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ORIGINAL ARTICLE

Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa

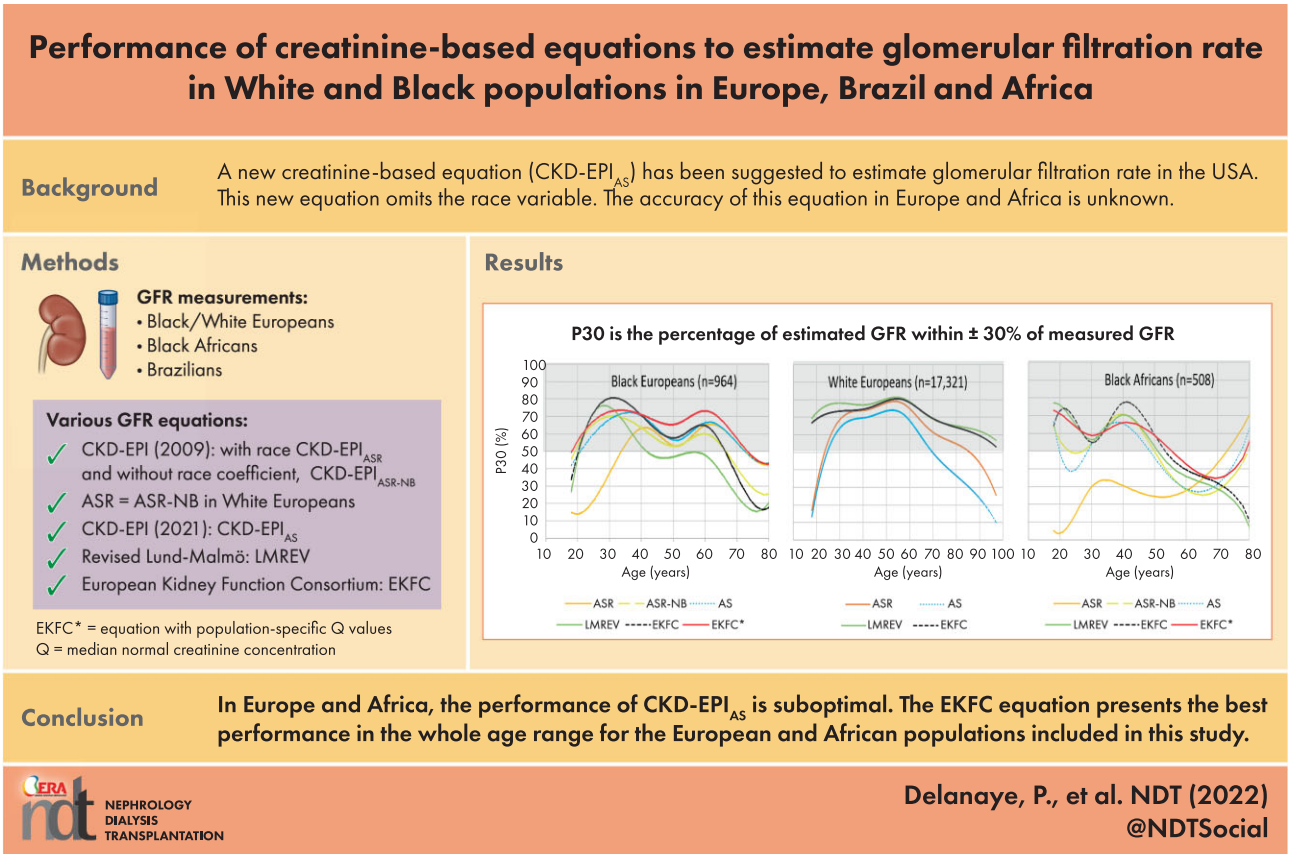
Pierre Delanaye[1,2,*], Emmanuelle Vidal-Petiot[3,*], Jonas Björk[4,5], Natalie Ebert[6], Björn O. Eriksen[7], Laurence Dubourg[8], Anders Grubb[9], Magnus Hansson[10], Karin Littmann[11], Christophe Mariat[12], Toralf Melsom[7], Elke Schaeffner[6], Per-Ola Sundin[13], Arend Bökenkamp[14], Ulla B. Berg[15], Kajsa Åsling-Monemi[15], Anna Åkesson[4,5], Anders Larsson[16], Etienne Cavalier[17], R. Neil Dalton[18], Marie Courbebaisse[19], Lionel Couzi[20], Francois Gaillard[21], Cyril Garrouste[22], Lola Jacquemont[23], Nassim Kamar[24], Christophe Legendre[25], Lionel Rostaing[26], Thomas Stehlé[27,28], Jean-Philippe Haymann[29], Luciano da Silva Selistre[30], Jorge P. Strogoff-de-Matos[31], Justine B. Bukabau[32], Ernest K. Sumaili[32], Eric Yayo[33], Dagui Monnet[33], Ulf Nyman[34], Hans Pottel[35,†] and Martin Flamant[36,†]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège, Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium, [2]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France, [3]Assistance Publique-Hôpitaux de Paris, Bichat Hospital, and Université Paris Cité, Paris, France, [4]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [5]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden, [6]Charité Universitätsmedizin Berlin, Institute of Public Health, Berlin, Germany, [7]Section of Nephrology, University Hospital of North Norway and Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsö, Norway, [8]Néphrologie, Dialyse, Hypertension et Exploration Fonctionnelle Rénale, Hôpital Edouard Herriot, Hospices Civils de Lyon, France, [9]Department of Clinical Chemistry, Skåne University Hospital, Lund, Lund University, Sweden, [10]Clinical Chemistry, Karolinska University Laboratory, Karolinska University Hospital Huddinge and Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden, [11]Department of Medicine, Karolinska Institute, Huddinge, Sweden, [12]Service de Néphrologie, Dialyse et Transplantation Rénale, Hôpital Nord, Centre Hospitalier Universitaire de Saint-Etienne, France, [13]Department of Geriatrics, School of Medical Sciences, Örebro University, Örebro, Sweden, [14]Department of Paediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, [15]Department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden, [16]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden, [17]Department of Clinical Chemistry, University of Liège, Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium, [18]The Wellchild Laboratory, Evelina London Children's Hospital, London, UK, [19]Physiology Department, Georges Pompidou European Hospital, Assistance Publique Hôpitaux de Paris, Paris University, Paris, France, [20]CNRS-UMR Immuno ConcEpT, Nephrologie – Transplantation-Dialyse, Centre Hospitalier Universitaire de Bordeaux, Université de Bordeaux, France, [21]Service de transplantation et immunologie clinique, Hôpital Edouard Herriot, Hospices civils de Lyon, Lyon, France, [22]Department of Nephrology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France, [23]Renal Transplantation Department, Centre Hospitalier Universitaire Nantes, Nantes University, Nantes, France, [24]Department of Nephrology, Dialysis and Organ Transplantation, Centre Hospitalier Universitaire Rangueil, University Paul Sabatier, Toulouse, France, [25]Hôpital Necker, Assistance Publique Hôpitaux de Paris, Paris University, France, [26]Service de Néphrologie, Hémodialyse, Aphérèses et Transplantation Rénale, Hôpital Michallon, Centre Hospitalier Universitaire Grenoble-Alpes, France, [27]Université Paris Est Créteil, Institut Mondor de Recherche Biomédicale, Créteil, France, [28]Service de Néphrologie et Transplantation, Fédération Hospitalo-Universitaire 'Innovative therapy for immune disorders' Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Henri Mondor, Service de Néphrologie et Transplantation, Créteil, France, [29]Physiology Department, Assistance Publique- Hôpitaux de Paris, Hôpital Tenon, Paris, France, [30]Ciências da Saúde, Universidade de Caxias do Sul, Hospital Geral de Caxias do Sul, Caxias do Sul, Brazil, [31]Nephrology Division, Department of Medicine, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil

*Pierre Delanaye and Emmanuelle Vidal-Petiot share first authorship.
†Hans Pottel and Martin Flamant share last/senior authorship.
Correspondence to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr

[32]Renal Unit, Department of Internal Medicine, Kinshasa University Hospital, University of Kinshasa, Kinshasa, Democratic Republic of Congo, [33]Département de Biochimie, UFR Sciences Pharmaceutiques et Biologiques, Université Felix Houphouët Boigny, Abidjan, Côte d'Ivoire, [34]Department of Translational Medicine, Division of Medical Radiology, Lund University, Malmö, Sweden, [35]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium and [36]Cordeliers Research Center, Assistance Publique-Hôpitaux de Paris, Bichat Hospital, and Université Paris Cité, Paris, France

GRAPHICAL ABSTRACT



ABSTRACT

Background. A new Chronic Kidney Disease Epidemiology Collaboration equation without the race variable has been recently proposed (CKD-EPI$_{AS}$). This equation has neither been validated outside USA nor compared with the new European Kidney Function Consortium (EKFC) and Lund-Malmö Revised (LMREV) equations, developed in European cohorts.

