Original Article

Carotid intima–media thickness, but not chronic kidney disease independently associates with noncardiac arterial vascular events in South Africa

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Aim: Although chronic kidney disease (CKD) as determined from estimated glomerular filtration rate (eGFR) is recommended for risk prediction by current hypertension guidelines, the equations to derive eGFR may not perform well in black Africans. We compared whether across the adult lifespan, eGFR or CKD are as closely associated with noncardiac arterial vascular events, as carotid intima–media thickness (IMT), in Africa.

Methods: In 1152 black South Africans [480 with noncardiac arterial events (294 with critical lower limb ischemia, 186 with stroke) of which 37% were premature] and 672 age, sex and ethnicity-matched controls from a randomly selected community sample, we assessed relations between eGFR, CKD or carotid IMT (B-mode ultrasound) and arterial events.

Results: From 20 years until old age, with or without adjustments, IMT was increased in those with as compared with without events ($P < 0.01$ at each decade of age). However, at any decade of age across the adult lifespan neither creatinine concentrations, nor eGFR were altered in those with arterial events ($P > 0.28$). Although IMT was strongly and independently associated with the odds of an event [odds ratio per 1 SD (0.171 mm) effect = 2.19, confidence interval = 1.75–2.78, $P < 0.0001$], neither creatinine concentrations ($P = 0.89$), modification of diet in renal disease-derived ($P = 0.07$), nor Chronic Kidney Disease Epidemiology Collaboration-derived [odds ratio per 1 SD (22.5 ml/min per 1.73 m^2) effect = 1.06, confidence interval = 0.89–1.27, $P = 0.51$] eGFR were independently associated with the odds of an event. Although many with premature events had an increased IMT (63%), few with either premature events (8%) or with events at an older age (21%) had CKD and CKD had a poor performance (0.539 ± 0.011) and low sensitivity (16%) for event detection.

Conclusion: In black South Africans, despite carotid IMT strongly associating with noncardiac arterial vascular events (stroke and critical lower limb ischaemia) consistently across the adult lifespan, few with events have CKD and CKD fails to associate with events.

Keywords: carotid intima–media thickness, critical limb ischaemia, estimated glomerular filtration rate, stroke

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CLI, critical lower limb ischemia; eGFR, estimating glomerular filtration rate; IMT, carotid intima–media thickness; MDRD, modification of diet in renal disease; MI, myocardial infarction; SOWETO, South West Township

INTRODUCTION

The kidney is a well recognized target for damage by several cardiovascular risk factors including hypertension. Risk factor-related renal injury results in a decrease in glomerular filtration rate (GFR) (the best overall measure of kidney function) and kidney dysfunction contributes to vascular changes through several mechanisms [1–3]. Importantly, the identification of chronic kidney disease (CKD) from a reduced GFR estimated from serum creatinine concentrations (eGFR) enhances the prediction of arterial vascular events beyond conventional risk factors [4,5]. Consequently, CKD identified from a reduced eGFR is included in hypertension guidelines for risk prediction [6]. In comparison with alternative measures of end-organ changes, eGFR is a simpler, cheaper and more cost-effective approach to risk prediction. Hence, hypertension

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guidelines in middle-income countries in Africa, give a higher priority to creatinine and eGFR assessments for risk prediction than more costly end-organ measures [7]. However, the role of CKD in enhancing risk prediction in Africa, is uncertain.

Several formulae have been developed for assessing eGFR [8,9], with a more systematic approach than that used to obtain previous equations resulting in the derivation of the recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. The CKD-EPI equation has been demonstrated to perform well with minimum bias across a range of GFR values in many ethnic groups [11]. In addition, the CKD-EPI equation more accurately categorizes individuals regarding clinical risk [12–16] than the modification of diet in renal disease (MDRD) study equation, the equation predating the CKD-EPI equation. However, because the relationship between creatinine and GFR varies between ethnicities, neither the MDRD, nor the CKD-EPI equations perform as well in African as they do in white populations [9,17], and the use of an ethnicity coefficient may not improve on performance in some African populations [11,18,19]. Moreover, arterial events in Africa are often premature, and hence occur at an age prior to when CKD more often occurs. Although in black South Africans eGFR derived from the CKD-EPI and MDRD equations associate with several alternative target organ measures, with more consistent associations noted for CKD-EPI-derived eGFR [20], whether estimates of glomerular dysfunction and CKD are independently associated with cardiovascular events across the adult lifespan in Africa, is unknown. Hence, in the current study we aimed to determine the independent association of creatinine concentrations, eGFR or CKD with arterial events that frequently occur across the adult lifespan in Africa (critical limb ischaemia and stroke) and to compare the associations with that of carotid intima–media thickness (IMT), a well accepted index of arterial end-organ changes.

METHODS

Study groups

The current study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval numbers: M11-08-29, M14-04-29, M16-04-11, M02-04-72, M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. 1152 black South Africans participated in the current study. 480 consecutive black South Africans with stroke ($n = 186$) or critical limb ischaemia (CLI) ($n = 294$) were recruited from the Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Patients with myocardial infarction (MI) were not included as MI most frequently occurs in older age groups in South Africans of African ancestry and the event may cause reductions in eGFR. The presence of CLI was defined as the occurrence of ischaemic leg pain at rest for more than 2 weeks, or the existence of ulcers or gangrene attributable to occlusive arterial disease. Patients with a new stroke, defined as a focal neurological deficit of vascular origin were evaluated. Participants with meningitis based on cerebrospinal fluid examination, or the presence of intracranial malignancy or intracranial mass lesions on imaging, or a vasculitis were excluded. Strokes were classified according to the Trial of Org 10172 in acute stroke treatment classification. Data obtained in patients with arterial vascular events were compared with data acquired over the same time period in 672 age-matched and sex-matched randomly recruited participants older than 16 years of black African descent living in the South West Township (SOWETO) of Johannesburg, South Africa, using the population census figures of 2001 [20]. In this regard, black African patients attending the Charlotte Maxeke-Johannesburg Academic Hospital are of the same socioeconomic class as those living in the SOWETO community. Of the patients with arterial vascular events and the controls, 448 and 406, respectively, had high-quality carotid images available for the assessment of IMT.

