ORIGINAL ARTICLE

Associations between serum uric acid levels and the incidence of hypertension and metabolic syndrome: a 4-year follow-up study of a large screened cohort in Okinawa, Japan

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The purpose of this study was to examine the associations between serum uric acid (SUA) levels and the incidences of hypertension and metabolic syndrome (MetS) in a large screened cohort of Japanese men and women. We evaluated 4812 subjects (males, 2528; females, 2284; mean age, 47.5 years) who underwent health checkups between 2006 and 2010 and were free of hypertension and MetS in 2006. After 4 years, 618 (13%), 764 (16%) and 158 (3%) subjects developed hypertension, MetS and hypertension with MetS, respectively. Increased SUA levels were significantly and positively associated with the incidences of hypertension, MetS and hypertension with MetS. Compared with the first quartile of SUA levels, the odds ratios (95% confidence intervals) for the third and fourth quartiles, respectively, were as follows: 1.5 (1.1–2.1; $P=0.0128$) and 1.8 (1.2–2.5; $P=0.0022$) for hypertension, 1.3 (0.9–1.9; $P=0.1910$) and 1.8 (1.2–2.7; $P=0.0039$) for MetS and 2.7 (1.1–6.6; $P=0.0276$) and 3.2 (1.3–8.0; $P=0.0115$) for hypertension with MetS. In conclusion, increased SUA levels were significantly and independently associated with the incidences of hypertension and MetS in subjects without hypertension or MetS at baseline. Increased SUA levels might also be correlated with the incidence of hypertension with MetS.

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INTRODUCTION

Elevated serum uric acid (SUA) levels are closely associated with hypertension and metabolic syndrome (MetS). MetS is characterized by the presence of multiple common cardiovascular risk factors, such as central obesity, atherogenic dyslipidemia (hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C)) levels, hyperglycemia and elevated blood pressure (BP). Elevated SUA levels are prevalent in patients with hypertension^{1,2} and MetS,^{3–7} and these levels can be a significant predictor of the development of hypertension^{3,8–10} and MetS.^{11–14} Although evidence has suggested that elevated SUA levels might have a role in hypertension,¹⁵ a causal relationship has not been established. Confirming the involvement of elevated SUA levels in the pathogenesis of hypertension has been difficult, because MetS can confound the relationship between elevated SUA levels and hypertension and because these conditions share common pathophysiological features, such as insulin resistance, endothelial dysfunction, oxidative stress and inflammation.^{16–18} For these reasons, controlling for MetS is important in clinical studies that

examine the association between elevated SUA levels and the incidence of hypertension.

We recently reported that hyperuricemia was a significant and independent predictor of MetS.¹¹ In that study, the prevalence of hypertension was significantly higher in women who developed MetS than in those who did not. Substantial evidence has also indicated a higher prevalence of insulin resistance among patients with hypertension than among normotensive individuals.^{19–21} These findings have also given rise to the clinical question of whether elevated SUA levels are associated with incident MetS (also called insulin resistance syndrome) in subjects without hypertension.

In subjects with hypertension, MetS was independently associated with insufficient BP control and lower effectiveness of antihypertensive therapy.²² Moreover, Ninomiya *et al.*²³ showed that, among middle-aged Japanese men and women, hypertensive subjects with MetS had a significantly higher risk of cardiovascular disease, compared with those without MetS. In this study, the risk of cardiovascular disease in normotensive subjects with MetS was similar to that in hypertensive

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subjects without MetS. Therefore, hypertension with MetS might confer a high risk of cardiovascular events.

The purpose of this study was to examine the associations between SUA levels and the incidence of hypertension, MetS and hypertension with MetS in subjects without hypertension or MetS in a large screened cohort of Japanese men and women.

METHODS

Subjects

In 2006, 13 668 individuals participated in a 1-day health checkup conducted by the Okinawa General Health Association. Of these participants, 6919 were re-examined in 2010; from this cohort, we excluded 17 participants because of a lack of available data on waist circumference (WC), as well as 1124 participants with hypertension, 314 with MetS and 652 with MetS in 2006. A total of 4812 individuals (male, 2528; female, 2284) were thus included in this study cohort. This study was approved by the ethics committee of the University Hospital of the Ryukyus.

