

Plasma Urate and Risk of a Hospital Stay with AKI: The Atherosclerosis Risk in Communities Study

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Abstract

Background and objectives Higher urate levels are associated with higher risk of CKD, but the association between urate and AKI is less established. This study evaluated the risk of hospitalized AKI associated with urate concentrations in a large population-based cohort. To explore whether urate itself causes kidney injury, the study also evaluated the relationship between a genetic urate score and AKI.

Design, setting, participants, & measurements A total of 11,011 participants from the Atherosclerosis Risk in Communities study were followed from 1996–1998 (baseline) to 2010. The association between baseline plasma urate and risk of hospitalized AKI, adjusted for known AKI risk factors, was determined using Cox regression. Interactions of urate with gout and CKD were tested. Mendelian randomization was performed using a published genetic urate score among the participants with genetic data ($n=7553$).

Results During 12 years of follow-up, 823 participants were hospitalized with AKI. Overall, mean participant age was 63.3 years, mean eGFR was 86.3 ml/min per 1.73 m², and mean plasma urate was 5.6 mg/dl. In patients with plasma urate >5.0 mg/dl, there was a 16% higher risk of hospitalized AKI for each 1-mg/dl higher urate (adjusted hazard ratio, 1.16; 95% confidence interval, 1.10 to 1.23; $P<0.001$). When stratified by history of gout, the association between higher urate and AKI was significant only in participants without a history of gout (P for interaction=0.02). There was no interaction of CKD and urate with AKI, nor was there an association between genetic urate score and AKI.

Conclusions Plasma urate >5.0 mg/dl was independently associated with risk of hospitalized AKI; however, Mendelian randomization did not provide evidence for a causal role of urate in AKI. Further research is needed to determine whether lowering plasma urate might reduce AKI risk.

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Introduction

AKI is a common problem affecting populations worldwide (1). In the United States, roughly 2%–5% of hospitalized patients develop AKI, and those who develop AKI experience significantly greater mortality and morbidity (1,2), including progressive CKD (3). No specific treatments for AKI are available, but many cases may be preventable with management of volume and hemodynamic status as well as avoidance of nephrotoxic pharmacologic agents and iodinated contrast material (4,5). Thus, identification of risk factors for AKI, especially potentially modifiable risk factors, is key to reducing the impact of AKI.

Urate may be one such modifiable risk factor. Renal injury due to deposition of urate crystals in conditions such as tumor lysis syndrome has been well described. Urate may also have several noncrystal mechanisms of nephrotoxicity, including systemic vasoconstriction, impaired autoregulation, and oxidative damage (6). If urate does increase renal vascular resistance, individuals with higher urate may be more susceptible to hemodynamically mediated AKI. Indeed, higher urate

has been associated with AKI in a cohort of Israeli patients with normal kidney function, as well as in patients undergoing cardiac surgery (7–10). The urate-AKI relationship has not been studied in broader populations, such as multiple racial groups and individuals with CKD.

Using participants from the Atherosclerosis Risk in Communities (ARIC) study, a prospective, community-based cohort with >25 years of follow-up, we examined the association of plasma urate level and AKI hospitalizations. To evaluate whether higher urate may simply be a proxy for diminished kidney function and not itself a contributor to AKI, we also evaluated the relationship between a genetic urate score and AKI risk in a subgroup of ARIC participants.

Materials and Methods

Study Population

Data were collected as part of the ARIC study, a prospective community-based cohort of individuals aged 45–64 years from four sites (Washington County, MD;

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Forsyth County, NC; Jackson, MS; and Minneapolis, MN) (11). A total of 15,792 individuals were initially enrolled between 1987 and 1989. Individuals were re-examined every 3 years, with examinations occurring during 1990–1992, 1993–1995, and 1996–1998. A fifth examination was recently completed (2011–2013). The ARIC study has been approved by institutional review boards at each study site and has been carried out in accordance with the Declaration of Helsinki. Because albuminuria (a key risk factor for AKI) was first quantified in 1996–1998, the fourth examination was considered the baseline for this study. Of the 11,656 participants of the fourth examination, 50 had a previous episode of AKI or eGFR <15 ml/min per 1.73 m², 168 were missing plasma urate level, and 423 were missing a covariate of interest and thus were excluded from the analysis. Four individuals with extreme urate levels (0.2 mg/dl, 0.9 mg/dl, 19 mg/dl, and 28 mg/dl) were excluded because of concern for laboratory error, for a final study population of 11,011 participants.

