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Rescaling creatinine makes GFR estimation equations generally applicable across populations – validation results for the Lund-Malmö equation in a French cohort of sub-Saharan ancestry

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Abstract

Objectives: To make glomerular filtration rate (GFR) estimating equations applicable across populations with different creatinine generation by using rescaled serum creatinine (sCr/Q) where sCr represents the individual creatinine level and Q the average creatinine value in healthy persons of the same population.

Methods: GFR measurements (mGFR, plasma clearance of ^{51}Cr-EDTA) were conducted in 964 adult Black Europeans. We established the re-expressed Lund-Malmö revised equation (r-LMR) by replacing serum creatinine (sCr) with rescaled creatinine sCr/Q. We evaluated the r-LMR equation based on Q-values of White Europeans (r-LMR$_{Q\text{-white}}$; Q-values females: 62 µmol/L, males: 80 µmol/L) and Black Europeans (r-LMR$_{Q\text{-Black}}$; Q-values females: 65 µmol/L, males: 90 µmol/L), and the European Kidney Function Consortium equation (EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$) regarding bias, precision (interquartile range, IQR) and accuracy (percentage of estimates within ±10 % [P_{10}] and ±30 % [P_{30}] of mGFR).

Results: Median bias of r-LMR$_{Q\text{-White}}$/r-LMR$_{Q\text{-Black}}$/EKFC$_{Q\text{-White}}$/EKFC$_{Q\text{-Black}}$ were −9.1/−4.5/−6.3/−0.9 mL/min/1.73 m^2, IQR 14.7/14.5/14.5/15.6 mL/min/1.73 m^2, P_{10} 25.1 %/34.8 %/30.3 %/37.2 % and P_{30} 74.2 %/84.1 %/80.6 %/83.6 %. The improvement of bias and accuracy when using proper Q-values was most pronounced in men. Similar improvements were obtained above and below mGFR 60 mL/min/1.73 m^2 and at various age and BMI intervals, except for BMI<20 kg/m^2 where bias increased, and accuracy decreased.

Conclusions: GFR estimating equations may be re-expressed to include rescaled creatinine (sCr/Q) and used across populations with different creatinine generation if population-specific average creatinine concentrations (Q-values) for healthy persons are established.

Keywords: chronic kidney disease; creatinine; glomerular filtration rate; kidney function tests

UN, JB, PD, HP and MF are members of the European Kidney Function Consortium, which is endorsed by the European Renal Association.

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Introduction

Glomerular filtration rate estimating equations (eGFR) as index test for renal function generally perform worse when validated outside the development population. This may be due to differences in population characteristics including morbidity, creatinine generation [1], methods to measure GFR (mGFR) used as reference test (e.g., renal clearance of the ionic X-ray contrast medium iothalamate vs. plasma clearance of the non-ionic X-ray contrast medium iohexol)

[2, 3] and in biomarker assays including differences in standardization [4].

Pottel et al. have introduced the principle of rescaled (normalized) serum creatinine to compensate for population differences in creatinine generation [5], mainly differences in muscle mass and dietary habits concerning e.g. meat [6]. Rescaled serum creatinine (sCr/Q) is a dimensionless ratio where sCr represents the actual serum creatinine level of the individual and Q the expected creatinine level of this individual if in a healthy state. Thus, the Q-value is a surrogate for the creatinine generation determinants in a given population. The European Kidney Function Consortium (EKFC) equation uses this rescaling principle that implies that the same basic expression of the equation can be used for both children and adults, females and males [7] as well as in different ethnic groups [8]. From this rescaling principle, it follows that any GFR estimating equation can be generalized to populations with creatinine generation different from the one where it was developed. Previous work has for example shown how GFR estimating equations developed for adults can be applied in children with satisfactory accuracy by converting their creatinine values to corresponding adult levels [9, 10].

The rescaling principle also implies that any GFR equation can be re-expressed mathematically so its estimation is based on rescaled serum creatinine (sCr/Q). In the current study, we establish the re-expressed Lund-Malmö Revised (r-LMR) equation, an equation that was originally developed in a White European (Swedish) population [11], for use with rescaled serum creatinine. As a proof of concept, we show how the rescaling with population-specific Q-values makes the LMR equation applicable as index test of renal function with satisfactory accuracy in a French Black population of sub-Saharan ancestry. Comparisons are made with the EKFC equation using the same Q-values.

