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ORIGINAL ARTICLE

Gender-specific risk factors for incident gout: a prospective cohort study

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Abstract Previous reports suggested that gout incidence increased with serum uric acid (sUA) level. In addition to sUA, we aimed to examine the gender-specific risk factors for incident gout. A prospective study was conducted using data of the MJ Health Screening Center and outcome database from Taiwan's National Health Insurance. Cox proportional hazard model was used for risk analysis of incident gout. During a mean follow-up of 7.31 years for 132,556 individuals aged ≥18 years, 1,606 subjects (1,341 men and 265 women) with clinical gout were defined. Hyperuricemia (sUA ≥7.7 mg/dL for men or ≥6.6 mg/dL for women) was the most important risk factor for gout development with a respective hazard ratio of 9.65 (95% confidence level, 8.53–10.9) for men and 9.28 (7.00–12.3) for women. The age-standardized sUA–gout relationship demonstrated a differential impact of sUA level on gout incidence between men and women. Metabolic comorbidities of hypertension, obesity, and hyperlipidemia were significantly associated with gout with respective HR of 1.32 (1.17–1.48), 1.30 (1.15–1.47), and 1.12 (0.99–1.26) for men and 1.34 (1.02–1.77), 2.15 (1.67–2.76), and 1.70 (1.32–2.19) for women. However, the relationship between diabetes and incident gout was not as prominent. The sex difference of sUA–gout relationship and the association between metabolic comorbidities and incident gout were demonstrated. Generalizability of these findings to other ethnic population needs further investigation.

Keywords Cohort study · Gout · Hyperuricemia · Sex

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Background

Gout is a common rheumatic disease which has recently drawn great research attention due to increasing incidence and prevalence reported worldwide in the past decades [1, 2]. Gouty arthritis occurs more frequently in men at younger ages than in women and is regarded as a result of interplays between genetic, metabolic, and environmental factors [3, 4].

Gouty arthritis is generally recognized as a result of monosodium urate (MSU) crystal deposition in the joint [3]. Using the level beyond 6.8–7.0 mg/dL at which extracellular uric acid supersaturates to define hyperuricemia [4] emphasizes crystal deposition property of urate in gout events [5]. The Normative Aging Study suggests that annual incidence of gout increases with increasing sUA levels [1, 2]. However, most gout-related reports studied

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men as contrast to the limited description of gout on women [6, 7]. Though sex difference has been observed for the age–hyperuricemia and age–gout relationships, impacts of sUA and other comorbidities on gout attack between sexes and difference between the pre- and post-menopausal women are not yet carefully examined [8].

In this study, we aimed to use baseline sUA data of health examinees collected from the MJ Health Screening Center and follow-up information from the Bureau of National Health Insurance (NHI) in Taiwan to determine the gender-specific risk factors for gout development.

Methods

Study population The study was conducted using health examinees' data collected by the privately owned nationwide MJ Health Screening Centers in Taiwan from 1994 to 1996. This dataset has been used in several recent publications on some timely and important research topics [9–11]. Detailed description of data for those health examinees and their socio-economic distribution has been described in our recent report [10]. This study was approved by the Institutional Review Boards of the China Medical University Hospital, Taichung and Academia Sinica, Taipei, Taiwan.

Exclusion criteria Data from 137,532 participants aged 18 years and above were included after excluding unclear data from 0.46% of the original cohort. 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 1994–1996 (n=189; see later description of gout definition). A total of 132,556 subjects (60,181 men and 72,375 women) free from gout at baseline were included in the statistical analyses.

