Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: Accuracy and Use for Population Estimates

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Introduction: We previously reported a modification to the Modification of Diet in Renal Disease (MDRD) Study equation for use in Japan. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed a new equation that is more accurate and yields a lower CKD prevalence estimate in the United States than the MDRD Study equation. We modified the CKD-EPI equation for use in Japan, compared its accuracy with the Japanese modification of the MDRD Study equation, and compared the prevalence of CKD in Japan using both equations.

Design: A diagnostic test study comparing the Japanese coefficient–modified CKD-EPI equation and Japanese coefficient–modified MDRD Study equation and a cross-sectional study comparing distribution of estimated glomerular filtration rate and prevalence of CKD in participants in a Japanese annual health check program.

Setting & Participants: 763 Japanese patients (413 for development and 350 for validation) were included. Prevalence estimates were based on 574,024 participants from the annual health check program.

Index Test: Japanese modification of the MDRD Study and CKD-EPI equations.

Reference Test: Inulin clearance.

Results: The Japanese coefficient of the modified CKD-EPI equation was 0.813 (95% CI, 0.794-0.833). In the validation data set, the modified CKD-EPI equation performed better than the modified MDRD Study equation. Bias (measured GFR [mGFR] − eGFR) was 0.4 ± 17.8 (SD) versus 1.3 ± 19.8 mL/min/1.73 m^2 overall, respectively ($P = 0.02$); 7.3 ± 20.6 versus 7.8 ± 22.2 mL/min/1.73 m^2 for participants with mGFR ≥60 mL/min/1.73 m^2, respectively ($P < 0.001$); and −4.4 ± 13.8 versus −3.3 ± 15.6 mL/min/1.73 m^2 for participants with mGFR <60 mL/min/1.73 m^2, respectively ($P = 0.5$). The modified CKD-EPI equation yields a lower estimated prevalence of CKD than the modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%).

Limitation: Most study participants had CKD. The study population contained a limited number of participants with mGFR ≥90 mL/min/1.73 m^2.

Conclusion: The Japanese coefficient–modified CKD-EPI equation is more accurate than the Japanese coefficient–modified MDRD Study equation and leads to a lower estimated prevalence of CKD in Japan.

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INDEX WORDS: Modification of Diet in Renal Disease (MDRD) Study equation; Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; CKD prevalence; Japanese coefficient.

Accurate estimation of glomerular filtration rate (GFR) is crucial for the detection of chronic kidney disease (CKD).[1] Calculating GFR by measuring the clearance of exogenous markers, such as inulin, is accurate, but the procedure is time consuming. The use of GFR-estimating equations has been recommended in clinical practice.[1] The Modification of Diet in Renal Disease (MDRD) Study equation[2] is the most commonly used worldwide. The equation was developed in mostly whites and African Americans. We previously reported that estimated GFR (eGFR) obtained using the isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation was significantly higher than measured GFR (mGFR) in Japanese patients.[3] Therefore, we calculated a correction coefficient of 0.808 for the MDRD

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Study equation and developed a new Japanese equation for GFR estimation.[3]

Recently, Levey et al[4] developed a more accurate new GFR estimation equation, the CKD Epidemiology Collaboration (CKD-EPI) equation, based on data from 5,504 participants. The equation yields a lower estimated prevalence of CKD than the MDRD Study equation in the United States. In this study, we explored the accuracy of this new equation in Japanese and estimated CKD prevalence in the general population in Japan using the equation. Because the CKD-EPI equation was developed mostly in whites and African Americans, we calculated a correction coefficient for the use of the CKD-EPI equation in Japanese and performed: (1) a diagnostic test study comparing the Japanese coefficient–modified CKD-EPI equation with the Japanese coefficient–modified MDRD Study equation, and (2) cross-sectional study comparing the distribution of eGFR and prevalence of CKD in participants in a Japanese annual health check program.

