RESEARCH ARTICLE

REVISED Chronic kidney disease (CKD) and associated risk in rural South Africa: a population-based cohort study [version 2; peer review: 2 approved]

June Fabian[1,2], Mwawi Gondwe[1], Nokthula Mayindi[1], Shingirai Chipungu[1], Bongekile Khoza[1], Petra Gaylard[3], Alisha N Wade[1], F. Xavier Gómez-Olivé[1], Laurie A Tomlinson[4], Michele Ramsay[5], Stephen Tollman[1,6], Cheryl Winkler[7], Jaya A George[8,9], Saraladevi Naicker[10]

[1]Medical Research Council/Wits University Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng, 2193, South Africa
[2]Wits Donald Gordon Medical Centre, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, Gauteng, 2193, South Africa
[3]Data Management and Statistical Analysis, (DMSA), Johannesburg, Gauteng, 2193, South Africa
[4]Department of non-communicable disease epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK
[5]Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng, 2193, South Africa
[6]International Network for the Demographic Evaluation of Populations and their Health, (INDEPTH), Accra, Ghana
[7]Molecular Genetic Epidemiology Section, Basic Research Laboratory, Frederick National Laboratory for Cancer Research, NCI, Frederick, MD 21701, USA
[8]Department of Chemical Pathology, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, Gauteng, 2193, South Africa
[9]Department of Chemical Pathology, National Health Laboratory Service, Johannesburg, Gauteng, 2193, South Africa
[10]Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, Gauteng, 2193, South Africa

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Abstract

Background: In Africa, true prevalence of chronic kidney disease (CKD) is unknown, and associated clinical and genetic risk factors remain understudied. This population-based cohort study aimed to investigate CKD prevalence and associated risk factors in rural South Africa.

Methods: A total 2021 adults aged 20-79 years were recruited between 2017-2018 from the Agincourt Health and Socio-Demographic Surveillance System in Bushbuckridge, Mpumalanga, South Africa. The following were collected: sociodemographic, anthropometric, and clinical data; venous blood samples for creatinine, hepatitis B serology; DNA extraction; spot urine samples for dipstick testing and urine albumin: creatinine ratio (UACR)

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1. **Jennifer Lees**, University of Glasgow, Glasgow, UK

measurement. Point-of-care screening determined prevalent HIV infection, diabetes, and hypercholesterolemia. DNA was used to test for apolipoprotein L1 (*APOL1*) kidney risk variants. Kidney Disease Improving Global Outcomes (KDIGO) criteria were used to diagnose CKD as low eGFR (<60mL/min/1.73m^2) and /or albuminuria (UACR $\geq$ 3.0mg/mmol) confirmed with follow up screening after at least three months. eGFR was calculated using the CKD-EPI$_{(creatinine)}$ equation 2009 with no ethnicity adjustment. Multivariable logistic regression was used to model CKD risk.

Results: The WHO age-adjusted population prevalence of CKD was 6.7% (95% CI 5.4 - 7.9), mostly from persistent albuminuria. In the fully adjusted model, *APOL1* high-risk genotypes (OR 2.1; 95% CI 1.3 - 3.4); HIV infection (OR 1.8; 1.1 - 2.8); hypertension (OR 2.8; 95% CI 1.8 - 4.3), and diabetes (OR 4.1; 95% CI 2.0 - 8.4) were risk factors. There was no association with age, sex, level of education, obesity, hypercholesterolemia, or hepatitis B infection. Sensitivity analyses showed that CKD risk factor associations were driven by persistent albuminuria, and not low eGFR. One third of those with CKD did not have any of these risk factors.

Conclusions: In rural South Africa, CKD is prevalent, dominated by persistent albuminuria, and associated with *APOL1* high-risk genotypes, hypertension, diabetes, and HIV infection.

Keywords
chronic kidney disease, Africa, South Africa, hypertension, HIV infection, diabetes, apolipoprotein L1

2. **Ifeoma Ulasi**, University of Nigeria, Enugu, Nigeria
Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Ugochi Onu, University of Nigeria Teaching Hospital, Enugu, Nigeria

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: June Fabian (june.fabian@mweb.co.za)

Author roles: Fabian J: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation; **Gondwe M**: Methodology, Project Administration, Writing – Review & Editing; **Mayindi N**: Methodology, Project Administration, Writing – Review & Editing; **Chipungu S**: Project Administration, Resources, Supervision, Writing – Review & Editing; **Khoza B**: Project Administration, Resources, Validation, Writing – Review & Editing; **Gaylard P**: Formal Analysis, Writing – Review & Editing; **Wade AN**: Conceptualization, Supervision, Writing – Review & Editing; **Gómez-Olivé FX**: Conceptualization, Methodology, Project Administration, Supervision, Validation, Writing – Review & Editing; **Tomlinson LA**: Conceptualization, Funding Acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing; **Ramsay M**: Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Tollman S**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Winkler C**: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Writing – Review & Editing; **George JA**: Conceptualization, Funding Acquisition, Resources, Supervision, Validation, Writing – Review & Editing; **Naicker S**: Conceptualization, Funding Acquisition, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED **Amendments from Version 1**

In response to reviewer 1:

1. The acronym for WHO (World Health Organization) was added to the text.
2. A reference was inserted in the "Chronic kidney disease prevalence" methods section for "eGFR was calculated using the CKD-EPI $_{(creatinine)}$ equation 2009 without adjusting for African American ethnicity".

In response to reviewers 2:

1. Reviewers refer to a sample size of 66,817: to clarify, the Agincourt HDSS population was 66,817 and study sample was 2021.
2. Request for CKD-EPI with race/ethnicity adjustment: we referred reviewers to our recent study comparing measured GFR to estimated GFR showing race-based adjustments overestimate GFR in this study population. https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00239-X/fulltext

   We added an explanation and reference to this publication in the methods section "Chronic kidney disease prevalence" where we state "eGFR was calculated using the CKD-EPI (creatinine) equation 2009 without adjusting for African American ethnicity as race-based coefficients have been shown to overestimate GFR in this rural South African population".
3. We included data regarding prior vs incidental HIV and hypertension status, stratified by sex, in the footnote of Table 1.
4. We clarified with reviewers that point of care screening was performed for hypertension, HIV, anaemia, hypercholesterolaemia, and hyperglycaemia. If indicated, participants were referred for further investigation and/or treatment. Samples for eGFR and albuminuria testing were batched and shipped for laboratory testing and after obtaining results for kidney function, those with low eGFR (<60ml/min/1.73m^2) and/or albuminuria (urine albumin: creatinine ratio >3mg/mmol) were rescreened after a minimum of 3 months. There were no interventions during this minimum 3-month period. However, there may have been some overlap between those referred because of their point of care results (who may also have had low eGFR and/or albuminuria). We have addressed this as a limitation in the discussion section of the revised manuscript.
5. A biostatistician, Dr Petra Gaylard (co-author of paper) performed the statistical analysis.

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

Introduction

Infectious and non-communicable disease comprise substantial risk for chronic kidney disease (CKD) in Africa, but its true prevalence remains unknown. Methodological differences in sampling frames and criteria used to diagnose CKD, and limited understanding of the best measures to assess kidney function in African populations make prevalence data difficult to interpret. Recent large epidemiological studies have highlighted regional differences in CKD prevalence - which was lower in West Africa (Ghana and Burkina Faso) compared to East (Kenya) and South Africa, and higher in eastern compared to southern Uganda[1,2].

