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The Protective Effects of Increasing Serum Uric Acid Level on Development of Metabolic Syndrome

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Background: It has not been determined whether changes in serum uric acid (SUA) level are associated with incident metabolic syndrome (MetS). The aim of the current study was to investigate the relationship between changes in SUA level and development of MetS in a large number of subjects.
Methods: In total, 13,057 subjects participating in a medical health check-up program without a diagnosis of MetS at baseline were enrolled. Cox proportional hazards models were used to test the independent association of percent changes in SUA level with development of MetS.
Results: After adjustment for age, systolic blood pressure, body mass index, fat-free mass (%), estimated glomerular filtration rate, smoking status, fasting glucose, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and baseline SUA levels, the hazard ratios (HRs) (95% confidence intervals [CIs]) for incident MetS in the second, third, and fourth quartiles compared to the first quartile of percent change in SUA level were 1.055 (0.936 to 1.190), 0.927 (0.818 to 1.050), and 0.807 (0.707 to 0.922) in male (P for trend <0.001) and 1.000 (0.843 to 1.186), 0.744 (0.615 to 0.900), and 0.684 (0.557 to 0.840) in female (P for trend <0.001), respectively. As a continuous variable in the fully-adjusted model, each one-standard deviation increase in percent change in SUA level was associated with an HR (95% CI) for incident MetS of 0.944 (0.906 to 0.982) in male (P=0.005) and 0.851 (0.801 to 0.905) in female (P<0.001).
Conclusion: The current study demonstrated that increasing SUA level independently protected against the development of MetS, suggesting a possible role of SUA as an antioxidant in the pathogenesis of incident MetS.

Keywords: Longitudinal studies; Metabolic syndrome; Uric acid

INTRODUCTION

Metabolic syndrome (MetS) is a comorbid condition of metabolic origin that includes abdominal obesity, atherogenic dyslipidemia, elevated blood pressure (BP), and elevated plasma glucose level [1]. MetS is increasing in prevalence globally and has become one of the most important health problems worldwide [2] due to its relationships with cardiovascular disease (CVD) and type 2 diabetes mellitus [3].

Uric acid is the end-product of purine catabolism in humans [4]. The prevalence of MetS has been reported to increase with increasing baseline serum uric acid (SUA) level [5]. We also

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observed this relationship after adjusting for body composition in our previous study, which included the same subjects as the current study [6]. Elevated SUA level has also been suggested to increase the risk for CVD mortality [7].

However, there is substantial evidence that uric acid might also have an antioxidant capacity as a free radical scavenger [8-13]. In addition, several studies have demonstrated that uric acid administration improves outcomes in patients with acute stroke [14-16]. Similarly, in our previous study, although elevated serum albumin level, which also has an antioxidant capacity, was linked to increased risk of incident MetS, change in serum albumin concentration was inversely associated with development of MetS, demonstrating that increase in serum albumin concentration might protect against the risk of MetS [17].

Considering these data, it has been hypothesized that the antioxidant effects of increasing SUA level might protect against the development of MetS. Nevertheless, the longitudinal association between changes in SUA level and the development of MetS has not yet been evaluated. Thus, we designed this study to investigate the longitudinal effects of changing SUA concentration on the development of MetS during a 7-year follow-up period in a healthy study group.

METHODS

Study population and design

A retrospective longitudinal study was designed to evaluate the association between changes in SUA level and development of MetS. The study subjects were adults aged ≥18 years who participated in a medical health check-up program at the Health Promotion Center of Samsung Medical Center, Sungkyunkwan University, Seoul, Korea [18]. The check-up included annual or biennial evaluations of medical history, smoking status, anthropometric data, and laboratory data. Initially, 24,185 participants who attended at least four follow-up visits between January 2006 and December 2012 were assessed for eligibility.

Among these participants, 11,003 were excluded because they were diagnosed with MetS at the baseline examination (n=3,475); developed MetS within 1 year of the first visit (n=1,443); had a history of CVD (myocardial infarction, bypass surgery, stroke, n=692); had total bilirubin or liver enzyme level more than twice the upper normal limit (n=248); had an estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2 (n=233); lacked waist circumference (WC) data at baseline or during follow-up (n=7,702); or lacked SUA data at baseline or during follow-up (n=237). Thus, 13,057 participants (7,694 male and 5,363 female) were included in the study (Fig. 1). The observation period for each patient continued until the patient was first diagnosed with MetS, or until the last follow-up visit if the patient was not diagnosed with MetS. The study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. SMC 2015-01-003-001). Informed consent was waived by the IRB.

Clinical and biochemical measurements

Weight, height, systolic BP, and diastolic BP were measured at

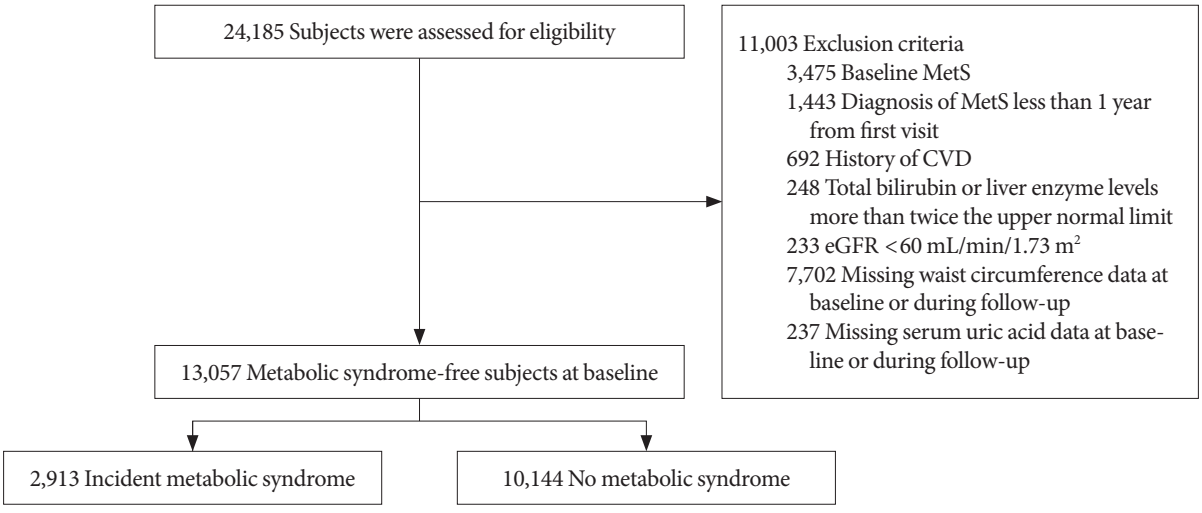

Fig. 1. Selection of study participants. MetS, metabolic syndrome; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

each visit. BP was measured by trained nurses with a mercury sphygmomanometer on the right arm after the participant had been seated comfortably for at least 5 minutes. WC was measured at the plane across the iliac crest, which usually represents the narrowest part of the torso. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m^2). The eGFR was calculated with the Modification of Diet in Renal Disease equation [19].

Venous blood samples were obtained after overnight fasting. Fasting plasma glucose (FPG), plasma insulin, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), SUA, and creatinine levels were measured. However, we were unable to obtain plasma insulin level for 5,115 participants (2,529 male and 2,586 female).

The FPG concentration was measured with hexokinase and Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany), and fasting plasma insulin concentration was measured with an immunoradiometric assay (TFB Co. Ltd., Tokyo, Japan). TG, LDL-C, HDL-C, and SUA levels were measured by an enzymatic colorimetric method with a Modular D2400 (Roche Diagnostics, Basel, Switzerland).

