Stroke Among Young West Africans

Evidence From the SIREN (Stroke Investigative Research and Educational Network) Large Multisite Case–Control Study

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Background and Purpose—Stroke in lower and middle-income countries affects a young and productive age group. Data on factors associated with stroke in the young are sorely lacking from lower and middle-income countries. Our objective is to characterize the nature of stroke and its risk factors among young West Africans aged <50 years old.

Methods—The SIREN (Stroke Investigative Research and Educational Network) is a multicenter, case–control study involving 15 sites in Nigeria and Ghana. Cases included adults aged ≥18 years with computed tomography/magnetic resonance imaging-confirmed stroke. Controls were age-and gender-matched stroke-free adults recruited from the communities in catchment areas of cases. Comprehensive evaluation for vascular, lifestyle, and psychosocial factors was performed. We used conditional logistic regression to estimate odds ratios and population attributable risks with 95% confidence intervals.

Results—Five hundred fifteen (24.3%) out of 2118 cases enrolled were <50 years old. Among subjects <50 years old, hemorrhagic stroke proportion was 270 (52.5%) versus 245 (47.5%) for ischemic strokes. Etiologic subtypes of ischemic strokes included large artery atherosclerosis (40.0%), small vessel disease (28.6%), cardioembolism (11.0%), and undetermined (20.4%). Hypertension (91.7%), structural lesions (3.4%), and others (4.9%) were causally associated with hemorrhagic stroke. Six topmost modifiable factors associated with stroke in descending order of population attributable risk (95% confidence interval) were hypertension: 88.7% (82.5%–94.8%), dyslipidemia: 48.2% (30.6%–65.9%), diabetes mellitus: 22.6% (18.7%–26.5%), low green vegetable consumption: 18.2% (−6.8%–43.2%), stress: 14.5% (4.9%–24.1%), and cardiac disease: 8.4% (5.8%–11.1%).

Conclusions—The high and rising burden of stroke among young Africans should be curtailed via aggressive, population-wide vascular risk factor control. **(*Stroke*. 2018;49:1116-1122. DOI: 10.1161/STROKEAHA.118.020783.)**

Key Words: diabetes mellitus ■ prevalence ■ public health ■ quality of life ■ stroke

Recent trends suggest that sub-Saharan Africa now bears the highest burden of stroke worldwide with age-standardized stroke incidence rates of up to 316 per 100 000, prevalence rates of up to 14 per 1000 population and 1-month fatality rates of up to 40%.[1–4] Stroke in these settings is characterized by a younger age of onset with poor long-term outcomes.[5] Stroke in the young has been defined by an age cut off of <50 years and contributes ≈10% to 14% of ischemic strokes in high-income countries.[6,7] Stroke among young adults has devastating consequences because of the longer lasting impact of stroke-related disability on quality of life and productivity.[8]

Very little is known about the burden, risk factors, and features of stroke among young West Africans. Given that stroke in sub-Saharan Africa levies a heavy economic toll by affecting a relatively younger age group, it is necessary to stem the rising tide of stroke by identifying risk factors for stroke among this productive segment of the population. Such data are crucial in designing evidence-based, context-specific public health interventions aimed at stroke prevention in a region at the throes of an epidemiological transition. Our aim for this study is to characterize the nature of strokes and quantify the contributions of modifiable risk factors for stroke among

Received January 14, 2018; final revision received February 28, 2018; accepted March 8, 2018.

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Presented in part at the International Stroke Conference, Los Angeles, CA, January 24–26, 2018.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.118.020783/-/DC1.

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young West Africans within the context of the SIREN (Stroke Investigative Research and Educational Network), the largest study of stroke in Africa to date.[9]

Methods

Study Design

The SIREN study is a multicenter case–control study involving several sites in northern and southern belts of Nigeria and Ghana. The study protocol has been published previously.[9] Briefly, stroke cases included consecutive consenting (in unconscious or aphasic patients, consent was obtained from next of kin) adults aged ≥18 years with first clinical stroke presenting within 8 days of current symptom onset or last seen without a deficit. All cases had neuroimaging confirmation with computed tomography or magnetic resonance imaging scan within 10 days of symptom onset. Although the stroke patients were recruited from hospitals to ensure accurate phenotyping, a robust community engagement core incorporated community sensitization programs to enhance early presentation at SIREN hospitals and minimize referral bias.[9] Controls were consenting stroke-free adults, mostly from the communities in the catchment areas of the SIREN hospitals where cases were recruited. Stroke-free status was confirmed with the 8-item questionnaire for verifying stroke-free status which has 98% negative predictive value.[10] Controls were matched by age (±5 years), sex and ethnicity to minimize the potential confounding effect of these variables on the relationship between stroke and the main environmental risk factors. Ethical approval was obtained from all study sites and informed consent was obtained from all subjects.[9] Data supporting the findings of this study are available on request from the corresponding author (M. Owolabi).