Clinical, demographic, anthropometric and blood pressure measurements

A questionnaire was administered to obtain demographic information including each participant's medical history, the use of medication and tobacco and alcohol use. Clinical information was also extracted from the hospital records and confirmed by the attending physician. Clinical data included the presence and duration of risk factors (hypertension, and diabetes mellitus and the therapy thereof). Height and weight were measured using standard approaches and in all participants obesity was defined as a BMI $\geq 30\,kg/m^2$. Blood tests were performed including a fasting lipid profile and glucose concentration. Participants were considered to have diabetes mellitus if they had a fasting plasma glucose concentration at least 7 mmol/l, or in whom glucose-lowering agents were prescribed. Brachial blood pressure (BP) was measured according to guidelines and taken as the mean of five measurements. Participants with a BP at least 140/90 mmHg or those receiving antihypertensive medication were considered to have hypertension.

Estimated glomerular filtration rate

Serum creatinine concentrations were measured from blood samples obtained before endovascular procedures or surgery and in clinically well hydrated patients, using the Advia Chemistry systems (Siemens) with calibration traceable to isotope dilution mass spectrometry. The 4-variable MDRD and CKD-EPI equations were employed to estimate GFR. The ethnicity factor as recommended in African Americans when calculating the MDRD and CKD-EPI eGFR was not applied in the current study as the use results in overestimation of kidney function in black Africans [17,18].

Carotid intima–media thickness

Carotid IMT was determined using high-resolution B-mode ultrasound (SonoCalc IMT; Sonosite Inc, Bothell, Washington, USA) employing a linear array 7.5 MHz probe as previously described [20]. Images of at least 1 cm length of the far wall of the distal portion of the right common carotid artery from an optimal angle of incidence (defined as the longitudinal angle of approach where both branches

of the internal and external carotid artery are visualized simultaneously) at least 1 cm proximal to the flow divider were obtained. Carotid IMT measurements were determined using semi-automated border-detection and quality control software.

Statistical analysis

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) was employed. Continuous variables were expressed as mean (SD), or median (interquartile range) when nonnormally distributed. Dichotomous variables were expressed as proportions or percentages. Age-related thresholds for IMT were derived from age-specific 75th and 95th percentiles of normotensive, nondiabetic participants from the community sample (Table S1, http://links.lww.com/HJH/A1000). CKD was identified not only from an eGFR less than 60 ml/min per 1.73 m^2, the currently accepted threshold, but also from age-specific thresholds derived from the 5th percentiles of normotensive, nondiabetic participants from the community sample (Table S2, http://links.lww.com/HJH/A1000). Multiple logistic regression analysis was performed to determine the independent relations between eGFR or carotid IMT and vascular events. Adjustments included in multivariate models were those associated with vascular events. Odds ratios were compared using z statistics. Performance of IMT or eGFR for the detection of noncardiac arterial vascular events was determined from the area under the receiver operator characteristic curve (AUC) and sensitivity and specificity for event detection using standard approaches.

RESULTS

Participant characteristics

The participant characteristics are given in Table 1. Differences in the characteristics between cases and controls were similar in those with vs. those without high-quality carotid imaging (Table S3, http://links.lww.com/HJH/A1000). Of the patients admitted with stroke, 11.3% were haemorrhagic, 17.2% had a cardio-embolic cause (as assessed from clinical features and echocardiography); 16.7% were classified as small artery occlusion (confirmed with intracranial imaging); 5.9% with large artery occlusion (atherosclerotic) (confirmed with computed tomography angiography); 41.4% were indeterminate in origin and 7.5% were from an alternative cause. 57.5% of stroke and 23.5% of those with CLI were chronologically premature (<55 years of age in women and 50 years of age in men).

Patients with arterial events had a greater prevalence of hypertension, diabetes mellitus and more patients smoked. HDL cholesterol concentrations were lower in patients with arterial events. Although LDL cholesterol concentrations were also lower in cases, 89.8% of these patients were receiving lipid-lowering therapy at the time of performing fasting blood analysis. BMI was also lower in cases as compared with controls in both younger and older age groups. 41.8% of patients had at least one of the modifiable conventional risk factors hypertension, diabetes mellitus or smoking, 36.2% had two of these risk factors and 5.4% had three of these risk factors.

Age-related changes in intima–media thickness and estimated glomerular filtration rate

Figure 1 shows the unadjusted and multivariate-adjusted age-related changes in IMT and eGFR (CKD-EPI equation) in the community sample and in patients experiencing arterial vascular events. Across the adult lifespan, age was associated with an increase in IMT and a decrease in eGFR in those with and without events. At all ages, IMT was increased in those with as opposed to without events. In contrast, CKD-EPI-derived eGFR was similar across all ages between those with and without events. The same results were noted when eGFR was determined from the MDRD equation (data not shown).