Baseline information and definition of comorbidities Baseline information of these health examinees was used. SUA, cholesterol, triglyceride, and plasma glucose of fasting blood were measured enzymatically by using the Hitachi 7150 autoanalyzer (Tokyo, Japan). We defined hyperuricemia as sUA ≥7.7 mg/dL for men or ≥6.6 mg/dL for women [12]. sUA was further divided into gender-specific quartile levels. Obesity was defined as a body mass index (BMI) of ≥27 kg/m^2. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg or by the use of antihypertensive medications [13]. Diabetes was defined as fasting blood sugar ≥126 mg/dL or by the use of anti-diabetic medications. A cholesterol level of ≥240 mg/dL and triglyceride level of ≥200 mg/dL were used to define hypercholesterolemia and hypertriglyceridemia, respectively. Hyperlipidemia was defined by the presence of either hypercholesterolemia or hypertriglyceridemia. Current alcohol drinking was defined if the subjects answered "drinking alcohol occasionally", "frequently or daily" as opposed to either "never drinking" or "abstaining". Likewise, current cigarette smoking was defined if the subjects answered "smoking occasionally", "frequently or daily" versus either "not smoking at all" or "ex-smokers".

Follow-up database and definition of incident gout We extracted data from the database of NHI, a national program that began in 1995, to provide outcome information of this study. This is an administrative database containing dispensed medical claim record [14]. Clinical gout diagnosis was recorded using 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 in database from January 1, 1996 to December 31, 2002. Four sets of criteria to define incident gout were established as described below: (1) having diagnostic code of gout assigned during follow-up period; (2) the first criteria+ having colchicine prescribed at least twice at these visits of gout diagnosis; (3) the second criteria+having urate lowering drugs (including allopurinol, probenecid, sulfinpyrazone, or benzbromarone) prescribed with colchicine at these visits; and (4) the third criteria specifically defined by rheumatologists. The onset time of gout was defined either when ICD code was assigned for the first criteria or when colchicine was initially prescribed to the patient for the rest of the criteria.

Statistical analysis Baseline characteristics between sexes and those between the gout-free and the incident-gout participants were compared by two-sample t tests or chi-square tests. A sensitivity analysis on gout definition was carried out by comparing four sets of criteria.

We used criteria to estimate the annual incidence of gout per 1,000 person-years (PYs), with respect to sUA levels from 4.0 to 9.0 mg/dL at an incremental interval of 0.5 mg/dL. Age-standardized rate of gout incidence was calculated, combining the above incidence rate and Taiwanese population age distribution at the end of year 2000 by 5-year age groups. The relationship between sUA level and incident gout was further examined in stratified age and sex subgroups (ages 18–39 years, 40–64 years, and ≥65 years for men; ages <50 and ≥50 years for women).

Cox proportional hazard model was used to estimate the relative risks of hyperuricemia, each metabolic risk factor, and those between three upper sUA quartiles and the lowest with respect to the incidence of gout. In the multivariate

Table 1 Baseline characteristics of the participants in the MJ Health Screening Center, stratified by gender (N=132,556)

	Men (n=60,181)	Women (n=72,375)
	Mean±SD	Mean±SD
Age (years)	42.5±14.6	42.3±14.3
BMI (kg/m^2)	23.6±3.3	23.0±8.2
Cholesterol (mg/dL)	184.3±37.0	183.6±37.9
Triglyceride (mg/dL)	132.3±115.6	102.2±79.0
Glucose (mg/dL)	98.5±23.0	96.8±23.6
Uric acid (mg/dL)	6.8±1.4	5.2±1.3
Serum uric acid by age groups	Mean±SD, mg/dL (n)	Mean±SD, mg/dL (n)
18–30 years	6.8±1.4 (13,444)	5.0±1.1 (16,858)
31–40 years	6.9±1.4 (18,121)	5.0±1.1 (19,888)
41–50 years	6.8±1.4 (10,323)	5.1±1.2 (12,891)
51–60 years	6.6±1.6 (8,562)	5.5±1.4 (12,798)
>60 years	6.6±1.4 (9,731)	5.7±1.5 (9.940)
Serum uric acid levels (mg/dL)	N (%)	N (%)
≤5.0	5,866 (9.7)	36,499 (50.4)
5.1–7.0	31,278 (52.0)	30,005 (41.5)
7.1–9.0	19.387 (32.2)	5,192 (7.2)
>9.0	3,650 (6.1)	679 (0.9)
Hyperuricemia[a]	13,269 (22.0)	8,838 (12.2)

