

## JAMA | Original Investigation

# Association of Estimated GFR Calculated Using Race-Free Equations With Kidney Failure and Mortality by Black vs Non-Black Race

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**IMPORTANCE** At a given estimated glomerular filtration rate (eGFR), individuals who are Black have higher rates of mortality and kidney failure with replacement therapy (KFRT) compared with those who are non-Black. Whether the recently adopted eGFR equations without race preserve racial differences in risk of mortality and KFRT at a given eGFR is unknown.

**OBJECTIVE** To assess whether eGFR equations with and without race and cystatin C document racial differences in risk of KFRT and mortality in populations including Black and non-Black participants.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective individual-level data analysis of 62 011 participants from 5 general population and 3 chronic kidney disease (CKD) US-based cohorts with serum creatinine, cystatin C, and follow-up for KFRT and mortality from 1988 to 2018.

**EXPOSURES** Chronic Kidney Disease Epidemiology Collaboration equation with serum creatinine (eGFR<sub>cr</sub> with and without race), cystatin C (eGFR<sub>cys</sub> without race), or both markers (eGFR<sub>cr-cys</sub> without race).

**MAIN OUTCOMES AND MEASURES** The prevalence of decreased eGFR at baseline and hazard ratios of KFRT and mortality in Black vs non-Black participants were calculated, adjusted for age and sex. Analyses were performed within each cohort and with random-effect meta-analyses of the models.

**RESULTS** Among 62 011 participants (20 773 Black and 41 238 non-Black; mean age, 63 years; 53% women), the prevalence ratio (95% CI; percent prevalences) of eGFR less than 60 mL/min/1.73 m<sup>2</sup> comparing Black with non-Black participants was 0.98 (95% CI, 0.93-1.03; 11% vs 12%) for eGFR<sub>cr</sub> with race, 0.95 (95% CI, 0.91-0.98; 17% vs 18%) for eGFR<sub>cys</sub>, and 1.2 (95% CI, 1.2-1.3; 13% vs 11%) for eGFR<sub>cr-cys</sub> but was 1.8 (95% CI, 1.7-1.8; 15% vs 9%) for eGFR<sub>cr</sub> without race. During a mean follow-up of 13 years, 8% and 4% of Black and non-Black participants experienced KFRT and 34% and 39% died, respectively. Decreased eGFR was associated with significantly greater risk of both outcomes for all equations. At an eGFR of 60 mL/min/1.73 m<sup>2</sup>, the hazard ratios for KFRT comparing Black with non-Black participants were 2.8 (95% CI, 1.6-4.9) for eGFR<sub>cr</sub> with race, 3.0 (95% CI, 1.5-5.8) for eGFR<sub>cys</sub>, and 2.8 (95% CI, 1.4-5.4) for eGFR<sub>cr-cys</sub> vs 1.3 (95% CI, 0.8-2.1) for eGFR<sub>cr</sub> without race. The 5-year absolute risk differences for KFRT comparing Black with non-Black participants were 1.4% (95% CI, 0.2%-2.6%) for eGFR<sub>cr</sub> with race, 1.1% (95% CI, 0.2%-1.9%) for eGFR<sub>cys</sub>, and 1.3% (95% CI, 0%-2.6%) for eGFR<sub>cr-cys</sub> vs 0.37% (95% CI, -0.32% to 1.05%) for eGFR<sub>cr</sub> without race. Similar patterns were observed for mortality.

**CONCLUSIONS AND RELEVANCE** In this retrospective analysis of 8 US cohorts including Black and non-Black individuals, the eGFR equation without race that included creatinine and cystatin C, but not the eGFR equation without race that included creatinine without cystatin C, demonstrated racial differences in the risk of KFRT and mortality throughout the range of eGFR. The eGFR<sub>cr-cys</sub> equation may be preferable to the eGFR<sub>cr</sub> equation without race for assessing racial differences in the risk of KFRT and mortality associated with low eGFR.

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JAMA. 2022;327(23):2306-2316. doi:10.1001/jama.2022.8801  
Published online June 6, 2022.

**S**tudies that used Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations with creatinine (alone or with cystatin C) and included a coefficient for race (Black or non-Black) to account for higher mean serum creatinine concentrations in Black vs non-Black individuals documented racial differences in the association of a low estimated glomerular filtration rate (eGFR) with risk of kidney failure with replacement therapy (KFRT) and mortality.<sup>1</sup> However, the use of race in GFR estimation and other clinical algorithms has been challenged because race is a social and not a biologic construct and does not fully capture the diversity within vs between racial groups.<sup>2</sup>

A creatinine-based eGFR equation that does not incorporate race was developed by CKD-EPI in 2021<sup>3</sup> and recommended for implementation in clinical laboratories by the National Kidney Foundation-American Society of Nephrology (NKF-ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.<sup>4</sup> This equation had small biases compared with directly measured GFR in Black and non-Black individuals, with a median of up to 4 mL/min/1.73 m<sup>2</sup> lower and higher values than measured GFR, respectively. As a result of eliminating race from eGFR, Black individuals are estimated to have a 2.0% higher prevalence of chronic kidney disease (CKD), and non-Black individuals a 1.5% lower prevalence, compared with older equations that included race. Whether these changes alter the association of decreased eGFR values with higher rates of KFRT and mortality within and between racial groups is unknown. This is important for assessing efforts to reduce the higher risk of KFRT in Black compared with non-Black individuals and tailoring risk-reduction strategies across the full spectrum of eGFR.

This study examined whether GFR estimating equations based on different filtration markers (creatinine [eGFR<sub>cr</sub>] vs cystatin C [eGFR<sub>cys</sub>] vs both [eGFR<sub>cr-cys</sub>]) and equations that included or excluded race altered risk estimates for KFRT and mortality for Black compared with non-Black participants.

## Methods

### Chronic Kidney Disease Prognosis Consortium

This study was approved for use of deidentified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health. The need for informed consent was waived by the institutional review board. The Chronic Kidney Disease Prognosis Consortium (CKD-PC) is a research group consisting of investigators representing cohorts from around the world. The consortium has been described elsewhere.<sup>5</sup> Investigators shared data for the purpose of collaborative meta-analyses to study prognosis in CKD. This study focused on cohorts that included both Black and non-Black individuals, had available creatinine and cystatin C (11 065 participants were excluded due to missing cystatin C data), and participated in analyses relating eGFR<sub>cr</sub> and eGFR<sub>cys</sub> to the outcomes of KFRT and mortality. The study included 5 general population cohorts (Atherosclerosis Risk in Communities [ARIC], Cardiovascular Health Study [CHS], Multi-Ethnic Study of Atherosclerosis [MESA], National

## Key Points

**Question** Compared with estimated glomerular filtration rate (eGFR) equations that include Black vs non-Black race or cystatin C, do eGFR equations without race or cystatin C alter estimates of racial differences in risk of kidney failure requiring replacement therapy and mortality?

