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Determinants of metabolic syndrome and its prognostic implications among stroke patients in Africa: Findings from the Stroke Investigative Research and Educational Network (SIREN) study

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ABSTRACT

Background: The prognostic implications of metabolic syndrome (METS) among African stroke patients are poorly understood. This study aimed to investigate the determinants of METS and its prognostic implications among Africans with newly diagnosed stroke in the SIREN study.
Methods: We included stroke cases (adults aged >18 years with CT/MRI confirmed stroke). The validated tools comprehensively evaluated vascular, lifestyle, and psychosocial factors. We used logistic regression to estimate adjusted odds ratios (OR) with 95% CIs for the association between METS and risk factors. We also computed the prediction power of the domain of covariates in a sequential manner using the area under the receiver operating curve (ROC) curve.

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Results: Among 3998 stroke subjects enrolled in the study, 76.8% had METS by at least one of the clinical definitions. Factors associated with METS were age > 50 years (OR- 1.46, CI-1.19-1.80), male gender (OR 4.06, CI-3.28-5.03), income >100USD (OR1.42, CI-1.17-1.71), stress (OR1.46, CI-1.14-1.87), family history of diabetes mellitus (OR1.38, CI-1.06-1.78), and cardiac disease (OR1.42, CI-1.18-1.65). Stroke severity was higher among those with METS (SLS = 5.8 ± 4.3) compared with those without METS (6.2 ± 4.5) at p = 0.037. METS was associated with higher odds (aOR 1.31, CI-1.08-1.58) of one-month fatality after adjusting for stroke severity, age > 50 years, and average monthly income >100USD.
Conclusion: METS is very common among African stroke patients and is associated with stroke severity and worse one-month fatality. Lifestyle interventions may prevent METS and attenuate its impact on stroke occurrence and outcomes.

1. Introduction

Metabolic syndrome (METS) is the constellation of multiple cardiovascular risk factors [1,2]. It is associated with an increased predisposition to cardiovascular disease and stroke [3,4]. METS is also associated with an increased risk for atrial fibrillation, diabetes mellitus, and coronary artery disease, which are interrelated to a high risk of stroke [5]. Recently, METS was proposed to be a predictor of ischaemic events culminating in ischaemic stroke in a population-based longitudinal cohort of Iranians [6]. A similar pattern was described among Polish citizens [7]. Also, the Atherosclerosis Risk in Communities (ARIC) study reported a direct relationship between the risk of stroke and the number of METS components [8].

The burden of stroke is rapidly rising across all African countries [2]. Stroke is a leading cause of death and disability, and medical admissions in most African hospitals due to epidemiological transition [12–14]. It is often preceded by multiple risk factors [9]. Some modifiable risk factors which could increase the odds of developing stroke include hypertension, diabetes mellitus, obesity, dyslipidaemia, physical inactivity, high sensitivity C-reactive proteins (hs-CRP), and fibrinogen [10,11]. METS may predict a cluster of subjects who could have benefited from intensive cardiovascular risk reduction. In Africa, the linkage between METS and stroke is not well described. The morbidity and outcome of stroke are also associated with specific gender differences across different populations [12–14]. Whether METS is associated with stroke among Africans has not been well described nor understood. Clinical correlates and prognostic potential of METS among stroke subjects are also yet to be clarified.

The burden of METS, like the burden of stroke, is rising significantly across the African continent [15–18]. However, factors responsible for the increasing burden of METS (particularly among stroke patients) are yet to be clearly understood. Similarly, whether METS could reliably predict stroke events among Africans is yet to be clarified.

This study aimed to investigate the determinants of METS and its prognostic implications among Africans with newly diagnosed stroke in the SIREN study and its related clinical correlate. It also described the implications of METS on stroke severity (measured using the SLS scale) as a covariate for METS, one-month fatality, and disability.

2. Methods

2.1. Study design

The Stroke Investigative Research and Educational Networks (SIREN) study is the most extensive African multicenter case-control study involving 15 sites in Ghana and Nigeria. The study commenced in August 2014, and the study protocol was published earlier [19]. Briefly, stroke cases included consecutive consenting adults aged >18 years with first clinical stroke within eight days of current symptom onset or 'last seen without deficit' with neuroimaging confirmation with Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scan within ten days of symptom onset (Details of the whole eligibility criteria are in). All the study sites obtained Ethical approval and informed consent from all subjects [19]. Clinical evaluations, brain neuroimaging (CT or MRI), electrocardiography (ECG), transthoracic echocardiography, and carotid Doppler ultrasound performed according to the standard operating procedures (SOP) were used for stroke diagnosis and phenotyping. The Oxfordshire Community Stroke Project (OCSP) criteria were used to clinically type ischemic stroke 20, and presumed etiological sub-types were defined using the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) [21] and the Atherosclerosis, Small vessel disease, Cardiac source, and Other (ASCO) [22] criteria. Intracerebral hemorrhage was classified into Structural, Medication-related, Amyloid angiopathy, Systemic/other diseases, hypertension-related, and Undetermined causes (SMASH-U) [23]. Stroke severity was measured by the modified National Institute of Health Stroke scale (mNHISS) [24] and the Stroke levity scale [25].

2.2. Data collection

Primary demographic and lifestyle data were obtained, including ethnicity and the native language of the subjects and their parents, socioeconomic status, cardiovascular risk profile, and dietary patterns. Validated instruments assessed physical activity, stress, depression, cigarette smoking, and alcohol use [26]. Fasting early morning venous blood samples were collected into serum separators in cases (the post-acute phase when fasting is feasible) and the control group. The serum was used to determine the plasma glucose levels, lipid panels total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), Triglyceride (TG), and Glycosylated haemoglobin (HbA1c) using a uniform standard operating case report forms across all the study sites.

2.3. Definition of METS

The study used two definitions of METS using the International Diabetes Federation (IDF) [27] and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III criteria) [28]. According to the Adult Treatment Panel III, METS was defined by the presence of at least three of five cardiovascular risk factors.