Risk factors associated with kidney disease are understudied. In many African studies traditional risk factors associated with CKD include hypertension, diabetes, HIV infection, older age, and female sex[1,3]. Studies from Tanzania, Malawi, Uganda and Kenya, suggest non-traditional risk factors are an important contributor to CKD risk[2,4,5]. These include endemic and other infectious diseases, such as undiagnosed genitourinary tuberculosis (TB), schistosomiasis, and viruses other than human immunodeficiency virus (HIV) which can manifest as nitrite-negative leukocyturia and/or hematuria, or tubulointerstitial injury related to occupational or environmental toxin exposure[3,5].

Compared to other US populations groups, African Americans have a three-to-four times higher risk of kidney failure associated with recessive inheritance of apolipoprotein L1 (*APOL1*) kidney risk variants (KRV)[6]. *APOL1* KRV comprise two missense single nucleotide polymorphisms (SNPs) defining the G1 allele and a six base pair-deletion defining the G2 allele. G1 and G2 alleles originated in West Africa with recent positive selection from protection against trypanosomal African sleeping sickness. *APOL1* KRV frequencies vary widely in Africa: Nigeria's Igbo and Yoruba people have the highest frequencies (40%), with lower frequencies in South Africa (18%), and near-absence in East Africa[7].

The role of *APOL1* KRV in the pathogenesis of CKD in African populations is unclear. *APOL1* KRV have been associated with hypertension-attributed and non-diabetic CKD in Democratic Republic of Congo and Nigeria, persistent albuminuria despite well-controlled HIV disease in Nigeria, and HIV-associated nephropathy, systolic hypertension and low eGFR in South Africa[2,8–11]. One familial study from South African failed to demonstrate an association between *APOL1* KRV and hypertension-attributed CKD compared to unaffected family members[12]. Recently, a large population-based study showed an association between *APOL1* KRV and albuminuria (but not eGFR), and this association was attenuated when compared to African American populations[13].

The aim of this study was to determine the prevalence of CKD and identify associated clinical and genetic risk factors in a rural South African population. We hypothesized that CKD prevalence would be high and associated with *APOL1* KRV, infectious and non-communicable disease.

Methods

Study setting and sampling strategy

This longitudinal cohort study was conducted from November 2017 to September 2018 in the Medical Research Council (MRC)/Wits Rural Public Health and Health Transitions Research Unit (otherwise referred to as "Agincourt") in Bushbuckridge, a rural subdistrict of the Mpumalanga province in north-eastern South Africa[14]. Agincourt is a health and socio-demographic surveillance system (HDSS) site that includes approximately

115,000 people. A minimum sample size of 1800 was required to provide at least 80% power to determine CKD prevalence of at least 5%, provided the true prevalence was equal to or more than 6.5%. Proportional allocation of Black African adults aged 20 to 79 years ensured a representative sample based on the most recent annual population census. Sample size was increased proportionately to 2759 individuals to accommodate a 25% non-participation rate.

Participant recruitment and study procedures

Ethics approval was obtained from the Medical Human Research Ethics Committee, University of the Witwatersrand (certificate number M170583). Trained fieldworkers and nurses performed home visits in 31 villages comprising the Agincourt HDSS. Written informed consent was obtained in the participant's first language (primarily Xitsonga). Participants with abnormal tests were referred to their local primary health care clinic for confirmatory testing and further management. Weight (kg) was measured using a digital scale and height was measured with a portable stadiometer (Seca, Germany). Height and weight were used to calculate body mass index (BMI) ((kg)/(m)^2. Blood pressure (BP) was measured using automated upper arm devices (Omron M6W, Intellisense BP785 large cuff, Japan). Participants were asked to sit comfortably with legs uncrossed for five minutes before taking readings. Three measurements were taken using an appropriate-sized cuff on the left arm at two-minute intervals. Of three BP readings, the first was discarded, and a mean of the second and third readings used for analyses. Nurses performed capillary point of care (POC) random cholesterol and random glucose testing (Cardiochek PA analyzer, PTS Panels test strips, PTS Diagnostics, USA). If a participant knew their HIV status as positive, this was recorded. If HIV status was unknown or participants previously tested negative, nurses offered voluntary POC screening and testing (Alere HIV Combo, Abbott, USA) according to South African Department of Health guidelines[15]. A positive test result was confirmed with a second test (Uni-Gold Recombigen HIV-1/2, Trinity BioTech, USA). Nurses collected blood samples and a freshly voided urine sample for laboratory testing. A spot urine pregnancy test was performed for premenopausal women (Abon One Step Pregnancy Test, Pharmaland, UAE). Samples were stored in isothermal bags (2 – 6 °C) with temperature monitoring (Easylog, Lascar Electronics, UK). After completing fieldwork, samples were delivered to the Agincourt Research laboratory for processing and storage at -80°C according to standard operation procedures.

Laboratory procedures

A 20µL aliquot of DNA was shipped to the Frederick National Laboratory at the National Cancer Institute, USA, for *APOL1* genotyping[16]. DNA was genotyped using TaqMan assays (ThermoFisher Scientific, USA). *APOL1* G1 KRV comprised a missense G nucleotide at rs73885319 (G1g) and either a T or G nucleotide at rs60910145; presence of only the G1g (p.342Gly) variant was sufficient to define the G1 KRV[17]. The *APOL1* G2 KRV consists of a six-base-pair in-frame deletion, rs717185313. The number of *APOL1* KRV (G1 or G2) carried by each participant was coded as 0 for the G0/G0 genotype, 1 for the G0/G1 or G0/G2 genotype, or 2 for the G1/G1, G1/G2, or G2G2 genotypes. *APOL1* genotypes were further coded as "high-risk (HR)" if the participant carried any combination of 2 risk alleles or "low-risk (LR)" if the participant had 0 or 1 risk allele. This classification was used for statistical analyses[16]. All remaining specimens were shipped at -80°C to the Central Laboratory Services (CLS) in Johannesburg, South Africa. Serum and urine creatinine was measured by an isotope-dilution mass spectrometry traceable modified Jaffe method, urine albumin by a colorimetric method (Cobas 6000/c501 analyzer), urine albumin:creatinine ratios (UACR) were calculated and reported (mg/mmol), and hepatitis B status was determined using Immulite serological assays (ARCHITECT i1000SR analyzer, Abbott USA). The CLS laboratory adhered to standard daily internal quality control procedures and complied with the requirements of the external quality control program through the College of American Pathologists.

Study procedures

For each participant, highest level of education was received from the Agincourt HDSS. Body mass index (BMI) was used to classify participants as underweight (< 18.5); normal (18.5 – 24.9); overweight (25.0 – 29.9); or obese (≥ 30.0)[18]. Participant blood pressure was classified according to the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as normotensive: systolic blood pressure (SBP) <120mmHg and diastolic blood pressure (DBP) <80mmHg; prehypertensive: SBP ≥120mmHg and <140mmHg or DBP ≥80mmHg and <90mmHg; and hypertensive: SBP ≥ 140mmHg or DBP ≥ 90mmHg[19]. Diabetes was defined as a non-fasting glucose ≥ 11.1mmol/L; and hypercholesterolaemia as a non-fasting total cholesterol > 5.0mmol/L[20,21].

