Brief report

Temporal trends in the prevalence and characteristics of hypouricaemia: A descriptive study of medical check-up and administrative claims data

Ruriko Koto[1,2], Izumi Sato[1,3], Masanari Kuwabara[4], Tomotsugu Seki[1,5], Koji Kawakami[1]

[1]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[2]Medical Science Department, Teijin Pharma Limited, Tokyo, Japan
[3]Department of Clinical Epidemiology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
[4]Intensive Care Unit and Department of Cardiology, Toranomon Hospital, Tokyo, Japan
[5]Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Correspondence to:
Koji Kawakami
Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
TEL. +81-75-753-9469
E-mail: kawakami.koji.4e@kyoto-u.ac.jp

ORCID ID:
Ruriko Koto http://orcid.org/0000-0001-9201-1273
Koji Kawakami http://orcid.org/0000-0002-7477-4071

Abstract

Objectives: To describe temporal trends in the prevalence and characteristics of hypouricaemia.

Methods: We analysed medical check-up and administrative claims data to calculate hypouricaemia prevalence from 2009 to 2019. Then, using data from 2018 to 2019, we compared the characteristics of individuals with and without hypouricaemia. We also compared the characteristics of those with lower (serum uric acid [sUA] ≤ 1.0 mg/dL) and higher (1.0 mg/dL < sUA ≤ 2.0 mg/dL) hypouricaemia.

Results: In total, 1,600,290 subjects underwent medical check-ups. The age-adjusted prevalence of hypouricaemia remained stable at 0.2% overall (men, 0.1%; women, 0.4%). We identified 1,704 subjects with hypouricaemia (598 men and 1,106 women) from among 796,508 subjects and studied their characteristics. The proportion of most pre-existing diseases, including urinary stones, was lower in those with hypouricaemia than in those without hypouricaemia. Cardio-metabolic diseases and Parkinson's disease were more frequent in men with hypouricaemia than those without hypouricaemia. Women with hypouricaemia tended to have healthier characteristics. Hypertension and dyslipidaemia were more common in the lower hypouricaemia group than in the higher hypouricaemia group.

Conclusions: The age-adjusted prevalence of hypouricaemia remained stable over 10 years. The characteristics of hypouricaemia subjects appear to differ between the sexes and between lower and higher hypouricaemia groups.

Key points:

- The prevalence of hypouricaemia remained almost unchanged over 10 years.
- Cardio-metabolic diseases and Parkinson's disease were more frequent in men with hypouricaemia than in those without hypouricaemia.
- Subjects with extremely low serum urate (sUA ≤ 1.0 mg/dL) appeared to have higher cardio-metabolic disease risks.
- Routine checks of sUA could be useful in screening or predicting these conditions.

Keywords: epidemiology, hypouricaemia, prevalence, uric acid

Introduction

Hypouricaemia is generally defined as a serum uric acid (sUA) level of ≤ 2.0 mg/dL [1-3]; the main cause is increased renal clearance of uric acid due to dysfunction of urate reabsorption transporters, termed renal hypouricaemia (RHUC) [2]. Other causes associated with hypouricaemia include decreased uric acid production due to a deficiency of xanthine oxidoreductase and acquired disorders, such as malignancy and diabetes mellitus, and therapeutic drugs [1, 4].

The reported prevalence of hypouricaemia varies depending on the setting of the study, such as populations and areas, ranging from 0.15 to 4.45% [1, 2, 4-7]. However, most epidemiological studies were limited to small sample sizes, and no studies have reported a temporal trend in hypouricaemia prevalence to date.

Complications of hypouricaemia include urinary stones and exercise-induced acute kidney injury in patients with RHUC [2]. Moreover, hypouricaemia is linked to reduced kidney function [7], endothelial dysfunction [8], and neurological diseases including Alzheimer's and Parkinson's diseases [9, 10]. However, whether the distribution of these conditions differs between subjects with and without hypouricaemia needs further clarification.

Additionally, recent studies suggested that lower (sUA level ≤1.0 mg/dL) and higher (1.0 mg/dL < sUA level ≤2.0 mg/dL) hypouricaemia groups may have different characteristics [5, 6]. Further studies are needed to explore the differences between the lower and higher hypouricaemia groups and to understand the underlying pathophysiology.

We used large-scale real-world data to identify a sufficiently large number of subjects with hypouricaemia in the general population. This study aimed (1) to observe temporal trends in hypouricaemia prevalence, (2) to compare the characteristics of subjects with and without hypouricaemia, and (3) to compare the characteristics between lower and higher hypouricaemia groups.

Methods

Study design and setting

This descriptive study utilised data from the JMDC Database, which includes medical check-up and administrative claims data from 2009 to 2019. JMDC Inc. (Tokyo, Japan) collects information from multiple health insurance societies for company employees and their dependents aged < 75 years [11]. The database contains records of check-ups, diagnostic codes, and drug prescriptions, and is widely used for epidemiological studies [12-16]. A

medical check-up is an annual standard check to ascertain the health statuses of health insurance enrolees. The database can track each person's medical information, even if the patient visited or was hospitalised in multiple medical institutions, and covers approximately 9.8 million people overall [11]. Participant eligibility criteria are shown in Fig. 1. This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (no. R2383).

Definitions

We defined hypouricaemia and hyperuricaemia as sUA levels of ≤ 2.0 mg/dL and > 7.0 mg/dL [2, 17], respectively. We evaluated sUA levels once a year, and if the subjects' sUA levels had been examined more than once during a fiscal year (FY) (from 1 April of a year to 31 March of the following year), the results from the first examination were used for the analysis.

