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Association between Serum Uric Acid and Impaired Endothelial Function: The Circulatory Risk in Communities Study

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Aims: Higher serum uric acid (UA) may impair endothelial function. However, population-based evidence examining the association between serum UA levels and endothelial function remains to be limited. Thus, in this study, we aimed to investigate this in the general population.

Methods: In this cross-sectional study, 1000 participants (496 males and 504 females), aged 30–79 years, free from a history of gout, have undergone both serum UA and brachial artery flow-mediated dilation (FMD) measurements. Participants were divided into four groups based on serum UA quartiles. Logistic regression models were used to calculate odds ratios (ORs) for low FMD according to the serum UA levels.

Results: In total, 203 participants (138 males and 65 females) with %FMD ≤ 5.0% were identified to have endothelial dysfunction. The multivariable OR of low FMD for highest quartiles vs. lowest quartiles was 2.39 (95% confidence interval [CI]: 1.32–4.34), while OR per 1-standard deviation (SD) increment was 1.28 (95% CI: 1.04–1.56). The positive association was noted to be more evident in females (OR per 1-SD increment: 1.46; 95% CI: 1.08–1.96) than in males and confined to individuals not using antihypertensive medications. The ORs per 1-SD increment were 1.01 (95% CI: 0.68–1.50) among individuals using antihypertensive medications and 1.43 (95% CI: 1.12–1.81) among individuals not using antihypertensive medications.

Conclusion: Higher serum UA was positively associated with the prevalence of endothelial dysfunction in samples of the general Japanese population and that positive association was confined to individuals not using antihypertensive medications.

Key words: Uric acid, Endothelial dysfunction, Flow-mediated dilation, Japanese, Cross-sectional study

1. Introduction

Endothelial cells are known to have distinct functions in vascular biology, and endothelial dysfunction has been associated with cardiovascular disease, diabetes, chronic kidney disease, and severe viral infections[1]. As a non-invasive method to evaluate vascular endothelial function[2], brachial artery flow-mediated dilation (FMD) has an independent predictive value for cardiovascular events and all-cause mortality[3].

Serum uric acid (UA) can stimulate vascular smooth muscle cell proliferation and angiotensin II production[4], induce oxidative stress and glycocalyx shedding[5], impair vascular nitric oxide activity[6], elevate the expression of inflammatory cytokines (such as interleukin [IL]-1β, IL-6, and tumor necrosis factor-alpha), and therefore impair endothelial function[7]. In addition, hyperuricemia has been associated with increased insulin resistance and the prevalence of metabolic syndrome[8].

Reactive oxygen species, including superoxides,

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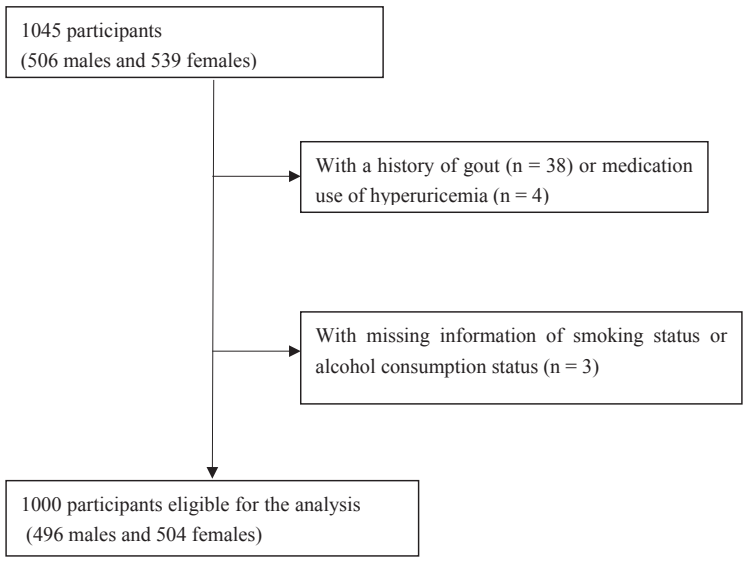

Fig. 1. Flowchart

are generated concomitantly with UA[9]. Thus, UA is considered a biomarker of oxidative stress level, which is an important endothelial dysfunction mechanism[10, 11], while UA is also identified as a powerful antioxidant[9]. An increase in UA levels could also be a compensatory mechanism to cope with the increased oxidative stress in patients with cardiovascular risk factors[9].

Higher serum UA levels have been associated with an increased risk of endothelial dysfunction in many studies[6, 12-24], especially in females[18, 22], postmenopausal females[19], and healthy males without metabolic syndrome[17]. However, several studies have shown no associations between serum UA and FMD[25-28], whereas UA was found to be negatively associated with microvascular function[26] and nitroglycerin-mediated dilatation[29]. These inconsistent results may be attributed to differences in the study populations, sample sizes, measurement methods, definitions of endothelial dysfunction, use of antihypertensive medications[30, 31], and genetic variance contributing to fractional excretion of UA[32, 33]. The association was observed to be stronger in females than in males[18, 22]. Different types of antihypertensive medications can increase (e.g., diuretics and beta-blockers) or decrease (e.g., calcium channel blockers) serum UA[30, 31], and certain antihypertensive medications (e.g., angiotensin-converting enzyme inhibitors and calcium channel blockers) can improve endothelial function[34]. Thus, we can assume that the associations between serum UA level and FMD might vary by sex and the usage of antihypertensive medications.

Therefore, in this study, we aimed to explore the associations in the general population and its discrepancies in sexes and with or without antihypertensive medications in this community-based cross-sectional study.

