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The dose-response effects of uric acid on the prevalence of metabolic syndrome and electrocardiographic left ventricular hypertrophy in healthy individuals

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Urate-lowering therapy

Abstract *Background and aim:* Hyperuricemia (HUA) is associated with the prevalence of metabolic syndrome (MetS) and cardiovascular risks in various populations. HUA is also able to induce cardiomyocyte hypertrophy in mouse models. However, the dose-response effects of serum uric acid (SUA) on the prevalence of MetS and electrocardiographic left ventricular hypertrophy (LVH) are unclear.
Methods and results: We retrospectively collected data from 18,932 individuals who underwent an annual health examination between 1/1/2016 and 12/31/2016. We excluded those with systemic diseases or missing questionnaires. The primary study endpoints were the prevalence of MetS and LVH, which were defined by the criteria for the Taiwanese population and the "SPRINT" trial. The cohort consisted of 17,913 individuals with a mean age of 31.2 years (SD 7.4) and a mean body mass index of 24.6 kg/m^2 (SD 3.6); 87.1% of the individuals were men. The prevalence rates of HUA, MetS, and LVH were 29.5%, 9.4%, and 0.32%, respectively, in the overall study population. The HUA group was predominantly male and had significantly poorer lifestyle choices and greater laboratory cardiometabolic biomarker values than did the normouricemic group. However, the frequencies of physical activity were comparable between the two groups. After adjusting for confounders, SUA was associated with MetS (OR:1.473, 95% CI:1.408–1.540, $P < 0.001$) and LVH (OR:1.301, 95% CI:1.064–1.591, $P = 0.01$).
Conclusion: We demonstrated that the dose-response effects of SUA are associated with the prevalence of MetS and electrocardiographic LVH in healthy individuals from Taiwan. Based on this evidence, future studies should investigate urate-lowering therapy and cardiovascular benefits in individuals with HUA (ClinicalTrials.gov number NCT03473951).

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Introduction

Serum uric acid (SUA) is the terminal product of purine metabolism through the oxidation–reduction reaction by xanthine oxidoreductase in humans [1]. Free radicals, such as superoxide and hydrogen peroxide, that are generated by xanthine oxidase during the electron transition induce systemic inflammatory responses and reactive oxygen species (ROS) [2]. Elevated SUA has multiple detrimental effects that decrease the viability of pancreatic beta cells by generating ROS, activating extracellular signal-regulated kinase signaling pathways [3], proliferating vascular smooth muscle cells, increasing intracellular expression of angiotensinogen mRNA [4], increasing lipid oxidation through activation of mitogen-activated protein kinases and accumulating citrate with stimulation of de novo lipogenesis by releasing citrate into the cytosol [5,6]. Therefore, the systemic inflammation and ROS induced by elevated SUA result in insulin resistance, elevated blood pressure and hypertriglyceridemia, all of which are components of metabolic syndrome (MetS).

Elevated SUA is commonly found in combination with excess purine intake, enhanced xanthine oxidoreductase activity, and decreased kidney excretion. Unhealthy dietary patterns are also related to hyperuricemia (HUA), dyslipidemia and obesity. A growing body of evidence consistently shows that HUA is strongly associated with the prevalence of MetS [7,8], but limited research on the dose-response effect of SUA on the prevalence of MetS has been performed [9]. In addition, few studies have discussed the relationship between elevated SUA and left ventricular hypertrophy (LVH) [10–12]. Therefore, the present study was conducted to investigate the dose-response effects of SUA on MetS and LVH.

Methods

Study population

Our hospital regularly performs annual health examinations for approximately twenty thousand military individuals [7]. We enrolled apparently healthy people without any known self-reported systemic diseases between January 1, 2016, and Dec 31, 2016. The major exclusion criteria included individuals who did not complete the comprehensive questionnaire and patients with systemic diseases. If an individual underwent the annual health examination twice, the results of the first examination were used. We excluded subjects who reported systemic diseases that interfered with the determination of blood pressure, fasting glucose levels, or lipid panels because these diseases can lead to an inaccurate diagnosis of MetS and LVH.