Chronic kidney disease prevalence

Kidney Disease Improving Global Outcomes (KDIGO) criteria were used to diagnose CKD[22]. eGFR was calculated using the CKD-EPI$_{(creatinine)}$ equation 2009 without adjusting for African American ethnicity as race-based coefficients have been shown to overestimate GFR in this rural South African population[23]. Albuminuria was quantified with spot UACR. Participants with low eGFR (<60ml/min/1.73m^2), and/or albuminuria (UACR ≥3.0mg/mmol) were followed up with repeated measures after a minimum of three months. CKD was defined as low eGFR, or albuminuria, or a combination (low eGFR and/or albuminuria) provided these measures were confirmed on repeat testing, and this definition was used for all analyses.

Statistical analysis

Continuous variables were represented as mean (standard deviation [SD]) if normally distributed and median (interquartile range) if non-normally distributed. Categorical variables were expressed as frequencies (percentage). Study variables were compared between sexes using the chi-squared test (Fisher's exact test was used for 2×2 tables). To identify factors associated with CKD, logistic regression analysis was used

to estimate odds ratios (OR), with corresponding 95% confidence intervals (CIs). Hierarchical models based on existing knowledge of known CKD risk factors were developed with all models, age- and sex-adjusted. Model 1 incorporated level of education and BMI. Model 2 added *APOL1* genotype status, and Model 3 added comorbid infectious and non-communicable conditions: hepatitis B, HIV, hypertension, diabetes, and hypercholesterolaemia. Nested models were compared using the likelihood ratio test. Because CKD was a composite variable (low eGFR and/or albuminuria), sensitivity analyses compared whether there were differences in association between risk factors and (i) low GFR alone, or (ii) albuminuria alone. Missing data were reported in figures and tables. CKD population prevalence was age-standardized using the revised World Health Organization (WHO) World Standard Population Distribution for ages 20–79 (direct method)[24,25]. Statistical analyses were performed using SAS (Stata Corp, Texas, USA) and can be performed in R (R Core Team, 2014)[26].

Results

The flow diagram in Figure 1 details sample selection, reasons for non-participation, and CKD screening procedures. Overall, 2021/2759 adults consented (73% participation rate), with the final study sample representative of the Agincourt HDSS population (Figure 2). Participant socio-demographic and clinical characteristics overall, and stratified by sex, are summarized in Table 1. For participants with complete data for eGFR and UACR (n=2004): 32 had low eGFR at first screening, and of these, 12/29 (41%) were confirmed with low eGFR at follow-up; 247 had albuminuria at first screening, and of

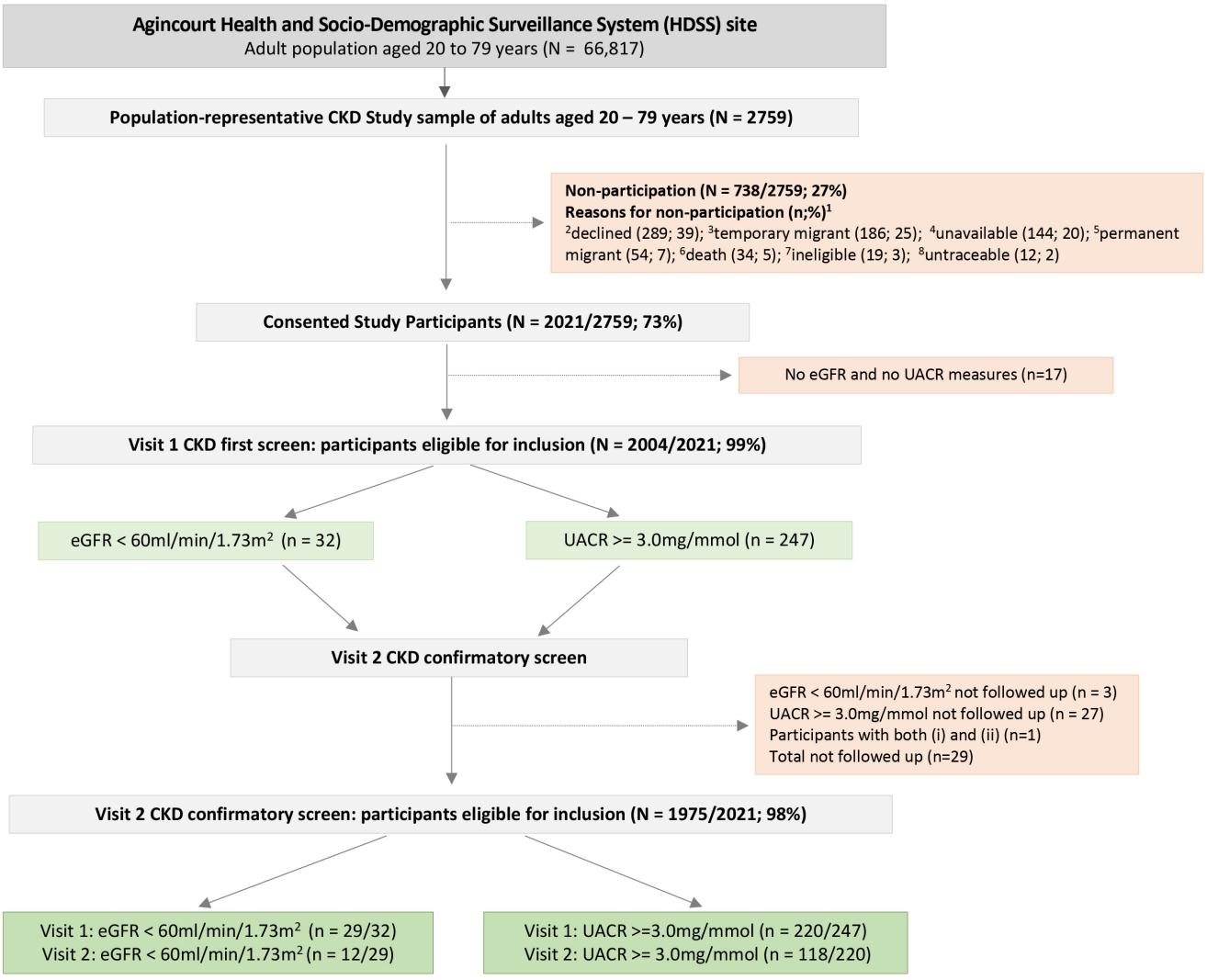

Figure 1. Flow diagram depicting study sample selection, participant recruitment, and CKD screening strategy.