METHODS

Diagnostic Test Study

Participants

To perform a diagnostic test study to compare the modified CKD-EPI and modified MDRD Study equations, we used same data sets from which the Japanese coefficient of the MDRD Study equation was developed and validated. Details of participants were reported previously.[3] Briefly, 763 Japanese patients in 80 medical centers were included. They were divided into a development data set (413 participants) and a validation data set (350 participants). GFR was measured using inulin renal clearance. Serum creatinine was measured using an enzymatic method in a single laboratory. The accuracy of creatinine measurement was validated using the calibration panel of the Cleveland Clinic.[3]

Calculation of a Coefficient of the CKD-EPI Equation

A coefficient for the CKD-EPI equation appropriate for use in Japanese was calculated in the development data set in the same way the Japanese MDRD Study equation coefficient was obtained previously.[3] The coefficient was determined by minimizing the sum of squared errors between eGFR and inulin renal clearance.

Performance of the Coefficient-Modified Equation

Performance of the Japanese coefficient–modified equations was studied using the development and validation data sets. Bias, root mean square error, and accuracy within 30% (P_{30}) were analyzed.

Cross-sectional Study

Population

We previously reported the prevalence of CKD based on data from the Japanese annual health check program in 2005 using an equation for Japanese.[5] In the present study, to compare eGFR distribution and CKD prevalence in participants in this health check program, we used the same population from the Japanese annual health check program, which consisted of 574,024 participants older than 20 years. Details of the data have been reported previously.[5] We calculated CKD prevalence using the Japanese coefficient–modified MDRD Study equation and Japanese coefficient–modified CKD-EPI equation using a Japanese adult population obtained from a census in 2005.

Statistical Analysis

Data are expressed as mean ± standard deviation. Differences in clinical characteristics between the development and validation

Table 1. Clinical Characteristics of the Study Population for the Diagnostic Test Study

Characteristic	Development Data Set	Validation Data Set	*P*
No. of participants	413	350	
Men	262 (63)	203 (58)	0.1
Age (y)	51.4 ± 16.5	53.9 ± 17.5	0.04
Height (cm)	163.2 ± 8.8	161.6 ± 9.5	0.01
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7	0.5
BSA (m^2)	1.65 ± 0.19	1.63 ± 0.19	0.2
BMI (kg/m^2)	22.8 ± 3.8	23.0 ± 3.8	0.4
Diabetes	82 (20)	77 (22)	0.5
Hypertension	235 (57)	202 (58)	0.8
Transplant	9 (2)	2 (1)	0.06
Kidney donor	1 (0)	10 (3)	0.003
Creatinine (mg/dL)	1.52 ± 1.59	1.88 ± 1.70	0.6
mGFR (mL/min/1.73 m^2)	59.1 ± 35.4	45 ± 25	0.5

Note: Data are expressed as mean ± standard deviation or number (percentage). Conversion factor for GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: BMI, body mass index; BSA, body surface area; mGFR, measured glomerular filtration rate.

Table 2. Performance of GFR-Estimating Equations in the Validation Data Set

Variable and Equation	All (N = 350)	mGFR <60 mL/min/1.73 m^2 (n = 206)	mGFR ≥60 mL/min/1.73 m^2 (n = 144)
Bias (mL/min/1.73 m^2)			
Japanese coefficient–modified MDRD Study equation	1.3 ± 19.4	−3.3 ± 15.6	7.8 ± 22.2
Japanese coefficient–modified CKD-EPI Study equation	0.4 ± 17.8	−4.4 ± 13.8	7.3 ± 20.6
P	0.02	0.5	<0.001
P_{30} (%)			
Japanese coefficient–modified MDRD Study equation	73 (69-78)	67 (61-74)	82 (75-87)
Japanese coefficient–modified CKD-EPI Study equation	75 (70-79)	65 (58-71)	88 (82-92)
P	0.7	0.6	0.1
Root mean square error (mL/min/1.73 m^2)			
Japanese coefficient–modified MDRD Study equation	19.4	15.9	23.5
Japanese coefficient–modified CKD-EPI Study equation	17.8	14.4	21.8