**Findings** In this retrospective individual-level data analysis of 62 011 participants, decreased eGFR was related to higher risk for all equations and within both racial groups. Compared with alternative equations, the creatinine-based eGFR equation without race attenuated racial differences in the risk of kidney failure requiring replacement therapy and mortality at normal eGFR and showed no significant racial differences in the risk at reduced eGFR.

**Meaning** Among eGFR equations without race, the equation including both creatinine and cystatin C, but not the equation including creatinine without cystatin C, demonstrated racial differences in the risk of kidney failure requiring replacement therapy and mortality.

Health and Nutrition Examination Survey [NHANES] III, and Reasons for Geographic and Racial Differences in Stroke [REGARDS]) and 3 CKD cohorts (African American Study of Kidney Disease and Hypertension [AASK], Modification of Diet in Renal Disease [MDRD], and Chronic Renal Insufficiency Cohort [CRIC]).<sup>6-11</sup> Data were collected from 1988 to 2018. Information on race was provided in the original cohort data and was self-reported by participants in most cohorts using fixed categories (eAppendix 1 in [Supplement 1](#)).

### eGFR Equations

Measurement of creatinine and cystatin C followed previously reported methods.<sup>12-15</sup> Values from each cohort were calibrated to the extent possible using the available information. Serum creatinine assays were calibrated to the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatinine Plus assay; Hoffman-La Roche Ltd), traceable to National Institute of Standards and Technology creatinine standard reference material 967.<sup>16</sup> Serum cystatin C assays were calibrated to the Siemens Dade Behring Nephelometer, traceable to International Federation of Clinical Chemistry and Laboratory Medicine Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements certified reference materials.<sup>17,18</sup>

Seven GFR estimating equations developed by the CKD-EPI collaboration and recommended or discussed by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines or the 2021 NKF-ASN Task Force were analyzed.<sup>1,4</sup> The primary focus was on 4 equations (2009 eGFR<sub>cr</sub>[ASR], 2021 eGFR<sub>cr</sub>[AS], 2012 eGFR<sub>cys</sub>[AS], and 2021 eGFR<sub>cr-cys</sub>[AS]), including those which calculate eGFR after removing race (AS [age and sex] vs ASR [age, sex, and race]) and using cystatin C (cr-cys vs cr) as recommended in 2021. Because the race coefficient for eGFR<sub>cr-cys</sub>(ASR) is small, results are presented in eTables 4 and 6 and eFigure 1 in [Supplement 1](#), as are those for 2 additional equations that were not recommended

by the NKF-ASN Task Force (eGFRcr[ASR-NB] and eGFRcys[ASR-NB]). The modifier non-Black (NB) in eGFRcr(ASR-NB) and eGFRcys(ASR-NB) denotes omitting the Black race coefficient from the 2009 equations without refitting other coefficients.<sup>2</sup> The abbreviations indicate the year of equation development (2009,<sup>12</sup> 2012,<sup>13</sup> or 2021<sup>3</sup>), the filtration markers used (creatinine [cr] and/or cystatin C [cys]), and the demographic variables included (age, sex, and/or race [ASR]), consistent with previous studies.<sup>3,4</sup> All of the equations evaluated were developed by CKD-EPI. Therefore, the abbreviations do not include CKD-EPI as a prefix. eGFRcr(ASR) was defined as the reference because it is the most widely used of these equations.<sup>12,13</sup> eTable 1 in [Supplement 1](#) summarizes the nomenclature, variables, recommended use, and performance of eGFR relative to measured GFR for each equation. eTable 2 in [Supplement 1](#) shows the formulas used for each equation.<sup>3,4</sup>

## Outcomes

The primary outcomes were KFRT, all-cause mortality, and cardiovascular mortality. Six cohorts had data on KFRT, defined as start of kidney replacement therapy or death due to kidney disease other than acute kidney injury. Mortality and cause of death were available for each cohort. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke.

## Statistical Analyses

Analyses were conducted retrospectively within each cohort, and meta-analyses were performed across cohorts using multivariable random-effects models (eAppendix 1.2 in [Supplement 1](#)). eGFR distribution analyses (density plots and prevalence estimates) were limited to the general population cohorts, and confidence intervals were estimated by bootstrap. For the association of eGFR with outcomes, eGFR from each equation was modeled as piece-wise linear splines with knots at 60 mL/min/1.73 m<sup>2</sup> and 90 mL/min/1.73 m<sup>2</sup>. Analyses were performed within each cohort using Cox proportional hazards regression models adjusted for age, sex, and interaction terms for eGFR splines and race (non-Black vs Black). eGFR spline coefficients were then combined across cohorts using multivariate meta-analysis and hazard ratios with 95% CIs, estimated for each 1 mL/min/1.73 m<sup>2</sup> of eGFR from 15 to 120 for Black and non-Black participants separately, compared with a reference of 80 mL/min/1.73 m<sup>2</sup> in non-Black participants. Log-log plots (ie, visual inspection) confirmed validity of the proportional hazards assumption using eGFR categories by different equations. Differences between Black and non-Black individuals for a given equation and eGFR level were expressed as hazard ratios and differences in estimated 5-year risk. Point estimates were displayed at eGFR values of 60 mL/min/1.73 m<sup>2</sup> and 30 mL/min/1.73 m<sup>2</sup>, because they define CKD stages. Difference in estimated 5-year risk was calculated by combining the meta-analyzed hazard ratio with the 5-year risk for the reference point estimated from the REGARDS cohort. For analyses of KFRT, death was a censoring event. To examine consistency across cohorts, relative hazard ratios were calculated as the ratio of the haz-

ard ratios at specific values of eGFR for each eGFR equation compared with eGFRcr(ASR) within each cohort (eAppendix 1.2 in [Supplement 1](#)).

In exploratory analysis, the predictive discrimination performance of each eGFR equation with demographic variables was examined using 5-fold cross-validation C statistics, separately within each cohort. C statistics were summarized across cohorts as the median and interquartile interval. Change in C statistics between different eGFR equations within each cohort was estimated with the user-written “somersd” command<sup>19</sup> and then with meta-analysis across cohorts. The significance threshold of each hypothesis test was set at 2-sided  $P < .05$ . Because of the potential for type I error due to multiple comparisons, findings of the analyses should be interpreted as exploratory. All analyses were conducted using Stata MP version 16 (StataCorp).

