Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities

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An equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) provides more accurate estimates of the glomerular filtration rate (eGFR) than that from the modification of diet in renal disease (MDRD) Study, although both include a two-level variable for race (Black and White and other). Since creatinine generation differs among ethnic groups, it is possible that a multilevel ethnic variable would allow more accurate estimates across all groups. To evaluate this, we developed an equation to calculate eGFR that includes a four-level race variable (Black, Asian, Native American and Hispanic, and White and other) using a database of 8254 patients pooled from 10 studies. This equation was then validated in 4014 patients using 17 additional studies from the United States and Europe (validation database), and in 1022 patients from China (675), Japan (248), and South Africa (99). Coefficients for the Black, Asian, and Native American and Hispanic groups resulted in 15, 5, and 1% higher levels of eGFR, respectively, compared with the White and other group. In the validation database, the two-level race equation had minimal bias in Black, Native American and Hispanic, and White and other cohorts. The four-level ethnicity equation significantly improved bias in Asians of the validation data set and in Chinese. Both equations had a large bias in Japanese and South African patients. Thus, heterogeneity in performance among the ethnic and geographic groups precludes use of the four-level race equation. The CKD-EPI two-level race equation can be used in the United States and Europe across a wide range of ethnicity.

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Chronic kidney disease (CKD) is a worldwide health problem, affecting all racial and ethnic groups that have been investigated.[1] In the United States, chronic kidney failure disproportionately burdens racial and ethnic minorities. Incidence rates for chronic kidney failure treated by dialysis and transplantation are 3.6 and 1.4 times higher in Blacks and Asians, respectively, compared with Whites, and 1.5 times higher in Hispanics compared with non-Hispanics.[2] Outside of the United States, Taiwan and Japan have the highest prevalence rates of treated kidney failure.[2,3] Data on the prevalence, etiology, and outcomes of earlier stages of kidney disease in these groups are likely to be inaccurate due, at least in part, to the lack of accurate glomerular filtration rate (GFR) estimates.

The Modification of Diet in Renal Disease (MDRD) Study equation utilizes a two-level variable for race (Black vs White and other). The coefficient for Blacks leads to higher values for estimated GFR (eGFR) compared with Whites for the same level of creatinine, because of differences between Blacks vs Whites in factors other than GFR that affect the serum level of creatinine (non-GFR determinants), especially higher creatinine generation from muscle and diet.[4,5] It is widely believed that there are also differences in creatinine generation in other racial, ethnic, and geographic groups, which are not captured by current equations.[6,7] Consistent with this assumption, introduction of coefficients for use in the MDRD Study equation in China and Japan improves its performance in these populations.[8,9]

We recently reported a new equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,

based on creatinine, age, sex, and a two-level variable for race, which is more accurate than the MDRD Study equation, particularly at higher levels of GFR and in populations without CKD,[5,10,11] and provides better risk prediction.[12,13] We hypothesized that the performance of the CKD-EPI equation could be further improved in Asians and in Native Americans and Hispanics by utilizing coefficients specific for these groups. In this study, we report on the development of an GFR-estimating equation that includes a four-level race variable in a diverse population from the United States and Europe, and its evaluation compared with the CKD-EPI (two-level race) equation in separate populations from the United States and Europe as well as in populations from other countries.

RESULTS

The clinical characteristics differed significantly among racial and ethnic groups. In the development data set (Table 1a), mean measured GFR ranged from 55 to 73 ml/min per 1.73 m^2 among racial/ethnic groups, and was lower in Blacks and Asians and higher in Native Americans and Hispanics compared with Whites and others. Blacks were older, more likely to be female, and had a larger body size compared with the other groups. In the CKD-EPI external validation data set, measured GFR ranged from 53 to 105 ml/min per 1.73 m^2 and was lower in Asians and higher in Native Americans and Hispanics compared with Whites and others (Table 1b). In the non-US and Europe validation data set, measured GFR ranged from 53 and 60 ml/min per 1.73 m^2, and body mass index (BMI) was lower than in the CKD-EPI development and validation data sets (Table 1b). Supplementary Appendix A and B describe the distribution of race and ethnic groups for each study.

Table 2 shows the coefficients for each race and ethnic groups refit in the CKD-EPI combined development and internal validation data set. The coefficients for Black and Asian are significantly larger than the reference group (White and other), resulting in higher eGFR for the same level of creatinine. The coefficient for Native American and Hispanic was smaller and not statistically significant, but was retained in the model. For both the two- and four-level race equations, eGFR is 15% higher for Blacks than for Whites or others. In the four-level race equation, eGFR is 5% higher in Asians but only 1% higher in Native Americans and Hispanics compared with Whites or others. Table 3 shows the two- and four-level race equations developed using the coefficients from the combined development and internal validation data sets, expressed for different combinations of race, sex, and serum creatinine.

