



URIC ACID IS ASSOCIATED WITH FUTURE ATRIAL FIBRILLATION: A 09-YEAR FOLLOW-UP OF 631 MEN AND WOMEN—STUDY AT TERTIARY CARE HOSPITAL FROM NORTH INDIA

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ABSTRACT

The aim of this study was to investigate the association between baseline Serum Uric Acid(SUA) and Atrial Fibrillation(AF) at single center tertiary care hospital from North India A total of 631 men and women from north India reporting to Medical OPD (MOPD)and Medical IPD(MIPD) of UP University of Medical Sciences, India. The mean age at baseline was 60 years. Information on angina, myocardial infarction, diabetes, anti-hypertensive and diuretic treatment, physical activity, smoking and alcohol, and measurements of height, weight, blood pressure, SUA, total cholesterol, and high density lipoprotein-cholesterol were obtained at baseline. The outcome measure was first-ever AF, documented on an electrocardiogram. We identified 57 cases of incident AF. In multivariable Cox proportional hazards regression analysis adjusted for cardiovascular risk factors and concomitant diseases, SUA was associated with AF in both sexes. Hazard ratio per 1 SD increase in SUA (91 $\mu\text{mol/L}$) was 1.40 [95% confidence intervals (CI), 1.14–1.72] in women and 1.17 (95% CI, 1.02–1.36) in men. The upper quartile of SUA conferred a 76% increased risk for AF in women and 49% in men as compared with the lowest quartile

- The association between SUA levels and AF remained when adjusted for factors known to predispose for AF, such as cardiovascular disease, diabetes, metabolic factors (body mass index, lipids) or blood pressure, and the association was non-significantly stronger in women.

INTRODUCTION

Serum uric acid (SUA) is the breakdown product of purine catabolism, catalysed by xanthine oxidase. Increased levels are associated with hypertension, kidney disease, obesity, hyperlipidaemia, diabetes, and cardiovascular disease (CVD). Serum uric acid levels in men are higher than in women throughout life, although SUA levels increase after menopause. Serum uric acid is influenced by diet, medication, and physical activity.

Atrial fibrillation (AF) is associated with conditions which are also associated with increased SUA, such as hypertension, obesity, CVD, and diabetes.^[1,2] A possible direct link between SUA and AF has barely been addressed. A cross-sectional Greek study reported an association between increased SUA and permanent AF^[3,4] The first population-based prospective study to investigate this topic reported that elevated SUA was associated with a greater risk of AF among African Americans and women^[5]

Alternatively, the association between SUA and AF may be linked through higher risk of coronary heart disease (CHD) or hypertension. Large studies have shown that hyperuricaemia is associated with increased incidence of CHD and increased mortality in persons with and without pre-existing CHD^[6] However, it is unclear if hyperuricaemia has a causal effect on CHD, or is just a marker for other risk factors, as some epidemiological studies did not observe significant associations between SUA and cardiovascular endpoints when adjusting for CVD risk factors^[7,8] The aim of this study was to investigate the association between SUA and future risk of incident AF in a large, general population of white, north-European descent.

METHODS

Prospective study of the general population in UP, India. The study was wef Apr-2008 to Apr 2017, with the main focus on determinants and distribution of CVDs. Eligible for the present study were participants at Medical OPD(MOPD) and IPD(MIPD) of UP University of Medical Sciences(UPUMS), India. All inhabitants 25

years and older were invited. All women 50–74 years, all men 55–74 years, and 5–10% samples in other 5-year age groups (25–54 years and 75–85 years) were invited to attend MOPD of UPUMS, India to which 100% attended. These participants constitute the study population.