Stroke Phenotyping

Stroke diagnosis and phenotyping were based on clinical evaluation and brain neuroimaging (computed tomography or magnetic resonance imaging), ECG, transthoracic echocardiography, and carotid Doppler ultrasound performed according to standardized protocols at each site. Presumed etiologic subtypes of ischemic stroke were defined using the TOAST (Trial of ORG 10172 in Acute Stroke Treatment)[11] and intracerebral hemorrhage was classified etiologically into SMASH-U causes (Structural, Medication-Related, Amyloid Angiopathy, Systemic/Other Disease, Hypertension and Undetermined).[12]

Definition of Risk Factors

We collected basic demographic and lifestyle data including, socioeconomic status, cardiovascular risk profile, dietary patterns, routine physical activity, stress using a validated INTERSTROKE instrument, depression, cigarette smoking, and alcohol use.[13] Hypertension: blood pressure (BP) was recorded at baseline and daily for 7 days. Hypertension was defined as a sustained elevation of BP ≥140/90 mm Hg >72 hours after stroke, a premorbid history of hypertension, use of antihypertensive drugs before stroke or >72 hours after stroke onset. Adjustments to systolic BP based on reported associations between premorbid BP and acute poststroke BP in the OXVASC (Oxford Vascular Study) were also applied in sensitivity analyses.[14] Definition of hypertension in controls was self-reported history of hypertension or use of antihypertensive drugs or average of 3 recorded BP at first clinical encounter ≥140/90 mm Hg.[13] Diabetes mellitus was defined based on history of diabetes mellitus, use of medications for diabetes mellitus, an HBA1c >6.5% or a fasting blood glucose levels of >7.0 mmol/L at first encounter in controls or measured after the postacute phase in cases because of the known acute transient elevation of glucose as a stress response after stroke.[15] Dyslipidemia was defined as fasting total cholesterol ≥5.2 mmol/L, HDL-C (high-density lipoprotein cholesterol) ≤1.03 mmol/L, triglyceride ≥1.7 mmol/L, or LDL-C (low-density lipoprotein cholesterol) ≥3.4 mmol/L according to National Cholesterol Education Program guidelines[16] or use of statin before stroke onset. Based on distribution of the LDL/HDL ratio in the present study, the LDL/HDL ratio was dichotomized using the lowest 2 tertiles (≤1.97 and 1.98–2.95) as normal versus highest tertile (≥2.96) as high. Cardiac disease was defined after evaluation by study cardiologists based on history or current diagnosis of atrial fibrillation, cardiomyopathy, heart failure, ischemic heart disease, rheumatic heart disease, or valvular heart diseases. For obesity, we assessed both waist-to-hip ratio and body mass index. Subjects were classified individually either using the World Health Organization guidelines cut offs of 0.90 (men) and 0.85 (women) for waist-to-hip ratio or 30 kg/m^2 for body mass index (obesity).[17] 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 hours or more per week.[13] Dietary history included regularity of intake of food items such as meat, fish, green leafy vegetables, addition of salt at table, nuts, sugar, and other local staple food items. Regular intake was defined as intake on daily, weekly, or at least once monthly versus none in a month. Alcohol use was categorized into current users (users of any form of alcoholic drinks) or never/former drinker, whereas alcohol intake 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; 1 drink or 1 U of alcohol=8 g of alcohol).[13] Smoking status was defined as current smoker (individuals who smoked any tobacco in the past 12 months) or never/former smoker.[13] We adapted the measures of psychosocial stress and depression in the INTERSTROKE study for assessment of psychosocial risk factors.[13] Psychosocial stress combined measures of stress at home/work (eg, irritability, anxiety, or sleeping difficulties) and life events, experienced in the 2 weeks preceding the stroke. 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 in the online-only Data Supplement. Family history of cardiovascular risk/diseases was defined based on self-reported history of any of hypertension, diabetes mellitus, dyslipidemia, stroke, cardiac disease, or obesity in participants' father, mother, sibling, or second-degree relative.

