Re-thinking kidney function: a new approach to kidney function estimation and the identification of chronic kidney disease

Jessica Dawson , Meg Jardine

Each serum creatinine pathology test result in Australia is routinely returned with a report on the estimated glomerular filtration rate (eGFR). The equation for calculating the eGFR has been updated, and Australian practitioners may be curious to know why this might concern them.

The eGFR equations were derived from multiple studies that used direct measurements of kidney function with accurate but intensive methods that are generally reserved for research, such as the clearance of the exogenous filtration markers inulin, iothalamate, or iohexol.[1] The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)$_{2009}$ equations included serum creatinine concentration, age, sex, and race (Black or non-Black) as variables.[1] A new, race-free equation was developed after concerns in the United States regarding the validity, accuracy, and implications of including a binary or non-binary race component.[2] In 2021 the CKD-EPI published a newly derived and validated race-free equation (CKD-EPI$_{2021}$), and reported that the new equations produced estimates of measured kidney function that were within the accepted 30% margin of error.[3] The CKD-EPI confirmed that equations based on creatinine and cystatin concentrations consistently produce more accurate estimates than equations based on creatinine alone. It also reconfirmed the clinical relevance of eGFR, reporting a strong inverse linear association with the risk of kidney failure, adverse cardiovascular events, and death. The association of lower eGFR with adverse event risk is the underlying rationale for risk-based categories in the widely used KDIGO classification of chronic kidney disease.[4] Using the new equation without a race coefficient is now the recommended standard.[5]

Practitioners may wonder about the implications of the change for Australia. At the individual level, the difference is mostly a minor, one-off change in eGFR that might only be apparent in people who are being frequently monitored at the time of the equation change. At the population level, even small changes in the calculated eGFR could affect how health systems anticipate and plan for chronic kidney disease (CKD)-associated health care.

CKD has a large impact on community health and on health budgets. It affects an estimated one in ten Australian adults, and one in five Aboriginal and Torres Strait Islander adults.[6] The association of CKD with adverse outcomes[4] is reflected by the prediction that CKD-associated death will be the fifth leading cause of years of lost life globally by 2040.[7] Even now, it has been estimated that CKD costs the Australian economy $9.9 billion each year.[8]

How the CKD-EPI$_{2021}$ equation performs in Australia could have substantial consequences, particularly for older people, who have greater health care needs. An estimated 22% of Australians aged 65–74 years and 44% of those aged 75 years or older have biomedical signs of CKD.[6] As the development and validation of the CKD-EPI$_{2009}$ and CKD-EPI$_{2021}$ equations were based on American populations predominantly under 65 years of age,[3] it is unclear how appropriate these equations are for older people outside the United States. The CKD-EPI authors emphasised the reliance of the equation on the populations used for its derivation and validation,[3] underscoring the need to test its impact in other populations.

In this issue of the *MJA*, Bongetti and colleagues shed light on the possible impact of estimating GFR in healthy older Australian with the updated CKD-EPI$_{2021}$ (creatinine) equation.[9] The authors undertook a secondary analysis of data from the ASPREE randomised controlled trial, which investigated the effect of daily aspirin on disability-free survival in a well characterised cohort of 16 244 Australian participants aged 70 years or older with relatively preserved kidney function.[10] With the old standard equation (CKD-EPI$_{2009}$) the median eGFR was 74 mL/min/1.73 m^2, and 17% of participants met the definition of CKD (eGFR below 60 mL/min/1.73 m^2). With the CKD-EPI$_{2021}$ equation, the median eGFR was about 4 mL/min/1.73 m^2 higher; individual changes were greatest for participants with well preserved estimated kidney function or aged 80 years or older. Overall, 20% of participants (3274 people) were classified to less advanced CKD stages with the CKD-EPI$_{2021}$ than with the CKD-EPI$_{2009}$, meaning that the proportion labelled with clinical CKD dropped from 17% to 12%. The re-estimation made no difference to the lack of effect of daily aspirin on disability-free survival or all-cause mortality, nor on the incidence of major adverse cardiovascular events or hospitalisations with heart failure. The previously reported higher risk of major adverse cardiovascular events in people with CKD was also noted using the CKD-EPI$_{2021}$ equation.[9]

The report by Bongetti and colleagues is largely reassuring. The lower prevalence among older people of meeting the definition for CKD is consistent with the original modelling for the CKD-EPI$_{2021}$ equation.[3] The slightly lower CKD prevalence is likely to mean that resources and programs can be targeted to a smaller group of older people at particular risk of adverse outcomes. The clinical characteristics of the cohort indicate that the equation still characterises CKD in familiar ways, such as its being associated with higher rates of cardiovascular disease.[9]