Changes in SUA level were determined by subtracting the baseline level from the final level, which was measured at the end of follow-up in participants without incident MetS or one year before the date of diagnosis of MetS. The percent change in SUA was calculated as follows:

Percent change in SUA = (Change in SUA)/(Baseline SUA) ×100

Definition of metabolic syndrome

The Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention was used to define MetS [20]. Participants were recognized as having MetS if they met three or more of the following criteria: (1) abdominal obesity (WC ≥90 cm in male, WC ≥80 cm in female); (2) high BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg) or medical treatment for hypertension; (3) high TG (≥150 mg/dL) or medical treatment for elevated TG; (4) low HDL-C (<40 mg/dL in male, <50 mg/dL in female) or medical treatment for low HDL-C; and (5) elevated fasting glucose (≥100 mg/dL) or treatment for diabetes.

Statistical analyses

Data were analyzed with SPSS version 21 (IBM Co., Armonk, NY, USA) and R version 3.3.2 (R Foundation, Vienna, Austria; http://www.r-project.org/). Continuous variables with normal distributions were expressed as mean±standard deviation, whereas continuous variables with non-normal distributions were expressed as median and interquartile range. Categorical data were expressed as frequencies and percentages. Student's *t*-test or the Mann-Whitney *U* test was used to compare participant characteristics according to the development of MetS. Pearson's chi-square test was used to compare frequency distributions. Natural logarithm-transformed high-sensitivity C-reactive protein (hs-CRP) values were used in a Pearson's correlation model. The percent changes in SUA level were analyzed in quartile groups and with 1SD (standard deviation) percent changes in SUA as a continuous variable.

Multivariate Cox proportional hazards analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident MetS according to changes in SUA level. Collinearity tests for variables used in the multivariate Cox proportional hazards analyses were performed through linear modeling of the outcome variables, and the variance inflation factor (VIF) was calculated for the independent predictors. A VIF <5 was considered optimal to warrant stability. The sets of variables adjusted in the model were previously selected according to clinical relevance (i.e., smoking status [21]).

The initial model was adjusted for age, systolic BP, BMI, fat-free mass (FFM, %), eGFR, and smoking status (Model 1). Then, we additionally adjusted for fasting glucose, TG, LDL-C, and HDL-C levels (Model 2). To determine the independent effect of the percent change in SUA level on the development of MetS, we also added baseline SUA level as a covariate (Model 3). Because fasting insulin data were only available for 7,980 participants (5,188 male and 2,792 female), we also formulated a model that included fasting insulin level as an additional confounder (Model 4). Two-tailed probability values <0.05 were considered to indicate statistical significance.

RESULTS

Clinical characteristics of the study participants

Table 1 displays the clinical characteristics and laboratory variables of the study participants with regard to the development of MetS. At baseline, the male who did not develop MetS were 51.7±8.4 years old, and those who did were 51.8±7.9 years old

Table 1. Baseline characteristics for both sexes according to development of metabolic syndrome

Characteristic	Incident MetS					
	Male (*n*=7,694)			Female (*n*=5,363)		
	No (*n*=5,682, 73.8%)	Yes (*n*=2,012, 26.2%)	*P* value	No (*n*=4,462, 83.2%)	Yes (*n*=901, 16.8%)	*P* value
Age, yr	51.7±8.4	51.8±7.9	0.502	48.6 ±7.2	52.4 ±7.5	<0.001
Smoking status			<0.001			0.155
Current smoker	1,440 (25.3)	638 (31.7)		84 (1.9)	11 (1.2)	
Ex-smoker	2,615 (46.0)	917 (45.6)		141 (3.2)	21 (2.3)	
Non-smoker	1,627 (28.6)	457 (22.7)		4,237 (95.0)	869 (96.4)	
BMI, kg/m^2	23.6±2.2	25.1±2.1	<0.001	21.7±2.3	23.8±2.5	<0.001
Waist circumference, cm	84.5±6.0	89.2±5.8	<0.001	73.5±6.1	79.0±6.5	<0.001
Fat-free mass, %	79.9±5.1	78.0±4.0	<0.001	72.7±5.3	69.3±5.1	<0.001
Systolic BP, mm Hg	111.9±13.9	115.0±13.2	<0.001	107.5±14.3	115.2±15.2	<0.001
Diastolic BP, mm Hg	70.0±9.7	72.2±8.9	<0.001	65.1±9.9	69.1±9.9	<0.001
eGFR, mL/min/1.73 m^2	87.9±11.5	87.7±11.6	0.429	90.8±12.5	89.6±12.9	0.006
Fasting glucose, mg/dL	89.4±13.9	92.7±14.5	<0.001	85.0±9.0	89.4±12.9	<0.001
Fasting insulin, μU/mL[a]	7.7 (6.0–9.7)	8.9 (7.0–11.4)	<0.001	7.8 (6.0–9.7)	8.9 (7.1–11.3)	<0.001
HOMA-IR[a]	1.7 (1.3–2.2)	2.0 (1.6–2.6)	<0.001	1.6 (1.3–2.1)	1.9 (1.5–2.6)	<0.001
Total cholesterol, mg/dL	188.7±30.2	190.9±30.8	0.004	190.5±32.4	198.1±35.1	<0.001
TG, mg/dL	101.0 (77.0–134.0)	134.0 (104.0–179.0)	<0.001	87.0±37.0	119.6±55.2	<0.001
LDL-C, mg/dL	123.6±27.2	127.7±28.0	<0.001	118.0±28.3	131.5±31.1	<0.001
HDL-C, mg/dL	57.2±12.3	51.3±10.5	<0.001	66.4±13.6	58.1±12.0	<0.001
hs-CRP, mg/L	0.11±0.34	0.15±0.46	0.004	0.07±0.30	0.12±0.29	<0.001
Baseline SUA, mg/dL	5.7±1.1	6.0±1.2	<0.001	4.0±0.8	4.4±0.9	<0.001
Change in SUA, %	0.5±14.1	–0.8±13.3	<0.001	6.3±17.2	1.8±15.5	<0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment index for insulin resistance; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SUA, serum uric acid.
[a]*n*=5,188 male, *n*=2,792 female.

(*P*=0.502). The female who did not develop MetS were 48.6±7.2 years old at baseline, whereas those who did were 52.4±7.5 years old (*P*<0.001).

In both sexes, baseline SUA level was lower in those who did not develop MetS than in those who did (5.7±1.1, 6.0±1.2 mg/dL for male; 4.0±0.8, 4.4±0.9 mg/dL for female, respectively; *P*<0.001). On the other hand, the changes in SUA level in both sexes were higher in those who did not develop MetS than in those who did (0.5%±14.1%, –0.8%±13.3% for male; 6.3%±17.2%, 1.8%±15.5% for female, respectively; *P*<0.001).

Participants who subsequently developed MetS had higher BMI, WC, systolic BP, diastolic BP, fasting glucose, fasting insulin, homeostasis model assessment index for insulin resistance (HOMA-IR), total cholesterol, TG, and LDL-C levels, but lower FFM (%) and HDL-C levels than those who did not develop MetS in both sexes.

