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CLINICAL RESEARCH

Cardiovascular Risk Factor Burden and Association With CKD in Ghana and Nigeria

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Introduction: Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD); however, the burden of cardiovascular risk factors in patients with CKD in Africa is not well characterized. We determined the prevalence of selected cardiovascular risk factors, and association with CKD in the Human Heredity for Health in Africa Kidney Disease Research Network study.

Methods: We recruited patients with and without CKD in Ghana and Nigeria. CKD was defined as estimated glomerular filtration rate of <60 ml/min per 1.73 m^2 and/or albuminuria as albumin-to-creatinine ratio <3.0 mg/mmol (<30 mg/g) for ≥3 months. We assessed self-reported (physician-diagnosis and/or use of medication) hypertension, diabetes, and elevated cholesterol; and self-reported smoking as cardiovascular risk factors. Association between the risk factors and CKD was determined by multivariate logistic regression.

Results: We enrolled 8396 participants (cases with CKD, 3956), with 56% females. The mean age (45.5 ± 15.1 years) did not differ between patients and control group. The prevalence of hypertension (59%), diabetes (20%), and elevated cholesterol (9.9%), was higher in CKD patients than in the control participants ($P < 0.001$). Prevalence of risk factors was higher in Ghana than in Nigeria. Hypertension (adjusted odds ratio [aOR] = 1.69 [1.43–2.01, $P < 0.001$]), elevated cholesterol (aOR = 2.0 [1.39–2.86, $P < 0.001$]), age >50 years, and body mass index (BMI) <18.5 kg/m^2 were independently associated with CKD. The association of diabetes and smoking with CKD was modified by other risk factors.

Conclusion: Cardiovascular risk factors are prevalent in middle-aged adult patients with CKD in Ghana and Nigeria, with higher proportions in Ghana than in Nigeria. Hypertension, elevated cholesterol, and underweight were independently associated with CKD.

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Cardiovascular disease has been recognized as the leading cause of morbidity and mortality in patients with CKD. Individuals with CKD are among the highest-risk group for cardiovascular events because of the presence of both traditional and CKD-related cardiovascular risk factors.[1] Cohorts of general populations from United States, Taiwan, and European countries have confirmed the association of CKD with cardiovascular disease.[2–4] The major traditional cardiovascular risk factors, hypertension, and diabetes mellitus, are notable risk factors, established causes, and progression factors for CKD.[5–8] Hypertension and diabetes are global public health problems but the burden is higher in low-income and middle income countries and especially in Africa. Epidemiologic studies have projected that the burden would be worse in the continent in the next decade if efforts toward their prevention are not scaled up.[9,10] This implies a potential parallel increase in the prevalence of CKD and associated cardiovascular events. The relationship of dyslipidemias with CKD has not been strongly established. Experimental studies in animals indicate that elevated cholesterols are associated with initiation and progression of CKD.[11,12] Epidemiologic studies in humans suggest that elevated total cholesterol and triglycerides contribute to rapid progression of CKD.[13–15] The randomized controlled trial of statin on progression of CKD however did not observe a significant benefit of statin in slowing the progression of CKD.[16] There is paucity of data in Africa that describe the relationship between cardiovascular risk factors and CKD burden. In this study, we describe the prevalence of hypertension, diabetes, and elevated cholesterol in indigenous African population enrolled in the Human Heredity and Health in Africa study and also determined the relationship between these factors and CKD. The findings may be helpful in planning large scale prevention and intervention programs that would enhance a reduction in the magnitude and socioeconomic impact of CKD and cardiovascular outcomes in Africa.

METHODS

Study Design and Population

The data were obtained from the ongoing Human Heredity and Health in Africa Kidney Disease Research, a multinational case-control study aimed at determining the environmental and genetic determinants of kidney disease in West African populations. The details of the methodology have been described earlier.[17] Briefly, 7 recruitment centers from urban-located tertiary hospitals in Nigeria and Ghana participated in the study. The study was approved by the ethics and research boards of participating institutions and we obtained written informed consents from all participants before enrollment in the study. Adults of at least 18 years of age, with established CKD because of hypertension, diabetes, sickle cell disease, HIV, glomerular diseases, and CKD of unclear etiology were recruited. Individuals with the aforementioned specific diseases but without CKD were recruited from the same hospitals as control group. Persons from the general population who do not have the diseases or CKD represent the control participants for CKD from unknown cause. The present analysis included 8396 participants.

