RESEARCH ARTICLE

REVISED Ultrasound appearance of the kidney among radiology department attendees of a tertiary centre in Malawi [version 2; peer review: 2 approved]

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Abstract

Background: Diagnostic and therapeutic decisions in nephrology in low-resource settings are frequently based on ultrasound assessment of kidney size. An understanding of reference values is critical, particularly given the rise of non-communicable disease and the expanding availability of point-of-care ultrasound. However, there is a paucity of normative data from African populations. We determined estimates of kidney ultrasound measures, including kidney size based on age, sex, and HIV status, among apparently healthy outpatient attendees of Queen Elizabeth Central hospital radiology department, Blantyre, Malawi.

Methods: We performed a cross-sectional cohort study of 320 adults attending the radiology department between October 2021 and January 2022. Bilateral kidney ultrasound was performed on all participants using a portable Mindray DP-50 machine and a 5MHz convex probe. The sample was stratified by age, sex, and HIV status. Predictive linear modelling was used to construct reference ranges for kidney size estimating the central 95 percentiles of 252 healthy adults. Exclusion criteria for the healthy sample were known kidney disease, hypertension, diabetes, BMI > 35, heavy alcohol intake, smoking and ultrasonographic abnormalities.

Results: There were 162/320 (51%) male participants. The median age was 47 (interquartile range [IQR] 34-59). Among people living with HIV

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134/138 (97%) were receiving antiretroviral therapy. Men had larger average kidney sizes: mean 9.68 cm (SD 0.80 cm), compared to 9.46 cm (SD 0.87 cm) in women (p = 0.01). Average kidney sizes in people living with HIV were not significantly different from those who were HIV-negative, 9.73 cm (SD 0.93 cm) versus 9.58 cm (SD 0.93 cm) (p = 0.63).

Conclusions: This is the first report of the apparently healthy kidney size in Malawi. Predicted kidney size ranges may be used for reference in the clinical assessment of kidney disease in Malawi.

Keywords
Ultrasound, Imaging, Africa, Malawi, kidney size, HIV

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REVISED **Amendments from Version 1**

Specific changes to the revised version include:

1. Reasons for stratification by HIV status
2. Further detail on ultrasound methods and quality control
3. Table 1, Table 3 and Table 4 have been presented stratified by sex
4. Limitations include absence of kidney function testing (due to resource constraints)
5. Limitations include potential confounding of the healthy sample with diabetes, pre-existing kidney disease and hypertension
6. Limitations include relatively small sample size for predicting kidney size by age category and sex
7. We refer specifically to practices in Malawi, or African populations rather than low resource settings or Sub-Saharan Africa
8. Further detail on how selection bias was minimised

Any further responses from the reviewers can be found at the end of the article

Introduction

Patients with kidney failure routinely undergo ultrasonography as part of their assessment. In Malawi when laboratory tests for kidney function are delayed or unavailable, therapeutic decisions are frequently made on ultrasound assessment. Kidney ultrasound is standard practice in Malawi as part of the assessment of acute kidney injury to identify chronic damage in the face of competition for dialysis beds. Patients with evidence of chronic kidney impairment are unlikely to be prioritized for kidney replacement therapy. Therefore, in Malawi, abnormal kidney size and appearance on ultrasound is often used as a surrogate marker for chronic kidney disease.

An understanding of reference kidney size values is critical, particularly given the rise of non-communicable disease and the expanding availability of point-of-care ultrasound in the region. A number of studies have reported reference values for kidney size in healthy adults measured by ultrasonography[1–4]. Data on ultrasound kidney size measurements for Africa, however, are scarce. Furthermore, there are established physiological differences between populations which underlie the need for population-based estimates for examining kidney size. For example, for the same height, the vital capacity and the forced expiratory volume in one second are about 14% smaller in adults of African lineage compared to Caucasian and Asian populations[5]. The purpose of this study was to investigate the normal ultrasound measurements of the kidney among adults in Malawi.

Methods

Queen Elizabeth Central Hospital (QECH) is a 1,300-bed government hospital providing free healthcare to Blantyre. QECH is the largest tertiary and teaching hospital in the country which manages severe trauma cases from the Southern and Eastern regions, and less severe cases from areas located near the hospital[6]. Malawi is a low-income country in South-East Africa, with an estimated adult HIV prevalence of 9%[7].

At QECH, we performed a cross sectional study of adults (≥18 years) attending the radiology department for any imaging modality, mostly relating to accidents and injury. Patients were approached for recruitment, Monday-Friday, 0700-1700. Exclusion criteria were people lacking capacity to consent with no proxy consent available. Radiology department attendees for imaging after accidents were targeted as they are less likely to have pre-existing kidney pathologies compared to other groups within the hospital. The sample was stratified by age, sex, and HIV status. The sample was stratified by HIV status to enable a separate reference range for those living with HIV.

Sampling and laboratory methods

Point-of-care HIV testing was done for those with unknown status or no recent negative test. Data on serum creatinine or estimated glomerular filtration rate were not available.

Ultrasound

Bilateral kidney ultrasound was performed by departmental sonographers experienced in performing kidney ultrasound, using a portable Mindray DP-50 machine and a 5MHz convex probe. For each individual, we evaluated the left and right kidney size, presence of hydronephrosis, loss of corticomedullary differentiation, echogenicity, and any other significant abnormality (such as cysts or pyonephrosis).

The examination was performed with the patient supine and the longitudinal dimensions of the kidneys were visually estimated to represent the largest longitudinal section. Quality control was performed before and after initiation of the study by experts to assess adequate image quality. Prior to commencement, a series of test images were reviewed by two experts for quality of view, detection of abnormalities and accuracy of length measurement. Where there was disparity, feedback was given to sonographers and further training in image acquisition. On data completion, 10% images were randomly selected for external review with expert opinion taken as the 'gold standard' against which to benchmark the accuracy of the sonographers' measurements. Images with insufficient quality as deemed by experts were rejected (n=4).

Because kidney length is related to body height, the relative kidney length was calculated using the kidney length: body height ratio (KBR) by dividing the absolute kidney length (millimetres) by the body height (centimetres) for each kidney[3].