Tables 4 and 5 show the performance of both models in the two external validation data sets. In the CKD-EPI

Table 1a | Clinical characteristics of the participants in development data sets

Variable	Overall	Race/ethnicity				*P*-values
		White and other	Black	Asian	Native American and Hispanic	
N	8254	5216	2585	100	353	
Age, mean (s.d.) in years	47 (15)	44 (15)	53 (12)	49 (15)	43 (12)	<0.001
Age categories, N *(%)*						<0.001
<40 years	3076 (37)	2464 (47)	422 (16)	36 (36)	154 (44)	
40–65 years	4154 (50)	2149 (41)	1766 (68)	50 (50)	189 (54)	
>65 years	1024 (12)	603 (11)	397 (16)	14 (11)	10 (3)	
Sex, N *(%)*						<0.001
Female	3606 (44)	2353 (45)	1019 (39)	41 (41)	193 (55)	
Male	4648 (56)	2863 (55)	1566 (61)	59 (59)	160 (45)	
Diabetes, N *(%)*						<0.001
Yes	2406 (29)	1885 (36)	280 (11)	33 (33)	208 (59)	
No	5848 (71)	3331 (64)	2305 (89)	67 (67)	145 (41)	
Transplant, N *(%)*						<0.001
Yes	360 (4)	330 (6)	24 (1)	5 (5)	1 (0.3)	
No	7894 (96)	4886 (94)	2561 (99)	95 (95)	352 (100)	
GFR mean (s.d.), ml/min per 1.73 m^2	68 (40)	73 (43)	55 (27)	57 (31)	90 (45)	<0.001
Serum creatinine, mean (s.d.), mg/dl	1.66 (1.16)	1.58 (1.19)	1.87 (1.09)	1.73 (0.91)	1.23 (1.02)	<0.001
Body surface area, mean (s.d.), m^2	1.91 (0.24)	1.90 (0.23)	2.00 (0.25)	1.77 (0.21)	1.91 (0.25)	<0.001
BMI, mean (s.d.), kg/m^2	28 (6)	27 (5)	31 (7)	26 (5)	31 (9)	<0.001
BMI categories, N *(%)*						<0.001
<20 kg/m^2	287 (3)	218 (4)	60 (2)	4 (4)	5 (1)	
20–25 kg/m^2	2447 (30)	1896 (36)	446 (17)	40 (40)	65 (18)	
26–30 kg/m^2	2922 (35)	1930 (37)	857 (33)	37 (37)	98 (28)	
>30 kg/m^2	2598 (31)	1172 (23)	1222 (47)	19 (19)	185 (52)	

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

Table 1b | Clinical characteristics of the participants in validation data sets

	CKD-EPI (US and Europe)				Non-US and Europe			
Variable	White and other	Black	Asian	Native American and Hispanic	Asian	Asian	Black	*P*-values
N	3378	384	67	185	248	675	99	
Age, mean (s.d.) in years	49 (15)	50 (15)	51 (15)	45 (12)	50 (18)	50 (15)	47 (17)	0.001
Age categories, N *(%)*								<0.001
<40 years	978 (29)	112 (29)	19 (28)	68 (37)	95 (38)	207 (31)	42 (43)	
40–65 years	1898 (56)	224 (58)	35 (52)	107 (58)	92 (37)	333 (49)	42 (43)	
>65 years	502 (15)	48 (13)	13 (19)	10 (5)	61 (25)	135 (20)	15 (15)	
Sex, N *(%)*								0.001
Female	1513 (45)	184 (48)	32 (48)	130 (70)	112 (45)	328 (49)	49 (49)	
Male	1865 (55)	200 (52)	35 (52)	55 (30)	136 (55)	347 (51)	50 (50)	
Diabetes, N *(%)*								<0.001
Yes	975 (29)	95 (25)	14 (21)	119 (64)	35(14)	21(3)	6 (6)	
No	2403 (71)	289 (75)	53 (79)	66 (67)	213 (86)	654 (97)	93 (94)	
Transplant, N *(%)*								<0.001
Yes	1072 (32)	52 (14)	7 (10)	3 (2)	0	0	0	
No	2306 (68)	332 (86)	60 (90)	182 (98)	0	0	0	
GFR, mean (s.d.), ml/min per 1.73 m^2	69 (36)	62 (34)	53 (31)	105 (47)	53 (31)	55 (35)	61 (32)	<0.001
Serum creatinine, mean (s.d.), mg/dl	1.48 (0.94)	1.80 (0.29)	1.99 (1.41)	0.90 (0.73)	1.24 (0.56)	2.25 (2.18)	1.77 (1.71)	<0.001
Body surface area, mean (s.d.), m^2	1.90 (0.23)	1.95 (0.23)	1.70 (0.20)	1.98 (0.29)	1.62 (0.18)	1.71 (0.18)	1.77 (0.17)	<0.001
BMI, mean (s.d.), kg/m^2	27 (5)	30 (7)	24 (4)	34 (8)	23 (4)	24 (4)	26 (5)	<0.001
BMI categories, N *(%)*								<0.001
<20 kg/m^2	225 (7)	17 (4)	5 (7)	2 (1)	55 (22)	107 (16)	15 (15)	
20–25 kg/m^2	1223 (36)	84 (22)	34 (51)	22 (12)	137 (55)	354 (52)	44 (44)	
25–30 kg/m^2	1178 (35)	115 (30)	24 (36)	49 (26)	45(18)	181 (27)	20 (20)	
>30 kg/m^2	752 (22)	168 (44)	4 (6)	112 (61)	11 (4)	33 (5)	20 (20)	