Serum uric acid was measured by photometry with COBAS[®] instruments (Roche diagnostics) using an enzymatic colorimetric test, the uricase/PAP method. Reference values were 140–340 $\mu\text{mol/L}$ (2.4–5.7 mg/100 mL) for women and 200–415 $\mu\text{mol/L}$ (3.4–7.0 mg/100 mL) for men. Creatinine was analysed by a modified Jaffe reaction, but since creatinine-based estimation of glomerular filtration rate (GFR) is better validated for enzymatic creatinine measurements, 111 plasma samples from the 1994/95 survey were thawed and reanalysed with an enzymatic method (Modular P/Roche). Values were fitted to a linear regression model, and recalibrated creatinine values were calculated for all participants. Estimated GFR (eGFR) was calculated according to the CKD-EPI formula where S_{Cr} is serum creatinine (mg/dL), k is 0.7 for females and -0.411 for males, min indicates the minimum of S_{Cr}/k , and max indicates the maximum of S_{Cr}/k . High-sensitive C-reactive protein (hs-CRP) was measured by a particle-enhanced immunoturbidimetric assay on a Modular P autoanalyser (Roche Diagnostics) with reagents from the manufacturer. Non-fasting serum total cholesterol was analysed by enzymatic colorimetric methods with commercial kits (CHOD-PAP, Boehringer-Mannheim). Serum high density lipoprotein (HDL)-cholesterol was measured after the precipitation of lower density lipoprotein with heparin and manganese chloride. The analyses were performed at the Department of Biochemistry, UP University of Medical Sciences India.

Information on diabetes, angina, myocardial infarction (MI), use of anti-hypertensive and diuretic treatment, physical activity, smoking, alcohol, and education was obtained from self-reported questionnaires. Diabetes was defined as self-reported diabetes and/or the use of anti-diabetic medication and/or glycosylated haemoglobin (HbA1c) $\geq 6.5\%$. Coronary heart disease was defined as previous MI and/or prevalent angina. Leisure-time physical activity was categorized into four levels. Smoking habits were classified as current daily smoking vs. non-smoking. Alcohol was reported as glasses per 2 weeks. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Blood pressure (BP) was recorded two times at 5min intervals of seated resting, by specially Resident Medicine Dept. UPUMS, India using an automated device. The mean of the first and second reading was used in the analysis. In addition, we manually searched paper versions of hospital records (used until Apr2017) for notes on AF, and performed text searches with the term 'atrial fibrillation' in the electronic hospital records. Study participants with

diagnoses of cerebrovascular or cardiovascular events but without a diagnosis of arrhythmia. Adjudication of hospitalized and out-of-hospital events was performed by Investigator s based on data from hospital and out-of-hospital records. All AF events and first time of occurrence were confirmed in medical records and validated by one of the investigators. Participants with transient AF occurring only during an acute MI, in connection with cardiac surgery, or in the last seven days of life, were not classified as having AF. Few participants ($n = 24$) were documented with atrial flutter only. These are not included in the AF group. The individuals were followed from the date of examination until the date of first documented AF, or date of censoring due to migration or death, or end of follow-up at 07 Apr2017, whichever came first. Those who had died or emigrated during follow-up were identified and included in the study.

Statistical analyses

Characteristics of the study population are presented as means (standard deviation, SD) or percentages (numbers) in those with/without AF and by quartiles of uric acid. Differences between groups were assessed by t -tests and χ^2 tests, and tests of linear trend across quartiles of uric acid were estimated using linear regression models for continuous variable and logistic regression for binary variables. Age-adjusted and multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for AF with 95% confidence intervals (CIs). The analyses were conducted separately for men, women, and the total study population. The following cardiovascular risk factors were included as covariates: age, BMI, systolic blood pressure (SBP), total cholesterol, HDL-cholesterol, eGFR, current smoking, use of alcohol, physical activity, prevalent CHD, diabetes, anti-hypertensive and diuretic treatment. Data were not censored for development of concomitant disorders such as occurrence of diabetes or CHD in conjunction with the AF diagnosis. Serum uric acid was included both categorized (in quartiles) and as a continuous variable. The proportional hazard assumption was assessed by visual inspection of log minus log plots of the survival curves. Analyses were conducted with SPSS version 19.0 for Windows. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Incident AF was identified in 26 women (8.1%) and 31 men (10.1%) during a mean follow-up of 9 years. The incidence rate of AF per 1000 person-years was 7.26 (95% CI, 6.36–8.16) in women and 9.60 (95% CI, 8.56–10.64) in men. Baseline characteristics for men and women with and without subsequent AF are as mentioned. Above Participants developing AF were significantly older, had higher BMI and BP, higher SUA levels, higher frequency of CHD, diabetes, and use of anti-hypertensive medication and diuretics. The proportion of daily smokers were lower in participants who developed AF. Women with subsequent AF had

higher total cholesterol, and men with subsequent AF had higher creatinine. There were no significant differences in HDL-cholesterol or alcohol consumption

in either sex, but women with subsequent AF were more likely to be teetotalers. Participants developing AF had lower baseline GFR.

