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REVIEW ARTICLE

Estimating glomerular filtration rate in African populations

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ABSTRACT

Without a strong bedrock of kidney research in African populations, we are vulnerable to extrapolating research findings derived from populations of non-African ancestry, mostly in high-income countries, with short- and long-term implications for individual and public health. This review tracks the evolution of kidney function monitoring, highlighting measured and estimated glomerular filtration rate (GFR) testing. While measured glomerular filtration rate (mGFR) is the most accurate method, there are potential sources of error for each reference compound so that regional preferences and availability dictate choice. Establishing mGFR testing as a research or clinical service is challenging and remains a barrier to its availability in Africa.

Estimated GFR (eGFR) is more practical but less accurate, and it is important for clinicians to understand the trade-offs, especially in an African context. Non-GFR determinants of serum creatinine lead to random error in measurement that is not a true reflection of kidney function: hereditable factors influence biomarker metabolism and excretion; biological variation results in intra- and inter-individual error; non-renal physiological factors include sex, age, environmental temperature (especially hot climes), ingestion of animal protein, levels of exercise, acute illness, chronic liver disease, enhanced gastrointestinal excretion with declining GFR, and concomitant medication that interferes with tubular handling of creatinine. There are likely to be additional factors (still unknown) in African populations, and analytic error that includes the Jaffe versus enzymatic methods, use of standard reference materials and methods for calibration, and adherence to internal and external quality assurance programmes. Laboratories also require age- and sex-based population-appropriate reference intervals for creatinine measure-ments in children, adolescents, adults, and older subjects, and these reference intervals do not exist in many African countries.

While the spotlight on racialised coefficients for eGFR has been largely confined to the United States, the effect of using GFR estimates that are US-based (and their racialised coefficients) throughout Africa remains overlooked. In Africa, recommended equations overestimate GFR, fewer individuals with chronic kidney disease (CKD) are diagnosed, and the population prevalence is underestimated. Downstream, there are fewer opportunities to investigate causes or initiate treatment to prevent progression – much more relevant since the advent of sodium-glucose co-transporter 2 (SGLT-2) and glucagon-like peptide (GLP)-1 agonists for managing early CKD.

Keywords: chronic kidney disease (CKD); glomerular filtration rate (GFR); measured GFR (mGFR); estimated GFR (eGFR); Africa; creatinine; cystatin C.

INTRODUCTION

In 2017, the Global Burden of Disease Study estimated that 9% of the world's population have all-stage chronic kidney disease (CKD) and that 1.2 million deaths were CKD-related [1]. Whether these global estimates accurately reflect CKD prevalence or associated mortality in African populations is questionable, given the lack of reliable data. Furthermore, appropriate care for managing kidney failure is severely restricted, rendering this condition uniformly fatal and creating a survival bias [2]. Of the available studies, cross-sectional prevalence estimates

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from several African countries are confounded by variations in study sample size, methodology, and the definitions used for CKD [3]. Also, very few longitudinal studies have determined critical outcomes such as CKD incidence, progression, all-cause and cardiovascular premature disability and death [4].

Without a strong bedrock of kidney research on African populations, we are vulnerable to extrapolating research findings based on non-African populations from (mostly) high-income countries. Implementing such findings in Africa without validation or critical reflection may compromise, rather than improve, individual care and impair the development of informed and appropriate public health policy.

This review focuses on how we assess kidney function in African populations, contrasting extrapolated practice with African-centred research findings that challenge long-held paradigms in nephrology, with careful consideration of the short- and long-term implications for individual health, public health, and future research in African populations.