Materials and methods

The present study cohort included 964 Black patients (henceforth designated Black Europeans) with self-reported partial or total ancestry from sub-Saharan Africa (of which about 1/3 were of Caribbean origin), who were referred for GFR measurements between October 2006 and October 2020 at Assistance Publique-Hôpitaux de Paris, Bichat Hospital (Table 1). The cohort included 28 % patients with diabetes mellitus, 7 % with human immunodeficiency virus, 15 % potential renal donors and 46 % renal transplant recipients. Serum concentration of creatinine, weight, height, age and gender were recorded at the time of the GFR examination and used to estimate GFR in cross-sectional analyses.

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 originally approved by the Regional Ethical Board in Lund, Sweden (reg no. 2018/220) with amendments subsequently reviewed and approved by the Swedish Ethical Review Authority (reg no. 2021–04177) and by the Institutional Review Board of Assistance-Publique Hôpitaux de Paris and Paris 7 University, France (IRB 00006477, study 14-051). All patients gave their written consent for scientific use of anonymous data. Relevant items of the 2015 Standards for Reporting of Diagnostic Accuracy checklist (STARD) were considered when preparing this report.

Table 1: Basic characteristics of the study cohort (n=964).

	All (n=964)	Females (n=368)	Males (n=596)
Age, years	51 (23–75)	51 (23–75)	51 (23–74)
Weight, kg	77 (50–118)	71 (45–109)	79 (53–119)
Height, cm	171 (153–189)	163 (151–176)	175 (159–191)
Body surface area, m^2	1.91 (1.48–2.42)	1.80 (1.40–2.29)	1.96 (1.56–2.46)
Body mass index, kg/m^2	26 (18–39)	27 (18–40)	26 (18–37)
Serum creatinine, µmol/L	124 (57–343)	103 (49–344)	133 (80–332)
Measured GFR, mL/min/1.73 m^2	59 (20–114)	58 (19–117)	61 (23–107)
Estimated GFR, mL/min/1.73 m^2			
r-$LMR_{Q\text{-}White}$	51 (16–99)	52 (15–108)	49 (17–89)
r-$LMR_{Q\text{-}Black}$	57 (18–104)	55 (15–111)	57 (19–96)
$EKFC_{Q\text{-}White}$	52 (16–107)	53 (14–111)	52 (18–100)
$EKFC_{Q\text{-}Black}$	59 (18–111)	56 (15–113)	60 (20–108)
Measured GFR, number (%)			
<30 mL/min/1.73 m^2	94 (10)	45 (12)	49 (8)
30–44 mL/min/1.73 m^2	170 (18)	78 (21)	92 (15)
45–59 mL/min/1.73 m^2	228 (24)	73 (20)	155 (26)
60–89 mL/min/1.73 m^2	346 (36)	116 (32)	230 (39)
≥90 mL/min/1.73 m^2	126 (13)	56 (15)	70 (12)s

Descriptive measures given as median values (2.5 and 97.5 percentiles) if not stated otherwise.

Laboratory methods for reference and index test

Measured GFR was determined from the plasma clearance of ^{51}Cr-labelled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), using 6–7 samples drawn between 105 and 255–285 min after injection, and with the Bröchner-Mortensen correction, as detailed elsewhere [12]. Plasma concentrations of creatinine were determined by a compensated-kinetic Jaffe assay on a Roche Hitachi analyser from 2006 to March 2008 and by an enzymatic assay on a Siemens Dimension Vista® analyser (Siemens Healthineers, Germany) thereafter (2008–2020). All assays were traceable to isotope dilution mass spectrometry (IDMS) by standard reference material (SRM) 967 (National Institute of Standards and Technology, NIST, Gaithersburg, MD, USA).

Q-values

For adult White Europeans, Q-values were based on sex-specific median creatinine values from non-nephrology units in three different European hospitals, two Belgian (n=18,757) and one Swedish (n=64,410):

62 µmol/L for females and 80 µmol/L for males [5, 7, 9]. For adult Black Europeans of sub-Saharan ancestry, mean Q-values have been established (females 65 µmol/L, males 90 µmol/L) based on creatinine values from 90 living kidney donors (48 females) in three centres in Paris, France [8].