Laboratory Measurements and Variable Definitions

Plasma urate was measured from samples stored at –80°C since collection at the ARIC Lipid Laboratory (at Baylor University) during 2010–2011 using Olympus AU400e analyzers. The coefficient of variation for this assay was 0.98% (12). Diabetes was defined as a single fasting serum glucose ≥126 mg/dl, nonfasting glucose ≥200 mg/dl, self-reported physician-diagnosed diabetes, or use of antidiabetic medications. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (from a mean of two measurements), or use of antihypertensive agents. Prevalent coronary heart disease was defined as history of myocardial infarction as identified by an adjudicated electrocardiogram, physician diagnosis, or history of coronary bypass or coronary artery angioplasty. Creatinine was measured by the modified kinetic Jaffe method in plasma samples and calibrated to the National Institute of Standards and Technology standard; eGFR was calculated using the CKD-Epidemiology Collaboration 2009 creatinine equation (13). Urine albumin-to-creatinine ratio (ACR) was measured from a spot urine sample by a nephelometric method. Use of allopurinol or losartan (which increases urinary urate excretion [14]) was identified among patient-reported medications at visit 4. Diuretic use was defined as patient-reported use of thiazide, loop, or potassium-sparing diuretics at visit 4. A history of gout was defined on the basis of self-reported, physician-diagnosed gout at visit 4; self-report of a physician diagnosis of gout is a reliable and a sensitive measure of gout (15) and has been used in previous studies (16–22). ESRD was identified through linkage to the US Renal Data System registry.

To evaluate whether urate might be a causal risk factor for AKI, we performed Mendelian randomization analysis, an instrumental variable approach in which genetic determinants of a risk factor are integrated into analyses (23). Using 7533 previously genotyped European American ARIC participants, we calculated their genetic urate score based on genotyping of eight single-nucleotide polymorphisms (24). The score, which reflects the expected difference in urate concentration from an individual homozygous for major alleles at each of the eight single-nucleotide polymorphisms, ranged from –1.1 to 1.3 mg/dl and captured 6.0% of the variation in urate levels (24).

Characteristic	Quartile 1 (n=2993)	Quartile 2 (n=2674)	Quartile 3 (n=2654)	Quartile 4 (n=2690)	P Value for Trend
Mean urate ±SD (range) (mg/dl)	3.9±0.6 (1.5–4.6)	5.1±0.3 (4.7–5.5)	6.0±0.3 (5.6–6.5)	7.6±1.0 (6.6–14.4)	N/A
Mean age ±SD (yr)	62.9±5.8	63.2±5.6	63.3±5.6	63.8±5.7	<0.001
Men (%)	20.9	40.3	54.0	63.8	<0.001
Black (%)	19.4	20.4	20.8	27.0	<0.001
Diabetes (%)	15.5	16.0	16.1	19.4	<0.001
Hypertension (%)	37.3	44.5	47.4	60.7	<0.001
Prevalent coronary heart disease (%)	4.6	7.7	8.2	13.6	<0.001
Mean eGFR ±SD (ml/min per 1.73 m ²)	91.1±13.4	87.6±14.3	85.7±15.0	80.4±18.5	<0.001
eGFR <60 ml/min per 1.73 m ² (%)	2.1	3.6	5.2	14.1	<0.001
ACR ≥30 mg/g (%)	6.5	7.1	7.5	11.9	<0.001
Diuretic use (%)	8.1	12.4	16.8	32.6	<0.001
Allopurinol use (%)	1.1	1.4	1.4	2.3	<0.001
Losartan use (%)	0.4	0.9	0.5	0.8	0.12
Gout (%)	2.8	4.0	4.7	12.8	<0.001

Participant numbers in quartiles are not identical because of large numbers of participants with the same urate level. N/A, not applicable; ACR, albumin-to-creatinine ratio.

