Cohort Study of Repeated Measurements of Serum Urate and Risk of Incident Atrial Fibrillation

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***Background*—**Current evidence on the association between serum urate and risk of atrial fibrillation (AF) is limited by cross-sectional designs and 1-time measurement of serum urate. The roles of serum urate, gout-related inflammation, and systemic inflammation in the etiology of AF are currently unknown. This gap is important, given that systemic inflammation is a recognized risk factor for AF.

***Methods and Results*—**We conducted a prospective cohort study of 123 238 Chinese patients from 2006 to 2014. Serum urate concentrations were measured in 2006, 2008, 2010, and 2012. Incident AF cases were identified via biennial 12-lead ECG assessment. We used a Cox proportional hazards model to examine the sex-specific associations of cumulative average serum urate and changes in serum urate accounting for baseline level with risk of incident AF. We also assessed the joint associations of serum urate and high-sensitivity C-reactive protein levels. Comparing extreme categories, participants with the highest quintile of serum urate had 1.91-fold higher risk of AF (adjusted hazard ratio: 1.91; 95% CI, 1.32–2.76; P=0.001 for trend). Participants with both high serum urate and high-sensitivity C-reactive protein had 2.6-fold elevated risk of incident AF compared with those with normal levels of serum urate and high-sensitivity C-reactive protein (adjusted hazard ratio: 2.63; 95% CI, 1.63–4.23).

***Conclusions*—**High serum urate levels and increases in serum urate over time were associated with increased risk of incident AF. Patients with high levels of both serum urate and high-sensitivity C-reactive protein had substantially higher risk of AF. **(*J Am Heart Assoc*. 2019;8:e012020. DOI: 10.1161/JAHA.119.012020.)**

Key Words: atrial fibrillation • epidemiology • uric acid

One of the most serious comorbidities in patients with gout is cardiovascular disease.[1,2] Although much of the focus regarding cardiovascular disease risk has been on myocardial infarction and heart failure, atrial fibrillation (AF), a disease of cardiac conduction with devastating consequences including fatal embolic stroke, is largely understudied and is not typically included in studies of cardiac outcomes. In the past decade, the prevalence of AF has increased dramatically. An evolving epidemic, AF can predispose to subsequent stroke, heart failure, and mortality. More than 33 million individuals worldwide have AF, with related mortality rising in parallel.[3,4] Limited insights currently exist regarding preventive opportunities. The potential impact of serum urate and related inflammation in the physiopathology of AF is unclear and represents an important gap, given that systemic inflammation is a recognized risk factor for AF.[5]

Serum urate could induce oxidative stress, inflammation, and vascular stiffness and is associated with metabolic syndrome, carotid atherosclerosis, endothelial dysfunction, and adverse effects on platelet adhesiveness and aggregation.[6] High serum urate is highly heritable,[7] has been associated with increased risk of AF,[8–15] and predicts new-onset AF after coronary artery

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Clinical Perspective

What Is New?

- Currently evidence on serum urate with risk of atrial fibrillation (AF) is mainly from cross-sectional studies, based on prevalent AF cases, and limited by only 1-time measurement of serum urate.
- In a large prospective cohort study with 123 238 participants followed from 2006 to 2012, both an increased cumulative average and elevations in serum urate over time were associated with increased risk of incident AF.
- The combination of high serum urate and high-sensitivity C-reactive protein levels was associated with a significant increased risk of incident AF.

What Are the Clinical Implications?

- This study provided important evidence of an association between a relatively common treatable metabolic alteration (higher serum urate) and a common cardiac rhythm disorder (AF) with substantial morbidity and mortality.
- This study suggested that hyperuricemia alone is important and that a complex interrelationship may exist between levels of serum urate and the role of inflammation in accelerating arrhythmia and atrial fibrillation.

bypass grafting[16] and AF recurrence after ablation.[17] However, prior studies were limited by only 1-time measurement of serum urate, cross-sectional study design, use of prevalent AF cases, and insufficient covariate adjustment.[10,12,13,15,16,18–20] Longitudinal data are needed to consider baseline serum urate level and further rule out issues of reverse causation. The long-term cumulative association of serum urate and risk of incident AF is unclear. The relationship between changes in serum urate level and risk of AF remains unknown. Furthermore, the joint effects of serum urate with inflammation level, measured by hs-CRP (high-sensitivity C-reactive protein), is also uncertain.

