Sex-specific association of hyperuricemia with cardiometabolic abnormalities in a military cohort
The CHIEF study

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Abstract

Hyperuricemia has been associated with metabolic syndrome, and the association with various cardiometabolic risk factors may be affected by sex.

We made a cross-sectional examination in a military cohort of 6738 men and 766 women, aged 18 to 50 years of Taiwan in 2013 to 2014. Hyperuricemia were defined as serum uric acid levels ≥ 7.0 mg/dL for men and ≥ 5.7 mg/dL for women, respectively. Multivariable logistic regression analyses were used to determine the associations between hyperuricemia and various metabolic abnormalities.

In the overall population, hyperuricemia was associated with high blood pressure (odds ratio [OR]: 1.59, and 95% confidence intervals: 1.42–1.77), low high-density lipoprotein (OR: 1.75, 1.56–1.97), high triglycerides (OR: 2.14, 1.90–2.42), high low-density lipoprotein (OR: 1.71, 1.51–1.93), high fasting plasma glucose (OR: 1.29, 1.13–1.48), and central obesity (OR: 2.85, 2.55–3.18) after adjusting for age and serum creatinine concentrations. However, the associations with atherogenic lipid profiles including high triglycerides and high low-density lipoprotein were merely significant in men but not in women. In addition, there was a tendency for a sex difference in the association of hyperuricemia and raised blood pressure $\geq 130/85$ mm Hg, which was greater in women than that in men (OR: 2.92, 1.37–6.25 and 1.54, 1.37–1.72, respectively; P for interaction = .059).

Our findings suggest that the association between hyperuricemia and various cardiometabolic abnormalities in young adults may differ by sex, possibly due to a regulation of sex hormones and uneven effects of uric acid at the same levels between sexes on lipid metabolisms and arterial stiffness.

Abbreviations: ANOVA = analysis of variance, CHIEF = cardiorespiratory fitness and hospitalization events in armed forces, OR = odds ratio, SD = standard deviation, SUA = serum uric acid.

Keywords: Arterial stiffness, cardiometabolic risk factors, hyperuricemia, sex difference

1. Introduction

Metabolic syndrome is characterized by presence of several cardiometabolic risk factors including central obesity, hyperglycemia, elevated blood pressure, elevated triglycerides, and decreased high density-lipoprotein cholesterol.[1,2] The prevalence of metabolic syndrome is increased largely with the obesity pandemic and affects 20% to 30% of the adult populations in most countries.[3,4] Previous studies have shown that metabolic syndrome is associated with the occurrence of type 2 diabetes,

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cardiovascular disease, and overall mortality.[2,5,6] Many unhealthy behaviors such as intake of cholesterol-rich foods, sedentary status, and tobacco smoking can result in these cardiometabolic abnormalities of the general populations. Rising epidemics of metabolic syndrome, particularly in young adults, is posing serious public health burden, and socioeconomic hazards.[7]

Uric acid is a final enzymatic product of purine metabolism. Elevated serum uric acid (SUA) concentrations, also referred as hyperuricemia, mostly comes from high intake of purine-rich foods or is due to reduced urinary excretion.[8] Uric acid, partly produced by vascular endothelium has been considered to be an antioxidant with anti-atherosclerotic effect in plasma.[9] In contrast, higher SUA concentrations may stimulate the production of aminocarbonyl radicals which have proinflammatory effects on vascular smooth muscle cells, leading to arterial stiffness and insulin resistance.[10,11] In fact, in addition to being the primary risk factor of gout flares,[12] high SUA concentrations are associated with other metabolic disorders including metabolic syndrome, non-alcoholic fatty liver disease and type 2 diabetes.[10,11,13]

Epidemiologic reports have shown that the incidence of both metabolic syndrome and hyperuricemia increase with aging. Many metabolic disorders such as obesity, dyslipidemia, and diabetes and the related comorbidities including hypertensive cardiovascular disease and chronic kidney disease are frequent among middle-to-old age individuals, especially in postmenopausal women.[14] Lack of estrogen, a dominant female sex hormone, may play a key role in the development of metabolic syndrome in women. In addition, postmenopausal women on sex hormone replacement therapy had lower SUA concentrations and lower risk of gout flare than those who did not take hormone replacement therapy.[15] This provides a basis regarding sex hormone mediated pathogenesis between hyperuricemia and metabolic syndrome in middle-to-old age individuals. However, the association in young adults is unclear. Therefore, we aimed to examine the association of hyperuricemia with cardiometabolic risk factors by sex in a military cohort of primarily young men and women.

