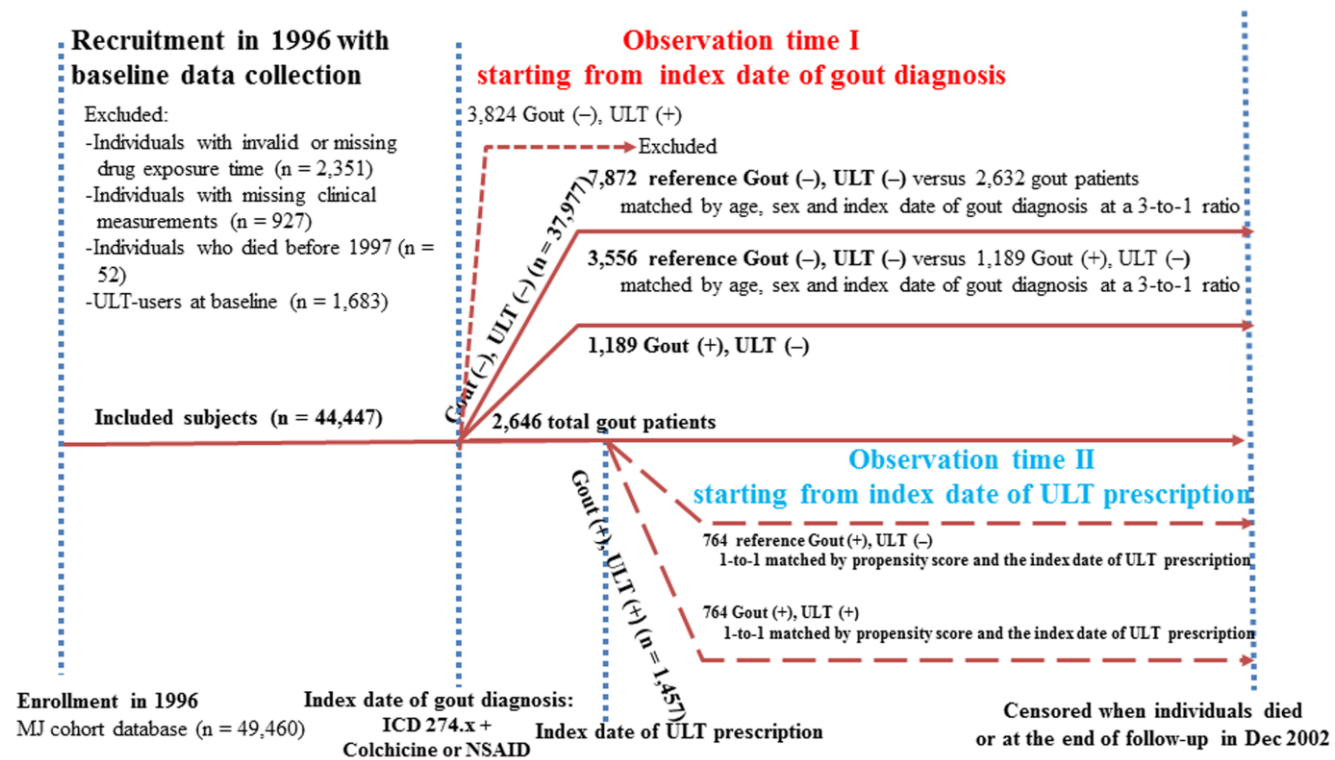


ONLINE SUPPLEMENTARY DATA

**Flow Diagram**

**Study Design: matched case-cohort study**



Supplementary Figure 1. Flow diagram of study design: matched case-cohort study

*Supplementary Table 1.* Demographic, lifestyle and clinical characteristics of the studied subjects (N = 40,623).

