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Association between serum uric acid and atrial fibrillation: a cross-sectional community-based study in China

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ABSTRACT

Objectives To investigate the effects of gender on the association of serum uric acid (SUA) levels and atrial fibrillation (AF) prevalence in a community-based Chinese population.

Setting Data were obtained from annual Jidong Oilfield employee and family member health checkups. The Jidong community is geographically located in Tangshan City in northern China.

Participants A total of 9078 residents were invited to take part in the survey and provided informed consents. Individuals without data of ECG or SUA were excluded, leaving 8937 residents in our study.

Primary and secondary outcome measures SUA was measured at baseline using the uricase-peroxidase method. Hyperuricaemia was defined as a SUA level >7.0 mg/dL in men and >5.7 mg/dL in women. AF was diagnosed based on ECG findings and/or any medical history of AF from referring physicians. The crude and independent association between SUA levels and AF prevalence was evaluated with logistic regression analysis.

Results AF prevalence was 0.6% (53/8937). Participants with hyperuricaemia had a higher AF prevalence compared with those with normal SUA levels (1.1% vs 0.5%; P=0.02). Hyperuricaemia was correlated with AF after adjustment for various cardiovascular risk factors in all participants (P=0.03, OR 2.051, 95% CI 1.063 to 3.856). This correlation was particularly stronger in women compared with men (P<0.001, OR 6.366, 95% CI 2.553 to 15.871 in women and P=0.96, OR 1.025, 95% CI 0.400 to 2.626 in men).

Conclusions We demonstrated a significant association between increased SUA levels and AF prevalence in a Chinese population. Our data indicate that there is a gender-specific mechanism underlying the relationship between SUA and AF.

Strengths and limitations of this study

► The subject group was based on a community-based population in China, and the sample size of the study was relatively large.
► Our data indicate that there is a gender-specific mechanism underlying the relationship between serum uric acid and atrial fibrillation (AF).
► This was a cross-sectional analysis with a low AF prevalence due to the low mean age of the participants.
► Some AF cases may not have been included in our analyses because participants with paroxysmal AF or asymptomatic AF 'escaped' ECG detection. Therefore, we may have underestimated the AF prevalence.

INTRODUCTION

Atrial fibrillation (AF) has become a health concern worldwide because of its significant association with increased risk of morbidity and mortality. The estimated prevalence of AF is between 2.3% and 3.4% in the general population and increases with ageing.[1 2] AF incidence and prevalence are expected to rise continuously over the next few decades.[3] A number of factors, including advancing age, male gender, obesity, hypertension, congestive heart failure, myocardial infarction (MI), chronic kidney disease and diabetes mellitus, have been identified as risk factors for AF development.[4–6] Mechanistically, AF occurrence and perpetuation depend on atrial electrophysiological and structural remodelling.[7] Although the pathophysiology of atrial remodelling is not well understood, recent studies have suggested that inflammation and oxidative stress have been shown to play a role in atrial electrical and/or structural remodelling.[8–11]

Serum uric acid (SUA) has been reported to be clearly associated with oxidative stress and inflammation in several pathological conditions.[12 13] Previous studies explored the role of SUA in AF aetiology and persistence.[14 15] For instance, several cross-sectional studies, which enrolled hospital patients, showed that elevated SUA levels were linked to a high risk of AF.[16 17] Another study investigated the relationship between SUA and AF based on a community cohort.[18] In addition, a large meta-analysis confirmed a potential association between SUA and AF.[19] Although some studies analysed the effect of gender on the

relationship between elevated SUA levels and AF and showed a gender-specific mechanism,[17 18] the findings were not consistent. Therefore, the aim of the present study was to further investigate the relationship between SUA levels and AF prevalence in a relatively large, community-based cohort in China and analyse the independent effects of gender on the association between SUA and AF.

METHODS
Study design and population
The current study included participants in the population-based Cohort Study in Outcome of Phased Progression of Atherosclerosis. Between April and August of 2014, data were obtained from annual Jidong Oilfield employee and family member health checkups. The Jidong community is geographically located in Tangshan City in northern China. All residents aged 18 years or older in the Jidong community were invited to participate in our study. A total of 9078 residents finally agreed to take part in the survey and provided informed consents; all of the 9078 residents underwent health examinations and filled in the questionnaires. Individuals without data of ECG or SUA were excluded, leaving 8937 residents in our study.