2. Methods

2.1. Study population

There were 9076 military participants enrolled in the cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) study between January 2013 and December 2014. Participants who had missing relevant data were further excluded, leaving a sample of 7504 subjects for the present analysis. Of these, 6738 were men and 766 were women, aged between 18 and 50 years. The research design has been described in detail previously.[16–21] All participants received regular annual health examination in Hualien Armed Forces General Hospital of Taiwan. Each participant was asked to self-report a questionnaire including demographic factors, medical history, first-, second-, and third-degree relatives' family history, cigarette smoking habits, alcohol consumption status and betel nut chewing status. Body height, weight, waist circumference, and blood pressure were measured by standardized protocols. Physical examinations and face-to-face interviews were made by experienced nurses and physicians. Height was measured in meters (without shoes), and weight was measured in kilograms (with heavy clothing removed and 1 kg deducted for remaining

garments). Body mass index was calculated as weight in kilograms divided by the square of height in meters. Obesity, overweight, normal-weight, and underweight were defined by a body mass index ≥ 30, 25–29.9, 18.5–24.9, and $<18.5\,kg/m^2$, respectively. Waist circumference was measured midway between the lower rib margin and iliac crest at standing position. Hemodynamic status of pulse rate and blood pressures were automatically measured once by the blood pressure monitor (Parama-Tech Co., Ltd, Fukuoka, Japan) over the right upper arm at sitting position, after taking a rest for at least 15 min. Overnight fasting blood specimens were collected to measure concentrations of fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and SUA. All these biochemical metabolic markers were analyzed enzymatically on an Olympus AU640 auto analyzer (Olympus, Kobe, Japan).

2.2. Definition of hyperuricemia

Participants were diagnosed with hyperuricemia if their SUA concentrations were $>7.0\,mg/dL$ in men or $>5.7\,mg/dL$ in women according to the criteria of the U.S. National Health and Nutrition Examination Survey.[22] The SUA levels of subjects were categorized into four levels using the quartiles (P25, P50, and P75) as cut-off values quartiles for both sexes. In this study, sex-specific SUA quartiles for subjects were as follows: Q1: <5.9 mg/dL (n = 1583), Q2: 5.9–6.6 mg/dL (n = 1717), Q3: 6.7–7.5 mg/dL (n = 1718), and Q4: >7.5 mg/dL (n = 1720) in men; Q1: <4.1 mg/dL (n = 170), Q2: 4.1–4.6 mg/dL (n = 209), Q3: 4.7–5.2 mg/dL (n = 180), and Q4: ≥ 5.2 mg/dL (n = 207) in women.

2.3. Definition of cardiometabolic risk factors

Metabolic syndrome was diagnosed as the existence of three or more of the following features:

1. central obesity: waist size $\geq 90\,cm$ in men and $\geq 80\,cm$ in women (ethnic-specifically for Han Chinese);
2. raised serum triglycerides $\geq 150\,mg/dL$ or on lipid-lowering therapy;
3. low high-density lipoprotein cholesterol $<40\,mg/dL$ in men and $<50\,mg/dL$ in women;
4. elevated systolic blood pressures $\geq 130\,mm\,Hg$ and/or diastolic blood pressure $\geq 85\,mm\,Hg$ or on antihypertensive therapy;
5. high fasting plasma glucose $\geq 100\,mg/dL$ or on antidiabetic therapy, according to an updated clinical criteria of International Diabetes Federation.[23]

Other metabolic risk factors including blood pressures $\geq 140/90\,mm\,Hg$ and low-density lipoprotein cholesterol $\geq 160\,mg/dL$ with or without medical therapy were defined as hypertension and hyper-cholesterolemia, respectively. This study protocol was approved by the Institutional Review Broad of Mennonite Christian Hospital (No. 16-05-008) in Taiwan and written informed consent was obtained from all participants.

2.4. Data analysis

The baseline characteristics were expressed as mean $\pm$ standard deviation (SD) for continuous variables, and absolute and relative numbers for categorical variables. For continuous variables, we used the independent samples t test to compare the means between men and women. Wilcoxon signed rank test was used

Table 1

Characteristics of the study participants by sex.

