

Received Date : 02-Jul-2013

Revised Date : 28-Nov-2013

Accepted Date : 27-Feb-2014

Article type : Research Article

Performance of formulas for estimating glomerular filtration rate in Indigenous Australians with and without Type 2 diabetes: the eGFR Study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dme.12426

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What's new?

- Diabetes is the leading cause of end-stage kidney disease in Indigenous Australians, a population at particularly high risk of diabetes and chronic kidney disease.
- Using a reference measure of glomerular filtration rate, performance of glomerular filtration rate-estimating equations was assessed in 564 Indigenous Australians according to diabetes status.
- The Chronic Kidney Disease Epidemiology Collaboration equation outperformed the Modification of Diet in Renal Disease equation and the Cockcroft–Gault formula overall in participants with and without diabetes.
- However, the Chronic Kidney Disease Epidemiology Collaboration formula had a greater bias in people with diabetes compared with those without diabetes, especially in those with normal renal function.

Abstract

Aims It has been proposed that the Chronic Kidney Disease Epidemiology Collaboration formula estimates glomerular filtration rate more accurately than the Modification of Diet in Renal Disease formula. With the very high incidence of diabetes and end-stage kidney disease in Indigenous Australians, accurate estimation of glomerular filtration rate is vital in early detection of kidney disease. We aimed to assess the performance of the Chronic Kidney Disease Epidemiology Collaboration, Modification of Diet in Renal Disease and Cockcroft–Gault formulas in Indigenous Australians with and without diabetes.

Methods Indigenous Australians with ($n = 224$) or without ($n = 340$) Type 2 diabetes had a

reference glomerular filtration rate measure using plasma disappearance of iohexol (measured glomerular filtration rate) over 4 h. Serum creatinine was measured by an enzymatic method. Performance was assessed by bias (measured glomerular filtration rate – estimated glomerular filtration rate) and accuracy (percentage of estimated glomerular filtration rate within 30% of measured glomerular filtration rate).

Results The median measured glomerular filtration rate (interquartile range) in participants with or without diabetes was 97 (68–119) and 108 (90–122) ml min⁻¹ 1.73 m⁻², respectively. The Chronic Kidney Disease Epidemiology Collaboration formula had smaller bias and greater accuracy than the Modification of Diet in Renal Disease and Cockcroft–Gault formulas overall, for participants both with and without diabetes. However, for estimated glomerular filtration rate > 90 ml min⁻¹ 1.73 m⁻², the Chronic Kidney Disease Epidemiology Collaboration formula had greater bias in participants with diabetes, underestimating measured glomerular filtration rate by 7.4 vs. 1.0 ml min⁻¹ 1.73 m⁻² in those without diabetes. The Chronic Kidney Disease Epidemiology Collaboration formula was less accurate across the whole range of estimated glomerular filtration rates in participants with vs. those without diabetes (87.1% vs. 93.3%).

Conclusions The Chronic Kidney Disease Epidemiology Collaboration formula outperforms the Modification of Diet in Renal Disease and Cockcroft–Gault formulas overall in Indigenous Australians with and without diabetes. However, the Chronic Kidney Disease Epidemiology Collaboration formula has greater bias in people with diabetes compared with those without diabetes, especially in those with normal renal function.

Abbreviations CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease

Introduction

The prevalence of diabetes and the incidence of end-stage kidney disease is much higher in Indigenous than in non-Indigenous Australians [1,2]. In order to detect and treat chronic kidney disease, to prevent end-stage kidney disease in this high-risk population, accurate measures of kidney function are necessary. Glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease [3]. As it is cumbersome to measure GFR in routine practice, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) formulas have been developed to estimate GFR. However, the MDRD formula underestimates measured GFR within the normal range and has limited precision [3]. The CKD-EPI formula was developed in an attempt to minimize these limitations and appears to have been successful in substantially reducing the underestimation of GFR in the normal range [4]. Possible factors limiting the universal applicability of the CKD-EPI formula include the under-representation of older people or people from non-Caucasian ethnic groups in the population that the formula was derived from [3]. The Cockcroft–Gault formula estimates creatinine clearance and remains in clinical use for medication dosing decisions, although it was derived and validated prior to the introduction of isotope-dilution mass spectrometry-aligned creatinine assays [5].