Definition of atrial fibrillation
In our study, all participants were subjected to a 12-lead ECG at rest for 5 min. All participants avoided drinking alcohol and tea before examination. Recordings were then transferred to a computer for data interpretation. Each ECG rhythm strip was read back-to-back by two research doctors from the Medical Centers of the Jidong Oilfield. If outcomes differed, ECGs were further reviewed by an experienced cardiologist. If anyone self-reported a medical history of AF, but the ECG was negative, we confirmed the case with referring physicians and obtained the data to confirm the diagnosis. AF was diagnosed if one of the following criteria was present: (1) irregular R-R intervals, (2) absence of repeating P waves and (3) irregular atrial activity.

Definition of hyperuricaemia
Baseline SUA measurements were reported in μmol/L, and we converted those values using the following conversion equivalence: 1 mg/dL=59.48 μmol/L. SUA was determined using the uricase-peroxidase method. Hyperuricaemia was defined as an SUA concentration >7.0 mg/dL in men and >5.7 mg/dL in women or current use of uric acid (UA)-lowering drugs.[20]

Biochemical measurements
Blood samples were drawn from the antecubital vein of each participant in the morning in the fasting state and stored in vacuum tubes containing EDTA. We measured serum creatinine, UA, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c) and fasting blood glucose

(FBG) in all participants. The estimated glomerular filtration rate (eGFR) was calculated using a formula based on the Chronic Kidney Disease Epidemiology Collaboration equation[21] as follows: $GFR=141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female, or) $\times 1.159$ (if black), where κ is 0.7 for female and 0.9 for male; α is 0.329 for female and 0.411 for male; min indicates the minimum of SC/κ or 1; and max indicates the maximum of SC/κ.

Definition of clinical variables
Demographic characteristics (age, sex, weight, body height, alcohol and cigarette use) and clinic characteristics (history of hypertension, diabetes mellitus, heart failure, gout, dyslipidaemia, MI, transient ischaemic attack (TIA), AF and medicine use) were obtained from physical examinations and questionnaires by research doctors from Medical Centers of Jidong Oilfield, as described in previous studies.[22 23] We measured body weight (to the nearest 0.1 kg) and body height (to the nearest 0.1 cm) with participants wearing light clothing and no shoes, and body mass index (BMI) was calculated as body weight (kg) divided by height (m^2). Hypertension was defined as a history of arterial hypertension or blood pressure ≥140/90 mm Hg (mean of three measurements) in the supine position or current treatment with any antihypertensive medications. Diabetes mellitus was defined by a self-reported history, the use of insulin, oral hypoglycaemic agents or FBG ≥7 mmol/L. Dyslipidaemia was defined by a self-reported history, current use of cholesterol-lowering medicine, TC level ≥5.7 mmol/L, TG ≥1.7 mmol/L or LDL ≥4.1 mmol/L.

Statistical analysis
All statistical analyses were performed with the SAS software V.9.4. The distributions (mean±SD) of the parameters were calculated. Continuous variables (with or without hyperuricaemia) were performed using the analysis of variance analysis, while the χ^2 test was applied for comparing categorical variables. We performed collinearity analysis of variables prior to logistic regression analysis, which showed that eGFR and BMI are collinear variables, and these two indexes were therefore excluded from the adjusted model. Univariate and multivariate logistic regression analysis was used to analyse the associations between SUA and AF prevalence. The OR was presented with their corresponding 95% CIs. A P value of <0.05 (two-tailed) was considered statistically significant.

RESULTS
Subject characteristics
Data were obtained from 8937 participants aged 18–82 years, including 4686 (52.4%) men and 4251 (47.6%) women, and the mean age was 42.1±13.1 years. Participants were divided into two groups on the basis of SUA levels: normal SUA-level group and hyperuricaemia

Table 1 Comparison of demographic and clinical characteristics of participants between normal and high SUA-level groups