Characteristics	Total (n = 7504)	Women (n = 766)	Men (n = 6738)	P^*
Age, years	28.93 ± 6.04	28.03 ± 6.61	29.03 ± 5.97	<.0001
Service specialty, %				
Air force	113 (1.51)	8 (1.04)	105 (1.56)	<.0001
Army	5909 (78.74)	655 (85.51)	5254 (77.98)	
Navy	1482 (19.75)	103 (13.45)	1379 (20.47)	
BMI, kg/m^2	24.96 ± 3.72	22.59 ± 3.11	25.23 ± 3.69	<.0001
Normal weight, %	4043 (53.88)	605 (78.91)	3438 (51.02)	<.0001
Overweight, %	2802 (37.34)	144 (18.80)	2658 (39.45)	
Obesity, %	659 (8.78)	17 (2.22)	642 (9.53)	
Current smoking, %	2537 (33.81)	78 (10.18)	2459 (36.49)	<.0001
Current alcohol intake, %	3391 (45.19)	167 (21.80)	3224 (47.85)	<.0001
WC, cm	83.44 ± 9.67	73.73 ± 8.06	84.54 ± 9.21	<.0001
High WC, %	2071 (27.60)	179 (23.37)	1892 (28.08)	.0055
BP ≥140/90 mm Hg, %	679 (9.05)	14 (1.83)	665 (9.87)	<.0001
BP ≥130/85 mm Hg, %	1922 (25.61)	46 (6.01)	1876 (27.84)	<.0001
FPG, mg/dL	92.07 ± 13.93	88.31 ± 10.30	92.49 ± 14.22	<.0001
High FPG, %	1083 (14.43)	40 (5.22)	1043 (15.48)	<.0001
Serum creatinine, mg/dL	0.94 ± 0.14	0.69 ± 0.10	0.96 ± 0.12	<.0001
Total cholesterol, mg/dL	174.08 ± 33.75	168.41 ± 29.87	174.72 ± 34.10	<.0001
TG, mg/dL	113.60 ± 94.26	79.03 ± 43.81	117.53 ± 97.60	<.0001
High TG, %	1497 (19.95)	47 (6.14)	1450 (21.52)	<.0001
HDL-C, mg/dL	48.73 ± 10.42	57.01 ± 11.04	47.79 ± 9.92	<.0001
Low HDL-C, %	1588 (21.16)	199 (25.98)	1389 (20.61)	.0008
LDL-C, mg/dL	106.00 ± 29.81	95.22 ± 25.44	107.23 ± 30.03	<.0001
High LDL-C, %	1453 (19.36)	108 (14.10)	1345 (19.96)	<.0001
Metabolic syndrome, %	1019 (13.58)	3 1 (4.05)	988 (14.66)	<.0001

Data is presented as means ± standard deviations (SD) or percentages (%).BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference; Metabolic syndrome was defined as the presence of three or more of the following indexes: WC ≥90 or ≥80 cm in men and women, respectively; BP ≥130/85 mm Hg or on antihypertensive therapy; TG ≥150 mg/dL or on lipid-lowering therapy; HDL-C <40 or <50 mg/dL in men and women, respectively or on lipid-lowering therapy; and FPG ≥100 mg/dL or on antidiabetic therapy.

* Independent samples *t* test was used to compare the means of continuous variables between men and women. Chi square test was used for categorical variables.

once the normality test, Kolmogorov–Smirnov test, was not fulfilled. In addition, the categorical variables were compared by chi square test. The Analysis of Variance (ANOVA) test for trend analysis was used to determine the characteristics of cardiometabolic risk factors according to SUA quartiles adjusted for age in both sexes. Finally, multivariable logistic regressions were used to determine the associations between hyperuricemia and various cardio-metabolic risk factors. In model 1, age was adjusted. In model 2, serum creatinine was additionally adjusted. Formal testing for interactions between men and women was performed. All data analyses were carried out with SAS statistical software (version 9.4, SAS Institute Inc, Cary, NC).

3. Results

3.1. Descriptive characteristics and Sex differences

The baseline characteristics of both sexes are displayed in Table 1. Men had higher serum creatinine concentrations and higher prevalent alcohol intake and cardiometabolic abnormalities compared with women. Table 2 shows that the prevalence of hyperuricemia in men was three times higher than that in women. The mean SUA in men was also higher than that in women. In addition, the mean SUA and prevalence of hyperuricemia in both sexes were constant in every 6-year intervals from 18 to 50 years of age. In contrast, the prevalence of metabolic syndrome and related components increased with

older ages in both men and women. Figure 1 demonstrates the distribution of SUA concentrations against frequency in men and women, respectively.

