Received: 19 May 2021 | Revised: 10 July 2021 | Accepted: 24 July 2021

DOI: 10.1002/joa3.12612

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Uric acid and incident atrial fibrillation of 14 years population-based cohort study: The Suita Study

Takashi Kobayashi MD, PhD[1,2,3] | Yoshihiro Kokubo MD, PhD[1] | Aya Higashiyama MD, PhD[1] | Makoto Watanabe MD, PhD[1] | Yoko M. Nakao MD, PhD[1,4] | Shiro Kamakura MD, PhD[3] | Kengo Kusano MD, PhD[3] | Yoshihiro Miyamoto MD, PhD[1,4]

[1]Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, Suita, Japan

[2]Division of Cardiovascular Medicine, Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa, Japan

[3]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

[4]Center for Cerebral and Cardiovascular Disease Information, Open Innovation Center, National Cerebral and Cardiovascular Center, Suita, Japan

Correspondence
Takashi Kobayashi, Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shinmachi, Suita, Osaka 564-8565, Japan.
Email: takashikobayashi.circ@gmail.com

Present address
Takashi Kobayashi, Division of Cardiovascular Medicine, Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, 1-7-1 Kohnodai, Ichikawa, Chiba 272-8516, Japan
Aya Higashiyama, Department of Hygiene, Wakayama Medical University, Kimiidera Campus 811-1 Kimiidera, Wakayama, Wakayama 641-8509, Japan
Yoshihiro Miyamoto, Open Innovation Center, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan

Funding information
This research was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-1-2, 22-4-5, and 20-4-9), and by grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (JSPS KAKENHI Grant Number 25293147, 16H05252, and 25860511).
IRB information: M25-043-4 (National Cerebral and Cardiovascular Center ethics committee).

Abstract

Background: Higher baseline uric acid (UA) was significantly associated with higher atrial fibrillation (AF) incidence in Japanese women. However, no prospective study is evident in the association between UA and incident AF in Japanese urban residents.
Methods: A total of 6863 participants (aged 30-79 years; 47% men) without prior AF were followed for 13.9 years on average in the Suita Study. According to the UA categories, cox proportional hazards regression models were used to estimating the Hazard Ratios (HRs) and 95% confidence intervals (CIs) for incident AF.
Results: During 95178 person-years of follow-up, we observed 311 cases of incident AF (204 cases in men and 107 cases in women). Compared to the subjects with UA of 4.0-4.9 mg/dL, multivariable-adjusted HR (95% CIs) of incident AF was 1.50 (1.01-2.25) ($P = .047$) for the subjects with UA ≥7.0 mg/dL.
Conclusion: High UA was associated with an increased risk for incident AF in the Japanese population.

KEYWORDS
atrial fibrillation, prospective study, uric acid

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] More than 33 million patients (the AF epidemic) are projected to impact morbidity, mortality, health care use, and cost.[1,2] There are great strides in stroke prevention and rhythm control strategies, yet reducing the incidence of AF has been insufficient.[1] However, only a few prospective studies have examined AF's risk factors among general populations, predominantly Asian countries. We have shown a basic risk score for incident AF in a general Japanese population for the first time.[3] In addition, the prevention of using factors other than classical AF risk score is increasingly important for AF strategy.

Serum UA is a byproduct of purine catabolism, the final steps are catalyzed by xanthine oxidoreductase.[4] There is no unified view on the relationship between cardiovascular disease and UA.[5,6] UA could be a marker of oxidative damage, representing the inflammation, which plays an essential role in the mechanism of initiation and perpetuation of AF.[7,8] American and European-studies showed that those with elevated serum UA at baseline would be at an increased risk of future AF and that this association would be independent of cardiovascular risk factors. The association of UA with AF risk differed by race and gender.[4,9] During the median observation period of 4.1 years, higher baseline UA was significantly associated with higher AF incidence in Japanese women but not in men.[10] We assessed the hypothesis using this Japanese urban cohort that higher UA is associated with increased incident AF in men and women.

