

Dominant modifiable risk factors for stroke in Ghana and Nigeria (SIREN): a case-control study

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Summary

Background Sub-Saharan Africa has the highest incidence, prevalence, and fatality from stroke globally. Yet, only little information about context-specific risk factors for prioritising interventions to reduce the stroke burden in sub-Saharan Africa is available. We aimed to identify and characterise the effect of the top modifiable risk factors for stroke in sub-Saharan Africa.

Methods The Stroke Investigative Research and Educational Network (SIREN) study is a multicentre, case-control study done at 15 sites in Nigeria and Ghana. Cases were adults (aged ≥ 18 years) with stroke confirmed by CT or MRI. Controls were age-matched and gender-matched stroke-free adults (aged ≥ 18 years) recruited from the communities in catchment areas of cases. Comprehensive assessment for vascular, lifestyle, and psychosocial factors was done using standard instruments. We used conditional logistic regression to estimate odds ratios (ORs) and population-attributable risks (PARs) with 95% CIs.

Findings Between Aug 28, 2014, and June 15, 2017, we enrolled 2118 case-control pairs (1192 [56%] men) with mean ages of 59.0 years (SD 13.8) for cases and 57.8 years (13.7) for controls. 1430 (68%) had ischaemic stroke, 682 (32%) had haemorrhagic stroke, and six (<1%) had discrete ischaemic and haemorrhagic lesions. 98.2% (95% CI 97.2–99.0) of adjusted PAR of stroke was associated with 11 potentially modifiable risk factors with ORs and PARs in descending order of PAR of 19.36 (95% CI 12.11–30.93) and 90.8% (95% CI 87.9–93.7) for hypertension, 1.85 (1.44–2.38) and 35.8% (25.3–46.2) for dyslipidaemia, 1.59 (1.19–2.13) and 31.1% (13.3–48.9) for regular meat consumption, 1.48 (1.13–1.94) and 26.5% (12.9–40.2) for elevated waist-to-hip ratio, 2.58 (1.98–3.37) and 22.1% (17.8–26.4) for diabetes, 2.43 (1.81–3.26) and 18.2% (14.1–22.3) for low green leafy vegetable consumption, 1.89 (1.40–2.54) and 11.6% (6.6–16.7) for stress, 2.14 (1.34–3.43) and 5.3% (3.3–7.3) for added salt at the table, 1.65 (1.09–2.49) and 4.3% (0.6–7.9) for cardiac disease, 2.13 (1.12–4.05) and 2.4% (0.7–4.1) for physical inactivity, and 4.42 (1.75–11.16) and 2.3% (1.5–3.1) for current cigarette smoking. Ten of these factors were associated with ischaemic stroke and six with haemorrhagic stroke occurrence.

Interpretation Implementation of interventions targeting these leading risk factors at the population level should substantially curtail the burden of stroke among Africans.

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Introduction

Stroke remains a leading cause of long-term disability and the second most common cause of death worldwide.^{1–3} Global estimates of stroke burden suggest that sub-Saharan Africa has the highest incidence (age-standardised incidence 316 per 100 000 people per year),⁴ prevalence (age-adjusted prevalence of up to 14.6 per 1000 people),⁵ and case fatality (up to 43% at 1 month and 84% at 3 years).^{6,7}

The Global Burden of Disease (GBD) Study⁸ showed regional variation in risk factors for stroke worldwide, and explored risk factors for stroke among Africans using a meta-analysis of the small amount of data available. INTERSTROKE,⁹ the largest case-control study on stroke so far, also reported regional differences in stroke types and leading risk factors globally. However, no significant association was found between stroke and important risk

factors such as diabetes, cigarette smoking, physical inactivity, and dietary and psychosocial factors among Africans in INTERSTROKE,⁹ probably because of the small representation of Africans. A Tanzanian community-based study¹⁰ investigated risk factors for stroke among Africans, but had 200 participants, of whom only 40% had neuroimaging to confirm stroke. Thus, the dominant risk factors for stroke and its subtypes in Africans are not yet clearly established.

Low-income and middle-income countries in Africa, have scant resources for acute care and rehabilitation.^{1–7} Hence, the most plausible strategy to reduce the burden of stroke in Africans is comprehensive and pragmatic preventive efforts targeted at its dominant risk factors.¹¹ We aimed to examine and quantify the contributions of the top modifiable risk factors for stroke among Africans within the context of the Stroke Investigative Research

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Research in context

Evidence before this study

Sub-Saharan Africa has the highest incidence, prevalence, and case fatality from stroke worldwide, yet detailed characterisation of risk factors for stroke on the continent remains elusive. Among large-scale studies on risk factors for stroke that included African people, we identified the Global Burden of Disease (GBD) Study, which used a meta-analytic approach to analyse the scant data available, and INTERSTROKE, which used a case-control design. No significant association was found between stroke and important factors such as diabetes, cigarette smoking, physical inactivity, and dietary and psychosocial factors among Africans in INTERSTROKE, probably because of the small representation of Africans.

Added value of this study

About 98% of population-attributable risk of stroke in 2118 case-control pairs of people from Ghana and Nigeria was

associated with 11 potentially modifiable factors. In descending order of population-attributable risk (PAR), hypertension, dyslipidaemia, regular meat intake, central obesity, diabetes, low consumption of green leafy vegetables, stress, added salt at the table, cardiac diseases, physical inactivity, and current cigarette smoking were independently associated with stroke occurrence. Our findings from the largest study on stroke among people in Nigeria and Ghana highlight novel associations in this population between stroke and dietary, lifestyle, and psychosocial factors, while underscoring the potent effect of hypertension on stroke occurrence among individuals of African descent.

Implication of all the evidence available

Although hypertension is the cardinal target for control of stroke in Africa, lifestyle and psychosocial factors also need to be addressed through strategic public health interventions.

and Educational Network (SIREN) study,¹² the largest study of stroke in Africa so far.

Methods

Study design

The SIREN study is a multicentre, case-control study done at 15 sites in Ghana and Nigeria (appendix). The study protocol has been published previously.¹² Briefly, stroke cases were consecutive consenting (in unconscious or aphasic patients, consent was obtained from next of kin) adults (aged ≥ 18 years) with a first clinical stroke within 8 days of current symptom onset or last seen without deficit, with neuroimaging confirmation on CT or MRI scan within 10 days of symptom onset. Exclusion criteria are listed in the appendix.

