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ORIGINAL ARTICLE

Prevalence, recognition and management of chronic kidney disease in Japan: population-based estimate using a healthcare database with routine health checkup data

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ABSTRACT

Background. We aimed to update information on the prevalence of chronic kidney disease (CKD) in Japan. We also explored whether CKD was properly recognized and managed.

Methods. We used data from annual health checkups in 2017, compiling records for 5 million persons. These included laboratory results and were linked to healthcare utilization records via personal identifiers. CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. The prevalence was compared with that in 2005. Healthcare utilization, including laboratory tests, disease coding and medication for comorbid diabetes mellitus (DM) and hypertension (HT), was used as an indicator for the recognition and management of CKD.

Results. Of the 761 565 records [median age 46 years (interquartile range 50–62)], CKD was found in 50 091 persons; the crude and age-adjusted prevalences were 63.1 and 71.8 per 1000 persons, respectively. CKD prevalence was significantly higher in 2017 than in 2005, with an increase of 14.1 per 1000 persons. Among persons with CKD, >95% sought medical services and 64.6% received laboratory tests within 180 days of the checkup. However, the diagnostic code suggestive of CKD was recorded in only 23.2% of patients and prescriptions for DM and HT were found in 31.2% (1590/5096) and 36.7% (8081/22 019) of comorbid persons, respectively.

Conclusions. The prevalence of CKD in Japan has increased over the past decade. However, recognition of CKD is likely suboptimal and there is room to improve the management of comorbid DM and HT.

Keywords: CKD, diabetes, epidemiology, hypertension

INTRODUCTION

The burden of chronic kidney disease (CKD) is substantial worldwide and the two major drivers of CKD are diabetes mellitus (DM) and hypertension (HT) [1, 2]. CKD is a precursor of end-stage kidney disease and a risk factor for cardiovascular disease and premature death [3, 4]. Such consequences of CKD lead to financial strain and reduce patients' quality of life [5, 6].

The epidemiology of CKD, including the prevalence and associated risk factors, namely, DM and HT, may change over time. In Japan, the prevalence of CKD was estimated at 13.2% of the adult population, or 13.3 million people, based on data from 2005 [7]. Unfortunately, up-to-date information is lacking. As a result of the promoting of a health lifestyle, salt intake and smoking have decreased over time in Japan [8], and the reduction in these risk factors could change the population-level burden and etiology of CKD. In addition, although studies from other countries have reported that the underdiagnosis of CKD is relatively common [9], the extent of CKD recognition remains unstudied in Japan. These knowledge gaps must be minimized to plan and implement a population-based strategy for the primary and secondary prevention of CKD.

The primary goal of this study was to update information on the prevalence of CKD in Japanese people of working age. We also examined how modifiable risk factors are prevalent in people with CKD, together with the recognition and management of CKD.

MATERIALS AND METHODS

Data source

We used data obtained from JMDC (Tokyo, Japan) [10, 11]. JMDC collects data from >100 employee-based insurances, and the number of cumulative enrollees from 2005 to 2016 was ~5 million. For people ≥75 years of age, a special insurance plan is offered by the government of Japan; the JMDC database does not include these individuals. In addition, due to the nature of employee-based insurance, people who have retired, which typically occurs at the age of 60–65 years in Japan, are not included in the JMDC database. Thus enrollees in the JMDC database represent working-age people and their dependents.

The JMDC database includes both annual health checkup data and medical claims records, which are linked via unique personal identifiers. The health checkup data involve two types of checkups: specific health checkups for all citizens ages 40–74 years and workplace checkups for employees provided by their companies [12]. Typically both checkups are performed on an annual basis and include information from physical assessments [e.g. blood pressure (BP)] and laboratory results, such as serum creatinine (SCr) and hemoglobin A1c (HbA1c). However, the uptake of specific health checkups is as low as ~50% [13].

Patients

Adult enrollees who had a recorded SCr value at the 2017 health checkup were eligible. Continuous enrollment of the JMDC database 12 months before and after a checkup was also required to search for comorbidities and medical-seeking behavior. The exclusion criterion waswomen who gave birth within 10 months following a checkup.