We excluded individuals with systemic diseases that caused symptoms resulting in receiving medical or surgical treatment; however, other diseases related to the study interest, such as hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, gout, and cardiovascular diseases, were not excluded. The exclusion due to systemic diseases mainly included admission within 30 days of the annual health examination due to an acute illness (N = 40); the other systemic diseases included chronic illnesses, such as overt cardiac disease, including acute myocardial infarction (N = 3), myocarditis (N = 2), protein S deficiency (N = 1), and young stroke (N = 1); endocrine diseases, including thyroid disorder (N = 26) and adrenal gland disorder (N = 1); autoimmune diseases, such as ankylosing spondylitis (N = 23), rheumatoid arthritis (N = 2), psoriasis (N = 3), and systemic lupus erythematous (N = 1); nephrotic syndrome (N = 2); glomerular nephritis (N = 1); pulmonary tuberculosis (N = 2); viral hepatitis undergoing antiviral therapy (N = 17); epilepsy (N = 13); and any malignancy (N = 23). We also excluded patients with medical histories of cardiovascular intervention, including radiofrequency ablation for cardiac arrhythmia (N = 3), aortic valve replacement (N = 3), mitral valve replacement (N = 1), aortic dissection (N = 1), coronary artery bypass surgery (N = 1), permanent pacemaker implantation (N = 1), and ventricular septum defect (N = 1).

Study protocol

The cohort was prospectively enrolled, and we retrospectively collected general data, the results of physical examinations, laboratory data, chest radiography data, and electrocardiography data from the electronic information system. Individuals with any abnormal results underwent a clinical examination at the outpatient department for safety issues and to ensure the accuracy of the data, and the study protocol was previously published (ClinicalTrials.gov number NCT03473951) [7]. We conducted the present study in accordance with the Declaration of Helsinki. Due to the low risk of the study, no informed consent was required from the study participants, and the study was approved by the Tri-service General Hospital with Institutional Review Board number TSGH 2-106-05-148.

Study definitions

Apparently healthy individuals were defined as individuals who did not have self-reported systemic diseases as reported by the study population, but individuals with medical histories of hypertension, diabetes mellitus, dyslipidemia, gout, and/or hyperuricemia were considered apparently healthy. Based on the Taiwan criteria, a MetS diagnosis must fulfill at least three of the following five criteria: 1) waist circumference greater than 90 cm in men and 80 cm in women; 2) blood pressure greater than 130/85 mm Hg or currently taking antihypertensive medication; 3) fasting glucose level of 100 mg/dl or greater or currently taking antidiabetic agents; 4) triglyceride level of 150 mg/dl or greater or currently receiving lipid lowering therapy for hypertriglyceridemia; and 5) high-density lipoprotein cholesterol of 40 mg/dl or less in men and 50 mg/dl or less in women. We replaced the criterion for waist circumference with a body mass index of 27 kg/m^2 in the definition of MetS [13].

We used the well-acknowledged definition of HUA of a serum uric acid level of 7 mg/dl or greater in men and 6 mg/dl or greater in women, which is widely used in clinical practice and in our previous study [7,14]. When the SUA level exceeds the physiological concentration of 6.8 mg/dl, urate starts to form and deposit in the joint space and kidneys [15]. We calculated estimated glomerular filtration rate by the Modification of Diet in Renal Disease study equation and creatinine clearance by Cockcroft-Gault formula. The stages of chronic kidney disease were classified as estimated glomerular filtration rate >90 ml/min/1.73 m^2 (stage I), 60–89 ml/min/1.73 m^2 (stage II), 30–59 ml/min/1.73 m^2 (stage III), 15–29 ml/min/1.73 m^2 (stage IV), and <15 ml/min/1.73 m^2 (stage V).

We used the same criteria for electrocardiographic LVH as those used in the "SPRINT" trial investigating its prognostic value [16]. LVH is defined by the Cornell voltage criteria (RaVL amplitude + SV3 amplitude) using the following sex-specific cutoff points: ≥2.2 mV in women and ≥2.8 mV in men. We also used other LVH criteria, including the Cornell voltage product ([RaVL amplitude + SV3 amplitude] × QRS duration), Sokolow-Lyon (SV1 amplitude + RV5 or V6 amplitude) LVH criteria, and the Minnesota Code ECG classification, which were used in the "SPRINT" trial in the sensitivity analyses, to ensure the accuracy of the LVH diagnosis.

Study endpoints

The primary endpoint of this study was the prevalence of MetS, and the secondary endpoint was the prevalence of electrocardiographic LVH.

Statistical analysis

We expressed continuous variables as the mean and standard deviation (SD), and categorical variables were expressed as a number or percentage. We used univariate logistic regression analyses to examine the association between the variables and the study endpoints, and we used multivariate logistic regression to investigate associations among SUA, confounders and study endpoints.

In our analysis of the primary study endpoint, we did not include waist circumference, systolic or diastolic blood pressure, fasting glucose level, total cholesterol level, high- or low-density lipoprotein cholesterol level, or triglyceride level in the statistical model as these variables are directly related to the diagnosis of MetS [7]. We performed sensitivity analyses to clarify the association between SUA and MetS regarding gender difference use of chronic medication, kidney function and the stages of chronic kidney disease. All P-values were two-tailed; $P < 0.05$ was considered significant. We performed the statistical analyses with R, version 3.4.1 (The R Project for Statistical Computing).

