



RESEARCH ARTICLE

Prevalence of impaired renal function among rural and urban populations: findings of a cross-sectional study in Malawi [version 1; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background: Sub-Saharan Africa faces region-specific risk factors for chronic kidney disease (CKD), such as nephrotoxic herbal medicines, antiretroviral therapy and infections, in addition to hypertension and diabetes. However, large epidemiological studies from this area are scarce.

Methods: In a cross-sectional survey of non-communicable diseases, we conducted a prevalence sub-study of CKD in two Malawian populations. Study participants (N=5264) of 18 years of age and above were recruited and data on demographics and CKD risk factors were collected. Glomerular filtration rate was estimated (eGFR) using the CKD-EPI equation.

Results: The prevalence of eGFR<60ml/min/1.73m² was 1.4% (95% CI 1.1 – 1.7%) and eGFR<90ml/min/1.73m² was 20.6% (95% CI 19.5 – 21.7%).

The rural area had higher age-standardized prevalence of both eGFR<60ml/min/1.73m², at 1.8% (95% CI 1.4 – 2.3) and eGFR <90 ml/min/1.73m², at 21.1% (95% CI 19.9 – 22.3), than urban location, which had a prevalence of 1.5%, (95% CI 1.0 – 2.2) and 19.4% (95% CI 18.0 – 20.8), respectively, with overlapping confidence intervals. The prevalence of CKD was lower in females than in males in both rural and urban areas. Older age ($p < 0.001$), a higher level of education ($p = 0.03$) and hypertension ($p < 0.001$) were associated with a higher adjusted odds ratio (aOR) of low eGFR. Diabetes was associated with a reduced aOR of eGFR<90ml/min/1.73m² of 0.69 (95% CI 0.49–0.96; $p=0.03$). Of participants with eGFR<60ml/min/1.73m², 14 (19.4%) had no history of hypertension, diabetes or HIV, while 36 (50%) had a single risk factor of being hypertensive.

Conclusions: Impaired renal function is prevalent, but lower than

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expected, in rural and urban Malawi. Further research is needed to increase understanding of CKD incidence, survival and validation of eGFR calculations in this population.

Keywords

Kidney Disease, Epidemiology, Sub Saharan Africa

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Introduction

Since 1990, the number of deaths from chronic kidney disease (CKD) has risen by 82%, representing the third largest increase in deaths, behind HIV/AIDS and diabetes^{1,2}. CKD, described as abnormalities of kidney structure or function present for longer than three months, is increasingly being recognized as an emerging public health problem globally and a key determinant of poor health outcomes of millions of people³⁻⁵. Sub-Saharan Africa (sSA) faces region-specific risk factors for CKD, such as nephrotoxic herbal medicines, antiretroviral therapy and infections, in addition to hypertension and diabetes^{6,7}. The few epidemiological studies in sSA show a large variation of CKD prevalence, ranging from 1.5% to 33.5%⁸.

However, current knowledge about the prevalence of CKD and renal disease in Malawi, as in most sSA countries, is scarce⁹. Published data on CKD have been based on opportunistic sampling, involving people seeking medical care, or of urban populations, who have a different epidemiological profile from the rural majority^{6,10}. It is thought that glomerulonephritis and CKD of unknown origin (CKDu), might account for a larger proportion of the total CKD burden in rural or disadvantaged populations, whilst hypertension and diabetes are more prevalent in urban areas^{3,11}.

The absence of community-based representative data on CKD is concerning, as strategies aimed at managing CKD in Africa critically depend on reliable assessment of the burden of the problem and the establishment of affordable early detection programs¹². As such, we conducted a cross-sectional survey to estimate and compare the prevalence of CKD in rural and urban Malawi and analyzed the factors associated with this condition.

Methods

Study setting

Participants were selected from a large cross-sectional population-based survey, designed to elucidate the burden and risk factors of non-communicable diseases in urban and rural Malawi^{13,14}. The survey was conducted in a rural area with a population of 40,000 people within southern Karonga District and Area 25 in Lilongwe, the capital city (Figure 1). Karonga is a lakeshore district, with a subsistence economy. Area 25 is an economically mixed urban economy with a population of around 66,000 individuals. Recruitment and data collection took place between May 16th 2013 to February 8th 2016.

Recruitment and data collection

Detailed study procedures of the survey and characteristics of the two populations have been previously described¹³ and all consenting adults age 18 years and over, residing within the defined study areas, were eligible to participate.

Briefly, the participants were visited in their homes. Written informed consent was obtained from all participants for interviewer-led questionnaires, documenting the participant's socio-demographic information, lifestyle (e.g. smoking, alcohol, diet and physical activity), personal and family health history (e.g. hypertension, diabetes, heart disease and HIV) and

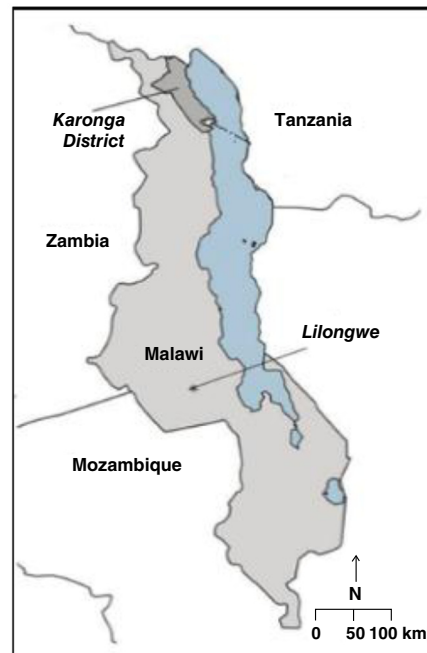


Figure 1. Map of Malawi Showing location rural Karonga and urban Lilongwe.

current medications. Anthropometric measurements, measured twice by two study staff independently, and three seated blood pressure measurements, with 5 minute rests in between, were taken, adhering to standard protocols. A rapid HIV test was conducted, and results were given to the participants.