Clinical characteristics of the study participants based on percent change in SUA quartile category

Table 2 presents the clinical characteristics and laboratory variables of the study participants based on the percent change in SUA quartile category. The percent change in SUA quartiles was positively related to the eGFR but negatively related to BMI, WC, total cholesterol, LDL-C, and baseline SUA levels in

Table 2. Baseline clinical and biochemical characteristic of study subjects based on percent change in serum uric acid levels quartile categories and sex

Characteristic	Percent changes in serum uric acid (male, *n*=7,694)					Percent changes in serum uric acid (female, *n*=5,363)				
	Quartile 1 (≤–9.1%, *n*=1,927)	Quartile 2 (–9.0% to –0.1%, *n*=1,930)	Quartile 3 (0% to 8.2%, *n*=1,908)	Quartile 4 (≥8.3%, *n*=1,929)	*P* value	Quartile 1 (≤–5.6%, *n*=1,346)	Quartile 2 (–5.5% to 4.1%, *n*=1,324)	Quartile 3 (4.2% to 14.6%, *n*=1,348)	Quartile 4 (≥14.7%, *n*=1,345)	*P* value
Age, yr	52.7±8.3	51.7±8.0	51.3±8.2	51.1±8.3	<0.001	50.2±8.4	49.5±7.4	49.1±7.2	48.3±6.3	<0.001
Smoking status					<0.001					0.910
Current smoker	478 (24.8)	493 (25.5)	517 (27.1)	590 (30.6)		22 (1.6)	22 (1.7)	24 (1.8)	27 (2.0)	
Ex-smoker	958 (49.7)	885 (45.9)	863 (45.2)	826 (42.8)		47 (3.5)	37 (2.8)	38 (2.8)	40 (3.0)	
Non-smoker	491 (25.5)	552 (28.6)	528 (27.7)	513 (26.6)		1,277 (94.9)	1,265 (95.5)	1,286 (95.4)	1,278 (95.0)	
BMI, kg/m^2	24.0±2.2	24.2±2.2	24.0±2.4	23.8±2.2	<0.001	22.4±2.6	22.1±2.5	21.9±2.3	21.9±2.3	<0.001
Waist circumference, cm	86.1±6.2	86.5±6.1	85.6±6.5	84.9±6.3	<0.001	75.2±7.1	74.5±6.5	73.9±6.2	74.0±6.1	<0.001
Fat-free mass, %	79.6±4.5	79.2±4.5	79.3±4.7	79.3±6.0	0.115	71.6±5.6	72.0±5.5	72.5±5.2	72.3±5.3	<0.001
Systolic BP, mm Hg	112.0±14.0	112.4±13.5	112.6±13.5	113.8±14.1	<0.001	108.8±15.4	108.8±14.9	108.5±14.4	109.1±14.4	0.728
Diastolic BP, mm Hg	70.2 ± 9.4	70.5±9.4	70.5±9.5	71.3±9.7	0.001	65.9±10.1	65.7±9.9	65.2±10.0	66.2±10.0	0.787
eGFR, mL/min/1.73 m^2	86.5±11.2	86.9±11.1	88.4±11.7	89.7±11.8	<0.001	88.1±12.4	90.3±12.8	91.3±11.9	92.9±12.7	<0.001
Fasting glucose, mg/dL	89.8±13.3	89.7±12.1	90.0±13.7	91.4±16.9	<0.001	86.1±10.9	85.7±8.5	85.3±9.7	85.8±10.2	0.314
Fasting insulin, μU/mL[a]	7.9 (6.1–10.3)	8.0 (6.3–10.2)	7.9 (6.1–10.3)	7.9 (6.1–10.3)	0.690	7.8 (6.0–9.9)	8.0 (6.1–9.8)	7.9 (6.2–10.1)	7.9 (6.3–10.3)	0.598
HOMA-IR[a]	1.8 (1.3–2.3)	1.8 (1.4–2.3)	1.7 (1.3–2.3)	1.8 (1.4–2.3)	0.514	1.7 (1.3–2.1)	1.7 (1.3–2.2)	1.7 (1.3–2.1)	1.7 (1.3–2.2)	0.562
Total cholesterol, mg/dL	190.7±30.9	189.8±30.2	188.6±30.3	187.8±30.0	0.001	194.2±34.3	193.4±32.1	191.3±32.6	188.0±32.6	<0.001
TG, mg/dL	108.0 (80.0–145.0)	110.0 (82.0–146.0)	107.0 (81.0–143.0)	111.0 (83.0–145.0)	0.238	84.0 (64.0–113.0)	86.0 (67.0–108.0)	84.0 (63.5–112.0)	81.0 (63.0–109.0)	0.059
LDL-C, mg/dL	126.5±28.2	125.8±27.4	124.3±27.1	122.1±27.0	<0.001	123.4±30.6	122.2±29.0	119.2±28.6	116.2±28.1	<0.001
HDL-C, mg/dL	56.3±12.4	55.5±12.1	55.3±12.0	55.5±12.0	0.038	64.7±13.4	64.9±14.0	65.8±13.6	64.9±13.7	0.363
hs-CRP, mg/L	0.12±0.25	0.12±0.35	0.12±0.46	0.13±0.41	0.564	0.10±0.46	0.07±0.16	0.07±0.16	0.08±0.29	0.150
Baseline SUA, mg/dL	6.2±1.2	6.0±1.1	5.7±1.1	5.3±1.0	<0.001	4.5±0.9	4.2±0.8	4.0±0.7	3.7±0.7	<0.001
Change in SUA, %	–16.3±6.2	–4.8±2.3	3.4±2.6	18.2±9.4	<0.001	–14.0±7.0	–0.7±2.7	9.0±3.0	27.6±12.8	<0.001
Incident MetS	545 (28.3)	544 (28.2)	485 (25.4)	438 (22.7)	<0.001	298 (22.1)	255 (19.3)	184 (13.6)	164 (12.2)	<0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Characteristics of the study population according to the serum uric acid quartile were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.
MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment index for insulin resistance; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SUA, serum uric acid.
[a]*n*=5,188 male, *n*=2,792 female.

both male and female. The incidence of MetS exhibited a decreasing trend across the percent change in SUA quartile category in both sexes (both $P<0.001$). Supplementary Table 1 displays the clinical characteristics and laboratory variables of the study participants based on baseline SUA quartile category. And Supplementary Tables 2 and 3 present the clinical characteristics and laboratory variables of the study participants based on baseline SUA quartile category according to incident MetS.

Correlations of SUA level and percent changes in SUA level with studied parameters

Table 3 displays the correlations of baseline SUA level and percent changes in SUA level with anthropometric and biochemical parameters according to sex. Baseline SUA level correlated positively with BMI, WC, systolic BP, diastolic BP, fasting glucose, fasting insulin, HOMA-IR, total cholesterol, TG, and LDL-C levels. In contrast, baseline SUA level correlated negatively with eGFR, HDL-C, and FFM (%) values in both male and female. The strongest correlation was observed between baseline SUA level and BMI ($r=0.206$, $P<0.001$ in male; $r=0.266$, $P<0.001$ in female).

Changes in SUA level correlated positively with eGFR, systolic BP, diastolic BP, and change in BMI. In contrast, changes in SUA level correlated negatively with WC, total cholesterol, TG, LDL-C, HDL-C, and percent change in log-transformed hs-CRP values in both male and female. The strongest correlation was observed between changes in SUA level and changes in BMI in male ($r=0.118$, $P<0.001$) and between changes in SUA level and eGFR in female ($r=0.122$, $P<0.001$). These factors were used as adjustments in the Cox proportional hazards models.

