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Measurement of kidney function in Malawi, South Africa, and Uganda: a multicentre cohort study

June Fabian, Robert Kalyesubula*, Joseph Mkandawire, Christian Holm Hansen, Dorothea Nitsch, Eustasius Musenge, Wisdom P Nakanga, Josephine E Prynn, Gavin Dreyer, Tracy Snyman, Billy Ssebunnya, Michele Ramsay, Liam Smeeth, Stephen Tollman, Saraladevi Naicker, Amelia Crampin, Robert Newton, Jaya A George, Laurie Tomlinson, on behalf of the African Research on Kidney Disease Consortium†*

Summary

Background The burden of kidney disease in many African countries is unknown. Equations used to estimate kidney function from serum creatinine have limited regional validation. We sought to determine the most accurate way to measure kidney function and thus estimate the prevalence of impaired kidney function in African populations.

Methods We measured serum creatinine, cystatin C, and glomerular filtration rate (GFR) using the slope-intercept method for iohexol plasma clearance (mGFR) in population cohorts from Malawi, Uganda, and South Africa. We compared performance of creatinine and cystatin C-based estimating equations to mGFR, modelled and validated a new creatinine-based equation, and developed a multiple imputation model trained on the mGFR sample using age, sex, and creatinine as the variables to predict the population prevalence of impaired kidney function in west, east, and southern Africa.

Findings Of 3025 people who underwent measured GFR testing (Malawi n=1020, South Africa n=986, and Uganda n=1019), we analysed data for 2578 participants who had complete data and adequate quality measurements. Among 2578 included participants, creatinine-based equations overestimated kidney function compared with mGFR, worsened by use of ethnicity coefficients. The greatest bias occurred at low kidney function, such that the proportion with GFR of less than 60 mL/min per 1·73 m² either directly measured or estimated by cystatin C was more than double that estimated from creatinine. A new creatinine-based equation did not outperform existing equations, and no equation, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 race-neutral equation, estimated GFR within plus or minus 30% of mGFR for 75% or more of the participants. Using a model to impute kidney function based on mGFR, the estimated prevalence of impaired kidney function was more than two-times higher than creatinine-based estimates in populations across six countries in Africa.

Interpretation Estimating GFR using serum creatinine substantially underestimates the individual and population-level burden of impaired kidney function in Africa with implications for understanding disease progression and complications, clinical care, and service provision. Scalable and affordable ways to accurately identify impaired kidney function in Africa are urgently needed.

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Introduction

The true prevalence of chronic kidney disease (CKD) in Africa is unknown. Current estimates of prevalence are 11–16% in people at high risk and 3–6% in population-representative studies, but these figures might not capture the true burden of kidney disease.[1] One reason these estimates might not be accurate is that creatinine-based equations to estimate glomerular filtration rate (eGFR) were developed in high-income countries, and have undergone little validation in African populations, partly because directly measured GFR (mGFR) using exogenous biomarkers, such as iohexol, to assess the accuracy of these equations is not possible due to limited access to compounds and to clinical services that offer mGFR testing.

The rationale for race-based adjustment of GFR-estimating equations has recently been called into question, sparking intense global debate. These equations were based on studies showing that African-American participants had higher mGFR for a given creatinine than other population groups in the USA.[2] The American Society of Nephrology and the National Kidney Foundation reviewed the use of race-based coefficients and recommended immediate adoption of a new race-neutral CKD-EPI (creatinine) 2021 equation.[3]

Another issue is whether eGFR equations—race-neutral or not—are transferable to continental African populations, despite their widespread use. Studies from Kenya, Ghana, South Africa, Democratic Republic of the Congo, and Côte d'Ivoire have consistently demonstrated that race-based adjustments for the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; creatinine) 2009 equations overestimate GFR, especially as GFR declines.

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For the Luganda translation of the abstract see **Online** for appendix 1

For the Chichewa translation of the abstract see **Online** for appendix 2

For the Xitsonga translation of the abstract see **Online** for appendix 3

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Research in context

Evidence before this study

Before conducting this work, we performed a systematic review to determine the available information from African countries regarding accurate assessment of kidney function. This included laboratory methods used to measure serum creatinine (Jaffe or enzymatic); measured glomerular filtration rate (mGFR) studies validating the performance of glomerular filtration rate (GFR) estimating equations; choice of GFR-estimating equations to assess kidney function, including whether ethnicity coefficients were used; and population prevalence of chronic kidney disease (CKD). The systematic review was registered with Prospero (CRD42017068151) and included all original research published from Jan 31, 2008, to Dec 31, 2018. The databases searched included PubMed, African Journals Online, and Web of Science. The medical subject headings used to search databases had the country name for each African country combined with the previously published search terms: kidney disease, renal disease, chronic kidney disease, CKD, chronic renal disease, chronic renal failure, CRF, glomerular filtration, glomerular filtration rate, GFR, proteinuria, albuminuria.

The results showed substantial variation in how kidney function is measured and reported in studies from African countries. Overall, 159 (63%) of 252 studies did not report their laboratory methods for creatinine measurement, but Jaffe was most common (80 [93%] of 86). Of the available GFR-estimating equations, the four-variable Modification of Diet in Renal Disease (MDRD) was most frequently used (146 [40%] of 363), followed by the CKD Epidemiology Collaboration (CKD-EPI) for creatinine 2009 (94 [26%] of 363), and Cockcroft-Gault (85 [23%] of 363). Ethnicity coefficients derived in the USA for the MDRD and CKD-EPI equations were commonly used to adjust eGFR: 45 (31%) of 146 studies adjusted for ethnicity using MDRD and 39 (42%) of 94 studies adjusted for ethnicity using CKD-EPI 2009. Only six studies, with a total sample of 777 participants, compared the performance of GFR-estimating equations with mGFR. These results showed that ethnicity coefficients for the MDRD and CKD-EPI creatinine equations overestimated GFR in Africans. When reporting CKD prevalence, only eight (3%) of 252 studies used population-based sampling frames.

Added value of this study

This is the largest study to robustly measure kidney function using serum creatinine and cystatin C and to directly measure GFR in a transparent and standardised prospective study across three countries in Africa. We used these data to evaluate the performance of ten GFR-estimating equations, four of which have not been previously assessed in African countries. In Malawi, South Africa, and Uganda, all creatinine-based eGFR equations substantially overestimate kidney function compared with mGFR, made worse by the inclusion of ethnicity coefficients when using the MDRD and CKD-EPI equations. Performance of the race-neutral CKD-EPI 2021 equation was no better than the 2009 equation, which is currently used in many parts of Africa. Failure to model an improved creatinine-based GFR-estimating equation and the poor performance of existing equations confirm that creatinine is limited as a biomarker of kidney function. Cystatin C-based equations performed better than creatinine-based equations overall and at all stages of mGFR, and might be a preferred biomarker in Africa. Multiple imputation modelling suggests kidney disease prevalence is substantially higher than that estimated from serum creatinine in African populations.