TABLE 1. Participant characteristics

	Controls, $n = 672$	Cases, $n = 480$
Strokes/CLI, *n*	–	186/294
Age (years)	54.5 ± 15.2	56.2 ± 14.4
Sex (% male)	55.2	60.6
BMI (kg/m^2)	27.7 ± 5.3	27.8 ± 8.2
Hypertensive (%)	61.6	65.8
Diabetes mellitus (%)	12.6	28.7*
Regular smoking (%)	22.5	40.4*
Regular alcohol intake (%)	26.2	50.0*
SBP/DBP (mmHg)	136 ± 22/87 ± 12	134 ± 22/80 ± 13*
Total cholesterol (mmol/l)	4.80 (4.20–5.30)	3.85 (3.20–4.60)*
LDL cholesterol (mmol/l)	2.72 (2.30–3.20)	2.26 (1.62–2.86)*
HDL cholesterol (mmol/l)	1.36 (1.10–1.50)	1.02 (0.83–1.27)*
Glycated haemoglobin (%)	5.85 (5.60–6.20)	6.10 (5.70–7.70)*
Serum creatinine (μmol/l)	76.0 (65.5–90.0)	77.0 (65.0–94.0)
MDRD–eGFR (ml/min per 1.73 m^2)	88.9 ± 25.1	91.3 ± 36.7
CKD-EPI–eGFR (ml/min per 1.73 m^2)	87.4 ± 20.7	85.4 ± 24.7
Average carotid IMT (mm)	0.686 ± 0.145 ($n = 406$)	0.800 ± 0.176* ($n = 448$)

Data shown are proportions, mean ± SD or median and interquartile range. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CLI, critical limb ischaemia; eGFR, estimated glomerular filtration rate; IMT, intima–media thickness; MDRD, modification of diet and renal disease.
*$P < 0.0001$ vs. controls.

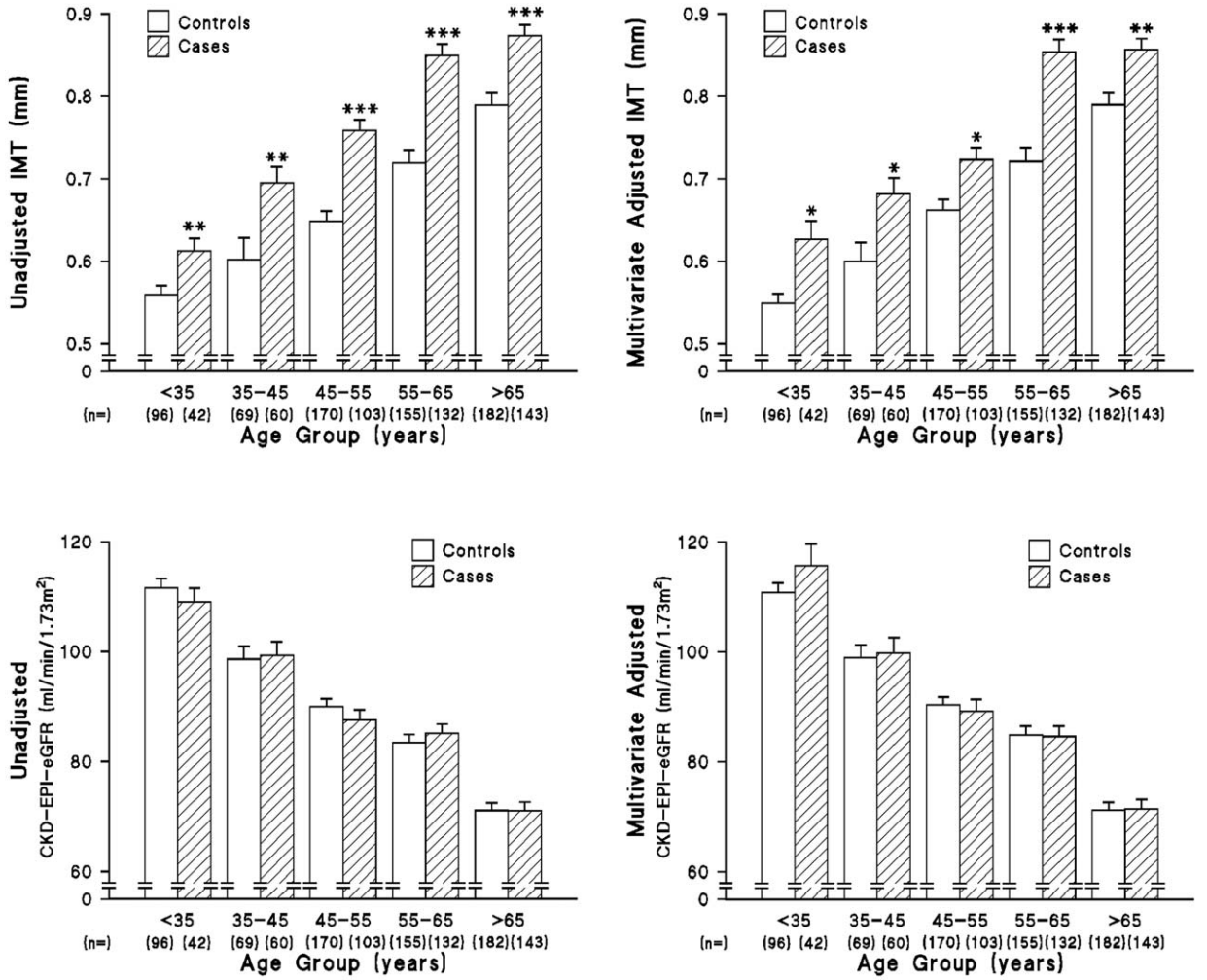

FIGURE 1 Unadjusted and multivariate-adjusted carotid intima–media thickness and estimated glomerular filtration rate (derived from the Chronic Kidney Disease Epidemiology Collaboration equation) across the adult lifespan in cases with noncardiac arterial vascular events (stroke and critical limb ischaemia) and age-matched, sex-matched and ethnicity-matched randomly selected community sample in Africa. Data shown are multivariate adjusted means and SEM. Adjustments are for sex, hypertension, diabetes mellitus, smoking and HDL cholesterol concentrations. See Table 1 footnote for abbreviations $^{*}P < 0.01$, $^{**}P < 0.001$, $^{***}P < 0.0001$ vs. controls.