All variables were tested by two-sample t test or chi-square test, and significant differences were found between sexes (p<0.05). Cholesterol 1 mg/dL=0.0259 mmol/L, triglyceride 1 mg/dL=0.0113 mmol/L, uric acid 1 mg/dL=0.059 mmol/L, glucose 1 mg/dL=0.055 mmol/L

[a] Hyperuricemia: sUA >7.7 mg/dL for men or >6.6 mg/dL for women

models, age, sex, obesity, hypertension, hyperlipidemia, diabetes, alcohol drinking, and cigarette smoking were adjusted. Significance of the interaction between sexes and each covariate was tested with two main effects (each covariate and sex) and their interaction term in the model. Sex stratification was subsequently performed. All hazard ratios (HR) were provided with a 95% confidence interval (CI). The statistical package SAS 9.01 (SAS Institute, Cary, NC, USA) was used for analysis.

Results

Baseline characteristics and comorbidities The mean (±SD) sUA level was 6.8±1.4 mg/dL in men (Table 1), which was significantly higher than that in women (5.2±1.3 mg/dL; p<0.001). sUA levels in men were similar across age groups, but women's sUA levels increased with age, especially after menopause at the age of 50 years. Serum uric acid quartiles were <5.8 mg/dL (reference), 5.8–6.6 mg/dL, 6.7–7.6 mg/dL, and >7.6 mg/dL for men; and <4.3 mg/dL (reference), 4.3–5.0 mg/dL, 5.1–5.9 mg/dL, and >5.9 mg/dL for women. The prevalence of hyperuricemia in this study population was as high as 16.7%, i.e., 22.0% in men (≥7.7 mg/dL sUA) and 12.2% in women (≥6.6 mg/dL). The mean levels of cholesterol (184.3±37.0 mg/dL), triglyceride (132.3±115.6 mg/dL), glucose (98.5±23.0 mg/dL), and BMI (23.6±3.3 kg/m^2) in men were also higher than those in women (183.6±37.9 mg/dL, 102.2±79.0 mg/dL, 96.8±23.6 mg/dL, and 23.0±8.2 kg/m^2, respectively; all p<0.05).

In this 132,556 study population, there were 14.0%, i.e., 18,587, subjects (10,047 men and 8,540 women) who had been prescribed at least once of urate-lowering drugs. All of them had been previously assigned ICD code of gout, which made them satisfy the first criteria (Table 2). It is worth noting that these subjects comprised 84% of 22,107 hyperuricemia individuals (i.e., 13,269 men and 8,838 women) at baseline (Table 1).

Table 2 Baseline characteristics of MJ participants who developed gout versus those who did not (N=132,556)

Variables	Controls (n=113,969)	1st criteria (n=18,587)	2nd criteria (n=2,930)	3rd criteria (n=1,606)	4th criteria (n=238)
Age (years)	41.3±14.2	48.9±14.2	49.6±15.0	49.8±14.8	49.5±14.8
Men N (%)	50,134 (44.0%)	10,047 (54.1%)	2,396 (81.8%)	1,341 (83.5%)	207 (87.0%)
Uric acid (mg/dL)	5.8±1.5	6.8±1.8	8.3±1.8	8.5±1.7	8.8±1.8
SBP (mmHg)	124.8±20.8	133.2±23.5	137.4±23.7	138.3±23.5	140.5±21.5
DBP (mmHg)	69.6±12.2	74.6±13.1	77.7±13.3	78.3±13.2	80.2±12.1
Glucose (mg/dL)	96.9±22.3	101.7±28.4	100.4±24.3	100.0±23.9	97.5±12.6
Cholesterol (mg/dL)	182.3±36.8	194.1±40.2	196.1±41.1	196.6±41.6	194.9±39.4
Triglyceride (mg/dL)	110.7±90.4	147.3±133.7	170.3±165.6	169.4±174.3	178.3±107.7
BMI (kg/m^2)	23.0±3.8	24.8±14.5	25.4±3.4	25.5±3.5	25.5±3.3