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per m^2, multiply by 0.0167.

Table 2 | Race/ethnicity coefficients (95% confidence intervals)[a]

Equation	White and other	Black	Asian	Native American and Hispanic
Two-level race	1.0 (reference group)	1.157 (1.144, 1.170)	1.0	1.0
Four-level race	1.0 (reference group)	1.160 (1.146, 1.173)	1.052 (1.004, 1.102)	1.010 (0.984, 1.037)

Coefficients are adjusted for creatinine, sex, and age.
[a]Corresponds to percent increase in estimated glomerular filtration rate (eGFR) for the same level of serum creatinine.

validation data set, performance of the equation with the two- and four-level race terms was similar in both the Black and White and other groups (Table 4). In Asians, there was a significant improvement in bias and root mean square error with the four-level compared with the two-level equation (0.8 (−2.2, 2.6) ml/min per 1.73 m^2 vs 2.1 (0.3, 4.4) ml/min per 1.73 m^2 ($P<0.005$) and 0.293 (0.178, 0.424) vs 0.302 (0.188, 0.436), $P=0.003$)), but there was a small higher interquartile range with the four-level equations (12.3 (9.0, 16.1) vs 10.5 (8.0, 14.6) ml/min per 1.73 m^2 ($P=0.001$)) and no significant difference in percentage of estimates within 30% of the measured GFR (P_{30}). There were no significant differences in performance between the two equations for Native Americans and Hispanics. In the Chinese data set (Table 5, column 1), as in the Asians in the CKD-EPI validation data set, there was an improvement in performance with the four-level race equation compared with the two-level race equation in bias (1.3 (0.6, 2.2) vs 2.7 (1.9, 3.7) ml/min per 1.73 m^2 ($P<0.0001$)), interquartile range (15.5 (14.4, 17.4) vs 16.7 (15.0, 18.5) ml/min per 1.73 m^2, $P<0.0001$), root mean square error (0.318 (0.295, 0.343) vs 0.325 (0.302, 0.348) ml/min per 1.73 m^2, $P=0.002$)), as well as in P_{30} (72.1 (68.7, 75.7) vs 73.2 (69.9, 76.6), $P=0.01$). In the Japanese data set (Table 5, column 2), performance for the two-level race equation was substantially worse than for the Asians in the CKD-EPI validation data set and not improved with the use of the four-level race equation. In the South African data set (Table 5, column 3), performance of both the two- and four-level race equations was substantially worse than for the Blacks in the CKD-EPI validation data set. Performance was better for the South African data set when the Black coefficient was not used (bias of −12.4 (−18.3, −7.6) with the use of the Black term vs −4.9 (−7.0, −0.5) ml/min per 1.73 m^2 without the use of the Black term).

Figure 1 summarizes the comparison of bias between the two- and four-level race equation by level of eGFR within

Table 3 | CKD-EPI equation for estimating GFR on the natural scale expressed for race, sex, and range of serum creatinine