Independent associations of intima–media thickness, creatinine or estimated glomerular filtration rate as continuous traits with vascular events

Figure 2 shows the unadjusted and conventional risk factor-independent relations between IMT, creatinine concentrations or eGFR values and the risk of an arterial event (a) and the performance (AUC) for events detection (b) of IMT and eGFR. Although IMT showed strong unadjusted or independent relations with events and a strong performance for event detection, neither creatinine concentrations nor eGFR were associated with events either before or after adjustments and showed a poor performance for event detection (Fig. 2). The relations between IMT and events, and the lack of relationship between creatinine concentrations, CKD-EPI derived or MDRD-derived eGFR and arterial events occurred for stroke or CLI considered separately; for haemorrhagic, small vessel and large vessel (atherosclerotic) strokes considered together, but separate from other causes of strokes; for cardio-embolic strokes considered separately from other causes of strokes; for premature events (<55 and 50 years of age for women and men respectively) or events in older age groups considered separately; and in hypertensive patients or normotensive patients (data not shown) considered separately (Table 2).

Independent associations of values above or below thresholds of intima–media thickness or estimated glomerular filtration rate with vascular events

Figure 3 shows the proportion of cases and controls with either increases in IMT or the presence of CKD [eGFR < 60 ml/min per 1.73 m^2 (CKD-EPI equation)] (a) and the performance (AUC) of increases in IMT or the presence of CKD for event detection (b). Table 3 shows the unadjusted or multivariate adjusted relations between IMT values more than 0.9 mm or IMT values above age-specific thresholds, stages 2 and 3 CKD, or CKD defined according to eGFR values below age-specific thresholds and vascular events. Importantly, few patients with arterial events had CKD defined according to either CKD-EPI or MDRD equations. This was particularly noticeable in those

