Table 1 Basic characteristics of participants vs. endpoint

	Total	No events	Stroke[a]	Cardiac disease[a]
Subjects (*n*)	2,41,159	2,34,512	2,441	4,541
Age (years)	64 ± 8	64 ± 8	67 ± 6	66 ± 6
Gender (% male)	38.6	38.4	47.5	47.1
Height (cm)	157.0 ± 8.5	157.0 ± 8.4	156.7 ± 8.3	157.7 ± 8.6
Weight (kg)	57.0 ± 10.2	56.9 ± 10.2	57.9 ± 10.1	58.6 ± 10.4
BMI (kg/m^2)	23.0 ± 3.2	23.0 ± 3.2	23.5 ± 3.2	23.5 ± 3.2
Comorbid conditions and habit				
Diabetes mellitus (%)	7.1	7.0	12.0	10.5
Hypertension (%)	40.6	40.2	59.9	54.1
Dyslipidemia (%)	15.2	15.1	22.3	20.4
Proteinuria (%)	4.3	4.2	7.9	7.4
Current smoker (%)	13.3	13.3	12.5	13.1
Kidney function				
Serum creatinine (mg/dL)	0.71 ± 0.22	0.71 ± 0.22	0.75 ± 0.28	0.75 ± 0.32
JPN-eGFR (mL/min/1.73 m^2)	75.83 ± 16.18	75.91 ± 16.15	72.84 ± 16.84	72.86 ± 16.71
mCKDEPI-eGFR (mL/min/1.73 m^2)	76.39 ± 9.61	76.48 ± 9.58	73.02 ± 10.54	73.39 ± 10.50

[a] A total of 335 participants experienced both stroke and cardiac disease

measure hemoglobin A1c and serum creatinine. Blood pressure was measured in all cohorts using a standard sphygmomanometer. Creatinine was measured using an enzymatic method. Hypertension was defined as ≥140/90 mmHg or on antihypertensive medication. Diabetes mellitus was defined as hemoglobin A1c ≥6.5 % (NSGP) or taking diabetes medication. Dyslipidemia was defined as taking medication for dyslipidemia.

In this study, a first CVD experiencer was defined as a participant who experienced CVD (cardiac disease or stroke, or both) in 2009.

Calculation of estimated GFR

We calculated estimated GFR using: (1) the Japanese GFR equation, and (2) the CKD-EPI equation modified for Japanese using Japanese coefficient, as follows:

(1) JPN-eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).

(2) mCKDEPI-eGFR (mL/min/1.73 m^2) = $141 \times \min(Cr/\kappa, 1)^{\alpha} \times \max(Cr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times$ 0.813 (Japanese coefficient) [12]. κ: 0.7 in female and 0.9 in male, α; −0.329 in female and −0.411 in male.

Data analysis

Statistical analyses were performed using SPSS Statistics version 21.0 (IBM Japan, Tokyo, Japan) and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing). EZR is a modified version of R commander (version 2.13.0, University of Vienna, Vienna, Austria) designed to add statistical functions frequently used in biostatistics [13].

Numeric data are presented as mean ± standard deviation. Categorical variables are expressed as percentages. The relationship between JPN-eGFR and mCKDEPI-eGFR was illustrated using a scatter diagram. For the magnitude of the correlation, we used Pearson's correlation coefficient (r). Receiver operating characteristics (ROC) curves were drawn and the areas under the curves (AUROC) were calculated for each equation to compare the discrimination abilities of the 2 models. A logistic regression model was used to adjust between-group differences in confounding factors; gender, age, BMI and presence of diabetes mellitus, hypertension, dyslipidemia and current smoking. For all analyses, two-tailed $p < 0.05$ was considered statistically significant. The authors had full access to the data and took responsibility for its integrity.

Results

The basic characteristics of the participants based in the data taken from the checkup in 2008 are shown in Table 1, and quartiles of GFR calculated from each GFR-estimating equation are shown in Table 2. The mean GFR derived from the Japanese GFR equation (JPN-eGFR) was 75.83 ± 16.18 mL/min/1.73 m^2, and the mean GFR from the coefficient-modified CKD-EPI equation (mCKDEPI-eGFR) was

Table 2 Quartiles of GFR calculated from each GFR-estimating equation

	Q1	Q2	Q3	Q4
JPN-eGFR (mL/min/1.73 m^2)	2.36–64.26	64.26–74.41	74.41–85.74	85.74–251.21
Age (years) (mean ± SD)	67.2 ± 5.6	64.8 ± 7.9	61.2 ± 7.4	61.8 ± 8.6
BMI (kg/m^2) (mean ± SD)	23.3 ± 3.2	23.1 ± 3.1	22.8 ± 3.2	22.8 ± 3.3
Gender (% male)	35.5	49.6	34.6	34.5
Number of events	2,193	1,784	1,289	1,381
mCKDEPI-eGFR (mL/min/1.73 m^2)	1.97–72.61	72.61–76.93	76.93–81.84	81.84–135.95
Age (years) (mean ± SD)	68.0 ± 5.5	67.1 ± 4.7	64.2 ± 5.4	55.9 ± 8.5
BMI (kg/m^2) (mean ± SD)	23.5 ± 3.1	23.0 ± 3.1	22.8 ± 3.2	22.8 ± 3.4
Gender (% male)	53.4	37.3	29.8	34.2
Number of events	2.417	1,737	1,486	1,007

