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Ann Rheum Dis

Supplemental Files

Serum uric acid control for prevention of gout flare in patients with asymptomatic hyperuricaemia: a retrospective cohort study of health insurance claims and medical check-up data in Japan

Contents:

Supplemental Methods

Methods of propensity score analysis

A multivariate logistic regression model was used to estimate the propensity score. Explanatory variables were age and estimated glomerular filtration rate (eGFR) at the follow-up date, number of measurements of serum uric acid levels (sUA) in period 1, number of comorbidities of interest in period 1, sex, presence of comorbidities in period 1 (hypertension, type 2 diabetes, ischemic heart disease, heart failure, cerebrovascular disease, hyperlipidaemia), and drug prescriptions in period 1 (antihyperlipidaemic drug, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), diuretic drug, antidiabetic drug). Goodness of fit of the propensity score was evaluated by the Hosmer-Lemeshow test and the C statistic. If eGFR measurements were missing for the follow-up date, values from the index date were used. Because goodness of fit was improved by adding quadratic terms to the explanatory variables, the propensity score was estimated from a model that included those quadratic terms.

We conducted 3 analyses to estimate effects: inverse probability weighting (IPW), propensity score matching (PS match), and analysis of the original cohort. IPW using the propensity score was employed to estimate the average treatment effect (ATE), as well as average treatment effect for the treated (ATT) in the groups having sUA ≤6.0 mg/dL, at the follow-up date. For PS match, 1:1 matching protocol without replacement (greedy nearest neighbour matching) was used, with calliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Analysis of the original cohort was also performed without using the propensity score. The primary analysis was the ATE, estimated by the IPW. Other analyses were performed to confirm the robustness of the primary analysis findings.

Before and after the propensity score analysis, standardized differences were calculated to assess between-group balance for all baseline characteristics. For a given covariate, standardized differences of <0.1 indicate a relatively small imbalance. Each analysis used Kaplan-Meier curves to estimate the time to first gout flare in period 2. Univariate analysis was performed using the Cox proportional hazards model, with group (sUA ≤6.0 mg/dL or >6.0 mg/dL) as a covariate. Multivariable analysis was also applied to the original cohort.

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Supplemental Tables

Table S1 List of definitions

Definitions of patient characteristics

- Hypertension: ICD10 code I10-I15 (Hypertensive diseases)
- Type 2 diabetes : ICD10 code E11 (Type 2 diabetes mellitus), E12 (Malnutrition-related diabetes mellitus), E13 (Other specified diabetes mellitus) or E14 (Unspecified diabetes mellitus)
- Ischemic heart disease: ICD10 code I20-I25 (Ischemic heart diseases)
- Heart failure: ICD10 code I50 (Heart failure)
- Cerebrovascular disease: ICD10 code I60-I69 (Cerebrovascular diseases)
- Hyperlipidaemia: ICD10 code E78 (Disorders of lipoprotein metabolism and other lipidaemias)

Definitions of drugs

- Antihyperlipidaemic drug: ATC codes C10A (Cholesterol and triglyceride regulating preparations), C10B (Anti-atheroma preparations of natural origin), or C11A (Lipid-regulating cardiovascular multitherapy combination products)
- ACE inhibitor: ATC code C09A (ACE inhibitors, plain)
- ARB: ATC code C09C (Angiotensin II antagonists, plain), C09D1 (Angiotensin II antagonists combinations with antihypertensive (C2) and/or diuretics) or C09D3 (Angiotensin II antagonists combinations with calcium antagonists)
- Diuretic drug: ATC code C03 (Diuretics)
- Antidiabetic drug: ATC code A10C (Human insulins and analogues), A10H (Sulphonylurea antidiabetic), A10J (Biguanide antidiabetics), A10K (Glitazone antidiabetics), A10L (Alpha-glucosidase inhibitor antidiabetics), A10M (Glinide antidiabetics), A10N (DPP-IV inhibitor antidiabetics), A10P (SGLT2 inhibitor antidiabetics), A10S (GLP-1 agonist antidiabetics), or A10X (Other drugs used in diabetes).

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ATC, anatomical therapeutic chemical; DPP-IV, dipeptidyl peptidase IV; GLP-1, glucagon like peptide-1; ICD, international statistical classification of diseases and related health problems; SGLT2, sodium-glucose cotransporter 2.