<b>Characteristics</b>	<b>Gout (-), ULT (-) N = 37,977</b>	<b>Gout (+), ULT (-) N = 1,189</b>	<b>Gout (+), ULT (+) N = 1,457</b>
Age, years	40.7 ± 14.2	47.6 ± 15.2	52.5 ± 15.1
Male, n (%)	16251 (42.8)	542 (45.6)	1097 (75.3)
Follow up time, years	6.5 ± 0.6	6.4 ± 0.8	6.5 ± 0.6
Uric acid, mg/dL	5.7 ± 1.4	6.5 ± 1.8	8.1 ± 1.8
SBP, mmHg	119.4 ± 19.9	124.3 ± 21.5	134.2 ± 22.8
DBP, mmHg	68.7 ± 11.3	71.8 ± 12.0	77.2 ± 12.2
Cholesterol, mg/dL	200.1 ± 37.6	204.0 ± 44.0	211.6 ± 39.9
HDL-C, mg/dL	46.8 ± 13.6	46.6 ± 14.0	44.2 ± 14.5
Triglyceride, mg/dL	106.6 ± 66.4	166.1 ± 87.2	159.3 ± 84.3
Glucose, mg/dL	98 ± 22.1	133.1 ± 94.3	104.6 ± 26.9
eGFR, mL/min per 1.73 m <sup>2</sup>	83.2 ± 15.6	77.6 ± 16.7	69.9 ± 16.8
BMI, kg/m <sup>2</sup>	23 ± 3.4	24.2 ± 3.6	25.5 ± 3.3
<b>Co-morbidity*</b>			
Hypertension, n (%)	429 (1.1)	33 (2.8)	74 (5.1)
Heart disease, n (%)	2176 (5.7)	146 (12.3)	307 (21.1)
Diabetes Mellitus, n (%)	145 (0.4)	14 (1.2)	18 (1.2)
<b>Alcohol drinking</b>			
Never, n (%)	4644 (12.2)	180 (15.1)	167 (11.5)

Abstained, n (%)	19212 (50.6)	571 (48.0)	565 (38.8)
1–2 drinks/week, n (%)	940 (2.5)	42 (3.5)	82 (5.6)
3–4 drinks/week, n (%)	9211 (24.2)	261 (22.0)	402 (27.6)
Daily, n (%)	3230 (8.5)	102 (8.6)	171 (11.7)
Missing data, n (%)	760 (2.0)	33 (2.8)	70 (4.8)
<b>Cigarette smoking</b>			
Never, n (%)	5925 (15.6)	208 (17.5)	209 (14.3)
Abstained, n (%)	19257 (50.7)	594 (50.0)	572 (39.3)
Occasionally, n (%)	1892 (5.0)	73 (6.1)	166 (11.4)
Often, n (%)	1349 (3.6)	45 (3.8)	66 (4.5)
Daily, n (%)	3702 (9.7)	111 (9.3)	149 (10.2)
Missing data, n (%)	5872 (15.5)	158 (13.3)	295 (20.3)
<b>Smoking amount</b>			
None or missing, n (%)	27450 (72.2)	871 (73.3)	871 (59.8)
<5 per day, n (%)	1791 (4.7)	49 (4.1)	74 (5.1)
5–10 per day, n (%)	2045 (5.4)	59 (5.0)	113 (7.8)
11–19 per day, n (%)	4699 (12.4)	133 (11.2)	258 (17.7)
1–2 packs per day, n (%)	1992 (5.2)	74 (6.2)	139 (9.5)
>2 packs per day, n (%)	20 (0.1)	3 (0.3)	2 (0.1)

\* Definition of co-morbidity: Hypertension is defined as systolic blood pressure (SBP)  $\geq$  140 mmHg or diastolic blood pressure (DBP)  $\geq$  90 mmHg or self-reported to have hypertension or use of antihypertensive medications. Heart disease is defined as abnormal ECG, or self-reported heart disease or medication use for heart disease. Diabetes is defined as fasting blood sugar  $\geq$  126 mg/dL or self-reported diabetes mellitus or use

of anti-diabetic medications. With respect to alcohol consumption and cigarette smoking, “Never” indicates the subjects have never been exposed to either alcohol or cigarette and “Abstained” indicates that although the subjects have been exposed before, they have stopped the usage. ULT: urate-lowering therapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; BMI: body mass index.