76.39 ± 9.61 mL/min/1.73 m^2. The prevalence of CKD stage 3–5 by JPN and mCKD-EPI equation were 13.1 and 5.1 %, respectively. The prevalence of CKD stage 3–5 by JPN equation in this study is slightly lower than that in previous report using same "specific health checkup" cohort (14.2 %) [14]: it is probably because past CVD experiencer was excluded in the present study. Within 1 year after the checkup in 2008, a total of 6,647 participants experienced their first CVD event (cardiac disease only, $n = 4{,}206$; stroke only, $n = 2{,}106$; both, $n = 335$). The distribution of each estimated GFR, and the relationship between age and each estimated GFR are shown as supplementary data (Figs. S1 and S2, respectively).

Figure 1 shows a scatter graph of JPN-eGFR and mCKDEPI-eGFR. The overall correlation between JPN-eGFR and mCKDEPI-eGFR was relatively good ($r = 0.866$, $p < 0.001$). Regarding mCKDEPI-eGFR as the standard, JPN-eGFR mildly to moderately underestimated GFR in persons with mCKDEPI-eGFR <70 mL/min/1.73 m^2. In contrast, JPN-eGFR moderately to greatly overestimated GFR in persons with mCKDEPI-eGFR >70 mL/min/1.73 m^2. Such condition was observed irrespective of gender difference.

Figure 2 shows ROC curves for predicting each endpoint according to JPN-eGFR and mCKDEPI-eGFR. The use of mCKDEPI-eGFR instead of JPN-eGFR results in a leftward shift of ROC curve in prediction of first CVD event, stroke and cardiac disease. AUROCs (95 % confidence level [95 % CI]) for mCKDEPI-eGFR vs. JPN-eGFR were 0.596 (0.589–0.603) vs. 0.562 (0.554–0.569) in predicting first CVD event, 0.601 (0.590–0.612) vs. 0.560 (0.549–0.572) in predicting first stroke and 0.591 (0.583–0.600) vs. 0.561 (0.552–0.570) in predicting first cardiac disease. We also evaluated ROC curves for predicting each endpoint according to JPN-eGFR and mCKDEPI-eGFR using the data of participants who did not have hypertension, diabetes mellitus or dyslipidemia ($n = 121{,}604$), who were 65 years or younger ($n = 117{,}240$), and whose JPN-eGFR was 15 mL/min/1.73 m^2 or higher ($n = 241{,}024$). And as a result, we observed a similar trend (supplementary data; Figs. S3–S5).

The participants were then divided into four groups (Q1–Q4) according to quartiles of GFR calculated from each equation (Table 2). The crude and adjusted odds ratios (ORs) for first CVD (cardiac disease or stroke, or both) incidence in each GFR group were calculated using multiple logistic regression analysis. The results are shown in Table 3. The crude likelihood of having a first CVD event in Q1 of mCKDEPI-eGFR (OR 2.46, 95 % CI 2.29–2.66) was far higher than double that in Q4. On

