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Original Article

ORIGINAL ARTICLE

Performance of the race-free CKD-EPI creatinine-based eGFR equation in a Danish cohort with measured GFR

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ABSTRACT

Background. In 2021, an updated Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimated glomerular filtration rate (eGFR) without a coefficient for race (CKD-EPI21) was developed. The performance of this new equation has yet to be examined among specific patient groups.

Methods. We compared the performances of the new CKD-EPI21 equation and the 2009 equation assuming non-Black race (CKD-EPI09-NB) in patients with GFR measured by chromium-51-EDTA plasma clearance at Aarhus University Hospital in Denmark during 2010–18. We examined bias, accuracy, precision and correct classification of chronic kidney disease (CKD) stage using chromium-51-EDTA clearance as the reference standard. We assessed the performance in the total cohort, cancer patients and potential living kidney donors. We also assessed the performance stratified by CKD stage in the total cohort.

Results. In this predominantly white population, the CKD-EPI21 equation performed slightly better than the CKD-EPI09-NB equation in both the total cohort ($N = 4668$), and in cancer patients ($N = 3313$) and potential living kidney donors ($N = 239$). In the total cohort, the CKD-EPI21 equation demonstrated a slightly lower median absolute bias (−0.2 versus −4.4 mL/min/1.73 m^2), and a similar accuracy, precision and correct classification of CKD stage compared with the CKD-EPI09-NB equation. When stratified by CKD stage, the CKD-EPI09-NB equation performed slightly better than the CKD-EPI21 equation among patients with a measured GFR (mGFR) <60 mL/min/1.73 m^2.

Conclusions. In a selected cohort of Danish patients with mGFR, the CKD-EPI21 equation performed slightly better than the CKD-EPI09-NB equation except for patients with a mGFR <60 mL/min/1.73 m^2, where CKD-EPI09-NB performed slightly better although the differences were considered clinically insignificant.

Keywords: CKD-EPI equation, GFR, race

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KEY LEARNING POINTS

What was known:

- An updated Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimated glomerular filtration rate (eGFR) without a coefficient for race (CKD-EPI21) was developed and published in 2021.

This study adds:

- In this study of predominantly white patients with GFR measured by chromium-51-EDTA plasma clearance, the overall performance of the CKD-EPI21 equation was slightly better than the original 2009 CKD-EPI equation assuming non-Black race (CKD-EPI09-NB), both overall and in cohorts of cancer patients and potential living kidney donors.
- However, the CKD-EPI09-NB equation performed slightly better than the CKD-EPI21 equation for patients with a measured GFR <60 mL/min/1.73 m^2.

Potential impact:

- There were slight differences in the performance of CKD-EPI21 and CKD-EPI09-NB depending on the kidney function; however, these differences may not be clinically significant.

INTRODUCTION

Accurate estimation of glomerular filtration rates (GFRs) is pivotal, as the estimated GFR (eGFR) is recommended to identify and monitor patients with chronic kidney disease (CKD) and to guide adjustments to medications and contrast medium [1]. The first version of the widely used Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based eGFR equation developed in 2009 (CKD-EPI09) based on patients included in American studies, included the variables serum creatinine, age, sex and race (Black versus non-Black) [2]. A new creatinine-based eGFR equation was proposed in 2021 that excludes the race term (CKD-EPI21) [3]. The authors concluded that the new equation is sufficiently accurate to be implemented in clinical practice. This led the National Kidney Foundation and American Society of Nephrology to recommend the use of this new equation in the USA [4]. However, Inker *et al.* [3] speculated that the new equation could lead to systematic differences in GFR estimation between race groups. This was confirmed by a recent study showing that exclusion of the race term would lead to fewer Black patients receiving the full dose of anticancer treatments, as more Black patients have an eGFR below kidney function cutoffs when using the CKD-EPI21 equation compared with the CKD-EPI09 equation [5]. Furthermore, in predominantly non-Black populations, such as Scandinavia [6, 7], the introduction of the CKD-EPI21 equation is observed to decrease the prevalence of CKD using eGFR by approximately 25%. Thus, the implementation of this new formula should be supported by studies establishing its accuracy compared with measured GFR (mGFR).

Some studies have examined the performance of the CKD-EPI21 equation in specific patient groups [8–14]. To further validate the new CKD-EPI21 equation, we examined its performance in a Danish and predominantly white population, including cohorts of cancer patients and potential living kidney donors, and compared the new equation with the original CKD-EPI09 equation considering all patients as non-Black (CKD-EPI09-NB). We assessed bias, precision, accuracy and the ability to categorize patients correctly according to CKD stage comparing the eGFR with mGFR using chromium-51-EDTA (^{51}Cr-EDTA) plasma clearance.

