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ORIGINAL ARTICLE

A Retrospective, Cross-Sectional Study on the Prevalence of Hyperuricemia Using a Japanese Healthcare Database

Shingo HIGA[1], Mizuki YOSHIDA[2], Daisuke SHIMA[1], Yoichi II[2], Shigeru KITAZAKI[3], Yuji YAMAMOTO[3], Yoko FUJIMOTO[1]

[1]*Pfizer Japan Inc., Medical Affairs, Pfizer Essential Health, Tokyo, Japan*
[2]*Pfizer Japan Inc., Clinical Statistics, Development Japan, Tokyo, Japan*
[3]*Minacare Co., Ltd., Tokyo, Japan*

ABSTRACT

Objectives: This study aims to evaluate the prevalence of hyperuricemia (HU) considering both serum uric acid (SUA) levels and medication status of urate-lowering drugs (ULDs), and the association between HU and its comorbidities using a Japanese healthcare database.

Materials and Methods: The study population consisted of 60,828 subjects who had at least one serum uric acid measurement between the fiscal years (FYs) 2010 and 2014 in a Japanese employment-based health insurance database (MinaCare Co., Ltd., Tokyo, Japan), which includes mutually linked medical/pharmaceutical claims data and health check-up data. Hyperuricemia was defined as a SUA level >7.0 mg/dL of the health check-up data and/or a prescription for a ULD. The association between HU and comorbidities were analyzed by comparing the prevalence of HU of each subgroup defined by presence or absence of comorbidity.

Results: The prevalence of HU in FY 2014 was 26.8% [95% confidence interval (CI): 26.2 to 27.3%] in male subjects and 0.9% (95% CI: 0.7 to 1.0%) in female subjects. According to the analyses by sex and age, a trend of increasing prevalence with age was observed in both males and females. The prevalence of HU remained stable both in males and females from FYs 2010 to 2014. The positive association between HU and well-known comorbidities were confirmed with the exception of diabetes mellitus and smoking status in male subjects.

Conclusion: Our results provided a more accurate prevalence of HU in Japanese population. It is important to increase the awareness on HU in the society to reduce the burden of HU-related diseases.

Keywords: Claims data, hyperuricemia, MinaCare database, prevalence.

Hyperuricemia (HU) is an important pathological condition that is not only a direct cause of gout,[1] but also an independent risk factor for the development of hypertension (HT),[2,3] chronic kidney disease (CKD),[4] and end-stage kidney disease.[5] In addition, accumulated evidence suggests that hyperuricemia may have a pathogenic role in the development of metabolic syndrome,[6] which is defined as a cluster of cardiovascular risk factors such as elevated glucose level, central obesity, HT, hypertriglyceridemia and low high-density lipoprotein cholesterol.[7] There are many unknown aspects in this area; for example, the etiological mechanisms of high blood pressure and renal damage caused by HU have not been clearly elucidated, and the causal relationship between HU and cardiovascular events is still controversial. The accurate prevalence of HU in Japan is also one of the unknown aspects.

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Correspondence: Yoko Fujimoto. Pfizer Japan Inc., Medical Affairs, Pfizer Essential Health, 1518589 Tokyo, Japan.
Tel: +81-80-6809-9575 e-mail: yoko.fujimoto@pfizer.com

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A few studies have reported the prevalence of HU in the Japanese population on the basis of the results of health check-ups in certain populations.[8,9] A study was performed at a health screening center and the results indicated that the prevalence of HU in males was 21.5% as of 2003.[8] Another population-based study conducted in Northern Japan reported a HU prevalence of 17.4% in male subjects and 2.2% in female subjects.[9] However, the estimations of HU prevalence in these studies did not consider the number of well-managed HU patients on urate-lowering drugs (ULDs), and are therefore presumed to underestimate the actual figures.

Previously reported age distributions of HU patients also imply underestimation of the HU prevalence. It was reported that the prevalence of HU increases with age in the USA and China,[10,11] whereas epidemiological studies conducted in Japan reported a higher prevalence of HU in male subjects in their 30s and 40s than in older age groups.[8,12] This age distribution of HU patients in Japan is considered to reflect the fact that well-controlled HU patients on ULDs are excluded, because HU is included in the indication of ULDs in Japan unlike in other countries. Similar considerations are also mentioned in the Japanese guideline for the management of HU and gout.[13] Therefore, in this study, we aimed to evaluate the prevalence of HU considering both serum uric acid (SUA) levels and medication status of ULDs, and the association between HU and its comorbidities using a Japanese healthcare database.