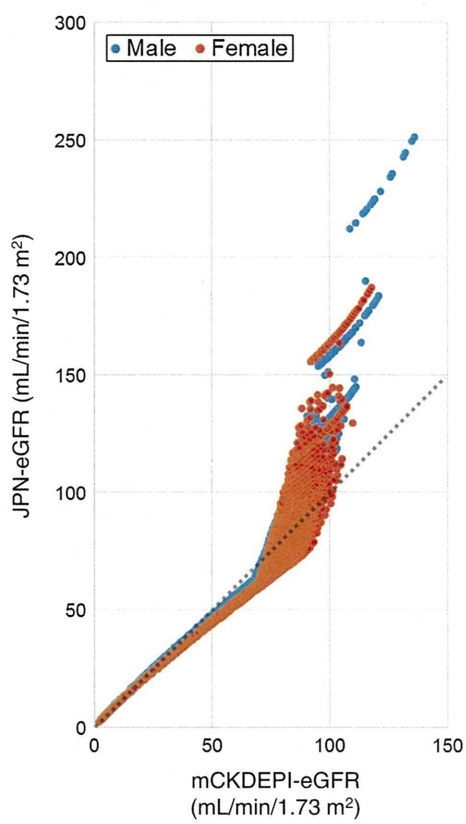
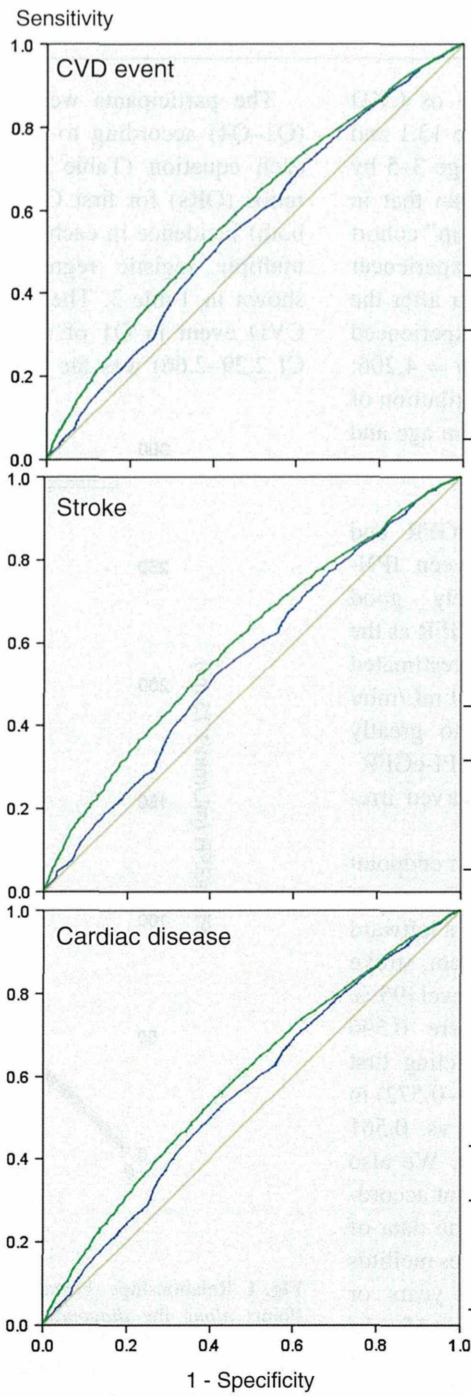


Fig. 1 Relationships between JPN-eGFR and mCKDEPI-eGFR. Points *along* the *diagonal dotted line*, accordance between JPN-eGFR and mCKDEPI-eGFR; points *below* the *diagonal dotted line*, underestimation by JPN-eGFR; points *over* the *diagonal dotted line*, overestimation by JPN-eGFR

the other hand, the crude OR in Q1 of JPN-eGFR (OR 1.61, 95 % CI 1.51–1.73 was less than double that in Q4. Such difference of OR in Q1 between mCKDEPI-eGFR and JPN-eGFR, however, almost disappeared by adjustment for age: age adjustment markedly lessened the OR in Q1 of mCKDEPI-eGFR (OR 1.31, 95 % CI 1.20–1.43) to near the same level of that of JPN-eGFR (OR 1.24, 95 % CI 1.15–1.33). Adjustment for BMI in addition to age further lessened the superior predictive value of low mCKDEPI-eGFR. Furthermore, adjustment for multiple confounding factors (age, gender, BMI, presence of proteinuria, hypertension, diabetes, dyslipidemia and current smoking) removed the difference of predictive value in Q1 between mCKDEPI-eGFR (OR 1.19, 95 % CI 1.09–1.30) and JPN-eGFR (OR 1.19, 95 % CI 1.10–1.27).



mCKDEPI-eGFR

JPN-eGFR

CVD event:

	AUROC (95%CI)
mCKDEPI-eGFR	0.596 (0.589-0.603)
JPN-eGFR	0.562 (0.554-0.569)

Stroke:

	AUROC (95%CI)
mCKDEPI-eGFR	0.601 (0.590-0.612)
JPN-eGFR	0.560 (0.549-0.572)

Cardiac disease:

	AUROC (95%CI)
mCKDEPI-eGFR	0.591 (0.583-0.600)
JPN-eGFR	0.561 (0.552-0.570)

Fig. 2 Receiver operating characteristics (ROC) curves in predicting each endpoint (first CVD event, stroke and cardiac disease) by JPN-eGFR and mCKDEPI-eGFR. The use of mCKDEPI-eGFR instead of JPN-eGFR resulted in a leftward shift of the ROC curve for predicting first CVD event, stroke and cardiac disease. *AUROC* area under the ROC curve, *CI* confidence interval

Table 3 Odds ratios (ORs) and 95% confidence intervals (95% CI) for the first cardiovascular incidence