2. Materials and Methods

2.1 Study Population

We conducted FMD measurements in two communities: Yao in Osaka Prefecture, an urban-suburban community, and Ikawa in Akita Prefecture, a rural community. Both communities were covered by the Circulatory Risk in Communities Study[35]. Informed consent was obtained from the community representatives. From 2013 to 2017, 1045 participants (506 males and 539 females) aged 30–79 years underwent both serum UA and FMD measurements. After excluding those with a history of gout (n=38) or those using medications for hyperuricemia (n=4), and those with missing information as regards smoking status or alcohol consumption status (n=3), 1000 participants (496 males and 504 females) were included in this study **(Fig. 1)**.

The study protocol was approved by the ethics committee of Osaka University and Osaka Center for Cancer and Cardiovascular Disease Prevention.

2.2 Measurement of FMD

FMD measurements were performed on resting supine participants by trained operators according to the current guidelines[2]. A 10 MHz high-resolution linear artery transducer with computer-assisted analysis software (UNEXEF18G, UNEX Co., Nagoya, Japan) was used to assess the right brachial artery

diameters of 5–10 cm above the elbow[36]. We then occluded artery inflow by pressurizing the cuff to 50 mmHg or more above the systolic blood pressure and deflated the cuff 5 min thereafter. %FMD was the percentage difference between the peak vessel diameter and baseline vessel diameter. The coefficient of intra-operator variability for FMD measurements was 11.1% and 10.8% after 2 months and 4 months, respectively. That of inter-operator variability was 5.7% in our laboratory[37].

2.3 Measurement of Serum UA and Other Cardiovascular Risk Factors

Serum UA was determined by the uricase-peroxidase method using a TBA-2000FR fully automated analyzer (Toshiba Medical System Corp., Japan).

All participants completed an interview and answered questions as regards their smoking and alcohol consumption status, physical activity, medical history, and use of medications for hypertension, diabetes mellitus, hyperlipidemia, and hyperuricemia. The participants wore stockings and light clothing when their height and weight were measured. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by the height squared (m^2). Blood pressure was measured by trained investigators using a standard mercury sphygmomanometer on the right arm after 5 min of rest[35]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg[38], or using antihypertensive medications. People who reported weekly consumption of 0.3 go-cups (7 g ethanol) or more were defined as current drinkers. Blood samples were also obtained on the same day, and the serum was immediately separated. Serum triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels were measured using enzymatic methods with a TBA-2000FR fully automated analyzer. Serum glucose measurements were performed using the hexokinase method/glucose-6-phosphate dehydrogenase method using the same analyzer. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL (7.0 mmol/L), non-fasting glucose ≥ 200 mg/dL (11.1 mmol/L)[39, 40], or using medication for diabetes.

2.4 Statistical Analysis

Low FMD was defined as the lowest quintile (%FMD ≤ 5.0%)[41-43]. Participants were divided into four groups according to the quartiles of serum UA. The characteristics of the participants in each group are presented as the mean ± SD or proportions. *P*-values of trend in categorical and continuous variables were tested using the median UA levels of each group with logistic linear regression and linear regression, respectively.

Logistic regression analyses were then used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for low FMD in the total population, in both sexes, and in individuals with or without antihypertensive medications. First, we made the analyses using an unadjusted model. In the second model, all analyses except for sex-specific analyses were age- and sex-adjusted, while age-adjusted models were used for sex-specific analyses. The third model was further adjusted for the community (Yao, Ikawa), sex-specific quartiles of BMI (kg/m^2), the use of antihypertensive medications (yes or no) except for stratified analyses by antihypertensive medication use, use of lipid-lowering medications (yes or no), diabetes mellitus (yes or no), smoking status (never-smoker, ex-smoker, and current smoker), alcohol drinking status (never-drinker, ex-drinker, and current-drinker), physical activity (yes or no), systolic blood pressure (mmHg), baseline brachial artery diameter (mm), and serum cholesterol (mmol/L) as continuous variables. The *p*-values for trends were tested using serum UA as a continuous variable. We then tested statistical interactions for the use of antihypertensive medications by adding a cross-product term for serum UA quartiles (1, 2, 3, and 4) and antihypertensive medication usage (0 and 1) to the model. Similarly, we tested the interaction by sex. We have also conducted total analyses and sex-specific analyses after excluding subjects using antihypertensive, anti-diabetic, or lipid-lowering medications. All the variables mentioned were obtained from the health checkup and interview on the same day as the FMD measurement. All *p*-values reported were two-sided, and statistical significance was set at $p<0.05$. All statistical analyses were performed using SAS version 9.4.

3. Results

The characteristics of the participants are summarized in **Table 1**. Mean values of serum UA from its lowest to highest quartiles were 3.6 mg/dL, 4.5 mg/dL, 5.4 mg/dL, and 6.9 mg/dL; moreover, males accounted for 17%, 29%, 65%, and 87% of these quartiles, respectively. For %FMD, the mean values were as follows: 7.9%, 7.4%, 7.2%, and 6.7%. The mean value of %FMD was 7.3% in the whole population (not shown in the table): 6.7% in males and 7.9% in females. In total, 203 participants (138 males and 65 females) with %FMD ≤ 5.0% were identified to have endothelial dysfunction.

