Lifestyle Risk Factors: Do they contribute to chronic kidney disease in developing countries?
I Ulasi, C Ijoma, E Arodiwe, J Okoye, N Ifebunandu

Citation

Abstract
Chronic kidney disease (CKD) is one of the world’s major public health issues. Many people in developing-countries adopt unhealthy western lifestyle which predisposes them to non-communicable diseases. Though, chronic glomerulonephritis may be the leading cause of CKD in these countries, studies in some developing-countries document that lifestyle risk factors are emerging as important in CKD. In Nigeria, though CKD constitutes 8% of hospital admissions, there is no known population-based study on CKD. This study, an arm of a larger project on early detection of CKD in Nigeria, examined modifiable lifestyle risk factors in relation to markers of CKD.

INTRODUCTION
The burden and magnitude of chronic kidney disease (CKD) is enormous especially in developing countries. CKD currently is one of the world’s major public health issues. Lifestyle related diseases are important causes of increased morbidity and mortality in the world today. The 2004 WHO report on global burden of disease includes lifestyle related diseases and kidney disorders in the top twenty leading causes of death [1].

The body of evidence for other modifiable risk factors such as lifestyle factors is growing as some studies suggest that tobacco use is positively associated with CKD [2,3]. Some other studies on the other hand have found no association between smoking and CKD [4,5]. Alcohol has been linked as cause of kidney disorders in some clinical and experimental studies [6,7]. Increased risk of CKD has been reported with obesity [4,8] but few studies have described an inverse relationship between BMI and CKD [9,10]. No studies have been done in developing countries.

In most developing countries, chronic glomerulonephritis often caused by infections and infestations may be the leading cause of CKD [11,12] followed by hypertension. Albeit, studies in some developing countries such as South Africa [13] and India [14] suggest that lifestyle factors are emerging as important risk factors for CKD. Non communicable diseases including lifestyle related diseases are emerging as significant causes of morbidity and mortality in developing countries prompting the WHO to highlight the problem of double burden of diseases in developing countries [1].

Presently in Nigeria, there is no known population based study on CKD, the last non-communicable disease nationwide survey sponsored by the Federal Ministry of Health in 1997,[15] did not include screening for CKD. Hospital based studies suggest that end-stage renal disease (ESRD) constitutes about 8% of hospital admissions. [12]. Most importantly, in Nigeria as in many other developing countries, majority of the individuals afflicted with CKD are young and in their economically productive years usually in their 4th decade of life.[12] Worse still, a large majority of them (>80%) first consult a Kidney specialist after they have reached the terminal stage[11]. These therefore underscore the need for screening for early detection of CKD.

In this arm of a larger project on screening for early detection and prevention of CKD in Nigeria, and bearing in mind the double burden of disease, the authors investigated several modifiable lifestyle risk factors (tobacco use, alcohol consumption, physical inactivity and increased BMI) associated with CKD in relation to markers of early CKD in a population-based study.

METHOD
STUDY AREA AND STUDY POPULATION
Nigeria is made up of 6 geo-political zones with a total of 36 states and the Federal Capital Territory. South East geo-political zone comprises of 5 states (Enugu, Ebonyi, Imo,
Abia and Anambra) with estimated population of 30 million people. The study area is Ujodo Nike Local Government Development Centre (LGDC) in Enugu North Local Government Area (LGA) of Enugu State. This LGDC comprises of three communities namely Mbulu-Ujodo, Mbulu-Awuli and Emene communitie. Emene-Nike and adjoining Eke-Obinagu were chosen as the only semi-urban area and Mbulu-Ujodo was randomly selected from the two rural communities. Mbulu-Ujodo comprises of villages or hamlets viz.: Obinagu Nike, Nchantancha, Akpuoga and Onuogba.

**STUDY POPULATION**

Most inhabitants in the study area are of the Igbo tribe. Majority of the inhabitants are of low socio-economic status mainly artisans, traders and low income workers who live in over-crowded homes with poor sanitary conditions. In the Igbo tribe, being overweight/obese is preferred to slim build.

