Comparison of Risk Prediction Using the CKD-EPI Equation and the MDRD Study Equation for Estimated Glomerular Filtration Rate

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Context The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation more accurately estimates glomerular filtration rate (GFR) than the Modification of Diet in Renal Disease (MDRD) Study equation using the same variables, especially at higher GFR, but definitive evidence of its risk implications in diverse settings is lacking.

Objective To evaluate risk implications of estimated GFR using the CKD-EPI equation compared with the MDRD Study equation in populations with a broad range of demographic and clinical characteristics.

Design, Setting, and Participants A meta-analysis of data from 1.1 million adults (aged ≥18 years) from 25 general population cohorts, 7 high-risk cohorts (of vascular disease), and 13 CKD cohorts. Data transfer and analyses were conducted between March 2011 and March 2012.

Main Outcome Measures All-cause mortality (84 482 deaths from 40 cohorts), cardiovascular mortality (22 176 events from 28 cohorts), and end-stage renal disease (ESRD) (7644 events from 21 cohorts) during 9.4 million person-years of follow-up; the median of mean follow-up time across cohorts was 7.4 years (interquartile range, 4.2-10.5 years).

Results Estimated GFR was classified into 6 categories (≥90, 60-89, 45-59, 30-44, 15-29, and <15 mL/min/1.73 m^2) by both equations. Compared with the MDRD Study equation, 24.4% and 0.6% of participants from general population cohorts were reclassified to a higher and lower estimated GFR category, respectively, by the CKD-EPI equation, and the prevalence of CKD stages 3 to 5 (estimated GFR <60 mL/min/1.73 m^2) was reduced from 8.7% to 6.3%. In estimated GFR of 45 to 59 mL/min/1.73 m^2 by the MDRD Study equation, 34.7% of participants were reclassified to estimated GFR of 60 to 89 mL/min/1.73 m^2 by the CKD-EPI equation and had lower incidence rates (per 1000 person-years) for the outcomes of interest (9.9 vs 34.5 for all-cause mortality, 2.7 vs 13.0 for cardiovascular mortality, and 0.5 vs 0.8 for ESRD) compared with those not reclassified. The corresponding adjusted hazard ratios were 0.80 (95% CI, 0.74-0.86) for all-cause mortality, 0.73 (95% CI, 0.65-0.82) for cardiovascular mortality, and 0.49 (95% CI, 0.27-0.88) for ESRD. Similar findings were observed in other estimated GFR categories by the MDRD Study equation. Net reclassification improvement based on estimated GFR categories was significantly positive for all outcomes (range, 0.06-0.13; all $P<.001$). Net reclassification improvement was similarly positive in most subgroups defined by age (<65 years and ≥65 years), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. The results in the high-risk and CKD cohorts were largely consistent with the general population cohorts.

Conclusion The CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and ESRD than did the MDRD Study equation across a broad range of populations.

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GLOMERULAR FILTRATION RATE (GFR) is used in the diagnosis of chronic kidney disease (CKD)[1,2] and is an independent predictor of all-cause and cardiovascular mortality and kidney failure in a wide range of populations.[3-6] Clinical guidelines recommend reporting estimated GFR when serum creatinine level is measured[1,2]; 84% of US laboratories report estimated GFR.[7] Although the Modification of Diet in Renal Disease (MDRD) Study equation is recommended for estimating GFR,[1,2,8,9] the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) has recently proposed an alternative equation, which applies different coefficients to the same 4 variables used in the MDRD Study equation (age, sex, race, and serum creatinine level).[10] The new CKD-EPI equation estimates measured GFR more accurately than the MDRD Study equation in most,[10-18] but

For editorial comment see p 1976.

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not all[19,20] studies. However; only 4% of US laboratories reporting estimated GFR used the CKD-EPI equation in June 2011; 92% of laboratories still used the MDRD Study equation and 4% used other equations.[7]

A few studies suggest that the better estimation of GFR by the CKD-EPI equation is reflected in better clinical risk prediction than by the MDRD Study equation.[21-24] However, these studies include predominantly white populations with higher levels of kidney function. In addition, the implications of use of the CKD-EPI equation in the elderly have yet to be elucidated.[25,26] The objective of this collaborative study was to comprehensively evaluate whether estimated GFR computed by the CKD-EPI equation predicts risk for adverse outcomes more accurately than the MDRD Study equation in a broad range of populations. Such information will help clinicians, laboratories, and policy makers decide whether estimated GFR reporting should be based on the MDRD Study equation or the CKD-EPI equation.

METHODS

Details of the Chronic Kidney Disease Prognosis Consortium (CKD-PC) were described previously.[3-6] To be included in the consortium, a study had to have at least 1000 participants (not applied to studies predominantly enrolling patients with CKD[6]), information at baseline on estimated GFR and urine albumin levels, and a minimum of 50 events for any of the outcomes of interest. As recommended,[1,2] we preferentially selected ratio of urine albumin to creatinine as the measure of albuminuria. However, we also accepted urine albumin excretion and ratio of urine protein to creatinine as well as a qualitative measurement using dipstick.[1] This analysis consists of data from 45 cohorts (25 general population cohorts, 7 high-risk cohorts with participants selected for cardiovascular or kidney disease risk factors, and 13 CKD cohorts). Data transfer (from collaborating cohorts to the CKD-PC Data Coordinating Center) and analyses for the present study were conducted between March 2011 and March 2012. This study is based on secondary data analysis of a preexisting, deidentified, and unlinked data set, and was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health. Information about ethical review of individual studies is available in the publications of the constituent cohorts.[21,24,27-69]