Subjects with higher serum UA levels had a

Table 1. Mean values ± standard deviations and proportions of cardiovascular risk factors according to quartiles of serum uric acid

	quartile of serum uric acid				*p* for trend*
	Q1	Q2	Q3	Q4	
Total, *n*	261	237	245	257	
Males, %	17	29	65	87	0.003
Age, year	50 ± 8	51 ± 8	53 ± 10	52 ± 10	< 0.001
Uric acid, mg/dL	3.6 ± 0.5	4.5 ± 0.2	5.4 ± 0.3	6.9 ± 0.8	< 0.001
Mean of flow-mediated dilation, %	7.9 ± 2.7	7.4 ± 2.6	7.2 ± 3.1	6.7 ± 3.0	< 0.001
Flow-mediated dilation ≤ 5.0, %	10	19	25	28	0.002
Baseline brachial artery diameter, mm	3.5 ± 0.6	3.6 ± 0.7	4.0 ± 0.7	4.3 ± 0.6	< 0.001
Current drinkers, %	37	41	58	75	0.45
Current smokers, %	12	17	23	32	0.12
Physical activity, %	62	53	51	57	0.01
Body mass index, kg/m^2	21.6 ± 3.1	22.6 ± 3.6	23.9 ± 3.6	24.7 ± 3.7	< 0.001
Systolic blood pressure, mmHg	119 ± 16	121 ± 17	125 ± 15	128 ± 17	< 0.001
Diastolic blood pressure, mmHg	77 ± 10	78 ± 10	80 ± 10	83 ± 12	< 0.001
Hypertension, %	21	28	44	53	0.04
Use of antihypertensive medications, %	8	14	22	25	0.009
Total cholesterol, mg/dL	208 ± 33	213 ± 38	210 ± 37	210 ± 44	0.97
HDL cholesterol, mg/dL	70 ± 15	67 ± 15	61 ± 14	56 ± 17	< 0.001
LDL cholesterol, mg/dL	121 ± 30	127 ± 32	127 ± 34	123 ± 36	0.73
Triglycerides, mg/dL	77 ± 40	89 ± 51	109 ± 73	171 ± 214	< 0.001
Use of lipid-lowering medications, %	6	5	9	9	0.91
Diabetes mellitus, %	5	8	10	9	0.10
Males, *n*	45	68	159	224	
Age, year	58 ± 8	53 ± 11	55 ± 11	53 ± 11	0.004
Uric acid, mg/dL	3.6 ± 0.6	4.6 ± 0.2	5.5 ± 0.3	6.9 ± 0.8	< 0.001
Mean of flow-mediated dilation, %	6.9 ± 3	6.7 ± 2.4	6.8 ± 3	6.6 ± 3.1	0.59
Flow-mediated dilation ≤ 5.0, %	20	25	30	29	0.48
Baseline brachial artery diameter, mm	4.4 ± 0.5	4.4 ± 0.6	4.3 ± 0.5	4.4 ± 0.6	0.63
Current drinkers, %	69	65	71	79	0.54
Current smokers, %	36	37	33	33	0.94
Physical activity, %	67	49	51	57	0.04
Body mass index, kg/m^2	23.5 ± 3.3	23.2 ± 3.4	23.8 ± 3.4	24.6 ± 3.4	0.02
Systolic blood pressure, mmHg	131 ± 14	124 ± 16	126 ± 15	128 ± 17	0.37
Diastolic blood pressure, mmHg	84 ± 9	79 ± 10	81 ± 10	83 ± 12	0.86
Hypertension, %	58	28	48	54	0.002
Use of antihypertensive medications, %	27	10	23	26	0.03
Total cholesterol, mg/dL	195 ± 31	200 ± 40	202 ± 29	206 ± 35	0.03
HDL cholesterol, mg/dL	61 ± 16	59 ± 14	58 ± 14	55 ± 17	0.02
LDL cholesterol, mg/dL	114 ± 28	119 ± 34	122 ± 27	122 ± 33	0.11
Triglycerides, mg/dL	91 ± 46	104 ± 68	115 ± 82	164 ± 145	< 0.001
Use of lipid-lowering medications, %	9	9	10	7	0.89
Diabetes mellitus, %	18	15	13	8	0.77
Females, *n*	216	169	86	33	
Age, year	48 ± 6	50 ± 6	52 ± 7	51 ± 6	0.03
Uric acid, mg/dL	3.5 ± 0.5	4.5 ± 0.2	5.3 ± 0.3	6.7 ± 0.8	< 0.001
Mean of flow-mediated dilation, %	8.1 ± 2.6	7.7 ± 2.7	7.8 ± 3.1	7.4 ± 2.8	0.18
Flow-mediated dilation ≤ 5.0, %	7	16	17	21	0.02
Baseline brachial artery diameter, mm	3.3 ± 0.4	3.3 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	0.001
Current drinkers, %	30	31	35	48	0.83
Current smokers, %	7	9	6	21	0.75
Physical activity, %	61	54	51	55	0.15
Body mass index, kg/m^2	21.3 ± 2.9	22.4 ± 3.6	24.2 ± 3.9	25.4 ± 5.4	< 0.001
Systolic blood pressure, mmHg	116 ± 16	120 ± 17	123 ± 15	131 ± 20	< 0.001
Diastolic blood pressure, mmHg	75 ± 10	78 ± 10	80 ± 9	84 ± 12	< 0.001
Hypertension, %	13	28	36	52	0.00
Use of antihypertensive medications, %	4	16	20	18	< 0.001
Total cholesterol, mg/dL	211 ± 32	219 ± 35	225 ± 44	234 ± 79	0.002
HDL cholesterol, mg/dL	72 ± 15	70 ± 15	67 ± 15	65 ± 16	0.009
LDL cholesterol, mg/dL	123 ± 30	130 ± 31	137 ± 41	133 ± 48	0.07
Triglycerides, mg/dL	74 ± 38	83 ± 41	99 ± 52	224 ± 466	< 0.001
Use of lipid-lowering medications, %	5	4	7	18	0.41
Diabetes mellitus, %	2	5	5	9	0.21

*p-values were non-adjusted and were estimated by the regression method (linear regression for continuous variables and logistic regression for categorical variables).

higher proportion of males and antihypertensive medication users. They had a larger baseline brachial artery diameter, higher BMI, higher blood pressure, higher HDL cholesterol, and lower triglyceride levels. Males with higher serum UA levels were more likely to be younger, with a higher BMI, higher serum cholesterol, higher serum triglyceride, and lower HDL cholesterol levels. Among females, those with higher serum UA levels were found to have a higher prevalence of hypertension and antihypertensive medication usage, a higher BMI, higher systolic and diastolic blood pressures, higher serum cholesterol, higher serum triglycerides, and lower HDL cholesterol. In contrast to males, females with higher serum UA levels were more likely to be older.