**SAMPLE DESIGN**

A 2-stage stratified sampling method with selection of all eligible consenting adult in Ujodo LGDC aged 25 to 64 years were selected from 20 sampling units – 12 semi-urban and 8 rural. The final stage of sampling was stratified by gender (50% men and 50% women) and by 10 year age group. Since the Nigerian national census list of 2006 was not available enumeration of the study community was done during the training of the interviewers. A total of 30 interviewers were trained by the field worker but 24 were selected one for each sampling unit and 4 as standby. All eligible subjects in the same household were invited for the study. Two thousand seven hundred persons (1010 men and 1,690 women) were randomly selected from 20 primary sampling units (streets in semi-urban areas, or hamlets in rural areas) and were invited to participate. The respondents were evaluated between July and Dec 2007. A total of 2182 persons (808 men and 1374 women) completed the survey and examination. The overall response rate was 80.8% (80.0% in men and 81.3% in women; 80.5% in semi-urban areas and 81.5% in rural areas). To remove sex bias the women recruited later were excluded from the study leaving a total of one thousand five hundred and fifty-six participants. Subject were evaluated following the World Health Organization Stepwise Approach to Chronic Disease Risk Factor Surveillance (STEPS), which included a questionnaire on socio-demographic and behavioral factors [16]. The socio-demographic characteristics— including age, gender, educational level/years in school, ethnicity, occupation, leisure and physical activity —was collected. Also information on medical and health history were obtained.

**DATA COLLECTION: ADMINISTRATION OF QUESTIONNAIRE, CLINICAL EVALUATION AND SAMPLE COLLECTION**

**ADMINISTRATION OF QUESTIONNAIRE**

Participants were interviewed in the evenings in their homes after their day’s work by the trained interviewers using the WHO STEPs questionnaire. Apart from questions on sociodemographic and behavioral factors information on demographic characteristics— including age, gender, educational level/years in school, ethnicity, occupation, leisure and physical activity —was collected. Also information on medical and health history were obtained.

All study investigators and staff members (comprising of doctors and nurses working with the department of Medicine, University of Nigeria Teaching Hospital, Enugu) successfully completed a training programme that oriented them both to the aims of the study and to the specific tools and methodologies employed. The interviewers who administered the questionnaires were trained over a month period during which time enumeration of the study community was done.

**THE CLINICAL EVALUATION AND COLLECTION OF SAMPLES WERE CARRIED OUT AT SCREENING CENTRES SET-UP AT SPOTS CONVENIENT FOR THE PARTICIPANTS: CHURCHES, MARKET SQUARE, TOWN HALL AND THE HEALTH CENTRE AT AKPUOGA, NIKE.**

The participants’ anthropometric data were taken: height, weight, waist and hip circumferences. The weight was measured using standardized bathroom scale (10kg weight was used). The heights were measured with a standiometer. The waist circumference was taken at mid-way between the sub-costal margin and the iliac crest while the hip circumference was taken at the widest diameter.

BP measurements were obtained from each participant by nurses according to a common protocol adapted from
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procedures recommended by the American Heart Association [17]. BP was measured three times, one minute apart with the participant in the sitting position after 5 minutes of rest with appropriately sized cuff using Accoson’s sphygmomanometer. The mean of the three measurements was used for analysis.

Three milliliters of fasting blood was collected into plain bottle for blood chemistry – serum creatinine. Urine was collected in universal container, dipsticks urinalysis was done on site and samples were sent to the laboratory for protein and creatinine analysis. All samples were analyzed at the Dept of Medicine Research Laboratory, University of Nigeria Teaching Hospital, Enugu. The concentration of total protein in urine was measured by a Biuret colorimetric assay and the urine creatinine was measured by a modified Jaffe test using semi-autoanalyser Mitra Photometer (Linear Chemicals S.L., Barcelona, Spain). The PCR in urine was expressed as mg/g of creatinine.