Race	Sex	Serum creatinine	eGFR (ml/min per 1.73 m^2)
Two-level race equation			
Black	Female	⩽0.7 mg/dl	$166 \times (0.993)^{Age} \times (Scr/0.7)^{-0.329}$
Black	Female	>0.7 mg/dl	$166 \times (0.993)^{Age} \times (Scr/0.7)^{-1.209}$
Black	Male	⩽0.9 mg/dl	$163 \times (0.993)^{Age} \times (Scr/0.9)^{-0.411}$
Black	Male	>0.9 mg/dl	$163 \times (0.993)^{Age} \times (Scr/0.9)^{-1.209}$
White and other	Female	⩽0.7 mg/dl	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-0.329}$
White and other	Female	>0.7 mg/dl	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-1.209}$
White and other	Male	⩽0.9 mg/dl	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-0.411}$
White and other	Male	>0.9 mg/dl	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-1.209}$
Four-level race equation			
Black	Female	⩽0.7	$167 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Black	Female	>0.7	$167 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Black	Male	⩽0.9	$164 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Black	Male	>0.9	$164 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
Asian	Female	⩽0.7	$151 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Asian	Female	>0.7	$151 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Asian	Male	⩽0.9	$149 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Asian	Male	>0.9	$149 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
Hispanic and Native American	Female	⩽0.7	$145 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Hispanic and Native American	Female	>0.7	$145 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Hispanic and Native American	Male	⩽0.9	$143 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Hispanic and Native American	Male	>0.9	$143 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
White and other	Female	⩽0.7	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
White and other	Female	>0.7	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
White and other	Male	⩽0.9	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
White and other	Male	>0.9	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167. To convert serum creatinine from mg/dl to μmol/l, multiply by 88.4. CKD-EPI equation coefficients derived from pooled development and internal validation data sets.
CKD-EPI two-level race equation expressed as a single equation: $GFR=141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [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.
The four-level equation expressed as a single equation: $GFR=141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.210} \times 0.993^{Age} \times 0.993$ [if female] $\times 1.16$ [if Black] $\times 1.05$ [if Asian] $\times 1.01$ [if Hispanic and Native American] where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.328 for females and −0.412 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ.
In the table, the multiplication factors for race and sex are incorporated into the intercept, resulting in different intercepts for age and sex combinations.

Table 4 | Performance in CKD-EPI external validation data set (US and Europe) by race/ethnicity

Measures	Equation	Total	White and other	Black	Asian	Native American and Hispanic
N		4014	3378	384	67	185
Bias, ml/min per 1.73 m^2	Two-level	2.5 (2.1, 2.9)	2.8 (2.4, 3.2)	−0.8 (−2.0, 0.6)	2.1 (0.3, 4.4)	2.3 (−2.1, 5.1)
	Four-level	2.5 (2.1, 2.9)	2.9 (2.5, 3.4)	−0.9 (−2.0, 0.6)	0.8 (−2.2, 2.6)	1.6 (−3.0, 4.2)
IQR, ml/min per 1.73 m^2	Two-level	17.0 (16.1, 17.6)	16.8 (16.0, 17.6)	15.1 (12.6, 17.6)	10.5 (8.0, 14.6)	25.6 (20.8, 32.0)
	Four-level	17.0 (16.2, 17.6)	16.8 (16.0, 17.6)	15.1 (12.6, 17.6)	12.3 (9.0, 16.1)	26.1 (20.8, 32.2)
P_{30}, %	Two-level	84 (83, 85)	84 (83, 86)	82 (78, 85)	85 (76, 93)	80 (74, 85)
	Four-level	84 (83, 85)	84 (83, 85)	82 (80, 85)	85 (76, 93)	81 (76, 87)
RMSE	Two-level	0.250 (0.242, 0.259)	0.250 (0.240, 0.258)	0.242 (0.221, 0.265)	0.302 (0.188, 0.436)	0.265 (0.223, 0.310)
	Four-level	0.250 (0.242, 0.259)	0.250 (0.240, 0.259)	0.243 (0.221, 0.266)	0.293 (0.178, 0.424)	0.264 (0.222, 0.310)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range, 25–75th percentile; P_{30}, percentage of GFR estimates within 30% of measured GFR; RMSE, root mean square error.
Bias is calculated as measured GFR−estimated GFR.
Numbers in brackets are 95% confidence intervals.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

each racial/ethnic category. In the CKD-EPI validation data set, using either the two- and four-level race equation, bias was less than ∼5 ml/min per 1.73 m^2 except for Blacks with eGFR >90 ml/min per 1.73 m^2, as we have previously reported. In the Asians in the CKD-EPI data set and in the Chinese data sets, the bias exceeded 5 ml/min per 1.73 m^2 for some eGFR groups, but improved with the use of the four-level race equation. For both equations, the bias varied substantially throughout the eGFR range in the Japanese and South African data sets.

DISCUSSION

Differences across race and ethnic groups in relationships between serum creatinine and measured GFR primarily

Table 5 | Performance in non-US and Europe external validation data set by country and race/ethnicity