Implications of all the available evidence

Our results are consistent with smaller studies from Africa suggesting that all creatinine-based GFR-estimating equations underestimate the prevalence of kidney disease in African populations with profound implications for individual and public health. Ethnicity coefficients for the MDRD and CKD-EPI equations should not be used for GFR estimation and the CKD-EPI (creatinine) 2021 race-neutral equation does not have improved performance. Scaleable and affordable alternative biomarkers to assess kidney function more accurately in Africa are urgently needed.

Even when omitted, these equations still perform poorly.[4–7] Potential explanations for the poor performance of eGFR equations within Africa might relate to smaller body surface area (BSA) and lower muscle mass compared with African-Americans, and non-GFR determinants of creatinine that differ from high-income countries.[5] In addition, wide biological and analytical variation in creatinine measurement has led to difficulties in estimating CKD prevalence and comparing results between countries and over time.[8]

To address these knowledge gaps, we formed the African Research on Kidney Disease (ARK) Consortium, based within three longitudinal population studies in Malawi (urban and rural),[9] Uganda (rural),[10] and a Health and Demographic Surveillance System in South Africa (rural).[11] Our primary aim was to measure GFR using plasma clearance of iohexol in large, community-based samples from each country, and to compare the performance of available eGFR equations to iohexol mGFR. If performance of available eGFR equations was inadequate, our secondary aim was to model and externally validate a better-performing eGFR equation. Lastly, using the optimal method, we would estimate the population prevalence of eGFR less than 60 mL/min per 1·73 m² in well-characterised datasets from six African countries.

Methods

Study setting and sampling strategy

Our study methods have been previously published.[12] In brief, ethical approval was obtained for studies within each country and all participants provided written informed

consent. Within each country we conducted a population-based study to determine CKD prevalence, henceforth known as the ARK-CKD Population Prevalence Studies (Malawi n=5264, South Africa n=2020, and Uganda n=5979). From these cohorts we sampled the population for the Iohexol Measured GFR Study;[13,14] for this study, the target sample size for each country was 1000 participants, stratified by sex and eGFR stage (appendix 4 pp 4–5).

Study procedures

Study protocols were harmonised across countries before starting the study, which was conducted from 2016 to 2019. We administered 5 mL of Omnipaque (350 mg iodine/mL; GE Healthcare, Chicago, IL, USA) as an intravenous bolus and calculated the dose of iohexol from preadministration and postadministration syringe weights, measured in mg to two decimal places. We drew venous samples from the contralateral arm at min 5, 120, 180, and 240 after iohexol administration, recording exact times for iohexol administration and sampling (appendix 4 p 6).[15] We used the slope-intercept method to calculate mGFR for three timepoints in the second (slow) exponential phase of iohexol elimination and applied the Bröchner-Mortensen correction to account for iohexol plasma clearance in the first (rapid) exponential phase.[16]

Laboratory methods and testing

Iohexol plasma samples were processed at each partner laboratory, stored at –80°C, and measured at a national reference laboratory in Johannesburg, South Africa. Iohexol plasma concentrations were assayed using ultra performance liquid chromatography (UPLC)-tandem mass spectrometry (MS/MS).[17] Coefficients of variation for internal quality control with the certified reference material for iohexol at 100 mg/L was 4·1% and at 1000 mg/L was 4·2%. The laboratory complied with Equalis external quality assurance requirements for iohexol (Uppsala, Sweden; appendix 4 p 7).[18]

In each country, laboratories performed standardised serum creatinine measurements using an isotope-dilution mass spectrometry-traceable assay calibrated to a standard reference material for creatinine. The modified Jaffe method was used in Malawi and South Africa, and the enzymatic method in Uganda. For cystatin C, samples from Malawi and Uganda were analysed in Uganda, whereas samples from South Africa were measured locally (appendix 4 pp 7–8). Intersite analytical bias was assessed with a split sample recalibration study for creatinine and cystatin C (appendix 4 pp 8–10): for our main analysis we adjusted all creatinine measures from South Africa and Malawi to align with the Uganda enzymatic method by adding 9·29 µmol/L, the median difference between enzymatic and Jaffe measures (appendix 4 pp 11). We also recalibrated cystatin C measurements using a linear regression equation with Cusum test to assess linearity, followed by Passing-Bablok regression analysis to determine the calibration function: Y=A(intercept) + B(slope) × X (appendix 4 pp 12).[19] Uganda and Malawi cystatin C measurements were adjusted with South Africa as the reference. Recalibrated values for both analytes were used for the main analysis and data presented.

Performance of GFR-estimating equations

We evaluated the following equations: Cockcroft-Gault (adjusted for BSA),[20] Four variable MDRD re-expressed for isotope-dilution mass spectrometry-traceable assays,[21] CKD-EPI (creatinine) 2009 and 2021,[22,23] CKD-EPI (cystatin C) 2012, CKD-EPI (creatinine-cystatin C) 2012 and 2021,[23,24] Revised Lund-Malmö Study,[25] Full Age Spectrum (FAS; creatinine),[26] and European Kidney Function Consortium (EKFC; creatinine;[27] appendix 4 pp 13–16). For the FAS equation we derived country-specific healthy population creatinine values (Q) from earlier population prevalence studies (appendix 4 p 17). For the MDRD and CKD-EPI 2009 and 2012 equations, we evaluated performance with and without ethnicity coefficients. AS refers to adjustment for age and sex;[23] AAE refers to adjustment for African-American ethnicity.

See Online for appendix 4

Data management and statistical analysis

We included participants who met all of the following criteria: complete recordings of age, sex, height, and weight; exact times for administering iohexol (T0) and subsequent sampling; iohexol plasma concentrations at each timepoint, and demonstrating a monotonic decline; pre-administration and post-administration syringe weights; and serum creatinine concentration of 30 µmol/L or more. We examined distributions of data overall and by country. For mGFR and volumes of distribution we plotted histograms and compared mean (SD) and median (IQR). We plotted cumulative distribution plots of the correlation coefficient (r) for the slope-intercept iohexol GFR derivation relative to an r of more than 0·985; and used kernel density plots to examine the distribution of GFR estimates from each equation compared with mGFR. We evaluated bias between mean differences (agreement) for each creatinine or cystatin C-based eGFR equation, or both, and the corresponding mGFR value using Bland-Altman plots.[28] Using mGFR as the reference, we compared performance of each equation and compared the proportion of participants correctly classified by mGFR stage. The parameters for performance included bias, measured as median (eGFR–mGFR) and expressed as mL/min per 1·73 m²; relative bias, measured as median (eGFR/mGFR) and reported as a percentage; precision, measured as log Root Mean Square Error (RMSE) and reported as standard deviation of log (eGFR–mGFR); and accuracy, measured as proportion of eGFR results within 30% of mGFR (P_{30}) and reported as a percentage.