Scatter plots figures **(Supplementary Fig. 1, 2, 3, 4, 5)** show the associations between serum UA level and FMD, age, BMI, systolic blood pressure, and total cholesterol. Regression lines and the 95% CIs were also demonstrated for all these variables.

The associations between the quartiles of serum UA and low FMD are shown in **Table 2**. We also showed sex-specific results, although there was no interaction by sex (p for interaction = 0.40, not shown in the tables), as the proportion of males in higher UA quartiles was significantly higher than that in the lowest quartile. Analyses stratified by antihypertensive medication usage were also performed since the borderline interaction by antihypertensive medication usage and quartiles of serum UA for low FMD (p for interaction = 0.05, not shown in tables).

As shown in **Table 2**, 1-standard deviation (SD) increment of serum UA (1.34 mg/dL) was determined to be associated with a higher risk of low FMD (OR: 1.28, 95% CI: 1.04–1.56, p for trend = 0.02). The multivariable ORs of low FMD compared with the lowest quartile were 2.18 (95% CI: 1.24–3.82) for the second quartile, 2.43 (95% CI: 1.38–4.29) for the third quartile, and 2.39 (95% CI: 1.32–4.34) for the highest quartile, respectively. Among males, a 1-SD increment of serum UA (1.25 mg/dL for males) was associated with a higher risk of low FMD, although not significant (OR: 1.23, 95% CI: 0.97–1.54, p for trend = 0.08). The multivariable ORs of low FMD compared with the lowest quartile were 1.88 (95% CI: 0.69–5.13) for the second quartile, 2.57 (95% CI: 1.06–6.24) for the third quartile, and 2.46 (95% CI: 1.03–5.87) for the highest quartile, respectively.

A positive association was more evident in females than in males. In females, the OR per 1-SD increment of serum UA (0.99 mg/dL for females) was 1.46 (95% CI: 1.08–1.96, p for trend = 0.01). The adjusted ORs from the second to the highest quartile were 2.28 (95% CI: 1.10–4.72), 2.37 (95% CI: 1.00–5.66), and 3.45 (95% CI: 1.10–10.81), respectively.

In the antihypertensive medication stratified analyses, the association confined to individuals not using antihypertensive medications, OR per 1-SD increment was 1.43 (95% CI: 1.12–1.81, p for trend = 0.004). The respective adjusted ORs (95% CIs) of low FMD compared with the lowest quartile were 2.25 (1.18–4.30), 2.86 (1.47–5.57), and 3.11 (1.54–6.27) from the second to the highest quartile. Results in individuals using antihypertensive medications showed no association between serum UA and low FMD, and the OR per 1-SD increment was found to be 1.01 (95% CI: 0.68–1.50, p for trend = 0.97).

In the sensitivity analyses, similar results were observed after excluding subjects using antihypertensive, anti-diabetic, or lipid-lowering medications **(Table 3)**.

4. Discussion

To the best of our knowledge, this is the first study to investigate the association between serum UA levels and the prevalence of endothelial dysfunction in community-based, middle-aged, older populations. In this cross-sectional study of 1000 males and females aged 30–79 years, we found that higher serum UA levels were positively associated with the prevalence of endothelial dysfunction in the general Japanese population. The positive association was noted to be more evident in females than in males, and the association was confined to individuals not using antihypertensive medications.

A number of previous studies[6, 12-24], but not all[25-28], suggest a positive association between serum UA and endothelial dysfunction. A cross-sectional study of 2732 Japanese males without cardiovascular diseases and medications (49 ± 8 years) found that mild or severe hyperuricemia (serum UA ≥ 425 μmol/L; ≥ 7.14 mg/dL) was negatively associated with FMD ($p < 0.05$ for both) among subjects without metabolic syndrome, and so was severe hyperuricemia (serum UA ≥ 461 μmol/L; ≥ 7.745 mg/dL) among subjects with metabolic syndrome ($p < 0.05$)[17]. In another cross-sectional study on 749 Japanese females aged 30–74 years recruited during health screening, serum UA was positively associated with the prevalence of endothelial dysfunction (FMD ≤ 4.90%) in postmenopausal females [OR 1.23 (95% CI: 1.01–1.50)] but not in premenopausal females [OR 0.98 (95% CI: 0.75–1.26)][19]. Similar associations were found between serum UA and FMD in healthy volunteers[14]; hospitalized patients[22]; patients with

Table 2. Odds Ratios (95% CIs) of low FMD according to quartiles of serum uric acid