We calculated estimated GFR from serum creatinine standardized to isotope dilution mass spectrometry using the MDRD Study equation[9] and the CKD-EPI equation.[10] For studies in which creatinine measurement was not standardized to isotope dilution mass spectrometry, we reduced the creatinine levels by 5%, which is the calibration factor used to adjust nonstandardized MDRD samples to this type of spectrometry.[70]

Diabetes mellitus was defined as fasting glucose level of 7.0 mmol/L or greater, nonfasting glucose level of 11.1 mmol/L or greater, hemoglobin A_{1c} of 6.5% or greater, use of glucose-lowering drugs, or self-reported diabetes (to convert glucose to mg/dL, divide by 0.0555; hemoglobin A_{1c} to a proportion, multiply by 0.01). Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of any antihypertensive medication. Hypercholesterolemia was defined as total cholesterol level of 6.0 mmol/L or greater ($\geq$5.0 mmol/L in people with prior cardiovascular disease) or use of lipid-lowering drugs (to convert cholesterol to mg/dL, divide by 0.0259). Cardiovascular disease history was defined as a history of myocardial infarction, coronary revascularization, heart failure, or stroke. Smoking was dichotomized as current vs former smokers or nonsmokers. Race/ethnicity was categorized as white, Asian, black, Hispanic, and other.

The outcomes of interest were all-cause mortality, cardiovascular mortality, and end-stage renal disease (ESRD). Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. End-stage renal disease was defined as the start of renal replacement therapy or death due to kidney disease other than acute kidney injury.

Statistics were first obtained within each study and then a meta-analysis was performed across studies using a random-effects model. Analyses were restricted to individuals aged 18 years or older. Any individual with missing values for estimated GFR or albuminuria at baseline was excluded. Missing values for all other covariates were estimated by mean imputation. The analysis overview and analytic notes for individual studies are described in the eAppendix 1 at http://www.jama.com). Heterogeneity was quantified using the χ^2 test and the I^2 statistic. We conducted a meta-regression analysis with a random-effects model to explore sources of heterogeneity. A meta-analysis was performed separately on the general population, high-risk, and CKD cohorts.

We evaluated the distribution and risk relationship for estimated GFR separately for both equations. Cox proportional hazards models were fitted with estimated GFR linear splines (knots at 30, 45, 60, 75, 90, and 105 mL/min/1.73 m^2 [the 105 mL/min/1.73 m^2 knot was not applied to CKD cohorts]). All Cox models were adjusted for age, sex, race/ethnicity (blacks vs nonblacks), smoking (current vs former or nonsmokers), history of cardiovascular disease, systolic blood pressure (continuous), diabetes, serum total cholesterol concentration (continuous), body mass index (continuous), and albuminuria (log-transformed ratio of urine albumin to creatinine, log-transformed ratio of urine protein to creatinine as continuous variables, or dipstick as a categorical variable [negative, trace, 1 +, 2 +, and 3 +]). From these models, hazard ratio (HR) was computed for each 1 mL/min/1.73 m^2 of estimated GFR from 15 to 120 mL/min/1.73 m^2 with a reference point at 95 mL/min/1.73 m^2

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(50 mL/min/1.73 m^2 for CKD cohorts). Model discrimination was assessed using the *c* statistic, which allows for censoring.[71]

We cross-tabulated estimated GFR using clinically relevant categories (≥90, 60-89, 45-59, 30-44, 15-29, <15 mL/min/1.73m^2)[1,2] and evaluated the proportion of participants in each category of estimated GFR by the MDRD Study equation that was reclassified by the CKD-EPI equation. To evaluate factors associated with reclassification, baseline characteristics of participants in each study were compared according to the reclassification status by the CKD-EPI equation (reclassified upward to a higher estimated GFR category, not reclassified, or reclassified downward to a lower estimated GFR category). Because there were few participants with an estimated GFR of less than 15 mL/min/1.73 m^2 in the general population cohorts (<0.1%) and in high-risk cohorts (0.2%), we only reported results for this estimated GFR category in the CKD cohorts.

Given that GFR category is a central measure for defining, staging, and managing CKD (including indications for referral),[1,2] we designated a priori the effect of reclassification in estimated GFR categories as the primary analysis.[21-23] We assessed risk of clinical outcomes among participants who were reclassified for estimated GFR compared with those who were not reclassified. Overall improvement in reclassification based on estimated GFR was assessed by applying net reclassification improvement (NRI).[21,72] To assess generalizability, we calculated NRI in subgroups according to age (<65 years and ≥65 years), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. Due to sparse data, we could not reliably investigate Hispanics and other racial/ethnic groups. The NRI also was estimated in subgroups according to albuminuria levels. All analyses were conducted using Stata version 11.2 (StataCorp). A *P* value of less than .05 was considered statistically significant.

RESULTS

Participants from 45 cohorts were from 40 countries or regions of Asia, Europe, North America and South America, the Middle East, and Oceania. Baseline characteristics of each cohort are shown in eTable 1 at http://www.jama.com. Overall, 1.1 million adults (940 366 from general population, 151 494 from high-risk, and 38 612 from CKD cohorts) were followed up for 9.4 million person-years (the median of mean follow-up time across collaborating cohorts was 7.4 years [interquartile range, 4.2-10.5 years]). Forty cohorts reported on 84 482 deaths (61 770 from general population, 13 693 from high-risk, and 9019 from CKD cohorts); 28 cohorts reported on 22 176 cardiovascular disease deaths (17 009 from general population, 4271 from high-risk, and 896 from CKD cohorts); and 21 cohorts reported on 7644 ESRD events (730 from general population, 954 from high-risk, and 5960 from CKD cohorts).