Methods. Standardized creatinine and measured glomerular filtration rate (GFR) from the European EKFC cohorts (n = 13 856 including 6031 individuals in the external validation cohort), from France (n = 4429, including 964 Black Europeans), from Brazil (n = 100) and from Africa (n = 508) were used to test the performances of the equations. A matched analysis between White Europeans and Black Africans or Black Europeans was performed.

Results. In White Europeans (n = 9496), both the EKFC and LMREV equations outperformed CKD-EPI$_{AS}$ (bias of –0.6 and –3.2, respectively versus 5.0 mL/min/1.73 m^2, and accuracy within 30% of 86.9 and 87.4, respectively, versus 80.9%). In Black Europeans and Black Africans, the best performance was observed with the EKFC equation using a specific Q-value (= concentration of serum creatinine in healthy males and females). These results were confirmed in matched analyses, which showed that serum creatinine concentrations were different in White Europeans, Black Europeans and Black Africans for the same measured GFR, age, sex and body mass index. Creatinine differences were more relevant in males.

Conclusion. In a European and African cohort, the performances of CKD-EPI$_{AS}$ remain suboptimal. The EKFC equation, using usual or dedicated population-specific Q-values, presents the best performance in the whole age range in the European and African populations included in this study.

Keywords: creatinine, glomerular filtration rate, race

INTRODUCTION

Glomerular filtration rate (GFR) is currently estimated by equations based on serum creatinine, a biomarker not free from criticism [1]. Among these limitations, the fact that GFR is different at the same level of serum creatinine in Black and

KEY LEARNING POINTS

What is already known about this subject?

- A new creatinine-based equation (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) has been suggested to estimate glomerular filtration rate in the USA. This new equation omits the 'race' variable. The accuracy of this new equation in Europe and Africa is unknown.

What this study adds?

- In a large cohort of subjects from Africa and Europe, we show that the new equation has a low accuracy among the different populations. This equation has no added value compared with the previous equation without the race correction. Moreover, the new European Kidney Function Consortium (EKFC) has the best performance, especially if a population-dedicated Q value is used.

What impact this may have on practice or policy?

- The new CKD-EPI equation without the race variable is not applicable in Europe and Africa. The prior CKD-EPI equation without the race correction, and better still, the EKFC equation should be preferred in these continents.

White American populations has been considered problematic [2–4]. This observation led the authors of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to use a race multiplier, but this correction has recently been considered a source of discrimination [2]. Accordingly, the original 2009 CKD-EPI equation with age, sex and race ($CKD\text{-}EPI_{ASR}$) has been replaced in 2021 by a new equation of the same mathematical form without a race coefficient ($CKD\text{-}EPI_{AS}$) [5]. Data were mathematically weighted to balance the bias between non-Black and Black individuals. Consequently, the authors deliberately introduced bias (thus reducing accuracy) in non-Black people, but the absolute bias was now similar in the two populations. The new $CKD\text{-}EPI_{AS}$ equation did not perform better in Black individuals (with a slight underestimation) and performed slightly worse in non-Black (with a slight overestimation) [5]. The equation has been rapidly endorsed by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) [6]. The vast majority of cohorts included in the development and validation of the $CKD\text{-}EPI_{AS}$ were from the USA [5, 7]. Studies outside the USA, notably from Europe, Brazil and Africa, have suggested that the $CKD\text{-}EPI_{ASR}$ equation performed better without the race multiplier ($CKD\text{-}EPI_{ASR\text{-}NB}$, NB for non-Black) than with the multiplier, or that the correction should be less than in the USA [8–13]. Thus, it is important to study and compare the performance of the $CKD\text{-}EPI_{AS}$ equation with the original $CKD\text{-}EPI_{ASR}$ both with and without the race coefficient in cohorts outside the USA [7]. Moreover, the new equation has been poorly compared with current European-developed creatinine-based equations, i.e. the Lund-Malmö Revised (LMREV) [14] and the new European Kidney Function Consortium (EKFC) equations, which was another aim of the current study [for an overview of estimated GFR (eGFR) equations, see Supplementary Table S1] [15].

MATERIALS AND METHODS

Design overview

This is a retrospective study with data from subjects representing 11 previously described cohorts from Europe (the EKFC cohort, $n = 13\,856$, including the external validation cohort, $n = 6031$) [15,16], and enhanced with data from Brazil ($n = 100$), France ($n = 4429$) and Africa (Democratic Republic of Congo and Côte d'Ivoire, $n = 508$) ($n = 18\,893$ for the whole cohort). As the CKD-EPI equations were developed for adults, we included subjects aged 18 years and older. Height and weight were missing in 149 subjects, but serum creatinine, age, sex and indexed measured GFR (mGFR) were available for all subjects. The EKFC cohort was considered as a non-Black population. All data from Africa were from Black individuals. In Brazil, participants were classified according to the three main race-ethnicity categories defined by the Brazilian Institute of Geography and Statistics: White, Black and mixed-race. The researcher in charge defined race-ethnicity according to the phenotypic appearance. In France, Black subjects, labeled as 'Black Europeans' in the current article, refers to partial or total ancestry from sub-Saharan Africa as self-reported by the patient. This cohort mainly came from the area of Paris (Île-de-France, France). Analysis was limited to the first GFR measurement obtained per patient (if more than one was available). Data were anonymized from the source cohorts for the analysis performed at Lund University, Sweden, for the EKFC cohort and locally for the three other cohorts analyzed separately. All procedures involving subjects and data agreed with the ethical principles for medical research involving human subjects established in the World Medical Association Declaration of Helsinki. The study was reviewed and approved by the Regional Ethical Board in Lund, Sweden (Registration No. 2018/220) for the EKFC cohort [15,16]. For Africa, the study protocol was approved by the Ethics Committee of the Public Health School of the University of Kinshasa, Democratic Republic of Congo (No. ESP/CE/029/2015) and the national ethnic committee under the number 039/MSLS/CNER-dkn in Côte d'Ivoire [10]. In Brazil, the project was approved by the research ethics committee of the Department of Medicine, Universidade Federal Fluminense, Niteroi, Rio de Janeiro, Brazil (CAAE 46 535 215.8.0000.5243) [12]. In Paris, France, the study was approved by the Institutional Review Board of Assistance-Publique Hôpitaux de Paris and Paris 7 University (IRB 00 006 477, study 14-051).

Participants

Data on GFR were collected and centralized by the EKFC, endorsed by the European Renal Association. Data were from participants in previously published research studies and patients undergoing mGFR as part of their clinical care at nephrology centers. An overview of the participating centers, the measurement methods used (both for mGFR and serum creatinine) in these centers and the patient characteristics in the centers have been published before and are summarized in Supplementary Table S2 and S3 [8,10,12,15–17].

Covariates

Age, gender, height, weight and serum creatinine were obtained from medical records. Serum creatinine was measured with assays traceable to the gold standard isotope dilution mass spectrometry (IDMS) method (Supplementary Table S3) [18].

Outcomes

mGFR was obtained using either plasma clearance (based on the decay of the plasma concentrations over time) or urinary clearance (based on urine excretion rate divided by plasma concentration) of exogenous filtration markers (iohexol, inulin, ^{99}Tc-DTPA or ^{51}Cr-EDTA), all methods with sufficient accuracy (Supplementary Table S3) [19–21]. All results of mGFR were indexed for body surface area with the Du Bois equation [22]. Sex- and age-specific median creatinine values (Q-values) in healthy subjects from different populations were established in independent cohorts. For White Europeans, Q-values were 0.70 mg/dL for females and 0.90 mg/dL for males [15]. For Black Africans, Q-values were 0.72 mg/dL for females and 0.96 mg/dL for males, as previously described [10]. For Black Europeans, the Q-values have been independently established with the mean serum creatinine concentration (measured with an IDMS enzymatic assay) obtained from 90 living kidney donors (48 females) in three centers in Paris, France. The distribution of creatinine values in living kidney donors was considered approximately normal and the mean and 95% confidence intervals (CI) were obtained using bootstrap resampling. Q-values at adult levels were calculated as 1.02 mg/dL 95% CI (0.98–1.07) for males and 0.74 mg/dL 95% CI (0.70–0.78) for females. The LMREV equation was tested in Black individuals by adjusting their creatinine value to the levels of White individuals: adjusted creatinine = original creatinine × Q (White individuals)/Q (specific for a Black population).

Statistical analyses

All analyses and calculations were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Data were presented as mean ± SD when the distribution was normal and as median with interquartile range (IQR) (quartile 1; quartile 3) when not. Normality was assessed using the Shapiro–Wilk test.

Performance of GFR equations was compared with usual metrics: median bias (i.e. eGFR – mGFR) with 95% CI, imprecision (IQR), as well as P30 and P20 accuracy (percentage of eGFR values within ±30% or 20% of mGFR) with 95% CI. The target for bias was zero, but an absolute bias of at most 5 mL/min/1.73 m² might be considered reasonable. Imprecision should be as low as possible [23]. The goal for P30 was 100%, yet P30 >75% has been considered as 'sufficient for good clinical decision making' by Kidney Disease Outcomes Quality Initiative (K/DOQI), although the goal was to reach a P30 >90% [24]. Median bias across the age spectrum was graphically presented using median quantile regression with 4th degree polynomials. Likewise, accuracy P30 (%) was graphically presented across the age spectrum using cubic splines with three free knots and using 3rd degree polynomials.