MATERIALS AND METHODS

Setting and data sources

We conducted this cross-sectional study using data from Danish medical databases. Denmark's National Health Service provides tax-supported healthcare to the Danish population, ensuring free access to general practitioners and hospitals [15]. All Danish residents are assigned a unique personal identifier that permits individual-level linkage among Danish registries, including the Danish National Patient Registry (patient registry) [16], laboratory databases providing data on creatinine measurements from general practices and hospitals [17, 18], and the Danish Civil Registration System [19]. The creatinine was measured based on isotope dilution mass spectrometry (IDMS)-traceable creatinine enzymatic assays. The mGFR was calculated from the plasma ^{51}Cr-EDTA clearance determined at Aarhus University Hospital, primarily for clinical purposes (e.g. before initiation of anticancer drug treatment or kidney donation). The ^{51}Cr-EDTA was administered intravenously followed by oral hydration. Plasma ^{51}Cr-EDTA was evaluated at 180, 200, 220 and 240 min after injection if the eGFR was >40 mL/min/1.73 m^2, at 180, 210, 240, 270 and 300 min after injection if the eGFR was 20–40 mL/min/1.73 m^2, and at 180, 210, 240, 270 and 300 min and 24 h after injection if the eGFR was <20 mL/min/1.73 m^2 [20, 21]. The mGFR was modeled using the Brochner Mortensen method. The body surface area was calculated using the DuBois equation. We did not have access to direct information about indications for the mGFR, but we used the patient registry to identify the most likely indication (see below).

Study cohort

We identified patients with an mGFR from 1 January 2010 to 31 December 2018 and included the first recorded measurement for each patient. We excluded patients without a creatinine measurement in the laboratory database within the 3 months prior to the date of the mGFR, patients receiving dialysis within the year prior to the date of GFR measurement as recorded in the patient registry and patients <18 years of age (Fig. 1). We identified three study cohorts for analysis: a total cohort consisting of all eligible patients, a cancer cohort consisting of patients with an inpatient or outpatient cancer diagnosis in the patient registry within the 3 months prior to the date of the mGFR, and a kidney donor cohort consisting of non-cancer patients with an outpatient diagnosis code for potential living kidney donation in the patient registry within the 3 months prior to the date of the mGFR or with a surgery code for living kidney donation in the patient registry within 1 year after the mGFR (see the Codebook in the Supplementary data for codes). The most recent creatinine

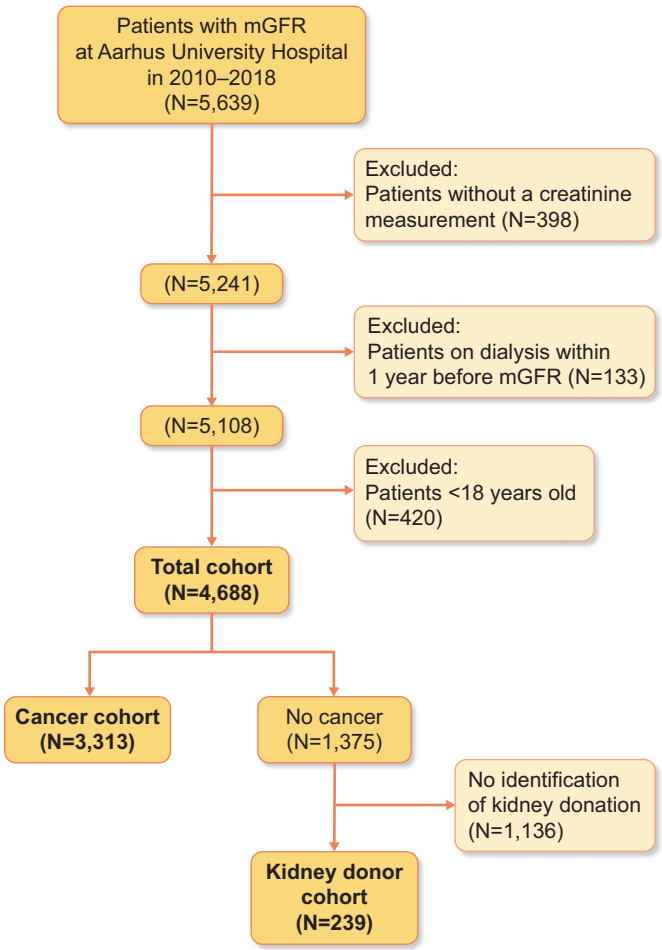

Figure 1: Flowchart of cohort construction.

measurement prior to the date of mGFR was used to estimate GFR (see Box 1 for definitions of the applied equations).

Box 1. Applied definitions of eGFR equations

(i) CKD-EPI21 $= 142 \times \min(S_{cr}/\kappa, L)^{\alpha} \times \max(S_{cr}/\kappa, L)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female], where:

S_{cr} = standardized serum creatinine in mg/dL
$\kappa = 0.7$ (female) or 0.9 (male)
$\alpha = -0.241$ (female) or -0.302 (male)

(ii) CKD-EPI09-NB $= 141 \times \min(S_{Cr}/k, L)^{\alpha} \times \max(S_{Cr}/k, L)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female], where:

S_{cr} = standardized serum creatinine in mg/dL
$\kappa = 0.7$ (female) or 0.9 (male)
$\alpha = -0.329$ (female) or -0.411 (male)

Covariates

We included the following covariates: age and sex obtained from the Civil Registration System; morbidities obtained from the patient registry, including diabetes, heart failure, liver disease and lung disease; the presumed indication for mGFR, including candidacy for a kidney, liver, lung or heart transplant, congenital malformation of the urinary system, benign tumor in the urinary system, palsy, and psoriasis or atopic dermatitis possibly related to administration of calcineurin inhibitors; and CKD identified from the laboratory databases, defined as two outpatient eGFR values <60 mL/min/1.73 m^2, according to either CKD-EPI21 or CKD-EPI09-NB, ≥90 days apart (see the Codebook in the Supplementary data for codes, definitions, and look-back and look-forward periods).