Subjects	Total (n = 8937)	Normal SUA level (n = 7740)	Hyperuricaemia (n = 1197)	P value
Age, years	42.1±13.1	42.2±13.0	41.6±13.6	0.10
Male, N (%)	4686 (52.4%)	3844 (49.7%)	842 (70.3%)	<0.001
BMI (kg/m^2)	24.5±3.7	24.2±3.6	26.8±3.7	<0.001
Smoking, N (%)	2324 (26.0%)	1912 (24.7%)	412 (34.4%)	<0.001
Alcohol use, N (%)	2971 (33.2%)	2421 (31.3%)	550 (45.9%)	<0.001
Hypertension, N (%)	2777 (31.1%)	2215 (28.6%)	562 (47.0%)	<0.001
Diabetes, N (%)	596 (6.7%)	512 (6.6%)	84 (7.0%)	0.60
Heart failure, N (%)	7 (0.08%)	5 (0.06%)	2 (0.17%)	0.24
Gout, N (%)	35 (0.39%)	17 (0.22%)	18 (1.50%)	<0.001
Dyslipidaemia, N (%)	3256 (36.4%)	2540 (32.8%)	716 (59.8%)	<0.001
MI, N (%)	41 (0.5%)	37 (0.5%)	4 (0.3%)	0.49
TIA/stroke, N (%)	82 (0.9%)	72 (0.9%)	10 (0.8%)	0.75
Statins use, N (%)	110 (1.2%)	87 (1.1%)	23 (1.9%)	0.02
Diuretic use, N (%)	51 (0.6%)	34 (0.4%)	17 (1.4%)	<0.001
TC (mmol/L)	4.4±0.9	4.4±0.9	4.7±0.9	<0.001
TG (mmol/L)	1.6±1.4	1.5±1.2	2.3±2.0	<0.001
HDL-c (mmol/L)	1.2±0.3	1.2±0.3	1.1±0.2	<0.001
LDL-c (mmol/L)	2.5±0.6	2.4±0.6	2.7±0.6	<0.001
FBG (mmol/L)	5.3±1.1	5.2±1.1	5.4±1.1	<0.001
Creatinine (µmol/L)	77.2±16.1	76.1±14.8	84.4±21.8	<0.001
eGFR (median) (mL/min/1.73 m^2)	97.6±16.3	98.1±15.8	94.1±18.3	<0.001
AF, N (%)	53 (0.6%)	40 (0.5%)	13 (1.1%)	0.02
SUA (mg/dL)	5.0±1.5	4.6±1.2	7.5±1.1	<0.001

Values are expressed as mean±SD or numbers (percentage).
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; MI, myocardial infarction; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; TIA, transient ischaemic attack .

group. The average SUA level was 5.0±1.5 mg/dL, and the prevalence of hyperuricaemia was 13.4%. Baseline characteristics, medical histories and biochemical markers of participants in the presence or absence of hyperuricaemia are presented in table 1. Male, hypertension, dyslipidaemia, gout, smoking, alcohol use, statin use and diuretic use were more prevalent in the subjects with hyperuricaemia (all P<0.05). Compared with patients with normal SUA levels, those with hyperuricaemia had a significantly higher BMI, TC, TG, LDL-c and FBG levels (all P<0.05). However, there were no significant differences between these two groups in terms of age, diabetes, heart failure, MI and TIA/stroke. We also summarised the clinical characteristics between the AF group and non-AF group in table 2.

Association of SUA level with AF

AF prevalence was 0.6% (53/8937) in all subjects, 0.7% (35/4686) in men and 0.4% (18/4251) in women. The correlation between hyperuricaemia and AF was assessed by logistic regression analysis for non-adjusted and adjusted models (table 3). Patients in the hyperuricaemia group had a higher AF prevalence compared with those in the normal SUA group in all subjects (P=0.02, OR 2.114, 95% CI 1.128 to 3.964) and in women (P<0.001, OR 7.104, 95% CI 2.737 to 18.442), but not in men (P=0.90, OR 0.944, 95% CI 0.391 to 2.281). The association with AF remained significant in all subjects following simultaneous adjustment for age, hypertension, diabetes mellitus, dyslipidaemia, smoking, alcohol use, statins use, diuretic use, history of MI, TIA/stroke, heart failure and gout (P=0.03, OR 2.051, 95% CI 1.063 to 3.856) and in women (P<0.001, OR 6.366, 95% CI 2.553 to 15.871). Additionally, we conducted a sensitivity analysis to evaluate the robustness of our findings. An almost identical result was found when we excluded participants with hypertension (P<0.001, OR 5.666, 95% CI 2.383 to 13.473). Similar correlations were observed when we excluded subjects with MI or heart failure (P=0.02, OR 2.183, 95% CI 1.132 to 4.212).

DISCUSSION

Several previous studies suggested that elevated SUA levels were positively associated with AF prevalence in

Table 2 Comparison of demographic and clinical characteristics of participants between AF and non-AF group