Table 3 shows the results of linear trend analyses after controlling for age. In men, an increase in body mass index, waist circumference, blood pressure, serum creatinine, total cholesterol, triglycerides, low-density lipoprotein, and a decrease in high-density lipoprotein cholesterol were found in parallel with an increase in SUA concentrations. In women, a similar trend was observed in body mass index, waist circumference, serum creatinine and blood pressure, but not seen in the lipid profile except high-density lipoprotein cholesterol concentrations. No correlation was found between SUA and fasting plasma glucose concentrations in both men and women.

3.2. Hyperuricemia with various cardiometabolic risk factors and sex differences

Table 4 reveals the results of multivariable logistic regression analyses for the overall cohort and between men and women. In the overall population, as compared with normal SUA, hyperuricemia was associated with higher risk of abdominal obesity, elevated blood pressure, high low-density lipoprotein cholesterol, high serum triglycerides, low high-density lipoprotein cholesterol, fasting plasma glucose, and metabolic syndrome in model 1 (odds ratios [OR]: 2.66, 1.54, 1.73, 2.05, 1.73, 1.29, and 2.51, respectively) and model 2 (OR: 2.85, 1.55, 1.71, 2.11,

Table 2

Sex-specific mean serum uric acid levels and prevalence of hyperuricemia, metabolic syndrome and related components stratified by age categories.

Age category, years	Mean SUA (95% CI)	High SUA, %	Obesity, %	High BP, %	High TG, %	Low HDL, %	High FPG, %	MetS, %
Men = 6738								
18–23 (n=1382)	6.77 (6.70–6.83)	526 (38.06)	220 (15.92)	297 (21.49)	125 (9.04)	242 (17.51)	121 (8.76)	89 (6.44)
24–29 (n=2105)	6.75 (6.70–6.81)	776 (36.86)	507 (24.09)	524 (24.89)	315 (14.96)	390 (18.53)	272 (12.92)	218 (10.36)
30–35 (n=2228)	6.83 (6.77–6.89)	875 (39.27)	783 (35.14)	677 (30.39)	670 (30.07)	490 (21.99)	398 (17.86)	423 (18.99)
36–41 (n=887)	6.79 (6.70–6.89)	360 (40.59)	337 (37.99)	314 (35.40)	294 (33.15)	232 (26.16)	208 (23.45)	222 (25.03)
42–50 (n=136)	6.86 (6.64–7.09)	51 (37.50)	45 (33.09)	64 (47.06)	46 (33.82)	35 (25.74)	44 (32.35)	36 (26.47)
Women = 766								
18–23 (n=197)	4.91 (4.79–5.03)	26 (13.20)	28 (14.21)	5 (2.54)	5 (2.54)	46 (23.35)	4 (2.03)	2 (1.02)
24–29 (n=306)	4.70 (4.60–4.80)	35 (11.44)	69 (22.55)	9 (2.94)	19 (6.21)	81 (26.47)	15 (4.90)	8 (2.61)
30–35 (n=122)	4.66 (4.50–4.81)	12 (9.84)	36 (29.51)	7 (5.74)	11 (9.02)	25 (20.49)	8 (6.56)	7 (5.74)
36–41 (n=117)	4.59 (4.41–4.76)	14 (11.97)	40 (34.19)	17 (14.53)	10 (8.55)	37 (31.62)	11 (9.40)	11 (9.40)
42–50 (n=24)	4.54 (3.99–5.10)	3 (12.50)	6 (25.00)	8 (17.39)	2 (8.33)	10 (41.67)	2 (8.33)	3 (12.50)

BP = blood pressure; CI = confidence interval; FPG = fasting plasma glucose; HDL = serum high-density lipoprotein; MetS = metabolic syndrome; SUA = serum uric acid; TG = serum triglycerides.
Definitions: (1) High SUA: SUA concentrations >7.0 mg/dL in men or >5.7 mg/dL in women; (2) obesity (central): waist circumference ≥90 cm in men and ≥80 cm in women; (3) high TG: fasting serum triglycerides concentrations ≥150 mg/dL or on lipid-lowering therapy; (4) low HDL: HDL concentrations <40 mg/dL in men and <50 mg/dL in women; (5) high BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg or on antihypertensive therapy; (6) high FPG: FPG concentrations ≥100 mg/dL or on antidiabetic therapy. MetS was defined as the existence of three or more of the features (2) to (6).