A BRIEF HISTORY OF OUR UNDERSTANDING OF KIDNEY FUNCTION

The study of kidney physiology in animals and humans tracks to the late 1800s: Max Jaffe described his laboratory method for measuring creatinine in 1886, unlocking the potential to quantify existing theories of kidney function. Otto Folin adapted this method to measure creatinine in body fluids in 1914. In 1926, Paul Rehberg performed the first creatinine clearance test on himself by ingesting large amounts of creatinine and plotting his plasma excretion curves [5,6]. After that, multiple studies linked renal blood flow, filtration and tubular secretion. Inulin was identified in 1935 by James Shannon and Homer Smith as an ideal marker of human glomerular filtration [7]. Clinicians began to appreciate the value of tracking glomerular filtration rate (GFR) estimates to monitor kidney disease and explored alternatives to measuring inulin clearance as early as 1938 [8]. Improved laboratory techniques for detecting creatinine in low concentrations enabled a transition from exogenous creatinine clearance (high doses administered orally) to endogenous creatinine clearance testing. Decades of intense debate on the validity of creatinine as a biomarker ensued because tubular creatinine secretion results in creatinine clearance overestimating GFR compared to inulin clearance and the contribution of tubular creatinine secretion varies depending on kidney function. However, the scales tipped in favour of using creatinine clearance rather than urea because creatinine was unaffected by urine flow rates [8-10]. In the late 1960s, there was a strong push to develop bedside nomograms for rapidly calculating creatinine clearance from serum creatinine and 24-hour urine creatinine for dose-adjusting drugs like kanamycin, digoxin, and gentamicin [11]. Given the impracticality of 24-hour urine collection, the drive to develop simpler and faster ways to estimate creatinine clearance was accelerated by "computer-aided" programs using variables such as serum creatinine, age, sex, height, and weight [12-16]. The first equations for calculating creatinine clearance at the bedside were proposed within three years of one another by Jelliffe (1973), Kampmann and colleagues (1974), and Cockcroft and Gault (1976) [15,17,18]. Sidestepping the pitfalls of creatinine clearance by developing estimating equations using measured GFR as the reference was the next step, heralding myriad equations: MDRD, Lund-Malmö, Mayo, FAS, EKFC, CKD-EPI, to name a few.

MEASURED GFR

Currently, measured glomerular filtration rate (mGFR) is the most accurate means to assess kidney function. Glomerular filtration markers (endogenous and exogenous) must be easily measurable in urine or blood, freely filtered by the glomerulus, not reabsorbed or secreted by kidney tubules, and not metabolised or excreted by the gastrointestinal tract or hepatobiliary system. The ideal "gold standard" marker remains inulin, but there is no standard reference to calibrate laboratory accuracy; it is expensive, not readily available, and requires constant intravenous infusion and urinary catheterisation for the duration of the procedure, up to eight hours [19]. Alternative markers that are easier to use, accessible, and more cost-effective are either radiolabelled with a nuclear isotope, such as tri-iodinated iothalamate (^{125}I-iothalamate), chromium-51 ethylenediamine tetraacetic acid (^{51}Cr-EDTA) or technetium-99 diethylenetriamine-pentaacetic acid (^{99}Tc-DTPA), or non-radiolabelled, such as iohexol or iothalamate, both radiocontrast media [20]. Irrespective of the marker, after administration of a bolus dose (normally intravenously), the concentration in urine or blood is measured at intervals and plotted as a concentration (y-axis) versus time (x-axis) curve. Clearance is calculated using the area under the curve and incorporated into various mathematical models to calculate mGFR [21].

Many potential sources of error affect mGFR testing. Intra- and inter-individual differences occur with repeated testing using the same dose of exogenous marker [21-23]. Methodological and analytic error may be introduced by (i) using non-standardised protocols; (ii) the time frame used for plasma sampling – longer sampling intervals are needed for impaired kidney function; (iii) single versus multi-sample techniques; (iv) laboratory methods to mea-

sure markers: high-pressure liquid chromatography can yield different results from liquid chromatography–mass spectrometry methods; (v) the choice of marker in relation to urinary clearance of inulin as the gold standard: urinary clearance of iothalamate, urinary and plasma clearance of ^{51}Cr-EDTA, plasma clearance of ^{99}Tc-DTPA, and plasma clearance of iohexol are accepted as sufficiently accurate for measuring GFR; urinary clearance of ^{99}Tc-DTPA and urinary clearance of iohexol have insufficient accuracy; and 24-hour creatinine clearance is the least accurate; (vi) the choice of marker compared to markers other than inulin: plasma clearances of ^{51}Cr-EDTA, ^{99}Tc-DTPA and iohexol have excellent agreement; plasma clearance of iothalamate consistently overestimates that of iohexol by approximately 10% because of the tubular secretion seen with iothalamate; and (vii) intra- and interlaboratory error [24]. Because of inherent difficulties associated with urinary clearance testing, plasma clearance-based methods are recommended as the procedures of choice [25].