Although patients with stroke were recruited from hospitals to ensure rapid and accurate phenotyping, a robust community engagement core incorporated community sensitisation programmes to enhance early presentation at SIREN study hospitals and minimise referral bias.¹² To minimise investigation bias, costs of neuroimaging, electrocardiography (ECG), echocardiography, carotid doppler, glycated haemoglobin A_{1c} (HbA_{1c}) testing, and lipid profiling were covered for all eligible patients who could not afford these procedures. Ghana has universal health coverage.

Controls were consenting stroke-free adults (aged ≥ 18 years), mostly from the communities in the catchment areas of the SIREN study hospitals where cases were recruited, while some were recruited from the study hospitals. Stroke-free status was confirmed with the eight-item Questionnaire for Verifying Stroke-Free Status (QVSFS), which had 98% negative predictive value in a validation study involving three major languages spoken in west Africa (Ashanti, Yoruba, and Hausa).¹³ Controls were matched by age (within 5 years),

sex, and ethnicity to minimise the potential confounding effect of these variables on the relationship between stroke and its risk factors. Ethical approval was obtained from all study sites and informed consent was obtained from all participants before enrolment.¹²

Stroke phenotyping

Stroke phenotyping was based on clinical assessment and brain neuroimaging (CT or MRI), ECG, transthoracic echocardiography, and carotid doppler ultrasound done in accordance with standard operating procedures. Ischaemic stroke was typed clinically with the Oxfordshire Community Stroke Project (OCSP) criteria¹⁴ and presumed causative subtypes were defined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST)¹⁵ and the Atherosclerosis, Small vessel disease, Cardiac source, and Other (ASCO)¹⁶ criteria. Intracerebral haemorrhage was classified causatively into structural, medication-related, amyloid angiopathy, systemic/other disease, hypertension, and undetermined causes (SMASH-U; appendix).¹⁷

Data collection

We collected basic demographic and lifestyle data including ethnic origin of the participants and their parents, socioeconomic status, cardiovascular risk profile, and dietary patterns. We used validated instruments to assess physical inactivity, stress, depression, cigarette smoking, and alcohol use while minimising potential biases (appendix).¹⁸ Using uniform standard operating procedures across all study sites, we collected blood samples for HbA_{1c} and early morning samples after an overnight fast in cases (after the acute phase when fasting is feasible) and controls for fasting blood glucose and fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride).

See Online for appendix

Definitions of risk factors

Blood pressure (mean of three measurements) was recorded at baseline and daily for 7 days or until death. A cutoff of at least 140/90 mm Hg for up to 72 h after stroke, a history of hypertension, or use of antihypertensive drugs before stroke or more than 72 h after stroke were regarded as indicators of hypertension. Adjustments to systolic blood pressure based on reported associations between premorbid blood pressure and acute post-stroke blood pressure in the Oxford Vascular Study (OXVASC)¹⁹ were also applied in sensitivity analyses. Hypertension in controls was defined as self-reported history of hypertension or use of antihypertensive drugs, or mean blood pressure at first clinical encounter of at least 140/90 mm Hg.¹⁸

Diabetes was defined in controls as a history of diabetes, use of drugs for diabetes, or a fasting blood glucose concentration greater than 7.0 mmol/L at first encounter. In cases, diabetes was defined as a history of diabetes, use of drugs for diabetes, an HbA_{1c} more than 6.5%, or a fasting blood glucose concentration greater than 7.0 mmol/L measured after the post-acute phase because of the known acute transient elevation of glucose as a stress response after stroke.²⁰

Dyslipidaemia was defined as a fasting total cholesterol concentration of at least 5.2 mmol/L, HDL cholesterol 1.03 mmol/L or lower, triglyceride at least 1.7 mmol/L, or LDL cholesterol at least 3.4 mmol/L according to National Cholesterol Education Program guidelines,²¹ or use of statin before stroke onset. Based on distribution of the LDL:HDL ratio in the present study, the LDL:HDL ratio was dichotomised using the lowest two tertiles (≤ 2.00 and 2.01–2.96) as normal versus the highest tertile (≥ 2.97) as high.

Cardiac disease was defined after assessment by study cardiologists as a history or current diagnosis of atrial fibrillation, cardiomyopathy, heart failure, ischaemic heart disease, rheumatic heart disease, or valvular heart diseases.

For obesity, we assessed both waist-to-hip ratio and body-mass index (BMI). Participants were classified individually either using the WHO guidelines with cutoffs of 0.90 (men) and 0.85 (women) for waist-to-hip ratio or 30 kg/m² for BMI (obesity).²² We categorised waist-to-hip ratio into thirds corresponding to low risk (≤ 0.90), moderate risk (0.91–0.96), and high risk (≥ 0.97) using the tertiles obtained from controls. 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 4 h or more per week.⁸

Dietary history included regularity of intake of food items such as meat, fish, green leafy vegetables, nuts, sugar, and other local staple food items, and addition of salt at the table. Regular intake was defined as intake daily, weekly, or at least once per month versus none in a month.

Alcohol users were categorised into current users (users of any form of alcoholic drinks) or never or former drinkers. Alcohol intake was categorised into low drinkers (1–2 drinks per day for women and 1–3 drinks per day for men) and high drinkers (>2 drinks per day for women and >3 drinks per day for men; 1 drink or 1 unit of alcohol=8 g of alcohol).¹⁸ Smoking status was defined as current smoker (individuals who smoked any tobacco in the past 12 months) or never or former smoker.⁹

For psychosocial risk factors, we adapted measures of psychosocial stress and depression from INTERSTROKE.¹⁸ Psychosocial stress combined measures of stress at home or work (eg, irritability, anxiety, or sleeping difficulties) and life events, experienced in the 2 weeks preceding the stroke. The definition of depression combined depressed mood and a checklist of other depression symptoms experienced in the 4 weeks preceding the stroke. Additional details on these assessments are presented in the appendix.

Family history of cardiovascular risk or diseases was defined as self-reported history of any of hypertension, diabetes, dyslipidaemia, stroke, cardiac disease, or obesity in a participant's father, mother, sibling, or second-degree relative.

Statistical analysis

Prevalence of stroke in Africa is up to 315 per 100 000 population.²³ Given the current prevalence and incidence of stroke in Africa, a sample size of 2000 cases and 2000 controls will be sufficient to give a power of 80% to detect an effect size of odds ratio at least 1.4, allowing for several types of exposures (categorical, count, or continuous).