We identified history of diseases and medications during the six months before the first check-up, using the International Classification of Diseases 10th revision codes and anatomical therapeutic chemical codes, respectively. Pre-existing diseases of our interest were included, such as cardio-metabolic and neurological diseases. We identified comorbidities with the definitions using laboratory values from medical check-up data (Supplemental Table S1).

Statistical analysis

We calculated the crude hypouricaemia prevalence and the age-adjusted prevalence by a direct method using a standard Japanese population from 1985.

We analysed the distribution of sUA levels and the subject characteristics for the final analysis population. Data were analysed overall and stratified by sex and were presented as the mean (standard deviation) or the median (interquartile range) as appropriate for continuous variables and as numbers and percentages for categorical variables. A comparison of subject characteristics according to sUA categories (hypouricaemia, normouricaemia, and hyperuricaemia) was performed using analysis of variance for continuous variables and chi-square tests for categorical variables. Subject characteristics were compared between the lower and higher hypouricaemia groups using t-tests for continuous variables and chi-square tests for categorical variables. All statistical tests were two-sided; $p < 0.05$ was considered statistically significant. All data analyses were performed using SAS version 9.4.

Results

We identified 1,600,290 subjects for the analysis of the prevalence of hypouricaemia, and 796,508 subjects for other measurements as the final analysis population (Fig. 1).

The crude and age-adjusted hypouricaemia prevalence from FY2009 to 2018 are shown in Supplemental Table S2 and in Fig. 2, respectively. The crude hypouricaemia prevalence had slightly decreased from FY2009 to FY2018. However, when adjusted for age, the prevalence remained stable, at approximately 0.2% overall, 0.1% in men, and 0.4% in women.

The distribution of sUA levels in the subjects of the final analysis population (n = 796,508) is shown in Supplemental Figure S1. Bimodal distribution was observed at sUA levels of ≤ 2.0 mg/dL for both sexes.

We observed the subject characteristics according to the sUA categories for the final analysis population (Supplemental Table S3). The proportion of male subjects varied significantly among the sUA categories; 35.1% (n = 598) for hypouricaemia, 55.1% (n = 375,944) for normouricaemia, and 96.1% (n = 107,561) for hyperuricaemia. Most comorbidities and pre-existing diseases tended to be less frequent in subjects with hypouricaemia than without hypouricaemia. The frequency of urinary stones was 0.8% in subjects with hypouricaemia, 1.0% in normouricaemia, and 1.4% in hyperuricaemia. In contrast, neurological diseases including Parkinson's disease were more frequent in subjects with hypouricaemia than without hypouricaemia. The frequency of Parkinson's disease was 0.8% in those with hypouricaemia, 0.2% in normouricaemia, and 0.2% in hyperuricaemia. Pre-existing diabetes mellitus, a possible cause of hypouricaemia, was found in 6.0% (n = 103) of subjects with hypouricaemia. Other possible causes, such as malignancy and history of urate-lowering therapy, were rarely found in subjects with hypouricaemia: 0.1% (n = 1) and 0.4% (n = 7), respectively.

Subject characteristics according to sUA categories by sex are shown in Tables 1 and 2. We identified 598 subjects (0.1%) with hypouricaemia among men and 1,106 (0.4%) among women, respectively. Pre-existing renal dysfunction, diabetes mellitus, ischaemic heart disease, and Parkinson's disease, were more frequent in men with hypouricaemia than without (Table 1). Most of the pre-existing diseases and comorbidities were less frequent in women with hypouricaemia than without (Table 2).

Characteristics of subjects in the lower (n=803) and higher (n=901) hypouricaemia groups and characteristics stratified by sex, are shown in Supplemental Tables S4 and S5, respectively. The proportion of men was significantly different: 58.8% (n = 472) in the lower

and 14.0% (n = 126) in the higher hypouricaemia group. Subjects in the lower group had more frequent comorbidities, such as hypertension and dyslipidaemia, than those in the higher hypouricaemia group (Table S4). Men in the higher group had a higher proportion of pre-existing hypertension, pre-existing dyslipidaemia, and reduced kidney function, than those in the lower hypouricaemia group (Table S5). Women in the lower group had a higher proportion of comorbidities, including reduced kidney function, hypertension, and dyslipidaemia, than those in the higher hypouricaemia group (Table S5).

Discussion

This study observed temporal trends in the prevalence of hypouricaemia and investigated the characteristics of subjects with hypouricaemia. The primary finding was that the age-adjusted prevalence of hypouricaemia remained almost unchanged over 10 years: consistently 0.2% overall, 0.1% in men, and 0.4% in women. These values were compatible with those previously reported in Japan [2, 7], but were lower than those reported from studies in other countries, in in- and outpatient settings [1, 4].

One well-known complication of hypouricaemia is urinary stones in patients with RHUC [2]; however, the exact prevalence thereof remains unknown. In our study, urinary stones were less observed: 1.0% (6/598) and 0.6% (7/1106) in men and women with hypouricaemia, respectively. These values were much lower than those previously reported in patients with RHUC (9.3% [4/43] in men and 7.1% [2/28] in women) [18], indicating that there was a marked gap in the frequency of urinary stones between patients with hypouricaemia overall and in those with RHUC.

We also found that pre-existing cardio-metabolic diseases and Parkinson's disease were more frequent in men with than in those without hypouricaemia. Since uric acid is a powerful antioxidant [19-21], low levels of sUA are possibly associated with increased oxidative stress and may be a risk factor for cardiovascular and neurodegenerative disease progression [8-10]. In contrast, this trend was not observed in women.