Definition

CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and eGFR was estimated using the following Japanese-specific equation [14]: eGFR (mL/min/1.73 m^2) = $194 \times SCr^{-1.094}$ (mg/dL) $\times age^{-0.287}$ (years) ($\times$ 0.739 for females). This equation was only applicable to SCr values measured by enzymatic methods, and most laboratories (>95%) in Japan employ this method [14]. Although urinary albumin is also a biomarker for CKD [15], it is rarely measured in a health checkup setting; thus we defined CKD based solely on eGFR. Patients on maintenance dialysis were classified as having CKD, regardless of eGFR at checkup; these patients were identified via a service code for dialysis on the claims record.

Among those identified as having CKD, we sought those with DM and HT comorbidities. Individuals with these comorbidities were defined as people under pharmacological treatment for DM/HT within 12 months of checkup and/or people whose HbA1c was ≥6.5% and/or fasting glucose level was ≥126 mg/dL for DM and those whose BP was ≥140/90 mmHg for HT. Information on medication use for DM and HT was extracted from medical claims records using the Anatomical Therapeutic Chemical' codes A10 for DM and C02 (antihypertensives), C03 (diuretics), C07 (beta-blockers), C08 (calcium channel blockers) and C09 (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) for HT [16].

Diagnosis and management of CKD

For people with CKD, we reviewed data from medical care visits, disease coding relevant to CKD, laboratory examinations for renal function and pharmacological interventions for comorbidities (inclusive of both the initiator and the prevalent user who had been prescribed before checkup). We regarded these factors as indicators for the diagnosis and management of CKD. This information was reviewed 180 days before and after the health checkup. For disease coding, International Classification of Diseases, Tenth Revision codes were used (Supplementary data, Table S1); these 34 codes were predetermined by the literature search and our expertise on disease coding practice in Japan [17, 18]. In the Japanese healthcare system, the recorded diagnosis is assigned by the physicians in charge or by trained staff under the supervision of a physician. Laboratory examinations included measurements of SCr, cystatin-C, albumin:creatinine ratio, urine protein:creatinine ratio, urinalyses and urine dipstick tests. The same aforementioned drug codes were used to define pharmacological management for DM and HT.

Statistical analysis

Descriptive statistics were used to represent the crude prevalence of CKD in the identified population, to report the percentage of recognition and to summarize the individual characteristics. Age- and sex-specific prevalence of CKD were also presented, with 95% confidence intervals (CIs) calculated via nonparametric bootstrap methods [19]. To compare the prevalence of CKD, age-adjusted prevalence was calculated using the population data from 2017 (Supplementary data, Figure S1). We also calculated the age-adjusted prevalence in 2005 that was reported using health checkups in different settings from this study [7]. Those analyses were repeated in the subgroup analyses, stratified by eGFR values of 50–59, 40–49, 30–39 and <30 mL/min/1.73 m^2. These categories were defined to be comparable with the previous estimate. We also performed subgroup analyses to coordinate with the current CKD grading

system [15]: 45–59, 30–44, 15–29 and <15 mL/min/1.73 m². All analyses were conducted in the R statistical environment, version 4.02 (R Foundation for Statistical Computing, Vienna, Austria; https://cran.r-project.org/).

RESULTS

Checkup participants and CKD prevalence

Of 4 441 302 adult beneficiaries in the JMDC database in 2017, 1 596 952 health checkup records were available. Of these, records without a Cr measurement (n = 833 088) and records of pregnant women (n = 2297) were removed. Hence 761 565 health checkup records were analyzed.

CKD was found in 50 091 people (Table 1). There were 410 people on maintenance dialysis, all of whom had an eGFR <60 mL/min/1.73 m² at the checkup (median 5.1 mL/min/1.73 m²). Among adults <75 years of age, the crude and age-adjusted prevalence of CKD was 63.1 per 1000 persons (95% CI 62.5–63.7) and 71.8 per 1000 persons (95% CI 71.1–72.6), respectively. Age- and sex-stratified data of CKD prevalence are shown in Table 2.

The age-adjusted prevalence of CKD in persons <70 years of age was higher in 2017 than in 2005: 71.8 versus 57.8, which corresponds to an increase of 14.1 per 1000 persons (95% CI 13.0–15.1). Table 3 represents the subgroup analyses grouped by eGFR stratum. In all strata, the prevalence of CKD was higher in 2017 than in 2005.

