Novel Pathological Implications of Serum Uric Acid with Cardiovascular Disease Risk in Obesity

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ABSTRACT

***Aims*:** This cohort study intended to elucidate the association between serum uric acid (SUA) levels and cardiovascular disease events in Japanese patients with obesity.

***Methods*:** Altogether, 450 obese Japanese outpatients were enrolled in a multicenter prospective cohort Japan, the Japan Obesity and Metabolic Syndrome Study. Primary analysis regarding the measurements of cardiovascular risk factors, including SUA levels, and the occurrence of macrovascular complications was based on following the participants over a 5-year period.

***Results*:** Of the eligible patients, 335 (74.4%) were followed into the fifth year. During the study period, 15 coronary heart disease, 7 stroke, and 6 arteriosclerosis obliterans events occurred in 39 patients. The CVD incidence rate was 15.8 per 1000 person-years. In the analysis of adjusted models for traditional risk factors, hyperuricemia was a significant factor for the incidence of CVD events, especially in female obese patients. Additionally, we estimated the association between SUA levels and CVD events using cubic spline models, which showed a U-shaped association in both male and female patients.

***Conclusions*:** SUA is an effective predictor of CVD events in female obese patients and a risk factor for CVD incident in obese patients.

Keywords:

obesity, uric acid, cardiovascular disease, U-shaped, effective predictor (6 limit)

1. Introduction

The prevalence of obesity is increasing worldwide [1]. Obesity, especially visceral obesity, is a risk factor of metabolic syndrome (MetS) that is closely implicated in the development and progression of cardiovascular disease (CVD) [1-3]. Obesity is also accompanied by hyperuricemia, and recent extensive studies have focused on the potential roles of hyperuricemia in CVD pathogenesis [4-6]; however, the relationship between hyperuricemia and a risk for CVD in patients with obesity has not been fully elucidated.

Uric acid (UA) is the final product of purine metabolism and has various bioactivities, including dual effects of pro-oxidant and antioxidant *in vivo* [4, 5]. UA is produced in the liver and vascular endothelium through xanthine oxidoreductase (XOR)-related pathways [5]. Adipose tissues also produced UA and obesity promoted UA production by elevating the XOR activity [7]. The serum UA (SUA) levels are positively associated with storage of visceral and hepatic fat in humans [8]. Regarding the pathological significance of SUA, hyperuricemia has been implicated in various health issues, including gout, metabolic diseases, cardiometabolic diseases, and kidney and liver dysfunction [4-6, 9-16]; however, whether SUA levels would be an independent risk factor for future incident CVD events remain unclear. SUA levels were reported to be not associated with incident coronary heart disease (CHD) and all-cause and CVD mortality in the general population [17]. A recent study also reported no significant association between SUA levels and all-cause and CVD mortality in a community-based obese population [18]. Conversely, another general population-based study revealed that hyperuricemia was related to incident CVD events in women and obese patients [19]. Furthermore, a significant association of higher SUA levels with increased risk of all-cause and CVD mortality in patients with diabetes

was shown by a recent epidemiological study [20]. Accordingly, these findings suggest the need to conduct a cohort study involving obese patients to better understand the pathological significance of SUA levels in incident CVD events in patients with obesity. Since SUA levels are higher in men than in women, sex-specific analyses are required for research on SUA [17]. Therefore, a cohort study addressing these issues would provide novel insights into the relationship between SUA and a risk for CVD events in patients with obesity.

We previously showed evidence of the pathological roles of obesity in CVD development and progression, using a database of a National Hospital Organization cohort comprising patients with obesity and/or diabetes. Our multicenter prospective cohort study (Japan Obesity and Metabolic Syndrome study: JOMS) demonstrated the utility of cardio-ankle vascular index, an index of arterial stiffness, as an effective predictor for CVD events in obese patients [21]. Moreover, urinary cystatin C was found to be a CVD and chronic kidney disease risk factor in patients with obesity and MetS [22]. In the present study, we conducted a 5-year longitudinal study to elucidate the relationship between SUA levels and incident CVD events in patients with obesity without a CVD history who underwent guideline-based diet and/or exercise therapy, using a cohort comprising patients with obesity.

2. Methods

2.1. Study participants and design

Study approval was obtained from the Central Ethics Committee for Clinical Research at the National Hospital Organization headquarters (approval number 05-27,14-034). The study was performed in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. Written informed consent was obtained from participants. The JOMS study was registered in the University Hospital Medical Information Network (UMIN) system (UMIN Study ID: 000000559).