1.77, 1.28, and 2.61, respectively). The results for men were consistent with that for the overall cohort. Notably, although the associations with fasting plasma glucose were significant in men and the overall cohort, probably due to a large sample size, the degree was very modest. However, the results for women show that hyperuricemia was not associated with high serum triglycerides, low-density lipoprotein cholesterol and fasting plasma glucose in model 1 (OR: 1.37, 1.19, and 1.70, respectively) and model 2. In addition, there tended to be a sex difference merely in the association between hyperuricemia and raised blood pressure ≥130/85 mmHg (OR: 1.51 for men and 3.37 for women, P-for-interaction = .059) or hypertension (OR: 1.52 for men and 4.91 for women, P-for-interaction = .057). The tendency remained after additionally adjusting for serum creatinine (P-for-interaction for raised blood pressure and hypertension was .059 and .057, respectively).

4. Discussion

In a military cohort of young individuals, our study showed a sex difference in the relationship between SUA concentrations and various cardiometabolic risk factors. In both young military men and women, higher SUA concentrations were correlated with higher serum creatinine concentrations, greater values of body mass index or waist size, lower high-density lipoprotein concentrations, and higher blood pressure values. However, sex-stratified analysis showed that hyperuricemia was associated with higher risk of elevated fasting plasma glucose, low-density lipoprotein, and triglycerides merely in men but not in women. We further uncovered that the extent of the association between hyperuricemia and raised blood pressure significantly differed by sex, which could not be explained by age and kidney function.

Obesity plays a fundamental role between SUA and other cardiometabolic risk factors in both sexes. An experimental
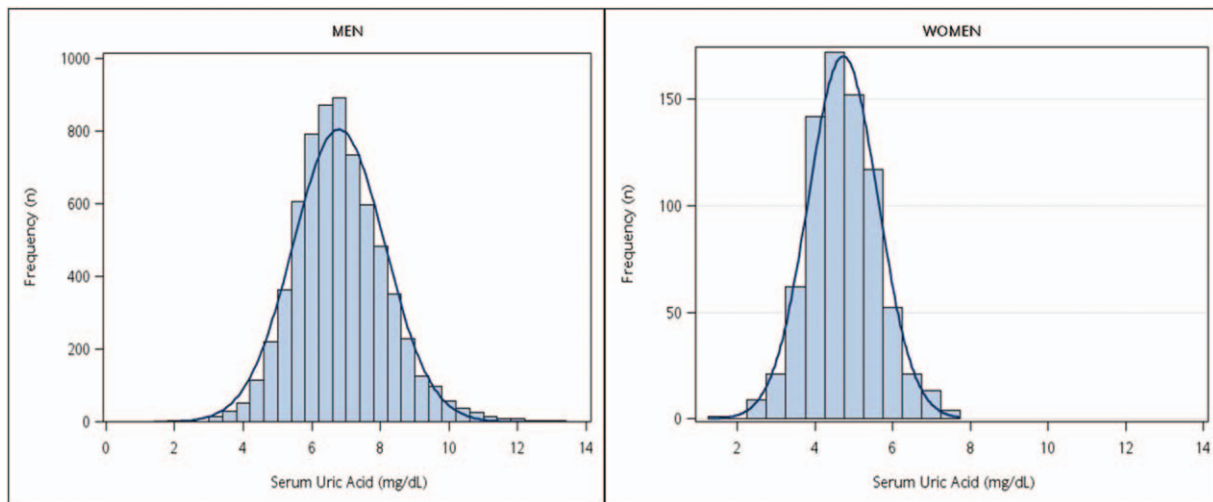
Figure 1. The serum uric acid levels against frequency in men and women.

Table 3

Anthropometric and biochemical characteristics according to sex-specific quartiles of serum uric acid levels.