Note: Bias is mGFR minus eGFR and is reported as mean ± standard deviation; P_{30} refers to percentage of GFR estimates that are within 30% of mGFR, with 95% confidence intervals given in parentheses. The Japanese coefficient–modified MDRD Study equation is the isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation multiplied by a Japanese coefficient of 0.808: eGFR = 0.808 × 175 × $SCr^{-1.154}$ × $Age^{-0.203}$ × 0.742 (if female). The Japanese coefficient–modified CKD-EPI Study equation is multiplied by a Japanese coefficient of 0.813; eGFR = 0.813 × 141 × $\min(SCr/\kappa, 1)^{\alpha}$ × $\max(SCr/\kappa, 1)^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

data sets were evaluated using χ^2 test and independent *t* test. Differences in the bias (absolute value) of eGFRs were evaluated using paired *t* test. Differences in accuracy (ie, P_{30}) were evaluated using χ^2 tests. Differences in the prevalence of specific GFR groups were evaluated using χ^2 test. A difference with $P < 0.05$ is considered statistically significant. Statview, version 4.02, and JMP 8.01 (both from SAS Institute, www.sas.com) were used for statistical analysis. JMP 8.01 was used for receiver operating characteristic curve analysis.

RESULTS

Modifying the CKD-EPI Equation for a Japanese Population

The coefficient to modify the CKD-EPI equation for Japanese, calculated from the development data set of 413 participants (for whom clinical characteristics are listed in Table 1), was found to be 0.813 (95% confidence interval, 0.794-0.833).

Diagnostic Test Study

We used a diagnostic test design to compare the Japanese coefficient–modified CKD-EPI and MDRD Study equations, which are listed in Table 2.

Comparison of Performance of Coefficient-Modified Equations

We analyzed all participants and subgroups in the validation data set, stratified by mGFR (<60 vs ≥60 mL/min/1.73 m^2; Table 2). As in the development data set, root mean square error was lower for the Japanese coefficient–modified CKD-EPI equation than the Japanese coefficient–modified MDRD Study equation in all participants and both subgroups stratified by mGFR. The coefficient-modified CKD-EPI equation had significantly less bias than the coefficient-modified MDRD Study equation in all participants (P = 0.02). This difference was due to improved bias in participants with GFR ≥60 mL/min/1.73 m^2 ($P < 0.001$); there was no significant difference in bias in participants with GFR <60 mL/min/1.73 m^2. Accuracy was not significantly different between equations.

Table 3 lists the performance of the equations in a validation data set (see Table 1 for details of participants in this data set) stratified by clinical characteristics. Compared with the coefficient-modified MDRD Study equation, the coefficient-modified CKD-EPI equation showed significantly lower bias in younger participants (aged

Table 3. Performance of Japanese Coefficient–Modified GFR-Estimating Equations in the Validation Data Set According to Clinical Characteristics

Clinical Characteristics	No. of Participants	Bias		P
		0.808 × MDRD	0.813 × CKD-EPI	
Sex				
Men	203	0.8 ± 15.8	0.4 ± 14.7	0.1
Women	147	1.9 ± 23.4	0.5 ± 21.5	0.1
Age (y)				
19-44	107	3.2 ± 18.7	−0.5 ± 17.1	0.03
45-64	130	1.0 ± 22.5	1.1 ± 20.7	0.5
≥65	113	−0.2 ± 15.9	0.5 ± 14.7	0.1
BMI (kg/m^2)				
<20	71	0.2 ± 26.4	−0.5 ± 25	0.9
20-25	190	−0.6 ± 17.2	−1.2 ± 14.8	0.01
>25	89	6.1 ± 16.2	4.6 ± 16.4	0.2
Diabetes				
Yes	83	−1.5 ± 15.2	−1.1 ± 14.5	0.9
No	264	2.2 ± 20.5	0.9 ± 18.8	0.02
Hypertension				
Yes	209	1.0 ± 15.9	0.1 ± 15.5	0.7
No	141	1.6 ± 23.6	0.9 ± 20.9	0.02
Total	350	1.3 ± 19.4	0.4 ± 17.8	0.02

Note: Unit of bias (mGFR − eGFR) is mL/min/1.73 m^2. Bias was reported as mean ± standard deviation. 0.808 × MDRD refers to the Japanese coefficient–modified isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation. 0.813 × CKD-EPI refers to the Japanese coefficient–modified CKD-EPI Study equation.