AKI Ascertainment

Participants were followed prospectively for intervening hospitalizations and death. Hospitalizations were reported during annual phone interviews (year 20 contact rate >90%) and active surveillance of community hospital discharge lists; at least 26 distinct discharge diagnostic codes were abstracted from hospitalization discharge records. Deaths were tracked by active surveillance of local obituaries, state death lists, and death certificates from the Department of Vital Statistics; all International Classification of Diseases (ICD), 10th Revision, Clinical Modification (ICD-10-CM) codes were abstracted from death certificates. As reported previously (25), hospitalization with AKI was defined by the ICD, 9th Revision, Clinical Modification codes 584.× and ICD-10-CM codes N17.× among discharge diagnoses or death certificates, respectively. This algorithm has been previously validated against Kidney Disease Improving Global Outcomes (KDIGO) criteria as having a high specificity (99.6%), but a low sensitivity (17.4%) (26). Sensitivity was higher if only KDIGO stages 2–3 AKI were considered (40.3%).

Statistical Analyses

Baseline characteristics of the study population were compared using linear or logistic regression for continuous and dichotomous characteristics, respectively, on quartile of plasma urate, expressed as an ordinal variable. A similar analysis was performed for quartile of genetic urate score. The association between urate and hospitalized AKI was modeled using Cox proportional hazards regression and a linear spline with knot at 5.0 mg/dl, a cut-point selected because of a nonlinear relationship between urate and hospitalized AKI observed with use of locally weighted smoothing plots. Death and ESRD were treated as censoring events. Multivariable analyses were adjusted for age; sex; race; eGFR (modeled as a linear spline with a knot at 60 ml/min per 1.73 m²); logACR; hypertension; diabetes; coronary heart disease; and use of diuretics, allopurinol, and losartan. These covariates are known risk factors for AKI that have also been shown to be associated with urate in observational studies (27–29).

Several sensitivity analyses were performed. To determine whether observed associations were driven primarily by the presence of CKD or gout, analyses were repeated in subgroups and interactions were formally tested. To limit confounding by urate-lowering medication use, analyses were repeated after exclusion of persons taking allopurinol at the time of study visit. A similar analysis was performed after exclusion of participants taking diuretics. Finally, instrumental analysis with the genetic urate score as an instrument (*i.e.*, Mendelian randomization) was performed to investigate for evidence of a causal effect of urate on AKI hospitalization. The relationship between genetic urate score and AKI was assessed in a fully adjusted (excluding plasma urate as a covariate) Cox proportional hazards model. This allowed for evaluation of the urate-AKI relationship with minimal confounding because the single-nucleotide polymorphisms used for the genetic urate score were randomly inherited and unlikely to be related to confounding factors. A causal relationship would be supported, but not proven (30), by a positive association between genetic urate score and AKI, with a hazard ratio (HR) for genetic urate score similar to that for plasma urate. Statistical analyses were performed using Stata software, version 13.1 (Stata Corp., College Station, TX).

Results

Baseline Characteristics of Participants

Of 11,011 participants with complete baseline data, 823 participants (7.5%) had an AKI hospitalization between baseline and December 31, 2010. Mean follow-up (\pm SD) was 12 \pm 3.1 years. Participants with higher plasma urate were older, more often male, and more often black (Table 1). They were also more likely to have diabetes, hypertension, coronary heart disease, an eGFR<60 ml/min per 1.73 m², albuminuria, and a history of gout and to be taking diuretics or allopurinol. Mean urate was 6.2 \pm 1.68 mg/dl in those with an AKI hospitalization and 5.6 \pm 1.46 mg/dl in participants without (P <0.001). When stratified by history of gout (available for 10,945 of the participants), similar distinctions applied: those with a history of gout were older, were more