MATERIALS AND METHODS

This was a retrospective, cross-sectional study conducted using a Japanese healthcare database (MinaCare Co., Ltd., Tokyo, Japan). The primary objective of this study was to estimate the prevalence of HU in Japan considering both SUA levels evaluated as health check-up and medication status of ULDs, and to investigate the trend of HU prevalence in recent years [fiscal year (FY) 2010 to FY 2014 (FY=April 1st to March 31st)].

The secondary objectives of this study were to examine the association of body mass index (BMI), smoking status, and well-known comorbidities of HU such as HT, diabetes mellitus (DM), and hyperlipidemia (HL) with the prevalence of HU.

The Japanese healthcare database that is managed by MinaCare Co., Ltd. was used for this study. The MinaCare database includes annual health check-up and medical/pharmaceutical claims data that are provided by employment-based health insurance societies.[14] The health check-up data include information on subjects' demographics, smoking status, blood pressure, BMI, and clinical laboratory test results. The medical/pharmaceutical claims data include information on prescriptions, medical procedures, diagnosis, and administrative data. Since these two types of data are linked in the subpopulation, this database enables us to estimate the prevalence of HU considering both the SUA levels at health check-ups and the prescriptions for ULDs in the claims data. The populations covered by this database comprise working individuals and their dependent family members. Since the employment-based insurance covers various large-scale, nationwide industries, this database includes healthcare information with minimal geographic or occupational bias.

The MinaCare database used for this research includes only the information that has already been anonymized unlinkably. Approval for this research by an ethical review committee and informed consent of each subject were not required, because studies using only unlinkably anonymized data are outside the scope of "Ethical Guidelines for Medical and Health Research Involving Human Subjects[15]" set by the Japanese government.

The data that support the findings of this study are available from MinaCare Co., Ltd., but restrictions apply to the availability of these data, which were used under license of the current study, and are not publicly available. Data are however available from the authors upon reasonable request and with the permission of MinaCare Co., Ltd.

The study population consisted of 60,828 subjects who had at least one SUA measurement in their health check-up data during the 2010 to 2014 FYs period. For analysis of a particular FY, subjects with missing SUA values were excluded from the analysis. For subjects with multiple observations of SUA in the same FY, the data of the examination date with the highest SUA value

were used. Hyperuricemia was defined as a SUA level >7.0 mg/dL in the health check-up data and/or a prescription for ULDs (benzbromarone, probenecid, bucolome, allopurinol, febuxostat, or topiroxostat) in the claims data.

Statistical analysis

The data analysis was conducted based on the study population. The characteristics of the study population as well as those by sex were descriptively summarized. As the primary analysis, the prevalence of HU by sex, and both sex and age was estimated for each FY (from FY 2010 to FY 2014). The prevalence was calculated as the number of subjects who met the definition of HU (described in the section of study population and case definition) divided by the total number of subjects who had at least one SUA measurement in each FY. The exact two-sided 95% confidence interval (CI) for the prevalence was calculated using the Clopper-Pearson method.[16]

As the secondary analysis, subgroup analyses of the prevalence of HU by the well-known comorbidities of HU (presence/absence of HT, DM, or HL), BMI (<18.5, 18.5 to <25, 25 to <30, and ≥30), and smoking status (yes, no) were performed. For subgroup analysis, comorbidities such as HT, DM, and HL were defined by prescriptions for each therapeutic medication (anti-hypertensive drugs, anti-diabetic drugs, and anti-hyperlipidemic drugs, respectively). Statistical comparison based on the prevalence of HU was conducted between categories for each subgroup using the chi-square test (for HT, DM, HL, and smoking status) and the Cochran-Armitage trend test (for BMI) at the two-sided significance level of 0.05.