Regional use of exogenous markers depends on preference and availability. For the abovementioned reasons, iothalamate, used in the United States to develop the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, tends to slightly overestimate GFR. On the other hand, iohexol, used in Scandinavia for modelling the Full Age Spectrum (FAS), Revised Lund-Malmö and, most recently, the European Kidney Function Consortium (EKFC) equations, is not secreted by the renal tubules and is the only exogenous marker with an external quality assurance programme aimed at reducing interlaboratory bias [20].

Establishing mGFR testing as a research or clinical service is challenging in many African countries [26]. However, equipment for radioactivity detection is robust and relatively inexpensive, which allows for substantial numbers of nuclear medicine facilities to be established in Africa. Whereas radionuclides such as ^{51}Cr-EDTA are expensive, many nuclear medicine units have switched to ^{99}Tc-DTPA based on its affordability and accessibility. Non-radionuclide markers such as iohexol are not available in many African countries. Where available, the necessary laboratory infrastructure, equipment, expertise, and adherence to the Equalis quality assurance programme may limit implementation. However, iohexol is affordable, heat stable, does not need to be processed in real-time (enabling pooled sample analysis), and can be measured using dried blood spot testing. Mindful that our priority is to capacitate African countries to measure GFR, the choice of technique, whether with non-radioactive or radioactive tracer, will most likely depend on resources available to each centre.

ESTIMATED GFR

non-GFR determinants

Estimated GFR (eGFR) is less accurate than mGFR. GFR estimates rely on kidney excretion of endogenous biomarkers such as creatinine and cystatin C and assume excretion rates are constant. Additionally, serum biomarker concentrations depend on non-renal physiological factors (non-GFR determinants) that contribute random variation to measurements. For creatinine, these include sex and age as indicators of muscle mass, time of day, environmental temperature (especially hot climes), ingestion of animal protein, levels of exercise, acute illness, chronic liver disease, enhanced gastrointestinal excretion with declining GFR, and concomitant medication that interferes with tubular handling of creatinine, most commonly trimethoprim and cimetidine [27]. Serum concentrations of cystatin C are influenced by age, sex, smoking, obesity, systemic inflammation, corticosteroid administration, and thyroid disease. However, renal tubules do not actively secrete cystatin C, nor is it dependent on dietary factors or muscle mass [28]. Some non-GFR determinants are factored into the modelling of GFR estimating equations; for example, creatinine-based eGFR adjusts for age and sex, providing more accurate estimates than using the serum level alone. However, the limitations are apparent, as equations capture only the average relationship and represent only a few non-GFR determinants [27].

Analytic error

Analytic methods contribute to errors in measurement of serum creatinine and cystatin C [29,30]. As serum creatinine decreases, the relative error increases, with implications for population screening because most individuals will have lower serum creatinine. The Jaffe method is subject to interference from non-creatinine chromogens, resulting in overreading true creatinine. Laboratories correct for this effect using a "compensated" Jaffe method that subtracts a manufacturer-recommended value of creatinine (18–26 µmol/L) from measured creatinine [31]. The compensated correction can lead to reporting artificially low creatinine concentrations, especially relevant in children and those with wasting conditions such as chronic liver failure, HIV infection, TB, and cancer. Standard reference materials and methods have been developed for creatinine and cystatin C, against which laboratories calibrate their assays, and laboratories must adhere to robust internal and external quality assurance programmes. Laboratories also require age- and sex-based population-appropriate reference intervals for creatinine in children, adolescents, adults, and older people. Such reference ranges exist in many high-income countries, but less so for other populations, particularly continental Africans [32,33].