1. Waist circumference > 102 cm in men or > 88 cm in women
2. Fasting triglyceride level of 150 mg/dL or higher
3. Blood pressure level of 130/85 mmHg or higher or the use of antihypertensive medication.
4. High-density lipoprotein cholesterol (HDL-C) level of <40 mg/dL in men or <50 mg/dL in women
5. Fasting glucose level of 100 mg/dL or higher

The International Diabetes Federation (IDF) defined METS as central obesity (race-specific) with at least two of the following four factors: raised triglycerides (TG >150 mg/dl or on specific treatment for the abnormality), reduced high-density lipoprotein (<1.03 mmol/l in males and <1.29 mmol/l in females) or on specific treatment for this abnormality, elevated blood pressure > 130/85 mmHg or antihypertensive treatment and increased fasting plasma glucose >5.6 mmol/l [27].

2.4. Definition of risk factors

- Hypertension: Blood pressure (average of three measurements used) was recorded at baseline and daily for seven days or until death. A cut-off BP ≥ 140/ 90 mmHg for up to 72 h after stroke, a history of hypertension, or use of antihypertensive drugs before stroke or > 72 h after stroke were regarded as indicators of hypertension. Adjustments to systolic BP (SBP) based on reported associations between pre-morbid BP and acute post-stroke BP in the Oxford Vascular Study (OXVASC) were also applied in sensitivity analyses [29]. Definition of hypertension in controls was a self-reported history of hypertension, use of antihypertensive drugs, or average BP at first clinical encounter ≥140/90 mmHg [29].
- Diabetes mellitus was defined based on a history of diabetes mellitus, use of medications for DM, and HBA1c >6.5% or a fasting blood glucose (FBG) level > 7.0 mmol/l at the first encounter in controls or measured after the post-acute phase in cases due to the known acute transient elevation of glucose as a stress response after stroke [30].
- Dyslipidemia was defined as TC ≥5.2 mmol/L, HDL-C ≤ 1.03 mmol/l for men and < 1.30 mmol/l for women, TG ≥ 1.7 mmol/l or LDL-C ≥ 3.4 mmol/l according to NCEP guidelines [28] or use of statin prior to stroke onset. Based on the distribution of the LDL/HDL ratio in the present study, the LDL/HDL ratio was dichotomized using the lowest two tertiles (≤1.97 and 1.98–2.95) versus the highest tertile (≥2.96) as normal versus high LDL/HDL ratio respectively [28].
- Cardiac disease was defined based on history or current diagnosis of atrial fibrillation, cardiomyopathy, heart failure, ischemic heart disease, and rheumatic heart disease. Cases had Electrocardiography (ECG) and echocardiography done to ascertain diagnosis where feasible.
- Obesity: We assessed waist-to-hip ratio (WHR) and body-mass index. Individuals were classified using the World Health Organization (WHO) guidelines using cut-offs of 94 cm (men) and 80 cm (women) for waist circumference, 0.90(men) and 0.85 (women) for WHR, and 30 kg/m2 for BMI (Obesity) [31].
- Physical Activity: Individuals were classified as physically active if they were regularly involved in moderate exercise (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for four hours or more per week [32].
- Dietary history: This included regular intake of food items such as meat, fish, green leafy vegetables, the addition of salt at the table, nuts, sugar, and other local staple food items. Regular intake was defined as intake daily, weekly, or at least once monthly versus none in a month.
- Alcohol use: This was categorized into current users (users of any form of alcoholic drinks) or never/former drinker, while alcohol intake (or drinking) was categorized as low drinkers (1–2 drinks per day for female and 1–3 drinks per day for male) and high drinker (>2 drinks per day for female and >3 drinks per day for male).
- Smoking status: This was defined as a current smoker (individuals who smoked any tobacco in the past 12 months) or never/former smoker [33].
- For psychosocial risk factors, we adapted psychosocial stress and depression measures in the INTERSTROKE study [34]. Psychosocial stress combined measures of stress at home/work (e.g., irritability, anxiety, or sleeping difficulties) and life events experienced in the two weeks prior to the stroke. Depression combined with depressed mood and a checklist of other depression symptoms experienced in the past four weeks prior to the stroke. Additional details on these assessments as presented in the appendix.
- Family history of cardiovascular risk/diseases was defined based on self-reported history of any of the following: hypertension, diabetes, dyslipidemia, stroke, cardiac disease, or obesity in participants' fathers, mothers, siblings, or second-degree relatives.

2.5. Statistical analysis

Statistical analyses were done with STATA MP Version 14. The primary outcome measure was METS, defined using the IDF [27] and ATP III [28] criteria. We assessed the bivariate association between risk factors and METS status (METS versus no METS) using chi-square or Fisher's exact test for categorical risk factors and a *t*-test for continuous risk factors. Further analysis was done to determine the adjusted associations between the risk factors and METS using multivariable logistic regression. The adjusted models included covariates depending on whether they were confirmed confounders in the bivariate analysis and considerations from the literature on MET risk factors. We also evaluated whether METS status was predictive of outcomes such as one-month fatality among study participants.

Constructed sequential models assessed independent socio-demographic variables, followed by clinical and behavioral variables associated with primary (MET_IDF) and secondary outcome (MET_ATP) measures. The odds ratio (OR) and 95% confidence intervals in the final models were estimated using the maximum likelihood method. The Hosmer-Lemeshow test assessed the goodness of fit of the models. Additionally, residual analysis assessed the final adjusted models for collinearity using variance inflation factor (VIF) and goodness of fit. All statistical tests of hypotheses are two-sided.