Blood was collected from an antecubital vein (following an overnight fast of at least 8h) in sodium fluoride tubes and plain serum tubes for fasting blood glucose (FBG) and serum creatinine tests, respectively. The samples were transported on the same day to the onsite project laboratory for the glucose assay and the serum was stored for creatinine analysis (mean time between collection and processing of 2.6h). We used the hexokinase glucose-6-phosphate dehydrogenase method using the AU480 Chemistry Analyzer (Beckman Coulter, California, USA), with sufficient sensitivity (range 0.555–44.4 mol/L) to determine glucose concentrations in the study samples.

Serum separation was done on a Sigma 6–16 centrifuge at 3000 RPM for 10 minutes. The separated serum was frozen in -80 freezer in 1.8ml Sarstedt tubes. On the day of analysis, the serum samples were taken out of the freezer, allowed to thaw at room temperature and then analysed on an AU480 analyser with ISE. Kinetic Jaffe (compensated) method, traceable to the isotope dilution mass spectrometry (IDMS) reference method was used. The AU480 analyser automatically computed the creatinine concentration of each sample and interference from protein was mathematically auto-corrected by the analyser by subtracting 18 $\mu\text{mol/L}$ from each test result. The instrument was equipped with reagent OSR6178, System Calibrator Cat. No. 66300 traceable to the IDMS method via National Institute of

Standards and Technology (NIST) Standard Reference Material (SRM) 967 and quality control material, all manufactured by Beckman Coulter (California, USA).

Participant ages were grouped into 10-year categories and education was categorized by the highest educational level achieved (no formal education, completed primary school standard 1–5, primary school standard 6–8, secondary, or tertiary). Occupation statuses were grouped into the following categories: not working, housework, farming or fishing, employed or self-employed. Household wealth scores were determined, based on the value of household assets, and then grouped into fifths across the total survey population. Physical activity was determined by self-reporting of the average duration (minutes) and intensity of exercise (pre-coded activities, grouped into high exertion, low exertion, or sedentary) in the previous week (both at work and during leisure time), used to establish whether participants met the World Health Organization (WHO) recommended level of activity per week. Alcohol consumption was divided into those who had consumed at least one alcoholic drink within the past 12 months and those who had not. Smoking status was divided into current smokers, ex-smokers and never-smokers.

Body mass index (BMI) categories were <18kg/m² (underweight), 18–24.99 kg/m² (healthy weight), 25–29.99 kg/m² (overweight) and >30 kg/m² (obese), in line with [World Health Organization recommendations](#). Hypertension was defined as one or more of: systolic blood pressure of 140mmHg or more; diastolic blood pressure of 90 mmHg or more; and any use of antihypertensive medication in the past two weeks. Diabetes was defined as fasting plasma glucose of at least 7.0 mmol/L or any self-reported prior diagnosis of diabetes, regardless of whether the participant was taking anti-diabetic medication.

Sampling participants for serum creatinine measurements

Serum samples were available for 24,780 participants; we sampled 5,264 serum samples for creatinine testing. With this sample size, we were able to determine a 0.1 standard difference, with power of 80% and p value of 0.01. Our sample was stratified by age (18–29, 30–39, 40–49, 50+), sex and site. We over-sampled older (aged 40 years plus) age groups in order to increase the numbers of individuals with impaired renal function to facilitate further analyses and prioritized participants recruited later in the study over those recruited earlier. Specifically, we tested 100 of each age/sex/site combination group for both 2015 and 2014, the remaining samples coming from participants aged 40 and older from 2015.

Method of calculating of eGFR

We used the CKD-EPI equation to calculate eGFR:

$$eGFR = 141 \times \min(S_{Cr}/K, 1)^\alpha \times \max(S_{Cr}/K, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}]$$

Where S_{Cr} is serum creatinine in $\mu\text{mol/L}$; K is 61.9 for females and 79.6 for males; α is -0.329 for females and -0.411 for males; Min indicates the minimum of S_{Cr}/K or 1, and max indicates the maximum of S_{Cr}/K or 1.

Using the this equation, not correcting for race, renal function was categorized as: eGFR <60 ml/min/1.73 m² (very low eGFR, representing CKD), <90 ml/min/1.73 m² (low GFR) and ≥ 90 ml/min/1.73 m² (normal), based on the [National Kidney Foundation guidelines](#).

Statistical analyses

We calculated the age-specific prevalence of eGFR<60ml/min/1.73m² and eGFR<90ml/min/1.73m² according to rural or urban residency and sex and estimated population prevalence, weighted to represent the age distribution of the underlying study population, using age groups of 18–29, 30–39, 40–49, and 50+, in line with the strategy used for sampling for the creatinine assay. In addition, the age-standardized prevalence (to the INDEPTH Standard population distribution 2000 – 2005¹⁵) was estimated.