Definition of CKD and Cardiovascular Risk Factors

We define CKD as estimated glomerular filtration rate <60 ml/min per 1.73 m^2 and/or albumin-to-creatinine ratio ≥ 3.0 mg/mmol (30 mg/g) for ≥ 3 months.[18] We determined estimated glomerular filtration rate using the CKD-Epidemiology equation based on age, sex, and serum creatinine, without race adjustment. Cardiovascular risk factors were defined as self-reported (physician-diagnosis and/or use of medication) hypertension, diabetes, and elevated cholesterol; and self-reported smoking.

Data Collection

Trained research nurses obtained sociodemographic and clinical data including self-reported hypertension, diabetes, elevated cholesterol, smoking, anthropometric indices (weight, height, and BMI), and past clinical events from the participants; using standardized case report forms containing questionnaires. The data were stored electronically in REDCap data management system which is licensed to the University of Michigan.

Statistical Analyses

The data were analyzed using statistical package for the social sciences IBM version 26.0 (SPSS Inc, Chicago, IL, USA). Quantitative data were reported as mean and standard deviation for normally distributed variables and median and interquartile range for skewed data. The prevalence of cardiovascular risk factors were reported in percentages. Differences in means were determined by student *t*-test for normally distributed data, whereas Mann-Whitney *U* test was used to compare skewed numerical data, and differences in proportions was assessed by chi-squared test. The association between the risk factors (hypertension, diabetes, elevated cholesterol, smoking, high BMI, and high waist circumference) and CKD was evaluated by multivariable logistic regression method. We used 'enter' method to build the multivariate logistic regression model, by entering in block cardiovascular risk factors that correlated with CKD. The goodness of fit of the regression model was assessed by Hosmer-Lemeshow test. We expressed the output as aOR with 95% confidence intervals. A 2-sided $P < 0.05$ was considered significant.

Table 1. Baseline characteristics[a] of the study participants of Human Heredity for Health in Africa Kidney Disease Research Network

Baseline characteristics	Total n (%)	Cases n (%)	Control n (%)	*P*-value
Gender (n %)				
Male	3670 (43.7)	1962 (49.6)	1708 (38.5)	<0.001
Age	45.5 ± 15.1	45.6 ± 16.0	45.4 ± 14.2	0.534
Ever smoked at least 100 cigarettes during entire life (n %)	539 (6.7)	285 (7.6)	254 (5.9)	0.003
Elevated cholesterol (n %)	470 (8.1)	271 (9.9)	199 (6.5)	<0.001
Heart attack (n %)	85 (1.1)	49 (1.3)	36 (0.8)	0.044
Heart failure (n %)	61 (0.8)	46 (1.2)	15 (0.4)	<0.001
Stroke (n %)	64 (0.8)	41 (1.1)	23 (0.5)	0.006
Medication use (n %)	457 (5.4)	446 (11.3)	11 (0.2)	<0.001
Peripheral vascular disease (n %)	26 (0.3)	18 (0.5)	8 (0.2)	0.023
Systolic blood pressure (mm Hg)	133.0 ± 27.6	136.7 ± 27.8	129.5 ± 27.2	<0.001
Diastolic blood pressure (mm Hg)	79.1 ± 16.7	81.1 ± 17.8	77.2 ± 15.5	<0.001
Body mass index (kg/m^2)	25.5 ± 6.3	25.0 ± 6.3	25.8 ± 6.1	<0.001
Hemoglobin (g/dl)	12.6 ± 2.2	12.4 ± 2.3	12.7 ± 2.2	<0.001
Albumin-creatinine Ratio (mg/g)	1.1 (0.6–4.0)	5.6 (1.2–40.3)	0.7 (0.5–1.3)	<0.001
Creatinine (μmol/l)	79.0 (62.0–129.0)	152.0 (76.0– 567.0)	70.0 (58.0–83.0)	<0.001
eGFR (ml/min/1.73 m^2)	99.3 (56.6–123.0)	45.8 (9.9– 104.0)	112.4 (93.5– 129.1)	<0.001

eGFR, estimated glomerular filtration.
[a]Characteristics are presented as mean ± SD, median (interquartile range) or number (%).