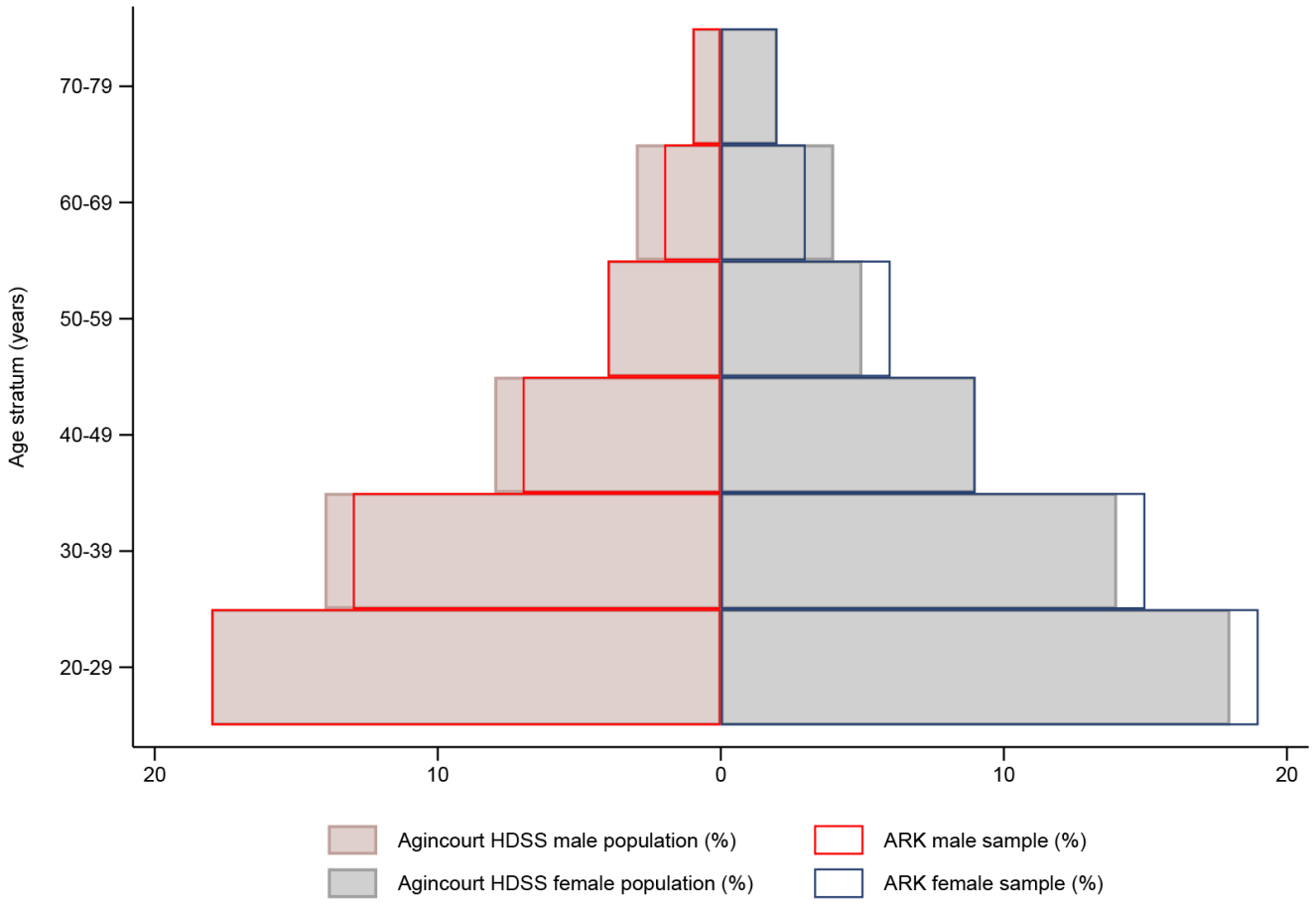

Figure 2. Comparison of the study sample with Agincourt HDSS population stratified by age and sex.

these, 118/220 (54%) were confirmed with albuminuria at follow-up (Figure 1). Overall, the WHO age-standardized prevalence for low eGFR was 0.9% (95% CI 0.4 - 1.4); for albuminuria was 6.2% (95% CI 5.0 - 7.4), and for CKD (low eGFR and/or albuminuria) was 6.7% (95% CI 5.4 - 7.9).

Results from multivariable adjusted logistic regression analyses are summarised in Table 2. In the fully adjusted model, CKD was associated with diabetes (OR 4.0; 95% CI 1.9 - 8.3), hypertension (OR 2.8; 95% CI 1.8 - 4.3), high-risk *APOL1* genotype (OR 2.1; 95% CI 1.3 - 3.4), and HIV infection (OR 1.8; 95% CI 1.1 - 2.8). CKD was not associated with age, sex, level of education, BMI, hepatitis B infection or hypercholesterolaemia. Because CKD was a composite variable, sensitivity analyses were conducted to determine whether the associations observed were driven by low eGFR or albuminuria. The number of events was too small for a sensitivity analysis restricted to eGFR <60mL/min/1.73m^2. Instead, a sensitivity analysis was performed using eGFR <90mL/min/1.73m^2 on initial screen which showed an association with advancing age, obesity, and diabetes, but not with *APOL1* high-risk genotypes, HIV infection, or hypertension (Table 3). For albuminuria, two sensitivity analyses were performed for those with albuminuria on (i) initial screening, and (ii) follow up screening (Table 4–Table 5). Both confirmed associations observed with the composite endpoint (CKD defined as low eGFR and/or albuminuria) were primarily driven by persistent albuminuria.

For participants with CKD, overall, there was no identified risk factor in 32% (37/117) of participants (Table 6), most had one risk factor, and none had more than three. Women had fewer identified risk factors than men. CKD risk factors included those identified in the multivariable regression analyses: high-risk *APOL1* genotype, hypertension, HIV infection, and diabetes.

Discussion

This rigorously conducted study determined CKD prevalence in a rural South African population using recommended KDIGO criteria for eGFR and albuminuria with confirmatory testing. Far more than low eGFR, persistent albuminuria was the

Table 1. Sociodemographic and clinical characteristics of the study participants.

Variable[1]	Men, N (%) (N = 851)	Women, N (%) (N = 1170)	Overall, N (%) (N = 2021)
Age (years) median (IQR)	35 (27 – 47)	34 (25 – 45)	35 (27 – 48)
20 – 39 years N (%)	557 (65.5)	705 (60.3)	1262 (62.4)
40 – 59 years N (%)	227 (26.7)	329 (28.1)	556 (27.5)
60 – 79 years N (%)	67 (7.9)	136 (11.6)	203 (10.0)
[2]**Serum creatinine (µmol/L)** mean (SD)	73 (15)	56 (13)	63 (16)
[2]**estimated GFR (ml/min/1.73m²)** mean (SD)	112 (17)	112 (19)	112 (18)
[3]**UACR (mg/mmol)** median (IQR)	0.3 (0.2 – 1.0)	0.5 (0.3 – 1.3)	0.4 (0.2 – 1.2)
[4]**Highest education level**			
No formal education N (%)	47 (5.6)	135 (11.7)	182 (9.1)
Less than six years completed N (%)	65 (7.7)	94 (8.1)	159 (7.9)
Six or more years completed N (%)	733 (86.8)	928 (80.2)	1661 (83.0)
[5]**BMI (kg/m²)**			
Normal (BMI 18.5 - 24.99)	493 (58.0)	277 (24.9)	770 (39.2)
Underweight (BMI < 18.5)	55 (6.5)	28 (2.5)	83 (4.2)
Overweight (BMI (25.0 - 29.99)	206 (24.2)	365 (32.8)	571 (29.1)
Obese (BMI >= 30.0)	96 (11.3)	444 (39.9)	540 (27.5)
[6]***APOL1* Low-risk** (zero or one risk allele) N (%)	745 (88.3)	1031 (89.0)	1776 (88.7)
[6]***APOL1* High-risk** (two risk alleles) N (%)	99 (11.7)	127(11.0)	226 (11.3)
[7]**Blood pressure**			
Normal N (%)	212 (24.9)	543 (46.4)	755 (37.4)
Pre-hypertension N (%)	452 (53.1)	445 (38.0)	897 (44.4)
Hypertension	187 (22.0)	182 (15.6)	369 (18.3)
[8]**Diabetes** N (%)	21 (2.5)	50 (4.3)	71 (3.5)
[9]**Hypercholesterolaemia** N (%)	144 (16.9)	321 (27.4)	465 (23.0)
[10]**Hepatitis B infection** N (%)	40 (4.7)	40 (3.4)	80 (4.0)
[11]**HIV infection** N (%)	102 (12.0)	278 (23.8)	380 (18.8)
[12]**Normoalbuminuric nitrite negative leukocyturia** N (%)	124 (16.9)	354 (38.0)	478 (28.7)
[13]**Normoalbuminuric haematuria** N (%)	179 (24.4)	294 (31.6)	473 (28.4)