3. Results

3.1. Participants' socio-demographic and clinical characteristics

Among 3998 stroke subjects enrolled in the study, 3070 (76.8%) had METS by at least one of the two definitions used (Table 1). Participants diagnosed with METS by either of the two criteria used in this study were significantly older than those without METS (Mean age was 60.5 ± 13.9 vs. 58.4 ± 15.7 years) (Table 1). The frequency of stress, physical inactivity, and tobacco use in the last twelve months was significantly higher among those with METS than those without METS. Stroke was more severe among those with METS than those without METS. One-month case fatality was also significantly higher among those with

Table 1
Patient demographic and clinical characteristics by METS status.

Characteristic		Without METS (n = 928)	With METS (n = 3070)	p-value
Age (years)	<50	249 (26.8)	641 (20.9)	**<0.001**
	>50	679 (73.2)	2429 (79.1)	
	Mean ± SD	58.6 ± 15.7	60.4 ± 13.8	**<0.001**
Sex	Male	703 (75.8)	1547 (50.4)	**<0.001**
	Female	225 (24.3)	1523 (49.6)	
Education	No education	150 (16.5)	600 (19.6)	**0.035**
	Some education	760 (83.5)	2461 (80.4)	
Income	≤100USD	435 (48.2)	1377 (45.2)	0.11
	>100USD	467 (51.8)	1669 (54.8)	
CVD factors	Hypertension (yes)	788 (89.6)	2987 (97.7)	**<0.001**
	Dyslipidemia (yes)	311 (35.5)	2697 (88.1)	**<0.001**
	Diabetes (yes)	170 (19.3)	1328 (43.4)	**<0.001**
	Cardiac Disease (yes)	94 (10.7)	360 (11.8)	0.391
	Depression (yes)	62 (7.3)	213 (7.2)	0.719
	Stress (yes)	123 (15.5)	575 (20.3)	**0.002**
	Physical inactivity (yes)	788 (96.7)	2756 (94.6)	**0.014**
	Tobacco Use (past 12 months)	47 (5.4)	80 (2.6)	**<0.001**
Stroke severity (SLS) score	Mean ± SD	6.2 ± 4.5	5.8 ± 4.3	<0.037
Stroke severity (SLS score)	Mild	177 (21.0)	495 (16.8)	**0.017**
	Moderate	269 (31.9)	966 (32.7)	
	Severe	398 (47.2)	1491 (50.5)	
One month outcome	Fatality	178 (19.2)	725 (23.6)	**0.005**
	Disability	367 (70.3)	1451 (73.3)	**0.169**

METS than those without METS (23.6% vs. 19.2%, $p < 0.05$), as shown in Table 1. Disability was not significantly different between the two groups.

Table 2 showed that mean body mass index (BMI) was significantly higher among subjects with METS (27.2 ± 5.3 kg/m^2) than those without (25.1 ± 4.8 kg/m^2). The mean waist-hip ratio among subjects with METS versus those without METS was 1.0 ± 0.1 vs. 0.9 ± 0.1, with 85.2% vs. 74.6% having increased waist-to-hip ratio, respectively. Furthermore, mean triglyceride and fasting glucose were significantly higher among subjects with METS (134.2 ± 88.7 mg/dl and 124.0 ± 51.2 mg/dl) than those without METS (95.1 ± 49.2 mg/dl and 88.2 ± 15.3 mg/dl) respectively. Those with METS had significantly higher mean arterial blood pressure (96.2 ± 22.2 vs. 86.7 ± 115.1), pulse pressure (64.2 ± 19.9 vs. 53.7 ± 17.9), and mean heart rate (88.7 ± 18.9 vs. 86.0 ± 19.2) compared to those without METS as shown in Table 2.

3.2. Family history and lifestyle factors associated with METS

Table 3 shows the family history and lifestyle factors associated with METS. As reported by the patients, family histories of cardiovascular diseases and stroke were not significantly different between those with METS and those without METS. Family history of hypertension (33.3% vs. 29.5% respectively) and diabetes (13.3% vs. 10.3% respectively) were more prevalent among those with METS than those without METS.

3.3. Adjusted odds of METS

Table 4 shows the factors associated with METS based on IDF definition. Model I represent the association with demographic characteristics in which patients with age > 50 years (OR = 1.41, CI: 1.18–1.68) and those with an average monthly income >100 USD per month (OR = 1.42, CI: 1.21–1.66) were more likely to have METS. Males were more likely to have METS than females (OR = 3.37, CI:2.83–4.0). In Model II, adding comorbidities to the first model showed that the demographic variables retained their influence. The presence of stress, positive family history of cardiovascular disease, and diabetes were significantly associated with METS. Model III controlled the analysis for demographic, comorbidities, and lifestyle characteristics. All previous parameters retained their effect as in model II, including an enhanced effect of the presence of cardiac diseases. Additionally, meat consumption was associated with METS (OR 1.11). The Area under the ROC (AUC), which signifies the predictive power of models I, II, and III, were 0.66, 0.67, and 0.69, respectively.

Another model set was fitted for METS defined according to ATP III criteria (Table 5). The socio-demographic model (Model I) showed that age > 50 (OR = 1.22, CI: 1.03–1.45), income >100 USD (OR = 1.36, CI: 1.18–1.57), and male gender (OR = 3.38, CI: 2.92–3.91) were positively associated with METS like what was found for the IDF definition. In Model II, all of the factors remained statistically significant in addition

Table 2
Patient anthropometric characteristics and laboratory investigations by METS status.