Altogether, 450 obese Japanese outpatients [body mass index (BMI) ≥25 kg/m^2] were enrolled in the JOMS study that involved five National Hospital Organization hospitals (Kyoto, Tokyo, and Nagoya Medical Centers and Kokura and Mie Hospitals) and the Ooishi Clinic in Japan as part of a study conducted by the Policy Based Medical Service Network for Endocrine and Metabolic Diseases from October 2005 to March 2007 [23]. The study was designed to assess the characteristics of MetS and CVD risk factors, and the onset of CVD events for 5 years in obese Japanese patients. During the follow-up period, the patients were recommended optimal treatments, especially weight-reduction therapy through lifestyle modifications to reduce energy intake, and an increase in physical activity [21, 22]. All patients undergoing weight-reduction therapy were instructed to maintain the same levels of energy intake and physical activity for the entire period, as recommended by the Japan Atherosclerosis Society's "Guidelines for the diagnosis and treatment of atherosclerotic cardiovascular disease" [21, 22]. The dietary therapy comprised 25 kcal/kg of ideal body weight per day. The participants consumed 60% of the total energy as carbohydrates, 20%–25% as fat, and 15%–20% as protein.

125 *2.2. Data Collection and Laboratory Measurements*

126 At enrollment and after 3 months in the JOMS study, the MetS-related [BMI, waist
127 circumference, and systolic and diastolic blood pressures (SBP and DBP)] and blood
128 parameters were measured. Fasting blood samples were drawn in the absence of
129 prescription drugs, and were analyzed for fasting plasma glucose (FPG), hemoglobin A1c
130 (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-
131 density lipoprotein cholesterol (HDL-C), triglycerides (TG), and serum C-reactive
132 protein (CRP) level.

133 Participants with SUA >7.0 mg/dL [24] and those with SUA ≤7.0 mg/dL but taking UA
134 drugs were defined as hyperuricemia in this study.

135 The MetS score was defined as the number of risk factors that corresponded to one of
136 the following 1–4 MetS diagnostic criteria (Japanese standard) [25]. The risk factors and
137 cut-off values are as follows: 1. abdominal circumference: men ≥85 cm, women ≥90 cm;
138 2. neutral fat: ≥150 mg/dL and/or HDL-C <40 mg/dL; 3. blood pressure: SBP ≥130
139 mmHg and/or DBP ≥85 mmHg; and 4. fasting blood glucose level: ≥110 mg/dL.

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141 *2.3. Study Endpoints*

142 The primary outcomes of the study were the occurrence of CVD: macrovascular
143 complication events defined as follows [21]. Macroangiopathy endpoints included the
144 occurrence of definite CHD (angina pectoris that is of arteriosclerotic origin and requiring
145 percutaneous coronary intervention or myocardial infarction), stroke (brain infarction,
146 atherosclerosis-originated brain hemorrhage, or transient ischemic attack), or
147 arteriosclerosis obliterans. The diagnosis of angina pectoris and myocardial infarction was
148 according to the criteria defined by the WHO/MONICA (Multinational Monitoring of

149 Trends and Determinants in Cardiovascular Disease) project, and the stroke diagnosis was
150 according to the guidelines defined by the Ministry of Health, Labour and Welfare of Japan
151 [26-28]. Information on each patient's primary outcome was collected through an annual
152 report from each physician. To verify the endpoints, medical records for events were further
153 confirmed by the researchers who were independent of the physician.
154
155 *2.4. Statistical Analysis*
156 Data are shown as the mean ± standard deviation or median with interquartile range
157 (IQR). Two-sided *p* values (at a significance level of 0.05) are provided in this article.
158 Linear and U-shaped correlations between SUA levels and baseline characteristics
159 were evaluated by performing tests of linear and quadratic contrasts in a general linear
160 model. A trend test for the mean SUA level stratified by the number of MetS components
161 was performed in a test of linear contrast in a general linear model adjusted for age, BMI,
162 and anti-hyperuricemia medication. Adjusted UA-estimated means and standard errors at
163 each MetS score were calculated.
164 The study endpoints were analyzed as time-to-event variables, and the Cox proportional
165 hazard model was used to calculate the unadjusted and adjusted hazard ratios (HRs) and
166 95% confidence intervals (CIs) for risk factors. The SUA values were divided into quartiles
167 by sex. The reference standard for HR was the SUA range with the lowest risk for each sex.
168 HRs were calculated by crude and adjusted analyses by age, BMI, and anti-hyperuricemia.
169 Restricted cubic splines with knots were used to further explore the shape of the dose–
170 response relationship between the SUA level and HR of CVD onset.
171 All statistical analyses were performed using SPSS 24.0 for Windows (SPSS Inc.,
172 Chicago, IL, USA).

3. Results

3.1. Clinical Variables and Their Changes

The patients' baseline clinical characteristics are shown in Table 1. The median follow-up time was 5.0 years and the total person-years were 1862.4. Of the eligible patients, 74.4% were followed into the fifth year. The dropout rate, which is the proportion of patients who were lost to follow-up until the fifth year, was 25.6%. During follow-up, one patient died of cancer and one died of old age. Of the 450 enrolled obese patients, 115 were lost to follow-up, and observations were discontinued for the following reasons: 41 patients stopped visiting the outpatient clinics (21 patients moved residence, 20 patients had a change in their work schedule), 56 patients moved to other clinics since they successfully lost weight, 11 patients stopped consultation visits for unknown reasons, and seven patients withdrew participation (Figure 1). There were no significant differences in the baseline characteristics between patients who completed the study and those who did not, except for BMI (31.1 ± 5.9 vs. 32.5 ± 7.8 kg/m^2, $p = 0.045$). The median SUA level at baseline for the entire cohort was 5.7 mg/dL (IQR: 4.7–6.7); it was higher in men [6.5 mg/dL (IQR: 5.5–7.5)] than in women [5.2 mg/dL (IQR: 4.3–6.0) (Table 1). The prevalence of hyperuricemia was 38.6% and 7.3% in men and women, respectively.