Exclusion

For normal size range estimates, to represent a 'healthy' population as closely as possible, participants were excluded after recruitment if they reported diabetes, current heavy smoking (> 20 cigarettes/day) or heavy alcohol intake (> 50 alcohol drinks/week), and if body mass index (BMI) > 35. Data did not contribute to normal range estimates where there were significant imaging abnormalities;

hydronephrosis, suspected pyonephrosis, and loss of corticomedullary differentiation.

Statistical analysis

Statistical analyses were performed using R version 4.0.2[8]. Summary statistics were calculated for the cohort, described using either median and interquartile range (IQR) or mean and standard deviation for continuous variables depending on data distribution, and proportions for categorical variables. Two-sample t-tests or non-parametric tests, depending on data distribution, were used to compare variables between groups.

To generate estimates of expected mean kidney size, predictive linear modelling was used to estimate the central 95th percentile for mean kidney size based on age and sex. To quantify the uncertainty of the lower and upper limits of these ranges, we fitted the same linear model to 1,000 bootstrap samples of the healthy dataset. Bootstrapped 95% confidence intervals were then constructed around the upper and lower limits of the prediction interval. Finally, a linear model was used to generate model fits of kidney size across the age ranges according to both sex and HIV status.

Sample size

The known mean kidney bipolar length in adult males in the USA is 12.40 cm with a standard deviation of 0.90 cm[9]. We aimed to estimate the bipolar length in the Malawi population with a margin of error of 0.15 cm using the following formula, where n is the sample size, $z^2_{a/2}$ = 1.96 (95% confidence level), $\sigma^2 = 0.90$ and $d = 0.15$ cm.

$$n = \frac{(z^2_{a/2} x \sigma^2)}{d^2} = \frac{(1.96^2 x 0.9^2)}{0.15^2} = 138$$

The number needed was inflated to 160 to cover for 15% unusable data. To recruit 50:50 HIV positive to negative, the total sample size was 320.

Results

Between 27 October 2021 and 31 January 2022, 320 participants were recruited. The study flow chart is summarised in Figure 1. Table 1 summarises the baseline characteristics of the participants. There were 162/320 (51%) male participants. The median age was 47 (interquartile range [IQR]34-59). Of those whose HIV status was positive, 138/320 (43%), 134/138 (97%) were receiving antiretroviral therapy. Tuberculosis (TB) history was known for 317/320, 303/320 (95%) had no prior TB history, 8/320 (3%) either received prior treatment or were receiving current treatment for TB, and 6/320 (2%) were diagnosed but never treated.

Social characteristics, symptoms, and reasons for attending the radiology department are shown in Table 2.

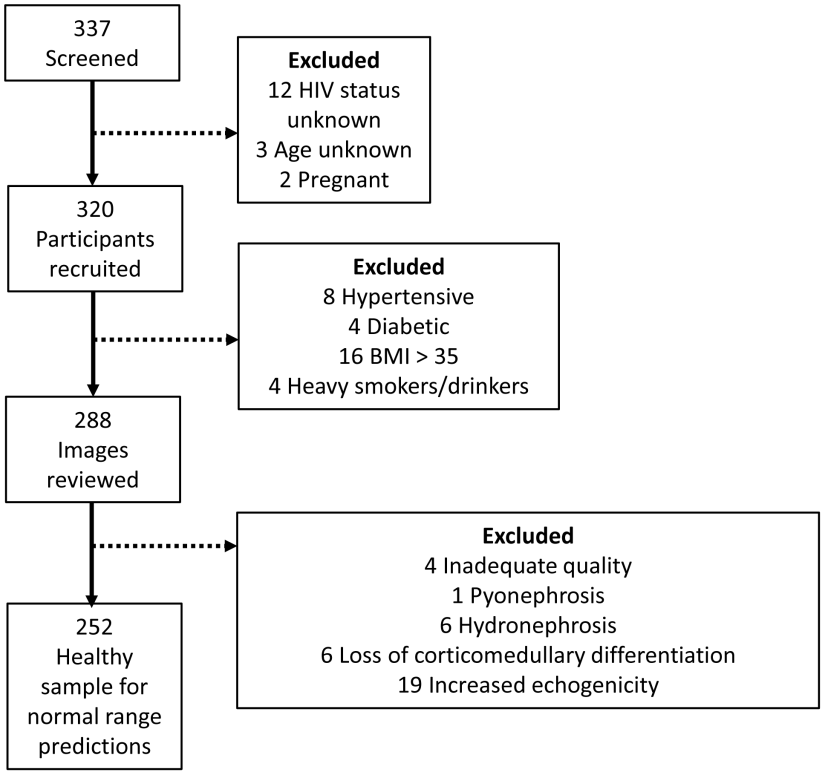

Figure 1. Study flow diagram demonstrating the number of participants recruited and selected for the healthy sample for normal range predictions.

Table 1. Baseline characteristics of participants.

TABLE 1: Baseline characteristics of included participants			
	All (n = 320)	**Female (n=158)**	**Male (n=162)**
Age (years), median (IQR)	47 (34-59)	47 (36-59)	48 (33-57)
HIV positive, n (%)	138/320 (43%)	61/158 (39%)	77/162 (48%)
HIV status unknown, n (%)	12/320 (4%)	6/158 (4%)	6/162 (4%)
Antiretroviral therapy			
TDF/3TC/DTG, n (%)	125/138 (91%)	50/61 (82%)	75/77 (97%)
TDF/3TC/EFV, n (%)	6/138 (4%)	6/61 (10%)	0/77 (0%)
AZT/3TC/LPVr, n (%)	1/138 (1%)	0/61 (0%)	1/77 (1%)
ABC/3TC/DTG, n (%)	1/138 (1%)	0/61 (0%)	1/77 (1%)
AZT/3TC/ATVr, n (%)	1/138 (1%)	1/61 (2%)	0/77 (0%)
Not taking antiretroviral therapy, n (%)	4/138 (3%)	4/61 (7%)	0/77 (0%)
Comorbidities			
No TB history, n (%)	303/320 (95%)	149/158 (94%)	154/162 (95%)
Treated TB, n (%)	8/320 (3%)	4/158 (3%)	4/162 (2%)
Untreated TB, n (%)	6/320 (2%)	3/158 (2%)	3/162 (2%)
TB history not known, n (%)	3/320 (1%)	2/158 (1%)	1/162 (1%)
Hypertension, n (%)	8/320 (3%)	5/158 (3%)	3/162 (2%)
Hypertension unknown, n (%)	0/320 (0%)	0/158 (0%)	0/162 (0%)
Diabetes, n (%)	4/320 (1%)	2/158 (1%)	2/162 (1%)
Diabetes unknown, n (%)	19/320 (6%)	12/158 (8%)	7/162 (4%)
Medications			
No medication/unknown, n (%)	306/320 (96%)	151/158 (96%)	155/162 (96%)
NSAIDS, n (%)	10/320 (3%)	4/158 (3%)	6/162 (4%)
Thiazides, n (%)	3/320 (1%)	3/158 (2%)	0/162 (0%)
ACE inhibitors, n (%)	1/320 (0%)	0/158 (0%)	1/162 (1%)