Characteristic		Without METS	With METS	*p*-value
BMI (mean ± SD)		25.1 ± 4.8	27.2 ± 5.3	**<0.001**
Waist circumference (mean ± SD)		79.5 ± 8.6	92.2 ± 14.3	**<0.001**
Hip circumference (mean ± SD)		85.7 ± 10.1	97.4 ± 14.4	**<0.001**
Waist to hip ratio	Normal	196 (25.4)	432 (14.8)	**<0.001**
	Raised	576 (74.6)	2484 (85.2)	
	Mean ± SD	0.9 ± 0.1	1.0 ± 0.1	**<0.001**
Systolic BP (mmHg)	≤140	337 (39.1)	775 (25.5)	**<0.001**
	>140	524 (60.9)	2268 (74.5)	
	Mean ± SD	152.6 ± 33.4	160.2 ± 30.0	**<0.001**
Diastolic BP (mmHg)	≤90	369 (42.9)	1047 (34.4)	**<0.001**
	>90	492 (57.1)	1996 (65.6)	
	Mean ± SD	98.9 ± 172.2	95.9 ± 17.8	0.345
Mean arterial Pressure (mean ± SD)		86.7 ± 115.1	96.2 ± 22.2	**<0.001**
Pulse pressure (mean ± SD)		53.7 ± 17.9	64.2 ± 19.9	**<0.001**
Heart rate (mean ± SD)		86.0 ± 19.2	88.7 ± 18.9	**<0.001**
Total Cholesterol (mg/dl)	<200	369 (61.1)	1590 (58.4)	0.23
	≥200	235 (38.9)	1131 (41.6)	
	Mean ± SD	191.5 ± 51.8	190.7 ± 58.8	0.758
Triglyceride (mg/dl)	<150	581 (96.0)	1915 (70.2)	**<0.001**
	≥150	24 (4.0)	812 (29.8)	
	Mean ± SD	95.1 ± 49.2	134.2 ± 88.7	**<0.001**
Fasting Glucose	Normal; ≤126	206 (97.6)	934 (69.7)	**<0.001**
	High; >126	5 (2.4)	406 (30.3)	**<0.001**
	Mean ± SD	88.2 ± 15.3	124.0 ± 51.2	**<0.001**

Table 3
Lifestyle characteristics by METS status.

Characteristic		Without METS	With METS	*p*-value
Family history	CVD (yes)	302 (34.6)	1143 (37.4)	0.119
	HTN (yes)	274 (29.5)	1023 (33.3)	0.030
	DM (yes)	96 (10.3)	409 (13.3)	0.017
	Stroke (yes)	133 (15.2)	446 (14.6)	0.654
Adding Salt	Never	767 (91.4)	2751 (93.4)	**0.043**
	Very Often	72 (8.6)	193 (6.6)	
Green leafy vegetable	None	225 (28.8)	774 (27.4)	0.429
	Some	556 (71.2)	2053 (72.6)	
Sugar Consumption	None	536 (70.5)	1973 (70.9)	0.832
	Some	224 (29.5)	809 (29.1)	
Meat consumption	None	197 (24.9)	713 (25.0)	0.945
	Some	594 (75.1)	2136 (75.0)	

Table 4
Multivariate regression analysis for the association between METS_IDF and risk factors.

	Adjusted OR (95%CI)		
Risk factors	Model I	Model II	Model III
Socio-demographic			
Age; ≥50	1.41 (1.18, 1.68)*	1.48 (1.23, 1.79)*	1.46 (1.19,1.80)*
Male gender	3.37 (2.83, 4.00)*	3.56 (2.95,4.28)*	4.06 (3.28,5.03)*
Income; ≥100USD	1.42 (1.21, 1.66)*	1.40 (1.18,1.65)*	1.42 (1.17,1.71)*
Co-morbidities			
Cardiac; Yes		1.04 (0.80,1.36)	1.29 (0.94,1.75)
Stress; Yes		1.39 (1.11,1.74)*	1.46 (1.14,1.87)*
Family history of CVD		1.10 (0.89,1.36)	1.01 (0.80,1.28)
Family history diabetes		1.14 (0.85,1.36)	1.20 (0.88,1.64)
Family history of stroke		0.85 (0.66,1.09)	0.86 (0.66,1.14)
Lifestyle/ Behavioral			
Physical activity; (Yes)			0.71 (0.44,1.16)
Tobacco; (Yes)			0.74 (0.48,1.16)
Salt intake			0.73 (0.53,1.00)
Green vegetables			0.96 (0.78,1.18)
Sugar consumption			1.00 (0.82, 1.23)
Meat consumption			1.11 (0.90, 1.38)
AUC (95% CI)	**0.66 (0.64, 0.68)***	**0.67 (0.65, 0.70)***	**0.69 (0.67, 0.72)***

AUC - Area under the curve; * $p < 0.05$

Table 5
Multivariate regression analysis for the association between METS_ATP and risk factors.

	Adjusted OR (95%CI)		
Risk factors	Model I	Model II	Model III
Socio-demographic			
Age; ≥50	1.22 (1.03,1.45) *	1.27 (1.06,1.52) *	1.25 (1.03,1.52) *
Male gender	3.38 (2.92,3.91) *	3.30 (2.84,3.85) *	3.58 (3.02,4.23) *
Income; ≥100USD	1.36 (1.18,1.57) *	1.33 (1.14,1.55) *	1.30 (1.10,1.54) *
Co-morbidities			
Cardiac dx; (Yes)		1.27 (1.01,1.59) *	1.26 (0.99,1.62)
Stress; (Yes)		1.48 (1.23,1.78) *	1.48 (1.21,1.81) *
Family history of CVD		1.22 (1.01,1.48) *	1.21 (0.99,1.49)
Family history diabetes		1.34 (1.05,1.72) *	1.38 (1.06,1.78) *
Family history of stroke		0.89 (0.71,1.12)	0.81 (0.64,1.03)
Lifestyle/Behavioral			
Physical inactivity; (Yes)			1.57 (1.06,2.32) *
Tobacco; (Yes)			1.00 (0.60,1.65)
Salt intake			0.98 (0.71,1.34)
Green vegetables			1.22 (1.01,1.48) *
Sugar consumption			0.96 (0.80,1.16)
Meat consumption			0.89 (0.74,1.07)
AUC (95% CI)	**0.66 (0.64,0.68)***	**0.67 (0.65,0.69)***	**0.69 (0.67,0.71)***

AUC - Area under the curve; * $p < 0.05$

Table 6
Multivariate regression analysis for the association between METS_IDF and one month fatality.