Mean estimated GFR was higher when computed by the CKD-EPI equation than by the MDRD Study equation in the general population cohorts (88.9 vs 81.5 mL/min/1.73 m^2, respectively; FIGURE 1A) and in the high-risk cohorts (84.6 vs 80.6 mL/min/1.73 m^2; eFigure 1A) but was comparable in the CKD cohorts (41.4 vs 40.6 mL/min/1.73 m^2) (eFigure 2A). The shift of distribution toward higher estimated GFR by the CKD-EPI equation was more evident in younger people (<65 years), females, and nonblacks (eFigures 3-5). Accordingly, the prevalence of CKD stages 3 to 5 (<60 mL/min/1.73 m^2) was lower by the CKD-EPI equation than by the MDRD Study equation in the general population cohorts (6.3% vs 8.7%, respectively) and in the high-risk cohorts (14.6% vs 17.7%). The lower prevalence of CKD stages 3 to 5 by the CKD-EPI equation was observed in most of the individual cohorts; there was a small increase in only 2 cohorts of elderly participants[30,39](eFigure 6).

The pattern of the estimated GFR risk relationship was similar for both equations in the general population cohorts after adjusting for potential confounders (Figure 1B-D). However, the adjusted HR of lower estimated GFR compared with estimated GFR of 95 mL/min/1.73 m^2 became significant at a higher level by the CKD-EPI equation than by the MDRD Study equation, particularly for cardiovascular mortality (77 vs 68 mL/min/1.73 m^2, respectively) and ESRD (82 vs 70 mL/min/1.73 m^2). Within the range of estimated GFR of less than 45 mL/min/1.73 m^2, the HRs were largely comparable between both equations for the mortality outcomes. The steeper risk gradient along with low estimated GFR was more evident in the unadjusted analysis for mortality (eFigure 7). The higher risk of all-cause and cardiovascular mortality in the higher estimated GFR range (105-120 mL/min/1.73 m^2) was more pronounced for the CKD-EPI equation than the MDRD Study equation. This effect was not observed in the unadjusted analysis. Similar estimated GFR risk relationships were observed in the high-risk and CKD cohorts (eFigure 1B-D and eFigure 2B-D), but the higher risk at higher levels of estimated GFR was not evident. Using these models with estimated GFR splines, traditional risk factors, and albuminuria, the *c* statistic, which focuses on ranking alone and ignores absolute levels and categories,[73] produced results that were almost identical for the CKD-EPI and MDRD Study equations in the general population cohorts for all-cause mortality (0.783 [95% CI, 0.758-0.807] vs 0.783 [95% CI, 0.759-0.808], respectively), for cardiovascular mortality (0.835 [95% CI, 0.800-0.869] vs 0.835 [95% CI, 0.801-0.869]) and for ESRD (0.920 [95% CI, 0.888-0.953] vs 0.919 [95% CI, 0.885-0.952]). Similar findings were observed in the high-risk and CKD cohorts (eTable 2).

In the general population cohorts, 25.0% of participants were reclassified by the CKD-EPI equation (24.4% to a higher estimated GFR category and 0.6% to a lower estimated GFR category) (FIGURE 2). Most reclassifica-

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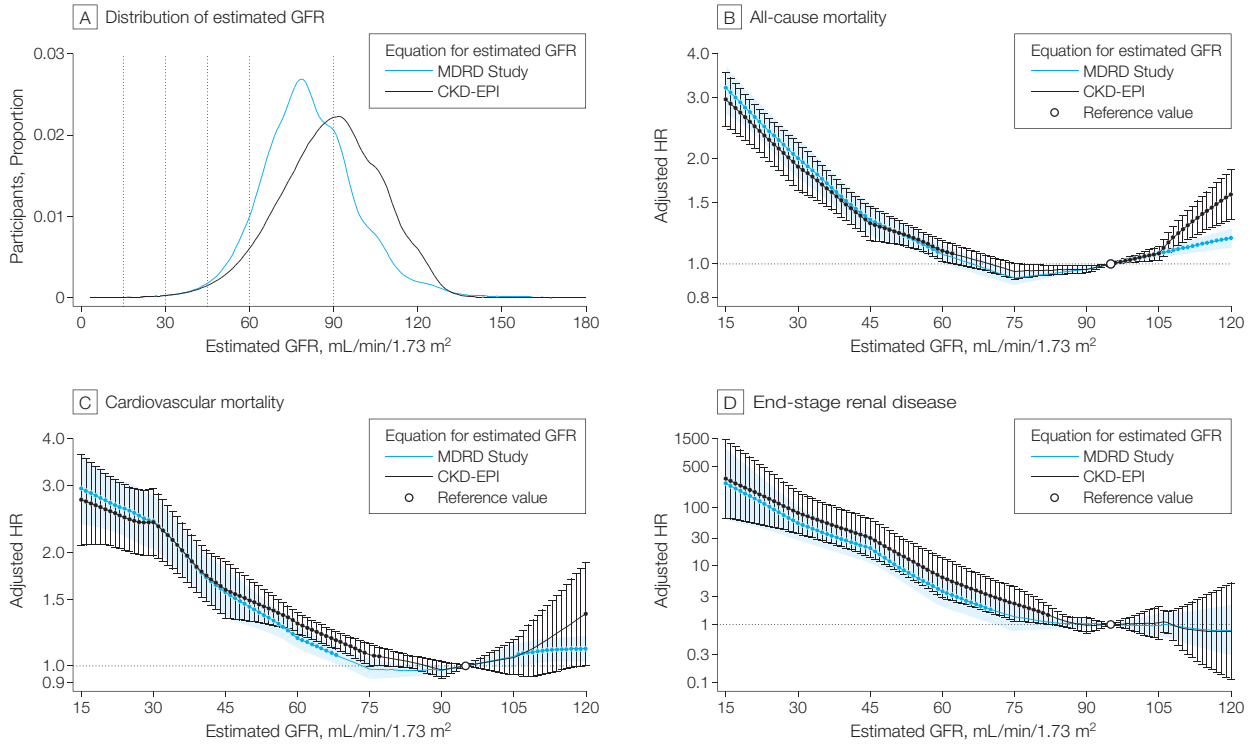
tion occurred among participants with estimated GFR between 45 and 89 mL/min/1.73 m^2 by the MDRD Study equation. A similar reclassification pattern was observed in the high-risk cohorts, although there was less reclassification (15.4% upward and 1.2% downward; eFigure 8). In the CKD cohorts, we observed much less upward reclas-

