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Estimated Versus Measured Glomerular Filtration Rate in Men at Risk for Mesoamerican Nephropathy

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To the Editor:

Equations for estimated glomerular filtration rate (eGFR) using serum creatinine (sCr) or cystatin C (CysC) may introduce bias when applied to populations with different ancestry, body type, or diet than the population where the equation was derived. The accuracy of eGFR equations has never been evaluated in persons with or at risk for Mesoamerican nephropathy (MeN), a syndrome of chronic kidney disease of unknown cause (CKDu) usually affecting young men from agricultural areas in Mesoamerica who are of mixed ancestry, perform strenuous manual labor, and live in poverty.[1] Andersson recently described markedly lower GFR estimates by CysC compared with sCr in this population,[2] raising questions about the accuracy of eGFR equations applied here.

We compared eGFR in a population with high rates of MeN against measured GFR (mGFR) determined by iohexol plasma disappearance.[3] Our primary analysis focused on three eGFR equations currently recommended by the National Kidney Foundation (NKF) / American Society of Nephrology (ASN),[4] which use sCr, CysC, or both; we secondarily evaluated three other eGFR equations used historically in MeN research in order to assess whether previous prevalence estimates may have been biased (**Table S1**).

Participants were from agricultural communities with high rates of MeN in Nicaragua. Eligible individuals were male, aged 18-50, with eGFR between 30 and 120 mL/min/1.73m^2. Individuals with diabetes, stage 2 hypertension, or kidney disease unrelated to MeN were excluded. We compared eGFR with mGFR by the following measures. *Bias* is the difference between eGFR and mGFR, with positive values indicating higher eGFR than mGFR. P_{30} is the percent of eGFR

values within 30% of the corresponding mGFR.[5] *Correct classification* is the percent agreement between mGFR and eGFR by CKD stage. *Correct MeN classification*, assessed only in individuals with mGFR between 45 and 90 ml/min/1.73m^2, is the percent agreement between mGFR and eGFR when dichotomized as above or below 60 ml/min/1.73m^2, a threshold frequently used to classify MeN. **Item S1** contains detailed methods.

Fifty individuals participated (**Figure S1)**. Age ranged from 19 to 45 (mean 34) years (**Table 1)**. mGFR ranged from 24 to 137 (median 82) ml/min/1.73m^2.

Among NKF/ASN-recommended equations, when compared with the 2021 CKD Epidemiology Collaboration (CKD-EPI) sCr equation without a black race term (eGFRcr$_{21}$),[6] the CKD-EPI CysC equation (eGFRcys)[7] had greater bias (median -9.9 vs -0.3 ml/min/1.73m^2), lower P_{30} (62% vs 90%), lower correct classification (52% vs 74%), and lower correct MeN classification (73% vs 85%). The 2021 CKD-EPI sCr-CysC equation without a black race term (eGFRcr-cys$_{21}$)[6] generally fell between these two models (**Figure 1a)**. **Figure S2** shows CKD staging by mGFR versus eGFR.

Among historically-used equations, bias, P30, correct classification, and Correct MeN classification were all best with the Cockcroft-Gault[8] and worst with the Modification of Diet in Renal Disease (MDRD)[9] equation (**Figure 1b, Figure S3**). The 2009 CKD-EPI sCr equation (eGFRcr$_{09}$),[5] the most frequently used equation in MeN research, performed more poorly than eGFRcr$_{21}$ but was better than eGFRcys across all four parameters.

Reliable eGFR models are important for estimating disease prevalence, correctly classifying participants in research studies, and delivering optimal clinical care. Among young men with or at risk for MeN, we found $eGFRcr_{21}$ to be accurate and unbiased overall, whereas equations incorporating CysC underestimated GFR and therefore overestimated the extent of kidney disease.

Our findings corroborate Andersson's description of lower eGFR by CysC than sCr,[2] and suggest this may occur due to systematic error in CysC-based equations when applied to populations at risk for MeN. The cause of this error is unknown, but differences in CysC production and metabolism due to unmeasured physiologic or environmental factors may contribute. In the context of MeN, two potential causes in particular warrant further investigation: Inflammation, increasing endogenous CysC production, and tubular damage, leading to incomplete renal metabolism of CysC and subsequent reabsorption.[10]

MDRD, eGFRcys, and, to a lesser extent, $eGFRcr_{09}$ underestimated GFR and may misclassify disease when applied to MeN populations. The use of $eGFRcr_{21}$ should mitigate this concern. Cockcroft-Gault, while no longer recommended due to its development with non-standardized creatinine, performed similarly to $eGFRcr_{21}$ and uniquely includes bodyweight; incorporating anthropometric measurements in equations for this population may warrant further investigation.