Statistical Analysis

We assessed the bivariate association between risk factors and stroke status (case versus control) using McNemar test for paired categorical outcomes with stratification by age (<50 years versus ≥50 years). Further analyses to determine the adjusted associations between the risk factors and stroke occurrence for the total sample and stratified by stroke types were made. We used conditional logistic regression to estimate the adjusted odds ratio (OR) and 95% confidence intervals (CIs) for the association between risk factors and odds of stroke. The adjusted models included selected covariates depending on whether or not they are confirmed confounders in the bivariate analysis and considerations from the literature on stroke risk factors. Additionally, the final adjusted models were assessed for collinearity using variance inflation factor and goodness of fit using residual analysis. We calculated the adjusted population attributable risks (PARs) with their respective 95% CI for each exposure variable included in the best-fitted adjusted models. The PARs were estimated as the proportion of the risk of the 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).[18] The 95% CI for the PAR were obtained using the AF R-package[19] where the variance is estimated via the delta method. Composite PARs for the dominant risk factors for stroke, stroke subtypes, and age <50 years versus ≥50 years were calculated using the ATTRIBRISK R package with its 95% CI computed via the bootstrap method. All statistical tests of hypotheses were 2-sided. Statistical analyses and graphics were performed with SAS 9.4 and R statistical program (version 3.4.2).

Table 1. Study Participant Characteristics by Case–Control Status for Each Age Group

	Age <50			Age ≥50		
Variable	Control (n=515)	Case (n=515)	*P* Value	Control (n=1603)	Case (n=1603)	*P* Value
Age, mean±SD	40.12±6.53	40.95±6.58	<0.0001	63.48±10.08	64.79±10.00	<0.0001
Monthly income >100 USD, %	48	60	<0.0001	43	56	<0.0001
Primary education or higher, %	92	94	0.222	77	80	0.004
Hypertension, (%)	35	90	<0.0001	65	97	<0.0001
Dyslipidemia, (%)	55	75	<0.0001	63	79	<0.0001
Diabetes mellitus, (%)	5	26	<0.0001	16	42	<0.0001
Cardiac disease, (%)	4	10	<0.0001	6	12	<0.0001
HDL-cholesterol, mmol/L, mean±SD	1.35±0.40	1.31±0.51	0.181	1.37±0.46	1.25±0.48	<0.0001
HDL-cholesterol ≤1.03 mmol/L, (%)	23	29	0.069	24	36	<0.0001
LDL-cholesterol, mmol/L, mean±SD	3.14±1.15	3.24±1.27	0.232	3.19±1.22	3.24±1.32	0.309
LDL-cholesterol ≥3.4 mmol/L, (%)	37	42	0.080	41	41	1.000
LDL/HDL ratio, mean±SD	2.56±1.30	2.86±2.10	0.010	2.59±1.43	2.96±1.74	<0.0001
LDL/HDL ratio >2.96, (%)	31	35	0.333	32	40	<0.0001
Total cholesterol mmol/L, mean±SD	5.0±1.2	5.1±1.5	0.200	5.1±1.3	5.1±1.5	0.986
Total cholesterol ≥5.2 mmol/L, (%)	38	46	0.006	43	45	0.310
Triglyceride mmol/L, mean±SD	1.1±0.6	1.5±1.0	0.0001	1.2±0.6	1.5±1.0	<0.0001
Triglyceride ≥1.7 mmol/L, (%)	10	28	<0.0001	16	26	<0.0001
Waist-to-hip ratio, mean±SD	0.89±0.10	0.94±0.08	<0.0001	0.92±0.09	0.94±0.08	<0.0001
Waist-to-hip ratio raised, (%)	49	78	<0.000	75	83	<0.000
BMI, mean±SD, kg/m^2	26.9±5.9	26.7±5.8	0.644	26.3±5.8	26.5±4.9	0.326
BMI >25 kg/m^2, (%)	26	25	0.928	22	20	0.465
Physical activity (some activity), (%)	99	97	0.012	97	95	0.001
Tobacco use in past 12 mo, (%)	1	5	<0.0001	1	3	0.013
Tobacco (any use), (%)	4	9	0.001	9	10	0.345
Alcohol (current user), (%)	16	25	<0.0001	15	17	0.113
Alcohol (any use), (%)	29	36	0.010	33	37	0.017
Stress, (%)	20	26	0.032	14	23	<0.0001
Cancer, (%)	0	0	1.000	0	1	0.092
Depression, (%)	7	8	0.795	7	9	0.077
Family history of CVD 1, (%)	35	44	0.006	27	40	<0.0001
Table added salt, (%)	8	9	0.561	5	8	<0.0001
Green vegetable consumption, (%)	82	69	<0.0001	82	71	<0.0001
Whole grains consumption, (%)	85	86	0.773	82	86	0.009
Legumes consumption, (%)	67	71	0.274	64	65	0.290
Fruit consumption, (%)	89	82	0.001	86	83	0.033
Sugar consumption or otherwise, (%)	46	43	0.374	33	28	0.005
Meat consumption or otherwise, (%)	87	90	0.256	77	81	0.002
Fish consumption or otherwise, (%)	94	94	0.683	93	93	0.654