[1]Percentages may sum to +/- 100 from rounding; for missing data : [2]Serum creatinine and estimated GFR from first screening: n=1169 for women; n=2020 overall; [3]UACR: urine albumin: creatinine ratio from first screening: n=845 for men; n=1160 for women; n=2005 overall; [4]Highest level of education: n=845 for men; n=1157 for women; n=2002 overall; [5]Body mass index (BMI) = weight (kg)/height (m²): excluded pregnant women n=53; n=850 for men; n=1114 for women; n=1964 overall; [6]*APOL1* risk genotypes: n=844 for men; n=1158 for women; n=2002 overall; [7]normal: SBP < 120mmHg and DBP < 80mmHg; pre-hypertension: SBP ≥ 120mmHg and < 140mmHg or DBP ≥ 80mmHg and < 90mmHg; hypertension: SBP ≥ 140mmHg or DBP ≥ 90mmHg; women with hypertension: 90/182 (49.5%) were previously tested and informed they were hypertensive; 78/182 (42.9%) were previously tested and informed they were normotensive; 14/182 (7.7%) had not been tested; men with hypertension: 55/187 (29.4%) were previously tested and informed they were hypertensive; 93/187 (49.7%) were previously tested and informed they were normotensive; 39/187 (20.9%) had not been tested; [8]Diabetes: non-fasting glucose >= 11.1mmol/L; [9]Hypercholesterolaemia: non-fasting total cholesterol > 5.0mmol/L; [10]Hepatitis B infection: n=851 for men; n=1169 for women; n=2020 overall; [11]HIV Infection: women testing positive: 259/278 (93.2%) had prior knowledge of their status; 15/278 (5.4%) had previously tested negative; 4/278 (1.4%) had no prior testing; men testing positive: 88/102 (86.2%) had prior knowledge of their status; and 7/102 (6.9%) each, had previously tested negative or had no prior testing. [12]Urine dipstick results from first screening; excluded pregnant women n=53; n=734 for men; n=931 for women; n=1665 overall; [13]Urine dipstick results from first screening; excluded pregnant women n=53; n=735 for men; n=931 for women; n=1666 overall.

Table 2. CKD prevalence and model-adjusted odds ratios for CKD risk by socio-demographic factors, *APOL1* status, infectious and non-communicable comorbidity.

Variable	Overall N = 1975[1] n (%)	CKD N = 124 (6.3%) n (%)	All models age- and sex-adjusted		
			Model 1[2] Adjusted for education, BMI	Model 2[2] Adjusted for education, BMI, *APOL1* genotype	Model 3[2] Adjusted for education, BMI, *APOL1* genotype, hepatitis B, HIV status, hypertension, diabetes, hypercholesterolemia
Age (years)					
20 – 39	1234 (62.5)	70 (5.7)	1.00 *reference*	1.00 *reference*	1.00 *reference*
40 – 59	546 (27.6)	34 (6.2)	1.07 (0.67 – 1.68)	1.08 (0.68 – 1.72)	0.70 (0.43 – 1.15)
60 – 79	195 (9.9)	20 (10.3)	1.52 (0.76 – 3.07)	1.55 (0.77 – 3.13)	0.82 (0.38 – 1.76)
Sex					
Male	829 (42.0)	55 (6.6)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Female	1146 (58.0)	69 (6.0)	0.85 (0.57 – 1.26)	0.85 (0.57 – 1.27)	0.88 (0.58 – 1.34)
Education					
No education	179 (9.2)	14 (7.8)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Less than six years	155 (7.9)	15 (9.7)	1.42 (0.65 – 3.13)	1.38 (0.63 – 3.04)	1.24 (0.55 – 2.80)
Six or more years	1622 (82.9)	93 (5.7)	0.93 (0.44 – 1.93)	0.91 (0.43 – 1.89)	0.86 (0.41 – 1.81)
[3]BMI (kg/m²)					
Non-obese	1388 (72.4)	89 (6.4)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Obese	530 (27.6)	31 (5.8)	0.89 (0.56– 1.42)	0.87 (0.55 – 1.39)	0.67 (0.41 – 1.09)
***APOL1* genotype**					
Low-risk	1737 (88.7)	99 (5.7)		1.00 *reference*	1.00 *reference*
High-risk	221 (11.3)	24 (10.9)		**2.16 (1.34 – 3.48)**	**2.10 (1.29 – 3.42)**
Hepatitis B status					
negative	1897 (96.1)	118 (6.2)			1.00 *reference*
positive	78 (3.9)	6 (7.7)			0.93 (0.33 – 2.63)
HIV status					
negative/unknown	1602 (81.1)	94 (5.9)			1.00 *reference*
positive	373 (18.9)	30 (8.0)			**1.78 (1.12 – 2.83)**
Blood pressure					
No hypertension	1617 (81.9)	80 (4.9)			1.00 *reference*
hypertension	358 (18.1)	44 (12.3)			**2.76 (1.78 – 4.27)**
Diabetes					
absent	1909 (96.7)	110 (5.8)			1.00 *reference*
present	66 (3.3)	14 (21.2)			**4.00 (1.93 – 8.29)**
Hypercholesterolaemia					
absent	1524 (77.2)	85 (5.6)			1.00 *reference*
present	451 (22.8)	39 (8.6)			1.37 (0.87 – 2.14)

Column percentages may sum to +/-100 due to rounding; odds ratios presented with 95% confidence intervals; categories presented as frequency (%); [1]N = 1975: total number eligible for inclusion after CKD screening and follow up; [2]N = 1885: total number with complete data for variables included in regression models; [3]BMI: body mass index: non-obese <30.0; obese BMI >= 30.0; Bold text indicates 5% level of significance (p-value <0.05).

Table 3. eGFR <90mL/min/1.73m² (on initial screen) and model-adjusted odds ratios by socio-demographic factors, *APOL1* status, infectious and non-communicable comorbidity.