DEFINITIONS

Significant alcohol consumption was defined as intake of 3 or more drinks. Heavy cigarette smoking was defined as smoking of 1 packet or 20 cigarettes/day for at least one year. Heavy snuffing was considered as use of about 35 gram (equivalent to 1.2 oz) of snuff per week daily for at least one year [18].

Obesity was defined according to the 1999 WHO criteria. Cutoff points for BMI were: overweight (BMI 25.0 – 29.99 kg/m\(^2\)) obesity (BMI ≥30 kg/m\(^2\)) [19].

Abdominal obesity was based on IDF classification viz. waist circumference ≥ 94 cm for males and ≥ 80 cm for females were considered abnormal [20].

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or and/or concomitant use of antihypertensive medications according to the WHO/ISH guidelines [21].

Estimated glomerular filtration rate (eGFR) was calculated using the Cockroft and Gault equation [22] which correlates well with measured creatinine clearance in Nigerians [23].

Creatinine clearance = (140-age) × weight (kg)

0.81 × serum creatinine (µmol/l)

For females multiply by a factor of 0.85.

Albuminuria was defined as the ratio of albumin to creatinine (ACR) in an un timed urine sample as recommended by The National Kidney Foundation Proteinuria, Albuminuria, Risk, Assessment, Detection, Elimination (NKF PARADE) and The American Diabetes Association in the assessment of proteinuria in CKD [24, 25]. The ACR was categorized as: a) normal, <30 mg/g; b) microalbuminuria, 30 ~ 299 mg/g; c) macroalbuminuria, >300 mg/g. Macroalbuminuria equates to 1+ proteinuria. Proteinuria creatinine ratio (PCR) was used in this instead of ACR.

Markers of early CKD were taken as proteinuria (PCR ≥30 mg/g), haematuria or estimated glomerular filtration rate (eGFR) stages 1 to 3 [26].

STATISTICAL METHODS

The Statistical Package for Social Sciences (SSPS Inc, Chicago, IL) version 16 statistical software was used for data analysis. Cross tabulation assessed the association between lifestyle risk factors and markers of chronic kidney disease as outcome variable. We examined the relationship between the various variables such as sex or gender, age, level of education or years in school, site (semi-urban or rural community), tobacco use, alcohol consumption, past history of hypertension, past history of DM, present history of hypertension and DM. The relationship between use of tobacco and CKD was examined by using heavy use of tobacco or less. We also examined the relationship between CKD and type of tobacco used (mostly as cigarette or snuff in the study area). We assessed alcohol consumption by number of drinks taken per day (≥3 or less).

Spearman’s correlation was used to assess these relationships. Significant variables were further analyzed using the stepwise method of multiple linear regression analysis to isolate possible predictors or determinants of CKD based on their level of importance. All tests were two-tailed with p<0.05 taken as statistically significant.

ETHICS

The Institutional Review Board at University Nigeria Teaching Hospital approved the study proposal and questionnaires. Informed consent was obtained from each participant before administration of questionnaire and data collection. During the study, participants with untreated conditions identified during the examination were referred to their usual primary health care provider, secondary or tertiary care providers as was deemed necessary.
RESULTS

Of the number screened, one thousand four hundred and fifty-eight (709 male and 749 female) respondents were analyzed and the others (73) did not have analyzable data. About two thirds of the respondents studied were from the semi-urban communities (540 male and 548 female respondents) and the other third were from the rural communities (169 male and 201 female respondents).

The study showed that the prevalence of markers of CKD in the populations studied was 26.8%. Prevalence of CKD increased with age, Table 1. The respondents with CKD had significantly higher mean age (52.3±12.4 years) than those without CKD (40.5±12.7 years), p-value 0.001. When stage 3 CKD and presence of albuminuria were considered separately 18.6% of the participants had CKD stage 3 and 17.1% had albuminuria only.