To support the primary analysis, exploratory analyses were performed by changing the definition of prevalence as follows:

- The prevalence of subjects who had SUA measurements exceeding 7.0 mg/dL at a health check-up (exploratory analysis 1)
- The prevalence of subjects to whom ULDs were prescribed (exploratory analysis 2)

In addition, tumor lysis syndrome, which is caused by the death of cancer cells during cancer treatment, causes a high SUA level.[17] Therefore, analysis that excluded cancer patients from the study population was also performed as a sensitivity analysis to evaluate the possibility of overestimation caused by subjects using ULDs

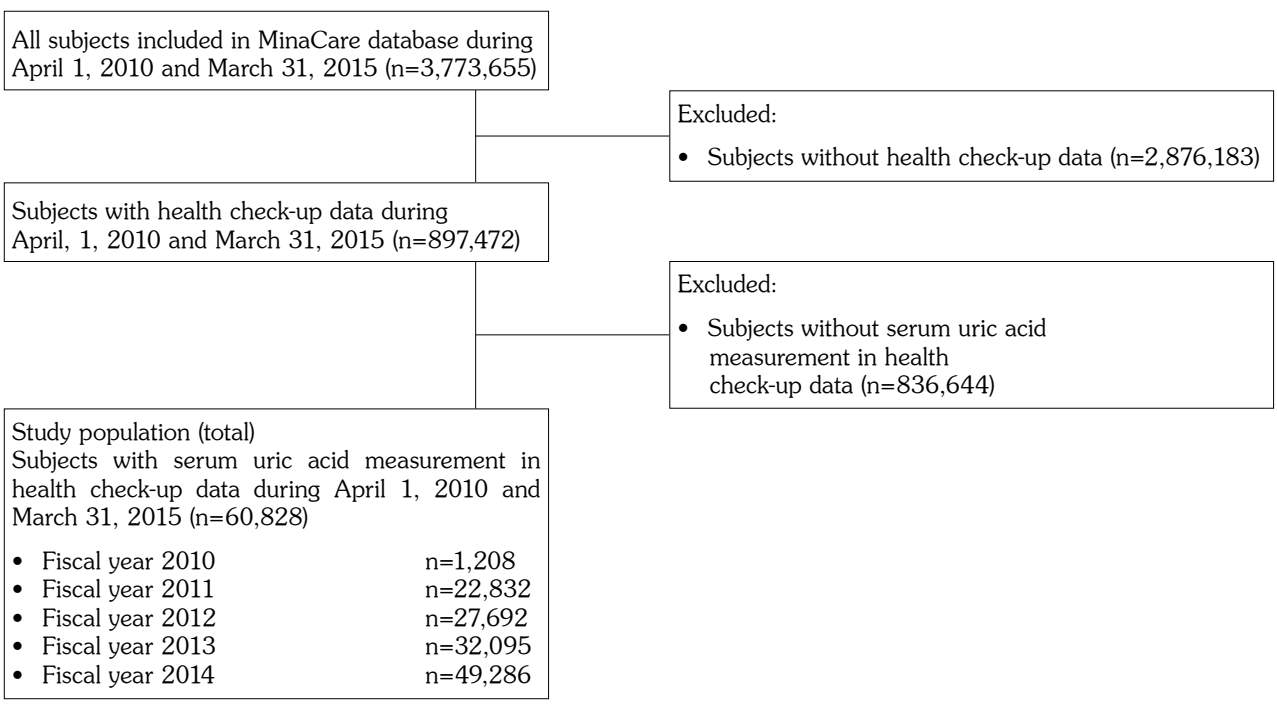

Figure 1. Flowchart of study population.
Study population was extracted from subjects included in MinaCare database at any time during study period (01 April 2010 - 31 March 2015).

for tumor lysis syndrome. All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Of the 3,773,655 subjects included in MinaCare database, 897,472 subjects had at least one health check-up data during the study period (from FY 2010 to FY 2014). Among them, a total of 60,828 subjects had at least one SUA measurement and were included in the analysis. A flowchart of the study population is presented in Figure 1. The numbers of subjects of each FY were 1,208, 22,832, 27,692, 32,095, and 49,286 in FYs 2010, 2011, 2012, 2013, and 2014, respectively. The characteristics of the study population in FY 2014 are shown in Table 1. A total of 49,286 subjects who had at least one SUA measurement in FY 2014 were analyzed. Of the 49,286 subjects, 51.7% were males and 48.3% were females. The study population mainly consisted of subjects in their 30s, 40s, and 50s. The proportion of male subjects with comorbidities, obesity (defined as BMI ≥25), and smoking habit was higher than that of female subjects. There were no big differences in the distribution of age, BMI, or smoking status between this study population, which consists of those who had at least one SUA measurement, and the overall population with any health check-up data in the MinaCare database.[14]

The prevalence of HU in FY 2014 was 26.8% (95% CI: 26.2 to 27.3%) in male subjects and 0.9% (95% CI: 0.7 to 1.0%) in female subjects

