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The Limits of Generalizability: Pitfalls of Applying Western GFR Estimation Models to Global Populations

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Glomerular filtration rate (GFR) is considered the best overall index of kidney function. Knowledge about its physiological role came from meticulous experiments using exogenous filtration markers to measure GFR (mGFR). Clinically, GFR is estimated (eGFR) from endogenous filtration markers such as serum creatinine and cystatin C and routinely reported with other laboratory data in the chemistry panel. The commonly used eGFR equations, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[1] and European Kidney Function Consortium (EKFC)[2] equations, were developed using cohorts of mainly Western populations. Statistically, equations were developed using linear regression to model the populations' average mGFR as a function of the marker (e.g., creatinine) and its non-GFR determinants that can easily be obtained from administrative data (e.g., age, sex). The non-GFR determinants of the endogenous filtration markers, such as muscle mass and cooked meat intake for creatinine, and adiposity and inflammation for cystatin C,[3] may differ significantly across populations in different parts of the world, affecting the coefficients that describe the relationship between them and mGFR. Thus, eGFR calculations using Western models are less likely to be reliable in populations with different body composition and food preferences, both in the West, and the rest of the world.

The "e" in the eGFR is a reminder that the eGFR is a population-average prediction (estimation) of mGFR at a given level of serum creatinine or cystatin C. One of the metrics used to evaluate eGFR is bias, the population-average of the difference between mGFR and eGFR of everyone. Bias is the average of the differences rather than the difference of the averages, an important distinction. Thus, the population-average bias can be negligible despite large differences at an individual level, as illustrated in Figure 1. The negligible population-average bias makes eGFR invaluable for population-level inferences for epidemiologic studies and disease prevalence modeling. However, the large individual-level differences mean that eGFR is inaccurate for clinical situations where reliable GFR information would change clinical management. We have shown in previous work that there is a substantial discrepancy between mGFR and eGFR; for persons with an eGFR of 60 ml/min per 1.73 m^2, 95% of corresponding mGFRs ranged from 36 to 87 ml/min per 1.73 m^2, spanning several chronic kidney diseases stages and implications for clinical care.[4]

With this context in mind, how do eGFR equations, derived predominantly from the Western cohorts, perform in populations from other parts of the world? Yadav *et al.*[5] present data to answer this question in this issue of *Kidney International Reports*. They evaluated the performance of 10 eGFR equations in 412 individuals from 1 center in Northern India. They included 187 individuals without known CKD and 225 with CKD. Participants were recruited for the research protocol, avoiding confounding by indication when patients are referred for GFR measurement as part of clinical care. GFR was measured initially (2014–2015) using urinary inulin clearance ($n = 130$) and later (2015–2020) by 4-hour, 1-compartment, plasma iohexol clearance ($n = 282$). The authors noted the limitations of their protocol, including the lack of bladder scanning for urinary inulin clearance and the lack of a late time point for plasma iohexol clearance in individuals with low GFR. The standardization of diet and medications before GFR measurement day was not described.

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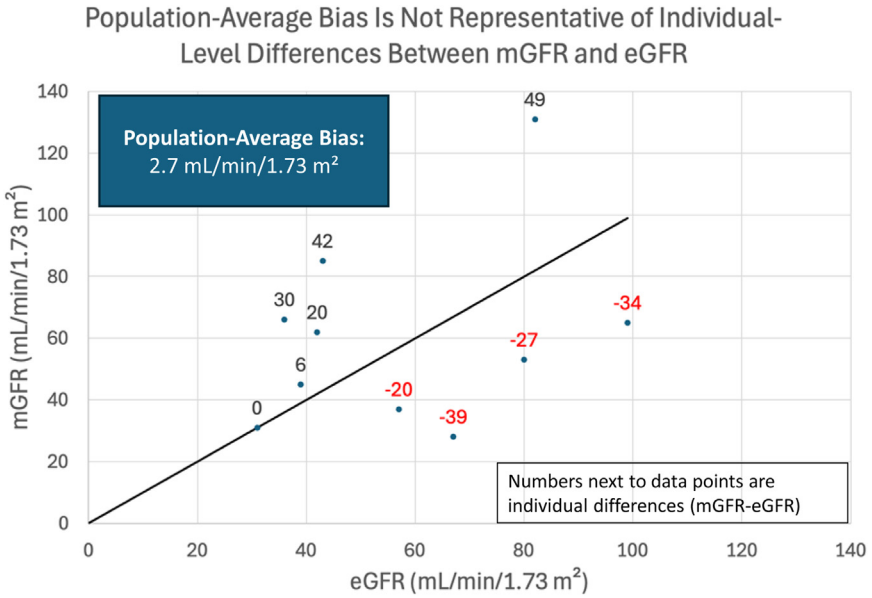

Figure 1. Population-average bias is not representative of individual-level differences between mGFR and eGFR. Plot of calculated eGFR against mGFR of 10 nonrandomly selected participants from an observational cohort study. Numbers above each datapoint represent the individual-level differences between mGFR and eGFR. This figure illustrates how large individual-level differences between mGFR and eGFR can still yield a low population-average bias. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate using an exogenous filtration marker.