Our study was constrained to men aged 18-50, the demographic historically most affected by MeN; these findings should not be extrapolated to women or those substantially outside this age

range. This is a single-center study in Nicaragua, and may not represent CKDu populations elsewhere.

Populations with MeN, and CKDu more broadly, are not well represented in eGFR equation development and validation cohorts and have never been the subject of a large-scale mGFR study. Continued work towards identifying appropriate eGFR equations for these and other underserved populations remains vital.

Supplementary Material

Item S1. Supplementary Methods

Table S1. Estimating equations for glomerular filtration rate.

Figure S1. Recruitment flow diagram.

Figure S2. Agreement in staging of chronic kidney disease (CKD) and Mesoamerican Nephropathy (MeN) diagnostic criteria by estimated glomerular filtration rate (eGFR) compared with measured GFR (mGFR).

Figure S3: Agreement in staging of chronic kidney disease (CKD) and Mesoamerican Nephropathy (MeN) diagnostic criteria by estimated glomerular filtration rate (eGFR) from historically-used estimating equations compared with measured GFR (mGFR).

Article Information

Authors' Contributions: Research idea and study design: NHR, DJF, MGQ; data acquisition: NHR, MGQ, JCS; data analysis/interpretation: NHR, JCS, LAI, MGQ, DJF; statistical analysis: NHR, LAI; supervision or mentorship: DJF, LAI, DRB; MGQ and DJF contributed equally to

this work. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Clinical Characteristics of Participants.

Variable	**Study Population (n=50)**
Age in years, mean (SD)	34 (8)
Age categories, n (%)	
18-29	14 (28)
30-39	22 (44)
40-50	14 (28)
Body mass index in kg/m^2, mean (SD)	24.3 (4.9)
Body mass index categories, n (%)	
<18.5 kg/m^2	3 (6)
18.5-24.9 kg/m^2	33 (66)
25-29.9 kg/m^2	9 (18)
≥30 kg/m^2	5 (10)
Body surface area in m^2, mean (SD)	1.74 (0.21)
Medical history, n (%)	
Stage 1 hypertension	4 (8)
NSAID use	7 (14)

ACEi/ARB use	8 (16)
Tobacco Smoking, n (%)	
Current	16 (32)
Former	6 (12)
Never	28 (56)
Blood pressure in mmHg, mean (SD) systolic/diastolic	121 (12) / 75 (8)
Serum creatinine in mg/dL, median (IQR)	1.14 (0.88 to 1.67)
Serum cystatin C in mg/dL, median (IQR)	1.10 (0.83 to 1.54)
Urine protein to creatinine ratio in g/g, median (IQR)	0.06 (0.04 to 0.11)
Current occupation or occupations, n (%)*	
Agricultural work	40 (80)
Sugarcane harvest cutting	15 (30)
Sugarcane seed cutting	18 (36)
Irrigation	3 (6)
Pesticide and herbicide application	9 (18)
Mechanic or supervisor	3 (6)

Subsistence agriculture	5 (10)
Work outside agriculture	21 (42)
Unemployed	1 (2)
Years working in agriculture, median (IQR)	10 (3 to 16)

Abbreviations: SD, standard deviation; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Conversion factors for units: serum creatinine in mg/dL to μmol/L, × 88.4.

* Percentages total >100% because participants could report more than one current occupation.

Figure Legend

Figure 1. Performance of estimating equations against measured glomerular filtration rate (mGFR) by iohexol disappearance in a Nicaraguan Mesoamerican Nephropathy (MeN) Population. Shown for each equation are correlation plots with linear regression between mGFR and estimated GFR (eGFR) above, and prediction plots with eGFR - mGFR plotted against eGFR below. (a) Equations currently recommended by the National Kidney Foundation - American Society of Nephrology Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.[4] (b) GFR estimating equations historically used in MeN populations. Bias is defined as the median of eGFR - mGFR, with interquartile range in parentheses. P_{30} is defined as the percentage of eGFR values with 30% of the mGFR. Correct classification is defined as the percent agreement between mGFR and eGFR when categorized as <30, 30 to <45, 45 to <60, 60 to <90, and 90 or greater ml/min/1.73m^2. Correct MeN classification is defined as the percent agreement between mGFR and eGFR when dichotomized as above or below 60 ml/min/1.73m^2, a threshold frequently used to classify MeN. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; $eGFRcr_{21}$, the 2021 CKD-EPI creatinine equation without a black race term; eGFRcys, the 2012 CKD-EPI cystatin C equation; $eGFRcr\text{-}cys_{21}$, the 2021 CKD-EPI equation incorporating both creatinine and cystatin C without a black race term; $eGFRcr_{09}$, the 2009 CKD-EPI creatinine equation which includes a black race term; MDRD, Modification of Diet in Renal Disease.