Stratified analysis in different GFR subgroups was done according to mGFR ranges (<15, 15–30, 30–45, 45–60, ≥60 mL/min/1.73 m²) [25,26]. We also performed analyses stratified by age (18–40, 40–65 and ≥65 years) and by body mass index (BMI) (<18, 18–25, 25–30, ≥30 kg/m²). These subanalyses were conducted in White Europeans, Black Africans and Black Europeans (not in the Brazilians because the sample was too small). Because equations generally performed better in the cohort used for its development, we repeated the analyses in the external validation cohort of the European cohorts included in the EKFC study (data from France, Lund, Amsterdam, Leuven and Kent) [15].

Because the characteristics of Black people were very different in the various cohorts in terms of age, sex, mGFR and BMI, we separately matched Black Europeans and Black Africans with White Europeans from the EKFC cohort (matching 1 for 5) using the matching criteria: age (±2 years), sex (equal), mGFR (±5 mL/min/1.73 m²) and BMI (±2.5 kg/m²). We wanted to investigate whether there are differences in serum creatinine in these matching cohorts. For the matched analyses, we considered the whole EKFC cohort, enriched by White Europeans from Paris.

RESULTS

All four populations

The participant characteristics and details for each cohort are summarized in Supplementary Tables S2 and S3. Median age was 56.7 (42.0; 67.8), 51.2 (41.3; 60.2), 39.0 (30.0; 53.0) and 59.5 (51.8; 66.0) years, in the White European (n = 17 321), Black European (n = 964), Black African (n = 508) and Brazilian cohort (n = 100), respectively.

The percentage of women was 47.6, 38.2, 46.7 and 54.0% in the four aforementioned cohorts.

Median mGFR was 74.0 (46.2; 95.0), 59.3 (43.4; 76.9), 86.8 (71.7; 99.2) and 42.0 (24.3; 61.3) mL/min/1.73 m², and median BMI was 25.3 (22.3; 28.7), 26.1 (23.1; 29.4), 23.7 (20.9; 27.6) and 27.1 (24.2; 30.8) kg/m², in the White European, Black European, Black African and Brazilian cohorts, respectively.

Results in White Europeans (n = 9465)

The results are those obtained in the external validation cohorts (EKFC external validation + Paris). In White

Table 1: Median bias (95% CI) and imprecision (interquartile range) expressed in mL/min/1.73 m², P20(%) (95% CI) and P30(%) (95% CI) accuracy for five different creatinine-based equations.

White Europeans (EKFC external validation + Paris cohort)	CKD-EPI$_{ASR}$	CKD-EPI$_{ASR-NB}$	CKD-EPI$_{AS}$	LMREV	EKFC
$N = 9496$					
Bias	1.8 (1.5; 2.1)	1.8 (1.5; 2.1)	5.0 (4.7; 5.2)	−3.6 (−3.9; −3.3)	−0.6 (−0.8; −0.3)
IQR (Q1; Q3)	15.7 (−5.2; 10.4)	15.7 (−5.2; 10.4)	16.0 (−2.2; 13.8)	15.0 (−11.3; 3.8)	14.7 (−7.6; 7.1)
P20	68.8 (67.9; 69.7)	68.8 (67.9; 69.7)	65.5 (64.5; 66.4)	70.7 (69.8; 71.7)	72.3 (71.4; 73.2)
P30	84.6 (83.9; 85.3)	84.6 (83.9; 85.3)	80.9 (80.1; 81.7)	87.4 (86.7; 88.1)	86.9 (86.3; 87.6)
White Europeans (Paris)					
$n = 3465$					
Bias	0.8 (0.3; 1.3)	0.8 (0.3; 1.3)	3.6 (3.0; 4.2)	−3.4 (−3.8; −3.0)	−0.5 (−0.9; −0.1)
IQR (Q1; Q3)	15.2 (−6.3; 8.9)	15.2 (−6.3; 8.9)	16.1 (−3.8; 12.3)	13.7 (−10.1; −3.4)	14.3 (−7.2; 7.2)
P20	66.4 (64.8; 68.0)	66.4 (64.8; 68.0)	65.1 (63.5; 66.7)	66.8 (65.3; 68.4)	68.7 (67.2; 70.3)
P30	83.5 (82.3; 84.8)	83.5 (82.3; 84.8)	80.9 (79.6; 82.2)	85.4 (84.2; 86.6)	85.5 (84.3; 86.7)
EKFC external validation					
$n = 6031$					
Bias	2.4 (2.1; 2.8)	2.4 (2.1; 2.8)	5.7 (5.3; 6.1)	−3.7 (−4.1; −3.3)	−0.6 (−0.9; −0.2)
IQR (Q1; Q3)	15.5 (−4.4; 11.1)	15.5 (−4.4; 11.1)	15.8 (−1.2; 14.6)	15.9 (−12.0; 3.9)	15.0 (−8.0; 7.0)
P20	70.2 (69.0; 71.3)	70.2 (69.0; 71.3)	65.7 (64.5; 66.9)	73.0 (71.9; 74.1)	74.4 (73.3; 75.5)
P30	85.2 (84.3; 86.1)	85.2 (84.3; 86.1)	80.9 (79.9; 81.9)	88.6 (87.8; 89.4)	87.8 (86.9; 88.6)
White Europeans (total EKFC cohort + Paris cohort)					
$n = 17\,321$					
Bias	3.0 (2.7; 3.2)	3.0 (2.7; 3.2)	6.0 (5.8; 6.3)	−3.2 (−3.4; −3.0)	−0.3 (−0.5; −0.1)
IQR (Q1; Q3)	16.8 (−4.4; 12.3)	16.8 (−4.4; 12.3)	17.2 (−1.5; 15.7)	15.5 (−11.3; 4.2)	15.1 (−7.7; 7.4)
P20	66.9 (66.2; 67.6)	66.9 (66.2; 67.6)	63.0 (62.3; 63.7)	71.0 (70.3; 71.7)	72.4 (71.8; 73.1)
P30	82.5 (82.0; 83.1)	82.5 (82.0; 83.1)	78.5 (77.9; 79.1)	87.3 (86.8; 87.8)	86.6 (86.1; 87.1)
Black Europeans					
$n = 964$					
Bias	0.8 (0.1; 2.2)	−6.1 (−7.0; −5.4)	−3.6 (−4.7; −2.9)	−9.1 (−10.2; −8.5)	−6.3 (−7.0; −5.5)
IQR (Q1; Q3)	19.1 (−6.8; 12.3)	15.5 (−13.2; 2.3)	16.3 (−11.1; 5.2)	14.7 (−16.5; −1.8)	14.6 (−13.4; 1.2)
P20	59.4 (56.3; 62.5)	57.3 (54.1; 60.4)	61.7 (58.6; 64.8)	49.8 (46.6; 53.0)	59.2 (56.1; 62.3)
P30	77.4 (74.7; 80.0)	78.3 (75.7; 80.9)	81.0 (78.5; 83.5)	74.2 (71.4; 76.9)	80.5 (78.0; 83.0)
Black Africans					
$n = 508$					
Bias	12.2 (10.7; 15.0)	−1.3 (−2.7; 0.7)	2.5 (0.7; 4.2)	−9.0 (−10.5; −7.6)	−4.4 (−5.3; −3.3)
IQR (Q1; Q3)	30.0 (−3.2; 26.8)	22.6 (−11.4; 11.2)	23.3 (−9.0; 14.3)	18.3 (−17.9; 0.4)	19.9 (−14.0; 5.9)
P20	43.7 (39.4; 48.0)	59.6 (55.4; 63.9)	59.6 (55.4; 63.9)	61.6 (57.4; 65.9)	62.4 (58.2; 66.6)
P30	63.6 (59.4; 67.8)	75.8 (72.0; 79.5)	74.4 (70.6; 78.2)	77.8 (74.1; 81.4)	79.3 (75.8; 82.9)

CKD-EPI$_{ASR}$: Chronic Kidney Disease Epidemiology Collaboration with variables age, sex and race; CKD-EPI$_{ASR-NB}$: Chronic Kidney Disease Epidemiology Collaboration with variables age, sex and race but without applying the race coefficient; CKD-EPI$_{AS}$: Chronic Kidney Disease Epidemiology Collaboration with variables age and sex; EKFC: European Kidney Function Consortium; IQR: Interquartile range; LMREV: Lund–Malmö Revised; P20: accuracy within 20%; P30: accuracy within 30% of mGFR; Pct: percentile.