Results

The HUA group exhibited poorer lifestyle choices and greater comorbidities than the normouricemic group

In total, 18,967 individuals underwent annual health examinations at our hospital in 2016. We excluded 35 individuals due to repetitive examinations, 846 individuals due to missing questionnaires, and 173 individuals due to systemic diseases (the details are described in Study population). The cohort ultimately consisted of 17,913 individuals with a mean age of 31.2 years (SD 7.4) and a mean body mass index of 24.6 kg/m^2 (SD 3.6), and 87.1% of the participants were men. The HUA group was predominantly male and had a significantly greater ratio of tobacco use, alcohol consumption, and betel nut chewing than the normouricemic group, but the frequencies of physical activity were comparable between the two groups. Table 1 shows the baseline characteristics and laboratory data of the study cohort. The prevalence rates of HUA, MetS, and LVH in the overall study population were 29.5%, 9.4%, and 0.32%, respectively. Figure 1 illustrates that the prevalence of MetS increased sequentially with each one mg/dl increment in SUA.

The dose-response effect of SUA on the prevalence of MetS

The HUA group had a greater prevalence of MetS than the normouricemic group (17.5% vs. 6.0%, $P < 0.001$). SUA and HUA were both significantly associated with MetS in univariate analyses (OR: 1.626, 95% CI: 1.569–1.686, $P < 0.001$ for SUA; OR: 3.314, 95% CI: 2.993–3.670, $P < 0.001$ for HUA). In multivariate analyses, SUA and HUA were still significantly associated with MetS after adjusting for potential confounders (adjusted OR: 1.473, 95% CI: 1.408–1.540, $P < 0.001$ for SUA; adjusted OR: 2.468, 95% CI: 2.198–2.772, $P < 0.001$ for HUA). Table 2 shows the results of univariate and multivariate logistic regression analyses.

The dose-response effect of SUA on the prevalence of electrocardiographic LVH

Sixty-eight patients from our electrocardiographic database were clinically diagnosed with LVH; however, after carefully reviewing the electrocardiography data, 11 of these patients did not meet the LVH criteria used in this study. The HUA group had a greater prevalence of LVH than the normouricemic group (0.47% vs. 0.25%, $P = 0.026$). Figure 2 demonstrates the significant difference in the prevalence of LVH between the two groups.

SUA was significantly associated with LVH in univariate analysis (OR: 1.626, 95% CI: 1.569–1.686, $P < 0.001$ for SUA; OR: 1.867, 95% CI: 1.106–3.154, $P = 0.02$ for HUA); other factors significantly associated with LVH included systolic and diastolic blood pressure and histories of hypertension, cardiac arrhythmia, cardiovascular disease, and

Table 1 Baseline characteristics, laboratory data, and study outcomes among 17,913 healthy individuals.