Table 3. Correlations between serum uric acid levels, percent changes in serum uric acid and metabolic parameters according to both sexes

Variable	Male				Female			
	Baseline serum uric acid		Percent changes in serum uric acid		Baseline serum uric acid		Percent changes in serum uric acid	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Age, yr	−0.088	<0.001	−0.050	<0.001	0.193	<0.001	−0.057	<0.001
BMI, kg/m^2	0.206	<0.001	−0.018	0.049	0.266	<0.001	−0.019	0.069
Waist circumference, cm	0.199	<0.001	−0.069	<0.001	0.264	<0.001	−0.051	<0.001
Fat-free mass, %	−0.148	<0.001	−0.015	0.096	−0.222	<0.001	0.026	0.014
eGFR, mL/min/1.73 m^2	−0.169	<0.001	0.104	<0.001	−0.275	<0.001	0.122	<0.001
Systolic BP, mm Hg	0.070	<0.001	0.049	<0.001	0.089	<0.001	0.021	0.040
Diastolic BP, mm Hg	0.089	<0.001	0.042	<0.001	0.071	<0.001	0.014	0.172
Fasting glucose, mg/dL	0.041	<0.001	0.003	0.781	0.104	<0.001	−0.018	0.089
Fasting insulin, μU/mL[a]	0.114	<0.001	0.013	0.248	0.129	<0.001	0.036	0.008
HOMA-IR[a]	0.115	<0.001	0.013	0.230	0.146	<0.001	0.024	0.072
Total cholesterol, mg/dL	0.109	<0.001	−0.051	<0.001	0.133	<0.001	−0.066	<0.001
TG, mg/dL	0.198	<0.001	−0.022	0.019	0.209	<0.001	−0.006	0.587
LDL-C, mg/dL	0.096	<0.001	−0.066	<0.001	0.172	<0.001	−0.073	<0.001
HDL-C, mg/dL	−0.107	<0.001	−0.018	0.045	−0.140	<0.001	−0.021	0.043
hs-CRP, mg/L	0.014	0.131	0.014	0.121	0.051	<0.001	0.008	0.043
Changes in log transformed hs-CRP, %	0.019	0.110	−0.028	0.003	0.044	0.011	−0.047	0.018
Changes in BMI, %	−0.016	0.099	0.118	<0.001	−0.030	0.006	0.058	<0.001

CRP was log transformed to meet the demands of normal distribution.
BMI, body mass index; eGFR, estimated glomerular filtration rate; BP, blood pressure; HOMA-IR, homeostasis model assessment index for insulin resistance; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.
[a]$n=5,188$ male, $n=2,792$ female.

Changes in SUA level during follow-up and the risk of MetS

During 62,458 person-years of follow-up between 2006 and 2012, there were 2,955 (2,012 male, 901 female) incident cases of MetS. Tables 4 and 5 display the HRs and 95% CIs for incident MetS according to percent change in SUA level, both in quartile groups and as a continuous variable.

Across quartile categories, although there was not exact linear relationship since the HR was highest in the second quartile in male, the HR for developing MetS decreased with a linear trend. In the unadjusted model, the HRs (95% CIs) for in-

Table 4. Hazard ratios and 95% confidence intervals for development of metabolic syndrome according to quartile of percent change in serum uric acid levels: male

	Percent changes in SUA levels (male, *n*=7,694)						
	Quartile 1 (≤–9.1%, *n*=1,927)	Quartile 2 (–9.0% to –0.1%, *n*=1,930)	Quartile 3 (0% to 8.2%, *n*=1,908)	Quartile 4 (≥8.3%, *n*=1,929)	*P* for trend	Continuous variable (1SD)	*P* value
Percent change in SUA levels	–16.3±6.2	–4.8±2.3	3.4±2.6	18.2±9.4		0.1±13.9	
Incident MetS	545 (28.3)	544 (28.2)	485 (25.4)	438 (22.7)		2,012 (26.2)	
Unadjusted	1 (reference)	1.034 (0.918–1.164)	0.908 (0.804–1.027)	0.804 (0.709–0.912)	<0.001	0.932 (0.897–0.968)	<0.001
Model 1	1 (reference)	1.003 (0.891–1.130)	0.895 (0.792–1.012)	0.804 (0.709–0.913)	<0.001	0.929 (0.894–0.965)	<0.001
Model 2	1 (reference)	1.042 (0.925–1.174)	0.909 (0.803–1.028)	0.779 (0.686–0.885)	<0.001	0.919 (0.885–0.955)	<0.001
Model 3	1 (reference)	1.055 (0.936–1.190)	0.927 (0.818–1.050)	0.807 (0.707–0.922)	<0.001	0.944 (0.906–0.982)	0.005
Model 4	1 (reference)	1.037 (0.891–1.207)	0.963 (0.824–1.126)	0.804 (0.681–0.948)	0.007	0.947 (0.903–0.993)	0.023

Values are presented as mean±standard deviation, number (%), hazard ratio (95% confidence interval). Model 1: adjusted for age, systolic blood pressure, body mass index, fat-free mass (%), estimated glomerular filtration rate, and smoking status; Model 2: adjusted for Model 1 plus fasting glucose, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol; Model 3: adjusted for Model 2 plus baseline SUA; Model 4: adjusted for Model 3 plus fasting insulin.[a]

SUA, serum uric acid; SD, standard deviation; MetS, metabolic syndrome.

[a]*n*=5,188 male.

Table 5. Hazard ratios and 95% confidence intervals for development of metabolic syndrome according to quartile of percent change in serum uric acid levels: female

	Percent changes in SUA levels (female, *n*=5,363)						
	Quartile 1 (≤–5.6%, *n*=1,346)	Quartile 2 (–5.5% to 4.1%, *n*=1,324)	Quartile 3 (4.2% to 14.6%, *n*=1,348)	Quartile 4 (≥14.7%, *n*=1,345)	*P* for trend	Continuous variable (1SD)	*P* value
Percent change in SUA levels	–14.0±7.0	–0.7±2.7	9.0±3.0	27.6±12.8		5.5±17.0	
Incident MetS	298 (22.1)	255 (19.3)	184 (13.6)	164 (12.2)		901 (16.8)	
Unadjusted	1 (reference)	0.860 (0.728–1.017)	0.590 (0.491–0.709)	0.524 (0.433–0.635)	<0.001	0.778 (0.779–0.873)	<0.001
Model 1	1 (reference)	0.977 (0.825–1.157)	0.684 (0.567–0.824)	0.635 (0.523–0.772)	<0.001	0.825 (0.894–0.965)	<0.001
Model 2	1 (reference)	0.981 (0.828–1.162)	0.713 (0.591–0.859)	0.634 (0.522–0.771)	<0.001	0.831 (0.785–0.880)	<0.001
Model 3	1 (reference)	1.000 (0.843–1.186)	0.744 (0.615–0.900)	0.684 (0.557–0.840)	<0.001	0.851 (0.801–0.905)	<0.001
Model 4	1 (reference)	0.971 (0.765–1.232)	0.760 (0.584–0.988)	0.740 (0.560–0.976)	0.011	0.856 (0.791–0.926)	<0.001

Values are presented as mean±standard deviation, number (%), or hazard ratio (95% confidence interval). Model 1: adjusted for age, systolic blood pressure, body mass index, fat-free mass (%), estimated glomerular filtration rate, and smoking status; Model 2: adjusted for Model 1 plus fasting glucose, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol; Model 3: adjusted for Model 2 plus baseline SUA; Model 4: adjusted for Model 3 plus fasting insulin.[a]

SUA, serum uric acid; SD, standard deviation; MetS, metabolic syndrome.

[a]*n*=2,792 female.

cident MetS in the second, third, and fourth quartiles compared to the first quartile of percent changes in SUA level were 1.034 (95% CI, 0.918 to 1.164), 0.908 (95% CI, 0.804 to 1.027), and 0.804 (95% CI, 0.709 to 0.912) in male (*P* for trend <0.001) and 0.860 (95% CI, 0.728 to 1.017), 0.590 (95% CI, 0.491 to 0.709), and 0.524 (95% CI, 0.433 to 0.635) in female (*P* for trend <0.001), respectively. These associations remained significant after further adjustments (Model 1: adjusted for age, systolic BP, BMI, FFM [%], eGFR, and smoking status; Model 2: Model 1 plus fasting glucose, TG, LDL-C, and HDL-C levels; Model 3: Model 2 plus baseline SUA level; Model 4: Model 3 plus fasting insulin level).