In sensitivity analyses, we determined whether results were affected by systematic bias from measurement error of creatinine between countries. We did all analyses

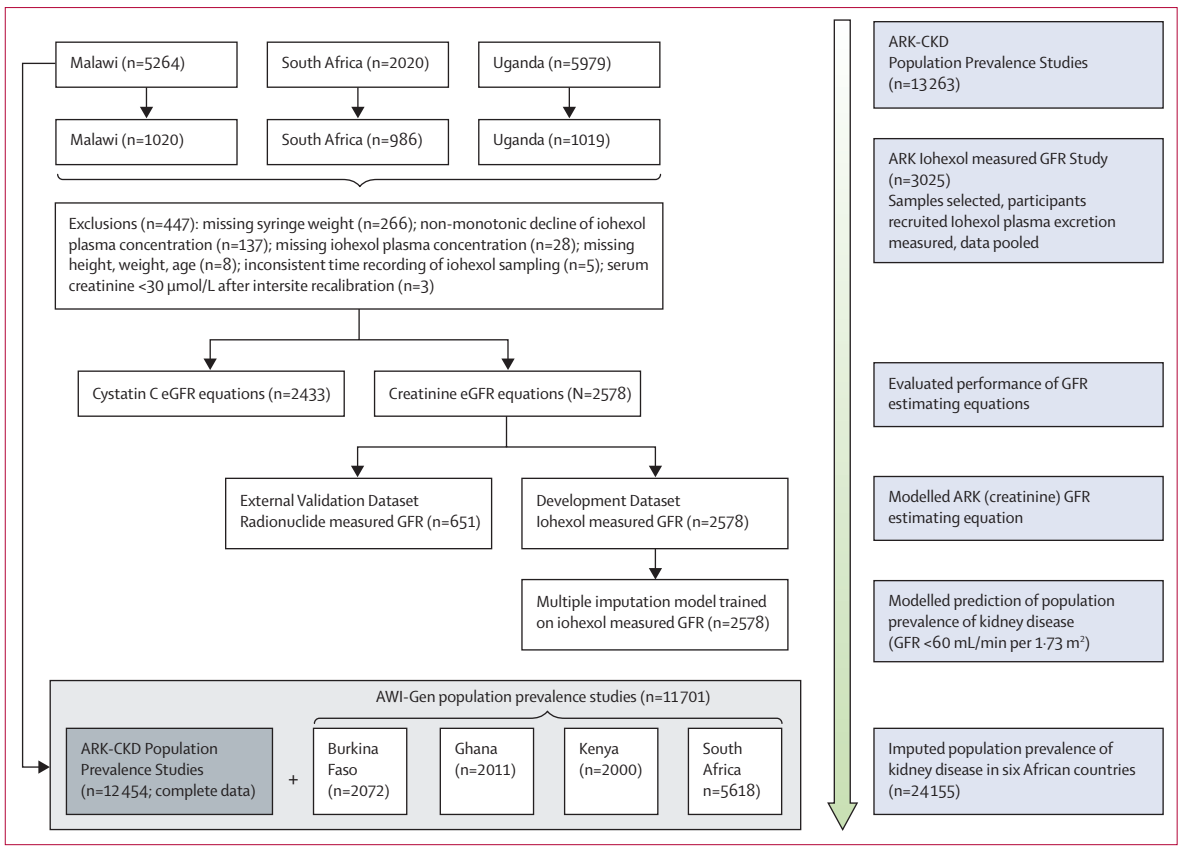


Figure 1: **Study procedures and datasets used for the Iohexol-Measured GFR Study**
ARK=African Research on Kidney Disease. ARK-CKD=African Research on Kidney Disease Chronic Kidney Disease. AWI-Gen=Africa Wits-International Network for the Demographic Evaluation of Populations and their Health Partnership for Genomic Studies.

without adjustment between creatinine measures, and after recalibrating creatinine between countries using Passing-Bablok regression analysis. We also examined whether our findings were influenced by the quality of the GFR measurement. To do so, we restricted the analysis to mGFR with an *r* of more than 0·985 for the slope-intercept measured GFR derivation and normal sex-specific calculated volumes of distribution, in accordance with the British Nuclear Medicine Society Guidelines.[15] Post hoc, we repeated the analysis after calibrating iohexol mGFRs upwards by 5%, to address whether our findings might be explained by methodological differences between iohexol and other measured GFR methods (in particular urinary iothalamate excretion, which can overestimate GFR due to tubular secretion).[29]

Modelling a new creatinine-based GFR-estimating equation

We sought to develop a better creatinine-based eGFR formula for African populations using some or all of age, sex, creatinine, weight, height, or body-mass index (BMI), aiming to keep the number of predictors at a minimum to ensure ease of use within clinical care. Candidate predictors were examined in models regressing the log of iohexol mGFR on log creatinine as well as age, sex, and BMI, mirroring the functional form of the CKD-EPI equations. Regression coefficients were allowed to vary by sex, and the model included a spline knot with the position chosen as indicated using Lowess plots. We also examined models regressing iohexol mGFR (on the natural scale) on log creatinine, sex, and age akin to the functional form of the Lund-Malmö equation. During model development we used likelihood ratio tests and adjusted R^2 to decide between candidate models. We assessed the performance of the ARK models by comparing GFR estimates with those of existing creatinine-based eGFR equations in development and external validation datasets. The development dataset comprised pooled data from all three countries in the Iohexol Measured GFR Study. The external validation dataset comprised people referred for mGFR plasma clearance studies using ^{51}Cr-EDTA or ^{99}DTPA as part of clinical evaluation for CKD, eligibility for living kidney donation, or participation in research studies.