We aimed to address the aforementioned knowledge gaps based on 2 large prospective cohort studies with 123 238 participants followed from 2006 to 2014 in China. We hypothesized that long-term high serum urate and increases in serum urate over time are associated with increased risk of incident AF. We further hypothesized that the association between serum urate and risk of AF is modified by inflammation, as indexed by hs-CRP levels.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set by qualified researchers trained in human subject confidentiality protocols may be sent to corresponding author Xiang Gao.

Study Population

Our study was based on Kailuan I and II, 2 large prospective cohort studies designed to investigate risk factors for common noncommunicable diseases. It is based in the Kailuan community in the city of Tangshan, in the southeast of Beijing, China, with low population mobility and relative internal stability. All residents in the Kailuan community (n=155 418) were current or retired employees of the Kailuan coal mining company and were invited to participate in the study. The Kailuan I study includes 101 510 resident participants (81 110 men and 20 400 women aged 18–98 years) who lived in the Kailuan community and completed the first survey between June 2006 and October 2007. Every 2 years all participants underwent questionnaire assessments, physical examinations, and laboratory tests in the hospitals. Similarly, the Kailuan II study consists of 35 856 Kailuan residents aged ≥18 years who were not part of the Kailuan I study and enrolled between June 2008 and October 2010. The studies were approved by the ethics committee of the Kailuan Medical Group. All participants gave written informed consent.

Our analytic sample consisted of 123 238 participants followed up from 2006 to 2014. We excluded 4343 participants with a history of stroke, myocardial infarction, or cancer before baseline; 871 participants with AF or atrial flutter at baseline based on ECG reading, self-reported AF, or atrial flutter history; 2292 participants with missing information on serum urate; and 28 273 participants without follow-up information. Participants were followed up until December 31, 2014, the event of interest, or death.

Measurement of Urate

Study participants returned fasting blood samples in the morning after an 8- to 12-hour overnight fast. Samples were transfused into vacuum tubes containing EDTA and were collected and measured in 2006, 2008, 2010, and 2012. We calculated a cumulative average of repeated measurements of serum urate to represent long-term urate level. We calculated the changes between adjacent measurements and calculated a per-year change variable to represent changes in serum urate over time. All calculations were based on available serum urate measurements from 2006 to the end of follow-up. Because men have higher serum urate levels than women, sex-specific quintiles were calculated.

Measurement of hs-CRP

Levels of hs-CRP were assessed by a commercial high-sensitivity nephelometry assay (Cias Latex CRP-H; Kanto Chemical) at the central laboratory of Kailuan Hospital. For hs-CRP, the lower limit of detection was 0.1 mg/L, and intra- and interassay coefficients of variation were 6.53% and 4.78%.

Assessment of Incident AF

Diagnosis of AF or flutter was based on a 12-lead ECG, which was conducted during follow-up visits every 2 years for all Kailuan participants. We defined *incident* AF cases according to the European Society of Cardiology guideline: (1) "absolutely" irregular RR intervals on the surface ECG; (2) no distinct P waves on the surface ECG and regular atrial electrical activity in some ECG leads, most often lead V1; and (3) atrial cycle length, the interval between 2 atrial activations, usually <200 ms (>300 beats/min).[21] *Paroxysmal* AF was defined as >2 AF outbreaks with duration of each outbreak <7 days. Other types were classified as *persistent* or *permanent* AF. Two cardiologists independently read all ECGs and confirmed AF cases. We defined the first signs of AF during follow-up as the incident AF cases.

Assessment of Covariates

Demographics, socioeconomic status, medical history, medication use, and psychosocial and lifestyle information were collected for all Kailuan participants at every clinical follow-up visit. Height, weight, and blood pressure were assessed by trained nurses during the survey interviews. Total cholesterol, triglycerides, HDL (high-density lipoprotein) cholesterol, LDL (low-density lipoprotein) cholesterol, and creatinine were assessed by autoanalyzer (Hitachi 747; Hitachi) at the central laboratory of Kailuan Hospital. We estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[22]

Statistical Analyses

We used a Cox proportional hazards model to examine the sex-specific associations of long-term average serum urate level and changes in serum urate with risk of incident AF. We modeled changes in serum urate as quintiles and as a continuous variable representing a 10-mmol/L increment. We tested the interactions between hs-CRP and serum urate level with incident AF risk at both multiplicative and additive scales. The relative excess risk due to interaction was calculated with 95% CI.

To examine whether those with a high serum urate level but with no history of gout have an elevated risk of AF, we excluded 500 participants with self-reported history of gout. As a sensitivity analysis, we also excluded participants with history of hypertension, high cholesterol, obesity or overweight, heart failure, renal failure, chronic kidney disease, AF-associated structural heart disease based on echocardiography, hypertrophic cardiomyopathy, valvular heart disease or hyperthyroidism, and impaired pulmonary function.