Europeans, the bias was closer to 0 with the EKFC equation [−0.6 (−0.8; −0.3)] than with the LMREV equation [−3.6 (−3.9; −3.3)] or CKD-EPI$_{ASR}$ [1.8 (1.5; 2.1)]. The largest bias [5.0 (4.7; 5.2)] was observed for the CKD-EPI$_{AS}$ equation (Table 1 and Figs 1A and 3A). In terms of precision, EKFC and LMREV equations performed better than the CKD-EPI equations (Table 1). Accuracy results were higher and similar for the EKFC and LMREV equations (with a P30 of 86.9 and 87.4%, respectively). In comparison, CKD-EPI$_{ASR}$ and CKD-EPI$_{AS}$ displayed significantly lower accuracy (with a P30 of 84.6 and 80.9%, respectively) (Table 1 and Figs 2A and 4A). We repeated analyses in White subjects from Paris (a cohort independent of the EKFC cohort), in the external validation cohort of the EKFC and in the whole cohort ($n = 17\,321$) (Table 1). We illustrated that the results in the total White European cohort ($n = 17\,321$), for bias (Supplementary Figs S1 and S3) and P30 (Supplementary Figs S2 and S4) for the EKFC and CKD-EPI$_{AS}$ equations according to age (Supplementary Figs S1 and S2) or mGFR (Supplementary Figs S3 and S4) were very similar to the results obtained in the external validation cohorts only (EKFC + Paris, $n = 9469$). Therefore, we presented the performance results of the whole cohort in the figures and in further sub-analyses.

Results in Black Europeans ($n = 964$)

The bias was closer to 0 with the CKD-EPI$_{ASR}$ equation [0.8 (0.1; 2.2)], than with the CKD-EPI$_{AS}$ equation [−3.6 (−4.7; −2.9)]. The bias of the CKD-EPI$_{ASR-NB}$ [−6.1 (−7.0; −5.4)] and the EKFC [−6.3 (−7.0; −5.5)] equations was similar and higher than for the two previous equations. The largest bias was for the LMREV equation [−9.1 (−10.2; −8.5)] (Table 1 and Figs 1B and 3B). The precision of the LMREV and EKFC equations was better than for the CKD-EPI equations (Table 1). Except for the LMREV equation, which had lower performance, results of accuracy were similar between equations, with P30 of 77.4, 78.3, 81.0 and 80.5% for the CKD-EPI$_{ASR}$, CKD-EPI$_{ASR-NB}$, CKD-EPI$_{AS}$ and EKFC equations, respectively (Table 1 and Figs 2B and 4B).

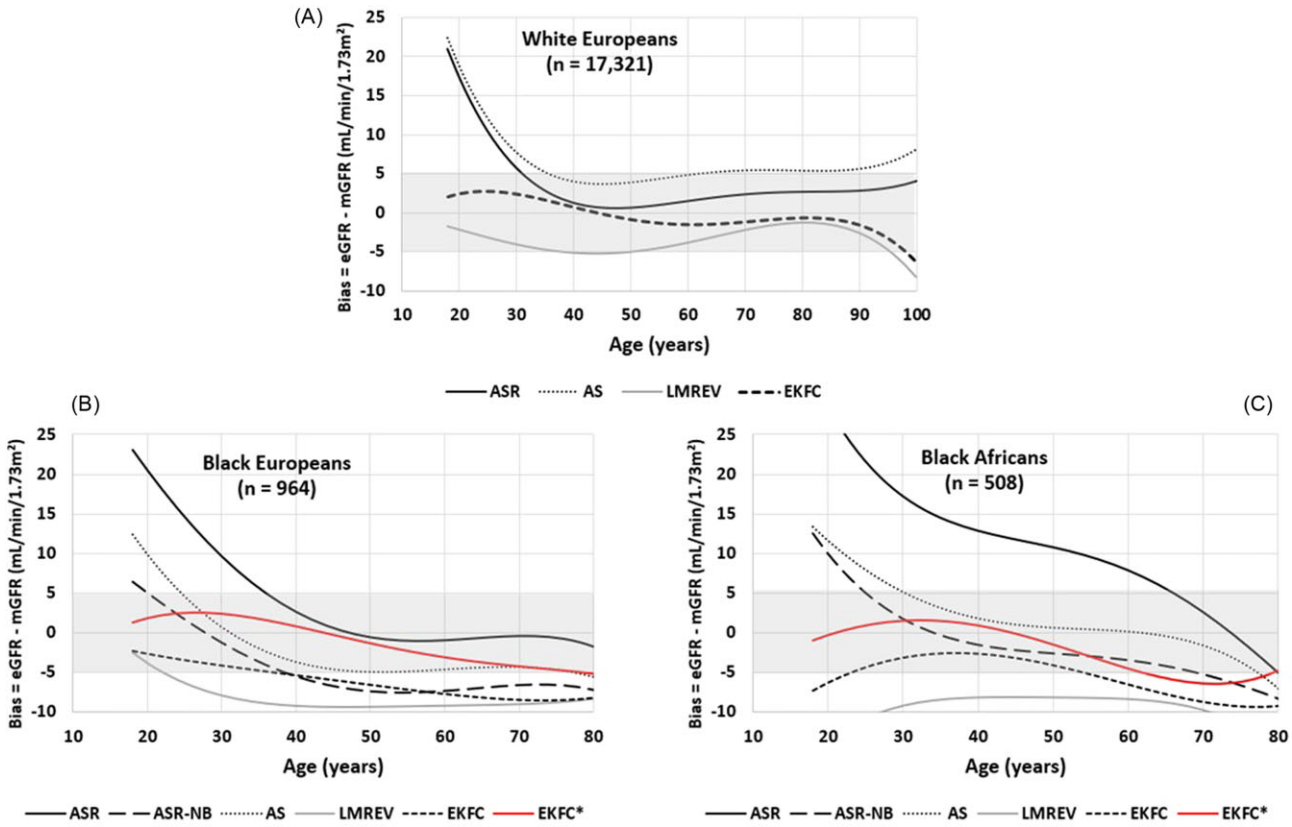


Figure 1: Bias versus age for the creatinine-based equations in White Europeans (**A**), Black Europeans (**B**) and Black Africans (**C**). The gray area indicates the region where bias was zero ±5 mL/min/1.73 m². The bias for the cases for EKFC with population-specific Q is shown in the red curve. ASR: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race; ASR-NB: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race but without applying the race coefficient; AS: Chronic Kidney Disease Epidemiology Collaboration equation with variables age and sex; EKFC: European Kidney Function Consortium; EKFC*: European Kidney Function Consortium with Q-value specific for Black populations; LMREV: Lund–Malmö Revised.

Results in Black Africans ($n = 508$)

The bias was closer to 0 with the CKD-EPI$_{ASR-NB}$ equation [−1.3 (−2.7; 0.7)] than with CKD-EPI$_{AS}$ [2.5 (0.7; 4.2)] and EKFC (−4.4 (−5.3; −3.3)]. The bias of the CKD-EPI$_{ASR}$ [12.2 (10.7; 15.0)] and the LMREV [−9.0 (−10.5; −7.6)] equations was similar (but with opposite sign) and significantly higher than for the three previous equations (Table 1 and Figs 1C and 3C). Precision of the LMREV and EKFC equations was better than for the other equations (Table 1). Except for the CKD-EPI$_{ASR}$ equation, which had lower performance, accuracy results were similar between CKD-EPI$_{ASR-NB}$, CKD-EPI$_{AS}$, LMREV and EKFC equations, with P30 of 75.8, 74.4, 77.8 and 79.3%, respectively (Table 1 and Figs 2C and 4C).

Results in Brazilians ($n = 100$)

The CKD-EPI$_{ASR}$ equation is the only biased equation in the Brazilian cohort, with the lowest P30 values, especially in Black Brazilians (Supplementary Table S4).

Results according to subgroups

A subgroup analysis according to age, mGFR, BMI and sex is shown in Table 2 and commented on in the Supplementary results. Briefly, the study according to age showed that all CKD-EPI equations in all cohorts had varying and mostly large bias in subjects younger than 30 years old. Figures 1–4 illustrate the results of bias or P30 (*y*-axis) according to age or mGFR (*x*-axis) and show superior or similar results of the EKFC equations compared with the CKD-EPI equations, especially in the White European and Black African cohorts.

EKFC with population-specific Q-values

Using the population-specific Q-values in the EKFC equation improved the bias (most bias results are close to zero both in males and females) compared with the EKFC equation with the Q-values defined for White Europeans. Consequently, P30 was also improved in the Black Europeans cohort (Table 3). This improvement made the EKFC equation with population-specific Q-values the equation with the best performances in terms of bias and accuracy in the whole range of ages and mGFR (Figs 1–4).