Measures	Equation	China (Asian)	Japan (Asian)	South Africa (Black)
N		675	248	99
Bias, ml/min per 1.73 m^2	Two-level	2.7 (1.9, 3.7)	−17.8 (−20.1, −14.7)	−12.4 (−18.3, −7.6)
	Four-level	1.3 (0.6, 2.2)	−21.4 (−23.3, −18.2)	−12.5 (−18.3, −7.6)
IQR, ml/min per 1.73 m^2	Two-level	16.7 (15.0, 18.5)	21.0 (18.5, 23.9)	28.0 (20.8, 33.3)
	Four-level	15.5 (14.4, 17.4)	23.5 (20.4, 26.0)	28.0 (20.8, 33.4)
P_{30}, %	Two-level	73.2 (69.9, 76.6)	29.4 (23.8, 35.1)	55.6 (46.5, 64.6)
	Four-level	72.1 (68.7, 75.7)	36.3 (30.6, 42.3)	55.6 (46.5, 64.6)
RMSE	Two-level	0.325 (0.302, 0.348)	0.469 (0.424, 0.515)	0.326 (0.292, 0.361)
	Four-level	0.318 (0.295, 0.343)	0.507 (0.463, 0.553)	0.327 (0.292, 0.362)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range, 25–75th percentile; P_{30}, percentage of GFR estimates within 30% of measured GFR; RMSE, root mean square error.
Bias is calculated as measured GFR−estimated GFR.
Numbers in brackets are 95% confidence intervals.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

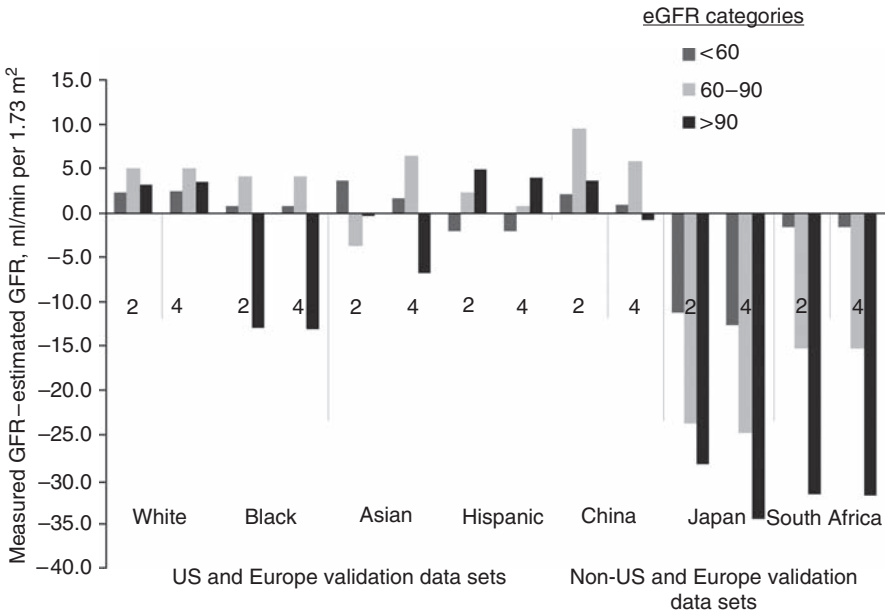

Figure 1 | Performance by level of estimated glomerular filtration rate (eGFR): Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) validation data set.

reflect variation in creatinine generation because of muscle mass or diet. The definition of the race coefficient as Black vs White and other in the MDRD Study does not account for differences in creatinine generation among other racial and ethnic groups. In the process of developing the CKD-EPI equation, we sought to develop an equation that better captures the variation in creatinine generation among racial and ethnic groups other than Blacks and Whites. The results of this process are described in this study. The four-level race equation that was developed is more accurate than the CKD-EPI (two-level race) equation in some, but not all, populations, and both equations demonstrated heterogeneous results within racial and ethnic groups across geographic regions. Given these results, we concluded that the four-level race equation was not sufficiently accurate to be implemented in clinical practice, and had selected the CKD-EPI equation with its two-level race variable.[10] Nevertheless, these results are informative for use of the two-level race CKD-EPI equation in these groups, and also suggest future research directions to derive generalizable racial and ethnic coefficients for GFR-estimating equations based on serum creatinine.

The coefficient for Blacks in the two- and four-level race term yielded a 15% higher eGFR for Blacks than for Whites at a given serum creatinine level, which is consistent with physiological data showing greater skeletal muscle mass in Blacks than otherwise equivalently matched White subjects.[14,15] Similarly, African Black athletes also have greater lean body mass compared with Whites.[16] Using either equation, the eGFR for Blacks in the CKD-EPI validation data set accurately estimated measured GFR. In contrast, these equations led to an overestimation of measured GFR by 12 ml/min per 1.73 m^2 in the South African data. This indicates a different relationship between serum creatinine and GFR for Black South Africans vs US and European Blacks, as shown previously for the MDRD Study equation

using these data[17] as well as in a separate population in Ghana.[18] This difference may be because of lower muscle mass in African Blacks compared with African Americans, potentially secondary to poorer diet or overall health, related to HIV infection or other chronic diseases. Indeed, the mean BMI in the Ghanaian and South African populations was lower than in the Blacks in the CKD-EPI validation data set. In a previous publication, we showed that the CKD-EPI equation overestimates measured GFR in people with low BMI.[5] Our data from South Africa, as well as the data from Ghana, demonstrated that GFR estimates are more accurate if the Black term is omitted. These data raise important questions about the appropriateness of use of the Black coefficient in the CKD-EPI and MDRD Study equations for GFR estimation in Blacks outside the United States and Europe.

