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.

ORIGINAL ARTICLE

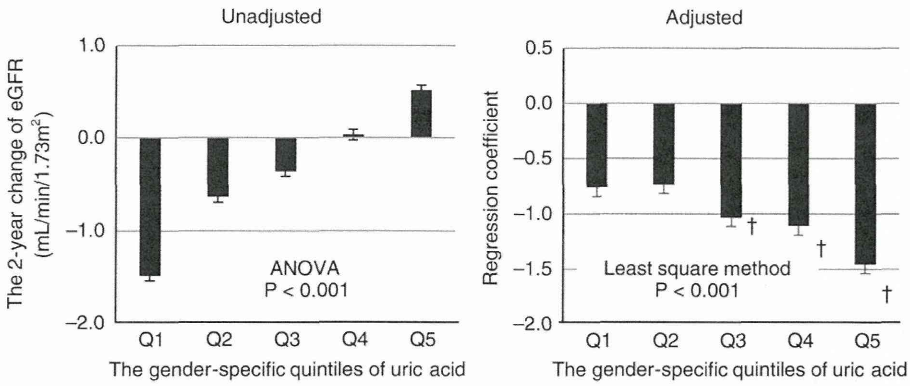

FIGURE 1: Serum uric acid at baseline and the 2-year change in eGFR. eGFR, estimated glomerular filtration rate. The gender-specific quintiles of uric acid (mg/dL), Q1: males (M) ≤4.9, females (F) ≤3.7; Q2: M 5.0–5.6, F 3.8–4.3; Q3: M 5.7–6.2, F 4.4–4.8; Q4: M 6.3–7.0, F 4.9–5.4 and Q5: M≥ 7.1, F ≥ 5.5. 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

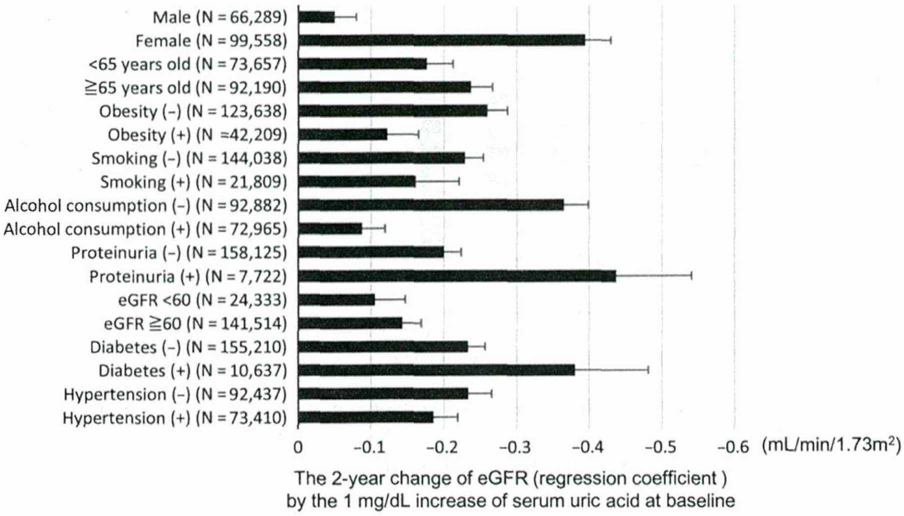

FIGURE 2: The 2-year change in eGFR by the 1 mg/dL increase of serum uric acid at baseline. eGFR, estimated glomerular filtration rate. Adjusted for gender, age, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking, alcohol consumption and proteinuria. Mean ± SE.

Table 2. OR of serum uric acid level categories for incidental renal insufficiency

Category	Unadjusted			Adjusted[a]		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.229	1.141–1.324	<0.001	0.995	0.920–1.077	0.909
Q3 (M 5.7–6.2, F 4.4–4.8)	1.576	1.466–1.696	<0.001	1.048	0.971–1.132	0.231
Q4 (M 6.3–7.0, F 4.9–5.4)	1.921	1.789–2.063	<0.001	1.104	1.024–1.191	0.010
Q5 (M ≥ 7.1, F ≥ 5.5)	2.399	2.236–2.575	<0.001	1.203	1.115–1.299	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.739	1.645–1.837	<0.001	1.117	1.051–1.187	<0.001
Uric acid (per 1 mg/dL increase)	1.280	1.260–1.300	<0.001	1.056	1.035–1.078	<0.001

OR, odds ratio; CI, confidence interval; M, males; F, females.
[a]Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR and proteinuria.

