Table 2. Predictors of 50% increase in serum creatinine level.

Predictors	Facility-adjusted model[a]		Multivariate model[b]	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age (per 10 year)	1.25 (1.04, 1.51)	0.016	1.08 (0.84, 1.39)	0.548
Male (vs female)	1.76 (1.06, 2.92)	0.028	1.54 (0.84, 2.82)	0.165
Current smokers (vs non-/past smokers)	2.33 (1.40, 3.86)	0.001	2.41 (1.38, 4.20)	0.002
Hypertension	1.36 (0.81, 2.27)	0.102	0.97 (0.53, 1.75)	0.915
eGFR ≥90 ml/min/1.73 m^2	1.00 (reference)		1.00 (reference)	
60–89 ml/min/1.73 m^2	1.29 (0.63, 2.66)	0.489	1.02 (0.46, 2.23)	0.969
45–59 ml/min/1.73 m^2	2.18 (1.00, 4.72)	0.049	1.32 (0.51, 3.41)	0.562
<45 ml/min/1.73 m^2	5.28 (2.31, 12.1)	<0.001	5.02 (1.94, 12.9)	0.001
Urinary protein < 0.50 g/day	1.00 (reference)		1.00 (reference)	
0.50–0.99 g/day	0.93 (0.44, 1.97)	0.858	0.80 (0.57, 1.73)	0.568
≥1.00 g/day	2.29 (1.21, 4.34)	0.011	1.84 (0.92, 3.67)	0.083
Urinary occult blood negative or trace	1.00 (reference)		1.00 (reference)	
1+ or 2+	1.44 (0.54, 3.83)	0.461	1.20 (0.42, 3.41)	0.735
3+ or more	1.10 (0.43, 2.84)	0.839	1.24 (0.46, 3.37)	0.668
ACE DD (vs ID/II)	1.97 (1.15, 3.40)	0.014	1.86 (1.03, 3.33)	0.038
RAS blockade[c]	1.21 (0.73, 2.00)	0.466	1.06 (0.59, 1.90)	0.847
Use of immunosuppressants[c]	0.91 (0.53, 1.58)	0.740	0.77 (0.41, 1.43)	0.406

eGFR: estimated glomerular filtration rate; 95% CI: 95% confidence interval; ACE: angiotensin-converting enzyme; I: insertion; D: deletion; RAS: renin-angiotensin system. [a]Adjusted for facility. [b]Adjusted for facility, clinical characteristics at kidney biopsy (age, gender, smoking status, hypertension, eGFR, urinary protein, and urinary occult blood); *ACE* I/D and therapeutic interventions within one year of kidney biopsy (RAS blockade and use of immunosuppressants). [c]RAS blockade and use of immunosuppressants within one year of kidney biopsy.

Table 3. Effect modification between three gene polymorphisms and RAS blockade.

	Facility-adjusted model[a]		Multivariate model[b]		*p* for interaction[c]
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	
ACE I/D					
DD vs ID/II	1.97 (1.15, 3.40)	0.014	1.86 (1.03, 3.33)	0.038	0.087
II vs ID/DD	0.90 (0.53, 1.52)	0.685	1.07 (0.61, 1.90)	0.807	0.712
AT1R A1166C					
AA vs AC/CC	1.04 (0.49, 2.20)	0.922	1.26 (0.56, 2.82)	0.583	0.761
AGT T704C					
CC vs CT/TT	0.99 (0.59, 1.65)	0.957	1.16 (0.68, 1.98)	0.595	0.891

RAS: renin-angiotensin system; 95% CI, 95% confidence interval; ACE: angiotensin-converting enzyme; I: insertion; D: deletion.
[a]Adjusted for facility. [b]Adjusted for facility, clinical characteristics at kidney biopsy (age, gender, smoking status, hypertension, eGFR, urinary protein, and urinary occult blood), *ACE* I/D and therapeutic interventions within one year of kidney biopsy (RAS blockade and use of immunosuppressants). [c]*p* for interaction between RAS-related gene polymorphisms and RAS blockade.

findings described above were hardly ascribed to blood pressure control because mean arterial pressures at one and two years after kidney biopsy were comparable between the patients with RAS blockade and those without RAS blockade (Figure 3).

Discussion

The present study showed that the *ACE* I/D predicted IgAN progression and the renoprotective effectiveness of RAS blockade in 237 IgAN patients. Compared with *ACE* II/ID patients, *ACE* DD patients were at higher risk of IgAN progression and RAS blockade halved their risk, mitigating their genetic disadvantage (Figure 1). These findings suggest that *ACE* I/D is a potentially useful marker to identify patients who will clinically benefit from RAS blockade. Compared with the previous studies assessing the associations between RAS-related gene polymorphisms and IgAN progression, this study is the third largest genetic study with 237 IgAN patients, following two larger studies ($n = 527$[34] and 267[35]), and has the longest observational period (9.9 ± 4.2 years). Furthermore, we performed a comparative assessment of three major RAS-related gene polymorphisms and carefully controlled for several

