# Supplementary Files

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

**Contents:**

# Supplementary 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 (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.

## Supplementary 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 hyperuricemia | | | 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; ULT, urate-lowering therapy.

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

(A) Subjects with asymptomatic hyperuricemia

| 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/1.73m$^2$*** | | | | | |
| ≥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/1.73m$^2$*** | | | | | |
| ≥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; ULT, urate-lowering therapy.

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

(A) Subjects with asymptomatic hyperuricemia

| 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 × 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; RR, relative incidence rate; sUA, serum uric acid; ULT, urate-lowering therapy.

**Table S5** Distribution of baseline characteristics between groups in the original, IPW, and PS matched cohorts (subjects with asymptomatic hyperuricemia 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 | >6.0 mg/dL | | ≤6.0 mg/dL | >6.0 mg/dL | | ≤6.0 mg/dL | >6.0 mg/dL | | ≤6.0 mg/dL | >6.0 mg/dL | |
| | n=337 | n=884 | | n=1184 | n=1232 | | n=337 | n=348 | | n=336 | 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/1.73m$^2$*** | | | | | | | | | | | | |
| 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) = $194 \times sCr^{-1.094} \times age^{-0.287}$, 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; 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; ULT, urate-lowering therapy.

**Table S6** Hazard ratio for sUA ≤6.0mg/dL compared to >6.0 mg/dL in subjects with asymptomatic hyperuricemia (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.

## Supplementary Figure

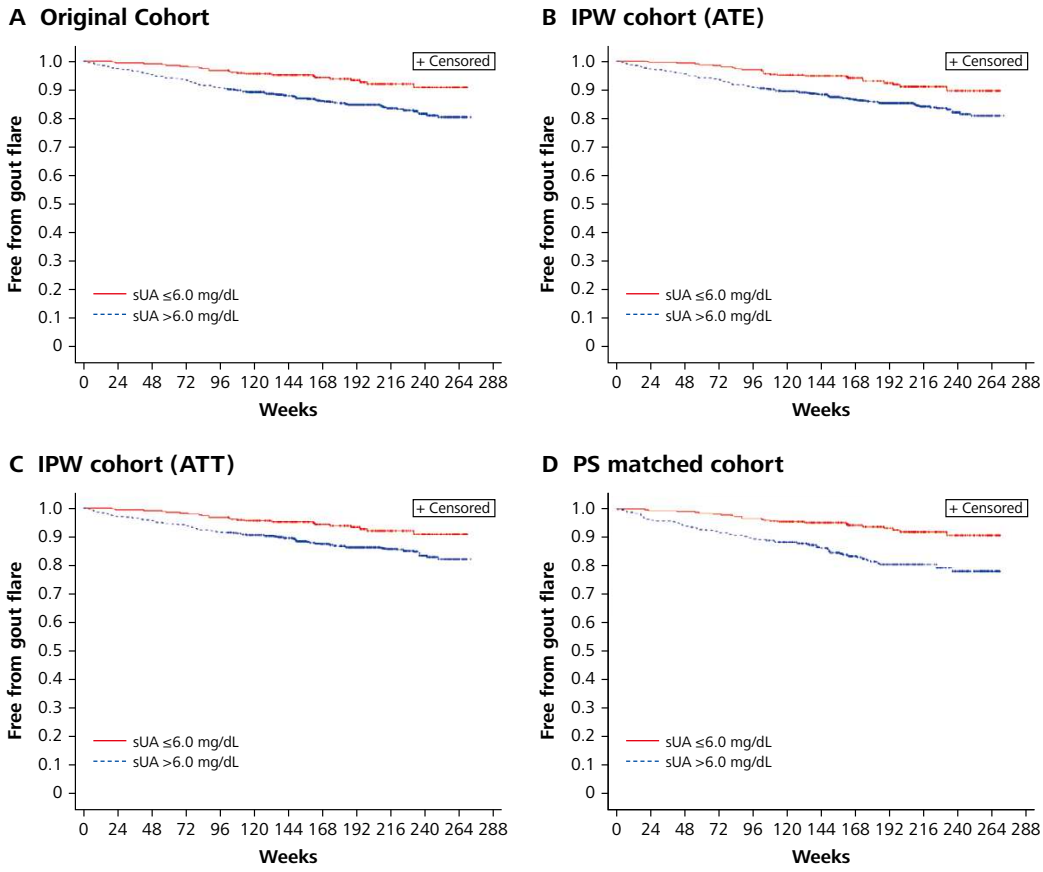


**Figure S1** Kaplan-Meier curves for time to first gout flare in Period 2 (subjects with asymptomatic hyperuricemia who were prescribed ULT)

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