Table 3. Adjusted OR of serum uric acid level categories for incidental renal insufficiency by gender.

Category	Males			Females		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.007	0.896–1.133	0.904	0.985	0.886–1.096	0.784
Q3 (M 5.7–6.2, F 4.4–4.8)	1.113	0.992–1.248	0.067	1.013	0.913–1.125	0.806
Q4 (M 6.3–7.0, F 4.9–5.4)	1.183	1.059–1.323	0.003	1.065	0.960–1.182	0.237
Q5 (M ≥ 7.1, F ≥ 5.5)	1.243	1.107–1.397	<0.001	1.216	1.098–1.348	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.134	1.045–1.230	0.003	1.136	1.036–1.245	0.007
Uric acid (per 1 mg/dL increase)	1.056	1.027–1.087	<0.001	1.076	1.043–1.109	<0.001

Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, proteinuria and eGFR.
OR, odds ratio; CI, confidence interval; M, males; F, females.

function could be modulated by the characteristics of the studied population.

Previous studies showed conflicting results on the association between uric acid levels and kidney disease, and this could be due to the insufficient statistical power resulting from a small sample size, the difference in characteristics of subjects and the analytical methods used [5]. In this study, we had a very large sample size to allow for subgroup analyses with sufficient statistical power, different classifications of uric acid levels (hyperuricemia, quintiles and the 1 mg/dL increase in uric acid), to include various correction factors and end points (GFR decrease and incidental renal insufficiency). Therefore, the findings obtained in this study appear to be robust.

Our study showed that the decline of renal function was significantly more rapid with the increased uric acid levels (≥5.7 mg/dL in males and ≥4.4 mg/dL in females), and the OR for incidental renal insufficiency was significantly increased with uric acid levels of ≥6.3 mg/dL in males and ≥5.5 mg/dL in females. This indicates that a slight increase within the normal range of serum uric acid might be a risk for renal function deterioration. This is consistent with the previous observation that cardiovascular mortality in females increases with serum uric acid levels of ≥5.5 mg/dL [1]. Together with previous observations, our finding suggests that the risk for reduced renal function might increase with increased serum uric acid levels, even within the normal range.

Although it is difficult to explain the mechanism of how uric acid causes renal function deterioration, a series of experimental studies provide a possible assumption that mild elevation of uric acid induces oxidative stress and endothelial dysfunction, resulting in the development of glomerular hypertension and arteriolosclerosis [15]. This assumption is supported by the clinical observations that uric acid levels are associated with renal arteriolopathy in biopsy specimens [16] and that an increase of uric acid (≥7 mg/dL for men, ≥6 mg/dL for women) was independent predictor for the development of albuminuria in a community-based population [17].

There was an interaction between uric acid and several clinical parameters such as eGFR, gender, age, BMI, triglycerides, HDL-C, presence of proteinuria and alcohol consumption. This indicates that the characteristics of the studied population might modulate the association between uric acid levels and renal changes. Its effect seems to be stronger in females, those with diabetes and proteinuria and those who do not drink alcohol. In females, serum uric acid levels are lower than males, because of estrogenic compounds that enhance the renal urate excretion [18], and after menopause serum uric acid is increased [19], suggesting an important role of estrogenic hormones in the regulation of uric acid. The estrogenic compounds are also known to have a vascular protective property. Therefore, it is speculated that the increase in uric acid in females is induced by the combination of the decrease of the protective estrogenic compounds and the overproduction of uric acid. This might enhance the effect of uric acid on renal function in females. Hyperuricemia increases intraglomerular pressure [20] and urinary albumin excretion [21]. Diabetes also develops glomerular hypertension and albuminuria, and massive proteinuria is a risk for ESKD [22]. Therefore, it is speculated that hyperuricemia and diabetes synergistically promote kidney injury by inducing glomerular hypertension and proteinuria. Several studies disclosed that regular light-to-moderate drinking appears to protect against incident hypertension and cardiovascular events [23]. Such protective effect of alcohol consumption might attenuate the aggravating effect of uric acid on renal function. The precise mechanism of how these factors interact with uric acid warrants a further research.

Interestingly, there was a positive association between uric acid levels and the change in eGFR in the unadjusted model that became inverse in the eGFR- and multivariate-adjusted models. A significant interaction between uric acid levels and renal function was detected. The baseline GFR was reported to be negatively correlated with GFR changes in the diabetic population [24]. Similarly, in this study, the baseline GFR shows a significant negative correlation with uric acid at baseline and GFR change. This indicates that subjects with high eGFR at baseline is likely to show a low uric acid at baseline and a rapid decline of eGFR. This observation suggests that eGFR at baseline should be regarded as a confounding factor to evaluate the independent effect of uric acid on renal function. Some previous studies did not include baseline eGFR in their multivariate-adjusted models, which may explain the conflicting results observed.