Table S2 Subject characteristics by disease status

	Asymptomatic hyperuricaemia			Gout			No treatment required	All
	ULT (+)		ULT (−)	ULT (+)		ULT (−)	ULT (−)	
	sUA ≤6.0 mg/dL	sUA >6.0 mg/dL	sUA ≥8.0 mg/dL	sUA ≤6.0 mg/dL	sUA >6.0 mg/dL	sUA ≥8.0 mg/dL	sUA <8.0 mg/dL	
	n=337	n=884	n=7049	n=101	n=303	n=107	n=10 480	n=19 261
Age, years								
Mean±SD	49.0 ± 8.8	46.2 ± 9.3	43.8 ± 9.2	50.1 ± 8.6	46.6 ± 8.8	45.5 ± 8.6	44.1 ± 9.5	44.2 ± 9.4
n (%)								
18-19	0	0	0	0	0	0	0	0
20-29	4 (1.2)	40 (4.5)	432 (6.1)	2 (2.0)	9 (3.0)	2 (1.9)	720 (6.9)	1209 (6.3)
30-39	47 (13.9)	152 (17.2)	1785 (25.3)	10 (9.9)	51 (16.8)	23 (21.5)	2495 (23.8)	4563 (23.7)
40-49	114 (33.8)	372 (42.1)	2904 (41.2)	35 (34.7)	134 (44.2)	49 (45.8)	4148 (39.6)	7756 (40.3)
50-59	136 (40.4)	261 (29.5)	1648 (23.4)	42 (41.6)	82 (27.1)	26 (24.3)	2629 (25.1)	4824 (25.0)
60-69	35 (10.4)	57 (6.4)	264 (3.7)	11 (10.9)	26 (8.6)	7 (6.5)	468 (4.5)	868 (4.5)
≥70	1 (0.3)	2 (0.2)	16 (0.2)	1 (1.0)	1 (0.3)	0	20 (0.2)	41 (0.2)
Sex, n (%)								
Male	330 (97.9)	872 (98.6)	6952 (98.6)	100 (99.0)	301 (99.3)	107 (100.0)	10 262 (97.9)	18 924 (98.3)
Female	7 (2.1)	12 (1.4)	97 (1.4)	1 (1.0)	2 (0.7)	0	218 (2.1)	337 (1.7)
eGFR, mL/min/1.73m^2*								
Mean±SD	72.93 ± 17.21	71.53 ± 15.11	74.45 ± 14.26	73.11 ± 12.07	72.43 ± 14.89	72.77 ± 12.83	78.52 ± 14.21	76.46 ± 14.51
n (%)								
≥90	40 (11.9)	93 (10.5)	897 (12.7)	7 (6.9)	36 (11.9)	11 (10.3)	2004 (19.1)	3088 (16.0)
≥60, <90	243 (72.1)	603 (68.2)	5226 (74.1)	80 (79.2)	212 (70.0)	81 (75.7)	7726 (73.7)	14 171 (73.6)
≥30, <60	46 (13.6)	183 (20.7)	910 (12.9)	14 (13.9)	55 (18.2)	15 (14.0)	737 (7.0)	1960 (10.2)
≥15, <30	3 (0.9)	4 (0.5)	10 (0.1)	0	0	0	6 (<0.1)	23 (0.1)
<15	5 (1.5)	1 (0.1)	6 (<0.1)	0	0	0	7 (<0.1)	19 (<0.1)
≥60	283 (84.0)	696 (78.7)	6123 (86.9)	87 (86.1)	248 (81.8)	92 (86.0)	9730 (92.8)	17 259 (89.6)
<60	54 (16.0)	188 (21.3)	926 (13.1)	14 (13.9)	55 (18.2)	15 (14.0)	750 (7.2)	2002 (10.4)
sUA, mg/dL								
Mean±SD	5.30 ± 0.65	7.48 ± 0.99	8.64 ± 0.61	5.28 ± 0.64	7.78 ± 1.21	8.74 ± 0.59	7.20 ± 0.57	7.71 ± 1.00
n (%)								
<8	337 (100.0)	617 (69.8)	0	101 (100.0)	180 (59.4)	0	10 480 (100.0)	11 715 (60.8)
≥8, <9	0	199 (22.5)	5393 (76.5)	0	73 (24.1)	77 (72.0)	0	5742 (29.8)
≥9, <10	0	56 (6.3)	1390 (19.7)	0	34 (11.2)	25 (23.4)	0	1505 (7.8)
≥10	0	12 (1.4)	266 (3.8)	0	16 (5.3)	5 (4.7)	0	299 (1.6)
Comorbidities of interest, n (%)								
Hypertension	173 (51.3)	339 (38.3)	990 (14.0)	29 (28.7)	55 (18.2)	17 (15.9)	1550 (14.8)	3153 (16.4)
Type 2 diabetes	62 (18.4)	134 (15.2)	391 (5.5)	11 (10.9)	28 (9.2)	12 (11.2)	703 (6.7)	1341 (7.0)
Ischemic heart disease	19 (5.6)	37 (4.2)	149 (2.1)	5 (5.0)	7 (2.3)	3 (2.8)	213 (2.0)	433 (2.2)
Heart failure	16 (4.7)	36 (4.1)	124 (1.8)	4 (4.0)	10 (3.3)	2 (1.9)	184 (1.8)	376 (2.0)
Cerebrovascular disease	20 (5.9)	35 (4.0)	79 (1.1)	3 (3.0)	6 (2.0)	3 (2.8)	180 (1.7)	326 (1.7)
Hyperlipidaemia	196 (58.2)	458 (51.8)	984 (14.0)	32 (31.7)	78 (25.7)	19 (17.8)	1716 (16.4)	3483 (18.1)
Number of comorbidities, n (%)								
0	61 (18.1)	228 (25.8)	4801 (68.1)	43 (42.6)	158 (52.1)	66 (61.7)	7291 (69.6)	12 648 (65.7)
1	116 (34.4)	306 (34.6)	1404 (19.9)	33 (32.7)	90 (29.7)	27 (25.2)	1872 (17.9)	3848 (20.0)
2	84 (24.9)	205 (23.2)	493 (7.0)	14 (13.9)	28 (9.2)	4 (3.7)	785 (7.5)	1613 (8.4)
3	52 (15.4)	94 (10.6)	214 (3.0)	7 (6.9)	16 (5.3)	4 (3.7)	342 (3.3)	729 (3.8)
4	20 (5.9)	32 (3.6)	86 (1.2)	4 (4.0)	10 (3.3)	6 (5.6)	136 (1.3)	294 (1.5)
5	4 (1.2)	14 (1.6)	41 (0.6)	0	1 (0.3)	0	41 (0.4)	101 (0.5)
6	0	4 (0.5)	8 (0.1)	0	0	0	12 (0.1)	24 (0.1)
7	0	1 (0.1)	2 (<0.1)	0	0	0	1 (<0.1)	4 (<0.1)
Concomitant medications, n (%)								
Antihyperlipidaemic drug	156 (46.3)	281 (31.8)	458 (6.5)	20 (19.8)	47 (15.5)	9 (8.4)	827 (7.9)	1798 (9.3)
ACE inhibitor	9 (2.7)	19 (2.1)	55 (0.8)	1 (1.0)	4 (1.3)	0	71 (0.7)	159 (0.8)
ARB	115 (34.1)	222 (25.1)	618 (8.8)	17 (16.8)	27 (8.9)	12 (11.2)	960 (9.2)	1971 (10.2)
Diuretic drug	18 (5.3)	53 (6.0)	141 (2.0)	2 (2.0)	3 (1.0)	3 (2.8)	186 (1.8)	406 (2.1)
Antidiabetic drug	24 (7.1)	47 (5.3)	140 (2.0)	1 (1.0)	5 (1.7)	6 (5.6)	249 (2.4)	472 (2.5)

*eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$. Data at the index date were used if data at the follow-up date were missing.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; SD, standard deviation; sUA, serum uric acid levels; ULT, urate-lowering therapy.

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Table S3 Cox proportional hazards model analysis of the time to first gout flare in period 2

(A) Subjects with asymptomatic hyperuricaemia

Parameter category	n	Median time (95% CI)	Unadjusted HR (95% CI)	Adjusted[†] HR (95% CI)	P value
Age, years					
18-29	476	− (−, −)	1.00	1.00	
30-39	1984	− (−, −)	1.54 (1.10, 2.16)	1.55 (1.10, 2.18)	0.012
40-49	3390	− (−, −)	2.05 (1.48, 2.83)	2.09 (1.49, 2.91)	<0.001
50-59	2045	− (−, −)	2.14 (1.53, 2.98)	2.32 (1.64, 3.27)	<0.001
≥60	375	− (−, −)	2.17 (1.44, 3.27)	2.48 (1.61, 3.82)	<0.001
Sex					
Male	8154	− (−, −)	1.00	1.00	
Female	116	− (−, −)	0.43 (0.20, 0.90)	0.42 (0.20, 0.89)	0.023
eGFR, mL/min/1.73m²*					
≥90	1030	− (−, −)	1.00	1.00	
≥60, <90	6072	− (−, −)	1.30 (1.07, 1.57)	1.11 (0.91, 1.35)	0.304
<60	1168	− (−, −)	1.67 (1.33, 2.09)	1.70 (1.30, 2.22)	<0.001
Number of comorbidities of interest					
0	5090	− (−, −)	1.00	1.00	
1	1826	− (−, −)	1.07 (0.93, 1.23)	0.81 (0.69, 0.96)	0.016
2	782	− (−, −)	0.87 (0.70, 1.07)	0.66 (0.52, 0.83)	<0.001
3	360	− (−, −)	0.68 (0.49, 0.95)	0.49 (0.34, 0.70)	<0.001
≥4	212	− (−, −)	0.66 (0.42, 1.03)	0.43 (0.27, 0.69)	<0.001
sUA control					
ULT (−), sUA (mg/dL) ≥8.0	7049	− (−, −)	1.00	1.00	
ULT (+), sUA (mg/dL) ≤5.0	88	− (−, −)	0.58 (0.29, 1.15)	0.64 (0.32, 1.29)	0.216
ULT (+), 5.0< sUA (mg/dL) ≤6.0	249	− (−, −)	0.40 (0.24, 0.66)	0.45 (0.27, 0.76)	0.002
ULT (+), 6.0< sUA (mg/dL) ≤7.0	358	− (−, −)	0.86 (0.64, 1.16)	0.97 (0.71, 1.32)	0.839
ULT (+), sUA (mg/dL) >7.0	526	− (−, −)	1.18 (0.95, 1.46)	1.29 (1.04, 1.61)	0.022