Table 1: Baseline characteristics by quartiles of uric acid and gender.

	Uric acid quartile				P for trend
	1	2	3	4	
<i>Women</i>					
Uric acid (µmol/L)	≤229.5	230.0–270.0	270.5–318.0	≥318.5	
Age (years)	58.3 (11.4)	60.2 (10.3)	61.3 (9.4)	63.2 (8.8)	<0.0001
Body mass index (kg/m ²)	23.8 (3.6)	25.2 (3.7)	26.5 (4.2)	28.3 (4.8)	<0.0001
Systolic blood pressure (mmHg)	138.2 (23.1)	142.1 (22.6)	147.3 (24.2)	152.7 (24.8)	<0.0001
Diastolic blood pressure (mmHg)	78.4 (12.6)	80.6 (12.5)	82.8 (13.6)	85.0 (13.8)	<0.0001
Cholesterol, total (mmol/L)	6.58 (1.35)	6.82 (1.33)	6.97 (1.31)	7.20 (1.31)	<0.0001
HDL-cholesterol (mmol/L)	1.77 (0.43)	1.71 (0.42)	1.65 (0.42)	1.48 (0.42)	<0.0001
Creatinine (µmol/L)	56.5 (8.8)	59.0 (9.2)	60.8 (10.2)	64.5 (14.6)	<0.0001
GFR (mL/min/1.73 m ²)	97.3 (12.0)	93.5 (11.9)	91.0 (12.6)	86.2 (14.8)	<0.0001
Smoking, % (n)	34.9 (280)	32.7 (263)	28.0 (225)	29.1 (235)	0.002
Coronary heart disease, % (n)	5.1 (41)	6.2 (50)	8.0 (64)	15.5 (125)	<0.0001
Diabetes, % (n)	2.5 (20)	3.1 (25)	4.0 (32)	7.6 (61)	<0.0001
Hypertension, % (n)	35.6 (283)	42.5 (340)	52.7 (420)	60.3 (485)	<0.0001
Anti-hypertensive treatment, % (n)	5.6 (45)	9.8 (79)	14.3 (115)	22.8 (184)	<0.0001
Diuretic treatment, % (n)	0.7 (6)	1.2 (10)	3.2 (26)	10.0 (81)	<0.0001
<i>Men</i>					
Uric acid (µmol/L)	≤303.5	304.0–349.5	350.0–404.0	≥404.5	
Age (years)	60.8 (9.7)	59.5 (9.8)	59.0 (10.8)	59.2 (9.7)	0.001
Body mass index (kg/m ²)	24.6 (3.0)	25.5 (2.9)	26.5 (3.3)	27.6 (3.4)	<0.0001
Systolic blood pressure (mmHg)	144.5 (20.7)	144.2 (19.9)	145.0 (20.7)	146.0 (19.8)	0.113
Diastolic blood pressure (mmHg)	84.0 (12.6)	84.2 (11.5)	85.2 (12.6)	86.1 (12.1)	<0.0001
Cholesterol, total (mmol/L)	6.31 (1.20)	6.45 (1.21)	6.52 (1.19)	6.78 (1.21)	<0.0001
HDL-cholesterol (mmol/L)	1.52 (0.41)	1.42 (0.40)	1.32 (0.35)	1.24 (0.38)	<0.0001
Creatinine (µmol/L)	69.8 (10.3)	73.4 (11.3)	75.7 (12.7)	81.3 (28.8)	<0.0001
GFR (mL/min/1.73 m ²)	96.6 (10.3)	95.0 (11.4)	93.5 (13.9)	89.8 (15.5)	<0.0001
Smoking, % (n)	39.1 (302)	35.7 (275)	32.2 (249)	30.1 (232)	<0.0001
Coronary heart disease, % (n)	11.1 (86)	12.6 (97)	16.4 (127)	20.6 (159)	<0.0001
Diabetes, % (n)	4.9 (38)	4.8 (37)	3.1 (24)	6.2 (48)	0.514
Hypertension, % (n)	45.5 (350)	48.3 (371)	51.1 (393)	54.6 (421)	<0.0001
Anti-hypertensive treatment, % (n)	8.1 (63)	10.0 (77)	13.5 (104)	20.6 (159)	<0.0001
Diuretic treatment, % (n)	0.8 (6)	1.0 (8)	1.9 (15)	4.4 (34)	<0.0001
<i>All</i>					
Uric acid (µmol/L)	≤257.5	258.0–309.0	309.5–368.5	≥369.0	
Age (years)	59.5 (10.9)	60.7 (9.7)	60.4 (10.1)	60.3 (9.7)	0.043
Body mass index (kg/m ²)	24.3 (3.6)	25.6 (3.8)	26.3 (3.7)	27.7 (3.9)	<0.0001
Systolic blood pressure (mmHg)	140.6 (22.9)	145.3 (22.4)	146.0 (21.7)	148.2 (22.0)	<0.0001
Diastolic blood pressure (mmHg)	80.1 (13.0)	82.9 (12.8)	84.0 (12.4)	86.1 (12.8)	<0.0001
Cholesterol, total (mmol/L)	6.62 (1.37)	6.69 (1.26)	6.67 (1.28)	6.84 (1.26)	<0.0001
HDL-cholesterol (mmol/L)	1.72 (0.43)	1.60 (0.42)	1.45 (0.41)	1.29 (0.39)	<0.0001
Creatinine (µmol/L)	59.2 (10.1)	64.4 (11.1)	69.6 (12.5)	76.8 (23.8)	<0.0001
GFR (mL/min/1.73 m ²)	96.1 (11.8)	93.5 (11.8)	92.5 (12.9)	89.2 (15.7)	<0.0001
Smoking, % (n)	35.9 (569)	32.0 (504)	32.5 (512)	30.2 (476)	0.002
Coronary heart disease, % (n)	6.6 (105)	8.6 (135)	12.3 (193)	20.1 (316)	<0.0001
Diabetes, % (n)	3.3 (53)	4.1 (64)	4.1 (65)	6.5 (103)	<0.0001
Hypertension, % (n)	38.9 (613)	49.2 (768)	50.5 (795)	56.6 (887)	<0.0001
Anti-hypertensive treatment, % (n)	7.1 (112)	11.3 (177)	13.7 (216)	20.5 (321)	<0.0001
Diuretic treatment, % (n)	0.8 (13)	1.8 (29)	2.7 (43)	6.4 (101)	<0.0001