	Overall	Normouricemia	Hyperuricemia	P value
	n = 17,913	n = 12,621	n = 5292	
Age (years)	31.2 (7.4)	31.0 (7.4)	31.5 (7.3)	<0.001
Male	15,595 (87.1)	10,480 (83.0)	5115 (96.7)	<0.001
Body mass index (kg/m^2)	24.6 (3.6)	24.0 (3.3)	26.3 (3.6)	<0.001
Waist circumference (cm)	80.2 (9.4)	78.5 (8.9)	84.3 (9.1)	<0.001
Tobacco use	3903 (21.8)	2657 (21.1)	1246 (23.5)	<0.001
Alcohol intake	3961 (22.1)	2513 (19.9)	1448 (27.4)	<0.001
Betel nut chewing	579 (3.2)	370 (2.9)	209 (3.9)	0.002
Physical activity				0.840
Never	1468 (8.2)	1040 (8.2)	428 (8.1)	
Less than once per week	4308 (24.0)	3012 (23.9)	1296 (24.5)	
1-2 times per week	6981 (39.0)	4927 (39.0)	2054 (38.8)	
More than 3 times per week	5156 (28.8)	3642 (28.9)	1514 (28.6)	
History of hypertension	382 (2.1)	214 (1.7)	168 (3.2)	<0.001
History of diabetes	59 (0.3)	46 (0.4)	13 (0.2)	0.254
History of dyslipidemia	112 (0.6)	66 (0.5)	46 (0.9)	0.008
History of virus hepatitis B or C	381 (2.1)	277 (2.2)	104 (2.0)	0.363
History of kidney disease	44 (0.2)	29 (0.2)	15 (0.3)	0.516
History of lung disease	71 (0.4)	50 (0.4)	21 (0.4)	1.000
History of gastrointestinal disease	118 (0.7)	93 (0.7)	25 (0.5)	0.057
History of cardiac arrhythmia	112 (0.6)	77 (0.6)	35 (0.7)	0.684
History of cardiovascular disease	61 (0.3)	35 (0.3)	26 (0.5)	0.032
History of gout	46 (0.3)	11 (0.1)	35 (0.7)	<0.001
Systolic blood pressure (mm Hg)	121 (13)	120 (12)	124 (13)	<0.001
Diastolic blood pressure (mm Hg)	73 (10)	72 (10)	76 (10)	<0.001
Laboratory data				
Fasting glucose (mg/dl)	93 (13)	92 (12)	94 (14)	<0.001
Serum uric acid (mg/dl)	6.3 (1.4)	5.6 (0.9)	7.9 (0.9)	<0.001
Total cholesterol (mg/dl)	178 (34)	175 (33)	186 (36)	<0.001
High-density lipoprotein-cholesterol (mg/dl)	51 (12)	52 (12)	47 (10)	<0.001
Low-density lipoprotein-cholesterol (mg/dl)	108 (30)	105 (29)	115 (32)	<0.001
Triglyceride (mg/dl)	106 (85)	96 (72)	131 (105)	<0.001
Creatinine (mg/dl)	0.9 (0.2)	0.9 (0.2)	1.0 (0.1)	<0.001
Estimated glomerular filtration rate by MDRD equation (ml/min/1.73 m^2)	104 (18)	106 (18)	99 (17)	<0.001
Creatinine Clearance by Cockcroft-Gault equation (ml/min)	122 (25)	120 (24)	125 (26)	<0.001
Normal kidney function or CKD stage I	14,115 (78.8)	10,467 (82.9)	3648 (68.9)	<0.001
CKD stage II	3770 (21.0)	2147 (17.0)	1623 (30.7)	
CKD stage III	25 (0.1)	6 (<0.1)	19 (0.4)	
CKD stage IV	2 (<0.1)	0 (0)	2 (<0.1)	
CKD stage V	1 (<0.1)	1 (<0.1)	0 (0)	
Alanine transaminase (IU/L)	25 (25)	23 (22)	32 (29)	<0.001
White blood cell count ($\times 10^3/\mu L$)	6.9 (1.7)	6.8 (1.7)	7.2 (1.7)	<0.001
Hemoglobin (g/dl)	15.2 (1.3)	15.0 (1.4)	15.5 (1.1)	<0.001
Study outcomes				
Metabolic syndrome	1687 (9.4)	760 (6.0)	927 (17.5)	<0.001
Left ventricular hypertrophy	57 (0.32)	32 (0.25)	25 (0.47)	0.026

Values were expressed as mean (standard deviation) or n (%). MDRD = Modification of Diet in Renal Disease study; CKD = chronic kidney disease.

gout, but the presence of MetS was not associated with LVH (OR: 1.132, 95% CI: 0.485–2.642, P = 0.774). In multivariate analyses, SUA was still an independent predictor of LVH (adjusted OR: 1.301, 95% CI: 1.064–1.591, P = 0.01 for SUA; adjusted OR: 1.803, 95% CI: 1.030–3.156, P = 0.039 for HUA) after adjusting for the aforementioned confounders. We also found a strong association between a medical history of gout and LVH (adjusted OR: 21.875, 95% CI: 6.036–79.277, P < 0.001) (shown in Table 2). If we excluded the individuals with histories of gout (n = 45), the association between SUA and LVH remained significant in the individuals without histories of gout (adjusted OR: 1.293, 95% CI: 1.045–1.599, P = 0.018).

In sensitivity analyses, we respectively excluded the individuals with chronic use of any medication (n = 500), urate lowering therapies (n = 44), anti-hypertensive agents (n = 221), anti-diabetic agents (n = 37), lipid-lowering therapies (n = 42), or any nutrition supplement (n = 444). The significant association did not change between SUA and the prevalence of MetS and between SUA and LVH (shown in Table 3).

We also performed another sensitivity analysis to ascertain whether the significant association were confounded by kidney function between SUA and prevalent MetS and between SUA and LVH. The significant association unchanged after we replaced creatinine by

