Accurate Assessment of Kidney Function in Indigenous Australians: the eGFR Study

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The incidence of end-stage kidney disease (ESKD) is up to 15 times higher in Indigenous than non-Indigenous Australians[1, 2], with the burden of ESKD in Indigenous Australians borne disproportionately by those in central and northern Australia.[3] This group of people is widely dispersed and heterogeneous, with wide variation in diet, body habitus, ethnic admixture and socioeconomic background.[4, 5] Aboriginal Australians traditionally had a 'linear' body build (narrow across the shoulders and hips, relatively long limbs and short torso), which in contrast to African Americans is associated with proportionately less muscle and more fat for a given weight.[4, 6] We hypothesised that: (i) the African American correction factor in estimated Glomerular Filtration Rate (eGFR) equations should not be used in Indigenous Australians; and (ii) differences in body build and body composition in Indigenous Australians will affect the utility of creatinine-based estimated measures of GFR. The aim of "The eGFR Study" was therefore to validate and improve if necessary the accuracy and precision of eGFR equations in Indigenous Australians.

The methods (Item S1) have been previously described in detail[8]. Participants were Indigenous Australians aged 18 years and above, recruited from urban, rural and remote centres within four geographical regions of Australia across five pre-defined strata of health, diabetes status and kidney function. A comparator group of Caucasian Australians was recruited from Darwin, Northern Territory, Australia. GFR was measured (mGFR) using an iohexol plasma disappearance technique over 4 hours. Estimates of GFR were calculated using the MDRD-4 and CKD-EPI equations[9]. Data analysis was performed using STATA v10.0 (Stata Corporation, TX, USA).

When compared to Caucasian participants, Indigenous participants were younger, with higher rates of albuminuria, diabetes and cigarette smoking (Table 1). Indigenous participants had equal or higher levels of eGFR and mGFR than Caucasians.

In Indigenous participants (Figure 1), use of the African American correction factor resulted in overestimation of GFR using both MDRD-4 and CKD-EPI equations. Without the African American correction factor, the median bias was greater using the MDRD-4 equation (8.9 [95%CI, 7.9 to 11.1] below mGFR) than with use of the CKD-EPI equation (3.8 [95% CI, 2.5 to 5.6] below mGFR). When stratified by mGFR group (Table S1), bias was highest in Indigenous participants with mGFR≥90mls/min/1.73m^2 when the MDRD-4 equation was used but improved with use of the CKD-EPI equation (without the correction factor). Accuracy of eGFR was not significantly different between use of MDRD-4 or CKD-EPI equations, for Indigenous and Caucasian participants.

Thus, we report that the magnitude of bias using the MDRD-4 equation in Indigenous participants was similar with or without use of the African American correction factor for Indigenous Australians, however the direction of bias differed, such that GFR was overestimated with use of the correction factor and underestimated without it. For the CKD-EPI equation, bias and accuracy were significantly improved with omission of the correction facotr.

With omission of African American correction factor, eGFR using the CKD-EPI equation provided a reasonably unbiased and accurate estimate of GFR, while the MDRD-4 equation

resulted in significant underestimation of GFR in Indigenous Australians (compared to a Caucasian Australian comparator group). This may relate to inherent limitations of the MDRD-4 equation rather than body build or other differences in Indigenous Australians. The CKD-EPI equation has been shown to perform better at higher mGFRs (approximately >60ml/min/1.73m^2) and the MDRD performs better at lower GFRs.[10] The mean mGFR of the Indigenous Australian cohort (93 ml/min/1.73m^2) was closer to that of the CKD-EPI than MDRD development cohort and this most likely explains why the CKD-EPI equation performed better than the MDRD-4 equation.[7, 9] Heterogeneity and ethnic admixture among the Indigenous Australian population makes the application of a single accurate correction factor for Indigenous Australians in the eGFR equation unlikely and impractical. Similar concerns about the limitations of the race coefficient used in North America have been recently raised.[11]