Statistical analysis

Descriptive analyses

We described the prevalence of the following conditions that were considered potential indications for mGFR: cancer, candidacy as a potential living kidney donor, congenital malformation of the urinary system, benign tumor in the urinary system, CKD, candidacy for a kidney, liver, heart or lung transplant, palsy, psoriasis and atopic dermatitis. We reported the number of patients and their distribution of age, sex, creatinine level, mGFR and year of mGFR, as well as the prevalence of diabetes, cancer, CKD, heart failure, liver diseas, and lung disease within 10 years before the mGFR (see the Codebook in the Supplementary data for codes and definitions). To investigate the time from the eGFR

Table 1: Characteristics of the study cohorts.

	Total cohort (*N* = 4688)	Cancer cohort (*N* = 3313)	Kidney donor cohort (*N* = 239)	Non-cancer, non-kidney donor cohort (*N* = 1136)
Age, median (IQR), years	64 (54–72)	66 (57–73)	54 (45–63)	58 (45–69)
Age <65 years	2446 (52)	1504 (45)	192 (80)	750 (66)
Female sex	2219 (47)	1688 (51)	140 (59)	391 (34)
mGFR, median (IQR), mL/min/1.73 m^2	84 (63–105)	86 (67–106)	101 (83–116)	73 (49–99)
Creatinine, median (IQR), μmol/L	75 (62–96)	72 (60–89)	71 (62–81)	92 (73–132)
Creatinine, median (IQR), μmol/L, women	65 (56–79)	64 (55–76)	65 (59–73)	75 (61–110)
Creatinine, median (IQR), μmol/L, men	85 (72–108)	81 (69–98)	79 (74–88)	100 (80–145)
Days from creatinine test to GFR, median (IQR)	5 (1–13)	6 (2–13)	3 (1–6)	3 (0–15)
Patients with an eGFR available within 5 days before the mGFR	2474 (53)	1649 (50)	176 (74)	649 (57)
Year of mGFR measurement				
2010–12	470 (10)	160 (5)	74 (31)	236 (21)
2013–15	797 (17)	408 (12)	86 (36)	303 (27)
2016–18	3421 (73)	2745 (83)	79 (33)	597 (53)
Diabetes	422 (9)	267 (8)	0 (0)	155 (14)
Cancer[a]	3550 (76)	3313 (100)	<5[c]	Masked[c]
Chronic kidney disease (CKD-EPI21)[b]	932 (20)	462 (14)	10 (4)	460 (40)
Chronic kidney disease (CKD-EPI09-NB)[b]	1094 (23)	592 (18)	13 (5)	489 (43)
mGFR level				
<30 mL/min/1.73 m^2	196 (4)	78 (2)	<5	Masked[c] (10)
30–59 mL/min/1.73 m^2	811 (17)	508 (15)	Masked[c] (4)	Masked[c] (26)
≥60 mL/min/1.73 m^2	3681 (79)	2727 (82)	Masked[c] (96)	Masked[c] (64)
Heart failure	349 (7)	131 (4)	0 (0)	218 (19)
Liver disease	64 (1)	40 (1)	<5[c]	Masked[c]
Lung disease	427 (9)	294 (9)	<5[c]	Masked[c]

Values are given as *N* (%) unless otherwise noted.
[a]The look-back period for the definition of cancer comorbidity was 3650 days, whereas the look-back period for the definition of the cancer cohort was 365 days.
[b]Two outpatient eGFRs <60 mL/min/1.73 m^2 ≥90 days apart within the look-back period.
[c]Cells are masked, so it is not possible to identify or back-calculate numbers less than 5.

determination to the mGFR, we calculated the median time from eGFR to mGFR in the three cohorts.

Performance

We assessed the performance of the CKD-EPI09-NB and CKD-EPI21 equation in each of the three cohorts. We examined bias by calculating the absolute bias (i.e. the difference between eGFR and mGFR) and the relative bias (i.e. the difference between eGFR and mGFR divided by the mGFR). Precision was defined as the interquartile range (IQR) of the absolute bias. We assessed accuracy by calculating the percentage of patients with eGFR within the range of ±30% of the mGFR (P_{30}). We plotted eGFR and the difference between the eGFR and mGFR against the mGFR. We then assessed bias, precision and accuracy in the three cohorts stratified by no CKD, or CKD stages 1/2, CKD stage 3 and CKD stages 4/5 based on mGFR (≥60, 30–59 and <30 mL/min/1.73 m^2). Finally, we calculated the percentage of patients correctly classified into the three CKD stages.

