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高尿酸血症對心血管疾病的前瞻性風險研究

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<center>報告內容</center>

INTRODUCTION

Prevalence of gouty arthritis, a common chronic arthritis, has steadily increased in different parts of the world[1]. Although hyperuricemia has been documented as a key precipitating factor of gout in the Normative Aging Study[2] and the UK General Practice Research Database from 1990-1995[3]; aging of the world population, growing prevalence of obesity and metabolic syndrome have been indicted for the worldwide increase of gout incidence and prevalence[4].

The Third National Health and Nutrition Examination Survey (NHANES III) reported a remarkably high prevalence of metabolic syndrome in individuals with hyperuricemia or gout[5-6] and have also found a close association between serum uric acid (sUA) level and the prevalence of metabolic syndrome[7]. Recent finding of an inverse correlation between sUA and insulin sensitivity[8] have suggested hyperuricemia as a possible marker of insulin resistance[9-10] or a reliable indicator of the "pre-metabolic syndrome"[11-13]. These findings raise attention on the role of metabolic syndrome on gout development[6].

Gender difference has been observed for the age-hyperuricemia and age-gout relationships[14]. However, most gout-related reports studied men as contrast to the limited description of gout on women[14-17]. Previous research indicates that women not only tend to develop gout later in life, but also use more diuretics, and have more co-morbidities of obesity, hypertension, dyslipidemia, cardiovascular disease (CVD), peripheral artery disease, diabetes mellitus, renal insufficiency, and habitual alcoholic intake[14, 18]. Therefore, this study sought to determine the gender-specific risk of gout in relation to the abnormalities of various metabolic risk factors, including sUA, cholesterol, triglyceride, glucose, blood pressure and overweight.

METHODS

Study population. This prospective cohort study used data collected from 1994-1996 to December 2002 with physical examination carried out and questionnaire administered in the privately-owned nationwide MJ Health Screening Centers in Taiwan[19-21]. Detailed description of the data for those health examinees and their socio-economic distribution has been described in our recent report[20].

Exclusion criteria. Data from 137,532 participants aged 18 years and above were included after excluding 0.46% of the original cohort due to unclear data. We further excluded subjects who did not have registered data with the NHI program (n=2,450), died before 1997 (n=612), had self-reported gout history (n=1,725) or were suspected to have had gout according to the NHI database during 1994-96 (n=189; see later description of gout definition). Data from a total of 132,556 subjects (60,181 men and 72,375 women) were analyzed. The Institutional Review Boards of both the China Medical University Hospital in Taichung and the Academia Sinica in Taipei, Taiwan approved the study.

Baseline characteristics and morbidities defined with clinical and chemistry data. Health examination and questionnaire data were used as baseline information for follow-up[20]. Plasma uric acid, cholesterol, triglyceride, and glucose were measured enzymatically using Hitachi 7150 autoanalyzer (Tokyo, Japan). Hyperuricemia was defined as sUA >6 mg/dl (0.354 mmol/L), overweight as body mass index (BMI) >24 kg/m^2 [22], high blood pressure as systolic blood pressure (SBP) >130 mmHg or diastolic blood pressure (DBP) >85 mmHg, hyperglycemia as fasting

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blood sugar >100 mg/dl (5.5 mmol/L), hypercholesterolemia as cholesterol >200 mg/dl (51.8 mmol/L), and hyper-triglyceridemia as triglyceride >150 mg/dl (16.9 mmol/L), respectively.

Incremental levels of sUA were stratified into <4.5 (reference), 4.5-5.9, 6.0-7.4, and $\geqq$7.5 mg/dl, BMI into <24 (reference), 24-26.9, 27-29.9, and $\geqq$30 Kg/m^2; cholesterol into <150 (reference), 150-199, 200-239, and $\geqq$240 mg/dl; triglyceride into <150 (reference), 150-199, 200-239, and $\geqq$240 mg/dl; blood pressure into <130/85 (reference), 130/85-139/89, 140/90-159/94, and $\geqq$160/95 mmHg; and glucose into <100 (reference), 100-125, 126-179, and $\geqq$180 mg/dl.

Outcome information: National Health Insurance (NHI) dataset and definition of incident gout. Use was made of claim data from the NHI that began in mid-1995. This administrative database was a pharmaco-medical claim cost record which has provided a longitudinal follow-up resource for epidemiologic research[23]. Clinical gout diagnosis was recorded using either the ninth version of the International Classification of Disease (ICD-9) code in the NHI database. The codes of gout (ICD-9: 274.x) were searched from January 1, 1994 to December 31, 2002. The criteria for gout in the MJ participants were (1) the diagnostic code of gout assigned in at least two visits to the physicians or rheumatologists, and (2) both colchicine and urate-lowering drugs (i.e. allopurinol, probenecid, sulfinpyrazone, or benzbromarone) prescribed in these visits. Subjects with gout developed prior to the end of 1996 were considered prevalent gout and excluded. Gout attacks developed after the beginning of 1997 were considered as incident event. The onset time of gout was defined as the initial colchicine prescription to the patient. Rheumatologists diagnosed gout endpoints was used for a sub-group analysis which was served as a validation study for the original analysis.