A potential limitation of our study is the use of iohexol clearance as the formal GFR measurement.[8] The study was designed with respect to what is practical and achievable in very remote regions of Australia. Collection over a time period longer than 4 hours was not practical, and this may explain reduced accuracy of eGFR in participants with reduced GFR.[12] The Indigenous and Caucasian Australian groups were not able to be matched for key factors such as age, GFR, diabetes diagnosis and albuminuria (due to population differences such as younger age of onset of chronic diseases and higher prevalence of diabetes as a comorbidity among Indigenous Australians with ESKD). However the Caucasian group was not intended to be a matched group, but a group in which the performance of eGFR equations could be assessed in comparison to other studies from North America, Europe and Australia, thereby supporting the reference GFR methodology used in the current study. Participants were volunteers, recruited

across five strata of health, diabetes status and kidney function, and we are unable to comment on how representative they are of their respective communities and ethnic groups. The majority of participants did not have CKD.

In conclusion, eGFR using the CKD-EPI equation (without the African American correction factor) provides a reasonably unbiased and accurate estimate of GFR in Indigenous Australians. These results support the proposed change to use of the CKD-EPI equation for routine reporting of eGFR in Australia.[13]

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Table 1: Characteristics of Participants. Data are mean ± standard deviation or n (%).

	All Participants		**Group 1: GFR<60**		**Group 2: GFR 60-89**		**Group 3: GFR≥90**		**p values**	
	Indigenous Australian	**Caucasian Australian**	**Indigenous Australian**	**Caucasian Australian**	**Indigenous Australian**	**Caucasian Australian**	**Indigenous Australian**	**Caucasian Australian**	Ethn-icity	GFR group
n	*576*	*99*	*72*	*20*	*115*	*32*	*389*	*47*		
Age (yrs)	45 ± 15	54 ± 14	59 ± 12	62 ± 14	53 ± 13	61 ± 11	40 ± 12	47 ± 13	**<0.001**	**<0.001**
Male*	217 (38%)	45 (45%)	23 (32%)	14 (70%)	43 (37%)	14 (44%)	151 (39%)	17 (36%)	0.194	0.530
Height (cm)	167 ± 8	169 ± 8	164 ± 7[†]	171 ± 9	167 ± 8	170 ± 8	167 ± 8	168 ± 8	-	-
Weight(kg)	83 ± 21	83 ± 18	78 ± 21	84 ± 19	81 ± 23	84 ± 16	85 ± 20	82 ± 19	0.879	**0.029**
BMI(kg/m^2)	30.0 ± 7.2	29.0 ± 5.7	28.9 ± 7.4	29.0 ± 6.0	29.1 ± 7.7	29.1 ± 5.4	30.5 ± 6.9	29.0 ± 5.9	0.337	0.117
Waist (cm)	101 ± 16	98 ± 17	102 + 15	103 ± 18	100 + 17	99 ± 15	101 + 16	95 ± 18	0.156	0.365
WHR	0.94 ±0.09	0.92 ±0.11	0.98 ±0.09	0.99 ±0.11	0.94 ±0.10	0.93 ±0.10	0.93 ±0.09	0.89 ±0.11	0.058	**<0.001**
Microalb-uminuria	101 (18%)	10 (10%)	13 (19%)	5 (25%)	21 (20%)	2 (6%)	67 (18%)	3 (7%)	**0.001**	**<0.001**
Macroalb-uminuria	116 (21%)	11 (11%)	48 (72%)	8 (40%)	26 (24%)	2 (6%)	42 (11%)	1 (2%)	**<0.001**	**<0.001**
Diabetes	234 (41%)	26 (26%)	51 (73%)	9 (45%)	53 (46%)	10 (31%)	130 (34%)	7 (15%)	**0.002**	**<0.001**
Current smoker	239 (42%)	12 (12%)	18 (25%)	0	33 (29%)	4 (13%)	188 (48%)	8 (17%)	**<0.001**	**<0.001**
Creatinine (umol/L)*	75 (72-77)	85 (77-93)	156 (139-175)	177 (145-216)	80 (76-84)	75 (70-81)	64 (63-66)	67 (63-72)	**0.002**	-
eGFR (MDRD)	82 (79-86)	70 (63-77)	33 (29-37)	31 (25-39)	73 (70-77)	78 (72-84)	101 (99-104)	92 (87-98)	**<0.001**	-
eGFR (MDRDbl)	100 (96-104)	70 (63-77)	40 (35-45)	31 (25-39)	89 (85-93)	78 (72-84)	123 (120-125)	92 (87-98)	**<0.001**	-
eGFR (CKD-EPI)*	88 (85-92)	76 (69-84)	36 (31-41)	33 (26-41)	83 (79-86)	85 (79-91)	107 (105-108)	100 (96-105)	**0.001**	-
eGFR (CKD-EPIbl)	103 (99-106)	76 (69-84)	42 (36-48)	33 (26-41)	96 (92-100)	85 (79-91)	123 (122-125)	100 (96-105)	**<0.001**	-
mGFR	93 (89-96)	76 (69-83)	37 (33-41)	34 (28-41)	78 (76-80)	78 (75-81)	116 (114-117)	105 (101-109)	**<0.001**	-