Additional analyses

We repeated the analysis of bias, precision and accuracy for the new European Kidney Function Consortium (EKFC) eGFR equation [22], while stratifying by sex and age (</≥65 years), and while restricting to patients with an eGFR available within 5 days prior to the mGFR.

RESULTS

We identified 5639 patients with an mGFR. After excluding 398 lacking a creatinine measurement, 133 in dialysis within 1 year before the mGFR and 420 aged <18 years, we included 4688 patients in the total cohort (Fig. 1). Based on the presumed indication for mGFR, the majority (3313 patients) were included in the cancer cohort, whereas 239 patients were included in the kidney donor cohort (Supplementary data, Table S1). Individuals in the kidney donor cohort were younger, and had fewer comorbidities and higher mGFR than the total and cancer cohorts (Table 1).

The median time from eGFR to mGFR was 5 days [first and third quartiles (Q1–Q3), 1–13 days] in the total cohort, 6 days (Q1–Q3, 2–13) in the cancer cohort and 3 days (Q1–Q3, 1–6) in the kidney donor cohort.

Performance

In all three cohorts, the biases were slightly closer to 0 using the CKD-EPI21 equation compared with the CKD-EPI09-NB equation, with biases being greatest in the kidney donor cohort (Table 2, Fig. 2 and Fig. 3). Precision (IQR of absolute bias) was similar for CKD-EPI21 and CKD-EPI09-NB in all three cohorts (Table 2), ranging from 24.1 to 25.7 mL/min/1.73 m^2. The accuracy (P_{30}) was markedly higher using the CKD-EPI21 equation than the CKD-EPI09-NB equation in the kidney donor cohort (88.3% versus 79.9%) and similar in the total cohort (72.4% versus 70.3%) and cancer cohort (73.4% versus 72.0%).

Table 2: Bias, precision and accuracy of eGFR for the CKD-EPI09-NB and CKD-EPI21 equations across cohorts.

		CKD-EPI09-NB	CKD-EPI21
Total cohort ($N = 4688$)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−4.4 (−17.1 to 8.0)	−0.2 (−13.2 to 12.1)
	Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−4.7 (−5.3 to −4.1)	−0.6 (−1.2 to 0.0)
	Precision, mL/min/1.73 m^2	25.1	25.3
	Relative bias, %, median (Q1–Q3)	−5.6 (−18.8 to 11.7)	−0.3 (−14.3 to 17.9)
	Relative bias, %, mean (95% CI)	1.9 (0.5–3.3)	7.6 (6.1–9.1)
	Accuracy, % (95% CI)	70.3 (69.0–71.6)	72.4 (71.1–73.6)
Cancer cohort ($N = 3313$)	Absolute bias, mL/min/1.73m^2, median (Q1–Q3)	−4.1 (−16.8 to 8.8)	0.5 (−12.6 to 13.1)
	Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−4.3 (−5.0 to −3.6)	0.0 (−0.7 to 0.7)
	Precision, mL/min/1.73 m^2	25.6	25.7
	Relative bias, %, median (Q1–Q3)	−4.8 (−17.6 to 12.2)	0.6 (−13.1 to 18.5)
	Relative bias, %, mean (95% CI)	2.6 (0.9–4.3)	8.4 (6.6–10.3)
	Accuracy, % (95% CI)	72.0 (70.4–73.5)	73.4 (71.9–74.9)
Kidney donor cohort ($N = 239$)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−9.9 (−22.0 to 2.1)	−5.8 (−17.6 to 6.6)
	Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−9.2 (−11.6 to −6.7)	−4.9 (−7.3 to −2.5)
	Precision, mL/min/1.73 m^2	24.1	24.2
	Relative bias, %, median (Q1–Q3)	−10.6 (−20.4 to 2.2)	−5.6 (−16.7 to 7.8)
	Relative bias, %, mean (95% CI)	−4.6 (−10.0 to 0.8)	−0.0 (−5.6 to 5.6)
	Accuracy, % (95% CI)	79.9 (74.5–84.6)	88.3 (83.8–91.9)
Non-cancer, non-kidney donor cohort ($N = 1136$)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−4.3 (−17.1 to 6.8)	−1.2 (−13.8 to 10.5)
	Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−4.8 (−6.1 to −3.5)	−1.4 (−2.7 to −0.1)
	Precision, mL/min/1.73 m^2	23.9	24.3
	Relative bias, %, median (Q1–Q3)	−7.0 (−22.1 to 11.9)	−1.7 (−17.9 to 18.0)
	Relative bias, %, mean (95% CI)	1.3 (−1.4 to 3.9)	6.7 (4.0–9.5)
	Accuracy, % (95% CI)	63 (61–66)	66 (63–69)

CI, confidence interval.
Absolute bias is calculated as the difference between eGFR and mGFR; relative bias is calculated as the difference between eGFR and mGFR divided by the mGFR; precision is calculated as the IQR of the bias; and the accuracy is calculated as the percentage of patients with eGFR within the range of ±30% of the mGFR (P_{30}).

