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Original Investigation

Accuracy of the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (CKD Epidemiology Collaboration) Equations for Estimation of GFR in the Elderly

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Background: Glomerular filtration rate (GFR) is a measure of kidney function, commonly estimated using equations that adjust serum creatinine concentration for age, race, and sex. The Modification of Diet in Renal Disease (MDRD) Study equation is widely used, but underestimates GFR at higher levels. The serum creatinine–based Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI$_{cr}$) equation generally provides more accurate estimation at GFR >60 mL/min/1.73 m^2. Newer equations have been reported using cystatin C concentration either alone (CKD-EPI$_{cys}$) or in combination with creatinine concentration (CKD-EPI$_{cr\text{-}cys}$). None of these equations has been well validated in older people. We tested the accuracy of these equations in people 74 years or older compared with GFR measured by a reference method.

Study Design: Diagnostic test evaluation in a prospective cohort.

Setting & Participants: Participants (n = 394; median age, 80 [range, 74-97] years) recruited from nephrology clinics and the community.

Index Test: GFR estimated using the MDRD Study, CKD-EPI$_{cr}$, CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ equations.

Reference Test: GFR measured using an iohexol clearance method.

Results: Median measured GFR was 53.4 (range, 7.2-100.9) mL/min/1.73 m^2. MDRD Study–, CKD-EPI$_{cr}$–, and CKD-EPI$_{cr\text{-}cys}$–estimated GFRs overestimated GFR (median differences of 3.5 [$P < 0.001$], 1.7 [$P < 0.001$], and 0.8 [$P = 0.02$] mL/min/1.73 m^2, respectively); the CKD-EPI$_{cys}$ equation was unbiased. Accuracy (percentage of estimates within 30% of measured GFR [P_{30}]) was 81%, 83%, 86%, and 86% for the MDRD Study, CKD-EPI$_{cr}$, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ equations, respectively. Accuracy of the MDRD Study equation was inferior ($P = 0.004$) to the CKD-EPI$_{cr}$ equation at GFR >60 mL/min/1.73 m^2.

Limitations: Those of non-European ancestry were not included. For practical reasons, only a 4-hour sampling protocol was used for iohexol clearance.

Conclusions: The CKD-EPI$_{cr}$ equation appeared less biased and was more accurate than the MDRD Study equation. No equation achieved an ideal P_{30} in the overall population. Our data suggest that GFR estimation is as satisfactory in older people of European ancestry as it has been reported to be in younger individuals.
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INDEX WORDS: Glomerular filtration rate; cystatin C; creatinine; kidney disease.

Glomerular filtration rate (GFR) is accepted as the best overall measure of kidney function. Measurement of GFR using reference procedures in which the clearance of an infused exogenous substance (eg, inulin, ^{125}I-iothlamate, ^{51}Cr-EDTA, or iohexol[1]) is measured is impractical for large-scale application. Estimation of GFR using equations based on serum creatinine concentration with adjustments for age, sex, and race are widely used as surrogate measures of GFR.

The Modification of Diet in Renal Disease (MDRD) Study equation, which estimates GFR adjusted for body surface area, originally was developed in 1999.[2] A simplified (4-variable) version of the equation subsequently was published[3] and later was re-expressed for use with a standardized serum creatinine assay.[4] Generally, the MDRD Study equation has been seen to perform better and offer practical advantages over other GFR estimating equations that had been used previously. Its use has been endorsed by national professional health care organizations.[5,6]

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The MDRD Study equation has been criticized on the basis that it significantly underestimates GFR in individuals with GFR >60 mL/min/1.73 m^2.[7] A revised equation, the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{cr}$) equation, has been published and is thought to partially address this issue, producing less biased estimates of GFR at higher levels of kidney function.[7] Recently, the same group has published 2 additional CKD-EPI equations: one based on cystatin C concentration ($CKD\text{-}EPI_{cys}$) and one using both cystatin C and serum creatinine concentrations ($CKD\text{-}EPI_{cr\text{-}cys}$).[8]

There has been limited evaluation of the CKD-EPI and MDRD Study equations in older people. CKD is common in the population in general and its prevalence increases markedly with age.[9,10] There have been suggestions that underestimation of GFR by estimating equations has led to overdiagnosis of CKD in the older population.[11] With an aging population and polypharmacy of growing complexity, accurately estimating GFR in older people and detecting and managing decreased kidney function in this group are undeniably critical issues.[12] In the present study, we assessed the accuracy of the MDRD Study and CKD-EPI equations for estimating GFR compared with an iohexol reference GFR measurement in older people of European ancestry.

METHODS

Participant Selection

Participants were either patients known to the Kent Kidney Care Centre or residents of the local population. The latter were recruited through a variety of means, including the researchers attending discussion groups in Age Concern centers, golf clubs, Rotary clubs, and residential care homes, and through advertising the study by media briefings in hospital newsletters, local newspapers, and radio stations. Overall, 38% of participants were recruited through nephrology clinics, and 62%, through other methods. Individuals 74 years and older were recruited and agreed to participate in the study from January 2008 to April 2011. All participants gave informed consent and the study had full ethical approval (East Kent REC number: 07/Q1803/37). The study took place in East Kent, a semirural area of Southern England.

Exclusion criteria included any history of untoward reactions to iodinated contrast media, known current active malignancy, life expectancy less than 3 months, inability to consent due to cognitive impairment, recent (within 3 months) episode of acute kidney injury, and receiving renal dialysis treatment.

Measurement and Estimation of GFR

Patients were invited to attend the hospital in the morning, having avoided any meat consumption on the day of the test. Demographic and comorbid condition data and prescription histories were recorded and blood pressure, weight, and height were documented. Blood samples were obtained at time zero for serum creatinine and cystatin C measurement, and a random urine sample was collected for total protein, albumin, and creatinine measurement.