Table 1. Characteristics of study population in fiscal year 2014

	Total (n=49,286)		Male (n=25,467)		Female (n=23,819)	
	n	%	n	%	n	%
Age (year)						
<20	91	0.2	38	0.1	53	0.2
20 to 29	7422	15.1	2542	10.0	4880	20.5
30 to 39	12155	24.7	5530	21.7	6625	27.8
40 to 49	15305	31.1	8229	32.3	7076	29.7
50 to 59	10742	21.8	6523	25.6	4219	17.7
60 to 64	3018	6.1	2193	8.6	825	3.5
≥65	553	1.1	412	1.6	141	0.6
Comorbidities						
HT (anti-hypertensive drugs* use)	4870	9.9	3717	14.6	1153	4.8
DM (anti-diabetic drugs** use)	1307	2.7	1069	4.2	238	1.0
HL (anti-hyperlipidemic drugs*** use)	3460	7.0	2488	9.8	972	4.1
BMI (kg/m^2)						
<18.5	5454	11.1	647	2.5	4807	20.2
18.5 to <25	33994	69.0	17353	68.1	16641	69.9
25 to <30	8201	16.6	6334	24.9	1867	7.8
≥30	1603	3.3	1132	4.4	471	2.0
Unknown	34	0.1	1	0.0	33	0.1
Smoking status						
Yes	9732	19.7	7812	30.7	1920	8.1
No	38180	77.5	17036	66.9	21144	88.8
Unknown	1374	2.8	619	2.4	755	3.2

HT: Hypertension; DM: Diabetes mellitus; HL: Hyperlipidemia; BMI: Body mass index; * Anti-hypertensive drugs include diuretics, calcium blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, selective aldosterone receptor antagonists, alpha blockers, alpha-2 agonists, reserpine, beta blockers, hydralazine, and sodium nitroprusside; ** Anti-diabetic drugs include insulin, glucagon-like peptide-1 receptor agonists, sulfonylureas, biguanides, pioglitazone, alpha-glucosidase inhibitors, glinides, dipeptidyl peptidase-4 inhibitors, and sodium-glucose co-transporter 2 inhibitors; *** Anti-hyperlipidemic drugs include statins, fibrates, ezetimibe, nicotinic acid, ion-exchange resin, probucol, gamma oryzanol, dextran sulfate sodium, polyene phosphatidylcholine, elastase, ethyl icosapentate, and omega-3 acid ethyl esters.

Table 2. Sex- and age-specific prevalence of hyperuricemia in fiscal year 2014

Sex	Age (years)	Prevalence	%	95% CI
Male	<30	510/2580	19.8	18.2 to 21.4
	30 to <40	1390/5530	25.1	24.0 to 26.3
	40 to <50	2232/8229	27.1	26.2 to 28.1
	50 to <60	1917/6523	29.4	28.3 to 30.5
	60 to <65	648/2193	29.5	27.6 to 31.5
	≥65	126/412	30.6	26.2 to 35.3
	Total	6823/25467	26.8	26.2 to 27.3
Female	<30	8/4933	0.2	0.1 to 0.3
	30 to <40	38/6625	0.6	0.4 to 0.8
	40 to <50	66/7076	0.9	0.7 to 1.2
	50 to <60	73/4219	1.7	1.4 to 2.2
	60 to <65	13/825	1.6	0.8 to 2.7
	≥65	5/141	3.5	1.2 to 8.1
	Total	203/23819	0.9	0.7 to 1.0

CI: Confidence interval.

(Table 2). According to the analyses by sex and age, the prevalence of HU increased with age in both male and female subjects (Table 2).

The proportion of subjects who had at least one SUA measurement that exceeded 7.0 mg/dL in FY 2014 was 22.6% (95% CI: 22.1 to 23.1%) in males and 0.8% (95% CI: 0.7 to 0.9%) in females. The proportion of subjects whose SUA levels exceeded 7.0 mg/dL was the highest in males in their 30s (exploratory analysis 1, data not shown). On the other hand, the prevalence of HU considering both SUA levels and medication status was the highest in subjects aged 65 years and older (Table 2). The proportion of subjects to whom ULDs were prescribed in FY 2014 was 6.7% (95% CI: 7.8 to 8.4%) in males and 0.1% (95% CI: 0.1 to 0.2%) in females. The proportion of subjects to whom ULDs were prescribed was