Statistical analysis. Baseline characteristics between men and women or between gout-free and incident-gout participants were tested by two-sample *t*-test or chi-square test. The age-standardized rate of gout was calculated according to the Taiwanese population structure at the end of year 2000 by five-year age groups. Hazard ratio (HR) of each metabolic risk factor on the incidence of gout in men and/or women was assessed by Cox proportional hazard model. In multivariate models, (1) the effects of age; and (2) those of age, hyperuricemia, hypercholesterolemia, hyper-triglyceridemia, hyperglycemia, high blood pressure, and overweight were adjusted. The interaction between gender and the aforementioned covariates was also tested. All HRs were provided with 95% confidence intervals (CI).

Mean gout incidence below cut-point of individual metabolic factor obtained from our study was used as the expected risk for subtraction in the process of estimating population-attributable risk (PAR)[24-25]. We used PAR to determine the percentage of gout cases in this population that theoretically would not have occurred if these metabolic risk factors had been lowered to the given levels. The degrees of impact from hyperuricemia, individual metabolic disorders, and different degrees of metabolic syndrome on gout were assessed by comparing above PARs. PAR was also estimated for (1) having hyperuricemia only, (2) at least one metabolic syndrome component, or (3) ≥3 of any metabolic risk factors, and (4) hyperuricemia combined with ≥3 metabolic factors. The statistical package SAS 9.01 (SAS Institute, Cary, NC) was used for analysis.

RESULTS

Incidence rate of gout and baseline characteristics. Table 1 shows the baseline

characteristics of the participants by genders. After a mean follow-up of 7.31±0.99 years, 1,606 clinical gout subjects (1,341 males and 265 females) were defined by the physicians' visit in the original study of the 132,556 individuals ≥18 years-old (60,181 men and 72,375 women). The standardized incidence of gout was 1.69 per 1,000 person-years (PYs) for adults aged 18 and above. The incidence in men was 3.09 per 1,000 PYs, which was six times higher than that in women (0.53 per 1,000 PYs). When we focused on older people (>60 years old), we found higher incidence of gout; however, the male to female ratio of incident gout reduced to three times higher in men than women (5.18 per 1,000 PYs for men and 1.69 per 1,000 PYs for women; $p<0.001$).

Among the physician-defined gout patients, the proportion of men was higher (83.5%) than women. The mean baseline age of participants who developed gout (49.8 years) was higher than that of participants without gout (42.3 years) (Table 2A). The mean onset age for gout was 62.3 years in women, which was older than that in men (52.3 years) (Table 1). Among the 238 gout subjects clinically defined by rheumatologists (207 males and 31 females), the proportion of male gout were 87.0% (Table 2B) and the mean age of gout onset was 51.9 years in men, and 64.4 years in women, respectively (no tabulated data shown). Both were comparable to the results derived from the original study (Table 2A). The comparability between both studies was shown not only in the baseline characteristics of the gout and gout-free participants (Tables 2) but also in the dose-responsive relations of gout with incremental levels of sUA, BMI, triglyceride, cholesterol, and blood pressure (Table 3).

Effects of hyperuricemia and metabolic risk factors on gout occurrence. Among all metabolic risk factors, hyperuricemia had the highest impact on gout (Figure 1A). Although the HR was higher in men (9.3; 95% CI, 7.1-12.0) than in women (7.0; 95% CI, 5.2-9.6), the gender difference was not statistically significant by multivariate regression model (*p* for gender-hyperuricemia interaction = 0.79). Nevertheless, the gender difference was significantly demonstrated for overweight, high blood pressure, hypercholesterolemia, and hyper-triglyceridemia, with respective HR (95% CI) higher in women [2.1 (1.5-2.8), 1.7 (1.2-2.3), 1.6 (1.2-2.0), and 1.6 (1.3-2.1)] than in men [1.5 (1.4-1.7), 1.4 (1.2-1.5), 1.1 (0.9-1.2), and 1.4 (1.3-1.6); all *p* for gender-metabolic disorder interactions < 0.05), respectively. In the validation study (Figure 1B) gender difference was similar but not statistically significant because there were only 31 female gout subjects defined by the rheumatologists.