The increase in uric acid was associated with a slow decline of eGFR, but a high incidence of renal insufficiency in the unadjusted model. One of the possible explanations for these contrasting results between the eGFR change and incident renal insufficiency is the difference in baseline eGFR among the quartiles. The subjects with high uric acid are likely to show low eGFR at baseline and to fall into a category of renal insufficiency with a small decline of eGFR. On the other hand, the subjects with low uric acid are likely to show high eGFR at baseline and not to develop renal insufficiency even with a relatively large decline of eGFR.

The strength of this study is the large number of nationwide samples that were prospectively followed. This adds reliability to our results, even in the subgroup analyses. However, this study has several limitations. First, the serum uric acid levels were measured only at the baseline. Therefore, the changes in serum uric acid levels during the follow-up period that might have an independent effect on renal outcome [25] were not evaluated. Second, the eGFR was evaluated only twice (at baseline and 2 years). These parameters are known to show day-to-day variations. Measuring them twice only might, therefore, underestimate the association between uric acid levels and renal outcomes. Third, renal function was estimated by using the Japanese equation for eGFR, not inulin clearance. Fourth, we have no information on uric acid-lowering medication use in this population.

In conclusion, our study showed that serum uric acid levels are an independent factor for a more rapid decline in renal function in a community-based population and that a slight increase in uric acid levels within the normal range might be a risk for a decline in renal function. To understand the effect of serum uric acid levels on the progression of renal disease, clinical trials of uric acid-lowering therapy are required.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ORIGINAL ARTICLE

Comparison of predictive value for first cardiovascular event between Japanese GFR equation and coefficient-modified CKD-EPI equation

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Abstract

Background The most superior GFR-estimating equation from the viewpoint of cardiovascular disease (CVD) prediction remains unclear. Thus, we performed cross-sectional comparison between two GFR-estimating equations (Japanese GFR equation and coefficient-modified CKD-EPI equation) and CVD incidence using Japanese nationwide "specific health checkup" data.

Methods We recruited Japanese residents (241,159 individuals; mean 63 years; male, 38.6 %) who had not experienced CVD event (cardiac disease or stroke, or both). We calculated estimated GFR using two equations, and compared their predictive value for first symptomatic CVD event within 1 year.

Results Of all subjects, the mean GFR estimated by the Japanese GFR equation (JPN-eGFR) modified for Japanese was 75.83 ± 16.18 mL/min/1.73 m^2, and that by the coefficient-modified CKD-EPI equation (mCKDEPI-eGFR) was 76.39 ± 9.61 mL/min/1.73 m^2. Area under the receiver operating characteristics curves (95 % confidence intervals) for predicting CVD event by mCKDEPI-eGFR vs. JPN-eGFR were 0.596 (0.589–0.603) vs. 0.562 (0.554–0.569). Using mCKDEPI-eGFR, the crude odds ratio (OR) for CVD incident in the 4th quartile group was far more than double (OR 2.46, 95 % CI 2.29–2.66) that in the 1st quartile group. Using JPN-eGFR, the crude OR in the 4th quartile group was less than double (OR 1.61, 95 % CI 1.51–1.73) that in the 1st quartile group. However, such superior predictive value of mCKDEPI-eGFR disappeared after adjustment for confounding factors (age, gender, BMI, presence of proteinuria, hypertension, diabetes, dyslipidemia and current smoking).

Conclusion GFR estimated by the coefficient-modified CKD-EPI equation was more closely related to CVD incidence than that estimated by the Japanese GFR equation. However, it is possible that low mCKDEPI-eGFR also

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reflects some cardiovascular risk(s) other than kidney dysfunction.

Keywords Chronic kidney disease · Cardiovascular disease · General population · MDRD · CKD-EPI · Japanese GFR equation

Introduction

Accumulated evidence has revealed that kidney dysfunction predicts both cardiovascular morbidity and all-cause mortality of the general population, not only in the Western population [1], but also in the Eastern population [2, 3]. Kidney dysfunction is associated with low-grade inflammation, endothelial dysfunction [4], and oxidative stress [5], all of which are known as nontraditional cardiovascular risk factors. Accordingly, from the epidemiological viewpoint, the main aim in estimating kidney function, or glomerular filtration rate (GFR), is to predict future events such as cardiovascular disease (CVD).