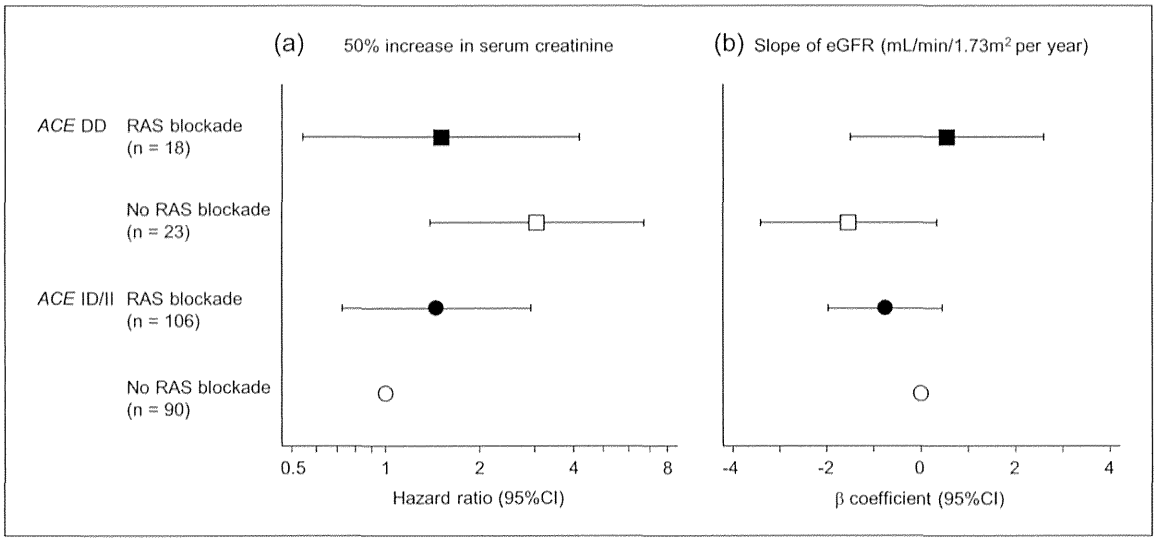

Figure 1. Effect modification between *ACE* I/D (recessive model) and RAS blockade. Associations of *ACE* I/D and RAS blockade with 50% increase in serum creatinine level (a) and slope of eGFR (b) were assessed using Cox proportional-hazards model and linear regression models, respectively, after adjusting for facility, clinical characteristics at kidney biopsy (age, gender, smoking status, hypertension, eGFR, urinary protein and urinary occult blood) and use of immunosuppressants within one year of kidney biopsy.
ACE: angiotensin-converting enzyme; I: insertion; D: deletion; RAS: renin-angiotensin system; eGFR: estimated glomerular filtration rate.

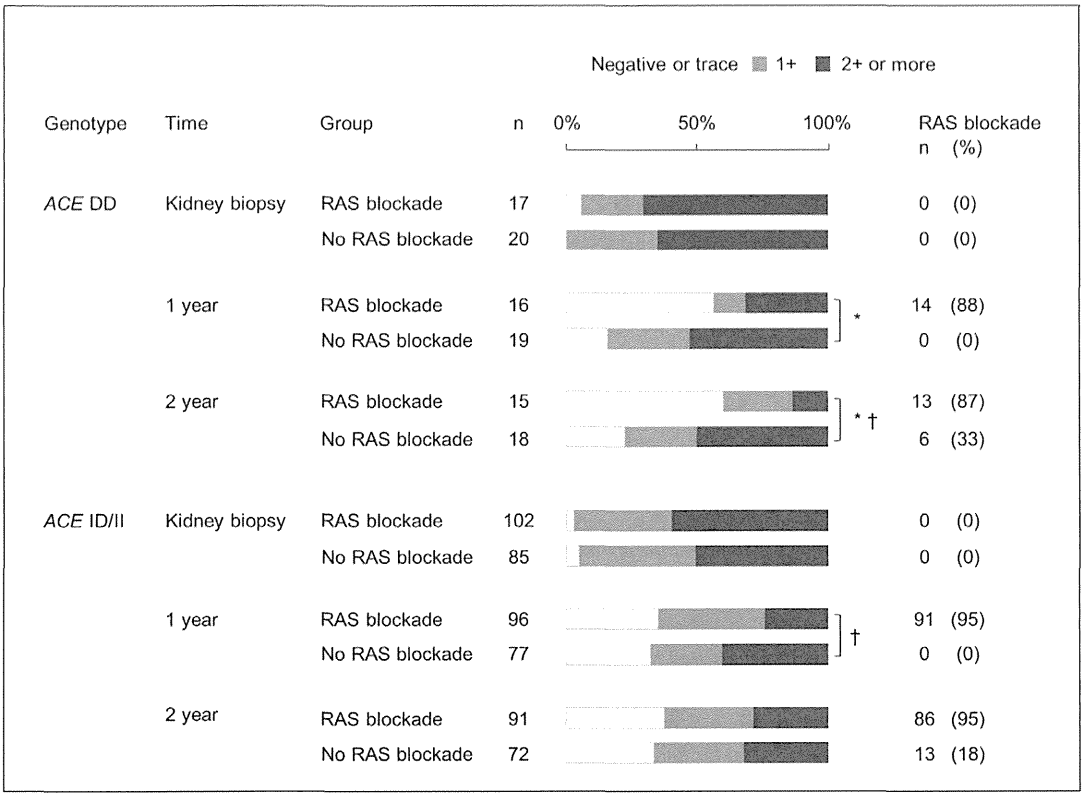

Figure 2. Urinary protein by dipstick test at kidney biopsy and one and two years after kidney biopsy. *ACE* DD patients with RAS blockade had higher proportions of negative or trace urinary protein at one year after kidney biopsy ($p = 0.012$) and negative or trace urinary protein and ≥1 of urinary protein at two years after kidney biopsy ($p = 0.027$ and 0.026, respectively), compared with those without RAS blockade. In contrast, no significant difference was observed at one and two years after kidney biopsy between *ACE* ID/II patients with RAS blockade and those without RAS blockade, except ≥2+ of urinary protein at one year after kidney biopsy ($p = 0.021$).
ACE: angiotensin-converting enzyme; I: insertion; D: deletion; RAS: renin-angiotensin system. *<0.05, negative or trace vs ≥1+ of urinary protein. †<0.05, ≤1+ vs ≥2+ of urinary protein.