Furthermore, the proportion of participants with diabetes was approximately 30% in the population used to derive the CKD-EPI formula [6]. In the pooled CKD-EPI study data set, an estimated GFR (eGFR) calculated from the CKD-EPI formula underestimated measured GFR in people with diabetes by $4.6 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ on average compared with only $1.3 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ in those without diabetes. This greater bias in people with diabetes was especially evident when eGFR was $> 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ [4]. Other studies have also shown that the CKD-EPI formula is less accurate in people with diabetes compared with healthy individuals [7] and that the CKD-EPI, MDRD and Cockcroft–Gault formulas underestimate GFR in patients with diabetes [8,9]. It has even been suggested that the CKD-EPI formula

may not offer any particular advantages over the MDRD formula in people with diabetes [10].

There are no studies that have specifically assessed the performance of eGFR derived from formulas based on serum creatinine in Indigenous Australians with and without diabetes [11]. Aboriginal Australians, and particularly those from remote areas with very high rates of treated end-stage kidney disease, have a light body build (narrow across the shoulders and hips, with relatively long limbs and shorter torso) with relatively less muscle mass for a given BMI than Australians of European origin [12]. Despite these physical differences, our group has demonstrated that an eGFR derived from the CKD-EPI formula (without the African-American correction factor) provides a reasonably unbiased and accurate estimate of GFR overall in the Indigenous Australian population, outperforming the MDRD formula [13]. However, the performance of the CKD-EPI formula in Indigenous Australians with diabetes remains unclear. The aim of this analysis was to assess the performance of the CKD-EPI, MDRD and Cockcroft–Gault formulas in Indigenous Australians with and without diabetes.

Patients and methods

Details of the methods have been previously described [14]. Participants were Indigenous Australians, which include people of Aboriginal and/or Torres Strait Islander background. The definition of ‘Aboriginal and/or Torres Strait Islander’ was according to the standard method used in National Census data collection: ‘(1) is of Aboriginal and/or Torres Strait Islander descent; (2) identifies as an Australian Aboriginal and/or Torres Strait Islander; and (3) is accepted as such by the community in which he or she lives or has lived’ [14].

Participants were recruited between 2007 and 2011 from urban, rural and remote centres (within Central Australia, Northern Territory, Queensland, Western Australia) of Australia across five predefined strata of health, diabetes status and kidney function. These predefined strata were: (1) ‘healthy’ group: with no diabetes, chronic kidney disease or albuminuria; (2)

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participants with diabetes or albuminuria and eGFR (MDRD-4) $> 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$; (3) eGFR $60\text{--}90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$; (4) eGFR $30\text{--}59 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$; (5) eGFR $< 15\text{--}29 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. Participants who received dialysis, women who were pregnant or breastfeeding and those who had a history of allergy to iodine-based contrast media were excluded. The Human Research Ethics Committees of the joint Menzies School of Health Research—Northern Territory Department of Health Human Research Ethics Committee, including approval by the Aboriginal subcommittee; Central Australian Human Research Ethics Committee; Western Australian Aboriginal Health Information and Ethics Committee, Royal Perth Hospital Ethics Committee and Cairns and Hinterland Health Services District Human Research Ethics Committee approved the study.

Reference GFR (mGFR)

Non-isotopic iohexol (300 mgI/ml, Omnipaque; GE Healthcare, Rydalmere, NSW, Australia) was injected (5.445 ml, including 0.445 ml of priming volume in the tubing of the butterfly cannula) into an antecubital vein and flushed with 10 ml of normal saline. Venous blood samples were collected for measurement of iohexol at 120, 180 and 240 min post-injection. Blood samples were refrigerated, centrifuged within 4 h and aliquoted for transportation on ice [or on dry ice or in liquid nitrogen ('Biological Shipper', CryoPak Series, Taylor-Wharton, AL, USA)] in remote locations, prior to storage at $-80 \text{ }^{\circ}\text{C}$ freezer [14].