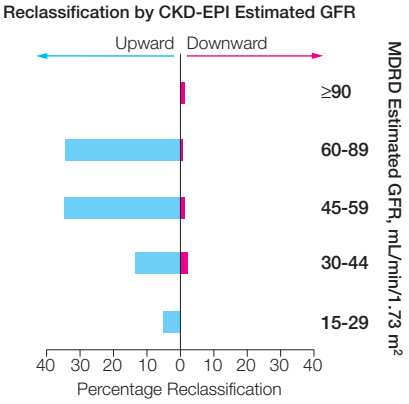
Figure 1. Distribution in General Population Cohorts for Estimated GFR and Adjusted Hazard Ratios (HRs) of All-Cause Mortality, Cardiovascular Mortality, and End-Stage Renal Disease



A, Distribution based on kernel density estimation (proportion is for each integer estimated glomerular filtration rate [GFR]). Dotted vertical lines define GFR categories used for chronic kidney disease staging.[1,2] B-D, Error bars indicate 95% confidence intervals for estimated GFR by the CKD-EPI equation. Tinted bands indicate 95% confidence intervals for estimated GFR by the MDRD Study equation. Reference (open circle) is estimated GFR of 95 mL/min/1.73 m^2. The filled circles (black and blue dots) represent statistical significance ($P<.05$). Adjustments were made for age, sex, race/ethnicity, smoking, history of cardiovascular disease, systolic blood pressure, diabetes, serum total cholesterol concentration, body mass index, and albuminuria. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

Figure 2. Reclassification Across Estimated GFR Categories by the CKD-EPI Equation From Estimated GFR Categories Based on the MDRD Study Equation

MDRD Estimated GFR, mL/min/1.73 m^2	CKD-EPI Estimated GFR Category, mL/min/1.73 m^2 ≥90	60-89	45-59	30-44	15-29	Total
≥90	259 906	3239 (1.2)				263 145
60-89	204 187 (34.3)	389 845	964 (0.2)			594 996
45-59		23 908 (34.7)	44 161	804 (1.2)		68 873
30-44			1476 (13.7)	9100	231 (2.1)	10 807
15-29				89 (4.8)	1772	1861
Total	464 093	416 992	46 601	9993	2003	



Reclassification by the CKD-EPI equation in the general population cohorts. The blue and red bars indicate upward reclassification to a higher estimated GFR category and downward reclassification to a lower estimated GFR category, respectively. Data in pink and blue type are the number (percentage) of participants who were reclassified.

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sification (6.6%) but slightly more downward reclassification (3.2%) by the CKD-EPI equation (eFigure 9).

Participants who were reclassified upward to a higher estimated GFR category by the CKD-EPI equation were more likely to be younger, female, and nonblack, and thus have fewer comorbid conditions such as hypertension, diabetes, and clinically significant albuminuria compared with individuals who remained in the same estimated GFR category (TABLE 1, TABLE 2, and eTable 3). In contrast, the participants reclassified downward to a lower estimated GFR category by the CKD-EPI equation were much older than those who were not reclassified in most studies (mean age in general population cohorts, 77 years vs 49 years, respectively). Blacks tended to be reclassified less frequently (in either direction) in the general population cohorts but were reclassified downward more frequently at a lower GFR range (CKD cohorts) compared with nonblacks.