We further studied the low risk subgroup with normal body weight, blood pressure, lipid and glucose levels, (n=41,351; 13,520 men and 27,831 women). HR of hyperuricemia on gout was 9.2 (95% CI, 4.8-17.6) in men, in contrast to the statistically insignificant relative risk in women (2.0; 95% CI, 0.4-9.7; *p*=0.11 for gender interaction) (Figure 3A). To further compare the contributions of metabolic factors to the risk of gout between gender, we demonstrated in women that the HRs of at least one and that of ≥3 factors of any of the aforementioned metabolic risk were 4.2 (95% CI, 2.1-8.4) and 2.7 (95% CI, 2.0-3.6), respectively, which were significantly higher than those in males (2.0; 95% CI, 1.6-2.4 and 1.6; 95% CI, 1.5-1.8, respectively). Furthermore, the HR of women with a combined condition of hyperuricemia and ≥3 factors of any metabolic risk (8.1; 95% CI, 6.2-10.5) were also statistically higher than that of men (2.8; 95% CI, 2.5-3.1).

Population-attributable risk of hyperuricemia and other individual metabolic risk factor on gout. Presented in figure 2 is the proportion of incident gout that might have been prevented (i.e. PAR), if participants' baseline levels of sUA, BMI, blood

pressure, glucose, cholesterol, triglyceride are lowered below clinical cut-points. Hyperuricemia was the most influential risk factor. Controlling sUA to below 6.0 mg/dl was estimated to account for 87.5% of incident gout prevention. The hyperuricemia control was slightly more effective in men (86.0%) than in women (73.1%). On the other hand, the PAR of overweight in women was 65.3%, which was higher than that in men (36.3%). This implied that 65.3% of gout may be attributable to overweight in women and 36.3% in men. Similarly, the PAR of metabolic risk factors, including high blood pressure, hypercholesterolemia, hyper-triglyceridemia, and hyperglycemia were all higher in women (corresponding PAR of 60.6%, 45.2%, 41.7%, and 21.1%, respectively) than in men (28.2%, 13.3%, 23.6%, and 6.8%, respectively). Moreover, the PAR of having any one or more metabolic risk factors were also higher in women (91.3%) than in men (60.7%) (Figure 3B), which means that if the population's body weight, blood pressure, lipid and glucose levels had been controlled within normal range, 91.3% of women and 60.7% of men can avoid gout. Furthermore, the PAR for usually defined metabolic syndrome was much higher in females than in males, regardless of whether hyperuricemia is combined or not.

DISCUSSION

The present study confirmed as expected that the risk of hyperuricemia on gout occurrence is the highest among all studied metabolic risk factors, and further demonstrated that the impact of metabolic syndrome components on gout attack are higher in women than in men, as illustrated by their relatively higher HR and PAR. From the perspective of PAR, metabolic syndrome can approximately explain more than 50% of the gout incidence in women and around 30% in men, regardless of the status of hyperuricemia. Further extending this perspective, if the population's body weight, blood pressure, lipid and glucose levels are all controlled within normal range, 91.3% of women and 60.7% of men may have avoided gouty attack. This study shows metabolic syndrome or individual metabolic component tends to be more important risk factors for gout development in women than in men.

While a recent report of Framingham Heart Study highlighted the importance of overweight and hypertension as risk factors for gout in women[18], the present study further demonstrated significant influences of other related metabolic risk factors in women, including hypercholesterolemia, hyper-triglyceridemia, and hyperglycemia. It is worth noting that although the prevalence of overweight in Taiwan (43.8% for men and 33.9% for women) was not as high as that in Caucasian (60% for men, and 40% for women)[26], estimates of the female to male relative risk of overweight (0.77) on gout were similar in our study and in the Framingham Heart Study (0.73).

The degrees of impact of individual metabolic factors on gout incidence in the current study is comparable to what previously reported by the NHANES III study[6] and American Health Professionals Follow-up Study[26]. Other than hyperuricemia, the importance of metabolic risk factors on incident gout follows the order of overweight, hyper-triglyceridemia, high blood pressure, hypercholesterolemia, and hyperglycemia. Among those who are free from metabolic disorders, hyperuricemia is still the most influential risk factor on gout occurrence, especially in men (Figure 3A). On the other hand, the risks of various metabolic morbidities on gout incidence are higher in women than in men (Figure 1). Therefore, controlling metabolic co-morbidities may be more critical or at least equally important as sUA control in women (Figure 3)[14].

We noticed that the mean age of this Taiwanese cohort was younger (42.5 year-old in men and 42.3 year-old in women) as compared to other cohorts[3, 18, 27]. Due to the younger onset of gout in males, the sex ratio of gout incidence in men was 6

times higher than that in women. Nevertheless, when we focused on the older people, we found the incidence was 5.18 per 1,000 PYs in men and 1.69 per 1,000 PYs in women, and the sex-ratio reduced to 3; both are comparable to previous reports[16-18].