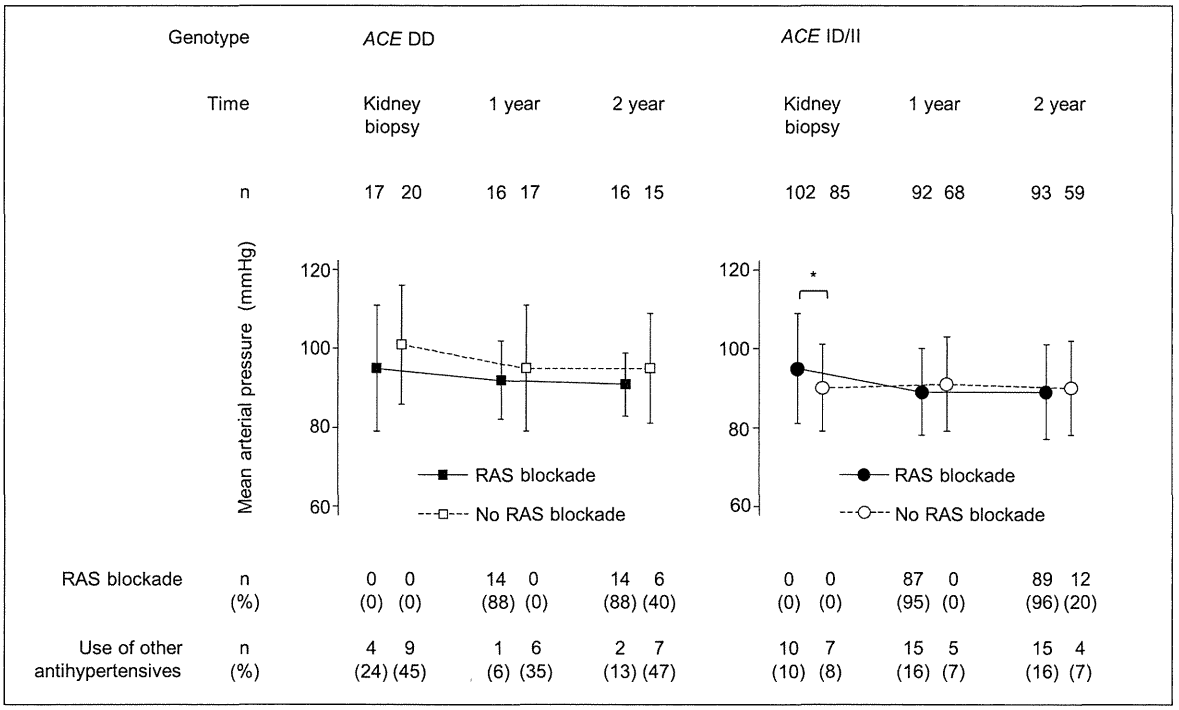

Figure 3. Mean arterial pressure at kidney biopsy and one and two years after kidney biopsy. No significant difference was observed between the patients with RAS blockade and those without RAS blockade at one and two years after kidney biopsy in *ACE* DD and II/ID patients, although *ACE* ID/II patients with RAS blockade had higher mean arterial pressure, compared with those without RAS blockade (95 ± 14 vs 90 ± 11 mmHg, $p = 0.011$).
RAS: renin-angiotensin system; *ACE*: angiotensin-converting enzyme; I: insertion; D: deletion. *<0.05, RAS blockade vs no RAS blockade.

critical biases in observational studies, which no previous study took into consideration.

Although multiple studies have described the association between *ACE* I/D and IgAN progression, including several systematic reviews identifying *ACE* I/D as a predictor of IgAN progression,[32,36,37] few studies assessed whether *ACE* I/D modified the renoprotective effect of RAS blockade. One exception was the largest genetic study by Suzuki and colleagues, which included 527 patients with IgAN.[34] Their study found that *ACE* I/D was not associated with the composite outcome of 100% increase in serum creatinine level or ESRD in all patients ($n = 527$) as well as in patients without RAS blockade during the entire observational period ($n = 333$), suggesting that *ACE* I/D did not modify the renoprotective effect of RAS blockade. In contrast, the present study revealed that RAS blockade remarkably improved renal prognosis in *ACE* DD patients, but not in *ACE* II/ID patients (Figure 1). These conflicting results may be owing to several biases such as the prevalent user bias[23] and survivor treatment bias,[28,29] which were deliberately controlled in our study. Interestingly, a randomized controlled trial, the Ramipril Efficacy in Nephropathy (REIN) study, including mostly nondiabetic proteinuric patients, described an effect modification between *ACE* I/D and RAS blockade similar to the present study.[38] The incidence of ESRD was significantly suppressed by ramipril in *ACE* DD patients, but not in II/ID patients, which corroborates our study findings.

The present study clarified that RAS blockade exerted a renoprotective effect in *ACE* DD patients, but not in ID/II patients. *ACE* I/D affects the level of circulating and tissue *ACE*.[39] Serum *ACE* level was higher in *ACE* DD subjects compared with ID/II subjects.[17,18] Furthermore, the local expression of *ACE* in T-lymphocytes[40] and cardiac tissue[19] were higher in *ACE* DD subjects compared with ID/II subjects. A Japanese study of 50 healthy kidney donors revealed that tubular and glomerular *ACE* messengerRNA (mRNA) signals measured using in situ hybridization were higher in *ACE* DD subjects than in ID/II subjects,[41] indicating that intrarenal RAS was more activated in DD patients compared to ID/II patients. Although its precise biological mechanism remains unknown, a recent study reported that *ACE* I/D regulated the transcriptional activity of *ACE* promoters,[42] providing new insight into the direct influence of *ACE* I/D on ACE activity. Therefore, *ACE* DD patients, who likely have higher activity of intrarenal RAS, might reap more renoprotective benefits from RAS blockade, compared to ID/II patients, as evidenced in the present study and REIN study.

The present study had several limitations. First, indication of RAS blockade was dependent on each physician and RAS blockade was not uniform in the present study because of its observational study design.