The effect of adjusting the Q-value by 0.01 mg/dL resulted in a change in EKFC-eGFR of 1.62% in females and 1.26% in males, e.g. changing the Q-value from 0.90 (White Q-value for males) to 1.02 (Black Q-value for males in Paris) increased eGFR by (1.02 − 0.90) ×

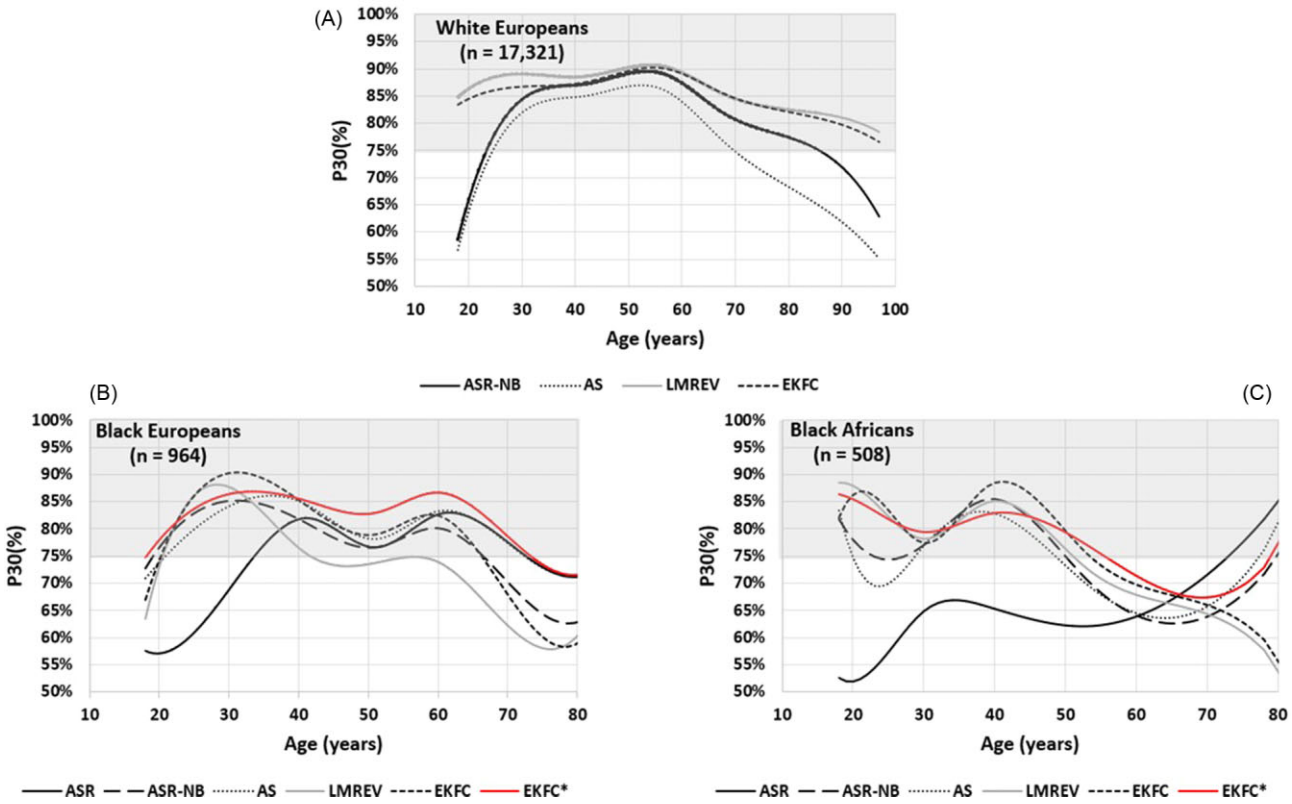


Figure 2: P30(%) accuracy versus age for the creatinine-based equations in White Europeans (**A**), Black Europeans (**B**) and Black Africans (**C**). The gray area indicates the region where P30 was >75%. P30 for the cases for EKFC with population-specific Q is shown in the red curve. ASR: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race; ASR-NB: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race but without applying the race coefficient; AS: Chronic Kidney Disease Epidemiology Collaboration equation with variables age and sex; EKFC: European Kidney Function Consortium; EKFC*: European Kidney Function Consortium with Q-value specific for Black populations; LMREV: Lund–Malmö Revised; P30: accuracy within 30% of mGFR.

100 × 1.26% = 15.1%, thus, at an average GFR level of approximately 60 mL/min/1.73 m², this would result in shifting the bias with approximately 9.1 mL/min/1.73 m². When the adjusted creatinine is used in LMREV, bias and P30 improve from –9.1 to –4.2 mL/min/1.73 m² and from 74.2 to 84.5% in Black Europeans, and from –9.0 to –6.1 mL/min/1.73 m² and from 77.8 to 80.9% in Black Africans.

Matched analyses

Black Europeans versus White Europeans

We matched individuals from the European Black population (n = 964) with the subjects from the White European population (n = 17 321) cohort, aiming at matching one for five. We could not identify matching partners for 50 subjects (5.2%). Five matches were identified for 649 subjects (67.3%), four matches for 70 subjects (7.3%), three matches for 65 subjects (6.7%), two matches for 59 subjects (6.1%) and one match for 71 (7.4%) subjects. Thus, in total, 3909 matches were found on the 4820 expected (5 × 964). The 50 subjects without matches were omitted from further analyses. The results of matching are shown in Supplementary Table S5. As expected, mean age, sex, mGFR and BMI were similar. Of interest, the median serum creatinine was quite different in the two populations, as illustrated in Fig. 5A. From Supplementary Figures S5–S10 and Table S6, it can be seen that the EKFC equations had the best performance in the two populations, especially if the population-specific Q-values were used. With the EKFC equations, compared with other equations, the results of bias were most frequently within 5 mL/min/1.73 m², and the results of P30 were most frequently above 75% in both populations and the whole age range, once again mainly when the population-specific Q-value was used.

Black Africans versus White Europeans

We matched the Black African population (n = 508) with the White European population. We could not identify matching partners for 35 subjects (6.9%). Five matches were identified for 348 subjects (68.5%), four matches for 31 subjects (6.1%), three matches for 27 subjects (5.3%), two matches for 29 subjects (5.7%) and one match for 38 (7.5%). In total, 2041 matches were found of the 2540 expected. The 35 subjects without matches were omitted from further analyses. Results of matching are shown in Supplementary Table S7. As expected, mean mGFR, age, sex and BMI were similar. Of interest, the median serum creatinine was only slightly different between Black Africans and White Europeans (Fig. 5B), whereas a large difference was observed between Black Europeans and White Europeans (Fig. 5A). From Supplementary Figures S11–S16 and Table S8, it can be seen that the EKFC equations showed the best performance in the two populations, especially if the population-specific Q-values were used. Performance of all

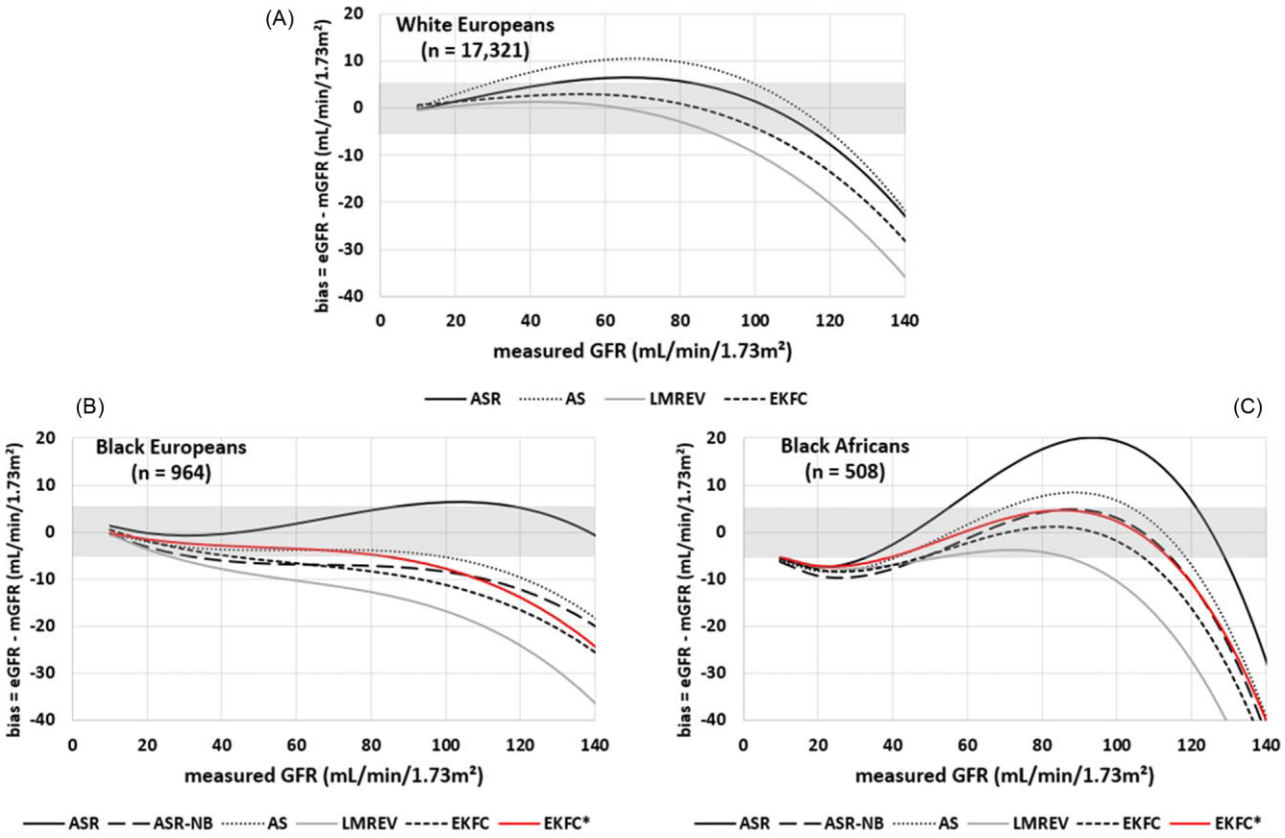


Figure 3: Bias versus measured GFR for the creatinine-based equations in White Europeans (**A**), Black Europeans (**B**) and Black Africans (**C**). The gray area indicates the region where bias was zero ± 5. The bias for the cases for EKFC with population-specific Q is shown in the red curve. ASR: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race; ASR-NB: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race but without applying the race coefficient; AS: Chronic Kidney Disease Epidemiology Collaboration equation with variables age and sex; EKFC: European Kidney Function Consortium; EKFC*: European Kidney Function Consortium with Q-value specific for Black populations; LMREV: Lund–Malmö Revised.