Estimating true population prevalence of impaired kidney function

We sought to estimate the population prevalence of eGFR of less than 60 mL/min per 1·73 m² (analogous

	Malawi		South Africa		Uganda		Overall (N=2578*)
	Females (n=474)	Males (n=424)	Females (n=636)	Males (n=311)	Females (n=413)	Males (n=320)	
Age, years	52 (45–62)	53 (42–64)	45 (34–55)	42 (29–58)	51 (41– 60)	52 (40–62)	50 (38–60)
Weight, kg	63 (53–75)	61 (55–70)	77 (66–91)	72 (63–83)	55 (49–65)	55 (50–63)	64 (55–77)
Height, cm	156 (152–160)	165 (161–170)	162 (158–166)	173 (168–177)	155 (151–160)	164 (160–169)	162 (156–167)
Body-mass index, kg/m²	26 (22–30)	23 (20–25)	30 (25–34)	24 (21–28)	23 (21–26)	21 (19–23)	24 (21–29)
Body surface area, m²†	1·7 (1·5–1·8)	1·7 (1·6–1·8)	1·9 (1·7–2·1)	1·9 (1·7–2·0)	1·6 (1·4–1·7)	1·6 (1·5–1·7)	1·7 (1·6–1·9)
Hypertension‡	194 (41%)	138 (33%)	207 (33%)	126 (41%)	139 (34%)	122 (38%)	935 (36%)
Diabetes§	43 (9%)	23 (5%)	27 (6%)¶	10 (4%)‖	21 (5%)	14 (4%)	138 (6%)
HIV positive**	49 (11%)	45 (11%)	136 (21%)	38 (12%)	44 (11%)	33 (10%)	345 (13%)
Serum creatinine, µmol/L	72 (63–82)	87 (77–99)	61 (54–69)	79 (69–89)	63 (55–73)	73 (65–85)	70 (61–84)
Serum cystatin C, mg/dL	1·03 (0·90–1·18)††	1·07 (0·95–1·23)‡‡	0·95 (0·80–1·12)§§	0·97 (0·82–1·13)¶¶	0·95 (0·86–1·07)‖‖	0·97 (0·86–1·08)***	0·99 (0·86–1·15)†††
Iohexol measured GFR, mL/min per 1·73 m²	73 (62–87)	79 (65–93)	79 (61–94)	84 (63–100)	83 (68–103)	97 (76–118)	81 (64–97)
Estimated GFR, mL/min per 1·73 m²‡‡‡	86 (72–100)	92 (77–104)	106 (93–117)	105 (92–118)	99 (84–110)	102 (93–114)	99 (84–111)

Data are median (IQR) or n (%). For sample sizes that differed from those reported in the column header, the appropriate denominator is give in the legend. *n=2578 for total number of creatinine samples; n=2433 for total number of cystatin-C samples. †Body surface area calculated using the Haycock formula.[20] ‡Defined as elevated systolic (≥140 mm Hg) or elevated diastolic (≥90 mm Hg) blood pressure, or self-report of taking antihypertensive treatment. §In Uganda this was defined as having HbA_{1c} of more than 6·5% or 48 mmol/mol, or being previously diagnosed with diabetes, or being on current treatment for diabetes; in Malawi this was defined as having a fasting blood glucose of more than 7·0 mmol/L or a random glucose >11·0 mmol/L, or self-report of taking antidiabetic treatment; in South Africa this was defined as having a random blood glucose of >11·0 mmol/L. ¶n=469. ‖n=248. **Self-report of previous test result as positive, or two rapid positive tests. ††n=457. ‡‡n=414. §§n=631. ¶¶n=311. ‖‖‖n=347. ***n=273. †††n=2433. ‡‡‡Estimated GFR calculated using the CKD-EPI (creatinine) equation 2021.[21]

Table 1: **Characteristics of ARK participants by sex, for each country and overall**

to CKD stages G3a-5 in six African countries) using the most accurate equation. However, because performance of all estimating equations was limited (including the novel ARK equation), we used a multiple imputation model trained on the mGFR sample (2578 participants, with 733 from Uganda, 898 from Malawi, and 947 from South Africa) to predict individual GFR based on creatinine, age, and sex in two distinct, large, population-representative datasets. The first dataset comprised data from our baseline ARK-CKD Population Prevalence Studies[13,14] (5715 from Uganda, 4719 from Malawi, and 2020 from South Africa). The second dataset was the Africa Wits-International Network for the Demographic Evaluation of Populations and their Health Partnership for Genomic Studies (AWI-Gen)[30] in which the prevalence of CKD was determined using creatinine-based estimates of GFR in four African countries (5618 from South Africa, 2011 from Ghana, 2000 from Kenya, and 2072 from Burkina Faso), henceforth referred to as the AWI-Gen Population Prevalence Studies. Samples from South Africa in each dataset did not overlap.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

A summary of the stages of the research and relevant data sources is shown in figure 1. We measured GFR using iohexol plasma excretion in 3025 adults and included 2578 participants in the final analysis (table 1). We compared characteristics of the whole sample to the final sample to investigate the effect of missing data (appendix 4 p 19). Median age was 50 years (IQR 38–60), weight was 64 kg (55–77), and height was 162 cm (156–167). South African participants were taller and weighed more, and had greater obesity in women according to a BMI of 30 kg/m² as compared with other countries assessed. Ugandan participants had the lowest BMI. Overall, 935 (36%) participants had hypertension; 138 (6%) had diabetes, with the highest prevalence among Malawian women; and 345 (13%) had HIV infection, with disproportionate seropositivity among South African women (136 [21%]). Using the CKD-EPI (creatinine) 2021 equation, median eGFR was 99 mL/min per 1·73 m² (IQR 84–111), which was significantly higher than the median iohexol mGFR of 81 mL/min per 1·73 m² (IQR 64–97). The distribution of iohexol mGFR, volume of distribution, and cumulative distribution plots with corresponding *r* were similar across countries (appendix 4 pp 20–22).

Across all three countries, performance of creatinine-based GFR-estimating equations was poor and none of

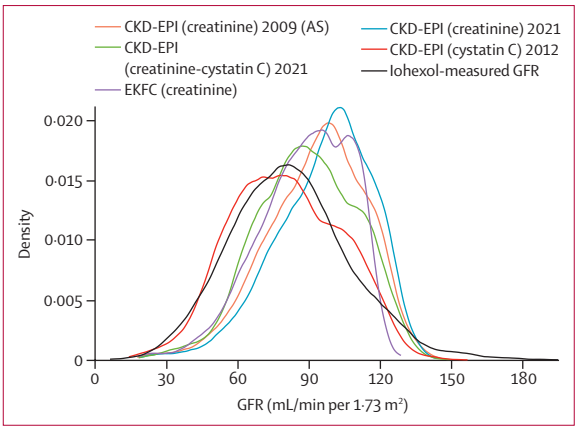


Figure 2: **Distributions of iohexol measured GFR compared with GFR estimates**
Kernel Density Distribution plot. GFR=glomerular filtration rate. CKD-EPI (creatinine) 2009 (AS)=Chronic Kidney Disease Epidemiology Collaboration creatinine 2009 equation adjusted for age and sex. CKD-EPI (creatinine) 2021=Chronic Kidney Disease Epidemiology Collaboration creatinine 2021 equation (race-neutral). CKD-EPI (creatinine-cystatin C) 2021=Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C 2021 equation (race neutral). CKD-EPI (cystatin C) 2012=Chronic Kidney Disease Epidemiology Collaboration cystatin C 2012 equation. EKFC (creatinine)=European Kidney Function Consortium creatinine equation.