For our main analysis of long-term serum urate, if serum urate information was missing, we carried forward serum urate information from the previous measurement. As a sensitivity analysis, we repeated our analyses using complete cases only with no carry-forward and performed multiple imputation for missing data in serum urate. For our analyses on changes in serum urate, we calculated change based on available data and did not perform carry-forward or multiple imputation. We also assessed the robustness of our results to unmeasured and residual confounders. We tested proportional hazards assumptions based on the Schoenfeld residuals and included an interaction term between covariates and time. All analyses were performed using SAS (v9.4; SAS Institute).

Results

Among 123 238 participants in our analytic sample, the mean age was 48 years, and 79% were men. Overall, 107 360 participants had repeated measurements of serum urate level. Participants included and excluded from this analysis were similar in terms of baseline characteristics, except that those excluded tended to drink less alcohol and were less likely to use antihypertensive, lipid lowering, and hypoglycemic medications and to have family history of cardiovascular disease (Table S1). Participants who had high serum urate tended to drink more alcohol and consume more salt; were more likely to be current smokers; had higher systolic and diastolic blood pressure and higher triglycerides; were more likely to use antihypertensive, lipid lowering, and hypoglycemic medications; and had higher levels of hs-CRP than those who did not have high serum urate (Table 1). Median level of serum urate was 244 umol/L (4.1 mg/dL) for women and 302 umol/L for men (Table S2).

During median follow-up of 6.7 years (interquartile range: 5.3–8.3 years) from 2006 to 2014, we identified a total of 352 incident AF cases from ECG readings. In the multivariable model, baseline serum urate was not significantly associated with risk of AF, with a hazard ratio (HR) comparing fifth and first quintiles (1.25 [95% CI, 0.88–1.78]; Table S3). Cumulative average serum urate level over time was significantly associated with incident risk of AF (Table 2). After multivariable adjustment for demographics, socioeconomic factors, medical history, and cardiovascular disease risk factors, participants with the highest quintiles of serum urate had 1.91 times higher risk of AF compared with those in the lowest quintile (adjusted HR: 1.91 [95% CI, 1.32–2.76]; P=0.001 for trend).

Table 1. Baseline Characteristics According to Cumulative Average Serum Urate Concentrations

	Q1	Q2	Q3	Q4	Q5
Total, n	24 642	24 631	24 614	24 695	24 656
Serum urate,* mmol/L	209±28	256±22	290±26	329±31	404±60
Age, y, mean±SD	48.5±12.5	49.2±12.9	48.7±13.4	48.0±14.1	46.9±15.1
Men, n (%)	19 530 (79.3)	19 505 (79.2)	19 514 (79.3)	19 594 (79.3)	19 535 (79.2)
Average income, ¥/mo, n (%)					
<500	4579 (18.6)	5564 (22.6)	5573 (22.6)	5327 (21.6)	4775 (19.4)
500–2999	17 437 (70.8)	16 464 (66.8)	16 333 (66.4)	16 378 (66.3)	16 253 (65.9)
≥3000	2112 (8.6)	2142 (8.7)	2222 (9.0)	2477 (10.0)	2849 (11.6)
Education, n (%)					
Illiteracy or elementary school	2008 (8.1)	2215 (9.0)	2111 (8.6)	2003 (8.1)	1826 (7.4)
Middle school	20 970 (85.1)	20 464 (83.1)	20 142 (81.8)	19 619 (79.4)	18 809 (76.3)
College/university	1588 (6.4)	1839 (7.5)	2217 (9.0)	2898 (11.7)	3702 (15.0)
Alcohol consumption, n (%)					
Never	17 162 (69.6)	15 197 (61.7)	14 022 (57.0)	13 203 (53.5)	11 991 (48.6)
Past	569 (2.3)	698 (2.8)	762 (3.1)	730 (3.0)	738 (3.0)
Current	6868 (27.9)	8679 (35.2)	9757 (39.6)	10 655 (43.1)	11 721 (47.5)
Smoking status, n (%)					
Never	16 727 (67.9)	14 928 (60.6)	14 167 (57.6)	13 691 (55.4)	13 122 (53.2)
Past	847 (3.4)	1104 (4.5)	1208 (4.9)	1400 (5.7)	1414 (5.7)
Current	7023 (28.5)	8540 (34.7)	9168 (37.2)	9498 (38.5)	9914 (40.2)
Sodium intake, g/d, n (%)					
≥10	2106 (8.5)	2507 (10.2)	2617 (10.6)	2927 (11.9)	3085 (12.5)
6–9	20 367 (82.7)	19 546 (79.4)	19 142 (77.8)	18 714 (75.8)	18 177 (73.7)
<6	2120 (8.6)	2502 (10.2)	2754 (11.2)	2917 (11.8)	3120 (12.7)
Physical activity, n (%)					
Never	2955 (12.0)	3374 (13.7)	3648 (14.8)	3701 (15.0)	4078 (16.5)
1–2 times/wk	18 930 (76.8)	17 797 (72.3)	17 049 (69.3)	16 861 (68.3)	16 303 (66.1)
≥3 times/wk	2708 (11.0)	3383 (13.7)	3816 (15.5)	3994 (16.2)	4001 (16.2)
Use of antihypertensive agent, %	2511 (10.2)	3303 (13.4)	3887 (15.8)	4677 (18.9)	6077 (24.6)
Use of lipid-lowering agent, n (%)	239 (0.97)	363 (1.47)	459 (1.86)	531 (2.15)	704 (2.86)
Use of hypoglycemic agent, n (%)	1375 (5.58)	1351 (5.48)	1121 (4.55)	1094 (4.43)	1012 (4.10)
Use of aspirin, n (%)	161 (0.65)	238 (0.97)	287 (1.17)	303 (1.23)	349 (1.42)
Father's CVD history	1274 (5.17)	1650 (6.70)	1841 (7.48)	1915 (7.75)	2060 (8.35)
Mother's CVD history	915 (3.71)	1110 (4.51)	1224 (4.97)	1253 (5.07)	1422 (5.77)
FBG,* mmol/L	5.68±1.72	5.62±1.46	5.55±1.33	5.55±1.26	5.54±1.18
BMI,* kg/m^2	24.1±3.0	24.4±3.0	24.8±3.1	25.3±3.2	26.1±3.3
eGFR,* mL/min/1.73 m^2	86.0±17.1	87.6±17.0	88.6±17.0	89.1±17.3	89.1±19.0
LDL-C,[1] mmol/L	2.51±0.60	2.53±0.65	2.54±0.69	2.54±0.72	2.53±0.75
TG,* mmol/L	1.40±0.94	1.46±0.99	1.56±1.11	1.74±1.27	2.11±1.55
SBP,* mm Hg	129±17	129±17	130±18	131±18	132±18