GFR was measured using an iohexol clearance method. A 5-mL bolus of Omnipaque 240 (518 g/L of iohexol, corresponding to 240 g/L of iodine; GE Healthcare, www.gelifesciences.com) was injected intravenously into the antecubital vein at time zero, followed by a 10-mL normal saline solution flush. A blood sample was obtained at 5 minutes from the opposite arm to confirm that the iohexol had been administered intravenously. Further blood samples were collected at 120, 180, and 240 minutes after injection. The exact timing of the samples in relation to the bolus injection was accurately recorded. All blood samples were collected in lithium heparin tubes, mixed, and centrifuged at the end of each study at 2,045*g* for 4 minutes. Plasma was stored at −80°C prior to analysis.

Iohexol GFR was calculated using a single-compartment model, in other words, GFR (mL/min) = 0.693 × iohexol volume of distribution (L) × 1,000/half-life of iohexol (min). GFR (milliliters per minute) was corrected for body surface area and the Brochner-Mortensen correction was applied.[13] GFR was estimated using the simplified isotope-dilution mass spectrometry (IDMS)-traceable version of the 4-variable MDRD Study equation[4] and the 3 CKD-EPI equations.[7,8]

Analytical Methods

Plasma creatinine and iohexol were measured simultaneously using a modified stable isotope-dilution electrospray tandem mass spectrometric method reported for creatinine.[14] The only modifications were the inclusion of both 25 μmol/L of $^5H_3$-iohexol and $^2H_3$-creatinine in the stable isotope reagent, the addition of the precursor/product ion pairs (mass to charge ratio [m/z]: 821.9/602.9, 826.9/607.9) for iohexol, and because of the higher sensitivity of the Applied Biosystems SCIEX API5000 (Applied Biosystems, www.appliedbiosystems.com) instrument used, the precursor/product ion pairs (m/z: 114.0/85.9, 117.0/88.9) were used for creatinine.

Between-assay imprecision for the plasma iohexol assay was assessed at 3 concentrations, covering the range 10-400 μmol/L, and was <7%. Accuracy of the plasma creatinine assay was assessed using NIST SRM 967 I and II (National Institute of Standards and Technology Standard Reference Material, www.nist.gov), included in each assay (n = 31): SRM 967 I (mean, 0.74 mg/dL; nominal value, 0.75 [0.73-0.77] mg/dL) and SRM 967 II (mean, 3.76 mg/dL; nominal value, 3.90 [3.82-3.98] mg/dL). Between-assay imprecision was 4.3% and 3.8%, respectively.

Cystatin C was measured by a particle-enhanced nephelometric immunoassay on a BN Prospec analyzer (Siemens Healthcare Diagnostics, www.medical.siemens.com). The reference range was 0.53-0.95 mg/L (manufacturer's product information) and between-day imprecision was 3.5% at a concentration of 2.3 mg/L. The assay was not calibrated against the international certified reference material ERM-DA471/IFCC for cystatin C,[15] but values were multiplied by 1.11 as recommended by the manufacturer (customer notification November 18, 2010) to convert them to ERM-DA471/IFCC–equivalent concentrations prior to their use in GFR estimating equations.

Urinary creatinine was measured using an enzymatic assay. Urinary albumin was measured using immunoturbidimetric assays and albumin concentration was expressed relative to urinary creatinine concentration. Urinary assays were undertaken using an Abbott Architect analyzer (Abbott Diagnostics Ltd, www.international.abbottdiagnostics.com) within 24 hours of sample collection.

All analyses were undertaken in accredited laboratories by scientists registered with the Health Professions Council. Readers of the index tests and iohexol reference standard were blinded (masked) to results of the other test and vice versa.

Statistical Analysis

Data were analyzed using Analyse-it (Analyse-it Software Ltd, www.analyse-it.com) and Stata, version 12.0 (StataCorp LP, www.stata.com). Bias, precision, and accuracy were measured to determine the performance of each equation as proposed by the NKF-KDOQI (National Kidney Foundation's Kidney Disease Outcomes Quality Initiative).[16] GFR and estimated GFR data sets were not normally distributed ($P < 0.001$, Shapiro-Wilk test); thus, nonparametric statistics were used throughout. Iohexol GFR was accepted as the reference measure of GFR against which estimated GFR was compared. Bias was calculated by subtracting measured GFR from estimated GFR; thus, a negative bias indicates that the prediction equation underestimates GFR and vice versa. Precision was assessed as interquartile range (IQR) for the differences. Accuracy was assessed as the percentage of estimates within 30% of measured GFR (P_{30}) and also as root mean square error (RMSE). Subanalyses were done for individuals with GFR <60 and ≥60 mL/min/1.73 m^2 and also for individuals younger than 80 and 80 years and older. Confidence intervals (CIs) for the IQR and RMSE were calculated using bootstrapping procedures. Wilcoxon matched-pairs signed rank test was used to compare the bias of each of the GFR estimates against measured GFR and of the MDRD Study, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ equations' GFR estimates against the CKD-EPI$_{cr}$ equation. McNemar test was used to compare P_{30} values of the MDRD Study, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ equations against those of the CKD-EPI$_{cr}$ equation. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 398 individuals were recruited to the study. An additional 27 individuals initially agreed to participate but subsequently withdrew, for reasons including intercurrent illness at the time of the scheduled test, refusal for participation from family members, and inability to provide alternative arrangements for their dependents. Three individuals of African-Caribbean ethnicity and one amputee were excluded from the final analyses on the basis that as subgroups, they were too small to provide meaningful data. The final study cohort therefore consisted of 394 individuals of European ancestry; characteristics of the group are listed in Table 1. Ten individuals lived in supported accommodation; the rest were free living.