the equations demonstrated a P_{30} of more than 75% (figure 2; table 2; appendix 4 pp 23–28).[31] When stratified by mGFR category, performance of equations worsened with declining kidney function. eGFR equations overestimated the proportion of people with G1 compared with measured GFR and underestimated the proportion with lower stages (G2–G5) of kidney function. Creatinine-based equations underestimated stages G2–G5 by at least 50% (figure 3; table 2; appendix 4 pp 27–31). Overestimation of individual GFR and misclassification by GFR stage was exacerbated when using ethnicity coefficients for the MDRD and CKD-EPI equations (figure 3; table 2; appendix 4 pp 23, 27–32). GFR estimation using cystatin C alone or in combination with creatinine led to smaller bias, reducing overestimation of mGFR when compared with creatinine-based estimates (figures 2–3; table 2; appendix 4 pp 29–31). This meant that estimates of prevalence of impaired kidney function using cystatin C were more than two-times higher than creatinine-based estimates. Performance of CKD-EPI (cystatin C) 2012 was better than combination creatinine-cystatin C equations (figure 3; table 2). The performance of GFR-estimating equations when compared with mGFR was similar between the three countries (appendix 4 pp 33–38).

Compared with results of the main analysis, using creatinine uncorrected for intersite measurement differences to calculate eGFR showed increased bias with lower precision and accuracy, while use of creatinine adjusted using a linear equation showed very similar results overall, and by country (appendix 4 pp 39–44). Restriction of eGFR comparisons to mGFR measurements with greater quality control indicators showed moderate improvement in performance (appendix 4 pp 45–51). For example, P_{30} for CKD-EPI 2009 (AS) compared with mGFR was 65% in the unrestricted dataset and 71% in the restricted dataset, whereas the best-performing equation, Lund-Malmö, had a P_{30} of 87% in the restricted dataset. The P_{30} for CKD-EPI cystatin 2012 increased from 70% to 78% in the restricted dataset; however, there was a disproportionate loss of people with low mGFR, from 6% to 2%, in the restricted dataset (appendix 4 p 49). Adjusting iohexol mGFR by an additional 5% resulted in slightly improved performance of MDRD and CKD-EPI creatinine-based equations with little effect on other equations such as the Revised Lund-Malmö and cystatin C-based equations (appendix 4 pp 52–53).

We fitted a model to the 2578 iohexol mGFRs (development dataset) with age, sex, and creatinine as potential predictors. Inspection of Lowess plots supported a piecewise linear model with one knot at 73 µmol/dL. Likelihood ratio testing showed evidence of a difference in slope in the regression line before and after the knot among men only (appendix 4 p 54). We found no evidence to support fitting separate coefficients for creatinine or age among men and women. Addition of BMI to the model increased adjusted R^2 marginally (from 0·225 to 0·234; appendix 4 p 55). The other predictors accounted for only 20–25% of the total variation in the data irrespective of the model form. If male, the model independent of BMI was $eGFR = 124 \times \min(1,SCr/0{\cdot}82)^{-0{\cdot}339} \times \max(1,SCr/0{\cdot}82)^{-0{\cdot}574} \times 0{\cdot}993^{age}$. If female the model was $eGFR = 103 \times (SCr/0{\cdot}82)^{-0{\cdot}339} \times 0{\cdot}993^{age}$.

We evaluated agreement and compared performance and predicted GFR stage between the ARK models and existing GFR-estimating equations in the development dataset (appendix 4 pp 56–58). Although the ARK estimates showed less bias than the CKD-EPI creatinine equations (2009 and 2021), they performed similarly to other GFR-estimating equations overall, categorising only 55% of people correctly across all GFR stages, underestimating high GFRs and overestimating low GFR measurements (appendix 4 pp 57–58). In addition, we compared performance of ARK models and creatinine-based GFR-estimating equations to measured GFR in the external validation dataset (appendix 4 pp 59–61). Overall, the ARK equations did not have better performance in terms of bias, precision, and accuracy (P_{30}; appendix 4 pp 60–61). Despite being substantially better at correctly identifying people in stage G2 than other GFR-estimating equations (95% accuracy *vs* 68% for CKD-EPI [creatinine] 2021) our model was poorer at identifying people in stages G3–G5 (39% sensitivity *vs* 67% and 73% for CKD-EPI and Lund-Malmö, respectively; appendix 4 pp 60–61).

Estimates of the proportion of people with a GFR of 60 mL/min per 1·73 m² using the multiple imputation model to predict individual GFR were similar to the

