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Original Investigation

Non-cigarette Tobacco Use and Stroke Among West Africans: Evidence From the SIREN Study

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Abstract

Introduction: Non-cigarette tobacco (NCT) represents a form of tobacco use with a misperceived significance in chronic disease events. Whether NCT use is sufficient to promote stroke events, especially among Africans, is yet to be understood. This study assessed the relationship between NCT use and stroke among indigenous Africans.

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Methods: A total of 7617 respondents (NCT users: 41 vs. non-NCT: 7576) from the Stroke Investigative Research and Educational Network (SIREN) study were included in the current analysis. NCT use was defined as self-reported use of smoked (cigars or piper) or smokeless (snuff or chewed) tobacco in the past year preceding stroke events. Stroke was defined based on clinical presentation and confirmed with a cranial computed tomography/magnetic resonance imaging. Multivariable-adjusted logistic regression was applied to estimate the odds ratio (OR) and 95% confidence interval (CI) for the relationship of NCT with stroke at a two-sided $p < .05$.

Results: Out of the 41 (0.54%) who reported NCT use, 27 (65.9%) reported using smokeless NCT. NCT users were older than non-NCT users (62.8 ± 15.7 vs. 57.7 ± 14.8 years). Overall, NCT use was associated with first-ever stroke (OR: 2.08; 95% CI: 1.02, 4.23) in the entire sample. Notably, smokeless NCT use was independently associated with higher odds of stroke (OR: 2.74; 95% CI: 1.15, 6.54), but smoked NCT use (OR: 0.16; 95% CI: 0.02, 1.63) presented a statistically insignificant association after adjusting for hypertension and other covariates.

Conclusions: NCT use was associated with higher odds of stroke, and public health interventions targeting NCT use might be promising in reducing the burden of stroke among indigenous Africans.

Implications: A detailed understanding of the relationship between NCT use and stroke will likely inform well-articulated policy guidance and evidence-based recommendations for public health prevention and management of stroke on the African continent.

Introduction

Cigarette smoking is the most common form of tobacco used worldwide, and it remains the leading single preventable cause of chronic disease, including cancer, cardiovascular diseases, and respiratory diseases,[1] with tobacco-related mortality occurring at least every 6 seconds.[2] Of these deaths, 75% occur in low- and middle-income countries, where more than 80% of the world's smokers live,[3] and the pooled crude incidence of stroke is approximately 106 persons per 100, 000 population in Africa.[4] The epidemic of smoking is being addressed by the World Health Organization through the Framework Convention on Tobacco Control—FCTC,[5] which is an intervention strategy to control tobacco production and its uses. This initiative was primarily driven by an emphasis on smoked cigarette tobacco,[6] with less attention to non-cigarette tobacco (NCT) products, particularly those commonly used in sub-Saharan Africa, such as cigars, pipers, snuff, or chewing tobacco, and pose significant health effects.[7,8] However, public health interventions on preventing tobacco use by the FCTC exclusively target cigarette tobacco, devoting little attention to NCT products.

The association between smoked cigarette tobacco use and cardiovascular diseases (CVDs) such as stroke among Black Africans has been widely documented.[9,10] However, few studies have explored the contribution of NCT use on the burden of stroke among Africans despite the growing use among Africans.[11] NCT products are attracting new markets worldwide,[12] but the reasons for these trends are not entirely clear, though concerns for smoking-related health effects may play a role.[13,14] In sub-Saharan Africa, the decision to change from cigarette tobacco to NCT products is multifactorial but may not be farfetched from the erroneous misconceptions that they are less harmful or perhaps price minimization strategy.[15] However, limited data are available on the health implications of using NCT products.[16,17] The prevalence of NCT use among adults aged 15 years and above was reported to be 1.9% in Nigeria[18] and 2.6% in Ghana.[19] Of note, several studies have revealed severe health consequences related to NCT use, specifically oral health impairment,[17,20] nutritional disorders,[21] co-use of psychoactive substances, and CVD, including coronary heart diseases,[22–24] but little is known about the significance of NCT use in the stroke events in this population.