The Okinawa General Health Association conducted the health checkups in Okinawa, Japan. Subjects who visited the clinic of the Okinawa General Health Association completed a questionnaire that included details on the following factors: family history of hypertension, diabetes mellitus, dyslipidemia, stroke and heart disease; lifestyle-related variables such as smoking and alcohol intake; medical history; and current medications. The participants were classified into one of the following three categories based on their smoking habits: non-smokers, ex-smokers, or current smokers. Regarding alcohol intake, subjects were classified as non-drinkers, ex-drinkers or current drinkers. Current medications included the use of antihypertensive medications (yes/no), anti-diabetic medications and/or insulin (yes/no) and antidyslipidemic medications (yes/no). The questionnaires were discussed during the physical examinations, and the subjects were further interviewed by a clinic physician.

All the subjects underwent clinical examinations that included height, weight and WC measurements. WC was measured using a graduated tape at the umbilical level with the subject in the standing position. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). A well-trained nurse or doctor measured the resting BP once using a standard

mercury sphygmomanometer (KENZMEDICO, Saitama, Japan) with the subject in the sitting position after at least 5 min of rest.

All the subjects fasted overnight for at least 12 h before blood sampling. A venous blood sample was obtained from the antecubital vein. SUA, triglycerides (TGs), HDL-C and fasting blood glucose (FBG) levels were determined for all the subjects using an autoanalyzer (Hitachi Automatic Analyzer Model 7700, Hitachi High-Technologies, Tokyo, Japan) in the laboratory of the Okinawa General Health Association.

Definitions

There is no universally accepted definition of hyperuricemia. In the present study, we defined hyperuricemia as SUA levels $>7.0 \text{ mg dl}^{-1}$ according to the Japanese criteria for hyperuricemia.²⁴ SUA levels were categorized by quartiles as follows: UA1, $\leq 4.4 \text{ mg dl}^{-1}$; UA2, $4.5\text{--}5.4 \text{ mg dl}^{-1}$; UA3, $5.5\text{--}6.4 \text{ mg dl}^{-1}$; and UA4, $\geq 6.5 \text{ mg dl}^{-1}$. In the subgroup analyses of men and women, SUA levels were categorized into three groups according to tertile: UA1, $\leq 5.8 \text{ mg dl}^{-1}$; UA2, $5.9\text{--}6.8 \text{ mg dl}^{-1}$; and UA3, $\geq 6.9 \text{ mg dl}^{-1}$ for the men and UA1, $\leq 4.1 \text{ mg dl}^{-1}$; UA2, $4.2\text{--}4.9 \text{ mg dl}^{-1}$; and UA3, $\geq 5.0 \text{ mg dl}^{-1}$ for the women. Hypertension was defined as a systolic blood pressure (SBP) of $\geq 140 \text{ mm Hg}$ and/or a diastolic blood pressure (DBP) of $\geq 90 \text{ mm Hg}$ and/or the current use of antihypertensive medication. Obesity was defined as a BMI of $\geq 25 \text{ kg m}^{-2}$. The estimated glomerular filtration rate (eGFR) was calculated using the modified Cockcroft–Gault formula for Japanese populations.²⁵

For this study, MetS was defined according to the Japanese Committee on the Criteria for MetS,²⁶ which are commonly used in routine clinical practice in Japan. Subjects with an increased WC ($\geq 85 \text{ cm}$ in men and $\geq 90 \text{ cm}$ in women) and those with ≥ 2 of the following factors were diagnosed with MetS: high BP (SBP $\geq 130 \text{ mm Hg}$, DBP $\geq 85 \text{ mm Hg}$ and/or the current use of antihypertensive medications); dyslipidemia (TG levels $\geq 150 \text{ mg dl}^{-1}$, HDL-C levels $< 40 \text{ mg dl}^{-1}$ and/or the current use of antidyslipidemic medications) or high blood glucose (FBG levels $\geq 110 \text{ mg dl}^{-1}$ and/or the current use of anti-diabetic medications).