All creatinine samples for determination of Q-values were analysed in clinical routine at the hospitals with enzymatic assays traceable to isotope dilution mass spectrometry (IDMS) by standard reference material (SRM) 967 (National Institute of Standards and Technology, NIST, Gaithersburg, MD, USA).

GFR estimating equations

Lund-Malmö revised (LMR) equation [11]: The original version of the LMR equation implicitly estimates GFR under the assumption that sCr is measured among White European adults or populations with similar creatinine generation:

$LMR=e^{X\ -\ 0.0158\ \times\ Age\ +\ 0.438\ \times\ lnAge}$		
Female	sCr<150 µmol/L:	$X=2.50 + 0.0121 \times (150 - sCr)$
Female	sCr≥150 µmol/L:	$X=2.50 - 0.926 \times \ln(sCr/150)$
Male	sCr<180 µmol/L:	$X=2.56 + 0.00968 \times (180 - sCr)$
Male	sCr≥180 µmol/L:	$X=2.56 - 0.926 \times \ln(sCr/180)$

The original formulation of the LMR equation was re-expressed mathematically to allow for rescaling (see Supplementary Material for details). In the re-expressed version of the LMR equation (r-LMR), the threshold sCr values (females: 150 µmol/L, males: 180 µmol/L) were replaced with corresponding thresholds for rescaled creatinine (females: 150/62, males: 180/80) where 62 and 80 µmol/L represent the Q-values of females and males, respectively, in the original LMR development cohort of White Europeans. sCr in the formula expression was then replaced by rescaled creatinine $62 \times sCr/Q$ for females and by $80 \times sCr/Q$ for males. Q in the formula expression represents the Q-values of the population where the equation is applied:

$r\text{-}LMR=e^{X\ -\ 0.0158\ \times\ Age\ +\ 0.438\ \times\ ln(Age)}$		
Female	sCr/Q<150/62≈2.42:	$X=4.315 - 0.7502 \times sCr/Q$
Female	sCr/Q/≥150/62≈2.42:	$X=3.3181 - 0.926 \times \ln(sCr/Q)$
Male	sCr/Q<180/80≈2.25:	$X=4.3024 - 0.7744 \times sCr/Q$
Male	sCr/Q≥180/80≈2.25:	$X=3.3109 - 0.926 \times \ln(sCr/Q)$

$r\text{-}LMR_{Q\text{-}Black}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for Black Europeans.

$r\text{-}LMR_{Q\text{-}White}$=re-expressed LMR equation based on rescaled creatinine with Q-values for White Europeans, which besides rounding errors yield identical estimates as the original formulation of the LMR equation.

European Kidney Function Consortium (EKFC) equation [7]:

$EKFC=107.3 \times (sCr/Q)^{-0.322} \times [0.990^{(Age-40)}$ if Age>40] for sCr/Q<1

$EKFC=107.3 \times (sCr/Q)^{-1.132} \times [0.990^{(Age-40)}$ Age>40] for sCr/Q≥1

$EKFC_{Q\text{-}Black}$=EKFC equation based on Q-values for Black Europeans

$EKFC_{Q\text{-}White}$=EKFC equation based on Q-values for White Europeans

Statistical evaluation

All statistical evaluations were conducted using IBM SPSS Statistics (version 25; IBM Corp.), STATA (version 14.2; StataCorp), PROC QUANTREG in SAS 9.4, (SAS Institute Inc., Cary, NC, US) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The analysis focused on bias, precision, and accuracy of the GFR estimating equations regarded as index test [13]. Bias was assessed as the median of estimated minus measured GFR (eGFR – mGFR) and precision as the interquartile range (IQR) of the differences eGFR – mGFR. Accuracy was assessed from the absolute error |eGFR – mGFR| and expressed in mL/min/1.73 m^2 and as the percentage of estimates within ±10 % and ±30 % of mGFR (P_{10} and P_{30}). P_{30} accuracy of at least 75 % has been considered sufficient "for good clinical decision-making" by the National Kidney Foundation but the benchmark is to reach P30>90 % [14].