The Asian coefficient in the four-level race equation translates into a 5% higher GFR at a given serum creatinine value compared with Whites and others. This is unexpected, given that some previous physiological and epidemiological data suggest that Asians have less muscle mass and lower dietary intake than Whites. For example, in an analysis of people in Pakistan, participants had lower mean creatinine excretion rates than those estimated for age- and gender-matched white individuals.[19] In other studies, Asians have been shown to have a higher percent body fat for the same level of BMI than Whites, suggesting lower levels of muscle mass.[20] The direction of the Asian coefficient is consistent with the modification of the MDRD Study equation for Chinese reported by Ma *et al.*,[8] whose data are included here as part of the non-US and Europe validation data set. Although the 5% higher eGFR was substantially lower than the 23% reported by Ma *et al.*,[8] they are both in contrast to the Japanese coefficient for the modification of the MDRD Study and CKD-EPI equations of 0.808 (ref. 9) and 0.8132 (ref. 21), respectively, which translate to a 19% lower GFR at a given serum creatinine.

The Asian coefficient in the four-level race equation led to more accurate GFR estimates in Asians in the CKD-EPI validation data set as well as in the Chinese data set, but neither the two-level or four-level equation resulted in accurate estimates in the Japanese. Both the Chinese and Japanese cohorts had a greater proportion of people with BMI $<20\,kg/m^2$ than the CKD-EPI development and validation data sets, but were similar to each other, suggesting that the overestimation of measured GFR in the Japanese cohort is not related solely to differences in levels of BMI. Factors other than muscle mass and diet may explain the difference between the Chinese and Japanese coefficients, such as differences in GFR measurement methods and the accuracy of creatinine calibration.[22] The countries of origin for the Asians in the CKD-EPI data sets are not known, and therefore we are not able to ascertain whether the Asian coefficient >1.0 in the four-level race CKD-EPI equation reflects Chinese origin. If future analyses establish that creatinine generation varies among Asian groups, then coefficients for subgroups of Asians in the CKD-EPI and other creatinine-based equations will need to reflect this variation.

The Native American and Hispanic coefficient resulted in a nonstatistically significant 1% higher eGFR for each serum creatinine value compared with Whites and others, and did not improve GFR estimation, suggesting that modification of the CKD-EPI equation may not be necessary for GFR estimation in Native Americans and Hispanics. To our knowledge, this is the only demonstration of the performance of the CKD-EPI equation in these groups. We are not aware of data on muscle mass in Native American and Hispanic populations. Data from NHANES (National Health and Nutrition Examination Survey) show a 5.3% lower mean level of serum creatinine for young healthy Mexican American men compared with Whites,[4] which has been interpreted as lower creatinine generation, but it may also reflect higher GFR. Furthermore, there is likely to be heterogeneity among Hispanic populations based on country of origin. There are only a small number of Native Americans and Hispanics in the CKD-EPI development data set and we do not have information on their country of origin.

The strengths of this study include the large diverse study population, with and without kidney diseases; calibration of the creatinine assays in each study to standardized values; rigorous and sophisticated statistical techniques for equation development; and evaluation of the equations in a separate data set of multiple studies that maximized external generalizability.

Our database had several limitations. First, it included only a small number of non-Blacks and non-Whites in both the CKD-EPI development and validation data sets. Nonetheless, the confidence intervals for the Asian and Native American and Hispanic coefficients were narrow, suggesting little variability among these groups in non-GFR determinants of serum creatinine. Second, the studies used a variety of methods to measure GFR that may have affected model evaluation. Finally, because we did not have information on country of origin for Asians and Hispanics in the CKD-EPI data sets, we grouped all Asians together and also grouped Hispanics and Native Americans, limiting a more nuanced analysis. Finally, the studies differed in their racial distributions, and hence the race effects cannot be entirely disentangled from study differences. Nevertheless, comparison of equations in a separate validation data set overcomes some of the limitations of differences among studies in patient characteristics and methods for measurement of GFR and serum creatinine, and provides support for the generalization of these results.