In Table 2, the baseline characteristics of obese patients are shown for each group divided by quartiles of SUA level (men: Q1, 1.9–5.4 mg/dL; Q2, 5.5–6.4 mg/dL; Q3, 6.5–7.5 mg/dL; Q4, 7.6–10.7 mg/dL; women: Q1, 0.6–4.2 mg/dL; Q2, 4.3–5.1 mg/dL; Q3, 5.2–5.9 mg/dL; Q4, 6.0–11.0 mg/dL). BMI tended to be higher with higher SUA level in both men and women ($p = 0.027$ and $p = 0.001$, respectively, in linear), but the FPG level and eGFR tended to be lower with higher SUA level in both men and women (FPG: $p = 0.015$ and $p = 0.003$, respectively; eGFR: $p = 0.011$ and $p = 0.004$, respectively). Contrarily, the TC and

LDL-C levels tended to be higher in men with higher SUA levels ($p = 0.004$ and $p = 0.026$, respectively), and age and antidiabetic rates tended to be lower in men with higher SUA ($p = 0.002$ and $p < 0.001$, respectively). Waist circumference and hs-CRP tended to be higher in women with higher SUA level ($p = 0.014$ and $p = 0.002$, respectively), and HbA1c level and antidiabetic rates tended to be lower in women with higher SUA level ($p = 0.043$ and $p < 0.001$, respectively).

The association between the number of MetS component and SUA level by sex is shown in Figure 2. In women, the more MetS score gained, the statistically significantly higher UA levels were observed ($p = 0.023$ for trend). Contrarily, no significant association was observed in men ($p = 0.089$ for trend).

3.2. Endpoint Analysis

During follow-up, 22 CHD, 11 stroke, and 6 arteriosclerosis obliterans events occurred. Among all CHD events, 63.6% (n = 14) were angina pectoris and 36.3% (n = 8) were myocardial infarction, and among all stroke events, 72.7% (n = 8) were brain infarction, 18.2% (n = 2) were atherosclerosis-originated brain hemorrhage, and 9.1% (n = 1) were transient ischemic attack. Therefore, all events (CHD, stroke, and arteriosclerosis obliterans) occurred in 39 patients, and the CVD incidence rate was 20.9 per 1,000 person-years (CHD, stroke, and arteriosclerosis obliterans: 11.8, 5.9, and 3.2 per 1,000 person-years, respectively).

The SUA levels were divided into sex-specific quartile groups and their association with CVD events were examined (Table 3), with 2nd quartile (5.5–6.4) in men and 3rd quartile (5.2–5.9) in women set as references. Using the Cox regression model, there is no significant difference among the male groups but, in the female groups, high SUA level (4th

221 quartile) showed significant difference compared to the reference (HR: 4.71, 95%CI: 1.03–
222 21.50, $p = 0.045$). Even after multivariable adjustment by age, BMI, and anti-hyperuricemia
223 medication, the results were similar to those before the adjustment.

224 Additionally, cubic spline models were used to estimate the association between SUA
225 levels and CVD events in more detail (Figure 3). Both men and women showed a U-shaped
226 association between SUA levels and CVD events (Figure 3A and B). The SUA level in the
227 bottom value of the HR was 6.6 and 5.2 mg/dL for men and women, respectively. In women,
228 the SUA level of >7.0 mg/dL confirmed that the lower 95% CI limit of the HR was >1.0.
229

4. Discussion

This is the first study to show that hyperuricemia is a novel marker to independently predict incident CVD events in women with obesity, a finding obtained by a longitudinal multicenter cohort study on obese patients without a CVD history over a 5-year follow-up period. Furthermore, a U-shaped relationship between SUA levels and HR of CVD events was found in both sexes, suggesting that lower and higher SUA levels are risk factors for incident CVD events in these patients. These findings highlight the novel clinical significance of SUA in preventing incident CVD events in patients with obesity.

We found a sex difference in the association of hyperuricemia with a risk for CVD events in obese patients. Similar female-specific relationships have been reported between SUA levels and a high risk for CVD events in a general population [19], arteriosclerotic CVD in patients with type 2 diabetes (T2D) [29], or all-cause mortality in obese or overweight patients with pre-existing T2D and/or CVD [30]. Since fructose is a carbohydrate that generates UA [31] and metabolic activity for fructose is suggested to differ between sexes [30], SUA elevation in women might reflect more severe metabolic derangements [30]; however, the underlying mechanisms remain unclear.