Bias and accuracy (P_{30}) were evaluated in subgroups defined by mGFR (<30, 30–44, 45–59, 60–89 and ≥90 mL/min/1.73 m^2), age (18–39, 40–64 and ≥65 years), BMI (<20, 20–24, 25–29 and ≥30 kg/m^2) and gender. We further stratified results by rescaled serum creatinine (sCr/Q) using thresholds implied by the formulations of the GFR equations: <1.0, 1.0–1.49, females: 1.50–2.24 and ≥2.25, males: 1.50–2.41 and ≥2.42. Non-parametric and asymptotic 95 % confidence intervals (CI) were calculated for the main results as measures of the statistical uncertainty in medians and proportions (P_{10} and P_{30}). We used McNemar's exact test for pairwise comparisons of P_{30} across different equations for the main results.

Results

In the current validation cohort, bias moved closer to zero, precision remained unchanged and P_{30} accuracy increased when appropriate population-specific Q-values were used. The re-expressed LMR equation used with the Q-values for Black Europeans ($r\text{-}LMR_{Q\text{-}Black}$) rather than Q-values for White Europeans ($r\text{-}LMR_{Q\text{-}White}$) led to performance improvements both overall and when stratified by mGFR (Tables 2 and 3). P_{30} increased overall by +10.4 percentage points (pp, 95 % CI 7.8–13.0 pp, p<0.001) and reached the same level as $EKFC_{Q\text{-}Black}$. The improvement in accuracy by using population-specific Q-values for Black Europeans was less marked for EKFC with an increase in P_{30} by only +3.0 pp (95 % CI 0.7–5.3 pp, p=0.01).

The improved performance of $r\text{-}LMR_{Q\text{-}Black}$ compared with $r\text{-}LMR_{Q\text{-}White}$ was more pronounced among males than among females (Table 4) and was consistently noted when results were stratified by rescaled serum creatinine (sCr/Q; Table S1). The improvement in performance for $r\text{-}LMR_{Q\text{-}Black}$ across levels of rescaled serum creatinine was less consistent among females (Table S2). The improvement of $EKFC_{Q\text{-}Black}$ was confined to males only (Table 4).

Improvement in P_{30} was noted in all age groups (18–39, 40–64 and ≥65 years) for both $r\text{-}LMR_{Q\text{-}Black}$ and $EKFC_{Q\text{-}Black}$ (Table 5). When stratifying for BMI (<20, 20–30 and ≥30 kg/m^2)

Table 2: Bias, precision and accuracy (95 % confidence intervals) of GFR estimating equations in the overall cohort (n=964).

Equations	r-LMR$_{Q\text{-White}}$	r-LMR$_{Q\text{-black}}$	EKFC$_{Q\text{-White}}$	EKFC$_{Q\text{-Black}}$
Bias	−9.1 (−10.2 to −8.5)	−4.5 (−5.3 to −3.8)	−6.3 (−7.0 to −5.5)	−0.9 (−1.7 to −0.3)
IQR	14.7	14.5	14.5	15.6
Accuracy				
–Absolute error	10.7 (10.0–11.4)	8.3 (7.4–8.9)	8.9 (8.3–9.5)	7.9 (7.4–8.5)
–P_{10}	25.1 (22.4–27.8)	35.5 (32.5–38.5)	30.3 (27.4–33.2)	37.2 (34.2–40.3)
–P_{30}	74.2 (71.4–82.3)	84.1 (81.8–86.4)	80.6 (78.1–83.1)	83.6 (81.3–85.9)

Median bias (eGFR-mGFR), precision (IQR, interquartile range) and accuracy in terms of absolute error |eGFR − mGFR| expressed in mL/min/1.73 m^2, and P_{10} and P_{30} accuracy expressed in percentage of GFR estimates within ±10 % and ±30 % of mGFR, respectively. r-LMR$_{Q\text{-White}}$ and r-LMR$_{Q\text{-Black}}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for White and Black Europeans, respectively. EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$=EKFC equation based on Q-values for White and Black Europeans, respectively.

