limit of urate solubility, and as such is generally the SUA concentration used to define hyperuricemia[30]. The additional cutpoints were chosen for the target of < 6 mg/dl in the treatment of chronic gout[31], while there is a theoretical concern that low SUA levels may be associated with adverse effects[32]. We also repeated analyses with sex-specific quartiles. We computed the sex-specific prevalence of carotid plaque for each SUA category. We examined the relation of SUA and prevalence of carotid plaques for men and women separately using logistic regression with generalized estimating equations[33] to account for correlation among members of a family in our study. In the multivariable regression model, we adjusted for age, body mass index (BMI), race, smoking, alcohol intake, education, low-dose aspirin use, hypertension and its treatments (including diuretics), diabetes and its treatments, renal insufficiency, and study center.

To assess whether the association of SUA and carotid plaques is modified by particular cardiovascular risk factors that are known to be associated with SUA, we performed further analyses stratified by such factors[34]. Specifically, we stratified by presence or absence of hypertension (and adjusted for mean arterial pressure in this analysis), of renal insufficiency, and of diabetes, respectively, as well as age (divided at the median age of 55 yrs) and BMI [obese (BMI ≥ 30 kg/m^2) vs nonobese (BMI < 30 kg/m^2)], to examine the association between SUA and prevalence of carotid plaques within each stratum and assessed effect-measure modification by each stratified variable. Further, we performed a stratified analysis by presence or absence of any of those 3 conditions (hypertension, renal insufficiency, and diabetes).

To account for the potential confounding effects of shared genetic or environmental factors within families, we performed a family-based case-control study to assess the relation of SUA and prevalence of carotid plaques. Specifically, cases (participants with carotid plaques) and controls (participants without carotid plaques) within a family were matched by sex and by age within a 5-year interval (using the caliper method of matching). We then conducted sex-specific conditional logistic regression, adjusting for the same potential confounding factors as in the main analyses.

All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Included were 4866 individuals who had both SUA and carotid plaque assessments. The mean age of this cohort was 52.2 years, and approximately 54% were women. Twenty-seven percent of men and 7.1% of women had SUA concentrations ≥ 6.8 mg/dl. The mean SUA in men was 6.2 [standard deviation (SD) 1.7)] mg/dl, and in women the mean SUA was 4.8 (SD 1.3). Participant characteristics for men are presented in Table 1A. Higher SUA levels were associated with higher BMI, alcohol consumption, aspirin use, hypertension, renal insufficiency, diabetes, and presence of coronary artery disease, but not with age, smoking, or race. Similar crude associations were noted in women, with the exception of age and race (Table 1B). In women, higher SUA categories were associated with older age and a lower proportion of Caucasians. A greater proportion of those in the higher SUA categories were postmenopausal and therefore older.

Higher SUA was associated with a higher prevalence of carotid plaques in men, but not women, after adjusting for potential confounders (Table 2). Compared with those whose SUA level was < 5 mg/dl, men with SUA level 5 to < 6 mg/dl, 6 to < 6.8 mg/dl, and ≥ 6.8 mg/dl had prevalence odds ratios (OR) of 1.29, 1.61, and 1.75, respectively, (p = 0.002 for linear trend) for the presence of carotid plaques. Although the crude OR in women appeared to indicate an association, after adjustment for age, no such association was found. Results were unchanged when individuals on urate-lowering therapy (n = 69) were excluded, SUA was

Table 1A. Participant characteristics according to serum uric acid (SUA) levels—men.

Variables in men	SUA categories, mg/dl				
	< 5 (mean 4.3) n = 360	5 to < 6 (mean 5.5) n = 685	6 to < 6.8 (mean 6.4) n = 595	≥ 6.8 (mean 7.8) n = 606	All men n = 2246*
Mean age, yrs	52.7	51.4	51.4	52.5	51.9 ± 14.0
Mean BMI	26.3	27.1	27.9	29.4	27.8 ± 4.5
Caucasian, %	96.4	97.2	96.0	97.4	96.8
> 16 yrs of education, %	53.1	54.3	56.5	51.8	54.0
Never smoker, %	45.6	45.4	46.6	43.2	45.2
> 14 alcoholic drinks/wk, %	6.4	8.4	10.6	15.4	10.6
No aspirin use, %	66.9	69.3	70.3	60.4	66.8
Presence of HTN, %	28.3	27.5	25.3	34.1	34.6
Presence of renal insufficiency, %	3.6	5.3	6.9	13.5	7.7
Presence of diabetes, %	17.5	8.2	7.1	10.2	9.9
Presence of CAD, %	19.2	16.8	17.3	32.5	18.9

BMI: body mass index; CAD: coronary artery disease; HTN: hypertension. * Mean ± standard deviation where appropriate.