We investigated 30 potential risk factors for stroke in Nigeria and Ghana that were carefully selected on the basis of a literature search, our clinical understanding of stroke risk, and empirical evidence from our data (significant associations observed in bivariate analyses). We assessed the bivariate association between risk factors and stroke status (case *vs* control) using the McNemar test for paired categorical outcomes. We did a similar analysis with stratification by stroke type (ischaemic *vs* haemorrhagic). We did further analyses to establish the adjusted associations between the risk factors and stroke occurrence for the total sample and stratified by stroke types and by age (<50 years *vs* ≥ 50 years) using conditional logistic regression with adjustment for potential confounders that were not used in the matching, apart from baseline age, which was included to adjust for residual confounding because of the non-exact age matching (appendix). The adjusted models included selected covariates depending on whether or not they were confirmed confounders in the bivariate analysis and whether or not they did not improve the model fit, or increased the SE of the parameter estimate of the primary exposure. Additionally, we assessed the final adjusted models for collinearity using variance inflation factor and goodness of fit in a residual analysis.

	Stroke status				Haemorrhagic stroke status				Ischaemic stroke status			
	Available data (n)	Control (n=2118)	Case (n=2118)	p value	Available data (n)	Control (n=682)	Case (n=682)	p value	Available data (n)	Control (n=1430)	Case (n=1430)	p value
Country, Ghana	2118	926 (44%)	917 (43%)	0.39	682	362 (53%)	360 (53%)	0.82	1430	561 (39%)	555 (39%)	0.47
Gender, male	2118	1192 (56%)	1192 (56%)	..	682	428 (63%)	428 (63%)	..	1430	762 (53%)	762 (53%)	..
Age (years)	2118	57.8 (13.7)	59.0 (13.8)	<0.0001	682	52.4 (12.8)	53.4 (12.8)	<0.0001	1430	60.4 (13.3)	61.6 (13.5)	<0.0001
Age >65 years	2118	623 (29%)	676 (32%)	<0.0001	682	106 (16%)	110 (16%)	0.54	1430	515 (36%)	562 (39%)	<0.0001
Domicile												
Rural	2112	302 (14%)	142 (7%)	<0.0001	682	83 (12%)	42 (6%)	0.02	1424	216 (15%)	98 (7%)	<0.0001
Semi-urban	2112	520 (25%)	574 (27%)	..	682	158 (23%)	182 (27%)	..	1424	360 (25%)	390 (27%)	..
Urban	2112	1290 (61%)	1396 (66%)	..	682	441 (65%)	458 (67%)	..	1424	848 (59%)	936 (66%)	..
Monthly income >US\$100	2062	905 (44%)	1169 (57%)	<0.0001	658	303 (46%)	376 (57%)	<0.0001	1398	600 (43%)	788 (56%)	<0.0001
Education (some)	2104	1692 (80%)	1761 (84%)	0.002	680	584 (86%)	606 (89%)	0.057	1418	1103 (78%)	1150 (81%)	0.01
Hypertension	2101	1210 (58%)	1998 (95%)	<0.0001	680	352 (52%)	664 (98%)	<0.0001	1415	855 (60%)	1329 (94%)	<0.0001
Dyslipidaemia	2118	1296 (61%)	1661 (78%)	<0.0001	682	427 (63%)	509 (75%)	<0.0001	1430	865 (60%)	1147 (80%)	<0.0001
Diabetes	2112	281 (13%)	800 (38%)	<0.0001	682	74 (11%)	185 (27%)	<0.0001	1424	208 (15%)	612 (43%)	<0.0001
Cardiac disease	2091	111 (5%)	249 (12%)	<0.0001	675	29 (4%)	45 (7%)	0.068	1410	80 (6%)	203 (14%)	<0.0001
HDL cholesterol (mmol/L)	2062	1.3 (0.4)	1.3 (0.5)	<0.0001	664	1.4 (0.4)	1.4 (0.5)	0.67	1392	1.4 (0.5)	1.2 (0.5)	<0.0001
HDL cholesterol ≤1.03 mmol/L	2062	495 (24%)	697 (34%)	<0.0001	664	159 (24%)	162 (24%)	0.90	1392	335 (24%)	535 (38%)	<0.0001
LDL cholesterol (mmol/L)	2060	3.2 (1.2)	3.2 (1.3)	0.14	662	3.2 (1.2)	3.4 (1.4)	0.09	1392	3.1 (1.2)	3.2 (1.3)	0.55
LDL cholesterol ≥3.4 mmol/L	2060	824 (40%)	853 (41%)	0.38	662	282 (43%)	292 (44%)	0.64	1392	539 (39%)	558 (40%)	0.48
LDL:HDL ratio	2031	2.6 (1.4)	2.9 (1.8)	<0.0001	653	2.6 (1.3)	2.8 (2.0)	0.04	1372	2.6 (1.4)	3.0 (1.7)	<0.0001
LDL:HDL ratio >2.96	2031	646 (32%)	778 (38%)	<0.0001	653	218 (33%)	221 (34%)	0.90	1372	425 (31%)	556 (41%)	<0.0001
LDL:HDL ratio												
≤2.00	2031	747 (37%)	609 (30%)	<0.0001	653	233 (36%)	223 (34%)	0.65	1372	512 (37%)	384 (28%)	<0.0001
2.01–2.96	2031	640 (32%)	644 (32%)	..	653	202 (31%)	210 (32%)	..	1372	435 (32%)	432 (31%)	..
≥2.97	2031	644 (32%)	778 (38%)	..	653	218 (33%)	220 (34%)	..	1372	425 (31%)	556 (41%)	..
Total cholesterol (mmol/L)	2109	5.1 (1.3)	5.1 (1.5)	0.52	680	5.1 (1.3)	5.2 (1.5)	0.07	1423	5.1 (1.3)	5.0 (1.5)	0.66
Total cholesterol ≥5.2 mmol/L	2109	877 (42%)	953 (45%)	0.02	680	286 (42%)	326 (48%)	0.04	1423	586 (41%)	625 (44%)	0.15
Triglyceride (mmol/L)	2102	1.2 (0.6)	1.5 (1.0)	<0.0001	676	1.1 (0.6)	1.4 (1.0)	<0.0001	1420	1.2 (0.6)	1.5 (1.0)	<0.0001
Triglyceride ≥1.7 mmol/L	2102	298 (14%)	561 (27%)	<0.0001	676	87 (13%)	157 (23%)	<0.0001	1420	210 (15%)	403 (28%)	<0.0001
WHR	1944	0.92 (0.09)	0.94 (0.08)	<0.0001	647	0.90 (0.08)	0.93 (0.07)	<0.0001	1291	0.92 (0.09)	0.94 (0.08)	<0.0001
WHR raised	1944	1328 (68%)	1582 (81%)	<0.0001	647	386 (60%)	511 (79%)	<0.0001	1291	939 (73%)	1068 (83%)	<0.0001
WHR												
≤0.90	1944	848 (44%)	552 (28%)	<0.0001	647	339 (52%)	203 (31%)	<0.0001	1291	506 (39%)	349 (27%)	<0.0001
0.91–0.96	1944	591 (30%)	721 (37%)	..	647	181 (28%)	244 (38%)	..	1291	407 (32%)	474 (37%)	..
≥0.97	1944	505 (26%)	671 (35%)	..	647	127 (20%)	200 (31%)	..	1291	378 (29%)	469 (36%)	..
WHR, lowest vs highest thirds	1226	462 (38%)	671 (55%)	<0.0001	402	115 (29%)	204 (51%)	<0.0001	515	218 (42%)	291 (57%)	<0.0001
WHR, first vs second and third thirds	1944	1096 (56%)	1392 (72%)	<0.0001	647	308 (48%)	445 (69%)	<0.0001	1291	785 (61%)	942 (73%)	<0.0001
BMI (kg/m ²)	1461	26.5 (5.8)	26.6 (5.1)	0.62	474	26.9 (6.1)	26.3 (5.1)	0.10	918	26.2 (5.7)	26.7 (5.1)	0.08
BMI >30 kg/m ²	1461	333 (23%)	314 (21%)	0.44	474	120 (25%)	92 (19%)	0.03	918	197 (21%)	207 (23%)	0.62
Physical activity (some activity)	2059	2010 (98%)	1960 (95%)	<0.0001	672	659 (98%)	642 (96%)	0.01	1381	1345 (97%)	1313 (95%)	0.002
Tobacco use in past 12 months	2050	29 (1%)	70 (3%)	<0.0001	667	9 (1%)	33 (5%)	<0.0001	1377	19 (1%)	36 (3%)	0.02