The explanation of greater gout incidence in men[14-15] may be attributable to higher mean sUA level, and higher prevalence of hyperuricemia in men (6.8 mg/dl and 67.8%) than in women (5.2 mg/dl and 21.7%)(Table 1). Estrogen may be responsible for the enhanced uricosuric effect on renal tubules and the lower incidence of hyperuricemia and gout in pre-menopausal women. This can also explain the later onset time of gout in women[15]. A greater impact of insulin on renal uric acid resorption in women, and a higher prevalence of abdominal obesity with insulin resistance in elderly women further evidence a central role of insulin resistance in the development of hyperuricemia[8] and a greater role of metabolic co-morbidities in women with gout than in their male counterpart[14]. To assess the potential effect of glomerular filtration of urate in our model, we did a subgroup analysis on individuals who had creatinine data. The multivariate HRs of individual risk factors did not change after including glomerular filtration rate (GFR) into the Cox regression model (see supplementary figure).

According to an American study[28], using administrative claim data with gout-related code assigned in at least two ambulatory visits in gout study achieved a positive predictive value of 61%, and evaluation by rheumatologists could substantially increase the positive predictive value to 92%. A relatively lower specificity in gout classification by using information from the National Health Insurance may be suspected. Since no information on chronic tophaceous gout or on acute arthritis with podagra has been provided by the NHI database, a subgroup analysis on gout subjects defined by rheumatologist was used to validate our findings. We found the respective metabolic characteristics by gout status (Table 2) and risk trends (Table 3) on gout incidence are comparable between the original and the validation studies. Furthermore, we included medical prescription data in defining gout in order to improve validity of gout diagnosis in this study. Since colchicine and urate-lowering drugs represent the most popular agents for treating chronic gout in Taiwan, and the non-steroidal anti-inflammatory drugs are primarily used to deal with acute arthritis, but not specifically for treating gouty arthritis; we included the former but not the latter in the definition. The criteria of incident gout defined by the current study may have underestimated gout incidence, but should not affect findings on the gender-specific or the overall relative risk on gout.

A gender difference concerning the impacts of hyperuricemia and metabolic co-morbidities on gout occurrence is shown in the present study. Although hyperuricemia has the greatest impact on gout development, the impacts of overweight, high blood pressure, hypercholesterolemia, and hyper-triglyceridemia as shown by HRs and PARs are all significantly higher in women than in men. In the subgroup analysis of participants free of metabolic risk factors, the HR of hyperuricemia on gout occurrence in women is not as prominent as in men. On the other hand, the importance of usually defined metabolic syndrome for incident gout in women again is evident, regardless of whether hyperuricemia is combined or not. This may suggest that controlling metabolic co-morbidities to prevent gout, especially among women, should not be overlooked, although clinical application warrants further investigation.

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Table 1. Baseline characteristics of the participants in the MJ Health Screening Center, stratified by gender.

	Male n=60181	Female n=72375
Incident Gout (Incidence per 1,000 person years)	1341 (3.09)	265 (0.53)
Age (year)	42.5 ± 14.6	42.3 ± 14.3
Age of gout onset (year)	52.3 ± 14.8	62.3 ± 11.1
BMI (kg/m^2)	23.6 ± 3.3	23.0 ± 8.2
Overweight (BMI > 24 kg/m^2)	26334 (43.8)	24504 (33.9)
Cholesterol (mg/dl)	184.3 ± 37.0	183.6 ± 37.9
Hypercholesterolemia (cholesterol > 200 mg/dl)	18478 (30.7)	21608 (29.9)
Triglyceride (mg/dl)	132.3 ± 115.6	102.2 ± 79.0
Hypertriglyceridemia (triglyceride > 150 mg/dl)	15916 (26.5)	10699 (14.8)
Systolic blood pressure (mmHg)	140.5 ± 21.5	125.9 ± 21.4
Diastolic blood pressure (mmHg)	80.2 ± 12.2	70.3 ± 12.4
Hypertension (SBP/DBP >130/85 mmHg)	25698 (42.7)	21270 (29.4)
Glucose (mg/dl)	98.5 ± 23.0	96.7 ± 23.6
Hyperglycemia (Glucose > 100 mg/dl)	15450 (25.7)	14847 (20.5)
Uric Acid (mg/dl)	6.8 ± 1.4	5.2 ± 1.3
Hyperuricemia (serum uric acid >6 mg/dl)	40814 (67.8)	15712 (21.7)

Values are mean±SD or the percentage with a given condition.

All variables were tested and found significantly different between genders ($p<0.01$) by either two-sample t-test or χ^2 test.