TDF = tenofovir, 3TC = lamivudine, EFV = efavirenz, AZT = zidovudine, LPVr = lopinavir/ritonavir, ABC = abacavir, DTG = dolutegravir, ATVr = atazanavir/ritonavir, NSAIDS = nonsteroidal anti-inflammatories.

Place of residence was known in 296/320, 218/320 (68%), reported living in an urban locality, 78/320 (24%) reported living rurally. proximity to the lake was known in 240/320, 14/320 (4%) reported living near Lake Malawi, where schistosomiasis is endemic.

Physiology and ultrasound variables are provided in Table 3. The prevalence of hydronephrosis, increased echogenicity and loss of corticomedullary differentiation was low (2–6%). The mean size of the right kidney was 9.38 cm (SD 0.98 cm) in women, and 9.61 cm (SD 0.93 cm) in men. The mean size of the left kidney was 9.54 cm (SD 0.97 cm) in women and 9.76 cm (SD 0.90 cm) in men. Men had larger average kidney sizes: mean 9.68 cm (SD 0.80 cm), compared to 9.46 cm (SD 0.87 cm) in women (p = 0.01). Average kidney sizes in HIV-positive participants were not significantly different from those who were HIV negative, 9.73 cm (SD 0.93 cm) versus 9.58 cm (SD 0.93 cm) (p = 0.63).

Absolute and relative kidney lengths are shown in Table 4. Absolute average (left and right) kidney lengths by sex and predicted range estimates with 95% confidence interval and bootstrapped upper and lower 95% prediction interval are shown in Table 5. The residuals plot for the multivariable

Table 2. Table of social characteristics, symptoms, and reason for attending radiology department.

Social	
Current smoker, n (%)	15/320 (5%)
Smoking unknown, n (%)	23/320 (7%)
Drinks alcohol, n (%)	62/320 (19%)
Alcohol intake unknown, n (%)	22/320 (7%)
Occupation	
Professionals, n (%)	45/320 (14%)
Sales and services, n (%)	13/320 (4%)
Craft and related trades, n (%)	11/320 (3%)
Labourer, n (%)	7/320 (2%)
Service workers, n (%)	6/320 (2%)
Armed forces, n (%)	5/320 (2%)
Agriculture, n (%)	5/320 (2%)
Machine operators, n (%)	3/320 (1%)
Legislators/officials/managers, n (%)	2/320 (1%)
Other/no occupation, n (%)	223/320 (70%)
Place of residence	
Urban, n (%)	218/320 (68%)
Rural, n (%)	78/320 (24%)
Unknown, n (%)	24/320 (8%)
Reason for attending	
Fall, n (%)	98/320 (31%)
Road traffic accident, n (%)	59/320 (18%)
Assault, n (%)	22/320 (7%)
Bike injury, n (%)	5/320 (2%)
Collapsed structure, n (%)	3/320 (1%)
Burn, n (%)	1/320 (0%)
Other, n (%)	132/320 (41%)
Symptoms	
None, n (%)	287/320 (90%)
Abdomen/Lower back pain, n (%)	8/320 (3%)
Fever, n (%)	6/320 (2%)
Chest pain, n (%)	3/320 (1%)
Cough, n (%)	2/320 (1%)
Headache, n (%)	2/320 (1%)
Other, n (%)	9/320 (3%)
Unknown, n (%)	3/320 (1%)
Imaging	
X-ray, n (%)	192/320 (60%)
Ultrasound, n (%)	106/320 (33%)
Other, n (%)	22/320 (7%)

model is in the GitHub repository (*Extended data*)[10]. Figure 2 and Figure 3 show the kidney size range estimates dependent on age, sex, and HIV status.

Discussion

This is the first report of ultrasound appearances of normal kidneys in a Malawian population. In our cohort, kidneys were larger in males compared to females. Prevalence of ultrasound abnormalities such as hydronephrosis, increased echogenicity and loss of corticomedullary differentiation was low. Kidney size was not significantly different in people living with HIV versus those without HIV, meaning the table of predicted ranges can be applied to both groups. This may be related to the successful scale up and subsequent high antiretroviral therapy coverage in our cohort, 97% (134/138), compared to the subnational estimate of 92% for Blantyre[11].

We found kidney sizes in our Malawi cohort to be smaller than in a Nigerian population, which reported 10.20 cm (SD 0.81 cm) and 9.85 cm (SD 0.90 cm) for left and right kidneys[12]. We also found kidney sizes in Malawi to be smaller than populations outside of SSA. For example, in the US the mean kidney bipolar length on ultrasound has been reported as 11.20 cm and 11.00 cm for left and right kidneys[9], in Kuwait 10.71 cm (SD 1.00 cm) cm and 10.68 cm (SD 1.40 cm) for left and right kidneys[2], and in Copenhagen, 11.20 cm and 10.90 cm for left and right kidneys[1].