As a continuous variable, the percent change in SUA level was also negatively associated with the risk of incident MetS. In the unadjusted model, the HR (95% CI) for incident MetS associated with each 1SD increase in the percent change in SUA level was 0.932 (95% CI, 0.897 to 0.968; *P*<0.001) in male and 0.778 (95% CI, 0.779 to 0.873; *P*<0.001) in female. These associations were apparent even after adjustments for multiple confounders in Models 1 and 2. After further adjustment for baseline SUA level (Model 3), the HR (95% CI) for incident MetS associated with each 1SD increase in the percent change in SUA level was 0.944 (95% CI, 0.906 to 0.982; *P*=0.005) in male and 0.851 (95% CI, 0.801 to 0.905; *P*<0.001) in female. These associations were still significant after additional adjustment for fasting insulin level (Model 4 [HR, 0.947; 95% CI, 0.903 to 0.993, *P*=0.023 in male]; [HR, 0.856; 95% CI, 0.791 to 0.926; *P*<0.001 in female]).

Supplementary Fig. 1 shows cumulative incidence of MetS using the Kaplan-Meier method and the log-rank test according to SUA quartile categories and percent change in SUA quartile categories according to both sexes. Fourth quartiles (Q4) of the percent change in SUA show a higher cumulative incidence of MetS than the other quartiles in both sexes (*P*< 0.001).

In subgroup analysis, Supplementary Tables 4 and 5 displays the HRs and 95% CIs for incident MetS according to percent change in SUA level as a continuous variable, regarding to the quartile categories of the basal SUA level separately. In the fully-adjusted model (Model 3) and additionally adjusted model for fasting insulin level (Model 4), each 1 SD increase in percent change in SUA level was negatively correlated with incident MetS regarding to the quartiles of the basal SUA levels in female. However, they lost statistical significance in male.

DISCUSSION

The novel finding of the present study was that there was a negative association between the percent change in SUA level and the incidence of MetS in mostly healthy participants, even after adjustment for baseline SUA level. Most epidemiological and cohort studies have identified positive relationships between baseline SUA level and prevalence of MetS. However, until this study, no attempt had been made to investigate the relationship between changes in SUA level and development of MetS.

In our study, both across quartile groups and as a continuous variable, the percent change in SUA level was negatively associated with incident MetS (Tables 4 and 5). Therefore, the percent change in SUA level could be an important measure, and increasing SUA level might protect against the development of MetS. The results of the current study support the idea that changes in SUA level could be one of the major anti-oxidative biomarkers predicting the development of MetS.

Uric acid is a water-soluble antioxidant mostly produced by the liver [4] and contributes up to 50% of the antioxidant capacity in the blood [22]. Additionally, it has been proposed that uric acid directly inhibits free radical-induced damage, thus protecting the cell membrane and DNA [23,24]. Furthermore, the increment of SUA level has been tested as a treatment in the clinical field of neurology. Some studies have demonstrated that systemic administration of uric acid increases the serum antioxidant capacity in healthy subjects [12,13]. In patients with acute stroke, the use of uric acid reduced several biomarkers of oxidative stress and was neuroprotective in combination with thrombolytic therapy [14,15]. More recently, uric acid therapy was reported to improve the clinical outcomes of acute stroke in female [16].

SUA has long been debated as either a prooxidant risk factor or an antioxidant protective factor. It has also been unclear whether increased SUA level in diseases associated with oxidative stress (such as CVDs) is a protective response or a primary cause [25,26]. SUA might be a prooxidant marker of oxidative stress [27], but it also could have a therapeutic role as an antioxidant [28,29]. Considering all of the above, the prolonged conflict could be resolved if it is hypothesized that the gradual elevation of SUA level is a protective factor, whereas chronic elevation is a risk factor for disease [30].

Although the mechanism was not completely delineated in the current study, the chronic inflammation and oxidative

stress involved in the initiation of MetS could explain the association between changes in SUA level and risk of developing MetS. To understand the mechanism whereby increasing SUA level protects against MetS, we investigated the correlation between changes in SUA level and changes in log-transformed hs-CRP (%). Changes in log-transformed hs-CRP (%) correlated inversely with changes in SUA level in both sexes, indicating that the protective/anti-inflammatory effects of SUA mainly contribute to its effects on incident MetS (Table 3). However, it remains unclear whether the increment in SUA level is an adaptive response to increasing oxidative stress, or whether failure to increase SUA level is a risk factor of MetS. Further studies are needed to resolve this question.

The relationship between changes in SUA level and development of MetS has been remained area of uncertainty; therefore, the findings of the current study are relevant for better defining the potentially protective role of SUA. Nevertheless, several limitations of this study should be mentioned. First, since participants were self-selected and this study was conducted with a single-center-based sample, we were unable to ascertain whether participants were representative of the general Korean population; thus, selection bias could limit the generalizability of the results. Second, we could not investigate the pattern of changes in SUA level in each participant since we used Multivariate Cox proportional hazards analysis. Third, participants who were taking medications known to influence SUA level (i.e., diuretics or allopurinol) could not be excluded. Forth, the reason and mechanism were still unclear what made the different results by sexes in subgroup analysis (Supplementary Tables 4 and 5). Finally, we did not include dietary habits or alcohol intake. Despite these limitations, we studied a large sample population with a relatively long follow-up period. Further, the measurements of factors associated with SUA level were standardized.

In conclusion, although higher baseline SUA level has been linked to an increased risk of incident MetS, increasing SUA level might protect against the risk of MetS, regardless of baseline SUA level, suggesting a possible role of SUA as an antioxidant in the pathogenesis of incident MetS.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2018.0079.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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Supplementary Table 1. Baseline clinical and biochemical characteristic of study subjects based on baseline serum uric acid quartile categories and both sexes