Slope–intercept GFR was calculated, multiplied by 1.73 and divided by the body surface area [calculated from the formula [15] $\text{body surface area} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$] as described previously [14]. The body surface area–slope intercept GFR value ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) was corrected by the Brochner–Mortensen correction factor = $(0.990778 \times \text{GFR}) - (0.001218 \times \text{GFR}^2)$ [16], providing a reference GFR value (mGFR; $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) [14]. Frozen samples were transported to Austin Health,

Melbourne, and iohexol measured using a validated HPLC assay modified from Niculescu-Duvaz *et al.* [14,17].

Measurement of enzymatic creatinine

Serum creatinine was measured in venous blood collected 120 minutes following iohexol injection. Creatinine was measured by a single laboratory (Melbourne Pathology, Melbourne Australia) using the Roche enzymatic assay. This method had traceability to isotope-dilution mass spectrometry as claimed by the manufacturer and supported by independent studies [18]. Thirteen participants for whom a centralised creatinine result was unavailable were excluded from this analysis.

Estimates of GFR (eGFR)

Estimates of GFR were calculated as using the previously described MDRD, CKD- EPI and Cockcroft–Gault formulas (noting the latter estimates creatinine clearance, in turn an estimate of GFR):

1. MDRD-4 variable formula (for creatinine measurements traceable to the isotope-dilution mass spectrometry method and reported in $\mu\text{mol/l}$):

$$\text{eGFR} = 175 \times [(\text{Scr} \times 0.0113)^{-1.154}] \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American}) \text{ [19]}$$

(where Scr is serum creatinine concentration in $\mu\text{mol/l}$, age in years, eGFR in ml min^{-1}

¹ 1.73 m^{-2}).

2. The CKD-EPI formula [3]:

eGFR = $141 \times \text{minimum} (\text{Scr} \times 0.0113/k, 1)^{\alpha} \times \text{maximum} (\text{Scr} \times 0.0113/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black), where k is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men.

The African-American correction factor in the above formulas was not used for Indigenous Australians [13].

3. The Cockcroft–Gault formula [20]:

Creatinine clearance (ml/min) = $\{[140 - \text{age}] \times \text{weight}/[\text{Scr} \times 0.814]\} \times (0.85 \text{ if female})$, where Scr is serum creatinine concentration in $\mu\text{mol/l}$, age in years, weight in kg.

Measurement of baseline characteristics:

Levels of non-fasting lipids and HbA_{1c} (120 min post-iohexol), a spot urine albumin:creatinine ratio were measured by local pathology services [14]. Diabetes was defined as a self-reported diagnosis of Type 2 diabetes or HbA_{1c} ≥ 48 mmol/mol (6.5%) [21]. The 234 participants with diabetes were diagnosed as follows: 24 by HbA_{1c}, 46 by history and 154 by both HbA_{1c} and history. Microalbuminuria was defined as urine albumin:creatinine ratio ≥ 2.5 and ≤ 25 mg/mmol in men and ≥ 3.5 and ≤ 25 mg/mmol in women.

Macroalbuminuria was defined as albumin:creatinine ratio > 25 mg/mmol [22]. Cigarette smoker was defined by self-report as current smoker, ex-smoker or never smoked.

Statistical analysis

Bias was defined as the median absolute difference between the measured GFR and the estimated GFR (i.e. mGFR–eGFR), and percentage bias as the median percentage difference relative to mGFR. Accuracy was defined as the percentage of eGFR values that fell within 30% of their corresponding mGFR value, and precision as the interquartile range of the

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absolute differences. Confidence intervals were calculated using the binomial exact method for proportions.

The performance of the CKD-EPI, the MDRD and the Cockcroft–Gault formulas was explored separately in participants with or without diabetes. Performance at different levels of eGFR was explored in two ways. Firstly, performance statistics including bias, % bias, precision and accuracy of eGFR formulas are reported for eGFR < 90 ml min⁻¹ 1.73 m⁻² and eGFR > 90 ml min⁻¹ 1.73 m⁻² for MDRD and CKD-EPI formulas (there were only a small number of participants who had eGFR < 60 ml min⁻¹ 1.73 m⁻²; 23 participants without diabetes and 49 participants with diabetes using the CKD-EPI formula). Performance statistics are reported stratified by eGFR < or > 90 ml/min for Cockcroft–Gault formula (with mGFR in ml/min used to assess performance). Secondly, quantile regression using the qreg command in Stata v12.1 (StataCorp., College Station, TX, USA) was used to examine how bias varied as a (cubic) function of eGFR. The function has been plotted across the whole range of eGFR, except for extreme values of eGFR (the lowest 10 and highest 10 values of eGFR).