(Table 1 continues on next page)

	Stroke status				Haemorrhagic stroke status				Ischaemic stroke status			
	Available data (n)	Control (n=2118)	Case (n=2118)	p value	Available data (n)	Control (n=682)	Case (n=682)	p value	Available data (n)	Control (n=1430)	Case (n=1430)	p value
(Continued from previous page)												
Tobacco (any use)	2075	162 (8%)	205 (10%)	0.02	670	42 (6%)	70 (10%)	0.006	1399	120 (9%)	134 (10%)	0.37
Alcohol (current user)	2083	321 (15%)	398 (19%)	0.001	672	118 (18%)	179 (27%)	<0.0001	1405	202 (14%)	218 (16%)	0.39
Alcohol (any use)	2083	671 (32%)	762 (37%)	0.001	672	231 (34%)	292 (43%)	<0.0001	1405	438 (31%)	468 (33%)	0.17
Alcohol use												
Never	1752	1433 (82%)	1351 (77%)	<0.0001	562	439 (78%)	392 (70%)	<0.0001	1184	989 (84%)	953 (80%)	0.01
Ever low	1752	310 (18%)	357 (20%)	..	562	121 (22%)	147 (26%)	..	1184	188 (16%)	210 (18%)	..
Ever high	1752	9 (1%)	44 (3%)	..	562	2 (<1%)	23 (4%)	..	1184	7 (1%)	21 (2%)	..
Stress	1945	296 (15%)	461 (24%)	<0.0001	628	109 (17%)	153 (24%)	0.004	1311	188 (14%)	307 (23%)	<0.0001
Cancer	2039	4 (<1%)	10 (<1%)	0.12	657	0 (0%)	2 (<1%)	NA*	1376	4 (<1%)	10 (1%)	0.27
Depression	1915	140 (7%)	170 (9%)	0.08	616	43 (7%)	54 (9%)	0.28	1293	97 (8%)	116 (9%)	0.20
Family history of CVD	2088	606 (29%)	852 (41%)	<0.0001	674	213 (32%)	283 (42%)	<0.0001	1408	391 (28%)	565 (40%)	<0.0001
Added salt at the table	2036	118 (6%)	173 (8%)	0.001	664	45 (7%)	68 (10%)	0.03	1366	74 (5%)	105 (8%)	0.02
Added salt at the table												
Never or rarely	2036	1653 (81%)	1433 (70%)	<0.0001	664	545 (82%)	464 (70%)	<0.0001	1366	1104 (81%)	966 (71%)	<0.0001
Occasionally	2036	265 (13%)	432 (21%)	..	664	73 (11%)	133 (20%)	..	1366	190 (14%)	296 (22%)	..
Very often	2036	118 (6%)	171 (8%)	..	664	46 (7%)	67 (10%)	..	1366	72 (5%)	104 (8%)	..
Regular green leafy vegetable consumption	1966	1606 (82%)	1390 (71%)	<0.0001	646	529 (82%)	450 (70%)	<0.0001	1314	1072 (82%)	934 (71%)	<0.0001
Regular whole grains consumption	1973	1636 (83%)	1693 (86%)	0.01	646	547 (85%)	552 (85%)	0.75	1321	1085 (82%)	1137 (86%)	0.006
Regular legumes consumption	1954	1258 (64%)	1303 (67%)	0.13	640	428 (67%)	438 (68%)	0.63	1308	825 (63%)	862 (66%)	0.14
Regular fruit consumption	1960	1703 (87%)	1627 (83%)	0.001	641	563 (88%)	526 (82%)	0.004	1313	1134 (86%)	1096 (83%)	0.04
Regular sugar consumption	1950	700 (36%)	614 (31%)	0.004	642	260 (40%)	224 (35%)	0.05	1302	438 (34%)	387 (30%)	0.04
Regular meat consumption	1972	1564 (79%)	1644 (83%)	0.001	650	532 (82%)	555 (85%)	0.09	1316	1026 (78%)	1083 (82%)	0.005
Regular fish consumption	1964	1827 (93%)	1838 (94%)	0.51	647	597 (92%)	610 (94%)	0.20	1311	1223 (93%)	1223 (93%)	1.00

Data are number (%) or mean (SD). Some percentages do not add up to 100 because of rounding. p values reported for paired t test, McNemar χ^2 , or test of marginal homogeneity. WHR=waist-to-hip ratio. BMI=body-mass index. NA=not applicable. CVD=cardiovascular disease. * χ^2 could not be computed because a cell had a 0 value.