2 | METHODS

2.1 | Study participants

The design and selection criteria of the Suita Study have been described.[11,12] As a baseline, 12 200 and 3000 participants were randomly selected from the municipality population registry of Suita city and stratified into groups by gender and age in 10-year increments in 1989 and 1996, respectively. Of these, participants attending the baseline examination of the original cohort (n = 6485; 1989-1996) and the secondary cohort (n = 1329; 1996-1998) were eligible for the present investigation. In addition, the baseline examination of a volunteer group (n = 546, 1992-2006) was also included in the present study. We excluded participants for the following reasons: prior or current illness of AF or atrial flutter (n = 42) or 80≥ years old (n = 34) at the baseline examination, missing covariate (n = 2), and failure to complete the baseline examination (n = 11) or the follow-up health surveys (n = 1408), resulting in a sample of 6863.[3] Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Suita, Japan (M25-043-4). This study adheres to the principles of medical research as laid down in the Declaration of Helsinki.

2.2 | Baseline examination

Blood samples were collected at the National Cerebral and Cardiovascular Center after the participants had fasted for at least 12h between 1989 and 2006.[11] The average of the second and third blood pressure measurements was used in the analysis. The definition of systolic prehypertension (120-139 mm Hg), systolic hypertension (≥140 mm Hg), under (body mass index: BMI <18.5 kg/m^2) or overweight (BMI ≥25 kg/m^2), non HDL-C (subtracting the HDL-C from the total cholesterol), excessive drinking, current or quit smoking, valvular disease, arrhythmia (other than AF), coronary heart disease, and chronic kidney disease (CKD)[13] were in the same way of previous Suita Study.[3] HU was defined as UA ≥7.0 mg/dL.[14,15] The medication of HU was defined as the use of antihyperuricemic agents.

2.3 | Definition of AF and follow-up

A standard 12-lead electrocardiogram was obtained from all participants in the supine position. Each record was coded independently using the Minnesota Code by two well-trained physicians. Participants were diagnosed with AF if AF (Minnesota Code 8-3-1 and 8-3-3) or atrial flutter (Minnesota Code 8-3-2 and 8-3-4) was present (n = 168) on an electrocardiogram from the routine Suita health check-up examination (every 2 years) or if AF was indicated as a present illness by the health check-up examination (n = 54), and hospital medical records (n = 80), and/or death records (n = 9) during follow-up. The end point of the follow-up period for each participant was whichever of the following options occurred first (1) the date of the first AF event, (2) the date of the last health examination and medical records, and (3) December 31, 2015 (censored).[3]

2.4 | Statistical analysis

We thought the critical cutoff point of serum UA level should be set at 7.0 mg/dL or higher because the level is thought to be adequate for recognizing subjects with increased risks for cardiovascular events. We used analyses of variances and chi-square tests to compare the mean values and frequencies, respectively. Age-, gender-, and multivariable-adjusted Cox proportional hazards models for incident AF were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in men and women. The following cardiovascular risk factors were included as covariate: age, male, components of the Suita atrial fibrillation risk score (systolic hypertension, overweight, excessive drinking, current smoking, non-HDL-C, arrhythmia except AF, coronary artery disease, and cardiac murmur) (Model 1), gamma-glutamyl transferase (γ-GTP), and medication of hyperuricemia (Model 2), and CKD (Model 3). All analyses were performed with SPSS (Version 20.0J; Japan IBM, Tokyo, Japan). A two-sided $P < .05$ was considered statistically significant.

3 | RESULTS

The baseline characteristics of the study participants according to the UA categories are presented in Table 1. The number in each of the lowest and highest UA groups was small because of a population study. The participants with the highest UA group were more likely to be male and had higher values of BMI (overweight), non-HDL-C, and γ-GTP, a greater prevalence of systolic hypertension, coronary heart disease, arrhythmia and CKD, frequency of current smoking, excessive alcohol drinking, and medication of HU compared to the participants with the reference UA (4.0-4.9 mg/dL) group. In each gender, the participants with the highest UA group had higher BMI values (overweight), non-HDL-C, and γ-GTP, a greater prevalence of systolic hypertension and CKD, frequency of excessive alcohol drinking, and medication of HU. In women, the participants with the highest UA group were also more likely to be older and had a greater prevalence of arrhythmia and frequency of current smoking (Table S1).