RESULTS

Baseline Characteristics of the Participants

The demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. The mean age of the participants (45.5 ± 15.1 years) did not differ between patients and the control group ($P = 0.534$), with preponderance of females of 56%. Patients who have had CKD, expectedly have significantly reduced estimated glomerular filtration rate, hemoglobin, and BMI compared with the control groups ($P < 0.001$); however, they are more likely to have smoked, and have elevated cholesterol, high blood pressure, and albuminuria. The CKD patients were also more likely to have had previous heart failure, heart attack, stroke, and peripheral vascular disease compared with the control individuals.

Prevalence of Cardiovascular Risk Factors in Patients With CKD

The prevalence of cardiovascular risk factors evaluated in the study is shown in Table 2. Values, when stratified by age and sex are shown in Figures 1 and 2, respectively. The prevalence of hypertension was significantly higher in CKD patients than among the control group ($P < 0.001$). Similarly, the prevalence of diabetes and elevated cholesterol are significantly higher in the patients than the control participants ($P < 0.001$, Table 2). However, BMI ≥ 25 kg/m^2, and wider waist circumference are less common in patients than the control participants (Table 2). The prevalence of the risk factors increased with age (Figure 1) and was higher among males (Figure 2). Risk factor prevalence was consistently higher in Ghana than in Nigeria (Table 3).

Association Between Selected Cardiovascular Risk Factors and CKD

The selected cardiovascular risk factors had significant inverse correlation with CKD as shown in Table 4, with age and hypertension having the strongest coefficient, although the strength of the correlation is generally weak. The crude and independent (adjusted) association of the risk factors with CKD are presented in Table 5. Age >50 years,

Table 2. Overall Prevalence of cardiovascular risk factors in the study population, Human Heredity for Health in Africa Kidney Disease Research Network

Cardivascular risk factors	Prevalence n (%[CI])		
	Cases	Control	*P*-value
Hypertension	1909 (52.6 [51.0–54.2])	1591 (39.2 [37.7–40.7])	<0.001
Diabetes	714 (20.7 [19.4–22.1])	474 (12.4 [11.4–13.4])	<0.001
Elevated cholesterol	271 (9.9 [8.8–11.0])	199 (6.5 [5.6–7.4])	<0.001
Smoking	324 (8.2 [7.4–9.1])	310 (7.0 [6.3–7.8%])	0.038
BMI (kg/m^2)[a]			
<18.5	356 (9.6 [8.7–10.6])	254 (5.9 [5.2–6.6])	<0.001
18.5–24.9	1727 (46.6 [44.9–48.2])	1902 (44.2 [42.7–47.7])	
≥25.0	1624 (43.8 [42.2–45.4])	2143 (49.8 [43.3–51.3])	
Waist circumference (cm)[b]			
High risk	1377 (50.8 [48.9–52.7])	1839 (59.3 [57.6–61.0])	<0.001
Normal	1335 (49.2 [47.3–51.1])	1262 (40.7 [38.9–42.4])	

BMI, body mass index; CI, confidence interval.
[a]BMI(kg/m^2) <18.5: underweight, 18.5–24.9: normal weight, ≥25.0: overweight or obesity.
[b]Waist circumference (cm) <90 for men and <80 for women: normal; ≥90 for men and ≥80 for women: high risk.