	quartile of serum uric acid				*p* for trend	OR per 1-SD** increment
	Q1	Q2	Q3	Q4		
Total, *n*	261	237	245	257		
Mean uric acid, mg/dL	3.6	4.5	5.4	6.9		
No. of low FMD ≤ 5.0%	25	44	62	72		
Proportion of low FMD ≤ 5.0, %	10	19	25	28		
Unadjusted OR (95% CI)	1	2.15 (1.27-3.64)	3.20 (1.93-5.29)	3.67 (2.24-6.02)	<0.001	1.49 (1.28-1.74)
Age- and sex-adjusted OR (95% CI)	1	1.99 (1.17-3.40)	2.22 (1.30-3.80)	2.45 (1.41-4.27)	0.005	1.30 (1.08-1.56)
Multivariable OR (95% CI)*	1	2.18 (1.24-3.82)	2.43 (1.38-4.29)	2.39 (1.32-4.34)	0.02	1.28 (1.04-1.56)
Males, *n*	45	68	159	224		
Mean uric acid, mg/dL	3.6	4.6	5.5	6.9		
No. of low FMD ≤ 5.0%	9	17	47	65		
Proportion of low FMD ≤ 5.0, %	20	25	30	29		
Unadjusted OR (95% CI)	1	1.33 (0.53-3.32)	1.68 (0.75-3.76)	1.63 (0.75-3.58)	0.26	1.12 (0.92-1.36)
Age- adjusted OR (95% CI)	1	1.62 (0.64-4.10)	1.95 (0.86-4.42)	2.08 (0.93-4.63)	0.06	1.21 (0.99-1.49)
Multivariable OR (95% CI)*	1	1.88 (0.69-5.13)	2.57 (1.06-6.24)	2.46 (1.03-5.87)	0.08	1.23 (0.97-1.54)
Females, *n*	216	169	86	33		
Mean uric acid, mg/dL	3.5	4.5	5.3	6.7		
No. of low FMD ≤ 5.0%	16	27	15	7		
Proportion of low FMD ≤ 5.0, %	7	16	17	21		
Unadjusted OR (95% CI)	1	2.38 (1.24-4.57)	2.64 (1.24-5.62)	3.37 (1.27-8.95)	0.006	1.40 (1.10-1.79)
Age- adjusted OR (95% CI)	1	2.21 (1.14-4.27)	2.28 (1.06-4.93)	3.06 (1.14-8.19)	0.02	1.34 (1.04-1.71)
Multivariable OR (95% CI)*	1	2.28 (1.10-4.72)	2.37 (1.00-5.66)	3.45 (1.10-10.81)	0.01	1.46 (1.08-1.96)
Individuals with antihypertensive medications, *n*	20	34	54	65		
Mean uric acid, mg/dL	3.4	4.5	5.4	7.0		
No. of low FMD ≤ 5.0%	7	13	21	24		
Proportion of low FMD ≤ 5.0, %	35	38	39	37		
Unadjusted OR (95% CI)	1	1.15 (0.36-3.63)	1.18 (0.41-3.44)	1.09 (0.38-3.10)	0.75	1.05 (0.78-1.43)
Age- and sex-adjusted OR (95% CI)	1	1.37 (0.41-4.58)	1.14 (0.39-3.35)	0.93 (0.32-2.75)	0.91	0.98 (0.70-1.38)
Multivariable OR (95% CI)*	1	1.78 (0.44-7.29)	1.35 (0.40-4.60)	1.10 (0.31-3.88)	0.97	1.01 (0.68-1.50)
Individuals without antihypertensive medications, *n*	241	203	191	192		
Mean uric acid, mg/dL	3.6	4.6	5.4	6.8		
No. of low FMD ≤ 5.0%	18	31	41	48		
Proportion of low FMD ≤ 5.0, %	7	15	21	25		
Unadjusted OR (95% CI)	1	2.23 (1.21-4.12)	3.39 (1.87-6.12)	4.13 (2.31-7.38)	<0.001	1.55 (1.29-1.86)
Age- and sex-adjusted OR (95% CI)	1	1.97 (1.06-3.69)	2.37 (1.25-4.49)	2.85 (1.47-5.51)	0.005	1.36 (1.10-1.70)
Multivariable OR (95% CI)*	1	2.25 (1.18-4.30)	2.86 (1.47-5.57)	3.11 (1.54-6.27)	0.004	1.43 (1.12-1.81)

*Adjusted further for community, baseline brachial artery diameter, body mass index, systolic blood pressure, serum cholesterol, use of lipid-lowering medications, diabetes mellitus defined by fasting glucose ≥ 126 mg/dL (7.0 mmol/L) or non-fasting glucose ≥ 200 mg/dL (11.1mmol/L) or taking medications for diabetes, smoking, drinking status, and physical activity. The use of antihypertensive medications was adjusted except for stratified analyses by antihypertensive medications use.
**1-SD serum UA is 1.34 mg/dL among all participants, 1.25 mg/dL among males, and 0.99 mg/dL among females.

cardiovascular disease[6], acute coronary syndrome[24], chronic kidney disease[12, 13, 25], hyperuricemia[20], human immunodeficiency virus[16], obstructive sleep apnea[21], and high cardiovascular risk but free from cardiovascular disease[23]; and normoglycemic first-degree relatives of type 2 diabetes mellitus complicated with hyperuricemia[15].

However, some studies found no association between serum UA levels and FMD. A Finnish cross-sectional study of 1985 young adults aged 30–45 years found no association between UA and FMD in both males ($\beta = 0.0011$, $p = 0.60$) and females ($\beta = -0.0047$, $p = 0.13$)[28]. In addition, no association was observed between UA and FMD in cross-sectional studies of

Table 3. Odds Ratios (95% CIs) of low FMD according to quartiles of serum uric acid after excluding subjects using antihypertensive, anti-diabetic, or lipid-lowering medications