Table 3. Sex- and age-specific proportion of subjects to whom urate-lowering drugs were prescribed in fiscal year 2014 (exploratory analysis 2)

Sex	Age (years)	Proportion	%	95% CI
Male	<30	21/2580	0.8	0.5 to 1.2
	30 to <40	118/5530	2.1	1.8 to 2.5
	40 to <50	483/8229	5.9	5.4 to 6.4
	50 to <60	718/6523	11.0	10.3 to 11.8
	60 to <65	311/2193	14.2	12.7 to 15.7
	≥65	60/412	14.6	11.3 to 18.3
	Total	1711/25467	6.7	6.4 to 7.0
Female	<30	0/4933	0	-
	30 to <40	3/6625	0.0	0.0 to 0.1
	40 to <50	7/7076	0.1	0.0 to 0.2
	50 to <60	12/4219	0.3	0.1 to 0.5
	60 to <65	3/825	0.4	0.1 to 1.1
	≥65	1/141	0.7	0.0 to 3.9
	Total	26/23819	0.1	0.1 to 0.2

CI: Confidence interval.

the highest in elderly persons, for both males and females (exploratory analysis 2, the results are shown in Table 3).

In the sensitivity analysis in which cancer patients were excluded from the study population, the prevalence of HU in FY 2014 was 26.0% (95% CI: 25.3 to 26.6%) in male subjects and 0.7% (95% CI: 0.6 to 0.9%) in female subjects (data not shown). There were no big differences between the results of the main analysis and the sensitivity analysis.

The five-year trend in the prevalence of HU by sex is shown in Figure 2a, and that by sex and age is shown in Figure 2b and 2c. From FY 2010 to FY 2014, the prevalence of HU remained stable both in male and female subjects (Figure 2a). In the subgroup analysis by sex and age, there were no big changes in the prevalence of HU over the course of five years (Figure 2b and 2c).

The prevalence of HU in the subgroups defined by well-known comorbidities (presence/absence of HT, DM, or HL), smoking habit (yes, no), and that defined by the BMI value (<18.5, 18.5 to <25, 25 to <30, ≥30) was estimated. The results of these subgroup analyses in male and female subjects in FY 2014 are shown in Figure 3a and 3b, respectively. In male subjects, the prevalence of HU in those with HT or HL was higher than in those without these respective conditions ($p<0.00001$ and $p<0.00001$, respectively). There was an increasing trend in the prevalence of HU along with the BMI value in male subjects ($p<0.00001$). However, there was no significant difference in the prevalence of HU between those with and without DM ($p=0.189$). The prevalence of HU in those with a smoking habit was lower than in those without a smoking habit ($p=0.00001$) (Figure 3a).

In female subjects, the prevalence of HU in those with HT, DM, HL, or those with a smoking habit was higher than in those without the above conditions ($p<0.00001$, $p<0.00001$, $p<0.00001$, and $p<0.00001$, respectively). There was also an increasing trend in the prevalence of HU with increasing BMI in female subjects ($p<0.00001$) (Figure 3b).