Furthermore, we compared the characteristics of the lower and higher hypouricaemia groups, because two peaks in sUA levels were observed, suggesting different pathophysiology between those groups [5, 6]. We found that sex distribution was significantly different, and the majority of subjects (86.0%) in the higher hypouricaemia group were female. Women in the higher hypouricaemia group tended to have healthier characteristics than those in the lower group. We considered that some subjects in the higher hypouricaemia group may have had transient hypouricaemia, under the influence of female

hormones, since oestrogen and progesterone decrease sUA levels. Subjects with extremely low serum urate (sUA ≤ 1.0 mg/dL) may be persistently hypouricaemic, due to RHUC caused by homozygous genetic urate transporter variants [5].

This study was strengthened by a large-scale real-world database from the general population that allowed us to describe the prevalence of hypouricaemia and its characteristics in > 1700 subjects. To our knowledge, no previous report has described the temporal trends in hypouricaemia prevalence over 10 years.

Our study had several limitations. First, there was a limitation to assessing the frequency of diseases that are common in older individuals, such as Alzheimer's and Parkinson diseases, because our population consisted of working-age individuals and their dependents who underwent annual medical check-ups. However, it is unlikely that bias occurred in examining the prevalence of hypouricaemia. Second, since sUA data was available only once a year, we could not verify whether hypouricaemia was transient or persistent. Third, it was not possible to estimate the causal relationship between hypouricaemia and other disorders, as this analysis was cross-sectional.

In conclusion, we demonstrated that the age-adjusted prevalence of hypouricaemia remained stable over 10 years. Hypouricaemia characteristics differ between sexes and between those with lower and higher serum uric acid levels. Cardio-metabolic diseases and Parkinson's disease were more frequently diagnosed in men with hypouricaemia than in those without hypouricaemia. Subjects in the lower hypouricaemia group had higher frequency of cardio-metabolic diseases. These findings suggest that routine checks of sUA could be useful in screening or predicting these conditions.

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Figure legends

Fig. 1 Flowchart for participant eligibility

Fig. 2 Age-adjusted prevalence of hypouricaemia from FY2009 to FY2018

Table 1 Characteristics of men in the final analysis population in FY2018

	Hypouricaemia		Normouricaemia		Hyperuricaemia		Overall		P value
	N	%	N	%	N	%	N	%	
Total	598		375,944		107,561		484,103		
Age, years, mean (SD)	45.4 (11.0)		44.8 (10.7)		44.4 (10.1)		44.7 (10.5)		<0.0001
BMI, kg/m^2, mean (SD)	24.1 (3.8)		23.5 (3.4)		25.3 (3.9)		23.9 (3.6)		<0.0001
Waist circumference, cm, mean (SD)	84.6 (10.1)		83.2 (9.4)		88.0 (9.9)		84.3 (9.7)		<0.0001
Smoking	206	34.5	131,217	34.9	37,630	35.0	169,053	34.9	0.8594
Drinking habits	384	64.2	249,405	66.3	79,501	73.9	329,290	68.0	<0.0001
Serum uric acid, mg/dL, median (IQR)	0.7 (0.6, 1.0)		5.8 (5.2, 6.4)		7.6 (7.3, 8.2)		6.1 (5.4, 6.9)		<0.0001
eGFR, mL/min/1.73 m^2, mean (SD)	81.1 (16.2)		80.2 (14.5)		75.2 (14.3)		79.1 (14.6)		<0.0001
Pre-existing diseases									
Renal dysfunction	19	3.2	5,458	1.5	1,834	1.7	7,311	1.5	<0.0001
Hypertension	93	15.6	56,004	14.9	18,123	16.9	74,220	15.3	<0.0001
Diabetes mellitus	57	9.5	34,170	9.1	7,496	7.0	41,723	8.6	<0.0001
Dyslipidaemia	84	14.1	56,898	15.1	15,869	14.8	72,851	15.1	0.0068
Urinary stones	6	1.0	5,165	1.4	1,558	1.5	6,729	1.4	0.132
Ischaemic heart disease	18	3.0	9,576	2.6	2,472	2.3	12,066	2.5	<0.0001
Heart failure	14	2.3	7,076	1.9	2,105	2.0	9,195	1.9	0.208
Cerebrovascular disease	12	2.0	8,155	2.2	2,092	1.9	10,259	2.1	<0.0001
Neurological disease	75	12.5	41,721	11.1	11,934	11.1	53,730	11.1	0.5315
Parkinson's disease	8	1.3	773	0.2	202	0.2	983	0.2	<0.0001
Alzheimer's disease	0	0.0	69	0.0	14	0.0	83	0.0	0.4741
Malignant tumour	0	0.0	47	0.0	13	0.0	60	0.0	0.958
History of medications									
Urate-lowering	6	1.0	21,537	5.7	7,806	7.3	29,349	6.1	<0.0001

therapy									
Antihypertensive drug	86	14.4	51,462	13.7	16,525	15.4	68,073	14.1	<0.0001
ACE inhibitors	6	1.0	2,529	0.7	769	0.7	3,304	0.7	0.2112
ARB	56	9.4	33,458	8.9	11,342	10.5	44,856	9.3	<0.0001
Diuretic drug	3	0.5	4,137	1.1	2,013	1.9	6,153	1.3	<0.0001
Antidiabetic drug	34	5.7	19,473	5.2	3,112	2.9	22,619	4.7	<0.0001
Antilipidemic drug	62	10.4	39,934	10.6	9,721	9.0	49,717	10.3	<0.0001
Comorbidities									
Reduced kidney function	34	5.7	21,542	5.7	13,102	12.2	34,678	7.2	<0.0001
Hypertension	96	16.1	58,389	15.5	25,145	23.4	83,630	17.3	<0.0001
Diabetes mellitus	41	6.9	23,408	6.2	4,600	4.3	28,049	5.8	<0.0001
Dyslipidaemia	243	40.6	152,693	40.6	64,704	60.2	217,640	45.0	<0.0001