Our findings suggest that the observed sex difference might be ascribed to the potential difference in vulnerability to detrimental effects of elevated SUA levels. UA is produced in various tissues [5] and obesity increases UA production in adipose tissue by elevating the XOR activity [7]. Elevated SUA levels would exert deleterious effects on oxidative stress, inflammation, and endothelial function, thereby leading to an increased CVD risk [4], potentially in both men and women. Conversely, SUA is mechanistically maintained at lower levels in women than in men in physiological settings through various mechanisms, such as estrogen-related pathways [32]. Accordingly, women may be more

vulnerable to elevation-induced pathological effects of SUA than men, thereby leading to increased risk for CVD events in women in conjunction with obesity and/or decrease in estrogen levels. Supporting these possibilities, SUA levels were positively associated with exacerbation of inflammation and MetS scores, which are risk factors for atherosclerosis, in women with obesity in this study. Alternatively, estrogen has potential protective effects against CVD [33], so that a decrease in estrogen levels and an increase in SUA levels would synergistically increase a risk for CVD events.

Another possibility concerning the sex difference is the potential masking effects of glucose metabolism. Diabetes is a risk factor for CVD [34], and higher SUA levels were correlated with improved glucose metabolism in this study, thereby leading to no significant relationship between higher SUA levels and CVD events in men. Our multivariate analysis also revealed that age, which was negatively correlated with SUA, was not a confounding factor affecting the relationship of SUA with CVD events in men. Thus, the significant relationship between SUA and CVD in women obtained in this study would highlight the more direct implications of SUA in CVD in women compared with men. Furthermore, androgen exhibits protective effects on the cardiovascular system [35], which would also contribute to no significant relationship between SUA and CVD in men. Although additional studies are required, our findings suggest the increased need to focus on hyperuricemia in women with obesity, as compared to men, to reduce the risk of incident CVD events.

In this study, a U-shaped relationship was observed between the SUA levels and incident CVD events in both sexes, suggesting the pathological roles of hypouricemia and hyperuricemia in CVD events development in obese patients. Although a similar U-shaped association of SUA with a CVD risk has been reported in various populations [36-

38], the mechanistic details have not been fully understood. Regarding hyperuricemia, detrimental effects of elevated SUA levels would be implicated in the increased risk of CVD in obesity, as discussed above. Conversely, the pathological roles of hypouricemia would be caused by the attenuation of beneficial effects of UA. Since UA is one of the major endogenous antioxidants in humans [4], hypouricemia would result in exacerbation of oxidative stress and subsequent vascular dysfunction, thereby leading to the increased risk for CVD [37]. Another possibility is that lower SUA levels reflect aggravation of hyperglycemia, a risk factor for CVD. Reportedly, exacerbation of glucose metabolism resulted in the decrease in SUA levels [39]. Our study also revealed a negative association of SUA levels with FPG and antidiabetic usage rate. Thus, reduction of UA-related beneficial activities and/or aggravation of glucose metabolism in hypouricemia would be implicated in a high CVD risk in obese patients.

As assumed by the U-shaped relationships, the pathological impacts of SUA levels would change according to its concentrations, thereby suggesting the need to control SUA levels within an appropriate range to prevent CVD events. In this respect, we found that the optimal target window of SUA levels to reduce the risk of CVD events differs between male and female obese patients. The SUA values corresponding to the lowest risk of incident CVD events were lower in women (5.2 mg/dL) than in men (6.6 mg/dL) with obesity in this study, suggesting that the optimal SUA values for male obese patients rather increased the CVD risk for female obese patients, as previously reported in a general population [19]. Similarly, the appropriate SUA values for women would not be applicable to men with obesity. These findings highlight the need to revisit the guideline recommendations for reference values of SUA that are the same between sexes, thereby contributing to the development of effective diagnostic guidelines and therapeutics for

preventing incident CVD events.

The main strength of this study is that this is the well-characterized, prospective longitudinal cohort study on patients with obesity of both sexes; this allowed analyses specialized for pathological significance of SUA in a risk of CVD in obesity. Nevertheless, this study has some limitations. First, the effects of potential confounding factors (e.g., alcohol consumption) were not investigated due to the limited sample size. A longitudinal cohort study with a larger sample size and a longer follow-up period is required to corroborate our findings. Second, we did not measure the sex hormone levels and XOR activity that would affect the SUA activity. Potential effects of renal functions on the relationship between SUA levels and CVD risk also remain unclear. Additional studies addressing these issues would elucidate the mechanisms underlying the association of SUA levels with CVD risk in obesity. Finally, racial and ethnic differences would exist among obese patients. Future studies across diverse groups would allow a comprehensive understanding of the pathological significance of SUA levels in incident CVD events in patients with obesity.

In conclusion, this study provided the first evidence that hyperuricemia is an independent predictive marker for incident CVD events in female obese patients without a CVD history. Accordingly, measuring the SUA levels would allow the identification of patients with an increased risk for CVD events, thereby indicating the need to reduce the CVD risk by intensive treatments in these patients. The U-shaped relationship suggests that hypouricemia and hyperuricemia would be implicated in an increased risk of CVD in both male and female obese patients. We further found a sex difference between the optimal windows of SUA levels to reduce the risk of incident CVD events. These findings would be helpful for developing novel strategies for predicting and preventing incident

CVD events in patients with obesity.