	Adjusted OR (95%CI)		
Factors	Model I	Model II	Model III
METS	1.31 (1.08, 1.58) *	1.21 (0.97, 1.50)	1.24 (0.98, 1.58)
Socio-demographic			
Age; ≥ 50	1.11 (0.93, 1.33)	1.01 (0.82, 1.24)	1.05 (0.84, 1.31)
Male gender	0.92 (0.78, 1.07)	0.90 (0.75, 1.08)	0.90 (0.74, 1.09)
Income; ≥100USD	0.99 (0.84, 1.15)	1.06 (0.90, 1.26)	0.95 (0.78, 1.15)
Co-morbidities			
Cardiac; (Yes)		0.79 (0.60, 1.04)	0.93 (0.69, 1.25)
Stress; (Yes)		1.11 (0.89, 1.37)	1.26 (0.99, 1.59)
Family history of CVD		0.75 (0.60, 0.94)	0.79 (0.62, 1.00)
Family history diabetes		1.02 (0.75, 1.40)	0.98 (0.70, 1.37)
Family history of stroke		0.89 (0.68, 1.18)	0.93 (0.69, 1.25)
Stroke severity			
Mild			
Moderate		4.86 (3.05, 7.75) *	4.45 (2.68, 7.38) *
Severe		15.15 (9.68, 23.70) *	13.58 (8.35, 22.09) *
Lifestyle/ Behavioral			
Physical activity; (Yes)			1.72 (1.07, 2.77) *
Tobacco; (Yes)			1.42 (0.86, 2.35)
Salt intake			0.99 (0.70, 1.39)
Green vegetables			0.48 (0.39, 0.59)*
Sugar consumption			1.14 (0.94, 1.40)
Meat consumption			0.89 (0.72, 1.10)
AUC (95% CI)	**1.00 (1.00, 1.00)**	**0.62 (0.59, 0.64) ***	**0.58 (0.56, 0.61) ***

AUC - Area under the curve; * $p < 0.05$

to comorbidities such as the presence of cardiac diseases (OR 1.27, CI1.01–1.59), stress (OR 1.48, CI: 1.23–1.78), presence of cardiovascular disease (OR 1.22, CI: 1.01–1.48) and positive family history of diabetes mellitus (OR 1.34, CI: 1.05–1.72) In the final model, the factors associated with METS were age > 50 years, male gender, income >100USD, stress, and diabetes. The AUCROC for the respective models were model I (0.66), model II (0.67), and model III (0.69).

3.4. Adjusted odds for one-month case fatality

Table 6 shows the factors associated with one-month case fatality among study participants. According to model I, the presence of METS as diagnosed by IDF is one of the most critical associated factors with one-month case fatality (OR 1.31, CI: 1.08–1.58) followed by age > 50 years old (OR 1.11, CI: 0.93–1.33). In model II, comorbidities were introduced, and the presence of METS as diagnosed by IDF criteria and age > 50 years retained its positive linear associations though not statistically significant. Stroke severity, especially moderate (OR 4.86, CI: 3.05–7.75) and high severity profile (OR 15.15, CI: 9.68–23.70), has significant associations with one-month case fatality compared to mild severity of stroke. In model III, lifestyle and behavioral factors were introduced, with most former associations maintained. The AUC for the respective models were model I (1.00), model II (0.62), and model III (0.58) (Figs. 1–4).

Factors associated with one-month case fatality in patients with METS diagnosed by ATP III are shown in Table 7. In model I, the presence of METS diagnosed by ATP III was significantly associated with one-month case fatality and, to a lesser extent, age > 50 years. In model II, comorbidities were introduced, and the two factors retained their direction of the association. Stroke severity remained the highest determinant factor of one-month fatality among stroke patients. Moderate (OR 4.89, CI: 3.07–7.80) and severe (OR 15.26, CI: 9.75–23.88) severity were significant predictors of one-month fatality. In model III, when lifestyle and behavioral factors were introduced, all the previous associations were maintained, while physical inactivity was significantly associated with one-month fatality among stroke patients. The AUC for the respective models were model I (1.00), model II (0.56), and model III (0.53).

4. Discussion

Stroke incidence is rapidly increasing in Africa, with higher stroke incidence rates and stroke prevalence than in Western Europe and the United States [3,6]. While age remains the most vital irreversible risk factor for stroke, various modifiable factors such as diet, lifestyle, physical activity, and psychosocial status affect the burden of stroke and cardiovascular diseases in Africa [3,6,35].

In this study, we examined the prevalence and characterized the association between METS (the clustering of cardiovascular risk factors and stroke in the largest study of stroke in Africans). This study revealed that METS was present in 77% of study participants using the IDF criteria and 31% using the Adult Treatment Panel III (ATP III) criteria. The difference in prevalence reported could be due to the race-specific cut-off for waist circumference used as a major criterion which is less than the value in the ATP III criteria [1,2]. This prevalence is higher than that reported in studies of stroke patients in Japan, Karachi, China, and other parts of the world using the same criteria [35–38]. This may highlight the rapid epidemiological transition underlying Africa's increasing morbidity and mortality among stroke patients.