	Japanese GFR equation								Coefficient-modified CKD-EPI equation							
	Crude		Adjusted[a]		Adjusted[b]		Adjusted[c]		Crude		Adjusted[a]		Adjusted[b]		Adjusted[c]	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Estimated GFR																
Q1	1.61	1.51–1.73	1.24	1.15–1.33	1.21	1.13–1.30	1.19	1.10–1.27	2.46	2.29–2.66	1.31	1.20–1.43	1.27	1.17–1.39	1.19	1.09–1.30
Q2	1.29	1.20–1.39	1.10	1.03–1.18	1.09	1.01–1.17	1.04	0.97–1.12	1.81	1.67–1.96	1.03	0.94–1.12	1.01	0.93–1.11	1.01	0.93–1.11
Q3	0.94	0.87–1.01	1.00	0.92–1.08	0.96	0.92–1.07	1.00	0.93–1.08	1.44	1.32–1.56	0.95	0.87–1.03	0.94	0.87–1.03	0.96	0.88–1.05
Q4	1	Ref.	1	Ref.	1	Ref.	1	Ref.	1	Ref.	1	Ref.	1	Ref.	1	Ref.
Age	–	–	1.06	1.06–1.07	1.06	1.06–1.07	1.06	1.05–1.06	–	–	1.06	1.05–1.06	1.06	1.05–1.07	1.05	1.05–1.06
BMI	–	–	–	–	1.04	1.03–1.05	1.02	1.01–1.02	–	–	–	–	1.04	1.03–1.05	1.02	1.01–1.02
Female gender	–	–	–	–	–	–	0.73	0.69–0.77	–	–	–	–	–	–	0.76	0.72–0.80
Proteinuria	–	–	–	–	–	–	1.40	1.27–1.54	–	–	–	–	–	–	1.39	1.27–1.54
Hypertension	–	–	–	–	–	–	1.47	1.39–1.55	–	–	–	–	–	–	1.47	1.39–1.55
Diabetes	–	–	–	–	–	–	1.21	1.12–1.32	–	–	–	–	–	–	1.21	1.12–1.32
Dyslipidemia	–	–	–	–	–	–	1.28	1.20–1.36	–	–	–	–	–	–	1.28	1.20–1.36
Smoking	–	–	–	–	–	–	1.01	0.94–1.09	–	–	–	–	–	–	1.02	0.94–1.10

[a] Adjusted for age

[b] Adjusted for age and BMI

[c] Adjusted for age, BMI, gender, and presence of proteinuria, hypertension, diabetes, dyslipidemia and current smoking

Discussion

In this nationwide community-based study, we compared risk predictabilities of first CVD event (stroke or cardiac disease, or both) between 2 models using GFR based on JPN-eGFR and that based on mCKDEPI-eGFR. Discriminating ability using mCKDEPI-eGFR was significantly higher than that using JPN-eGFR to predict first CVD event, stroke and cardiac disease (Fig. 2). Such superior discriminating ability of mCKDEPI-eGFR was observed in participants who did not have traditional risk factors such as hypertension, diabetes mellitus and dyslipidemia (Fig. S3), who were 65 years or younger (Fig. S4), and whose JPN-eGFR was 15 mL/min/1.73 m^2 or higher (Fig. S5). Such superior discriminating ability of CKD-EPI equation is thought to be owing to improved accuracy via avoidance of overestimation among subjects with lower serum creatinine level ($\leq$0.7 mg/dL in female and $\leq$0.9 mg/dL in male), at least in part. These results imply that an estimation of mCKDEPI-eGFR is more effective than that of JPN-eGFR to identify CVD risks in the general population.

Kidney dysfunction causes several detrimental conditions which relate to CVD such as angina pectoris and stroke. Kimoto et al. reported the relationship between kidney dysfunction and elevated arterial, particularly aorta, stiffness in type-2 diabetic subjects [15]. Kumai et al. [16] reported the higher prevalence of atrial fibrillation in ischemic stroke patients with CKD. Otani et al. [17] showed using MRI that kidney dysfunction is associated with profound brain damage (silent lacunar infarcts and white matter hyperintensity) in the general population. Therefore, from the viewpoint of CVD risk screening, the accuracy of GFR estimation for general checkup is very important.

As shown in Table 3, superiority in discriminating ability in the mCKDEPI-eGFR model markedly lessened after age adjustment and we found almost similar predictability in the 2 models. From the result of age-adjusted logistic regression analysis, it is suggested that the contribution of age to prediction of initial CVD event (stroke or cardiac disease, or both) was greater in the mCKDEPI-eGFR model. Ohsawa et al. reported the same trend in their "Iwate KENCO Study" [10]. Moreover, adjustment for multiple confounding factors further diminished the superior discriminating ability of mCKDEPI-eGFR over JPN-eGFR. These results highly suggest the possibility that low mCKDEPI-eGFR reflects some cardiovascular risk(s) other than kidney dysfunction such as aging and cachexia (low BMI). We suppose the reason of this phenomenon as follows. Both GFR-estimating equations (Japanese GFR and coefficient-modified CKD-EPI equation) are based on serum creatinine level. Serum creatinine is determined not only by kidney function (namely, "real" GFR), but also by muscular metabolism. Persons with muscle wasting due to ill condition such as aging, malnutrition, chronic inflammatory disease or malignancy, who have a lower serum creatinine level irrespective of their "real" GFR, is common in the elderly population. CKD-EPI equation had been designed to avoid "overestimation" among such subjects with lower serum creatinine level (<0.7 mg/dL in female and <0.9 mg/dL in male). Consequently, lower eGFR value estimated by the coefficient-modified CKD-EPI equation (in comparison with Japanese GFR equation) could reflect not only lower kidney function, but also such ill conditions.