We conducted multivariable logistic regression to examine the association of different exposures with having an eGFR<90ml/min/1.73m². Exposures were considered in a conceptual framework of distal exposures (age, sex, urban or rural study site, education, occupation and household wealth score), behavioral exposures (smoking, alcohol consumption and physical activity) and pathological exposures (obesity, hypertension and impaired fasting glucose), displayed in [Figure 2](#). We report the odds ratios (ORs) with 95% confidence intervals (CIs) for each of these exposures, adjusted for age and sex only, for distal exposures only, and for both distal and behavioral exposures. Complete case analysis was used as a strategy to deal with missing data. All analysis was done using Stata version 15.0 (StataCorp, College Station, TX).

Ethical statement

All participants gave written consent to participate. Ethical approval was obtained from Malawi National Health Sciences Research Committee protocol number #1072, and London School of Hygiene and Tropical Medicine (UK) Ethics Committee protocol number #6303.

Results

Participant demographic characteristics

The creatinine assay was conducted on serum from 5264 participants. BMI was missing for 123 participants, mainly as it was not calculated in pregnant women. Blood pressure and diabetes data were missing for 3 and 2 participants, respectively. HIV status was not available for 1382 participants.

Socio-demographic characteristics of the participants are described in [Table 1](#). 55.2% were from the rural area, 27.6% were between age 18 to 29, and 43.4% were farmers or fishermen. The rural sample was generally poorer, less well educated, and most participants were farmers or fishermen. The urban sample comprised more overweight or obese participants and had a higher prevalence of hypertension and diabetes.

Crude and age-specific prevalence

The prevalence of eGFR<60ml/min/1.73m² in our sample overall was 1.4% (95% CI 1.1 – 1.7) and the prevalence of eGFR<90ml/min/1.73m² was 20.6% (95% CI 19.5 – 21.7). This is

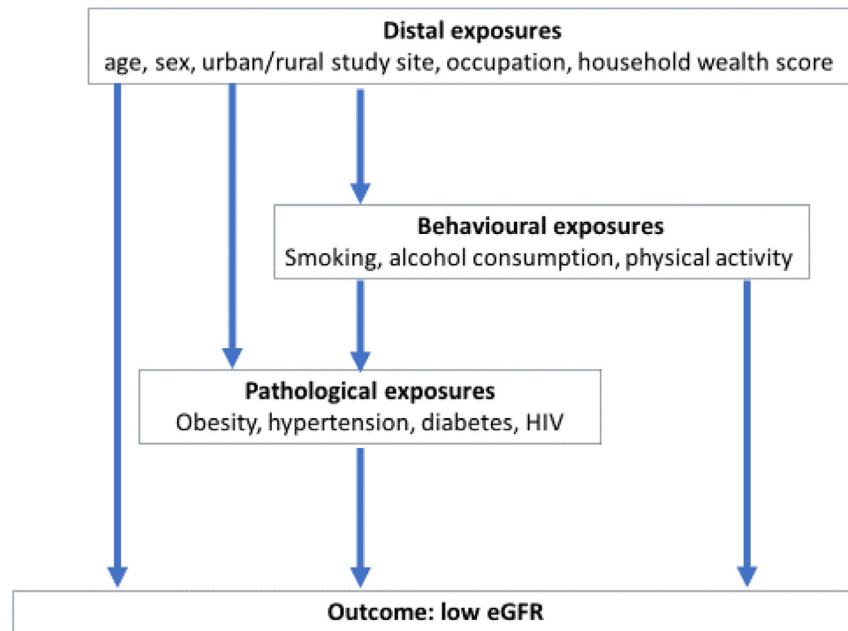


Figure 2. Conceptual framework of exposures potentially contributing to low estimated glomerular filtration rate (eGFR).

Table 1. Baseline characteristics of the stratified sample by urban and rural study site.

	Rural		Urban	
	Female n (%)	Male n (%)	Female n (%)	Male n (%)
Age				
18–29	388 (24.5)	318 (24.3)	447 (32.2)	302 (31.2)
30–39	327 (20.7)	304 (21.7)	329 (23.7)	222 (22.9)
40–49	367 (23.2)	316 (23.5)	328 (23.6)	222 (22.9)
50–59	255 (16.1)	190 (15.3)	177 (12.7)	111 (11.5)
60–69	152 (9.6)	92 (8.4)	74 (5.3)	80 (8.3)
70+	92 (5.8)	105 (6.8)	34 (2.5)	32 (3.3)
Household possession score				
1 (poorest)	419 (26.5)	319 (24.1)	126 (9.1)	99 (10.2)
2	450 (28.5)	380 (28.7)	121 (8.7)	118 (12.2)
3	297 (18.8)	258 (19.5)	253 (18.2)	175 (18.1)
4	332 (21.0)	291 (22.0)	416 (30.0)	234 (24.2)
5 (wealthiest)	83 (5.3)	77 (5.8)	473 (34.1)	343 (35.4)
Occupation				
Farming/fishing	1297 (82.0)	966 (72.9)	14 (1.0)	6 (0.6)
Self-employed	113 (7.2)	126 (9.6)	308 (22.2)	245 (25.3)
Employed	30 (1.9)	93 (7.0)	178 (12.8)	378 (39.0)
Not working	63 (4.0)	135 (10.2)	283 (20.4)	271 (28.0)
Housework	78 (4.9)	5 (0.4)	606 (43.6)	69 (7.1)