Table 1: Comparison of characteristics of participants by case-control status and by stroke type

We estimated the odds ratios (ORs) and 95% CIs in the final models using conditional likelihood. We calculated the adjusted population-attributable risks (PARs) with their respective 95% CIs for each exposure variable included in the best-fitted adjusted models. The PARs were estimated as the proportion of the risk of stroke in the population that is attributable to the individual risk factors (ie, the proportion of cases that would not occur in the population if the factor were eliminated).²⁴ The 95% CIs for the PAR were obtained using the AF R package,²⁴ in which the variance is estimated via the delta method. The advantage of the AF package is that it allows for an empirical variance estimator to be used in building the 95% CI. Composite PARs for the dominant risk factors for stroke, stroke subtypes and age (<50 years vs \geq 50 years) were calculated, adjusted for covariates (intermediate or non-modifiable covariates: age, family history of

cardiovascular disease, education, and income), using the ATTRIBRISK R package with 95% CIs computed via the bootstrap method. We also did several sensitivity analyses using different definitions for hypertension, sources of control cohort (community-based controls vs hospital-based controls), and sources of case respondents to questionnaires (cases vs proxy respondents), as well as by country. All statistical tests of hypotheses are two sided. Statistical analyses and graphics were produced with SAS (version 9.4) and R statistical program (version 3.4.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MOO had full access to all the data in the study and final responsibility for the decision to submit for publication.

	Odds ratio (95% CI)	Population-attributable risk (%, 95% CI)
Baseline age ≥50 years	4.54 (1.87 to 11.01)	58.8% (48.8 to 68.7)
Education (some vs none)	1.38 (0.97 to 1.96)	23.5% (3.1 to 44.0)
Monthly income >US\$100	1.35 (1.07 to 1.71)	14.9% (3.8 to 26.0)
Hypertension	19.36 (12.11 to 30.93)	90.8% (87.9 to 93.7)
Dyslipidaemia	1.85 (1.44 to 2.38)	35.8% (25.3 to 46.2)
Diabetes	2.58 (1.98 to 3.37)	22.1% (17.8 to 26.4)
Cardiac disease	1.65 (1.09 to 2.49)	4.3% (0.6 to 7.9)
Elevated waist-to-hip ratio	1.48 (1.13 to 1.94)	26.5% (12.9 to 40.2)
Physical inactivity	2.13 (1.12 to 4.05)	2.4% (0.7 to 4.1)
Current cigarette smoker	4.42 (1.75 to 11.16)	2.3% (1.5 to 3.1)
Stress	1.89 (1.40 to 2.54)	11.6% (6.6 to 16.7)
Family history of CVD	1.29 (1.00 to 1.66)	9.2% (-0.5 to 18.9)
Added salt at the table	2.14 (1.34 to 3.43)	5.3% (3.3 to 7.3)
Low green leafy vegetable consumption	2.43 (1.81 to 3.26)	18.2% (14.1 to 22.3)
Regular sugar consumption	1.16 (0.90 to 1.48)	4.4% (-2.4 to 11.2)
Regular meat consumption	1.59 (1.19 to 2.13)	31.1% (13.3 to 48.9)
Composite PAR	..	98.2% (97.2 to 99.0)

PAR=population-attributable risk. CVD=cardiovascular disease.

Table 2: Adjusted odds ratios and PARs for stroke

Results

Between Aug 28, 2014, and June 15, 2017, we approached 3000 cases and 2200 controls, of whom we enrolled 2118 patients with stroke (cases) and 2118 controls. 1192 (56%) participants in each group were men, and the mean age was 59.0 years (SD 13.8) for cases versus 57.8 years (13.7) for controls (table 1). 1758 (83%) controls were recruited from communities where stroke cases were recruited, 328 (15%) were hospital-based controls from the same hospitals, and 32 were invited during community outreaches and recruited in the hospitals. MRI or CT scan was available for 2118 (100%) cases, 2113 (>99%) had a lipid profile, 1717 (81%) had HBA_{1c} measurements, and 1530 (72%) had fasting blood glucose results, whereas 1597 (75%) had ECG, 916 (43%) had transthoracic echocardiography, and 974 (46%) had carotid doppler studies. Among cases with discrete ischaemic or haemorrhagic strokes (n=2112), study questionnaires for cases were completed by 1621 (76%) proxy respondents, 414 (20%) by patients, and 77 (4%) by both patients and proxy respondents. Six cases and seven controls self-reported sickle-cell anaemia and eight cases and eight controls reported previously diagnosed HIV/AIDS.

Among stroke cases, 1396 (66%) resided in urban, 574 (27%) in semi-urban, and 142 (7%) in rural settings. Comparing cases with controls, 1998 (95%) of 2101 versus 1210 (58%) had hypertension; 1661 (78%) of 2118 versus 1296 (61%) had dyslipidaemia; 800 (38%) of 2112 versus 281 (13%) had diabetes; 249 (12%) of 2091 versus 111 (5%) had cardiac diseases; and 70 (3%) versus 29 (1%) were current cigarette smokers (p<0.0001 for all comparisons). Waist-to-hip ratio (p<0.0001), but not BMI (p=0.62), was significantly higher among patients with stroke than

controls (table 1). Furthermore, patients with stroke were more likely to add salt at the table (p<0.0001), consume meat (p=0.001) and whole grains (p=0.01) on a regular basis, but less likely to consume green leafy vegetables regularly (p<0.0001) compared with controls.

1430 (68%) patients had ischaemic stroke, 682 (32%) had haemorrhagic stroke, and six (<1%) had both discrete ischaemic and haemorrhagic lesions (appendix). Cases with both ischaemic and haemorrhagic lesions were excluded from stroke type analyses. Using the TOAST classification (n=1216), 455 (37%) had small-vessel occlusions, 411 (34%) had large artery atherosclerotic strokes, 102 (8%) had cardioembolic strokes, and 248 (20%) had stroke of undetermined cause or other causes. Haemorrhagic strokes (n=598 with available causative information) were caused by hypertension in 520 (87%) people, structural lesions in 40 (7%), cerebral amyloid angiopathy in 12 (2%), systemic diseases in ten (2%), medication use in six (1%), and undetermined cause in ten (2%), with some causative overlaps. Regarding the functional status and severity of patients with stroke at presentation (n=1928), the modified Rankin scores were as follows: 24 (1%) had a score of 0, 80 (4%) a score of 1, 115 (6%) a score of 2, 130 (7%) a score of 3, 902 (47%) a score of 4, and 677 (35%) a score of 5 (appendix).