The most important limitation of this study is that mortal cases were not censored in this study. Perhaps this is why the incidence of first CVD event was relatively low in this study (2.8 % per year). Further investigation regarding mortal cases is needed to clarify "real" CVD incidence in this study population.

Conclusions

Our present study demonstrated that GFR estimated by the coefficient-modified CKD-EPI equation was more closely related to the first occurrence of cardiovascular disease than those estimated by the Japanese GFR equation. However, adjustment for multiple confounding factors diminished the superior discriminating ability of mCKD-EPI-eGFR over JPN-eGFR. These results suggest the possibility that low mCKDEPI-eGFR also reflects some cardiovascular risk(s) other than kidney dysfunction.

Acknowledgments This study was supported by Health and Labour Sciences Research Grants for "Study on the appropriate states of Specific Health Checkups and Specific Health Guidance for prevention of CKD progression" and "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health Checkups" from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest The authors have declared that no conflict of interest exists.

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Received for publication: 24.2.2014; Accepted in revised form: 27.6.2014

Nephrol Dial Transplant (2014) 29: 2286–2292
doi: 10.1093/ndt/gfu256
Advance Access publication 24 July 2014

A slight increase within the normal range of serum uric acid and the decline in renal function: associations in a community-based population

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ABSTRACT

Background. Hyperuricemia is a risk factor for adverse renal outcomes in patients with chronic kidney disease. This study investigated the effect of uric acid on renal function in a community-based population.

Methods. We used a nationwide database of 165 847 subjects (aged 29–74, male 40%) who participated in the annual 'Specific Health Check and Guidance in Japan' checkup between 2008 and 2010; we examined the relationship between serum uric acid levels at baseline and 2-year change in the estimated glomerular filtration rate (eGFR) obtained by using the Japanese equation.

Results. After adjusting for possible confounders, the eGFR change was inversely correlated with uric acid at baseline. In the multivariable analysis, the decline in eGFR was significantly more rapid in subjects with the slight increase in uric acid (males ≥5.7 mg/dL, females ≥4.4 mg/dL), and the risk for incidental renal insufficiency (eGFR <60 mL/min/1.73 m^2) was increased at uric acid of ≥6.3 mg/dL in males and ≥5.5 mg/dL in females, compared with the lowest quintile. The multiple linear regression analysis revealed that the effect of uric acid on eGFR changes was significant, especially in females, those with proteinuria and diabetes and those without alcohol consumption.
Conclusion. This study showed that serum uric acid is independently associated with a more rapid decline of eGFR and incident renal insufficiency, and that a slight increase within the normal range of serum uric acid might be a risk for renal damage in the general population.

Keywords: cohort study, renal function, uric acid

INTRODUCTION

Recent studies have showed that hyperuricemia increases the risk for cardiovascular diseases [1] and mortality [2, 3]. Chronic kidney disease (CKD) is also a risk for cardiovascular events and premature death [4], and the association between uric acid and kidney disease has been previously investigated in the literature [5]. An increase in uric acid was thought to be associated with an increased risk of incidental CKD [6–8], and end-stage kidney disease (ESKD) [9] in the general population. However, studies have reported conflicting results. In the general population, increased uric acid levels were independently associated with ESKD in women but not men [10]. In patients with CKD, hyperuricemia was an incidental factor for all-cause and CVD mortality but not kidney failure [3]. In the elderly population, uric acid levels had a significant but weak association with the progression of kidney disease [11]. Furthermore, previous reports documented that a risk for ESKD was increased at different threshold values for men (≥7 mg/dL) and women (≥6 mg/dL) [10]. Therefore, the association between an increase in serum uric acid and kidney disease is still unclear.

This inconsistency might be due to several reasons including small sample sizes, differences in the characteristics of the studied populations, the varying classification of serum uric acid levels (hyperuricemia ≥7 mg/dL, quartiles/quintiles and per the 1 mg/dL increase), the end points [incident CKD, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2); glomerular filtration rate (GFR) decrease and ESKD] and the correction factors used in multivariate analyses. Furthermore, renal insufficiency itself decreases urinary excretion of uric acid, resulting in an increase in serum uric acid levels. This makes it difficult to determine whether hyperuricemia is the cause or result of renal damage. To address this issue, we accessed a nationwide large-scale database and prospectively examined the independent effect of uric acid on the change of renal function, using plural classifications of uric acid levels and end points, and subgroup analyses.