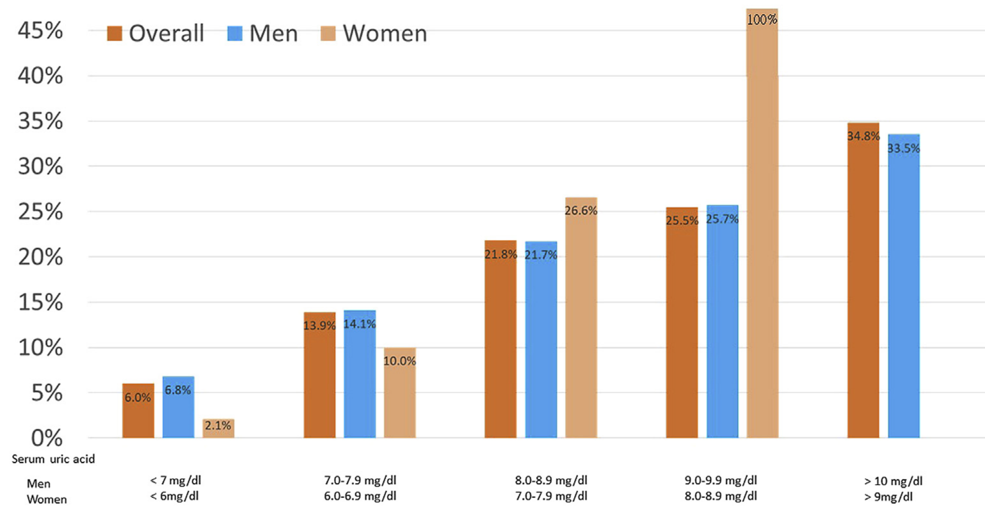

Figure 1 The prevalence of metabolic syndrome increased subsequently across the strata of each one increment of serum uric acid in the apparently healthy individuals (N = 17,932, 87.1% male). Only three women in the fourth stratum. No women had serum uric acid more than 9.0 mg/dl.

estimated glomerular filtration rate or creatinine clearance or chronic kidney disease stages, respectively (shown in Supplemental Table 1–3).

Discussion

The dose-response effect of SUA on the prevalence of LVH was demonstrated in the present study independently of a medical history of cardiovascular diseases, systolic blood pressure and other metabolic components, and kidney function. These results suggest that SUA is directly associated with LVH but not through hypertension, cardiometabolic abnormality, and chronic kidney disease. Another study also showed a similar result in which elevated SUA was associated with echocardiographic LVH independently of MetS in non-diabetic patients with essential hypertension [10]. A study conducted by Cudpidi et al. further demonstrated that elevated SUA was associated with new-onset echocardiographic LVH during a 10-year follow-up [12].

The results of our study appear to be inconsistent with those of another study showing that compared with subjects with normal SUA values and no MetS, concomitant HUA and MetS were independently associated with echocardiographic LVH [11]; this inconsistency might be related to a discrepancy in the modality of LVH. As demonstrated in our multivariate analysis, waist circumference and body mass index were both inversely associated with electrocardiographic LVH. Thus, the high electrical resistance in the obese individuals might have resulted in the underestimation of the prevalence of electrocardiographic LVH in the present study; however, echocardiographic LVH was not confounded by obesity because the wall thickness of the left ventricle was measured directly by echocardiography. In addition, the individuals in the present study were much younger and therefore had a lower prevalence of LVH than did the subjects in the study by Yu et al. Despite the conflicting results between the present study and the study by Yu et al., the dose-response effect of SUA on LVH observed in our study is still worth exploring in clinical practice because electrocardiography has the advantages of easy reproducibility, time-efficiency, and cost-effectiveness. Therefore, electrocardiography is appropriate for use for massive screenings and was used as a prognostic modality in the “SPRINT” trial [16]. Furthermore, elevated SUA was associated with ischemic alternations and cardiac arrhythmia in electrocardiography in the general population [17,18].

The association between SUA and LVH in human studies could be explained by the observation that SUA is elevated in experimental LVH through the activation of the S6 kinase-1 growth pathway in mice fed a Western diet [19]. Administration of xanthine oxidase (XO) inhibitors further prevents cardiac fibrosis in mice, which may be indirect evidence of elevated SUA and LVH. SUA serves as a surrogate biomarker of XO in individuals with normal kidney function, and elevated XO activity might be a true indicator of LVH because XO activity has been reported to be associated with the severity of heart failure [20].

The dose-response effects of elevated SUA were not only associated with the prevalence of MetS and LVH in the present study but have also been reported to be associated with the incidence of MetS [9,21]. A growing body of evidence from several systematic reviews and meta-analyses consistently shows the detrimental effects of elevated SUA on the incidence of coronary heart disease in apparently healthy populations [22]. Each one mg/dl increase in SUA doubles the risk of cardiac death in patients with suspected or definite coronary heart disease [23]. Additionally, the reported harmful effects of elevated SUA include increased mortality in patients with acute myocardial infarction regardless of receiving percutaneous coronary intervention [24]. Therefore, contemporary

Table 2 Variables associated with metabolic syndrome and left ventricular hypertrophy in univariate and multivariate logistic regression analyses.