(B) Subjects with gout

Parameter category	n	Median time (95% CI)	Unadjusted HR (95% CI)	Adjusted[†] HR (95% CI)	P value
Age, years					
18-29	13	76.0 (26.0, −)	1.00	1.00	
30-39	84	− (187.7, −)	0.58 (0.27, 1.24)	0.59 (0.27, 1.28)	0.178
40-49	218	146.9 (94.9, 186.7)	0.89 (0.43, 1.81)	0.99 (0.47, 2.08)	0.977
50-59	150	164.6 (114.6, −)	0.80 (0.39, 1.65)	0.99 (0.46, 2.12)	0.970
≥60	46	142.1 (72.4, −)	0.78 (0.35, 1.75)	1.09 (0.45, 2.60)	0.851
Sex					
Male	508	164.6 (139.9, 220.4)	1.00	1.00	
Female	3	− (22.0, −)	0.61 (0.09, 4.35)	0.80 (0.11, 5.93)	0.826
eGFR, mL/min/1.73m²*					
≥90	54	112.7 (50.3, −)	1.00	1.00	
≥60, <90	373	169.7 (131.6, 220.4)	0.89 (0.61, 1.32)	0.81 (0.54, 1.22)	0.314
<60	84	164.6 (133.4, −)	0.80 (0.50, 1.28)	0.64 (0.37, 1.10)	0.109
Number of comorbidities of interest					
0	267	169.7 (128.6, 216.7)	1.00	1.00	
1	150	158.3 (110.3, −)	1.02 (0.78, 1.35)	1.09 (0.81, 1.48)	0.572
2	46	− (99.4, −)	0.81 (0.50, 1.32)	0.82 (0.49, 1.38)	0.454
3	27	70.6 (18.0, −)	1.15 (0.66, 1.99)	1.13 (0.64, 2.01)	0.667
≥ 4	21	164.6 (71.1, −)	0.96 (0.52, 1.78)	1.08 (0.55, 2.12)	0.815
sUA control					
ULT (−), sUA (mg/dL) ≥8.0	107	158.3 (120.6, −)	1.00	1.00	
ULT (+), sUA (mg/dL) ≤5.0	33	127.6 (14.9, −)	1.24 (0.73, 2.12)	1.22 (0.71, 2.10)	0.465
ULT (+), 5.0< sUA (mg/dL) ≤6.0	68	− (164.6, −)	0.70 (0.44, 1.11)	0.65 (0.40, 1.05)	0.078
ULT (+), 6.0< sUA (mg/dL) ≤7.0	102	− (176.3, −)	0.78 (0.53, 1.17)	0.76 (0.51, 1.14)	0.179
ULT (+), sUA (mg/dL) >7.0	201	125.6 (87.3, 157.1)	1.23 (0.89, 1.69)	1.23 (0.89, 1.70)	0.207

*eGFR (male) = 194 × sCr$^{-1.094}$ × age$^{-0.287}$, eGFR (female) = 194 × sCr$^{-1.094}$ × age$^{-0.287}$ × 0.739. Data at the index date were used if data at the follow-up date were missing.

[†] Sex, number of comorbidities of interest in period 1, and age, eGFR, and sUA control at the follow-up date were included in the model.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; sUA, serum uric acid levels; ULT, urate-lowering therapy.

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Table S4 Negative binomial regression model analysis for incidence rate of gout flare (flares/person-year) in period 2