## Results

### Study Populations

For these analyses, the 5 population-based cohorts included 18 073 Black participants and 38 017 non-Black participants (2% Asian, 8% Hispanic, 89% non-Hispanic White, and 1% other race and ethnicity [listed for each individual cohort in eAppendix 1.4 in [Supplement 1](#)]) and the 3 CKD cohorts included 2700 Black participants and 3221 non-Black participants (15% Hispanic, 78% non-Hispanic White, and 7% other race and ethnicity) for a total of 62 011 participants. The mean (SD) age was 63 (12) years, and 53% were women, with no missing data for age, sex, or race (Table 1; eTable 3 in [Supplement 1](#)).

### Prevalences of Decreased eGFR by Race and Their Ratios Across Equations

The prevalences of eGFR less than 60 mL/min/1.73 m<sup>2</sup> (CKD stage G3+) in Black vs non-Black individuals were 11% vs 12% for eGFRcr(ASR), 17% vs 18% for eGFRcys(AS), and 13% vs 11% for eGFRcr-cys(AS) compared with 15% vs 9% among Black vs non-Black individuals for eGFRcr(AS) (Table 2, Figure 1; eTable 4 in [Supplement 1](#)). As a result, the Black relative to non-Black prevalence ratios of eGFR less than 60 mL/min/1.73 m<sup>2</sup> were 0.98 (95% CI, 0.93-1.03) for eGFRcr(ASR), 0.95 (95% CI, 0.91-0.98) for eGFRcys(AS), 1.2 (95% CI, 1.2-1.3) for eGFRcr-cys(AS), and 1.8 (95% CI, 1.7-1.8) for eGFRcr(AS).

### Comparison of Risk Associations for KFRT

A total of 3265 KFRT events occurred over a mean (SD) follow-up of 12 (5) years in Black participants and 13 (6) years in non-Black participants. The 5-year estimated absolute risks of KFRT were 7.3% (95% CI, 6.9%-7.7%) in Black and 3.9% (95% CI, 3.7%-4.1%) in non-Black participants overall. For all equations, in both Black and non-Black populations, the risk of KFRT was significantly greater at lower vs higher eGFR (Figure 1; eFigure 1 in [Supplement 1](#)). Age- and sex-adjusted risks of KFRT were significantly higher in Black compared with non-Black participants for eGFRcr(ASR), eGFRcys(AS), and eGFRcr-cys(AS) across all

Table 1. Baseline Characteristics and Outcomes Among Study Participants by Cohort and Self-reported Race Group

Source	Participant race	No.	Age, mean (SD), y	Female, %	Mean (SD), mL				Kidney failure requiring treatment		All-cause mortality		
					eGFRcr	eGFRcys	eGFRcr-cys			Follow-up, mean (SD), y	5-y risk, %	Follow-up, mean (SD), y	5-y risk, %
					Age, sex, and race	Age and sex	Age and sex	Age and sex					
General population													
ARIC	Black	2484	62 (6)	64	92 (21)	83 (18)	89 (19)	89 (18)	21.0 (2.7)	0.65 (0.40-1.05)	17.2 (6.0)	6.1 (5.2-7.1)	
	Non-Black	8731	63 (6)	53	85 (14)	89 (14)	83 (18)	89 (14)	21.3 (1.7)	0.31 (0.21-0.45)	17.8 (5.6)	5.1 (4.6-5.6)	
CHS	Black	495	77 (5)	65	71 (19)	66 (17)	69 (20)	70 (19)			10.7 (5.4)	19.4 (16.2-23.2)	
	Non-Black	2489	78 (5)	58	65 (16)	69 (16)	65 (18)	69 (17)			10.0 (5.4)	22.5 (20.9-24.2)	
MESA	Black	1846	62 (10)	55	86 (19)	79 (16)	90 (20)	88 (18)			12.7 (3.3)	4.9 (4.0-6.0)	
	Non-Black	4848	62 (10)	52	82 (15)	86 (15)	89 (20)	91 (17)			13.2 (3.0)	3.4 (2.9-3.9)	
NHANES III	Black	1742	51 (20)	52	96 (29)	86 (25)	98 (27)	95 (26)			18.0 (7.8)	9.9 (8.6-11.4)	
	Non-Black	5280	59 (20)	53	86 (24)	90 (23)	88 (28)	92 (26)			16.5 (8.1)	12.7 (11.8-13.6)	
REGARDS	Black	11 506	65 (9)	61	88 (24)	80 (21)	79 (24)	82 (23)	11.3 (3.6)	1.62 (1.40-1.88)	11.9 (3.8)	9.0 (8.5-9.5)	
	Non-Black	16 669	66 (9)	50	82 (17)	86 (17)	77 (22)	84 (20)	11.4 (3.4)	0.36 (0.27-0.46)	12.0 (3.6)	8.0 (7.6-8.4)	
Overall	Black	18 073	63 (11)	60	89 (24)	81 (21)	83 (24)	85 (22)	12.7 (5.2)	1.47 (1.28-1.68)	13.2 (5.2)	8.6 (8.2-9.0)	
	Non-Black	38 017	65 (12)	52	82 (18)	86 (18)	81 (23)	86 (20)	14.0 (5.9)	0.41 (0.34-0.50)	14.0 (5.7)	8.3 (8.1-8.6)	
CKD population													
AASK	Black	949	55 (11)	39	46 (15)	42 (13)	48 (18)	45 (15)	7.4 (3.4)	16.5 (14.3-19.1)	7.7 (3.4)	9.3 (7.5-11.4)	
CRIC	Black	1650	58 (11)	51	44 (15)	40 (13)	51 (23)	46 (18)	8.0 (4.5)	22.7 (20.7-24.9)	9.8 (4.1)	14.4 (12.8-16.2)	
	Non-Black	2277	58 (11)	41	45 (15)	47 (16)	54 (24)	51 (20)	8.8 (4.4)	15.7 (14.2-17.3)	10.1 (3.7)	11.2 (10.0-12.6)	
MDRD	Black	101	50 (12)	44	36 (17)	33 (15)	35 (16)	33 (15)	7.7 (6.0)	37.0 (28.2-47.4)	13.4 (5.4)	9.9 (5.5-17.6)	
	Non-Black	944	52 (13)	39	35 (15)	36 (16)	32 (14)	33 (15)	7.8 (5.7)	39.3 (36.2-42.5)	14.1 (5.0)	8.1 (6.5-10.0)	
Overall	Black	2700	56 (11)	47	44 (15)	38 (13)	49 (21)	45 (17)	7.8 (4.2)	21.1 (19.5-22.7)	9.2 (4.1)	12.5 (11.3-13.9)	
	Non-Black	3221	56 (12)	40	42 (16)	44 (16)	47 (24)	46 (20)	8.5 (4.8)	22.8 (21.3-24.3)	11.3 (4.5)	10.3 (9.3-11.4)	
Populations combined													
Overall	Black	20 773	62 (11)	59	83 (27)	72 (23)	79 (26)	80 (26)	12.0 (5.3)	7.3 (6.9-7.7)	12.7 (5.3)	9.1 (8.7-9.5)	
	Non-Black	41 238	64 (12)	51	79 (21)	83 (21)	78 (24)	83 (23)	13.4 (6.0)	3.9 (3.7-4.1)	13.8 (5.6)	8.5 (8.2-8.8)	