	Rural		Urban	
	Female	Male	Female	Male
	n (%)	n (%)	n (%)	n (%)
Education				
No formal	145 (9.2)	30 (2.3)	115 (8.3)	24 (2.5)
Standard 1–5	337 (21.3)	169 (12.8)	154 (11.1)	52 (5.4)
Standard 6–8	843 (53.3)	636 (48.0)	345 (24.8)	199 (20.5)
Secondary	243 (15.4)	459 (34.6)	602 (43.3)	474 (48.9)
Tertiary	13 (0.8)	31 (2.3)	173 (12.5)	220 (22.7)
Alcohol consumption				
No alcohol in past year	1509 (95.5)	787 (59.4)	1319 (95.0)	635 (65.5)
Alcohol in past year	72 (4.6)	538 (40.6)	70 (5.0)	334 (34.5)
Smoking				
Never smoked	1581 (100)	1071 (80.8)	1380 (99.4)	788 (81.3)
Ex-smoker	0 (0)	65 (4.9)	6 (0.4)	88 (9.1)
Current smoker	0 (0)	189 (14.3)	3 (0.2)	93 (9.6)
Physical activity level				
Did not meet WHO recommendations	26 (1.6)	36 (2.7)	31 (2.2)	50 (5.2)
Met WHO recommendations	1555 (98.4)	1289 (97.3)	1358 (97.8)	919 (94.8)
Body Mass Index (kg/m²)¹				
<18	75 (5.0)	80 (6.1)	36 (2.7)	36 (3.7)
18–24.99	1029 (68.1)	1110 (83.9)	598 (44.7)	679 (70.1)
25–29.99	290 (19.2)	118 (8.9)	370 (27.7)	196 (20.2)
30+	118 (7.8)	15 (1.1)	333 (24.9)	58 (6.0)
Hypertension				
Hypertension	262 (16.6)	195 (14.7)	305 (22.0)	217 (22.4)
No hypertension	1317 (83.4)	1129 (85.3)	1084 (78.0)	752 (77.6)
Diabetes				
Diabetes	56 (3.5)	50 (3.8)	74 (5.3)	53 (5.5)
No diabetes	1525 (96.5)	1275 (96.2)	1314 (94.6)	915 (94.4)
HIV status				
HIV positive	140 (14.3)	101 (13.7)	140 (10.7)	72 (8.4)
HIV negative	840 (85.7)	638 (86.3)	1162 (89.3)	789 (91.6)

¹Missing data on 123 participants (69 rural women, 2 rural men, 52 urban women).

²Missing data on 3 participants (2 rural women, 1 rural man).

³Missing data on 2 participants (1 urban woman, 1 urban man).

⁴Missing data on 1382 participants (601 rural women, 586 rural men, 87 urban women, 108 urban men).

shown by age and urban or rural location in [Table 2](#) and [Table 3](#) and [Figure 3](#) and [Figure 4](#). The rural area had higher prevalence of both eGFR<60ml/min/1.73m², at 1.8% (95% CI 1.4 – 2.3), and eGFR<90ml/min/1.73m², at 21.1% (95% CI 19.9 – 22.3), than the urban location, which had a prevalence of 1.5% (95% CI 1.0 – 2.2) and 19.4% (95% CI 18.0 – 20.8), respectively, although with overlapping confidence intervals when standardized to the INDEPTH standard age distribution. The prevalence

of eGFR<60ml/min/1.73m² was also slightly lower in females than in males in both rural and urban areas.

Exposures associated with low eGFR

Low eGFR was strongly associated with increasing age ([Table 4](#)), with participants in the over-70 age group having 148 times the odds of low eGFR than those in the 18–39 age group, when adjusted for distal and behavioral exposures

Table 2. Prevalence (%) of chronic kidney disease (CKD) (eGFR<60 ml/min/1.73m²).

Prevalence	Rural			Urban		
	Female	Male	Total	Female	Male	Total
	27/1581	23/ 1325	50/ 2906	10/ 1389	12/ 969	22/ 2358
Stratified study population	1.7 (1.2-2.5)	1.7 (1.2-2.6)	1.7 (1.3-2.3)	0.7 (0.4-1.3)	1.2 (0.7-2.2)	0.9 (0.6-1.4)
Standardized to age distribution of underlying population	1.3 (0.9-1.9)	1.3 (0.9-1.9)	1.4 (1.0-1.8)	0.4 (0.2-0.7)	0.7 (0.4-1.2)	0.6 (0.4-0.8)
Standardized to INDEPTH standard age distribution	1.5 (1.1-2.1)	1.8 (1.2-2.6)	1.8 (1.4-2.3)	1.0 (0.5-0.2)	1.6 (1.0-2.7)	1.5 (1.0-2.2)

Table 3. Prevalence (%) of low estimated glomerular filtration rate (eGFR<90 ml/min/1.73m²).

Prevalence	Rural			Urban		
	Female	Male	Total	Female	Male	Total
	399/ 1581	291/ 1325	690/ 2906	213/ 1389	180/ 969	393/ 1965
Stratified study population	25.24 (23.2-27.4)	21.96 (19.8-24.3)	23.7 (22.2-25.3)	15.3 (13.5-17.3)	18.6 (16.3-21.2)	16.7 (15.2-18.2)
Standardized to age distribution of underlying population	19.9 (18.4-21.5)	18.0 (16.4-19.7)	19.1 (18.0-20.3)	10.6 (9.4-12.0)	12.4 (10.7-14.3)	11.3 (10.3-12.5)
Standardized to INDEPTH standard age distribution	22.2 (20.1-23.9)	19.5 (17.8-21.4)	21.1 (19.9-22.3)	18.7 (16.9-21.6)	20.2 (18.1-22.3)	19.4 (18.0-20.8)

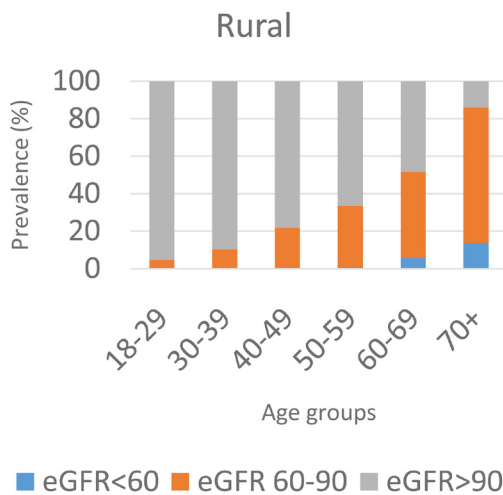


Figure 3. Age specific prevalence of low estimated glomerular filtration rate (eGFR) in the rural site.