Table 2. Baseline characteristics of participants by gout diagnosis

Characteristic	No Gout Diagnosis (n=10,291)	Gout (n=654)	P Value
Mean urate \pm SD (range) (mg/dl)	5.5 \pm 1.4 (1.5–12.6)	6.8 \pm 1.9 (2.5–14.4)	<0.001
Mean age \pm SD (yr)	63.2 \pm 5.7	64.4 \pm 5.7	<0.001
Men (%)	42.9	63.9	<0.001
Black (%)	21.1	29.8	<0.001
Diabetes (%)	15.6	31.7	<0.001
Hypertension (%)	45.8	66.2	<0.001
Prevalent coronary heart disease (%)	7.9	15.4	<0.001
Mean eGFR \pm SD (ml/min per 1.73 m ²)	86.7 \pm 15.5	81.0 \pm 19.5	<0.001
eGFR<60 ml/min per 1.73 m ² (%)	5.6	15.0	<0.001
ACR \geq 30 mg/g (%)	7.5	18.3	<0.001
Diuretic use (%)	16.2	31.5	<0.001
Allopurinol use (%)	0.2	23.1	<0.001
Losartan use (%)	0.5	2.0	<0.001

Information on gout diagnosis was not available for 66 of 11,011 participants. ACR, albumin-to-creatinine ratio.

often male, and had a higher burden of comorbidities (Table 2). As expected, urate, allopurinol use, and gout prevalence were associated with higher genetic urate score (Table 3). Otherwise, most covariates were not associated with genetic urate score. Diabetes showed a decreasing prevalence with higher urate score.

Association of Plasma Urate Level and Hospitalization with AKI

In unadjusted analysis, plasma urate was significantly associated with hospitalized AKI with an HR of 1.34 (95% confidence interval [95% CI], 1.28 to 1.42; $P < 0.001$) for each 1-mg/dl higher urate > 5.0 mg/dl. Among participants with values < 5.0 mg/dl, the HR for each 1-mg/dl higher urate was slightly attenuated and not statistically significant (HR, 1.16; 95% CI, 0.98 to 1.37; $P = 0.08$). After adjustment for age; sex; race; eGFR; log-transformed ACR values (logACR); hypertension; diabetes; coronary heart disease; and use of diuretics, allopurinol, and losartan, there remained a significant association between urate and hospitalized AKI at levels > 5.0 mg/dl (Table 4). The adjusted HR (aHR) for each 1-mg/dl higher urate > 5.0 mg/dl was 1.16 (95% CI, 1.10 to 1.23; $P < 0.001$) (Figure 1). For urate of ≤ 5.0 mg/dl, the risk of hospitalized AKI with higher urate remained nonsignificant, with an aHR of 1.10 for each 1-mg/dl higher urate (95% CI, 0.92 to 1.30; $P = 0.30$). In sensitivity analyses excluding participants taking allopurinol and diuretics, the association between urate and AKI was similar if slightly attenuated (excluding allopurinol use: aHR, 1.09 [95% CI, 0.91 to 1.29], $P = 0.35$ for urate ≤ 5.0 mg/dl; aHR, 1.18 [95% CI, 1.11 to 1.25], $P < 0.001$ for urate > 5.0 mg/dl; excluding diuretic use: aHR, 1.19 [95% CI, 0.98 to 1.44], $P = 0.08$ for urate ≤ 5.0 mg/dl; aHR, 1.09 [95% CI, 1.00 to 1.18], $P = 0.04$ for urate > 5.0 mg/dl). The association between urate and AKI was very similar when cases of primary AKI (AKI code limited to the primary position) and all other cases of AKI were examined separately.

Subgroup Analysis by eGFR < 60 ml/min per 1.73 m^2 , Albuminuria, and Gout History

When stratified by eGFR < 60 ml/min per 1.73 m^2 , albuminuria, or CKD stages 1–5 (presence of eGFR < 60 ml/min per 1.73 m^2 or ACR ≥ 30 mg/g), the associations between urate and hospitalized AKI were similar to results obtained in the full population (Table 4). When stratified by history of gout at baseline, higher urate was associated with AKI only in those without a history of gout (P for interaction = 0.02).