This study has several implications for clinical practice and research. First, the MDRD Study equation is currently widely used by clinicians, researchers, and public health officials, and is automatically reported by clinical laboratories whenever serum creatinine is ordered in the United States and Canada as well as in several countries in Europe.[23] In these countries, we suggest that the CKD-EPI (two-level race) equation could be used across a wide range of race and ethnicity, with the understanding that there is likely to be variation in accuracy of GFR estimates among and within

racial and ethnic groups based on factors associated with variation in creatinine generation, just as there is variation in accuracy within age and sex groups. Additional studies with a greater number and better characterization of participants from racial and ethnic minorities are necessary to develop more accurate estimates. Second, in geographic regions outside the United States and Europe, differences in creatinine generation within race and ethnic groups may limit the application of any creatinine-based estimating equation, unless the equation was specifically developed in that region. This limitation could possibly apply to immigrants of the same race and ethnicity from one region to another. Before recommending the CKD-EPI equation (or any creatinine-based estimating equation) in clinical practice, studies are required to determine whether modifications to the CKD-EPI (two-level race) equation are necessary.[8,21] Third, emphasis should be placed on investigation of filtration markers that may be less affected than creatinine by race and ethnicity, such as cystatin C and other novel markers.

In summary, racial differences in performance of creatinine-based estimating equation likely reflect geographic and ethnic differences rather than race *per se*. The four-level race equation was more accurate in some populations but not all. The CKD-EPI (two-level race) equation can be used in the United States and Europe across a wide range of race and ethnicity with appropriate attention to factors that affect creatinine generation.

MATERIALS AND METHODS

Sources of data and measurements

CKD-EPI is a research group funded by the NIDDK (National Institute of Diabetes, Digestive and Kidney Disease) to address challenges in the study and care of CKD, including development and validation of improved GFR-estimating equations by pooling data from research studies and clinical populations (hereafter referred to as 'studies').[10] The design and studies have been previously described and are briefly reviewed here.[10] We developed and internally validated the CKD-EPI equation in a database of 10 studies with a total of 8254 participants, divided randomly into separate data sets for development ($n = 5504$) and internal validation ($n = 2750$). The equations were then externally validated in a separate data set of 16 other studies with a total of 3896 participants. In the current report, we use the same data set as previously described for development and internal validation.[10] We also use the same external validation data set as previously described,[10] with the addition of data from Native Americans that were not available in the original report because of absence of creatinine calibration at the time of the original report, but now available to us (herein referred to as 'CKD-EPI validation data set') ($N = 4014$). We also evaluated the equations in three separate studies from outside of United States and Europe; two are from Asia[8,21] (referred to as 'China' and 'Japan') and one is from South Africa[17] (referred to as 'South Africa'), each of which has been previously described (herein referred together as 'non-US and Europe validation data sets').

GFR was measured using urinary clearance of iothalamate in the development data set and iothalamate and other filtration markers in the external validation data sets (Supplementary Appendix A and Appendix B). Serum creatinine values were calibrated to standardized creatinine measurements using the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffmann–La Roche, Basel, Switzerland) at the Cleveland Clinic Research Laboratory (Cleveland, OH).[24,25]

Development and validation

Methods for development and validation have been previously described in detail.[10] In brief, we used least squares linear regression to relate measured GFR to serum creatinine and clinical characteristics available in the development data set. Predictor variables included serum creatinine, age, sex, and race in all equations. GFR was adjusted for body surface area.[26] GFR and serum creatinine were transformed to natural logarithms to reflect their inverse relationship and satisfy the assumption of a normal error distribution to stabilize variance across the range of GFR. We tested multiple forms of creatinine and age, and the final model includes a piecewise linear spline of log serum creatinine with a knot at 0.7 mg/dl in men and 0.9 mg/dl in women, and linear age.

Information on race and ethnicity was provided in the original study data. Race was defined as a two-level variable (Black vs White and other) and as a four-level variable (Black, Asian, Native American and Hispanic vs White and other). The specific origin of Asians was not specified in the original studies. The rationale for grouping Native Americans and Hispanics together is that the majority of non-Black Hispanics in the United States are from Mexico, and they are considered to be of mixed European-Native American descent.[27,28] The rationale for grouping others with White is that many of the other groups are defined as of Caucasian descent (for example, Arabs, non-Black, and non-Native American Hispanics). In some studies, information on ethnicity is not available, and it is possible that some Blacks or Whites were also Hispanics. We developed models in parallel using two- and four-level variables for race. Race groups were defined using a categorical variable with all levels necessarily included in the models using indicator variables. We selected models to bring forth from development into internal and then external validation based on analyses of the two-level race variable, with models using the four-level race variable brought along in parallel. For clarity of presentation, we will refer to the two equations as two- and four-level race equations.

Models created in the development database were first validated in the internal validation database. The development and internal validation data sets were then combined and equations were refit to yield more precise final coefficients to be used in subsequent analyses. Models were then evaluated in the CKD-EPI validation data set and a final two-level race model was selected using a prespecified series of steps, as has been previously described.[10] The four-level race variable model presented here is the parallel model to the final two-level race model, which is known as the CKD-EPI equation.[10] Results are also presented in the non-US and Europe validation data set by study.