Results

Participants

In total, 656 Indigenous Australians were recruited to the study. Of these participants, 65 were excluded as they did not have measured GFR, 13 were excluded as they did not have available data for centralized enzymatic creatinine, 13 were excluded because they were less than 18 years of age, and one person was excluded because diabetes status was not able to be determined. Accordingly, 564 Indigenous participants had complete data for this analysis: 224 with diabetes (40%) and 340 without diabetes (Table 1). Participants with diabetes were shorter and had a greater BMI, waist circumference and waist–hip ratio, as well as a higher

frequency of microalbuminuria and macroalbuminuria. There were fewer smokers in participants with diabetes, and participants with diabetes were on average 12 years older than participants without diabetes.

Participants with diabetes had a lower measured/estimated GFR than participants without diabetes, although they also had a greater spread of GFR (Table 1); the median (interquartile range) mGFR in participants with diabetes was 97 (68–119) ml min⁻¹ 1.73 m⁻² and 108 (90–122) ml min⁻¹ 1.73 m⁻² in participants without diabetes. On average, eGFR derived from the CKD-EPI formula was lower than mGFR, while eGFR derived from the MDRD formula was lower still.

CKD-EPI vs. MDRD

The performance of the CKD-EPI and the MDRD formulas in participants with or without diabetes is illustrated in Fig. 1 and summarized in Table 2. For participants with or without diabetes, the CKD-EPI formula performed better than the MDRD formula. In both participants with and without diabetes, the CKD-EPI formula had a smaller bias and greater accuracy than the MDRD formula overall, as well as for the eGFR < 90 and eGFR > 90 ml min⁻¹ 1.73 m⁻² groups. Figure 1 shows that the CKD-EPI formula had a smaller bias than the MDRD formula for participants without diabetes and eGFR between 40 and 110 ml min⁻¹ 1.73 m⁻², as well as for participants with diabetes and eGFR between 30 and 110 ml min⁻¹ 1.73 m⁻².

There was a greater range of the mGFR, CKD-EPI eGFR and MDRD eGFR in Indigenous Australians with diabetes than in those without diabetes (Fig. 1b). There was no correlation between bias and HbA_{1c} in those with diabetes and CKD-EPI > 90 ml min⁻¹ 1.73 m⁻² (Spearman's rho = -0.04).

Bias and accuracy of the CKD-EPI formula

Overall, the CKD-EPI formula underestimated the measured GFR by $7.0 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ in participants with diabetes. The CKD-EPI formula underestimated the measured GFR by 6.2 and $7.4 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ at $\text{eGFR} < 90$ and $> 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ levels, respectively, in participants with diabetes.

Overall, the CKD-EPI formula underestimated the mGFR by $3.3 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ in participants without diabetes. The CKD-EPI formula underestimated the measured GFR by 8.8 and $1.0 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ at $\text{eGFR} < 90$ and $> 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ levels, respectively, in participants without diabetes. Furthermore, there was less accuracy of the CKD-EPI formula in participants with diabetes compared with participants without diabetes (87.1% and 93.5%, respectively, $P = 0.009$). This was also the case for the groups with $\text{eGFR} < 90$ and $> 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$.

Cockcroft–Gault formula

The performance of the Cockcroft–Gault formula is illustrated in Fig. 2 and presented in Table 2. For all participants, the Cockcroft–Gault formula overestimated mGFR (ml/min) by 9.9 ml/min, with no difference in performance for those with or without diabetes. The Cockcroft–Gault formula performed well for participants both with and without diabetes at levels of $< 90 \text{ ml/min}$, with a smaller bias but reduced accuracy for participants with diabetes compared with those without diabetes when Cockcroft–Gault was $< 90 \text{ ml/min}$.