Nevertheless, our results were compatible with the REIN study,[38] which is the largest randomized control trial assessing the efficacy of RAS blockade mainly in nondiabetic proteinuric patients. The similar findings support the validity of the present study. Second, minor genotype frequencies of *ATIR* A1166C and *AGT* T704C were too small to examine their clinical impact on effectiveness of RAS blockade. A larger cohort is essential for further investigation. Third, our study used the candidate gene approach and examined only one of a large number of gene polymorphisms in *ACE*. A previous study of 267 IgAN patients reported an effect modification between *ACE* A2350G and RAS blockade, though this was not ascertained in a multivariate model adjusting for clinically relevant factors.[35] A broader investigation of RAS-related gene polymorphisms is required to identify genetic predictors of the renoprotective effect of RAS blockade. Fourth, the present study assessed the associations between RAS blockade and RAS-related gene polymorphisms but did not measure systemic or intrarenal RAS activity. The precise biological mechanism of effect modification between the renoprotective effect of RAS blockade and *ACE* I/D-dependent RAS activity needs further clarification. Fifth, a lack of information on the histopathological lesion, one of the conventional prognostic factors, might affect the results of the present study. A slightly higher hazard ratio and lower β coefficient of *ACE* ID/II with RAS blockade compared with ID/II without RAS blockade might be due to the unmeasured histopathological lesion (confounding by indication).

Conclusions

The present study clarified that *ACE* I/D predicted renal outcomes and the renoprotective effectiveness of RAS blockade in IgAN patients. Recognition of *ACE* I/D potentially provides pivotal information for treatment optimization to prevent further progression of IgAN. Further studies are required to establish a therapeutic strategy based on both genetic and clinical evidence.

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Conflict of interest

None declared.

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ORIGINAL ARTICLE

Underestimating chronic kidney disease by urine dipstick without serum creatinine as a screening tool in the general Japanese population

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Abstract
Background It is not known if urine dipstick alone can identify chronic kidney disease (CKD) in the general Japanese population.
Methods We designed a cross-sectional study using data obtained in 2008 from a nationwide community-based health examination program for adults aged 40–74. The data consisted of blood tests, urine tests and questionnaire related to metabolic disorders. Those who had both serum creatinine measured and urine dipstick tested were analyzed.
Results Data were obtained from 538,846 people with a mean age of 62.8 years, consisting of 41.6 % males. Our study showed that 14.4 % had an eGFR below 60 mL/min/1.73 m^2, 5.2 % had proteinuria and 18.1 % had CKD. Within the population with CKD, non-proteinuric CKD accounted for 71.4 %. The proportion of non-proteinuric CKD was highest in stage G3a (91.8 %) followed by G3b (77.0 %) disease, and was greater in the more elderly and in females. The proportion of non-proteinuric CKD was 47.9 % in diabetes mellitus, 69.3 % in dyslipidemia, 66.8 % in hypertension and 57.1 % in metabolic syndrome. Furthermore, non-proteinuric CKD accounted for 78.1 % of the population without these lifestyle diseases, suggesting that even in the population without apparent risk, CKD is still prevalent and can be missed when urine dipstick is the only screening method used.

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Conclusions This study showed that a considerable population of CKD might be overlooked when only dipstick proteinuria is assessed for CKD screening. Hence, we strongly recommend that both urinalysis and serum creatinine measurement should be a part of the nationwide CKD screening system.

Keywords Chronic kidney disease · Screening · Urine dipstick test

Introduction

The current epidemic of chronic kidney disease (CKD) is a health problem worldwide. Individuals with CKD are at a significantly increased risk of both cardiovascular disease (CVD) and end-stage kidney disease (ESKD). In Japan, urinalysis by urine dipstick for CKD screening in schoolchildren, working adults and non-workers older than 40 years has been a mandatory and routine part of annual medical check-ups since 1983. Concurrently, there has been a drastic decrease in ESKD caused by glomerulonephritis and an increase in the mean age of those treated for ESKD [1]. In 1992, measurement of serum creatinine was added to both the company-based and community-based annual health examination program in adults aged 40 or more, for early detection of CKD. The combination of urinalysis and measurement of serum creatinine has contributed to better detection of early-stage CKD in Japanese adults aged 40 years or more [1].

In 2000, the Ministry of Health, Labour and Welfare devised the "Healthy Japan 21" policy, to maintain and improve the health of the Japanese public in the 21st century. The primary focus of this policy was prevention of CVD, malignancy, diabetes mellitus and metabolic syndrome (MS), by advocating an improvement in diet, exercise, mental health, smoking, alcohol and dental health. In 2008, the Ministry of Health, Labour and Welfare started a new surveillance project to prevent and reduce the number of people with MS, the prevalence of which is 25 % among Japanese men aged 40 years or more [2]. This specific health check, consists of a physical check-up, including height, weight, waist circumference, blood pressure, and blood tests related to metabolic disorders, such as those of glucose, lipids, hepatic enzymes and urine. Questionnaire surveys for a past history of stroke, cardiac disease, kidney disease, lifestyles such as smoking, alcohol intake, exercise, etc., and treatment for hypertension, diabetes mellitus and dyslipidemia are also performed. However, serum creatinine measurement was deleted from the list of mandatory tests for adults aged 40 years or more because urinalysis by urine dipstick was previously thought to be superior to measurement of serum creatinine level for early detection of CKD. This was also due to the political aim of reducing the cost of disease screening, which was based on the assumption that detecting high-risk people, such as those with hypertension or metabolic disorders, may be enough to identify those with CKD. However, this may overlook a certain number of people with CKD who do not have proteinuria. Furthermore, there remains a concern that limiting screening to people with hypertension or MS may not sufficiently decrease the incidence of new ESKD in Japanese people, because glomerulonephritis, the second leading cause of ESKD, is not associated with hypertension or MS [1].

The aim of this study was to clarify the accuracy and validity of CKD screening only by dipstick assessment of urine proteinuria without measurement of serum creatinine in the Japanese general population.