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; cr, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate;

MESA, Multi-Ethnic Study of Atherosclerosis; MDRD, Modification of Diet in Renal Disease; NHANES, National Health and Nutrition Examination Survey III; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

eGFR levels (Figure 1). For example, the age- and sex-adjusted hazard ratio of KFRT at an eGFR of 60 mL/min/1.73 m<sup>2</sup> (compared with the referent of non-Black persons at an eGFR of 80 mL/min/1.73 m<sup>2</sup>) was 9.3 (95% CI, 4.9-17.9) in Black vs 3.3 (95% CI, 2.5-4.4) in non-Black individuals using eGFRcr(ASR), resulting in a significantly higher risk of KFRT in Black relative to non-Black participants (hazard ratio, 2.8 [95% CI, 1.6-4.9], Table 2; 5-year absolute estimated risk difference, 1.4% [95% CI, 0.2%-2.6%], eTable 4 in Supplement 1). Similar hazard ratios were observed for eGFRcys

(AS) and eGFRcr-cys(AS): the Black relative to non-Black participant hazard ratios of KFRT at an eGFR of 60 mL/min/1.73 m<sup>2</sup> compared with the reference of eGFR of 80 mL/min/1.73 m<sup>2</sup> were 3.0 (95% CI, 1.5-5.8) and 2.8 (95% CI, 1.4-5.4), respectively (5-year risk differences of 1.1% [95% CI, 0.2%-1.9%] and 1.3% [95% CI, 0%-2.6%]). In contrast, racial differences in KFRT risk were smaller for eGFRcr(AS) at values of 60 mL/min/1.73 m<sup>2</sup> or lower (Figure 1), with the Black relative to non-Black participant hazard ratio of KFRT at an eGFR of 60 mL/min/1.73 m<sup>2</sup> no longer significantly different



Table 2. Prevalence of Decreased eGFR and Age- and Sex-Adjusted Hazard Ratios of KFRT for Different GFR Estimating Equations, by Race<sup>a</sup>

Equation	Participant race	Prevalence in general population cohorts and their ratio by race, % (95% CI)		Hazard ratios of KFRT vs eGFR = 80 mL/min/1.73 m <sup>2</sup> and their ratio by race (95% CI)		
		eGFR <30 mL/min/1.73 m <sup>2</sup>	eGFR <60 mL/min/1.73 m <sup>2</sup>	eGFR = 30 mL/min/1.73 m <sup>2</sup>	eGFR = 60 mL/min/1.73 m <sup>2</sup>	eGFR = 80 mL/min/1.73 m <sup>2</sup>
2009 eGFRcr (age, sex, and race)	Black	1.7 (1.5-1.9)	11 (11-12)	119 (41-351)	9.3 (4.9-17.9)	3.7 (2.0-6.7)
	Non-Black	0.70 (0.61-0.78)	12 (11-12)	74 (35-160)	3.3 (2.5-4.4)	1 [Reference]
	Ratio, Black vs non-Black	2.5 (2.0-2.9)	0.98 (0.93-1.03)	1.6 (1.1-2.3)	2.8 (1.6-4.9)	3.7 (2.0-6.7)
2021 eGFRcr (age and sex)	Black	1.9 (1.7-2.2)	15 (15-16)	78 (27-226)	5.1 (2.6-9.9)	2.3 (1.2-4.2)
	Non-Black	0.52 (0.44-0.59)	8.7 (8.4-9.0)	74 (32-172)	3.8 (2.6-5.7)	1 [Reference]
	Ratio, Black vs non-Black	3.8 (3.1-4.4)	1.8 (1.7-1.8)	1.0 (0.8-1.4)	1.3 (0.8-2.1)	2.3 (1.2-4.2)
2012 eGFRcys (age and sex)	Black	2.7 (2.5-2.9)	17 (16-17)	84 (24-299)	8.0 (3.6-17.8)	3.2 (2.0-5.0)
	Non-Black	1.8 (1.7-1.9)	18 (17-18)	41 (14-126)	2.7 (1.7-4.3)	1 [Reference]
	Ratio, Black vs non-Black	1.5 (1.3-1.7)	0.95 (0.91-0.98)	2.0 (1.0-4.0)	3.0 (1.5-5.8)	3.2 (2.0-5.0)
2021 eGFRcr-cys (age and sex)	Black	2.2 (1.9-2.4)	13 (13-14)	119 (37-377)	9.7 (5.0-18.9)	2.9 (1.6-5.3)
	Non-Black	0.81 (0.72-0.90)	11 (10-11)	74 (32-170)	3.5 (2.6-4.8)	1 [Reference]
	Ratio, Black vs non-Black	2.7 (2.3-3.1)	1.2 (1.2-1.3)	1.6 (1.1-2.4)	2.8 (1.4-5.4)	2.9 (1.6-5.3)

Abbreviations: cr, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate; KFRT, kidney failure with replacement therapy.

<sup>a</sup> Total sample size of 56 090 for prevalence estimates in general population cohorts, and 45 311 in hazard ratio estimation of KFRT. Ratios in Black compared with non-Black participants are prevalence ratios for the first 2 data columns and hazard ratios for the last 3 columns, and calculated by dividing

the estimate in Black participants by the estimate in non-Black participants. Note that the ratio of 2 hazard ratios with the same reference group, eg, non-Black participants at eGFR of 80 mL/min/1.73 m<sup>2</sup>, is itself a hazard ratio. For example, 1.6 is the hazard ratio of KFRT in Black compared with non-Black participants at an eGFRcr(ASR) of 30 mL/min/1.73 m<sup>2</sup>.

(hazard ratio, 1.3 [95% CI, 0.8-2.1]; 5-year risk difference, 0.37% [95% CI, -0.32% to 1.05%]). Results were similar at an eGFR of 30 mL/min/1.73 m<sup>2</sup>, with absence of statistically significant racial differences in risk of KFRT for eGFRcr(AS) in contrast to the other 3 equations (Table 2; eFigure 2 in Supplement 1). Similar patterns of significantly higher estimated risk of KFRT in Black relative to non-Black participants were observed for eGFRcr-cys(ASR) and eGFRcr-cys(ASR-NB), whereas eGFRcr(ASR-NB) was similar to eGFRcr(AS), which showed attenuation of racial differences in risk (eTable 4 in Supplement 1).