1st criteria for gout definition: having diagnostic code of gout assigned during follow-up period; 2nd criteria for gout definition: 1st criteria+having colchicine prescribed at least twice at these visits of gout diagnosis; 3rd criteria for gout definition: 2nd criteria+having urate-lowering drugs (including allopurinol, probenecid, sulfinpyrazone, or benzbromarone) prescribed with colchicine at these visits; 4th criteria for gout definition: 3rd criteria specifically defined by rheumatologists

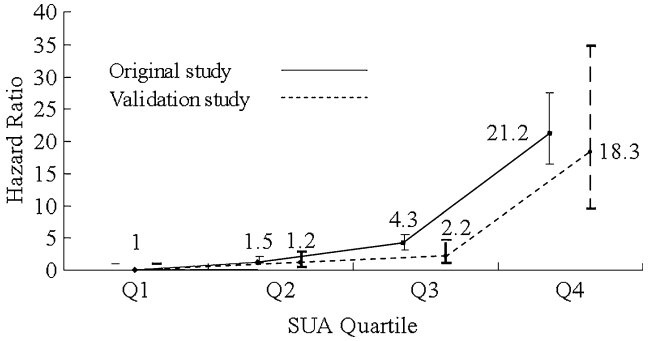


Fig. 1 Hazard ratios of gout attack comparing higher serum uric acid quartiles to the lowest quartile. Among 132,556 participants, there are 1,606 gout events defined by the third criteria in the original study and 238 events in the validation study defined by the fourth criteria. Serum uric acid quartiles are <5.8 mg/dL (reference), 5.8–6.6 mg/dL, 6.7–7.6 mg/dL, and >7.6 mg/dL for men, and <4.3 mg/dL (reference), 4.3–5.0 mg/dL, 5.1–5.9 mg/dL, and >5.9 mg/dL for women. All confidence intervals for HR in each quartile overlap between the original and validation studies

Sensitivity analysis of definition criteria for incident gout The results of sensitivity analysis on four sets of gout definition through comparing demographic information between gout patients and controls were summarized (Table 2). The results derived from the second, third, and fourth criteria were comparable, deviated from the first criteria. For instance, the mean sUA level of gout patients was from 8.3 mg/dL to 8.8 mg/dL. However, the mean sUA level derived from the first criteria was 6.8 mg/dL which was closer to 5.8 mg/dL of the controls. On the other hand, the proportion between men and women defined by the first criteria was almost equal, which does not satisfy the usual expectation for higher prevalence of men to have gout than women [7].

There was 1.2% of this study population, i.e., 1,606 subjects (1,341 men and 265 women), who satisfied the third criteria for incident gout defined by the general physicians (Table 2). The mean age of the gout subjects was 49.8±14.8 years. Most of the gout patients were men (83.5%). Although the case number of gout was only 238 (207 men and 31 women) according to the fourth criteria defined by the rheumatologists, the mean age of gout subjects (49.5±14.8 years) or the proportion of men (87.0%) was respectively close to those derived from the third criteria. Figure 1 shows the sex-combined HRs for gout attack (all p for interaction between sexes and sUA quartiles >0.20), defined by the third and fourth criteria, that compare risks of the higher sUA quartiles with the lowest one among patients. A marked increase in the HR (21.2; 95% confidence interval, 16.4–27.5) for the gout patients defined by the third criteria was noted in the fourth quartile (sUA ≥7.6 mg/dL for men and ≥5.9 mg/dL for women). In the meantime, a study validated by the patients of gout defined by the fourth criteria exhibited a similar

Table 3 Hazard ratios (95% confidence interval) of each metabolic risk factor on the future incidence of gouty arthritis (men=60,181; women=72,375; pre-menopausal women=49,637; post-menopausal women=22,738)