Variables	Crude OR	95% CI		P value	Adjusted OR	95% CI		P value
Metabolic syndrome								
Age (years)	1.094	1.087	1.102	<0.001	1.095	1.086	1.104	<0.001
Male	1.094	1.087	1.102	<0.001	0.745	0.545	1.018	0.065
Tobacco use	1.724	1.545	1.924	<0.001	1.103	0.960	1.268	0.166
Alcohol intake	0.578	0.518	0.645	<0.001	0.996	0.870	1.140	0.951
Betel nut chewing	0.372	0.302	0.457	<0.001	0.558	0.433	0.720	<0.001
Physical activity	0.846	0.802	0.892	<0.001	0.851	0.799	0.906	<0.001
History of hypertension	6.419	5.188	7.942	<0.001	2.267	1.764	2.912	<0.001
History of diabetes	8.817	5.276	14.73	<0.001	3.568	1.901	6.694	<0.001
History of dyslipidemia	8.569	5.891	12.46	<0.001	3.300	2.115	5.150	<0.001
History of virus hepatitis B or C	1.827	1.381	2.418	<0.001	1.001	0.728	1.376	0.997
History of kidney disease	2.481	1.191	5.171	0.015	1.476	0.628	3.467	0.371
History of lung disease	0.728	0.293	1.809	0.494				
History of gastrointestinal disease	1.514	0.891	2.570	0.125				
History of cardiac arrhythmia	1.729	1.029	2.903	0.039	1.112	0.596	2.071	0.739
History of cardiovascular disease	3.443	1.942	6.105	<0.001	0.712	0.343	1.477	0.362
History of gout	3.412	1.763	6.601	<0.001	0.879	0.415	1.863	0.737
Serum uric acid (mg/dl)	1.626	1.569	1.686	<0.001	1.473	1.408	1.540	<0.001
Creatinine (mg/dl)	5.891	4.192	8.277	<0.001	0.736	0.475	1.140	0.170
Estimated glomerular filtration rate (ml/min/1.73 m^2)[a]	0.979	0.976	0.982	<0.001				
Creatinine clearance (ml/min)[a]	1.026	1.025	1.028	<0.001				
CKD stages[a]	2.026	1.824	2.251	<0.001				
Alanine transaminase (IU/L)	1.030	1.027	1.032	<0.001	1.018	1.016	1.021	<0.001
White blood cell count ($\times10^3/\mu L$)	1.308	1.275	1.342	<0.001	1.251	1.214	1.289	<0.001
Hemoglobin (g/dl)	1.534	1.466	1.605	<0.001	1.237	1.170	1.307	<0.001
Left ventricular hypertrophy								
Age (years)	0.992	0.957	1.028	0.659	0.980	0.942	1.019	0.309
Male	4.098	0.999	16.81	0.050	3.241	0.696	15.08	0.134
Body mass index (kg/m^2)	0.952	0.882	1.027	0.204	0.836	0.764	0.916	<0.001
Waist circumference (cm)	0.983	0.955	1.011	0.236				
Tobacco use	0.763	0.385	1.512	0.438				
Alcohol intake	0.727	0.407	1.296	0.280				
Betel nut chewing	>999	0.001	>999	0.993				
Physical activity	0.844	0.640	1.112	0.228				
History of hypertension	4.458	1.771	11.22	0.002	3.029	1.005	9.132	0.049
History of diabetes	5.480	0.746	40.25	0.095				
History of dyslipidemia	2.855	0.392	20.80	0.301				
History of virus hepatitis B or C	0.821	0.113	5.948	0.845				
History of kidney disease	0.001	<0.001	>999	0.998				
History of lung disease	0.001	<0.001	>999	0.997				
History of gastrointestinal disease	2.707	0.372	19.72	0.326				
History of cardiac arrhythmia	5.866	1.413	24.35	0.015	3.072	0.572	16.51	0.191
History of cardiovascular disease	10.969	2.615	46.01	0.001	6.457	1.171	35.61	0.032
History of gout	23.01	6.928	76.44	<0.001	21.88	6.036	79.27	<0.001
Systolic blood pressure (mm Hg)	1.033	1.014	1.052	0.001	1.042	1.007	1.079	0.019
Diastolic blood pressure (mm Hg)	1.029	1.005	1.054	0.017	0.989	0.946	1.035	0.642
Fasting glucose (mg/dl)	1.007	0.994	1.020	0.306				
Serum uric acid (mg/dl)	1.321	1.111	1.570	0.002	1.301	1.064	1.591	0.010
Total cholesterol (mg/dl)	1.006	0.999	1.013	0.109				
HDL-C (mg/dl)	1.003	0.981	1.026	0.782				
LDL-C (mg/dl)	1.007	0.998	1.015	0.118				
Triglyceride (mg/dl)	1.000	0.998	1.003	0.713				
Creatinine (mg/dl)	1.726	0.458	6.498	0.420				
Estimated glomerular filtration rate (ml/min/1.73 m^2)	1.006	0.992	1.020	0.389				
Creatinine clearance (ml/min)	0.998	0.987	1.009	0.737				
CKD stages	1.420	0.806	2.500	0.225				
Alanine transaminase (IU/L)	0.994	0.979	1.010	0.449				
White blood cell count ($\times10^3/\mu L$)	1.074	0.934	1.234	0.316				
Hemoglobin (g/dl)	1.207	0.975	1.493	0.084				
Metabolic syndrome	1.470	0.728	2.969	0.283				