Discussion

There is a large burden of Type 2 diabetes [1] and end-stage kidney disease [2] among Indigenous Australians. Diabetes is the leading cause of end-stage kidney disease in

Australia [23] and, in 2007, 77% of Indigenous Australians commencing dialysis treatment had Type 2 diabetes as a co-morbidity compared with 33% of non-Indigenous Australians [24]. In order to treat chronic kidney disease to prevent end-stage kidney disease, it is necessary to detect kidney disease early. In this study, we have analysed the performance of the Cockcroft–Gault, CKD-EPI and MDRD formulas (without African-American correction factors) in Indigenous Australians with diabetes. We have reported that the CKD-EPI equation outperformed the MDRD and Cockcroft–Gault formulas overall in participants with and without Type 2 diabetes. However, the CKD-EPI equation had a greater bias in people with diabetes than without diabetes, especially in those with $eGFR > 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$.

For participants with or without diabetes, the CKD-EPI formula outperformed the MDRD and Cockcroft–Gault formulas. The CKD-EPI formula had a smaller bias, at least for $eGFR$ in the range $40\text{--}110 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ and had a greater accuracy than the MDRD and Cockcroft–Gault formulas. These findings in Indigenous Australians largely concur with the findings of the CKD-EPI study [4], which showed that the CKD-EPI formula had a smaller bias than the MDRD formula for people with diabetes in the groups with $eGFR < 60/60\text{--}90/\geq 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, and also for people without diabetes in the groups with $eGFR < 60/60\text{--}90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. However, our findings also support the findings of Camargo *et al.*, who similarly found that the CKD-EPI formula was less accurate in people with Type 2 diabetes when compared with healthy individuals [7]. The study by Camargo *et al.* was a small study of 56 patients with Type 2 diabetes and 55 healthy volunteers from a single centre. Furthermore, in that study, creatinine was measured using the Jaffe reaction and, unlike the enzymatic method used in the present study, may be prone to interference from plasma glucose [25].

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For participants with or without diabetes, the relationship between bias and eGFR level in our study using the CKD-EPI formula was broadly similar to that of the CKD-EPI study. In the CKD-EPI study, the bias was also greater in those with diabetes compared with those without diabetes. In people with diabetes, the CKD-EPI formula underestimated measured GFR by 2.6/4.0/12.3 ml min⁻¹ 1.73 m⁻² at eGFR < 60/60–90/> 90 ml min⁻¹ 1.73 m⁻² levels, respectively. In contrast, the underestimation for people without diabetes was only 1.6/4.4 ml min⁻¹ 1.73 m⁻² at eGFR < 60/60–90, with an overestimation of the measured GFR by 3.3 ml min⁻¹ 1.73 m⁻² at eGFR > 90 ml min⁻¹ 1.73 m⁻² [4]. Likewise, when our data were evaluated across the whole eGFR range, the bias was greater in Indigenous Australians with diabetes than in those without diabetes (7.0 vs. 3.5 ml min⁻¹ 1.73 m⁻², respectively), and this was a consistent finding in the > 90 ml min⁻¹ 1.73 m⁻² subgroup. Despite this, the performance of the CKD-EPI formula was superior to that of the MDRD and Cockcroft–Gault formulas in people with and without diabetes, reinforcing the recommended use of the CKD-EPI formula in people with diabetes [3,11].

Participants with diabetes had a lower measured GFR and CKD-EPI eGFR than those without diabetes. Hence, it may be impossible to determine the effect of ‘diabetes’ status per se on the formulas, as it is often difficult to match participants in terms of their diabetes status and other characteristics essential for the formulas. Indeed, we observed a greater range of mGFR in those with diabetes compared with those without diabetes. At the higher end of mGFR, it is likely that this is an effect of hyperfiltration in people with diabetes [26]. Indeed, a recent assessment of 15 creatinine-based formulas in 600 participants with Type 2 diabetes questioned the use of any formula to identify hyperfiltration and monitor progression of kidney disease in those with Type 2 diabetes without overt nephropathy [27].

The strengths of the current study include the measurement of GFR using iohexol clearance, the relatively large number of participants in the high GFR range, the presence of a similar

number of participants with diabetes and participants without diabetes and the use of enzymatic creatinine.

