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Original Article

Hyperuricemia is Associated With an Increased Prevalence of Metabolic Syndrome in a General Population and a Decreased Prevalence of Diabetes in Men

Hyemin Jeong, M.D., Ph.D.[1], Ji Eun Moon, Ph.D.[2], Chan Hong Jeon, M.D., Ph.D.[1]

[1]Division of Rheumatology, Department of Internal Medicine, [2]Department of Biostatistics, Soonchunhyang University Hospital Bucheon, Bucheon, Korea

Objective. Elevated uric acid is associated with cardiovascular disease and metabolic syndrome. However, uric acid is also an antioxidant with beneficial effect on comorbidities. The aim of this study was to evaluate the relationship of serum uric acid with diabetes, metabolic syndrome, and cardiovascular disease in a Korean adult population. **Methods.** A total of 5,887 (weighted n=40,251,868) participants aged ≥19 years from the 2016 Korean National Health and Nutrition Examination Survey were included for analysis. Weighted prevalence and odds ratio (OR) of comorbidities were analyzed according to the presence of hyperuricemia and uric acid quartile. **Results.** Participants of both sexes with hyperuricemia showed higher prevalence of metabolic syndrome, hypertension, hypertriglyceridemia, and obesity than those without hyperuricemia. After adjusting for socioeconomic and lifestyle characteristics, hyperuricemia was associated with a decreased prevalence of diabetes mellitus in men (OR: 0.44, 95% confidence interval [CI]: 0.28～0.72, p=0.001) and a decreased prevalence of myocardial infarction or angina (OR: 0.25, 95% CI: 0.08～0.75, p=0.013) in women. Hyperuricemia was significantly associated with an increased prevalence of metabolic syndrome in both men (OR: 1.81, 95% CI: 1.33～2.45, p<0.001) and women (OR: 1.95, 95% CI: 1.22～3.13, p=0.006). **Conclusion.** Hyperuricemia was associated with a decreased prevalence of diabetes mellitus in men and a decreased prevalence of myocardial infarction or angina in women. Hyperuricemia was associated with an increased prevalence of metabolic syndrome in both men and women. **(J Rheum Dis 2020;27:247-260)**

Key Words. Uric acid, Metabolic syndrome, Diabetes mellitus

INTRODUCTION

Uric acid, the final oxidation product of purine metabolism in humans and higher primates, is influenced by genetics, diet, alcohol consumption, and renal insufficiency. Hyperuricemia is involved in the pathogenesis of gout. Excess serum uric acid concentrations are associated with comorbidities such as coronary artery disease, stroke, metabolic syndrome, diabetes, and hypertension [1-4]. Uric acid can induce endothelial dysfunction [5] and contribute to systemic inflammation [6]. It is also a prooxidant and a marker of oxidative stress [7]. Fructose-induced uric acid generation can cause mitochondrial oxidative stress and result in insulin resistance [8]. These might be potential mechanisms involved in the role of uric acid as a cardiovascular risk factor.

However, serum uric acid concentrations are positively associated with longevity in humans and mammals [9], implying that uric acid might have an physiologic role in the human body. Uric acid is an endogenous antioxidant that provides an antioxidant defense in humans against oxidant-and radical-caused diseases [10]. Extremely low serum uric acid concentrations have been associated with endothelial dysfunction and adverse cardiovascular events [11]. Uric acid administration can restore endothelial function of patients with diabetes and smokers [12]. Uric

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Corresponding to : Chan Hong Jeon http://orcid.org/0000-0002-2430-7264
Division of Rheumatology, Department of Internal Medicine, Soonchunhyang University Hospital Bucheon, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea. E-mail : chjeon@gmail.com

acid levels are inversely associated with diabetes in a US population [13]. On the other hand, serum uric acid is negatively associated with diabetes in Japanese men, but not in women [14]. Serum uric acid levels are associated with severe coronary artery disease only in women [15]. The relationship between uric acid and cardiovascular risk is still controversial. Therefore, the aim of this study was to evaluate the relationship of serum uric acid with diabetes, metabolic syndrome, and cardiovascular disease in men and women Korean adults.

MATERIALS AND METHODS

Study population

The Korean National Health and Nutrition Examination Survey (KNHANES) is a nationwide survey that is conducted periodically by the Korean Centers for Disease Control and Prevention to investigate the health and nutritional status of the Korean population [16]. This survey assesses the general health and nutritional status of individuals in South Korea through interviews regarding health and nutrition and basic health assessments. Study participants were selected using a proportional allocation-systematic sampling method with multistage stratification to derive a representative Korean population. Although individual participants were not generally representatives of the Korean population, this survey provided representative estimates of the noninstitutionalized Korean civilian population using the power of sample weight. Every year, 10,000 to 12,000 individuals in approximately 3,800 to 4,600 households are selected from a panel based on National Census Data. Participation rates of selected households in the past several cycles of the KNHANES have been high, ranging from 75% to 80%. This study analyzed the 2016 KNHANES [17]. In the 2016 KNANES, 10,806 individuals in 4,416 households were selected. Participation rate was 75.4%. Among 8,150 participants in the 2016 KNHANES, 1,768 participants who were younger than 19 years old were excluded. Among 6,382 participants, 495 participants with missing data of serum uric acid levels were also excluded. Thus, a total of 5,887 participants were selected for final analysis. Written informed consent was obtained from all participants before completing the survey. This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Hospital Bucheon (IRB no. 2018-05-017).

Demographic variables and data collection

The KNHANES was conducted by four special research teams. Each team was composed of eight experts including nurses, nutritionists, and students majoring in public health. The selected professional investigator was placed at the investigation site after completing one month of education and practice. Subsequently, the ability of the investigator to conduct research was verified through regular education and on-site quality management. A standardized interview was performed in participants' homes. An established questionnaire was used to collect information on demographic and socioeconomic characteristics, including age, sex, income, region, education, marital status, alcohol consumption, and smoking status. Alcohol consumption was categorized into the following four groups based on the frequency of alcohol consumption during the past year: never, ≤1 time/week, 2～3 times/week, and ≥4 times/week. Income levels were categorized into quartiles based on average individual monthly income. Urban and rural areas were classified by administrative district. Blood pressure was measured by nurses using standard methods. After at least five minutes of rest in a sitting position, blood pressure was measured using a mercury sphygmomanometer on the right arm. Blood pressure was measured three times. The mean of the second and third measurements was calculated and used for analysis. Blood samples were collected from each participant after at least eight hours of fasting. All blood samples were immediately refrigerated and transported in cold container to a central testing facility.

