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. 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.
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. 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. Another population-based study conducted in Northern Japan reported a HU prevalence of 17.4% in male subjects and 2.2% in female subjects. 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, 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. 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. 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 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...
Prevalence of Hyperuricemia in Japan

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

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**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).
overestimation caused by subjects using ULDs 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

<table>
<thead>
<tr>
<th>Table 1. Characteristics of study population in fiscal year 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>&lt;20</td>
</tr>
<tr>
<td>20 to 29</td>
</tr>
<tr>
<td>30 to 39</td>
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<td>40 to 49</td>
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<td>50 to 59</td>
</tr>
<tr>
<td>60 to 64</td>
</tr>
<tr>
<td>≥65</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
</tr>
<tr>
<td>HT (anti-hypertensive drugs* use)</td>
</tr>
<tr>
<td>DM (anti-diabetic drugs** use)</td>
</tr>
<tr>
<td>HL (anti-hyperlipidemic drugs*** use)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td>&lt;18.5</td>
</tr>
<tr>
<td>18.5 to &lt;25</td>
</tr>
<tr>
<td>25 to &lt;30</td>
</tr>
<tr>
<td>≥30</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

*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, polynene phosphatidylcholine, elastase, ethyl icosapentate, and omega-3 acid ethyl esters.
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 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

<p>| Table 2. Sex- and age-specific prevalence of hyperuricemia in fiscal year 2014 |
|-----------------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Prevalence</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>&lt;30</td>
<td>510/2580</td>
<td>19.8</td>
<td>18.2 to 21.4</td>
</tr>
<tr>
<td></td>
<td>30 to &lt;40</td>
<td>1390/5530</td>
<td>25.1</td>
<td>24.0 to 26.3</td>
</tr>
<tr>
<td></td>
<td>40 to &lt;50</td>
<td>2232/8229</td>
<td>27.1</td>
<td>26.2 to 28.1</td>
</tr>
<tr>
<td></td>
<td>50 to &lt;60</td>
<td>1917/6523</td>
<td>29.4</td>
<td>28.3 to 30.5</td>
</tr>
<tr>
<td></td>
<td>60 to &lt;65</td>
<td>648/2193</td>
<td>29.5</td>
<td>27.6 to 31.5</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>126/412</td>
<td>30.6</td>
<td>26.2 to 35.3</td>
</tr>
<tr>
<td>Total</td>
<td>6823/25467</td>
<td>26.8</td>
<td>26.2 to 27.3</td>
<td></td>
</tr>
</tbody>
</table>

| 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.

<p>| Table 3. Sex- and age-specific proportion of subjects to whom urate-lowering drugs were prescribed in fiscal year 2014 (exploratory analysis 2) |
|-----------------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Proportion</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>&lt;30</td>
<td>21/2580</td>
<td>0.8</td>
<td>0.5 to 1.2</td>
</tr>
<tr>
<td></td>
<td>30 to &lt;40</td>
<td>118/5530</td>
<td>2.1</td>
<td>1.8 to 2.5</td>
</tr>
<tr>
<td></td>
<td>40 to &lt;50</td>
<td>483/8229</td>
<td>5.9</td>
<td>5.4 to 6.4</td>
</tr>
<tr>
<td></td>
<td>50 to &lt;60</td>
<td>718/6523</td>
<td>11.0</td>
<td>10.3 to 11.8</td>
</tr>
<tr>
<td></td>
<td>60 to &lt;65</td>
<td>311/2193</td>
<td>14.2</td>
<td>12.7 to 15.7</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>60/412</td>
<td>14.6</td>
<td>11.3 to 18.3</td>
</tr>
<tr>
<td>Total</td>
<td>1711/25467</td>
<td>6.7</td>
<td>6.4 to 7.0</td>
<td></td>
</tr>
</tbody>
</table>

| 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.
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 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.
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 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 countries18 and a relationship between the prevalence of HU and aging in the USA10 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. 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. Although other
risk factors of HU such as CKD may influence the
prevalence of HU, 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. 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, as well as
HU and HL. Obesity is also a well-known risk
factor of HU, and several studies have reported a
relationship between HU and BMI. 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, and difference
between sexes with regards to this association have
been reported previously. 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. 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. 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. 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. 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. 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
SH, MY, DS, YI, and YF are full-time employees of Pfizer Japan Inc. YY is the founder and CEO of MinaCare Co., Ltd., and SK is full-time employee of MinaCare Co., Ltd.

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