Table 1B. Participant characteristics according to serum uric acid (SUA) levels—women.

Variables in women	SUA categories, mg/dl				
	< 5 (mean 4.0) n = 1589	5 to < 6 (mean 5.4) n = 587	6 to < 6.8 (mean 6.4) n = 259	≥ 6.8 (mean 7.8) n = 185	All women n = 2620*
Mean age, yrs	49.6	54.8	59.7	59.9	52.5 ± 13.6
Postmenopausal, %	37.1	55.4	70.3	69.2	46.7
Mean BMI	25.5	29.4	31.1	33.2	27.5 ± 6.2
Caucasian, %	95.6	93.4	92.7	86.0	94.2
> 16 yrs of education, %	50.0	41.2	32.1	32.4	45.0
Never smoker, %	58.1	53.7	65.6	61.1	58.1
> 14 alcoholic drinks/wk, %	1.6	3.3	3.2	3.3	2.3
No aspirin use, %	80.6	73.8	64.5	63.8	76.3
Presence of HTN, %	21.6	36.1	56.0	65.4	31.3
Presence of renal insufficiency, %	5.3	13.8	23.2	31.4	10.8
Presence of diabetes, %	5.9	10.6	12.0	26.5	9.0
Presence of CAD, %	4.6	6.1	13.5	15.1	6.6

BMI: body mass index; CAD: coronary artery disease; HTN: hypertension. * Mean ± standard deviation where appropriate.

Table 2. Association of SUA and prevalence of carotid plaques in men and in women.

SUA, mg/dl	No. Subjects	Prevalence of Carotid Plaques, %	Crude OR	Adjusted OR (95% CI)
		Men		
< 5	360	26.1	1.0 (reference)	1.0 (reference)
5 to < 6	685	28.0	1.10	1.29 (0.92–1.82)
6 to 6.8	595	30.4	1.24	1.61 (1.12–2.30)
≥ 6.8	606	35.2	1.53	1.75 (1.21–2.51)
Test for trend				p = 0.002
		Women		
< 5	1589	18.6	1.0 (reference)	1.0 (reference)
5 to < 6	587	25.4	1.49	1.05 (0.79–1.39)
6 to < 6.8	259	31.3	1.99	1.03 (0.69–1.52)
≥ 6.8	185	33.5	2.20	1.06 (0.70–1.59)
Test for trend				p = 0.08

examined as a continuous variable, sex-specific SUA quartiles were used, and when the highest category of SUA was further divided as ≥ 6.8 to < 8 mg/dl and ≥ 8 mg/dl.

When analyses were stratified by factors that were potentially associated with both SUA and carotid plaques, men in the higher categories of SUA continued to demonstrate a positive association across all strata compared to those in the lowest category of SUA (Table 3), suggesting that there may be an independent effect of SUA on prevalence of carotid plaques irrespective of the coexistence of hypertension, renal insufficiency, or diabetes. Further, when we evaluated men who did not have any of these comorbidities, the prevalence OR for the presence of carotid plaques were 1.0, 1.34, 1.40, and 1.95 (p = 0.02 for linear trend) for each increasing SUA-level category. The corresponding prevalence OR were 1.0, 1.26, 1.94, and 1.71 (p = 0.02 for linear trend; p = 0.6 for interaction) among men with at least one of these comorbidities, demonstrating consistency in the effect estimates among those with and without these comorbidities. Additionally, consistent associations were found among men ≥ 55 versus < 55 years of age, and among obese and nonobese men. In contrast, there was no association found in women across strata of these potential confounding factors (Table 4).