OR = odds ratio; CI = confidence interval; HDL-C = High-density lipoprotein-cholesterol; LDL-C = Low-density lipoprotein-cholesterol; MDRD = Modification of Diet in Renal Disease study; CKD = chronic kidney disease.

[a] The association between serum uric acid and the prevalence of metabolic syndrome was respectively adjusted for kidney function represented by estimated glomerular filtration rate, creatinine clearance, and CKD stages in Supplemental Table 1–3.

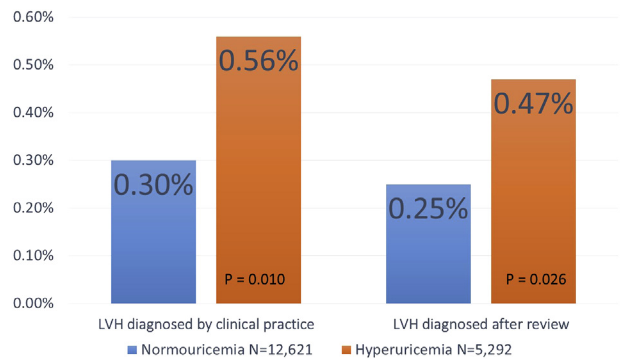

Figure 2 The prevalence of electrocardiographic LVH was significantly higher in the hyperuricemic group than in the normouricemic groups regardless of the diagnostic criteria of left ventricular hypertrophy.

guidelines may suggest SUA as a nontraditional risk factor of cardiovascular disease [25].

Urate-lowering therapies might attenuate the harmful effects of elevated SUA, including all-cause and cardiovascular mortality, in the general population based on a Taiwanese study [26], and xanthine oxidase inhibitors can reduce major adverse cardiovascular events based on a meta-analysis [27]. Another study found that the prescription of XO inhibitors was not associated with increased or decreased cardiovascular risks in gout patients [28]; a meta-analysis showed that urate-lowering therapies did not improve cardiovascular events [29]. The discrepancy in the therapeutic effect of urate-lowering therapies is possibly due to the ethnic and genetic differences among these studies. Asian patients undergoing allopurinol treatment are prone to develop a severe cutaneous skin reaction and even allopurinol-hypersensitivity-related death due to carrying the HLA-B*5801 gene [30], whereas this gene is not prevalent in Western countries. Thus, Asian patients may not benefit from allopurinol treatment due to the much higher prevalence of the HLA-B*5801 gene, which is as high as 19.6% in Taiwan [31]. It is currently unclear whether urate-lowering therapies provide cardiovascular benefits in gout patients, and it is unknown which therapies, i.e., XO inhibitors or uricosuric agents, are superior in attenuating the detrimental effects of elevated SUA on cardiovascular outcomes [32].

The present study had the strength of a large sample size with nearly no missing data, and life style choices and physical activities that induces MetS were well adjusted in our statistical analyses. We can therefore clearly and concomitantly elucidate the association of each one mg/dl increment of SUA with the prevalence of MetS and LVH; we also discussed the association in the various study subgroup, such as the individual with gender difference, normal kidney function, and medication that interfere metabolism and excretion of SUA. The comprehensive data and analysis provided more solid evidence among SUA, MetS and LVH, complementary to our previous study and

Table 3 The association between serum uric acid and the prevalence of metabolic syndrome and between serum uric acid and left ventricular hypertrophy in the overall and various study population.