			All models age- and sex-adjusted		
Variable[1]	**Overall N = 1975 n (%)**	**eGFR <90[2] N = 220 n (%)**	**Model 1 Adjusted for education, BMI**	**Model 2 Adjusted for education, BMI, *APOL1* genotype**	**Model 3 Adjusted for education, BMI, *APOL1* genotype, hepatitis B, HIV status, hypertension, diabetes, hypercholesterolemia**
Age (years)					
20 – 39	1234 (62.5)	43 (3.5)	1.00 *reference*	1.00 *reference*	1.00 *reference*
40 – 59	546 (27.6)	81 (14.8)	**4.60 (3.08 – 6.86)**	**4.59 (3.07 – 6.85)**	**4.13 (2.73 – 6.26)**
60 – 79	195 (9.9)	96 (49.2)	**26.1 (15.5 – 43.7)**	**26.0 (15.5 – 43.7)**	**22.1 (12.9 – 37.9)**
Sex					
Male	829 (42.0)	90 (10.9)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Female	1146 (58.0)	130 (11.3)	0.74 (0.52 – 1.04)	0.75 (0.52 – 1.04)	0.75 (0.53 – 1.07)
Education					
No education	179 (9.2)	53 (32.4)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Less than six years	155 (7.9)	34 (21.9)	0.83 (0.48 – 1.43)	0.83 (0.48 – 1.44)	0.75 (0.53 – 1.07)
Six or more years	1622 (82.9)	127 (7.8)	0.99 (0.61 – 1.61)	1.00 (0.61 – 1.62)	0.82 (0.47 – 1.42)
[3]BMI (kg/m²)					
Non-obese	1388 (72.4)	133 (9.6)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Obese	530 (27.6)	86 (16.2)	**1.61 (1.13 – 2.28)**	**1.61 (1.13 – 2.28)**	**1.46 (1.02 – 2.49)**
***APOL1* genotype**					
Low-risk	1737 (88.7)	197 (11.3)		1.00 *reference*	1.00 *reference*
High-risk	221 (11.3)	22 (10.0)		0.93 (0.55 – 1.55)	0.93 (0.56 – 1.57)
Hepatitis B status					
negative	1897 (96.1)	207 (10.9)			1.00 *reference*
positive	78 (3.9)	13(16.7)			1.33 (0.65 – 2.71)
HIV status					
negative/unknown	1602 (81.1)	177 (11.0)			1.00 *reference*
positive	373 (18.9)	43 (11.5)			1.07 (0.71 – 1.61)
Blood pressure					
No hypertension	1617 (81.9)	150 (9.3)			1.00 *reference*
hypertension	358 (18.1)	70 (19.6)			1.18 (0.82 – 1.71)
Diabetes					
absent	1909 (96.7)	192 (10.1)			1.00 *reference*
present	66 (3.3)	28 (42.4)			**2.06 (1.13 – 3.75**)
Hypercholesterolaemia					
absent	1524 (77.2)	137 (9.0)			1.00 *reference*
present	451 (22.8)	83 (18.4)			1.09 (0.77 – 1.56)

[1]Column percentages may sum to +/-100 due to rounding; odds ratios presented with 95% confidence intervals; categories presented as frequency (%); [2]eGFR<90: estimated GFR less than 90ml/min/1.73m²; [3]BMI: body mass index: non-obese <30.0; obese BMI >= 30.0; Bold text indicates 5% level of significance (p-value <0.05)

Table 4. Albuminuria (on initial screen) and model-adjusted odds ratios by socio-demographic factors, *APOL1* status, infectious and non-communicable comorbidity.

			All models age- and sex-adjusted		
Variable[1]	**Overall N = 1975 n (%)**	**Albuminuria N= 220 n (%)**	**Model 1 Adjusted for education, BMI**	**Model 2 Adjusted for education, BMI, *APOL1* genotype**	**Model 3 Adjusted for education, BMI, *APOL1* genotype, hepatitis B, HIV status, hypertension, diabetes, hypercholesterolemia**
Age (years)					
20 – 39	1234 (62.5)	122 (9.9)	1.00 *reference*	1.00 *reference*	1.00 *reference*
40 – 59	546 (27.6)	70 (12.8)	1.34 (0.95 – 1.89)	1.36 (0.96 - 1.91)	1.00 (0.70 - 1.45)
60 – 79	195 (9.9)	28 (14.4)	1.33 (0.76 – 2.35)	1.34 (0.76 – 2.37)	0.81 (0.44 - 1.50)
Sex					
Male	829 (42.0)	84 (10.1)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Female	1146 (58.0)	136 (11.9)	1.08 (0.79 – 1.48)	1.08 (0.79 - 1.48)	1.12 (0.81 - 1.55)
Education					
No education	179 (9.2)	22 (12.3)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Less than six years	155 (7.9)	25 (16.1)	1.53 (0.81 – 2.89)	1.50 (0.80 – 2.83)	1.47 (0.76 – 2.77)
Six or more years	1622 (82.9)	171 (10.5)	1.06 (0.60 – 1.87)	1.04 (0.59 – 1.85)	1.00 (0.57 – 1.84)
[2]BMI (kg/m²)					
Non-obese	1388 (72.4)	146 (10.5)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Obese	530 (27.6)	64 (12.1)	1.08 (0.77 – 1.52)	1.07 (0.76 – 1.50)	0.90 (0.63 - 1.28)
***APOL1* genotype**					
Low-risk	1737 (88.7)	186 (10.7)		1.00 *reference*	1.00 *reference*
High-risk	221 (11.3)	33 (14.9)		**1.57 (1.05 – 2.36)**	**1.54 (1.02 – 2.33)**
Hepatitis B status					
negative	1897 (96.1)	209 (11.0)			1.00 *reference*
positive	78 (3.9)	11 (14.1			1.03 (0.48 - 2.21)
HIV status					
negative/unknown	1602 (81.1)	170 (10.6)			1.00 *reference*
positive	373 (18.9)	50 (13.4)			1.43 (0.99 - 2.06)
Blood pressure					
No hypertension	1617 (81.9)	155 (9.6)			1.00 *reference*
hypertension	358 (18.1)	65 (18.2)			**1.94 (1.36 – 2.76)**
Diabetes					
absent	1909 (96.7)	198 (10.4)			1.00 *reference*
present	66 (3.3)	22 (33.3)			**3.79 (2.08 – 6.88)**
Hypercholesterolaemia					
absent	1524 (77.2)	154 (10.1)			1.00 *reference*
present	451 (22.8)	66 (14.6)			1.26 (0.89 – 1.79)

[1]Column percentages may sum to +/-100 due to rounding; odds ratios presented with 95% confidence intervals; categories presented as frequency (%);[2]BMI: body mass index: non-obese <30.0; obese BMI >= 30.0; Bold text indicates 5% level of significance (p-value <0.05).

Table 5. Albuminuria (confirmed with follow up) and model-adjusted odds ratios by socio-demographic factors, *APOL1* status, infectious and non-communicable comorbidity.

			All models age- and sex-adjusted		
Variable[1]	**Overall N = 1975 n (%)**	**Albuminuria N = 118 n (%)**	**Model 1 Adjusted for education, BMI**	**Model 2 Adjusted for education, BMI, *APOL1* genotype**	**Model 3 Adjusted for education, BMI, *APOL1* genotype, hepatitis B, HIV status, hypertension, diabetes, hypercholesterolemia**
Age (years)					
20 – 39	1234 (62.5)	69 (5.6)	1.00 *reference*	1.00 *reference*	1.00 *reference*
40 – 59	546 (27.6)	33 (6.0)	1.02 (0.64 – 1.63)	1.05 (0.65 - 1.68)	0.69 (0.42 – 1.15)
60 – 79	195 (9.9)	16 (8.2)	1.11 (0.52 – 2.36)	1.13 (0.53 – 2.40)	0.61 (0.27 – 1.48)
Sex					
Male	829 (42.0)	53 (6.4)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Female	1146 (58.0)	65 (5.7)	0.82 (0.54 – 1.23)	0.82 (0.55 - 1.24)	0.85 (0.55 – 1.30)
Education					
No education	179 (9.2)	13 (7.3)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Less than six years	155 (7.9)	13 (8.4)	1.25 (0.55 – 2.87)	1.21 (0.53 – 2.78)	1.08 (0.46 – 2.54)
Six or more years	1622 (82.9)	90 (5.5)	0.81 (0.38 – 1.73)	0.79 (0.37 – 1.70)	0.76 (0.35 – 1.63)
[2]BMI (kg/m^2)					
Non-obese	1388 (72.4)	84 (6.1)	1.00 *reference*	1.00 *reference*	1.00 *reference*
Obese	530 (27.6)	30 (5.7)	0.95 (0.59 - 1.51)	0.92 (0.58 – 1.48)	0.72 (0.44 - 1.18)
***APOL1* genotype**					
Low-risk	1737 (88.7)	93 (5.4)		1.00 *reference*	1.00 *reference*
High-risk	221 (11.3)	24 (10.9)		**2.31 (1.43 – 3.72)**	**2.23 (1.37 – 3.64)**
Hepatitis B status					
negative	1897 (96.1)	112 (5.9)			1.00 *reference*
positive	78 (3.9)	6 (7.7)			0.97 (0.34 - 2.77)
HIV status					
negative/unknown	1602 (81.1)	90 (5.6)			1.00 *reference*
positive	373 (18.9)	28 (7.5)			**1.70 (1.06 - 2.73)**
Blood pressure					
No hypertension	1617 (81.9)	78 (4.8)			1.00 *reference*
hypertension	358 (18.1)	40 (11.2)			**2.56 (1.63 – 4.00)**
Diabetes					
absent	1909 (96.7)	106 (5.6)			1.00 *reference*
present	66 (3.3)	12 (18.2)			**3.54 (1.64 – 7.60)**
Hypercholesterolaemia					
absent	1524 (77.2)	81 (5.3)			1.00 *reference*
present	451 (22.8)	37 (8.2)			1.45 (0.92 – 2.30)