(A) Subjects with asymptomatic hyperuricaemia

Parameter category	n	Univariable		Multivariable[†]		
		Incidence rate (95% CI), flares/person-year	RR (95% CI)	Incidence rate (95% CI), flares/person-year	RR (95% CI)	P value
Age, years						
18-29	476	0.040 (0.029, 0.056)	1.00	0.015 (0.009, 0.025)	1.00	
30-39	1984	0.060 (0.052, 0.069)	1.47 (1.03, 2.11)	0.023 (0.014, 0.035)	1.52 (1.06, 2.17)	0.023
40-49	3390	0.081 (0.073, 0.090)	2.00 (1.42, 2.82)	0.031 (0.021, 0.048)	2.12 (1.49, 3.02)	<0.001
50-59	2045	0.092 (0.080, 0.105)	2.26 (1.59, 3.22)	0.038 (0.025, 0.058)	2.56 (1.77, 3.71)	<0.001
≥60	375	0.094 (0.068, 0.130)	2.33 (1.47, 3.69)	0.040 (0.024, 0.066)	2.67 (1.65, 4.32)	<0.001
Sex						
Male	8154	0.077 (0.072, 0.083)	1.00	0.044 (0.035, 0.056)	1.00	
Female	116	0.033 (0.016, 0.067)	0.43 (0.21, 0.87)	0.017 (0.008, 0.036)	0.39 (0.19, 0.79)	0.009
eGFR, mL/min/1.73m^2*						
≥90	1030	0.064 (0.052, 0.078)	1.00	0.024 (0.015, 0.038)	1.00	
≥60, <90	6072	0.074 (0.068, 0.081)	1.17 (0.94, 1.45)	0.023 (0.015, 0.036)	0.97 (0.77, 1.22)	0.799
<60	1168	0.101 (0.085, 0.121)	1.59 (1.21, 2.08)	0.038 (0.024, 0.059)	1.58 (1.15, 2.17)	0.004
Number of comorbidities of interest						
0	5090	0.078 (0.072, 0.085)	1.00	0.044 (0.028, 0.068)	1.00	
1	1826	0.082 (0.071, 0.095)	1.05 (0.89, 1.25)	0.033 (0.021, 0.052)	0.76 (0.62, 0.93)	0.007
2	782	0.071 (0.057, 0.089)	0.91 (0.71, 1.16)	0.031 (0.020, 0.049)	0.71 (0.54, 0.93)	0.013
3	360	0.057 (0.040, 0.082)	0.73 (0.51, 1.06)	0.024 (0.014, 0.040)	0.54 (0.37, 0.81)	0.002
≥ 4	212	0.044 (0.027, 0.072)	0.57 (0.34, 0.93)	0.015 (0.008, 0.028)	0.34 (0.20, 0.58)	<0.001
sUA control						
ULT (−), sUA (mg/dL) ≥8.0	7049	0.078 (0.073, 0.084)	1.00	0.035 (0.024, 0.051)	1.00	
ULT (+), sUA (mg/dL) ≤5.0	88	0.048 (0.023, 0.102)	0.62 (0.29, 1.31)	0.023 (0.010, 0.053)	0.65 (0.31, 1.39)	0.269
ULT (+), 5.0< sUA (mg/dL) ≤6.0	249	0.028 (0.017, 0.046)	0.36 (0.21, 0.59)	0.014 (0.008, 0.027)	0.40 (0.24, 0.68)	0.001
ULT (+), 6.0< sUA (mg/dL) ≤7.0	358	0.063 (0.044, 0.089)	0.81 (0.56, 1.15)	0.032 (0.019, 0.053)	0.91 (0.64, 1.31)	0.624
ULT (+), sUA (mg/dL) >7.0	526	0.092 (0.071, 0.120)	1.18 (0.90, 1.55)	0.043 (0.027, 0.068)	1.23 (0.93, 1.63)	0.141

(B) Subjects with gout

Parameter category	n	Univariable		Multivariable[†]		
		Incidence rate (95% CI), flares/person-year	RR (95% CI)	Incidence rate (95% CI), flares/person-year	RR (95% CI)	P value
Age, years						
18-29	13	0.446 (0.188, 1.061)	1.00	0.245 (0.061, 0.982)	1.00	
30-39	84	0.302 (0.211, 0.432)	0.68 (0.27, 1.73)	0.170 (0.054, 0.539)	0.69 (0.27, 1.76)	0.442
40-49	218	0.503 (0.408, 0.621)	1.13 (0.46, 2.75)	0.307 (0.101, 0.932)	1.25 (0.51, 3.04)	0.622
50-59	150	0.446 (0.345, 0.578)	1.00 (0.41, 2.47)	0.271 (0.091, 0.804)	1.10 (0.44, 2.74)	0.832
≥60	46	0.426 (0.265, 0.687)	0.96 (0.36, 2.57)	0.286 (0.089, 0.916)	1.16 (0.42, 3.21)	0.769
Sex						
Male	508	0.447 (0.388, 0.514)	1.00	0.427 (0.314, 0.580)	1.00	
Female	3	0.151 (0.018, 1.265)	0.34 (0.04, 2.84)	0.147 (0.017, 1.244)	0.34 (0.04, 2.87)	0.324
eGFR, mL/min/1.73m^2*						
≥90	54	0.467 (0.305, 0.716)	1.00	0.319 (0.099, 1.028)	1.00	
≥60, <90	373	0.455 (0.386, 0.536)	0.97 (0.62, 1.54)	0.271 (0.090, 0.818)	0.85 (0.53, 1.35)	0.490
<60	84	0.385 (0.269, 0.550)	0.82 (0.47, 1.44)	0.183 (0.059, 0.566)	0.57 (0.31, 1.05)	0.072
Number of comorbidities of interest						
0	267	0.425 (0.351, 0.516)	1.00	0.202 (0.068, 0.603)	1.00	
1	150	0.391 (0.301, 0.507)	0.92 (0.66, 1.27)	0.197 (0.065, 0.600)	0.97 (0.68, 1.39)	0.876
2	46	0.580 (0.371, 0.908)	1.36 (0.84, 2.22)	0.309 (0.096, 0.993)	1.53 (0.91, 2.55)	0.105
3	27	0.804 (0.452, 1.430)	1.89 (1.03, 3.47)	0.439 (0.130, 1.480)	2.17 (1.13, 4.18)	0.021
≥ 4	21	0.330 (0.160, 0.678)	0.77 (0.37, 1.63)	0.183 (0.050, 0.677)	0.91 (0.41, 2.01)	0.807
sUA control						
ULT (−), sUA (mg/dL) ≥8.0	107	0.495 (0.366, 0.669)	1.00	0.298 (0.096, 0.924)	1.00	
ULT (+), sUA (mg/dL) ≤5.0	33	0.436 (0.253, 0.754)	0.88 (0.47, 1.64)	0.263 (0.077, 0.894)	0.88 (0.48, 1.63)	0.690
ULT (+), 5.0< sUA (mg/dL) ≤6.0	68	0.278 (0.185, 0.419)	0.56 (0.34, 0.93)	0.162 (0.051, 0.516)	0.54 (0.33, 0.91)	0.020
ULT (+), 6.0< sUA (mg/dL) ≤7.0	102	0.455 (0.333, 0.622)	0.92 (0.60, 1.42)	0.273 (0.091, 0.823)	0.92 (0.59, 1.42)	0.694
ULT (+), sUA (mg/dL) >7.0	201	0.470 (0.377, 0.587)	0.95 (0.65, 1.38)	0.286 (0.094, 0.869)	0.96 (0.66, 1.39)	0.822

*eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$. Data at the index date were used if data at the follow-up date were missing.

† Sex, number of comorbidities of interest in period 1, and age, eGFR, and sUA control at the follow-up date were included in the model.

CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative incidence rate; sUA, serum uric acid levels; ULT, urate-lowering therapy.

Table S5 Distribution of baseline characteristics between groups in the original, IPW, and PS matched cohorts (subjects with asymptomatic hyperuricaemia who were prescribed ULT)

	Original cohort			IPW cohort (ATE)			IPW cohort (ATT)			PS matched cohort		
	sUA		Standardized difference	sUA		Standardized difference	sUA		Standardized difference	sUA		Standardized difference
	≤6.0 mg/dL n=337	>6.0 mg/dL n=884		≤6.0 mg/dL n=1184	>6.0 mg/dL n=1232		≤6.0 mg/dL n=337	>6.0 mg/dL n=348		≤6.0 mg/dL n=336	>6.0 mg/dL n=336	
Age, years												
Mean±SD	49.0 ± 8.8	46.2 ± 9.3	0.32	47.6 ± 9.2	47.1 ± 9.3	0.05	49.0 ± 8.8	49.4 ± 8.9	−0.04	49.0 ± 8.8	49.1 ± 8.3	−0.01
n (%)												
18-19	0	0	–	0	0	–	0	0	–	0	0	–
20-29	4 (1.2)	40 (4.5)	−0.20	31 (2.6)	47 (3.8)	−0.07	4 (1.2)	7 (1.9)	−0.06	4 (1.2)	6 (1.8)	−0.05
30-39	47 (13.9)	152 (17.2)	−0.09	211 (17.8)	187 (15.2)	0.07	47 (13.9)	35 (10.2)	0.12	47 (14.0)	29 (8.6)	0.17
40-49	114 (33.8)	372 (42.1)	−0.17	413 (34.9)	501 (40.6)	−0.12	114 (33.8)	129 (37.0)	−0.07	113 (33.6)	133 (39.6)	−0.12
50-59	136 (40.4)	261 (29.5)	0.23	425 (35.9)	399 (32.4)	0.07	136 (40.4)	138 (39.7)	0.01	136 (40.5)	136 (40.5)	0.00
60-69	35 (10.4)	57 (6.4)	0.14	103 (8.7)	94 (7.7)	0.04	35 (10.4)	37 (10.7)	−0.01	35 (10.4)	30 (8.9)	0.05
≥70	1 (0.3)	2 (0.2)	0.01	2 (0.2)	4 (0.3)	−0.03	1 (0.3)	2 (0.5)	−0.04	1 (0.3)	2 (0.6)	−0.04
Sex, n (%)												
Male	330 (97.9)	872 (98.6)	−0.06	1168 (98.6)	1214 (98.5)	0.01	330 (97.9)	342 (98.2)	−0.02	329 (97.9)	330 (98.2)	−0.02
Female	7 (2.1)	12 (1.4)		16 (1.4)	18 (1.5)		7 (2.1)	6 (1.8)		7 (2.1)	6 (1.8)	
eGFR, mL/min/1.73m²*												
Mean±SD	72.93 ± 17.21	71.53 ± 15.11	0.09	71.67 ± 16.85	72.36 ± 16.22	−0.04	72.93 ± 17.21	74.45 ± 18.61	−0.08	72.69 ± 16.62	72.52 ± 15.90	0.01
n (%)												
≥90	40 (11.9)	93 (10.5)	0.04	117 (9.8)	150 (12.2)	−0.07	40 (11.9)	57 (16.4)	−0.13	39 (11.6)	46 (13.7)	−0.06
≥60, <90	243 (72.1)	603 (68.2)	0.09	822 (69.4)	841 (68.3)	0.03	243 (72.1)	238 (68.5)	0.08	243 (72.3)	237 (70.5)	0.04
≥30, <60	46 (13.6)	183 (20.7)	−0.19	217 (18.4)	233 (18.9)	−0.01	46 (13.6)	50 (14.3)	−0.02	46 (13.7)	50 (14.9)	−0.03
≥15, <30	3 (0.9)	4 (0.5)	0.05	7 (0.6)	7 (0.5)	0.00	3 (0.9)	3 (0.8)	0.01	3 (0.9)	2 (0.6)	0.03
<15	5 (1.5)	1 (0.1)	0.15	21 (1.8)	1 (0.1)	0.17	5 (1.5)	0	0.16	5 (1.5)	1 (0.3)	0.13
≥60	283 (84.0)	696 (78.7)	0.13	939 (79.3)	992 (80.5)	−0.03	283 (84.0)	296 (84.9)	−0.02	282 (83.9)	283 (84.2)	−0.01
<60	54 (16.0)	188 (21.3)		245 (20.7)	241 (19.5)		54 (16.0)	53 (15.1)		54 (16.1)	53 (15.8)	