Several studies have shown associations between CV risk factors such as hypertension, diabetes, dyslipidemia, heart disease, obesity, atrial fibrillation, smoking, and stroke among the general population [39,40]. Newer risk factors for cardiovascular diseases, such as increased blood

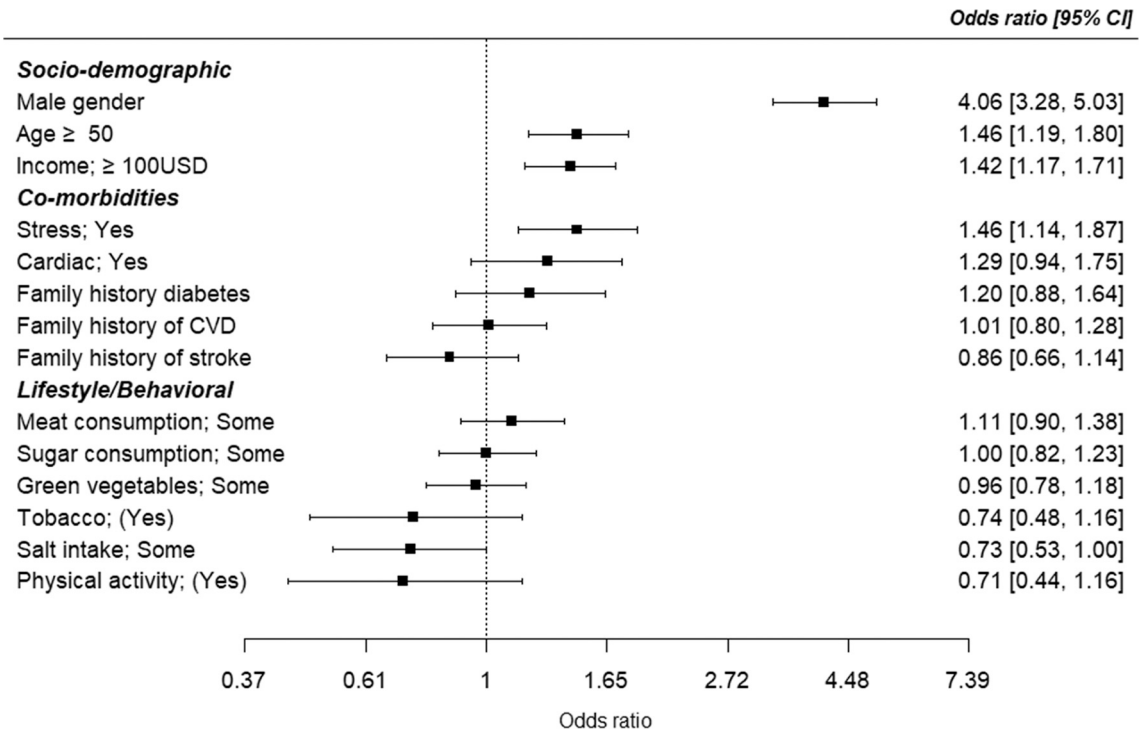

Fig. 1. Showing the odd ratio of lifestyle/behavioral factors and demographic characteristics for developing METS by IDF criteria.

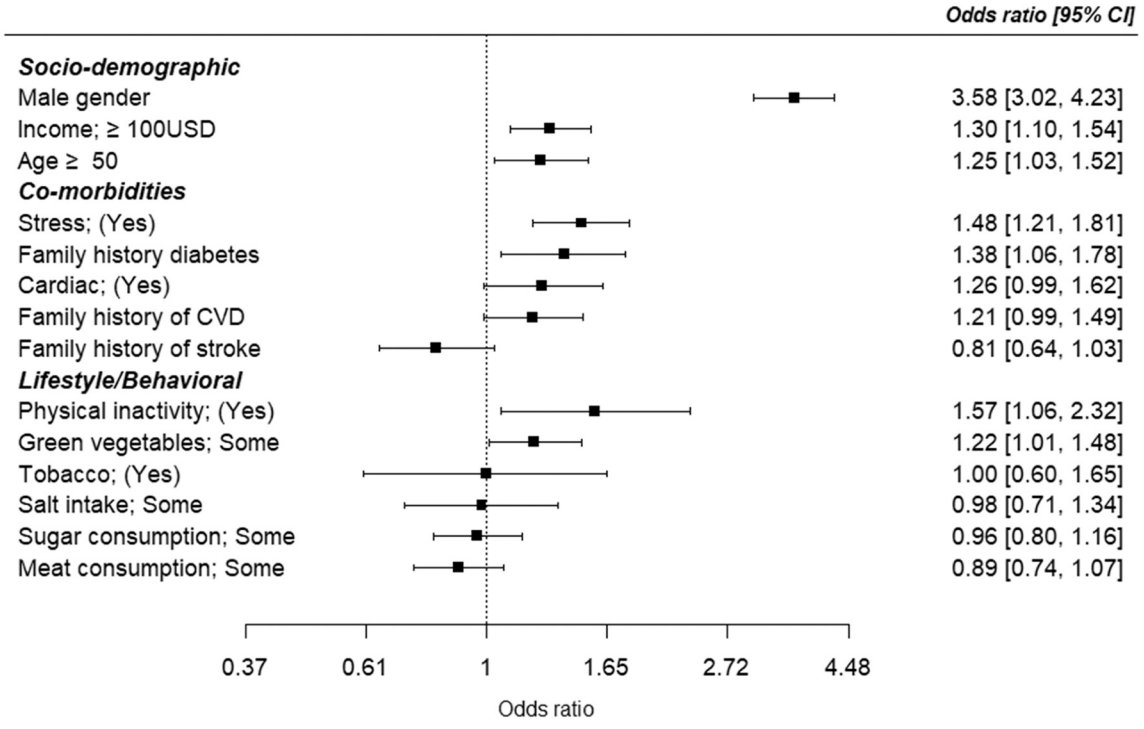

Fig. 2. Showing the odd ratio of lifestyle/behavioral factors and demographic characteristics for developing METS by ATP criteria.

levels of C-reactive protein, carotid intima-media thickness, METS, older age, and gender, have also been described [41]. These risk factors independently increase the risk of cardiovascular disease, stroke, and diabetes mellitus, but the outcome is multiplicative if they are present in clusters [42,43]. Despite the shreds of evidence of inflammation and arterial stiffness in acute ischemic stroke patients with METS [44,45], reports linking METS and stroke in Africa are very few. In this study, we demonstrated an increased risk of stroke in those with MET, which increased with age and was stronger in the males, similar to what obtains in other parts of the world [46]. However, other studies have shown significant association with the female gender due mainly to the influence of obesity [47,48]. The mechanism leading to greater risk for METS in men in this study may be attributed to a higher prevalence of clusters of cardiovascular risk factors, smoking and alcohol intake, and