Characteristic	Baseline serum uric acid (male, *n*=7,694)					Baseline serum uric acid (female, *n*=5,363)				
	Quartile 1 (≤5.1 mg/dL, *n*=2,146)	Quartile 2 (5.2–5.8 mg/dL, *n*=1,938)	Quartile 3 (5.9–6.6 mg/dL, *n*=1,905)	Quartile 4 (≥6.7 mg/dL, *n*=1,705)	*P* value	Quartile 1 (≤3.5 mg/dL, *n*=1,392)	Quartile 2 (3.6–4.0 mg/dL, *n*=1,259)	Quartile 3 (4.1–4.6 mg/dL, *n*=1,449)	Quartile 4 (≥4.7 mg/dL, *n*=1,263)	*P* value
Age, yr	52.7±8.3	51.7±8.1	51.2±8.2	51.1±8.2	<0.001	47.9±6.7	48.5±6.6	49.7±7.3	51.0±8.4	<0.001
Smoking status					0.074					0.178
Current smoker	584 (27.2)	515 (26.6)	544 (28.6)	435 (25.5)		21 (1.5)	15 (1.2)	27 (1.9)	32 (2.5)	
Ex-smoker	944 (44.0)	893 (46.1)	870 (45.7)	825 (48.4)		43 (3.1)	35 (2.8)	40 (2.8)	44 (3.5)	
Non-smoker	618 (28.8)	530 (27.3)	491 (25.8)	445 (26.1)		1,328 (95.4)	1,209 (96.0)	1,382 (95.4)	1,187 (94.0)	
BMI, kg/m^2	23.5±2.2	23.8±2.3	24.2±2.1	24.6±2.3	<0.001	21.5±2.2	21.8±2.3	22.2±2.5	22.9±2.6	<0.001
WC, cm	84.4±6.4	85.3±6.2	86.3±6.1	87.4±6.1	<0.001	73.0±6.0	73.6±6.1	74.8±6.6	76.4±6.9	<0.001
Fat-free mass, %	79.9±5.9	79.6±4.6	79.2±4.5	78.7±4.3	<0.001	73.2±5.2	72.7±5.1	71.8±5.5	70.6±5.5	<0.001
Systolic BP, mm Hg	112.0±13.6	112.4±13.7	113.1±13.8	113.5±14.0	<0.001	108.2±14.1	108.0±14.8	109.2±15.1	109.8±15.1	0.001
Diastolic BP, mm Hg	69.8±9.3	70.4±9.5	71.0±9.6	71.3±9.6	<0.001	65.3±9.8	65.5±10.2	66.0±10.0	66.2±10.0	0.011
eGFR, mL/min/1.73 m^2	90.6±11.9	88.7±11.0	86.8±11.0	84.8±11.2	<0.001	95.1±12.6	91.6±12.0	89.7±11.9	85.8±11.9	<0.001
Fasting glucose, mg/dL	92.6±19.3	90.0±12.7	89.0±11.0	88.9±9.9	<0.001	85.5±10.3	85.3±9.9	85.7±9.6	86.5±9.7	0.012
Fasting insulin, μU/mL[a]	7.6 (6.0–9.8)	7.9 (6.1–10.2)	8.0 (6.3–10.3)	8.4 (6.5–10.9)	<0.001	7.9 (6.2–9.9)	7.7 (6.2–9.5)	7.9 (6.2–10.2)	8.1 (6.1–10.6)	0.061
HOMA-IR[a]	1.7 (1.3–2.2)	1.7 (1.3–2.3)	1.7 (1.3–2.3)	1.8 (1.4–2.4)	0.001	1.7 (1.3–2.1)	1.6 (1.3–2.1)	1.7 (1.3–2.1)	1.8 (1.3–2.3)	0.017
TC, mg/dL	185.8±29.4	187.2±30.2	191.1±30.9	193.9±30.3	<0.001	186.4±31.8	189.2±31.7	194.2±32.8	197.3±34.5	<0.001
TG, mg/dL	101.0 (77.0–135.0)	105.0 (78.0–139.0)	112.0 (84.0–148.0)	123.0 (90.0–162.0)	<0.001	78.0 (60.0–102.0)	81.0 (64.0–106.0)	87.0 (66.0–112.0)	91.0 (69.0–122.0)	<0.001
LDL-C, mg/dL	121.2±26.5	122.7±27.0	126.7±28.0	129.0±27.8	<0.001	114.4±27.8	117.7±27.7	122.1±28.7	127.0±31.1	<0.001
HDL-C, mg/dL	56.7±12.6	56.1±12.5	55.0±11.7	54.6±11.5	<0.001	66.4±13.4	65.4±14.0	65.2±13.8	63.1±13.3	<0.001
hs-CRP, mg/L	0.13±0.46	0.11±0.23	0.12±0.37	0.13±0.41	0.513	0.07±0.24	0.07±0.23	0.07±0.17	0.11±0.47	<0.001
Baseline SUA, mg/dL	4.5±0.6	5.5±0.2	6.2±0.2	7.4±0.7	<0.001	3.1±0.4	3.8±0.1	4.3±0.2	5.2±0.5	<0.001
Change in SUA, %	5.5±15.3	1.4±13.1	−1.9±12.3	−5.8±11.7	<0.001	14.1±19.4	7.5±15.3	3.0±14.3	−3.1±13.2	<0.001
Incident MetS	491 (22.9)	395 (20.4)	532 (27.9)	594 (34.8)	0.002	151 (10.8)	169 (13.4)	253 (17.5)	328 (26.0)	<0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Characteristics of the study population according to the serum uric acid quartile were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

BMI, body mass index; WC, waist circumference; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment index for insulin resistance; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SUA, serum uric acid; MetS, metabolic syndrome.

[a]*n*=5,188 male, *n*=2,792 female.

Supplementary Table 2. Baseline clinical and biochemical characteristic of study subjects based on baseline serum uric acid quartile categories and both sexes according to incident metabolic syndrome: male

Characteristic	Percent changes in serum uric acid (not incident MetS in male, *n*=5,682)					Percent changes in serum uric acid (incident MetS in male, *n*=2,012)				
	Quartile 1 (≤–9.1%, *n*=1,382)	Quartile 2 (–9.0% to –0.1%, *n*=1,386)	Quartile 3 (0% to 8.2%, *n*=1,423)	Quartile 4 (≥8.3%, *n*=1,491)	*P* value	Quartile 1 (≤–9.1%, *n*=545)	Quartile 2 (–9.0% to –0.1%, *n*=544)	Quartile 3 (0% to 8.2%, *n*=485)	Quartile 4 (≥8.3%, *n*=438)	*P* value
Age, yr	52.8±8.4	51.7±8.2	51.2±8.5	51.0±8.3	0.000	52.5±8.0	51.9±7.6	51.3±7.6	51.5±8.6	0.025
Smoking status					0.000					0.090
Current smoker	316 (22.9)	315 (22.7)	379 (26.6)	430 (28.8)		162 (29.7)	178 (32.7)	138 (28.5)	160 (36.5)	
Ex-smoker	695 (50.3)	652 (47.0)	626 (44.0)	642 (43.1)		263 (48.3)	233 (42.8)	237 (48.9)	184 (42.0)	
Non-smoker	371 (26.8)	419 (30.2)	418 (29.4)	419 (28.1)		120 (22.0)	133 (24.4)	110 (22.7)	94 (21.5)	
BMI, kg/m^2	23.6±2.2	23.8±2.1	23.5±2.3	23.4±2.1	0.012	25.1±2.1	25.2±2.0	25.3±2.1	25.0±2.1	0.822
Waist circumference, cm	84.8±5.9	85.2±5.8	84.2±6.2	83.9±6.1	0.000	89.3±5.8	89.6±5.6	89.5±5.9	88.2±5.7	0.010
Fat-free mass, %	80.2±4.5	79.7±4.6	79.9±4.8	79.8±6.4	0.090	78.2±4.2	78.2±4.1	77.7±4.0	77.8±4.0	0.056
Systolic BP, mm Hg	110.9±13.9	111.3±13.6	111.9±13.7	113.3±14.3	0.000	115.0±13.6	115.2±12.8	114.4±12.8	115.6±13.4	0.757
Diastolic BP, mm Hg	69.3±9.5	69.9±9.5	70.1±9.6	70.8±9.9	0.000	72.5±8.8	71.9±9.0	71.7±8.9	72.9±8.7	0.656
eGFR, mL/min/1.73 m^2	86.4±11.3	87.1±11.1	88.5±11.6	89.7±11.7	0.000	86.8±10.9	86.4±11.2	88.1±12.1	90.0±12.2	0.000
Fasting glucose, mg/dL	88.7±12.3	88.7±11.5	89.3±13.8	90.6±16.9	0.000	92.5±15.0	92.2±13.0	92.1±13.3	94.2±16.6	0.120
Fasting insulin, μU/mL[a]	7.6 (5.9–9.7)	7.8 (6.1–10.0)	7.6 (5.9–9.5)	7.7 (6.0–9.7)	0.120	9.0 (6.9–11.4)	8.5 (6.9–10.9)	9.3 (7.1–11.5)	8.9 (7.1–11.6)	0.110
HOMA-IR[a]	1.7 (1.2–2.2)	1.7 (1.3–2.3)	1.6 (1.3–2.1)	1.7 (1.3–2.2)	0.073	2.1 (1.5–2.6)	1.9 (1.5–2.5)	2.1 (1.6–2.7)	2.1 (1.6–2.7)	0.133
Total cholesterol, mg/dL	189.4±30.8	189.5±30.1	188.3±30.0	187.5±29.8	0.052	194.0±30.9	190.6±30.4	189.7±31.0	188.8±30.6	0.006
TG, mg/dL	100.0 (76.0–133.0)	100.0 (77.0–134.0)	100.0 (76.0–133.0)	105.0 (79.0–135.0)	0.028	129.0 (100.0–174.0)	135.0 (106.0–180.5)	134.0 (106.0–170.0)	136.0 (104.0–186.0)	0.321
LDL-C, mg/dL	124.7±28.0	124.8±27.5	123.4±26.8	121.7±26.6	0.001	131.2±28.4	128.4±27.0	126.8±27.7	123.4±28.6	0.000
HDL-C, mg/dL	58.0±12.8	57.2±12.1	57.0±12.2	56.6±12.1	0.002	52.1±10.2	51.0±10.7	50.3±9.8	51.9±11.2	0.415
hs-CRP, mg/L	0.1±0.3	0.1±0.4	0.1±0.3	0.1±0.4	0.803	0.1±0.2	0.1±0.3	0.2±0.8	0.2±0.4	0.377
Baseline SUA, mg/dL	6.1±1.2	5.9±1.0	5.7±1.0	5.3±1.0	0.000	6.4±1.3	6.1±1.2	5.9±1.1	5.5±1.1	0.000
Change in SUA, %	–16.5±6.3	–4.9±2.3	3.5±2.6	18.3±9.5	0.000	–15.7±5.8	–4.8±2.3	3.4±2.6	18.1±9.2	0.000