During 95 178 person-years of follow-up, we identified 311 participants (204 men and 107 women) with incident AF. In all, compared to the participants with the reference UA (4.0-4.9 mg/dL) group, the age- and gender-, and multivariable-adjusted HRs (95% CIs) of models 1, 2, and 3 for incident AF in the participants with the highest UA (≥7.0 mg/dL) group, were 1.73 (1.17-2.55), 1.53 (1.03-2.27), 1.52 (1.02-2.27), and 1.50 (1.01-2.25). (Table 2). In each man or woman, multivariable-adjusted HRs (95% CIs) for incident AF in the participants with the highest UA (≥7.0 mg/dL) group showed a similar tendency. However, there was no statistical significance in each gender mainly because of statistical power (Data not shown). The sample size of the participants with the UA ≥7.0 mg/dL group was not enough and we could detect the distribution shifted to low UA value in the general population of the Suita study.

4 | DISCUSSION

High UA level in combined men and women was associated with the AF risks after adjusting for traditional cardiovascular risk factors in the prospective cohort study of Japanese living in an urban area. Considering the AF real world, the data collection of this AF study, including hospitalization and underlying cause of death, is better than the standard cohort study. However, we could not find a significant association either in the analysis targeting only men or women. We showed a clue for future studies that examine the association between serum UA levels and the risk of incident AF in Japan. The larger sample size study would yield statistically significant findings in both genders, and future studies should be conducted. It is

TABLE 1 Baseline characteristics of the study participants according to the uric acid categories: the Suita Study, 1989-2015, Japan

	Men and women				
UA, mg/dL	**<4.0**	**4.0-4.9**	**5.0-5.9**	**6.0-6.9**	**>7.0**
n	1284	1929	1787	1157	706
Age, year, mean (SD)	53.5 (12.7)	55.4 (12.6)	57.0 (12.4)	56.8 (12.7)	55.7 (13.1)
Gender, men, %	14.5	24.9	55.4	80.4	90.1
SBP					
120-139 mm Hg , %	32.3	34.3	36.1	37	36.8
≥140 mm Hg , %	18	22.2	27.4	29.3	34.8
Body composition					
Underweight, %	13.3	10	6.2	4.2	3.1
Overweight, %	9.2	16	21.7	28.4	34.6
Non-HDL-C					
130-189 mg/dL, %	52.5	57.4	57.4	62.2	56.5
≥190 mg/dL, %	11	15.8	17.5	18.3	21.5
Smoking status					
Current smoking, %	16.5	21.4	31.6	41.4	41.9
Quit smoking, %	10.4	13	21.8	28.1	35.1
Excessive drinking, %	2.4	3.9	10.9	16.9	25.5
CHD, %	1.6	1.7	1.9	2.4	2.7
Valvular disease, %	2.5	2.4	2.7	1.7	2.1
Arrhythmia, %	3.7	3.5	4.1	4.1	4.5
Medication of HU, %	0.5	0.5	0.9	1.6	3.8
γ-GTP, mg/dL, mean (SD)	21.8 (25.7)	25.5 (27.5)	36.2 (43.4)	48.3 (49.6)	70.4 (91.6)
CKD, %	17.4	19.6	25.5	29.1	33.9

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; HU, hyperuricemia; SBP, systolic blood pressure; SD, standard deviation; UA, uric acid; γ-GTP, gamma-glutamyl transferase.

TABLE 2 Multivariable-adjusted hazard ratios (95% CIs) for incident AF according to Serum UA in men and women: the Suita Study, 1989-2015, Japan

UA, mg/dL	<4.0	4.0-4.9	5.0-5.9	6.0-6.9	>7.0	UA per 1 mg/dL
Men and women						
Person-years, py	18 171	27 624	24 980	15 218	9184	
Cases, n	39	64	88	67	53	
Incident of AF, n/1000 py	2.2	2.3	3.5	4.4	5.8	
Age- and gender-adjusted						
HRs (95% CIs)	1.15 (0.77-1.72)	1 (reference)	1.14 (0.82-1.59)	1.27 (0.88-1.82)	1.73 (1.17-2.55)*	1.12 (1.02-1.23)
Model 1 adjusted HRs (95% CIs)	1.31 (0.88-1.97)	1 (reference)	1.16 (0.83-1.62)	1.22 (0.84-1.76)	1.53 (1.03-2.27)*	1.06 (0.97-1.23)
Model 2 adjusted HRs (95% CIs)	1.31 (0.88-1.97)	1 (reference)	1.16 (0.83-1.61)	1.21 (0.84-1.76)	1.52 (1.02-2.27)*	1.06 (0.96-1.17)
Model 3 adjusted HRs (95% CIs)	1.30 (0.87-1.95)	1 (reference)	1.12 (0.80-1.57)	1.20 (0.83-1.74)	1.50 (1.01-2.25)*	1.06 (0.96-1.17)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; py, person-years; UA, uric acid.