Median iohexol GFR was 53.4 (range, 7.2-100.9) mL/min/1.73 m^2. Performance of the equations is summarized in Table 2, and bias plots of the 4 equations against measured (iohexol) GFR are shown in Fig 1. In the entire population studied, the MDRD Study, CKD-EPI$_{cr}$, and CKD-EPI$_{cr\text{-}cys}$ equations overestimated GFR, whereas the CKD-EPI$_{cys}$ equation was unbiased. The MDRD Study and CKD-EPI$_{cr}$ equations overestimated measured GFR when GFR was <60 mL/min/1.73 m^2; under the same conditions, the CKD-EPI$_{cys}$ equation underestimated measured GFR. All equations overestimated GFR when GFR was ≥60 mL/min/1.73 m^2. The 3 CKD-EPI equations appeared to be more accurate (higher P_{30}) than the MDRD Study equation in all participants overall, but the inferiority of the MDRD Study equation was significant only for individuals with GFR ≥60 mL/min/1.73 m^2. No equation achieved P_{30} ≥90% in the overall cohort, but the 3 CKD-EPI equations achieved this level of accuracy at GFR ≥60 mL/min/1.73 m^2. The CKD-EPI$_{cr\text{-}cys}$ equation had the lowest IQR and RMSE.

Similar trends in equation performance were seen whether individuals were younger than 80 or 80 years or older, but the CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ equations were unbiased in individuals 80 years or older overall. The MDRD Study equation performed poorly in individuals 80 years or older with GFR ≥60 mL/min/1.73 m^2 (Table 2).

In men, the CKD-EPI$_{cys}$ equation underestimated measured GFR (bias, −2.8; 95% CI, −3.8 to −1.8 mL/min/1.73 m^2; $P = 0.005$), whereas the MDRD Study (1.6; 95% CI, 0.0 to 3.9 mL/min/1.73 m^2; $P = 0.07$), CKD-EPI$_{cr}$ (0.1; 95% CI, −1.9 to 1.1 mL/min/1.73 m^2; $P = 0.9$), and CKD-EPI$_{cr\text{-}cys}$ (−1.9; 95% CI, −3.2 to −0.1 mL/min/1.73 m^2; $P = 0.1$) equations were unbiased. In women, the MDRD Study (bias, 4.8; 95% CI, 3.0 to 6.6 mL/min/1.73 m^2; $P < 0.001$), CKD-EPI$_{cr}$ (4.3; 95% CI, 1.8 to 5.9 mL/min/1.73 m^2; $P < 0.001$), CKD-EPI$_{cys}$ (0.8; 95% CI, −0.7 to 3.7 mL/min/1.73 m^2; $P = 0.01$), and CKD-EPI$_{cr\text{-}cys}$ (2.9; 95% CI, 1.2 to 5.1 mL/min/1.73 m^2; $P < 0.001$) equations all overestimated measured GFR.

DISCUSSION

We present a large prospective evaluation of the performance of contemporary GFR estimating equations in older people. Overall, our data suggest that these equations perform as well in the older population as in younger people and that there may be marginal benefits in using one of the CKD-EPI equations compared to the MDRD Study equation.

Several studies have been undertaken directly comparing the MDRD Study and CKD-EPI$_{cr}$ equations: a variety of statistical approaches have been used. In this discussion, we focus on the use of P_{30} as a measure of accuracy because it incorporates elements of both bias and precision. Typically and understandably, equations generally have performed less well outside the cohorts in which they were developed.[17] In the original MDRD Study validation cohort,[2] the MDRD Study equation achieved P_{30} of 91%, whereas in the CKD-EPI cohort,[7] this decreased to 81% compared with 84% for the CKD-EPI$_{cr}$ equation itself. In studies that subsequently have directly compared the CKD-EPI$_{cr}$ and MDRD Study equations in large (n > 100) adult European-ancestry populations using standardized serum creatinine assays, the CKD-EPI equation has been superior to the MDRD Study equation at higher GFRs (>60 mL/min/1.73 m^2), whereas the MDRD Study equation performs better at lower