equations was poorer in the Black African cohort than in the matched White Europeans. In contrast, in the matched analysis of White and Black Europeans, the performance was comparable. With the EKFC equations, compared with other equations, the results of bias were most frequently within 5 mL/min/1.73 m², and the results of P30 were most frequently above 75% in both populations and the whole age range, once again mainly when the population-specific Q-values were used.

DISCUSSION

In the present study, we compared the performance of the EKFC and LMREV creatinine-based equations with the new 2021 CKD-EPI equation based on age and sex but without a race multiplier (CKD-EPI$_{AS}$) [5,15] in a large cohort from Europe (enhanced with a new cohort of both Black and White subjects from Paris, France), and additional data from Africa and Brazil. The EKFC equation outperformed the original CKD-EPI$_{ASR}$, and still more the CKE-EPI$_{AS}$, in the three cohorts, mainly when population-specific Q-values were used. These better performances are also observed in the external validation cohort of the EKFC study (European cohorts only) and in the White cohort from Paris, the last one being totally independent of the cohorts used for the development and validation of the EKFC equation. Compared with CKD-EPI$_{AS}$, the EKFC equation has 8.1% more patients with eGFR results within 30% of mGFR, corresponding to 1530 individuals in our cohort. The EKFC equation was superior primarily in White Europeans and in Black Africans. In contrast, the performance of CKD-EPI$_{AS}$ in the European Black cohort was slightly better in terms of bias, however the precision (IQR) was better and P30 was similar for the EKFC equations. At the population level (for epidemiological studies or large interventional trials), a bias close to zero and little imprecision (scatter around the bias) is important. However, at the individual level, a prediction of the equation 'on target' is most relevant [23]. It must be underlined that the precision (IQR) of the EKFC and LMREV were systematically better in all cohorts and all subgroups. Moreover, compared with the EKFC equation, the new CKD-EPI$_{AS}$ shares the same important and underrecognized limitations of the previous CKD-EPI equations: a large bias in subjects younger than 30 years, also explaining the abrupt jump of eGFR results at the transition between adolescence and young adulthood [15,27,28]. This is a consequence of the choice to keep the

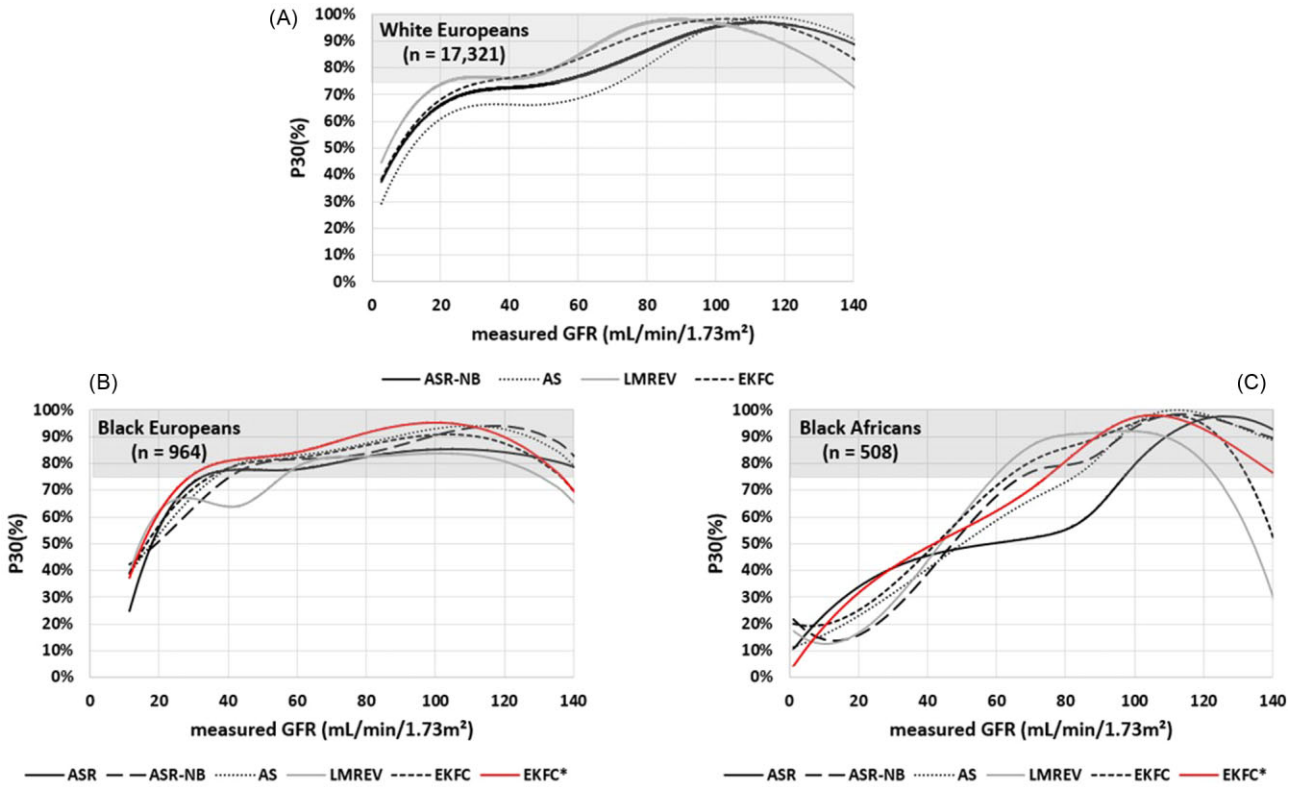


Figure 4: P30(%) accuracy versus measured GFR for the creatinine-based equations in White Europeans (**A**), Black Europeans (**B**) and Black Africans (**C**). The gray area indicates the region where P30 was >75%. P30 for the cases for EKFC with population-specific Q is shown in the red curve. ASR: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race; ASR-NB: Chronic Kidney Disease Epidemiology Collaboration equation with variables age, sex and race but without applying the race coefficient; AS: Chronic Kidney Disease Epidemiology Collaboration equation with variables age and sex; EKFC: European Kidney Function Consortium; EKFC*: European Kidney Function Consortium with Q-value specific for Black populations; LMREV: Lund–Malmö Revised; P30: accuracy within 30% of mGFR.

original mathematical form when constructing the new CKD-EPI$_{AS}$ equation, which is unable to describe the actual course of the overarching GFR–age relationship.

The new CKD-EPI$_{AS}$ was purposefully constructed to yield a similar absolute bias in the Black and non-Black populations, allowing a single equation for both populations, without a race variable [5]. This new CKD-EPI$_{AS}$ also has the advantage of better estimating eGFR in Black American women, for whom the previous CKD-EPI$_{ASR}$ was particularly inaccurate (a better performance that is also observed in the Black European cohort) [3,29]. In the seminal study, the price to pay for this CKD-EPI$_{AS}$ equation without race is a lower performance in White populations [5,30]. Because the CKD-EPI$_{AS}$ was a mathematical construction developed in a US population, it is important to test its performances outside the USA. In our large cohort of White Europeans, we showed that the performance of the CKD-EPI$_{AS}$ was inferior to that in White American cohorts. Absolute bias was higher than in the American cohort (6.0 in Europeans versus 3.9 in Americans) and both precision and accuracy was much lower (P30 of 78.5% versus 86.5%). Several explanations can be proposed. First, an equation always performs better in the cohort in which it has been developed. Second, contrary to American cohorts with mGFR predominantly obtained via renal clearance of iothalamate, Europeans cohorts used a majority of plasma clearance techniques to measure GFR and enzymatic assays to measure serum creatinine [18,31,32]. Third, *sensu stricto*, US cohorts are considering non-Black populations as a whole (including Native Americans, Mexican, Asian and Hispanic people), whereas non-Black European populations included here are potentially more homogenous.