(cholesterol 1 mg/dl = 0.0259 mmol/L; triglyceride 1 mg/dl = 0.0113 mmol/L; uric acid 1mg/dl = 0.059 mmol/L; glucose 1 mg/dl = 0.055 mmol/L)

Table 2. Baseline characteristics of MJ participants who developed gout and those who did not (n=132556)

Variables	A. Original study, gout defined by physicians			B. Validation study, gout defined by rheumatologists		
	Gout (n=1606)	Non-gout (n=130950)	p	Gout [a] (n=238)	Non-gout [a] (n=132318)	p
Gout-onset Age (years)	54.0 ± 14.7			53.5 ± 14.7		
Age (year)	49.8 ± 14.8	42.3 ± 14.4	<0.001	49.5 ± 14.8	42.4 ± 14.4	<0.001
Male gender	1341 (83.5)	58840 (44.9)	<0.001	207 (87.0)	59974 (45.3)	<0.001
Educational >9 years	341 (21.2)	34018 (26.0)	<0.001	58 (24.4)	34301 (25.9)	0.81
Sedentary job	502 (31.3)	49307 (37.7)	<0.001	76 (31.9)	49733 (37.6)	0.98
No exercise	694 (43.2)	58127 (44.4)	0.63	93 (39.1)	58728 (44.4)	0.99
Alcohol drinking	1055 (65.7)	79050 (60.4)	<0.001	148 (62.2)	79957 (60.4)	0.01
Cigarette smoking	861 (53.6)	57406 (43.8)	<0.001	111 (46.6)	58156 (44.0)	0.02
Uric acid (mg/dl)	8.5 ± 1.7	5.9 ± 1.5	<0.001	8.8 ± 1.8	5.9 ± 1.6	<0.001
Hyperuricemia	*1490 (92.8)*	*55036 (42.0)*	<0.001	*224 (94.1)*	*56307 (42.6)*	<0.001
SBP (mmHg)	138.3 ± 23.5	125.8 ± 21.4	<0.001	140.5 ± 21.5	125.9 ± 21.4	<0.001
DBP (mmHg)	78.3 ± 13.2	70.2 ± 12.3	<0.001	80.2 ± 12.2	70.3 ± 12.4	<0.001
High Blood Pressure	*977 (60.8)*	*45991 (35.1)*	<0.001	*157 (66.0)*	*46811 (35.4)*	<0.001
Anti-hypertensive	189 (11.8)	5614 (4.3)	<0.001	33 (13.9)	5,770 (4.4)	<0.001
Glucose (mg/dl)	100.0 ± 23.9	97.5 ± 23.3	<0.001	97.5 ± 12.6	97.5 ± 23.3	0.97
Hyperglycemia	*503 (31.3)*	*29794 (22.8)*	<0.001	*77 (32.4)*	*30220 (22.8)*	<0.001
Anti-diabetics	53 (3.3)	2705 (2.1)	<0.001	2 (0.8)	2,756 (2.1)	<0.001
Cholesterol (mg/dl)	196.6 ± 41.6	183.8 ± 37.4	<0.001	194.9 ± 39.4	183.9 ± 37.5	<0.001
Hypercholesterolemia	*687 (42.8)*	*39399 (30.1)*	<0.001	*96 (40.3)*	*39990 (30.2)*	<0.001
Triglyceride (mg/dl)	169.4 ± 174.3	115.2 ± 97.0	<0.001	178.3 ± 107.8	115.8 ± 90.4	<0.001
Hypertriglyceridemia	*718 (44.7)*	*25897 (19.8)*	<0.001	*122 (51.3)*	*26493 (20.0)*	<0.001
BMI (kg/m^2)	25.5 ± 3.5	23.2 ± 6.5	<0.001	25.5 ± 3.3	23.3 ± 6.5	<0.001
Overweight	*1063 (66.2)*	*49775 (38.0)*	<0.001	*160 (67.2)*	*50678 (38.3)*	<0.001

[a] Values are mean±SD or the number (percentage) unless otherwise indicated. All variables were tested by two-sample *t*-test or chi-square test.

Table 3. Hazard ratios of incremental serum levels of each metabolic risk factor on gouty arthritis

Hazard Ratio [a]	G1	G2	G3	G4
Uric acid (mg/dl)	<4.5	4.5-5.9	6.0-7.4	≧7.5
I (original study)	1	1.3 (0.8-2.1)	4.6 (3.0-6.9)	27.1 (18.0-40.8)
II (validation study)	1	0.6 (0.2-1.8)	2.1 (0.8-5.6)	16.7 (6.6-42.3)
BMI (kg/m2)	<24	24-26.9	27-29.9	≧30
I	1	1.4 (1.2-1.6)	1.9 (1.6-2.1)	2.2 (1.8-2.7)
II	1	1.4 (1.0-1.9)	1.7 (1.2-2.5)	1.8 (1.0-3.0)
Triglyceride (mg/dl)	<150	150-199	200-239	≧240
I	1	1.4 (1.2-1.6)	1.5 (1.3-1.8)	1.6 (1.4-1.9)
II	1	1.7 (1.2-2.4)	1.9 (1.2-3.0)	2.5 (1.8-3.6)
Cholesterol (mg/dl)	<150	150-199	200-239	≧240
I	1	1.1 (0.9-1.3)	1.2 (1.0-1.5)	1.3 (1.1-1.7)
II	1	1.0 (0.6-1.5)	0.9 (0.6-1.5)	1.1 (0.6-1.9)
Blood pressure (mmHg)	<130/85	130/85-139/89	140/90-159/94	≧160/95
I	1	1.2 (1.0-1.3)	1.2 (1.1-1.4)	1.7 (1.5-1.9)
II	1	1.2 (0.9-1.6)	1.8 (1.4-2.3)	2.0 (1.4-2.7)
Glucose (mg/dl)	<100	100-125	126-179	≧180
I	1	0.9 (0.8-1.0)	0.7 (0.5-1.0)	0.8 (0.5-1.1)
II	1	1.0 (0.7-1.3)	0.6 (0.2-1.3)	0.2 (0.03-1.4)