Across all three cohorts, both eGFR equations overestimated the GFR at low values and underestimated GFR at high values (Fig. 2). When we stratified the total cohort by CKD stage, we observed that bias was slightly greater using the CKD-EPI21 equation compared with the CKD-EPI09-NB equation when mGFR was <60 mL/min/1.73 m^2 (Table 3). When mGFR was ≥60 mL/min/1.73 m^2, the reverse was seen—the bias of the CKD-EPI21 equation was slightly smaller than the bias of the CKD-EPI09-NB equation (Table 3).

Overall, the classification according to no CKD, or CKD stages 1/2, CKD stage 3 and CKD stages 4/5 was very similar using the CKD-EPI21 and CKD-EPI09-NB equations in all three cohorts (Table 4). However, for CKD stage 3 and CKD stages 4/5, the CKD-EPI09-NB equation classified the patients more accurately than the CKD-EPI21 equation, whereas the CKD-EPI21 equation classified CKD stage more accurately than the CKD-EPI09-NB equation for mGFR ≥60 mL/min/1.73 m^2 (Table 4).

Additional analysis

For the EKFC equation in the total cohort, the absolute median bias was −8.4 mL/min/1.73 m^2, precision was 24.6 mL/min/1.73 m^2 and accuracy was 67% (Supplementary data, Table S3), suggesting that the EKFC performs slightly worse than both the CKD-EPI09-NB and CKD-EPI21 equations in these selected patient cohorts. When stratifying by sex we observed that both CKD-EPI equations performed worse for men than for women (Supplementary data, Table S4). The CKD-EPI09-NB equation performed slightly better than the CKD-EPI21 equation in women, while the reverse was seen for men. When stratifying by age, we observed that the CKD-EPI09-NB and CKD-EPI21 equation were equally biased for patients aged ≥65 years (Supplementary data, Table S5). The CKD-EPI21 equation performed slightly better than CKD-EPI09-NB equation for patients aged <65 years. Lastly, we did not observe major differences from the main analysis when restricting analysis to patients with an eGFR available within 5 days prior to the mGFR (Supplementary data, Table S6).

DISCUSSION

In a Danish cohort of patients with mGFR, we found an overall slightly lower bias, and similar accuracy, precision and classification of CKD stages with the CKD-EPI21 equation compared with the CKD-EPI09-NB equation. The performances were virtually consistent in both the total cohort, and the cohorts of cancer patients and potential living kidney donors. When stratifying by GFR, the CKD-EPI21 equation performed slightly better than the CKD-EPI09-NB equation when the mGFR was ≥60 mL/min/1.73 m^2, whereas the CKD-EPI09-NB equation performed slightly better than the CKD-EPI21 when mGFR was <60 mL/min/1.73 m^2. We found that the accuracy was considerable higher in the kidney donor cohort compared with the total and cancer cohort. This could potentially be explained by our findings that kidney donors generally had a higher mGFR compared with the total and cancer cohort, and that the CKD-EPI equations are more accurate at high mGFR. Furthermore, we observed that the new EKFC equation performed slightly worse than both the CKD-EPI09-NB and the CKD-EPI21 equation.

Our findings of a slightly better performance of the new CKD-EPI21 equation compared with the CKD-EPI09-NB equation are in contrast to the original validation study [3]. As there is a difference in creatinine between Black and non-Black individuals independent of kidney function [2], we expected that