Hypertension was defined as mean systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or by the presence of antihypertensive agents. Prehypertension was defined as an average SBP of 120～139 mmHg or DBP of 80～89 mmHg. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL or current use of antidiabetic drugs or insulin due to a previous diagnosis of diabetes. Impaired fasting glucose was determined if fasting plasma glucose level was ≥100 mg/dL and <126 mg/dL. Hypercholesterolemia was defined as a total plasma cholesterol ≥240 mg/dL after eight hours of fasting or current use of cholesterol-lowering agents. Hypertriglyceridemia was defined as triglyceride levels >200 mg/dL after 12 hours of fasting. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition [18]. Current ATP III criteria were used to define metabolic syndrome if

any three of the following five traits were present: (1) central obesity (waist circumference ≥90 cm in Asian men or ≥80 cm in Asian women), (2) hypertriglyceridemia (fasting serum triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides), (3) decreased high density lipoprotein (HDL) cholesterol (serum HDL cholesterol <40 mg/dL in men or <50 mg/dL in women or drug treatment for low HDL cholesterol), (4) elevated BP (SBP

Table 1. Clinical characteristics of participants

Variables	Total (n=5,887)	Men (n=2,568)	Women (n=3,319)	p-value
Age (yr)	46.7±0.3	45.7±0.3	47.7±0.4	<0.001
Sex	6,129	2,647 (49.75)	3,482 (50.25)	
Income				0.688
Low	1,464 (25.8)	638 (26.1)	826 (25.4)	
Mid-low	1,468 (24.4)	638 (24.0)	830 (25.0)	
Mid-high	1,476 (25.0)	640 (24.7)	836 (25.3)	
High	1,458 (24.8)	641 (25.2)	817 (24.3)	
Education				<0.001
Elementary school	1,189 (15.1)	369 (9.7)	820 (20.5)	
Middle school	576 (9.1)	252 (8.7)	324 (9.5)	
High school	1,794 (36.2)	808 (37.0)	986 (35.4)	
College graduation	2,045 (39.6)	998 (44.6)	1,047 (34.6)	
Marital status				<0.001
Married	4,970 (77.3)	2,081 (72.4)	2,889 (82.2)	
Not married	917 (22.7)	487 (27.6)	430 (17.8)	
Region				0.660
Urban	4,740 (84.3)	2,066 (84.5)	2,674 (84.2)	
Rural	1,147 (15.7)	502 (15.5)	645 (15.8)	
Alcohol consumption				<0.001
Never	928 (15.1)	318 (10.0)	610 (20.8)	
≤1/week	2,889 (58.1)	1,168 (52.0)	1,721 (64.9)	
2~3/week	877 (18.5)	581 (24.9)	296 (11.4)	
≥4/week	418 (8.3)	339 (13.1)	79 (2.9)	
Smoking				<0.001
Never smoker	3,490 (56.2)	579 (24.7)	2,911 (87.9)	
Ex-smoker	1,204 (20.9)	1,028 (35.9)	176 (5.8)	
Current smoker	1,098 (22.9)	919 (39.4)	182 (6.3)	
Uric acid (mg/dL)	5.09±0.02	5.83±0.03	4.36±0.02	<0.001
BMI (kg/m^2)	24.0±0.1	24.5±0.1	23.4±0.1	<0.001
Hypertension	1,909 (28.0)	938 (31.4)	971 (24.6)	<0.001
Diabetes	744 (10.8)	373 (11.6)	371 (10.0)	<0.001
Hypercholesterolemia	1,209 (19.1)	465 (18.0)	744 (20.3)	0.040
Hypertriglyceridemia	677 (16.1)	388 (22.0)	289 (10.9)	<0.001
Stroke	121 (1.6)	68 (1.9)	53 (1.3)	0.003
Myocardial infarction or angina	165 (2.2)	94 (2.7)	71 (1.7)	0.012
Number of MetS components				<0.001
0	1,291 (21.9)	448 (17.4)	843 (25.4)	
1	1,225 (20.8)	546 (21.3)	679 (20.5)	
2	1,196 (20.3)	573 (22.3)	623 (18.8)	
3	965 (16.4)	496 (19.3)	469 (14.1)	
4	793 (13.5)	348 (13.6)	445 (13.4)	
5	417 (7.1)	157 (6.1)	260 (7.8)	
MetS	2,175 (36.9)	1,001 (39.0)	1,174 (35.4)	0.004

Values are presented as mean±standard deviationor unweighted n (weighted %). BMI: body mass index, MetS: metabolic syndrome.

Table 2. Clinical characteristics of participants with or without hyperuricemia

Variables	Men			Women		
	Normal UA (UA < 7) (n = 2,085)	Hyperuricemia (UA ≥ 7) (n = 483)	p-value	Normal UA (UA < 6) (n = 3,088)	Hyperuricemia (UA ≥ 6) (n = 231)	p-value
Age (yr)	46.5 ± 0.4	42.6 ± 0.8	< 0.001	47.3 ± 0.5	55.1 ± 1.5	< 0.001
Income			0.088			0.211
Low	500 (25.1)	138 (30.2)		755 (25.2)	71 (30.1)	
Mid-low	529 (24.8)	109 (20.6)		771 (24.9)	59 (24.7)	
Mid-high	517 (24.2)	123 (26.7)		778 (25.2)	58 (26.7)	
High	531 (25.9)	110 (22.5)		776 (24.7)	41 (18.5)	
Education			0.043			0.003
Elementary school	321 (10.5)	48 (6.3)		737 (19.8)	83 (30.4)	
Middle school	200 (8.3)	52 (10.0)		303 (9.7)	21 (7.2)	
High school	646 (36.3)	162 (39.8)		914 (35.2)	72 (37.1)	
College graduation	807 (44.9)	191 (43.9)		1,001 (35.3)	46 (25.3)	
Marital status			0.001			0.431
Married	1,720 (74.3)	361 (64.6)		2,684 (82.0)	205 (84.7)	
Unmarried	365 (25.7)	122 (35.4)		404 (18.0)	26 (15.3)	
Region			0.374			0.040
Urban	1,669 (84.1)	397 (86.1)		2,497 (84.5)	177 (79.2)	
Rural	416 (15.9)	86 (13.9)		591 (15.5)	54 (20.8)	
Alcohol consumption			0.671			0.122
Never	261 (9.8)	57 (10.3)		558 (20.7)	52 (23.1)	
≤ 1/week	960 (52.5)	208 (50.1)		1,622 (65.2)	99 (60.8)	
2 ~ 3/week	463 (25.0)	118 (24.6)		276 (11.4)	20 (10.0)	
≥ 4/week	259 (12.7)	80 (15.0)		70 (2.7)	9 (6.1)	
Smoking			0.821			0.004
Never smoker	475 (24.4)	104 (25.8)		2,718 (88.2)	193 (84.2)	
Ex-smoker	846 (36.2)	182 (34.5)		167 (5.9)	9 (3.8)	
Current smoker	724 (39.4)	195 (39.7)		157 (5.9)	25 (12.0)	
Glucose (mg/dL)	103.4 ± 0.8	100.6 ± 0.8	0.019	97.5 ± 0.5	104.3 ± 1.8	0.001
Hemoglobin A1c	5.69 ± 0.03	5.58 ± 0.03	0.003	5.59 ± 0.02	5.86 ± 0.06	< 0.001
HDL-C (mg/dL)	48.2 ± 0.3	44.6 ± 0.6	< 0.001	55.1 ± 0.3	49.9 ± 0.9	< 0.001
Triglyceride (mg/dL)	160.5 ± 4.5	213.5 ± 16.1	0.002	114.8 ± 1.9	168.4 ± 9.4	< 0.001
WC (cm)	85.6 ± 0.2	89.4 ± 0.5	< 0.001	78.7 ± 0.2	87.1 ± 0.9	< 0.001
SBP (mmHg)	120.0 ± 0.4	122.4 ± 0.6	0.002	114.8 ± 0.4	121.6 ± 1.3	< 0.001
DBP (mmHg)	78.0 ± 0.3	80.6 ± 0.5	< 0.001	73.3 ± 0.2	74.6 ± 0.8	0.117
Number of MetS components			< 0.001			< 0.001
0	399 (22.8)	49 (11.6)		831 (30.3)	12 (6.2)	
1	469 (22.8)	77 (18.4)		655 (23.1)	24 (14.4)	
2	464 (21.9)	109 (21.1)		584 (18.4)	39 (16.7)	
3	369 (15.9)	127 (25.9)		418 (12.0)	51 (21.2)	
4	267 (12.8)	81 (16.2)		394 (11.0)	51 (19.9)	
5	117 (4.8)	40 (6.8)		206 (5.2)	54 (21.6)	
MetS	753 (32.5)	248 (48.8)	< 0.001	1,018 (28.3)	156 (62.6)	< 0.001
Classification			0.001			< 0.001
Normal range	1,110 (60.3)	256 (59.5)		2,103 (73.7)	92 (43.4)	
IFG	572 (26.9)	166 (33.6)		564 (17.2)	83 (34.4)	
Diabetes mellitus	325 (12.8)	48 (6.9)		320 (9.1)	51 (22.2)	
Classification			0.013			< 0.001
Normal range	722 (38.5)	132 (29.9)		1,634 (57.7)	63 (31.2)	
Prehypertension	615 (31.2)	148 (34.2)		603 (19.4)	43 (20.4)	
Hypertension	735 (30.3)	203 (35.9)		846 (22.9)	125 (48.4)	