Sex (*n*/*N*) person years	Men (1,341/60,181)		Women (265/72,375)		Post-menopause (213/22,783)		Pre-menopause (52/49,637)	
	436,852.7 PYs		531,625.3 PYs		165,382.0 PYs		366,270.3 PYs	
Incidence	3.09×10^{-3} PYs		0.53×10^{-3} PYs		1.29×10^{-3} PYs		0.14×10^{-3} PYs	
HR (95% CI)	Age-adjusted	Multi-adjusted	Age-adjusted	Multi-adjusted	Age-adjusted	Multi-adjusted	Age-adjusted	Multi-adjusted
Age	–	1.03	–	1.05	–	1.02	–	1.09
	–	(1.02–1.03)	–	(1.04–1.06)	–	(1.00–1.04)	–	(1.04–1.13)
Hyperuricemia	10.5	9.65	12.3	9.28	9.54	7.68	25.3	17.2
	(9.27–11.8)	(8.53–10.9)	(9.33–16.1)	(7.00–12.3)	(7.08–12.9)	(5.66–10.4)	(13.7–47.0)	(8.98–33.1)
Obesity	2.13	1.30	3.70	2.15	2.97	1.90	6.48	2.50
	(1.88–2.40)	(1.15–1.47)	(2.90–4.72)	(1.67–2.76)	(2.27–3.88)	(1.44–2.51)	(3.67–11.5)	(1.38–4.52)
Hypertension	1.74	1.32	2.11	1.34	1.76	1.23	3.53	1.70
	(1.54–1.95)	(1.17–1.48)	(1.59–2.79)	(1.02–1.77)	(1.32–2.34)	(0.92–1.65)	(1.92–6.50)	(0.91–3.18)
Hyperlipidemia	1.81	1.12	2.77	1.70	2.36	1.59	4.34	1.79
	(1.61–2.04)	(0.99–1.26)	(2.16–3.57)	(1.32–2.19)	(1.80–3.09)	(1.20–2.09)	(2.37–7.96)	(0.96–3.35)
Diabetes	0.82	0.85	1.62	1.15	1.65	1.27	1.18	0.51
	(0.65–1.03)	(0.67–1.07)	(1.17–2.24)	(0.83–1.60)	(1.18–2.30)	(0.90–1.79)	(0.29–4.90)	(0.12–2.13)

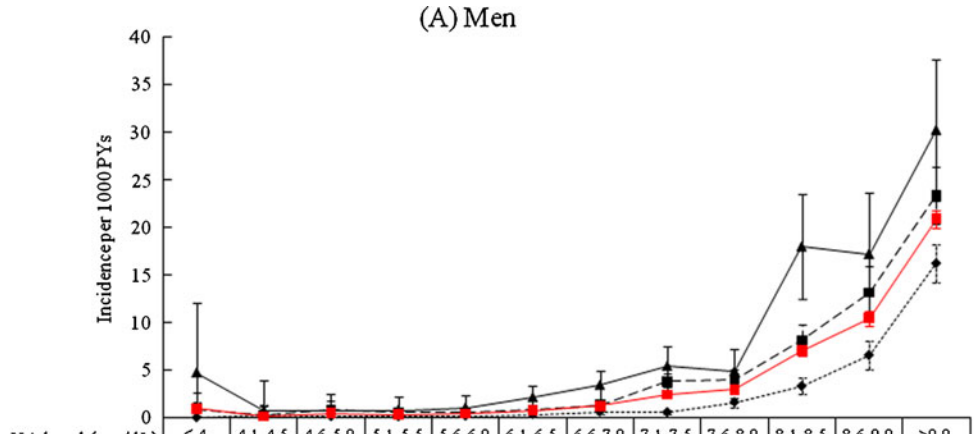
The multi-adjusted model of hyperuricemia was adjusted by age, obesity, hypertension, hyperlipidemia, diabetes, alcohol drinking, and cigarette smoking

pattern with a conspicuously sharp increase at the fourth quartile (18.3; 9.63–34.8). Confidence intervals for all HR estimates in each quartile overlapped substantially between the studies defined by the third and fourth criteria.