In 2006, after reviewing the available evidence, the US National Kidney Disease Education Program (NKDEP) Laboratory Working Group, in collaboration with international professional organizations, recommended that all clinical laboratories worldwide use the enzymatic method for creatinine measurement [34]. Despite these recommendations, today most laboratories throughout Africa still use the Jaffe method because of the cost–benefit, exposing barriers to implementation that have not been addressed. The downstream consequences of continuing use of the Jaffe method require consideration. International studies show that CKD classification stage can differ by up to 19% depending on the laboratory method [35]. A comparative study in South Africa, Malawi, and Uganda showed serum creatinine was higher (by +9.3 µmol/L) with the enzymatic compared to the Jaffe method [36]. Results from a local clinic in Johannesburg, South Africa, demonstrated that delays in sample processing of more than 6 hours artificially increased serum creatinine using the Jaffe but not the enzymatic method [37]. Such delays are frequent in local clinics, and it is reasonable to anticipate longer delays in more peripheral urban and rural clinics in South Africa. In rural South Africa, when evaluating the performance of point-of-care (POC) creatinine devices (all of which are calibrated to the enzymatic method), POC eGFR showed improved performance over laboratory Jaffe eGFR, again highlighting the need for chemical pathology laboratories to use enzymatic methods [38].

ESTIMATED GFR IN THE USA

The US National Kidney Foundation Kidney (NFK) Disease Outcomes Quality Initiative (KDOQI) published the definition and classification of chronic kidney disease guidelines in 2002 [39]. Subsequently, the guidelines were adopted with minor modifications by the international guideline group, Kidney Disease Improving Global Outcomes (KDIGO), in 2004 and revised in 2012 [40]. Journaling the guidelines has undoubtedly benefited clinical practice, research, and public health globally, but not without controversy.

The 2002 NKF guidelines recommended the Modification of Diet in Renal Disease Study (MDRD) equation as first-line evaluation of kidney function [41]. The MDRD equation was published in 1999 and derived from a US-based study by the same name. The study recruited 1,628 adults, of whom 197 were of self-reported Black ethnicity, hereafter referred to as Black participants. Compared to other ethnic groups, Black participants had higher serum creatinine levels for a given mGFR – seen more commonly in men and with lower mGFR. On this basis, an "ethnicity coefficient" was developed to increase eGFR by a factor of 1.18 (18%) in the Black American population. The authors postulated that higher creatinine levels were due to greater muscle mass in Black participants, stating, "Previous studies have shown that, on average, black persons have greater muscle mass than white persons" [41]. Three studies were cited supporting this statement: the first was published in 1978 and showed that Black children had lower percentage body fat than White children, with no reference to lean muscle mass or adults [42]; the second, from 1977, showed that total body potassium, as a proxy for lean muscle mass, was higher in Black adults (47 participants) than in Whites [43]; and the last study, from the UK in 1990, demonstrated racial differences in serum creatine kinase with no link to populations in the US, nor creatinine and its association with lean muscle mass [44].

In 2012, the updated KDIGO guidelines switched their recommendation from the MDRD to the CKD-EPI (creatinine) 2009 equation [40]. The CKD-EPI Consortium accessed pooled mGFR data from 12,150 participants, of whom 2,969 were Black, and modelled an ethnicity coefficient that increased eGFR by a factor of 1.159 (16%) [45]. Between 1999 and 2012, dual X-ray absorptiometry (DXA) became available for assessing body composition. Hsu et al. used DXA to evaluate muscle mass differences in patients with kidney failure, showing that differences in creatinine ascribed to Black ethnicity could not be explained by muscle mass alone [46]. Given these DXA findings and that racial disparities in creatinine measures attenuate at higher GFR in men and are less prominent in women for any GFR [47], one could argue that the scientific rationale for racialised coefficients was not justified for either GFR equation.

ESTIMATED GFR IN AFRICA

The authors who developed the MDRD and CKD-EPI (creatinine) 2009 equations stated as a limitation that the equations would need to be validated in other populations [41,45]. However, after KDIGO recommended these US-derived estimating equations in guidelines intended for global use, there were (unintended) consequences. Aside from evaluating the equations themselves, the relevance of the ethnicity coefficients was questioned for indigenous Australians with varying admixture, multiethnic Asian populations, continental African and non-US-based African diaspora populations [48-50]. Evaluation of eGFR equations was conducted in countries that were able to do so, followed by population-appropriate recommendations for use [51,52]. Studies from China [53,54], South Korea [55], Thailand [56], Taiwan [57], and Japan [58,59] revealed discrepancies, fuelling ongoing debate that remains unresolved [49].