Values are means±SD or percentages. Values of polytomous variables may not sum to 100% because of rounding. Age of stroke case determines age group for matched control. *P* values reported for Paired *t* test, McNemar χ^2, or test of marginal homogeneity. BMI indicates body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Results

Demographic and Clinical Characteristics of Stroke Subjects by Age

Of the 2118 stroke cases in the SIREN cohort, 515 (24.3%) were <50 years and 306 (59.4%) were males. Compared with age- and gender-matched controls, stroke subjects <50 years had higher income levels, were more likely to be hypertensive, dyslipidemic, diabetic, have cardiac diseases and higher waist-to-hip ratios as shown in Table 1. Furthermore, young stroke subjects were less physically active, smoked cigarette more commonly compared with age-matched controls. They were less likely to consume green vegetables and fruits, with higher rates of reported stress than controls (Table 1).

Stroke Types and Subtypes by Age

Among subjects <50 years old, hemorrhagic stroke occurred at a higher frequency than ischemic stroke 270 (52.5%) versus 245 (47.5%). Among stroke subjects aged ≥50 years, there were significantly more ischemic strokes 1174 (73.5%) than hemorrhagic stroke 423 (26.5%), $P<0.0001$. Six subjects with both ischemic and hemorrhagic stroke were excluded. Among young subjects <50 years, the etiologic subtypes of ischemic strokes included large artery atherosclerosis (40.0%), small vessel disease (28.6%), cardioembolism (11.0%), and undetermined (20.4%). Hypertension (91.7%), structural lesions (3.4%), and others (4.9%) were causally associated with hemorrhagic stroke in the young. Hemorrhagic stroke was nonlobar 155 (68.3%) and lobar 48 (21.1%) in location in the <50 years group with intraventricular extension in 93 (35.9%) cases (Table 2).

Table 2. Ischemic and Hemorrhagic Stroke Subtype Distribution by Age Group

	Age <50 n (%)	Age ≥50 n (%)	*P* Value
TOAST ischemic stroke subtypes			
Large artery atherosclerosis	84 (40.0)	330 (32.6)	0.04
Cardioembolism	23 (11.0)	79 (7.8)	0.13
Small vessel disease	60 (28.6)	396 (39.2)	0.004
Undetermined (≥2 causes)	1 (0.4)	0 (0.0)	0.03
Undetermined (negative evaluation)	42 (20.0)	206 (20.4)	0.90
Undetermined (incomplete evaluation)	0 (0.0)	0 (0.0)	
Missing	35	163	
SMASH-U hemorrhagic subtypes			
Structural	7 (3.4)	14 (3.8)	0.81
Medication-associated	2 (1.0)	1 (0.3)	0.29
Cerebral amyloid angiopathy	0 (0.0)	6 (1.6)	0.09
Systemic illness	1 (0.5)	0 (0.0)	0.36
Hypertensive	188 (91.7)	340 (92.6)	0.74
Undetermined	7 (3.4)	6 (1.6)	0.24
Missing	65	56	
Location of hemorrhagic strokes			
Lobar	48 (21.1)	61 (16.5)	0.15
Nonlobar	155 (68.3)	278 (75.1)	0.07
Both	24 (10.6)	31 (8.4)	0.90
Missing	32	53	
Intraventricular hemorrhage			
Yes	93 (35.9)	157 (37.1)	0.48

SMASH-U indicates Structural, Medication-Related, Amyloid Angiopathy, Systemic/Other Disease, Hypertension and Undetermined; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Factors Associated With Stroke Among Young Africans