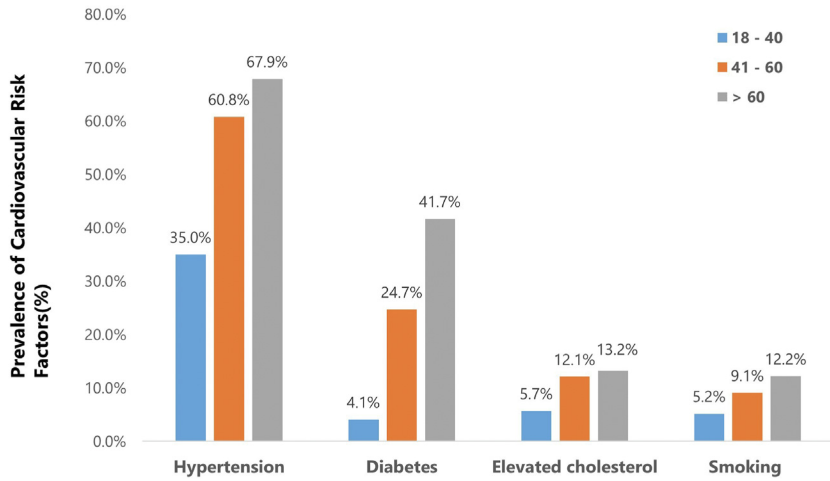

Figure 1. Prevalence of cardiovascular risk factors stratified by age groups (years) among CKD patients, Human Heredity for Health in Africa Kidney Disease Research Network.

hypertension, elevated cholesterol, and BMI <18.5 kg/m^2 are independently associated with CKD. The odds of CKD was strongest with hypertension (aOR = 1.69 [1.43–2.0, $P < 0.0001$]). Diabetes and smoking were associated with CKD in the presence of other risk factors whereas increased waist circumference was inversely associated with CKD (aOR = 0.84 [0.71–0.99, $P = 0.037$]).

DISCUSSION

In this large West African population, we estimated the prevalence of specific traditional cardiovascular risk factors among patients with CKD, and we determined the association of the risk factors with CKD. Our results show that in Ghana and Nigeria, patients with CKD are young, they have high prevalence of hypertension, diabetes, smoking, elevated cholesterol, overweight, and high waist circumference. The prevalence of the cardiovascular risk factors are generally higher in Ghana than Nigeria, and they are associated with CKD.

Prevalence of Cardiovascular Risk Factors in Patients With CKD

We observed substantially higher prevalence of hypertension and diabetes but moderately higher prevalence of smoking and elevated cholesterol in patients than the control participants. Similar studies in

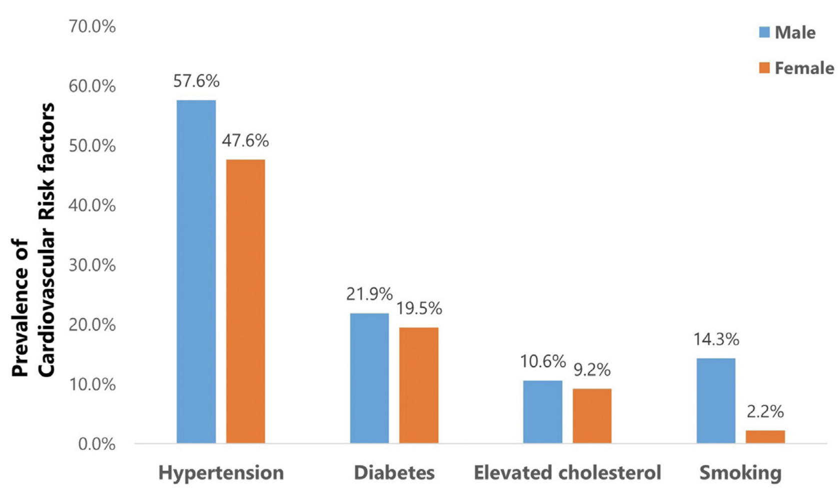

Figure 2. Prevalence of cardiovascular risk factors stratified by sex among CKD patients, Human Heredity for Health in Africa Kidney Disease Research Network.