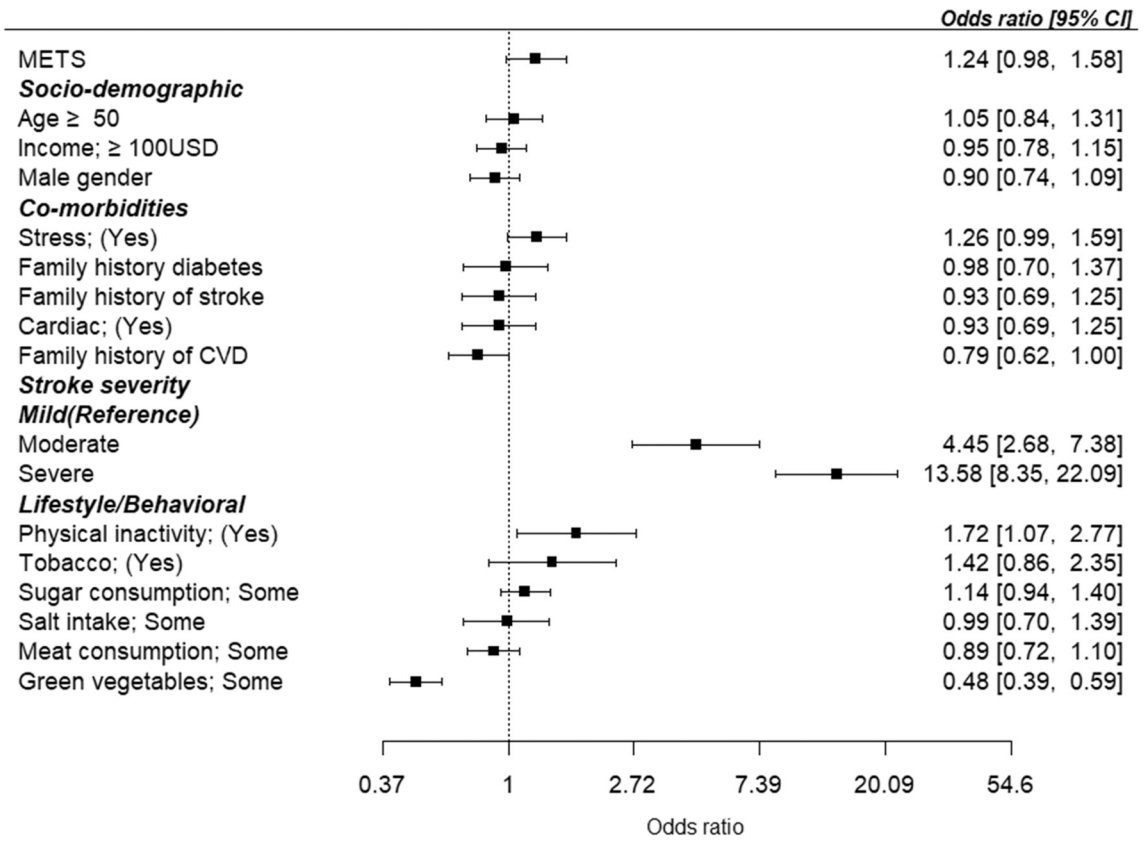

Fig. 3. Showing the odds for association between METS diagnosed by IDF and one-month case fatality in the study population.

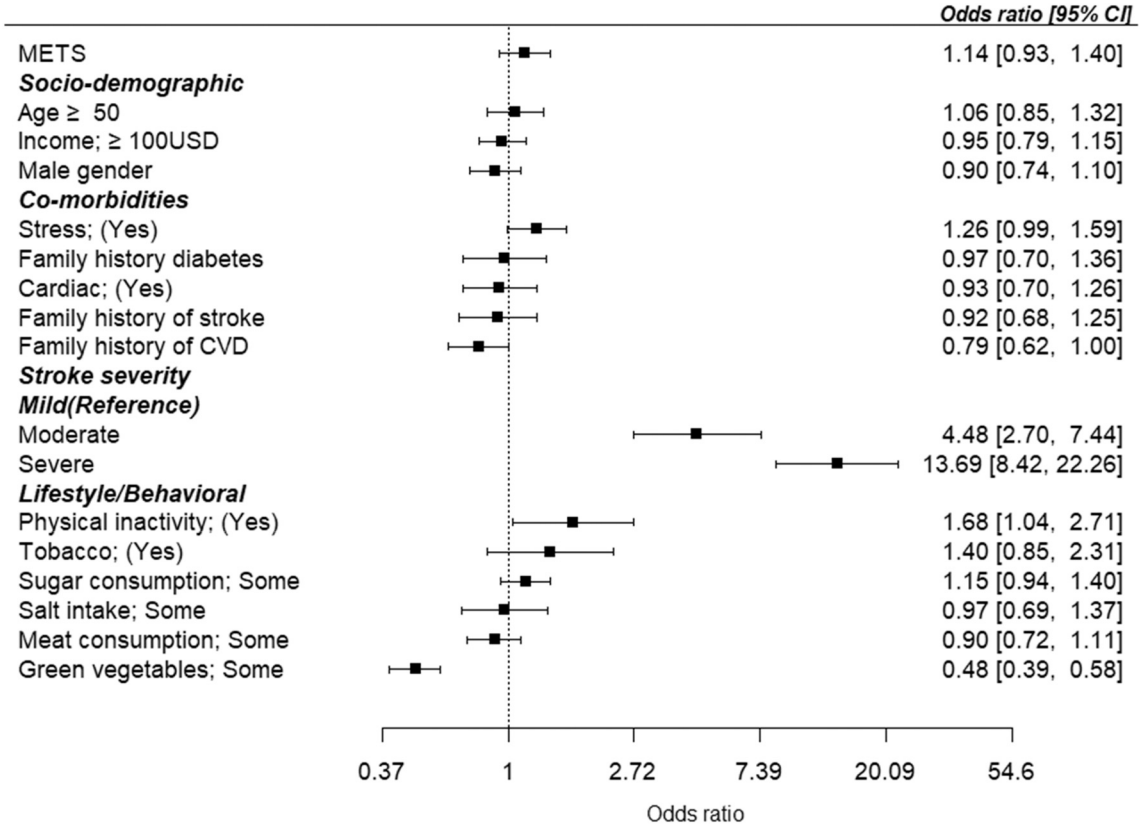

Fig. 4. Showing the odd risk for association between METS diagnosed by ATP and one-month case fatality in the study population.