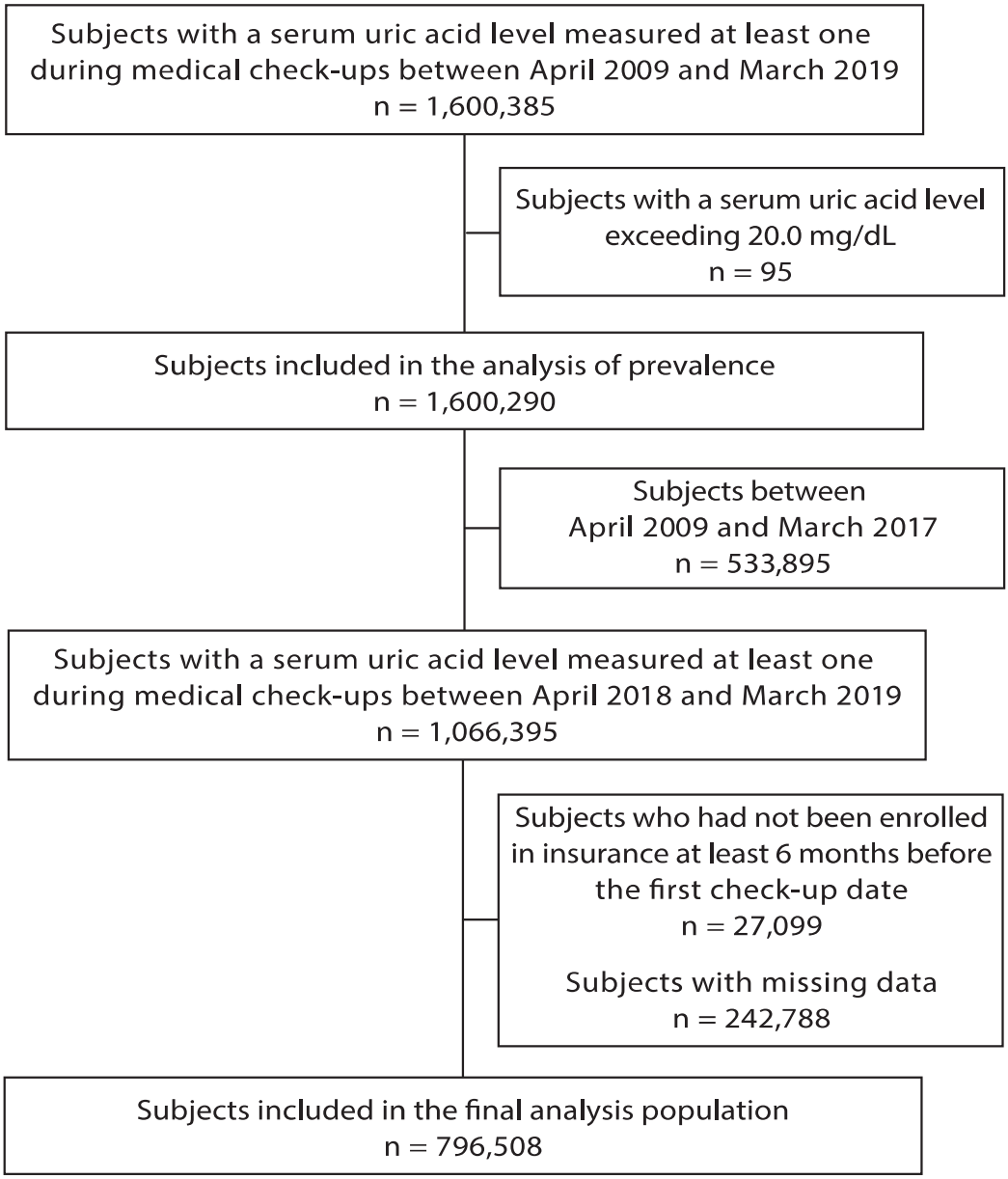
SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

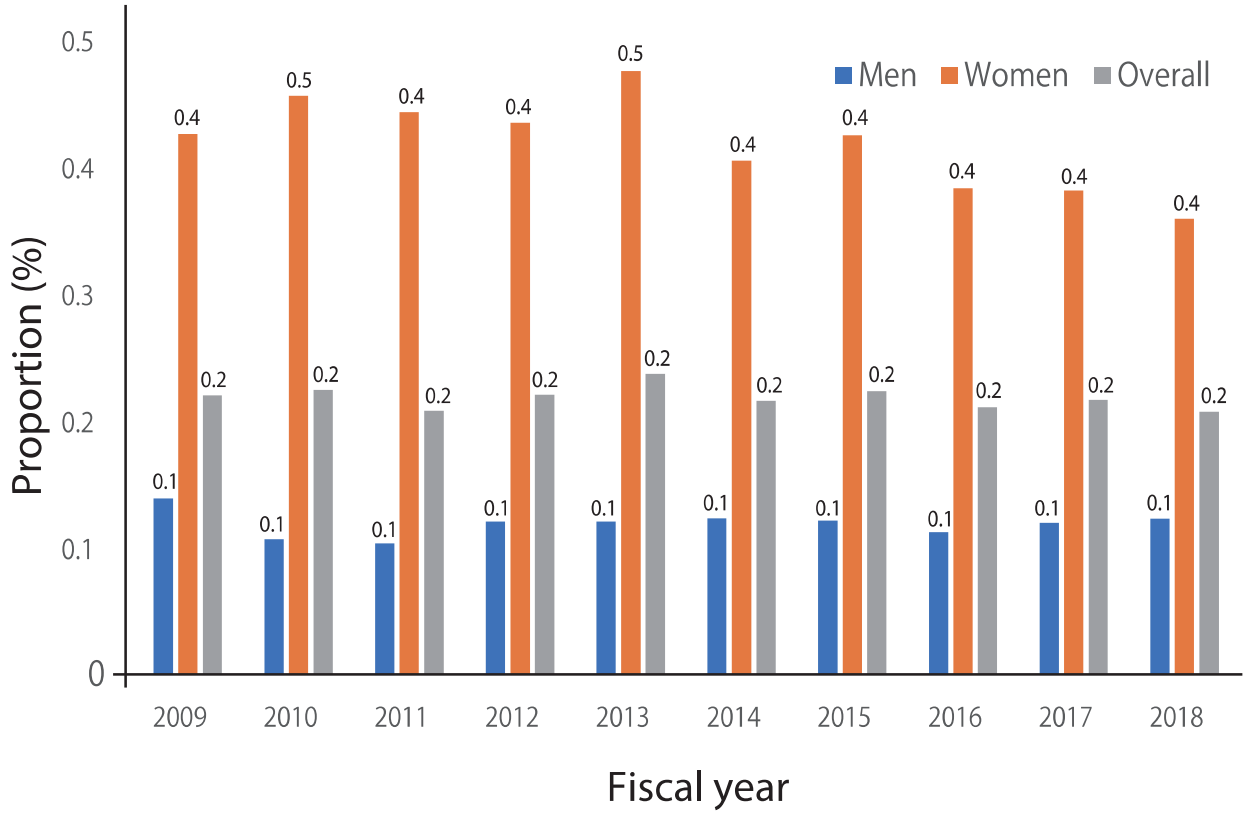
Table 2 Characteristics of women in the final analysis population in FY2018