Table 3. Prevalence of cardiovascular risk factors among CKD patients stratified by the country of the participants, Human Heredity for Health in Africa Kidney Disease Research network

	Country				
	Nigeria	Ghana	Total		
Cardivascular risk factors	n (%)	n (%)	N (%)	χ^2	*P*-value
Age					
<50	714 (57.0)	494 (52.7)	1208 (55.2)	3.937	0.047
Hypertension	442 (35.5)	599 (67.2)	1041 (48.8)	208.772	<0.001
Diabetes	177 (15.1)	163 (24.1)	340 (18.4)	23.251	<0.001
Elevated cholesterol	39 (3.2)	83 (9.9)	122 (5.9)	40.367	<0.001
Smoking	93 (7.4)	105 (11.2)	198 (9.0)	9.284	0.002
BMI (kg/m^2)					
<18.5	104 (8.5)	97 (11.6)	201 (9.8)	14.325	0.001
18.5–24.9	617 (50.5)	356 (42.5)	973 (47.3)		
≥25.0	500 (41.0)	384 (45.9)	884 (43.0)		
Waist circumference[a] (cm)					
High risk	615 (51.3)	123 (59.1)	738 (52.5)	4.323	0.038
Normal	583 (48.7)	85 (40.9)	669 (47.5)		

BMI, body mass index.
[a]Waist circumference (cm) <90 for men and <80 for women: normal; ≥90 for men and ≥80 for women: high risk.

Nigeria were affected by small sample sizes to allow comparison of the results,[19,20] however, these observations agree with previous reports from large studies in the United States,[21] China,[22] and Taiwan,[23] which showed that these traditional cardiovascular risk factors are prevalent in patients with CKD. The prevalence of hypertension, diabetes, hypercholesterolemia, and smoking in our patients are less than figures reported in these countries. Further studies are required to unravel possible causes of the disparity between these countries and our populations. Cardiovascular risk factors are common and often cluster in patients with CKD. The clustering of the traditional cardiovascular risk factors and the CKD-related cardiovascular risk factors amplify cardiovascular events in patients with CKD. Thus, they die more of cardiovascular disease before the need for renal replacement therapy.

Table 4. Correlation between selected cardiovascular risk factors and CKD, Human Heredity for Health in Africa Kidney Disease Research Network

	eGFR	
Cardivascular risk factors	r[a]	*P*-value
Age	−0.207[b]	<0.001
Hypertension	−0.221	<0.001
Diabetes	−0.097	<0.001
Elevated cholesterol	−0.075	<0.001
Smoking	−0.023	0.032
Body mass index	−0.051	<0.001
Waist circumference	−0.060	<0.001

eGFR, estimated glomerular filtration rate.
[a]Spearman's rho correlation coefficient.
[b]Pearson correlation coefficient.

Table 5. Association between cardiovascular risk factors and CKD, Human Heredity for Health in Africa Kidney Disease Research Network

	Unadjusted		Adjusted[a]	
Cardivascular risk factors	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age				
<50 REF	1		1	
≥50	1.14 (1.04–1.24)	0.004	1.18 (1.00–1.39)	0.049
Hypertension	1.72 (1.57–1.88)	<0.001	1.69 (1.43–2.00)	<0.001
Diabetes	1.84 (1.62–2.09)	<0.001	1.15 (0.92–1.44)	0.234
Elevated cholesterol	1.59 (1.31–1.92)	<0.001	1.99 (1.39–2.86)	<0.001
Smoking	1.19 (1.01–1.40)	0.038	0.84 (0.64–1.12)	0.244
BMI (kg/m^2)				
18.5–24.9 REF	1			
<18.5	1.54 (1.30–1.84)	<0.001	1.68 (1.21–2.323)	0.002
≥25.0	0.84 (0.76–0.92)	<0.001	0.92 (0.77–1.09)	0.311
Waist circumference (cm)[b]				
High risk	0.69 (0.62–0.76)	<0.001	0.84 (0.71–0.99)	0.037
Normal REF	1		1	

95% CI, 95% confidence interval; CKD, chronic kidney disease; REF, reference category; OR, odds ratio.
[a]Each factor was adjusted for all others, gender and country of residence.
[b]Waist circumference (cm) <90 for men and <80 for women: normal; ≥90 for men and ≥80 for women: high risk.