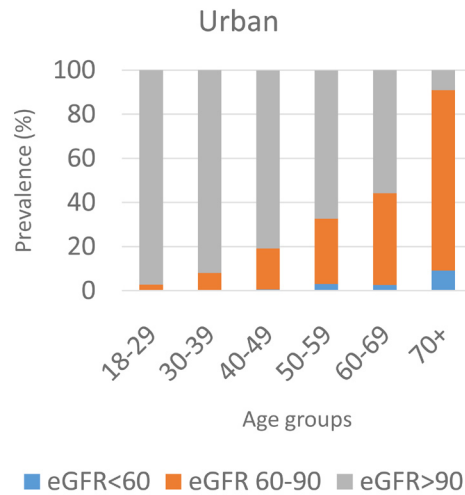


Figure 4. Age-specific prevalence of low estimated glomerular filtration rate (eGFR) in the urban study site.

(95% CI 90.88 – 242.27). Other exposures associated with low eGFR in the fully-adjusted model were having a higher education level (p=0.03), being a farmer or fisherman, and hypertension (p<0.001). Being underweight was associated with reduced odds of low eGFR (p=0.03). In our sample, diabetes was associated

with a reduced adjusted odds ratio (aOR) of eGFR<90ml/min/1.73m², with an aOR of 0.57 (95% CI 0.40 – 0.81; p=0.001), adjusting for distal and behavioral exposures. Place of residence was associated with eGFR<90ml/min/1.73m² with an age- and sex-adjusted OR of 0.84 (95% CI 0.72 – 0.98; p=0.03)

Table 4. Factors associated with estimated glomerular filtration rate (eGFR) <90 adjusted for age and sex only, adjusted for distal factors, and adjusted for both distal and behavioral factors.

	Adjusted for age and sex only		Adjusted for distal factors (age, sex, site, education, occupation, wealth score)		Adjusted for distal and behavioral factors (age, sex, site, occupation, wealth score, smoking, alcohol and physical activity), and diabetes and hypertension	
	OR (95% CI)	p ¹	OR (95% CI)	p ¹	OR (95% CI)	p ¹
Sex						
Female	1		1		1	
Male	0.91 (0.78-1.07)	0.26	0.81 (0.68-0.96)	0.02	0.92 (0.76-1.12)	0.39
Age group						
18–29	1		1.00		1.00	
30–39	2.61 (1.87-3.66)	<0.001	2.59 (1.83-3.66)	<0.001	2.50 (1.77-3.54)	<0.001
40–49	6.77 (4.99-9.19)		6.68 (4.86-9.18)		6.27 (4.55-8.64)	
50–59	12.86 (9.41-17.57)		12.98 (9.37-18.00)		11.32 (8.09-15.83)	
60–69	24.71 (17.67-34.56)		26.01 (18.37-36.83)		20.69 (14.35-29.83)	
70+	176.55 (112.37-277.37)		199.27 (124.15-319.84)		148.38 (90.88-242.27)	
Site						
Rural	1		1		1	
Urban	0.84 (0.72-0.98)	0.03	1.01 (0.77-1.34)	0.92	0.97 (0.73-1.28)	0.82
Household wealth score						
1 (poorest)	1		1.00		1.00	
2	1.12 (0.87-1.44)	0.53*	1.12 (0.87-1.44)	0.54*	1.10 (0.85-1.42)	0.78*
3	1.00 (0.77-1.29)		1.03 (0.79-1.35)		1.00 (0.76-1.31)	
4	1.06 (0.83-1.35)		1.06 (0.83-1.37)		1.02 (0.79-1.32)	
5 (wealthiest)	1.14 (0.88-1.48)		1.15 (0.86-1.54)		1.11 (0.82-1.49)	
Education						
No formal	0.82 (0.60-1.11)	0.03*	0.86 (0.63-1.19)	0.03*	0.85 (0.62-1.17)	0.03*
Standard 1–5	0.88 (0.69-1.11)		0.87 (0.69-1.11)		0.90 (0.71-1.14)	
Standard 6–8	1.00		1.00		1.00	
Secondary	0.92 (0.75-1.12)		1.01 (0.81-1.24)		1.01 (0.82-1.26)	
Tertiary	1.42 (1.07-1.90)		1.47 (1.04-2.07)		1.53 (1.08-2.17)	
Occupation						
Not working	1.25 (0.89-1.76)	<0.001	1.17 (0.83-1.66)	0.003	1.09 (0.77-1.56)	0.003
Housework	0.86 (0.63-1.18)		0.89 (0.65-1.23)		0.87 (0.63-1.20)	
Farming/fishing	1.44 (1.13-1.84)		1.55 (1.14-2.12)		1.58 (1.15-2.15)	
Self-employed	1.00		1.00		1.00	
Employed	1.58 (1.18-2.13)		1.42 (1.04-1.93)		1.37 (1.00-1.88)	