Table 1 Baseline characteristics of subjects according to serum uric acid quartiles

	UA1 (n = 1187)	UA2 (n = 1217)	UA3 (n = 1184)	UA4 (n = 1224)	P-values
Age (years)	47.1 $\pm$ 9.0	48.8 $\pm$ 9.4	47.8 $\pm$ 10.1	46.3 $\pm$ 9.4	<0.0001
Male (%)	10.8	32.5	72.4	93.7	<0.0001
BMI (kg m^{-2})	22.0 $\pm$ 2.8	22.9 $\pm$ 3.0	23.7 $\pm$ 2.9	24.8 $\pm$ 3.1	<0.0001
Obesity (%)	14.1	22.8	29.4	45.1	<0.0001
WC (cm)	79.1 $\pm$ 8.0	81.6 $\pm$ 8.2	83.7 $\pm$ 7.7	86.4 $\pm$ 7.6	<0.0001
SBP (mm Hg)	112.0 $\pm$ 11.6	114.3 $\pm$ 11.2	116.1 $\pm$ 10.3	117.4 $\pm$ 9.7	<0.0001
DBP (mm Hg)	69.8 $\pm$ 7.8	71.5 $\pm$ 7.9	73.2 $\pm$ 7.3	74.6 $\pm$ 6.8	<0.0001
eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	81.5 $\pm$ 12.9	77.3 $\pm$ 12.0	76.1 $\pm$ 12.9	73.1 $\pm$ 12.3	<0.0001
TG (mg dl^{-1})	83.9 $\pm$ 51.2	101.8 $\pm$ 63.1	123.0 $\pm$ 96.2	155.4 $\pm$ 109.9	<0.0001
HDL-C (mg dl^{-1})	64.5 $\pm$ 14.2	61.5 $\pm$ 13.7	56.5 $\pm$ 13.7	52.6 $\pm$ 12.7	<0.0001
FBG (mg dl^{-1})	94.5 $\pm$ 13.7	96.4 $\pm$ 14.8	98.6 $\pm$ 14.9	99.4 $\pm$ 13.2	<0.0001
UA (mg dl^{-1})	3.8 $\pm$ 0.5	4.9 $\pm$ 0.3	5.9 $\pm$ 0.3	7.4 $\pm$ 0.8	<0.0001
Increased WC (%)	11.0	21.0	35.1	52.4	<0.0001
High BP (%)	4.2	5.9	5.7	6.0	<0.0001
Dyslipidemia (%)	9.2	17.6	28.7	44.3	<0.0001
High BG (%)	3.1	5.8	7.9	8.7	<0.0001
Diabetes mellitus (%)	1.9	2.5	4.0	2.5	<0.0001
Current drinker (%)	37.7	47.5	69.4	83.3	<0.0001
Current smoker (%)	10.7	17.4	28.8	33.4	<0.0001
Anti-DL drug use (%)	2.4	2.9	2.2	3.0	0.5622
Anti-DM drug use (%)	1.0	1.4	2.1	1.6	0.1218

Abbreviations: Anti-DL, antidyslipidemic; Anti-DM, anti-diabetic; Anti-HT, antihypertensive; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HU, hyperuricemia; SBP, systolic blood pressure; TG, triglyceride; UA, uric acid; UA1, $\leq 4.4 \text{ mg dl}^{-1}$; UA2, $4.5\text{--}5.4 \text{ mg dl}^{-1}$; UA3, $5.5\text{--}6.4 \text{ mg dl}^{-1}$; UA4, $\geq 6.5 \text{ mg dl}^{-1}$; WC, waist circumference. Data for categorical variables are presented in percentages (%), and data for continuous variables are presented as means $\pm$ s.d. $P < 0.05$ was considered statistically significant.

Statistical analyses

The data for continuous variables are reported as the means $\pm$ s.d., and the data for categorical variables are reported as percentages (%). Independent *t*-tests were used to compare the results for continuous variables between groups with and without hyperuricemia. Data for the categorical variables were compared using the chi-square test. Odds ratios (ORs, 95% confidence intervals (CIs)) for the incidence of MetS were determined using multivariate logistic regression models. We used two logistic models: Model 1 (adjusted for age and sex) and Model 2 (adjusted for age, sex, alcohol consumption, eGFR, WC values and SBP, TG, HDL-C, low-density lipoprotein cholesterol and FBG levels). The TG levels were transformed logarithmically to improve skewing before analyses. The lifestyle factors and variables that were correlates with hypertension, MetS and UA levels were selected as adjustment variables. The statistical analyses were performed using the JMP software, version 10.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

RESULTS

At baseline, the mean age of the subjects was 47.5 ± 9.5 years, and 52.5% were male. The baseline characteristics of the subjects according to the SUA quartiles are shown in Table 1. BMI and WC values, SBP, DBP, TG and FBG levels, and the prevalence of male sex, obesity, dyslipidemia, current drinking and smoking significantly increased with increasing SUA levels. In contrast, eGFR and HDL-C levels significantly decreased with increasing SUA levels.