*Supplementary Table 2.* Demographics of gout patients with allopurinol-only use or benzbromarone-only use and their matched references.

<b>Characteristics</b>	<b>Gout (+), Allopurinol (+)</b>	<b>Gout (+), ULT (-)</b>	<b><i>p</i></b>	<b>Gout (+) Benzbromarone (+)</b>	<b>Gout (+), ULT (-)</b>	<b><i>p</i></b>
Age, years	52.7 ± 15.4	53.2 ± 15.3	0.67	51.0 ± 15.1	50.8 ± 15.6	0.81
Male, n (%)	89 (31.1)	95 (33.2)	0.59	357 (70.8)	364 (72.2)	0.99
Follow-up time, years	6.4 ± 0.8	6.2 ± 1.1	0.07	6.5 ± 0.5	6.4 ± 0.9	<0.01
Uric acid, mg/dL	7.7 ± 1.7	7.5 ± 1.8	0.29	7.7 ± 1.7	7.7 ± 1.7	0.99
SBP, mmHg	130.5 ± 22.5	130.5 ± 22.1	0.99	132.3 ± 22.5	130.9 ± 22.0	0.35
DBP, mmHg	78.4 ± 12.1	77.7 ± 10.6	0.32	78.4 ± 11.8	77.5 ± 11.7	0.29
Cholesterol, mg/dL	211.2 ± 47.3	211.9 ± 38.4	0.83	210.8 ± 41.3	208.0 ± 42.0	0.29
HDL-C, mg/dL	43.9 ± 12.8	45.4 ± 18.4	0.22	41.9 ± 13.7	43.7 ± 16.2	0.35
Triglyceride, mg/dL	146.8 ± 78.9	158.9 ± 136.3	0.19	159.2 ± 89.6	158.4 ± 118.1	0.90
Glucose, mg/dL	103.6 ± 24.7	109.0 ± 36.1	0.04	104.3 ± 25.3	105.2 ± 29.7	0.60
eGFR, mL/min per 1.73 m <sup>2</sup>	70.2 ± 16.1	71.7 ± 16.4	0.27	73.0 ± 16.0	73.4 ± 16.4	0.68
BMI, kg/m <sup>2</sup>	25.3 ± 3.5	25.4 ± 3.5	0.68	25.4 ± 3.3	25.0 ± 3.3	0.13
<b>Co-morbidity</b>						

Hypertension, n (%)	11 (3.8)	13 (4.5)	0.68	33 (6.5)	53 (10.5)	<0.01
Heart disease, n (%)	51 (17.8)	54 (18.9)	0.75	146 (29.0)	330 (65.5)	<0.01
Diabetes Mellitus, n (%)	4 (1.4)	6 (2.1)	0.52	14 (2.8)	30 (6.0)	0.30
<b>Alcohol drinking</b>			0.13			0.51
Never, n (%)	29 (10.1)	43 (15)		53 (10.5)	65 (12.9)	
Abstained, n (%)	130 (45.5)	116 (40.6)		187 (37.1)	199 (39.5)	
1–2 drinks/week, n (%)	10 (3.5)	20 (7)		27 (5.4)	26 (5.2)	
3–4 drinks/week, n (%)	77 (26.9)	67 (23.4)		151 (30)	148 (29.4)	
Daily, n (%)	31 (10.8)	27 (9.4)		61 (12.1)	46 (9.1)	
Missing data, n (%)	9 (3.1)	13 (4.5)		25 (5)	20 (4)	
<b>Cigarette smoking</b>			0.62			0.53
Never, n (%)	38 (13.3)	46 (16.1)		73 (14.5)	75 (14.9)	
Abstained, n (%)	118 (41.3)	121 (42.3)		196 (38.9)	215 (42.7)	
Occasionally, n (%)	35 (12.2)	28 (9.8)		49 (9.7)	44 (8.7)	
Often, n (%)	15 (5.2)	13 (4.5)		19 (3.8)	24 (4.8)	
Daily, n (%)	19 (6.6)	26 (9.1)		64 (12.7)	48 (9.5)	
Missing data, n (%)	61 (21.3)	52 (18.2)		103 (20.4)	98 (19.4)	
<b>Smoking amount</b>			0.62			0.04
None or missing, n (%)	174 (60.8)	184 (64.3)		311 (61.7)	317 (62.9)	
<5 per day, n (%)	17 (5.9)	12 (4.2)		22 (4.4)	16 (3.2)	
5–10 per day, n (%)	19 (6.6)	16 (5.6)		44 (8.7)	31 (6.2)	
11–19 per day, n (%)	41 (14.3)	39 (13.6)		96 (19)	84 (16.7)	