Table 2. Continued

Variables	Men			Women		
	Normal UA (UA < 7) (n = 2,085)	Hyperuricemia (UA ≥ 7) (n = 483)	p-value	Normal UA (UA < 6) (n = 3,088)	Hyperuricemia (UA ≥ 6) (n = 231)	p-value
Hypercholesterolemia	380 (18.2)	85 (17.1)	0.658	673 (19.5)	71 (31.7)	< 0.001
Hypertriglyceridemia	268 (18.4)	120 (36.5)	< 0.001	242 (9.8)	47 (24.7)	< 0.001
BMI (kg/m^2)	24.26 ± 0.09	25.93 ± 0.20	< 0.001	23.22 ± 0.09	26.09 ± 0.36	< 0.001
Variable			< 0.001			< 0.001
Underweight	60 (3.0)	5 (1.1)		154 (5.8)	3 (1.2)	
Normal range	1,233 (58.1)	223 (44.9)		2,020 (67.2)	86 (38.6)	
Overweight	789 (38.9)	254 (54.1)		885 (27.0)	140 (60.1)	
Stroke	59 (2.1)	9 (1.3)	0.288	46 (1.3)	7 (2.0)	0.407
Myocardial infarction or angina	81 (2.8)	13 (1.9)	0.240	66 (1.8)	5 (1.7)	0.985

Values are presented as mean ± standard deviation or unweighted n (weighted %). UA: uric acid, HDL-C: high-density lipoprotein cholesterol, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, MetS: metabolic syndrome, IFG: impaired fasting glucose, BMI: body mass index.

≥ 130 mmHg and/or DBP ≥ 85 mmHg or drug treatment for elevated BP), and (5) hyperglycemia (fasting plasma glucose ≥ 100 mg/dL or drug treatment for elevated blood glucose).

Myocardial infarction or angina and stroke were defined in the questionnaire (question: was your myocardial infarction or angina diagnosed by a physician?) as "myocardial infarction or angina diagnosed by a physician" through a standardized interview. The questionnaire consisted of three responses (1, Yes; 2, No; 3, I have never been sick before). Participants who chose 1 (Yes) were classified as having hypertension. Each interview was conducted individually by a trained professional investigator. Height and weight were assessed using standardized techniques and equipment. Height was measured to the nearest 0.1 cm using a portable stadiometer Seca 225 (Seca, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using a GL-6000-20 (G-tech, Uijeongbu, Korea). Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). For waist circumference measurement, participants were asked to breathe out and the waist girth at the mid-point between the lower margin of ribs and the iliac crest was measured to the nearest 0.1 cm using a Seca 200 (Seca).

Statistical analyses

To reflect representative estimates of the noninstitutionalized Korean civilian population, survey sample weights were applied in all analyses. Sample weights were calculated by taking into account sampling rate, response rate, and age/sex proportions of the reference population (2005 Korean National Census registry). Clinical characteristics were analyzed according to dichotomized serum uric acid or quartiles of uric acid. Due to sex difference in uric acid level, the definition of hyperuricemia was different between men and women (> 7 mg/dL for men and > 6 mg/dL for women). To analyze the effect of uric acid on morbidity, univariable logistic regression models were computed with comorbidities as dependent variables and serum uric acid level as an independent variable. Multivariable logistic regression analyses were performed after adjusting for age, income, region, education, marriage, smoking, alcohol consumption, BMI, and estimated glomerular filtration rate (eGFR). The strength of association was estimated using odds ratio (OR) and 95% confidence intervals (95% CIs). All statistical analyses were performed using SPSS statistics version 20.0 (IBM Corp., Armonk, NY, USA). All p-values were two-sided and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the study population are summarized in Table 1. Their mean age was 46.7 years. Males accounted for 49.7%. Prevalence of hypertension, diabetes, hypertriglyceridemia, stroke, myocardial infarction or angina, and metabolic syndrome were significantly higher in men than in women. Serum uric acid was higher in men than in women. Clinical characteristics

Table 3. Clinical characteristics of women according to the menopause and uric acid