The top 11 potentially modifiable risk factors associated with stroke occurrence in decreasing order of magnitude by PAR were hypertension, dyslipidaemia, regular meat consumption, elevated waist-to-hip ratio, diabetes, low green leafy vegetable consumption, stress, added salt at the table, cardiac disease, physical inactivity, and current use of cigarettes (table 2). These 11 factors compositely accounted for 98.2% (95% CI 97.2–99.0) of PAR associated with stroke (table 2, appendix). Five factors—hypertension, diabetes, dyslipidaemia, stress, and green leafy vegetable consumption—were associated with both stroke types; obesity, physical inactivity, regular meat intake, salt intake, and cardiac diseases were associated with ischaemic strokes, whereas tobacco was associated with haemorrhagic strokes (table 3; appendix).

Hypertension, dyslipidaemia, diabetes, stress, and low consumption of green leafy vegetables were associated with stroke regardless of age cutoff. Cardiac diseases were significantly more associated with stroke in people younger than 50 years, whereas current cigarette smoking, added table salt, and regular meat consumption were significantly associated with stroke in those 50 years and older (table 4). Hypertension, diabetes, dyslipidaemia, and low consumption of green leafy vegetables were independently associated with stroke in both Ghana and Nigeria (appendix). However, obesity, stress, regular meat consumption, and regular sugar consumption were significantly associated with stroke occurrence among Nigerians, whereas cardiac diseases, physical inactivity, current cigarette smoking, and salt consumption were

	Haemorrhagic stroke		Ischaemic stroke	
	Adjusted odds ratio (95% CI)	PAR (% , 95% CI)	Adjusted odds ratio (95% CI)	PAR (% , 95% CI)
Baseline age ≥50 years	5.45 (0.89 to 33.28)	49.7% (31.3 to 68.1)	3.93 (1.39 to 11.06)	61.2% (48.6 to 73.9)
Education (some vs none)	1.64 (0.82 to 3.28)	30.9% (-14.2 to 76.1)	1.40 (0.92 to 2.13)	23.8% (0.0 to 47.5)
Monthly income >US\$100	0.98 (0.62 to 1.54)	19.0% (7.1 to 30.9)	1.50 (1.13 to 1.99)	19.0% (7.1 to 30.9)
Hypertension	75.91 (22.81 to 252.63)	96.6% (94.4 to 98.9)	11.93 (7.09 to 20.10)	86.6% (81.6 to 91.6)
Dyslipidaemia	1.80 (1.11 to 2.92)	32.7% (11.2 to 54.1)	1.90 (1.40 to 2.58)	37.6% (24.3 to 50.8)
Diabetes	2.30 (1.35 to 3.93)	14.6% (5.9 to 23.3)	2.70 (1.96 to 3.71)	26.2% (20.8 to 31.6)
Cardiac disease	0.50 (0.19 to 1.28)	-6.0% (-18.1 to 6.2)	2.21 (1.38 to 3.54)	7.4% (3.1 to 11.8)
Raised waist-to-hip ratio	1.23 (0.75 to 2.03)	16.4% (-7.2 to 40.1)	1.58 (1.14 to 2.21)	30.4% (13.1 to 47.8)
Physical inactivity	1.92 (0.56 to 6.60)	21.3% (-1.6 to 5.8)	2.21 (1.01 to 4.82)	2.5% (0.5 to 4.6)
Current cigarette smoker	7.45 (1.15 to 48.20)	3.8% (2.3 to 5.2)	2.93 (0.97 to 8.87)	1.5% (0.4 to 2.5)
Stress	2.35 (1.34 to 4.10)	14.0% (6.6 to 21.4)	1.86 (1.28 to 2.69)	11.4% (4.4 to 18.3)
Family history of CVD	1.23 (0.77 to 1.97)	7.5% (-13.5 to 28.5)	1.33 (0.97 to 1.83)	10.1% (-0.9 to 21.0)
Added salt at the table	2.42 (0.99 to 5.90)	6.6% (2.3 to 11.0)	2.10 (1.18 to 3.76)	4.7% (2.6 to 6.8)
Low green leafy vegetable consumption	2.81 (1.57 to 5.06)	20.7% (13.1 to 28.2)	2.36 (1.66 to 3.34)	17.5% (12.2 to 22.9)
Regular sugar consumption	0.83 (0.52 to 1.33)	-6.3% (-27.3 to 14.7)	1.30 (0.96 to 1.76)	7.3% (-0.4 to 15.1)
Regular meat consumption	1.79 (0.99 to 3.25)	38.8% (3.8 to 73.9)	1.50 (1.06 to 2.12)	27.7% (3.5 to 52.0)
Composite PAR	..	99.3 (98.5 to 99.9)	..	97.7% (96.2 to 98.8)

PAR=population-attributable risk. CVD=cardiovascular disease.