MATERIALS AND METHODS

Study population

This study was part of an ongoing 'Research on design of the comprehensive health care system for CKD based on the individual risk assessment by Specific Health Checkup' study. The Specific Health Check and Guidance is an annual health checkup for all inhabitants between the ages of 40 and 74 and is covered by Japanese national health insurance. We utilized the nationwide database obtained from 16 prefectures (administrative regions), Hokkaido, Tochigi, Saitama, Chiba, Nagano, Niigata, Ishikawa, Fukui, Gifu, Hyogo, Tokushima, Fukuoka, Saga, Nagasaki, Kumamoto and Okinawa, in keeping with our study aims. We collected data from 87 750 men and 131 485 women (total 219 235, age range 40–74) who took part in the health checkups in both 2008 and 2010. The study was conducted according to the Declaration of Helsinki and was approved by the respective institutional ethics committees. The details of this study have been described elsewhere [12].

Among the 219 235 participants, 53 388 were excluded from this study because the essential data, including serum uric acid and serum creatinine levels, were incomplete. Therefore, data from 66 289 males and 99 558 females (total 165 847, age range 40–74) were included in our statistical analyses. We examined the association between serum uric acid levels at baseline and 2-year change in renal function, as measured by the eGFR. In our analysis of the incidence of renal insufficiency, we used 141 514 subjects (54 152 males and 87 362 females) without renal insufficiency at baseline, after excluding 24 333 subjects who showed renal insufficiency at baseline.

Measurements

Subjects used a self-reporting questionnaire to document their medical history, current medications, smoking habits (smoker or non-smoker) and alcohol consumption (drinker or non-drinker). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained staff by using a standard sphygmomanometer or an automated device, with subjects in the sitting position for at least 5 min prior to measurement. Hypertension was defined as a SBP ≥140 mmHg or DBP ≥90 mmHg, or being on antihypertensive medication. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height (m^2). For both men and women, obesity was defined as BMI ≥25.0 kg/m^2 [13]. Plasma glucose levels were measured by using the hexokinase enzymatic reference method. Subjects with diabetes were identified either by a fasting plasma glucose concentration of ≥126 mg/dL, an HbA1c value of ≥6.5% or on antidiabetic medication. Triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations were measured by using enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) concentration was measured directly. Dyslipidemia was defined as triglycerides ≥150 mg/dL, HDL-C <40 mg/dL, LDL-C ≥140 mg/dL or being on lipid-lowering medication. Serum uric acid was measured by using an enzymatic method, and hyperuricemia was defined as serum uric acid ≥7 mg/dL in males and ≥6 mg/dL in females, according to the previous report [10].

Urinalysis was performed with a single spot urine specimen collected in the early morning after overnight fasting and measured by using a dipstick. The results of the urinalysis were recorded as negative (−), trace, 1+, 2+ and 3+. Positive proteinuria was defined as ≥1+. Serum creatinine was measured by using an enzymatic method, and the eGFR was obtained by using the Japanese equation [14]. According to the universal definition, CKD was defined as the presence of proteinuria and/or renal insufficiency (eGFR <60 mL/min/1.73 m^2). Incidental renal insufficiency was defined as the new development of renal insufficiency at a 2-year follow-up examination among the subjects who had no renal insufficiency at baseline.

Statistical analysis

We divided the subjects into gender-specific quintiles [Q1: males (M) ≤4.9, females (F) ≤3.7; Q2: M 5.0–5.6, F 3.8–4.3; Q3: M 5.7–6.2, F 4.4–4.8; Q4: M 6.3–7.0, F 4.9–5.4 and Q5: M ≥ 7.1, F ≥ 5.5 mg/dL] by their serum uric acid level at baseline. The χ^2-test was used to evaluate differences in proportions. To compare the mean values in the unadjusted model and regression coefficients in the adjusted model among the quintile groups, we used a one-factor analysis of variance (ANOVA) test and the least squares analyses. We adjusted for possible confounders that showed significant correlation across the quintiles of uric acid levels, such as age, gender, BMI, SBP, DBP, eGFR, HbA1c, triglyceride levels, LDL-C, HDL-C, smoking habits, alcohol consumption and proteinuria. Additionally, we performed *post hoc* analyses by using the Dunnett–Hsu test using the quintile with the lowest values as a reference. To examine the factors relating to the 2-year changes in eGFR, we performed a multivariate linear regression analysis and adjusted for the abovementioned confounding factors. To examine the factors related to incidental renal insufficiency, we performed a multivariate logistic regression analysis and adjusted for possible confounding factors such as age, gender, obesity, hypertension, diabetes, dyslipidemia, smoking habits, alcohol consumption, eGFR and proteinuria. Continuous data are expressed as the mean ± SD. All statistical analyses were performed by using JMP version 10 software (SAS Institute Inc., Cary, NC). A P-value of <0.05 was used to define statistical significance.

RESULTS

The mean age of the total subjects was 63.3 years, and the prevalence of obesity, hypertension, diabetes, dyslipidemia and hyperuricemia was 25.5, 44.3, 6.4, 55.1 and 12.0%, respectively. Subjects were divided into the quintiles (Q1–Q5) by their serum uric acid levels at baseline, and their baseline characteristics are described in Table 1. Along with an increase in serum uric acid levels, the prevalence of alcohol drinkers, obesity, proteinuria, hypertension and dyslipidemia and the mean values of BMI, SBP, DBP, triglycerides and LDL-C increased significantly. In contrast, the mean values of eGFR and HDL-C significantly decreased. The correlation between these parameters and uric acid at baseline was similar in both males and females (data not shown).