[a] Model adjusted by multiple covariates including age, sex, hyperuricemia, obesity, high blood pressure, hypercholesterolemia, hyper-triglyceridemia, and hyperglycemia.

I, indicates hazard ratios derived from the original study of gout patients diagnosed by either general physicians or rheumatologists; II, indicates relative risks derived from the validation study of gout patients diagnosed by rheumatologists.
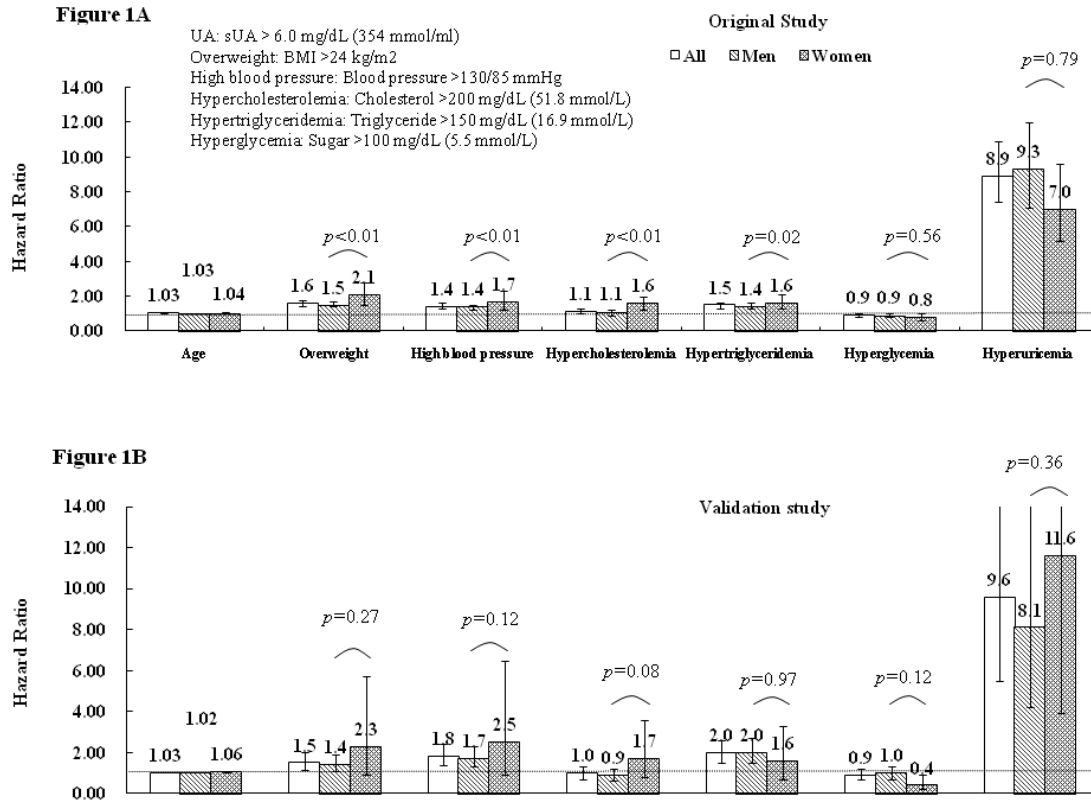
FIGURES

Figure 1A

UA: sUA > 6.0 mg/dL (354 mmol/ml)
Overweight: BMI >24 kg/m2
High blood pressure: Blood pressure >130/85 mmHg
Hypercholesterolemia: Cholesterol >200 mg/dL (51.8 mmol/L)
Hypertriglyceridemia: Triglyceride >150 mg/dL (16.9 mmol/L)
Hyperglycemia: Sugar >100 mg/dL (5.5 mmol/L)