Model performance

Performance of the equations was evaluated using similar metrics in both the development and two validation databases. Bias was expressed as the difference (mGFR–eGFR) and percent difference ($100 * [\text{mGFR} - \text{eGFR}]/\text{mGFR}$) between measured GFR (mGFR) and eGFR, with positive values indicating lower eGFR than mGFR (underestimation). Precision was expressed as interquartile range for the differences. Accuracy was expressed as P_{30} that takes into

account higher errors at higher values. We defined the probability of a large error as $1–P_{30}$.

Performance was evaluated within subgroups defined by the following clinical characteristics: age (<40, 40–65, and >65 years), sex, race (Black, Asian, Native American and Hispanic, and White and other), diabetes (yes, no), previous organ transplant (yes, no), and BMI (<20, 20–25, 26–30, and $>30\,kg/m^2$). Level of eGFR was categorized as <60, 60–90, and >90 ml/min per $1.73\,m^2$.

Confidence intervals were calculated by bootstrap methods (2000 bootstraps) for difference, percent difference, and for P_{30}. Significance testing between metrics for each equation was computed using the Wilcoxon rank test on the bootstrapped estimates. Analyses were computed using R (Version 2, Free Software Foundation, Boston, MA) and SAS software (version, 9.1, Cary, NC). Smooth estimates of the mean in the figures were created using the lowess function in R.

The institutional review boards of all participating institutions approved the study.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Appendix A. Development and internal validation race/ethnic group, *N* (%).

Appendix B. External validation.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Levey AS, Atkins R, Coresh J *et al.* Chronic kidney disease as a global public health problem: approaches and initiatives — a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; **72**: 247–259.
2. U.S. Renal Data System. *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2008.
3. U.S. Renal Data System. *USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2007.
4. Jones CY, Jones CA, Wilson IB *et al.* Cystatin C and creatinine in an HIV cohort: the nutrition for healthy living study. *Am J Kidney Dis* 2008; **51**: 914–924.
5. Stevens LA, Schmid CH, Zhang YL *et al.* Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant* 2010; **25**: 449–457.
6. Baxmann AC, Ahmed MS, Marques NC *et al.* Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 2008; **3**: 348–354.
7. Banfi G, Del Fabbro M, Lippi G. Relation between serum creatinine and body mass index in elite athletes of different sport disciplines. *Br J Sports Med* 2006; **40**: 675–678; discussion 678.
8. Ma YC, Zuo L, Chen JH *et al.* Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; **17**: 2937–2944.
9. Matsuo S, Imai E, Horio M *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
10. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
11. Stevens LA, Schmid CH, Greene T *et al.* Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 ml/min/1.73 m(2). *Am J Kidney Dis* 2010; **56**: 486–495.
12. White SL, Polkinghorne KR, Atkins RC *et al.* Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* 2010; **55**: 660–670.
13. Matsushita K, Selvin E, Bash LD *et al.* Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2010; **55**: 648–659.
14. Gallagher D, Visser M, De Meersman RE *et al.* Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 1997; **83**: 229–239.
15. He Q, Heo M, Heshka S *et al.* Total body potassium differs by sex and race across the adult age span. *Am J Clin Nutr* 2003; **78**: 72–77.
16. Holden C. Peering under the hood of Africa's runners. *Science* 2004; **305**: 637–639.
17. van Deventer HE, George JA, Paiker JE *et al.* Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. *Clin Chem* 2008; **54**: 1197–1202.
18. Eastwood JB, Kerry SM, Plange-Rhule J *et al.* Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. *Nephrol Dial Transplant* 2010; **25**: 2178–2187.
19. Jafar TH, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. *J Am Soc Nephrol* 2005; **16**: 1413–1419.
20. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002; **3**: 141–146.
21. Horio M, Imai E, Yasuda Y *et al.* Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 2010; **56**: 32–38.
22. Rule AD, Teo BW. GFR estimation in Japan and China: what accounts for the difference? *Am J Kidney Dis* 2009; **53**: 932–935.
23. College of American Pathologists. Current Status of Reporting Estimated Glomerular Filtration Rate (eGFR). Accessed 10 August 2010. Available from http://www.cap.org/apps/docs/committees/chemistry/current_status_of_reporting_eGFR.pdf.
24. Levey AS, Coresh J, Greene T *et al.* Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766–772.
25. Stevens LA, Manzi J, Levey AS *et al.* Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. *Am J Kidney Dis* 2007; **50**: 21–35.
26. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**: 1098.
27. US Census Bureau. Hispanic Population of the United States. Accessed 11 April 2010. Available from http://www.census.gov/population/www/socdemo/hispanic/tables.html.
28. U.S. Census Bureau. The Hispanic Population. Census 2000 Brief. Accessed 23 April 2010. Available from http://www.census.gov/prod/2001pubs/c2kbr01-3.pdf.