Table 1. Characteristics of the Study Population

	Entire Cohort	Age <80 y	Age ≥80 y
No.	394	193	201
Age (y)	80 (74-97)	—	—
Age stratification			
74-79 y	193 (49)	—	—
80-84 y	132 (34)	—	—
85-89 y	51 (13)	—	—
≥90 y	18 (5)	—	—
Male sex	189 (48)	90 (47)	99 (49)
Height (m)	1.67 (1.24-1.94)	1.67 (1.43-1.94)	1.67 (1.24-1.85)
Weight (kg)	74 (32-126)	78 (46-126)	71 (32-109)
Body surface area (m^2)	1.87 (1.14-2.59)	1.92 (1.35-2.59)	1.82 (1.14-2.38)
Body mass index (kg/m^2)	26.1 (13.7-47.6)	27.2 (18.9-47.6)	25.5 (13.7-36.7)
Systolic BP (mm Hg)	140 (78-203)[c]	140 (95-203)[c]	141 (78-198)[c]
Diastolic BP (mm Hg)	74 (42-115)[c]	75 (50-115)[c]	74 (42-110)[c]
Prescription data			
RAS antagonists	154 (39)	82 (43)	72 (36)
Calcium channel antagonists	105 (27)	46 (24)	59 (29)
β-Blockers	97 (25)	49 (25)	48 (24)
α-Blockers	42 (11)	20 (10)	22 (11)
Diuretics	145 (37)	66 (34)	79 (39)
Nitrates	42 (11)	21 (11)	21 (10)
NSAIDs	37 (9)	20 (10)	17 (9)
Comorbid conditions			
Hypertension	215 (55)	104 (54)	111 (55)
Diabetes	76 (19)	37 (19)	39 (19)
Vascular disease[a]	172 (44)	77 (40)	95 (47)
History of malignancy	51 (13)	28 (15)	23 (11)
Urine ACR ≥30 mg/g	110 (30)[b]	49 (28)[b]	61 (32)[b]
Urine ACR ≥300 mg/g	31 (8)[b]	10 (6)[b]	21 (11)[b]
Serum creatinine (mg/dL)	1.07 (0.39-4.30)	1.00 (0.46-3.71)	1.15 (0.39-4.30)
Serum cystatin C (mg/L)	1.19 (0.68-3.45)	1.12 (0.68-3.45)	1.37 (0.77-3.40)
mGFR ($mL/min/1.73\ m^2$)	53.4 (7.2-100.9)	60.6 (7.2-96.3)	46.9 (15.0-100.9)
mGFR category			
<30 $mL/min/1.73\ m^2$	64 (16.2)	22 (11.4)	42 (20.9)
30-44 $mL/min/1.73\ m^2$	79 (20.1)	27 (14.0)	52 (25.9)
45-59 $mL/min/1.73\ m^2$	91 (23.1)	46 (23.8)	45 (22.4)
60-89 $mL/min/1.73\ m^2$	154 (39.1)	95 (49.2)	59 (29.4)
>90 $mL/min/1.73\ m^2$	6 (1.5)	3 (1.6)	3 (1.5)
eGFR			
MDRD Study ($mL/min/1.73\ m^2$)	57.6 (13.3-156.0)	62.0 (16.0-129.8)	52.3 (13.3-156.0)
CKD-EPI$_{cr}$ ($mL/min/1.73\ m^2$)	57.0 (12.0-98.2)	63.1 (14.9-94.4)	50.3 (12.0-98.2)
CKD-EPI$_{cys}$ ($mL/min/1.73\ m^2$)	55.2 (13.6-98.7)	60.3 (14.1-98.7)	45.7 (13.6-97.8)
CKD-EPI$_{cr\text{-}cys}$ ($mL/min/1.73\ m^2$)	56.1 (12.5-102.1)	60.9 (14.5-98.6)	47.3 (12.5-102.1)

Note: Data were available for each participant unless stated otherwise. Values for continuous variables expressed as median (range); values for categorical values expressed as number (percentage). Conversion factors for units; GFR in $mL/min/1.73\ m^2$ to $mL/s/1.73\ m^2$, ×0.01667; serum creatinine in mg/dL to μmol/L, ×88.4; ACR in mg/g to mg/mmol, ×0.113.

Abbreviations and definitions: ACR, albumin-creatinine ratio; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI$_{cr}$, serum creatinine–based CKD-EPI equation; CKD-EPI$_{cys}$, cystatin C–based CKD-EPI equation; CKD-EPI$_{cr\text{-}cys}$, serum creatinine– and cystatin C–based CKD-EPI equation; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate (using iohexol); NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system.

[a]Considered present if there was a history of myocardial infarction, angina, arrhythmia, valvular disease, congestive cardiac failure, requirement for coronary intervention (angioplasty, coronary artery bypass graft, or pacemaker), or cerebrovascular or peripheral vascular disease.

[b]Albuminuria data available for 368 (177 individuals <80 years and 191 ≥80 years).

[c]BP data available for 374 (187 individuals <80 years and 187 ≥80 years).

Table 2. Performance of the MDRD Study and CKD-EPI Equations Compared With mGFR

All Participants

	Overall (n = 394)	mGFR <60 (n = 234)	mGFR ≥60 (n = 160)
	Bias: Median Difference, ie, eGFR – mGFR (95% CI)[a]		
MDRD Study	3.5 (1.9 to 4.8); $P_1 < 0.001$, $P_2 < 0.001$	2.0 (0.8 to 3.9); $P_1 < 0.001$, $P_2 < 0.001$	5.5 (3.4 to 8.1); $P_1 < 0.001$, $P_2 < 0.001$
$CKD\text{-}EPI_{cr}$	1.7 (0.3 to 3.2); $P_1 < 0.001$	0.6 (−0.7 to 2.3); $P_1 = 0.03$	4.3 (1.2 to 6.2); $P_1 < 0.001$
$CKD\text{-}EPI_{cys}$	−1.2 (−2.2 to 0.0); $P_1 = 0.9$, $P_2 < 0.001$	−2.9 (−3.7 to −1.9); $P_1 < 0.001$, $P_2 < 0.001$	3.4 (0.7 to 6.5); $P_1 < 0.001$, $P_2 = 0.6$
$CKD\text{-}EPI_{cr\text{-}cys}$	0.8 (−0.4 to 1.9); $P_1 = 0.02$, $P_2 < 0.001$	−1.6 (−2.8 to −0.2); $P_1 = 0.2$, $P_2 < 0.001$	4.8 (2.1 to 6.8); $P_1 < 0.001$, $P_2 = 0.2$
	Precision: IQR of the Difference (95% CI) [range]		
MDRD Study	13.7 (11.4 to 16.0) [101.3]	11.4 (9.5 to 13.3) [78.0]	18.3 (14.3 to 22.3) [94.3]
$CKD\text{-}EPI_{cr}$	13.1 (11.7 to 14.6) [68.5]	11.7 (9.8 to 13.6) [68.5]	15.8 (13.0 to 18.7) [46.7]
$CKD\text{-}EPI_{cys}$	14.2 (12.5 to 15.9) [81.5]	10.7 (8.1 to 13.2) [63.6]	14.4 (11.9 to 16.8) [79.0]
$CKD\text{-}EPI_{cr\text{-}cys}$	12.7 (11.5 to 13.9) [67.9]	10.3 (8.4 to 12.2) [62.9]	13.3 (9.6 to 17.1) [59.6]
	Accuracy: P_{30} (95% CI)[b]		
MDRD Study	81 (77 to 85); $P = 0.2$	78 (72 to 83); $P = 0.5$	86 (79 to 91); $P = 0.004$
$CKD\text{-}EPI_{cr}$	83 (79 to 87)	76 (70 to 81)	93 (88 to 97)
$CKD\text{-}EPI_{cys}$	86 (82 to 89); $P = 0.3$	82 (77 to 87); $P = 0.1$	91 (86 to 95); $P = 0.7$
$CKD\text{-}EPI_{cr\text{-}cys}$	86 (82 to 90); $P = 0.07$	81 (75 to 86); $P = 0.07$	94 (90 to 97); $P = 0.8$
	Accuracy: RMSE (95% CI)		
MDRD Study	13.4 (11.8 to 14.9)	11.1 (9.5 to 12.6)	16.2 (13.4 to 18.6)
$CKD\text{-}EPI_{cr}$	10.9 (10.0 to 11.7)	10.7 (9.5 to 11.8)	11.1 (10.1 to 12.1)
$CKD\text{-}EPI_{cys}$	10.5 (9.6 to 11.4)	9.2 (8.2 to 10.2)	12.2 (10.4 to 13.7)
$CKD\text{-}EPI_{cr\text{-}cys}$	9.8 (9.0 to 10.5)	8.9 (7.8 to 9.8)	11.0 (9.8 to 12.1)