Some of the concerns regarding the use of creatinine in eGFR formulas include issues associated with production of creatinine, excretion and secretion of creatinine and measurement of creatinine. Several factors affect the level of serum creatinine other than GFR, including the generation of creatinine from muscle metabolism; i.e. muscle mass [6]. Aboriginal Australians have a more slender body build than Australians of European origin, with relatively longer limbs and shorter torso [12] and relatively less muscle mass for a given BMI. This could result in lower serum creatinine than for Australians of European origin for a given BMI. However, we have recently reported that eGFR using the CKD-EPI formula provided a reasonably unbiased and accurate estimate of GFR, while the MDRD formula resulted in significant underestimation of GFR in Indigenous Australians [13]. We note that revision of the CKD-EPI equation to include a four-level (rather than two-level) ethnicity variable (including African-American, Asian, Native American, Hispanic) was not recommended for clinical use because of heterogeneity in performance among various ethnic and geographic groups [28].

The use of the CKD-EPI formula, through reclassification of low-risk individuals, has led to a lower estimated prevalence of chronic kidney disease [29]. In people with diabetes and an eGFR < 60 ml min⁻¹ 1.73 m⁻² (Fig. 1), this might provide greater certainty for clinical decision making regarding the need for dose reductions of diabetes medications such as metformin or sitagliptin. This is particularly relevant in disadvantaged communities, including Indigenous Australian communities, where it can be challenging to institute insulin or additional medications for the management of diabetes. Another advantage of the use of the CKD-EPI formula is that there is greater accuracy and lower bias for results of < 90 ml min⁻¹ 1.73 m⁻², which can more accurately alert the clinician to the reduction in eGFR over time. However,

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future studies are necessary in these high-risk populations, in people with and without diabetes, to determine rates and predictors of progression of chronic kidney disease and the clinical utility of the CKD-EPI formula for predicting kidney function loss over time.

The limitations of the study are recognized. Research studies have reported a GFR measurement error of 5–20% variation within a single clearance procedure or between clearance procedures on different days [30,31]. The variation is greater in the higher ranges of GFR on the absolute scale [31]. Furthermore, hydration status and hyperglycaemia can routinely affect the measurement of GFR. Whilst the GFR can be determined precisely by measuring the clearance of inulin [32], the measurement using iohexol is more practical in real-world settings, particularly in remote locations. Another limitation in the current study has also been alluded to by Stevens *et al.* and relates to the populations in which the formulas were derived [6]. There may have been selection bias in those who volunteered to participate in this study; that is, healthier people may choose to participate in studies such as this in general. Furthermore, in the current study, the participants were asked not to have a protein-based meal prior to their non-fasting blood test, which would have minimized the impact of dietary variations, which may have influenced measured creatinine. Creatinine levels can also be affected by drugs [33,34], including the commencement of angiotensin-converting enzyme inhibitors [35]; however, no specific medication changes were made before participation in this study.

In summary, the CKD-EPI formula outperforms the MDRD and Cockcroft–Gault formulas overall in Indigenous Australians with and without diabetes. However, the CKD-EPI formula has a greater bias in people with diabetes compared with those without diabetes, especially in those with normal renal function.

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Funding sources

The eGFR Study was funded by the National Health and Medical Research Council of Australia (NHMRC, project grant no. 545202). The views expressed are those of the authors and do not reflect the views of the NHMRC. Additional support was obtained from Kidney Health Australia, NHMRC no. 320860, the Colonial Foundation, Diabetes Australia Research Trust, Rebecca L. Cooper Foundation and SeaSwift, Thursday Island. LJMB is supported by an Australian NHMRC Early Career Fellowship in Aboriginal and Torres Strait Islander Health Research (no. 605837). EIE is supported by an NHMRC Early Career Fellowship: Health Professional Research Fellowship (part-time, no. 1054312). JTH is supported by NHMRC Scholarship no. 490348, Rio Tinto Aboriginal Fund and the Centre of Clinical Research Excellence in Clinical Science of Diabetes, University of Melbourne. PDL is supported by NHMRC Scholarship no. 1038529. AC holds an NHMRC Principal Research Fellowship no. 1027204, and WEH holds an NHMRC Australia Fellowship no. 511081. Funding bodies had no role in the study design, in the collection, analysis or interpretation of data, in the writing of the manuscript or the decision to submit the manuscript for publication.

Competing interests

None declared.