In 2010, 618 subjects (13%) had developed hypertension, and 764 (16%) had developed MetS. Hypertension with MetS was found in 158 subjects (3%). Figure 1 shows the incidences of hypertension, MetS

Figure 1 Incidences of hypertension, metabolic syndrome and hypertension with metabolic syndrome with and without hyperuricemia. MetS, metabolic syndrome; HT, hypertension; HT+MetS, hypertension with metabolic syndrome; HU, hyperuricemia. * $P < 0.05$ compared with the HU (-) group using the chi-square test.

and hypertension with MetS in subjects with and without hyperuricemia. The incidences of hypertension, MetS and hypertension with MetS were significantly higher in subjects with hyperuricemia than in those without. ORs (95% CIs) for hyperuricemia and for the incidences of hypertension, MetS and hypertension with MetS are shown in Table 2. Hyperuricemia was significantly associated with the incidence of both hypertension and MetS in both Model 1 and Model 2. In contrast, no significant association was found in the incidence of hypertension with MetS in Model 2.

Figure 2 shows the incidences of hypertension, MetS (Figure 2a) and hypertension with MetS (Figure 2b) according to SUA quartiles. The incidences of hypertension, MetS and hypertension with MetS significantly increased with increasing SUA levels.

ORs (95% CIs) for the incidences of hypertension, MetS and hypertension with MetS in the second, third and fourth SUA quartiles, compared with that in the first SUA quartile, are shown in Table 3. In Model 1, the third and fourth quartiles were significantly associated with the incidences of hypertension, MetS and hypertension with MetS. In Model 2, the fourth quartile was significantly associated with the incidences of hypertension, MetS and hypertension with MetS. The analyses were repeated using SUA levels as a continuous variable. Significant associations were observed between increased SUA levels (1 mg dl^{-1}) and the risk of hypertension, MetS and hypertension with MetS in Model 1 (hypertension: OR, 1.2; 95% CI, 1.1–1.3; $P < 0.0001$; MetS: OR, 1.5; 95% CI, 1.4–1.7; $P < 0.0001$; hypertension with MetS: OR, 1.5; 95% CI, 1.4–1.8; $P < 0.0001$) and Model 2 (hypertension: OR, 1.1; 95% CI, 1.0–1.2; $P = 0.0073$; MetS: OR, 1.2; 95% CI, 1.1–1.3; $P < 0.0001$; hypertension with MetS: OR, 1.3; 95% CI, 1.1–1.5; $P = 0.0002$).

Because SUA levels differed by sex, we conducted subgroup analyses of men and women. Table 4 shows the incidences of hypertension, MetS and hypertension with MetS according to the presence of hyperuricemia and the UA tertile in men and women. Female subjects with hyperuricemia accounted for a small fraction of the incidences of hypertension, MetS and hypertension with MetS. In Model 2 (Table 4), male subjects with hyperuricemia had significant associations with the incidences of both hypertension and MetS. Compared with the first SUA tertile, the third tertile was significantly associated with the incidences of MetS and hypertension with MetS only in men. In contrast, in women, hyperuricemia had no significant association with the incidences of hypertension or MetS (Table 4).