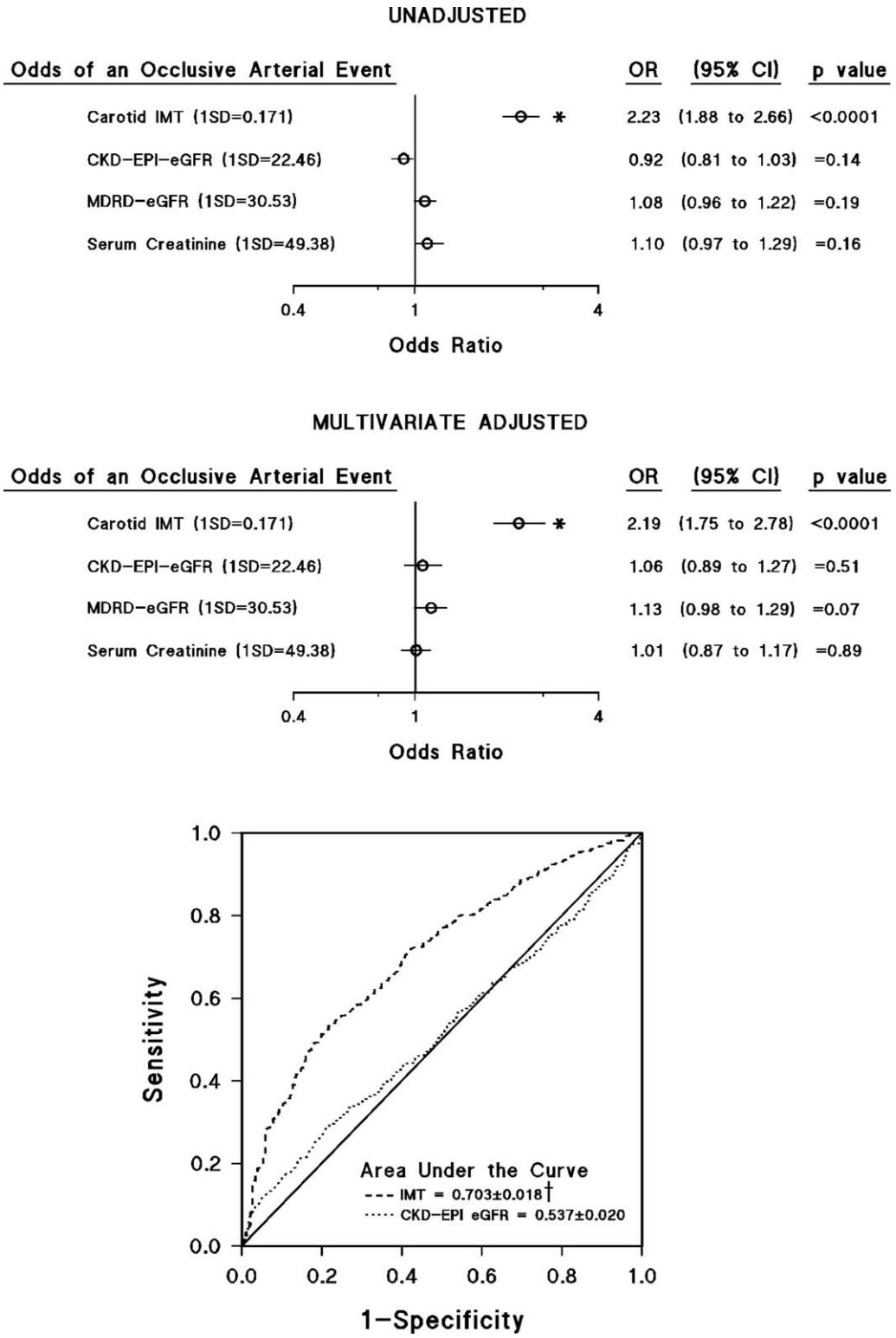

FIGURE 2 Unadjusted and multivariate adjusted relations between an one SD change in carotid intima–media thickness, creatinine concentrations or estimated glomerular filtration rate (estimated glomerular filtration rate derived from the Chronic Kidney Disease Epidemiology Collaboration equation) and noncardiac arterial vascular events (stroke and critical limb ischaemia) in Africa (a) and the performance (area under the receiver operator characteristic curves) for event detection of intima–media thickness and estimated glomerular filtration rate (b). Adjustments are for age, sex, hypertension, diabetes mellitus, smoking and HDL cholesterol concentrations. One SD effects for intima–media thickness are in mm, for creatinine is in μmol/l and for estimated glomerular filtration rate are in ml/min per 1.73 m^2. AUC, area under the receiver operator characteristic curves. *$P < 0.0001$ vs. odds ratio for relations between creatinine or estimated glomerular filtration rate and events; †$P < 0.0001$ vs. area under the receiver operator characteristic curves for estimated glomerular filtration rate.

TABLE 2. Multivariate adjusted relations between carotid intima–media thickness, creatinine concentrations or estimated glomerular filtration rate and subgroups of noncardiac arterial vascular events (stroke and critical limb ischaemia) in Africa

Event vs.	One SD effect	Odds ratios (95% CI)	*P* value
Stroke			
IMT	0.160 mm	2.33 (1.75–3.14)	<0.0001
Creatinine concentrations	52.6 μmol/l	1.17 (0.96–1.52)	0.21
CKD-EPI–eGFR	21.6 ml/min per 1.73 m^2	0.82 (0.63–1.07)	0.14
MDRD–eGFR	25.7 ml/min per 1.73 m^2	0.87 (0.68–1.10)	0.26
Critical limb ischaemia			
IMT	0.169 mm	2.08 (1.63–2.68)	<0.0001
Creatinine concentrations	37.6 μmol/l	0.86 (0.68–1.03)	0.15
CKD-EPI–eGFR	22.0 ml/min per 1.73 m^2	1.19 (0.97–1.46)	0.11
MDRD–eGFR	31.0 ml/min per 1.73 m^2	1.18 (0.98–1.41)	0.08
Haemorrhagic, small vessel and large vessel strokes ($n = 63$)			
IMT	0.152 mm	2.25 (1.56–3.29)	<0.0001
Creatinine concentrations	56.2 μmol/l	1.15 (0.94–1.49)	0.20
CKD-EPI–eGFR	20.9 ml/min per 1.73 m^2	0.78 (0.57–1.08)	0.13
MDRD–eGFR	25.1 ml/min per 1.73 m^2	0.78 (0.56–1.06)	0.12
Cardio-embolic strokes ($n = 32$)			
IMT	0.150 mm	1.76 (1.14–2.75)	0.01
Creatinine concentrations	37.1 μmol/l	1.28 (0.72–1.67)	0.15
CKD-EPI–eGFR	20.8 ml/min per 1.73 m^2	0.63 (0.35–1.18)	0.14
MDRD–eGFR	25.0 ml/min per 1.73 m^2	0.66 (0.34–1.19)	0.19
Premature events			
IMT	0.140 mm	1.79 (1.28–2.58)	0.001
Creatinine concentrations	57.6 μmol/l	1.35 (0.93–2.81)	0.37
CKD-EPI–eGFR	20.4 ml/min per 1.73 m^2	0.97 (0.74–1.26)	0.81
MDRD–eGFR	29.6 ml/min per 1.73 m^2	1.10 (0.86–1.38)	0.43
Events at an older age			
IMT	0.163 mm	2.12 (1.65–2.79)	<0.0001
Creatinine concentrations	42.6 μmol/l	0.85 (0.65–1.06)	0.21
CKD-EPI–eGFR	20.1 ml/min per 1.73 m^2	1.09 (0.89–1.33)	0.41
MDRD–eGFR	29.8 ml/min per 1.73 m^2	1.17 (0.96–1.42)	0.13
Hypertensive patients			
IMT	0.166 mm	1.80 (1.39–2.36)	<0.0001
Creatinine concentrations	59.5 μmol/l	1.00 (0.83–1.21)	0.98
CKD-EPI–eGFR	21.9 ml/min per 1.73 m^2	1.09 (0.89–1.35)	0.40
MDRD–eGFR	30.7 ml/min per 1.73 m^2	1.15 (0.95–1.38)	0.15

Adjustments are for age, sex, hypertension, diabetes mellitus, smoking and HDL cholesterol concentrations. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMT, intima–media thickness; MDRD, modification of diet and renal disease.

with premature vascular events (<55 and 50 years of age for women and men, respectively) (8%) (Fig. 3). An increased IMT based on values above either an absolute threshold of 0.9 mm or age-specific thresholds was independently associated with arterial events and showed a strong performance (Fig. 3) and a reasonable sensitivity (Table S4, http://links.lww.com/HJH/A1000) for event detection. Although in unadjusted models stages 2 and 3 CKD was associated with events (Table 3), with adjustments for conventional risk factors neither stages 2 and 3 CKD, nor CKD defined according to age-specific thresholds were associated with arterial events (Table 3) and stage 2 and 3 CKD showed a poor performance (Fig. 3) and a very low sensitivity (Table S4, http://links.lww.com/HJH/A1000) for event detection.