These differences may be explained, in part, by population differences in height; however very few studies report relative kidney size, and none in Africa. After accounting for height using kidney length: body height ratio (KBR) our data suggest smaller relative kidney sizes among Malawians compared to European populations. For example, data from Croatia suggest KBRs in adults younger than 60 without kidney disease, are between 0.60 and 0.74 for the left kidney and 0.57 to 0.72 for the right kidney[3]. In a Swiss autopsy series of 635 adults without diabetes or known kidney disease, mean (standard deviation) KBRs were 0.67 (0.07) for men and 0.69 (0.07) for women[13].

There were limitations to our study. We were unable to measure kidney function to confirm absence of pre-existing kidney disease. However, we excluded participants with comorbidities, social behaviours, and ultrasound abnormalities likely to affect glomerular filtration rate (GFR). The healthy sample may have included participants with kidney impairment. We relied on self-reporting of hypertension and diabetes and were unable to perform glucose measurements for diabetes screening. It is therefore possible that some participants with undiagnosed hypertension and diabetes contributed to the healthy sample. The quality control process did not include a formal assessment of interobserver variability. Only 10% of images were reviewed by experts for quality. There may be images remaining of insufficient quality which were not assessed. The relatively small sample for predicting kidney size within age and sex categories and sex, and the lower proportion of HIV-positive participants in the younger age categories may have biased the size estimates. We did not collect data on CD4

Table 3. Physiology and ultrasound variables.

Variable	Overall	Female	Male
Height (cm)	162.40 (SD 99.01)	158 (153-163)	167 (160-172)
Weight (kg)	67.30 (IQR 57.00-76.67)	64 (56-80)	63 (59-73)
Body mass index (kg m^{-2})	24.00 (IQR 22.00-28.00)	26 (23-31)	24 (21-26)
Systolic blood pressure (mm Hg)	136.00 (SD 23.61)	130 (116-158)	138 (125-156)
Diastolic blood pressure (mm Hg)	80.00 (SD 12.11)	80 (75-89)	81 (74-89)
Average kidney size (cm)	9.58 (SD 0.83)	9.46 (SD 0.87)	9.68 (SD 0.80)
Kidney size left (cm)	9.66 (SD 0.94)	9.54 (SD 0.97)	9.76 (SD 0.90)
Kidney size right (cm)	9.50 (SD 0.96)	9.38 (SD 0.98)	9.61 (SD 0.93)
Kidney length: height right (KBR)	0.59 (SD 0.06)	0.59 (SD 0.06)	0.58 (SD 0.06)
Kidney length: height left (KBR)	0.60 (SD 0.06)	0.60 (SD 0.06)	0.59 (SD 0.06)
Loss of corticomedullary differentiation, n (%)	6/320 (2%)	2/158 (1%)	4/162 (2%)
Increased echogenicity, n (%)	19/320 (6%)	9/158 (6%)	10/162 (6%)
Hydronephrosis, n (%)	6/320 (2%)	3/158 (2%)	3/162 (2%)
Pyonephrosis, n (%)	1/320 (0%)	1/158 (1%)	0/162 (0%)

Table 4. Absolute and relative kidney lengths*. Abbreviation: KBR, ratio of kidney length in millimetres to subject height in centimetres. * Values are means (± 2 standard deviations).

	Age, years						
	18–29 ***(n = 52)***	**30–39** ***(n = 55)***	**40–49** ***(n = 52)***	**50–59** ***(n = 58)***	**60–69** ***(n = 55)***	**70+** ***(n = 48)***	**All** ***(n = 320)***
Absolute kidney length, cm							
Left	9.76 (8.19, 11.34)	9.77 (8.40, 11.13)	9.68 (7.73, 11.64)	9.55 (7.49, 11.62)	9.58 (7.43, 11.73)	9.56 (7.43, 11.68)	9.65 (7.76, 11.53)
Right	9.81 (8.15, 11.46)	9.36 (7.61, 11.10)	9.66 (7.66, 11.67)	9.38 (7.50, 11.26)	9.39 (7.38, 11.40)	9.41 (7.25, 11.57)	9.50 (7.57, 11.42)
Relative kidney length, KBR							
Left	0.60 (0.49, 0.70)	0.61 (0.52, 0.70)	0.59 (0.48, 0.71)	0.60 (0.46, 0.73)	0.59 (0.46, 0.72)	0.58 (0.45, 0.72)	0.60 (0.48, 0.71)
Right	0.60 (0.48, 0.71)	0.59 (0.46, 0.72)	0.59 (0.47, 0.71)	0.59 (0.47, 0.70)	0.58 (0.45, 0.71)	0.58 (0.44, 0.71)	0.59 (0.46, 0.71)
	Women Age, years						
	18–29 ***(n =22)***	**30–39** ***(n =27)***	**40–49** ***(n =24)***	**50–59** ***(n =36)***	**60–69** ***(n =28)***	**70+** ***(n =21)***	**All** ***(n =158)***
Absolute kidney length, cm							
Left	9.69 (8.80 -10.58)	9.71 (8.97-10.46)	9.56 (8.63-10.49)	9.59 (8.52-10.67)	9.27 (8.23-10.31)	9.42 (8.30-10.54)	9.54 (8.57-10.51)
Right	9.77 (8.92-10.62)	9.19 (8.20-10.18)	9.53 (8.42-10.64)	9.37 (8.52-10.22)	9.26 (8.34-10.17)	9.22 (8.02-10.42)	9.38 (8.40-10.36)
Relative kidney length, KBR							
Left	0.61 (0.55-0.67)	0.62 (0.57-0.67)	0.60 (0.55-0.66)	0.61 (0.54-0.67)	0.58 (0.52-0.64)	0.60 (0.53-0.66)	0.60 (0.54-0.66)
Right	0.62 (0.56-0.67)	0.59 (0.52-0.66)	0.60 (0.53-0.66)	0.59 (0.54-0.65)	0.58 (0.52-0.64)	0.58 (0.51-0.66)	0.59 (0.53-0.65)