Variables	N	study interest	adjusted OR	95% CI		P value
Metabolic syndrome[a]						
Overall study population	17,913	1687	1.473	1.408	1.540	<0.001
Study individuals without use of any medication	17,413	1532	1.468	1.402	1.538	<0.001
Study individuals without use of urate-lowering therapy	17,869	1668	1.476	1.411	1.544	<0.001
Study individuals without use of anti-hypertensive agents	17,692	1593	1.469	1.403	1.538	<0.001
Study individuals without use of anti-diabetic agents	17,876	1665	1.476	1.412	1.544	<0.001
Study individuals without use of lipid-lowering therapy	17,871	1670	1.475	1.411	1.542	<0.001
Study individuals without any nutrition supplement	17,469	1625	1.471	1.406	1.539	<0.001
Study individuals with male gender	15,595	1617	1.449	1.385	1.516	<0.001
Study individuals with female gender	2318	70	2.363	1.804	3.095	<0.001
Study individuals with eGFR of 60 ml/m^2/1.73 or more	17,885	1675	1.472	1.408	1.540	<0.001
Study individuals without histories of gout	17,868	1669	1.481	1.416	1.549	<0.001
Left ventricular hypertrophy[b]						
Overall study population	17,913	57	1.301	1.064	1.591	0.010
Study individuals without use of any medication	17,413	52	1.315	1.061	1.629	0.012
Study individuals without use of urate-lowering therapy	17,869	56	1.341	1.093	1.646	0.005
Study individuals without use of anti-hypertensive agents	17,692	53	1.268	1.028	1.565	0.026
Study individuals without use of anti-diabetic agents	17,876	57	1.299	1.062	1.589	0.011
Study individuals without use of lipid-lowering therapy	17,871	57	1.298	1.061	1.587	0.011
Study individuals without any nutrition supplement	17,469	55	1.309	1.069	1.603	0.009
Study individuals with male gender	15,595	55	1.314	1.073	1.608	0.008
Study individuals with female gender	2318	2	0.051	0.001	2.043	0.114
Study individuals with eGFR of 60 ml/m^2/1.73 or more	17,885	55	1.312	1.069	1.611	0.009
Study individuals without histories of gout	17,868	56	1.343	1.094	1.648	0.005
Study individuals without metabolic syndrome	16,226	51	1.262	1.016	1.568	0.035

eGFR = estimated glomerular filtration rate; OR = odds ratio; CI = confidence interval.

[a] Adjusted for age, male, tobacco use, alcohol intake, betel nut chewing, physical activity, creatinine, alanine transaminase, white blood cell, hemoglobin, histories of hypertension, histories of diabetes, histories of hyperlipidemia, histories of virus hepatitis B or C, histories of kidney disease, histories of cardiac arrhythmia, histories of cardiovascular disease, and histories of gout.

[b] Adjusted for age, male, body mass index, systolic blood pressure, diastolic blood pressure, histories of hypertension, histories of cardiac arrhythmia, histories of cardiovascular disease, and histories of gout.

others [7–12]. We also showed that the hyperuricemic women even had a greater risk of the prevalence of MetS compared with the hyperuricemic men, complementary to our previous study due to underpowered [7]. However, several limitations should be addressed. First, we may have underestimated the prevalence of smoking, alcohol intake, and betel nut use in this study as these factors were self-reported by the study individuals. Similar to the above factors, the real numbers of systemic diseases and the use of medication for systemic diseases were estimated. We used office blood pressure readings rather than automated blood pressure measurements; thus, the prevalence of prehypertension and hypertension might have been overestimated. These factors possibly contributed to the prevalence of MetS. Purine-rich foods and fructose intake from beverages with sugar increases a concentration of SUA, but we did not have dietary record in the questionnaire. The above informative bias and measurement error should be non-differential and had little chance of changing the significant associations among SUA, MetS and LVH. Second, the diagnosis of electrocardiographic LVH was clinically made by two cardiologists (the first author and third author), and non-differential errors in the voltage measurements in each lead could have occurred. We only reviewed the electrocardiography data of individuals with LVH but not the electrocardiography data of the remaining seventeen thousand individuals without LVH. We confidently believe that the impact of the misinterpretation of the prevalence of LVH should not alter the study results because all individuals with electrocardiographic abnormalities must undergo a clinical examination including a second electrocardiography at our out-patient department. Artificial intelligence may help cardiologists manage the large demand for electrocardiography, especially when massively screening hundreds of apparently healthy individuals by electrocardiography is required daily. Third, we reported the prevalence rather than the incidence of both MetS and LVH; therefore, the significant association between elevated SUA and MetS might only be related to an unhealthy dietary pattern. However, a low-purine diet might be enough to attenuate the cardiometabolic risks in hyperuricemic individuals. Although we cannot demonstrate the casual effect of elevated SUA on the incidence of MetS in the present study, we intend to extend the present study with a longitudinal follow-up to elucidate the casual relationship among elevated SUA and the incidences of MetS, LVH, and even cardiovascular events.

In conclusion, we demonstrated that the dose-response effects of SUA were associated with the prevalence of MetS and electrocardiographic LVH in healthy individuals from Taiwan. These results demonstrate the need for future studies to investigate urate-lowering therapy and cardiovascular benefits in individuals with HUA.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2018.10.001.

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