DISCUSSION

The main findings of the current study are as follows: In a large case–control study conducted in a group of African ancestry, despite carotid IMT being uniformly greater across the adult lifespan in those with noncardiac arterial vascular events (stroke and CLI) as compared with controls, creatinine-based indexes of glomerular function or after adjustments the presence of CKD based on these estimates were no different between those with and without events. Although, beyond all risk factors, IMT was independently associated with arterial events, neither creatinine concentrations, nor eGFR estimated using the CKD-EPI or the MDRD equations were associated with events either before or after multivariate adjustments. Importantly, few cases (16.3%), particularly those with premature events (8%), had CKD and assuming that similar eGFR values existed prior to as at the time of the event, eGFR showed a low sensitivity and poor performance for event detection. In sensitivity analyses, these relations were consistent for both stroke and CLI considered separately; after excluding strokes that were not necessarily haemorrhagic, small vessel or large vessel strokes (where the cause may not have been through conventional risk factors); for premature events and events occurring at an older age considered separately; as well as in hypertensive patients and normotensives considered separately.

Although controls were carefully age-matched sex-matched and ethnicity-matched participants from a randomly selected community sample and the sample size was reasonably large, as with any case–control analysis, the results of the current study may be subject to selection bias

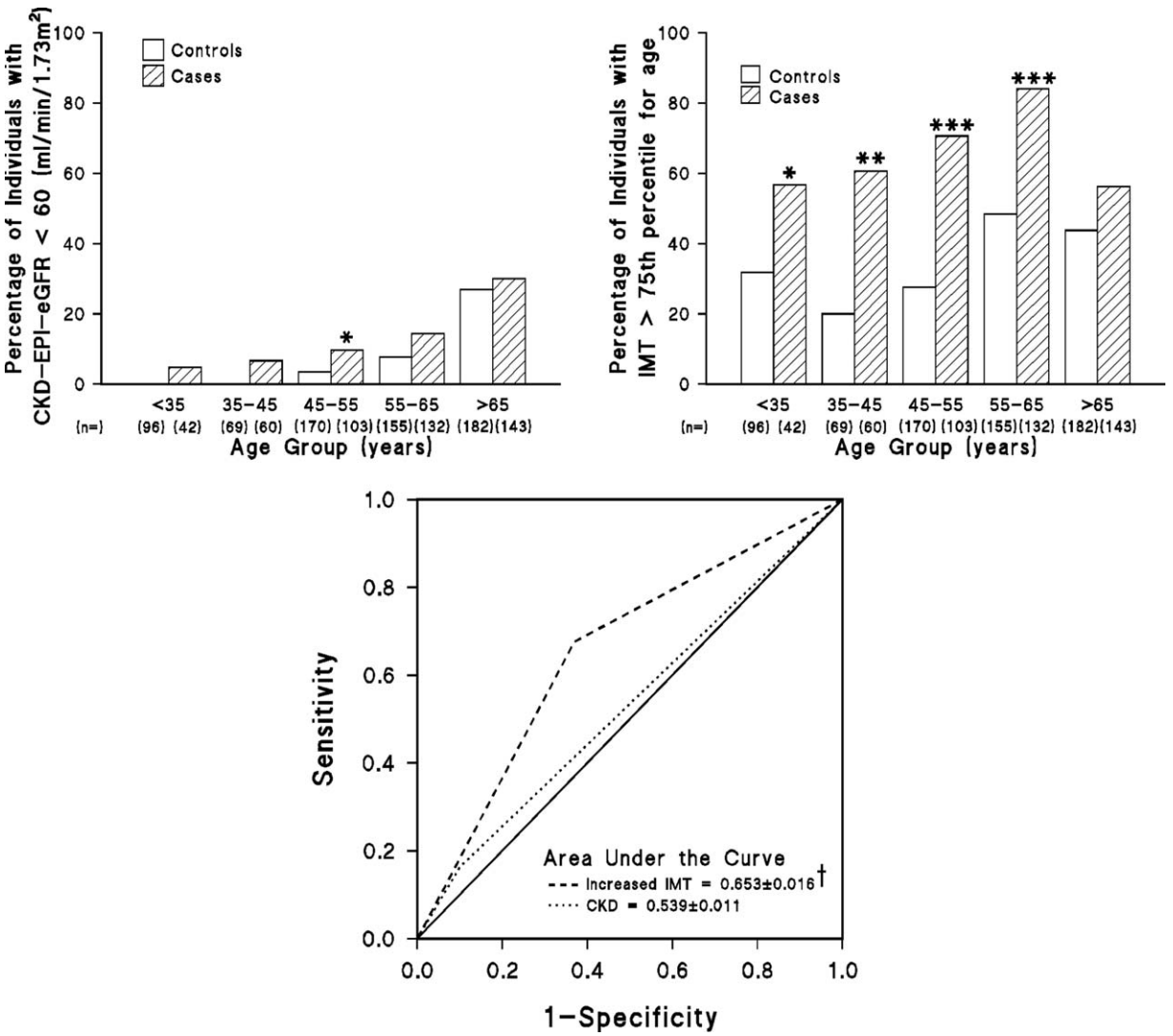

FIGURE 3 Proportion of cases with noncardiac arterial vascular events (stroke and critical limb ischaemia) and age-matched, sex-matched and ethnicity-matched randomly selected community sample in Africa with increased carotid intima–media thickness or decreased estimated glomerular filtration rate (estimated glomerular filtration rate derived from the Chronic Kidney Disease Epidemiology Collaboration equation) less than 60 ml/min per 1.73 m^2 (chronic kidney disease) across the adult lifespan (a) and the performance (area under the receiver operator characteristic curves) for event detection of an increased intima–media thickness or chronic kidney disease (b). Data shown are unadjusted data. AUC, area under the receiver operator characteristic curves. $^{*}P < 0.01$, $^{**}P < 0.001$, $^{***}P < 0.0001$ vs. controls; $^{\dagger}P < 0.0001$ vs. area under the receiver operator characteristic curves for chronic kidney disease.