It has previously been shown that the CKD-EPI$_{ASR}$ equation was inaccurate in Brazil and Africa [9–13]. CKD-EPI$_{ASR-NB}$ was thus preferred in these regions of the world. We here confirmed these observations, and we showed that the CKD-EPI$_{AS}$ had no added value in the Black African cohort compared with the CKD-EPI$_{ASR-NB}$ and the EKFC equations. In Black Europeans, there is no clear added value of the CKD-EPI$_{AS}$ in comparison with CKD-EPI$_{ASR-NB}$ and with EKFC, whereas CKD-EPI$_{ASR}$ and EKFC using dedicated Q-values yielded the best performance, with bias closest to zero (for males for the CKD-EPI$_{ASR}$ and for both males and females for EKFC). The same can be concluded from the small-sized cohort of CKD patients from Brazil. LMREV was developed in White populations from Sweden (no data used for the development of the LMREV are used in the current work, in either the development or validation of the EKFC equation) and its lower performance in Black populations was not unexpected. Using an adjusted creatinine value improved the results, especially in Black Europeans.

Table 2: Median bias (mL/min/1.73 m²) and P30 (%) for the five different creatinine-based equations according to mGFR, age, sex and BMI.

	Sample (%)	Bias CKD-EPI$_{ASR}$/CKD-EPI$_{ASR-NB}$/CKD-EPI$_{AS}$/LMREV/EKFC	P30 CKD-EPI$_{ASR}$/CKD-EPI$_{ASR-NB}$/CKD-EPI$_{AS}$/LMREV/EKFC
mGFR (mL/min/1.73 m²)			
mGFR >60			
White Europeans	11 013 (63.6)	3.1/3.1/6.7/−6.6/−2.4	89.4/89.4/86.5/93.6/93.6
Black Europeans	472 (49.0)	3.1/−8.1/−5.0/−12.7/−9.5	81.6/83.9/86.7/80.7/85.0
Black Africans	411 (80.9)	17.0/1.7/4.9/−8.7/−3.3	69.6/86.9/84.4/89.1/89.5
mGFR 45–60			
White Europeans	2187 (12.6)	5.2/5.2/8.5/1.5/2.6	73.4/73.4/66.5/80.7/79.6
Black Europeans	228 (23.7)	0.7/−6.8/−3.9/−9.2/−5.6	76.8/82.5/84.2/72.8/82.9
Black Africans	16 (3.1)	12.9/3.8/6.9/2.4/3.1	50.0/43.8/43.8/50.0/50.0
mGFR 30–45			
White Europeans	2057 (11.9)	2.6/2.6/5.2/−0.8/1.8	74.6/74.6/68.2/75.2/77.0
Black Europeans	170 (17.6)	0.5/−4.9/−3.3/−8.1/−4.5	76.5/69.4/72.9/64.1/74.7
Black Africans	30 (5.9)	−7.3/−11.2/−10.0/−14.0/−10.7	46.7/46.7/50.0/40.0/53.3
mGFR 15–30			
White Europeans	1638 (9.5)	1.4/1.4/3.2/−0.4/1.4	65.2/65.2/60.7/74.9/68.6
Black Europeans	89 (9.2)	−0.7/−4.1/−3.1/−4.9/−2.8	60.7/57.3/60.7/64.0/64.0
Black Africans	34 (6.7)	−9.6/−11.8/−11.2/−10.5/−10.6	32.4/11.8/17.6/20.6/20.6
mGFR <15			
White Europeans	426 (2.5)	1.6/1.6/2.7/2.1/1.9	58.5/58.5/51.6/64.1/58.7
Black Europeans	5 (0.5)	1.0/−0.7/−0.3/0.9/0.2	40.0/40.0/40.0/40.0/40.0
Black Africans	17 (3.3)	−3.3/−3.7/−3.6/−2.4/−3.3	23.5/17.6/17.6/11.8/23.5
Age (years)			
Age 18–40			
White Europeans	3978 (23.0)	10.7/10.7/12.4/−3.4/2.2	75.9/75.9/73.7/87.9/85.8
Black Europeans	219 (22.7)	9.1/−2.4/0.2/−8.2/−4.6	71.2/83.1/83.1/82.2/86.3
Black Africans	258 (50.8)	17.6/2.1/5.0/−10.2/−3.6	62.4/78.7/76.7/81.0/81.8
Age 40–65			
White Europeans	8254 (47.7)	1.1/1.1/4.6/−4.4/−1.0	88.0/88.0/85.1/89.4/89.1
Black Europeans	618 (64.1)	−0.1/−6.8/−4.4/−9.0/−6.3	79.8/78.5/81.1/73.9/81.4
Black Africans	210 (41.3)	8.7/−3.2/0.8/−8.5/−4.8	62.4/73.3/71.4/75.2/77.6
Age ≥65			
White Europeans	5089 (29.4)	2.2/2.2/5.4/−1.8/−0.7	78.9/78.9/71.6/83.4/83.2
Black Europeans	127 (13.2)	−1.6/−7.5/−5.5/−10.5/−9.5	76.4/69.3/77.2/61.4/66.1
Black Africans	40 (7.9)	4.7/−3.4/−0.0/−7.4/−6.3	77.5/70.0/75.0/70.0/72.5
Sex			
Male			
White Europeans	9068 (52.4)	2.2/2.2/5.7/−4.1/−0.4	81.9/81.9/77.4/86.3/85.5
Black Europeans	596 (61.8)	−0.6/−8.1/−5.5/−11.5/−7.8	81.4/78.2/81.5/70.3/79.4
Black Africans	271 (53.3)	10.9/−2.7/1.2/−11.3/−5.1	66.8/74.2/72.3/75.3/78.2
Female			
White Europeans	8253 (47.6)	3.7/3.7/6.5/−2.3/−0.2	83.2/83.2/79.7/88.4/87.8
Black Europeans	368 (38.2)	5.9/−2.3/−0.5/−5.3/−3.7	70.9/78.5/80.2/80.4/82.3
Black Africans	237 (46.7)	15.4/1.4/4.2/−5.5/−3.6	59.9/77.6/76.8/80.6/80.6
BMI (kg/m²)			
BMI <18			
White Europeans	751 (4.3)	13.1/13.1/15.6/1.9/5.2	62.6/62.6/59.0/78.0/75.5
Black Europeans	23 (2.4)	19.3/9.9/11.7/5.8/7.2	34.8/73.9/69.6/69.6/78.3
Black Africans	20 (3.9)	5.8/−4.7/−2.0/−10.3/−6.3	45.0/65.0/65.0/75.0/75.0
BMI (18–25)			
White Europeans	7556 (43.6)	4.7/4.7/7.7/−2.8/0.7	81.8/81.8/77.5/87.9/86.5
Black Europeans	369 (38.3)	4.0/−4.1/−1.6/−7.6/−4.5	73.2/78.0/78.6/76.4/79.4
Black Africans	291 (57.3)	14.2/−0.2/3.0/−10.1/−4.0	62.5/73.2/72.5/77.3/78.0
BMI (25–30)			
White Europeans	5814 (33.6)	1.4/1.4/4.7/−4.2/−1.3	85.8/85.8/81.9/88.9/88.7
Black Europeans	350 (36.3)	0.2/−7.3/−4.8/−10.1/−7.2	86.0/82.0/87.1/76.0/85.1
Black Africans	128 (25.2)	10.8/−2.0/1.0/−7.8/−4.3	66.4/80.5/76.6/78.9/80.5
BMI ≥30			
White Europeans	3200 (18.5)	0.8/0.8/3.8/−3.4/−1.1	83.0/83.0/79.3/85.2/85.8
Black Europeans	222 (23.0)	−1.5/−7.9/−5.7/−10.7/−7.7	75.2/73.4/76.6/68.0/75.2
Black Africans	69 (13.6)	11.9/−2.3/1.8/−6.7/−5.0	68.1/81.2/81.2/78.3/84.1

CKD-EPI$_{ASR}$: Chronic Kidney Disease Epidemiology Collaboration with variables age, sex and race; CKD-EPI$_{ASR-NB}$: Chronic Kidney Disease Epidemiology Collaboration with variables age, sex and race but without applying the race coefficient; CKD-EPI$_{AS}$: Chronic Kidney Disease Epidemiology Collaboration with variables age and sex; EKFC: European Kidney Function Consortium; LMREV: Lund–Malmö Revised; P20: accuracy within 20%; P30: accuracy within 30% of mGFR.

Table 3: EKFC with and without population-specific Q-values (all results in Black populations).