Original Study

□ All ▨ Men ▨ Women

Figure 1B

Validation study

Figure 1. Hazard ratio of each metabolic risk factor on gout occurrence. (A) Hazard ratios of subjects with gouty arthritis diagnosed by general physicians or rheumatologists. **(B)** Hazard ratio derived from the gout patients diagnosed by rheumatologists. Cox proportional hazard model estimated the hazard ratios with adjustments for age, (sex), hyperuricemia, obesity, high blood pressure, hypercholesterolemia, hyper-triglyceridemia, and hyperglycemia. Difference by gender was further tested between gender and each metabolic risk factor by multivariate regression model. *P*-value corresponds to the gender-metabolic disorder interaction.
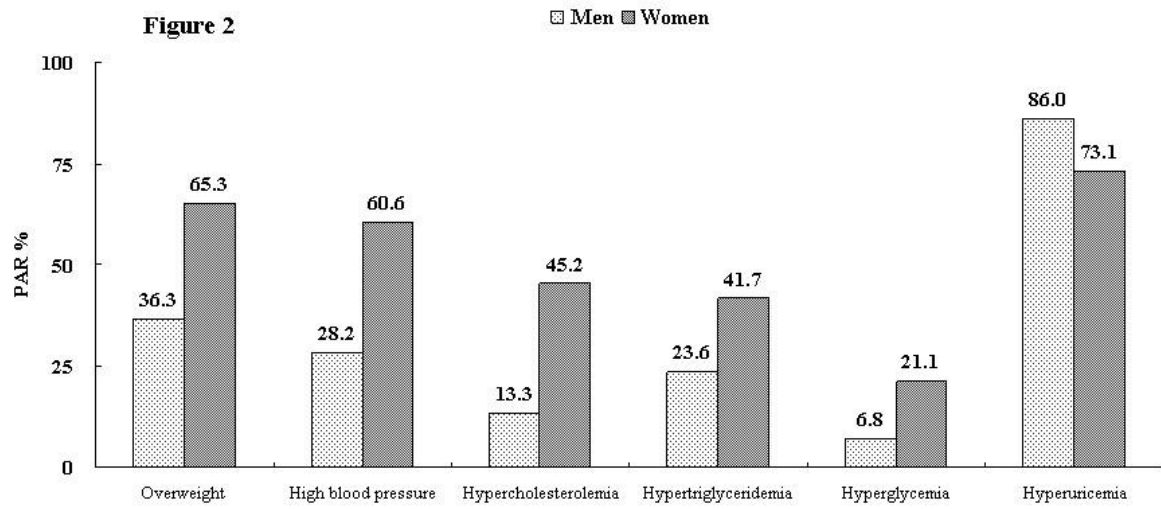
Figure 2. Population-attributable risk (PAR) for each metabolic factor on gout. Of the total 132,556 patients, 60181 were male and 72375 were female. Of the 1606 gout events, 1341 were in men and 265 in women.
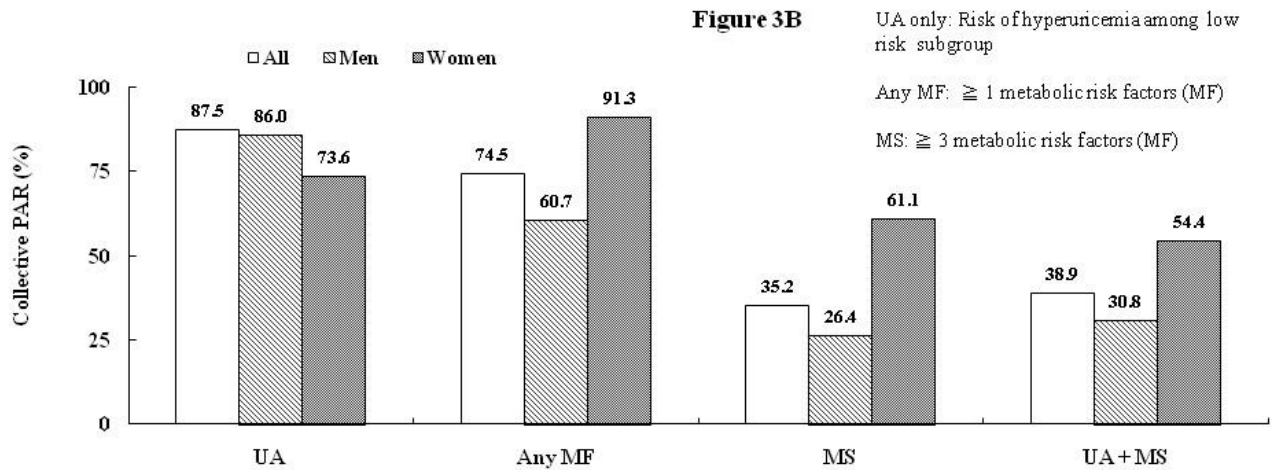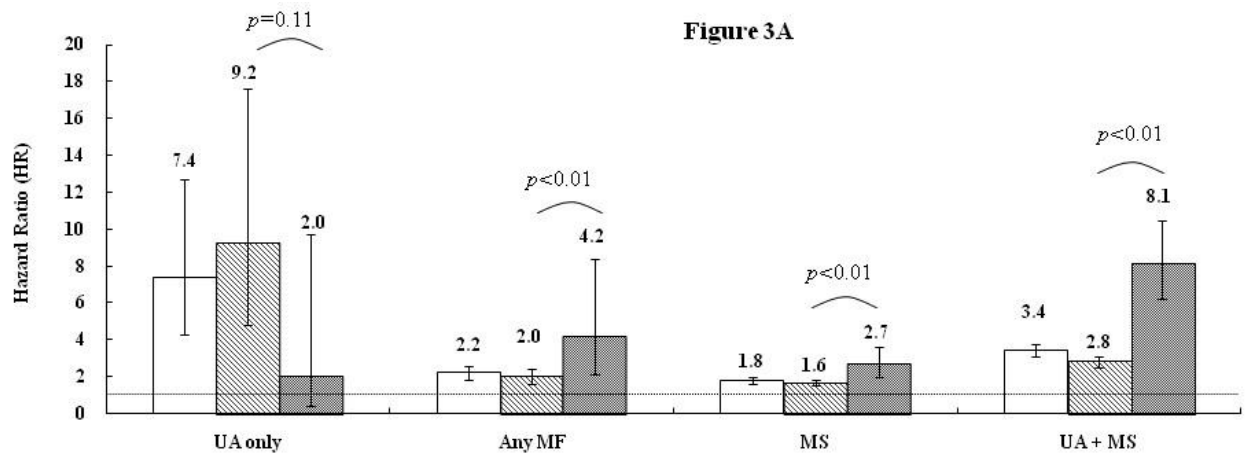
Figure 3A