	Men Age, years						
	18–29 ***(n =30)***	**30–39** ***(n =28)***	**40–49** ***(n =28)***	**50–59** ***(n =22)***	**60–69** ***(n =27)***	**70+** ***(n =27)***	**All** ***(n =162)***
Absolute kidney length, cm							
Left	9.82 (9.10-10.53)	9.82 (9.20-10.44)	9.79 (8.77-10.81)	9.49 (8.51-10.47)	9.90 (8.86-10.94)	9.66 (8.64-10.68)	9.76 (8.85-10.66)
Right	9.83 (9.01-10.66)	9.51 (8.78-10.24)	9.78 (8.87-10.68)	9.39 (8.29-10.48)	9.53 (8.44-10.62)	9.56 (8.58-10.53)	9.61 (8.68-10.55)
Relative kidney length, KBR							
Left	0.58 (0.54-0.63)	0.60 (0.56-0.65)	0.58 (0.52-0.64)	0.58 (0.51-0.65)	0.60 (0.53-0.66)	0.58 (0.51-0.64)	0.59 (0.53-0.65)
Right	0.59 (0.53-0.64)	0.59 (0.53-0.65)	0.58 (0.53-0.64)	0.57 (0.51-0.64)	0.58 (0.51-0.64)	0.57 (0.51-0.63)	0.58 (0.52-0.64)

Table 5. Absolute average (left and right) kidney lengths and predicted range estimates with 95% confidence interval and bootstrapped upper and lower 95% prediction interval. Absolute values are means (± 2 standard deviations) of the complete dataset n = 320. Predicted ranges and 95% confidence intervals were generated using a linear model to predict kidney size according to sex and age category: lm(kidneysize ~ age + sex, data= healthy). The model was then fitted to a bootstrapped sample of the healthy dataset with 1,000 replicates and bootstrapped 95% confidence intervals were constructed around the upper and lower limits of the prediction interval. Abbreviation: F, female, M, male.

	Age, years						
	18–29 ***F = 22*** ***M = 30***	**30–39** ***F = 27*** ***M = 28***	**40–49** ***F = 24*** ***M = 22***	**50–59** ***F = 36*** ***M = 22***	**60–69** ***F = 28*** ***M = 27***	**70+** ***F = 21*** ***M = 27***	**All** ***n = 320***
Absolute average (left and right) kidney length, cm							
Male	9.83 (8.60, 11.06)	9.67 (8.54, 10.79)	9.78 (8.16, 11.40)	9.44 (7.52, 11.35)	9.71 (7.82, 11.61)	9.61 (7.85, 11.36)	9.68 (8.09, 11.28)
Female	9.73 (8.18, 11.28)	9.45 (8.08, 10.82)	9.55 (7.76, 11.33)	9.48 (7.70, 11.27)	9.26 (7.48, 11.05)	9.32 (7.17, 11.47)	9.46 (7.72, 11.20)
Predicted ranges (95% confidence interval) *Healthy sample only (n=252)*							
Male	8.26-11.43 (9.60-10.14)	8.16-11.30 (9.53-9.96)	8.06-11.19 (9.43-9.82)	7.95-11.08 (9.30-9.71)	7.84-10.98 (9.16-9.63)	7.71-10.88 (8.98-9.56)	7.71-11.43 (8.98-10.14)
Female	8.05-11.22 (9.38-9.94)	7.95-11.09 (9.31-9.75)	7.84-10.98 (9.21-9.62)	7.74-10.87 (9.09-9.50)	7.63-10.77 (8.95-9.41)	7.50-10.67 (8.78-9.35)	7.50-11.22 (8.78-9.94)
Bootstrapped lower and upper 95% prediction interval *Healthy sample only (n = 252)*							
Male	Lower 8.08-8.46 Upper 11.15-11.67	Lower 8.00-8.35 Upper 11.07-11.49	Lower 7.88-8.27 Upper 10.99-11.35	Lower 7.74-8.20 Upper 10.88-11.25	Lower 7.59-8.14 Upper 10.76-11.16	Lower 7.41-8.06 Upper 10.63-11.10	Lower 7.41-8.06 Upper 11.15-11.67
Female	Lower 7.83-8.31 Upper 10.92-11.48	Lower 7.74-8.19 Upper 10.84-11.30	Lower 7.65-8.09 Upper 10.77-11.16	Lower 7.52-7.80 Upper 10.67-11.04	Lower 7.39-7.94 Upper 10.57-10.95	Lower 7.23-7.87 Upper 10.45-10.88	Lower 7.23-7.87 Upper 10.92-11.48

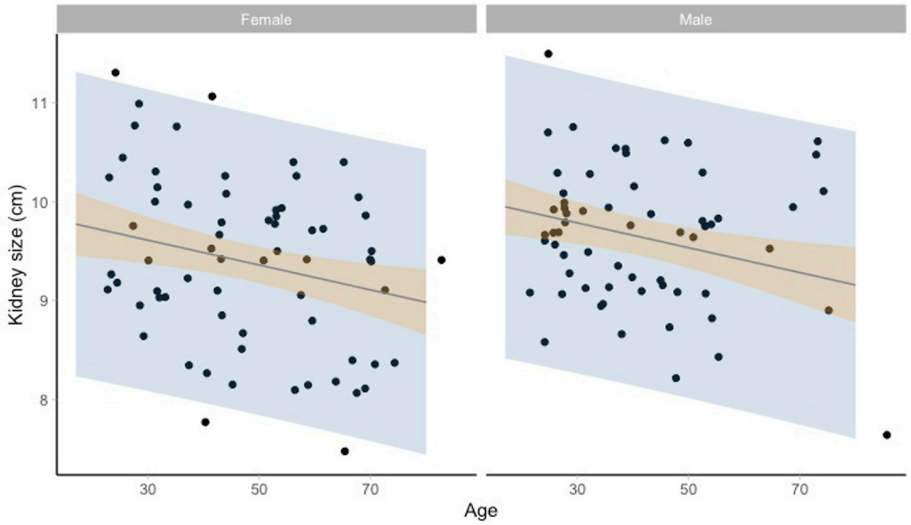

Figure 2. Kidney size range estimates dependent on age and sex for HIV negative participants. Model fit (grey line) of the linear regression model: lm(kidneysize ~ age + sex + hiv_status, data = noHIV) and 95% prediction intervals (blue) and 95% confidence intervals around the mean (orange).