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

19-44 years; $P = 0.03$), those with optimal body mass index (20-25 kg/m^2; $P = 0.01$), those without diabetes ($P = 0.02$), and those without hypertension ($P = 0.02$).

Receiver operating characteristic curves to detect GFRs less than 90, 60, and 30 mL/min/1.73 m^2 did not differ between the Japanese coefficient–modified CKD-EPI and MDRD Study

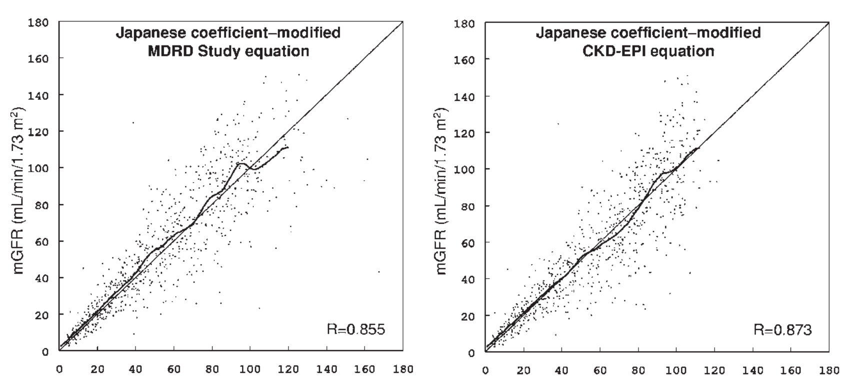

Figure 1. Correlation between estimated (eGFR) and measured glomerular filtration rate (mGFR) in the combined data set. (Left) mGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR versus eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Smoothed lines show the fit of the data.

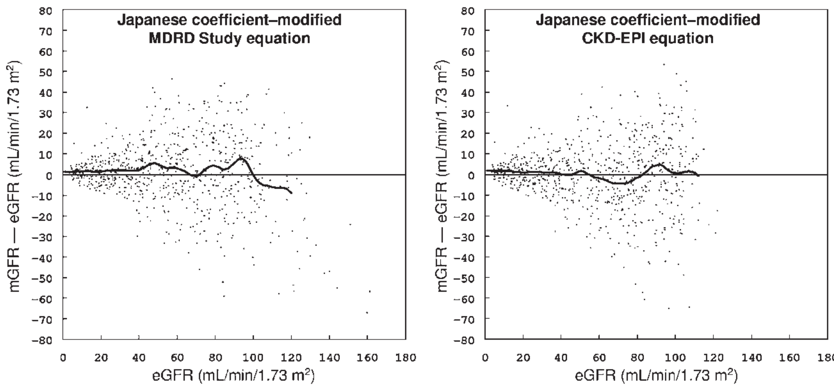

Figure 2. Difference between measured (mGFR) and estimated glomerular filtration rate (eGFR) versus eGFR in the combined data set. (Left) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

equations. Areas under the receiver operating characteristic curves were 0.93, 0.94 and 0.96 for both equations, respectively.

Correlation Between Modified CKD-EPI eGFR and mGFR

The correlation coefficient between mGFR and eGFR calculated using the coefficient-modified CKD-EPI equation in the combined data set was higher than the corresponding value for the coefficient-modified MDRD Study equation (0.872 vs 0.855, respectively; Fig 1). Smoothed lines show the fit of the data. Plots of mGFR minus eGFR versus eGFR were evaluated as shown in Fig 2. Smoothed lines show the fit of the data. The Japanese coefficient–modified CKD-EPI equation showed good performance.