	Hypouricaemia		**Normouricaemia**		**Hyperuricaemia**		**Overall**		**P value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Total	1,106		306,950		4,349		312,405		
Age, years, mean (SD)	42.7 (9.2)		44.5 (10.2)		48.9 (10.0)		44.6 (10.2)		<0.0001
BMI, kg/m^2, mean (SD)	20.8 (3.1)		21.8 (3.6)		26.5 (5.7)		21.8 (3.7)		<0.0001
Waist circumference, cm, mean (SD)	74.7 (8.6)		77.4 (9.6)		89.3 (12.9)		77.6 (9.7)		<0.0001
Smoking	92	8.3	27,438	8.9	685	15.8	28,215	9.0	<0.0001
Drinking habits	410	37.1	132,562	43.2	2,124	48.8	135,096	43.2	<0.0001
Serum uric acid, mg/dL, median (IQR)	1.8 (0.8, 2.0)		4.4 (3.8, 5.0)		7.5 (7.2, 7.9)		4.4 (3.8, 5.1)		<0.0001
eGFR, mL/min/1.73 m^2, mean (SD)	90.2 (20.1)		81.6 (15.6)		70.1 (17.1)		81.4 (15.7)		<0.0001
Pre-existing diseases									
Renal dysfunction	5	0.5	2,848	0.9	177	4.1	3,030	1.0	<0.0001

Hypertension	54	4.9	25,273	8.2	1313	30.2	26,640	8.5	<0.0001
Diabetes mellitus	46	4.2	13,695	4.5	581	13.4	14,322	4.6	<0.0001
Dyslipidaemia	80	7.2	32,832	10.7	1107	25.5	34,019	10.9	<0.0001
Urinary stones	7	0.6	1,612	0.5	56	1.3	1675	0.5	<0.0001
Ischaemic heart disease	10	0.9	3,782	1.2	148	3.4	3,940	1.3	<0.0001
Heart failure	12	1.1	3,086	1.0	187	4.3	3,285	1.1	<0.0001
Cerebrovascular disease	8	0.7	4,833	1.6	177	4.1	5,018	1.6	<0.0001
Neurological disease	147	13.3	38,837	12.7	880	20.2	39,864	12.8	<0.0001
Parkinson's disease	6	0.5	799	0.3	36	0.8	841	0.3	<0.0001
Alzheimer's disease	0	0.0	51	0.0	3	0.1	54	0.0	0.0303
Malignant tumour	1	0.1	371	0.1	6	0.1	378	0.1	0.9096
History of medications									
Urate-lowering therapy	1	0.1	615	0.2	133	3.1	749	0.2	<0.0001
Antihypertensive drug	53	4.8	23,542	7.7	1,266	29.1	24,861	8.0	<0.0001
ACE inhibitors	0	0.0	682	0.2	50	1.2	732	0.2	<0.0001
ARB	27	2.4	12,335	4.0	860	19.8	13,222	4.2	<0.0001
Diuretic drug	8	0.7	2,910	1.0	249	5.7	3,167	1.0	<0.0001
Antidiabetic drug	24	2.2	5,008	1.6	227	5.2	5,259	1.7	<0.0001
Antilipidemic drug	54	4.9	22,353	7.3	759	17.5	23,166	7.4	<0.0001
Comorbidities									
Reduced kidney function	21	1.9	16,591	5.4	1142	26.3	17,754	5.7	<0.0001
Hypertension	61	5.5	25,941	8.5	1115	25.6	27,117	8.7	<0.0001
Diabetes mellitus	25	2.3	6,275	2.0	383	8.8	6,683	2.1	<0.0001
Dyslipidaemia	204	18.4	81,502	26.6	2604	59.9	84,310	27.0	<0.0001

SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker


Subjects with a serum uric acid level measured at least one during medical check-ups between April 2009 and March 2019
n = 1,600,385
Subjects with a serum uric acid level exceeding 20.0 mg/dL
n = 95
Subjects included in the analysis of prevalence
n = 1,600,290
Subjects between April 2009 and March 2017
n = 533,895
Subjects with a serum uric acid level measured at least one during medical check-ups between April 2018 and March 2019
n = 1,066,395
Subjects who had not been enrolled in insurance at least 6 months before the first check-up date
n = 27,099
Subjects with missing data
n = 242,788
Subjects included in the final analysis population
n = 796,508