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Declaration of interests

No potential conflicts of interest relevant to this article were reported.

Author contributions

D. Wakabayashi, S. Kato, M. Tanaka, H. Yamakage, and N. Satoh-Asahara conceptualized the study; D. Wakabayashi, S. Kato, H. Yamakage, and N. Satoh-Asahara were responsible for validation; H. Yamakage were responsible for formal analysis; D.

Wakabayashi, S. Kato, H. Yamakage, and N. Satoh-Asahara were responsible for investigation; N. Satoh-Asahara were responsible for resources; D. Wakabayashi, S. Kato, and N. Satoh-Asahara were responsible for data curation; D. Wakabayashi, S. Kato, M. Tanaka, H. Yamakage, and N. Satoh-Asahara wrote original draft; and D. Wakabayashi, S. Kato, M. Tanaka, H. Yamakage, Hisashi. Kato, N. Ozu, S. Kasama, M. Kasahara, and N. Satoh-Asahara reviewed and edited the manuscript.

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Tables

Table 1. Baseline characteristics of the study obese patients stratified by sex

Valuables	Total	Men	Women
N (men/women)	450 (202 / 248)	202	248
Age (years)	51.5 ± 14.2	49.7 ± 14.4	53.0 ± 13.8
BMI (kg/m^2)	31.1 ± 5.9	31.3 ± 6.5	31.0 ± 5.4
SBP (mmHg)	140.4 ± 19.0	140.6 ± 18.1	140.2 ± 19.7
DBP (mmHg)	84.1 ± 11.7	85.5 ± 12.5	82.9 ± 10.9
FPG (mg/dL)	123.6 ± 52.0	121.0 ± 43.5	125.8 ± 58.0
HbA1c (%)	6.3 [5.8, 7.4]	6.1 [5.7, 7.3]	6.3 [5.8, 7.4]
IRI (μU/mL)	14.6 [8.3, 26.9]	15.5 [9.1, 28.6]	13.8 [7.7, 24.9]
Total cholesterol (mg/dL)	211.1 ± 58.2	205.9 ± 37.3	215.3 ± 70.7
Triglyceride (mg/dL)	145.0 [103.0, 220.3]	150.5 [107.0, 256.5]	139.5 [101.3, 203.0]
HDL-cholesterol (mg/dL)	54.7 ± 14.0	50.0 ± 12.9	58.5 ± 13.8
LDL-cholesterol (mg/dL)	126.1 ± 31.5	125.8 ± 32.9	126.4 ± 30.4
eGFR	82.8 ± 24.4	83.0 ± 24.7	82.7 ± 24.2
UA (mg/dL)	5.7 [4.7, 6.7]	6.5 [5.5, 7.5]	5.2 [4.3, 6.0]
hs-CRP (μg/ml)	0.81 [0.43, 1.92]	0.79 [0.44, 1.89]	0.83 [0.41, 1.99]
Proportion of			
hypertension (n, %)	285 , 63.3	122 , 60.4	163 , 65.7
dyslipidemia (n, %)	344 , 76.4	156 , 77.2	188 , 75.8
diabetes (n, %)	212 , 47.1	94 , 46.5	118 , 47.6
hyperuricemia (n, %)	96 , 21.3	78 , 38.6	18 , 7.3
taking calcium antagonist (n, %)	103 , 22.9	44 , 21.8	59 , 23.8
taking ACE/ARB (n, %)	126 , 28.0	59 , 29.2	67 , 27.0
taking statins (n, %)	102 , 22.7	30 , 14.9	72 , 29.0
taking antidiabetic medications (n, %)	142 , 31.6	56 , 27.7	86 , 34.7
taking UA drug (n, %)	6 , 1.3	4 , 2.0	2 , 0.8
current smoking (n, %)	77 , 17.1	45 , 22.3	32 , 12.9

Data are expressed as mean ± standard deviation, median [interquartile range], or the number and percentage of patients. BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, IRI: immunoreactive insulin, TG; triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, UA: uric acid, hs-CRP: high sensitive C-reactive protein, ACE: angiotensin-converting enzyme, ARB: angiotensin II type 1 receptor blocker.

Table 2. Correlation between serum uric acid level and baseline characteristics stratified by sex