The adjusted ORs and PAR (95% CI) of the 6 topmost modifiable risk factors associated with stroke occurrence <50 years in decreasing order of magnitude by PAR were hypertension (30.84, 11.37–83.61; 88.7%, 82.5%–94.8%), dyslipidemia (2.75, 1.34–5.61; 48.2%, 30.6%–65.9%), diabetes mellitus (5.80, 2.05–16.36; 22.6%, 18.7%–26.5%), low green vegetable consumption (2.31, 1.02–5.22; 18.2%, −6.8 to 43.2), stress (2.26, 1.04–4.93; 14.5%, 4.9%–24.1%), and cardiac disease (8.03, 1.91–33.82; 8.4%, 5.8%–11.1%). Having no education was independently associated with stroke with adjusted OR of 3.68 (1.01–13.41) and a PAR of 68.9% (36.0%–101.7%). Altogether, these 7 factors compositely accounted for 98.1% (95% CI, 96.0%–99.8%) of PAR associated with stroke. (Table 3; Figure I in the online-only Data Supplement). Four factors were independently associated with ischemic stroke occurrence, namely hypertension, cardiac disease, raised waist-to-hip ratio, and stress while hypertension, dyslipidemia, and diabetes mellitus were associated with hemorrhagic stroke occurrence (Table 3). Factors associated with stroke occurrence on univariate analyses are presented as Table I in the online-only Data Supplement. In sensitivity analyses, the effect size of the association between hypertension and stroke varied depending on the definition of hypertension used and whether adjustments were made for the acute rise in systolic BP after stroke onset (Table II in the online-only Data Supplement). For instance, an adjusted OR of 8.57 (4.52–16.26) for hypertension was found if BP was adjusted for the acute rise and hypertension was defined based on BP measured on the morning after admission and 36.70 (12.98–103.76) if new antihypertensive medications were introduced after stroke occurrence.

Discussion

Burden of Stroke

Approximately 25% of strokes in this West African cohort occurred among young adults <50 years old. Reports from high-income countries in North America and Europe indicate a slightly lower frequency of stroke burden in this age group ranging between 5% to 20%.[4–7] This would concur with findings from the Global Burden of Disease study where 31% of the global burden of stroke was contributed to by children aged <20 years and young and middle adults (20–64 years)

Table 3. Adjusted OR, Population Attributable Risk, and 95% CI Using Conditional Logistic Regression for Stroke and Its Subtypes Among Africans Aged <50 Y

	Stroke Overall		Hemorrhagic Stroke		Ischemic Stroke	
Predictor	Adjusted OR (95% CI)	PAR% (95% CI)	Adjusted OR (95% CI)	PAR% (95% CI)	Adjusted OR (95% CI)	PAR% (95% CI)
Education, some vs none	3.68 (1.01 to 13.41)	68.9 (36.0 to 101.7)	3.26 (0.74 to 14.35)	66.2 (31.2 to 101.2)	1.30 (0.24 to 6.89)	21.5 (–129.75 to 172.84)
Monthly income >$100 (USD)	1.37 (0.69 to 2.75)	17.0 (–44.1 to 78.0)	0.92 (0.39 to 2.16)	–5.3 (–58.9 to 48.3)	1.62 (0.73 to 3.55)	24.5 (–17.9 to 66.8)
Hypertension	30.84 (11.37 to 83.61)	88.7 (82.5 to 94.8)	120.0 (16.0 to 898.13)	96.0 (92.6 to 99.4)	11.23 (4.16 to 30.32)	77.5 (68.1 to 86.9)
Dyslipidemia	2.75 (1.34 to 5.61)	48.2 (30.6 to 65.9)	2.52 (1.06 to 6.01)	43.8 (–12.9 to 100.5)	2.26 (0.99 to 5.16)	42.0 (–2.3 to 86.2)
Diabetes mellitus	5.80 (2.05 to 16.36)	22.6 (18.7 to 26.5)	8.71 (1.86 to 40.8)	21.4 (11.0 to 31.8)	3.16 (0.94 to 10.59)	19.1 (11.4 to 26.8)
Cardiac disease	8.03 (1.91 to 33.82)	8.4 (5.8 to 11.1)	2.67 (0.37 to 18.91)	3.1 (0.4 to 5.8)	11.05 (2.11 to 57.89)	11.8 (8.0 to 15.6)
Raised waist-to-hip ratio	1.99 (0.95 to 4.18)	38.5 (7.8 to 69.2)	NA	NA	2.70 (1.03 to 7.07)	49.9 (11.7 to 88.1)
Physical activity	7.42 (0.59 to 93.98)	2.8 (0.8 to 4.7)	NA	NA	NA	NA
History of tobacco use	5.52 (0.36 to 84.59)	3.7 (–3.4 to 10.7)	NA	NA	NA	NA
Stress in the last 2 wk	2.26 (1.04 to 4.93)	14.5 (4.9 to 24.1)	NA	NA	2.84 (1.04 to 7.80)	20.2 (8.5 to 31.9)
Family history of CVD	1.27 (0.60 to 2.70)	9.4 (–30.6 to 49.3)	1.31 (0.55 to 3.08)	11.7 (–53.6 to 77.0)	0.89 (0.37 to 2.14)	–4.5 (–62.1 to 53.2)
Sprinkle salt at table	1.23 (0.36 to 4.13)	1.8 (–7.4 to 11.1)	NA	NA	4.17 (0.78 to 22.37)	6.9 (1.8 to 12.0)
Low consumption of green leafy vegetables	2.31 (1.02 to 5.22)	18.2 (–6.8 to 43.2)	2.15 (0.91 to 5.10)	17.1 (–9.0 to 43.2)	1.74 (0.59 to 5.19)	12.2 (–15.2 to 39.6)
Regular sugar consumption	1.36 (0.65 to 2.85)	11.7 (–13.5 to 37.0)	NA	NA	NA	NA
Meat consumption	1.50 (0.52 to 4.35)	30.4 (–38.8 to 99.5)	1.66 (0.52 to 5.29)	36.1 (–40.7 to 113.0)	NA	NA
Composite PAR		98.1 (96.0 to 99.8)				