In Africa, eGFR equations have been implemented for widespread use without validation. Isolated studies emerged from Ghana [60], South Africa [50,61], Kenya [62], Ivory Coast, and the Democratic Republic of Congo [63,64], all with a common theme: US-derived ethnicity coefficients substantially overestimated eGFR in continental Black Africans. More recently, a prospective, multicentre, iohexol mGFR study was performed in Malawi, South Africa, and Uganda [36]. The cohorts comprised diverse urban and rural populations and compared the performance of creatinine- and cystatin C-based eGFR equations. In all three countries, creatinine-based eGFR equations substantially overestimated kidney function compared to iohexol mGFR (Figure 1); the overestimation was exacerbated by the inclusion of US-derived ethnicity coefficients. Cystatin C-based equations performed better than creatinine-based equations; but none of the eGFR equations achieved an accuracy considered adequate for individual clinical decision-making. At population level, using creatinine-based eGFR equations substantially underestimated the prevalence of kidney disease. Modelling a new creatinine-based equation to estimate GFR more accurately was not possible due to wide age- and sex-independent variability in the relationship between creatinine and mGFR, even with weight or BMI adjustment.

Understanding why creatinine is a relatively poor biomarker in African populations is critical. Extrapolating from US findings, many have assumed that serum creatinine in continental African populations would be higher than in White North American or European populations. Creatinine data from two large studies in West Africa (Burkina Faso and Ghana), East Africa (Kenya and Uganda), and Southern Africa (Malawi and South Africa) [65,66] were compared with creatinine data from the Health Survey for England [67]. All studies used population-representative sampling; thus, all African participants were Black, compared to ~3% of participants in the UK study [67]. In Africa and the UK, women had lower age-stratified creatinine than men, as expected. However, for all age strata, African men and women had lower serum creatinine than their UK counterparts, with attenuation of the age-related rise in serum creatinine, particularly in women (Figure 2). These results go some way to explaining the poor performance of creatinine-based eGFR equations in Africa. With low population creatinine, the creatinine/GFR ratio is low, predisposing to analytic biases already discussed. Additional