	Serum uric acid concentration quartiles				*p*	*p*
	Q1	Q2	Q3	Q4	linear	U-shape
Men						
n	48	50	54	50		
UA (mg/dL)	1.9 - 5.4	5.5 - 6.4	6.5 - 7.5	7.6 - 10.7		
Age (years)	54.7 ± 14.5	51.1 ± 12.2	46.4 ± 14.4	47.1 ± 15.2	**0.002**	0.277
BMI (kg/m^2)	29.4 ± 5.1	31.2 ± 6.8	32.6 ± 7.3	32.0 ± 6.4	**0.027**	0.214
Waist circumference (cm)	100.4 ± 11.1	101.8 ± 12.7	105.9 ± 17.0	103.8 ± 16.4	0.127	0.392
SBP (mmHg)	139.7 ± 16.5	141.3 ± 17.7	141.2 ± 19.3	140.2 ± 18.9	0.917	0.602
DBP (mmHg)	83.6 ± 9.7	86.1 ± 9.2	86.8 ± 15.2	85.5 ± 14.4	0.423	0.277
FPG (mg/dL)	127.0 ± 49.8	129.4 ± 48.2	120.2 ± 40.1	107.7 ± 32.3	**0.015**	0.220
HbA1c (%)	6.6 ± 1.7	6.3 ± 1.5	6.3 ± 1.4	6.0 ± 1.3	0.080	0.950
TC (mg/dL)	195.1 ± 36.1	201.4 ± 34.2	211.8 ± 37.4	214.3 ± 38.9	**0.004**	0.714
TG (mg/dL)	164.9 ± 92.0	220.6 ± 251.9	201.4 ± 149.0	211.2 ± 117.0	0.255	0.323
HDL-C (mg/dL)	48.5 ± 12.5	48.5 ± 11.6	53.1 ± 15.5	49.4 ± 11.0	0.366	0.309
LDL-C (mg/dL)	120.0 ± 35.6	120.4 ± 33.3	129.9 ± 28.2	132.4 ± 33.7	**0.026**	0.828
eGFR	86.4 ± 19.8	87.1 ± 28.7	84.8 ± 22.8	73.6 ± 24.5	**0.011**	0.089
hs-CRP (μg/mL)	6.6 ± 1.1	6.7 ± 1.4	7.0 ± 1.2	6.9 ± 1.1	0.125	0.507
Medications						
antihypertension	24 , 50.0	13 , 26.0	21 , 38.9	15 , 30.0	0.122	0.262
antidiabetic	23 , 47.9	12 , 24.0	15 , 27.8	6 , 12.0	**<0.001**	0.506
antidyslipidemia	21 , 43.8	18 , 36.0	21 , 38.9	18 , 36.0	0.516	0.725
Women						
n	57	64	60	67		
UA (mg/dL)	0.6 - 4.2	4.3 - 5.1	5.2 - 5.9	6.0 - 11.0		
Age (years)	53.1 ± 13.5	55.6 ± 12.2	53.8 ± 12.9	49.8 ± 15.8	0.134	0.063
BMI (kg/m^2)	28.9 ± 3.5	31.1 ± 5.9	31.0 ± 6.1	32.6 ± 5.1	**0.001**	0.599
Waist circumference	96.1 ± 9.7	100.4 ± 14.3	99.3 ± 13.3	102.3 ± 11.7	**0.014**	0.667
SBP (mmHg)	139.2 ± 17.1	140.4 ± 17.8	140.8 ± 19.1	140.5 ± 24.0	0.972	0.772
DBP (mmHg)	83.1 ± 9.7	81.0 ± 9.6	82.8 ± 12.3	84.8 ± 11.6	0.259	0.132
FPG (mg/dL)	140.9 ± 73.2	133.6 ± 65.0	116.0 ± 36.8	114.1 ± 48.0	**0.003**	0.713
HbA1c (%)	6.6 ± 1.4	6.6 ± 1.6	6.4 ± 1.3	6.1 ± 1.1	**0.043**	0.355
TC (mg/dL)	204.7 ± 28.9	212.5 ± 36.5	217.0 ± 34.6	225.5 ± 124.2	0.098	0.971
TG (mg/dL)	158.9 ± 124.7	176.2 ± 105.3	147.7 ± 78.2	175.7 ± 80.3	0.696	0.671
HDL-C (mg/dL)	60.4 ± 13.7	57.8 ± 13.4	61.8 ± 13.7	54.8 ± 13.5	0.101	0.201
LDL-C (mg/dL)	119.3 ± 26.2	127.5 ± 29.3	131.0 ± 34.1	127.3 ± 31.0	0.111	0.123
eGFR	88.6 ± 23.8	85.1 ± 19.7	81.2 ± 23.9	76.6 ± 27.5	**0.004**	0.866
hs-CRP (μg/mL)	6.2 ± 1.1	6.9 ± 1.2	6.9 ± 1.2	7.0 ± 1.2	**0.002**	0.068
Medications						
antihypertension	21 , 36.8	20 , 31.3	26 , 43.3	24 , 35.8	0.744	0.876
antidiabetic	29 , 50.9	25 , 39.1	20 , 33.3	12 , 17.9	**<0.001**	0.760
antidyslipidemia	26 , 45.6	30 , 46.9	26 , 43.3	32 , 47.8	0.919	0.804

Data are expressed as mean ± standard deviation, or the number and percentage of patients. Abbreviations used in this table are the same as in Table 1.

Linear and U-shaped correlations between serum uric acid levels and baseline characteristics were evaluated by tests of first and second order contrasts in a general linear model.