Model 1: adjusting by components of the Suita atrial fibrillation risk score.

Model 2: Model 1 + Gamma-glutamyl transferase and medication of hyperuricemia.

Model 3: Model 2 + CKD.

*$P < .05$ (compared with subjects with UA 4.0-4.9 mg/dL)

expected that future studies based on this study form the foundation for novel risk scores for AF.

The serum UA level is closely associated with cardiovascular risk factors such as BMI, and hypertension.[4] In both gender, BMI and present illness of systolic hypertension increased in the highest UA group. Therefore, we found that this study was similarly associated with BMI and hypertension with the ARIC and Tromsø study. In the Tromsø study, baseline serum UA was associated with an increased risk for future AF in both gender, but no gender interaction was observed.[9] In the ARIC and Kagoshima study, significant associations between high UA levels and incident AF, were observed in all and women.[4,10] In the ARIC study, all were not equally divided into gender, and the percentages of the women from <5.0 to ≥7.0 UA group were 87%, 63%, 39%, and 26%, respectively. Similarly, all in this study were not equally divided into gender, and the percentages of the women from <4.0 to ≥7.0 UA group were 85%, 75%, 45%, 20%, and 10%, respectively. We could show that a high UA level (UA ≥7.0 mg/dL) was associated with the risks for AF after adjusting for traditional cardiovascular risk factors in all but not each gender. The study's numerical value categories are useful to understand the critical cutoff point of serum UA level because of recognizing subjects with high risks for AF events in Japanese. Since alcohol exposure increases UA levels, the higher UA levels could be associated with the heavy drinker. Since alcohol is a known factor associated with AF,[16] we evaluated excessive drinkers such as the Suita atrial fibrillation risk score, and the highest UA group had a frequency of excessive alcohol drinking.

HR of AF was J-shaped associated with serum UA in this study. UA has a known characteristic that possesses an anti-oxidative effect even UA could act as a marker of oxidative stress.[17,18] Therefore, higher UA levels might indicate higher values of oxidative stress and higher activity of anti-oxidative. In contrast, lower values of UA might indicate lower activity of anti-oxidative effect. The low and high UA level values of UA level could be associated with high levels of oxidative stress. Since γ-GTP could act as a marker of oxidative stress, γ-GTP could be an efficient tool to evaluate the magnitude of oxidative stress in UA's levels.[19] In all, men, and women, the value of γ-GTP was the highest in this study's highest UA group. Therefore, we analyzed Model 2 (Model 1 plus γ-GTP and HU), and multivariable-adjusted HR for incident AF was not significantly different (1.53 in Model 1 and 1.52 in Model 2). When focused on the UA, it is crucial to consider CKD. In addition to the previous study,[3] we could not show that CKD was associated with the risks for AF after adjusting for traditional cardiovascular risk factors. We also evaluated the influence of medication that lowers serum UA. However, there was a low frequency of UA medication in this study. Multivariable-adjusted HR for incident AF was not significantly different (1.53 in Table 2 and 1.37 in Table S2). It is difficult to clarify risk factors or disease markers. It cannot conclude with only our work, whether UA is a treatment target or merely an identification of mediator molecule.

From a preventive medical perspective, we should focus on the high UA condition of liability to AF. Being overweight is strongly associated with HU. For high UA people such as HU who keep diet and exercise sufficiently, prescribing medication for these high UA people to prevent incident AF needs future studies of UA lowering therapy on AF.[20,21] Finally, even if UA was added to the Suita AF risk score, the C statistic did not increase significantly (data not shown). Thus, from the above results, UA is a risk factor for AF, but there is a possibility that it can be explained by a component of the Suita AF risk score, and further research is required in the future.

4.1 | Limitations

This study had several limitations. First, this study is a small sample size and a small number of incident AF cases in Japan. Therefore,

the generalizability of the results might not be adequate. The results need to be confirmed by further studies with more subjects in Japanese and various Asians. Atrial flutter was counted as AF in this study. Though most AF was frequently accompanied by atrial flutter, counting exact AF only was more correct and ideal. Second, as we did not perform Holter electrocardiography, we may miss participants with paroxysmal AF. Third, there may be a dilution bias. Fourth, serum UA was measured only once. Finally, participants without follow-up were excluded from our baseline data.