First, we compared the changes seen at the 2-year follow-ups in the eGFR among the quintiles at baseline. The ANOVA showed that the eGFR declined significantly more rapidly in subjects with low uric acid levels in the unadjusted model (P < 0.001) (Figure 1). It is well known that factors such as gender, age and renal function affect serum uric acid levels; therefore, to avoid the confounding effect of such factors, we performed a least squares analysis with an adjustment for gender, age, baseline eGFR, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking habits, alcohol consumption and

Table 1. Baseline characteristics of the study population

	Total subjects	Gender-specific quintiles of serum uric acid (mg/dL)					
		Q1 (M ≤ 4.9, F ≤ 3.7)	Q2 (M 5.0–5.6, F 3.8–4.3)	Q3 (M 5.7–6.2, F 4.4–4.8)	Q4 (M 6.3–7.0, F 4.9–5.4)	Q5 (M ≥ 7.1, F ≥ 5.5)	P-value
Number	165 847	32 630	34 870	32 558	32 918	32 871	
Age (years)	63.3 ± 7.4	63.1 ± 7.7	63.2 ± 7.5	63.4 ± 7.3	63.5 ± 7.3	63.5 ± 7.3	<0.001
Male (%)	40.0	40.6	37.6	39.1	43.2	39.6	<0.001
Smoker (%)	13.2	13.4	12.5	12.7	13.4	13.8	<0.001
Alcohol consumption (%)	44.0	40.2	40.8	44.1	47.2	47.9	<0.001
Obesity (%)	25.5	16.5	18.9	23.2	23.1	39.3	<0.001
BMI (kg/m^2)	23.1 ± 3.2	22.2 ± 3.0	22.5 ± 3.0	23.0 ± 3.0	23.6 ± 3.1	24.4 ± 3.4	<0.001
SBP (mmHg)	128.9 ± 17.3	126.6 ± 17.4	127.4 ± 17.3	128.5 ± 17.1	129.9 ± 17.1	131.9 ± 17.0	<0.001
DBP (mmHg)	76.2 ± 10.5	74.6 ± 10.5	75.3 ± 10.4	76.1 ± 10.4	76.9 ± 10.5	78.0 ± 10.5	<0.001
eGFR (mL/min/1.73 m^2)	74.5 ± 15.2	80.6 ± 15.8	77.1 ± 14.5	74.4 ± 14.1	72.0 ± 14.0	68.1 ± 14.7	<0.001
Triglyceride (mg/dL)	119.4 ± 77.3	103.5 ± 62.5	108.8 ± 65.8	116.0 ± 70.7	125.4 ± 78.6	144.0 ± 96.7	<0.001
LDL-C (mg/dL)	125.9 ± 29.8	122.0 ± 28.6	125.0 ± 29.1	126.5 ± 29.2	127.3 ± 29.9	129.0 ± 31.6	<0.001
HDL-C (mg/dL)	62.1 ± 15.9	64.3 ± 16.1	63.5 ± 16.0	62.3 ± 15.8	60.9 ± 15.8	59.2 ± 15.6	<0.001
HbA1$_c$ (%)	5.3 ± 0.6	5.4 ± 0.8	5.3 ± 0.6	5.3 ± 0.6	5.3 ± 0.5	5.4 ± 0.5	<0.001
Proteinuria (≥1+) (%)	4.7	3.8	3.6	4.0	4.8	7.1	<0.001
Hypertension (%)	44.3	36.4	38.7	42.8	48.1	55.6	<0.001
Diabetes (%)	6.4	8.4	6.0	6.0	5.7	6.1	<0.001
Dyslipidemia (%)	55.1	46.1	50.4	54.9	58.5	66.0	<0.001

M, males; F, females; BP, blood pressure; eGFR, estimated glomerular filtration rate. Mean ± SD.