Participants <80 y

	Overall (n = 193)	mGFR <60 (n = 95)	mGFR ≥60 (n = 98)
	Bias: Median Difference, ie, eGFR – mGFR (95% CI)[a]		
MDRD Study	3.0 (0.8 to 5.1); $P_1 < 0.001$, $P_2 = 0.005$	2.1 (−0.9 to 5.0); $P_1 = 0.01$, $P_2 < 0.001$	4.6 (0.8 to 7.2); $P_1 = 0.003$, $P_2 = 0.2$
$CKD\text{-}EPI_{cr}$	3.1 (0.3 to 4.9); $P_1 < 0.001$	1.2 (−1.5 to 4.8); $P_1 = 0.04$	3.6 (0.3 to 6.6); $P_1 = 0.006$
$CKD\text{-}EPI_{cys}$	−0.1 (−1.9 to 1.9); $P_1 = 0.4$, $P_2 = 0.01$	−2.0 (−4.3 to 0.0); $P_1 = 0.08$, $P_2 < 0.001$	3.2 (−0.6 to 6.7); $P_1 = 0.01$, $P_2 = 0.8$
$CKD\text{-}EPI_{cr\text{-}cys}$	2.0 (−0.1 to 2.0); $P_1 = 0.02$, $P_2 = 0.03$	−0.6 (−3.1 to 2.0); $P_1 = 0.7$, $P_2 < 0.001$	4.7 (1.9 to 6.8); $P_1 = 0.002$, $P_2 = 0.3$
	Precision: IQR of the Difference (95% CI) [range]		
MDRD Study	13.3 (10.4 to 16.2) [78.0]	11.9 (8.0 to 15.7) [78.0]	15.7 (10.9 to 20.5) [64.8]
$CKD\text{-}EPI_{cr}$	13.0 (11.0 to 15.0) [68.5]	12.8 (8.9 to 16.7) [68.5]	13.2 (9.9 to 16.5) [46.7]
$CKD\text{-}EPI_{cys}$	15.0 (12.6 to 17.4) [81.5]	11.6 (8.3 to 14.9) [63.6]	14.5 (11.4 to 17.7) [79.0]
$CKD\text{-}EPI_{cr\text{-}cys}$	13.0 (10.9 to 14.1) [67.9]	11.0 (8.0 to 13.9) [62.9]	13.8 (9.2 to 18.3) [59.6]
	Accuracy: P_{30} (95% CI)[b]		
MDRD Study	84 (78 to 89); $P = 0.7$	79 (69 to 87); $P = 0.1$	89 (81 to 94); $P = 0.7$
$CKD\text{-}EPI_{cr}$	83 (77 to 88)	75 (65 to 83)	91 (83 to 96)
$CKD\text{-}EPI_{cys}$	86 (80 to 91); $P = 0.5$	80 (71 to 88); $P = 0.4$	92 (85 to 96); $P = 0.9$
$CKD\text{-}EPI_{cr\text{-}cys}$	88 (82 to 92); $P = 0.1$	80 (71 to 88); $P = 0.4$	95 (88 to 98); $P = 0.3$
	Accuracy: RMSE (95% CI)		
MDRD Study	13.3 (11.3 to 15.0)	12.0 (9.1 to 14.3)	14.4 (11.7 to 16.7)
$CKD\text{-}EPI_{cr}$	11.5 (10.2 to 12.6)	12.0 (10.0 to 13.8)	11.0 (9.6 to 12.3)
$CKD\text{-}EPI_{cys}$	11.7 (9.9 to 13.2)	10.7 (8.6 to 12.5)	12.5 (9.8 to 14.8)
$CKD\text{-}EPI_{cr\text{-}cys}$	10.6 (9.3 to 11.8)	10.1 (8.1 to 11.8)	11.1 (9.6 to 12.5)

(Continued)

Table 2 (Cont'd). Performance of the MDRD Study and CKD-EPI Equations Compared With mGFR