	quartile of serum uric acid				*p* for trend	OR per 1-SD** increment
	Q1	Q2	Q3	Q4		
Total, *n*	195	195	199	193		
Mean uric acid, mg/dL	3.5	4.4	5.3	6.8		
No. of low FMD ≤ 5.0%	14	27	40	49		
Proportion of low FMD ≤ 5.0, %	7	14	20	25		
Unadjusted OR (95% CI)	1	2.08 (1.05-4.10)	3.25 (1.71-6.20)	4.40 (2.34-8.28)	<0.001	1.59 (1.32-1.91)
Age- and sex-adjusted OR (95% CI)	1	1.89 (0.95-3.77)	2.13 (1.07-4.25)	2.73 (1.32-5.64)	0.005	1.39 (1.11-1.74)
Multivariable OR (95% CI)*	1	2.11 (1.03-4.31)	2.52 (1.22-5.20)	3.13 (1.44-6.80)	0.003	1.47 (1.15-1.89)
Males, *n*	23	48	113	170		
Mean uric acid, mg/dL	3.6	4.5	5.4	6.8		
No. of low FMD ≤ 5.0%	2	12	28	46		
Proportion of low FMD ≤ 5.0, %	9	25	25	27		
Unadjusted OR (95% CI)	1	3.50 (0.71-17.18)	3.46 (0.76-15.69)	3.90 (0.88-17.27)	0.13	1.21 (0.95-1.53)
Age- adjusted OR (95% CI)	1	4.65 (0.92-23.38)	4.12 (0.89-19.02)	5.67 (1.25-25.73)	0.02	1.37 (1.06-1.78)
Multivariable OR (95% CI)*	1	5.66 (1.02-31.33)	6.18 (1.20-31.70)	7.88 (1.57-39.68)	0.005	1.53 (1.14-2.05)
Females, *n*	172	147	86	23		
Mean uric acid, mg/dL	3.5	4.4	5.2	6.7		
No. of low FMD ≤ 5.0%	12	15	12	3		
Proportion of low FMD ≤ 5.0, %	7	10	14	13		
Unadjusted OR (95% CI)	1	1.52 (0.69-3.35)	2.16 (0.93-5.04)	2.00 (0.52-7.70)	0.07	1.31 (0.98-1.76)
Age- adjusted OR (95% CI)	1	1.47 (0.66-3.25)	2.03 (0.86-4.76)	1.95 (0.51-7.54)	0.10	1.28 (0.95-1.73)
Multivariable OR (95% CI)*	1	1.83 (0.77-4.34)	2.80 (1.05-7.44)	3.12 (0.69-14.16)	0.01	1.59 (1.10-2.29)

*Adjusted further for community, baseline brachial artery diameter, body mass index, systolic blood pressure, serum cholesterol, diabetes mellitus defined by fasting glucose ≥ 126 mg/dL (7.0 mmol/L) or non-fasting glucose ≥ 200 mg/dL (11.1mmol/L), smoking, drinking status, and physical activity.
**1-SD serum UA is 1.31 mg/dL among all participants, 1.22 mg/dL among males, and 0.96 mg/dL among females.

kidney transplant recipients (n=124)[25], patients with cardiovascular disease or diabetes (n=304)[29], and subjects with hypertension (n=506)[26]. The different results may be due to discrepancies in the study population, sample sizes, measurement methods, definitions of endothelial dysfunction, use of antihypertensive medications[30, 31], and genetic variance contributing to fractional excretion of UA[32].

The association was reported to be stronger in females than in males[18, 22]. Cross-sectional research on 140 patients (females=86) in the Mayo Clinic suggested that elevated serum UA (≥ 5 mg/dL) was associated with an increased risk of peripheral endothelial dysfunction assessed by reactive hyperemia peripheral arterial tonometry (OR 2.45; 95% CI: 1.08–5.52; p=0.031). The association remained significant in females (OR 2.69; 95% CI: 1.01–7.19; p=0.048), but not in males (OR 1.65; 95% CI: 0.36–7.54; p=0.515)[22]. In a cross-sectional study of Chinese males (n=1891) and females (n=620), aged 46.86±9.52 years, serum UA was not entered in the stepwise regression equation in the multivariate linear regression analysis; however, in the univariate correlations, UA was significantly correlated with FMD in totality (r=–0.102; p<0.001) and females (r=–0.213; p<0.001) but not in males (r=–0.015; p=0.511)[18]. Similarly, a stronger association was observed among females in our study. The possible explanations may be the sexual difference in hormone levels and lower serum UA levels in females than in males.

The association between UA and low FMD was confined to individuals not using antihypertensive medications. UA is a powerful antioxidant, and hyperuricemia can be considered a compensatory mechanism to reduce the increased oxidative stress in individuals with high cardiovascular risk[9]. The use of medications can affect UA excretion. Certain antihypertensive medications, including diuretics and beta-blockers, can increase serum UA[30, 31], while others, such as calcium channel blockers, decrease serum UA[30]. Furthermore, certain antihypertensive medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium

channel antagonists, can improve endothelial function and vascular inflammation regardless of the lowering of blood pressure[34]. Angiotensin-converting enzyme inhibitors and calcium channel blockers are the two most commonly used antihypertensive medications from 2013 to 2017[44], when we collect the data. Both two medications can improve endothelial function, and calcium channel blockers are associated with the reduced serum UA level. Therefore, we can assume that hyperuricemia may not be accompanied by an increased risk of endothelial dysfunction in participants using antihypertensive medications.

Pemafibrate, a lipid-lowering medication, can improve endothelial function in diabetic mice[45]. Another lipid-lowering drug, that is, rosuvastatin, and some anti-diabetics, including insulin, metformin, and BLX-1002, could increase the viability and regeneration and reduce apoptosis of human coronary artery endothelial cells[46], suggesting using lipid-lowering and anti-diabetic medication is beneficial on endothelial function. However, after excluding subjects using antihypertensive, anti-diabetic, or lipid-lowering medications, the results did not change substantially **(Table 3)**.

In this study, both continuous and categorical analyses showed that serum UA levels were associated with an increased risk of endothelial dysfunction. This could imply that not only the highest level of UA showed impaired endothelial function, but a higher serum UA at any level could be associated with endothelial dysfunction. However, because of the cross-sectional design of this study, further longitudinal studies are needed to confirm this.

Our study had several strengths, including the use of general population samples, the non-invasive method for assessing endothelial function, and the standardized evaluations of cardiovascular risk factors that assured the quality of the study. In addition, we analyzed the association stratified by antihypertensive medication usage, which allowed us to investigate the associations among subjects with potential medication-induced hyperuricemia. However, this study also has several limitations. First, we could not confirm a causal relationship with the cross-sectional design. Additionally, oxidative stress is an important endothelial dysfunction mechanism[10, 11], and UA is not only an antioxidant but also a biomarker of oxidative stress[9]. Unfortunately, we have no measurements of oxidative stress and inflammatory markers. Furthermore, we did not collect information on the types of antihypertensive medications. Diuretics and beta-blockers increase serum UA[30, 31], while calcium channel blockers decrease serum UA[30].