The study participants were drawn from 1193 families (median 4 persons/family). The sex-specific matched case-control study approach also demonstrated higher levels of SUA to be associated with carotid plaques in men but not women. The prevalence OR of having carotid plaques for men with SUA levels of 5 to < 6 mg/dl, 6 to < 6.8 mg/dl, and ≥ 6.8 mg/dl were 3.38 (95% CI 1.15–9.95), 2.84 (95% CI 0.96–8.45), and 6.54 (95% CI 1.83–23.37), respectively, compared with those with levels < 5 mg/dl (p = 0.01 for linear trend) by this approach. In women, the respective preva-

Table 3. Association of SUA and prevalence of carotid plaques in men stratified by hypertension, renal insufficiency, diabetes, age, BMI.

Risk Factor	Presence of Carotid Plaques, n/N	Adjusted OR by Category of SUA, mg/dl <5	5 to < 6	6 to < 6.8	≥ 6.8	p for Linear Trend	p for Interaction
Hypertension*							
Absent	343/1468	1.0	1.34	1.41	2.04	0.008	0.2
Present	337/778	1.0	1.23	2.06	1.52	0.09	
Renal insufficiency							
Absent	585/2074	1.0	1.36	1.61	1.68	0.01	0.6
Present	95/172	1.0	0.66	1.79	3.04	0.02	
Diabetes							
Absent	571/2023	1.0	1.25	1.53	1.53	0.04	0.5
Present	109/223	1.0	1.72	1.40	3.43	0.009	
Age							
< 55 yrs	143/1180	1.0	0.95	1.31	1.82	0.03	0.3
≥ 55 yrs	537/1066	1.0	1.42	1.67	1.67	0.03	
BMI							
< 30 kg/m^2	513/1663	1.0	1.34	1.66	1.66	0.02	0.8
≥ 30 kg/m^2	167/583	1.0	1.36	1.73	2.06	0.05	

* Additionally adjusted for mean arterial pressure. BMI: body mass index.

Table 4. Association of SUA and prevalence of carotid plaques in women stratified by hypertension, renal insufficiency, diabetes, age, BMI.

Risk Factor	Presence of Carotid Plaques, n/N	Adjusted OR by Category of SUA, mg/dl <5	5 to < 6	6 to < 6.8	≥ 6.8	p for Linear Trend	p for Interaction
Hypertension*							
Absent	282/1799	1.0	1.13	1.08	0.81	0.9	0.7
Present	306/821	1.0	0.95	1.00	1.16	0.7	
Renal insufficiency							
Absent	480/2337	1.0	1.09	1.13	0.90	0.9	0.4
Present	108/283	1.0	0.89	0.85	1.31	0.7	
Diabetes							
Absent	495/2384	1.0	1.06	1.07	0.95	0.9	0.5
Present	93/236	1.0	0.80	0.75	1.23	0.8	
Age							
< 55 yrs	123/1371	1.0	0.99	1.24	0.22	0.3	0.1
≥ 55 yrs	465/1249	1.0	1.06	1.03	1.37	0.3	
BMI							
< 30 kg/m^2	435/1874	1.0	1.05	1.08	1.28	0.5	0.9
≥ 30 kg/m^2	153/746	1.0	1.10	1.03	0.91	0.8	

* Additionally adjusted for mean arterial pressure. BMI: body mass index.

lence OR were 0.87 (95% CI 0.48–1.60), 1.25 (95% CI 0.51–3.11), and 1.33 (95% CI 0.48–3.71), compared with those with SUA < 5 mg/dl (p = 0.7 for linear trend).

DISCUSSION

Our findings based on data from a large multicenter cross-sectional study demonstrated that higher levels of SUA were associated with a higher prevalence of carotid plaques in men. This association was consistent regardless of the presence or absence of conditions that may be associated with both uric acid and carotid atherosclerosis. While the uricosuric effects of estrogen[35] and the lower likelihood of preclinical atherosclerotic disease in premenopausal women may account for lack of association noted among women, hyperuricemia appeared to be associated with a higher prevalence of carotid plaques among postmenopausal women (women ≥ age 55 yrs).