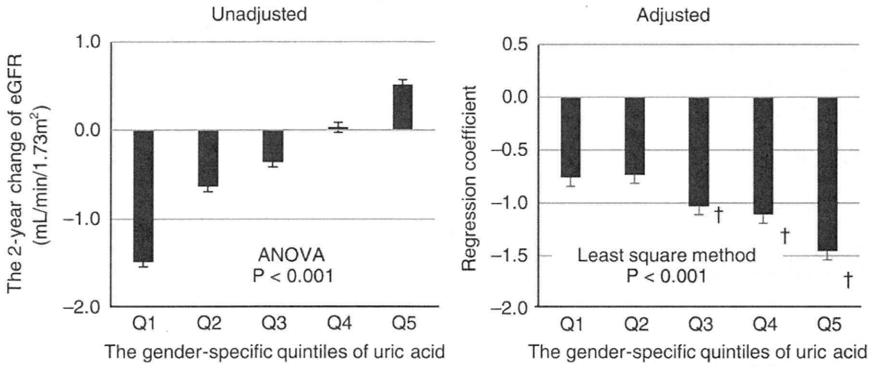

FIGURE 1: Serum uric acid at baseline and the 2-year change in eGFR. eGFR, estimated glomerular filtration rate. The gender-specific quintiles of uric acid (mg/dL), Q1: males (M) ≤4.9, females (F) ≤3.7; Q2: M 5.0–5.6, F 3.8–4.3; Q3: M 5.7–6.2, F 4.4–4.8; Q4: M 6.3–7.0, F 4.9–5.4 and Q5: M≥ 7.1, F ≥ 5.5. Adjusted for gender, age, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking, alcohol consumption and proteinuria. †P < 0.05 versus Q1. Mean ± SE.

proteinuria. The adjusted analysis showed that the change in eGFR observed at the 2-year follow-up was inversely correlated with serum uric acid levels at baseline (P < 0.001) and the decline was significantly more rapid in subjects with high uric acid (Q3–Q5: M ≥5.7 mg/dL, F ≥4.4 mg/dL), as compared with those with low uric acid levels (Q1: M ≤4.9 mg/dL, F ≤3.7 mg/dL) (Figure 1). We performed a sensitivity analysis in the subjects without renal insufficiency at baseline. It showed similar results as presented in total population that the subjects with high uric acid at baseline showed a slow decline of eGFR in the unadjusted analysis and, in contrast, a faster decline of eGFR in the adjusted analysis (Supplementary Data, Figure S1). Furthermore, the adjusted analysis was performed in males and females separately, and it showed that the eGFR decline was significantly more rapid in subjects with high uric acid (Q3–Q5) in both males and females (Supplementary Data, Figure S2).

Second, we evaluated the independent effect of the increase in serum uric acid per 1 mg/dL on the changes in renal function. In the unadjusted model of linear regression analysis, the uric acid levels at baseline were positively correlated with the changes in eGFR (regression coefficient of the 1 mg/dL increase of uric acid, 0.355; SE 0.019; P < 0.001). The baseline GFR shows a significant negative correlation with uric acid at baseline (regression coefficient −0.024, SE 0.001, P < 0.001) and GFR change (regression coefficient −0.237, SE 0.001, P < 0.001). Therefore, we performed a further analysis with the adjustment for baseline eGFR. It showed that the increase of serum uric acid was inversely correlated with change in eGFR (regression coefficient −0.362, SE 0.019, P < 0.001). In the multiple linear regression analysis fully adjusted for the confounders, the regression coefficient of the 1 mg/dL increase of uric acid was −0.213 (SE 0.023, P < 0.001). There was a significant interaction between uric acid and other baseline parameters such as gender, age, eGFR, BMI, triglycerides, HDL-C, presence of proteinuria and alcohol consumption (P < 0.05). The subgroup analyses, divided by the characteristics of the participants at baseline, showed that the effect of the increase in serum uric acid on eGFR was statistically significant in all subgroups except in males and was especially prominent in females, those with diabetes and proteinuria and those who did not drink alcohol (Figure 2).

Third, we examined the association between uric acid and renal damage by using incidental renal insufficiency as the end point. We analyzed 141 514 subjects without renal insufficiency at baseline; the characteristics of these subjects were similar to those of the total population (Supplementary Data, Table S1). At the 2-year follow-up, there were 9169 cases (6.5%) of incidental renal insufficiency. The incidence of renal insufficiency increased along with the increase in uric acid levels at baseline (Q1: 4.2%, Q2: 5.2%, Q3: 6.5%, Q4: 7.8% and Q5: 9.6%, respectively, P < 0.001). In the multivariable logistic regression analysis adjusted for confounders (age, gender, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR and proteinuria), the odds ratio (OR) significantly increased along with the increase of uric acid [OR: 1.104, 95% confidence interval (CI): 1.024–1.191 in Q4, OR: 1.203, 95% CI: 1.115–1.299 in Q5, using Q1 as a reference] (Table 2). The adjusted analysis was performed in males and females separately and revealed that the risk for incidental renal insufficiency was increased at uric acid of Q4–Q5 (≥6.3 mg/dL) in males and Q5 (≥5.5 mg/dL) in females, compared with the lowest quintile Q1 (Table 3). The OR for hyperuricemia and the 1 mg/dL increase in serum uric acid for incidental renal insufficiency were 1.117 (95% CI: 1.051–1.187) and 1.056 (95% CI: 1.035–1.078), respectively, after adjustment for confounders (Table 2).

DISCUSSION

In this longitudinal nationwide cohort study, our results showed that an increase in serum uric acid levels is independently associated with a more rapid decline in eGFR and incidental renal insufficiency and showed that a slight increase within the normal range of serum uric acid levels might be a risk for renal damage in the general population. Furthermore, the association between uric acid and a decline in renal