As the authors note, the Northern Indian population differs systematically from CKD-EPI and EKFC's predominantly Western populations. The Indian population had a lower body mass index (mean of 25 kg/m^2 vs. 28 kg/m^2 in CKD-EPI) and lower protein intake (mean protein intake of 47.5 g/d; approximately 0.68 g/kg/d for a 70 kg person) with less protein coming from meat because 61% were vegetarians. With low meat intake and potentially lower muscle mass, serum creatinine is expected to be systematically lower in this population, translating to a higher eGFR-creatinine. Conversely, lower meat intake could also translate to a lower mGFR due to the elimination of meat-induced glomerular hyperfiltration.[6] The authors noted that all eGFRs from serum creatinine were markedly higher than mGFRs regardless of equation used. On average, eGFR-creatinine was higher than mGFR by 19, 17, and 15 ml/min per 1.73 m^2 using CKD-EPI 2021, CKD-EPI 2009, and EKFC equations, respectively. Accuracy of the eGFR-creatinine equations was also poor, with the distribution of the population-average bias (95% limits of agreement or 1.96 SD) ranging from eGFR-creatinine being approximately 20 ml/min per 1.73 m^2 lower to 20 ml/min per 1.73 m^2 higher than mGFR. In contrast, the use of noncreatinine biomarkers eliminated the large population-average bias; it was insignificant for CKD-EPI 2012 eGFR-creatinine-cystatin C (−0.9 ml/min per 1.73 m^2; 95% CI: −2.7 to 1.0) and EKFC eGFR-cystatin C (−0.2 ml/min per 1.73 m^2; 95% CI: −2.0 to 1.8). The population-average bias was also insignificant for eGFRs incorporating multiple markers in persons with mGFR $>$ 30 ml/min per 1.73 m^2. However, the accuracy of eGFR equations using noncreatinine biomarkers was still low.

What are the implications of these findings? First, from a population-level perspective, Western equations are likely to calculate population-average eGFRs higher than mGFRs in parts of the world where muscle mass or meat intake are lower. Thus, the burden of CKD in these regions may be underestimated by eGFR-creatinine. Using eGFR-cystatin C may ameliorate this problem; however, it is not feasible to use it worldwide solely for evaluating CKD burden. Large region-specific studies employing multiple markers and measuring GFR concurrently may address this issue, but the cost may not be justified. Statistical modeling to account for region-specific non-GFR determinants of creatinine may partially address this problem but may have unintended consequences. Second, results from this study demonstrate yet again that population-average eGFR values are inadequate in important clinical decisions that are contingent on accurate knowledge of GFR, such as donor nephrectomy; assessing eligibility and dosing of chemotherapy; and initiating, withholding, or withdrawing medications such as sodium-glucose transport protein 2 inhibitors and mineralocorticoid receptor antagonists. A multipronged approach is required to address this.

We need to reconsider whether, despite its inaccuracy, eGFR should continue to be reported as a single number alongside other highly precise and accurate components of the serum chemistry or instead be reported with its prediction interval or the range of expected mGFRs for a given eGFR. This can alert clinicians to pursue GFR measurement when the clinical decision requires a more accurate GFR assessment. Applying multiple biomarkers for GFR estimation can also improve accuracy.[3] The recent Kidney Disease: Improving Global Outcomes CKD guidelines noted, "All nephrologists…should have access to at least one method to measure GFR using plasma or urinary clearance of exogenous markers." The EKFC plasma iohexol clearance consensus is one such step in the right direction toward standardizing and operationalizing mGFR for widespread use.[7] Finally, for clinical care, eGFR is but one component of CKD progression risk assessment. An individual's CKD progression risk varies considerably within the strata of eGFR, depending on albuminuria and other clinical factors.[8,9] Utilizing both eGFR and CKD progression risk can be helpful in both prognostication and guiding medical management with kidney function–preserving therapies.

In conclusion, this meticulous work by Yadev *et al*.[5] illustrates the issues of generalizability of population-average eGFR in non-Western populations. It also serves as a reminder of the potential concerns when using eGFR alone for individualizing patient care.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. https://doi.org/10.1056/NEJMoa2102953
2. Pottel H, Björk J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate : a cross-sectional analysis of pooled data. *Ann Intern Med*. 2021;174:183–191. https://doi.org/10.7326/m20-4366
3. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol*. 2020;16:51–64. https://doi.org/10.1038/s41581-019-0191-y
4. Shafi T, Zhu X, Lirette ST, et al. Quantifying individual-level inaccuracy in glomerular filtration rate estimation : a cross-sectional study. *Ann Intern Med*. 2022;175:1073–1082. https://doi.org/10.7326/m22-0610
5. Yadav AK, Kaur J, Kaur P, et al. Evaluation of race-neutral glomerular filtration rate estimating equations in an Indian population. *Kidney Int Rep*. 2024;9:3414–3426. https://doi.org/10.1016/j.ekir.2024.09.020
6. Hostetter TH. Human renal response to meat meal. *Am J Physiol*. 1986;250:F613–F618. https://doi.org/10.1152/ajprenal.1986.250.4.F613
7. Ebert N, Schaeffner E, Seegmiller JC, et al. Iohexol plasma clearance measurement protocol standardization for adults: a consensus paper of the European Kidney Function Consortium. *Kidney Int*. 2024;106:583–596. https://doi.org/10.1016/j.kint.2024.06.029
8. Grams ME, Brunskill NJ, Ballew SH, et al. Development and validation of prediction models of adverse kidney outcomes in the population with and without diabetes. *Diabetes Care*. 2022;45:2055–2063. https://doi.org/10.2337/dc22-0698
9. Tio MC, Butler J, Zhu X, et al. Individualized risk of CKD progression among US adults. *J Am Soc Nephrol*. 2024;35:1076–1083. https://doi.org/10.1681/asn.0000000000000377