CI indicates confidence interval; CVD, cardiovascular disease; NA, not computed; OR, odds ratio; and PAR, population attributable risk.

with 78% of the young and middle-aged stroke cases emanating from lower and middle-income countries.[1] Hence, the contribution of stroke between ages 18 to 50 is quite substantial among West Africans.

Stroke Types

The most striking finding of our study is the overwhelming preponderance of hemorrhagic stroke accounting for 52.5% of all strokes in this young population relative the middle-aged to elderly cohort. This contrasts sharply with published studies from high-income countries such as Germany,[20] where primary intracerebral hemorrhage among adults <55 years old contributed only 5.5%, and from a review of 29 studies (with age cut off of 45 years), mostly involving European and Northern American countries, where the proportions of hemorrhagic stroke ranged between 3.7% and 38.5%.[21] A report from the Korean Stroke Statistics collaboration identified 34.3% of stroke <55 years were of hemorrhagic variety.[22] Among subjects with ischemic stroke, large artery atherosclerosis was the commonest etiologic subtype in agreement with findings from a Chinese young stroke cohort between 18 and 45 years.[23] Although cardioembolic stroke account for up to a third of ischemic stroke among young Europeans[23] and up to 47% among a young US cohort,[24] we found a lower rate of 12.4% highlighting possible differences in etiologic profile of ischemic stroke among young Africans or a limited gamut of investigative capabilities in our study sites.

Factors Associated With Stroke Occurrence

Six topmost modifiable factors in decreasing order by rank namely hypertension, dyslipidemia, diabetes mellitus, low consumption of green leafy vegetables, psychosocial stress, and cardiac disease were associated with stroke occurrence among young West Africans. Among the subcohort aged <55 years in the global INTERSTROKE case–control study, hypertension, physical inactivity, dyslipidemia, central obesity, and current smoking were the leading 6 factors associated with stroke.[13] Furthermore, hypertension, low physical activity, smoking, and alcohol consumption explained 78% of stroke among young Germans.[20] A common emerging theme is that the established traditional vascular risk factors are now potent contributors to stroke risk among young and middle age adults globally. The differences observed in PARs for specific risk factors in between studies may be because of regional differences in prevailing behavioral and lifestyle practices. For instance, cigarette smoking is a less commonly reported risk factor for stroke among Africans perhaps because smoking is an expensive habit to sustain in a resource-limited setting. Racial differences in vascular risk factor predisposition and expression have been shown to

account for some of the differences in stroke burden in the US and indigenous Africans.[25]