Table 3: Bias and P_{30} accuracy (95 % confidence intervals) of GFR estimating equations stratified by measured GFR (mGFR mL/min/1.73 m^2).

mGFR intervals	Number (%)	r-LMR$_{Q\text{-White}}$	r-LMR$_{Q\text{-Black}}$	EKFC$_{Q\text{-White}}$	EKFC$_{Q\text{-Black}}$
Bias					
<30	94 (10)	−4.4 (−5.4 to −2.5)	−2.7 (−4.4 to −0.7)	−2.8 (−5.3 to −1.4)	−0.8 (−3.2 to 1.0)
30–44	170 (18)	−8.1 (−8.8 to −6.6)	−4.2 (−6.1 to −2.5)	−4.5 (−5.4 to −2.9)	−0.7 (−2.1 to 1.0)
45–59	228 (24)	−9.2 (−10.8 to −6.9)	−3.0 (−4.9 to −0.5)	−5.6 (7.4 to −4.1)	0.4 (−1.1 to 1.5)
60–89	346 (36)	−11.0 (−12.6 to −9.5)	−4.2 (−6.6 to −2.7)	−9.1 (−10.7 to −6.6)	−1.0 (−2.8 to 1.1)
≥90	126 (13)	−17.6 (−21.6 to −15.2)	−11.5 (−14.9 to −9.2)	−12.9 (16.2 to −8.6)	−5.2 (−8.1 to −2.5)
P_{30}					
<30		62.8 (53.0–72.5)	72.3 (63.3–81.4)	62.8 (53.0–72.5)	67.0 (57.5–76.5)
30–44		64.1 (56.9–71.3)	71.8 (65.0–78.5)	74.7 (68.2–81.2)	78.8 (72.7–85.0)
45–59		72.8 (67.0–78.6)	82.5 (77.5–87.4)	82.9 (78.0–87.8)	82.9 (78.0–87.8)
60–89		79.5 (75.2–83.7)	91.0 (88.0–94.0)	83.5 (79.6–87.4)	87.3 (83.8–90.8)
≥90		84.1 (77.7–90.5)	93.7 (89.4–97.9)	89.7 (84.4–95.0)	93.7 (89.4–96.8)

Median bias (eGFR-mGFR) expressed in mL/min/1.73 m^2 and P_{30} accuracy in percentage of GFR estimates within ±30 % of mGFR. r-LMR$_{Q\text{-White}}$ and r-LMR$_{Q\text{-Black}}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for White and Black Europeans, respectively. EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$=EKFC equation based on Q-values for White and Black Europeans, respectively.

Table 4: Bias and P_{30} accuracy (95 % confidence intervals) of GFR estimating equations stratified by females (n=368) and males (n=596).

mGFR intervals	r-LMR$_{Q\text{-white}}$	r-LMR$_{Q\text{-Black}}$	EKFC$_{Q\text{-White}}$	EKFC$_{Q\text{-Black}}$
Bias females	−5.3 (−7.3 to −4.2)	−3.5 (−5.1 to −1.7)	−3.8 (−5.0 to −2.5)	−0.9 (−2.4 to 0.5)
Bias males	−11.5 (−12.5 to −10.4)	−5.2 (−6.0 to −4.0)	−7.8 (−8.7 to −6.8)	−0.8 (−2.1 to 0.0)
P_{30} females	80.4 (76.4–84.5)	83.2 (79.3–87.0)	82.3 (78.4–86.2)	81.3 (77.3–85.2)
P_{30} males	70.3 (66.6–74.0)	84.7 (81.8–87.6)	79.5 (76.3–82.8)	85.1 (82.2–87.9)

Median bias (eGFR-mGFR) expressed in mL/min/1.73 m^2 and P_{30} accuracy in percentage of GFR estimates within ±30 % of mGFR. r-LMR$_{Q\text{-White}}$ and r-LMR$_{Q\text{-Black}}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for White and Black Europeans, respectively. EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$=EKFC equation based on Q-values for White and Black Europeans, respectively.

bias increased and P_{30} decreased at BMI<20 kg/m^2 for both equations based on Q-values for blacks while bias decreased with improved P_{30} at BMI≥20 kg/m^2 (Table 6).

Discussion

We showed in the present study how the generalizability of GFR estimation equations can be improved by re-expressing the equation formulation using the biomarker rescaling principle and apply population-specific Q-values. We used the creatine-based LMR-equation as an example, but similar rescaling should be possible to apply also for other GFR estimating equations and other biomarkers. Our validation results suggest that rescaling may substantially improve estimation performance when a GFR equation developed in one population is applied to another population with anticipated different creatinine generation. Recently it was also

Table 5: Bias and P_{30} accuracy (95 % confidence intervals) of GFR estimating equations stratified by age (years).