Acknowledgements

Thanks to participants, study staff and investigators of the eGFR Study. Thanks to Roche Diagnostics for supplying the enzymatic creatinine reagent kits and Melbourne Pathology, Australia for the technical support for the analysis of enzymatic creatinine.

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Table 1 Baseline characteristics of participants

	With diabetes	Without diabetes	<i>P</i> -value†
	<i>n</i> = 224	<i>n</i> = 340	
Age (years)	52 ± 12	40 ± 14	< 0.001
Male	81 (37%)	131 (39%)	0.570
Height (cm)	166 ± 8	167 ± 9	0.013
Weight (kg)	89 ± 22	80 ± 20	< 0.001
BMI (kg/m ²)	32 ± 7	28 ± 7	< 0.001
Waist (cm)*	108 ± 14	96 ± 16	< 0.001
Waist–hip ratio*	0.99 ± 0.09	0.91 ± 0.08	< 0.001
HbA _{1c} [mmol/l, (%)]*	60 (49–77) [7.6 (6.6–9.2)]	39 (36–42) [5.7 (5.4–6.0)]	< 0.001
Normoalbuminuria*	74 (34%)	257 (79%)	< 0.001

Microalbuminuria*	61 (28%)	37 (11%)	< 0.001
Macroalbuminuria*	82 (38%)	30 (9%)	< 0.001
Current smoker	68 (31%)	167 (49%)	< 0.001
Creatinine ($\mu\text{mol/l}$)	72 (57–97)	69 (58–83)	0.057
MDRD eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	84 (61–106)	95 (80–111)	< 0.001
CKD-EPI eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	93 (66–107)	105 (90–116)	< 0.001
Cockcroft–Gault (ml/min)	120 (76–164)	126 (95–158)	0.199
mGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	97 (68–119)	108 (90–122)	< 0.001
mGFR (ml/min)	109 (73–139)	114 (94–136)	0.083

Data are summarized as mean \pm standard deviation, median (interquartile range) or n (%).

Microalbuminuria was defined as urine albumin:creatinine ratio ≥ 2.5 and ≤ 25 mg/mmol in men and ≥ 3.5 and ≤ 25 mg/mmol in women; macroalbuminuria was defined as albumin:creatinine ratio > 25 mg/mmol.

*Because of missing data, the number of each group for the following variables was: waist, 212, 330; waist–hip ratio, 209, 330; HbA_{1c}, 217, 332; albuminuria, 217, 324.

† P -values calculated using t -test for normally distributed continuous variables (those presented as mean \pm standard deviation), Mann–Whitney U -test for other continuous variables and χ^2 -test for categorical variables.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease.

Table 2 Comparison of performance of eGFR (MDRD and CKD-EPI) and Cockcroft–Gault formula to reference GFR in Indigenous Australians with and without diabetes overall, stratified by eGFR above and below 90 ml min⁻¹

¹ 1.73 m⁻² (90 ml/min for Cockcroft–Gault)

	All participants				eGFR* ≤ 90			eGFR* > 90		
		Diabetes	No diabetes	P-value	Diabetes	No diabetes	P-value	Diabetes	No diabetes	P-value
MDRD	<i>n</i>	224	340		122	145		102	195	
	Bias	8.8 (6.4–10.7)	9.0 (7.1–12.9)	0.390	9.3 (6.8–12.3)	16.3 (13.7–19.1)	0.015	7.2 (4.2–11.1)	5.8 (3.4–8.0)	0.994
	% bias	9.6 (8.0–13.9)	9.9 (7.4–12.7)	0.903	16.8 (13.1–20.8)	19.2 (16.8–20.8)	0.444	6.1 (3.4–8.7)	5.2 (3.0–6.8)	0.923
	Precision	24.1 (–1.9 to 22.1)	22.9 (–0.4 to 22.5)	0.785	22.1 (0.4–22.5)	20.0 (4.9–24.9)	0.509	28.8 (–9.8 to 19.0)	21.4 (–4.2 to 16.6)	0.223
	Accuracy	79.5 (73.6–84.6)	88.8 (85.0–92.0)	0.002	74.6 (65.9–82.0)	82.1 (74.8–87.9)	0.137	85.3 (76.9–91.5)	93.8 (89.5–96.8)	0.015
	% < –30%	5	3		2	1		9	4	
% > 30%	15	9		23	17		6	2		
CKD-EPI	<i>N</i>	224	340		103	86		121	254	
	Bias	7.0 (5.1–8.6)	3.3 (1.3–6.4)	0.006	6.2 (1.7–8.3)	8.8 (5.6–12.7)	0.061	7.4 (5.2–12.4)	1.0 (–2.1 to 3.0)	<0.001
	% bias	8.5 (5.2–11.2)	3.5 (1.3–6.9)	0.001	11.9 (3.4–15.4)	11.5 (8.4–15.0)	0.419	6.2 (4.6–10.5)	0.8 (–1.7 to 2.8)	<0.001
	Precision	22.3 (–3.1 to 19.3)	20.0 (–6.4 to 13.6)	0.209	18.0 (–3.1 to 14.8)	15.6 (0.85–16.4)	0.450	26.0 (–3.0 to 22.9)	21.4 (–8.8 to 12.6)	0.208
	Accuracy	87.1 (81.9–	93.3 (90.4 to	0.009	81.6 (72.7–	86.0 (76.9–	0.406	91.7 (85.3–	96.1 (92.9–	0.089