Table 3. Adjusted hazard ratio for cardiovascular disease onset by Cox regression models according to serum uric acid level by sex

	Serum uric acid concentration quartiles			
	Q1	Q2	Q3	Q4
Men				
N	50	48	54	50
UA (mg/dL)	1.9 – 5.4	5.5 – 6.4	6.5 – 7.5	7.6 – 10.7
HR for CVD (HR [95%CI], *p*)				
Crude model	2.91 [0.77, 10.98], 0.114	reference	1.04 [0.21, 5.15], 0.962	1.40 [0.31, 6.26], 0.659
Adjusted model	2.37 [0.62, 9.02], 0.205	reference	1.15 [0.23, 5.67], 0.868	1.52 [0.34, 6.78], 0.586
Women				
N	64	57	60	67
UA (mg/dL)	0.6 – 4.2	4.3 – 5.1	5.2 – 5.9	6.0 – 11.0
HR for CVD (HR [95%CI], *p*)				
Crude model	2.20 [0.40, 12.02], 0.362	1.90 [0.35, 10.38], 0.459	reference	**4.71 [1.03, 21.50], 0.045**
Adjusted model	2.24 [0.41, 12.25], 0.351	1.81 [0.33, 9.88], 0.495	reference	**5.05 [1.10, 23.08], 0.037**

HR: hazard ratio, 95%CI: 95% confidence interval, other abbreviations used in this table are the same as in Table 1. Adjusted model: adjusted for age, BMI, and anti-hyperuricemia medication.

515 **Figure legends**

516 Figure 1. Flow diagram of the JOMS. CVD: cardio vascular disease.

517

518 Figure 2. Severity of metabolic syndrome (MetS) risk factors and SUA level among men
519 (A) and women (B). Association between the number of MetS components and SUA
520 levels is shown for men (p for trend = 0.089) and women (p for trend = 0.023) adjusted
521 for age, BMI and anti-hyperuricemia medication. n indicates the number of patients
522 included in the group with the cumulative MetS components. Bars show adjusted SUA-
523 estimated means and standard errors at each MetS score.

524

525 Figure 3. Cubic spline models for the association between serum uric acid (SUA) level
526 and hazard ratios (HRs) for cardiovascular disease (CVD) events among men (A) and
527 women (B). The reference standard for the hazard ratio was the median SUA. The dashed
528 line indicates the 95% confidence interval (CI). 95%CI+: the upper limit of the 95%
529 confidence interval, 95% - : the lower limit of the 95% confidence interval. The SUA
530 level corresponding to the lowest hazard ratio of CVD events is 6.6 mg/dL for men and
531 5.2 mg/dL for women.