[1]Column percentages may sum to +/-100 due to rounding; odds ratios presented with 95% confidence intervals; categories presented as frequency (%);
[2]BMI: body mass index: non-obese <30.0; obese BMI >= 30.0; Bold text indicates 5% level of significance (p-value <0.05).

Table 6. Distribution of risk factors in those with and without CKD overall, and by sex.

Number of CKD risk factors[1]	Overall N (%)	No CKD N(%)	CKD N (%)
Overall	**N = 1885**	**N = 1768**	**N = 117**
0	1059 (56.2)	1022 (57.8)	37 (31.6)
1	682 (36.2)	628 (35.5)	54 (46.2)
2	131 (6.9)	109 (6.2)	22 (18.8)
3	13 (0.7)	9 (0.5)	4 (3.4)
Men	**N = 815**	**N = 760**	**N = 55**
0	482 (59.1)	467 (61.4)	15 (27.3)
1	280 (34.4)	251 (33.0)	29 (52.7)
2	47 (5.8)	38 (5.0)	9 (16.4)
3	6 (0.7)	4 (0.5)	2 (3.6)
Women	**N = 1070**	**N = 1008**	**N = 62**
0	577 (53.9)	555 (55.1)	22 (35.5)
1	402 (37.6)	377 (37.4)	25 (40.3)
2	84 (7.9)	71 (7.0)	13 (21.0)
3	7 (0.7)	5 (0.5)	2 (3.2)

[1]CKD risk factors: from multivariable regression analysis we identified as APOL1 high-risk genotype; HIV infection, hypertension, and diabetes.

dominant kidney function abnormality and the primary driver of observed associations with *APOL1* high-risk genotypes, HIV infection, hypertension, and diabetes. There were no significant associations with age, sex, level of education, obesity, hepatitis B infection, or hypercholesterolemia.

There are several strengths to the study including the rural population-based sampling frame, combined evaluation of eGFR and albuminuria, and confirmation with follow-up testing which reduced the risk of over-reporting prevalent kidney disease. The strong contribution of persistent albuminuria to CKD prevalence is relevant, as many large epidemiological studies rely solely on the estimation of GFR. Limitations include evaluation of few non-traditional risk factors for CKD, and low power for evaluating risk in those with eGFR <60mL/min/1.73m^2. Participants with hypertension, HIV (not on treatment), anaemia, hypercholesterolaemia, and hyperglycaemia were referred to their local care facility for further investigation and/or treatment. In so doing, those with concomitant low eGFR and / or albuminuria at baseline might have received treatment that affected subsequent kidney function testing. The relatively small proportion of participants with low eGFR might be explained by the absence of appropriate care for those with severe kidney disease, thus creating a survival bias, or potential to overestimate creatinine-based GFR with the CKD-EPI$_{(creatinine)}$ equation with consequent underdiagnosis of CKD[27].

The association of *APOL1* high-risk genotypes with persistent albuminuria is consistent with population-based studies in continental African and African American populations[13,28,29]. While the population frequencies of *APOL1* high-risk genotypes approximated those reported in African Americans (~10–15%) and the association with persistent albuminuria similar, our study did not show any association with low eGFR[7]. This might relate to limited analytic power because so few had low eGFR, but it is worth noting that similar findings have been described in a population-based study from West, East, and Southern Africa[13]. The absence of longitudinal follow-up to evaluate the impact of *APOL1* status on incident CKD, CKD progression, and survival restrict interpretation of current findings.

The study confirmed known associations with HIV infection, hypertension, and diabetes[2,30,31], but one third of participants with CKD had none of these risk factors. Potential context-specific risk for kidney disease not accounted for in this study include endemic malaria, endemic genitourinary schistosomiasis, genitourinary tuberculosis, ingestion of traditional and over-the-counter medicines, and environmental exposures such as agricultural pesticides and heavy metal toxins[32–34]. Such exposures might result in repeated bouts of acute, or acute-on-chronic kidney injury, or comprise the "second hit" needed for *APOL1*-induced kidney injury.

Our findings show that CKD is prevalent and those with HIV infection, hypertension, and diabetes may benefit from screening strategies to control risk and prevent progression. Research is needed to evaluate performance of creatinine-based eGFR equations in African populations and investigate the contribution of genetic and non-traditional risk factors to CKD risk in South Africa.

Data availability

Underlying data

WIReDSpace: Dataset from: Chronic kidney disease (CKD) and associated risk in rural South Africa: a population-based cohort study, https://doi.org/10.54223/uniwitwatersrand-10539-33016[35]

This project contains the following underlying data:

- Readme Orginal
- data in github format
- plain text data
- dataset in xlsx

Acknowledgments

Study data were collected and managed using opensource REDCap electronic data capture tools hosted at the University of the Witwatersrand[36,37].

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Version 2

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✔ **Ifeoma Ulasi**
[1] Department of Medicine, College of Medicine, University of Nigeria, Enugu, Nigeria
[2] Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Ugochi Onu
Department of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

We have reviewed the revised version. We are satisfied.

Thank you for the opportunity to be part of this review process.

Competing Interests: No competing interests were disclosed.

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

Version 1

Reviewer Report 19 October 2022

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? **Ugochi Onu**
Department of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

Ifeoma Ulasi
[1] Department of Medicine, College of Medicine, University of Nigeria, Enugu, Nigeria
[2] Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria

Thank you for inviting us to review this manuscript. Knowing that there are not many large population community studies on kidney disease emanating from Africa, this is a step in the right direction. Most of the CKD data in Africa are hospital-based.

The paper presents a much-needed perspective to studying kidney disease in Africa, looking at traditional risk factors as well as chronic viruses (HIV, hepatitis B virus except for hepatitis C virus) and some other non-traditional risk factors.

The strengths of this study, including the large number of adults recruited (66,817), are quite commendable, as rural community recruitment of participants for a study is certainly an enormous task. However, the reason for selecting adults from 20 years of age was not stated. Recruiting participants from 18 years recognized globally as the onset of adulthood may have been more inclusive and good for comparison with other studies.

Furthermore, there is still a paucity of data on genetic studies in Africa, including the link between CKD and genes; this study going beyond the traditional CKD risk factors in Africa to include genomics is remarkable.