The mean BMI was significantly lower in respondents with CKD (23.8±4.6kg/m$^2$) than those without CKD (26.2±4.7kg/m$^2$), p-value 0.001. BMI was negatively and significantly associated with markers of CKD – correlation coefficient (r): -0.260, p < 0.001. Further analysis showed that odds ratios (ORs) (obese versus non-obese) [95% CI] for all respondents were 0.48 [0.33–0.68], p < 0.001; when the sexes were analyzed separately similar pattern was seen viz. female respondents – correlation coefficient (r): -0.266, p <0.001; ORs [95% CI] 0.48 [0.31-0.74], p=0.001 and male respondents correlation coefficient (r): -0.25822, p<0.001; ORs [95% CI] 0.43 [0.22 – 0.87], p < 0.016. Similar trend was noted when overweight respondents (BMI >24.9 - <30kg/m$^2$) was compared with those not overweight (BMI <25kg/m$^2$); for all respondents, ORs [95% CI] 0.44 [0.33 – 0.58], p<0.001; female respondents ORs [95% CI] 0.45 [0.30 – 0.67], p<0.001, and for male respondents ORs [95% CI] 0.43 [0.29 – 0.64], p<0.001.

The mean estimated glomerular filtration rate (eGFR) for the respondents with early markers of CKD was 61.6±23.8ml/min as against 92.1±22.2ml/min for the respondents without, p<0.001. Increasing age, past history of hypertension and presence of hypertension were associated with CKD, Table 1.

The association between those who took alcohol (≥3 drinks) compared with those who took less and CKD was significant, OR [95% CI] 2.67 [1.30 – 5.49], p=0.006, table 1. After controlling for variables such as age, sex, use of tobacco, presence of diabetes mellitus or hypertension there was no association between alcohol consumption and CKD, r=0.052, p-0.100. There was no significant association between use of tobacco when combined (i.e cigarette smoking and use of snuff) and presence of markers of chronic kidney disease (ORs [95% CI]: 1.30[0.87–1.93], p <0.196. However, further analysis showed that use of tobacco as snuff when considered alone was significantly associated with CKD no such association was found with smoking of cigarette, table 2.

Table 3 shows the Spearman’s correlation values for CKD and factors that affect it in the study population. Of all factors, decreasing BMI correlated best with CKD (r= -0.260, p-value <0.001). BMI therefore had inverse relationship with CKD. Significant variables were further analyzed using the stepwise method of multiple linear regression analysis to isolate variables based on their level of importance. Decreasing body mass index, reduced physical activity, use of tobacco as snuff, waist circumference and alcohol were isolated as predictors with decreasing BMI being the best predictor, table 4.

Figure 1

Characteristics of the respondents by presence or absence of CKD

Figure 2

Prevalence of CKD with type of tobacco used
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Figure 3
: Correlation table of the lifestyle risk factors with CKD

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Correlation coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Use (combined)</td>
<td>0.037</td>
<td>&lt;0.196</td>
</tr>
<tr>
<td>Snuff</td>
<td>0.091</td>
<td>0.002*</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.260</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-0.130</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.086</td>
<td>0.006*</td>
</tr>
<tr>
<td>Activity</td>
<td>-0.077</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

*P-value significant

Figure 4
: Stepwise multiple linear regression analysis of lifestyle factors that correlate with CKD in respondents

<table>
<thead>
<tr>
<th>Model</th>
<th>Standardized Beta</th>
<th>Coefficients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.756</td>
<td>0.125</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.009</td>
<td>0.122</td>
<td>0.001</td>
</tr>
<tr>
<td>Activity</td>
<td>-0.023</td>
<td>0.011</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of snuff</td>
<td>0.027</td>
<td>0.014</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.080</td>
<td>0.014</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-0.175</td>
<td>-0.078</td>
<td>0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

In this population-based study of adult Nigerians aged 25 to 64 years we found a high prevalence of early markers of CKD – 26.8%. In studies in developed countries, prevalence range from 7.2% in Iceland [27], 10.2% in Norway [28] to 13.1% in US [29]. Whilst the US [29] and Norwegian [28] studies looked at people with CKD stages 1 to 4 which is close to stages 1 to 3 done in this current study, the study in Iceland essentially looked at participants who had stages 3 to 5 CKD. Other developing countries have documented prevalence rates of 12.4% [30], 13% [31] and 13.3% [32] in Congo, China and India respectively. These later studies however looked at respondents with eGFR <60ml/min (stages 3 to 5 CKD). The difference in the degree of CKD as represented by stages of CKD can mostly explain the discrepancy between our studies and others in the developing world.