	Adjusted for age and sex only		Adjusted for distal factors (age, sex, site, education, occupation, wealth score)		Adjusted for distal and behavioral factors (age, sex, site, occupation, wealth score, smoking, alcohol and physical activity), and diabetes and hypertension	
Smoking status						
Never smoker	1		1		1	
Ex-smoker or current smoker	0.70 (0.52-0.94)	0.02	0.71 (0.53-0.97)	0.03	0.80 (0.59-1.10)	0.17
Alcohol consumption						
Never	1		1		1	
Rarely/often	0.81 (0.65-1.01)	0.06	0.80 (0.64-1.00)	0.05	0.83 (0.65-1.04)	0.11
Physical activity²						
Did not meet WHO recommendation	1.48 (0.96-2.28)	0.08	1.44 (0.93-2.23)	0.10	1.32 (0.85-2.07)	0.22
Met WHO recommendation	1.00		1.00		1.00	
BMI (kg/m²)³						
<18	0.58 (0.38-0.89)		0.57 (0.38-0.87)		0.62 (0.41-0.94)	
18–24.99	1		1.00		1.00	
25–29.99	1.12 (0.92-1.36)	0.03	1.19 (0.97-1.45)	0.009	1.16 (0.94-1.43)	0.04
30+	1.04 (0.82-1.34)		1.13 (0.87-1.48)		1.04 (0.79-1.37)	
Hypertension⁴						
No hypertension	1		1		1	
Hypertension	1.57 (1.30-1.88)	<0.001	1.69 (1.40-2.05)	<0.001	1.77 (1.46-2.16)	<0.001
Diabetes⁵						
No diabetes	1		1		1	
Diabetes	0.71 (0.51-0.98)	0.03	0.70 (0.50-0.97)	0.03	0.57 (0.40-0.81)	0.001
HIV						
Negative	1		1		1	
Positive	1.09 (0.84-1.41)	0.50	1.09 (0.84-1.42)	0.52	1.16 (0.89-1.51)	0.29

1. Likelihood ratio tests for association. Values marked with * are test-for-trend p-values.

2. High defined as meeting recommended WHO physical activity levels.

3. Missing data on 123 participants

4. Defined as blood pressure $\geq 140/90$ or on antihypertensive medication, missing data on 3 participants

5. Defined as fasting plasma glucose ≥ 7.1 or self-report, missing data on 3 participants

BMI, body mass index; OR, odds ratio; CI, confidence intervals

for urban residence, with rural as the reference. The association was no longer seen when also adjusting for distal or behavioral exposures.

Of those who had $eGFR < 60 \text{ ml/min/1.73m}^2$, 14 (19.4%) had no history of hypertension, diabetes or HIV (Table 5). Thirty-six (50.0%) of the participants with $eGFR < 60 \text{ ml/min/1.73m}^2$ had a single risk factor of being hypertensive, eight (11.1%) had a single risk factor of HIV and nine (19.4%) had two known risk factors of CKD.

Discussion

In this large, population-based, cross-sectional stratified sample, we found an overall standardized prevalence of $eGFR < 90 \text{ ml/min/1.73m}^2$ of 20.6% and $eGFR < 60 \text{ ml/min/1.73m}^2$ of 1.4% using the CKD-EPI equation. A study conducted in Lilongwe by Glaser *et al.* found a prevalence of $eGFR < 60 \text{ ml/min/1.73m}^2$ of 3.1%, in individuals seeking HIV testing in urban Malawi⁸. These estimates are comparable to those found in other regional studies and validate a growing body of research indicating presence of undiagnosed CKD at population level^{16,17}.

Table 5. Number and proportion of participants with known hypertension, diabetes and HIV with low and very low estimated glomerular filtration rate (eGFR)¹.

		eGFR>90	eGFR 60-90	eGFR<60	Total
		n (%)	n (%)	n (%)	n (%)
No known risk factors	No hypertension, diabetes, or HIV	3259 (88.0%)	547 (54.1%)	14 (19.4%)	3820 (72.6%)
Single known risk factor	Hypertension only	433 (10.4%)	315 (31.2%)	36 (50.0%)	784 (14.9%)
	Diabetes only	58 (1.4%)	14 (1.4%)	0	72 (1.4%)
	Known HIV only	304 (7.3%)	68 (6.7%)	8 (11.1%)	380 (7.2%)
2 known risk factors	Hypertension and diabetes	83 (2.0%)	43 (4.3%)	9 (12.5%)	135 (2.6%)
	Hypertension and HIV	25 (0.6%)	17 (1.7%)	5 (6.9%)	47 (0.9%)
	Diabetes and HIV	11 (0.3%)	2 (0.2%)	0	13 (0.2%)
3 known risk factors	Hypertension, diabetes and HIV	8 (0.2%)	5 (0.5%)	0	13 (0.2%)
	Overall	4181	1011	72	5264

¹ Participants with missing data on any of the three risk factors examined were classified as not having known risk factor