To date, a few studies have specifically evaluated the association of SUA and carotid atherosclerosis, with some reporting higher SUA levels to be associated with carotid atherosclerosis[20,22,23,26], consistent with our findings, while others found no association[21,24,25]. Prior epidemiologic studies of hyperuricemia and adverse clinical cardiovascular outcomes have also been conflicting.

Contradictory results can be due to differences in adjustment for certain covariates and definitions used for such covariates, resulting in residual confounding. Some prior studies, with both negative and positive associations reported, have either failed to adjust for low-dose aspirin use or for renal insufficiency (both of which can increase SUA and risk for CVD[36,37]), have not used current standard definitions for hypertension, and/or have adjusted for the presence of hypertension and use of antihypertensive agents, which may cause problems of collinearity[1-3,5,8,10,21,23,24]. Finally, as any effect of SUA is likely to be small given the multifactorial nature of CVD, studies with relatively small numbers of events may not be able to demonstrate an association, particularly when populations studied are at low risk for the outcome under study[8-10]. Nevertheless, a recent metaanalysis with close to 9500 cases from 16 studies found a 13% increased risk (risk ratio 1.13, 95% CI 1.07–1.20) of coronary heart disease among those in the top tertile of SUA levels compared to the lowest tertile[38].

There are many potential mechanisms linking SUA to CVD. While not all individuals with hyperuricemia have clinical gout despite urate's ability to promote inflammation, a proinflammatory state is likely associated with hyperuricemia[39,40]. Further, in addition to its elevated levels in atherosclerotic plaques[41], urate can promote proliferative and proinflammatory responses in cultured vascular smooth-muscle cells[42,43]. Other evidence exists that uric acid may have a pathogenic role through vascular effects. In 2 rat models of hypertension, urate-lowering therapy modulated vascular remodeling, while direct treatment of hypertension did not[12,44]. On the other hand, direct effects of soluble urate on the vasculature have not been conclusively established. For example, urate infusion into the human circulation *in vivo* failed to demonstrate impairment of cardiovascular function[45], possibly related to antioxidant effects of soluble urate. However, urate may also be pro-oxidative under certain conditions. The net effects of these complex and, in some cases, competing functions of uric acid are unknown, although they provide considerable support for the possibility that uric acid may have direct biological effects on the vasculature.

Several characteristics of our study are noteworthy. First,

we were able to control for many known potential confounders, which were assessed according to standardized methods. Second, we were able to assemble a large sample not only to examine the association between SUA and carotid plaques, but also to assess whether the association was modified by potential confounders. Third, the consistent associations across strata of various factors that could act as potential confounders or effect measure modifiers suggest that our findings were unlikely to be confounded by these cardiovascular risk factors. As well, finding the same effect of SUA among subjects without major comorbidities minimizes the possibility of reverse causation and further lowers the likelihood that confounding explains our findings. Finally, we performed additional analyses to explore whether the relation of SUA with carotid plaques may be explained by other mechanisms, such as potentially shared genetic or environmental factors, a mutual association with inflammation (C-reactive protein, homocysteine), medications that have beneficial cardiovascular effects that also lower SUA (atorvastatin, fenofibrate, losartan), or mediation through the presence of gout, and found that the results remained similar.

Our study has some limitations. First, definitive conclusions about causality cannot be made given that our findings are cross-sectional. Second, it is possible that the observed association was imparted indirectly via effects of hypertension. However, the association was present among men both with and without hypertension, indicating that SUA has an association with carotid plaques independent of hypertension. Nevertheless, because multiple factors are likely to play a role in the development of carotid plaques, residual confounding may still potentially account for our findings despite our various analytic strategies.

SUA may have a pathophysiologic role in atherosclerosis. Given the cross-sectional expression of these data, evaluation of these preclinical cardiovascular outcomes in randomized trials of urate-lowering drugs (for example, those trials being conducted for gout) appears warranted. Current clinical treatment guidelines do not recommend treatment of asymptomatic hyperuricemia. Should SUA be confirmed as a risk factor for preclinical CVD, this may provide another indication for urate-lowering therapy irrespective of the presence of clinical gout.

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