Variables	Women					
	Premenopause (n=1,715)			Menopause (n=1,598)		
	Normal UA (UA<6) (n=1,638)	Hyperuricemia (UA≥6) (n=77)	p-value	Normal UA (UA<6) (n=1,444)	Hyperuricemia (UA≥6) (n=154)	p-value
Age (yr)	36.79±0.33	36.81±1.80	0.992	62.68±0.33	66.76±0.98	<0.001
Income			0.023			0.893
Low	401 (25.1)	32 (38.6)		352 (25.0)	39 (24.7)	
Mid-low	408 (25.0)	17 (19.6)		362 (24.8)	42 (28.0)	
Mid-high	409 (25.1)	21 (31.0)		367 (25.3)	37 (23.8)	
High	415 (24.8)	7 (10.8)		360 (24.9)	34 (23.5)	
Education			0.932			0.063
Elementary school	38 (2.3)	1 (2.5)		698 (43.9)	82 (45.9)	
Middle school	52 (3.7)	3 (2.2)		251 (18.0)	18 (9.9)	
High school	593 (42.1)	29 (41.1)		320 (25.6)	43 (34.9)	
College graduation	826 (51.9)	35 (54.2)		172 (12.5)	11 (9.3)	
Marital status			0.196			0.643
Married	1,248 (70.3)	52 (61.7)		1,430 (99.1)	153 (99.4)	
Unmarried	390 (29.7)	25 (38.3)		14 (0.9)	1 (0.6)	
Region			0.032			0.808
Urban	1,390 (87.3)	56 (78.7)		1,102 (80.4)	121 (79.5)	
Rural	248 (12.7)	21 (21.3)		342 (19.6)	33 (20.5)	
Alcohol consumption			<0.001			0.589
Never	256 (16.4)	12 (12.6)		300 (28.5)	40 (31.4)	
≤1/week	998 (68.2)	37 (60.2)		622 (59.8)	62 (61.1)	
2~3/week	201 (13.1)	12 (15.0)		75 (8.2)	8 (6.1)	
≥4/week	37 (2.3)	8 (12.2)		33 (3.5)	1 (1.4)	
Smoking			<0.001			0.543
Never smoker	1,383 (85.8)	56 (76.8)		1,331 (91.6)	137 (88.7)	
Ex-smoker	125 (8.2)	4 (4.9)		41 (2.6)	5 (3.1)	
Current smoker	96 (6.0)	13 (18.3)		61 (5.8)	12 (8.2)	
Glucose (mg/dL)	93.26±0.58	95.5±1.82	0.245	103.82±0.85	109.99±0.38	0.019
Hemoglobin A1c	5.39±0.01	5.42±0.07	0.003	6.10±0.04	6.12±0.07	<0.001
HDL-C (mg/dL)	56.91±0.36	52.56±1.95	0.028	52.53±0.46	48.34±1.02	<0.001
Triglyceride (mg/dL)	100.65±1.98	169.51±19.68	0.001	135.86±3.36	167.76±8.45	0.001
WC (cm)	76.28±0.34	85.24±1.74	<0.001	82.33±0.33	88.29±0.98	<0.001
SBP (mmHg)	108.79±0.37	115.20±1.99	0.001	123.88±0.59	125.68±1.58	0.001
DBP (mmHg)	72.06±0.27	77.17±1.54	0.001	75.19±0.32	73.08±0.91	0.023
Number of MetS components			<0.001			<0.001
0	685 (43.1)	7 (11.3)		146 (11.5)	5 (3.0)	
1	430 (27.0)	16 (25.4)		223 (17.1)	8 (7.5)	
2	281 (17.0)	21 (22.1)		301 (20.4)	18 (13.3)	
3	129 (6.9)	9 (11.5)		228 (19.5)	42 (27.5)	
4	82 (4.4)	15 (14.8)		301 (20.8)	36 (23.1)	
5	31 (1.6)	9 (14.9)		175 (10.7)	45 (25.6)	
MetS	242 (12.9)	33 (41.2)	<0.001	774 (51.0)	123 (76.2)	<0.001
Classification			<0.001			<0.001
Normal range	1,304 (83.7)	44 (61.5)		796 (59.0)	48 (31.9)	
IFG	224 (12.9)	26 (34.7)		338 (23.3)	57 (34.2)	
Diabetes mellitus	63 (3.4)	5 (3.8)		257 (17.7)	46 (33.9)	

Table 3. Continued

Variables	Women					
	Premenopause (n=1,715)			Menopause (n=1,598)		
	Normal UA (UA<6) (n=1,638)	Hyperuricemia (UA≥6) (n=77)	p-value	Normal UA (UA<6) (n=1,444)	Hyperuricemia (UA≥6) (n=154)	p-value
Classification			<0.001			0.002
Normal range	1,226 (75.9)	34 (46.8)		405 (30.7)	29 (21.2)	
Prehypertension	259 (16.3)	23 (29.3)		343 (24.0)	20 (14.8)	
Hypertension	149 (7.8)	20 (23.9)		696 (45.3)	105 (64.0)	
Hypercholesterolemia	131 (7.4)	21 (29.8)	<0.001	542 (37.7)	50 (32.9)	0.350
Hypertriglyceridemia	78 (6.4)	13 (20.6)	<0.001	164 (14.7)	34 (27.3)	0.001
BMI (kg/m^2)	22.59±0.12	26.05±0.64	<0.001	24.14±0.11	26.12±0.39	<0.001
Variable			<0.001			<0.001
Underweight	122 (8.2)	2 (1.9)		32 (2.4)	1 (0.8)	
Normal range	1,134 (70.9)	27 (39.2)		885 (61.8)	59 (38.3)	
Overweight	359 (20.9)	47 (58.9)		526 (35.8)	93 (60.9)	
Stroke	5 (0.3)	0 (0)	0.077	41 (2.7)	7 (3.2)	0.717
Myocardial infarction or angina	4 (0.2)	0 (0)	0.706	62 (3.9)	5 (2.7)	0.438

Values are presented as mean±standard deviation or unweighted n (weighted %). UA: uric acid, HDL-C: high-density lipoprotein cholesterol, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, MetS: metabolic syndrome, IFG: impaired fasting glucose, BMI: body mass index.

according to the presence of hyperuricemia are shown in Table 2. The mean age of those in the hyperuricemia group was 42.6 years for men and 55.1 years for women. Participants with hyperuricemia showed higher prevalence of hypertension, metabolic syndrome, and hypertriglyceridemia than participants without hyperuricemia for both sexes. Diabetes was found more frequently in men with normal uric acid than in men with hyperuricemia. On the other hand, prevalence of diabetes was lower in women with normal uric acid than in women with hyperuricemia. Metabolic syndrome parameters were significantly higher in the hyperuricemia group than in the normal uric acid group for both sexes. Subgroup analysis was performed for women according to menopause (Table 3). Among 3,319 women, six participants who had no information about menopause were excluded. Among 3,316 women participants, 1,715 were premenopausal women and 1,598 were postmenopausal women. For postmenopausal women, the mean age was higher in the hyperuricemia group than in the normal uric acid group. However, the mean age was not significantly different between the hyperuricemia group and the normal uric acid group for premenopausal women. Hyperuricemia was associated with frequent use of alcohol and tobacco, particularly in premenopausal women. There was no association between hyperuricemia and alcohol consumption or smoking in postmenopausal women. In both premenopausal women and postmenopausal women, proportions of those with metabolic syndrome, hypertension, and obesity were higher in the hyperuricemia group than in the normal uric acid group. Proportion of diabetes was also significantly higher in the hyperuricemia group than in the normal uric acid group for both premenopausal women and premenopausal women, although the difference was greater in the postmenopausal group. For premenopausal women, proportions of those with diabetes in the normal uric acid group and the hyperuricemia group were 3.4% and 3.8%, respectively. For postmenopausal women, proportions of diabetes in the normal uric acid group and the hyperuricemia group were 17.7% and 33.9%, respectively.