DISCUSSION

In this 4-year follow-up study, we observed that elevated SUA levels were significantly and independently associated with the incidences of

Table 2 Odds ratios for the incidence of hypertension, metabolic syndrome and hypertension with metabolic syndrome according to the presence or absence of hyperuricemia

	Incidence (n, %)		Model 1			Model 2		
	HU(-) (n = 4131)	HU(+) (n = 681)	OR	95% CI	P-values	OR	95% CI	P-values
HT	487 (11.8)	131 (19.2)	1.6	1.2–2.0	0.0002	1.3	1.0–1.7	0.0278
MetS	515 (12.5)	249 (36.6)	2.3	1.9–2.7	<0.0001	1.3	1.0–1.6	0.0217
HT+MetS	105 (2.5)	53 (7.8)	2.0	1.4–2.8	0.0002	1.4	0.9–2.0	0.1117

Abbreviations: CI, confidence interval; HT, hypertension; HT+MetS, hypertension with metabolic syndrome; MetS, metabolic syndrome; OR, odds ratio.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, alcohol consumption, estimated glomerular filtration rate, waist circumference values and systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting blood glucose levels.

Hyperuricemia was defined as serum uric acid levels of $> 7.0 \text{ mg dl}^{-1}$.

$P < 0.05$ was considered statistically significant.

Figure 2 (a and b) Incidences of hypertension and metabolic syndrome (a) and of hypertension with MetS (b) according to serum uric acid quartiles. MetS, metabolic syndrome; HT, hypertension; HT+MetS, hypertension with metabolic syndrome. UA, uric acid; UA1, <4.5 mg dl $^{-1}$; UA2, 4.5–5.4 mg dl $^{-1}$; UA3, 5.5–6.4 mg dl $^{-1}$; UA4, ≥ 6.5 mg dl $^{-1}$. * $P < 0.05$ compared with the HT (+) group using the chi-square test.

hypertension, MetS and hypertension with MetS in subjects who did not have hypertension or MetS at baseline. These associations were independent of age, sex, lifestyle variables, MetS-component levels and renal function. In the subgroup analysis, hyperuricemia showed significant associations with the incidences of both hypertension and MetS in males.

The Multiple Risk Factor Intervention Trial (MRFIT) study recently investigated the effect of hyperuricemia on the risk of hypertension in normotensive men without MetS.¹⁰ In that study, subjects with hyperuricemia were at an 80% higher risk of developing hypertension, compared with those without hyperuricemia. The MRFIT study was a randomized, controlled trial in a cohort of men who were at high risk for adverse coronary events. In contrast, our study included both male and female subjects in good health. Despite differences in some of the results between these two studies, both studies found that hyperuricemia was significantly associated with the incidence of hypertension in men who did not have MetS at baseline. No significant associations were found between hyperuricemia and the incidences of hypertension or MetS in women in our study. One reason for this result might have been the small number of female participants who developed hypertension or MetS in this study, resulting in low statistical power for female subjects (Table 4).

Four epidemiological studies, including our previous study, have recently shown that SUA levels were closely associated with an increase in the incidence of MetS.^{11–14} In the present study, a different approach was used to assess the association between elevated SUA levels and the incidence of MetS. As a result, elevated SUA levels showed a significant and independent association with the incidence of MetS, even in subjects without hypertension.

The principal pathophysiological abnormalities underlying MetS are central obesity and insulin resistance.²⁷ Therefore, subjects without MetS might have a lower degree of insulin resistance than those with MetS. SUA levels have been positively correlated with insulin resistance.^{28,29} We observed that WC increased with increasing SUA levels (Table 1). WC is a marker of visceral obesity, and a larger WC was correlated with a higher degree of insulin resistance.³⁰ Visceral

Table 3 Odds ratios for the incidence of hypertension, metabolic syndrome and hypertension with metabolic syndrome according to serum uric acid quartiles