Subjects and methods

This study was a cross-sectional study using data obtained in 2008 from a nationwide community-based health examination program for adults aged 40–74 years. The data of those in whom both urine dipstick and serum creatinine had been measured were analyzed. Proteinuria was diagnosed by a dipstick test result of 1+ or more and CKD was diagnosed by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or positive dipstick proteinuria. Diabetes mellitus was defined as fasting plasma glucose of at least 126 mg/dL, hemoglobin A1c (National Glycohemoglobin Standardization Program; NGSP) of at least 6.5 % or a history of anti-diabetic medication. Dyslipidemia was defined as fasting triglyceride levels of at least 150 mg/dL, high-density lipoprotein (HDL) cholesterol levels below 40 mg/dL, low-density lipoprotein (LDL) cholesterol levels of at least 140 mg/dL or history of anti-dyslipidemic medication. Hypertension was defined as a systolic blood pressure of 140 mmHg and above, diastolic

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blood pressure of 90 mmHg and above, or a history of antihypertensive medication. MS was defined in accordance with the current Japanese definition [3]. That is a waist size of at least 85 cm in males and 90 cm in females, and 2 or more of the following: blood pressure of at least 130/85 mmHg, fasting triglyceride levels of at least 150 mg/dL or HDL cholesterol below 40 mg/dL, and fasting plasma glucose of at least 110 mg/dL. Estimated GFR was calculated by the equation for Japanese adults [194 × serum Cre − 1.094 × Age − 0.287 (×0.739 in females)] [4]. Comorbidities included diabetes, dyslipidemia, hypertension and MS.

The data are presented as average ± standard deviation (SD) or percentages. All analyses were performed with SPSS version 17.0 (IBM, Chicago, IL).

The study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research (December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare of Japan). Ethical

Table 1 Characteristics of the whole cohort

	Total $n = 538,846$	Non-CKD $n = 441,550$	CKD without proteinuria $n = 69,506$	CKD with proteinuria $n = 27,790$
Age, years	62.8 ± 8.7	62.3 ± 8.9	65.6 ± 7.2	63.9 ± 8.6
Males, *n* (%)	223,881 (41.6)	176,754 (40.0)	30,982 (44.6)	16,145 (58.1)
Diabetes mellitus, *n* (%)	44,255 (8.2)	32,500 (7.4)	5,629 (8.1)	6,126 (22.0)
Dyslipidemia, *n* (%)	238,096 (44.2)	191,110 (43.3)	32,584 (46.9)	14,402 (51.8)
Hypertension, *n* (%)	216,639 (40.2)	167,499 (37.9)	32,825 (47.2)	16,315 (58.7)
Metabolic syndrome, *n* (%)	48,544 (9.0)	35,266 (8.0)	7,584 (10.9)	5,693 (20.5)
Chronic kidney disease, *n* (%)	97,296 (18.1)	–	69,506 (100)	27,790 (100)
Body height (cm)	157.5 ± 8.6	157.4 ± 8.6	157.6 ± 8.3	159.0 ± 8.7
Body weight (kg)	57.9 ± 10.7	57.5 ± 10.6	58.8 ± 10.3	61.9 ± 11.9
Body mass index (kg/m$^{2)}$	23.2 ± 3.3	23.1 ± 3.3	23.6 ± 3.2	24.4 ± 3.9
Waist size (cm)	83.8 ± 9.3	83.4 ± 9.2	84.8 ± 9.0	86.8 ± 10.1
Systolic blood pressure (mmHg)	129.1 ± 17.8	128.5 ± 17.6	130.0 ± 17.6	136.0 ± 19.3
Diastolic blood pressure (mmHg)	76.5 ± 10.9	76.3 ± 10.8	76.7 ± 10.7	79.6 ± 11.6
Pulse/min	52.6 ± 12.8	52.2 ± 12.7	53.2 ± 12.9	56.4 ± 14.5
Fasting plasma glucose (mg/dL)	97.7 ± 20.8	97.1 ± 19.8	97.1 ± 17.3	109.5 ± 35.9
HbA1c (NGSP) (%)	5.3 ± 0.69	5.3 ± 0.66	5.3 ± 0.57	5.7 ± 1.2
Triglycerides (mg/dL)	121.3 ± 82.3	118.9 ± 81.0	127.1 ± 76.6	144.3 ± 107.5
HDL cholesterol (mg/dL)	62.0 ± 16.2	62.6 ± 16.1	59.5 ± 15.8	58.3 ± 16.3
LDL cholesterol (mg/dL)	125.4 ± 30.6	125.3 ± 30.5	126.3 ± 30.3	124.5 ± 32.8
AST, IU/L	24.4 ± 11.3	24.2 ± 11.0	24.6 ± 10.0	27.1 ± 16.5
ALT, IU/L	22.0 ± 14.4	21.9 ± 14.2	21.5 ± 13.0	25.5 ± 18.8
GGTP, IU/L	37.0 ± 48.7	36.3 ± 47.1	35.6 ± 44.0	52.8 ± 75.4
Hemoglobin (g/dL)	13.5 ± 2.1	13.4 ± 2.1	13.7 ± 2.1	13.8 ± 2.2
Uric acid (mg/dL)	5.2 ± 1.4	5.1 ± 1.3	6.0 ± 1.4	5.8 ± 1.5
Creatinine (mg/dL)	0.72 ± 0.25	0.67 ± 0.13	0.97 ± 0.38	0.87 ± 0.58
eGFR categories, mL/min/1.73 m^2, *n* (%)				
G1, ≥90	107,085 (19.9)	102,921 (23.3)	–	4,164 (15.0)
G2, 60–89	354,118 (65.7)	338,629 (76.7)	–	15,489 (55.7)
G3a, 45–59	68,906 (12.8)	–	63,279 (91.0)	5,627 (20.2)
G3b, 30–44	7,320 (1.4)	–	5,637 (8.1)	1,683 (6.1)
G4, 15–29	996 (0.18)	–	404 (0.6)	592 (2.1)
G5, <15	421 (0.08)	–	186 (0.3)	235 (0.8)
G3a–G5, <60	77,643 (14.4)	–	69,506 (100)	8,137 (29.3)
Proteinuria, *n* (%)				
Negative or trace	511,056 (94.8)	441,550 (100)	69,506 (100)	–
1+ or more	27,790 (5.2)	–	–	27,790 (100)

Expressed as Mean ± SD unless noted otherwise

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *eGFR* estimated glomerular filtration rate, *GGTP* gamma-glutamyl transpeptidase, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NGSP* national glycohemoglobin standardization program

approval was also obtained from the respective institutional review boards.