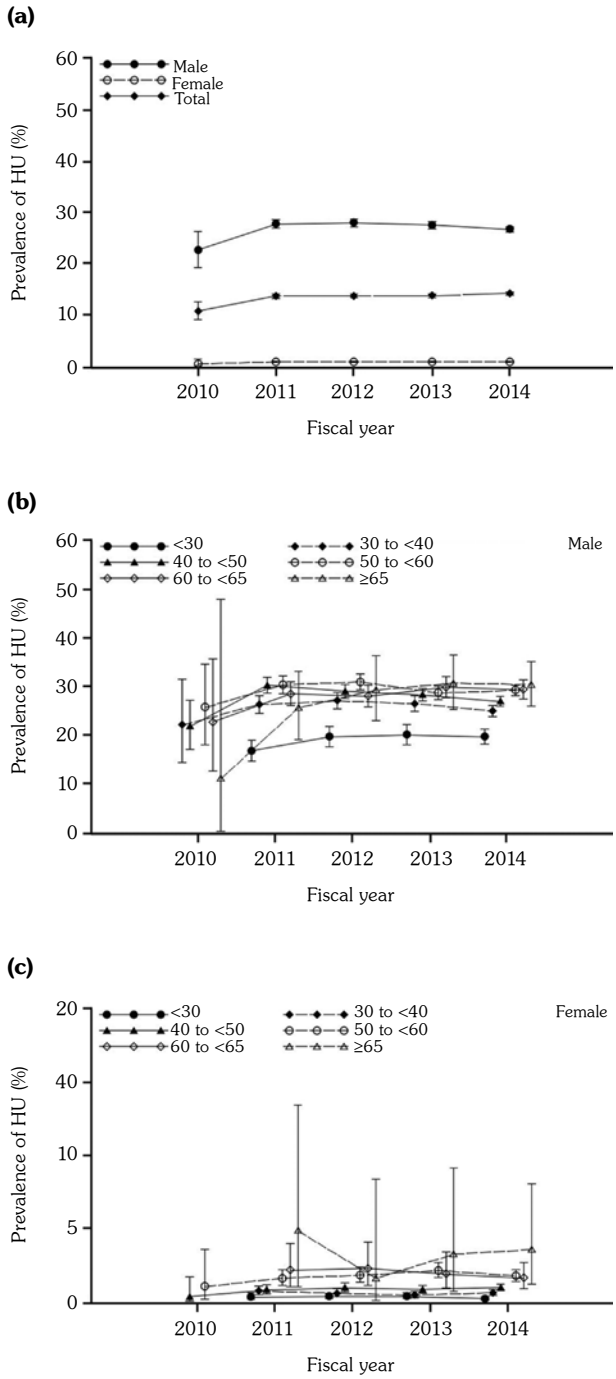

Figure 2. Five-year trend in prevalence of hyperuricemia. **(a)** Overall and sex-specific prevalence of HU (FY 2010 to FY 2014). **(b)** Age-specific prevalence of HU in male subjects (FY 2010 to FY 2014). **(c)** Age-specific prevalence of HU in female subjects (FY 2010 to FY 2014). 95% confidence intervals (shown with bars) were calculated using Clopper-Pearson method.

HU: Hyperuricemia; FY: Fiscal year.

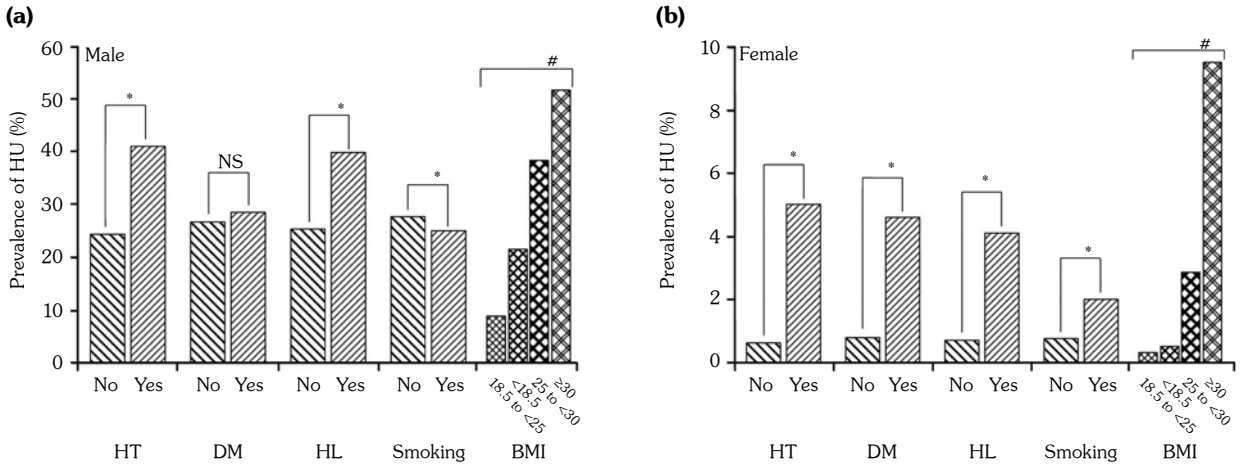

Figure 3. Prevalence of hyperuricemia by major comorbidities of hyperuricemia. Prevalence of hyperuricemia in subgroup defined by presence or absence of comorbidities (hypertension, diabetes mellitus, and hyperlipidemia), smoking habit, and that defined by body mass index value in **(a)** male subjects and **(b)** female subjects in fiscal year 2014.

* p<0.0001 (chi-square test); # p<0.0001 (Cochran-Armitage trend test); NS: Not significant; HU: Hyperuricemia; HT: Hypertension; DM: Diabetes mellitus; HL: Hyperlipidemia; BMI: Body mass index.