To calculate estimated GFR, the Modification of Diet in Renal Disease (MDRD) Study equation is currently used worldwide. In Japan, not the original MDRD equation, but the Japanese GFR equation in which coefficient for age, gender and serum creatinine was directly derived from Japanese data is used nationwide [6]. However, in 2009 the chronic kidney disease epidemiology collaboration (CKD-EPI) proposed an alternative equation [7], which applies different coefficients to the same three variables used in the MDRD Study equation and Japanese GFR equation (age, gender, and serum creatinine level). The CKD-EPI equation was developed to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR (i.e., above 60 mL/min/1.73 m^2) [7]. Compared with the MDRD equation, the most different point of the CKD-EPI equation is the avoidance of overestimation among subjects with lower serum creatinine level (<0.7 mg/dL in female and <0.9 mg/dL in male). Although which of these two equations (or modifications thereof) is favored by a general practice is unclear [8], results of meta-analysis have recently been published showing that the predictive value of the CKD-EPI equation for CVD is superior to that of the MDRD equation [9]. Regarding the precise conditions regarding the issue of which GFR-estimating equation is superior in terms of CVD prevention, recent report from rural community in Iwate, Japan demonstrated the superiority of the CKD-EPI equation over Japanese GFR equation [10]. However, nationwide condition regarding this problem is not clear as yet.

The aim of this study was to prove which GFR-estimating equation is superior in terms of CVD prediction using national "specific health checkup" data. The present study provides us with information regarding the predictive values of each GFR-estimating equation among the Japanese general population.

Methods and subjects

The "Specific Health Checkup" system

The "Specific Health Checkup" system ("Tokutei-Kenshin" in Japanese) is a health checkup and guidance system for adult Japanese citizens and carried out nationwide annually. The system was initiated in April 2008 in Japan by the Ministry of Health, Labour and Welfare to detect metabolic syndrome, and if confirmed, to provide individual instructions to modify lifestyle and necessary treatment [11].

Study population ("Specific Health Checkup" participants)

Individual records of 1,030,679 participants who participated in the "Specific Health Checkup" in both 2008 and 2009 were anonymously provided and included in this study. Among these participants, those who had data for serum creatinine, age, gender, and body weight were selected, as serum creatinine test had not been mandatory. Data from the nationwide database was obtained for 24 prefectures (Hokkai-do, Yamagata, Miyagi, Ibaraki, Tochigi, Saitama, Tokyo, Kanagawa, Ishikawa, Niigata, Nagano, Gifu, Osaka, Okayama, Tokushima, Kochi, Fukuoka, Saga, Kumamoto, Nagasaki, Oita, Miyazaki, Okinawa, and Fukushima) that agreed with the study aims. Ethical approval was obtained from Fukushima Medical University (Accept No. 1485). Data were sent to a data center called the NPO Japan Clinical Research Support Unit to be verified. Outliers accounted for 0.01–0.1 % of the total and were treated with winsorization (Supplementary data; Table S1) [12]. Of the 1,030,679 participants in the databases, 765,653 were excluded due to missing serum creatinine level, gender, or past CVD history. We also excluded 23,867 people who already had experienced CVD in 2008. Thus, the present study comprised 241,159 subjects, representing 23.4 % of the residents who participated in the "specific health checkup" held in 2008 and 2009.

Eligible participants visited a pre-assigned clinic or hospital and responded to a questionnaire regarding past history of stroke and cardiac disease, and medications for hypertension, diabetes mellitus, and dyslipidemia. Physical measurements including height, weight and blood pressure were taken, and then blood samples were collected to

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) × 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