A detailed understanding of the relationship between NCT use and the risk of stroke will likely inform well-articulated policy guidance and evidence-based recommendations for public health prevention and management of stroke on the African continent. As far as we know, this study is the largest and the first to characterize NCT use in relation to stroke epidemiology on the African continent. Given the increased morbidity and mortality due to stroke and the priority of its treatment and prevention, numerous studies have assessed the relationship between smoking and stroke with limited information on the significance of NCT use in stroke epidemiology, particularly among indigenous Africans. Therefore, this present study investigated the relationship of NCT use with the odds of first-ever stroke among adults in West Africa.

Methods

Study Design, Population, and Setting

Respondents for this current study were from the Stroke Investigative Research and Educational Network (SIREN) study. SIREN is a multicenter case–control study initiated in 2014 and carried out in Ghana and Nigeria to characterize the burden and risk factors of stroke among indigenous Africans. Ethical approval was obtained across 15 study sites in Ghana and Nigeria, and informed consent was obtained from respondents (≥18 years) before participation. The SIREN study recruited stroke cases with a first clinical stroke within eight days of current symptom onset or last seen without deficit, with neuroimaging confirmation on computed tomography (CT) or magnetic resonance imaging (MRI) scan within ten days of symptom onset. Population-based stroke-free controls were recruited primarily from catchment communities of the study sites. Stroke-free status was verified using the eight-item validated questionnaire for verifying stroke-free status.[25] Details of methods and preliminary findings have been documented elsewhere.[9,26] This current report included 3531 stroke cases and 4086 stroke-free population-based controls from the SIREN dataset who have never used cigarette tobacco in their lifetime. In-person interviews and physical examinations were conducted by trained medical personnel to extract data on demographic and lifestyle factors (including NCT use) and fasting blood samples (after an overnight fast) using validated instruments and uniform standard operating procedures across all study sites.

Definition of First-Ever Stroke (Outcome)

Based on clinical evaluation and brain imaging (CT or MRI), stroke cases were defined and phenotyped using electrocardiography, transthoracic echocardiography, and carotid Doppler ultrasound. Details of the definition and phenotyping procedure have been published elsewhere.[9] Ischaemic stroke subtypes were defined using Oxfordshire community stroke project guidelines[27] and the Trial of ORG 10172 in acute stroke treatment guidelines.[28] Intracerebral haemorrhage was defined using structural, medication-related, amyloid angiopathy, systemic/other diseases, hypertension, and undetermined.[9,29] Stroke-free controls were verified using a prevalidated eight-item scale to verify stroke-free status (with 98% negative predictive value) in three main local languages in West Africa (Ashanti Twi, Hausa, and Yoruba).[25]

NCT Use (Exposure)

The current study included respondents who reported having never used cigarette tobacco in a lifetime. NCT use was defined as self-reported use of at least one of the following NCTs: cigars or piper (for at least 50 times) or snuff or chewing tobacco (for at least 20 times) in the past year before the onset of stroke as described in the protocol.[26] NCT use was classified as smoked (if respondents reported using cigars or piper) or smokeless (if respondents reported using snuff and chewed tobacco).[12]

Sociodemographic, Lifestyle, and Clinical Characteristics (Covariates)

Respondents provided information on country of residence (Ghana or Nigeria), sex (male or female), age in years, education status (classified as none, primary, secondary, or secondary school education and above), income (classified as "low" if respondent's monthly earnings was <\$100 or "high" if respondent's monthly earnings was ≥\$100)[30], alcohol use (no or yes), and family history of CVD (no or yes). Physical activity was defined as regular involvement in moderate exercise (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for at least 4 hours per week.[30,31]

Body mass index (BMI) was estimated from weight (in kg) divided by the square of height (in meters), and waist-to-hip ratio (WHR) was a function of the waist circumference divided by hip circumference (in cm). Obesity was defined as BMI ≥30 kg/m^2, and WHR ≥0.90—males and ≥0.85—females used as the cutoff for respondents at risk of metabolic disorders.[32] Diabetes mellitus (DM) was defined as any of the following conditions: self-reported DM diagnosis by a trained physician, current use of medications for DM, HbA1c ≥6.5%, or fasting blood glucose ≥7.0 mmol/L.[33] Hypertension was defined as any of the following conditions: a one-off or sustained systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, a prior diagnosis of hypertension by a trained physician or use of antihypertensive medications.[34] Dyslipidemia was defined as any of the following conditions: fasting total cholesterol ≥5.2 mmol/L, high-density lipoproteins ≤1.03 mmol/L, triglycerides ≥1.7 mmol/L, or low-density lipoproteins ≥3.4 mmol/L or use of statin prior before stroke onset.[35]