	≥90 mL/min per 1·73 m² of BSA; CKD stage G1	60 to 89 mL/min per 1·73 m² of BSA; CKD stage G2	45–59 mL/min per 1·73 m² of BSA; CKD stage G3a	<45 mL/min per 1·73 m² of BSA; CKD stage G3b-5	Overall
Iohexol GFR, mL/min per 1·73 m² of BSA	909 (35%)	1168 (45%)	340 (13%)	161 (6%)	n=2578*
Categories by GFR stage for GFR estimating equations†					
CKD-EPI (creatinine) 2009 (AS)	1534 (60%)	874 (34%)	116 (5%)	54 (2%)	1265 (49%)‡
CKD-EPI (creatinine) 2021	1680 (65%)	764 (30%)	90 (4%)	44 (2%)	1227 (48%)‡
CKD-EPI (creatinine-cystatin C) 2021	1184 (49%)	1055 (43%)	138 (6%)	56 (2%)	1291 (53%)‡
CKD-EPI (cystatin C) 2012	826 (34%)	1098 (45%)	381 (16%)	128 (5%)	1196 (49%)‡
EKFC (creatinine)	1331 (52%)	1029 (40%)	160 (6%)	58 (2%)	1364 (53%)‡
Bias, mL/min per 1·73 m²§					
CKD-EPI (creatinine) 2009 (AS)	−1 (−3 to 0)	16 (15 to 17)	26 (24 to 30)	41 (33 to 47)	12 (11 to 13)
CKD-EPI (creatinine) 2021	2 (−1 to 4)	20 (19 to 21)	31 (28 to 35)	45 (37 to 51)	15 (14 to 16)
CKD-EPI (creatinine-cystatin C) 2021	−5 (−7 to −3)	10 (9 to 12)	20 (17 to 23)	30 (26 to 39)	7 (6 to 8)
CKD-EPI (cystatin C) 2012	−15 (−17 to −13)	0·5 (−1 to 2)	10 (7 to 12)	21 (14 to 28)	−2 (−3 to −1)
EKFC (creatinine)	−7 (−8 to −5)	12 (10 to 14)	22 (20 to 26)	36 (29 to 43)	7 (6 to 8)
Relative bias¶					
CKD-EPI (creatinine) 2009 (AS)	−1% (−3 to 1)	21% (19 to 23)	50% (43 to 56)	112% (93 to 126)	15% (13 to 16)
CKD-EPI (creatinine) 2021	1% (0 to 3)	26% (25 to 28)	58% (52 to 64)	123% (103 to 137)	19% (17 to 20)
CKD-EPI (creatinine-cystatin C) 2021	−5% (−6 to −3)	14% (12 to 16)	38% (31 to 44)	77% (65 to 102)	9% (7 to 11)
CKD-EPI (cystatin C) 2012	−14% (−16 to −12)	1% (−2 to 3)	17% (13 to 24)	55% (37 to 73)	−2% (−4 to −1)
EKFC (creatinine)	−6% (−8 to −5)	15% (14 to 18)	41% (37 to 47)	101% (74 to 114)	9% (7 to 9)
Precision, log RMSE‖					
CKD-EPI (creatinine) 2009 (AS)	0·23 (0·21 to 0·25)	0·22 (0·20 to 0·23)	0·29 (0·27 to 0·32)	0·52 (0·44 to 0·60)	0·33 (0·31 to 0·35)
CKD-EPI (creatinine) 2021	0·22 (0·20 to 0·24)	0·21 (0·19 to 0·22)	0·28 (0·25 to 0·30)	0·51 (0·43 to 0·60)	0·33 (0·31 to 0·34)
CKD-EPI (creatinine-cystatin C) 2021	0·22 (0·20 to 0·23)	0·22 (0·21 to 0·23)	0·28 (0·26 to 0·30)	0·53 (0·45 to 0·61)	0·32 (0·30 to 0·33)
CKD-EPI (cystatin C) 2012	0·27 (0·25 to 0·29)	0·28 (0·26 to 0·29)	0·34 (0·30 to 0·37)	0·56 (0·47 to 0·64)	0·35 (0·34 to 0·37)
EKFC (creatinine)	0·22 (0·20 to 0·24)	0·21 (0·20 to 0·22)	0·29 (0·26 to 0·32)	0·52 (0·44 to 0·59)	0·32 (0·31 to 0·34)
Accuracy**					
CKD-EPI (creatinine) 2009 (AS)	88% (85 to 90)	63% (61 to 66)	32% (27 to 37)	15% (10 to 21)	65% (63 to 67)
CKD-EPI (creatinine) 2021	88% (86 to 90)	55% (51 to 59)	25% (17 to 36)	14% (5 to 27)	60% (58 to 62)
CKD-EPI (creatinine-cystatin C) 2021	88% (86 to 90)	72% (69 to 75)	42% (34 to 51)	19% (10 to 32)	70% (68 to 72)
CKD-EPI (cystatin C) 2012	77% (74 to 80)	74% (72 to 77)	58% (52 to 63)	34% (26 to 42)	70% (69 to 73)
EKFC (creatinine)	88% (86 to 90)	74% (71 to 77)	39% (31 to 47)	20% (11 to 33)	71% (69 to 73)

Data are n (%) or value (95% CI). Percentages might sum to more than 100% due to rounding. GFR=glomerular filtration rate. CKD=chronic kidney disease. BSA=body surface area. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. AS=adjustment for age and sex. EKFC=European Kidney Function Consortium. RMSE=Root Mean Square Error. *n=2578 for creatinine-based equations; n=2433 for cystatin C-based equations where for G1 n=838 (34%), G2 n=1121 (46%), G3a n=320 (13%), and G3b-5 n=154 (6%). †Proportion correctly classified by GFR stage. ‡Percentage within same GFR stage as iohexol GFR. §Median (estimated GFR–iohexol measured GFR). ¶Median (estimated GFR/iohexol measured GFR). ‖SD log (estimated GFR–iohexol measured GFR). **Proportion of estimated GFR results within 30% of iohexol-measured GFR.

Table 2: **Overall performance of GFR estimating equations compared with iohexol-measured GFR, by GFR range and CKD stage**

measured proportions in the iohexol mGFR study (n=2578; Uganda observed 14% *vs* predicted 11%; Malawi observed 20% *vs* predicted 25%; South Africa observed 23% *vs* predicted 21%). In the external validation dataset (n=651), the same model estimated the proportion of people with GFR at less than 60 mL/min per 1·73 m² to be 21% versus observed 17%. Prevalence of GFR at less than 60 mL/min per 1·73 m² in countries in the ARK-CKD and AWI-Gen Population Prevalence Studies, estimated with the same imputation model, was 5–15% higher than that estimated from creatinine-based equations (appendix 4 pp 62–63). Comparison of prevalence estimates of imputed GFR with the CKD-EPI (creatinine) 2021 equation for each country is shown in figure 4.

Discussion

Our results show that within three African countries, creatinine-based eGFR equations substantially overestimate kidney function compared with mGFR. The overestimation worsened at lower levels of mGFR, and at all levels was further exacerbated by inclusion of ethnicity coefficients. The most commonly used equation in Uganda and South Africa, the CKD-EPI (creatinine) 2009 equation (without adjusting for ethnicity), did not achieve an accuracy (P_{30} >75%) considered appropriate for individual clinical decision making, even in sensitivity analyses.[31] Performance of the race-neutral CKD-EPI (creatinine) 2021 equation was no better than the CKD-EPI 2009 equation in current use. Cystatin C-based