		91.2)	95.9)		88.5)	92.6)		96.0)	98.1)	
	% < -30%	4	3		7	1		2	4	
	% > 30%	8	4		12	13		6	0	
Coc croft- Gault	N	224	340							
	Bias	-10.5 (-14.9 to -6.7)	-9.9 (-11.7 to -6.0)	0.6 13	0.3 (-3.9 to 3.1)	3.2 (1.2-7.6)	0.03 2	-20.3 (-24.5 to -15.8)	-15.1 (-20.1 to -11.2)	0.12 0
	% bias	-11.0 (-15.4 to -8.3)	-9.6 (-11.9 to -6.4)	0.3 38	0.5 (-6.5 to 9.1)	5.4 (1.5-12.2)	0.06 9	-16.4 (-22.7 to -11.3)	-12.6 (-17.1 to -9.9)	0.13 1
	Precision	34.1 (-31.1 to 3.0)	33.2 (-30.0 to 3.2)	0.9 28	15.2 (-6.4 to 8.8)	18.2 (-2.9 to 15.3)	0.49 7	39.5 (-42.1 to -2.6)	35.4 (-35.9 to -0.6)	0.46 8
	Accuracy	71.4 (65.0 to 77.2)	77.4 (72.5-81.7)	0.1 12	84.1 (73.3-91.8)	93.7 (84.5-98.2)	0.08 3	65.8 (57.8 to 73.2)	73.6 (68.0-78.7)	0.08 6
	% < -30%	27	21		12	4		34	26	
	% > 30%	2	1		2	5		1	1	

*Definition varies according to whether results relate to use of the MDRD, CKD-EPI or Cockcroft-Gault formula

(see first column). Units for eGFR and mGFR are $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ for results relating to MDRD and CKD-EPI, and ml/min for those relating to Cockcroft-Gault.

Bias and % bias are median (95% CI), Precision is interquartile range of the bias (25th, 75th percentile of the bias),

Accuracy is % of eGFR within 30% of reference GFR (95% CI). '% < -30%' is the % of eGFR below 30% of reference GFR, '% > 30%' is the % of eGFR above 30% of reference GFR.

Bias is (mGFR-eGFR); % bias is the median percentage difference relative to mGFR; and precision is the interquartile range of the absolute differences.

P-values were calculated using the Mann-Whitney *U*-test for bias and % bias, interquartile range regression for precision, χ^2 -test for accuracy.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease.

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Figure 1 Performance of the CKD-EPI and MDRD formulas in Indigenous Australians with and without diabetes, by eGFR level. (a) Data inside the wedge are 'accurate' (i.e. within 30% of measured GFR). The thick lines shows the modelled (see Methods) bias. (b) The thick lines from the top panel have been overlaid onto the same graph. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Figure 2 Performance of the Cockcroft–Gault formula in Indigenous Australians with and without diabetes, by Cockcroft–Gault level (ml/min). (a) Data inside the wedge are 'accurate' (i.e. within 30% of measured GFR). The thick lines shows the modelled (see Methods) bias. (b) The thick lines from the top panel have been overlaid onto the same graph. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