Comorbidities and medical resource use in CKD

DM and HT comorbidities identified by checkup data and/or prescription records were found in 10.2% and 44.0% of the population, respectively (Table 1). Within 180 days of checkup, ~96% of people with CKD visited medical institutions for any reason; referral to specialists, such as nephrologists and urologists, cannot be specified in the Japanese healthcare system. CKD-related diagnoses within 180 days of checkup were found in 23.2% (11 613/50 091) of people with CKD. Any laboratory assessments relevant to renal function were performed in 64.6% (32 332/50 091) of patients within 180 days of checkup (Table 4). This proportion was 87.4% when the analysis was limited to people with an eGFR <45 mL/min/1.73 m². Of the laboratory markers examined, SCr was most frequently tested (59.1% of the population) and cystatin C was the least frequently tested (2.0% of the population), as shown in Table 4. Among people with DM and HT comorbidities, at least one medication for a comorbidity was prescribed for 31.2% (1590/5096) and 36.7% (8081/22 019) of the population, respectively, within 180 days of checkup.

DISCUSSION

We found that the crude and age-adjusted prevalences of CKD in 2017 were 63.1 and 71.8 per 1000 people <75 years of age, respectively. This prevalence was higher than in 2005, with an increase of 14.1 per 1000 people. Most people with CKD visited medical institutions and ~65% received laboratory assessment within 180 days of checkup. However, the recognition of CKD may be suboptimal, as the coding of CKD was infrequently recorded and CKD-specific laboratory tests were performed infrequently. Furthermore, prescriptions for DM and HT comorbidities were found in only one-third of the population. These results indicate that there is still room to improve the recognition and management of CKD.

Globally the prevalence of CKD is estimated to have increased since 1990, but it is estimated to be stable when standardized by age [1]. The prevalence of CKD in this study was higher than that in 2005. Although both of these values were based on health checkup data, the characteristics of the checkups were somewhat different. In Japan, the coverage of public health checkups has expanded over time and since 2009 it has been open to virtually all segments of the population in a semiobligatory manner [12]. Before 2009, however, checkups were obligatory only for full-time employees; otherwise, checkups were available on a voluntary basis, with or without fees.

Table 1. Characteristics of persons with CKD

Variable (% missing, if any)	Value[a]
Age (years), median (IQR)	56 (50–62)
Sex (male), % (n/N)	69.4 (34 770/50 019)
eGFR (mL/min/1.73 m²), median (IQR)	56.1 (52.4–58.3)
Persons with eGFR <45 mL/min/1.73 m² , % (n/N)	7.1 (3541/50 091)
Chronic dialysis, % (n/N)	0.82 (410/50 091)
DM, % (n/N)	10.2 (5094/50 091)
HbA1c (12.6%) (%), median (IQR)	5.72 (5.40–5.90)
FBS (9.2%) (mg/dL), median (IQR)	96.0 (89.0–104.0)
Medication use[a], % (n/N)	3.1 (1538/50 091)
Medication use in comorbid persons[a], % (n/N)	31.1 (1538/5094)
HT, % (n/N)	44.0 (22 020/50 091)
SBP (0.22%) (mmHg), median (IQR)	124 (113–135)
DBP (0.22%) (mmHg), median (IQR)	78 (70–85)
Medication use[a], % (n/N)	15.6 (7789/50 091)
Medication use in comorbid persons[a], % (n/N)	35.4 (7789/22 020)
BMI (0.21%) (kg/m²), median (IQR)	23.7 (21.5–26.1)
Smoking[b] (7.1%), % (n/N)	32.4 (16237/50091)

[a]Within 12 months prior to check-up (identified from claims record).
[b]Self-report at checkup.
FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Table 2. Age- and sex-specific prevalence of CKD (per 1000 persons)

Male		Female	
Age (years)	Prevalence (95% CI)	Age (years)	Prevalence (95% CI)
20–29 (n = 41 000)	1.0 (0.73–1.3)	20–29 (n = 22 319)	1.3 (0.81–1.7)
30–39 (n = 101 521)	8.4 (7.8–9.0)	30–39 (n = 48 009)	7.4 (6.6–8.1)
40–49 (n = 163 949)	42.7 (41.7–43.6)	40–49 (n = 96 005)	30.8 (29.8–31.9)
50–59 (n = 133 844)	110.0 (108.3–111.7)	50–59 (n = 71 912)	100.0 (97.9–102.4)
60–75 (n = 54 544)	222.6 (219.3–226.1)	60–75 (n = 28 422)	168.6 (164.1–173.1)