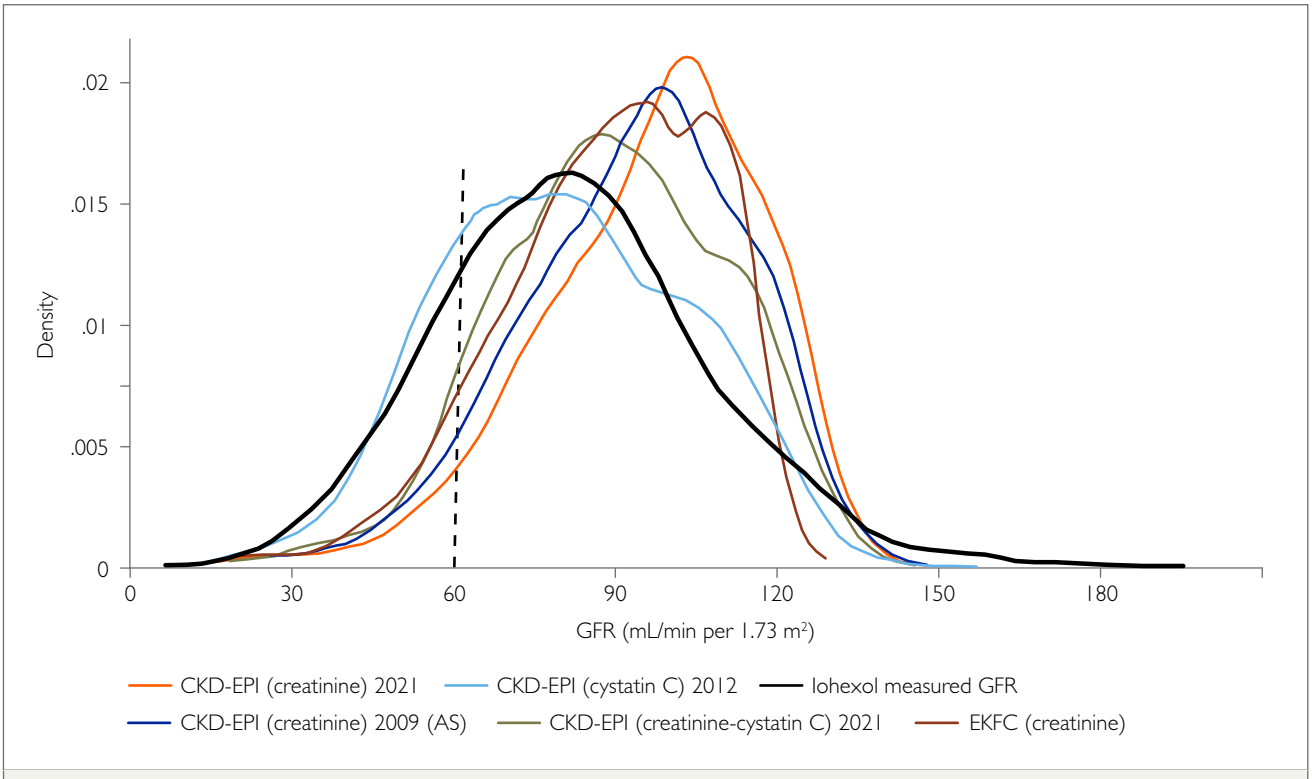


Figure 1. Performance of creatinine-based GFR equations compared to iohexol GFR as the reference in Malawi, South Africa, and Uganda [36]. Kernel density distribution plots of iohexol measured GFR compared with GFR estimates.
Abbreviations: GFR, glomerular filtration rate; CKD-EPI (creatinine) 2009 (AS), 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.