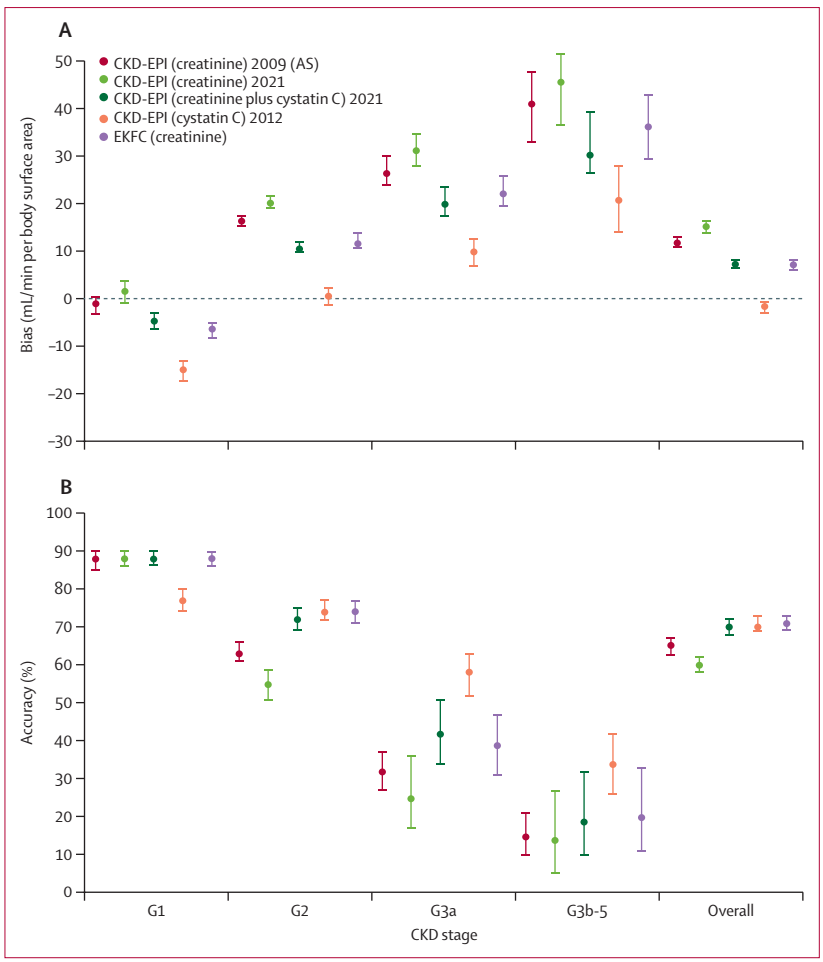


Figure 3: **Performance of GFR estimating equations using bias and accuracy**
(A)Bias measured as median (estimated GFR–iohexol measured GFR). (B) Accuracy measured as proportion of estimated GFR results within 30% of iohexol measured GFR. GFR=glomerular filtration rate. CKD-EPI (creatinine) 2009 (AS)=Chronic Kidney Disease Epidemiology Collaboration creatinine 2009 equation adjusted for age and sex. CKD-EPI (creatinine) 2021=Chronic Kidney Disease Epidemiology Collaboration creatinine 2021 equation (race-neutral). CKD-EPI (creatinine-cystatin C) 2021=Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C 2021 equation (race neutral). CKD-EPI (cystatin C) 2012=Chronic Kidney Disease Epidemiology Collaboration cystatin C 2012 equation. EKFC (creatinine)=European Kidney Function Consortium creatinine equation.

equations performed better than all creatinine-based equations. A new creatinine-based equation to better estimate GFR based on measured GFR samples was not possible due to wide age-independent and sex-independent variability in the relationship between creatinine and mGFR, even with BMI adjustment. Use of a multiple imputation method suggested population prevalence of CKD was substantially higher in countries across west, east, and southern Africa than that determined from creatinine-based GFR estimates.

Our large, community-based study of measured GFR has several strengths. Using both creatinine and cystatin to estimate GFR, we evaluated the performance of the EKFC[26] and Revised Lund-Malmö Study equations[25] for the first time in African populations, as well as US-derived equations, including the most recent CKD-EPI creatinine and creatinine-cystatin C 2021 equations. We used a gold-standard multisample method for iohexol plasma clearance. Measurements were centralised in a reference laboratory with extensive experience using UPLC-MS/MS assays and compliant with the iohexol Equalis quality assurance programme. We addressed intersite analytical bias for creatinine and cystatin C and recalibrated measurements accordingly, and separately quantified the potential impact of methodological differences (iothalamate *vs* iohexol) and measurement error with transparently reported sensitivity analyses.

However, there are limitations to this work. We measured creatinine and mGFR at a single timepoint, so did not fulfil the temporal requirements for defining CKD, although our approach is consistent with other large cohort studies.[32] Our sampling frame was community-derived with higher mean kidney function compared with CKD cohorts used to develop GFR equations elsewhere.[24–26] Since measurement of low creatinine values is more prone to biological and analytical variation than high levels, this could have contributed to poor performance of GFR-estimating equations; however, performance was worse at lower levels of measured GFR. Variability in iohexol mGFR measurement inherent to a study done in rural areas, despite rigorous quality control procedures, might also have impacted performance of GFR-estimating equations. Restriction of iohexol GFR measurements to those with the highest quality control parameters resulted in levels of accuracy similar to those reported in studies elsewhere,[24,33] but persistently higher levels of bias, as well as disproportionate exclusion of people with low GFR. We chose not to restrict the dataset to a subsample meeting higher quality control standards because people with impaired kidney function might have abnormal fluid balance, normal volumes of distribution have not been validated in Africa, and guideline-recommended parameters for GFR measurement might not be appropriate at low levels of kidney function.[34] Given the risk of creating systematic bias through data restriction and only modest increase in performance for the equations in sensitivity analyses, we used the complete dataset for further analyses. Supporting the validity of our findings, prevalence of impaired kidney function with iohexol mGFR was similar to that estimated from cystatin, reinforcing that it is variability in the association between creatinine and GFR that leads to poor performance of eGFR equations in this population, rather than measurement error of iohexol GFR. The reference method for measuring GFR could also be a potential source of bias. Although an advantage of this work was that iohexol mGFR measurement was consistent across all countries, poor performance of GFR-estimating equations could be partly explained by comparison with studies using other methods to measure GFR. However, upward recalibration of iohexol mGFR towards that obtained by iothalamate did not alter our findings. Finally, while our study is, to our knowledge, the largest of its kind from Africa and

includes iohexol mGFR from three countries, the diversity of African populations means there is potentially greater variability in the relationship between creatinine and GFR than we have measured. This could affect the accuracy of the imputed GFR estimates in the AWI-GEN datasets. However, in internal validation, the imputation model estimated prevalence of CKD close to that from measured GFR, and with differences substantially less than the variation we see between creatinine-based eGFR derived and imputed estimates in the population prevalence datasets.

Our finding that creatinine-based eGFR equations overestimate well preserved kidney function (stages G1–G2), but underestimate declining kidney function (stages G3–G5) supports results from studies in low-income to middle-income[5,33] and high-income countries.[23,25] Non-GFR determinants of creatinine, rather than ethnicity, might underlie greater inaccuracy from creatinine-based GFR estimation in Asian countries compared with derivation populations and might also be important in Africa.[35] Our study corroborates previous research showing lower BMI, and possibly lower muscle mass and creatinine levels in continental Africans.[4,5,13,14] Perinatal and childhood factors resulting in growth stunting predispose people to low lean muscle mass and short stature in adulthood, even in the presence of adult obesity.[11] Wasting from chronic infection or inflammation, such as tuberculosis and HIV, low dietary protein ingestion, and undiagnosed liver disease impact muscle mass and creatinine generation.[36] Renal tubular handling of creatinine might be affected by antiretroviral therapy (which is particularly relevant in countries in which HIV is highly prevalent, such as South Africa) and by variants in genes affecting creatinine production and tubular secretion.[37] These issues, as well as prevalence of comorbidities such as hypertension, affect the likelihood of individuals developing kidney dysfunction. Furthermore, normative ranges for GFR have not been established in African populations and whether a cutoff of GFR of less than 60 mL/min per 1·73 m² is appropriate is unknown. Although our imputed prevalence estimates of kidney dysfunction appear high, there is no precedent to compare with because all earlier studies used creatinine-based estimates of GFR, and they are consistent with the observation that the African diaspora in high-income countries have consistently higher rates of advanced kidney disease.[38]