Continued

Table 1. Continued

	Q1	Q2	Q3	Q4	Q5
DBP,* mm Hg	82.8±9.1	83.0±9.1	83.4±9.4	84.1±9.6	85.3±9.8
hs-CRP,* mg/mL	0.85 (1.16)	1.01 (1.31)	1.14 (1.41)	1.28 (1.58)	1.55 (1.91)

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.
*Updated cumulative average (see the Methods section), shown as mean±SD.

To examine the association of hyperuricemia in the absence of gout, we repeated our analyses in a subset of 122 738 participants who were free of gout at baseline and follow-up. Similar results were observed (adjusted HR comparing fifth and first quintiles: 1.89 [95% CI, 1.30–2.73]; $P<0.001$ for trend; Table 2).

Changes in serum urate over time were similar in women compared with men (Table S4). Greater increases in serum urate were associated with higher risk of AF, adjusting for baseline serum urate level (HR comparing fifth and first quintiles: 2.63 [95% CI, 1.85–3.76]; $P<0.001$ for trend after further adjusting for baseline serum urate level; Table 3). Results were similar when we modeled changes in serum urate as a continuous variable representing a 10-mmol/L increment (HR: 1.28 [95% CI, 1.18–1.39] after adjusting for baseline serum urate; Table 3).

We further examined AF risk by the joint associations between serum urate and hs-CRP levels. We defined hyperuricemia by cutoff values of >420 μmol/L for men and >360 μmol/L for women. High hs-CRP level was defined as hs-CRP level >3 mg/L. Participants with both high serum urate and hs-CRP had 2.6-fold higher risk of incident AF compared with those with normal serum urate and hs-CRP levels (Table 4). There were significant interactions between serum urate and hs-CRP levels on both multiplicative and additive scales (Table 4).

In our sensitivity analyses, we found consistent results for the association between long-term serum urate and elevated risk of AF, regardless of analytic strategies to handle missing data in serum urate. For an unmeasured confounder to totally explain away the observed 1.9-fold increased risk with long-term serum urate, the unmeasured confounder would need to associate with serum urate and AF with a relative risk of 3.2. In our study, given the wide range of potential confounders adjusted, it is highly unlikely that we would have such a strong unmeasured confounder. For an unmeasured confounder to totally explain away the observed 1.3-fold increased risk with changes in serum urate, the unmeasured confounder would need to associate with changes in serum urate and AF with a relative risk of 1.9, which is possible with an unmeasured confounder of modest strength. We did not find violation of the proportional hazards assumption (Tables 2 and 3).