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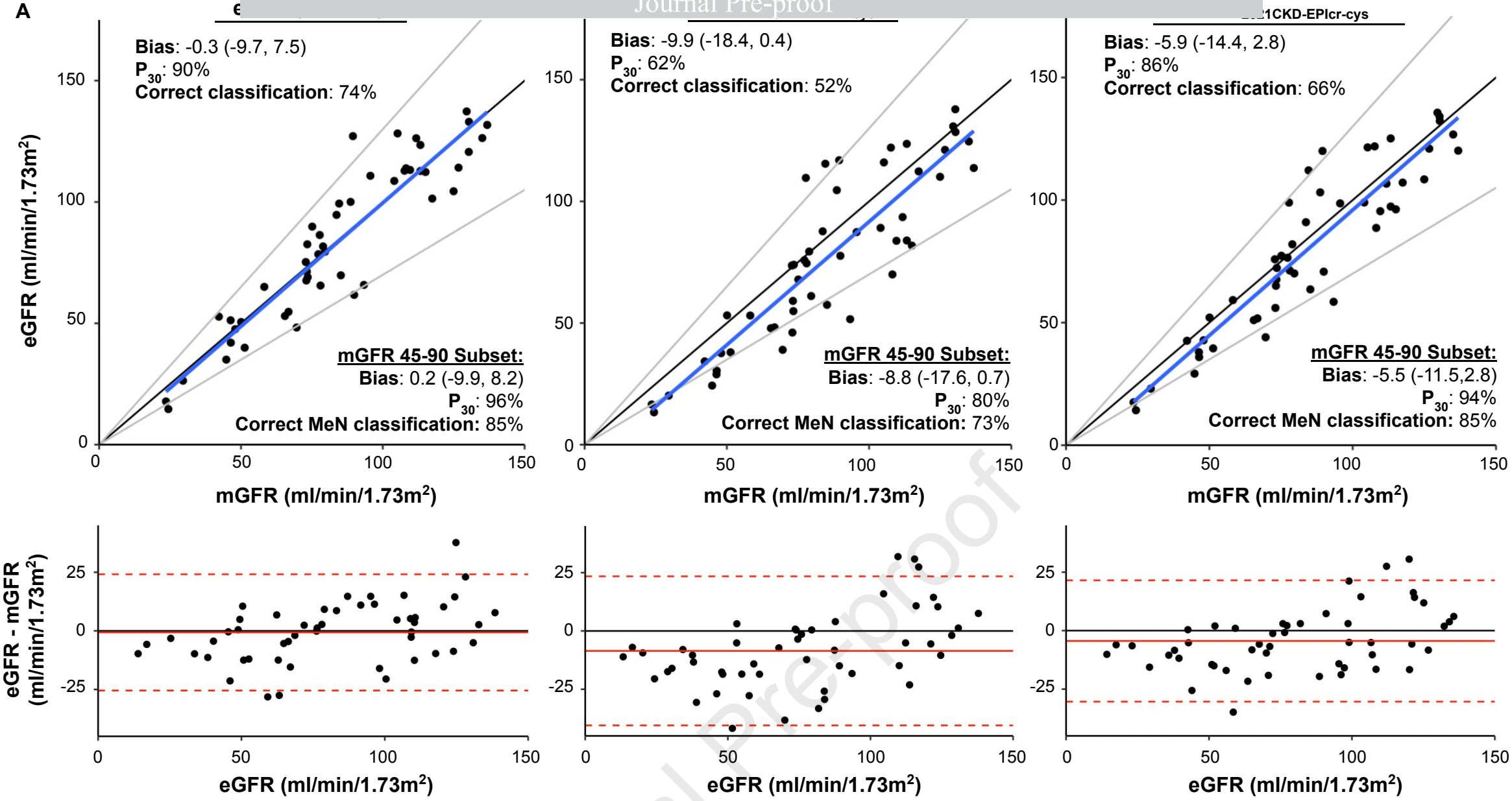

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