This current paper however considers the contribution of lifestyle factors in prevalence of CKD in the study population. The use of tobacco was not associated with markers of early CKD. Interestingly, further analysis showed that the form of tobacco product used was relevant as respondents who used tobacco in form of snuff had significantly higher prevalence of CKD. This raises the possibility that the additives to the tobacco in snuff could be accountable for the risk of CKD in these respondents. While some population-based studies have demonstrated significant association between smoking and CKD even independent of confounders such as body mass index, physical inactivity, use of NSAIDs, alcohol consumption, hypertension, diabetes mellitus and others [2,3], other studies have found no association between CKD and smoking[4].

Alcohol has been reported as a possible risk factor for CKD in clinical and experimental studies and several pathogenic mechanisms have been suggested. Shankar et al [2] have shown in their study that heavy drinking is associated with CKD. In this current study, alcohol consumption increased the risk of CKD in respondents. But the effect was not independent. Also few participants consumed alcohol in significant quantity.

Living in the rural area seemed to be a risk factor for CKD. The reasons for this finding were not explored in this present paper as it is a subject for another study. We found a contradictory protective effect with increased BMI in this population i.e. the non-obese respondents had two fold odds of developing CKD than the obese. Most literatures suggest obesity [4,8] and metabolic syndrome as risk factors for CKD [33]. However, some studies done in Japan have found decreased body mass index as an independent risk factor for CKD [9,10]. This seems to have been borne out in this current study. We opine the use of Cockroft and Gault equation as possible explanation as extremes of weight are known to adversely affect the accuracy of correlation of eGFR with renal function using this formula. This indeed calls for research in this area to further elucidate the reasons for this observation. It is important to note that waist circumference a measure of abdominal obesity had positive correlation with CKD in this current study.

Of the variables tested, decreasing BMI, physical inactivity, use of tobacco as snuff, waist circumference and alcohol consumption predicted the occurrence of markers of early CKD. While alcohol consumption, use of tobacco as snuff and waist circumference had positive correlation, BMI and physical activity had inverse relationship with CKD.

In spite of the strengths of this study which include: the fact that this is a population-based study, there were some limitations for example: the cross sectional design of the study instead of longitudinal design which is better for establishing causality. The use of self report for alcohol consumption and use of tobacco may not be entirely accurate because the veracity of the response cannot be ascertained. Kidney function and indicators of kidney damage were based on single measurements. In assessing proteinuria, PCR
was used instead of ACR which is preferred.

In conclusion, in this population-based study, the prevalence of CKD was high. The consumption of three or more servings of drink was found to be associated with chronic kidney disease. Use of tobacco as snuff was associated with CKD but not cigarette smoking. BMI had inverse relationship with CKD.

SPONSORSHIP

This project was part sponsored by the International Society of Nephrology (ISN) through their Research Committee Programme for Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes and Cardiovascular Disease in Developing Countries (KHDC) which offers grant for befitting proposals.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

ACKNOWLEDGEMENTS

The authors acknowledge their gratitude to Dr Elvis N Shu, Pharmacology Department, College of Medicine, University of Nigeria for his invaluable guidance. We also appreciate Mr. Soludo Eze, the sociologist, Mr. Eric Obikeze, who assisted with translating the questionnaire and Mr. Eke U Kalu, the field worker who trained the interviewers.

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Author Information

Ifeoma I Ulasi
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Chinwuba K Ijoma
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Ejikeme B Arodiwe
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Julius U Okoye
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Ngozi A Ifebunandu
Department of Medicine, Ebonyi State University Teaching Hospital