Discussion

In this study of 123 238 participants with 6.7 years of follow-up, we found that long-term elevated serum urate was associated with 1.9-fold increased risk of incident AF. The risk

Table 2. Association Between Sex-Specific Quintile of Cumulative Average Serum Urate and Risk of Incident AF

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Population, n (cases)	24 642 (48)	24 631 (63)	24 614 (71)	24 695 (71)	24 656 (99)	
Incidence rate, per 1000 person-years	0.31	0.40	0.46	0.46	0.68	
Age- and sex-adjusted HR	1 (ref)	1.25 (0.86–1.82)	1.42 (0.99–2.05)	1.45 (1.01–2.10)	2.11 (1.49–2.98)	<0.001
Multivariable-adjusted HR*	1 (ref)	1.25 (0.86–1.82)	1.42 (0.98–2.06)	1.39 (0.96–2.03)	1.91 (1.32–2.76)	0.001
Sensitivity analyses						
Among participants without gout[†]	1 (ref)	1.25 (0.86–1.82)	1.42 (0.98–2.06)	1.40 (0.96–2.04)	1.89 (1.30–2.73)	<0.001

AF indicates atrial fibrillation; HR, hazard ratio; ref, referent.
*Model adjusted for age (years), sex, smoke status (current, past, or never), alcohol consumption status (current, past, or never), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–2999, or ≥3000¥), education (illiteracy/elementary school, middle school, or college/university), sodium intake (<6.0, 6.0–9.9, or ≥10.0 g/d), father and mother's cardiovascular disease history (yes or no), use of aspirin (yes/no), antihypertensive medication (yes/no), hypoglycemic medication (yes/no), lipid-lowering agents (yes/no), use of diuretics (yes/no), systolic blood pressure (quintile), diastolic blood pressure (quintile), fasting blood glucose (<4.0, 4.0–5.5, 5.6–6.9, or ≥7 mmol/L), triglycerides (<1.7, 1.7–2.2, 2.3–5.5, or ≥5.6 mmol/L), LDL (low-density lipoprotein) cholesterol (<1.80, 1.80–3.33, 3.34–4.91, or ≥4.92 mmol/L), body mass index (<25.0, 25.0–29.9, or ≥30 kg/m^2), high-sensitivity C-reactive protein (<1, 1–2.9, or ≥3 mg/mL), and estimated glomerular filtration rate (<30, 30–59, 60–89, or ≥90 mL/min/1.73 m^2). As sensitivity analysis, we excluded participants with a history of hypertension, high cholesterol, obesity or overweight, heart failure, renal failure, chronic kidney disease, AF-associated structural heart disease based on echocardiography, hypertrophic cardiomyopathy, valvular heart disease or hyperthyroidism, and impaired pulmonary function.
Test for proportional hazards assumption: $P=0.88$.
[†]We excluded 500 participants with a history of gout.

Table 3. Association Between Sex-Specific Quintile of Changes in Serum Urate and Risk of Incident AF

	Q1	Q2	Q3	Q4	Q5	Per 10 mmol/L	P_{trend}
Population, n (case)	21 469 (69)	21 531 (56)	21 415 (49)	21 482 (62)	21 463 (95)		
Incidence rate, per 1000 person-years	0.52	0.37	0.32	0.41	0.73		
Age- and sex-adjusted HR	1 (ref)	0.75 (0.53–1.07)	0.71 (0.49–1.02)	1.01 (0.72–1.43)	2.00 (1.46–2.73)	1.20 (1.12–1.29)	<0.001
Multivariable adjusted HR*	1 (ref)	0.88 (0.61–1.26)	0.88 (0.60–1.29)	1.28 (0.88–1.85)	2.63 (1.85–3.76)	1.28 (1.18–1.39)	<0.001

Test for proportional hazards assumption: P=0.94. AF indicates atrial fibrillation; HR, hazard ratio; ref, referent.