Prevalence of Cardiovascular Risk Factors in Patients With CKD Stratified by Age and Gender

The observed high prevalence of cardiovascular risk factors in older age groups may reflect the epidemiology of cardiovascular risk factors in the general population. Increasing age is associated with vascular aging, insulin resistance, impaired cholesterol metabolism, and progressive atherosclerosis. We also noted that cardiovascular risk factors are higher in men than women. Our result supports a previous study in the United States which showed that men have higher prevalence of hypertension, diabetes, and triglyceride (but lower low-density lipoprotein cholesterol) than women.[24] This disparity may explain why men progressed faster to end-stage kidney disease despite women having higher prevalence of CKD.[23,25] In our population, access to health care, and other psychosocial, and economic factors that were not analyzed in our study may be contributory. For example, health-seeking or prevention habit differs significantly between men and women in Africa. Women present more to hospital for health care and they tend to adhere more to preventive measures for diseases.[26,27] In West Africa, because of the poor income of households, men are often the sole income earners, and they engage in prolonged working hours to meet their families' needs such that they have little time to care for their personal health. This disproportion in prevalence of cardiovascular risk factors between men and women suggests that gender should be considered in approaches to manage cardiovascular risk factors in patients with CKD.

Prevalence of Cardiovascular Risk Factors in Patients With CKD Stratified by Country

We observed a higher prevalence of cardiovascular risk factors in Ghana than in Nigeria in this study.The observed disparity in the prevalence of the cardiovascular risk factors may be related to the differences in the health awareness between the 2 countries. For instance, studies have shown that Ghanaians are more aware of hypertension and other cardiovascular disease risk factors than Nigerians.[28–30] In addition, more studies are needed to explore the sociocultural lifestyles, including dietary habits and underlying genetic composition, which may also account for the discrepancy. These imply that county-specific approaches may be adopted to control the cardiovascular risk factors.

Association of Cardiovascular Risk Factors With CKD

The independent association of hypertension with CKD, with 70% increased odds of CKD confirmed reports from previous studies,[21–23,31] though our study has smaller effect size. Our report is analogous to the effect size reported for the overall sample of a 6-continent study by the International Society of Nephrology,[12] but there was no association in the African (Nigeria) subgroup of the study probably because of the difference in study design and the population. The International Society of Nephrology study used cross-sectional design in general population, whereas we used case-control design. The moderate effect size may be attributed to the competing glomerulonephritis from infectious diseases as one of the leading causes of CKD in West Africa. Hypertension is a global burden, and a potent predictor and driver of CKD. A recent study conducted in East Africa and West Africa showed that the prevalence of hypertension is high with low rates of awareness, treatment, and control.[32] The cumulative effects result in premature deaths from hypertension-related cardiovascular events in the general population and in patients with CKD. The poor outcomes reinforce the need to strengthen efforts to prevent and control hypertension in West Africa. The strategies may include adoption of universal health insurance, subsidizing the medications, investment in indigenous production of drugs, and use of fixed-dose combinations of the drugs.

In this study, diabetes was associated with CKD in the presence of other cardiovascular risk factors, with the increased unadjusted odds of CKD of 84% that was attenuated to insignificant 14% when adjusted for other cardiovascular risk factors. This contrasts other studies that documented independent association of diabetes with CKD.[21–23] In agreement with our study, diabetes was not independently associated with CKD in the Nigerian subgroup of the multicontinent study.[31] These observations suggests that the occurrence of CKD in patients with diabetes is modified by other cardiovascular risk factors such as hypertension and elevated cholesterol. In West Africa, diabetes often coexists with hypertension and obesity, and other cardiovascular risk factors and may explain the increasing prevalence in diabetic kidney disease. Diabetes is the leading cause of CKD globally. The prevalence of diabetes is rising at alarming rates in developing countries. The observation of enhancing effects of other cardiovascular risk factors in the association of diabetes with CKD implies that the approach to reduce diabetes-associated CKD should incorporate coexisting risk factors.