Men
Women
Overall
Proportion (%)
0.5
0.4
0.3
0.2
0.1
0
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Fiscal year

Supplemental Files

Temporal trends in the prevalence and characteristics of hypouricaemia: A descriptive study of medical check-up and administrative claims data

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Supplemental Tables

Table S1 List of definitions

Pre-existing diseases	ICD-10 codes
Renal dysfunction	N17-19, N26-28
Hypertension	I10-15
Diabetes mellitus	E10-14
Dyslipidaemia	E78
Urinary stones	N20-23
Ischemic heart disease	I20-25
Heart failure	I50
Cerebrovascular disease	I60-69
Neurological disease	G00-99
Parkinson's disease	G20-22
Alzheimer's disease	G30
Malignant tumour	C00-97, D00-09
History of medications	**ATC codes**
Urate-lowering therapy	M04, except for colchicine
Antihypertensive drug	C02, C03, C07, C08, C09, C11
ACE inhibitors	C09A
ARB	C09C, C09D1, C09D3
Diuretic drug	C03
Antidiabetic drug	A10C, A10H, A10J, A10K, A10L, A10M, A10N, A10P, A10S, A10X
Antilipidemic drug	C10A, C10B, C11A
Comorbidities	**Laboratory values**
Reduced kidney function	less than 60 ml/min/1.73 m^2 in eGFR* *eGFR (ml/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ (× 0.739, if female)
Hypertension	systolic blood pressure (BP) of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg
Diabetes mellitus	HbA1c level of ≥ 6.5%
Dyslipidemia	low-density lipoprotein cholesterol level ≥ 140 mg/dl, high-density lipoprotein cholesterol level < 40 mg/dL, and/or triglyceride level ≥ 150 mg/dL

ICD-10, International Classification of Diseases 10th revision; ATC, anatomical therapeutic chemical; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated Haemoglobin A1C

Table S2 Demographics of the study population, showing the prevalence of hypouricaemia for each fiscal year (FY) and the crude prevalence of hypouricaemia from FY2009 to FY2018

	FY2009		FY2010		FY2011		FY2012		FY2013	
	N	%	N	%	N	%	N	%	N	%
Total	99,421		127,548		201,901		286,042		442,948	
Age, years, mean (SD)	42.5 (10.0)		42.7 (10.0)		42.6 (10.6)		42.0 (10.8)		43.1 (10.6)	
Age										
16-19	900	0.9	861	0.7	1,750	0.9	2,263	0.8	2,967	0.7
20-29	8,329	8.4	10,758	8.4	21,769	10.8	37,415	13.1	48,287	10.9
30-39	29,245	29.4	36,497	28.6	55,263	27.4	78,127	27.3	111,924	25.3
40-49	36,300	36.5	47,314	37.1	69,461	34.4	95,763	33.5	153,007	34.5
50-59	20,351	20.5	25,830	20.3	41,864	20.7	56,110	19.6	98,472	22.2
60-69	4,056	4.1	6,004	4.7	11,261	5.6	15,592	5.5	26,932	6.1
70-74	240	0.2	284	0.2	533	0.3	772	0.3	1,359	0.3
Sex										
Men	69,953	70.4	90,361	70.8	140,913	69.8	197,190	68.9	300,764	67.9
Women	29,468	29.6	37,187	29.2	60,988	30.2	88,852	31.1	142,184	32.1
SUA, mg/dL, mean (SD)	5.4 (1.4)		5.4 (1.4)		5.5 (1.4)		5.5 (1.4)		5.5 (1.4)	
Men	5.9 (1.2)		5.9 (1.2)		6.0 (1.2)		6.0 (1.2)		6.0 (1.2)	
Women	4.2 (0.9)		4.2 (0.9)		4.3 (1.0)		4.3 (1.0)		4.3 (1.0)	
Hypouricaemia	273	0.3	346	0.3	495	0.3	674	0.2	1,054	0.2
Men	111	0.2	132	0.2	185	0.1	251	0.1	363	0.1
Women	162	0.6	214	0.6	310	0.5	423	0.5	691	0.5

	FY2014		FY2015		FY2016		FY2017		FY2018	
	N	%	N	%	N	%	N	%	N	%
Total	557,673		682,277		801,381		928,307		1,066,395	
Age, years, mean (SD)	43.4 (10.8)		44.1 (10.8)		43.9 (11.0)		44.1 (11.0)		44.2 (11.1)	
Age										
16-19	3,290	0.6	3,595	0.5	4,688	0.6	5,141	0.6	6,871	0.6
20-29	62,156	11.2	66,896	9.8	86,512	10.8	95,535	10.3	110,676	10.4
30-39	134,298	24.1	155,573	22.8	181,730	22.7	211,553	22.8	243,056	22.8
40-49	190,486	34.2	236,954	34.7	270,414	33.7	314,124	33.8	351,621	33.0
50-59	128,052	23.0	164,956	24.2	193,520	24.2	226,513	24.4	264,832	24.8
60-69	36,350	6.5	50,374	7.4	60,495	7.6	70,923	7.6	83,487	7.8
70-74	3,041	0.6	3,929	0.6	4,022	0.5	4,518	0.5	5,852	0.6
Sex										
Men	377,944	67.8	442,465	64.9	508,979	63.5	586,730	63.2	680,414	63.8
Women	179,729	32.2	239,812	35.2	292,402	36.5	341,577	36.8	385,981	36.2
SUA, mg/dL, mean (SD)	5.5 (1.4)		5.5 (1.4)		5.5 (1.4)		5.5 (1.4)		5.5 (1.4)	
Men	6.0 (1.2)		6.1 (1.2)		6.1 (1.2)		6.1 (1.2)		6.1 (1.2)	
Women	4.3 (1.0)		4.4 (1.0)		4.4 (1.0)		4.4 (1.0)		4.5 (1.0)	
Hypouricaemia	1,312	0.2	1,629	0.2	1,848	0.2	2,101	0.2	2,267	0.2
Men	457	0.1	535	0.1	594	0.1	699	0.1	811	0.1
Women	855	0.5	1094	0.5	1254	0.4	1402	0.4	1456	0.4