Table 3: Adjusted odds ratios and PARs by stroke type

	Age <50 years		Age ≥50 years	
	Adjusted odds ratio (95% CI)	PAR (% , 95% CI)	Adjusted odds ratio (95% CI)	PAR (% , 95% CI)
Education (some vs none)	3.68 (1.01 to 13.41)	68.9% (36.0 to 101.7)	1.16 (0.80 to 1.68)	11.5% (-11.2 to 34.2)
Monthly income >US\$100	1.37 (0.69 to 2.75)	17.0% (-44.1 to 78.0)	1.37 (1.06 to 1.77)	15.0% (3.5 to 26.5)
Hypertension	30.84 (11.37 to 83.61)	88.7% (82.5 to 94.8)	17.82 (9.99 to 31.18)	91.6% (87.6 to 95.7)
Dyslipidaemia	2.75 (1.34 to 5.61)	48.2% (30.6 to 65.9)	1.74 (1.32 to 2.31)	33.6% (21.3 to 45.9)
Diabetes	5.80 (2.05 to 16.36)	22.6% (18.7 to 26.5)	2.40 (1.81 to 3.19)	22.9% (17.6 to 28.3)
Cardiac disease	8.03 (1.91 to 33.82)	8.4% (5.8 to 11.1)	1.34 (0.86 to 2.08)	2.9% (-2.0 to 7.8)
Raised waist-to-hip ratio	1.99 (0.95 to 4.18)	38.5% (7.8 to 69.2)	1.33 (0.99 to 1.81)	20.8% (4.0 to 37.6)
Physical inactivity	7.42 (0.59 to 93.98)	2.8% (0.8 to 4.7)	1.92 (1.00 to 3.71)	2.3% (0.3 to 4.3)
Current cigarette smoker	5.52 (0.36 to 84.59)	3.7% (-3.4 to 10.7)	3.88 (1.42 to 10.61)	1.9% (1.0 to 2.7)
Stress	2.26 (1.04 to 4.93)	14.5% (4.9 to 24.1)	1.78 (1.28 to 2.48)	10.4% (4.7 to 16.1)
Family history of CVD	1.27 (0.60 to 2.70)	9.4% (-30.6 to 49.3)	1.32 (1.00 to 1.75)	10.0% (0.0 to 20.0)
Added salt at the table	1.23 (0.36 to 4.13)	1.8% (-7.4 to 11.1)	2.47 (1.45 to 4.19)	5.8% (3.8 to 7.8)
Low green leafy vegetable consumption	2.31 (1.02 to 5.22)	18.2% (-6.8 to 43.2)	2.33 (1.69 to 3.23)	17.4% (13.2 to 21.7)
Regular sugar consumption	1.36 (0.65 to 2.85)	11.7% (-13.5 to 37.0)	1.18 (0.89 to 1.55)	4.3% (-2.5 to 11.1)
Regular meat consumption	1.50 (0.52 to 4.35)	30.4% (-38.8 to 99.5)	1.56 (1.15 to 2.13)	29.3% (10.5 to 48.2)
Composite PAR	..	98.1% (96.0 to 99.8)	..	98.3% (97.1 to 99.2)

PAR=population-attributable risk. CVD=cardiovascular disease.

Table 4: Adjusted odds ratios and PARs by age group

associated with stroke among Ghanaians (appendix). Intake of vegetables showed a dose-response relationship with stroke, occasional or regular salt intake was associated with a higher risk of stroke than no or rare salt intake, and weekly meat consumption was associated

with a higher risk of stroke than no or less than monthly meat consumption (figure).

Several sensitivity analyses were done to assess the effect of using different definitions for risk factors and sources of controls. For example, the effect size of the

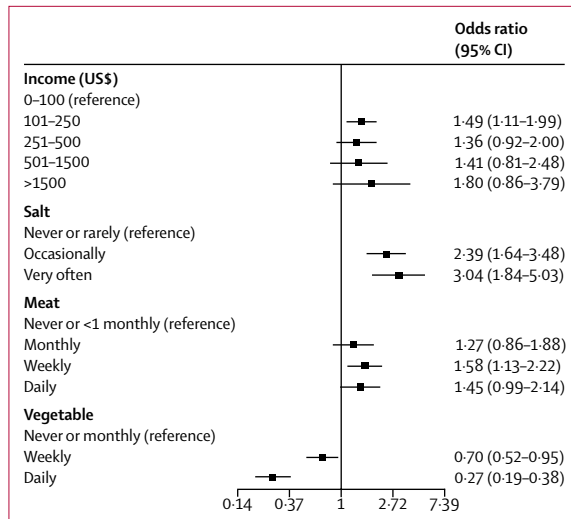


Figure: Dose-response relationships with stroke

association and the corresponding PAR between hypertension and stroke occurrence varied depending upon the definition of hypertension used and whether adjustments were made for the acute rise in systolic blood pressure after stroke onset. We calculated an adjusted OR of 5.79 (95% CI 4.32–7.76) if blood pressure was adjusted for the acute rise and hypertension was defined based on blood pressure measured on the morning after admission, and an OR of 17.87 (11.49–27.78) if blood pressure at the time of interview was elevated or new antihypertensive drugs were introduced after stroke occurrence (appendix).

The effect sizes of factors associated with stroke occurrence were also affected by the source of controls used to match cases and source of respondents for cases. Eight of the 11 modifiable factors associated with stroke from the overall analyses maintained significant associations in sensitivity analyses limited to the 1758 community-recruited controls versus case pairs (83% of entire sample size), whereas three of 11 factors maintained significant associations in the 328 hospital-recruited controls versus stroke case pairs (17% of entire sample size; appendix). Furthermore, because of the high frequency of severe stroke, responses to questions were obtained from 1621 proxy respondents (77%) and 414 (20%) from patients themselves (appendix). Similarly in the sensitivity analyses, nine of 11 modifiable risk factors—namely, hypertension, diabetes, physical inactivity, stress, added salt at table, regular meat consumption, low consumption of green leafy vegetables, current cigarette smoking, and cardiac disease—maintained significant associations with stroke in the proxy respondents, whereas three factors—hypertension, stress, and low consumption of green leafy vegetables—maintained association in self respondents. Higher monthly income and lower educational status were associated

with stroke occurrence but were considered socioeconomic indicators, hence were not included as modifiable risk factors (appendix).

Discussion

We have identified the top 11 modifiable risk factors that account for 98.2% of PAR associated with stroke among people from Ghana and Nigeria in the largest study done on stroke in Africa. Our findings build on those of INTERSTROKE,⁹ but there are important differences in effect sizes of risk factors, and novel factors among Africans are worth noting. First, the adjusted OR for hypertension reported among Africans of 4.01 (99% CI 2.59–6.21) in INTERSTROKE was the highest for any region.⁹ However, in the SIREN study, we found an even higher estimate of 19.36 (95% CI 12.11–30.93) for stroke overall, with a higher effect size for haemorrhagic compared with ischaemic strokes. This high effect size persisted even after adjustment for rise in systolic blood pressure after stroke¹⁹ and with various definitions of hypertension in a sensitivity analysis. Initiation of antihypertensive therapy after haemorrhagic stroke contributed to the observed high effect size of hypertension. The high OR for haemorrhagic stroke is consistent with a high OR of up to 28.8 for hypertension reported elsewhere.²⁶ Second, although diabetes was not associated with stroke among Africans in INTERSTROKE, it was associated with both stroke types, with a higher effect size for ischaemic stroke, in this study. Third, economic and psychosocial factors were associated with stroke in the present study, but not among the African subset of INTERSTROKE. With a sample size of 2118, more than twice the sample size of 973 dyads of Africans in INTERSTROKE, the SIREN study has greater power to detect differences with fewer false negatives.