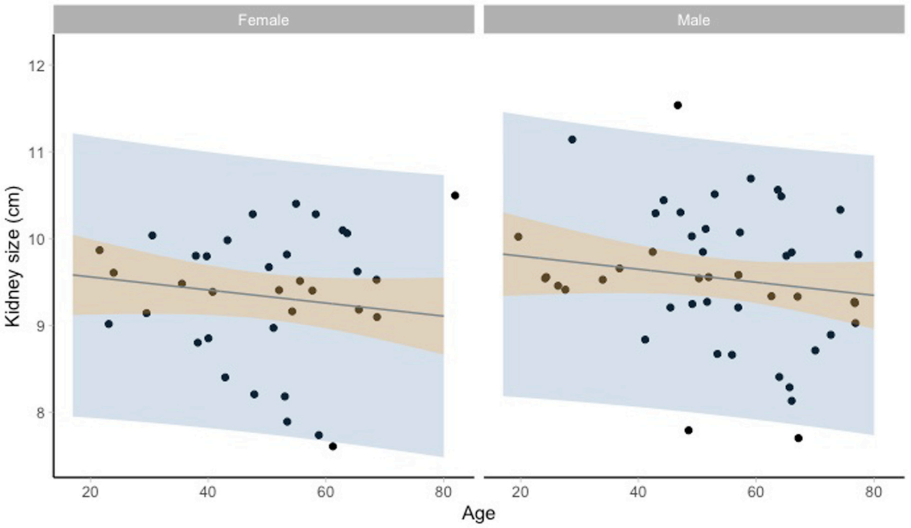

Figure 3. Kidney size range estimates dependent on age and sex for HIV positive participants. Model fit (grey line) of the linear regression model: lm(kidneysize ~ age + sex + hiv_status, data = HIV) and 95% prediction intervals (blue) and 95% confidence intervals around the mean (orange).

count or viral load, and future studies should aim to correlate kidney size with stage of HIV infection.

We recruited participants attending a tertiary centre for imaging following accidents as they were less likely to have a pre-existing kidney disease than other hospital-based cohorts. Future studies should aim to develop nomograms for adults and children, derived from a larger demographic sample. Ideally, these would also include GFR measurement, CD4 count and viral load for HIV positive participants.

In conclusion, we demonstrate the range of kidney sizes expected in adult Malawians without known kidney disease. We found a low prevalence of ultrasound abnormalities in our population. Our predicted size estimates within age categories can be referred to in the assessment of patients with kidney failure.

Ethical statement

Participants gave written informed consent under ethical approvals from the College of Medicine Research Ethics Committee, University of Malawi (P.03/19/2625) and the

Liverpool School of Tropical Medicine Ethics Committee (18-062). Study information including purposes, benefits and risk was provided to all participants in both English and Chichewa.

Data availability

Underlying data

Zenodo: careyla/Normal-kidney: v1.0.0, https://doi.org/10.5281/zenodo.7231616[10]

This project contains the following underlying data:

- baseline.csv210.0 kB
- fulldata.csv117.5 kB
- tidyclean2.csv117.6 kB
- uss_data.csv

Extended data

Zenodo: careyla/Normal-kidney: v1.0.0, https://doi.org/10.5281/zenodo.7231616[10]

This project contains the following extended data:

- Residualsplot

Analysis code

Analysis code available from: https://github.com/careyla/Normal-kidney/tree/v1.0.0

Archived analysis code at time of publication: https://doi.org/10.5281/zenodo.7231616[10]

License: MIT

Reporting guidelines

Zenodo: STROBE checklist for 'Ultrasound appearance of the kidney among radiology department attendees of a tertiary centre in Malawi', https://doi.org/10.5281/zenodo.7231616[10]

Acknowledgements

We thank all the participants who contributed to the study. We are grateful to the radiology department at QECH.

References

1. Emamian SA, Nielsen MB, Pedersen JF, *et al.*: **Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers.** *AJR Am J Roentgenol.* 1993; **160**(1): 83–86.
PubMed Abstract | Publisher Full Text

2. El-Reshaid W, Abdul-Fattah H: **Sonographic assessment of renal size in healthy adults.** *Med Princ Pract.* 2014; **23**(5): 432–436.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Miletić D, Fuckar Z, Sustić A, *et al.*: **Sonographic measurement of absolute and relative renal length in adults.** *J Clin Ultrasound.* 1998; **26**(4): 185–189.
PubMed Abstract | Publisher Full Text

4. Brandt TD, Neiman HL, Dragowski MJ, *et al.*: **Ultrasound assessment of normal renal dimensions.** *J Ultrasound Med.* 1982; **1**(2): 49–52.
PubMed Abstract | Publisher Full Text

5. Quanjer PH, Stanojevic S, Cole TJ, *et al.*: **Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations.** *Eur Respir J.* 2012; **40**(6): 1324–1343.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Chokotho LC, Mulwafu W, Nyirenda M, *et al.*: **Establishment of trauma registry at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi and mapping of high risk geographic areas for trauma.** *World J Emerg Med.* 2019; **10**(1): 33–41.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Gupta-Wright A, Corbett EL, van Oosterhout JJ, *et al.*: **Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial.** *Lancet.* 2018; **392**(10144): 292–301.
PubMed Abstract | Publisher Full Text | Free Full Text

8. **R: The R Project for Statistical Computing.** Accessed May 24, 2022.
Reference Source

9. Cheong B, Muthupillai R, Rubin MF, *et al.*: **Normal values for renal length and volume as measured by magnetic resonance imaging.** *Clin J Am Soc Nephrol.* 2007; **2**(1): 38–45.
PubMed Abstract | Publisher Full Text

10. careyla: **careyla/Normal-kidney: v1.0.0 (v1.0.0).** *Zenodo*. [data set]. 2022.
http://www.doi.org/10.5281/zenodo.7231616

11. **HIV sub-national estimates viewer.** Accessed December 15, 2022.
Reference Source