1–2 packs per day, n (%)	35 (12.2)	33 (11.5)	31 (6.2)	55 (10.9)
>2 packs per day, n (%)	0 (0)	2 (0.7)	0 (0)	1 (0.2)

Gout (+), allopurinol (+): gout patients treated with allopurinol-only (n = 286). Gout (+), benzbromarone (+): gout patients treated with benzbromarone-only (n = 504). Gout (–), ULT (–): 1-to-1 matched counterparts of non-ULT-users to subgroups of Gout (+), allopurinol (+) (n = 286) and Gout (+), benzbromarone (+) (n = 504) by propensity score and index date of the ULT prescription. ULT: urate-lowering therapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; BMI: body mass index.

*Supplementary Table 3.* Mortality risk according to the presence of ULT use in subgroups stratified by concomitant medications and by duration of ULT use.

Characteristics	ULT	Number	Person-years	All-cause mortality				
				Event number	Mortality (10 <sup>-3</sup> P-Y)	MRR	<sup>a</sup> HR (95% CI)	<i>p</i>
<b><i>Concomitant drugs</i></b>								
Anti-hypertensive (–)	–	121	785	2	<b>2.55</b>		Reference	
	+	121	800.4	0	<b>0.00</b>	0	NA	NA
Anti-hypertensive (+)	–	243	1524.2	26	<b>17.06</b>		Reference	
	+	243	1577.4	11	<b>6.97</b>	0.41	0.41(0.20–0.82)	0.01
Anti-diabetic (–)	–	496	3184.3	22	<b>6.91</b>		Reference	
	+	496	3237.1	11	<b>3.40</b>	0.49	0.50(0.24–1.00)	0.05
Anti-diabetic (+)	–	10	60.4	1	<b>16.56</b>		Reference	
	+	10	65.6	0	<b>0.00</b>	0	NA	NA
Lipid-lowering agent (–)	–	563	3604.7	33	<b>9.15</b>		Reference	
	+	563	3661.5	16	<b>4.37</b>	0.48	0.47(0.26–0.86)	0.01
Lipid-lowering agent (+)	–	6	38.8	0	<b>0.00</b>		Reference	

	+	6	40.6	0	<b>0.00</b>	NA	NA	NA
<b><i>Duration of ULT use</i></b>								
<60 days	–	256	1664.7	5	<b>3.00</b>		Reference	
	+	256	1653.2	7	<b>4.23</b>	1.41	1.44(0.46–4.52)	0.54
60–364 days	–	121	768.9	8	<b>10.40</b>		Reference	
	+	121	786.9	9	<b>11.44</b>	1.10	1.09(0.42–2.83)	0.86
1–2 years	–	90	587.1	3	<b>5.11</b>		Reference	
	+	90	581.3	3	<b>5.16</b>	1.01	1.10(0.22–5.46)	0.91
>2 years	–	297	1865.8	28	<b>15.01</b>		Reference	
	+	297	1944.6	4	<b>2.06</b>	0.14	0.14(0.05–0.39)	<0.01

<sup>a</sup> HRs were adjusted for age, gender, lifestyle (smoking, drinking and exercise) and comorbidity (obesity, hypertension, diabetes, renal failure and hepatitis). ULT: urate-lowering therapy; P-Y: person-years; MRR: mortality rate ratio; NA: result not available.