UA variable	HT			MetS			HT+MetS		
	OR	(95% CI)	P-values	OR	(95% CI)	P-values	OR	(95% CI)	P-values
Model 1									
UA1	1.0	Reference	—	1.0	Reference	—	1.0	Reference	—
UA2	1.6	(1.2–2.1)	0.0012	1.8	(1.3–2.6)	0.0011	1.7	(0.7–4.2)	0.2457
UA3	1.8	(1.4–2.5)	<0.0001	2.5	(1.7–3.6)	<0.0001	4.1	(1.7–9.7)	0.0013
UA4	2.4	(1.7–3.3)	<0.0001	5.0	(3.5–7.1)	<0.0001	6.5	(2.7–15.4)	<0.0001
UA as a continuous variable (per 1 mg dl $^{-1}$)	1.2	(1.1–1.3)	<0.0001	1.5	(1.4–1.7)	<0.0001	1.5	(1.4–1.8)	<0.0001
Model 2									
UA1	1.0	Reference	—	1.0	Reference	—	1.0	Reference	—
UA2	1.5	(1.1–2.0)	0.0129	1.2	(0.8–1.8)	0.3330	1.3	(0.5–3.5)	0.5503
UA3	1.5	(1.1–2.1)	0.0128	1.3	(0.9–1.9)	0.1910	2.7	(1.1–6.6)	0.0276
UA4	1.8	(1.2–2.5)	0.0022	1.8	(1.2–2.7)	0.0039	3.2	(1.3–8.0)	0.0115
UA as a continuous variable (per 1 mg dl $^{-1}$)	1.1	(1.0–1.2)	0.0073	1.2	(1.1–1.3)	<0.0001	1.3	(1.1–1.5)	0.0002

Abbreviations: CI, confidence interval; HT, hypertension; HT+MetS, hypertension with metabolic syndrome; MetS, metabolic syndrome; OR, odds ratio; UA, uric acid.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, alcohol consumption, estimated glomerular filtration rate, waist circumference values and systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting blood glucose levels.

UA1, ≤ 4.4 mg dl $^{-1}$; UA2, 4.5–5.4 mg dl $^{-1}$; UA3, 5.5–6.4 mg dl $^{-1}$; and UA4, ≥ 6.5 mg dl $^{-1}$.

$P < 0.05$ was considered statistically significant.

Table 4 Odds ratios for the incidence of hypertension, metabolic syndrome and hypertension with metabolic syndrome according to serum uric acid tertile or the presence of hyperuricemia

	Males					Females				
	UA1 (n = 846)	UA2 (n = 869)	UA3 (n = 813)	HU(+) (n = 654)	HU(−) (n = 1874)	UA1 (n = 783)	UA2 (n = 752)	UA3 (n = 749)	HU(+) (n = 27)	HU(−) (n = 2257)
Incidence of HT (n, %)	120 (14.2)	115 (13.2)	155 (19.1)	127 (19.4)	263 (14.0)	54 (6.9)	75 (10.0)	99 (13.2)	4 (14.8)	224 (9.9)
Incidence of MetS (n, %)	138 (16.3)	212 (24.4)	293 (36.0)	247 (37.8)	396 (21.1)	19 (2.4)	29 (3.9)	73 (9.7)	2 (7.4)	119 (5.3)
Incidence of HT+MetS (n, %)	23 (2.7)	46 (5.3)	66 (8.1)	53 (8.1)	82 (4.4)	3 (0.4)	4 (0.5)	16 (2.1)	0 (0)	23 (1.0)
HT										
OR	1.0	1.0	1.5	1.5		1.0	1.4	1.8	1.3	
95% CI	Reference	0.7–1.3	1.2–2.0	1.2–1.9		Reference	1.0–2.1	1.3–2.6	0.4–3.8	
P-values	—	0.7237	0.0012	0.0004		—	0.00507	0.0007	0.6429	
MetS										
OR	1.0	2.9	2.9	2.2		1.0	1.6	4.1	1.2	
95% CI	Reference	1.3–2.1	2.3–3.7	1.8–2.7		Reference	0.9–2.8	2.4–6.8	0.3–5.3	
P-values	—	<0.0001	<0.0001	<0.0001		—	0.2024	<0.0001	0.7812	
HT+MetS										
OR	1.0	2.0	3.3	2.0		1.0	1.4	5.2	—	
95% CI	Reference	1.2–3.4	2.1–5.4	1.4–2.8		Reference	0.3–6.1	1.5–18.2	—	
P-values	—	0.0060	<0.0001	0.0002		—	0.6932	0.0091	—	
HT										
OR	1.0	0.8	1.3	1.5		1.0	1.5	1.5	0.5	
95% CI	Reference	0.6–1.1	1.0–1.8	1.1–1.9		Reference	1.0–2.2	1.0–2.2	0.2–1.7	
P-values	—	0.2652	0.0562	0.0057		—	0.0696	0.0590	0.2858	
MetS										
OR	1.0	1.3	1.6	1.4		1.0	1.2	1.5	0.3	
95% CI	Reference	1.0–1.7	1.2–2.1	1.1–1.7		Reference	0.6–2.2	0.8–2.8	0.1–1.6	
P-values	—	0.0882	0.0010	0.0088		—	0.6311	0.1714	0.1470	
HT+MetS										
OR	1.0	1.8	2.4	1.5		1.0	1.1	1.9	—	
95% CI	Reference	1.0–3.1	1.4–4.2	1.0–2.3		Reference	0.2–5.0	0.5–7.4	—	
P-values	—	0.0381	0.0015	0.0403		—	0.9121	0.3380	—	