12. Zira JD, Salisu AY, Sani MU, *et al.*: **ULTRASONOGRAPHIC NOMOGRAM OF THE KIDNEYS IN APPARENTLY HEALTHY ADULTS IN A NIGERIAN POPULATION.** *PJR.* 2017; **27**(4).
Reference Source

13. Kalucki SA, Lardi C, Garessus J, *et al.*: **Reference values and sex differences in absolute and relative kidney size. A Swiss autopsy study.** *BMC Nephrol.* 2020; **21**(1): 289.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 16 February 2023

https://doi.org/10.21956/wellcomeopenres.20908.r54643

✔ **Robert Kalyesubula**
[1] Department of Medical Physiology, School of Biomedical Sciences, Makerere University, Kampala, Uganda
[2] Medical Research Council/UVRI & London School of Hygiene and Tropical Medicine Research Unit, Entebbe, Uganda

I have reviewed the responses and agree with indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a nephrologist working in the area of determination of kidney function among people of African origin. I am also an actively practicing clinician from Uganda, Kampala.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 February 2023

https://doi.org/10.21956/wellcomeopenres.20908.r54644

✔ **June Fabian**
Wits Donald Gordon Medical Centre, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

I am happy with the changes and happy to recommend the paper be accepted for indexing without further revisions.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Specialist physician and nephrologist, research interest is the epidemiology of kidney disease in African populations

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 13 December 2022

https://doi.org/10.21956/wellcomeopenres.20466.r53281

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June Fabian
Wits Donald Gordon Medical Centre, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Thank you for this important work which, as the authors have stated, is much needed in African populations.

The authors state that in Malawi, because of the absence of additional diagnostic capabilities, kidney size on ultrasound is often used as a proxy for determining whether there is underlying chronic kidney disease in those who need dialysis (usually presenting as acute kidney injury). However, such interpretation is hampered by the absence of population-appropriate references for normal kidney size. They also make the point that POCUS is becoming more accessible and NCDs are rising in prevalence - implying (perhaps) that kidney disease is on the rise and more clinicians will have access to POCUS. The authors screened 320 apparently healthy adults presenting at Queen Elizabeth Central hospital radiology department, Blantyre, Malawi. The authors found non-significant differences in kidney size between HIV + and HIV - participants, larger kidney sizes in men than women (expected), and relative kidney length seems to be smaller than in other studies (Nigeria, and high-income settings). They used predictive linear modelling to estimate kidney size stratified by age and sex that might be used in future.

I have a few questions that I would like to ask the authors for clarity:

1. The stated purpose of the study was to investigate normal US measurements in apparently heathy Malawian adults. If so, I am not sure I understand why the sample was stratified by HIV status as we know that untreated HIV can result in loss of coticomedullary differentiation or larger than normal kidney sizes. It is a valuable finding in this study that for PLWHIV who have high ART

coverage, kidney sizes are not significantly different from apparently healthy Malawians. Following on from this, it feels a little incongruent that NCDs are mentioned, yet excluded when we know that hyperfiltrating dabetics can have larger than normal kidney size and hypertension is linked to kidney size in the setting of CKD. One might argue that those with HIV should have been excluded?
Perhaps asked another way, was the original study about kidney size in PLWHIV - and because no difference was found, these data could contribute to an apparently normal dataset. If so, it would be helpful to explain this in the paper and perhaps reframe it as such? Also, in clinical prcatice elsewhere, kidney size in the setting of HIV is/was used to ration access to short term dialysis support - perhaps this is also why the authors focused in HIV? If so, again, it would be very helpful to include this.

2. It would be helpful to describe the US methods in more detail that would enable replication:
- Who did the ultrasound scans - was it only sonographers - any radiologists?
- How did you account for interobserver variability?
- Can you explain what QC measures were undertaken for each sonographer prior to starting the study?

3. Tables 1, 3, 4 - since we describe differences in kidney size stratified by sex - can these tables describe the overall data and be stratified by sex with sample sizes for each category in the top tab for each column?

4. No screening was conducted (other than HIV) and it is well known that many with hypertension, kidney disease, and diabetes are unaware - so the apparently healthy population may indeed have had comorbidity. I think this is a significant limitation of the study and needs to be stated as such. Likewise, the relatively small sample sizes for predicting kidney size (by age caegory and sex) are also limitations that need to be stated.

One nitpicky edit (if I may): sub-Saharan Africa (SSA): the "sub" should be capitalised ("Sub-Saharan") - and using this terminology has been questioned as colonial in origin - perhaps for the authors to consider that African / African populations might suffice?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Specialist physician and nephrologist, research interest is the epidemiology of kidney disease in African populations

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jan 2023

Laura Carey, Malawi-Liverpool Wellcome Trust, Blantyre, Malawi

1. Thanks for making this very important point. The original plan to stratify by HIV status was because we wanted sufficient power to detect a difference in kidney size, had there been one. With the high prevalence of HIV in Malawi, it was important for us to provide a reference range for both people living with HIV and those without, expecting there to be a difference. We agree with both statements. Untreated HIV can result in larger than normal kidney sizes. However, perhaps reassuringly, kidney sizes were not significantly different from apparently healthy Malawians in our study. Which could be related to high ART coverage, as you suggest. Given that we found little differences one could argue for combining the ranges. It is our experience in Blantyre, that kidney size regardless of HIV status is used to ration access to short term dialysis support. We have added the statement "*The sample was stratified by HIV status to enable a separate reference range for those living with HIV*" to hopefully give more clarity to the rationale behind the stratification. With regards to NCDs, the reported prevalence is lower than HIV. The argument for exclusion is related to minimizing selection bias in the context of a hospital-based cohort without access to GFR measurement. We therefore excluded those who were more likely to have abnormal GFR (diabetics, and hypertensives).