Comparisons of equations applied within each cohort showed that compared with eGFRcr(ASR), eGFRcys(AS) and eGFRcr-cys(AS) resulted in similar estimates (7 of the 8 relative hazard ratios were close to 1.0 with confidence intervals including 1.0; Figure 2; eTable 5 in Supplement 1). In contrast, the comparison of eGFRcr(AS) with eGFRcr(ASR) resulted in relative hazard ratios significantly less than 1.0 in all 4 cohorts with data, indicating lower Black relative to non-Black participant hazard ratio estimates with eGFRcr(AS).

### Comparison of Risk Associations for All-Cause and Cardiovascular Mortality

Decreased eGFR was associated with significantly higher age- and sex-adjusted risk for all-cause and cardiovascular mortality for all equations (Table 3; eFigure 1 in Supplement 1). Compared with non-Black participants, mortality risk at an eGFR of 60 mL/min/1.73 m<sup>2</sup> was significantly higher in Black participants for nearly all estimates for eGFRcr(ASR), eGFRcys(AS), and eGFRcr-cys(AS). For example, eGFRcys(AS) showed Black compared with non-Black participant hazard ratios of 1.2 (95% CI, 1.1-1.4) for all-cause mortality and 1.4 (95% CI, 1.2-1.7) for car-

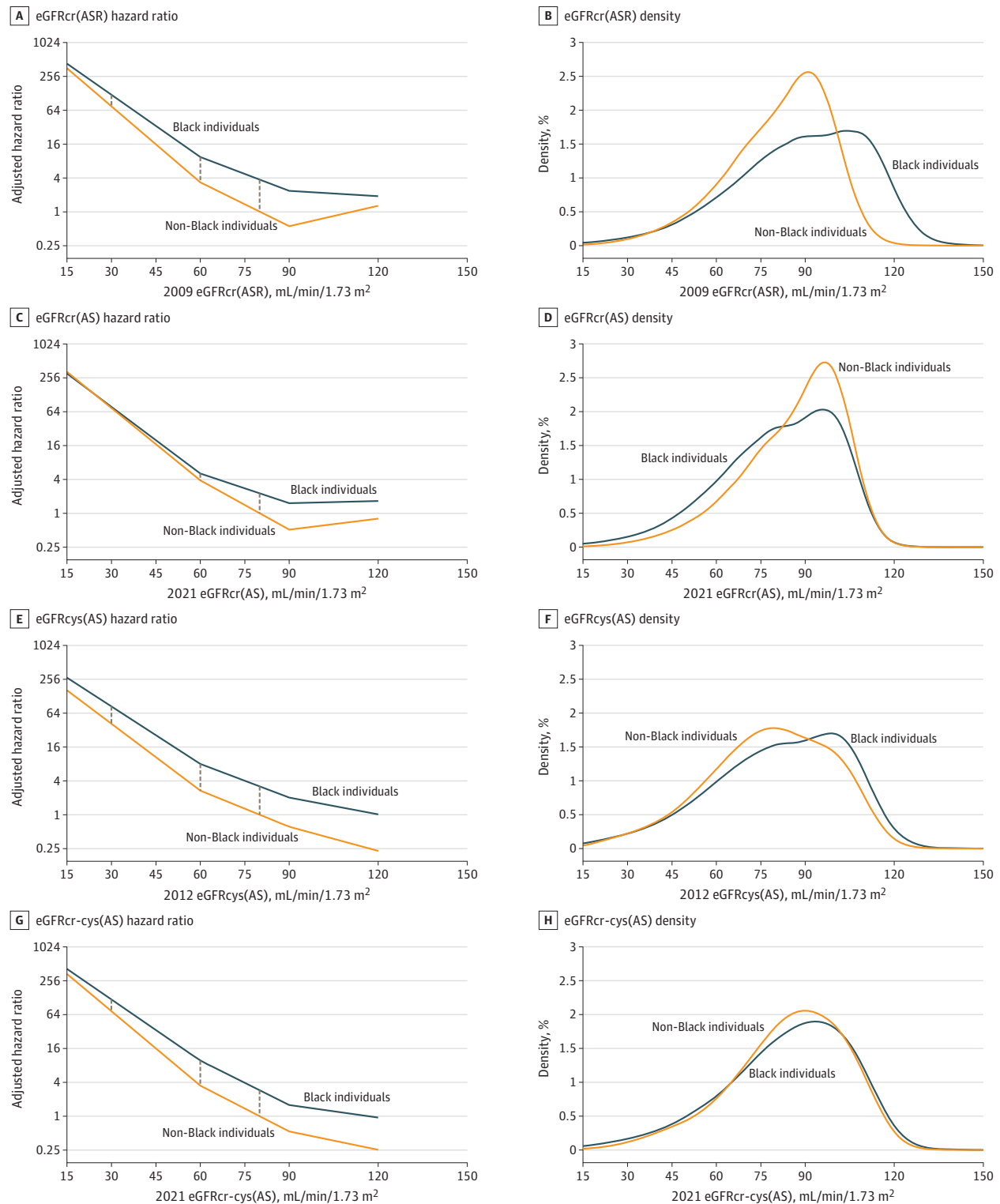
diovascular mortality, with 5-year risk differences of 1.0% (95% CI, 0.4%-1.7%) and 0.71% (95% CI, 0.38%-1.03%), respectively. In contrast, when the eGFRcr(AS) equation was used, risks were not significantly different in Black compared with non-Black participants, with hazard ratios of 1.0 (95% CI, 0.9-1.1) for all-cause mortality and 1.1 (95% CI, 0.9-1.3) for cardiovascular mortality, with 5-year risk differences of -0.04% (95% CI, -0.49% to 0.42%) and 0.08% (95% CI, -0.19% to 0.35%), respectively (Table 3; eTable 6 in Supplement 1).

Within each cohort, comparing equations for all-cause and cardiovascular mortality showed that, similar to KFRT, eGFRcr(AS) resulted in a smaller estimate of the Black to non-Black participant hazard ratio (relative hazard ratios significantly <1.0 for 13 of 14 estimates in Figure 2). In contrast, eGFRcys(AS) and eGFRcr-cys(AS) were similar to eGFRcr(ASR) (25 of 28 relative hazard ratios not significantly different from 1.0).