Table 7
Multivariate regression analysis for the association between METS_ATP and one month fatality.

	Adjusted OR (95%CI)		
Factors	Model I	Model II	Model III
METS	1.24 (1.05, 1.46) *	1.21 (1.00, 1.45)	1.14 (0.93, 1.40)
Socio-demographic			
Age; ≥50	1.12 (0.93, 1.34)	1.01 (0.83, 1.24)	1.06 (0.85, 1.32)
Male gender	0.91 (0.78, 1.07)	0.89 (0.75, 1.07)	0.90 (0.74, 1.10)
Income; ≥100USD	0.99 (0.85, 1.15)	1.06 (0.90, 1.26)	0.95 (0.79, 1.15)
Co-morbidities			
Cardiac; Yes		0.79 (0.60, 1.03)	0.93 (0.70, 1.26)
Stress; Yes		1.10 (0.89, 1.37)	1.26 (0.99, 1.59)
Family history of CVD		0.75 (0.60, 0.94)	0.79 (0.62, 1.00)
Family history diabetes		1.02 (0.75, 1.39)	0.97 (0.70, 1.36)
Family history of stroke		0.89 (0.67, 1.18)	0.92 (0.68, 1.25)
Stroke severity			
Mild			
Moderate		4.89 (3.07, 7.80) *	4.48 (2.70, 7.44) *
Severe		15.26 (9.75, 23.88) *	13.69 (8.42, 22.26) *
Lifestyle/Behavioral			
Physical activity; Yes			1.68 (1.04, 2.71) *
Tobacco; Yes			1.40 (0.85, 2.31)
Salt intake			0.97 (0.69, 1.37)
Green vegetables consumption			0.48 (0.39, 0.58)*
Sugar consumption			1.15 (0.94, 1.40)
Meat consumption			0.90 (0.72, 1.11)
AUC (95% CI)	**1.00 (1.00, 1.00)**	**0.58 (0.56, 0.60)***	**0.53 (0.51, 0.55)***

AUC - Area under the curve; * $p < 0.05$

stress in men. This is similar to findings in the United Kingdom, which showed that the association between the metabolic syndrome and exposure to health damaging behaviours was stronger among men than women [3]. The significantly higher prevalence of METS with increasing age may not be unconnected with the association of advancing age with hypertension, insulin resistance, and obesity which constitute the cluster risk factors for METS.

Our observation that stroke patients with METS had a stronger family history of CVD and diabetes mellitus compared to those without METS suggests genetic contributions to the relationship between stroke and METS [49,50]. A significant proportion of stroke patients with METS were also shown to have reported significant stress levels, meat consumption, and physical inactivity, which could be a predisposing lifestyle for increased CV risk factors clustering. These could be possible targets for intervention in primary and secondary stroke prevention.

Furthermore, this study revealed that METS was associated significantly with a higher one-month mortality suggesting that METS, apart from increased predisposition to stroke, is also associated with poor outcome. It was also associated significantly with a higher stroke severity compared to those without METS. This has also been shown in similar studies [55]. In another study in Cameroon, patients with ischemic stroke and METS died significantly faster compared with those without METS Overall, METS was associated with a higher mortality rate and independent predictor of 5-year post-stroke death. A similar trend was observed for deaths from cardiovascular-related conditions [56]. Furthermore, several studies have also shown that METS is associated with an increased risk of cardiovascular morbidity and mortality, with risk estimates ranging from 1.4 to 4.5, as found in this study [5,8–59]. However, the mechanism for this excess morbidity and mortality risk is still unclear. Meanwhile, targeting METS might effectively prevent early mortality associated with stroke and improve overall outcome.

5. Strengths, limitations and future directions

Our study has several strengths: including establishing the burden of metabolic syndrome among patient in the largest stroke study in Africa. Our findings also have implications for early risk stratification of patients for prompt management for best post-stroke outcome. We plan to develop a post-stroke outcome prediction tool for metabolic risk factors that will be validated for use in people of African ancestry.

6. Conclusions

In this study, METS was prevalent in stroke patients and independently associated with lifestyle factors including average income, family history of diabetes, physical inactivity, and regular meat consumption. In unadjusted models, METS was associated with stroke severity and one-month fatality, in stroke survivors. The association between METS and stroke as well as stroke-related mortality in Africa indicates that stroke and stroke-related mortality can be mitigated by recognizing and treating the various components of METS. Furthermore, regular physical activity, reduction in meat consumption, and stress can reduce the burden of METS and stroke in Africa.

Ethical approval statement

The Stroke Investigative Research and Educational Network (SIREN) study is a multi-centre study, and 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).

Patient consent

All respondents in the SIREN provided written informed consent before participating in the study.

CRediT authorship contribution statement

Abiodun M. Adeoye: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. **Adeseye A. Akintunde:** Methodology, Writing - original draft. **Joshua Akinyemi:** Data curation, Formal analysis, Methodology, Validation, Writing - review & editing. **Mayowa Owolabi:** Conceptualization, Supervision, Funding acquisition, Investigation, Methodology, Resources, Writing - review & editing. All other authors contributed to the review, editing and final approval of the manuscript

Declaration of Competing Interest

The authors declare they have no conflict of interests.

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