2. Sonographers performed the scans. Interobserver variability was not formally assessed, however, quality control was undertaken by two independent experts (including one radiologist). Prior to starting data collection, experts reviewed a series of test images performed by the sonographers and gave feedback and further training. After completion of data collection, 10% images were reviewed by the experts and images of insufficient quality rejected, accepting that there were likely to be images of insufficient quality remaining in the sample. This approach was chosen for pragmatic reasons, and is a limitation of the study which has now been made more explicit in the methods and limitations section. Methods: *Prior to commencement, a series of test images were reviewed by two experts for quality of view, detection of abnormalities and accuracy of length measurement. Where there was disparity, feedback was given to sonographers and further training in image acquisition. On data completion, 10% images were randomly selected for external review with expert opinion taken as the 'gold standard' against which to benchmark the accuracy of the sonographers' measurements. Images with insufficient quality as deemed by experts were*

rejected (n=4). Limitations: *The quality control process did not include a formal assessment of inter-observer variability. Only 10% of images were reviewed by experts for quality. There may be images remaining of insufficient quality which were not assessed.*

3. Thank you for this helpful comment, the three tables are now presented stratified by sex as suggested.

4. We have now expanded the limitations section to makes these limitations clearer: *There were limitations to our study. We were unable to determine measured kidney function to confirm absence of pre-existing kidney disease. However, we excluded participants with comorbidities, social behaviours, and ultrasound abnormalities likely to affect glomerular filtration rate (GFR). The healthy sample may have included participants with kidney impairment. We relied on self-reporting of hypertension and diabetes and were unable to perform glucose measurements for diabetes screening. It is therefore possible that some participants with undiagnosed hypertension and diabetes contributed to the healthy sample. The quality control process did not include a formal assessment of inter-observer variability. Only 10% of images were reviewed by experts for quality. There may be images remaining of insufficient quality which were not assessed. The relatively small sample for predicting kidney size within age and sex categories and sex, and the lower proportion of HIV-positive participants in the younger age categories may have biased the size estimates.*

Competing Interests: No competing interests were disclosed.

Reviewer Report 25 November 2022

https://doi.org/10.21956/wellcomeopenres.20466.r53279

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Robert Kalyesubula
[1] Department of Medical Physiology, School of Biomedical Sciences, Makerere University, Kampala, Uganda
[2] Medical Research Council/UVRI & London School of Hygiene and Tropical Medicine Research Unit, Entebbe, Uganda

This is a wonderful study undertaken by Carey *et al.* in an attempt to report on the normal kidney sizes among people from Malawi. The researchers provide very useful information that would help in determination of kidney pathology in SSA.

I have a few comments that may need to be addressed:

1. The introductory statement sounds rather interesting. I would argue that most low-resource centers do not have access to ultrasound scans and therefore it is unlikely that decisions to treat kidney disease would be based on an ultrasound scan - perhaps

proteinuria which is available on a dipstick. You may want to have this statement restricted to Malawi.

2. How was selection bias minimized in the selection of the participants? People who present to hospitals are sick and are therefore less likely to represent the general population.

3. The use of creatinine or proteinuria would have been of additional value in excluding those with underlying kidney dysfunction at least GFR less than 60mls/min/1.73m2. Why was this not done?

4. Please provide more details on how you did the radiography. Was the interpretation done centrally or was this as used in routine practice? What happened if there was a disagreement in the 10% of images which were randomly selected for routine control? In the exclusion criteria; was diabetes only on self report? How reliable is this in excluding DM? I believe this would be a great confounder in the size of the kidney as would HIV since the kidneys tend to be bigger. Many DM patients do not know that they have it.

5. The standardization for body size is a strong point for this study. Is there any major difference in size between the rural and urban dwellers in the study and overall in Malawi?

The STROBE guidelines for cross sectional studies were dully followed which streamlined the reporting.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a nephrologist working in the area of determination of kidney function among people of African origin. I am also an actively practicing clinician from Uganda, Kampala.

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jan 2023

Laura Carey, Malawi-Liverpool Wellcome Trust, Blantyre, Malawi

"The introductory statement sounds rather interesting. I would argue that most low-resource centers do not have access to ultrasound scans and therefore it is unlikely that decisions to treat kidney disease would be based on an ultrasound scan - perhaps proteinuria which is available on a dipstick. You may want to have this statement restricted to Malawi."

Response: This is a very good point, thank you for raising it. The introduction has been changed to only refer to practices in Malawi.

"How was selection bias minimized in the selection of the participants? People who present to hospitals are sick and are therefore less likely to represent the general population."

Response: Thank you for raising this important question. We employed several methods to minimize selection bias in the population presenting to hospital. Firstly, because we wanted to ensure participants would be unlikely to have pre-existing kidney disease, we selected those who were attending for imaging and injury as a result of accidents. Secondly, we excluded participants who were pregnant, diabetic, hypertensive or smokers and alcohol drinkers. Thirdly, we excluded those who had imaging abnormalities identified on ultrasound.

"The use of creatinine or proteinuria would have been of additional value in excluding those with underlying kidney dysfunction at least GFR less than 60mls/min/1.73m2. Why was this not done?"

Response: We are wholly in agreement with this, but unfortunately due to the very limited study budget we were unable to offer kidney function tests to the participants.

"Please provide more details on how you did the radiography. Was the interpretation done centrally or was this as used in routine practice? What happened if there was a disagreement in the 10% of images which were randomly selected for routine control?"
In the exclusion criteria; was diabetes only on self report? How reliable is this in excluding DM? I believe this would be a great confounder in the size of the kidney as would HIV since the kidneys tend to be bigger. Many DM patients do not know that they have it."

Response: Thank you for raising this important point. The quality control was done externally by two experienced consultant radiologists. After the initial quality check, specific feedback and further training was given to the sonographers on image optimisation. After the final quality check, 4/41 images (10%) were deemed unusable and were excluded from the analysis. Diabetes was on self-report and so unfortunately yes, there is likely to be unknown undiagnosed diabetes among the cohort. This could potentially have biased kidney sizes to larger dimensions. Given that we found kidneys to be small in size, this

potentially makes our findings even more interesting. However, the population prevalence of diabetes in 20-79 year olds in Malawi is 7.3%[1].

"The standardization for body size is a strong point for this study. Is there any major difference in size between the rural and urban dwellers in the study and overall in Malawi?"

Response: Thank you for raising this most interesting question. We have looked into it and compared height and BMI between the urban and rural locations and found no evidence of a difference (please see the box plots found in the PDF file linked here).

Competing Interests: No competing interests were disclosed.