Age intervals	Number (%)	r-LMR$_{Q\text{-White}}$	r-LMR$_{Q\text{-Black}}$	EKFC$_{Q\text{-White}}$	EKFC$_{Q\text{-Black}}$
Bias					
18–39	219 (23)	−8.2 (−8.8 to −7.6)	−3.7 (−4.0 to −3.0)	−4.6 (−5.0 to −3.6)	2.4 (1.4–3.1)
40–64	618 (64)	−9.0 (−10.2 to −8.2)	−4.3 (−5.6 to −3.4)	−6.3 (−7.2 to −5.3)	−1.0 (−2.1 to 0.0)
≥65	127 (13)	−10.5 (−12.4 to −8.4)	−6.7 (−8.0 to −4.9)	−9.4 (−11.2 to −7.3)	−5.2 (−8.2 to −3.4)
P_{30}					
18–39		82.2 (77.1–87.3)	90.4 (86.5–94.3)	86.8 (82.3–91.2)	84.0 (79.2–88.9)
40–64		73.9 (70.5–77.4)	83.7 (80.7–86.6)	81.4 (78.3–84.5)	84.8 (82.0–87.6)
≥65		61.4 (53.0–69.9)	75.6 (68.1–83.1)	66.1 (57.9–74.4)	77.2 (69.9–85.5)

Median bias (eGFR-mGFR) expressed in mL/min/1.73 m^2 and P_{30} accuracy in percentage of GFR estimates within ±30 % of mGFR. r-LMR$_{Q\text{-White}}$ and r-LMR$_{Q\text{-Black}}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for White and Black Europeans, respectively. EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$=EKFC equation based on Q-values for White and Black Europeans, respectively.

Table 6: Median bias and P_{30} accuracy (95 % confidence intervals) of GFR estimating equations stratified by body mass index (BMI, kg/m^2).

BMI intervals	Number (%)	r-LMR$_{Q\text{-White}}$	r-LMR$_{Q\text{-Black}}$	EKFC$_{Q\text{-White}}$	EKFC$_{Q\text{-Black}}$
Bias					
<20	80 (8)	1.6 (−1.1 to 5.7)	7.5 (4.5–10.0)	5.4 (1.1–8.6)	10.4 (7.7–14.0)
20–29	662 (69)	−9.7 (−10.7 to −8.7)	−4.5 (−5.4 to −3.4)	−6.7 (−7.5 to −5.9)	−0.9 (−1.9 to −0.2)
≥30	222 (23)	−10.7 (−12.2 to −8.9)	−6.2 (−75 to −4.6)	−7.7 (−9.5 to −6.3)	−3.7 (−5.4 to −2.0)
P_{30}					
<20		77.5 (68.3–86.7)	68.8 (58.6–78.9)	75.0 (65.8–84.2)	57.5 (47.1–67.9)
20–29		75.8 (72.6–79.1)	87.5 (84.9–90.0)	83.1 (80.2–85.9)	88.4 (85.9–90.8)
≥30		68.0 (61.9–74.2)	79.7 (74.4–85.0)	75.2 (69.6–80.8)	78.8 (73.5–84.1)

Median bias (eGFR-mGFR) expressed in mL/min/1.73 m^2 and P_{30} accuracy in percentage of GFR estimates within ±10 % and ±30 % of mGFR. r-LMR$_{Q\text{-White}}$ and r-LMR$_{Q\text{-Black}}$=re-expressed Lund-Malmö revised equation based on rescaled creatinine values with Q-values for White and Black Europeans, respectively. EKFC$_{Q\text{-White}}$ and EKFC$_{Q\text{-Black}}$=EKFC equation based on Q-values for White and Black Europeans, respectively.

shown how the rescaling principle can be used to generalize a GFR estimation equation developed for one biomarker (creatinine) to another biomarker (cystatin C) by developing biomarker-specific Q-values [15]. This suggests that the GFR-age evolution is generally applicable to all populations, while the biomarker-age evolution is population-specific. Thus, rescaling the biomarker makes the biomarker-GFR relationship less complex, which comes with many advantages for the GFR equations: i) applicable and continuous for all ages, ii) applicable to males and females, iii) applicable for different populations (ethnicities), iv) applicable for different biomarkers and v) stable performance in comparison with equations not based on rescaled biomarkers [7, 15].