Furthermore, to increase the applicability of our findings in routine clinical settings, we analysed intake of various dietary components individually, not as a composite dietary score,⁹ and also measured routinely used lipid fractions in the estimation of cardiovascular disease risk. Some of the modifiable factors in our study (including hypertension, smoking, physical inactivity, and a diet low in green leafy vegetables) are consistent with those identified in the GBD Study,⁸ with differences in ranking. The GBD Study, however, did not examine stress, meat consumption, and income level, whereas we did not identify an independent association of certain factors suggested by the GBD Study, such as BMI, alcohol consumption, and fruit consumption. However, like the SIREN study, INTERSTROKE showed a stronger relationship between stroke and waist-to-hip ratio than BMI.⁹

Dietary and socioeconomic factors seem to play more important roles in predisposition to stroke among Africans than previously appreciated. Regular intake of meat, added table salt, and low consumption of green

leafy vegetables were associated with stroke in both countries in the present study. Higher income was independently associated with stroke (significantly in the US\$101–250 band) and was also associated with increased salt and meat intake, but decreased vegetable intake in cases, suggesting that poor dietary choices might be underpinned by higher income level (appendix). Although the effect of high salt intake might be mediated via hypertension occurrence or control, red meat is a source of saturated fatty acids and cholesterol, and has been associated with increased risk of stroke in a dose-dependent manner elsewhere.²⁷ Conversely, regular consumption of green leafy vegetables was associated with reduced risk of stroke among 75 000 stroke-free Swedes after a decade of follow-up.²⁸ Although the precise biological pathways remain to be clarified, green leafy vegetables contain high concentrations of folic acid, which is inversely associated with homocysteine,²⁹ a risk factor for cerebral small vessel disease.

We found consistent associations between stress and occurrence of ischaemic and haemorrhagic strokes. An almost doubled risk of fatal stroke has been reported among participants with self-reported high stress intensity compared with those without stress.³⁰ Cigarette smoking was associated with stroke, but contributed little to the attributable risk because of the low prevalence of smoking among west Africans.^{8,9} Altogether, our study highlights the contributions of context-specific risk factors such as household income levels, poor dietary habits, and stress as risk factors to stroke occurrence among Africans, probably reflecting the effect of adoption of western lifestyles.

Pathophysiologically, ischaemic strokes were commonly of lacunar subtype followed by large-artery atherosclerosis and cardioembolic strokes. 87% of haemorrhagic strokes were attributed to hypertension on the basis of the SMASH-U classification,¹⁷ providing further impetus to address this risk factor at the population level to mitigate the occurrence of this fatal stroke type among Africans. Indeed, although hypertension and current alcohol use were significantly associated with haemorrhagic stroke compared with ischaemic stroke, dyslipidaemia, diabetes, and cardiac disease were conversely more associated with ischaemic than haemorrhagic strokes (appendix).

The mean age of the study population was 59 years, which shows the heavy economic toll stroke exerts in sub-Saharan Africa by affecting a relatively young and productive population. Although there were differences in effect sizes, the spectrum of risk factors associated with stroke occurrence among young Africans (age <50 years) were similar to those among the older population. The emergence of traditional vascular risk factors as dominant predispositions for stroke occurrence in those younger than 50 years is an indication of a rapid emergence of cardiovascular risk factors at early ages in sub-Saharan Africa. An implication is that public health

interventions aimed at remediation of the traditional risk factors and the novel dietary and psychosocial factors identified are likely to lead to a reduction in stroke burden across the different age strata among the adult population.

Case-control studies such as ours cannot establish causality, but rather seek to show associations and quantify effect sizes of risk factors. Furthermore, we adopted measures similar to INTERSTROKE⁹ to minimise bias due to the study design. Although there are likely to be subregion-specific variations in stroke risk factor burden within Africa itself, our findings provide the context-specific information needed to combat the burden of stroke on the continent. Our estimates of diabetes should be interpreted cautiously given that only fasting blood glucose was used to diagnose diabetes in controls, whereas HbA_{1c}, or fasting blood glucose, or both, were used in stroke cases. Similarly, the burden of cardiac diseases might have been underestimated because ECG and echocardiographic assessments were only available for some participants.

A substantial number of patients with stroke in our study had severe strokes at the time of recruitment, necessitating a proxy investigation of lifestyle and behavioural history (appendix). Valid proxies were spouses or first-degree relatives who had lived with the patient within the year before the stroke. The associations observed among proxies were in the same direction as for patients with direct assessment. Because of the high proportion of critically ill patients with stroke, not all patients could undergo exhaustive investigations to establish the cause of ischaemic and haemorrhagic strokes before their death. Nevertheless, we have provided comprehensive data on the burden of causative subtypes of stroke among Africans, to our knowledge, for the first time.

An important strength of our study was an active community engagement arm throughout the study duration to minimise presentation bias for cases and controls thereby enhancing representativeness to promote generalisability (appendix). 83% of our controls were community based and recruited from the catchment population of the cases, thereby fulfilling the ideal recommendation of community-based controls.¹⁸ Some investigators have suggested that the validity of case-control studies, which is contingent on selecting controls independently of risk factor status, could be compromised by matching.³¹ Hence, we individually matched cases to controls in a 1:1 fashion and used conditional logistic regression analysis to attain unbiased ORs. Finally, a strength of this study is the quantification and ranking of the unique contributions of behavioural, psychosocial, and traditional vascular risk factors for stroke, which jointly account for a huge proportion of stroke in the region. Our findings might help to explain the higher rates of strokes among individuals of African ancestry,

with a greater vascular risk factor load in diasporan people (ie, people dispersed beyond their traditional homeland), as recently shown in a comparison of risk factor profiles of patients with stroke in the SIREN study with African Americans and European Americans in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.³² The SIREN study has thus established a crucial platform to lead the efforts in stroke research and control on the continent.

Indeed, the risk factors identified in the SIREN study provide context-specific potential targets for public health control of stroke on the African continent and potentially in other low-income and middle-income countries. First, given the effect of hypertension on stroke occurrence globally and among Africans in particular, the need for enhanced awareness, detection, and control of this risk factor for stroke is urgent. Second, clusters of other metabolic risk factors such as dyslipidaemia, diabetes, and obesity have become important targets for multi-pronged interventions for stroke prevention. Third, health promotion campaigns geared towards healthy dietary choices and exercise are likely to help curb the rising burden of stroke among Africans.

Contributors

MOO and BO designed the study and planned analyses. MOO and FS wrote the first draft of the report. MG and OA did the statistical analyses. RA, OA, AA, KW, RO and LO were study site lead investigators. All authors contributed to the collection of data, discussions and interpretation of the data, and to the writing and review of the manuscript.

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Declaration of interests

We declare no competing interests.

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