532

533 **Figure 1. Flow diagram of the JOMS.**

534

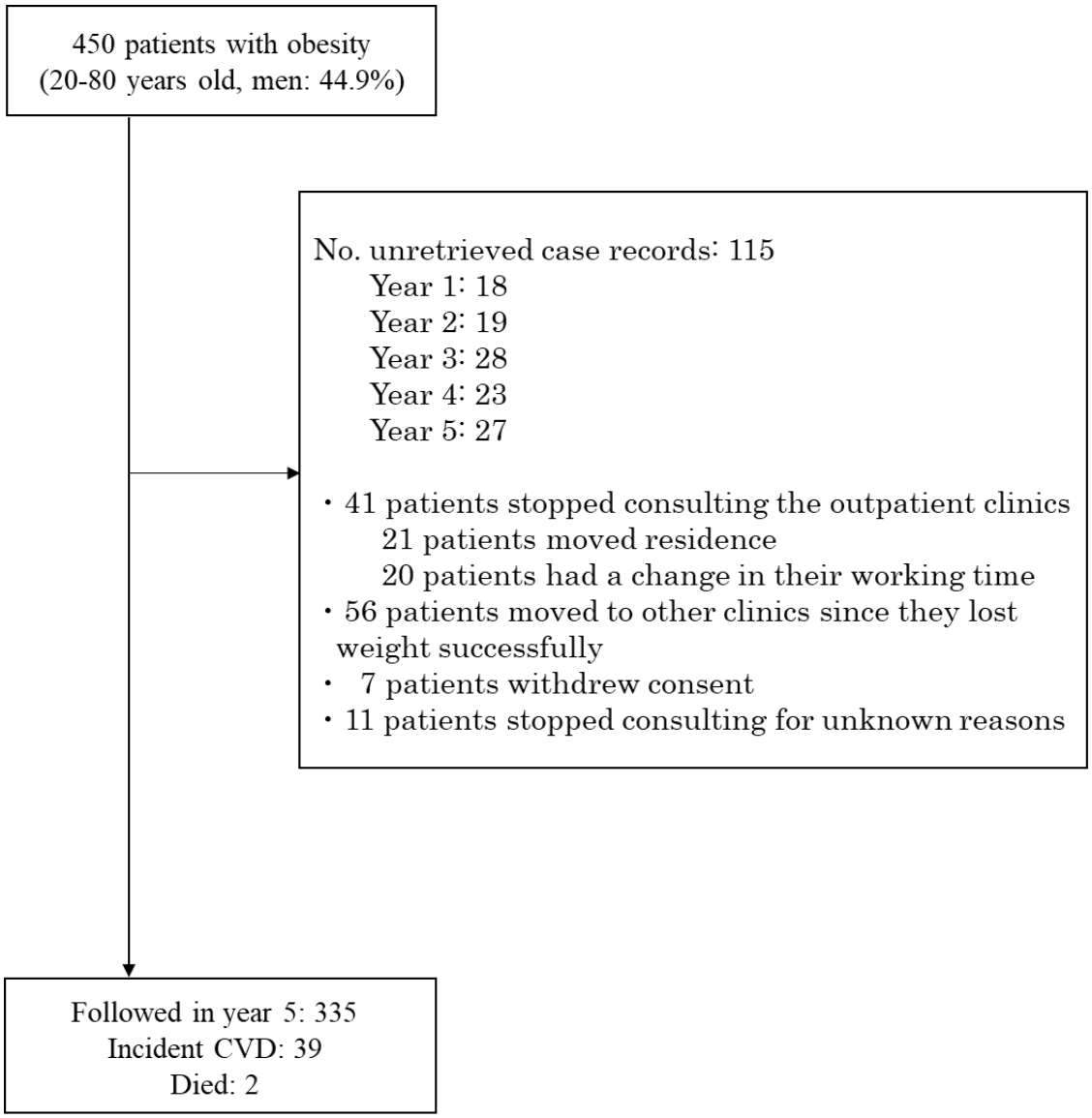

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Figure 2. Severity of metabolic syndrome (MetS) risk factors and SUA level among men(A) and women(B).

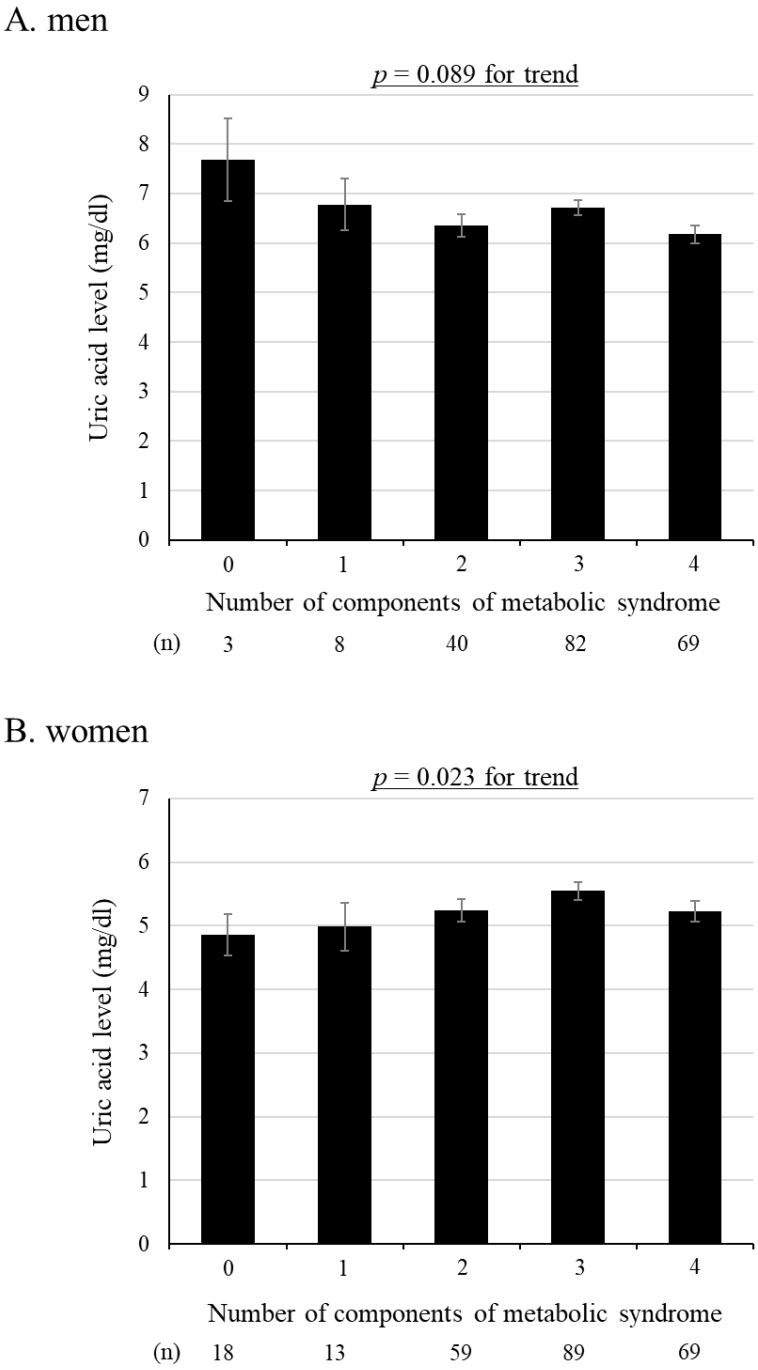

Figure 3. Cubic spline models of the association between serum uric acid (SUA) level and hazard ratios (HRs) for cardiovascular disease (CVD) events among men (A) and women (B).