	Men (n = 6738)				
	Q1 (<5.9) (N = 1583)	Q2 (5.9–6.7) (N = 1717)	Q3 (6.7–7.5) (N = 1718)	Q4 (>7.5) (N = 1720)	P for trend
Age, years	29.05 ± 5.87	28.76 ± 5.99	28.89 ± 5.98	29.43 ± 6.01	.0069
BMI, kg/m^2	23.82 ± 3.28	24.60 ± 3.34	25.38 ± 3.53	27.01 ± 3.78	<.0001
WC, cm	81.29 ± 8.39	82.98 ± 8.69	85.01 ± 8.70	88.67 ± 9.34	<.0001
FPG, mg/dL	92.56 ± 19.67	92.09 ± 12.67	92.43 ± 12.58	92.90 ± 10.85	.4049
Serum creatinine, mg/dL	0.93 ± 0.10	0.95 ± 0.11	0.97 ± 0.11	1.00 ± 0.13	<.0001
Total cholesterol, mg/dL	168.46 ± 31.30	171.79 ± 32.80	174.43 ± 32.52	183.69 ± 37.42	<.0001
TG, mg/dL	99.57 ± 88.41	107.78 ± 87.48	115.98 ± 81.62	145.34 ± 121.14	<.0001
HDL-C, mg/dL	49.87 ± 10.00	48.53 ± 9.72	47.25 ± 9.84	45.69 ± 9.68	<.0001
LDL-C, mg/dL	101.20 ± 27.67	104.88 ± 29.19	108.01 ± 28.52	114.33 ± 32.79	<.0001
Systolic BP, mmHg	118.17 ± 13.21	118.93 ± 12.88	120.29 ± 13.77	122.92 ± 13.55	<.0001
Diastolic BP, mmHg	70.41 ± 9.89	71.25 ± 10.44	71.83 ± 10.39	74.06 ± 11.02	<.0001
	Women (n = 766)				
	Q1 (<4.1) N = 170	Q2 (4.1–4.7) N = 209	Q3 (4.7–5.2) N = 180	Q4 (>5.2) N = 207	P for trend
Age, years	29.82 ± 6.90	28.03 ± 6.25	26.86 ± 6.13	27.56 ± 6.85	.0002
BMI, kg/m^2	21.86 ± 2.81	21.92 ± 2.83	22.63 ± 3.11	23.83 ± 3.26	<.0001
WC, cm	72.75 ± 8.40	71.72 ± 7.04	73.82 ± 8.51	76.48 ± 7.62	<.0001
FPG, mg/dL	87.48 ± 7.70	87.63 ± 8.39	89.43 ± 14.96	88.70 ± 8.83	.2185
Serum creatinine, mg/dL	0.66 ± 0.11	0.68 ± 0.09	0.70 ± 0.09	0.72 ± 0.10	<.0001
Total cholesterol, mg/dL	168.16 ± 31.87	168.87 ± 30.04	165.83 ± 27.50	170.40 ± 30.04	.5096
TG, mg/dL	80.62 ± 46.09	75.17 ± 40.72	79.64 ± 47.62	81.08 ± 41.44	.5069
HDL-C, mg/dL	58.84 ± 11.61	57.40 ± 10.28	57.08 ± 10.56	55.05 ± 11.47	.0094
LDL-C, mg/dL	92.85 ± 25.51	95.38 ± 24.68	92.98 ± 23.16	98.95 ± 27.67	.0621
Systolic BP, mmHg	105.63 ± 12.95	106.88 ± 12.13	108.51 ± 10.90	109.77 ± 13.25	.0068
Diastolic BP, mmHg	63.95 ± 9.30	65.75 ± 8.60	66.46 ± 8.72	67.21 ± 10.31	.0064

BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference. The trend analysis was performed by ANOVA and adjusted for age.

Table 4

Clinical outcomes of study participants by hyperuricemia status by sex.