*Model adjusted for age (years), sex, smoke status (current, past, or never), alcohol consumption status (current, past, or never), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–2999, or ≥3000¥), education (illiteracy/elementary school, middle school, or college/university), sodium intake (<6.0, 6.0–9.9, or ≥10.0 g/d), father and mother's cardiovascular disease history (yes or no), use of aspirin (yes/no), antihypertensive medication (yes/no), hypoglycemia (yes/no), lipid-lowering agents (yes/no), use of diuretics (yes/no), systolic blood pressure (quintile), diastolic blood pressure (quintile), fasting blood glucose (<4.0, 4.0–5.5, 5.6–6.9, or ≥7 mmol/L), triglycerides (<1.7, 1.7–2.2, 2.3–5.5, or ≥5.6 mmol/L), LDL (low-density lipoprotein) cholesterol (<1.80, 1.80–3.33, 3.34–4.91, or ≥4.92 mmol/L), body mass index (<25.0, 25.0–29.9, or ≥30 kg/m^2), high-sensitivity C-reactive protein (<1, 1–2.9, or ≥3 mg/mL), estimated glomerular filtration rate (<30, 30–59, 60–89, or ≥90 mL/min/1.73 m^2), and baseline serum urate (mmol/L).

of AF increased by 1.3-fold per 10-mmol/L increment in serum urate. This association was significantly modified by hs-CRP, with participants with both high serum urate and high hs-CRP having a 2.6-fold elevated risk of incident AF compared with those with normal serum urate and hs-CRP levels.

Several biological explanations have been proposed for the link between serum urate and risk of AF. Serum urate could induce oxidative stress and inflammation, both of which are implied among the mechanisms of cardiac hypertrophy. [23] Serum urate is also associated with vascular stiffness,[24–29] atrial remodeling, ionic channel remodeling, and large left atrial size. [19] Conversely, use of allopurinol, a medication that lowers urate through inhibition of xanthine oxidase,[30] is associated with lower risk of AF. [31]

The current literature suggests a potentially elevated AF risk associated with serum urate,[10,20,32,33] but inferences were limited by the fact that prior studies have only 1-time measurement of serum urate. [34] Serum urate is time varying by nature. One measurement at baseline may be subject to measurement errors and may lead to biased results. With a longitudinal study design and repeated measurements of serum urate, we investigated whether the risk of AF (1) differs by long-term elevated serum urate and (2) increases with increase in serum urate over time—both key gaps in knowledge. We provided evidence of the association of long-term serum urate and changes in urate levels and found a consistently increased risk of AF associated with high serum urate. Prior studies were based on either 1-time measurement of serum urate in cohort studies[12,13,16,19,20] or gout in claim databases without detailed information on serum urate level, body mass index, and lifestyle factors. [18,35] Our study has unique information on repeated measurements of serum urate and detailed individual lifestyle and medical information. We were able to provide direct evidence that an increase in serum urate over time subsequently increases AF risk.

Development of AF as a result of elevated serum urate among healthy individuals has not been well studied, nor have

Table 4. Joint Association of Serum Urate and hs-CRP With Risk of Incident AF

	Low hs-CRP and Low Serum Urate	Low hs-CRP and High Serum Urate	High hs-CRP and Low Serum Urate	High hs-CRP and High Serum Urate	RERI for Multiplicative Interaction	RERI for Additive Interaction
Population, n (cases)	95 235 (240)	6027 (18)	16 108 (72)	2133 (20)		
Incidence rate, per 1000 person-years	0.39	0.51	0.75	1.67		
Age- and sex-adjusted HR	1 (ref)	1.20 (0.75–1.94)	1.43 (1.10–1.87)	3.37 (2.13–5.33)		
Multivariable adjusted HR*	1 (ref)	1.08 (0.66–1.76)	1.26 (0.96–1.65)	2.63 (1.63–4.23)	1.93 (1.46–2.57)	1.29 (1.01–1.82)

Hyperuricemia was defined by cutoff values >420 μmol/L for men and >360 μmol/L for women. High hs-CRP was defined as >3 mg/L. AF indicates atrial fibrillation; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; ref, referent; RERI, relative excess risk due to interaction.

*Model adjusted for age (years), sex, smoke status (current, past, or never), alcohol consumption status (current, past, or never), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–2999, or ≥3000¥), education (illiteracy/elementary school, middle school, or college/university), sodium intake (<6.0, 6.0–9.9, or ≥10.0 g/d), father and mother's cardiovascular disease history (yes/no), use of aspirin (yes/no), antihypertensive medication (yes/no), hypoglycemia (yes/no), lipid-lowering agents (yes/no), use of diuretics (yes/no), systolic blood pressure (quintile), diastolic blood pressure (quintile), fasting blood glucose (<4.0, 4.0–5.5, 5.6–6.9, or ≥7 mmol/L), triglycerides (<1.7, 1.7–2.2, 2.3–5.5, or ≥5.6 mmol/L), LDL (low-density lipoprotein) cholesterol (<1.80, 1.80–3.33, 3.34–4.91, or ≥4.92 mmol/L), body mass index (<25.0, 25.0–29.9, or ≥30 kg/m^2), and estimated glomerular filtration rate (<30, 30–59, 60–89, or ≥90 mL/min/1.73 m^2).