Results

The health examination data were obtained from 20 prefectures around Japan. A total of 538,846 people had both urine dipstick tested and serum creatinine measured, together with other mandatory tests. The average age of the study population was 62.8 ± 8.7 years and males constituted 41.6 % of the population.

Prevalence of CKD

The characteristics of the entire cohort are shown in Table 1. Estimated GFR below 60 mL/min/1.73 m^2 was found in 14.4 % (n = 77,643) of the population and proteinuria was found in 5.2 % (n = 27,790). CKD (either or both low eGFR and proteinuria) was identified in 18.1 % (n = 97,296) of the population.

Proportion of CKD without proteinuria

Of the 97,296 people with CKD, 69,506 (71.4 %) had no proteinuria, indicating the possibility that 71.4 % of people with CKD (91.8 % with stage G3a, 77.0 % with stage G3b, 40.6 % with stage G4, and 44.2 % with stage G5 disease) might be overlooked when only the urine dipstick method is used for CKD screening (Table 2). With advancing age, the population with CKD increased, especially those without proteinuria (Fig. 1). Thus, we are more likely to overlook CKD in the elderly when CKD screening only involves urine dipstick tests. The proportion of CKD without proteinuria was greater in females than in males (76.5 vs. 65.7 %, $p < 0.001$).

Table 2 Distribution of GFR category and proteinuria in subjects with CKD

CKD	Proteinuria		Total
	Negative or trace	1+ or more	
GFR category, *n* (%)			
G1	–	4,164 (100)	4,164
G2	–	15,489 (100)	15,489
G3a	63,279 (91.8)	5,627 (8.17)	68,906
G3b	5,637 (77.0)	1,683 (23.0)	7,320
G4	404 (40.6)	592 (59.4)	996
G5	186 (44.2)	235 (55.8)	421
G3a–G5	69,506 (89.5)	8,137 (10.5)	77,643
Total	69,506 (71.4)	27,790 (28.6)	97,296

CKD chronic kidney disease

Proportion of those with eGFR below 60 mL/min/1.73 m^2 and without proteinuria

Of the 77,643 people who had an eGFR below 60 mL/min/1.73 m^2, as many as 69,506 (89.5 %) subjects showed no proteinuria (Table 2). Moreover, among the 511,056 people who did not have proteinuria, 69,506 (13.6 %) were found to have an eGFR below 60 mL/min/1.73 m^2.

Proportion of CKD with/without comorbidities and no proteinuria

Table 3 shows the prevalence of CKD according to eGFR categories, proteinuria and comorbidities. The main purpose of the Japanese specific health check is to reveal those who may have MS and to give lifestyle guidance to prevent disease onset. Indeed, among those with MS (n = 48,544), 19.5 % had an eGFR below 60 mL/min/1.73 m^2, 11.7 % had proteinuria, and 27.4 % had CKD. This also indicates the possibility of overlooking CKD in 57.1 % of the people

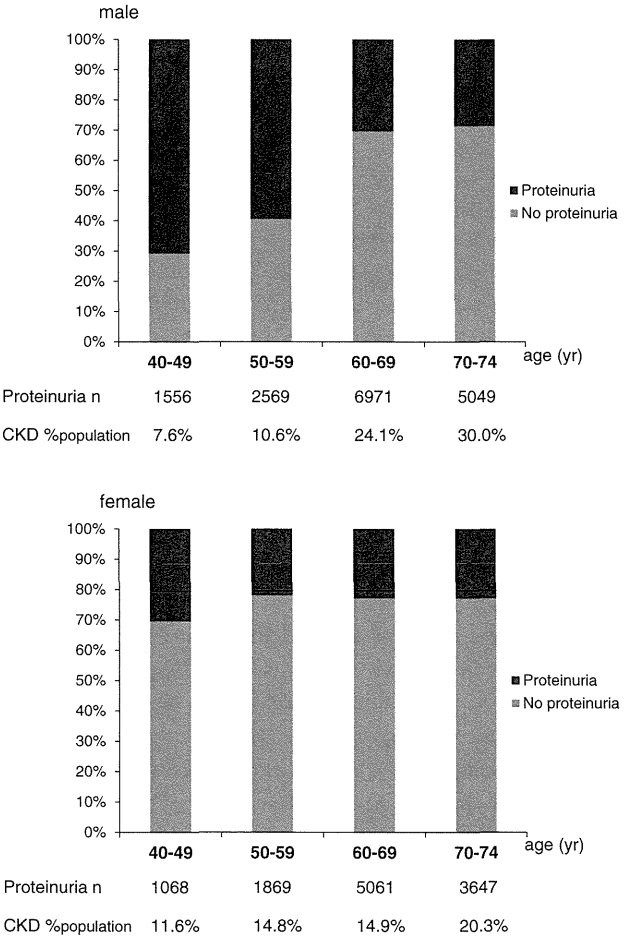

Fig. 1 Distribution of proteinuria according to age in those with CKD

Table 3 Comparison of age, gender, GFR category, proteinuria and coexisting morbidities in subjects grouped according to the comorbidities of diabetes mellitus (DM), dyslipidemia (DL), hypertension (HTN) and metabolic syndrome (MS)