Data are presented as means (SD) for continuous variables, percentages (number of cases) for categorical variables. GFR, glomerular filtration rate.

Hypertension = SBP > 140 or DBP > 90 or anti-hypertensive treatment.

Table 2: Baseline characteristics by quartiles of uric acid and gender.

	Uric acid quartile				P for trend
	1	2	3	4	
Women					
Uric acid (µmol/L)	≤229.5	230.0–270.0	270.5–318.0	≥318.5	
Age (years)	58.3 (11.4)	60.2 (10.3)	61.3 (9.4)	63.2 (8.8)	<0.0001
Body mass index (kg/m ²)	23.8 (3.6)	25.2 (3.7)	26.5 (4.2)	28.3 (4.8)	<0.0001
Systolic blood pressure (mmHg)	138.2 (23.1)	142.1 (22.6)	147.3 (24.2)	152.7 (24.8)	<0.0001
Diastolic blood pressure (mmHg)	78.4 (12.6)	80.6 (12.5)	82.8 (13.6)	85.0 (13.8)	<0.0001
Cholesterol, total (mmol/L)	6.58 (1.35)	6.82 (1.33)	6.97 (1.31)	7.20 (1.31)	<0.0001
HDL-cholesterol (mmol/L)	1.77 (0.43)	1.71 (0.42)	1.65 (0.42)	1.48 (0.42)	<0.0001
Creatinine (µmol/L)	56.5 (8.8)	59.0 (9.2)	60.8 (10.2)	64.5 (14.6)	<0.0001
GFR (mL/min/1.73 m ²)	97.3 (12.0)	93.5 (11.9)	91.0 (12.6)	86.2 (14.8)	<0.0001
Smoking, % (n)	34.9 (280)	32.7 (263)	28.0 (225)	29.1 (235)	0.002
Coronary heart disease, % (n)	5.1 (41)	6.2 (50)	8.0 (64)	15.5 (125)	<0.0001
Diabetes, % (n)	2.5 (20)	3.1 (25)	4.0 (32)	7.6 (61)	<0.0001
Hypertension, % (n)	35.6 (283)	42.5 (340)	52.7 (420)	60.3 (485)	<0.0001
Anti-hypertensive treatment, % (n)	5.6 (45)	9.8 (79)	14.3 (115)	22.8 (184)	<0.0001
Diuretic treatment, % (n)	0.7 (6)	1.2 (10)	3.2 (26)	10.0 (81)	<0.0001
Men					
Uric acid (µmol/L)	≤303.5	304.0–349.5	350.0–404.0	≥404.5	
Age (years)	60.8 (9.7)	59.5 (9.8)	59.0 (10.8)	59.2 (9.7)	0.001
Body mass index (kg/m ²)	24.6 (3.0)	25.5 (2.9)	26.5 (3.3)	27.6 (3.4)	<0.0001
Systolic blood pressure (mmHg)	144.5 (20.7)	144.2 (19.9)	145.0 (20.7)	146.0 (19.8)	0.113
Diastolic blood pressure (mmHg)	84.0 (12.6)	84.2 (11.5)	85.2 (12.6)	86.1 (12.1)	<0.0001
Cholesterol, total (mmol/L)	6.31 (1.20)	6.45 (1.21)	6.52 (1.19)	6.78 (1.21)	<0.0001