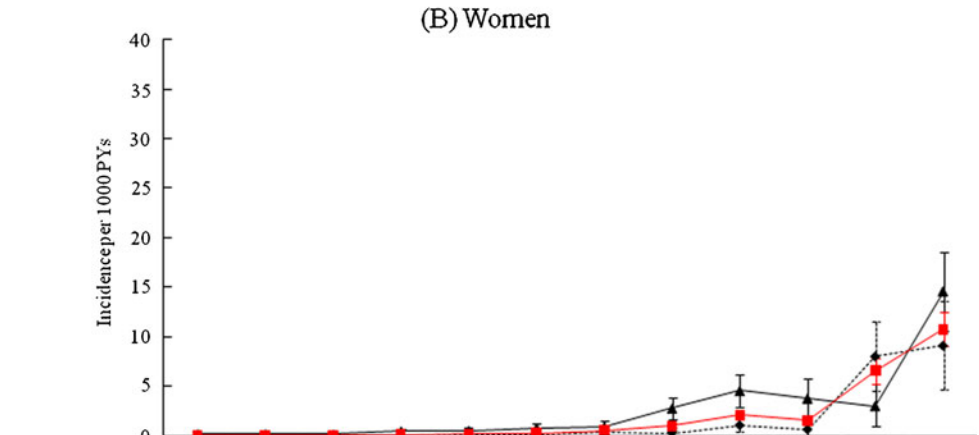
We decided to present estimates derived from the third criteria because the estimates of demographic characteristics (Table 2) and HRs of quartile sUA (Fig. 1) were comparable with those derived from the second and fourth criteria. Besides, the relationship between the metabolic risk factors and gout development was consistent for the second to the fourth criteria.

Age, sex, sUA, metabolic comorbidities, and incident gout The standardized overall incidence was 1.69 per 1,000 PYs. Incidence in men (3.09 per 1,000 PYs) was six times higher than that in women (0.53 per 1,000 PYs) (Table 3). The standardized incidence increased with each increment of sUA level (Fig. 2). The effect of sUA level increment on gout incidence elevation was greater in men than women. Gout occurred at a mean age of 54.0± 14.7 years (ages 52.3±14.8 years for men and 62.2± 11.1 years for women; $p<0.001$; no tabulated data shown). Older people had a higher incidence of gout at all levels of sUA.

The multivariate adjusted HR of hyperuricemia was 9.65 (95% CI, 8.53–10.9) in men, which was followed by hypertension (1.32; 1.17–1.48), obesity (1.30; 1.15–1.47), and hyperlipidemia (1.12; 0.99–1.26) (Table 3). On the other hand, adjusted HR of hyperuricemia in women was 9.28 (7.00–12.3), which was followed by obesity (2.15; 1.67–2.76), hyperlipidemia (1.70; 1.32–2.19), and hypertension (1.34; 1.02–1.77). For the post-menopausal



sUA level (mg/dL)	≤4	4.1-4.5	4.6-5.0	5.1-5.5	5.6-6.0	6.1-6.5	6.6-7.0	7.1-7.5	7.6-8.0	8.1-8.5	8.6-9.0	>9.0
18-39 y/o	0.00	0.25	0.12	0.11	0.17	0.35	0.61	0.56	1.63	3.31	6.58	16.26
40-64 y/o	0.91	0.22	0.87	0.51	0.56	0.86	1.35	3.83	4.02	8.13	13.17	23.37
≥65 y/o	4.72	0.72	0.70	0.77	1.02	2.10	3.39	5.40	4.84	17.97	17.19	30.26
Standardized	0.95	0.12	0.48	0.35	0.43	0.77	1.25	2.44	2.96	7.03	10.48	20.89



sUA level (mg/dL)	≤4	4.1-4.5	4.6-5.0	5.1-5.5	5.6-6.0	6.1-6.5	6.6-7.0	7.1-7.5	7.6-8.0	8.1-8.5	8.6-9.0	>9.0
<50 y/o	0.05	0.00	0.04	0.03	0.07	0.07	0.41	0.32	1.10	0.68	8.07	9.16
≥50 y/o	0.24	0.23	0.21	0.52	0.58	0.87	0.99	2.82	4.59	3.82	3.07	14.57
Standardized	0.11	0.07	0.09	0.17	0.22	0.30	0.58	1.05	2.12	1.60	6.60	10.75