Abbreviations: CI, confidence interval; HT, hypertension; HT+MetS, hypertension with metabolic syndrome; MetS, metabolic syndrome; OR, odds ratio; UA, uric acid.

Model 1: adjusted for age.

Model 2: adjusted for age, alcohol consumption, estimated glomerular filtration rate, waist circumference values and systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting blood glucose levels.

UA1, ≤ 5.8 mg dl^{−1}; UA2, 5.9–6.8 mg dl^{−1}; and UA3, ≥ 6.9 mg dl^{−1} for males.
UA1, ≤ 4.1 mg dl^{−1}; UA2, 4.2–4.9 mg dl^{−1}; and UA3, ≥ 5.0 mg dl^{−1} for females.

Hyperuricemia was defined as serum uric acid levels of > 7.0 mg dl^{−1}.

The value of $P < 0.05$ was considered statistically significant.

adipose tissues secrete several adipocytokines, including adiponectin, leptin and tumor necrosis factor- α . Elevated production of these proinflammatory adipocytokines contributes to the development of insulin resistance.³¹ Moreover, evidence that elevated SUA levels increase the risk of developing insulin resistance has been reported.³²

In the present study, significant associations between elevated SUA levels and the incidences of hypertension and MetS were determined using a multivariate adjusted model that included WC. Therefore, other contributing factors such as endothelial dysfunction and oxidative stress are also involved in the pathophysiological mechanisms leading to elevated SUA levels and the incidences of hypertension and MetS.^{16–18} UA potentially decreases endothelial nitric oxide bioavailability and induces endothelial dysfunction.³³ Elevated SUA levels were also associated with the increased generation of free radicals³⁴ and oxidative stress, which could abolish endothelium-dependent vasodilatation, leading to hypertension.³⁵ However, other studies have suggested that UA was an effective antioxidant,^{36,37} and the exact role

of UA in oxidation (pro-oxidant or antioxidant) remains to be elucidated. Further studies are needed to clarify the role of UA in the context of hypertension and MetS.

The present study had several limitations. First, we showed significant associations between elevated SUA levels and the incidences of hypertension and MetS; however, no causal relationship could be inferred because this study was observational. In addition, although insulin resistance, endothelial dysfunction, oxidative stress and inflammation might have roles in the incidences of hypertension and MetS, epidemiological studies such as ours cannot directly demonstrate pathophysiological evidence. Second, variables were measured only once; therefore, misclassifications might have occurred. A lack of data regarding the use of antihyperuricemic medications might have led to underestimation of the prevalence of hyperuricemia. Because the frequency of diuretics used as antihypertensives is low in Japan,³⁸ the influence of diuretics on our results was most likely small. Third, information on menopause was not available for our female subjects. Estrogen increases the excretion of UA, and SUA levels increase after

menopause.³⁹ The biological mechanism explaining the relationships between estrogen levels and the development of hypertension or MetS has still not been elucidated. Fourth, we could not assess the dietary statuses of our subjects. Finally, the subjects in this study participated voluntarily and represented a relatively healthy population, and this voluntary participation might have led to selection bias. Despite these limitations, our results offer new insight into the relationships between SUA levels and the incidences of hypertension and MetS.

In conclusion, increased SUA levels were significantly and independently associated with the incidences of hypertension and MetS in subjects without hypertension or MetS at baseline. Increased SUA levels might also be associated with the incidence of hypertension with MetS. To prevent cardiovascular events, this relationship between increased SUA levels and an increased incidence of hypertension and MetS should be noted, even in subjects without hypertension or MetS at baseline.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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