The application of the re-expressed LMR-equation with population-specific Q-values resulted in decreased bias and improved accuracy both overall and when stratified by GFR and age. Rescaled creatinine led to larger improvement in performance for r-LMR than for EKFC and after rescaling the two equations had similar performance overall. LMR and EKFC also perform similar in White Europeans with median bias of −0.6 and −3.5 mL/min/1.73 m^2, respectively, and P_{30} accuracy of 87.4 and 86.8 %, respectively, (Table S4b and S7a in reference [7]). It should also be noted that imprecision, a major drawback of GFR estimating equations, did not improve by using rescaled creatinine with population-specific Q-values.

The implication of the rescaling was a bit different for the two equations. For EKFC, rescaling creatinine to Black Europeans implied that eGFR was increased with a constant (1.152 for males, 1.065 for females) for all rescaled creatinine values above one. By contrast, the increase in eGFR from rescaling is for r-LMR dependent on how elevated the biomarker is. In the present study the rescaling factor for r-LMR varied between 1.10 and 1.21 for males and between 1.04 and 1.09 for females. It was beyond the scope of the present study to optimize the rescaling at various creatinine levels, but this is a topic for additional investigations.

The improved performance with respect to bias and accuracy was more pronounced and consistent in males, most likely due to a larger difference in Q-values between Black and White male Europeans than between females. However, at BMI<20 kg/m^2 both r-LMR$_{Q\text{-Black}}$ and EKFC$_{Q\text{-Black}}$ showed increased overestimation resulting in decreased

accuracy. This was expected since both LMR and EKFC are known to overestimate mGFR in White Europeans with low creatinine values due to low muscle mass [16–18]. By using the lower Q-values for White Europeans two different errors cancelled out, thus explaining the lower bias and higher accuracy when not using the Q-values specific for Black Europeans in underweight patients. As this group was small it was not possible to stratify any further.

A similar technique has previously been proposed by Björk et al. [9] for the LMR equation to make it applicable in European children by converting childhood levels of sCr to corresponding adult levels and apply the equation as though the child was 18 years old. Future studies are warranted to establish creatinine growth curves and hence Q-values for children of different ethnicities, thereby further extending the applicability of the rescaling principle for equations like LMR.

Despite the generality of the outlined rescaling principle, the generalizability of the present validation results to other black populations should be considered as a potential study limitation. The validation was based on a single cohort in Paris and the applicability to persons of sub-Saharian origin or other black populations living elsewhere in Europe is a topic for additional investigations [19]. A related limitation is that ethnicity was self-reported in the Paris cohort, although it has been recently shown that genetic ancestry may not be add more accuracy in the GFR estimation than self-reports [1]. It should also be noted that the Q-values utilized for the black population in the present study are subject to statistical uncertainty as the sample size used when they were established was small. Another limitation was that the validation did not include children. While creatinine growth curves and hence Q-values have been established in Swedish children [9], it is yet unclear to what extent they can be generalized with sufficient accuracy to children of other origin. Finally, the choice of reference method may impact the validation results. We considered plasma clearance a coherent choice of reference method in this study, as LMR was developed against plasma clearance (iohexol) and EKFC was initially mainly validated against plasma clearance methods. However, there is some concern that mGFR determined by plasma clearance yields overestimations in patients with low GFR [20, 21]. If this is the case, then the present validation study may have overrated the performance improvement of r-LMR$_{\text{Q-Black}}$ in patients with severe renal impairment. However, it does not affect the generality of the proposed rescaling principle as such.

In conclusion, any well-established eGFR equation may be re-expressed to include rescaled creatinine (sCr/Q) and used in other populations with anticipated different creatinine generation if average creatinine concentration (Q-values) for healthy persons is established. The applied Q-values may either be sex-specific (as in adults) or be both age- and sex-specific (as in children).