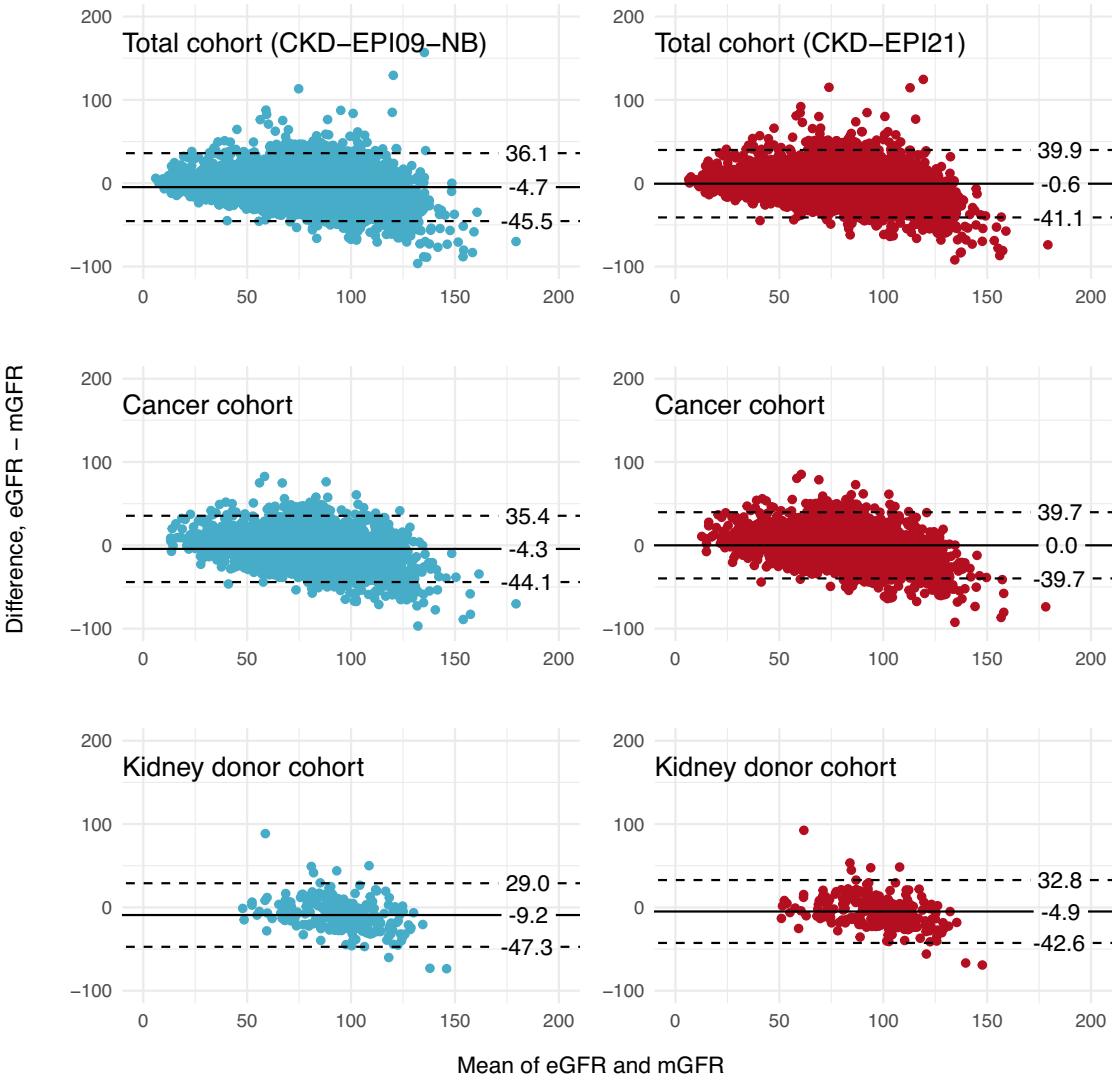

Figure 2: Bland–Altman plots of the difference between eGFR and mGFR against the mean of estimated and measured GFR for the CKD-EPI09-NB and CKD-EPI21 equations across cohorts. CI, confidence interval.

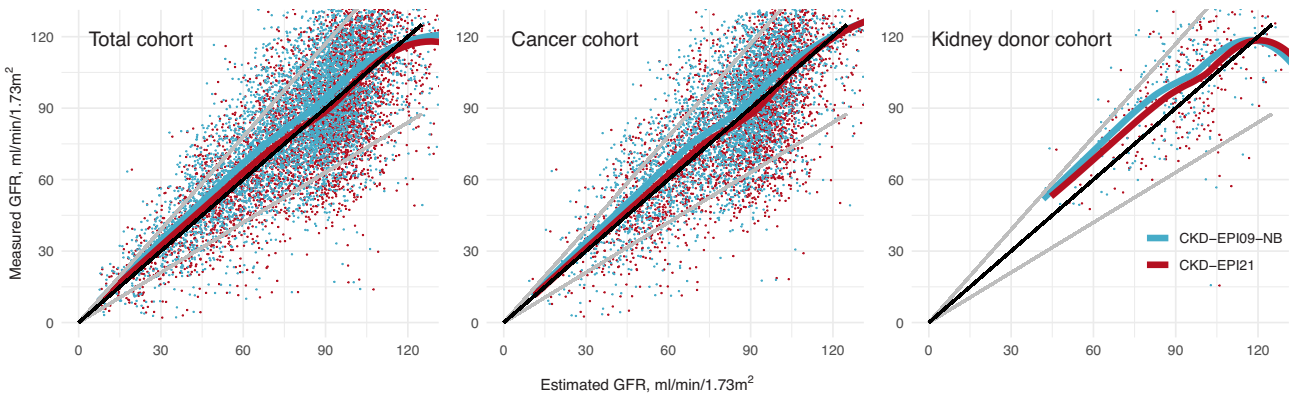

Figure 3: Comparison of mGFR and eGFR values across cohorts. CI, confidence interval.

Table 3: Bias, precision and accuracy of eGFR for the CKD-EPI09-NB and CKD-EPI21 equations across CKD stages in the total cohort.