Table 4 shows clinical comorbidities according to uric acid quartile. Prevalence of metabolic syndrome, hypertension, and BMI were significantly higher in the highest quartile compared to those in the lowest quartile for both sexes. Interestingly, the lowest uric acid quartile group showed the highest prevalence of diabetes in men. In contrast, the highest uric acid quartile group showed the highest prevalence of diabetes in women. Increasing uric acid concentration was associated with increasing preva-

Table 4. Clinical comorbidities according to serum uric acid quartiles

Variables	Men					Women				
	Q1 (<4.9) (n=587)	Q2 (4.9~5.7) (n=697)	Q3 (5.8~6.5) (n=606)	Q4 (≥6.6) (n=678)	p-value	Q1 (<3.7) (n=755)	Q2 (3.7~4.2) (n=832)	Q3 (4.3~4.9) (n=896)	Q4 (≥5.0) (n=836)	p-value
Glucose (mg/dL)	117.7±2.2	100.4±0.8	99.6±0.7	100.8±0.8	<0.001	97.6±1.0	96.0±0.7	97.6±1.1	100.6±0.9	0.002
Hemoglobin A1c	5.97±0.07	5.61±0.30	5.54±0.02	5.59±0.03	<0.001	5.63±0.04	5.51±0.21	5.59±0.03	5.71±0.03	<0.001
HDL-C (mg/dL)	48.7±0.5	49.1±0.5	47.3±0.5	45.1±0.4	<0.001	56.0±0.5	56.2±0.5	54.7±0.6	52.2±0.5	<0.001
Triglyceride (mg/dL)	160.6±9.8	146.0±5.0	162.6±5.7	210.8±13.8	<0.001	101.3±2.4	107.1±3.4	116.8±3.4	147.6±4.7	<0.001
WC (cm)	85.0±0.4	84.6±0.3	86.4±0.3	89.0±0.4	<0.001	77.2±0.41	77.6±0.4	79.1±0.4	83.0±0.5	<0.001
SBP (mmHg)	121.1±0.7	120.2±0.5	118.8±0.7	121.6±0.5	0.009	114.6±0.7	113.2±0.6	115.3±0.6	118.3±0.7	<0.001
DBP (mmHg)	77.7±0.4	78.2±0.3	78.0±0.5	79.9±0.5	0.006	72.5±0.3	72.5±0.4	73.7±0.3	74.7±0.4	<0.001
Number of MetS components					<0.001					<0.001
0	111 (18.9)	148 (21.2)	114 (18.8)	75 (11.1)		240 (34.0)	264 (35.1)	220 (28.5)	119 (16.3)	
1	127 (21.6)	145 (20.8)	149 (24.6)	125 (18.4)		176 (25.7)	184 (23.4)	191 (23.3)	128 (17.4)	
2	140 (23.9)	166 (23.8)	113 (18.6)	154 (22.7)		146 (18.7)	158 (19.0)	180 (17.8)	139 (17.3)	
3	102 (17.4)	121 (17.4)	113 (18.7)	160 (23.6)		82 (8.8)	104 (10.3)	127 (14.2)	156 (18.5)	
4	73 (12.4)	83 (11.9)	83 (13.7)	109 (16.1)		72 (9.0)	78 (8.5)	123 (11.1)	172 (18.0)	
5	34 (5.8)	34 (4.9)	34 (5.6)	55 (8.1)		39 (3.8)	44 (3.7)	55 (5.1)	122 (12.5)	
MetS	209 (34.9)	238 (29.3)	230 (33.1)	324 (44.9)	<0.001	193 (21.5)	226 (22.5)	305 (30.1)	450 (47.8)	<0.001
Classification					<0.001					<0.001
Normal range	272 (52.8)	385 (62.7)	346 (63.3)	363 (60.8)		535 (74.9)	596 (78.6)	617 (74.3)	447 (59.3)	
IFG	146 (25.6)	191 (26.6)	171 (28.2)	230 (32.0)		125 (15.6)	136 (15.2)	159 (17.0)	227 (25.3)	
Diabetes mellitus	144 (21.6)	97 (10.7)	66 (8.5)	66 (7.2)		73 (9.5)	67 (6.2)	88 (8.7)	140 (15.4)	
Classification					0.029					<0.001
Normal range	192 (34.9)	245 (39.9)	218 (40.4)	200 (32.2)		417 (58.8)	494 (65.1)	459 (56.3)	327 (43.4)	
Prehypertension	165 (31.0)	202 (29.7)	188 (33.2)	208 (33.4)		153 (20.8)	138 (16.0)	187 (20.7)	168 (20.4)	
Hypertension	226 (34.1)	248 (30.4)	195 (26.4)	269 (34.4)		184 (20.4)	197 (18.9)	249 (23.0)	341 (36.2)	
Hypercholesterolemia	122 (21.4)	116 (17.2)	105 (15.8)	122 (17.9)	0.215	143 (17.2)	171 (18.0)	194 (19.3)	236 (26.7)	<0.001
Hypertriglyceridemia	55 (16.2)	82 (16.2)	94 (20.5)	157 (33.6)	<0.001	36 (6.0)	60 (9.0)	62 (9.0)	131 (18.6)	<0.001
BMI	23.9±0.1	23.9±0.1	24.6±0.1	25.6±0.1	<0.001	22.6±0.1	22.8±0.1	23.3±0.1	24.7±0.1	<0.001
Classification					<0.001					<0.001
Underweight	27 (3.8)	19 (3.0)	9 (2.2)	10 (1.5)		44 (6.1)	38 (5.0)	46 (6.7)	29 (4.3)	
Normal range	377 (61.0)	423 (61.9)	337 (54.9)	319 (45.3)		540 (74.4)	577 (72.1)	584 (65.9)	405 (49.4)	
Overweight	181 (35.2)	254 (35.1)	260 (42.9)	348 (53.2)		156 (19.5)	206 (22.9)	263 (27.4)	400 (46.3)	
Stroke	23 (3.2)	19 (1.9)	14 (1.4)	12 (1.3)	0.385	6 (0.9)	8 (0.8)	17 (1.2)	22 (2.3)	0.239
Myocardial infarction or angina	29 (3.9)	28 (2.8)	20 (2.3)	17 (1.8)	0.165	16 (2.1)	18 (1.6)	19 (1.8)	18 (1.4)	0.727

Values are presented as mean±standard deviation or unweighted n (weighted %). HDL-C: high-density lipoprotein cholesterol, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, MetS: metabolic syndrome, IFG: impaired fasting glucose, BMI: body mass index.