Mendelian Randomization Using Genetic Urate Score

Among European Americans with available genotyping, genetic urate score was significantly associated with plasma urate in demographic (age, sex, and study center)-adjusted analyses. Each 1-mg/dl higher urate score was associated with a 1.04-mg/dl higher plasma urate (95% CI, 0.94 to 1.13; $P < 0.001$). However, there was no association between genetic urate score and hospitalized AKI in unadjusted or adjusted analyses (HR, 0.95 [95% CI, 0.72 to 1.26], $P = 0.74$; aHR, 1.01 [95% CI, 0.77 to 1.34], $P = 0.92$), although the 95% CIs overlapped with those observed in the association of urate and AKI (Table 4).

Table 3. Baseline characteristics of participants by quartiles of genetic urate score

Characteristic	Quartile 1 (n=1884)	Quartile 2 (n=1883)	Quartile 3 (n=1883)	Quartile 4 (n=1883)	P Value for Trend
Mean urate \pm SD (range) (mg/dl)	5.2 \pm 1.4 (1.5–11.1)	5.5 \pm 1.4 (1.6–11.1)	5.6 \pm 1.4 (1.8–13.0)	6.0 \pm 1.5 (1.5–12.3)	< 0.001
Mean age \pm SD (yr)	63.7 \pm 5.6	63.6 \pm 5.6	63.5 \pm 5.7	63.5 \pm 5.6	0.22
Men (%)	48.0	46.6	46.5	44.9	0.07
Diabetes (%)	15.3	13.3	13.1	12.8	0.03
Hypertension (%)	41.8	42.7	42.5	41.8	0.99
Prior coronary heart disease (%)	8.8	9.0	8.8	8.4	0.63
Mean eGFR \pm SD (ml/min per 1.73 m^2)	84.4 \pm 14.1	84.3 \pm 14.2	85.5 \pm 14.1	84.6 \pm 14.5	0.23
eGFR < 60 ml/min per 1.73 m^2 (%)	5.7	6.3	2.4	2.5	0.19
ACR ≥ 30 mg/g (%)	6.1	6.5	7.5	6.5	0.37
Diuretic use (%)	13.9	15.4	14.4	15.7	0.21
Allopurinol use (%)	0.6	1.1	1.5	2.8	< 0.001
Losartan use (%)	0.5	0.5	1.1	0.8	0.09
Gout (%)	3.4	3.9	6.2	8.4	< 0.001

Race is not included as a covariate because genetic urate score was available for white participants. ACR, albumin-to-creatinine ratio.