Cross-sectional Study

We also performed a cross-sectional study to compare the eGFR distribution and CKD prevalence obtained using the Japanese coefficient–modified equations in participants in a Japanese annual health check program. Characteristics of the study population are shown in Table 4 and results of the cross-sectional analysis are shown in Fig 3. Percentages of specific GFR ranges (15-29, 30-59, 60-89, 90-119, and ≥120 mL/min/1.73 m^2) indicated that the coefficient-modified CKD-EPI equation increased the prevalence of GFR within the range of 90-119 mL/min/1.73 m^2 from 28.6% to 34.0% and decreased the prevalence of GFR within the range of 30-59 mL/min/1.73 m^2 from 7.5% to 5.2%. The coefficient-modified CKD-EPI equation yields a lower estimated prevalence of CKD than the coefficient-modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%).

Table 4. Characteristics of the Study Population in the Annual Health Check Program

	Men	Women
No. of participants	240,594	333,430
Age (y)	57.8	58.6
Creatinine (mg/dL)	0.86	0.63
Mean eGFR (mL/min/1.73 m^2)		
0.808 × MDRD	78.5	81.9
0.813 × CKD-EPI	77.5	79.6
Median eGFR (mL/min/1.73 m^2)		
0.808 × MDRD	77 (68-88)	79 (70-93)
0.813 × CKD-EPI	78 (70-86)	80 (73-87)
Prevalence (%)		
Diabetes	5.9	3.5
Hypertension	30.3	24.7
Proteinuria	4.7	2.5

Note: Values in parentheses are interquartile ranges. 0.808 × MDRD refers to the Japanese coefficient–modified isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation. 0.813 × CKD-EPI refers to the Japanese coefficient–modified CKD-EPI Study equation.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