Participants in general population cohorts who were reclassified upward and downward by the CKD-EPI equation had consistently lower and higher incidence rates for all outcomes, respectively, than those who remained in the same estimated GFR category (TABLE 3). This association remained the same even after adjustment for potential confounders, with only a few exceptions (none of which were significant). When we focused on clinically important upward reclassification from CKD stage 3a (estimated GFR 45 to 59 mL/min/1.73 m^2) to mildly reduced estimated GFR (60 to 89 mL/min/1.73 m^2), this reclassification was associated with lower incidence rates compared with no reclassification (incidence rate per 1000 person-years, 9.9 vs 34.5 [difference, –24.6] for all-cause mortality, 2.7 vs 13.0 [–10.3] for cardiovascular mortality, and 0.5 vs 0.8 [–0.3] for ESRD). Of note, this reclassification was associated with a 20% to 51% lower risk of these outcomes even after the adjustment for traditional risk factors and albuminuria. We obtained similar results for the groups either younger or older than 65 years of age (eTable 4 and eTable 5). Among the statistically significant reclassifications

Table 1. Characteristics of Participants in General Population Cohorts According to Reclassification Status by CKD-EPI Equation Compared With MDRD Study Equation for Estimated GFR

		Moved Upward to Higher GFR Category			No Reclassification			Moved Downward to Lower GFR Category		
General Population Cohorts[a]	Total No.	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]
Aichi[27]	4731	19	48	20; 0; 3	81	48	20; 0; 2	0	NA	NA; NA; NA
ARIC[21,c]	11 441	8	59	58; 15; 7	90	63	56; 23; 8	2	71	21; 6; 12
AusDiab[24,c]	11 179	25	45	60; 0; 4	74	54	54; 0; 7	1	77	27; 0; 23
Beaver Dam CKD[28]	4857	16	54	64; 0; 2	81	63	55; 0.03; 5	2	77	40; 0; 5
Beijing[29,c]	1559	17	54	65; 0; 8	83	61	48; 0; 5	1	74	20; 0; 23
CHS[30,c]	2988	0.3	73	89; 0; 33	88	78	60; 17; 21	11	81	46; 14; 20
CIRCS[31]	11 871	21	52	69; 0; 3	79	54	59; 0; 3	0	NA	NA; NA; NA
COBRA[32,c]	2872	9	52	49; 0; 12	89	51	53; 0; 9	2	81	40; 0; 15
ESTHER[33]	9641	14	59	67; 0; 9	85	62	53; 0; 12	1	72	33; 0; 12
Framingham[34,c]	2956	17	55	58; 0; 9	82	59	52; 0; 13	1	75	25; 0; 21
Gubbio[35,c]	1681	23	53	52; 0; 3	77	55	56; 0; 4	0	NA	NA; NA; NA
HUNT[36,c]	9659	12	53	64; 0; 6	84	63	54; 0; 13	4	77	45; 0; 19
IPHS[37]	95 451	18	53	77; 0; 2	81	60	64; 0; 3	0.3	76	12; 0; 4
MESA[38,c]	6733	12	56	61; 13; 7	86	63	52; 29; 10	2	78	32; 44; 25
MRC[39]	12 371	1	77	100; 0; 5	91	81	62; 0; 8	8	84	42; 0; 8
NHANES III[40,c]	15 563	13	44	55; 16; 8	86	46	53; 29; 12	2	81	35; 19; 27
Ohasama[41]	1956	14	58	80; 0; 7	85	64	62; 0; 8	1	83	22; 0; 39
Okinawa 1983[42]	9599	22	43	61; 0; 17	78	54	59; 0; 22	0.4	83	52; 0; 32
Okinawa 1993[43]	93 216	21	46	60; 0; 3	79	57	57; 0; 4	1	81	36; 0; 6
PREVEND[44,c]	8385	27	44	58; 0.4; 8	73	51	47; 1; 12	0.2	72	15; 0; 30
RanchoBernardo[45,c]	1474	10	58	66; 0; 8	83	71	59; 0.1; 15	7	84	56; 0; 18
REGARDS[46,c]	27 306	11	59	68; 18; 8	85	65	53; 43; 16	4	77	36; 30; 21
Severance[47]	76 201	29	42	53; 0; 5	71	47	48; 0; 5	0.1	77	20; 0; 16
Taiwan[48]	515 573	29	37	52; 0; 1	71	43	50; 0; 2	0.1	80	22; 0; 9
ULSAM[49,c]	1103	1	71	0; 0; 11	93	71	0; 0; 16	6	71	0; 0; 19
Total	**940 366**	24	43	57; 1; 3	75	49	52; 2; 4	1	77	24; 2; 10

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NA, data not applicable.
[a] The study acronyms and abbreviations are listed in eAppendix 2 at http://www.jama.com.
[b] For albuminuria, this is the proportion of participants with ratio of urine albumin to creatinine of 30 mg/g or greater, ratio of protein to creatinine of 50 mg/g or greater, or dipstick protein level of 1 or greater.
[c] This study included ratio of urine albumin to creatinine.

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in Table 3, heterogeneity across studies was minimal to moderate (I^2=0% to 52.5%; P values ranged from 0.82 to 0.006). Similar findings were observed in the high-risk (eTable 6) and CKD cohorts (eTable 7). For ESRD, analysis with mortality as a competing risk provided similar findings (eTable 8).

In the general population cohorts, NRI was significantly positive (favoring the CKD-EPI equation) for all outcomes (0.11 [95% CI, 0.09-0.13] for all-cause mortality, 0.13 [95% CI, 0.09-0.16] for cardiovascular mortality, and 0.06 [95% CI, 0.02-0.10] for ESRD) (FIGURE 3). There was high heterogeneity between individual cohorts for overall NRI (I^2=71%-97%; all $P<.01$). However, this heterogeneity reflected quantitative rather than qualitative differences because the CKD-EPI equation was favored in almost all general population cohorts (eFigures 10-12). We conducted a meta-regression analysis with the covariates (eTable 9). Studies with higher mean age and prevalence of diabetes tended to have lower NRI for cardiovascular mortality (eFigure 13 and eFigure 14). The NRI for other associations did not vary significantly across studies.