Table 5. Clinical comorbidities of women according to menopause and serum uric acid quartiles

Variables	Women									
	Premenopause (n=1,715)					Postmenopause (n=1,598)				
	Q1 (<3.7) (n=404)	Q2 (3.7~4.2) (n=473)	Q3 (4.3~4.9) (n=469)	Q4 (≥5.0) (n=369)	p-value	Q1 (<3.7) (n=351)	Q2 (3.7~4.2) (n=358)	Q3 (4.3~4.9) (n=423)	Q4 (≥5.0) (n=466)	p-value
Glucose (mg/dL)	93.66±1.1	92.28±0.7	93.8±1.4	93.8±0.9	0.480	103.5±1.9	102.4±1.5	103.2±1.5	107.7±1.3	0.031
Hemoglobin A1c	5.43±0.04	5.34±0.02	5.40±0.05	5.38±0.03	0.157	5.9±0.07	5.79±0.05	5.87±0.04	6.05±0.04	<0.001
HDL-C (mg/dL)	57.2±0.7	57.6±0.7	56.8±0.6	55.0±0.9	0.148	54.3±0.7	53.9±0.8	51.8±1.1	49.3±0.6	<0.001
Triglyceride (mg/dL)	92.3±3.2	93.8±3.5	103.2±3.6	129.5±6.1	<0.001	114.5±3.4	129.9±6.0	137.0±6.6	166.6±7.0	<0.001
WC (cm)	75.4±0.5	75.4±0.5	76.6±0.6	79.8±0.7	<0.001	80.1±0.6	81.4±0.5	82.7±0.6	86.4±0.6	<0.001
SBP (mmHg)	108.2±0.7	107.3±0.6	109.6±0.6	111.6±0.9	<0.001	123.9±1.2	123.2±1.2	123.6±1.0	125.2±0.9	0.437
DBP (mmHg)	71.3±0.5	71.0±0.4	72.6±0.5	74.6±0.6	<0.001	74.3±0.6	75.2±0.7	75.4±0.6	75.0±0.5	0.524
Number of MetS components					<0.001					<0.001
0	191 (46.7)	217 (47.3)	184 (41.0)	100 (30.0)		49 (15.4)	47 (14.3)	36 (10.6)	19 (4.4)	
1	108 (29.2)	125 (27.1)	129 (27.8)	84 (23.5)		68 (20.8)	59 (17.3)	61 (17.0)	43 (11.0)	
2	62 (14.6)	74 (16.1)	86 (17.2)	80 (21.6)		84 (24.9)	84 (24.0)	92 (18.6)	59 (13.2)	
3	23 (5.0)	37 (5.9)	41 (8.2)	37 (9.3)		59 (14.2)	67 (17.8)	85 (22.0)	119 (25.3)	
4	15 (3.5)	16 (3.0)	18 (3.7)	48 (10.2)		57 (16.9)	61 (17.7)	105 (22.1)	124 (26.0)	
5	5 (1.0)	4 (0.6)	11 (2.1)	20 (5.4)		34 (7.8)	40 (8.9)	44 (9.7)	102 (20.1)	
MetS	43 (9.6)	57 (9.6)	70 (14.0)	105 (25.0)	<0.001	150 (38.9)	168 (44.4)	234 (53.8)	345 (71.3)	<0.001
Classification					0.017					<0.001
Normal range	321 (83.5)	388 (86.0)	376 (84.0)	263 (76.3)		214 (62.5)	208 (65.8)	239 (59.6)	183 (41.2)	
IFG	57 (12.3)	57 (12.0)	60 (12.7)	76 (19.5)		68 (20.3)	79 (20.8)	97 (23.2)	151 (31.5)	
Diabetes mellitus	16 (4.2)	13 (2.0)	17 (3.3)	22 (4.2)		60 (17.2)	54 (13.4)	71 (17.2)	118 (27.3)	
Classification					<0.001					<0.001
Normal range	313 (76.3)	380 (81.9)	339 (73.5)	228 (65.2)		104 (33.3)	114 (36.4)	118 (31.0)	98 (20.9)	
Prehypertension	57 (16.1)	60 (12.8)	89 (19.2)	76 (19.7)		96 (27.7)	78 (21.3)	97 (22.8)	92 (21.2)	
Hypertension	33 (7.6)	31 (5.3)	40 (7.3)	65 (15.1)		151 (39.0)	166 (42.3)	208 (46.2)	276 (57.9)	
Hypercholesterolemia	21 (5.8)	33 (5.5)	40 (8.2)	58 (15.0)	<0.001	122 (33.7)	138 (39.7)	154 (36.2)	178 (39.0)	0.363
Hypertriglyceridemia	11 (3.7)	20 (6.5)	19 (5.8)	40 (13.2)	0.003	25 (9.3)	40 (14.7)	43 (13.6)	90 (24.0)	<0.001
BMI	22.2±0.2	22.3±0.2	22.7±0.2	24.0±0.2	<0.001	23.2±0.2	24.0±0.2	24.2±0.2	25.6±0.2	<0.001
Classification					<0.001					<0.001
Underweight	32 (8.0)	31 (6.9)	39 (9.9)	22 (6.8)		12 (3.3)	7 (1.7)	7 (2.2)	7 (1.8)	
Normal range	300 (77.8)	343 (75.9)	316 (67.1)	200 (56.4)		240 (69.8)	233 (65.9)	267 (64.7)	204 (42.1)	
Overweight	58 (14.2)	88 (17.2)	11 (23.0)	146 (36.8)		98 (26.9)	118 (32.4)	149 (33.1)	254 (56.1)	
Stroke	1 (0.3)	2 (0.4)	0 (0)	2 (0.3)	0.629	5 (1.7)	6 (1.5)	17 (3.0)	20 (4.4)	0.088
Myocardial infarction or angina	2 (0.5)	2 (0.2)	0 (0)	0 (0)	0.306	14 (4.4)	16 (3.9)	19 (4.4)	18 (2.8)	0.619

Values are presented as mean±standard deviation or unweighted n (weighted %). HDL-C: high-density lipoprotein cholesterol, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, MetS: metabolic syndrome, IFG: impaired fasting glucose, BMI: body mass index.