We agree and applaud the use of CKD-EPI without race/ethnicity adjustment. Still, it will be good to include that with race/ethnicity adjustment for clarity and future reference. The jury is not quite out in considering the use or not of the race/ethnicity adjustments.

It will be nice to state how many hypertensive participants had pre-existing hypertension or incidental diagnosis. Similarly, prior vs. incidental HIV diagnosis should have been documented.

At the first screening, certain patients had hypertension and/or impaired renal function (eGFR /albuminuria); any intervention done between the initial and second screenings should have been documented. Perhaps, these interventions could explain the drop in the number of participants with eGFR <60mls/min/1.73m^2 or albuminuria from 220 to 118 and 29 to 12, respectively.

Though the statistical analysis seems adequate, a statistician may also review that aspect.

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.

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

Author Response 26 Oct 2022

June Fabian, University of the Witwatersrand, Johannesburg, South Africa

Thank you for your review.

Response to reviewers:

1. "The strengths of this study, including the large number of adults recruited (66,817), are quite commendable, as rural community recruitment of participants for a study is certainly an enormous task."
   - *To clarify, the Agincourt Health and Demographic Surveillance System had a population of 66,817 adults aged 20-79 years from which our representative sample of 2021 consented participants was derived (Figures 1 and 2).*

*2. "*We agree and applaud the use of CKD-EPI without race/ethnicity adjustment. Still, it will be good to include that with race/ethnicity adjustment for clarity and future reference. The jury is not quite out in considering the use or not of the race/ethnicity adjustments."

Thank you for your comments. We would like to bring the following to the reviewers' attention, as this addresses your concerns:
   - *As a sequel to this study, we selected a subgroup of participants stratified by eGFR and sex (N=986) for a measured GFR study using iohexol as the reference. We showed that inclusion of race-based coefficients overestimated GFR in this rural South African population, and our findings were replicated in our partner country study sites, Malawi and Uganda. Please see reference:*

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00239-X/fulltext
Fabian J, Kalyesubula R, Mkandawire J, et al.: Measurement of kidney function in Malawi, South Africa, and Uganda: a multicentre cohort study. The Lancet Global Health. 2022;10(8):e1159-e1169.

Given the biodiversity of African populations, we cannot assume our findings are generalisable. However, the participants in the iohexol measured GFR study were the same as those in our population-based sample, and we have shown unequivocally that race-based coefficients overestimate measured GFR in this population, so this effect on eGFR is clear. As such, we do not

feel it is necessary to include the eGFR results with a race-based adjustment in this paper, as it has been addressed separately with reference to measured GFR - the gold standard for evaluating performance of eGFR equations.

To make this clear in the revised manuscript, we added the above reference to the methods section "Chronic kidney disease prevalence" where we state "eGFR was calculated using the CKD-EPI $_{(creatinine)}$ equation 2009 without adjusting for African American ethnicity as race-based coefficients have been shown to overestimate GFR in this rural South African population". (tracked changes)

3. "It will be nice to state how many hypertensive participants had pre-existing hypertension or incidental diagnosis. Similarly, prior vs. incidental HIV diagnosis should have been documented."
Thank you, we collected these data, stratified by sex:

Women: HIV prevalence was 23.8% (278/1170). Of those who tested positive:
- *259/278 (93.2%) had prior knowledge of their status*
- *15/278 (5.4%) had previously tested negative*
- *4/278 (1.4%) had no prior testing*

Men: HIV prevalence was 12.0% (102/851). Of those who tested positive:
- *88/102 (86.2%) had prior knowledge of their status*
- *7/102 (6.9%) each, had previously tested negative or had no prior testing*

Women: Hypertension prevalence was 15.6% (182/1170). Of those with hypertension:
- *90/182 (49.5%) were previously tested and informed they were hypertensive*
- *78/182 (42.9%) were previously tested and informed they were normotensive*
- *14/182 (7.7%) had not been tested*

Men: Hypertension prevalence was 22.0% (187/851). Of those with hypertension:
- *55/187 (29.4%) were previously tested and informed they were hypertensive*
- *93/187 (49.7%) were previously tested and informed they were normotensive*
- *39/187 (20.9%) had not been tested*

These data for HIV and hypertension have been added to the footnote for Table 1 (tracked changes).

4. "At the first screening, certain patients had hypertension and/or impaired renal function (eGFR /albuminuria); any intervention done between the initial and second screenings should have been documented. Perhaps, these interventions could explain the drop in the number of participants with eGFR <60mls/min/1.73m2 or albuminuria from 220 to 118 and 29 to 12, respectively."

Thank you for raising this point. At baseline screening, participants with hypertension, HIV (not on treatment), anaemia, hypercholesterolaemia, and hyperglycaemia were referred to their local care facility for further investigation and/or treatment – made possible because tests were performed in real time using point of care technology. The eGFR and albuminuria testing was not

done in real time. Rather, samples were batched and shipped for laboratory testing to Johannesburg, South Africa. After obtaining results for kidney function from the laboratory, those with low eGFR (<60ml/min/1.73m^2) and/or albuminuria (urine albumin:creatinine ratio >3mg/mmol) were rescreened after a minimum of 3 months (KDIGO CKD diagnosis guidelines). There were no interventions during this minimum 3-month period based on kidney function. However, there may have been some overlap between those referred because of their point of care results (who may also have had low eGFR and/or albuminuria). We have addressed this as a limitation in the revised manuscript (tracked changes).

5. "Though the statistical analysis seems adequate, a statistician may also review that aspect."
Thank you. A biostatistician, Dr Petra Gaylard (co-author in the paper) performed the statistical analysis.

Competing Interests: none

Reviewer Report 07 October 2022

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Jennifer Lees
School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK

I enjoyed reading this study investigating the prevalence of CKD – as defined by current international guidelines – for the diagnosis of chronic kidney disease in a rural south African population. The authors have further explored potential risk factors for CKD relevant to an African population. The authors acknowledge that the risk factors explored are not exhaustive, and they have detailed other potential risk factors that it was not possible to assess in this study.

The manuscript is clearly written. The methods are thoroughly detailed and appropriate for the current investigation. Sensitivity analyses are appropriate and justified in the text. The results are clearly displayed in tables and described in text. The strengths and limitations of the study are clearly described. I agree with the authors that there is a major limitation in identifying prevalence of (and risk factors for) CKD in African populations using creatinine-based eGFR, when these estimates of kidney function and the guidelines for their use have been primarily derived and validated in developed countries.

I believe the manuscript is scientifically valid in its current form. I have only a couple of very minor comments for clarity:

Abstract and throughout:

- "WHO" is not defined (though presumably is World Health Organisation) – please specify on first use

Methods, section on "Chronic kidney disease prevalence":

- Authors wrote: "as these coefficients overestimate GFR in African populations". Can the authors provide a reference for this statement?

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: Outside the review of this work, I have received personal lectureship fees within the last 5 years from Bristol Myers Squibb, Pfizer and AstraZeneca.

Reviewer Expertise: Estimated GFR equations; CKD epidemiology (risk factors and outcomes)

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.

Author Response 26 Oct 2022

June Fabian, University of the Witwatersrand, Johannesburg, South Africa

Thank you for your review.
As requested, I have included the full name for the "World Health Organization" (WHO) on first use; and I have added a reference for the statement "as these coefficients overestimate GFR in African populations" in the methods for the section titled "Chronic kidney disease prevalence"
The above changes are tracked in the revised version of the paper that has been resubmitted.

Competing Interests: No competing interests were disclosed.