Statistical Analysis

Multiple imputation technique, enabled by the MICE package in the R statistical software, was used to fill in the missing data on NCT use in the dataset. A chi-square and independent-sample *t* test were used for categorical and continuous variables respectively to compare respondents' characteristics according to NCT use status. Furthermore, we used logistic regression to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for NCT use and first-ever stroke, controlling for covariates. We included covariates in the regression models based on whether they were of statistical significance in the bivariate analysis and our clinical understanding of stroke. The following covariates were included in the final regression model: age (in years, continuous), highest education completed (none, primary, or secondary school and above), monthly income (<\$100 vs. ≥\$100), current alcohol use (no vs. yes), family history of CVD (no vs. yes), physical inactivity (no vs. yes), obesity (<30 kg/m^2 vs. ≥30 kg/m^2), DM status (no vs. yes), dyslipidemia (no vs. yes), and hypertension (no or yes). Furthermore, we carried out subgroup analyses by NCT type, which included smoked and smokeless NCT use. All statistical analyses were performed using SPSS (version 25) and the R statistical program (version 3.6.2) at a two-sided $p < .05$.

Results

Characteristics of Respondents

The characteristics of respondents are presented in Table 1. NCT users were older than non-NCT users (62.8 ± 15.7 vs. 57.7 ± 14.8 years). Among NCT users, 65.9% were males while 34.1% were females and a higher proportion of respondents who earn ≥\$100 reported NCT use compared to non-NCT users (57.5% vs. 44.5%). However, current alcohol use, family history of CVD, physical inactivity, mean WHR, and BMI differed insignificantly by NCT use status, but the prevalence of obesity was higher among NCT users (48.8%) than non-NCT users (23.5%). Similarly, the prevalence of dyslipidemia was higher among NCT users compared to non-NCT users (26.4% vs. 23.3%), and the proportion of NCT users 34 (0.6%) with hypertension was higher compared to non-NCT users 7 (0.4%).

NCT Use, Stroke Status, and Stroke Subtype

Of the total 41 (0.5%) who reported NCT use, 27/41 (65.9%) were stroke cases, while 14/41 (34.1%) were stroke-free controls. Among stroke cases that reported NCT use, 20 (0.8%) and 7 (0.7%) had ischaemic and hemorrhagic stroke subtypes, respectively.

NCT Use and Odds of First-Ever Stroke

The OR and 95% CI for the association of NCT use with all stroke events are presented in a single model (Table 2). In the unadjusted model, overall NCT use was significantly associated with higher odds of stroke (OR: 2.74; 95% CI: 1.35, 5.56). Overall, NCT use was associated with first-ever stroke (OR: 2.08; 95% CI: 1.02, 4.23) in the entire sample after adjusting for age, highest education completed, monthly income, current alcohol use, family history of CVD, physical inactivity, obesity status, DM status, and dyslipidaemia status—Table S1. However, the association was attenuated (OR: 1.98; 95% CI: 0.91, 4.28) after additionally adjusting for hypertension—Table S2. Notably, smokeless NCT was independently associated with higher odds of stroke (OR: 2.74; 95% CI: 1.15, 6.54), but smoked NCT use (OR: 0.16; 95% CI: 0.02, 1.63) presented a statistically insignificant association with stroke odds, even after adjusting for hypertension and other covariates (Figure 1).