Socioeconomic factors may play differential underpinning roles for cardiovascular disease risk in diverse regional blocks worldwide. We identified a potent independent association between no educational attainment and stroke occurrence in the young. A prospective cross-sectional survey among >200 000 Chinese demonstrated an inverse relationship between educational status and stroke.[26] Low educational status associated with poor functional health literacy may contribute to a lack of awareness, detection, and control of vascular risk factors in particular hypertension which is often asymptomatic. Consequently, the contribution of hypertension to stroke occurrence among young Africans is quite astronomical with a PAR of 88.7% for stroke overall and explained 100% of all hemorrhagic strokes. Additionally, novel psychosocial factors such as stress, recently demonstrated to be causally associated with stroke occurrence[27] via elaboration of proatherogenic cytokines, was identified to be independently associated with ischemic stroke risk among young West Africans in this study. Interestingly, our group has identified associations between *IL6* (interleukin-6) rs1800796 single nucleotide polymorphisms and ischemic stroke in men with hypertension in the model but not in women.[28]

Strengths and Limitations

This is one of the largest studies to examine factors associated with stroke risk among young West Africans. Previous studies in this population have been limited by sample size and had no control group.[29] A limitation of case–control studies is that causality between putative risk factors and event/outcome measure of interest cannot be conclusively established. Indeed, it has been suggested that the validity of case–control studies is contingent on selecting controls independently of risk factor status and could be compromised by matching.[30] Hence, we performed individual matching of cases to controls (age, gender, and ethnicity not risk factor status) in a 1:1 fashion and used conditional logistic regression analysis to attain unbiased ORs. Furthermore, although the study paid for the cost of investigation of all study participants, specific investigations such as thrombophilia screening, bubble echocardiographic studies, and others investigations pertinent in establishing causes of stroke in the young were unavailable at study sites.

Implications and Future Directions

The cluster of factors identified in the present study strongly support urgent population-wide interventions aimed at primary prevention of stroke across the lifespan of continental Africans. Further studies are clearly warranted to characterize the outcomes of stroke among young Africans over the longer term including mortality, control of vascular risk factors, and reintegration back into a society with limited social support services.

Conclusions

The high and rising burden of stroke among young Africans should be curtailed via aggressive, population-wide vascular risk factor control.

Sources of Funding

SIREN (Stroke Investigative Research and Educational Network) was funded by the National Institutes of Health Grant U54 HG007479 under the H3Africa initiative.

Disclosures

None.

References

1. Walker R, Whiting D, Unwin N, Mugusi F, Swai M, Aris E, et al. Stroke incidence in rural and urban Tanzania: a prospective, community-based study. *Lancet Neurol*. 2010;9:786–792. doi: 10.1016/S1474-4422(10)70144-7.
2. Ezejimofor MC, Uthman OA, Maduka O, Ezeabasili AC, Onwuchekwa AC, Ezejimofor BC, et al. Stroke survivors in Nigeria: a door-to-door prevalence survey from the Niger Delta region. *J Neurol Sci*. 2017;372:262–269. doi: 10.1016/j.jns.2016.11.059.
3. Sarfo FS, Awuah DO, Nkyi C, Akassi J, Opare-Sem OK, Ovbiagele B. Recent patterns and predictors of neurological mortality among hospitalized patients in Central Ghana. *J Neurol Sci*. 2016;363:217–224. doi: 10.1016/j.jns.2016.02.041.
4. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;383:245–254. doi: 10.1016/S0140-6736(13)61953-4.
5. Sarfo FS, Akassi J, Kyem G, Adamu S, Awuah D, Kantanka OS, et al. Long-term outcomes of stroke in a Ghanaian outpatient clinic. *J Stroke Cerebrovasc Dis*. 2018;27:1090–1099. doi: 10.1016/j.jstrokecerebrovasdis.2017.11.017.
6. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke*. 2009;40:1195–1203. doi: 10.1161/STROKEAHA.108.529883.
7. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70:713–721. doi: 10.1002/ana.22539.
8. Edwards JD, Kapoor A, Linkewich E, Swartz RH. Return to work after young stroke: a systematic review [published online ahead of print January 1, 2017]. *Int J Stroke*. doi: 10.1177/1747493017743059.
9. Akpalu A, Sarfo FS, Ovbiagele B, Akinyemi R, Gebregziabher M, Obiako R, et al; SIREN as part of the H3Africa Consortium. Phenotyping stroke in Sub-Saharan Africa: Stroke Investigative Research and Education Network (SIREN) phenomics protocol. *Neuroepidemiology*. 2015;45:73–82. doi: 10.1159/000437372.
10. Sarfo F, Gebregziabher M, Ovbiagele B, Akinyemi R, Owolabi L, Obiako R, et al; Stroke Investigative Research Educational Networks. Multilingual validation of the questionnaire for verifying stroke-free status in West Africa. *Stroke*. 2016;47:167–172. doi: 10.1161/STROKEAHA.115.010374.
11. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32:2735–2740.
12. Meretoja A, Strbian D, Putaala J, Curtze S, Haapaniemi E, Mustanoja S, et al. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. *Stroke*. 2012;43:2592–2597. doi: 10.1161/STROKEAHA.112.661603.
13. O'Donnell M, Xavier D, Diener C, Sacco R, Lisheng L, Zhang H, et al; INTERSTROKE Investigators. Rationale and design of INTERSTROKE: a global case-control study of risk factors for stroke. *Neuroepidemiology*. 2010;35:36–44. doi: 10.1159/000306058.
14. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *Lancet Neurol*. 2014;13:374–384. doi: 10.1016/S1474-4422(14)70031-6.
15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553. doi: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.

16. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation; Treatment of high blood cholesterol in adults (Adult treatment panel). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation.*2002;106:3143–3421.
17. World Health Organization. Waist Circumference and Waist-Hip Ratio. Report of a WHO Expert Consultation. http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/. Accessed May 27, 2017.
18. Llorca J, Delgado-Rodríguez M. A comparison of several procedures to estimate the confidence interval for attributable risk in case-control studies. *Stat Med*. 2000;19:1089–1099.
19. Dahlqwist E, Sjölander A. AF Package- Model Based Estimation of Confounder-Adjusted Attributable Fractions. https://cran.r-project.org/web/packages/AF/index.html. Accessed May 27, 2017.
20. Aigner A, Grittner U, Rolfs A, Norrving B, Siegerink B, Busch MA. Contribution of established stroke risk factors to the burden of stroke in young adults. *Stroke*. 2017;48:1744–1751. doi: 10.1161/STROKEAHA.117.016599.
21. Marini C, Russo T, Felzani G. Incidence of stroke in young adults: a review. *Stroke Res Treat*. 2010;2011:535672. doi: 10.4061/2011/535672.
22. Hong KS, Bang OY, Kang DW, Yu KH, Bae HJ, Lee JS, et al. Stroke statistics in Korea: part I. Epidemiology and risk factors: a report from the Korean stroke society and clinical research center for stroke. *J Stroke*. 2013;15:2–20. doi: 10.5853/jos.2013.15.1.2.
23. Smajlović D. Stroke in young adults: epidemiology and prevention. *Vasc Health Risk Manag*. 2015;11:157–164.
24. Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol*. 2013;70:51–57. doi: 10.1001/jamaneurol.2013.575.
25. Owolabi M, Sarfo F, Howard VJ, Irvin MR, Gebregziabher M, Akinyemi R, et al; SIREN-REGARDS Collaboration (Stroke Investigative Research and Educational Network–Reasons for Geographic and Racial Differences in Stroke). Stroke in indigenous Africans, African Americans, and European Americans: interplay of racial and geographic factors. *Stroke*. 2017;48:1169–1175. doi: 10.1161/STROKEAHA.116.015937.
26. Li Q, Wu H, Yue W, Dai Q, Liang H, Bian H, et al. Prevalence of stroke and vascular risk factors in China: a Nationwide Community-based Study. *Sci Rep*. 2017;7:6402. doi: 10.1038/s41598-017-06691-1.
27. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet*. 2017;389:834–845. doi: 10.1016/S0140-6736(16)31714-7.
28. Akinyemi R, Arnett DK, Tiwari HK, Ovbiagele B, Sarfo F, Srinivasasainagendra V, et al; SIREN Investigators. Interleukin-6 (IL-6) rs1800796 and cyclin dependent kinase inhibitor (CDKN2A/CDKN2B) rs2383207 are associated with ischemic stroke in indigenous West African Men. *J Neurol Sci*. 2017;379:229–235. doi: 10.1016/j.jns.2017.05.046.
29. Owolabi LF, Ibrahim A. Stroke in young adults: a prospective study from northwestern Nigeria. *ISRN Neurol*. 2012;2012:468706. doi: 10.5402/2012/468706.
30. Rose S, van der Laan, MJ. Why match? Investigating matched case-control study designs with causal effect estimation. *Int J Biostat*. 2009;5:1. doi: 10.2202/1557–4679.1127.