FY, fiscal year; SD, standard deviation; SUA, serum uric acid

Table S3 Characteristics of subjects in the final analysis population in the 2018 fiscal year

	Hypouricaemia		Normouricaemia		Hyperuricaemia		Overall		P value
	N	%	N	%	N	%	N	%	
Total	1,704		682,894		111,910		796,508		
Age, years, mean (SD)	43.7 (9.9)		44.7 (10.5)		44.6 (10.1)		44.7 (10.4)		<0.0001
Men	598	35.1	375,944	55.1	107,561	96.1	484,103	60.8	<0.0001
BMI, kg/m^2, mean (SD)	21.9 (3.7)		22.7 (3.6)		25.3 (4.0)		23.1 (3.8)		<0.0001
Waist circumference, cm, mean (SD)	78.2 (10.3)		80.6 (9.9)		88.1 (10.0)		81.6 (10.2)		<0.0001
Smoking	298	17.5	158,655	23.2	38,315	34.2	197,268	24.8	<0.0001
Drinking habits	794	46.6	381,967	55.9	81,625	72.9	464,386	58.3	<0.0001
Serum uric acid, mg/dL, median (IQR)	1.3 (0.7, 1.9)		5.2 (4.3, 6.0)		7.6 (7.3, 8.1)		5.5 (4.4, 6.5)		<0.0001
eGFR, mL/min/1.73m^2, mean (SD)	87.0 (19.3)		80.8 (15.0)		75.0 (14.4)		80.0 (15.1)		<0.0001
Pre-existing diseases									
Renal dysfunction	24	1.4	8,306	1.2	2,011	1.8	10,341	1.3	<0.0001
Hypertension	147	8.6	81,277	11.9	19,436	17.4	100,860	12.7	<0.0001
Diabetes mellitus	103	6.0	47,865	7.0	8,077	7.2	56,045	7.0	0.0114
Dyslipidaemia	164	9.6	89,730	13.1	16,976	15.2	106,870	13.4	<0.0001
Urinary stones	13	0.8	6,777	1.0	1,614	1.4	8,404	1.1	<0.0001
Ischaemic heart disease	28	1.6	13,358	2.0	2,620	2.3	16,006	2.0	<0.0001
Heart failure	26	1.5	10,162	1.5	2,292	2.1	12,480	1.6	<0.0001
Cerebrovascular disease	20	1.2	12,988	1.9	2,269	2.0	15,277	1.9	0.0014
Neurological disease	222	13.0	80,558	11.8	12,814	11.5	93,594	11.8	0.0010
Parkinson's disease	14	0.8	1,572	0.2	238	0.2	1,824	0.2	<0.0001
Alzheimer's disease	0	0.0	120	0.0	17	0.0	137	0.0	0.7368
Malignant tumour	1	0.1	418	0.1	19	0.0	438	0.1	<0.0001
History of medications									
Urate-lowering therapy	7	0.4	22,152	3.2	7,939	7.1	30,098	3.8	<0.0001
Antihypertensive drug	139	8.2	75,004	11.0	17,791	15.9	92,934	11.7	<0.0001
ACE inhibitors	6	0.4	3,211	0.5	819	0.7	4,036	0.5	<0.0001
ARB	83	4.9	45,793	6.7	12,202	10.9	58,078	7.3	<0.0001
Diuretic drug	11	0.7	7,047	1.0	2,262	2.0	9,320	1.2	<0.0001
Antidiabetic drug	58	3.4	24,481	3.6	3,339	3.0	27,878	3.5	<0.0001
Antilipidemic drug	116	6.8	62,287	9.1	10,480	9.4	72,883	9.2	0.0001
Comorbidities									
Reduced kidney function	55	3.2	38,133	5.6	14,244	12.7	52,432	6.6	<0.0001
Hypertension	157	9.2	84,330	12.4	26,260	23.5	110,747	13.9	<0.0001
Diabetes mellitus	66	3.9	29,683	4.4	4,983	4.5	34,732	4.4	0.1682
Dyslipidaemia	447	26.2	234,195	34.3	67,308	60.1	301,950	37.9	<0.0001

SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

Table S4 Characteristics of subjects in the hypouricaemia group with lower and higher serum uric acid levels in the 2018 fiscal year