The NRI was positive in most of the subgroups according to age, sex, race/ethnicity, and presence or absence of diabetes and hypertension (Figure 3). The NRI was comparable between females and males and between those younger than 65 years and those aged 65 years or older except for a lower NRI in those aged 65 years or older for ESRD. The NRI was positive even in the age category of 75 years or older for all-cause mortality (0.03 [95% CI, 0.02 to 0.05]) and cardiovascular mortality (0.02 [95% CI, 0.01 to 0.03]). The NRI was negative but not significant for ESRD (–0.04 [95% CI, –0.10 to 0.02], P=.15). The NRI for mortality outcomes was lower in blacks compared with whites and Asians but still significantly favored the CKD-EPI equation. With further stratification by the combination of these demographic variables, the NRI was positive (favoring the

Table 2. Characteristics of Participants in High-Risk and Chronic Kidney Disease (CKD) Cohorts According to Reclassification Status by CKD-EPI Equation Compared With MDRD Study Equation for Estimated GFR

		Moved Upward to Higher GFR Category			No Reclassification			Moved Downward to Lower GFR Category		
Cohort[a]	Total No.	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]	Overall, %	Mean Age, y	Females; Blacks; Albuminuria, %[b]
High-risk										
ADVANCE[50,c]	10 595	10	62	57; 0.4; 31	88	66	41; 0.3; 31	2	74	25; 1; 26
CARE[51]	4098	17	54	17; 2; 12	83	60	13; 4; 14	0.2	73	0; 0; 57
KEEP[52]	77 902	15	48	72; 21; 10	84	55	68; 33; 13	1	79	51; 36; 21
KP Hawaii[53,d]	39 884	15	51	54; 0; 29	84	60	50; 0; 34	2	82	38; 0; 45
MRFIT[54]	12 854	28	44	0; 3; 4	72	47	0; 9; 4	0	NA	NA; NA; NA
Pima[55,c]	5066	4	46	68; 0; 37	96	32	56; 0; 19	0.2	76	50; 0;t50
ZODIAC[56,c]	1095	10	58	56; 0; 25	88	69	58; 0; 41	2	79	27; 0; 46
Subtotal	151 494	15	49	59; 11; 17	83	56	53; 18; 19	1	72	40; 18; 28
CKD										
AASK[57,d]	1094	6	46	66; 100; 63	92	55	37; 100; 62	2	66	21; 100; 54
BC CKD[58,c]	17 426	6	52	56; 0.1; 76	90	70	45; 0.4; 75	4	82	34; 1; 74
CRIB[59,c]	308	3	49	38; 0; 63	95	62	34; 6; 87	2	77	17; 17; 100
Geisinger[60]										
ACR[c]	3361	3	59	63; 3; 50	96	71	54; 2; 43	1	79	6; 0; 56
Dipstick	4509	3	57	80; 6; 32	96	72	62; 1; 25	2	81	27; 3; 27
GLOMMS-1[61]										
ACR[c]	537	2	54	33; 0; 67	93	73	52; 0; 51	4	80	42; 0; 38
PCR[d]	470	4	41	47; 0; 88	91	70	48; 0; 95	5	83	43; 0; 100
KPNW[62]	1627	10	62	72; 1; 25	86	72	54; 3; 32	4	82	53; 3; 31
MASTERPLAN[63,c]	636	11	49	47; 3; 78	88	62	29; 3; 86	1	72	50 0; 75
MDRD[64,d]	1730	14	45	50; 5; 80	86	52	38; 13; 83	1	67	29; 64; 86
MMKD[65,d]	202	17	39	41; 0; 94	83	48	33; 0; 95	0	NA	NA; NA; NA
NephroTest[66,c]	928	9	48	33; 8; 51	89	61	31; 10; 65	2	75	0; 13; 73
RENAAL[67,c]	1513	9	55	34; 8; 100	90	61	37; 15; 100	1	68	0; 67; 100
STENO[68,c]	886	26	42	48; 0; 46	74	44	42; 0; 50	0.1	74	0; 0; 0
Sunnybrook[69,c]	3385	6	52	52; 0; 83	89	71	44; 0; 84	5	82	26; 0; 86
Subtotal	38 612	7	53	58; 5; 67	90	68	47; 5; 66	3	79	28; 10; 65

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NA, data not applicable.
[a] The study acronyms and abbreviations are listed in eAppendix 2 at http://www.jama.com.
[b] For albuminuria, this is the proportion of participants with ratio of urine albumin to creatinine (ACR) of 30 mg/g or greater, ratio of protein to creatinine (PCR) of 50 mg/g or greater, or dipstick protein level of 1 or greater.
[c] This study included ACR.
[d] This study included PCR.