DISCUSSION

This study was designed to estimate the prevalence of HU in the Japanese population more accurately by using data on SUA levels as well as medication status. The MinaCare database, which includes linked health check-up data and claims data, enabled us to estimate the prevalence that also covers well-managed HU patients. Considering the existence of HU patients whose SUA levels were controlled at 7.0 mg/dL or less with ULDs, the prevalence of HU in FY 2014 in Japanese male subjects observed in this study (26.8%) was higher than that previously reported (21.5%, 17.4%),[8,9] which is in alignment with our hypothesis. In the analysis using only the SUA level (exploratory analysis 1, data not shown), the overall prevalence and age specific prevalence in male subjects in FY 2014 were very similar to that in a previous study,[8] in which prevalence of HU was evaluated based only on the SUA level. In addition, the prevalence of male subjects to whom ULDs were prescribed increased dramatically with age (exploratory analysis 2, Table 3). These data indicate that the previously reported prevalence of HU based only on the SUA levels were underestimated, particularly in older male patients, as stated in the Japanese guideline for the management of hyperuricemia and gout.[13] Given the previous study results showing a relationship between the prevalence of gout and aging in several countries[18] and a relationship between the prevalence of HU and aging in the USA[10] and China,[11] where HU is not an indication for ULDs, the results observed in this study are considered reasonable.

The prevalence of HU increased dramatically in female subjects aged between 40 (0.9%) and 50 (1.7%) years in accordance with a previous study in Japan (1.3% and 3.7% in the age group of under 50 years, and more than or equal to 50 years, respectively).[13] This substantial difference in the prevalence of HU between the ages of 40 and 50 years was also observed in the Third US National Health and Nutritional Examination Survey (NHANES III, 1988 to 1994) study.[10] It is considered that this exponential increase of the prevalence is caused by menopause because estrogen enhances the renal urate clearance.[19] The increased use of diuretics in association with increasing age is also considered to be one of the explanations for the exponential increase in prevalence because diuretics are a well-known cause of HU.[20]

Although an increasing trend in the prevalence of HU and age specific prevalence over the five-year period from FY 2010 to FY 2014 were not observed either in male or female subjects (Figure 2a-c) in this study, a previous study

using the health check-up data reported that the prevalence of HU in Japanese male subjects showed an increasing trend in all age groups from 1996 to 2004.[12] This changing trend in the prevalence of HU suggests changes in the prevalence of the risk factors of HU between the 1990s to 2000s and 2010s. According to the results of the National Health and Nutrition Survey in Japan, there was an increasing trend in the prevalence of obesity (BMI ≥25) in male subjects in the 1990s to 2000s (22.0% in 1996 and 27.3% in 2004), while the prevalence has not changed in recent years (29.3% in 2010 and 27.8% in 2014) without big change in blood pressure, triglyceride, blood glucose or total cholesterol during the period.[21] Although other risk factors of HU such as CKD may influence the prevalence of HU,[22] it is considered that obesity or BMI was one of the major factors that triggered the changing trend in the prevalence of HU.

It is well known that SUA is associated with the prevalence of metabolic syndrome and its components.[23-25] In this study, we conducted subgroup analyses by the presence or absence of well-known comorbidities, BMI category, and smoking status, to investigate the consistency between previous studies and this study regarding the association of these cardiovascular risk factors with the prevalence of HU. As a result, the positive associations of HU with its comorbidities, BMI and smoking status were confirmed with the exception of DM and smoking status in male subjects.

There is much evidence that indicates a relationship between HU and HT,[2,26] as well as HU and HL.[24,27] Obesity is also a well-known risk factor of HU, and several studies have reported a relationship between HU and BMI.[28-30] This study showed that the prevalence of HU in male and female subjects who had HT or HL was higher than that in subjects who did not have HT or HL, as well as a clear positive association between BMI and the prevalence of HU (Figure 3a and 3b), which were consistent with the results of previous studies.

In regard to the association between HU and DM, sex differences in the prevalence of HU between DM and non-DM subjects were observed in this study (Figure 3a and 3b). Interestingly, a negative association between HU and the occurrence of DM in males,[27,31] and difference between sexes with regards to this association have been reported previously.[28,32] There is evidence that mean serum urate increases with increasing glucose concentration up to 7.0 mmol/L in males and 9.0 mmol/L in females, and thereafter increasing glucose values are accompanied by a decrease in serum urate.[33] This difference in the flexion point of the glucose concentration between the sexes may be one of the explanations of the sex differences in the prevalence of HU between DM and non-DM subjects, observed in this study. However, further research is necessary to elucidate the reason of the sex differences in the relationship between HU and DM.