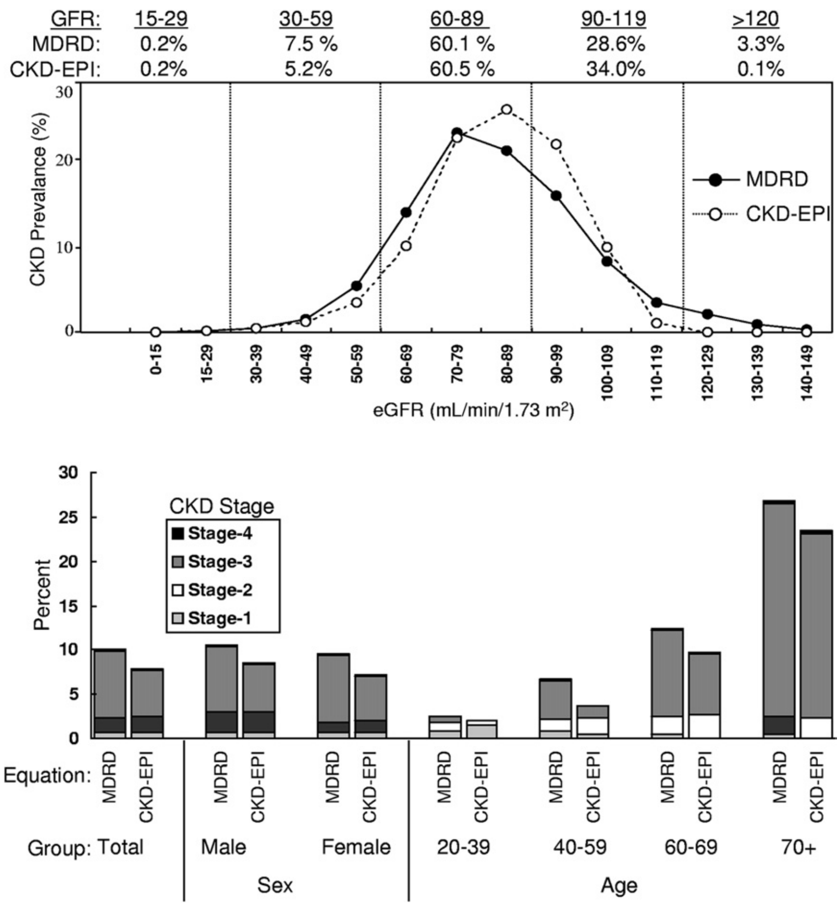

Figure 3. Comparison of distributions of estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) prevalence. (Top) Distribution in a Japanese general adult population of eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation (solid line) compared with eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (dotted line). Percentages of specific GFR ranges (15-29, 30-59, 60-89, 90-119, and ≥120 mL/min/1.73 m^2) are shown. (Bottom) Estimated prevalence of CKD by sex and age when GFRs are obtained using either the Japanese coefficient–modified MDRD Study or CKD-EPI equation.

DISCUSSION

We previously reported a Japanese coefficient of 0.808 for the MDRD Study equation.[3] In the present study, we obtained the Japanese coefficient of 0.813 (95% confidence interval, 0.794-0.833) for the CKD-EPI equation. The values are similar in both equations. The observation that correction coefficients are less than 1.0 indicates lower serum creatinine levels in Japanese than in whites with equivalent GFRs, probably because of the lower skeletal muscle mass found in Japanese compared with North Americans.[3]

The coefficient-modified CKD-EPI equation had lower bias ($P = 0.02$) than the coefficient-modified MDRD Study equation because of lower bias in participants with mGFR ≥60 mL/min/1.73 m^2. As reported by Levey et al,[4] the improvement in bias likely depends on the use of a 2-slope linear spline with sex-specific knots to model the relationship between log(GFR) and log(serum creatinine), which allows for a steeper slope of GFR versus serum creatinine at creatinine levels above the knots and a less steep slope at creatinine levels below the knots.[4] Differences in bias between subgroups defined by age, body mass index, diabetes, and hypertension also were noted, but larger studies are needed to confirm these results.

The eGFR distribution and CKD prevalence indicated that the Japanese coefficient–modified CKD-EPI equation increased the prevalence of GFR within the range of 90-119 mL/min/1.73 m^2 even as it decreased the prevalence of GFR within the range of 30-59 mL/min/1.73 m^2. The coefficient-modified CKD-EPI equation yields a lower estimated prevalence of CKD than the coefficient-modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%). This result may be explainable by the characteristics of the coefficient-modified CKD-EPI equation that increased eGFR in participants stratified by mGFR >60 or <60 mL/min/1.73 m^2 compared with the coefficient-modified MDRD Study equation. Levey et al[4] reported that the CKD-EPI equation decreased the prevalence estimate for CKD in the United States from 13.1% to 11.5% compared with the MDRD Study equation. These results are consistent with our results.

Limitations of the present study are as follows. (1) We obtained and validated the Japanese coefficient for the CKD-EPI equation from 763 participants. Most study participants had CKD. The study population contained a limited number of participants with mGFR $\geq$90 mL/min/1.73 m^2, and performance of the coefficient-modified equation was not studied sufficiently in the healthy population. (2) We compared performances between coefficient-modified equations, but the best performance of the equations may not be shown by a simple coefficient correction. The CKD-EPI equation uses log(serum creatinine) with 2-slope linear spline with sex-specific knots at 0.7 mg/dL in women and 0.9 mg/dL in men. That the coefficient was found to be less than 1.0 indicates lower serum creatinine levels in Japanese than in whites with equivalent GFRs. It is unknown whether creatinine values for sex-specific knots are suitable for Japanese.

In conclusion, the CKD-EPI equation modified with the Japanese coefficient performed better than the Japanese coefficient–modified MDRD Study equation. The Japanese coefficient–modified CKD-EPI equation yields a lower estimated prevalence of CKD than the Japanese coefficient–modified MDRD Study equation, primarily because of a lower estimated prevalence of CKD stage 3.

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