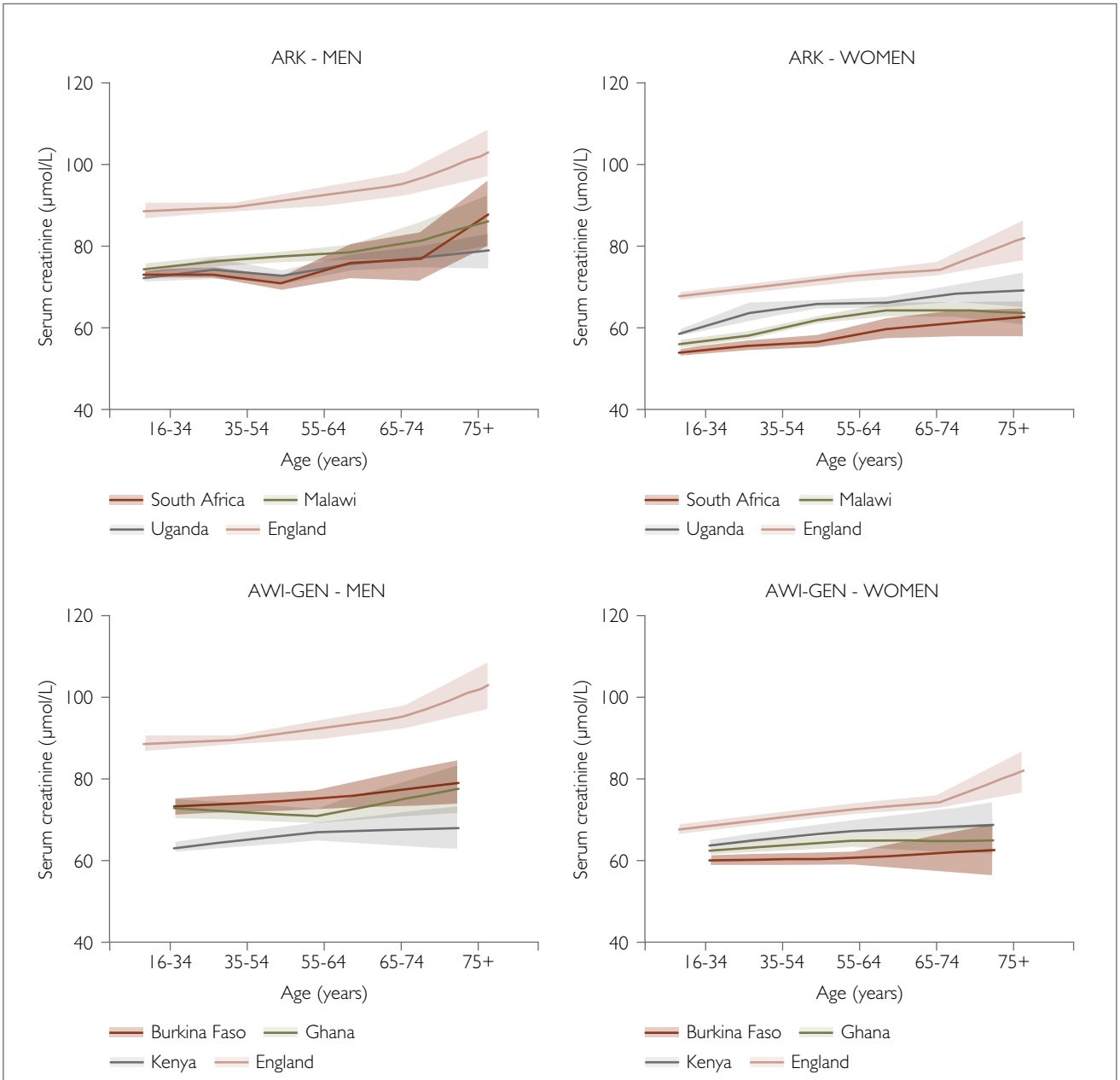


Figure 2. Sex-stratified population-based serum creatinine levels by age in West, East, and Southern Africa, and England (mean and 95% confidence intervals). Population-based mean serum creatinine (solid line) with the 95% confidence interval (shadow) for each age-group, stratified by sex. Data were derived from the African Research on Kidney Disease (ARK) Study: Malawi, South Africa, and Uganda [65]; AWI-GEN (Africa Wits-International Network for the Demographic Evaluation of Populations and their Health Partnership for Genomic Studies): Ghana, Burkina Faso, Kenya, and South Africa [66]; and the Health Survey for England [67]. All creatinine assays were IDMS-traceable, and each laboratory adhered to standard internal and external quality control procedures.

factors contributing to lower population creatinine include lower BMI and BSA, with likely lower muscle mass and lower baseline creatinine [60,62,68,69]. Perinatal and early childhood factors resulting in undernutrition predispose to low lean muscle mass and short stature in adulthood (even in adult obesity) and remain common in many African countries [70-73]. Wasting from chronic infection or inflammation, such as caused by tuberculosis and HIV infection, low dietary protein ingestion as consequences of poverty and food insecurity, and undiagnosed liver disease also affect muscle mass, muscle quality, and creatinine generation [74-77].

ESTIMATING GFR – UNTANGLING RACIALISED MEDICINE AND THE HEREDITABILITY OF KIDNEY FUNCTION

Recently, race-based adjustments of eGFR have been heavily criticized for perpetuating health inequalities in

American medicine. Within US nephrology, fierce debate has ensued regarding the effect of overestimating GFR based on an individual's self-identified race, with implications for patient management, treatment decisions, and access to healthcare resources such as nephrology referral, treatment of CKD, and kidney replacement therapy [78,79]. Consequently, changes have been initiated such as recommending removal of race-based adjustments of GFR in clinical practice (likewise for the UK, according to the revised NICE guidelines [80]), reworking a race-free CKD-EPI equation, and evaluating the utility of alternative biomarkers like cystatin C [81]. However, the silence regarding the impact of race-based coefficients in continental African populations is deafening and the implications profound: based on findings in Black Americans, a sequence of assumptions have been (and continue to be) made about continental African populations that include the biology of creatinine, performance of estimating equations, and utility of ethnicity coefficients resulting in substantial overestimation of GFR. Overestimating GFR means fewer individuals with CKD are diagnosed and population prevalence is underestimated. Downstream of missing a CKD diagnosis, there are fewer opportunities to investigate causes or initiate treatment to prevent progression – much more relevant since the advent of sodium-glucose co-transporter 2 (SGLT-2) and glucagon-like peptide (GLP)-1 agonists for managing CKD [82].