Table 6. Adjusted odds ratios of comorbidities according to sex and serum uric acid level

Variables	Hyperuricemia		UA quartiles				
	OR (95% CI)	p-value	Q1	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	Trend p-value
Men							
Hypertension	1.46 (1.11～1.90)	0.006	1.00 (ref)	1.21 (0.87～1.68)	0.85 (0.59～1.22)	1.36 (0.98～1.91)	0.891
Diabetes	0.44 (0.28～0.72)	0.001	1.00 (ref)	0.54 (0.34～0.84)*	0.36 (0.22～0.59)*	0.26 (0.16～0.44)*	<0.001
Hypercholesterolemia	0.90 (0.62～1.30)	0.593	1.00 (ref)	0.89 (0.60～1.33)	0.83 (0.57～1.21)	0.91 (0.61～1.34)	0.593
Hypertriglyceridemia	2.22 (1.59～3.10)	<0.001	1.00 (ref)	1.21 (0.74～1.96)	1.46 (0.85～2.49)	2.59 (1.54～4.35)*	<0.001
Metabolic syndrome	1.81 (1.33～2.45)	<0.001	1.00 (ref)	0.98 (0.70～1.39)	1.01 (0.69～1.47)	1.61 (1.11～2.31)*	0.018
Stroke	0.50 (0.20～1.26)	0.144	1.00 (ref)	0.82 (0.38～1.78)	0.81 (0.34～1.91)	0.39 (0.14～1.07)	0.065
Myocardial infarction or angina	0.71 (0.33～1.53)	0.222	1.00 (ref)	0.82 (0.41～1.65)	0.79 (0.35～1.77)	0.61 (0.28～1.34)	0.222
Women, premenopause							
Hypertension	2.01 (0.75～5.42)	0.164	1.00 (ref)	0.65 (0.30～1.14)	0.88 (0.41～1.85)	1.69 (0.74～3.86)	0.172
Diabetes	0.32 (0.04～2.31)	0.259	1.00 (ref)	0.31 (0.10～0.96)	0.57 (0.21～1.49)	0.38 (0.11～1.27)	0.199
Hypercholesterolemia	5.51 (2.53～11.99)	<0.001	1.00 (ref)	1.11 (0.53～2.32)	1.87 (0.82～4.24)	3.21 (1.38～7.47)*	0.003
Hypertriglyceridemia	1.69 (0.61～4.71)	0.309	1.00 (ref)	1.83 (0.77～4.36)	1.74 (0.68～4.39)	3.88 (1.34～11.21)*	0.210
Metabolic syndrome	1.91 (0.76～4.82)	0.167	1.00 (ref)	1.17 (0.63～2.21)	1.86 (0.97～3.56)	2.87 (1.46～5.66)*	0.001
Women, postmenopause							
Hypertension	1.41 (0.83～2.39)	0.195	1.00 (ref)	1.10 (0.75～1.61)	1.28 (0.88～1.86)	1.43 (0.94～2.19)	0.066
Diabetes	1.50 (0.87～2.57)	0.140	1.00 (ref)	0.65 (0.42～1.03)	0.81 (0.48～1.38)	1.08 (0.68～1.72)	0.477
Hypercholesterolemia	0.61 (0.36～1.05)	0.079	1.00 (ref)	1.23 (0.86～1.74)	0.06 (0.74～1.51)	1.05 (0.71～1.54)	0.982
Hypertriglyceridemia	2.21 (1.24～3.92)	0.007	1.00 (ref)	1.74 (0.90～3.37)	1.45 (0.81～2.60)	3.52 (2.04～6.06)*	<0.001
Metabolic syndrome	1.99 (1.14～3.47)	0.016	1.00 (ref)	1.18 (0.79～1.77)	1.84 (1.18～2.86)*	2.99 (1.95～4.57)*	<0.001
Stroke	0.47 (0.12～1.83)	0.277	1.00 (ref)	0.86 (0.24～3.13)	1.42 (0.44～4.58)	1.87 (0.45～7.66)	0.287
Myocardial infarction or angina	0.22 (0.07～0.65)	0.006	1.00 (ref)	0.75 (0.29～1.97)	0.75 (0.31～1.80)	0.23 (0.08～0.65)*	0.006

Adjusted for age, income, region, education, marital status, alcohol consumption, smoking, body mass index, and eGFR. Patients were categorized according to quartiles of UA level: In men, Q1, <4.9 mg/dL; Q2, 4.9～5.7 mg/dL; Q3, 5.8～6.5 mg/dL; and Q4, ≥6.6 mg/dL. In women, Q1, <3.7 mg/dL; Q2, 3.7～4.2 mg/dL; Q3, 4.3～4.9 mg/dL; and Q4, ≥5.0 mg/dL. UA: uric acid, OR: odds ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate. *p<0.05.

lence of metabolic syndrome, hypertension, and diabetes regardless of menopause (Table 5). In postmenopausal women, increasing uric acid concentration was significantly associated with increasing glucose and hemoglobin A1c levels, whereas there was no significant association between uric acid and glucose or hemoglobin A1c in the premenopausal group.

ORs and 95% CIs of comorbidities after adjusting for age, socioeconomic characteristics, and eGFR in men are shown in Table 6. In men, hyperuricemia was significantly associated with a reduced prevalence of diabetes. Hyperuricemia was significantly associated with increased prevalence of hypertriglyceridemia. In women, hyperuricemia was significantly associated with increased prevalence of hypertriglyceridemia (OR: 2.12, 95% CI: 1.33～3.38, p=0.002) and metabolic syndrome (OR: 1.95, 95% CI: 1.22～3.13, p=0.006) after adjusting for age, socioeconomic characteristics, and eGFR. Hyperuricemia was negatively associated with the prevalence of myocardial infarction or angina (OR: 0.25, 95% CI: 0.08～0.75, p=0.013) in women. However, diabetes was not significantly associated with uric acid after adjustment (OR: 1.25, 95% CI: 0.72～2.18, p=0.418) in women. When analysis was performed according to menopause, higher uric acid concentration was significantly associated with a reduced prevalence of myocardial infarction or angina in postmenopausal women. In premenopausal women, stroke, myocardial infarction, and angina could not be estimated due to a small number of patients. Increasing uric acid concentration was significantly associated with hypercholesterolemia in premenopausal women, whereas increasing uric acid concentration was significantly associated with hypertriglyceridemia in postmenopausal women. In both sexes, increasing uric acid concentration was significantly associated with increased prevalence of metabolic syndrome.

DISCUSSION

The association of serum uric acid and cardiovascular risk was investigated in the present study. Results showed that hyperuricemia was associated with an increased prevalence of metabolic syndrome in both sexes. Hyperuricemia was associated with a decreased prevalence of diabetes in men. Myocardial infarction or angina was negatively associated with uric acid in women. Associations of hyperuricemia with obesity, insulin resistance, and type 2 diabetes have been reported previously [3]. It has been found that hyperuricemia contributes to insulin resistance by various mechanisms. Uric acid might cause direct oxidative stress on pancreatic islet cells and result in islet cell dysfunction [19]. It can also cause mitochondrial dysfunction in the liver by oxidative stress [20]. Uric acid can induce adipose tissue inflammation and result in decreased production of adiponectin [21]. However, studies on the association between type 2 diabetes and serum uric acid level have shown conflicting results. The current study found that serum uric acid was negatively associated with the prevalence of diabetes in men. These results correspond to those of a previous study reporting that subjects with the 3rd and the 4th quartiles of uric acid level had significantly lower prevalence of diabetes compared to those with the 1st quartile of uric acid level in Japanese men [14]. In Austrian men, serum uric acid was negatively correlated with fasting glucose level [22].