sUA, mg/dL												
Mean±SD	5.30 ± 0.65	7.48 ± 0.99	−2.60	5.26 ± 0.72	7.44 ± 0.98	−2.54	5.30 ± 0.65	7.33 ± 0.94	−2.52	5.30 ± 0.65	7.30 ± 0.90	−2.56
Comorbidities of interest, n (%)												
Hypertension	173 (51.3)	339 (38.3)	0.26	533 (45.0)	524 (42.5)	0.05	173 (51.3)	185 (53.2)	−0.04	172 (51.2)	163 (48.5)	0.05
Type 2 diabetes	62 (18.4)	134 (15.2)	0.09	205 (17.3)	207 (16.8)	0.01	62 (18.4)	73 (20.8)	−0.06	62 (18.5)	66 (19.6)	−0.03
Ischemic heart disease	19 (5.6)	37 (4.2)	0.07	62 (5.2)	57 (4.6)	0.03	19 (5.6)	20 (5.7)	0.00	19 (5.7)	22 (6.5)	−0.04
Heart failure	16 (4.7)	36 (4.1)	0.03	64 (5.4)	53 (4.3)	0.05	16 (4.7)	17 (4.9)	−0.01	16 (4.8)	19 (5.7)	−0.04
Cerebrovascular disease	20 (5.9)	35 (4.0)	0.09	55 (4.6)	55 (4.5)	0.01	20 (5.9)	20 (5.8)	0.01	19 (5.7)	14 (4.2)	0.07
Hyperlipidaemia	196 (58.2)	458 (51.8)	0.13	651 (55.0)	664 (53.9)	0.02	196 (58.2)	206 (59.1)	−0.02	195 (58.0)	191 (56.8)	0.02
Number of comorbidities, n (%)												
0	61 (18.1)	228 (25.8)	−0.19	257 (21.7)	286 (23.2)	−0.04	61 (18.1)	58 (16.6)	0.04	61 (18.2)	61 (18.2)	0.00
1	116 (34.4)	306 (34.6)	0.00	410 (34.7)	423 (34.3)	0.01	116 (34.4)	117 (33.5)	0.02	116 (34.5)	120 (35.7)	−0.02
2	84 (24.9)	205 (23.2)	0.04	263 (22.2)	300 (24.3)	−0.05	84 (24.9)	95 (27.2)	−0.05	84 (25.0)	92 (27.4)	−0.05
3	52 (15.4)	94 (10.6)	0.14	164 (13.9)	151 (12.2)	0.05	52 (15.4)	57 (16.3)	−0.02	51 (15.2)	38 (11.3)	0.11
4	20 (5.9)	32 (3.6)	0.11	60 (5.1)	47 (3.9)	0.06	20 (5.9)	15 (4.4)	0.07	20 (6.0)	16 (4.8)	0.05
5	4 (1.2)	14 (1.6)	−0.03	29 (2.5)	20 (1.6)	0.06	4 (1.2)	6 (1.7)	−0.05	4 (1.2)	8 (2.4)	−0.09
6	0	4 (0.5)	−0.10	0	5 (0.4)	−0.09	0	1 (0.2)	−0.06	0	1 (0.3)	−0.08
7	0	1 (0.1)	−0.05	0	1 (0.1)	−0.04	0	0	−0.03	0	0	–
Concomitant medications, n (%)												
Antihyperlipidaemic drug	156 (46.3)	281 (31.8)	0.30	450 (38.0)	450 (36.5)	0.03	156 (46.3)	169 (48.6)	−0.05	155 (46.1)	160 (47.6)	−0.03
ACE inhibitor	9 (2.7)	19 (2.1)	0.03	30 (2.6)	28 (2.3)	0.02	9 (2.7)	9 (2.5)	0.01	9 (2.7)	12 (3.6)	−0.05
ARB	115 (34.1)	222 (25.1)	0.20	336 (28.4)	338 (27.4)	0.02	115 (34.1)	116 (33.3)	0.02	114 (33.9)	114 (33.9)	0.00
Diuretic drug	18 (5.3)	53 (6.0)	−0.03	71 (6.0)	72 (5.8)	0.01	18 (5.3)	19 (5.4)	0.00	18 (5.4)	22 (6.5)	−0.05
Antidiabetic drug	24 (7.1)	47 (5.3)	0.07	75 (6.3)	81 (6.6)	−0.01	24 (7.1)	34 (9.7)	−0.09	24 (7.1)	26 (7.7)	−0.02

*eGFR (male) = 194 × sCr$^{-1.094}$ × age$^{-0.287}$, eGFR (female) = 194 × sCr$^{-1.094}$ × age$^{-0.287}$ × 0.739. Data at the index date were used if data at the follow-up date were missing.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ATE, average treatment effect; ATT, average treatment effect for treated; eGFR, estimated glomerular filtration rate; IPW, inverse probability weighting; PS, propensity score; SD, standard deviation; sUA, serum uric acid levels; ULT, urate-lowering therapy.