Table 3. Prevalence of CKD (per 1000 persons) stratified by eGFR

eGFR category (mL/min/1.73 m^2)	2005	2017	Difference
50–<60	47.5 (46.9–48.1)	60.3 (59.5–61.0)	12.8 (11.9–13.7)
40–<50	8.1 (7.9–8.3)	8.9 (8.7–9.3)	0.9 (0.5–1.3)
30–<40	1.3 (1.2–1.4)	1.4 (1.3–1.5)	0.07 (−0.08–0.21)
<30	0.92 (0.83–1.01)	1.3 (1.1–1.3)	0.31 (0.18–4.4)
Current grading system			
45–<60	NA	66.9 (66.1–67.7)	NA
30–<45	NA	3.8 (3.6–4.0)	NA
15–<30	NA	0.59 (0.52–0.66)	NA
<15	NA	0.64 (0.58–0.71)	NA

The prevalence was age adjusted, limited to persons ≤70 years of age.
NA: not available.

Table 4. Laboratory markers examined at medical encounters (N = 50 091 persons)

Item	Frequency[a] (for persons with eGFR <45 mL/min/1.73 m^2)[b]
SCr	59.1% (85.7%)
Cystatin C	2.0% (6.8%)
Albumin:creatinine ratio	5.3% (4.4%)
Urine protein:creatinine ratio	5.1% (15.5%)
Semiqualitative urine dipstick	34.0% (45.6%)
Urinary sedimentation	15.1% (29.7%)
Any of the above	64.6% (87.4%)

[a]Within 180 days post-checkup.
[b]n = 3541 persons.

Voluntary checkup recipients may be healthier than the general population. The population in 2005 was derived from a mixture of obligatory and voluntary checkups (i.e. company-, community- and hospital-based checkups) [7, 20], thus the increase in CKD prevalence observed could be partially explained by the difference in the checkup participants. A second possible explanation for the increase in CKD prevalence is changing patterns of risks for CKD, particularly DM and HT comorbidities. Unfortunately, the prevalence of these comorbidities in 2005 was reported using different definitions (e.g. DM for HbA1c >6.0% with or without medication use) from those used in our study. In addition, the disease duration of DM and HT is associated with CKD burden, but such information was not available from cross-sectional data. Thus it is difficult to directly compare comorbidities between the 2005 and 2017 populations. A third explanation is measurement error of laboratory values, as even a 0.04 mg/dL higher mean SCr can contribute to a 23% higher CKD prevalence [21]. In contrast to the results in 2005, the laboratory values were not standardized in this study and may be variable at each laboratory center. However, such a measurement error was expected to bidirectionally occur at random. If the observed increase in CKD prevalence could be explained by measurement error alone, it is possible only when most measurement errors were biased towards higher Cr measurements. Another possible, but unlikely, explanation for the increase in CKD prevalence is increased exposure to nephrotoxic agents [22]. Continuous, regular updates may be required regarding the prevalence of CKD in Japan, along with its risk factors [23].

There is no single metric to measure the recognition of CKD [9], and several studies have used various measures, such as surveys, chart audits and referrals to nephrologists [24–27]. Even with different measures, the recognition of CKD is consistently reported as low at both the patient and physician levels [9]. In this study we used healthcare utilization, such as laboratory assessments and disease coding for CKD, as an indicator of recognition. The diagnosis of CKD was only found in 23% of the population despite the comprehensive list suggestive of CKD. The low proportion of CKD coding was in line with reports from other countries [27, 28]. Although nearly two-thirds of the population received laboratory assessment within 180 days of checkup, this proportion may yield optimistic estimates for CKD diagnosis, because the indication of laboratory assessment was undetermined. In particular, SCr measurement is often performed as one of the laboratory screening panels to evaluate some acute or chronic conditions unrelated to CKD. Laboratory items more specific to CKD, such as cystatin C and albuminuria, were examined in 2.0% and 5.3% of the population, respectively (Table 4). Thus our data might be interpreted as indicating that opportunities to diagnose and classify CKD were largely missed in Japan, despite the frequent medical encounters. These data collectively suggest that CKD was underrecognized.

We also found that the pharmacological management of DM and HT was less than optimal for people with these comorbidities; medications for these comorbidities were prescribed to only one-third of the population within 180 days of a health checkup. It is possible that lifestyle modifications, such as weight management and salt intake reduction, were utilized first before introducing medication. However, it is uncertain whether lifestyle modification alone is sufficient for people with CKD, and there is ample evidence that adequate pharmacological management for DM and HT can delay the progression towards end-stage kidney disease [2]. As such, the management of DM and HT was unlikely sufficient in our cohort, which would also support the underrecognition of CKD.