The study by Bongetti and colleagues does not answer all questions. The accuracy of the CKD-EPI$_{2021}$ needs to be further investigated in studies that reflect the ethnic diversity of Australia, particularly Aboriginal and Torres Strait Islander people, for whom the burden of CKD is higher than among non-Indigenous people.[6] Interestingly, the CKD-EPI$_{2009}$ equation provided a

NHMRC Clinical Trials Centre, the University of Sydney, Sydney, NSW. jessica.dawson@sydney.edu.au • doi: 10.5694/mja2.52560 • See Research (Bongetti)

reasonably accurate estimate of GFR in Aboriginal and Torres Strait Islander people when used without a correction for race.[11] Some of the recent debate in the United States was foreshadowed by the authors of an Australian study who proposed that a single correction factor was unlikely to be useful in Australia, given the heterogeneity and ethnic diversity of Aboriginal and Torres Strait Islander peoples.[11]

The accuracy of the equations for Australians of Asian background requires further investigation, given both the composition of the Australian population and the anticipated growth in the incidence of kidney failure in Asia.[12] In Chinese[13,14] and South Asian[15] populations, the CKD-EPI$_{2021}$ equation yields median eGFR values median 4 to 6 mL/min/1.73 m^2 higher than the CKD-EPI$_{2009}$. However, the CKD-EPI$_{2021}$ equation is reported to perform poorly when compared with measured GFR, and some investigators have attempted to develop ethnic background-specific equations.[14,15]

The equitable allocation of health care resources and lower health care costs each require the appropriate identification and response to CKD in the diverse Australian population. The findings of Bongetti and colleagues suggest that adopting the updated equation may result in fewer older people being classified as having CKD. Whether this improves the effective use of resources targeted to those at greatest risk remains to be seen.

Competing interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed. ■

1 Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: core curriculum 2021. *Am J Kidney Dis* 2021; 78: 736-749.

2 Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis* 2022; 79: 268-288.e1.

3 Inker LA, Eneanya ND, Coresh J, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C–based equations to estimate GFR without race. *New Engl J Med* 2021; 385: 1737-1749.

4 Writing Group for the CKD Prognosis Consortium; Grams ME, Coresh J, Matsushita K, et al. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *J Am Med Assoc* 2023; 330: 1266-1277.

5 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024; 105 (4 Suppl): S117-S314.

6 Australian Institute of Health and Welfare. Chronic kidney disease: Australian facts. Updated 17 June 2024. https://www.aihw.gov.au/reports/chronic-kidney-disease/chronic-kidney-disease (viewed Dec 2024).

7 Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018; 392: 2052-2090.

8 Deloitte Access Economics. Changing the chronic kidney disease landscape: the economic benefits of early detection and treatment [report commissioned by Kidney Health Australia]. 8 Mar 2023. https://www.deloitte.com/au/en/services/economics/analysis/changing-chronic-kidney-disease-landscape.html (viewed Dec 2024).

9 Bongetti EK, Wolfe R, Wetmore JB, et al. Classification of chronic kidney disease in older Australian adults by the CKD-EPI 2009 and 2021 equations: secondary analysis of ASPREE study data. *Med J Aust* 2025; 222: 74-81.

10 ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. *Contemp Clin Trials* 2013; 36: 555-564.

11 Maple-Brown LJFP, Hughes JTF, Lawton PDF, et al. Accurate assessment of kidney function in Indigenous Australians: the Estimated GFR Study. *Am J Kidney Dis* 2012; 60: 680-682.

12 Liyanage TM, Ninomiya TP, Jha VP, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 385: 1975-1982.

13 Shen Y, Wu H, Liu X, et al. Comparison of the 2021 and 2009 chronic kidney disease epidemiology collaboration creatinine equation for estimated glomerular filtration rate in a Chinese population. *Clin Biochem* 2023; 116: 59-64.

14 Pei X, Zhao W, Du X. A validation study of the 2021 CKD-EPI equations: data from two cohort studies in Nanjing, *China J Nephrol* 2022; 35: 2155-2156.

15 Safdar A, Akram W, Khan MA, et al. Comparison of EKFC, Pakistani CKD-EPI and 2021 race-free CKD-EPI creatinine equations in South Asian CKD population: a study from Pakistani CKD community cohort. *PLoS One* 2024; 19: e0300428. ■