Subjects	Total (n=8937)	Non-AF group (n=8884)	AF group (n=53)	P value
Age (years)	42.1±13.1	42.1±13.1	56.1±11.6	<0.001
Male, N (%)	4686 (52.4%)	4651 (52.4%)	35 (66.0%)	0.04
BMI (kg/m^2)	24.5±3.7	24.5±3.7	25.2±2.8	0.08
Smoking, N (%)	2324 (26.0%)	2308 (26.0%)	16 (30.2%)	0.49
Alcohol use, N (%)	2971 (33.2%)	2951 (33.2%)	20 (37.7%)	0.49
Hypertension, N (%)	2777 (31.1%)	2750 (31.0%)	27 (50.9%)	0.01
Diabetes, N (%)	596 (6.7%)	586 (6.6%)	10 (18.9%)	<0.001
Heart failure, N (%)	7 (0.08%)	6 (0.1%)	1 (1.9%)	<0.001
Gout, N (%)	35 (0.39%)	34 (0.4%)	1 (1.9%)	0.08
Dyslipidaemia, N (%)	3256 (36.4%)	3228 (36.3%)	28 (52.8%)	0.01
MI, N (%)	41 (0.5%)	38 (0.4%)	3 (5.7%)	<0.001
TIA/stroke, N (%)	82 (0.9%)	80 (0.9%)	2 (3.8%)	0.03
Statins use, N (%)	110 (1.2%)	103 (1.2%)	7 (13.2%)	<0.001
Diuretic use, N (%)	51 (0.6%)	50 (0.6%)	1 (1.9%)	0.20
TC (mmol/L)	4.4±0.9	4.4±0.9	4.4±0.9	0.99
TG (mmol/L)	1.6±1.4	1.6±1.3	2.0±1.1	0.37
HDL-c (mmol/L)	1.2±0.3	1.2±0.3	1.1±0.3	0.13
LDL-c (mmol/L)	2.5±0.6	2.5±0.6	2.5±0.5	0.82
FBG (mmol/L)	5.3±1.1	5.3±1.1	5.8±1.3	<0.001
Creatinine (µmol/L)	77.2±16.1	77.1±16.1	80.1±12.3	0.09
eGFR (median) (mL/min/1.73 m^2)	97.6±16.3	97.6±16.2	87.8±15.8	<0.001
Hyperuricaemia, N (%)	1197 (13.4%)	1184 (13.3%)	13 (24.5%)	0.02
SUA (mg/dL)	5.0±1.5	5.0±1.5	5.5±1.4	0.01

Values are expressed as mean±SD or numbers (percentage).
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; MI, myocardial infarction; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; TIA, transient ischaemic attack .

both hypertensive[24] and chronic systolic heart failure patients.[25] A recent meta-analysis, which included both cross-sectional and cohort studies, also demonstrated a positive relationship between SUA and AF.[26] In the present study, we explored the relationship between SUA levels and AF in a Chinese community-based population and found that elevated SUA levels were significantly correlated with AF, and that the independent association between these two persisted after adjusting for multiple clinical factors in the general population, especially in women. In addition, the AF prevalence was relatively low on account of the low mean age (42 years), which contributed to AF's association with other risk factors. The logistic regression analysis was helpful for adjusting this bias and increasing the reliability of the findings. In the present study, we found that the width and magnitude of the observed CIs of total subjects and men were acceptable; however, the CIs of women were relatively wide. The reasons were probably linked to the low AF prevalence and the difference of AF prevalence in different genders with hyperuricaemia, as evidenced by the finding that AF

prevalence was higher in women with hyperuricaemia. In addition, although hyperuricaemia was more prevalent in men than women (18% vs 8.4%, P<0.001), hyperuricaemia was associated with AF in women but not in men, partly because being a woman affects the relationship between SUA and AF.

Consistent with a previous report,[15] we show here that elevated SUA levels are positively correlated with an increased risk of AF in a general Chinese population. Moreover, we found that SUA has gender-specific, independent effects on AF prevalence in women, but not in men, which was in accordance with a previous study in Japan,[17] which was based on a relatively large hospital-based cohort with a high prevalence of AF and divided patients according to sex-specific UA tertiles. This study showed that gender affected the independent relationship between SUA and AF after adjusting for well-known cardiovascular risk factors. Our findings were also consistent with several previous studies that reported gender-specific effects of SUA on the prevalence of hypertension and kidney disease in women.[27 28]

Table 3 OR and 95% CI between hyperuricaemia and AF prevalence

Group	Subjects (n)	AF	Prevalence (%)	Unadjusted model OR (95% CI)	P value	Adjusted model OR (95% CI)	P value
Men*	4686	35	0.74				
Normal SUA level	3844	29	0.75	1.000	1.0000	1.000	1.0000
Hyperuricaemia	842	6	0.71	0.944 (0.391 to 2.281)	0.90	1.025 (0.400 to 2.626)	0.96
Women*	4251	18	0.42				
Normal SUA level	3896	11	0.28	1.000	1.0000	1.000	1.0000
Hyperuricaemia	355	7	1.97	7.104 (2.737 to 18.442)	<0.001	6.366 (2.553 to 15.871)	<0.001
Total †	8937	53	0.60				
Normal SUA level	7740	40	0.52	1.000	1.0000	1.000	1.0000
Hyperuricaemia	1197	13	1.09	2.114 (1.128 to 3.964)	0.02	2.051 (1.063 to 3.856)	0.03
Sensitive analysis							
Total ‡							
Normal SUA level	5525	17	0.31	1.000	1.0000	1.000	1.0000
Hyperuricaemia	635	9	1.42	4.658 (2.068 to 10.494)	<0.001	5.666 (2.383 to 13.473)	<0.001
Total §							
Normal SUA level	7699	37	0.48	1.000	1.0000	1.000	1.0000
Hyperuricaemia	1191	13	1.09	2.285 (1.211 to 4.312)	0.01	2.183 (1.132 to 4.212)	0.02