			CKD-EPI09-NB	CKD-EPI21
Total cohort	GFR <30 (*N* = 196)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	7.7 (−0.1 to 16.5)	9.7 (1.2–19.7)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	11.7 (9.1–14.3)	13.9 (11.1–16.6)
		Precision, mL/min/1.73 m^2	16.6	18.5
		Relative bias, %, median (Q1–Q3)	39.4 (−0.7 to 95.0)	49.6 (7.2–110.6)
		Relative bias, %, mean (95% CI)	90.2 (65.0–115.4)	103.6 (76.6–130.6)
		Accuracy, % (95% CI)	30.6 (24.5–37.3)	30.1 (24.0–36.8)
	30 ≤ GFR < 60 (*N* = 811)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	4.7 (−4.7 to 16.5)	8.4 (−1.7 to 21.0)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	7.7 (6.5–9.0)	11.4 (10.1–12.6)
		Precision, mL/min/1.73 m^2	21.2	22.7
		Relative bias, %, median (Q1–Q3)	10.0 (−10.5 to 36.5)	18.3 (−3.7 to 45.9)
		Relative bias, %, mean (95% CI)	16.4 (13.7–19.0)	24.2 (21.5–26.9)
		Accuracy, % (95% CI)	60.4 (57.0–63.7)	54.7 (51.3–58.2)
	GFR ≥60 (*N* = 3681)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−7.8 (−20.9 to 4.7)	−3.3 (−16.5 to 9.2)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−8.3 (−8.9 to −7.6)	−4.0 (−4.6 to −3.3)
		Precision, mL/min/1.73 m^2	25.6	25.8
		Relative bias, %, median (Q1–Q3)	−8.5 (−20.2 to 5.5)	−3.5 (−15.8 to 10.8)
		Relative bias, %, mean (95% CI)	−6.0 (−6.7 to −5.3)	−1.2 (−1.9 to −0.5)
		Accuracy, % (95% CI)	75 (73–76)	78 (77–80)
Cancer cohort	GFR <30 (*N* = 78)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	15.8 (9.1–30.3)	18.8 (11.4–33.2)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	20.0 (16.2–23.7)	22.9 (19.0–26.8)
		Precision, mL/min/1.73 m^2	21.2	21.9
		Relative bias, %, median (Q1–Q3)	80.5 (38.1–175.6)	93.3 (49.3–197.7)
		Relative bias, %, mean (95% CI)	156.5 (104.4–208.5)	175.7 (119.5–231.8)
		Accuracy, % (95% CI)	12 (6–20)	12 (6–20)
	30 ≤ GFR < 60 (*N* = 508)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	8.0 (−1.3 to 20.7)	11.8 (2.2–25.5)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	10.5 (9.0–11.9)	14.6 (13.1–16.1)
		Precision, mL/min/1.73 m^2	22.0	23.4
		Relative bias, %, median (Q1–Q3)	16.6 (−2.8 to 45.1)	25.9 (4.4–56.0)
		Relative bias, %, mean (95% CI)	22.4 (19.3–25.5)	31.0 (27.8–34.2)
		Accuracy, % (95% CI)	58 (54–63)	50 (45–54)
	GFR ≥60 (*N* = 2727)	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−7.1 (−19.8 to 4.9)	−2.7 (−15.3 to 9.5)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−7.8 (−8.5 to −7.1)	−3.4 (−4.1 to −2.6)
		Precision, mL/min/1.73 m^2	24.7	24.9
		Relative bias, %, median (Q1–Q3)	−7.7 (−19.4 to 5.8)	−2.7 (−14.8 to 11.4)
		Relative bias, %, mean (95% CI)	−5.5 (−6.3 to −4.8)	−0.6 (−1.3 to 0.2)
		Accuracy, % (95% CI)	76 (75–78)	80 (78–81)
Kidney donor cohort[a]	GFR ≥60 (*N* = masked[b])	Absolute bias, mL/min/1.73 m^2, median (Q1–Q3)	−11.8 (−22.2 to 1.2)	−6.7 (−18.0 to 5.6)
		Absolute bias, mL/min/1.73 m^2, mean (95% CI)	−10.1 (−12.5 to −7.8)	−5.8 (−8.2 to −3.5)
		Precision, mL/min/1.73 m^2	23.4	23.6
		Relative bias, %, median (Q1–Q3)	−10.9 (−20.4 to 1.4)	−7.1 (−16.9 to 7.1)
		Relative bias, %, mean (95% CI)	−7.7 (−10.0 to −5.4)	−3.3 (−5.7 to −1.0)
		Accuracy, % (95% CI)	80 (75–85)	89 (84–92)

CI, confidence interval.

Absolute bias is calculated as the difference between eGFR and mGFR; relative bias is calculated as the difference between eGFR and mGFR divided by the mGFR; precision is calculated as the IQR of the bias; and the accuracy is calculated as the percentage of patients with eGFR within the range of ±30% of the mGFR (P_{30}).

[a]We did not report the results for potential living kidney donors with mGFR <60 mL/min/1.73 m^2 because of the low number of these patients.

[b]Cells are masked, so it is not possible to identify or back-calculate numbers less than 5.

ignoring race, and thereby omitting information, would lead to more biased estimates. There are a couple of possible explanations behind this observation. First, the study population may not have been representative of the non-Black individuals used to model the CKD-EPI equations, which may have biased the equations. Second, the method used to measure GFR differed by study. The development of the CKD-EPI equation was mainly based on iothalamate [3]. This may have provided mGFR values that were different from those obtained by ^{51}Cr-EDTA plasma clearance, since iothalamate clearance and ^{51}Cr-EDTA plasma clearance have been shown to yield slightly different results [23]. Likewise, the difference in performance of the EKFC equation between our study and the original validation study may have been due to the fact that the EKFC equation was developed in a cohort where the GFR was measured mainly based on inulin and iohexol [22]. Thus there is a need to achieve better standardizations of the mGFR methods.