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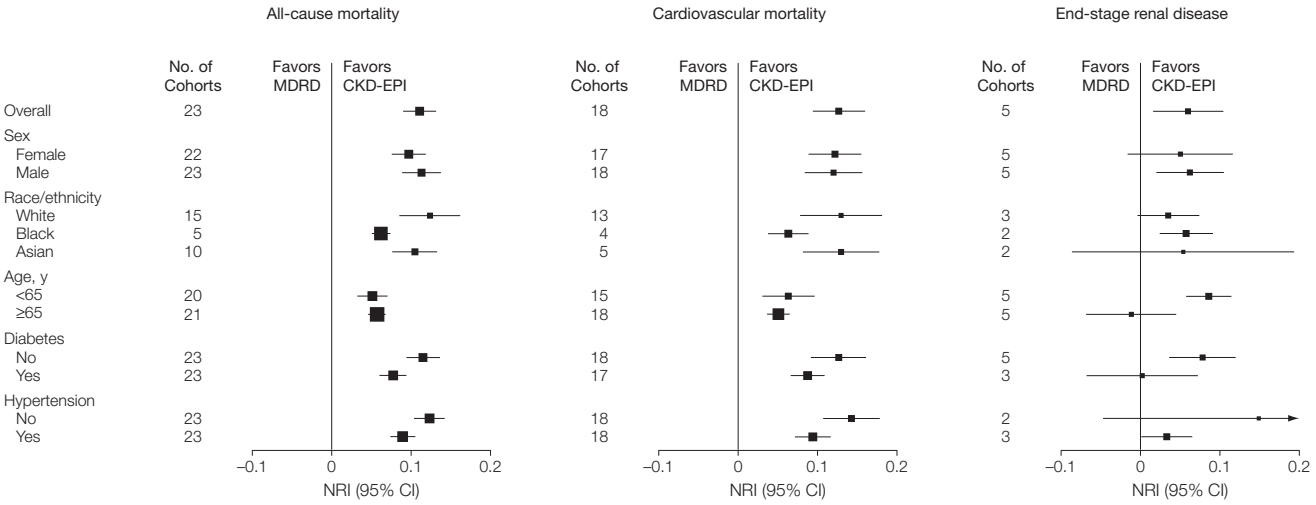
CKD-EPI equation) in 33 of 36 comparisons and was statistically significant in 17 comparisons (eTable 10). None of 3 negative NRIs (favoring the MDRD Study equation) were significant. Similarly, the NRI was positive in most subgroups in the high-risk and CKD cohorts (eFigure 15, eFigure 16, eTable 11, and eTable 12). The NRI also was positive in most subgroups defined according to albuminuria level (eTable 13).

Table 3. Clinical Outcomes for the General Population Cohorts According to Reclassification Status by CKD-EPI Equation Compared With MDRD Study Equation for Estimated GFR

MDRD Estimated GFR Category, mL/min/1.73 m^2		All-Cause Mortality (n = 61 426 Events) by CKD-EPI GFR Reclassification			Cardiovascular Mortality (n = 16 923 Events) by CKD-EPI GFR Reclassification			End-Stage Renal Disease (n = 666 Events) by CKD-EPI GFR Reclassification		
		Upward (n = 5586 Events)	None (n = 53 601 Events)	Downward (n = 2239 Events)	Upward (n = 1113 Events)	None (n = 14 979 Events)	Downward (n = 831 Events)	Upward (n = 60 Events)	None (n = 588 Events)	Downward (n = 18 Events)
≥90	CIR[a]	NA[b]	3.8	52.9	NA[b]	0.8	22.3	NA[b]	0.3	0.4
	AHR[c]	NA[b]	1 [Reference]	1.02 (0.89-1.18)	NA[b]	1 [Reference]	1.24 (1.01-1.53)	NA[b]	1 [Reference]	1.54 (0.50-4.78)
60-89	CIR[a]	2.2	10.2	95.1	0.4	3.0	46.0	0.1	0.2	2.3
	AHR[c]	1.03 (0.98-1.08)	1 [Reference]	0.98 (0.85-1.14)	0.93 (0.85-1.02)	1 [Reference]	1.21 (1.01-1.43)	0.47 (0.24-0.93)	1 [Reference]	4.44 (1.52-13.00)
45-59	CIR[a]	9.9	34.5	111.6	2.7	13.0	52.3	0.5	0.8	1.6
	AHR[c]	0.80 (0.74-0.86)	1 [Reference]	1.15 (1.03-1.27)	0.73 (0.65-0.82)	1 [Reference]	1.25 (1.07-1.48)	0.49 (0.27-0.88)	1 [Reference]	2.67 (0.73-9.72)
30-44	CIR[a]	18.2	66.4	134.5	6.0	27.3	56.4	4.6	7.0	13.7
	AHR[c]	0.74 (0.61-0.88)	1 [Reference]	1.11 (0.79-1.55)	0.75 (0.54-1.05)	1 [Reference]	1.25 (0.68-2.31)	0.95 (0.43-2.07)	1 [Reference]	1.35 (0.51-3.56)
15-29	CIR[a]	33.4	88.1	NA[d]	15.7	33.6	NA[d]	59.5	59.7	NA[d]
	AHR[c]	1.04 (0.51-2.15)	1 [Reference]	NA[d]	1.66 (0.44-6.30)	1 [Reference]	NA[d]	1.13 (0.36-3.54)	1 [Reference]	NA[d]

Abbreviations: AHR, adjusted hazard ratio; CIR, crude incidence rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
[a] Per 1000 person-years.
[b] NA indicates inapplicable.
[c] Adjusted for age, sex, race/ethnicity, smoking, systolic blood pressure, total cholesterol, diabetes, history of cardiovascular disease, body mass index, and albuminuria.
[d] NA indicates unreliable due to the small number of participants.

Figure 3. Meta-analyses of Net Reclassification Improvements (NRIs) for All-Cause Mortality, Cardiovascular Mortality, and End-Stage Renal Disease



The sizes of the data markers are proportional to the inverse of the variance of the NRIs.