The first implication of our results is need for awareness that creatinine-based GFR-estimating equations perform poorly in African populations. Ethnicity coefficients for creatinine-based equations, which are still widely used in Africa, exaggerate the overestimation of GFR and should not be used. The performance of the race-neutral CKD-EPI (creatinine) 2021 equation was not better than CKD-EPI 2009, with greater bias at lower eGFR levels, so should not be adopted for immediate use in Africa. Overestimation of kidney function at lower levels of GFR impacts clinical care and public health. For an individual,

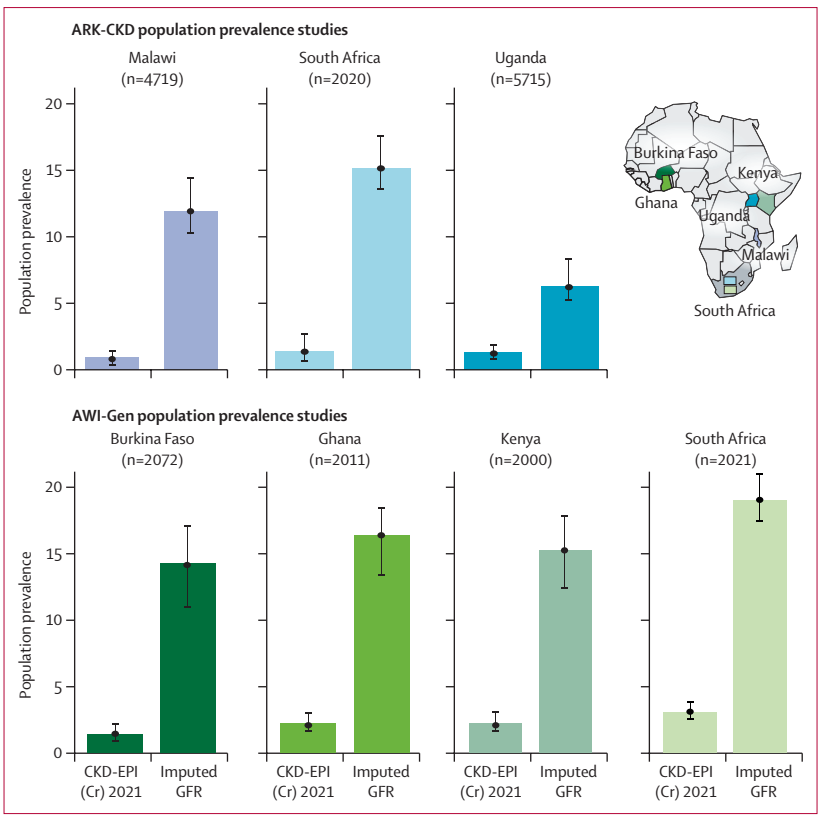


Figure 4: **Population prevalence of GFR of less than 60 mL/min per 1·73 m², comparing imputed GFR modelled on iohexol measured GFR to estimated GFR using the CKD-EPI (creatinine) 2021**
Data are % (95% CI). Datasets for South Africa did not overlap. Reported prevalence was unadjusted. ARK-CKD=African Research on Kidney Disease Chronic Kidney Disease. AWI-Gen=Africa Wits-International Network for the Demographic Evaluation of Populations and their Health Partnership for Genomic Studies. CKD-EPI (Cr) 2021=Chronic Kidney Disease Epidemiology Collaboration (creatinine) 2021 equation. GFR=glomerular filtration rate.

inaccurate estimation of GFR risks a missed diagnosis of CKD and the opportunity to address modifiable risk factors to slow kidney disease progression, and possible harm from unadjusted doses of renally cleared drugs. At the population level, underestimation of the burden of CKD in Africa reduces focus on strategies to minimise CKD progression and manage end-stage kidney disease. Poor access to specialist renal care in many African countries compounds the individual risk for progression, premature disability, and death.[39] However, the optimal method to diagnose kidney disease at present is unclear: there is urgent need for further research to develop accurate and low-cost alternatives to creatinine for measuring kidney function in Africa. Cystatin C demonstrated improved performance in our cohort, consistent with data from the USA,[23] but remains largely inaccessible. However, clinical need might drive improvements in cost and assay reliability. The role of other biomarkers to estimate GFR in this context should also be evaluated.

In this large collaborative study from Malawi, Uganda, and South Africa, we prospectively measured kidney function using consistent and robust techniques. We

showed that creatinine-based GFR-estimating equations overestimate kidney function compared with iohexol and cystatin C measures. Our results suggest the burden of kidney disease is markedly underestimated in Africa, with substantial implications for individual health-care and public health interventions to address the challenge of kidney disease in resource-limited settings.

Collaborators

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Contributors

Authors from each study site had access to site-related data. For the pooled dataset, CHH and EM verified the data, and CHH, JF, RK, EM, JAG, and LT had access to the pooled dataset. All authors agreed to be accountable for all aspects of this work and all authors approved the final version of the manuscript. JF designed the study, acquired and analysed data in South Africa, interpreted data, wrote the first and subsequent revisions of the manuscript, and had final responsibility for submission of the manuscript. RK designed the study, acquired data in Uganda, interpreted data, and edited the first and subsequent revisions of the manuscript. JM, WPN, and JEP acquired data in Malawi. CHH analysed and interpreted data, analysed data for manuscript revisions, and wrote the first and subsequent revisions of the manuscript. DN interpreted data and edited the first and subsequent revisions of the manuscript. EM designed the study for South Africa and analysed data. GD designed the study and interpreted data. TS established the iohexol method, analysed all iohexol samples, and conducted intersite calibration studies for creatinine and cystatin C. BS acquired data in Uganda. MR designed the study in South Africa, and contributed data from AWI-Gen. LS, ST, SN, RN, and AC designed the study, interpreted data, and edited the first and subsequent revisions of the manuscript. JAG had oversight for all laboratory methods for the study including the iohexol method, iohexol sample testing, and intersite calibration studies for creatinine and cystatin C; interpreted data; and edited the first and subsequent revisions of the manuscript. LT designed the study, acquired data in Uganda, interpreted data, wrote the first and subsequent revisions of the manuscript, and edited the final version of the manuscript.

Declaration of interests

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Data sharing

To facilitate research into kidney disease in Africa, the African Research on Kidney Disease (ARK) Consortium is committed to sharing a standardised set of relevant data from all three study sites; namely, Malawi, South Africa, and Uganda. The dataset includes deidentified individual participant data related to estimated and measured GFR, with accompanying analytic code used for development of the creatinine-based GFR-estimating equation. The dataset will be available indefinitely from the date of publication at https://github.com/ARKconsortium/iohexol_mGFR_eGFR.

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