As for the relationship between smoking and HU, an inverse association between smoking and SUA levels has been described.[34,35] In accordance with these findings, male subjects with a smoking habit showed a lower prevalence of HU (Figure 3a). On the other hand, smoking habit was associated with a higher prevalence of HU in female subjects (Figure 3b). However, to our knowledge, the difference in the effect of smoking on SUA levels by sex has never been reported before. The reason for the negative correlation between SUA levels and smoking is partially explained as a reduced production and increased consumption of endogenous antioxidant uric acid caused by cigarette smoking, which is a source of oxidative stress.[34] Further research is needed to understand the exact mechanism of this association.

Several limitations due to the characteristics of health insurance claims data, health check-up data, and the method of analysis should be considered in this study. Since the MinaCare database includes healthcare information of working individuals and their dependents, it may not cover general retired people. Therefore, generalizability of the prevalence in subjects aged 65 years and older is possibly lower than that in other age categories. It is also considered that the precision of the prevalence in subjects aged under 20 years and those aged 65 years and older is lower than that in other age categories due to the small sample sizes. However, it is reported that age trends by sex for the parameters such as blood pressure, lipid parameters and blood glucose levels were generally consistent across the MinaCare database and national survey data sources.[14] In addition, since HU is not a

life-threatening disease, it is considered that most HU patients can continue working. Therefore, there are no major differences between working individuals and the general population in terms of the distribution of SUA levels in the same age group and the generalizability of the estimated prevalence of HU is considered sufficiently high, particularly in young and middle-aged people.

There is another limitation associated with the health check-up data, particularly the arbitrary property of SUA measurements of health check-ups. We cannot completely deny the possibility of selection bias because we included those who had at least one SUA measurement of health check-up data as the study subjects. However, the characteristics of this study population are similar to those in a previous study using the same database, which included those who had at least one set of health check-up data as the study subjects.[14] This suggests that the existence or non-existence of SUA measurements do not depend on the individual SUA levels, but depend on the health insurance to which insured persons belong. Therefore, it is considered that selection bias caused by the extraction of the study population is not major in this study.

Some limitations based on the analysis method should also be considered. We only performed univariate analyses and did not adjust for other risk factors in the analysis that investigated the association between the prevalence of HU and its comorbidities, because these subgroup analyses were exploratory ones. Since the major comorbidities of HU such as HT, DM, HL, and obesity are associated with each other, we cannot deny overestimation of the strength of association between HU and these comorbidities.

In addition to this, other limitations derived from the definition of HU are conceivable. We defined HU patients as people to whom ULDs were prescribed in this study, while there are some anti-hypertensive and anti-hyperlipidemic drugs that have a moderate SUA-lowering effect. Therefore, if these drugs were intentionally prescribed to HT or HL patients with a high SUA level, we cannot deny the possibility of underestimation of HU prevalence due to a lack of coverage of the potential HU patients whose SUA levels were controlled at 7.0 mg/dL or below by the administration of these drugs.

Finally, similar to studies using administrative or claims databases, there are several limitations that may affect the validity and reproducibility of the results such as incomplete coding, coding errors, and correction or duplication of claims.

The strengths of this study are that the MinaCare database, which includes linked health check-up data and claims data, enabled us to estimate the prevalence of HU in the Japanese population that also includes well-managed HU patients, and the sample size of this study was also larger than those of previous studies.

In conclusion, this is the first study using a Japanese healthcare database to estimate the prevalence of HU in Japan considering both SUA levels and medication status. The increment in prevalence reported by this study compared with those in previous studies may reflect the number of well-managed HU patients whose SUA levels were controlled at 7.0 mg/dL or below by the administration of ULDs. The fact that medication with ULDs in males increased dramatically with age supports the hypothesis of the underestimation of the previously reported prevalence in older male patients stated in the Japanese guideline for the management of hyperuricemia and gout. Considering the administration of ULDs, the prevalence of HU in the Japanese population increased with age in this study. These results suggest that the number of HU patients in Japan is higher than had previously been assumed. In addition, the association between HU and its comorbidities which are also major cardiovascular risk factors were confirmed in this study. Therefore, it is important to increase awareness on HU in society to reduce the social and health burden of HU-related diseases.

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Declaration of conflicting interests

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