In summary, we observed that higher serum UA levels were associated with the risk of endothelial dysfunction in the general Japanese population.

Conflict of Interest

All the authors have no conflicts of interest concerning this study.

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Author Contributions

The authors' responsibilities were as follows: All the authors and other CIRCS investigators made the study design and data collection; HI, JT, and KL: coordinated the entire work and primary responsibility for the final content; JT and KL: performed the statistical analysis; JT wrote the draft of the manuscript; All the authors: provided comments on the draft, read and approved the final manuscript.

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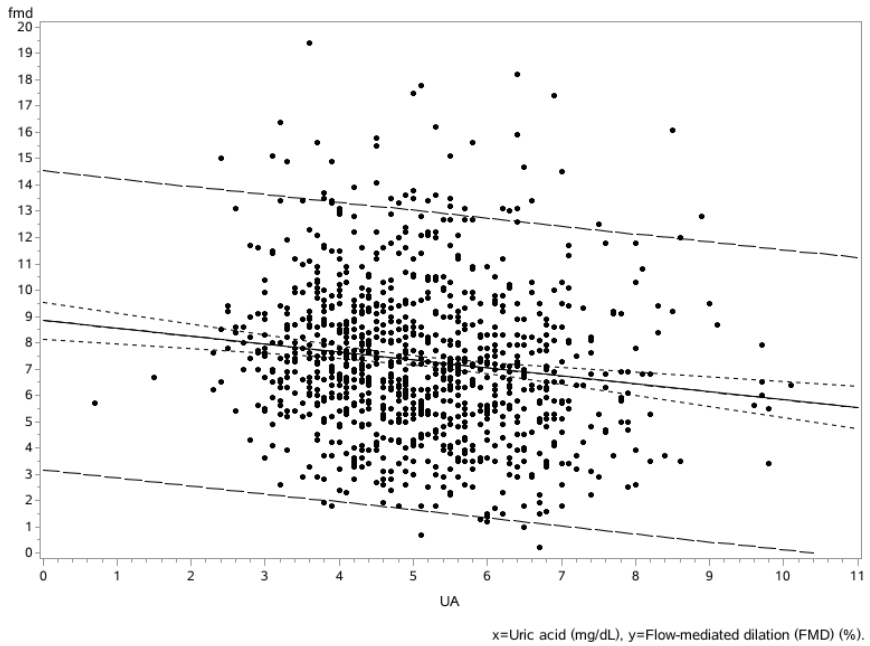
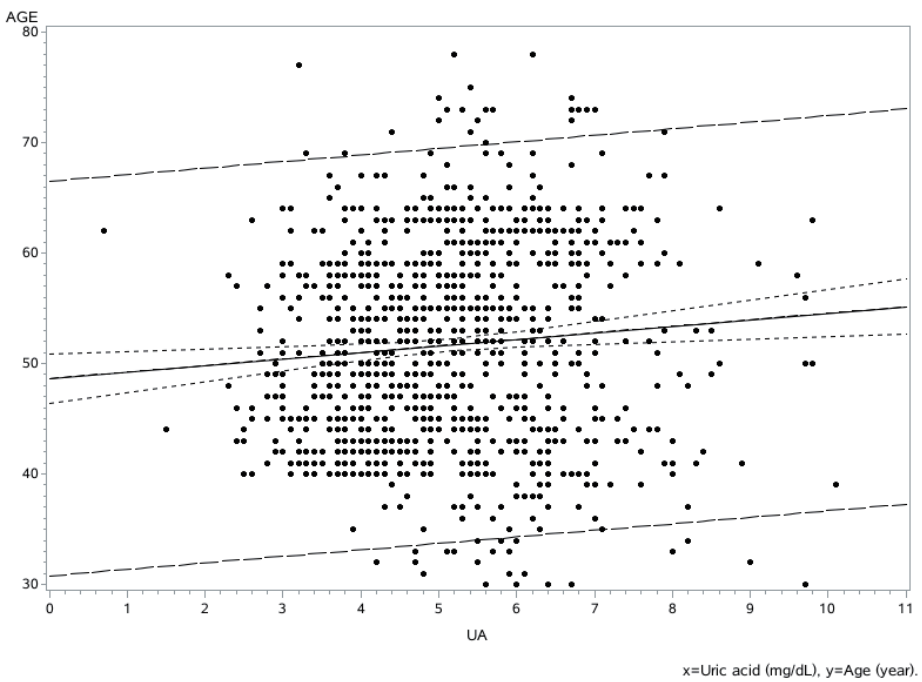
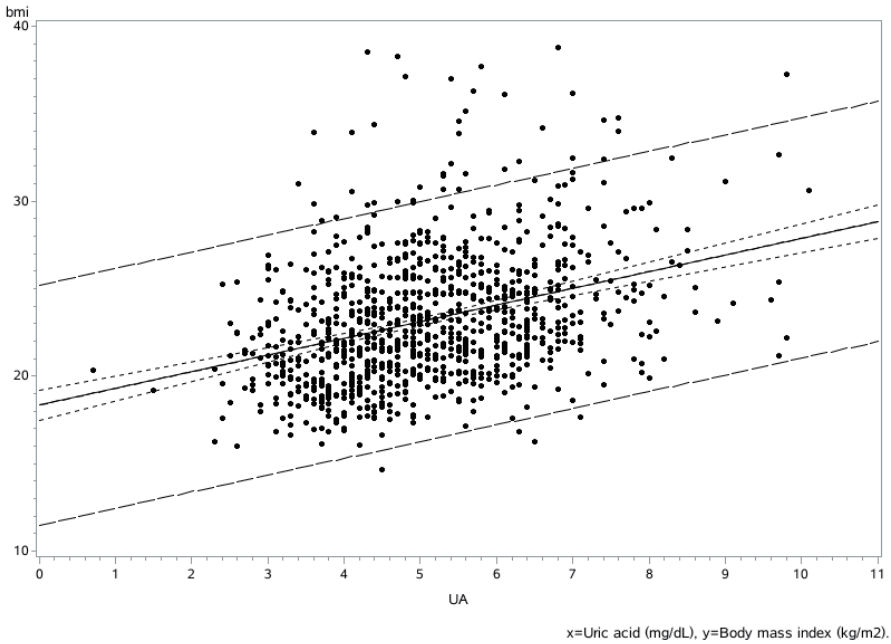