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Characteristics of the study population according to the serum uric acid quartile were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.
MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment index for insulin resistance; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SUA, serum uric acid.
[a]*n*=5,188 male.

Supplementary Table 3. Baseline clinical and biochemical characteristic of study subjects based on baseline serum uric acid quartile categories and both sexes according to incident metabolic syndrome: female

Characteristic	Percent changes in serum uric acid (not incident MetS in female, n=4,462)					Percent changes in serum uric acid (incident MetS in female, n=901)				
	Quartile 1 (≤–5.6%, n=1,048)	Quartile 2 (–5.5% to 4.1%, n=1,069)	Quartile 3 (4.2% to 14.6%, n=1,164)	Quartile 4 (≥14.7%, n=1,181)	P value	Quartile 1 (≤–5.6%, n=298)	Quartile 2 (–5.5% to 4.1%, n=255)	Quartile 3 (4.2% to 14.6%, n=184)	Quartile 4 (≥14.7%, n=164)	P value
Age, yr	49.2±8.2	48.9±7.3	48.5±7.0	47.9±6.2	0.000	53.4±8.0	51.7±7.2	52.8±7.7	51.3±6.4	0.014
Smoking status					0.886					0.655
Current smoker	19 (1.8)	20 (1.9)	20 (1.7)	25 (2.1)		3 (1.0)	2 (0.8)	4 (2.2)	2 (1.2)	
Ex-smoker	39 (3.7)	29 (2.7)	36 (3.1)	37 (3.1)		8 (2.7)	8 (3.1)	2 (1.1)	3 (1.8)	
Non-smoker	990 (94.5)	1,020 (95.4)	1,108 (95.2)	1,119 (94.8)		287 (96.3)	245 (96.1)	178 (96.7)	159 (97.0)	
BMI, kg/m^2	21.9±2.4	21.7±2.3	21.7±2.3	21.7±2.1	0.115	24.1±2.7	23.8±2.5	23.4±2.2	23.7±2.6	0.006
Waist circumference, cm	73.9±6.6	73.5±6.2	73.3±6.0	73.4±5.8	0.031	80.0±7.1	79.0±6.2	78.1±5.9	78.5±6.5	0.003
Fat-free mass, %	72.4±5.4	72.7±5.4	72.9±5.2	72.7±5.2	0.137	68.8±5.2	69.2±5.0	70.1±4.7	69.6±5.2	0.018
Systolic BP, mm Hg	107.1±15.0	107.3±14.4	107.4±14.0	108.1±14.0	0.092	114.7±15.2	115.1±15.3	115.3±15.0	116.2±15.1	0.355
Diastolic BP, mm Hg	65.2±10.2	64.9±9.7	64.6±9.9	65.5±9.8	0.612	68.4±9.6	68.8±10.1	68.7±9.7	71.1±10.0	0.014
eGFR, mL/min/1.73 m^2	88.2±12.3	90.3±12.5	91.2±11.9	93.4±12.7	0.000	87.6±12.6	90.2±13.9	91.9±12.1	89.6±12.2	0.017
Fasting glucose, mg/dL	85.2±10.0	85.0±8.2	84.7±8.6	85.1±8.9	0.741	89.4±13.0	88.7±8.7	89.3±14.3	90.9±16.0	0.271
Fasting insulin, μU/mL[a]	7.5 (5.9–9.4)	7.8 (5.8–9.5)	7.8 (6.1–10.0)	7.8 (6.3–10.1)	0.131	8.9 (7.0–11.7)	9.1 (7.4–10.9)	8.4 (7.0–10.7)	9.0 (7.0–11.5)	0.540
HOMA-IR[a]	1.6 (1.2–2.0)	1.6 (1.2–2.1)	1.6 (1.3–2.1)	1.7 (1.3–2.2)	0.182	2.0 (1.5–2.6)	2.0 (1.6–2.4)	1.9 (1.5–2.4)	2.0 (1.4–2.6)	0.826
Total cholesterol, mg/dL	192.9±34.2	192.3±31.0	190.1±32.5	187.0±31.6	0.000	199.0±34.6	197.9±36.1	199.2±32.2	195.4±37.8	0.421
TG, mg/dL	79.0 (61.0–102.5)	81.0 (64.0–102.0)	80.0 (61.0–105.0)	78.0 (61.0–103.0)	0.352	109.5 (82.0–140.0)	106.0 (86.5–141.0)	115.0 (89.0–143.0)	106.0 (83.5–137.0)	0.560
LDL-C, mg/dL	120.9±29.9	119.9±27.8	117.2±28.1	114.4±27.0	0.000	132.3±31.2	131.9±32.0	131.6±28.8	129.3±32.3	0.370
HDL-C, mg/dL	66.3±13.3	66.5±14.0	66.9±13.6	66.0±13.5	0.709	58.9±11.8	57.8±11.8	58.5±11.4	56.8±13.0	0.132
hs-CRP, mg/L	0.1±0.5	0.1±0.2	0.1±0.1	0.1±0.2	0.178	0.1±0.2	0.1±0.2	0.1±0.2	0.1±0.5	0.558
Baseline SUA, mg/dL	4.4±0.9	4.2±0.8	4.0±0.7	3.6±0.7	0.000	4.7±0.9	4.5±0.8	4.2±0.8	3.9±0.8	0.000
Change in SUA, %	–14.0±7.1	–0.7±2.7	9.0±3.0	27.9±13.0	0.000	–13.8±6.6	–0.5±2.6	8.9±3.1	25.9±11.1	0.000

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Characteristics of the study population according to the serum uric acid quartile were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.
MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment index for insulin resistance; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SUA, serum uric acid.
[a]n=2,792 female.