Participants ≥80 y

	Overall (n = 201)	mGFR <60 (n = 139)	mGFR ≥60 (n = 62)
	Bias: Median Difference, ie, eGFR – mGFR (95% CI)[a]		
MDRD Study	3.8 (1.6 to 5.2); $P_1 < 0.001$, $P_2 < 0.001$	2.0 (0.8 to 4.1); $P_1 < 0.001$, $P_2 < 0.001$	8.3 (3.8 to 12.9); $P_1 < 0.001$, $P_2 < 0.001$
CKD-EPI$_{cr}$	1.2 (−0.1 to 2.6); $P_1 = 0.008$	0.5 (−1.2 to 2.2); $P_1 = 0.2$	4.4 (−0.1 to 10.0); $P_1 = 0.005$
CKD-EPI$_{cys}$	−2.2 (−2.9 to −0.9); $P_1 = 0.3$, $P_2 < 0.001$	−2.9 (−4.0 to −1.9); $P_1 = 0.002$, $P_2 < 0.001$	3.5 (−0.9 to 8.5); $P_1 = 0.03$, $P_2 = 0.6$
CKD-EPI$_{cr\text{-}cys}$	−0.1 (−1.6 to 1.0); $P_1 = 0.3$, $P_2 < 0.001$	−1.7 (−3.2 to −0.4); $P_1 = 0.1$, $P_2 < 0.001$	4.9 (1.1 to 8.2); $P_1 < 0.001$, $P_2 = 0.5$
	Precision: IQR of the Difference (95% CI) [range]		
MDRD Study	13.8 (11.3 to 16.3) [89.3]	11.4 (9.0 to 13.8) [53.2]	19.2 (13.7 to 24.6) [89.3]
CKD-EPI$_{cr}$	13.3 (10.9 to 15.7) [51.4]	10.9 (8.4 to 13.4) [50.9]	19.1 (15.3 to 22.9) [40.7]
CKD-EPI$_{cys}$	13.4 (10.8 to 15.9) [53.8]	9.2 (5.3 to 13.1) [48.5]	14.9 (10.5 to 19.2) [48.6]
CKD-EPI$_{cr\text{-}cys}$	12.4 (10.5 to 14.3) [48.8]	9.3 (6.9 to 11.6) [43.3]	12.6 (8.0 to 17.2) [44.5]
	Accuracy: P_{30} (95% CI)[b]		
MDRD Study	78 (72 to 84); $P = 0.05$	77 (69 to 84); $P = 0.9$	81 (69 to 90); $P = 0.002$
CKD-EPI$_{cr}$	83 (77 to 88)	77 (69 to 84)	97 (89 to 100)
CKD-EPI$_{cys}$	86 (80 to 90); $P = 0.5$	83 (76 to 89); $P = 0.2$	90 (80 to 96); $P = 0.2$
CKD-EPI$_{cr\text{-}cys}$	85 (79 to 90); $P = 0.5$	81 (74 to 87); $P = 0.2$	94 (84 to 98); $P = 0.6$
	Accuracy: RMSE (95% CI)		
MDRD Study	13.6 (10.9 to 15.9)	10.5 (8.6 to 12.2)	18.1 (12.9 to 23.2)
CKD-EPI$_{cr}$	10.2 (9.1 to 11.3)	9.7 (8.1 to 11.1)	11.3 (9.8 to 12.6)
CKD-EPI$_{cys}$	9.3 (8.4 to 10.2)	8.1 (7.1 to 8.9)	11.6 (9.7 to 13.2)
CKD-EPI$_{cr\text{-}cys}$	8.9 (7.9 to 9.8)	7.9 (6.9 to 8.8)	10.8 (8.9 to 12.4)

Note: mGFR given in milliliters per minute per 1.73 m^2.

Abbreviations and definitions: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI$_{cr}$, serum creatinine–based CKD-EPI equation; CKD-EPI$_{cys}$, cystatin C–based CKD-EPI equation; CKD-EPI$_{cr\text{-}cys}$, serum creatinine– and cystatin C–based CKD-EPI equation; eGFR, estimated GFR; GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR; P_{30}, percentage of estimates within 30% of mGFR; RMSE, root mean square error.

[a]Wilcoxon matched-pairs signed rank test was used to compare the bias of each of the GFR estimates against mGFR (P_1) and of the MDRD Study, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ equation GFR estimates against the CKD-EPI$_{cr}$ equation (P_2).

[b]McNemar test was used to compare P_{30} values of the MDRD, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ equation GFR estimates against the CKD-EPI$_{cr}$ equation.

GFRs.[18] Observed P_{30} values have ranged from 73%-93% for the MDRD Study equation and 80%-95% for the CKD-EPI$_{cr}$ equation.[18] Most studies[19-25] have included very few individuals older than 75 years. In the external validation data sets of Inker et al,[8] the CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ equations achieved P_{30} values of 86% and 92%, respectively, although performance was slightly worse in individuals older than 65 years. There have been no independent evaluations of these newer CKD-EPI equations incorporating cystatin C concentration.

Comparing against previous studies, the P_{30} values we have observed for all 4 equations in older people appear reasonable, being slightly lower than those observed in the original validation cohorts,[2,7,8] but consistent with other independent evaluations.[19-25] Further, bias against the reference method, although significant for the MDRD Study, CKD-EPI$_{cr}$, and CKD-EPI$_{cr\text{-}cys}$ equations, was small in clinical terms. Notably, the underestimation of GFR reported for the MDRD Study equation in some other studies[7,21,22,24] was not seen, with a small positive bias being observed even and especially at higher GFRs. The CKD-EPI$_{cr}$ equation was more accurate than the MDRD Study equation at higher GFRs. Bias, precision, and accuracy appeared broadly equivalent among the 3 CKD-EPI equations: no single CKD-EPI equation showed consistent superiority in any of these measures across different age and GFR strata, although IQR and RMSE tended to be superior for equations incorporating cystatin C concentration (Table 2). Demonstrable improvements in GFR estimation using newer equations are likely to be marginal, and it is possible that our study was underpowered to detect such differences.