### Comparison of Risk Discrimination Across Equations

When included in a model with age and sex, the 5-fold cross-validated C statistics for KFRT had a median value of greater than 0.78 for all eGFR equations within race groups. Compared with eGFRcr(ASR), equations that included cystatin C in addition to creatinine had significantly higher cross-validated discrimination in race-stratified analyses or overall in race-adjusted analyses (0.013 to 0.018 increase in the C statistic, all *P* values < .03, eTable 4 in Supplement 1). Similarly, equations that included cystatin C in addition to creatinine had higher discrimination for mortality and cardiovascular mortality compared with eGFRcr(ASR) (0.008 to 0.013 increase in the C statistic, all *P* values < .05 except *P* = .06 for eGFRcr-cys[ASR-NB]; eTable 6 in Supplement 1). Within race groups, or overall when adjusting for race, the

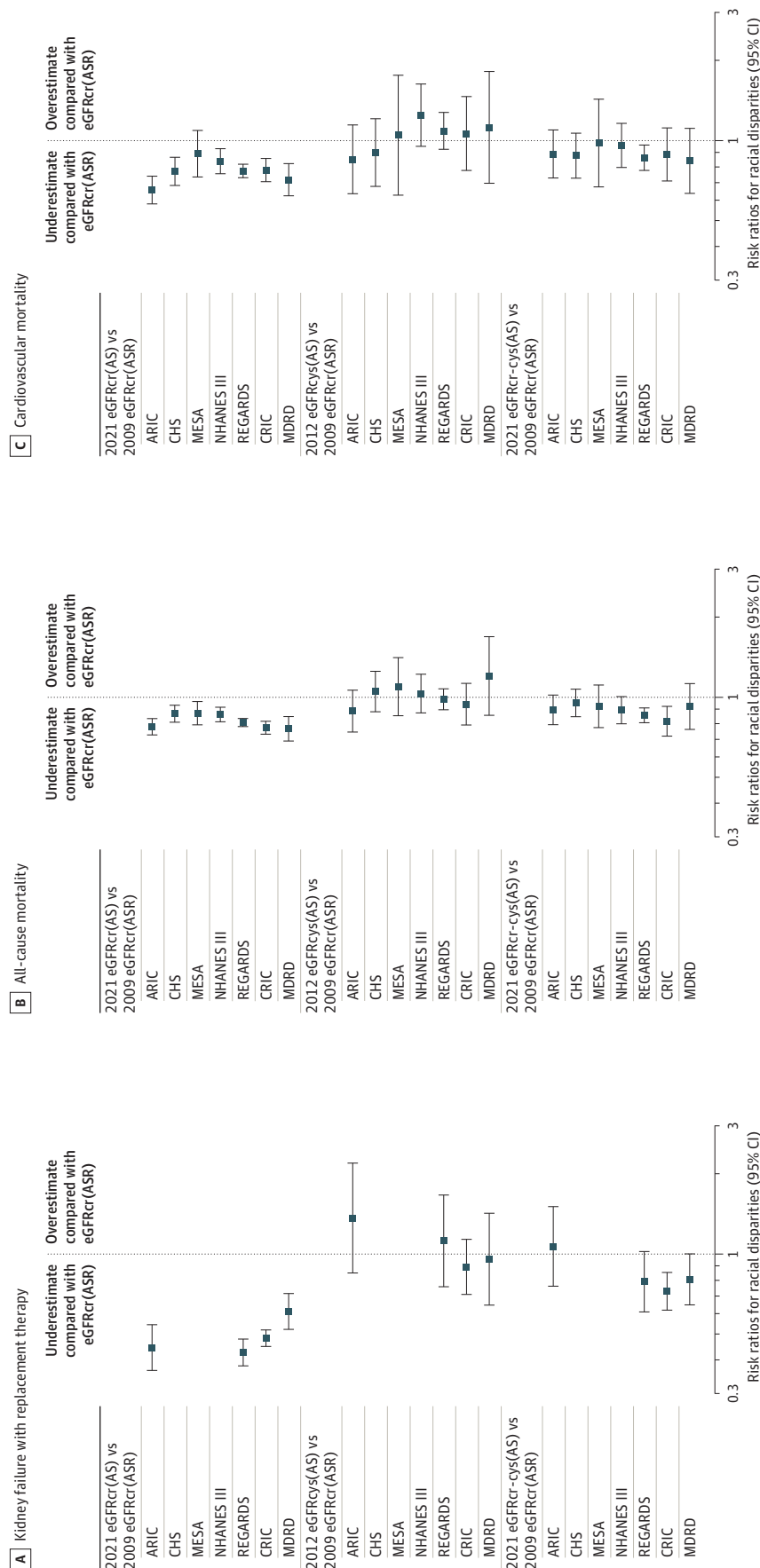
**Figure 1. Risk of Kidney Failure With Replacement Therapy (KFRT) Associated With Level of Estimated Glomerular Filtration Rate (eGFR) in Black and Non-Black Participants for Different GFR Estimating Equations**



Vertical lines show the difference in log hazard ratios between Black and non-Black participants for a given eGFR, which are smaller for 2021 eGFRcr(AS) than for the other equations. The hazard ratio is adjusted for age and sex and calculated vs the reference point (80 mL/min/1.73 m<sup>2</sup> in the non-Black population). Point estimates at eGFRs of 30, 60, and 80 mL/min/1.73 m<sup>2</sup> are

reported in Table 2. The KFRT meta-analysis included participants from AASK, ARIC, CRIC, MDRD, and REGARDS. Density plots show the distribution of eGFR in the population-based cohorts (ARIC and REGARDS). AS indicates age and sex and ASR, age, sex, and race.

Figure 2. Relative Hazard Ratios for Black vs Non-Black Participants Using Different Glomerular Filtration Rate (GFR) Estimating Equations Compared With 2009 eGFRcr(ASR) in Each Participating Cohort



Estimates are the ratio of Black vs non-Black participant hazard ratio at eGFR of 60 mL/min/1.73 m<sup>2</sup> using each equation compared with the corresponding hazard ratio for the 2009 eGFRcr(ASR) adjusted for age and sex. The 2021 eGFRcr(AS) results in a significant attenuation of racial differences compared with the 2009 eGFRcr(ASR) in 17 of 18 relative hazard ratios (95% CIs did not include 1.0). In contrast, for the 2012 eGFRcys(AS) and 2021 eGFRcr-cys(AS), 32 of 36 95% CIs for the relative hazard ratios contain 1.0. Risk ratios less than 1 represent

underestimation compared with eGFRcr (age, sex, and race). The data are available in eTable 5 in Supplement 1. ARIC indicates Atherosclerosis Risk in Communities; AS, age and sex; ASR, age, sex, and race; CHS, Cardiovascular Health Study; CRIC, Chronic Renal Insufficiency Cohort; MDRD, Modification of Diet in Renal Disease; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

Table 3. Age- and Sex-Adjusted Hazard Ratios of All-Cause and Cardiovascular Mortality Across Different GFR Estimating Equations by Race<sup>a</sup>