Discussion

In this study, we investigated the relationship between NCT use and first-ever stroke and found that NCT was independently associated with higher odds of stroke among indigenous Africans, with smokeless NCT presenting higher odds for all stroke events. Our study is the largest and the first to characterize NCT use, including smokeless NCT and its association with stroke, even after adjusting for vascular risk factors for

Table 1. Characteristics of All Nonsmokers According to NCT Use in the SIREN Study

Characteristics	NCT use status		
	NCT (no)	NCT (yes)	*p*-value
Country	7576	41	
Ghana	2220 (29.9)	10 (24.4)	.491
Nigeria	5356 (70.1)	31 (76.6)	
Sex			
Females	3865 (51.0)	14 (34.1)	.02
Males	3711 (49.0)	27 (65.9)	
Age (years), mean ± *SD*	57.7 ± *14.8*	62.8 ± *15.7*	.01
<60 years	4000 (52.8)	13 (31.7)	.007
≥60 years	3576 (47.2)	28 (68.3)	
Education			
None	1569 (20.7)	7 (17.5)	.87
Primary school	1678 (22.2)	9 (22.5)	
Secondary school and above	4317 (57.1)	24 (60.0)	
Monthly income			
<$100	4132 (55.5)	17 (42.5)	.09
≥$100	3311 (44.5)	23 (57.5)	
Lifestyle factors			
Current alcohol use (yes)	7334 (96.8)	39(95.1)	.54
Family history of CVD (yes)	4623 (61.0)	26 (63.4)	.75
Physical inactivity (yes)	251 (3.3)	2 (4.9)	.57
Anthropometric measurements			
WHR, mean ± *SD*	0.92 ± *0.8*	0.93 ± *0.09*	.53
WHR ≥ 0.90 (men) and 0.85 (women)	5522 (72.9)	28 (68.3)	.92
BMI (kg/m^2), mean ± *SD*	26.5 ± *5.6*	26.2 ± *5.2*	.79
BMI ≥ 30 kg/m^2	1781 (23.5)	20 (48.8)	<.0001
Blood pressure and metabolic factors			
SBP (mm Hg), mean ± *SD*	146.1 ± *30.0*	152.1 ± *28.7*	.21
DBP (mm Hg), mean ± *SD*	89.1 ± *60.6*	92.4 ± *15.1*	.73
Hypertension (yes)	7 (0.4)	34 (0.6)	.20
Diabetes (yes)	3360 (44.4)	24 (58.5)	.068
Dyslipidemia (yes)	1767 (23.3)	11 (26.8)	<.0001

NCT: non-cigarette tobacco; CVD: cardiovascular diseases; WHR: waist-to-hip ratio; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Continuous data are presented as mean ± *SD* and compared using paired *t* test; categorical data are presented as *n* (%) and compared using the chi-square test.

stroke. NCT remains the main form of tobacco consumption by almost a quarter of all tobacco users worldwide.[36] Nevertheless, its regulation and control lag behind cigarette tobacco use. Our findings will contribute to identifying the neglected environmental risk factors of stroke and necessitate its inclusion in designing culturally relevant primary prevention strategies for controlling stroke and other CVDs among Africans.

Several published reports have documented the significance of active and passive smoking in the epidemiology of stroke and other CVD events,[37–39] with limited evidence on the implications of NCT use in stroke occurrence. Our findings corroborate reports from a few epidemiological studies.[40,41] Two meta-analyses demonstrated a higher risk of stroke among current NCT users, especially for studies from the United States.[42,43] A similar observational study in Iran reported a three-fold risk of first-ever ischaemic stroke among users of Hookah—an NCT product.[44]

Our findings revealed the significance of smokeless NCT use (chewing and snuffing tobacco) in stroke events. To date, a significant gap is the lack of observational studies on the risks associated with various types of smokeless NCT used within and between countries.[36] The few epidemiological reports on the association between smokeless NCT use and stroke have been inconsistent, with some studies showing a slightly elevated risk of stroke and others reporting no association.[45,46] Our study found that smokeless NCT was strongly and significantly associated with all stroke events, even after adjusting for related covariates, especially hypertension. Our report did not account for subgroup analysis by stroke type due to fewer stroke cases, but a recent study by Hergens et al.[41] reported an increased risk of fatal ischaemic stroke subtype only and not overall stroke among current snuff users. A possible explanation could be the inclusion of snuffers and tobacco chewers in the current analysis as opposed to only snuffers in the study by Hergens et al.[41]