	DM $n = 44,255$	DL $n = 238,096$	HTN $n = 216,639$	MS $n = 48,543$	No. comorbidities $n = 72,297$
Age, years	65.22 ± 7.22	63.43 ± 8.02	65.07 ± 7.36	64.12 ± 8.00	60.58 ± 9.55
Males, *n* (%)	25,494 (57.6)	100,405 (42.2)	100,387 (46.3)	33,325 (68.6)	26,084 (36.0)
eGFR, mL/min/1.73 m^2					
G1, ≥90	9,886 (22.3)	43,678 (18.3)	37,683 (17.4)	7,458 (15.4)	14,452 (20.0)
G2, 60–89	26,826 (60.6)	157,429 (66.1)	140,680 (64.9)	33,634 (69.3)	50,462 (69.8)
G3a, 45–59	6,045 (13.7)	32,540 (13.7)	32,902 (15.2)	8,053 (16.6)	6,968 (9.6)
G3b, 30–44	1,148 (2.6)	3,714 (1.6)	4,397 (2.0)	1,134 (2.3)	381 (0.53)
G4, 15–29	277 (0.63)	534 (0.22)	726 (0.34)	220 (0.45)	21 (0.029)
G5, <15	73 (0.16)	201 (0.084)	251 (0.12)	44 (0.091)	13 (0.018)
G3a–G5, <59	7,543 (17.0)	36,989 (15.5)	38,276 (17.7)	9,451 (19.5)	7,383 (10.2)
Proteinuria					
Negative to trace	38,129 (86.2)	223,694 (94.0)	200,324 (92.5)	42,850 (88.3)	70,330 (97.3)
1 + to more	6,126 (13.8)	14,402 (6.0)	16,315 (7.5)	5,693 (11.7)	1,967 (2.7)
DM, *n* (%)	–	22,501 (9.5)	18,662 (8.6)	12,763 (26.3)	–
DL, *n* (%)	22,501 (50.8)	–	102,595 (47.4)	42,250 (87.0)	–
HTN, *n* (%)	18,662 (42.2)	102,595 (43.1)	–	35,383 (72.9)	–
MS, *n* (%)	12,763 (28.8)	42,250 (17.7)	35,383 (16.3)	–	–
CKD, *n* (%)	11,755 (26.7)	46,986 (19.7)	49,140 (22.7)	13,277 (27.4)	9,000 (12.4)
Within those w CKD					
CKD w/o UProt, *n* (%)	5,629 (47.9)	32,584 (69.3)	32,825 (66.8)	7,584 (57.1)	7,033 (78.1)
CKD w UProt, *n* (%)	6,126 (52.1)	14,402 (30.7)	16,315 (33.2)	5,693 (42.9)	1,967 (21.9)

CKD chronic kidney disease, *UProt* proteinuria, *w* with, *w/o* without

($n = 7,584$) who have CKD and no proteinuria if serum creatinine is not measured. Furthermore, among the people without MS, the frequency of CKD patients with no proteinuria was estimated to be 56.3 %, which means a considerable number of people with CKD may be overlooked by the current specific health check. The proportion of the population of CKD patients without proteinuria who will be overlooked by having only urine dipstick screening for CKD is 47.9 % in patients with diabetes mellitus, 69.3 % of those with dyslipidemia, and 66.8 % in hypertensive patients, indicating that even in those with a high risk, CKD may be overlooked if screening does not include serum creatinine assessments.

It is also important to note that non-proteinuric CKD accounted for 78.1 % of the CKD population without comorbidities. This suggests that even in the population without apparent risk, CKD is still prevalent and that we will miss these people when CKD screening is only done by the urine dipstick test.

Discussion

From this large cross-sectional study of the general Japanese population, we found that a significant portion of people with CKD would have been overlooked if screened only by the urine dipstick test without measurement of serum creatinine. This study shows that as many as 71.4 % of people with CKD would have been missed if they had been screened using only the urine dipstick test and when limited to people with an eGFR below 60 mL/min/1.73 m^2, 89.5 % may have been overlooked. And the proportion of overlooking is the highest in people without comorbidities such as MS, diabetes, dyslipidemia, or hypertension.

Previous studies showed that proteinuria is independent of eGFR as a predictor of mortality and is also the strongest risk factor for CKD progression, with its associated risks of cardiovascular (CV) morbidity and mortality [5–7]. Along with proteinuria, Matsushita et al. [6] have shown in a meta-analysis of worldwide general population cohorts that, indeed, CV mortality and all-cause mortality increase when eGFR is about 70 mL/min/1.73 m^2 and lower. It has been shown that independent of proteinuria, the risk of ESKD is prominently higher in people with a lower eGFR [8]. Our study showed that the probability of overlooking CKD by screening only with urine dipstick is highest in stage G3a followed by G3b disease, and, in general, from these early stages, CVD, renal failure and mortality risk significantly increase, suggesting the need for detection of CKD at this early stage. The risk of such outcomes was

independent of proteinuria, and, more importantly, showed a multiplicatively associated risk of mortality with the existence of proteinuria along with low eGFR [9].

Detection of CKD would be even more important in a population possessing other risk factors for CV events. Muntner et al. have reported that compared to a non-CKD population, people with CKD (defined by eGFR below 60 mL/min/1.73 m^2) possessing other risk factors, such as hypertension, diabetes or dyslipidemia, had a threefold greater risk of CVD [9]. Nakayama et al. [10] have shown in a Japanese cohort that compared to patients with primary renal disease, patients with diabetic and hypertensive nephropathy are at a 3–5 times higher risk of CV events. Present Japanese health screening tests focus mainly on the detection of MS, thereby aiming to prevent CV mortality and morbidity. Our study showed that 27.4 % of those with MS had associated CKD, which strongly suggests that MS is a high-risk factor for CKD. On the other hand, our study also revealed that as many as 57.1 % of MS subjects with CKD might have been overlooked if serum creatinine had not been measured along with urine dipstick, indicating that even in high-risk patients, we cannot recognize CKD without measuring serum creatinine. Furthermore, within the population with CKD, 69.3 % with dyslipidemia, 66.8 % with hypertension and 47.9 % with diabetes could not be diagnosed as CKD only with urine dipstick.