HDL-cholesterol (mmol/L)	1.52 (0.41)	1.42 (0.40)	1.32 (0.35)	1.24 (0.38)	<0.0001
Creatinine (µmol/L)	69.8 (10.3)	73.4 (11.3)	75.7 (12.7)	81.3 (28.8)	<0.0001
GFR (mL/min/1.73 m ²)	96.6 (10.3)	95.0 (11.4)	93.5 (13.9)	89.8 (15.5)	<0.0001
Smoking, % (n)	39.1 (302)	35.7 (275)	32.2 (249)	30.1 (232)	<0.0001
Coronary heart disease, % (n)	11.1 (86)	12.6 (97)	16.4 (127)	20.6 (159)	<0.0001
Diabetes, % (n)	4.9 (38)	4.8 (37)	3.1 (24)	6.2 (48)	0.514
Hypertension, % (n)	45.5 (350)	48.3 (371)	51.1 (393)	54.6 (421)	<0.0001
Anti-hypertensive treatment, % (n)	8.1 (63)	10.0 (77)	13.5 (104)	20.6 (159)	<0.0001
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All					
Uric acid (µmol/L)	≤257.5	258.0–309.0	309.5–368.5	≥369.0	
Age (years)	59.5 (10.9)	60.7 (9.7)	60.4 (10.1)	60.3 (9.7)	0.043
Body mass index (kg/m ²)	24.3 (3.6)	25.6 (3.8)	26.3 (3.7)	27.7 (3.9)	<0.0001
Systolic blood pressure (mmHg)	140.6 (22.9)	145.3 (22.4)	146.0 (21.7)	148.2 (22.0)	<0.0001
Diastolic blood pressure (mmHg)	80.1 (13.0)	82.9 (12.8)	84.0 (12.4)	86.1 (12.8)	<0.0001
Cholesterol, total (mmol/L)	6.62 (1.37)	6.69 (1.26)	6.67 (1.28)	6.84 (1.26)	<0.0001
HDL-cholesterol (mmol/L)	1.72 (0.43)	1.60 (0.42)	1.45 (0.41)	1.29 (0.39)	<0.0001
Creatinine (µmol/L)	59.2 (10.1)	64.4 (11.1)	69.6 (12.5)	76.8 (23.8)	<0.0001
GFR (mL/min/1.73 m ²)	96.1 (11.8)	93.5 (11.8)	92.5 (12.9)	89.2 (15.7)	<0.0001
Smoking, % (n)	35.9 (569)	32.0 (504)	32.5 (512)	30.2 (476)	0.002
Coronary heart disease, % (n)	6.6 (105)	8.6 (135)	12.3 (193)	20.1 (316)	<0.0001
Diabetes, % (n)	3.3 (53)	4.1 (64)	4.1 (65)	6.5 (103)	<0.0001
Hypertension, % (n)	38.9 (613)	49.2 (768)	50.5 (795)	56.6 (887)	<0.0001
Anti-hypertensive treatment, % (n)	7.1 (112)	11.3 (177)	13.7 (216)	20.5 (321)	<0.0001
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Data are presented as means (SD) for continuous variables, percentages (number of cases) for categorical variables. GFR, glomerular filtration rate.