Fig. 2 Relationship between incidence of gout and serum uric acid levels by sex and by age. Incidence estimates (per 1,000 person-years) and 95% confidence intervals are provided. Age-standardized incidence (*bold line*) of gout is calculated from Taiwanese population at year 2000. The tables below show the respective age–sUA incidence per 1,000 PYs

women, risk of hyperuricemia was comparatively lower with a HR of 7.68 (5.66–10.4); however, due to less case number, HR of hyperuricemia for the pre-menopausal women was 17.2 (8.98–33.1). Both risks of obesity and hyperlipidemia were of importance for gout development in the post- and pre-menopausal women. Their respective HRs were 1.90 (1.44–2.50) and 2.50 (1.38–4.52) for obesity, and 1.59 (1.20–2.09) and 1.79 (0.96–3.35) for hyperlipidemia. The relationship between diabetes and incident gout was not as prominent.

Discussion

We found that hyperuricemia was the most import risk factor for gout development. HRs of hyperuricemia for men with sUA at 7.7 mg/dL and women at 6.6 mg/dL in the present study were almost equal (HR 9.65 for men and 9.28 for women, respectively), and the 95% confidence intervals overlapped, while a HR of 7.68 for the post-menopausal women was comparatively lower. The sUA–gout relationship with higher impact of sUA on men than women is further demonstrated in Fig. 2. The greater impact of sUA elevation on gout incidence in men [7, 15] may be attributable to a higher mean sUA level and a higher prevalence of hyperuricemia in men (6.8 mg/dL and 22.0%, respectively) than in women (5.2 mg/dL and 12.2%, respectively). Enhanced uricosuric effect of estrogen [8] on renal tubules in women may be responsible for lower incidence of hyperuricemia and gout in women [15].

We observed that women's mean gout onset age (62.2 years) was 10 years older than that of men's (52.3 years). The age and sex difference of gout occurrence with respect to sUA levels has been explained by a greater impact of insulin on renal uric acid resorption in women [16] and a higher prevalence of abdominal obesity with insulin resistance in post-menopausal women [7]. In the present study, obesity and hyperlipidemia were shown as important risk factors especially in women. Contribution of hypertension for incident gout was also demonstrated. A close association between these metabolic comorbidities for gout development is suggested [17]. On the other hand, patients with diabetes was noted to have a lower future risk of gout, which is also compatible with the previous report hypothesizing that glycosuria may result in uricosuria [18].

Presence of MSU crystal in the synovial fluid by arthrocentesis is considered essential for gout diagnosis in the past [19]. However, sensitivity of crystal diagnosis for gouty arthritis can be low in a large population study. Recent epidemiologic research using administrative claim data in gout study has suggested that diagnosis of gout with at least two ambulatory visits may present a positive predictive value of 61%. An evaluation by rheumatologists can substantially increase the value up to 92% [20]. The current study used information from NHI in Taiwan, which may have the weakness in classifying "true" gout subjects [21]. We thus used sensitivity analysis for different sets of criteria to define gout and found comparability between these definitions especially that made between general physicians and rheumatologists. Incident gout defined by linking medical dispensed record of colchicine and/or urate-lowering drugs may add to the validity for defining chronic gout and would not change the relationship between respective risk factor and gout development.

Conclusions

In this study, a sex difference of sUA–gout relationship has supported a higher risk impact of sUA level for men than that for women. Metabolic comorbidities of hypertension, obesity, and hyperlipidemia are shown as important risk factors for incident gout, and obesity is especially worth noting for women. Further replication studies for the generalizability of our findings are needed in the future.

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