However, the apparent direct association between NCT use and stroke was not statistically significant after adjusting for hypertension, except for smokeless NCT use. Possible reasons could include the following. First, unlike smoked cigarettes, smokeless NCTs are consumed discretely without combustion, either nasally or orally, which aids regular consumption, thereby resulting in the absorption of nicotine and other chemicals across mucus membranes. Smokeless NCT products vary significantly in composition and contain high levels of free nicotine, total nicotine, and various carcinogens.[47] In contrast to our findings, a meta-analysis has reported a significantly increased risk of stroke due to exposure to some toxicants and nicotine in smoked NCT.[48,49] It is likely that misclassification of NCT status, particularly regarding underreporting of smoked NCT use, may partly explain the association toward the null for smoked NCT use in our study. Unlike smokeless NCT use, smoking is not considered socially desirable among African young adults due to cultural values and beliefs.[50] Hence, smoked NCT use is likely to be underreported. Second, this might be due to the low statistical power to discriminate associations due to the few NCT users in the dataset. Third, it is likely that NCT use could trigger stroke events via hypertension risk due to early reports[51,52] that have demonstrated a direct link between passive tobacco use and hypertension. A common ingredient in all tobacco products is nicotine, and the plasma level of nicotine in NCT is as high as in passive tobacco.[53] Some authors have demonstrated an increase in heart rate and blood pressure measurements along with elevation of plasma epinephrine after administration of NCT.[54] A secondary data analysis of the South African Demographic and Health Survey among 4092 South African women aged 20–75 years reported a significantly increased blood pressure to levels shown to increase CVD risk due to heavy snuff use.[55] Also, combined lifetime use of both snuff and cigarettes has been reported to increase the odds of developing osteoporosis among women aged ≥40 years.[56] Studies reporting a positive association of NCT use with hypertension postulated that frequent use of NCT could lead to continuous moderate levels of nicotine in the blood, causing sympathetic nervous system activation and a rise in

Table 2. Odds Ratio (95% Confidence Interval) of the Multivariate Adjustment for the Association of Smokeless and Smoked NCT Use by Odds of Stroke Using Non-NCT as Reference

	All stroke events
NCT use (yes)	2.74 (1.35, 5.56)
Crude odds	
Non-NCT (ref)	1
Smoked	0.29 (0.03, 2.60)
Smokeless	2.75 (1.36, 5.57)
Adjusted odds	1.93 (0.89, 4.17)
Non-NCT (ref)	1
Smoked	0.16 (0.02, 1.63)
Smokeless	2.74 (1.15, 6.54)
Covariates	
Age (in years continuous)	1.00 (0.99, 1.01)
Sex (males)	1.34 (1.19, 1.50)
Secondary school and above	1.24 (1.10, 1.40)
Monthly income (≥$100)	0.1 (0.62, 0.80)
Current alcohol use (yes)	1.29 (1.04, 1.61)
Family history of CVD (yes)	1.40 (1.25, 1.56)
Physical inactivity (yes)	2.33 (1.71, 3.19)
BMI (≥30 kg/m^2)	0.85 (0.72, 1.01)
Diabetes (yes)	1.68 (1.50, 1.88)
Dyslipidemia (yes)	3.66 (3.20, 4.18)
Hypertension (yes)	15.45 (12.85, 18.58)

NCT: non-cigarette tobacco; CVD: cardiovascular diseases; BMI: body mass index.