Inverse association between diabetes and hyperuricemia can be explained by uricosuric effect of glycosuria. Uricosuric effect of glycosuria occurs when blood glucose level is greater than approximately 10 mmol/L (180 mg/dL) [23]. Osmotic diuresis caused by glycosuria might enhance uric acid excretion. Uric acid is filtered in the glomerulus. Approximately 90% of uric acid is reabsorbed in the proximal renal tubule. Insulin resistance might enhance renal sodium retention, decrease urinary uric acid clearance, and increase serum uric acid concentration [24]. However, glucose competitively inhibits uric acid reabsorption at the same proximal tubule in diabetic individuals, resulting in decreased serum uric acid [25]. National Health and Nutritional Examination Survey (NHANES) III in US data showed that serum uric acid levels were increased with increasing HbA1c level up to the category of 6%～6.9%, but decreased with further increasing of HbA1c level, showing a bell-shaped relation [26]. Serum uric acid has been reported to be increased in the prediabetic stage but decreased in overt diabetes [27].

In the current study, a negative association between uric acid and diabetes was not found in women. In women, the prevalence of diabetes was higher in the hyperuricemia group than in the normouricemia group. After adjusting for age, income, region, education, marital status, alcohol consumption, smoking, BMI, and eGFR, there was no significant association between diabetes and uric acid concentration in women. This finding was in line with results of previous studies. Uric acid levels were associated with insulin resistance and plasma glucose levels more strong-

ly in women than in men in a Taiwanese nondiabetic population [28]. A British primary care database study has shown that individuals with diabetes have a lower risk of gout independent of risk factors and that the inverse association between diabetes and gout is stronger in men than in women [29]. A population based cohort study in UK has shown that individuals with type 2 diabetes are at increased risk of gout and that this association is stronger in women. However, after adjusting for renal function and comorbidities, the risk disappeared in women and reversed in men [30]. The NHANES III study has reported that individuals with moderately elevated HbA1c levels (prediabetes) might be at an increased risk of hyperuricemia and gout in women, whereas those with highly elevated HbA1c levels (diabetes) might be at a lower risk of hyperuricemia and gout in men [26].

Reasons for these sex-specific differences are unclear. Sex hormone might impact uric acid metabolism [31]. Serum uric acid levels in women are lower than in men. However, uric acid levels increase around menopause. Thus, the relative physiologic impact of hyperuricemia on women might be stronger than on men [32]. A possible hypothesis for this sex difference is that the effect of glucose on uric acid reabsorption in the kidney tubule is different between men and women [30]. We performed a subgroup analysis for women according to menopause. The prevalence of diabetes was higher in the hyperuricemia group than in the normal uric acid group for both premenopausal and postmenopausal women. However, after adjusting for age, income, region, education, marital status, alcohol consumption, smoking, BMI, and eGFR, there was no significant association between diabetes and uric acid concentration in premenopausal women or menopausal women. Sex difference in the association between uric acid and diabetes cannot be fully explained by sex hormone alone. The effect of sex on the association between uric acid and diabetes clearly needs further exploration.

We found that risks of a number of metabolic syndrome components increased with increasing levels of serum uric acid, in agreement with a previous study showing that serum uric acid was positively associated with metabolic syndrome in a Chinese community population [33]. A nationwide prospective follow-up study in Taiwan has found that hyperuricemia is a significant independent risk determinant for metabolic syndrome [34]. Currently available evidence suggests that uric acid might play a role in the development of metabolic syndrome. Since serum insulin reduces renal excretion of uric acid, elevated uric acid might be a consequence of hyperinsulinemia in metabolic syndrome [35]. However, hyperuricemia has been detected prior to the development of hyperinsulinemia [36]. Hyperuricemia-induced endothelial dysfunction and direct oxidative changes in adipocytes might be mechanisms underlying the association between hyperuricemia and metabolic syndrome [37].

The current study showed that elevated uric acid concentration was associated with a decreased prevalence of myocardial infarction or angina in women participants. Previous studies have reported that uric acid and cardiovascular disease have a J-shaped relationship [38]. Extremely low levels of uric acid have been associated with endothelial dysfunction, resulting in increased cardiovascular events and all-cause deaths. Low uric acid levels have been associated with adverse clinical outcomes in patients with vasospastic angina in a Korean population [39]. Patients with Prinzmetal's angina are predominantly younger women who might not have classical cardiovascular risk factors compared to those with classic atherosclerotic myocardial infarction or angina. Although pathophysiology of variant angina is not fully understood yet, hypouricemia-induced endothelial dysfunction might result in a U-shaped relationship between uric acid and outcomes of variant angina. The protective effect of uric acid on myocardial infarction or angina in women may be partially explained by pure variant angina or mixed angina patients. However, those with the highest quartile of uric acid level showed significantly increased risk of hypertension in participants of the present study compared to those with the lowest quartile of uric acid level. Moreover, the current study showed that hyperuricemia was associated with dyslipidemia and metabolic syndrome as other risk factors for coronary artery disease in women. Previous studies have reported that women with hyperuricemia show higher incidence of atherosclerosis and cardiovascular mortality than men [40]. In the current study, the definition of myocardial infarction or angina was based on self-report whereas definitions of diabetes, metabolic syndrome, and hypertension were based on laboratory results. Additionally, the total number of premenopausal women with myocardial infarction or angina was small. Moreover, multivariable analysis was not performed for premenopausal women. Although uric acid was negatively associated with myocardial infarction or angina in postmenopausal women, these results should be cautiously applied considering these

factors.

This study had some limitations. First, the definition of myocardial infarction or angina and stroke depended on self-reported information provided by participants in an interview. Although trained researchers asked participants in face-to-face interviews, recall bias might have influenced self-reported data. Second, we could not assess medications for gout or cardiovascular diseases. Therefore, we were unable to evaluate the potential effect of medications on comorbidities or serum uric acid. Third, we could not determine causality due to the cross-sectional design of this study. The strength of this study was that we analyzed association of uric acid with cardiovascular risk factors using a nationwide representative sample of the Korean adult population after adjusting for socioeconomic and lifestyle characteristics. Our comprehensive cross-sectional data could provide additional evidence for the relationship between uric acid and cardiovascular risk factors.

CONCLUSION

Results of this study revealed that participants with hyperuricemia showed increased prevalence of metabolic syndrome. Hyperuricemia was associated with decreased prevalence of diabetes mellitus in men and decreased prevalence of myocardial infarction or angina in women. Thus, clinicians should be aware of comorbidities in patients with hyperuricemia and take appropriate preventive and management measures.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

H.J. designed this study, data collection, performed statistical analysis, and drafted the manuscript. J.E.M. collect the data, performed statistical analysis. C.H.J. designed this study and critically reviewed the manuscript.

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