Until recently, SCr was not an essential laboratory item requested by the government at specific health checkups. This was because this checkup was aimed at the primary prevention of conditions associated with metabolic syndrome. Incorporating a request from nephrology specialists, since 2018, SCr measurements and eGFR reports have been integrated into essential laboratory panels in checkups. This policy change might increase the recognition of CKD, which requires future research.

This study provided comprehensive estimates regarding the prevalence, diagnosis and management of CKD using large-scale population-level data. In previous studies, such estimates were often determined using data from consumers of healthcare resources [27, 29]. Our estimates were derived from a rather

unselected population, which we believe is the strength of our study. A similar report with a different scope also used a combination of health checkup data and medical claims records from Japan [30]. Our study provided a more comprehensive analysis of CKD with larger samples, including a comparison with a previous estimate.

This study has several limitations. First, our analyses were limited to people <75 years old. Second, although the diagnosis of CKD requires a minimum of two eGFR measurements to avoid overdiagnosis due to acute kidney damage [31], our study defined CKD from only a single measurement. This was because health checkups are typically performed only once a year. However, in Japan, health checkups are often performed in the workplace in a grouped way. Thus people with acute conditions were not expected to receive checkups, and we assumed that a stable Cr measurement could be obtained for each person from checkup data. Third, we could not account for the absence of albuminuria measurements, which might lead to underestimation of CKD prevalence. At the time of writing this report, new evidence has emerged indicating that urine protein detected by dipstick tests is moderately correlated with a urine albumin:creatinine ratio of 30 mg/g, which is a threshold for CKD inclusion [32]. Given this, as a preliminary post hoc analysis we changed our definition of CKD as follows: eGFR of 60 mL/min/1.73 m^2 and/or the presence of urine protein by dipstick test (available for ∼96% of the population in our cohort). This operation led to a 3-fold increase in CKD prevalence compared with that in 2005 (see Supplemental Methods and Supplemental Table 2), which is likely incorrect. Although it is possible that urine protein provides a more accurate estimate of CKD prevalence when the albumin:creatinine ratio is unavailable [33], this was not the case in our study. Thus we did not include the urine protein identified by dipstick test in the composite CKD definition. Fourth, the prevalence of HT could be overestimated due to the temporal increase in checkup settings, such as white coat HT. In such cases, the repeated measure would return to normal; a phenomenon known as 'regression toward the mean' [34]. Finally, we could not determine whether the underrecognition of CKD occurred at either the patient or care provider level. This information is important, however, to define the target population to disseminate and implement the primary and secondary prevention program efficiently; thus future research may be needed.

In summary, we reported the crude and age-adjusted prevalence of CKD in 2017 as 63.1 and 71.8 per 1000 people <75 years of age, respectively. This prevalence was higher than in 2005, with an increase of 14.1 per 1000 people. CKD was underrecognized, as assessed by the infrequent recorded diagnosis, along with infrequent laboratory tests to diagnose or classify CKD. Furthermore, pharmacological management for DM and HT was found in only one-third of the affected people. All these findings indicate that there is still room to improve the secondary prevention of CKD.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

M.T., K.S. and K.K. conceived the study design. M.T. analyzed the data and wrote the first draft. K.S., M.Y. and K.K. provided the critical review for the draft and the draft was revised upon their comments. All authors approved the manuscript as submitted.

CONFLICT OF INTEREST STATEMENT

M.T. received a consultation fee from Eisai. M.Y. received research grants from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Fujiyakuhin, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD KK, Nippon Boehringer Ingelheim and Torii Pharmaceutical. K.K. received advisory fees from Shin Nippon Biomedical Laboratories, Chugai Pharmaceutical, AstraZeneca KK, TAIHO Pharmaceutical, Santen Pharmaceutical and IQVIA Services Japan; research funds from Sumitomo Dainippon Pharma, Pfizer, Stella Pharma, CMIC, Suntory Beverage & Food, Medical Platform, Real World Data, Eisai, Kyowa Hakko Kirin and Mitsubishi and holds stock in Real World Data. K.S. has no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not permitted under JMDC policy. If readers are interested in our dataset, please contact JMDC for data availability (https://www.jmdc.co.jp/).

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