Supplementary Table 4. Hazard ratios and 95% confidence intervals for development of metabolic syndrome according to percent change in serum uric acid level as a continuous variable, regarding to the quartile categories of the basal serum uric acid level: male

	Baseline serum uric acid (male, *n*=7,694)							
	Quartile 1 (≤5.1 mg/dL, *n*=2,146)	*P* value	Quartile 2 (5.2–5.8 mg/dL, *n*=1,938)	*P* value	Quartile 3 (5.9–6.6 mg/dL, *n*=1,905)	*P* value	Quartile 4 (≥6.7 mg/dL, *n*=1,705)	*P* value
Incident MetS	491 (22.9)		395 (20.4)		532 (27.9)		594 (34.8)	
Unadjusted	0.954 (0.888–1.025)	0.202	1.025 (0.936–1.122)	0.598	1.023 (0.946–1.106)	0.567	0.987 (0.912–1.069)	0.987
Model 1	0.932 (0.869–0.999)	0.048	0.954 (0.870–1.046)	0.315	0.987 (0.912–1.069)	0.749	0.965 (0.889–1.046)	0.385
Model 2	0.933 (0.869–1.002)	0.057	0.926 (0.844–1.016)	0.106	0.920 (0.848–0.999)	0.046	0.972 (0.895–1.055)	0.494
Model 3	0.932 (0.868–1.001)	0.052	0.929 (0.847–1.019)	0.119	0.921 (0.849–1.000)	0.050	0.991 (0.911–1.078)	0.836
Model 4	0.921 (0.848–1.001)	0.052	0.954 (0.855–1.064)	0.395	0.917 (0.834–1.008)	0.072	0.997 (0.899–1.105)	0.950

Values are presented as number (%) or hazard ratio (95% confidence interval). Model 1: adjusted for age, systolic blood pressure, body mass index, fat-free mass (%), estimated glomerular filtration rate, and smoking status; Model 2: adjusted for Model 1 plus fasting glucose, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol; Model 3: adjusted for Model 2 plus baseline serum uric acid; Model 4: adjusted for Model 3 plus fasting insulin.[a]

MetS, metabolic syndrome.

[a]*n*=5,188 male.

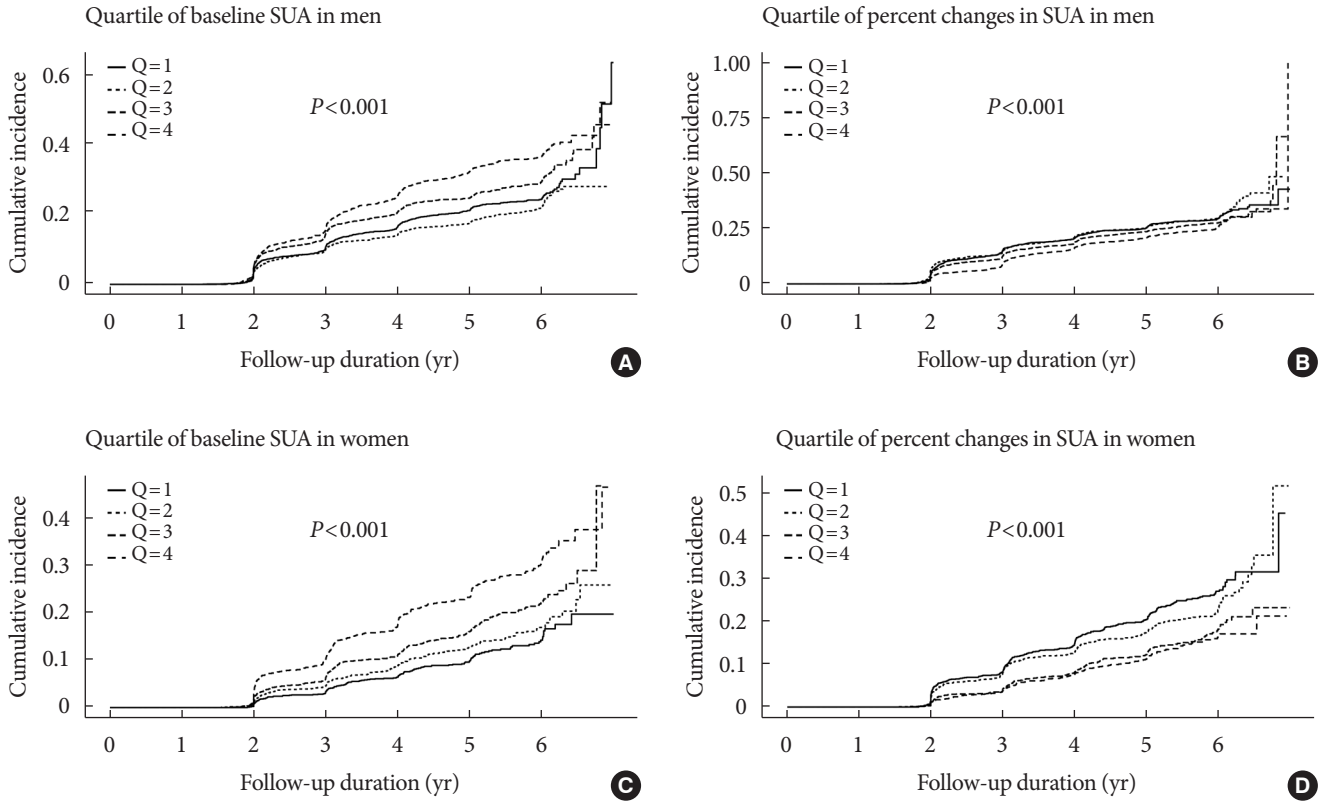
Supplementary Table 5. Hazard ratios and 95% confidence intervals for development of metabolic syndrome according to percent change in serum uric acid level as a continuous variable, regarding to the quartile categories of the basal serum uric acid level: female

	Baseline serum uric acid (female, *n*=5,363)							
	Quartile 1 (≤3.5 mg/dL, *n*=1,392; continuous variable [1SD])	*P* value	Quartile 2 (3.6–4.0 mg/dL, *n*=1,259; continuous variable [1SD])	*P* value	Quartile 3 (4.1–4.6 mg/dL, *n*=1,449; continuous variable [1SD])	*P* value	Quartile 4 (≥4.7 mg/dL, *n*=1,263; continuous variable [1SD])	*P* value
Incident MetS	151 (10.8)		169 (13.4)		253 (17.5)		328 (26.0)	
Unadjusted	0.817 (0.719–0.929)	0.002	0.948 (0.824–1.090)	0.451	0.895 (0.791–1.012)	0.076	0.844 (0.755–0.944)	0.003
Model 1	0.829 (0.732–0.940)	0.003	0.893 (0.784–1.019)	0.093	0.919 (0.813–1.040)	0.180	0.840 (0.752–0.939)	0.002
Model 2	0.819 (0.722–0.930)	0.002	0.869 (0.759–0.995)	0.043	0.869 (0.768–0.983)	0.025	0.833 (0.745–0.931)	0.001
Model 3	0.825 (0.726–0.939)	0.004	0.868 (0.758–0.994)	0.041	0.871 (0.770–0.986)	0.029	0.843 (0.752–0.944)	0.003
Model 4	0.833 (0.706–0.985)	0.032	0.842 (0.708–1.000)	0.050	0.839 (0.717–0.983)	0.030	0.832 (0.715–0.967)	0.017

Values are presented as number (%) or hazard ratio (95% confidence interval). Model 1: adjusted for age, systolic blood pressure, body mass index, fat-free mass (%), estimated glomerular filtration rate, and smoking status; Model 2: adjusted for Model 1 plus fasting glucose, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol; Model 3: adjusted for Model 2 plus baseline serum uric acid; Model 4: adjusted for Model 3 plus fasting insulin.[a]

MetS, metabolic syndrome.

[a]*n*=2,792 female.



Supplementary Fig. 1. Cumulative incidence of metabolic syndrome (MetS) using the Kaplan-Meier method and the log-rank test according to serum uric acid (SUA) quartile categories and percent change in SUA quartile categories according to both sexes. Fourth quartile (Q4) of the percent change in SUA shows a higher cumulative incidence of MetS than the other quartiles in both sexes ($P<0.001$). (A) Cumulative incidence of MetS according to baseline SUA quartile categories in male. (B) Cumulative incidence of MetS according to percent change in SUA quartile categories in male. (C) Cumulative incidence of MetS according to baseline SUA quartile categories in female. (D) Cumulative incidence of MetS according to percent change in SUA quartile categories in female.