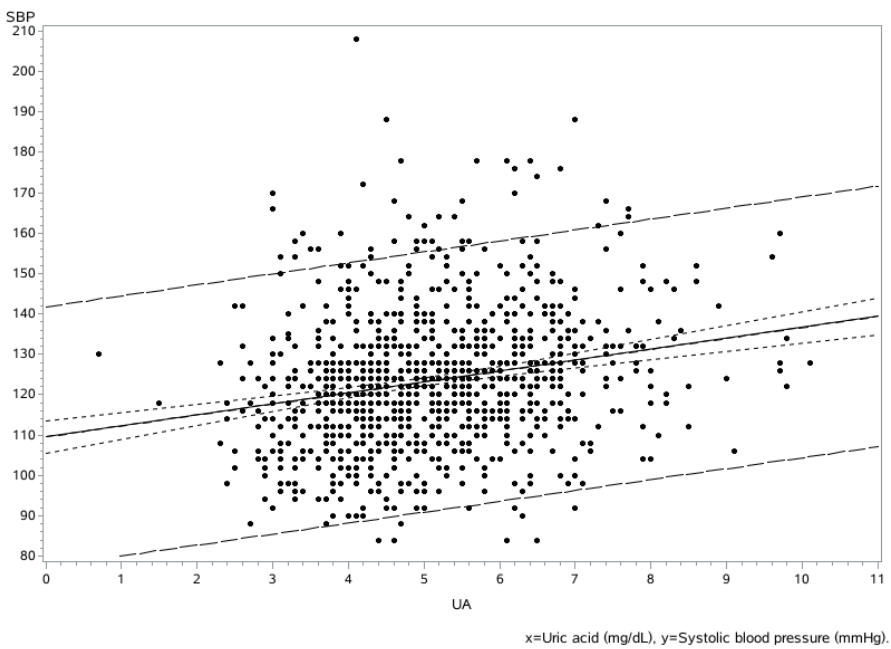
Supplementary Fig. 1. The scatter plot shows the association between serum uric acid level and flow-mediated dilation (FMD)
Straight lines show the regression line and the 95% confidence interval (CI), whereas the curves show the 95% CI for the mean of FMD.



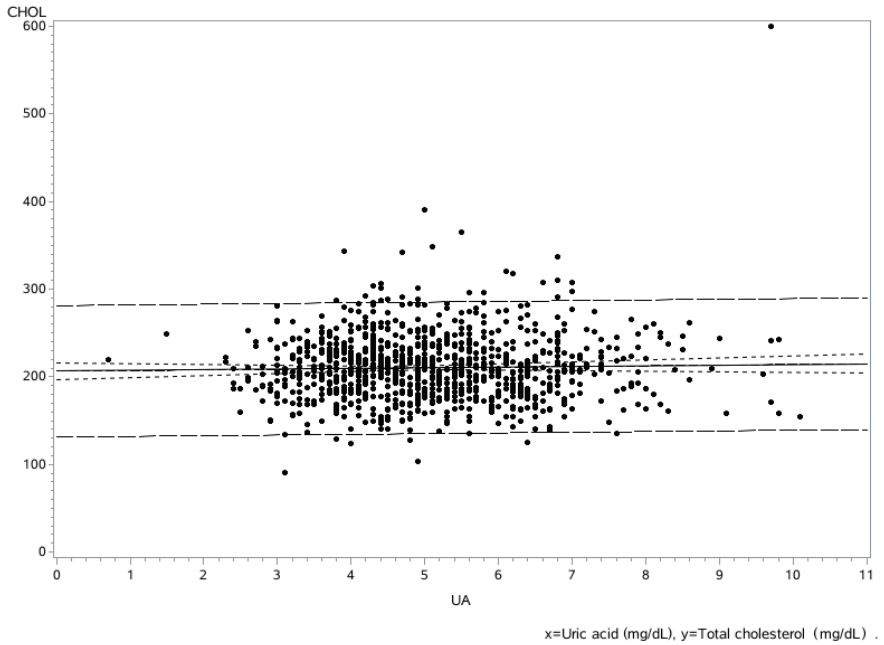
Supplementary Fig. 2. The scatter plot shows the association between serum uric acid level and age
Straight lines show the regression line and the 95% confidence interval (CI), whereas the curves show the 95% CI for the mean of age.



Supplementary Fig. 3. The scatter plot shows the association between serum uric acid level and body mass index (BMI)
Straight lines show the regression line and the 95% confidence interval (CI), whereas the curves show the 95% CI for the mean of BMI.



Supplementary Fig. 4. The scatter plot shows the association between serum uric acid level and systolic blood pressure
Straight lines show the regression line and the 95% confidence interval (CI), whereas the curves show the 95% CI for the mean of systolic blood pressure.



Supplementary Fig. 5. The scatter plot shows the association between serum uric acid level and total cholesterol

Straight lines show the regression line and the 95% confidence interval (CI), whereas the curves show the 95% CI for the mean of total cholesterol.