The MDRD Study equation originally was validated in 1,085 patients with CKD with a mean age of 51 ± 13 years (22% were >65 years).[2] The authors subsequently evaluated the equation in a larger (n = 5,504) and more diverse population, but again, few people were older than 75 years (mean age, 47 ± 15 years; 13% were >65 years).[26] Although few very elderly people were included, it is interesting to note that the bias they observed in their older-than-65-year

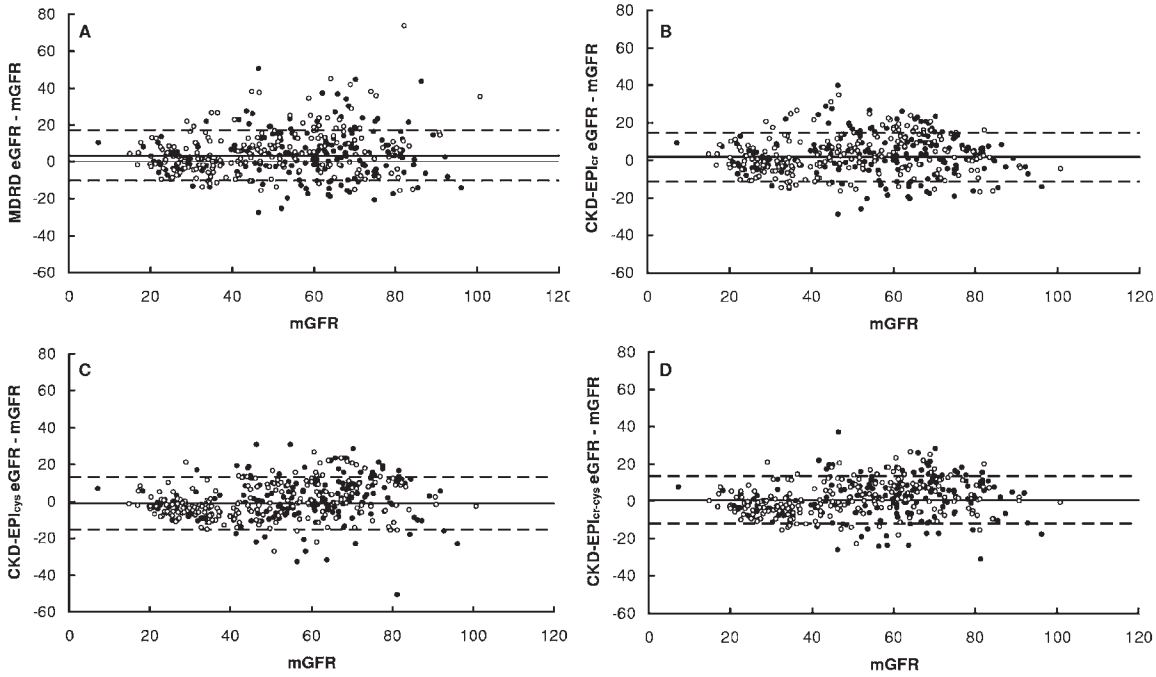

Figure 1. Bias plots show the differences between (A) MDRD (Modification of Diet in Renal Disease) Study, (B) CKD-EPI$_{cr}$ (serum creatinine–based CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation), (C) CKD-EPI$_{cys}$ (cystatin C–based CKD-EPI equation), and (D) CKD-EPI$_{cr\text{-}cys}$ (serum creatinine– and cystatin C–based CKD-EPI equation) estimated glomerular filtration rate (eGFR) and measured GFR (mGFR), plotted against mGFR. All data in milliliters per minute per 1.73 m^2. Individuals younger than 80 years are represented by filled circles, and those 80 years and older, by open circles. Horizontal lines indicate zero bias (gray line), median bias (solid line), and the 25th and 75th percentiles of the bias (long dashes).

subgroup was smaller than that in younger individuals and was minimal (−0.3 mL/min/1.73 m^2) even when GFR was >60 mL/min/1.73 m^2, with P_{30} of 88% being observed in this subgroup. By contrast, they found that the MDRD Study equation underestimated measured GFR in younger individuals with higher GFRs (by −6.4 and −10.6 mL/min/1.73 m^2 in individuals 40-65 and <40 years, respectively).

The development and external validation data sets for the CKD-EPI$_{cr}$ equation had mean ages of 47 ± 15 and 50 ± 15 years, respectively, and again included very few elderly people.[7] Nevertheless, bias of the CKD-EPI$_{cr}$ and MDRD Study estimates in the external validation data set were minimal and broadly equivalent (−1.3 and −1.4 mL/min/1.73 m^2, respectively) in individuals older than 65 years, whereas larger biases were observed in younger individuals, in particular for the MDRD Study equation (eg, −9.7 mL/min/1.73 m^2 for individuals <40 years).[27] A study of Australian individuals also reports a similar age-related shift,[23] and CKD-EPI$_{cr}$–estimated GFR was reported to be 3 mL/min/1.73 m^2 lower than MDRD Study–estimated GFR in North American octogenarians.[28] The recent large study of Murata et al[29] observed that both equations overestimate GFR (MDRD Study, 9%; CKD-EPI$_{cr}$, 5%) in individuals older than 70 years with CKD and underestimate GFR in younger healthy individuals (eg, in 40-69 year olds: CKD-EPI$_{cr}$, −9%; MDRD, −17%).