Hypertension = SBP > 140 or DBP > 90 or anti-hypertensive treatment.

HRs for AF across quartiles and per 1 SD (91 $\mu\text{mol/L}$) increase in SA levels, shown in the total study population and in women and men separately. Adjustments were done in different steps. Systolic blood pressure and DBP were highly correlated (Pearson's $r = 0.77$ for women and 0.74 for men) and only SBP was entered in the analyses. The use of a composite hypertension variable instead (SBP ≥ 140 or DBP ≥ 90 or current diuretics or anti-hypertensive treatment) rendered almost identical HRs and P values. Since diuretic treatment exerts a direct effect on SUA, diuretic treatment was included as adjustment variable in the final step. We also tested the combination of SBP and DBP, which rendered identical estimates in all models. Replacing the composite variable 'coronary heart disease' (self-reported MI and/or angina) with validated MI at baseline, rendered a somewhat higher HR for AF, but with a wider CI and a lower P value. In Model 4, the HR was 1.47 ($P = 0.014$) in women and 1.24 ($P = 0.041$) in men. In Model 5, we have censored for incident MI.

There was an increased risk in both sexes of AF in the two upper SUA quartiles (SUA levels >270 $\mu\text{mol/L}$ in women and >350 $\mu\text{mol/L}$ in men), compared with the lowest quartile (SUA level <229 $\mu\text{mol/L}$ in women and <303 $\mu\text{mol/L}$ in men). In multivariable analyses, 1 SD increase in SUA was associated with a risk increment of 17% in men and 40% in women. Cross-product terms between sex and SUA were added to the models to assess interaction. No significant interaction was found, $P = 0.46$. Adjustment for covariates known to predispose for AF did not modify the estimates worthily.

DISCUSSION

In the present study, SUA was a significant risk factor for future AF. The association appeared stronger in women, however, no sex interaction was observed. This is in contrast with the ARIC study^[5], the only population-based prospective study published so far, where a significant association between SUA and AF was observed in women, but not in men. A cross-sectional Japanese study with more than 7000 patients also reported a sex-specific relationship between SUA level and prevalence of AF^[11]. A sex difference was also demonstrated in NHANES 1^[6] where ischaemic heart disease mortality, total cardiovascular mortality, and all-cause mortality was higher in women, with increasing SUA levels.

Serum uric acid levels in women increase during the fifth to seventh decade due to reduced renal excretion post-menopausally, caused by the loss of uricosuric effect of oestrogens^[12]. Flat or slightly declining SUA levels are seen with ageing in men^[7] probably due to age-related loss of skeletal muscle mass and reduced production of SUA. Age-related change in SUA could influence the sex differences observed in studies of SUA associated endpoints. However, many studies support a true difference in the impact of SUA in women and men^[5,6,11-14]. In the present study, no sex interaction was observed

in the associations between SUA and AF, although risk estimates were higher in women. Occurrence of AF increases with age, and the fact that SUA levels in women, in contrast to men, increase with age may account for the higher risk estimates seen in women. The aetiology of AF may also differ slightly in women and men. This is not investigated thoroughly, but in many studies the risk factors for AF have shown different strength of association in women and men. One may speculate that women may be more likely to develop AF in older age due to increase in BP, structural changes in the myocardium, or metabolic disturbances with accompanying rise in SUA levels^[2,3,15,16] while men may be more likely to develop AF due to additional factors, such as exercise-induced AF in younger age^[14,15]. In the present study, however, the proportion of persons reporting heavy physical activity was low, and sex differences in exercise-induced AF probably did not influence the results. In a previous report from the Tromsø Study, we found no association in any age groups between high physical activity and future AF.^[6]