Equations	Participant race	Hazard ratio vs eGFR = 80 mL/min/1.73 m <sup>2</sup> and their ratio by race (95% CI)					
		All-cause mortality			Cardiovascular mortality		
		eGFR = 30 mL/min/1.73 m <sup>2</sup>	eGFR = 60 mL/min/1.73 m <sup>2</sup>	eGFR = 80 mL/min/1.73 m <sup>2</sup>	eGFR = 30 mL/min/1.73 m <sup>2</sup>	eGFR = 60 mL/min/1.73 m <sup>2</sup>	eGFR = 80 mL/min/1.73 m <sup>2</sup>
2009 eGFRcr (age, sex, and race)	Black	3.3 (2.4-4.6)	1.3 (1.2-1.5)	1.1 (1.1-1.2)	4.3 (2.4-7.7)	1.8 (1.4-2.2)	1.3 (1.2-1.6)
	Non-Black	3.0 (2.6-3.4)	1.1 (1.0-1.2)	1 [Reference]	3.7 (2.9-4.7)	1.3 (1.1-1.5)	1 [Reference]
	Ratio, Black vs non-Black	1.1 (0.9-1.4)	1.2 (1.1-1.4)	1.1 (1.1-1.2)	1.2 (0.8-1.7)	1.4 (1.1-1.7)	1.3 (1.2-1.6)
2021 eGFRcr (age and sex)	Black	3.0 (2.2-4.1)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	3.9 (2.3-6.6)	1.5 (1.2-1.8)	1.3 (1.1-1.4)
	Non-Black	3.3 (2.8-3.8)	1.2 (1.1-1.3)	1 [Reference]	3.8 (3.0-4.8)	1.4 (1.2-1.6)	1 [Reference]
	Ratio, Black vs non-Black	0.9 (0.7-1.2)	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.0 (0.7-1.5)	1.1 (0.9-1.3)	1.3 (1.1-1.4)
2012 eGFRcys (age and sex)	Black	4.4 (3.2-6.1)	1.8 (1.5-2.1)	1.4 (1.2-1.6)	5.7 (3.5-9.2)	2.4 (1.9-3.1)	1.6 (1.4-1.9)
	Non-Black	3.8 (3.1-4.8)	1.4 (1.3-1.6)	1 [Reference]	4.6 (3.5-6.0)	1.7 (1.5-2.0)	1 [Reference]
	Ratio, Black vs non-Black	1.2 (0.8-1.6)	1.2 (1.1-1.4)	1.4 (1.2-1.6)	1.2 (0.8-1.9)	1.4 (1.2-1.7)	1.6 (1.4-1.9)
2021 eGFRcr-cys (age and sex)	Black	4.0 (2.9-5.5)	1.6 (1.4-1.8)	1.2 (1.1-1.3)	5.1 (3.0-8.6)	2.1 (1.6-2.6)	1.4 (1.2-1.5)
	Non-Black	3.9 (3.3-4.5)	1.4 (1.3-1.5)	1 [Reference]	4.5 (3.7-5.5)	1.6 (1.4-1.9)	1 [Reference]
	Ratio, Black vs non-Black	1.0 (0.8-1.4)	1.1 (1.0-1.2)	1.2 (1.1-1.3)	1.1 (0.7-1.7)	1.3 (1.0-1.6)	1.4 (1.2-1.5)

Abbreviations: cr, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate.

<sup>a</sup> Total sample of 62 011 for hazard ratio estimation for all-cause mortality, and 61 062 for cardiovascular mortality. Ratios in Black compared with non-Black participants are hazard ratios, and calculated by dividing the estimate in Black

participants by the estimate in non-Black participants. Note that the ratio of 2 hazard ratios with the same reference group, eg, non-Black participants at eGFR of 80 mL/min/1.73 m<sup>2</sup>, is itself a hazard ratio. For example, 1.2 is the hazard ratio of all-cause mortality in Black compared with non-Black participants at an eGFRcr(ASR) of 60 mL/min/1.73 m<sup>2</sup>.

discrimination of eGFRcr(ASR), eGFRcr(AS), and eGFRcr (ASR-NB) were not significantly different (0.000 with confidence intervals of < ±0.001).

## Discussion

This retrospective analysis of Black and non-Black adults participating in 8 US cohort studies showed that decreased eGFR values, calculated with the eGFRcr(AS) equation, were significantly associated with higher KFRT risk within each race group. However, this equation attenuated racial differences in risk of KFRT and mortality at decreased eGFR values compared with the eGFRcr(ASR), eGFRcys(AS), and eGFRcr-cys(AS) equations. The eGFRcr-cys(AS) equation, which provides a more accurate estimate of measured GFR than these other equations,<sup>3</sup> was significantly associated with both KFRT and mortality risk in both Black and non-Black participants, and demonstrated a higher risk of these outcomes in Black relative to non-Black individuals. These data suggested that eGFRcr-cys(AS) may be preferred for measuring the higher risk of KFRT and mortality among Black individuals at both normal and moderately decreased eGFR because this equation was an accurate estimate of measured GFR and also documented the higher risk of KFRT and mortality compared with alternative eGFR equations.

Valid measures of the racial differences in the risk of KFRT and mortality are important for tailoring intervention strategies and documenting progress toward racial equity in kidney health. Overall, the findings of this study support the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease recommendations that the new 2021 CKD-EPI creatinine equation without race (the eGFRcr[AS] equation)<sup>3,4</sup> be imple-

mented in clinical laboratories, because creatinine remains the dominant filtration marker for estimating GFR and this equation discriminates risk well within each racial group. However, data presented here showed that adding cystatin C to the eGFR equation without race is necessary to estimate racial difference in risk and improve accuracy at the individual patient level.