In our study, low eGFR was associated with occupation (farmers/fisherman more likely to have decreased eGFR), increasing age, and hypertension and was inversely associated with being underweight in fully adjusted analyses. These associations are similar to those found by Kalyesubula *et al.* in rural Uganda¹⁷. The high prevalence of CKD amongst rural participants and farmers has been documented in other literature¹⁸. Rural agricultural communities from Central America, Egypt, India, and Sri Lanka have reported a high prevalence of CKD of unknown etiology, and a clinical presentation suggestive of interstitial nephritis, confirmed by renal biopsies, with male farm workers affected disproportionately³. The rural site investigated in the study has a high population of males working in agricultural fields in similar circumstances to those studied in other regions and we could postulate that it has similar epidemiology, but more research is required. Alternately, the result could be confounded by higher creatinine levels due to the high muscle mass in this physically active group. Similarly, the lower odds of CKD in underweight participants may reflect reduced muscle bulk with lower creatinine production. As expected, loss of renal function in our study was associated with an older age. CKD may be a consequence of expected age-related renal function decline, accelerated in hypertension, diabetes, obesity, and primary renal disorders⁵. Similar studies in other settings have shown that an age of over 60, female gender, low educational status, increased waist circumference, hypertension, and diabetes were associated with low eGFR¹⁶. The high prevalence of CKD amongst hypertensive participants is in keeping with several similar studies carried out in SSA¹⁶. Inadequate blood pressure control may explain the prevalence of CKD observed⁷; however, poor renal function may also lead to an increase in blood pressure.

Our study also suggests an inverse association between renal impairment and diabetes. A survivor bias in the cross-sectional design may explain this association¹⁶, as it is possible that people with diabetes die before developing renal impairment, or that people with diabetes who develop renal impairment

have very poor survival. Additionally, hyperfiltration is a feature of early diabetic nephropathy, associated with a high eGFR. Early diabetic kidney disease would not be picked up from the eGFR alone, and may bias the results in the direction of diabetes being protective for kidney disease¹⁹.

The results of the study are useful because of the large sample size, the study of the general population rather than patients in a clinical setting, and the ability to compare between rural and urban populations. The previous study conducted in Lilongwe recruited participants attending a HIV Testing and Counselling Centre and may not be a good estimate of population prevalence. In particular, the prevalence of HIV in the study was greater than in the general population and the HIV-negative patients may have been symptomatic for other conditions, prompting self-referral for HIV testing⁹. As our study population is of a similar age and sex structure to the Malawian population and represent typical rural and urban populations, our results are likely to be representative of the rest of the country, and possibly to other similar populations in low resource and low income countries¹.

A limitation of our study was relying on serum creatinine for the measurement of CKD with no urine albumin:creatinine ratio, since classification of CKD stages one and two includes other evidence of renal damage including proteinuria, haematuria, or evidence of abnormal anatomy or systemic disease. Furthermore, CKD can only be formally diagnosed if low eGFR and/or a high urine albumin:creatinine ratio have been found at two different times, with at least a three month gap², and 30–40% of patients labelled as CKD stage 3A when the diagnosis is based on only a single eGFR determination move to 'normal'². Therefore, the reported prevalence of CKD might be overestimated⁷. However, as nearly all other prevalence studies have defined CKD based on a one-off measurement of eGFR <60 mL/min/1.73m², this does allow our results to be directly comparable to much of the published data^{2,20}. Furthermore, the study used CKD-EPI

equation in the determination of eGFR, which is considered to be a more accurate predictor of clinical risk than other serum-based equations, including the Modification of Diet in Renal Disease (MDRD) equation⁵. However, the CKD-EPI equation has not been validated for the African population, so it is possible that calculated eGFR is not reflecting the underlying kidney function accurately in our population. Finally, cross-sectional studies do not allow one to derive a causal inference, which is particularly important when considering the relationship between hypertension, diabetes and CKD.

Conclusion

Our study is the first to estimate population-level prevalence of CKD in urban and rural Malawi, and highlights that there is already a substantial burden of disease. With an ageing population and increasing prevalence of hypertension, this is likely to increase over the coming decades. Furthermore, in the absence of screening of high-risk individuals, diagnosis, and appropriate service provision, poor survival with CKD is likely and this estimated prevalence may mask a much higher incidence. Longitudinal research is urgently needed to increase understanding of CKD incidence, survival and validation of eGFR calculations in this population.

Data availability

Underlying data

The cross-sectional NCD data underlying this analysis are available for download via the LSHTM Data Compass Repository (<https://doi.org/10.17037/DATA.00000961>). However, owing

to data protection concerns, there are restrictions on access to this underlying data. Given their linkages to the longitudinal data produced by MEIRU, these data require anonymization using statistical disclosure control techniques to make them sufficiently safe for direct access. The anonymization process is scheduled for the last quarter of 2019. In the meantime, data access to bona fide researchers for specific research purposes is possible through completing a data request form on the LSHTM data compass repository. Once the anonymization process has been completed, direct access will be granted via the same repository.

Grant information

The baseline survey was funded by the Wellcome Trust through a Strategic Award (098610/Z/12/Z and 098610/B/12/A) awarded to Prof Moffat Nyirenda. The creatinine testing was supported by a project grant from the GSK Africa Non Communicable Disease Open Lab (Project number:8111) as part of a broader multicenter collaborative study between South Africa, Uganda, Malawi and the London School of Hygiene and Tropical Medicine, which is collectively identified as the African Research in Kidney Disease (ARK) Network.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We acknowledge GSK Open Lab and Wellcome Trust for their financial support during the different stages of this research.

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[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:



Version 1

Reviewer Report 17 October 2019

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Nombulelo P Magula 

Department of Internal Medicine, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal (UKZN), Durban, South Africa

The study compares renal function in a rural and urban population in sub-Saharan Africa. The authors have presented population data on renal function and risk factors.

The work adds to an important body of knowledge. The rationale for the study is clearly articulated. The methodology is sound and the results very well presented and interpreted.

Some of the variables used need justification.