TABLE 3. Unadjusted and multivariate adjusted associations between increases in carotid intima–media thickness or chronic kidney disease and noncardiac arterial vascular events

Event vs.	% Cases/% controls with ↑IMT or CKD	Unadjusted Odds ratios[a] (95% CI)	Unadjusted *P* value	Multivariate adjusted Odds ratios[a] (95% CI)	Multivariate adjusted *P* value
IMT > 0.9 mm	24.3/5.9	5.12 (3.21–8.15)	<0.0001	4.31 (2.56–7.27)	<0.0001
IMT > age-specific thresholds (75th percentile)	67.6/36.9	3.57 (2.69–4.73)	<0.0001	3.06 (2.22–4.22)	<0.0001
IMT > age-specific thresholds (95th percentile)	42.9/12.6	5.22 (3.69–7.39)	<0.0001	4.24 (2.89–6.23)	<0.0001
CKD (-EPI) stages 2 and 3	16.3/10.0	1.58 (1.09–2.30)	<0.05	1.48 (0.95–2.30)	0.08
CKD (-EPI) (<age-specific 5th percentile)	14.4/8.9	1.32 (0.88–1.97)	0.18	1.50 (0.95–2.36)	0.08
CKD (-MDRD) (<age-specific 5th percentile)	14.4/8.5	1.39 (0.92–2.09)	0.12	1.39 (0.89–2.18)	0.15
Creatinine (>age-specific 95th percentile)	14.8/10.0	1.32 (0.89–1.93)	0.16	1.20 (0.77–1.86)	0.42

CI, confidence interval; CKD, chronic kidney disease; CKD, Chronic Kidney Disease Epidemiology Collaboration; IMT, intima–media thickness; MDRD, modification of diet and renal disease.
[a]Adjustments are for age, sex, hypertension, diabetes mellitus, smoking and HDL cholesterol concentrations.

or residual confounding and consequently false negative or positive findings. However, the very low prevalence of CKD as defined by eGFR values less than 60 ml/min per 1.73 m^2 in those with premature events (8%) and thus the low sensitivity of CKD for event detection markedly limits the value of CKD for detecting risk for a significant proportion of patients with events. Thus, even if residual confounding or a selection bias had limited associations between eGFR and events, too few patients experiencing noncardiac arterial vascular events would have been identified as being at risk prior to the event, to place a high value on employing CKD identification as a sensitive marker for risk prediction. Against a notion that in the current study an inability of CKD to associate with noncardiac arterial vascular events represents false negative findings is that in similar participants, an increased IMT was strongly and consistently associated with vascular events across the adult lifespan. Indeed, because conventional risk factors account for all end-organ changes, population stratification and an inability to adjust for residual confounding effects are likely to have generated a bias against a role for all indices of end-organ changes, rather than a bias against a role for one (eGFR), but not another (IMT) end-organ measure.

Stroke may be caused by several pathophysiological mechanisms, and a significant proportion of patients in the current study had a stroke that may not have been caused by risk factors that affect glomerular function. Indeed, 17.2% were cardio-embolic, where the cardiac disorder may have been other than coronary artery or hypertensive heart disease, 41.4% were indeterminate in origin and 7.5% were from an alternative cause. However, in the 11.3% that were haemorrhagic (without congenital aneurysms on imaging); 16.7% classified as small artery occlusion (confirmed with intracranial imaging); and 5.9% with large artery occlusion (atherosclerotic) (confirmed with CT angiography) similar findings were noted as with all patients with stroke or those with critical limb ischaemia. Consequently, it is unlikely that the inclusion of patients with cardio-embolic or indeterminate causes (not caused by conventional risk factors) influenced the interpretation of the present results.

The current study suggests that in the majority of patients with noncardiac-related arterial vascular events in South Africa and hence possibly other African regions, the event precedes the development of CKD. These data are contrary to alternative populations [4,5,12–16], where CKD may be useful in predicting a significant number of arterial events. Hence, generalized screening of either hypertensive patients or normotensives for CKD using creatinine-based estimations of GFR are unlikely to be of use in predicting the majority of noncardiac-related arterial vascular events in South African and possibly other African populations. These findings oppose the proposal by hypertension guidelines in middle-income countries in Africa [7]. In this regard, because of the low cost of eGFR assessments, these guidelines assign a greater priority to eGFR than more costly ultrasound-based assessments, such as carotid IMT, in detecting end-organ changes.