5 | CONCLUSION

During over 13.9 years, serum high UA was an independent risk factor for incident AF in the general Japanese general population after adjusting for established cardiovascular risk factors. Given preventive medicine, it is expected that future studies based on this study form the foundation for novel risk scores for AF.

ACKNOWLEDGEMENTS

We sincerely appreciate the members of the Suita Medical Foundation and the Suita City Health Center. Furthermore, we thank all researchers and co-medical staff in the Department of Preventive Cardiology, the National Cerebral and Cardiovascular Center, for their excellent medical examinations and follow-up surveys. We also thank the Satsuki-Junyukai, the society members of the Suita Study.

CONFLICT OF INTEREST

Nakao has received grants from Bayer and Pfizer.

ORCID

Takashi Kobayashi https://orcid.org/0000-0002-4742-819X

REFERENCES

1. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, et al. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. Circulation. 2020;141:e750–72.
2. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation. 2017;136:583–96.
3. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a basic risk score for incident atrial fibrillation in a Japanese genereal population-The Suita Study. Circulation J. 2017;81:1580–8.
4. Tamariz L, Agarwal S, Soliman EZ, Chamberlain AM, Prineas R, Folsom AR, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol. 2011;108:1272–6.
5. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANESI Epidemiologic Follow-up Study, 1971–1992. JAMA. 2000;283:2404–10.
6. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH; MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med. 2008;168:1104–10.
7. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21:1064–70.
8. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108:3006–10.
9. Nyrnes A, Toft I, Njolstad I, Mathiesen EB, Wilsgaard T, Hansen J-B, et al. Uric acidis associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women–the Tromso study. Europace. 2014;16:320–6.
10. Kawasoe S, Kubozono T, Yoshifuku S, Ojima S, Miyata M, Miyahara H, et al. Uric acid level and new-onset atrial fibrillation in the Japanese General Population-Longitudinal Study. Circ J. 2019;83:156–63.
11. Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: The Suita Study. Hypertension. 2008;52:652–9.
12. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kobayashi T, Watanabe T, et al. Interaction of blood pressure and body mass index with risk of incident atrial fibrillation in a Japanese urban cohort: The Suita Study. Am J Hypertens. 2015;28:1355–61.
13. Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, et al. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: The Suita Study. Stroke. 2009;40:2674–9.
14. Mikkelsen WM, Dodge HJ, Valkenburg H, Himes S. The distribution of serum uric acid values in a population unselectedas to gout or hyperuricemia: Tecumseh, Michigan 1959–1960. Am J Med. 1965;39:242–51.
15. Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum. 1972;15:189–92.
16. Anadon MJ, Almendral P, Gonzalez P, Zaballos M, DIcan JL, Guevara LD. Alcohol concentration determines the type of atrial arrhythmia induced in porcine model of acute alcoholic intoxication. Pacing Clin Electropgysiol. 1996;19:1962–7.
17. Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. J Cardiol Fail. 2020;26:977–84.
18. Becker BF, Reinholz N, Ozcelik T, Leipert B, Gerlach E. Uric acid as radical scavenger and antioxidant in the heart. Pflugers Arch. 1989;415:127–35.
19. Uçar H, Gür M, Gözükara MY, Kalkan GY, Baykan AO, Türkoğlu C, et al. Gamma glutamyl transferase activity is independently associated with oxidative stress rather than SYNTAX score. Scand J Clin lab Invest. 2015;75:7–12.
20. Zhou J, Wang YU, Lian F, Chen D, Qiu Q, Xu H, et al. Physical exercises and weight loss in obese patients help to improve uric acid. Oncotarget. 2017;8:94893–9.
21. Zhang C-H, Huang D-S, Shen D, Zhang L-W, Ma Y-J, Wang Y-M, et al. Association between serum uric acid levels and atrial fibrillation risk. Cell Physiol Biochem. 2016;38:1589–95.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kobayashi T, Kokubo Y, Higashiyama A, et al. Uric acid and incident atrial fibrillation of 14 years population-based cohort study: The Suita Study. J Arrhythmia. 2021;37:1215–1219. https://doi.org/10.1002/joa3.12612