Supplemental material

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Table S6 Hazard ratio for sUA ≤6.0mg/dL compared to >6.0 mg/dL in subjects with
asymptomatic hyperuricaemia (Cox proportional hazards model)

| Analysis	Analysis set	HR (95% CI)	P value
Weighted*	IPW cohort (ATE)	0.48 (0.30, 0.79)	0.004
Weighted*	IPW cohort (ATT)	0.48 (0.30, 0.75)	0.002
Unadjusted	PS matched cohort	0.36 (0.22, 0.58)	<0.001
Unadjusted	Original cohort	0.43 (0.27, 0.66)	<0.001
Multivariable adjusted[†]	Original cohort	0.44 (0.28, 0.69)	<0.001

* Using Robust variance.

[†] Sex, number of comorbidities of interest in period 1, and age, eGFR, and sUA (≤6.0mg/dL/>6.0mg/dL) at the follow-up date were included in
the model.

ATE, average treatment effect; ATT, average treatment effect for the treated; CI, confidence interval; eGFR, estimated glomerular
filtration rate; HR, hazard ratio; IPW, inverse probability weighting; PS, propensity score; sUA, serum uric acid levels.

Supplemental Figure
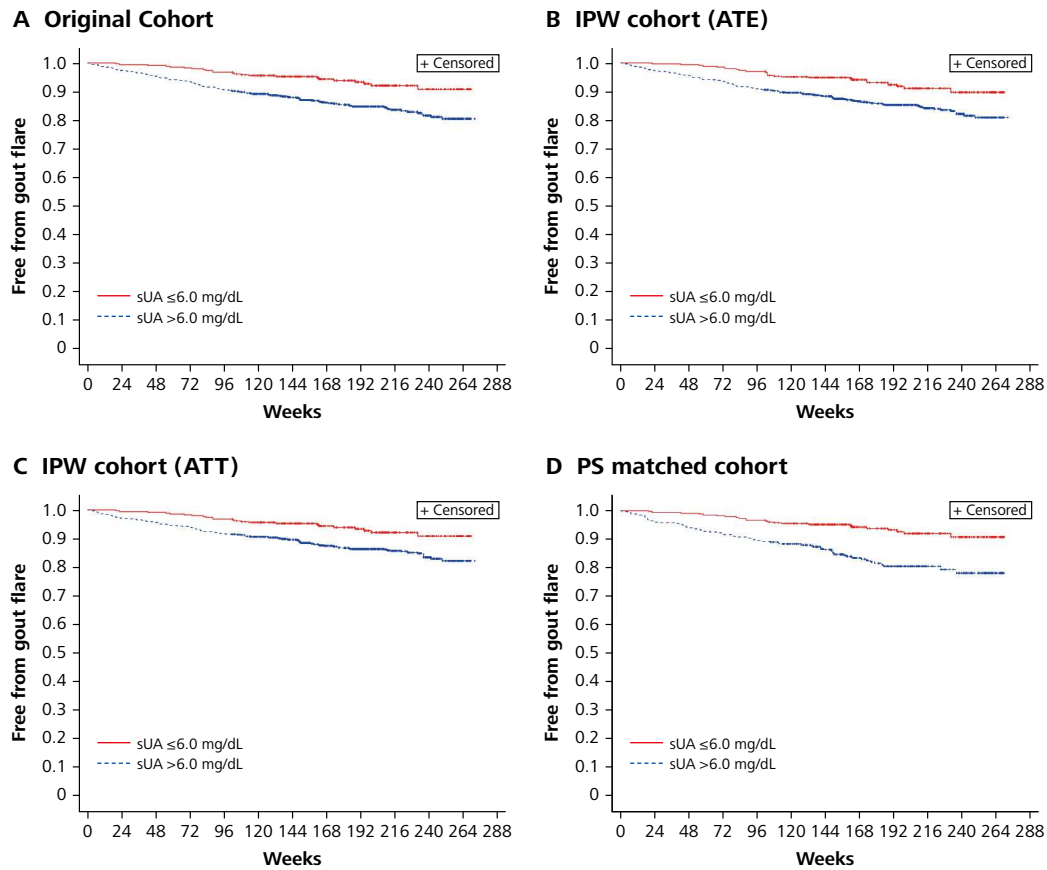
Figure S1 Kaplan-Meier curves for time to first gout flare in period 2 (subjects with asymptomatic hyperuricaemia who were prescribed ULT)

ATE, average treatment effect; ATT, average treatment effect for treated; IPW, inverse probability weighting; PS, propensity score; sUA, serum uric acid levels; ULT, urate-lowering therapy.