Research ethics: 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 originally approved by the Regional Ethical Board in Lund, Sweden (reg no. 2018/220) with amendments subsequently reviewed and approved by the Swedish Ethical Review Authority (reg no. 2021–04177) and by the Institutional Review Board of Assistance-Publique Hôpitaux de Paris and Paris 7 University, France (IRB 00006477, study 14-051). Data were anonymized from the source cohort for the analysis performed at Lund University, Sweden.

Informed consent: Informed consent was obtained from all individuals included in this study.

Author contributions: J.B. and U.N. conceived the study, conducted the statistical analyses and draughted the article. M.F, E.V.P. and A.L. contributed with data. All authors contributed with analysis and interpretation of data, provided intellectual content of critical importance to the work described, revising the article and have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability: Legal and ethical restrictions prevent public sharing of the dataset. Data can be made available for collaborations upon request to interested researchers but would generally require a new ethical permission and the permission of each of the data-owners.

References

1. Hsu CY, Yang W, Parikh RV, Anderson AH, Chen TK, Cohen DL, et al. Race, genetic ancestry, and estimating kidney function in CKD. N Engl J Med 2021;385:1750–60.
2. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol 2019;16:51–64.
3. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? Clin Kidney J 2016; 9:682–99.

4. Björk J, Bäck SE, Nordin G, Nyman U. How valid are GFR estimation results from the CKD-EPI databases? Am J Kidney Dis 2018;71:446.
5. Pottel H, Hoste L, Dubourg L, Ebert N, Schaeffner E, Eriksen BO, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016;31:798–806.
6. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38: 1933–53.
7. Pottel H, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. Ann Intern Med 2021;174:183–91.
8. Delanaye P, Vidal-Petiot E, Björk J, Ebert N, Eriksen BO, Dubourg L, et al. Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa. Nephrol Dial Transplant 2023;38:106–18.
9. Björk J, Nyman U, Delanaye P, Grubb A, Larsson A, Vranken L, et al. A novel method for creatinine adjustment makes the revised Lund-Malmö GFR equation applicable in children. Scand J Clin Lab Invest 2020;80:456–63.
10. Björk J, Nyman U, Larsson A, Delanaye P, Pottel H. Estimation of the glomerular filtration rate in children and young adults using the CKD-EPI equation with age-adjusted creatinine values. Kidney Int 2021; 99:940–7.
11. Björk J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. Scand J Clin Lab Invest 2011;71:232–9.
12. Vidal-Petiot E, Courbebaisse M, Livrozet M, Corrégé G, Rusu T, Montravers F, et al. Comparison of (51)Cr-EDTA and (99m)Tc-DTPA for glomerular filtration rate measurement. J Nephrol 2021;34:729–37.
13. Stevens LA, Zhang Y, Schmid CH. Evaluating the performance of equations for estimating glomerular filtration rate. J Nephrol 2008;21: 797–807.
14. NKF5. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. Guideline 4. Estimation of GFR. Am J Kidney Dis 2002;39:S76–92.
15. Pottel H, Björk J, Rule AD, Ebert N, Eriksen BO, Dubourg L, et al. Cystatin C-based equation to estimate GFR without the inclusion of race and sex. N Engl J Med 2023;388:333–43.
16. Nyman U, Grubb A, Larsson A, Hansson LO, Flodin M, Nordin G, et al. The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med 2014;52:815–24.
17. Björk J, Nyman U, Courbebaisse M, Couzi L, Dalton RN, Dubourg L, et al. Prospects for improved GFR estimation based on creatinine – results from a transnational multicentre study. Clin Kidney J 2020;13: 674–83.
18. Delanaye P, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Performance of creatinine-based equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment. Br J Clin Pharmacol 2022;88:2118–27.
19. Gama RM, Clery A, Griffiths K, Heraghty N, Peters AM, Palmer K, et al. Estimated glomerular filtration rate equations in people of self-reported black ethnicity in the United Kingdom: inappropriate adjustment for ethnicity may lead to reduced access to care. PLoS One 2021;16:e0255869.
20. Soveri I, Berg UB, Björk J, Elinder CG, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. Am J Kidney Dis 2014;64:411–24.
21. Stolz A, Hoizey G, Toupance O, Lavaud S, Vitry F, Chanard J, et al. Evaluation of sample bias for measuring plasma iohexol clearance in kidney transplantation. Transplantation 2010;89:440–5.

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