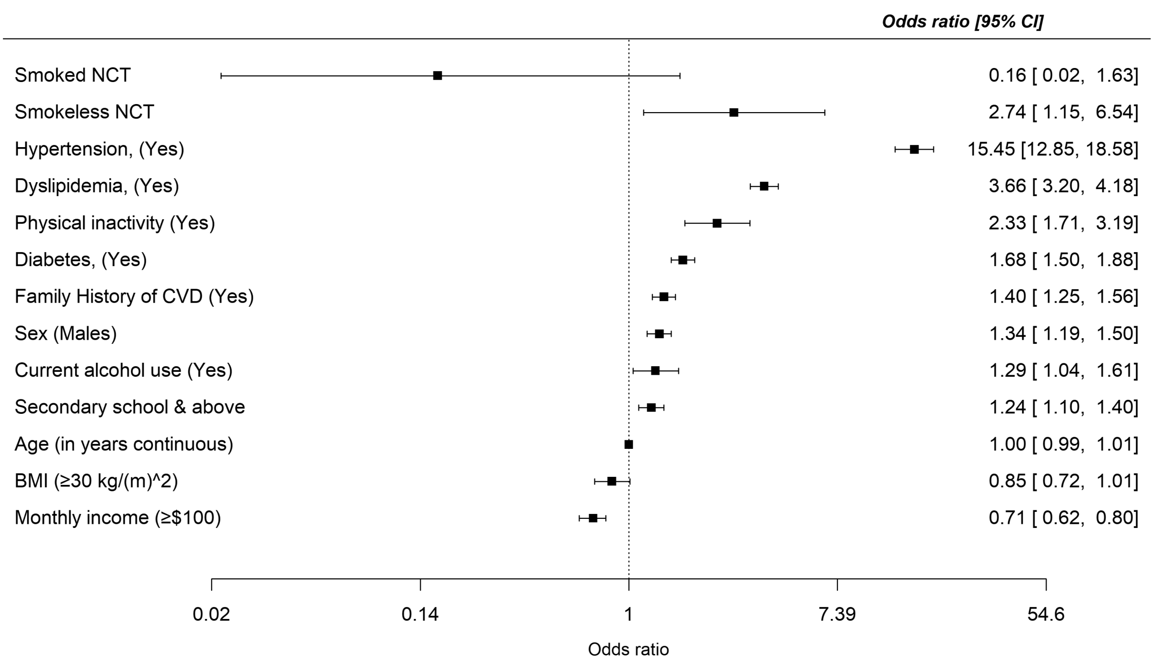

Figure 1. Multivariate adjustment for the association of smokeless and smoked non-cigarette tobacco (NCT) use by odds of stroke.

blood pressure.[57] The impact of NCT on stroke events may be attributable to the apparent effect of exposure to nicotine from tobacco products.[45,58]

Short-term NCT use has been linked to increased blood pressure and heart rate (primarily due to nicotine),[59] which are risk factors for stroke events. Some studies have also linked smokeless NCT use with CVD.[42,60] Biologic mechanisms by which NCT might result in stroke events are not implausible. Results from animal studies show that nicotine can induce cardiac arrhythmias.[58] About 20% of all strokes are cardioembolic, and atrial fibrillation is a risk factor for this type of ischaemic stroke.[61] Also, results from in vitro studies suggest that nicotine opens the blood-brain barrier, increasing the severity of the stroke by allowing post-ischaemic brain edema.[62]

There are some limitations in our study. The small number of stroke cases among non-cigarette smokers included in the study is a major limitation that could significantly underpower the study. A possibility is that NCT usage is underreported in the SIREN population because they are not generally acceptable products in Nigeria and Ghana. Also, NCT users might alongside NCT also smoke cigarette tobacco, and this might be underreported, making it challenging to exclusively isolate cigarette tobacco use in these associations. A larger sample of exclusive NCT users would improve the reliability of the associations between NCT use and stroke events, but this will be difficult to achieve in practice, given that most NCT users might have previously smoked cigarettes or used other forms of combustible tobacco. These limitations notwithstanding, this is one of the largest and most comprehensive efforts at delineating the association between NCT use and first-ever stroke among indigenous Africans. The physician-adjudicated stroke case ascertainment and multicenter setting are additional strengths of this study. Future longitudinal studies are necessary to infer causal associations between NCT use and stroke, including the contribution of the different forms of NCT.

Conclusions

NCT use, especially smokeless NCT, is associated with higher odds of stroke in this sample of Africans. Although NCT use is a relatively neglected aspect of tobacco use epidemiology, it might play a significant role in the global burden of stroke, especially among Africans. Tailored interventions directed against NCT use, might be necessary to manage the increasing burden of stroke among Africans.

Supplementary Material

Supplementary material is available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

None declared.

Ethical Approval

The Stroke Investigative Research and Educational Network (SIREN) study is a multicenter study, and the Institutional Review Board (IRB) at all study sites provided ethical approval for the study. The overall coordinating IRB for the SIREN study was the University of Ibadan/University College Hospital Ibadan, Nigeria (IRB Approval No.: UI/EC/13/0105).

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Data Availability

Individual participant data that underlie the results reported in this article (text, tables, and figures) has been deidentified. The joint dataset is available upon reasonable request, and a proposal to access the data should be directed to MO (PI: mayowaowolabi@yahoo.com). Data requestors will need to sign a data access agreement.

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