Hereditability of GFR in US and UK diaspora

While there is no justification for using race as a biological variable, some argue that race or ethnicity is a proxy for genetic ancestry. The relationship between creatinine and genetic ancestry was investigated in the Coronary Artery Risk Development in Young Adults (CARDIA) study in the US [45]. Based on race, Black men had greater odds of elevated creatinine than White men after adjusting for sociodemographic characteristics and comorbidities; with a much weaker association seen in Black women. While African ancestry was similar for men and women (72–73%), the association between elevated creatinine and African ancestry was only significant in men and increased with increasing percentages of African ancestry. The Chronic Renal Insufficiency Cohort (CRIC) study showed that adjusting for non-GFR determinants of creatinine could not correct for adjustments of race or ancestry, but estimation of GFR using cystatin C generated accurate GFR estimates independent of race [83]. In an analysis of multi-ethnic groups (Black, East Asian, South Asian, White, Mixed, Other) from the UK biobank, positive associations with creatinine were observed for African ancestry (the strongest association), Black ethnicity, male sex, and height. There was no association with creatinine and socioeconomic deprivation [84].

Hereditability of GFR in African populations

Genome-wide association studies (GWAS) of kidney function have uncovered hundreds of risk loci, primarily in populations of European ancestry. The first African GWAS of kidney function based on creatinine-eGFR was performed in East Africa (Uganda) and identified a novel locus mapped to the *GATM* gene that encodes the enzyme glycine amidinotransferase involved in tubular creatinine secretion [85]. Unfortunately, the functional significance of this novel locus cannot be inferred, and the sample size was small. The second GWAS, from the same group in Uganda, assessed cystatin C eGFR, identifying two novel single nucleotide polymorphisms (SNPs) that had not been associated previously with $eGFR_{cys}$ in other populations, and replicated a SNP associated with cystatin C eGFR among those of European ancestry [86]. One novel SNP was a variant of the *ANK3* gene, highly expressed in human kidney tissue and associated with polycystic kidney disease in mice; the second novel variant of the *OR51B5* gene encodes kidney receptors involved in blood pressure control and glucose excretion; and the last replicated variant of the *CST3* gene encodes cystatin C. While both GWAS are limited, the findings support the need for large-scale GWAS from multiple, diverse African populations to deepen our understanding of the genetic architecture of kidney function and CKD in Africa.

FUTURE DIRECTIONS FOR ASSESSING KIDNEY FUNCTION IN AFRICA

From the available data there are grounds for regional recommendations regarding eGFR testing that include: (i) transitioning from Jaffe to enzymatic methods for laboratory creatinine assays; (ii) developing population-appropriate laboratory reference ranges for creatinine and cystatin C; (iii) omitting ethnicity coefficients from eGFR if using the MDRD or CKD-EPI equations; (iv) use of the CKD-EPI (creatinine) 2009 equation for the initial screening test as there is no evidence that the revised race-free CKD-EPI (creatinine) 2021 equation confers improved performance; (v) utilising cystatin C eGFR as a confirmatory test for CKD diagnosis with improved sensitivity compared to creatinine-based eGFR (especially relevant in the absence of access to measured GFR testing); and using simple tools to calibrate current estimating equations where limited GFR measurement facilities exist [87]. Thus, establishing a framework of clinical guidelines would be an appropriate next step. Future work will need to evaluate region-specific explanations for the poor performance of creatinine in monitoring kidney function by including the effect on functioning nephron mass of adverse developmental and life course events, investigating factors that influence non-

GFR determinants of creatinine (including muscle mass), and identifying mechanisms for tubular secretion of creatinine and genetic variation that might be specific to African populations. Whether cystatin C performs better as an indicator than creatinine with serial monitoring (to detect changes in eGFR) or whether it predicts increased risk for adverse outcomes in African populations would add critical evidence to inform eGFR screening strategies.

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Conflict of interest

The author has no conflict of interest to declare.

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