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

Variable and Equation	All (N = 350)	mGFR <60 mL/min/1.73 m² (n = 206)	mGFR ≥60 mL/min/1.73 m² (n = 144)
Bias (mL/min/1.73 m²)			
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 m²)			
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: $eGFR = 0.808 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female). The Japanese coefficient–modified CKD-EPI Study equation is multiplied by a Japanese coefficient of 0.813; $eGFR = 0.813 \times 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [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 m²; 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 m² ($P < 0.001$); there was no significant difference in bias in participants with GFR <60 mL/min/1.73 m². 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

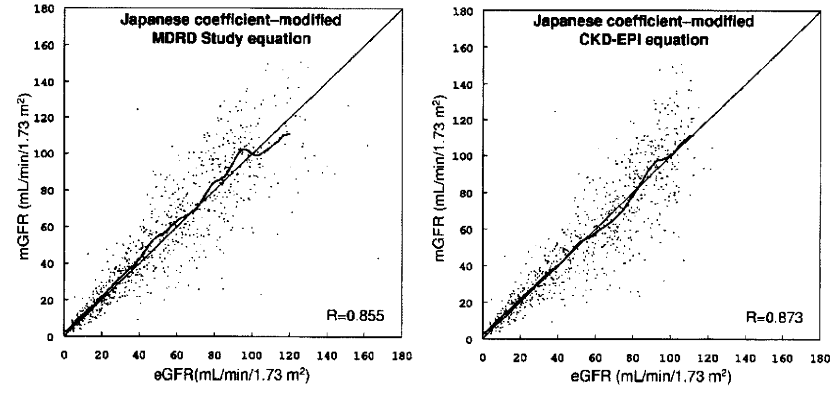

Figure 1. Correlation between estimated (eGFR) and measured glomerular filtration rate (mGFR) in the combined data set. (Left) mGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR versus eGFR obtained using the Japanese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

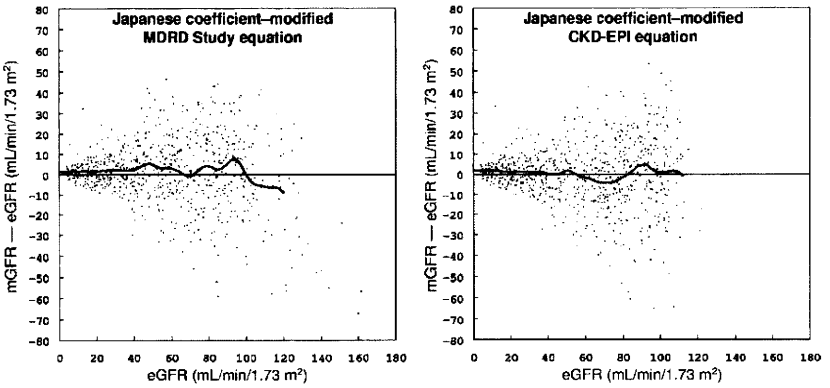

Figure 2. Difference between measured (mGFR) and estimated glomerular filtration rate (eGFR) versus eGFR in the combined data set. (Left) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR minus eGFR versus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

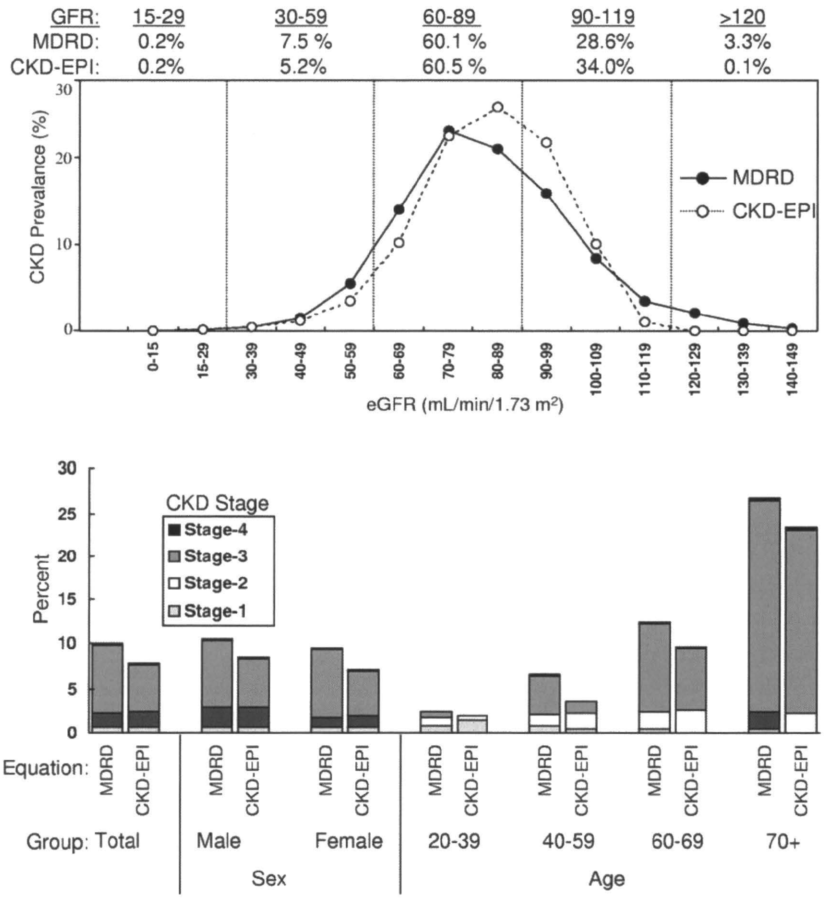

Figure 3. Comparison of distributions of estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) prevalence. (Top) Distribution in a Japanese general adult population of eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation (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 ≥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.

ACKNOWLEDGEMENTS

Support: This study was supported by a grant from the Japanese Society of Nephrology.

Financial Disclosure: The authors declare that they have no relevant financial interests.

REFERENCES

1. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function. *N Engl J Med.* 2006;354:2473-2483.

2. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-254.

3. Matsuo S, Imai E, Horio M, et al. Revised equations for estimating glomerular filtration rate (GFR) from serum creatinine in Japan. *Am J Kidney Dis.* 2009;53:982-992.

4. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.

5. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol.* 2009;13:621-630.