Black individuals have higher rates of incident KFRT and mortality than non-Black individuals.<sup>20,21</sup> eGFR has been used to detect, stage, and treat CKD and to examine disparities in CKD prevalence and risk for adverse outcomes.<sup>1,22</sup> Most of the US literature has used eGFRcr equations that include a race coefficient (predominantly the MDRD Study and 2009 CKD-EPI eGFRcr[ASR]). These equations showed a similar or slightly lower prevalence of moderately reduced eGFR in Black compared with non-Black individuals, in contrast to the higher KFRT incidence in Black than in non-Black adults.<sup>23,24</sup> Possible causes for the discrepancy in racial differences in prevalence of reduced eGFR vs incidence of KFRT have been documented, including faster decline in measured GFR, more severe albuminuria, and other risk factors for CKD progression, underdiagnosis and undertreatment of CKD, as well as adverse social determinants of health, racial discrimination, and structural racism disproportionately experienced by Black compared with White individuals in the US.<sup>4,24-26</sup>

Consistent with findings in NHANES,<sup>3</sup> the current study showed that the eGFRcr(AS) equation resulted in a higher estimated prevalence of reduced eGFR among Black individuals and lower estimated prevalence in non-Black individuals as compared with eGFRcr(ASR). This is likely due to eGFRcr(AS) having an approximate 4-mL/min/1.73 m<sup>2</sup> systematic underestimation of measured GFR in Black individuals and similar overestimation of measured GFR in non-Black individuals.<sup>3</sup> The higher prevalence of decreased eGFR among Black individuals



based on eGFRcr(AS) has the potential benefit of increasing awareness of CKD and promoting earlier interventions to reduce disease progression in Black individuals, but also the potential harm of overdiagnosis. However, the lower estimation of racial differences in KFRT and mortality risk by eGFR(AS) could have unintended consequences for research and public health policies, such as reduced emphasis on understanding existing risk factors for racial disparities in KFRT and mortality risk.

The present analysis focused on eGFR, because eGFR is routinely used in clinical practice to assess the presence and severity of kidney disease and to assess the risk of progression to kidney failure. Risk tools, such as the kidney failure risk equation, are increasingly used in clinical decision-making and benefit from the incorporation of other risk factors in addition to eGFR.<sup>27</sup> The current study built on this work to show that including cystatin C in the eGFR equation may improve the predictive capability of eGFRcr: the eGFRcr-cys(AS) equation had significantly greater discrimination of KFRT relative to eGFRcr(ASR) and eGFRcr(AS). These findings support the NKF-ASN Task Force recommendations to increase cystatin C testing, because it is less affected by muscle mass and race group than serum creatinine. This recommendation is further supported by its recommendation for confirmation of CKD in the KDIGO 2012 guidelines.<sup>28</sup> Cystatin C has been standardized since 2010,<sup>18</sup> improves risk prediction compared with equations that include creatinine alone,<sup>6,29</sup> and is now integrated into early CKD detection guidelines<sup>30</sup> and CKD curricula.<sup>31</sup>

### Limitations

This study has several limitations. First, the study lacked specific information on factors that may differ between racial groups,

such as measures of social determinants of health, and therefore could not statistically adjust for all potential causes for observed racial differences. Second, there may be unmeasured heterogeneity in methods of measurement across cohorts, although the overall results were consistent across all cohorts. Third, insufficient numbers of individuals from racial and ethnic groups other than Black and White preclude comparing outcomes across other race and ethnic groups.<sup>32</sup> Fourth, other outcomes of interest, such as cardiovascular disease events and heart failure, were not examined. Fifth, physicians' decisions to start KFRT may have been influenced by serum creatinine and eGFRcr reporting or other factors, whereas cystatin C is not widely available in clinical practice. Sixth, data on measured GFR were not available in all cohorts. Seventh, none of the models underwent external validation outside the cohorts in which they were developed. Eighth, this study assessed discrimination, but not calibration, which is important in assessing how accurately an estimated probability of an outcome can be applied to an individual patient.

### Conclusions

In this retrospective analysis of 8 US cohorts including Black and non-Black individuals, the eGFR equation without race that included creatinine and cystatin C, but not the eGFR equation without race that included creatinine without cystatin C, demonstrated racial differences in the risk of KFRT and mortality throughout the range of eGFR. The eGFRcr-cys equation may be preferable to the eGFRcr equation without race for assessing racial differences in the risk of KFRT and mortality associated with low eGFR.

### ARTICLE INFORMATION

**Accepted for Publication:** May 11, 2022.

**Published Online:** June 6, 2022.  
doi:10.1001/jama.2022.8801

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**Conflict of Interest Disclosures:** Dr Gutiérrez reported receiving grants from Akebia, Amgen, and GlaxoSmithKline and personal fees from AstraZeneca, Reata, and Ardelyx, and serving on a data monitoring committee for QED outside the submitted work. Dr Grams reported receiving grants from the National Institutes of Health (NIH) and National Kidney Foundation (NKF) during the conduct of the study; receiving grants from the NIH

and NKF and nonfinancial support from Kidney Disease: Improving Global Outcomes (KDIGO) outside the submitted work; and being a member of the USRDS Scientific Advisory Committee and NKF Scientific Advisory Committee and KDIGO Executive Committee. Dr Matsushita reported receiving grants from the NIH during the conduct of the study and personal fees from Akebia and Kyowa Kirin and grants from Kyowa Kirin outside the submitted work. Dr Go reported receiving grants from the National Institute of Diabetes, Digestive, and Kidney Diseases during the conduct of the study. Dr Shlipak reported receiving personal fees from Cricket Health, Intercept Pharmaceuticals, Bayer Pharmaceuticals, AstraZeneca, and Boehringer Ingelheim and grants from Bayer Pharmaceuticals outside the submitted work. Dr Inker reported funding to Tufts Medical Center for research, consulting, or contracts with the NIH, NKF, Reata, Omers, Chinnocks Tricida, and Goldfinch Bio. Dr Inker also reported receiving consulting fees from Diametrix and being a member of the NKF-American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease; the views presented here are hers and the authors' and do not reflect the views of the NKF-ASN Task Force. Dr Crews reported receiving grants from Somatus and Baxter International outside the submitted work and being a member of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing

Kidney Disease. Dr Levey reported receiving grants from the NIH, NKF (grant support for Chronic Kidney Disease Epidemiology Collaboration and Chronic Kidney Disease Prognosis Consortium [CKD-PC]) during the conduct of the study and personal fees from AstraZeneca for participation in data and safety monitoring boards for dapagliflozin clinical trials. Dr Coresh reported receiving grants from the NIH and NKF during the conduct of the study and being a consultant and owning stock options of Healthy.io outside the submitted work. No other disclosures were reported.

**Funding/Support:** The CKD-PC data coordinating center is funded in part by a program grant from the NKF and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK100446). A variety of sources have supported enrollment and data collection including laboratory measurements and follow-up in the collaborating cohorts of the CKD-PC (eAppendix 2 in Supplement 1). These funding sources include the NIH for the African American Study of Kidney Disease and Hypertension (AASK), Atherosclerosis Risk in Communities, Cardiovascular Health Study, Chronic Renal Insufficiency Cohort (CRIC), Multi-Ethnic Study of Atherosclerosis, and Reasons for Geographic and Racial Differences in Stroke, a number of pharmaceutical companies donated medications for the trial component of AASK, a number of clinical and translational science institutional awards funded part of CRIC, and the US Centers for Disease Control and Prevention provided support for the National Health and Nutrition Examination Survey.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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**Additional Information:** An earlier version of these analyses was presented to the NKF-ASN Task Force.

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