We also found that smoking is not independently associated with CKD, which is similar to the studies in China and Taiwan,[22,23] but we recorded only modest increased odds of CKD in the presence of other risk factors. Smoking has been identified as a risk factor for CKD; it increased the risk for cardiovascular events, end-stage kidney disease, and mortality in CKD patients.[33–35] Smoking is less prevalent in West Africa than in high-income countries; nonetheless more people are now smoking in Africa. The small number of people that smoked in this study may be responsible for the dependent association with CKD.

Elevated cholesterol was independently associated with CKD at almost a twice the odds of CKD risk. This finding is similar to the prior study,[22] but shows stronger association compared with other studies that documented only 22% to 36% increased odd of CKD.[23,31] There was no association in the Nigeria subgroup of the multicontinent study[31] probably because of difference in the methods. Although our study cannot detect causality in the relationship between elevated cholesterol and CKD, the strong association discovered in this study suggests a call to reduce cholesterol in CKD population to prevent cardiovascular disease.

Overweight by elevated BMI and waist circumference are not associated with CKD in our study. Although obesity is not the focus of our study, it is inclusive in the definition of overweight. The finding of nonassociation of overweight with CKD is in parallel with other studies[22] and contrary to others that found association.[23] Our observation corroborates the Nigeria subgroup of the 6-continent study[31]; and in their overall sample, the odds of the association was increased by only 7%. However, the association between obesity and CKD in the general population has been documented.[36] In our study, reduced BMI compared with normal weight was associated with CKD. Reduced BMI may represent malnutrition or underlying disease, which predicts mortality in patients with CKD. A systematic review and meta-analysis has shown obesity paradox in which underweight was associated with higher risk of death; and overweight or obese was associated with a lower risk (protective) of death.[37] Because substantial numbers of patients have advanced disease, obesity paradox may explain this finding. Obesity paradox has been succinctly described elsewhere.[38–40] In addition, muscle wasting may occur in CKD because of inflammatory process with release of cytokines and humoral factors that deplete systemic calorie reserve. Furthermore, poor nutrition, inadequate intake, and hypermetabolism that characterize inflammatory state are additional factors that may contribute to reduce BMI in CKD. We observed that higher BMI and waist circumference seem to protect against risk of CKD, implying that boosting the nutritional needs of the patients may reduce their risk.

Strength and Limitations

The strength of this study is the large population of the participants. It is the largest study of CKD in Africa. The study involved Ghana and Nigeria that hosts about 20% of African population. The case-control design of the study also strengthens the results obtained. The limitation of the study is the use of self-reported variables for the cardiovascular risk factors rather than measured variables. Self-reported variables may be subject to recall and reporting biases, however, in this study, we used self-reported physician-diagnosis and use of medication to reduce the biases. In addition, the data were meticulously collected after validation in various ethnic groups and languages of the participants to ensure accuracy of the data. Moreover, data from Atherosclerosis Risk in Communities study showed that using self-reported tool to predict cardiovascular events compare well with atherosclerotic cardiovascular disease risk score that relies on several measured variables.[41]

Conclusion

In summary, in the largest study of CKD in Africa to date, self-reported cardiovascular risk factors are prevalent among middle-age adult patients, with higher proportion in Ghana than in Nigeria. Hypertension, elevated cholesterol, and reduced body weight are independently associated with CKD. Diabetes and smoking are associated with CKD in the presence of other cardiovascular risk factors, whereas increased body weight and waist circumference may protect against risk of CKD. This study describes the association of common determinants of cardiovascular disease and suggests that a comprehensive multifactorial approach to cardiovascular risk factor control should be implemented to reduce cardiovascular burden in patients with CKD in Ghana and Nigeria.

APPENDIX

List of H3Africa Kidney Disease Research Network (Case-Control Study) Investigators

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DISCLOSURE

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