GFR data are presented as ml/min/1.73m^2. Groups defined according to mGFR.
p values refer to overall differences across groups using analysis of variance (continuous variables) and logistic regression models (categorical variables). Comparison group for microalbuminuria and macroalbuminuria is participants with normoalbuminuria. Comparison of creatinine, eGFR and mGFR was performed only between all Indigenous and Caucasian participants, not by mGFR strata.
†p<0.05 compared to Caucasian group of same mGFR group for variables where there was a significant interaction between ethnicity and mGFR group.
Significant interaction between ethnicity and mGFR group for height only (p=0.027).
eGFR, estimated glomerular filtration rate; BMI, body mass index; WHR, waist-hip ratio; ACR, albumin-creatinine ratio.
*log transformed.
eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MDRDbl, MDRD with Afircan American correction factor; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration, CKD-EPIbl, CKD-EPI with African American correction factor.
Diabetes was defined as a previous diagnosis of diabetes or HbA1c≥6.5%. Microalbuminuria was defined as urine ACR ≥2.5 and ≤25 mg/mmol in men and ≥3.5 and ≤25 mg/mmol in women. Macroalbuminuria was defined as ACR > 25mg/mmol.
Number of participants with missing data:
eGFR<60: Indigenous, waist (4), WHR (4), urine ACR (5), diabetes (2), smoking (1).
eGFR 60-89: Indigenous, waist (1), WHR (2), urine ACR (8), diabetes (1), smoking (3).
eGFR≥90: Indigenous, waist (17), WHR (19), urine ACR (12), diabetes (4), smoking (1); Caucasian, waist (1), WHR (1), urine ACR (2).

Figure 1: Differences between reference and estimated glomerular filtration rate (GFR), for estimating equations, according to the level of estimated GFR, by ethnicity.

Caucasian participants (■), Indigenous participants (○). Dashed lines eGFR +/- 30% different from mGFR. The +/- 30% lines are not evenly spaced above and below the x-axis as they indicate percent difference relative to mGFR rather than eGFR which is used on the x-axis.

A: MDRD (without African American correction factor)
Median bias: Caucasian, 3.4 (-0.2, 6.3); Indigenous, 8.9 (7.9, 11.1).
Accuracy (P30): Caucasian, 87 (79-93); Indigenous, 85 (82-88).

B: CKD-EPI (without African American correction factor)
Median bias: Caucasian, -1.9 (-5.5, 1.4); Indigenous, 3.8 (2.5, 5.6).
Accuracy (P30): Caucasian, 87 (79-93); Indigenous, 88 (85-90).

C: MDRD (with African American correction factor)
Median bias: Caucasian, 3.4 (-0.2, 6.3); Indigenous, -8.3 (-10.0, -5.7).
Accuracy (P30): Caucasian, 87 (79-93); Indigenous, 81 (78-84).

D: CKD-EPI (with African American correction factor)
Median bias: Caucasian, -1.9 (-5.5, 1.4); Indigenous, -10.4 (-11.9, -8.0).
Accuracy (P30): Caucasian, 87 (79-93); Indigenous, 79 (75-82).

Table S1: Comparison of performance of eGFR (MDRD and CKD-EPI) to reference GFR in different ethnic groups

Item S1: online supplementary methods