*Model 1: adjusted for age, smoking, alcohol use, diuretics use, statins use, hypertension, diabetes, MI, TIA/stroke and dyslipidaemia, heart failure and gout.
†Model 2: adjusted for model 1 and sex.
‡Model 3: adjusted for model 2 and further excluded subjects with hypertension.
§Model 4: adjusted for model 2 and further excluded subjects with MI or heart failure.
AF, atrial fibrillation; MI, myocardial infarction; SUA, serum uric acid; TIA, transient ischaemic attack.

Possible mechanism of gender difference is potentially linked, in part, to menopause, as oestrogen is known to be uricosuric. In our study, nearly one-third of women (26.11%) were postmenopausal, thus, we believe that age-related postmenopause potentially contributed to the possible mechanism underlying the gender difference. A recent study proposed that independent association with SUA was only observed in the total population and in men after adjusting for other cardiovascular risk factors. However, this study only enrolled patients aged ≥35 years in the rural Liaoning province of China.[18] Thus, it is possible that the differences in age, region and dietary customs account for the observed discrepancies between the present and previous studies. Further studies with a larger sample size are needed to confirm the regional and gender-specific link between SUA and AF.

As noted above, some epidemiological studies suggested an association between elevated SUA levels and AF, but little is known about the pathophysiological mechanism underlying this link. However, SUA biology may point to a potential mechanism. SUA is the final product of purine metabolism catalysed by xanthine oxidase, which plays an important role in the formation of free radical superoxide anion and oxidative stress, consequently resulting in calcium overload and decreasing sodium channels and aggravating cellular damage. These pathological processes promote electrical remodelling of the left atria.[29 30] In addition, SUA promotes inflammation via releasing pro-inflammatory cytokines (eg, interleukin-6, interleukin-8, tumour necrosis factor and monocyte chemoattractant protein 1)[31–33] or local activation of the renin–angiotensin system (RAS).[34] It is well known that chronic inflammation leads to endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation and elevated expression of fibrinogen.[35 36] Inflammation also upregulates the RAS and increases angiotensin II (Ang II) levels, which activate the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway. It has been shown that the Ang II/Rac1/STAT3 pathway is an important signalling pathway that can promote AF.[37] Both JAK/STAT and RAS signalling play a role in left atrial structural remodelling, and both electrical and structural remodelling contribute to the occurrence and development of AF.[38] Another potential epidemiological explanation for the relationship between SUA and AF could be that SUA is an independent predictor of various cardiovascular diseases, including stroke, hypertension, coronary heart disease and congestive heart failure.[39–41] Thus, elevated SUA levels may lead to increased AF prevalence via increasing the risk of cardiovascular diseases.

Our study has several limitations. First, this was a cross-sectional analysis with a low AF prevalence due to the low mean age of the participants. Furthermore, we did not explore the cause and effect of elevated SUA levels

and AF because this association may have been affected by reverse causality and survivor bias in the cross-sectional study. Second, the data were obtained from a population in northern China, and the lifestyle and diet customs (eg, meat, seafood and milk), which are different from other regions of China, played a significant role in SUA metabolism.[42] Therefore, this study was not nationally representative or regionally diverse. Third, some AF cases may not have been included in our analyses because participants with paroxysmal AF or asymptomatic AF 'escaped' ECG detection, and some subjects with valvular AF might not be excluded. Therefore, AF prevalence may be biased. Despite these limitations, our study has some important strengths. Specifically, the subject group was based on community-based population in China, and the sample size of the study was relatively large.

CONCLUSION

In conclusion, SUA levels were significantly associated with AF prevalence in a particular Chinese population. Also, women, but not men, with higher SUA levels tended to have an increased AF prevalence after adjusting for multiple clinical AF risk factors, suggesting a gender-specific mechanism. Further research should focus on confirming our finding and elucidating the exact pathophysiological and prognostic mechanisms underlying the link between SUA and AF.

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