mechanisms of such consequences been fully elucidated. The CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial suggested that autoimmunity and inflammation play key mechanistic roles in the development of cardiovascular consequences.[36,37] In our study, we observed a significant interaction between serum urate and an inflammatory marker (hs-CRP), at both multiplicative and additive scales. This result suggests a complex interrelationship between levels of serum urate and the role of inflammation in accelerating arrhythmia and AF. Future studies are needed to examine whether such interactions are mechanistic and whether they exist for inflammatory biomarkers besides hs-CRP.

To the best of our knowledge, our work is the first longitudinal prospective study that establishes an association between long-term serum urate levels obtained over years and risk of incident AF. Consequently, it provides new and important evidence suggesting an association between a relatively common treatable metabolic alteration (higher serum urate) and a common cardiac rhythm disorder associated with substantial morbidity and mortality. Other than its mechanistic relevance, our findings might have direct therapeutic implications as this association was robust in participants both with and without a clinical diagnosis of gout. Urate-lowering therapies are currently not prescribed to patients without gout. Current guidelines recommend annual screening for myocardial infarction risk factors in patients with hyperuricemia and gout,[38–41] but despite its increasing prevalence, no guidelines are currently available for screening AF because of a knowledge gap about the link between serum urate and AF. Our study suggests that hyperuricemia alone is also important. Whether urate concentrations should be treated even among people without cardiovascular disease risk factors and gout is speculative. To the best of our knowledge, only a few studies have looked at this issue in an Asian population.[11,42,43] It is estimated that ≈10 million Chinese people have AF, and prevalence is still rising with the obesity epidemic.[42–45] The findings of this study could be useful to inform public health policy.

The strengths of our study include repeated measurements of serum urate and hs-CRP, large sample size, and detailed covariate information including lifestyle factors, medical conditions, medication use, and laboratory measures. We were also able to examine the interaction between serum urate and hs-CRP, which provided novel insights regarding the etiology of AF. Our study also has some limitations. All participants in our study underwent ECG every 2 years through clinical examinations. The occurrence of AF in our analytic sample was obtained through ECG readings, and our estimation of AF incidence may underestimate the true prevalence and burden of AF in the general Asian population, although Asian people have low AF rates compared with non-Hispanic white people. However, the measurement errors in AF identification were highly likely to be nondifferential with respect to serum urate level. Thus, our effect estimates of the association between serum urate and AF would be an underestimation of the true effect and attenuate toward the null. Only hs-CRP as an inflammatory marker was available in the current study. Future studies are needed to examine and confirm the joint effects of serum urate and hs-CRP on risk of AF, as well as the joint effects with other inflammatory markers. Even though we had extensive covariates in our study, we may still have some residual and unmeasured confounding. For example, we do not have detailed information regarding use of medication to lower serum urate and reduce inflammation, although such medication use may be associated with AF risk. Because our study was observational, we cannot establish a causal relation between urate levels and AF.

In conclusion, both increases and elevations in serum urate over time were associated with increased risk of incident AF. A combination of high serum urate with high hs-CRP level significantly increased risk of incident AF. Future studies should examine whether lowering serum urate levels and associated inflammation provides a relevant goal for AF prevention in patients both with and without clinically diagnosed gout.

Author Contributions

Li and Gao designed the study, interpret data, and drafted and revised the article. Cheng performed statistical analyses. All authors provided important intellectual content and revisions of this article.

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Supplemental Material

Table S1. Baseline characteristics of participants included and excluded in the analytic sample.

	Excluded	Included
N	30565	123238
UA, mmol/L	309±89	298±75
Age, year	50.5±18.7	48.2±13.7
Men, n (%)	24424(81.5)	97678(79.6)
Average income, n (%)		
<500¥/month	2280(11.4)	25818(21.4)
500- 2999¥/ month	15425(77.4)	82865(68.8)
≥3000¥/ month	2214(11.1)	11802(9.8)
Education, n (%)		

	Excluded	Included
Illiteracy or elementary school	2599(10.5)	10163(8.3)
Middle school	18844(75.8)	100004(81.7)
College /university	3416(13.7)	12244(10.0)
Alcohol consumption status, n (%)		
Never	16122(64.2)	71575(58.3)
Past	652(2.6)	3497(2.8)
Current	8333(33.2)	47680(38.8)
Smoking status, n (%)		
Never	15621(62.2)	72635(59.2)
Past	1120(4.5)	5973(4.9)