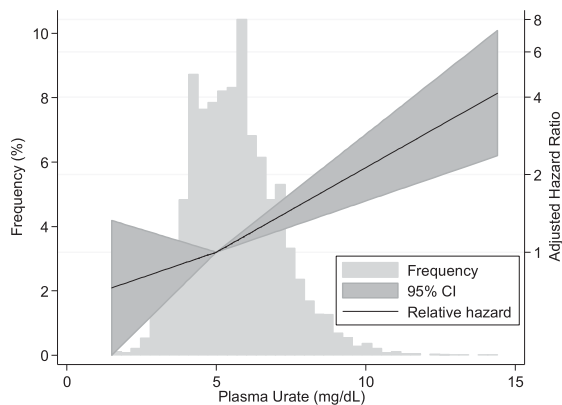
Group	Plasma Urate, per 1 mg/dl ^a						Genetic Urate Score, per 1 mg/dl ^b			
	Urate ≤5.0 mg/dl		Urate >5.0 mg/dl		P Value for Interaction	Participants (n)	aHR (95% CI)	Participants (n)	aHR (95% CI)	P Value
	aHR (95% CI)	P Value	aHR (95% CI)	P Value						
All participants	1.10 (0.92 to 1.30)	0.30	1.16 (1.10 to 1.23)	<0.001	N/A	7533	1.01 (0.77 to 1.34)	7533	1.01 (0.77 to 1.34)	0.92
eGFR					0.55					
≥60 ml/min per 1.73 m ²	1.07 (0.90 to 1.29)	0.43	1.17 (1.10 to 1.26)	<0.001		7063	0.98 (0.72 to 1.32)	7063	0.98 (0.72 to 1.32)	0.87
<60 ml/min per 1.73 m ²	1.31 (0.64 to 2.72)	0.45	1.11 (0.99 to 1.25)	0.08		470	1.20 (0.64 to 2.26)	470	1.20 (0.64 to 2.26)	0.57
Proteinuria					0.88					
ACR<30 mg/g	1.13 (0.93 to 1.37)	0.22	1.15 (1.07 to 1.23)	<0.001		7032	0.95 (0.70 to 1.30)	7032	0.95 (0.70 to 1.30)	0.76
ACR≥30 mg/g	0.92 (0.62 to 1.37)	0.67	1.18 (1.05 to 1.33)	0.007		501	1.13 (0.57 to 2.27)	501	1.13 (0.57 to 2.27)	0.72
CKD^c					0.92					
No	1.10 (0.90 to 1.34)	0.34	1.15 (1.06 to 1.24)	<0.001		6662	0.89 (0.64 to 1.23)	6662	0.89 (0.64 to 1.23)	0.48
Yes	1.05 (0.74 to 1.50)	0.79	1.16 (1.06 to 1.28)	0.001		871	1.24 (0.75 to 2.06)	871	1.24 (0.75 to 2.06)	0.40
Gout status					0.02					
No gout	1.06 (0.89 to 1.27)	0.52	1.23 (1.15 to 1.31)	<0.001		7095	0.96 (0.72 to 1.29)	7095	0.96 (0.72 to 1.29)	0.81
Gout	1.14 (0.52 to 2.51)	0.74	1.00 (0.86 to 1.15)	0.96		411	0.88 (0.36 to 2.11)	411	0.88 (0.36 to 2.11)	0.77

aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; N/A, not applicable; ACR, albumin-to-creatinine ratio.

^aAdjusted for age, sex, race, hypertension, diabetes, coronary heart disease, eGFR, logACR, diuretic use, allopurinol use, losartan use. Urate is modeled as a linear spline with knot at 5 mg/dl.

^bAdjusted for age, sex, and study center.

^ceGFR<60 ml/min per 1.73 m² or eGFR≥60 ml/min per 1.73 m² with ACR≥30 mg/g.



Note: Of the 823 AKI hospitalizations, 215 occurred among participants with urate ≤ 5.0 mg/dL, and 608 occurred among those with urate > 5.0 mg/dL.

Figure 1. | Relationship between plasma urate and relative hazard for hospitalization with AKI. 95% CI, 95% confidence interval.

Discussion

In this community-based study of $>11,000$ participants followed for an average of 12 years, plasma urate >5.0 mg/dl was independently associated with risk of subsequent hospitalized AKI, even after adjustment for age, sex, race, eGFR, logACR, hypertension, diabetes, coronary heart disease, and use of medications that affect urate. For each 1-mg/dl higher urate >5.0 mg/dl, the risk of AKI was 16% higher. This association did not differ by CKD status and, interestingly, was observed only in participants without a history of physician-diagnosed gout. While the results of Mendelian randomization were null, suggesting that the association between urate and AKI may not be causal, there was limited statistical power.

This study extends prior work primarily done in smaller clinical populations. In participants with normal baseline renal function from the Jerusalem Lipid Research Clinic cohort, individuals with the highest quintile of serum urate had a higher risk of AKI (aHR, 2.87; 95% CI, 1.45 to 5.69) compared to all other individuals (7). Both preoperative and postoperative serum urate have been associated with higher risk of postoperative AKI (based on creatinine criteria as defined by the AKI Network [31]) in patients undergoing cardiac surgery. In individuals undergoing high-risk cardiothoracic surgery, a preoperative urate ≥ 6.1 mg/dl was associated with a 4-fold higher risk of developing AKI postoperatively (odds ratio, 3.98; 95% CI, 1.10 to 14.33) compared to urate <6.1 mg/dl (8). In a subsequent study of additional cardiac surgery patients, patients with the highest tertile of postoperative urate (>5.77 mg/dl) had a 7-fold higher AKI risk (odds ratio, 6.98; 95% CI, 1.75 to 27.85) compared with those with the lowest tertile of urate (≤ 4.53 mg/dl) (10). Our study extends these findings to the general population and suggests a more modest association between urate and AKI.