	Lower hypouricaemia		Higher hypouricaemia		P value
	N	%	N	%	
Total	803		901		
Age, years, mean (SD)	44.8 (10.8)		42.6 (9.0)		<0.0001
Men	472	58.8	126	14.0	<0.0001
BMI, kg/m^2, mean (SD)	23.1 (3.7)		20.9 (3.4)		<0.0001
Waist circumference, cm, mean (SD)	81.6 (10.2)		75.1 (9.3)		<0.0001
Smoking	187	23.3	111	12.3	<0.0001
Drinking habits	455	56.7	339	37.6	<0.0001
SUA, mg/dL, median (IQR)	0.7 (0.6, 0.8)		1.9 (1.7, 2.0)		<0.0001
eGFR, mL/min/1.73m^2, mean (SD)	82.0 (14.2)		91.5 (22.0)		<0.0001
Pre-existing diseases					
Renal dysfunction	13	1.6	11	1.2	0.4864
Hypertension	85	10.6	62	6.9	0.0066
Diabetes mellitus	45	5.6	58	6.4	0.4712
Dyslipidaemia	85	10.6	79	8.8	0.2042
Urinary stones	7	0.9	6	0.7	0.6260
Ischaemic heart disease	16	2.0	12	1.3	0.2842
Heart failure	11	1.4	15	1.7	0.6200
Cerebrovascular disease	11	1.4	9	1.0	0.4779
Neurological disease	85	10.6	137	15.2	0.0047
Parkinson's disease	5	0.6	9	1.0	0.3904
Alzheimer's disease	0	0.0	0	0.0	—
Malignant tumour	0	0.0	1	0.1	0.3450
History of medications					
Urate-lowering therapy	1	0.1	6	0.7	0.0811
Antihypertensive drug	83	10.3	56	6.2	0.0019
ACE inhibitors	4	0.5	2	0.2	0.3367
ARB	47	5.9	36	4.0	0.0754
Diuretic drug	8	1.0	3	0.3	0.0879
Antidiabetic drug	19	2.4	39	4.3	0.0257
Antilipidemic drug	55	6.9	61	6.8	0.9484
Comorbidities					
Reduced kidney function	31	3.9	24	2.7	0.1629
Hypertension	107	13.3	50	5.6	<0.0001
Diabetes mellitus	26	3.2	40	4.4	0.1994
Dyslipidaemia	270	33.6	177	19.6	<0.0001

SUA, serum uric acid; SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

Table S5 Characteristics by sex in subjects in the hypouricaemia group with lower and higher serum uric acid levels in the 2018 fiscal year

	Men					Women				
	Lower hypouricaemia		Higher hypouricaemia		P value	Lower hypouricaemia		Higher hypouricaemia		P value
	N	%	N	%		N	%	N	%	
Total	472		126			331		775		
Age, years, mean (SD)	44.8 (11.2)		47.9 (9.7)		0.0039	45.0 (10.0)		41.8 (8.6)		<0.0001
BMI, kg/m^2, mean (SD)	24.0 (3.5)		24.3 (4.6)		0.4663	21.8 (3.5)		20.4 (2.7)		<0.0001
Waist circumference, cm, mean (SD)	84.5 (9.7)		84.9 (11.4)		0.7040	77.5 (9.5)		73.5 (7.9)		<0.0001
Smoking	162	34.3	44	34.9	0.9000	25	7.6	67	8.7	0.5469
Drinking habits	308	65.3	76	60.3	0.3044	147	44.4	263	33.9	0.0010
SUA, mg/dL, median (IQR)	0.7 (0.6, 0.8)		1.8 (1.3, 1.9)		<0.0001	0.6 (0.5, 0.7)		1.9 (1.8, 2.0)		<0.0001
eGFR, mL/min/1.73m^2, mean (SD)	82.2 (14.2)		77.1 (21.7)		0.0017	81.8 (14.2)		93.8 (21.2)		<0.0001
Pre-existing diseases										
Renal dysfunction	12	2.5	7	5.6	0.0867	1	0.3	4	0.5	0.6271
Hypertension	63	13.4	30	23.8	0.0040	22	6.7	32	4.1	0.0752
Diabetes mellitus	34	7.2	23	18.3	0.0002	11	3.3	35	4.5	0.3629
Dyslipidaemia	56	11.9	28	22.2	0.0030	29	8.8	51	6.6	0.1998
Urinary stones	5	1.1	1	0.8	0.7904	2	0.6	5	0.7	0.9373
Ischaemic heart disease	12	2.5	6	4.8	0.1952	4	1.2	6	0.8	0.4847
Heart failure	10	2.1	4	3.2	0.4862	1	0.3	11	1.4	0.1005
Cerebrovascular disease	10	2.1	2	1.6	0.7055	1	0.3	7	0.9	0.2800
Neurological disease	51	10.8	24	19.1	0.0131	34	10.3	113	14.6	0.0532
Parkinson's disease	5	1.1	3	2.4	0.2513	0	0.0	6	0.8	0.1085
Alzheimer's disease	0	0.0	0	0.0	—	0	0.0	0	0.0	—
Malignant tumour	0	0.0	0	0.0	—	0	0.0	1	0.1	0.5132
History of medications										
Urate-lowering therapy	1	0.2	5	4.0	0.0002	0	0.0	1	0.1	0.5132
Antihypertensive drug	59	12.5	27	21.4	0.0112	24	7.3	29	3.7	0.0124
ACE inhibitors	4	0.9	2	1.6	0.4591	0	0.0	0	0.0	—
ARB	35	7.4	21	16.7	0.0015	12	3.6	15	1.9	0.0954
Diuretic drug	3	0.6	0	0.0	0.3696	5	1.5	3	0.4	0.0435
Antidiabetic drug	16	3.4	18	14.3	<0.0001	3	0.9	21	2.7	0.0594
Antilipidemic drug	38	8.1	24	19.1	0.0003	17	5.1	37	4.8	0.7982
Comorbidities										
Reduced kidney function	18	3.8	16	12.7	0.0001	13	3.9	8	1.0	0.0012
Hypertension	75	15.9	21	16.7	0.8329	32	9.7	29	3.7	<0.0001
Diabetes mellitus	20	4.2	21	16.7	<0.0001	6	1.8	19	2.5	0.5127
Dyslipidaemia	188	39.8	55	43.7	0.4379	82	24.8	122	15.7	0.0004

SUA, serum uric acid; SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

Supplemental Figure

Figure S1 Distribution sUA levels in subjects of the final analysis population in the 2018 fiscal year. (a) Men, (b) Women