	Total population (N = 7504)				
Characteristics	Normal SUA (n = 4826)	Hyperuricemia (n = 2678)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
BP ≥140/90 mmHg	355 (7.36)	324 (12.10)	1.73*** (1.48- 2.03)	1.55*** (1.32- 1.83)	1.57*** (1.33–1.86)
BP ≥130/85 mmHg	1052 (21.80)	870 (32.49)	1.73*** (1.55- 1.92)	1.54*** (1.38- 1.71)	1.55*** (1.39–1.73)
FPG ≥100 mg/dL	619 (12.83)	464 (17.33)	1.42*** (1.25- 1.62)	1.29*** (1.13- 1.48)	1.28*** (1.12–1.47)
LDL-C ≥160 mg/dL	773 (16.02)	680 (25.39)	1.78*** (1.59- 2.00)	1.75*** (1.55- 1.97)	1.71*** (1.51–1.93)
TG ≥150 mg/dL	738 (15.29)	759 (28.34)	2.19*** (1.95–2.46)	2.03*** (1.80–2.29)	2.11*** (1.86–2.38)
Low HDL-C	874 (18.11)	714 (26.66)	1.64*** (1.47–1.84)	1.73*** (1.54–1.94)	1.77*** (1.58–2.00)
High WC	991 (20.53)	1080 (40.33)	2.62*** (2.36- 2.90)	2.66*** (2.30- 2.97)	2.85*** (2.55–3.18)
Obesity	245 (5.08)	414 (15.46)	3.42*** (2.90- 4.04)	3.15*** (2.66- 3.72)	3.32*** (2.79–3.94)
Metabolic syndrome	445 (9.22)	574 (21.43)	2.69*** (2.35- 3.07)	2.51*** (2.18- 2.88)	2.61*** (2.26–3.01)
	Men (N = 6738)				
Characteristics	Normal SUA (n = 4150)	Hyperuricemia (n = 2588)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
BP ≥140/90 mmHg	346 (8.34)	319 (12.33)	1.55*** (1.32- 1.82)	1.52*** (1.30–1.79)	1.55*** (1.31–1.83)

Table 4

(continued).

Characteristics	Men (N = 6738)				
	Normal SUA (n = 4150)	Hyperuricemia (n = 2588)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
BP ≥130/85 mm Hg	1018 (24.53)	858 (33.15)	1.53*** (1.37–1.70)	1.51*** (1.36–1.69)	1.53*** (1.37–1.72)
FPG ≥100 mg/dL	586 (14.12)	457 (17.66)	1.30** (1.14–1.49)	1.29** (1.12–1.47)	1.27*** (1.11–1.46)
LDL-C ≥160 mg/dL	679 (16.36)	666 (25.73)	1.77*** (1.57–2.00)	1.78*** (1.57–2.01)	1.72*** (1.51–1.95)
TG ≥150 mg/dL	698 (16.82)	752 (29.06)	2.03*** (1.80, 2.28)	2.05*** (1.82, 2.31)	2.10*** (1.85–2.38)
HDL-C <40 mg/dL	711 (17.13)	678 (26.20)	1.72*** (1.52–1.93)	1.71*** (1.51–1.92)	1.74*** (1.54–1.96)
WC ≥90 cm	852 (20.53)	1040 (40.19)	2.60*** (2.33–2.90)	2.63*** (2.36–2.94)	2.76*** (2.47–3.10)
Obesity	233 (5.61)	409 (15.80)	3.16*** (2.66–3.74)	3.14*** (2.65–3.72)	3.30*** (2.78–3.93)
Metabolic syndrome	422 (10.17)	566 (21.87)	2.47*** (2.16–2.84)	2.50*** (2.17–2.87)	2.60*** (2.25–3.00)

Characteristics	Women (N = 766)				
	Normal SUA (n = 676)	Hyperuricemia (n = 90)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
BP ≥140/90 mm Hg	9 (1.33)	5 (5.56)	4.36** (1.43–13.31)	4.91**† (1.55–15.58)	4.69*† (1.43–15.41)
BP ≥130/85 mm Hg	34 (5.03)	12 (13.33)	2.91** (1.44–5.84)	3.37**‡ (1.60–7.10)	2.82**‡ (1.31–6.07)
FPG ≥100 mg/dL	33 (4.88)	7 (7.78)	1.64 (0.70–3.83)	1.70 (0.72–3.98)	1.89 (0.78–4.56)
LDL-C ≥160 mg/dL	94 (13.91)	14 (15.56)	1.14 (0.62–2.10)	1.19 (0.64–2.22)	1.40 (0.73–2.66)
TG ≥150 mg/dL	40 (5.92)	7 (7.78)	1.34 (0.58, 3.09)	1.37 (0.59, 3.17)	2.13 (0.87–5.19)
HDL-C <50 mg/dL	163 (24.11)	36 (40.00)	2.10** (1.33–3.31)	2.13** (1.35–3.37)	2.41*** (1.50–3.87)
WC ≥80 cm	139 (20.56)	40 (44.44)	3.09*** (1.96–4.88)	3.28*** (2.06–5.22)	4.09*** (2.51–6.66)
Obesity	12 (1.78)	5 (5.56)	3.26* (1.12–9.47)	3.42* (1.16–10.05)	3.98* (1.31–12.15)
Metabolic syndrome	23 (3.40)	8 (8.89)	2.77* (1.20–6.39)	2.99* (1.27–7.06)	3.10* (1.28–7.50)