An interesting finding of our study was that higher urate was a risk factor in participants without a history of gout but not in those with a history of gout. These results should be treated cautiously, however, because the subgroup with a history of gout was small and limited our power to detect associations. Urate measurements in persons with gout may reflect treated levels (23% of those with gout were receiving

allopurinol at baseline), although our analyses were adjusted for allopurinol use. In addition, the results of Mendelian randomization analysis suggest that the association between urate and AKI may not be causal, although this is not definitive given overlapping 95% CIs between the risk associated with serum urate and the risk associated with urate score. The Mendelian randomization analysis is similar to previous studies that have used a genetic urate score or individual genes associated with urate levels as instrumental variables (24,32–34). While an association between urate score and gout has been demonstrated, no association has been observed between urate genes and BP, fasting glucose, CKD, coronary artery disease, or metabolic syndrome in these studies. Of course, Mendelian randomization is not a definitive test of causation given potential gene-gene and gene-environment interactions that may exist (30).

Several potential mechanisms by which urate may cause kidney injury have been suggested, including activation of the renin-angiotensin-aldosterone system, reduction of nitric oxide production, inhibition of renal tubule cell proliferation, and increased production of cytokines and other systemic factors (6,35–37). In animal studies, lowering urate reduced glomerular hypertension, preserved renal function, and decreased tubulointerstitial fibrosis, supporting a potential causal role of hyperuricemia in kidney disease (35,38). If a causal relationship exists, urate might also be useful in identifying individuals at substantial risk for AKI, particularly AKI that occurs in the setting of hemodynamic instability or tubulointerstitial damage. Despite this experimental evidence, however, a causal relationship for higher levels of urate and the development of AKI and CKD has not been established in humans, although trials of urate-lowering medications for prevention of CKD progression are ongoing (39,40). Hyperuricemia may simply be an indicator of reduced renal function (perhaps the strongest risk factor for AKI), or a proxy for other AKI susceptibilities, such as treatment with nonsteroidal anti-inflammatory drugs, commonly used in gout.

Our study has several strengths. To our knowledge this is the first large population-based study with lengthy follow-up to investigate the relationship between urate and AKI. Unlike the studies by Ejaz and colleagues, urate levels were measured in an outpatient setting, often many years before the AKI event, thus reducing the possibility of reverse causation. However, plasma urate, creatinine, and albuminuria were measured only once, and longitudinal measurements of urate have shown mild increases over time (41). Further, all data were collected prospectively, and hospitalization data were gathered by active surveillance.

Our study also has limitations. AKI events were identified by diagnostic codes, a method that may have missed cases of AKI and does not include cases of AKI identified and managed in the ambulatory setting. Use of diagnostic codes instead of serum creatinine to identify AKI has low sensitivity but is unlikely to introduce bias because coding of AKI is likely not related to urate independent of eGFR, which was included in analysis. Second, variability in creatinine and albuminuria levels may have led to participants being miscategorized. Third, this cohort was also at low risk for AKI, with only 823 AKI hospitalizations in $>11,000$ participants, which may have limited our ability to precisely characterize the association between urate and AKI. Finally, as in all observational studies, residual

confounding is possible. In several instances, baseline characteristics substantially differed between participants in the lowest and highest quartiles of urate (e.g., sex, diuretic use), raising the possibility that the observed association between urate and AKI may be spurious and motivating the subsequent Mendelian randomization analysis.

In summary, this study demonstrates an association between urate and hospitalized AKI independent of markers of kidney function and other known risk factors for AKI. The risk of AKI was higher even at levels of urate within the normal range. Interestingly, the association was not present in participants with gout, a population with demonstrated adverse effects of hyperuricemia, and results from the Mendelian randomization analysis did not provide supportive evidence for a causal relationship between urate and AKI risk. Further work is needed to determine whether urate-lowering therapy might be beneficial in modifying risk of AKI.

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Some of the data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the United States government.

Disclosures

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