Serum uric acid has emerged as a marker of CVD and a measure of cardiovascular risk factor load^[1,6]. Risk estimates of CVD by SUA vary in epidemiological studies, probably^[6,7] related to population differences, and also insufficiently accounted for confounding risk factors strongly related to SUA levels. In the Framingham Study, SUA was no longer associated with CHD, death from CVD, or death from all causes after adjustment for diuretics and CVD risk factors, and the SUA effect was strongly interrelated with traditional CVD risk factors and medication.^[7,17] By contrast, the present study showed a significant association between SUA levels and AF, adjusted for factors known to predispose for AF, such as CVD, diabetes, metabolic factors (BMI, lipids), or BP. This may suggest that either superoxide production linked with augmented xanthine oxidase activity^[17] or uric acid *per se* may cause myocardial dysfunction and influence the electro-mechanical system of the heart. In animal experiments, hyperuricaemia activates the renin-angiotensin system and reduces nitric oxide. Both superoxide and nitric oxide may modulate cardiac mechanosensitive ion channels^[19]. In patients with ischaemic cardiomyopathy, uric acid lowering therapy improved contractility thought to be mediated by beneficial effects on the myocardial redox state^[20]. Thus, one may speculate that uric acid, or increased xanthine oxidase activity, or both, are involved in important pathophysiological mechanisms of AF, independent of other risk factors.

Serum uric acid predicts the development of hypertension,¹ which is a known risk factor for AF. However, in the present study, adjustments for BP did not influence the associations between SUA and AF. Experimental animal and human studies have shown that treatment with allopurinol (a xanthine oxidase inhibitor) can lower BP^[21,22] and also have anti-ischaemic effects in patients with angina^[23]. In a recent, double-blinded,

placebo-controlled study of pre-hypertensive adolescents, SUA lowering by the xanthine oxidase independent drug probenecid resulted in normalization of BP^[24] This suggests a direct effect of SUA on vascular muscle cells or an indirect effect on renin-angiotensin activation or nitric oxide production These mechanisms may also explain the hypertension independent association between SUA and AF demonstrated²⁵ in the present study.

Serum uric acid promotes inflammation through the activation of pro-inflammatory cytokines.^[29,30,31,32] On the other hand, inflammation also increases SUA through augmented cell destruction. Chronic inflammation has been shown to be associated with AF, but results are inconsistent Whether inflammation is an initiator, a consequence or merely an innocent bystander of AF is debated. Many studies support the concept that inflammation contributes to at least some types of AF^[28,30,31,32,33,24,35] The most studied inflammatory biomarker is CRP, considered to reflect underlying disease processes associated with AF. Whether CRP contributes directly to the development of AF is debated.^[28,29] We therefore also performed multivariable analyses where we included hs-CRP as a covariate in Model 4. This did not change the results. The HRs and CIs after inclusion of hs-CRP were 1.39 (1.13–1.71) in women and 1.18 (1.03–1.37) in men. Thus, the association between SUA and AF does not seem to be mediated by inflammation in the Tromsø cohort. The ARIC study did not account for inflammation^[27,28,29,39,23] The MONICA/KORA survey reported that SUA was associated with all-cause and cardiovascular mortality independent of systemic inflammation in a general population^[31,32] Atrial fibrillation was not an endpoint in that study.

The angiotensin receptor blocker (ARB) losartan exerts a uricosuric effect and may also have anti-inflammatory effects^[14,28,33,39,40] angiotensin receptor blockers were not in common use in UPUMS India in 2008

Some limitations should be mentioned. The population is white European, and the results may not be generalizable to other ethnic groups. Serum uric acid was measured only once. Risk factor levels, including SUA, may have changed during follow-up.

Unfortunately, we were not able to adjust for congestive heart failure, as this information was available for AF cases only. This introduces a possible bias. Heart failure is an important risk factor for AF, and is included in the Framingham risk score^[32,34,35,36,37] Also, we lack information about incident hypertension and diabetes, which could influence the results.

The real number of AF cases may be understated, because there may be many persons in our study population with an undiagnosed AF. Persons with paroxysmal or asymptomatic AF would fail to get their

arrhythmia documented on an ECG. Some patients may be taken care of by their general practitioner without hospital contact. A British study found that this applied to one-third of AF patients in primary care.^[38,39,40] We have no corresponding data from Norway.

CONCLUSION

In summary, this prospective, population-based study showed that SUA is associated with future risk of AF in both sexes one one may benefit if uricosuric drugs are given when there is high Serum uric acid.

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