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COMMENT

In our data from more than 1 million participants residing in 40 countries or regions, approximately one-fourth of participants were reclassified to a higher estimated GFR category by the CKD-EPI equation compared with the MDRD Study equation (24.4% in the general population cohorts, 15.4% in the high-risk cohorts, and 6.6% in the CKD cohorts), lowering the prevalence of CKD in all cohorts except for the elderly. Participants who were reclassified upward had lower risks of mortality and ESRD compared with those not reclassified even after adjusting for age, sex, race/ethnicity, and other potential confounders. Individuals who were reclassified downward (0.7%) had higher risk than those who were not reclassified. Positive NRIs also support better overall reclassification by the CKD-EPI equation. Although we observed quantitative heterogeneity in some analyses, most of the studies were in agreement with the pooled results (eFigures 10-12). Importantly, a better risk categorization by the CKD-EPI equation compared with the MDRD Study equation was consistent in almost all subgroups defined by age, sex, race/ethnicity, and clinical characteristics.

Our results confirm and extend results from previous literature.[21-24] First, we observed that the CKD-EPI equation is a better predictor of risk than the MDRD Study equation in CKD cohorts as well as in cohorts with higher estimated GFR. Improved or similar performance across the range of estimated GFR is important for clinical implementation. Second, although the elderly were less often reclassified by the CKD-EPI equation compared with younger people, their future risk also was more correctly classified. Third, we found that the CKD-EPI equation predicts clinical risk more accurately than the MDRD Study equation in Asians. Although there is debate about which estimated GFR equation to use in Asia,[74,75] our results suggest that the CKD-EPI equation would be a better option for risk prediction than the MDRD Study equation. Fourth, we showed that the CKD-EPI equation categorizes risk slightly more accurately than or at least as well as the MDRD Study equation in blacks, even though reclassification is less common in blacks than in whites and Asians. Fifth, we showed that the CKD-EPI equation provides more accurate risk categorization than the MDRD Study equation even after considering albuminuria, a measure of kidney damage. Recent reports suggest using albuminuria in addition to GFR for CKD staging and risk classification.[76,77] Our findings suggest the CKD-EPI equation will be more useful than the MDRD Study equation for this application. Finally, we showed improved risk prediction for ESRD, in addition to mortality and cardiovascular disease shown in most of the previous studies.[21-24]

The CKD-EPI and MDRD Study equations estimate the same physiological function (GFR) using identical variables, thus the comparison of outcome prediction by 2 equations differs from the more common comparison of 2 models with and without a new biomarker. Because the same variables appear in both equations in our study, the difference in predicted risk between the 2 equations should not be expected to be as large as would be sought when adding a new biomarker. Consequently, we did not anticipate improvements in less sensitive statistics (such as the *c* statistic), which ignore absolute levels and categories and focus on ranking alone.[73] This is particularly the case when age, sex, and race/ethnicity are included in the prediction model because coefficients for these variables can compensate for worse prediction by estimated GFR by the MDRD Study equation compared with the CKD-EPI equation.[21]

From another perspective, the use of the identical variables in the CKD-EPI equation requires no additional laboratory costs and enables relatively easy implementation with computerized algorithms. Therefore, a significant overall improvement in risk categorization by the CKD-EPI equation, even if small, would support its clinical use in place of the MDRD Study equation. At this time, only a small proportion of clinical laboratories in the United States have switched to the CKD-EPI equation for estimated GFR reporting.[7] In this context, clinically important reclassification crossing the threshold for CKD definition from CKD stage 3a to mildly reduced estimated GFR (60 to 89 mL/min/1.73m^2) was observed in our study in one-third of individuals with estimated GFR by the MDRD Study equation between 45 and 59 mL/min/1.73m^2. In the general population cohorts, these individuals had lower risk of mortality and ESRD compared with those who were not reclassified (crude incidence rate difference of −24.6 to −0.3 per 1000 person-years and 20% to 51% lower adjusted HR). Given both lower CKD prevalence estimates and better risk categorization, the use of the CKD-EPI equation would contribute to a more appropriate allocation of health care resources and more targeted prevention and management of CKD complications.

The paradoxically increased mortality risk at higher estimated GFR is noted in several studies and may be due to confounding by muscle wasting secondary to ill health.[21] With the CKD-EPI equation, this risk was not evident in the unadjusted analysis but was evident after age adjustment, suggesting the CKD-EPI equation does not fully overcome this limitation inherent to creatinine-based estimated GFR equations. Other filtration markers not related to muscle mass such as serum cystatin C[78,79] might help to resolve this issue.

Some limitations to our study should be mentioned. Measurements of creatinine were not standardized in all studies; however, we observed similar results when we limited our analysis to studies with serum creatinine measurements standardized to isotope dilution mass spectrometry (data not shown). Most of the participants recorded as blacks were from studies in the United States. Although there are various ethnic groups within Asia (eg,

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South Asian and Eastern Asian), we analyzed these groups together. Further analyses will be required for racial/ethnic groups not tested in this study.

Overall, the CKD-EPI creatinine-based equation more accurately classified individuals with respect to risk of mortality and ESRD compared with the MDRD Study equation. Given more accurate GFR estimation,[10] lower CKD prevalence estimates, and better risk categorization by the CKD-EPI equation without additional laboratory costs, its implementation for estimated GFR reporting could contribute to more efficient and targeted prevention and management of CKD-related outcomes.

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Online-Only Material: 3 eAppendices, 13 eTables, 16 eFigures, and eReferences are available at http://www.jama.com.

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