	Excluded	Included
Current	8377(33.4)	44143(36.0)
Sodium intake, n (%)		
≥10 gram/day	2707(10.8)	13242(10.8)
6–9 gram/day	19793(79.2)	95946(78.3)
<6 gram/day	2490(10.0)	13413(10.9)
Physical activity, n (%)		
Never	4232(16.9)	17756(14.5)
1-2 times/week	17379(69.5)	86940(70.9)
3+ times/week	3381(13.5)	17902(14.6)
Use of antihypertensive agent, %	2263(7.4)	20455(16.6)

	Excluded	**Included**
Use of lipid-lower agent, n (%)	122(0.40)	2296(1.86)
Use of hypoglycemic agent, n (%)	636(2.08)	5953(4.83)
Use of aspirin, n (%)	140(0.46)	1338(1.09)
Father's CVD history	496(1.62)	8740(7.09)
Mother's CVD history	280(0.92)	5924(4.81)
FBG1, mmol/L	5.57±1.74	5.59±1.41
BMI[*], Kg/m^2	24.7±3.6	24.9±3.2
eGFR[1], mL/min/1·73m^2	86.9±22.7	88.1±17.6
LDL-c[*], mmol/L	2.50±0.87	2.53±0.68
TG[*], mmol/L	1.63±1.45	1.65±1.22

	Excluded	**Included**
SBP*, mmHg	130±21	130±17
DBP*, mmHg	83.3±11.9	83.7±9.4
hs-CRP*, †, mg/mL	1.20(2.11)	1.15(1.51)

* updated cumulative average (see the Methods section)

† present as median (interquartile range)

UA, uric acid; FBG, fasting blood glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate

LDL-c, low-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high sensitive C-reactive protein.

Table S2. Median and range of serum urate by sex-specific quintiles.

	Q1	Q2	Q3	Q4	Q5
	Cumulative average uric acid				
Women	186(33-203)	219(204-230)	244(231-256)	272(257-291)	323(292-631)
Men	222(12-244)	265(245-283)	302(284-320)	342(321-367)	407(368-794)
	Baseline uric acid				
Women	161(21-185)	204(186-217)	234(218-250)	270(251-292)	330(293-817)
Men	206(12-233)	256(234-275)	295(276-314)	339(315-367)	410(368-1457)

Table S3. The association between sex-specific quintile of baseline uric acid and atrial fibrillation.

	Q1	Q2	Q3	Q4	Q5	p for trend
Population # (case)	24596(56)	24596(62)	24819(69)	24537(76)	24690(89)	
Incidence rate, per 1000 person-year	0.35	0.40	0.44	0.50	0.60	
Age and sex adjusted HR	1(ref)	1.08(0.75-1.54)	1.17(0.83-1.67)	1.30(0.92-1.84)	1.41(1.00-1.97)	0.02
Multivariable adjusted HR*	1(ref)	1.09(0.76-1.56)	1.14(0.80-1.63)	1.24(0.87-1.76)	1.25(0.88-1.78)	0.12

*Model adjusted for age (year), sex, smoke status (current, past, or never), alcohol consumption status (current, past, or never), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500-2999, or ≥3000¥), education (illiteracy/elementary school, middle school, or college/university), sodium intake (<6.0, 6.0-9.9, or ≥10.0 gram/day), father and mother's cardiovascular disease history(yes or no), use of aspirin (yes/no), antihypertensive (yes/no), hypoglycemic (yes/no), lipid-lowering agents (yes/no), use of diuretics (yes/no), systolic blood pressure(quintile), diastolic blood pressure(quintile), fasting blood glucose(<4.0, 4.0-5.5,5.6-6.9, or ≥7 mmol/L), triglycerides(<1.7, 1.7-2.2, 2.3-5.5, or ≥5.6 mmol/L), low-density lipoprotein cholesterol(<1.80, 1.80-3.33, 3.34-4.91, or 4.92,≥mmol/L), body mass index (<25.0, 25.0-29.9, or ≥30Kg/m^2), high sensitive C-reactive protein (<1, 1-2.9, or≥3mg/ml), and estimated glomerular filtration rate(<30, 30-59, 60-89, or ≥90 mL/min/1.73m^2).

Table S4. Median and range of changes in serum urate per year by sex-specific quintiles.

	Q1	Q2	Q3	Q4	Q5
Women	-14(-120 to -7)	-3(-6 to 1)	4(2 to 7)	11(8 to 15)	23(16 to 177)
Men	-19(-230 to -10)	-4(-9 to 0)	4(1 to 8)	12(9 to 18)	28(19 to 267)