Figure 3B

UA only: Risk of hyperuricemia among low risk subgroup

Any MF: ≧ 1 metabolic risk factors (MF)

MS: ≧ 3 metabolic risk factors (MF)

Figure 3. Gender-stratified hazard ratio and collective population-attributable risks of hyperuricemia and metabolic risk factors on gout. These metabolic risk factors (MF) were overweight, hypercholesterolemia, hyper-triglyceridemia, high blood pressure, and hyperglycemia. Multivariate Cox proportional hazard model was applied with adjustment of age, (sex), hyperuricemia and MF. The hazard risk (HR) and collective population-attributable risk (PAR) shown were those with hyperuricemia, with at least one MF, with metabolic syndrome (MS), or hyperuricemia with MS.

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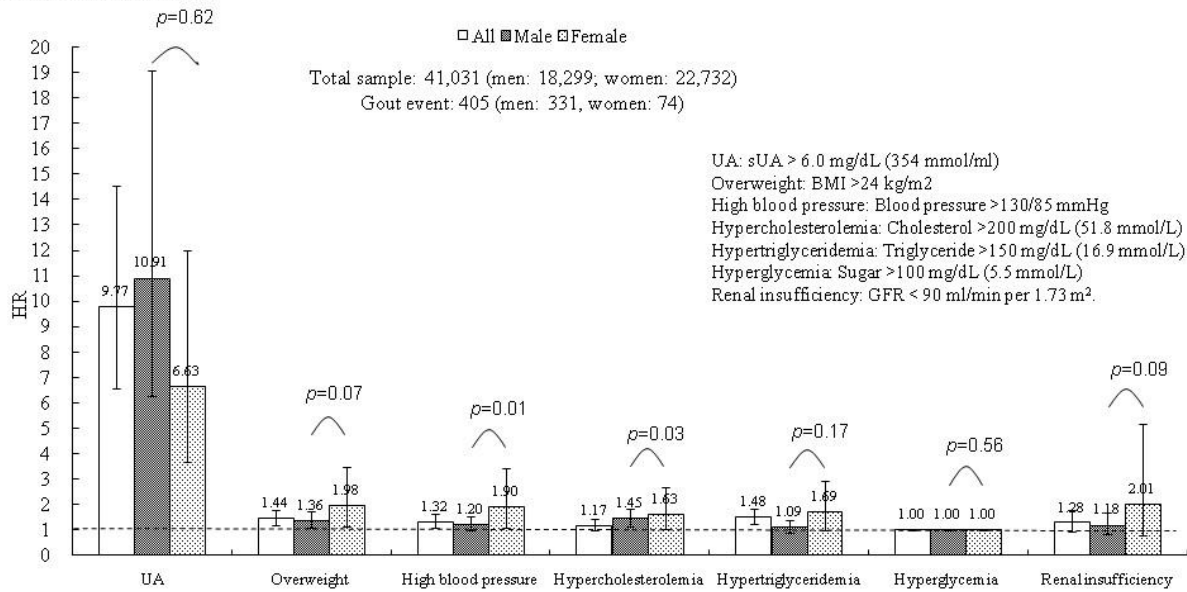
Supplementary Figure. Gender-stratified HR of hyperuricemia and metabolic risks on gout among individuals who had creatinine data. Of the total 41,031 patients, 18,293 were men and 22,743 were women. Renal insufficiency was defined in subjects whose glomerular filtration rate (GFR) <90 ml/min per 1.73 m^2. Multivariate Cox proportional hazard model was applied.