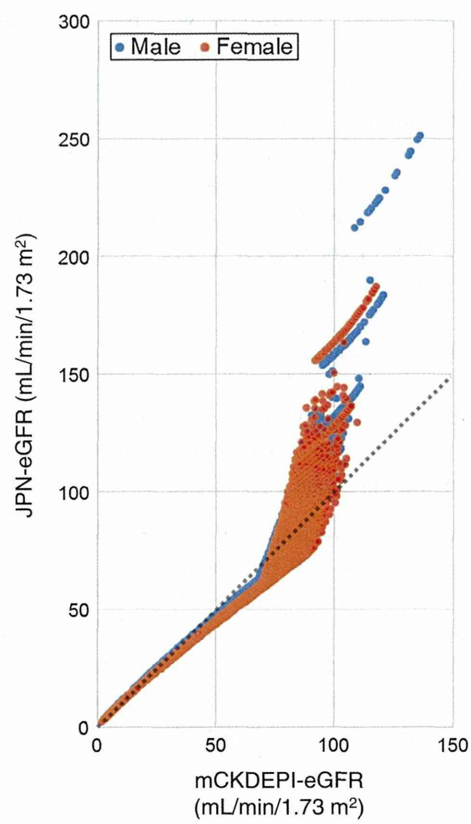
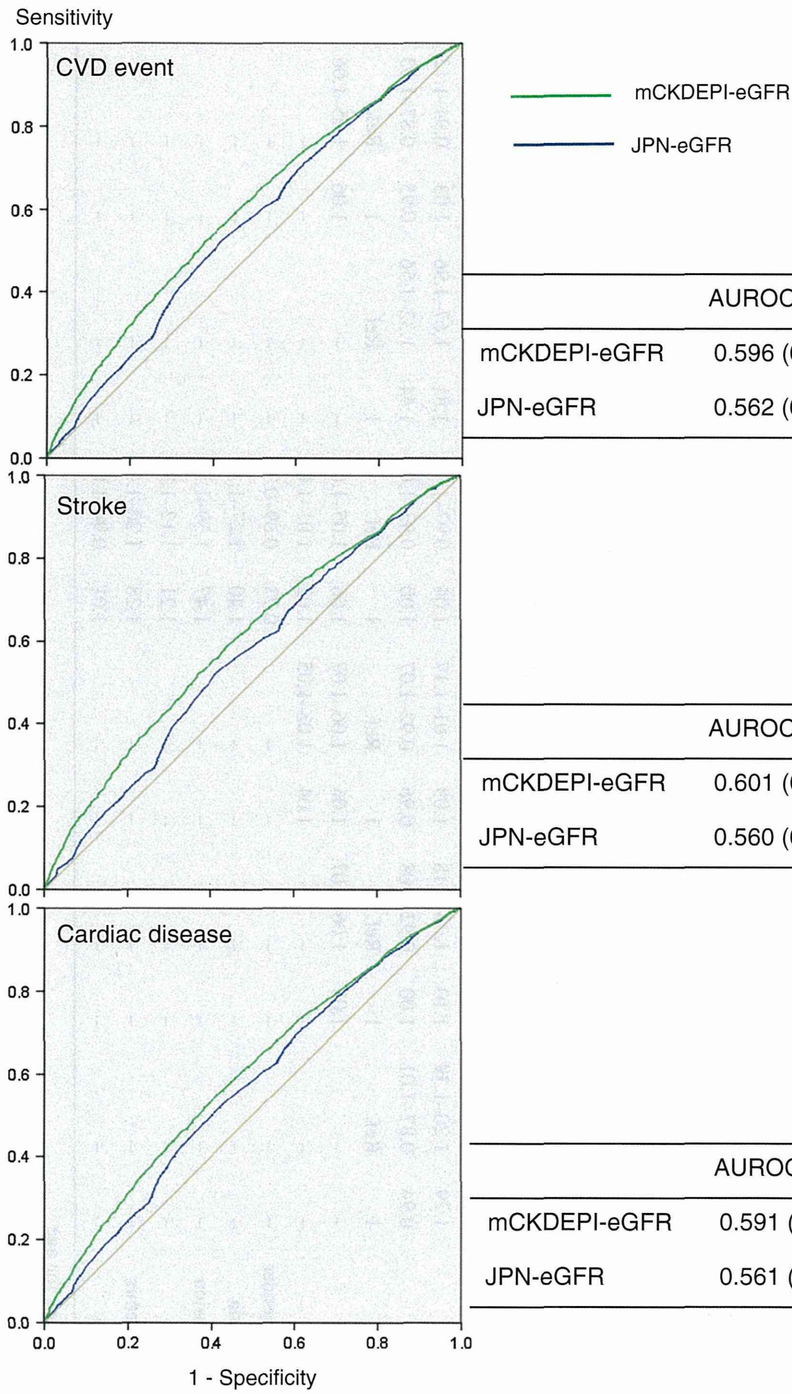


Fig. 1 Relationships between JPN-eGFR and mCKDEPI-eGFR. Points *along* the *diagonal dotted line*, accordance between JPN-eGFR and mCKDEPI-eGFR; points *below* the *diagonal dotted line*, underestimation by JPN-eGFR; points *over* the *diagonal dotted line*, overestimation by JPN-eGFR

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).



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

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

	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