Overall, a picture emerges of differences between the CKD-EPI and MDRD Study equations and differences between these equations and the reference methods, being diminished in older compared with younger people. The MDRD Study equation was developed in a cohort of patients with CKD (mean GFR, 40 mL/min/1.73 m^2). Its underperformance in healthy individuals with higher GFRs has been attributed to the fact that few such individuals were included in the original development data set. The CKD-EPI$_{cr}$ equation was developed in a broader cohort with better kidney function (68 mL/min/1.73 m^2), purposefully including healthy individuals and thus explaining its superior performance at higher GFRs. Nevertheless, it was developed predominantly in cohorts of diseased individuals, in particular, patients with CKD and/or diabetes.

In our hands, in the elderly, both equations appear to work reasonably and broadly equivalently. We speculate that the relationship among muscle mass, dietary protein intake (and thus creatinine concentration), and GFR in older people is more akin to that of the diseased development cohorts of the MDRD Study and CKD-EPI$_{cr}$ equations than some of the various younger populations in which they subsequently have

been tested. Consequently these equations work well in older people. This is fortunate because the major burden of CKD in most populations resides in the elderly. Accumulating evidence suggests that the CKD-EPI$_{cr}$ equation better identifies clinical risk than the MDRD Study equation,[30,31] including for older people.[32] It will be interesting to see whether CKD-EPI equations incorporating cystatin C concentration add extra information in terms of clinical risk in older people given the increasing evidence suggesting cystatin C as a risk marker for poor outcomes in the elderly.[28,33]

Our observations also fit well with data from studies that have looked at the relative prevalence of CKD in populations and across age strata.[7,9,31] In all cases, although a decrease in CKD prevalence when assessed using the CKD-EPI$_{cr}$ equation rather than the MDRD Study equation has been observed in middle-aged populations, due to virtual abolition of negative bias at GFR >60 mL/min/1.73 m^2, in older people, the 2 equations give similar prevalence estimates. For example, in the East Kent population, we observed mean estimated GFR using the CKD-EPI$_{cr}$ equation to be 11.2% higher than that estimated using the MDRD Study equation for individuals aged 40-49 years: this difference gradually diminished to 0.7% in the 70-79 year olds.[9] In people older than 80 years, the MDRD Study equation gave a lower CKD prevalence estimate than the CKD-EPI$_{cr}$ equation, again in keeping with the slight positive bias (MDRD minus CKD-EPI$_{cr}$) observed in the present study.[9]

Our study incorporated a large number of older people drawn from a range of settings, many of whom were not under the care of nephrologists. The comorbid conditions and prescription data are typical of such populations in the western world, and a broad and balanced range of GFRs was included. Plasma creatinine was measured using an IDMS assay with NIST-traceable standards, and standard reference materials included in each assay and cystatin C concentrations were adjusted to be equivalent to those derived using the international reference standard. Our participants were asked to avoid meat consumption, a known confounder.[34]

Nevertheless, our study has some limitations. The Kent population is predominantly Caucasian: population data shows only 0.7% of the population to be black and a further 1.7% recorded as Asian.[35] Hence, we have validated the use of these equations in only the older European ancestry population. Further studies will need to be performed in other ethnically diverse groups. Our reference GFR method was plasma iohexol clearance over a 4-hour period. Due to problems of ensuring complete bladder emptying in this population, we were unable to collect timed urine samples. Practical limitations meant that collecting a delayed (eg, 24-hour) blood sample was not feasible. Standard clearance of inulin, including urine collection, remains the gold-standard method for GFR measurement, but few studies use this. Most evaluations of GFR equations have used radiolabelled plasma clearance methods, which are assumed to be closely related to inulin clearance, although it is increasingly appreciated that such methods are not all equivalent.[36] Radiolabelled iothalamate plasma clearance was the method used for developing the MDRD Study[2] and CKD-EPI$_{cr}$[7] equations, whereas the CKD-EPI$_{cr}$ equation validation data set used a variety of reference GFR methods, including iohexol.[7] One study suggested that iothalamate clearance overestimated urinary inulin clearance by 20 mL/min/1.73 m^2.[37] Plasma clearance of iohexol using a 4-hour procedure has been shown to significantly overestimate,[38] underestimate,[39] or accurately reflect reference urinary clearance measures.[40] The variety of sampling protocols, compartmental models used, patient mix, and GFR ranges studied in the literature makes interpretation of these various reports difficult. Iohexol clearance is used widely in clinical and research practice, and there is no convincing evidence that it is better or worse than other reference GFR procedures compared to urinary inulin clearance.[41] Prior to clinical introduction of the iohexol GFR method used in this study, it was compared with our existing GFR method (plasma clearance of Inutest [Fresenius Kabi, www.fresenius-kabi.com]) primarily used in children: results were not significantly different. Furthermore, irrespective of how accurately we have assessed "true" GFR, our conclusions regarding the relative performance of the 4 GFR estimating equations remain valid.

In conclusion, although falling short of the >90% P$_{30}$ aspiration of the 2002 NKF-KDOQI guideline,[16] GFR estimating equations appear to work just as well in older compared with younger populations. We found no evidence that the MDRD Study equation was underestimating GFR, irrespective of the level of GFR. The CKD-EPI equations performed marginally better than the MDRD Study equation, particularly at GFR ≥60 mL/min/1.73 m^2. It is possible that other markers, such as β-trace protein and symmetric dimethyl arginine (SDMA), may further improve equation performance in the future. Further studies are required to confirm that the equations perform well in older cohorts of non-European ancestry.

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