Intriguingly, 56.5 % of people with CKD had no proteinuria and no MS, which means that even in a low risk population, CKD is very common but can be overlooked. Furthermore, 12.4 % of those without apparent comorbidities had CKD and 78.1 % of these people had no proteinuria. Since those without apparent risks would have significantly fewer opportunities to get further medical work-up, their CKD has a much higher risk of being overlooked compared to those with risk factors. Thus, screening by serum creatinine measurement is extremely important in detecting CKD.

This study also brought to light the fact that the elderly population is more inclined to have non-proteinuric CKD. The Japanese society is aging rapidly. Considering the increasing proportion of elderly people in the general population and the increasing age of those on dialysis and initializing dialysis, screening for CKD in this at-risk population is anticipated to result in appropriate treatment at an early stage. Kondo et al. [11] have reported that the use of urine dipstick and serum creatinine is each cost effective as a screening tool for CKD and combination of the two would be even more cost effective. Thus, both urinalysis and serum creatinine measurement in the specific health check are necessary not only for early detection of CKD but also for the reduction of medical cost.

A limitation of this study is that it was not a longitudinal study following up the eGFR of each individual for an extended period of time, but a cross-sectional study. Further, diagnosis of CKD was based on a single test, which may have misestimated renal function. However, the large number of data collected from a nationwide screening test seems adequate to prove its validity. Measuring the urinary protein excretion was analyzed by urine dipstick alone that was a quantitation method which cannot detect microalbuminuria.

Chronic kidney disease is fully established as an independent and powerful risk for CV events. In this regard, early detection of CKD is thought to be important, and this study highlights the fact that this population-based screening test is an ideal opportunity to detect CKD simultaneously with evaluation of other metabolic risk factors. However, there is concern that the current specific health check for CKD will be inadequate without serum creatinine measurement. Hence, we strongly recommend that both urinalysis and serum creatinine measurement should be a part of the nationwide health examination program.

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Conflict of interest All authors declare that they have no competing interests.

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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) $\times$ 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

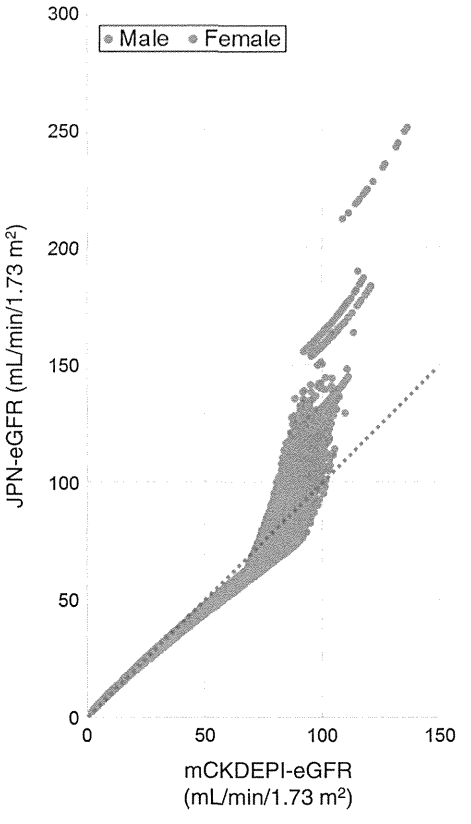
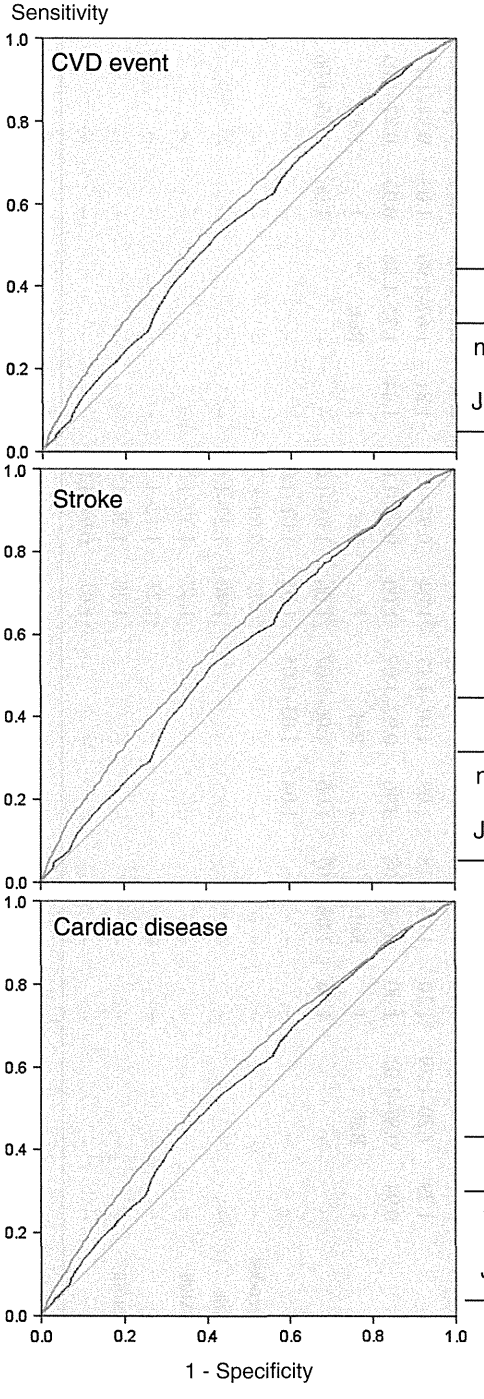


Fig. 1 Relationships between JPN-eGFR and mCKDEPI-eGFR. Points *along* the *diagonal dotted line*, accordance between JPN-eGFR and mCKDEPI-eGFR; points *below* the *diagonal dotted line*, underestimation by JPN-eGFR; points *over* the *diagonal dotted line*, overestimation by JPN-eGFR

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).



	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

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.

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

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