EKFC	Q female/male	Sample	Bias (95% CI)	IQR (Q1; Q3)	P30 (95% CI)
European cohort	0.70/0.90	Overall $n = 964$	−6.3 (−7.0; −5.5)	14.6 (−13.4; 1.1)	80.5 (78.0; 83.0)
		Females $n = 368$	−3.7 (−4.9; −2.6)	15.3 (−10.8; 4.5)	82.3 (78.4; 86.3)
		Males $n = 596$	−7.8 (−8.6; −6.8)	14.4 (−15.3; −0.9)	79.4 (76.1; 82.6)
European cohort	0.74/1.02	Overall $n = 964$	−0.9 (−1.8; −0.3)	15.6 (−8.2; 7.4)	83.7 (81.4; 86.0)
		Females $n = 368$	−0.9 (−2.4; 0.4)	15.8 (−8.2; 7.6)	81.3 (77.2; 85.3)
		Males $n = 596$	−0.9 (−2.1; −0.0)	15.5 (−8.3; 7.3)	85.2 (82.4; 88.1)
African cohort	0.70/0.90	Overall $n = 508$	−4.4 (−5.3; −3.3)	19.9 (−14.0; 5.9)	79.3 (75.8; 82.9)
		Females $n = 237$	−3.6 (−5.0; 0.1)	20.0 (−12.7; 7.3)	80.6 (75.5; 85.7)
		Males $n = 271$	−5.1 (−7.0; −3.5)	19.6 (−15.0; 4.5)	78.2 (73.3; 83.2)
African cohort	0.72/0.96	Overall $n = 508$	−1.4 (−2.8; 0.6)	20.4 (−10.6; 9.9)	78.9 (75.4; 82.5)
		Females $n = 237$	−1.0 (−3.3; 1.6)	20.4 (−10.9; 9.5)	80.6 (75.5; 85.7)
		Males $n = 271$	−2.2 (−4.1; 1.3)	20.7 (−10.4; 10.3)	77.5 (72.5; 82.5)

EKFC: European Kidney Function Consortium; IQR: Interquartile range; P30: accuracy within 30% of mGFR.

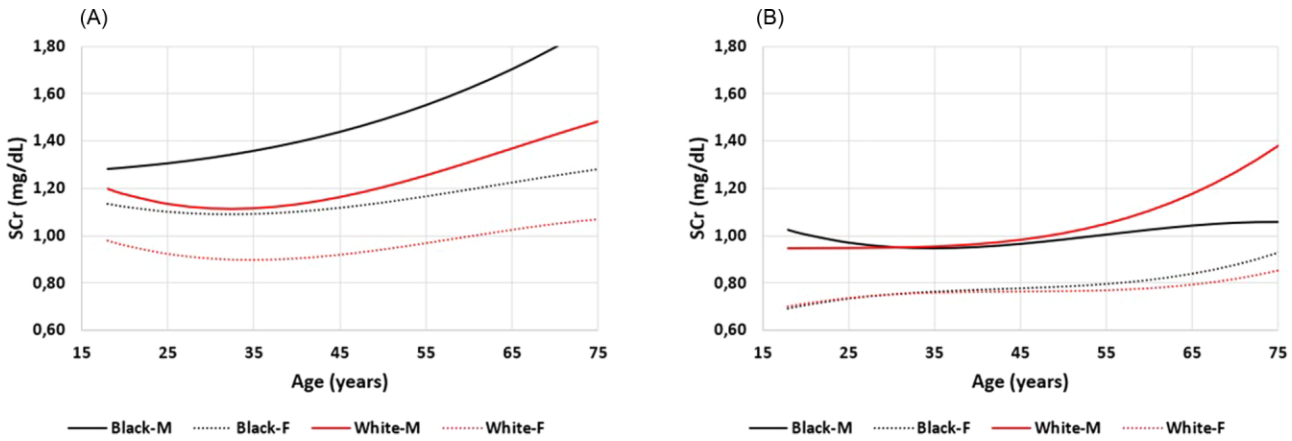


Figure 5: Median quantile lines for serum creatinine in the age/sex/mGFR/BMI-matched Black Europeans and White Europeans (**A**) and matched Black Africans and White Europeans (**B**), separately for males and females. F: females; M: males; SCr: serum creatinine.

It is well known that serum creatinine is not a perfect biomarker for GFR [1,4]. Its concentration differs between females and males, and varies in different populations for the same mGFR value. However, as illustrated in Fig. 5 in the matched analysis, it is probably not closely related to race (neither ethnicity nor ancestry), and still less to skin color. For a similar level of mGFR, age, BMI and the same sex, serum creatinine was different in Black Europeans compared with White Europeans from the EKFC cohort. However, the same analysis showed that serum creatinine versus age in Black Africans is very close to White Europeans. Also, the difference in serum creatinine between Black Europeans and White Europeans is more pronounced in males than in females (an observation also made in Black Americans) [3]. The reason for such a disparity in serum creatinine is still not fully understood, and cannot be simplified by a difference in muscular mass only (as we matched for BMI) or kidney function (matched for age, sex and mGFR) [2]. Other factors, such as nutritional habits and diet, may play a role [4,33].

The EKFC with the population-specific Q-values takes the impact of such variables into account for a more accurate estimation of GFR. Of importance, the specific Q-values are dedicated to the populations at hand. We used independently developed Q-values for specific populations, and therefore, these are not just a 'correction' of results obtained in White populations. Moreover, as illustrated here, the dedicated Q-values are applied to serum creatinine, not to the global estimation at the GFR level, as it has been shown that mGFR is not different in Black and White populations [10,34]. The Q-value can be determined by different methods (from large laboratory databases or from healthy populations), and the population of choice can be multiple, from a very large (as in White Europeans) to a more limited one (as in Black Europeans) [17]. One can even imagine an ideal, personalized 'baseline' Q-value, which would be the Q-value of a given individual when he/she is healthy and between 20 and 40 years of age.

There are several strengths of this study. We used a very large cohort of White Europeans, and to the best of our knowledge, the largest cohort of Black individuals from Europe and Africa ever described for this topic. The large EKFC cohort of White Europeans allowed an original matched analysis, reinforcing the conclusions of the study. There are also limitations. Firstly, the results obtained in Black Europeans are coming from Black people living in the area of Paris and may not be readily applicable to other Black populations living elsewhere in Europe [13]. In Paris, most Black subjects

originate from West Africa. The Black African cohort data are from Central and West Africa, thus additional work is required in other regions of Africa (notably to establish the Q-values) [10,11]. Secondly, in the EKFC cohort, ethnicity could not be identified for legal reasons ('ethnic' studies are not allowed in some countries or require specific ethical requirement). However, the number of Black subjects in the different cohorts of EKFC was limited. Thirdly, the Black African cohort does not cover the entire GFR and age range, and further studies in older people and in patients with moderate chronic kidney disease (GFR between 45 and 60 mL/min/1.73 m^2) are necessary. Also, the sample of the Brazilian cohort includes CKD patients and is relatively small to draw solid conclusions. Fourth, mGFR was measured by different techniques which may have contributed to differences between cohorts. Fifth, ethnicity was self-reported in the Paris cohort and assigned by researchers in Brazil. However, it has been recently shown that genetic ancestry was not better than 'self-reported ethnicity' in the context of eGFR [4]. The question of mixed populations remains important, as practitioners might be embarrassed to manage the ethnicity variable in these subjects. To overcome this problem, a dedicated Q-value can be easily established, using data from healthy kidney donors or large databases from laboratories [17] (a mean Q-value in a mixed population may also be used). EKFC displays the best overall performances, and the use of population-specific Q-values reduces the bias in all Black populations and further improves accuracy, notably in Black European males. Finally, cystatin C samples were not available in the current analysis for all subjects. This biomarker could be of particular interest because race, but also sex, seem to have less impact on its concentration compared with that of creatinine [35,36]. A dedicated cystatin C–based EKFC equation is under development. However, cystatin C measurement at a large scale can be challenging for pragmatic reasons, especially in developing countries [10,37].

In conclusion, the new CKD-EPI_{AS} has been developed in the USA for societal reasons and is now recommended by the NKF and ASN. In Europe and Africa, the performance of CKD-EPI_{AS} is, however, suboptimal. The EKFC equation, using the usual Q-values or dedicated, population-specific Q-values (when available), presents the best performance in the whole age range for the European and African populations included in this study.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

P.D., J.B., U.N., M.F., E.V.-P. and H.P. contributed to the conception and design, analysis and interpretation of the data. H.P., M.F., J.B., U.N., E.V.-P. and P.D. drafted the manuscript. All other co-authors were involved in the acquisition of data [M.F., E.V.-P., T.S., J.-P.H. (Paris), N.E., E.S. (Berlin), L.D. (Lyon), R.N.D. (Kent), H.P. (Leuven), A.B. (Amsterdam), C.M. (Saint-Etienne), T.M., B.O.E. (Tromsö), K.A.-M., K.L., U.B.B., M.H. (Stockholm), A.G., A.A. (Lund), A.L. (Uppsala), P.-O.S. (Örebro), J.B.B., E.K.S., E.C. (Congo), E.Y., D.M., E.C. (Côte d'Ivoire), M.C., L.C., F.G., C.G., L.J., N.K., C.L., L.R. (for the French Kidney Donor Study), L.d.S.S., J.P.S.d.M. (Rio de Janeiro)], and revised the manuscript, before giving final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

All the authors declare no competing interests.

(See related article by Fu *et al.* Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population. *Nephrol Dial Transplant* 2023; 38: 119–128; See related article by Gansevoort *et al.* What should European nephrology do with the new CKD-EPI equation? *Nephrol Dial Transplant* 2023; 38: 1–6)

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