Data is presented as numbers with percentages, and odds ratio with 95% confidence intervals. BP = blood pressure; CI = confidence intervals; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio; TG = triglycerides; WC = waist circumference.
Definitions: High WC: ≥90 cm in men and ≥80 cm in women, respectively. Low HDL-C <40 mg/dL for men or <50 mg/dL for women, respectively.
Model 1 adjusted for age; and Model 2 additionally adjusted for creatinine concentrations.
*P < .05; **P < .01; ***P < .001; †P-for-interaction = .057; ‡P-for-interaction = .059.

study of mouse models has uncovered that uric acid could be produced and secreted from adipocytes, which were abundant and had higher xanthine oxidoreductase (XOR) activity in obesity.[24] In another study,[25] uric acid induced monocyte chemotactic protein-1, a pro-inflammatory adipokine, production in vitro evidenced by mRNA expression within adipocytes in obesity. In addition, uric acid decreased the production of adiponectin, an anti-inflammatory agent and insulin sensitizer, for adipocytes. Using allopurinol to inhibit XOR could lower SUA concentrations in obese mice and thereby reduce macrophage infiltration in the adipose tissue and improve insulin resistance. Accordingly, obesity might be a moderator of hyperuricemia to abnormal lipid profiles, hyperglycemia, and elevated blood pressure.

Estrogens may play a critical role in modification of the relationship between hyperuricemia, dyslipidemia, and prediabetes in women. The National Health and Nutrition Examination Survey showed premenopausal women had lower serum triglycerides, non-high-density lipoproteins, and uric acid compared with men of similar ages.[26] Estrogens have uricosuric effect on kidney to excrete uric acid,[27] and regulate lipid metabolism in adipose tissues, muscle, and liver. More triglycerides-rich very low-density lipoproteins are secreted by liver to prevent hepatic fat accumulation and free fatty acids clearance rates of muscle are increased in young women,[28,29] which reduces atherogenic lipid levels and hyperuricemia mediated inflammatory process with obesity.[30] In addition, the protective effect of estrogens on hyperuricemia from

prediabetes or diabetes has been reported in young women in previous studies.[31,32]

Previous studies have uncovered that in young adults of the general population, the association between SUA and blood pressure was stronger in women than in men.[33] Also, the relationship was found greater in women than in men of the elderly,[34] implying that SUA might have an adverse effect on the arterial vasculatures to elevate blood pressure, which is not influenced by estrogens.[35] Uric acid inhibits nitrite oxide, and induces C-reactive protein and major reactive oxygen species productions in smooth muscle and vascular endothelial cells, resulting in cell proliferation, endothelial dysfunction, renin–angiotensin–aldosterone system activation, and vascular contractility impairment.[36–38] Several cohort studies have shown that SUA were dose-dependently associated with maximal intima-media thickness and peripheral arterial stiffness among apparently healthy individuals and those at high vascular risk.[33,39,40] In addition, most of these studies reported that the SUA relationship with arterial stiffness or hypertension in men was null or weaker than that in women.[33,35,39,40] This sex difference could be reasoned partially by that at higher SUA levels, women may have greater xanthium oxidase activity and reactive oxygen species productions, resulting in severer renal vascular inflammation, arterial stiffness, and elevated blood pressure as compared with men.[36–38]

There were a number of strengths in this study. First, the sample size of this study was large enough to provide sufficient power for sex-specific analyses. Second, although 1572 participants were excluded for missing data initially, the demographic characteristics were similar to the study population, reducing the selection bias (supplemental Table 1). Third, all measurements were standardly performed in one referral hospital to avoid potential bias. Several limitations should be denoted. First, our study was a cross-sectional design, which restricts the temporal relationship of SUA with cardio-metabolic risk factors. Second, although the association of SUA with triglycerides and low-density lipoprotein was null in women, the sex difference was not statistically significant, requiring more investigations. Third, our cohort was confined in the military of Taiwan; therefore, the results might not be proper to apply to the general public.

5. Conclusion

Our findings suggest that the relationship of hyperuricemia with various metabolic abnormalities in young adults may differ by sex. There tended to be a sex difference in the association between hyperuricemia and raised blood pressure, which was greater in women than in men, possibly related to a regulation of female sex hormones and uneven effects of uric acid at the same levels between sexes on lipid metabolisms and arterial stiffness.

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Author contributions

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