The rationale to use the categorization of at least one alcoholic drink in the past 12 months versus no alcohol needs to be explained. The biological or clinical effects of one alcoholic drink in 12 months compared to an excessive alcohol drinker would be vastly different.

In this paper, hypertension was defined as "...one or more of: systolic blood pressure of 140mmHg or more; diastolic blood pressure of 90 mmHg or more; and any use of antihypertensive medication in the past two weeks." Yet in the published methods paper (Crampin AC et. al 2016¹), this was defined as "three blood pressure measurements, with 5 min resting time in between,...., and the average of the last two readings was used". The definition used in the methods of the two papers needs to be aligned.

The relationship found between diabetes and renal function is surprising and the attempt to explain the finding of diabetes being protective is reasonably explained. The limitation of urine examination not being done has been explicitly described.

In diabetes, retinal changes occur before the onset of nephropathy and this clinical detail should be alluded to in the attempts to explain the unexpected protective findings of diabetes. The lack of retinal examination in the study should be highlighted as a limitation in making the link between diabetes and nephropathy as found in this study. If the examination confirmed absence of retinopathy, then this would support a possibility that those with diabetes had early disease.

The effects of HIV infection are alluded to in the background, however, the stage of HIV disease or effects of antiretroviral treatment has not been explored. This needs to be addressed in the limitations.

Excellent work overall.

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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: HIV, TB, Non-Communicable diseases (cardiovascular, renal disease)

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 29 August 2019

<https://doi.org/10.21956/wellcomeopenres.16651.r35849>

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Richard K.D. Ephraim

Department of Medical Laboratory Technology, University of Cape Coast, Cape Coast, Ghana

A very good work which adequately reviewed existing data and used a rigorous methodology to establish the prevalence of CKD in urban and rural Malawi

However, though the authors examined the population for the presence of hypertension and diabetes mellitus I did not see any data on the duration of the diabetes and hypertension and even the therapy these patients or participants used. I think this is relevant since earlier studies have established a relationship between duration of these chronic conditions and CKD as well as the medications and CKD

Secondly the study of Ephraim *et al*¹ and also Janmohammed *et al*² estimated or identified evidence of kidney damage by measuring microalbuminuria or dipstick proteinuria

I realized that the authors did not mention anything on evidence of renal damage. Authors should provide reasons for this omission.

CKD diagnosis is either based on the KDIGO or KDOQI guidelines
Which of these did the authors use and why?

References

1. Ephraim RK, Biekpe S, Sakyi SA, Adoba P, Agbodjakey H, Antoh EO: Prevalence of chronic kidney disease among the high risk population in South-Western Ghana; a cross sectional study. *Can J Kidney Health Dis.* 2015; **2**: 40 [PubMed Abstract](#) | [Publisher Full Text](#)
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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?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephropathy (AKI and CKD) diagnosis hypertensive disorders of pregnancy

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.

Reviewer Report 15 August 2019

<https://doi.org/10.21956/wellcomeopenres.16651.r35749>

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Robert N. Peck 

Center for Global Health, Department of Medicine, Weill Cornell Medicine, New York City, NY, USA

In this large, population based, cross-sectional study of 5264 adults in urban and rural Malawi, the authors investigate the epidemiology of impaired renal function. The study population is a nested cohort within a much larger population based survey in Malawi that was conducted between 2013-2016. The outcome (impaired renal function) is defined by eGFR < 60 or <90 based on a single creatinine measurement. The methods are generally rigorous and well described and limitations are noted. The resulting analysis provides a useful snapshot of the distribution of kidney disease that will be valuable in guiding public health efforts to prevent and treat this important disease.

I recommend that several major and minor revisions should be made to this manuscript before it is indexed. I have described these concerns below.

Methods:

- Were the study areas truly either urban or rural? Were any of the areas peri-urban? is there any mining conducted in any of the study sites?
- A brief description of the sampling procedure that was used for selecting the 24,780 study participants from the source population should be provided in this manuscript. Authors can refer to the prior publications for details related to sampling procedure.
- What was the method for selecting the 5,264 serum samples that were tested from the 24,780 total study participants? The stratification is well described but was the sampling random within these strata?
- 3 blood pressure measurements were taken. How many of these were used to calculate the average blood pressure? Did participants with elevated blood pressure have repeat measurements conducted according to the guidelines?
- Diagnosis of diabetes mellitus depended on fasting glucose. What methods were used to ensure that the participant had actually fasted?
- Why was the CKD EPI equation without race correction chosen for this analysis? References should be provided to support this choice since this is the primary outcome and multiple GFR calculator options exist.

Statistical analysis/Interpretation

- Complete case analysis was used to deal with missing data. The pattern of missingness should be described in the methods section. Did missingness impact the selection of serum samples?

- 123 participants included in this analysis were pregnant. BMI was not calculated for these participants. Pregnancy is known to be related to eGFR (the outcome variable) and several of the exposure variables such as blood pressure. Could this be a hidden confounder in your analysis? What was the association between pregnancy and eGFR?

- In Table 2, some of the superscripts listed in the footnote are not clearly visible within the table.

Conclusions

- If I am interpreting Table 5 correctly, 58/72 of the participants with eGFR < 60 had HTN. This point should be emphasized in the discussion and the implications for linking HTN and kidney disease screening should be discussed.
- Are the fisherman/farmers exposed to schistosomiasis? Could this or some other helminthic infection explain the link between fisherman/farmers and CKD? This possibility should be discussed and references should be listed.

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?

Partly

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

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Epidemiology of NCDs in Africa

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.