Several explanations are thought to account for the ability of CKD to predict events caused by vascular abnormalities beyond conventional risk factors [1–3]. Importantly, the kidney is a well recognized target organ for conventional risk factors including hypertension. Consequently, decreases in GFR are thought to provide an index of the accrual of the overall adverse effects of uncontrolled conventional risk factors, such as hypertension or diabetes mellitus, over time. In this regard, in Africa both CLI and stroke occur across the adult lifespan starting at an age as young as 20 years. It may therefore be argued that in younger individuals there is insufficient time for risk factors such as hypertension to cause the development of CKD based on current definitions. In these circumstances, it is possible that a predisposition to prothrombotic conditions rather than vascular pathology is a more important cause of premature events [21–25]. However, in the current study a strong, independent relationship between IMT and events was noted across the adult lifespan. Hence, vascular pathology is likely to have been a major cause of events across the adult lifespan. Moreover, risk factors are likely to have been present for sufficiently long, even in those with events at a younger age, to have caused carotid vascular changes. In addition, the lack of association of creatinine-based assessments of CKD and events was noted in both the young and the elderly and we assume that in the elderly, risk factors would have prevailed for a significant time-period. Moreover, the presence of CKD in the current study was defined not only according to standard approaches (at least <60 ml/min per 1.73 m^2), but also according to age-specific thresholds. Hence, inadequate definitions of CKD in the young cannot account for the lack of association of CKD with arterial events.

An alternative explanation for the lack of relationship between creatinine concentrations, eGFR or CKD and arterial events in the current study is that creatinine concentrations and eGFR are a poor index of glomerular function in Africa. Indeed, although the CKD-EPI equation has been demonstrated to perform well with minimum bias across a range of GFR values in many ethnic groups [6], the relationship between creatinine and GFR varies between ethnicities [6,19]. Thus, neither the MDRD, nor the CKD-EPI equations perform as well in African as they do in white populations [8,17]. Moreover, the use of an ethnicity coefficient may not improve on performance in some African populations [10,18,19]. However, prior studies [20,26] conducted in black African patients with rheumatoid arthritis and in the general population have demonstrated distinct independent associations between eGFR determined using CKD-EPI or MDRD equations and several alternative end-organ measures, including indexes of atheroma (plaque) [26]. Hence, eGFR, determined using either MDRD or CKD-EPI equations may indeed be considered to be an appropriate end-organ measure in Africa. However, the current study suggests that the relationship between eGFR or CKD and noncardiac arterial vascular events in Africa is remarkably limited.

A third possible explanation for the lack of relationship between creatinine concentrations, eGFR or CKD and arterial events in the current study is that eGFR and CKD mainly predict cardiac rather than cerebral or peripheral vascular events. Cardiac events were not evaluated in the current study as they do not occur across the adult lifespan in groups of African ancestry in South Africa and they cause

reductions in eGFR. In this regard, 50% of events predicted by CKD are coronary events and a substantial portion of events predicted by CKD are caused by heart failure [2]. A dominant effect of CKD on cardiac as opposed to alternative cardiovascular events may occur through the cardiorenal syndrome. Indeed, eGFR is strongly and independently associated with left ventricular (LV) mass beyond all haemodynamic factors in groups of African ancestry in Africa [27]. Although eGFR associates with LV mass beyond all risk factors in African populations [27], the relationship between eGFR and carotid IMT is not independent of age [20]. Thus, the adverse effects of CKD in Africa may be specific to cardiac rather than peripheral or cerebral vascular arterial events.

A fourth potential explanation for the lack of independent association between estimates of glomerular function or the presence of CKD and noncardiac arterial vascular events in Africa is that the major risk factors that determine arterial events are those that do not affect renal function. In this regard, dyslipidaemia may be a major determinant of atherosclerosis, but have little impact on renal function. Indeed, in the current study although we could not determine the relationship between LDL cholesterol concentrations and occlusive arterial events (lipid lowering therapy was initiated on admission to hospital), a strong relationship between reduced HDL cholesterol concentrations and events was noted. However, in the current study, 68.1% of those with arterial events had either hypertension or diabetes mellitus and these risk factors are well established as determinants of both CKD and occlusive arterial events. Moreover, at least for stroke, hypertension is well recognized as the major risk factor in Africa.

An important limitation of the current study is that few possible confounding factors were determined and hence in statistical analysis adjustments for these unmeasured confounders could not be performed. Hence, with adjustments for these unmeasured confounders, differences in eGFR between cases and controls may have been noted. This limitation would nevertheless not have influenced the remarkably low number of cases with CKD, rendering identification of CKD a measure with a negligible sensitivity (16.3%) for predicting events. An additional important limitation of the current study is that it was conducted at a single site (Johannesburg, South Africa) where extensive special investigations are available to ensure an appropriate diagnosis of the event. Although black Africans living in Johannesburg are largely representative of most chiefdoms in South Africa, whether the results of the current study can be extrapolated to alternative black African populations in Africa is uncertain. However, in this regard, black African populations living in South Africa are thought to originate from the Bantu expansion from West Africa, and hence at least from a genetic perspective are thought to be similar. Nevertheless, further studies are warranted to explore whether the presence of CKD is as sensitive an index of noncardiac arterial vascular events as vascular indexes of end-organ changes in other regions of Africa.

In conclusion, in the current study we show that in groups of African ancestry in South Africa, despite a consistent independent relationship between carotid IMT and noncardiac-related arterial vascular events (stroke and CLI) across the adult lifespan, neither creatinine concentrations, eGFR calculated from either the MDRD or CKD-EPI equations, nor the presence of CKD associate with these events. Importantly, few patients in this study with noncardiac arterial vascular events had eGFR values below currently accepted CKD thresholds and consequently the presence of CKD offered a negligible sensitivity for event detection. Thus, current creatinine-based assessments of glomerular function and the identification of CKD based on these thresholds is unlikely to significantly add to the prediction of the majority of noncardiac arterial vascular events in South Africa. Whether current creatinine-based assessments of glomerular function enhance the ability to predict cardiac pathology in Africa or whether there is a necessity for identifying alternative equations that more accurately assess eGFR in Africa, requires further study.

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Conflicts of interest

There are no conflicts of interest.

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