Notably, both eGFR equations tended to overestimate GFR at lower values and to underestimate GFR at higher values in all three cohorts. mGFR is often prescribed when a highly accurate GFR is required or when the eGFR is thought to be exceptionally inaccurate (e.g. if muscle mass is abnormal). This may have contributed to the discrepancy between eGFR values and mGFR in the total cohort and the cancer cohort. However, GFR is measured in virtually all patients undergoing kidney donor eligibility screening regardless of muscle mass. Thus, selection of patients with extreme body composition is unlikely to explain the non-uniform bias that we observed.

Table 4: Proportions of participants correctly classified according to GFR cut-offs.

		GFR <30 mL/min/1.73 m^2	30 ≤ GFR < 60 mL/min/1.73 m^2	GFR ≥60 mL/min/1.73 m^2	Overall
Total cohort (N = 4688)	CKD-EPI09-NB	110/196, 56% (49%–63%)	473/811, 58% (55%–62%)	3408/3681, 93% (92%–93%)	3991/4688, 85% (84%–86%)
	CKD-EPI21	100/196, 51% (44%–58%)	449/811, 55% (52%–59%)	3495/3681, 95% (94%–96%)	4044/4688, 86% (85%–87%)
Cancer cohort (N = 3313)	CKD-EPI09-NB	23/78, 29% (20%–40%)	280/508, 55% (51%–59%)	2541/2727, 93% (92%–94%)	2844/3313, 86% (85%–87%)
	CKD-EPI21	18/78, 23% (15%–33%)	256/508, 50% (46%–55%)	2607/2727, 96% (95%–96%)	2881/3313, 87% (86%–88%)
Kidney donor cohort (N = 239	CKD-EPI09-NB	Masked[a]	Masked[a]	Masked[a], 99% (97%–100%)	232/239, 97% (94%–99%)
	CKD-EPI21	Masked[a]	Masked[a]	Masked[a], 99% (97%–100%)	232/239, 97% (94%–99%)

95% confidence intervals are given in parentheses.
[a]Cells are masked, so it is not possible to identify or back-calculate numbers less than 5.

In the original validation study, which included data from various studies, Inker *et al.* found that the CKD-EPI21 equation provided equally biased estimates in Black individuals and slightly more biased estimates in non-Black individuals compared with estimates obtained using the CKD-EPI09 equation [3]. Inker *et al.* reported considerably higher accuracy than in our study. A couple of studies have subsequently validated the CKD-EPI21 equation in different patient groups [8–14, 24]. In line with our study, the studies generally reported no or only minor differences in the performance between CKD-EPI09-NB and CKD-EPI21 equations in patients with mGFR including kidney transplant recipients, living kidney donors, patients with CKD and cancer patients, among others [8–14, 24]. Although our study took advantage of comprehensive, routinely collected health data in Denmark, some limitations should be considered when interpreting our results. First, we lacked information on race, though the vast majority are thought to be white because approximately 90% of Danes have a Danish ancestor [25]. In addition, as the study was conducted in a predominantly non-Black population, our results may not be generalizable to other populations. Second, the cohorts consisted of patients whose GFR was measured due to a clinical indication, so the estimates may not be applicable to the general population or to cancer patients in general. Third, we lacked direct information on the indication for the mGFR. However, we expect that our algorithm for categorizing patients based on diagnosis and surgery codes identified the correct indication for the vast majority of the patients. Fourth, the median time of 5 days between the eGFR and mGFR could potentially affect the performance of the equations; however, we did not see major differences in the performance when restricting analysis to patients with an eGFR available within 5 days prior to the mGFR.

In conclusion, in a selected cohort of predominantly white Danish patients, including cancer patients and potential living kidney donors, the CKD-EPI21 equation performed slightly better than the CKD-EPI21-NB equation except for patients with a GFR <60 mL/min/1.73 m^2; however, these differences may not be clinically significant.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

C.F.C., H. B., H.T.S., J. F., P.V.M., S.K. J., S.V.V., and U. H.-J. conceptualized the study. C.F.C., P.V.M., S.K.J., S.V.V., and U.H.-J. designed the study. P.V.M. reviewed the literature and wrote the initial draft of the article. U.H.-J. conducted the formal analysis. All authors interpreted the results and reviewed and edited the article.

DATA AVAILABILITY STATEMENT

The data underlying this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data. Researchers may apply for data access through the Danish Health Data Authority.

CONFLICT OF INTEREST STATEMENT

C.F.C., H.B., H.T.S., J.F., P.V.M., S.K.J., S.V.V. and U.H.-J. report employment with Aarhus University and Aarhus University Hospital. The Department of Clinical Epidemiology, Department of Biomedicine, Department of Renal Medicine, Department of Clinical Pharmacology and Department of Nuclear Medicine and PET-Centre at Aarhus University Hospital are involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these is related to this study. H.B. also reports consultancy agreements with AstraZeneca, Galapagos and Vifor Pharma, as well as research funding from GlaxoSmithKline (GSK) and Vifor Pharma, and reports honoraria from Alexion, AstraZeneca, MSD, Novartis Healthcare, NOVO Nordisk and Otsuka Pharmaceuticals. None of these is related to this study.

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