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**Title:**

**Risk Factor Characterization of Ischemic Stroke Subtypes among West Africans**

**Running title:** *Ischemic Stroke in West Africa*

**Authors:**

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## Table I: Comparison of demographic and clinical characteristics of stroke-free controls to ischemic stroke cases

| Characteristic | Control N=2431 | Cases N=2431 | p-value |
|---|---|---|---|
| Gender, Male, n (%) | 1283(52.78) | 1284(52.82) | 0.868 |
| Age, mean ± SD | 60.1±13.8 | 62.1 ± 14.0 | 0.471 |
| Age categories, n (%) | | | |
| <30 | 38(1.56) | 52(2.14) | 0.002 |
| 30-49 | 491(20.20) | 355(14.60) | |
| 50-69 | 1240(51.01) | 1210(49.77) | |
| >=70 | 662(27.23) | 803(33.03) | |
| Age >65years, n (%) | 864(35.54) | 984(40.44) | <0.001 |
| Domicile | | | |
| *Rural, n (%)* | 457(18.80) | 221(9.09) | <0.001 |
| *Semi-urban, n (%)* | 632(26.00) | 713(29.33) | |
| *Urban, n (%)* | 1341(55.16) | 1482(60.96) | |
| Monthly Income >$100, n (%) | 897(36.90) | 983(40.44) | <0.001 |
| Education, (some) n (%) | 1846(75.94) | 1898(78.7) | 0.031 |
| Country, Ghana, n (%) | 864(35.54) | 735(30.23) | <0.001 |
| *Akan* | 526(2.14) | 524(21.55) | <0.001 |
| *Gal/Adange* | 130(5.35) | 92(3.78) | |
| *Ewe* | 99(4.07) | 70(1.93) | |
| *others* | 109(4.48) | 49(2.02) | |
| Country, Nigeria, n (%) | 1558(64.09) | 1680(69.11) | <0.001 |
| *Yoruba* | 880(36.20) | 877(36.08) | 0.001 |
| *Igbo* | 85(3.50) | 102(4.20) | |
| *Hausa* | 425(17.48) | 438(18.02) | |
| *Others* | 168(6.91) | 253(10.41) | |
| Hypertension, n (%) | 1496(61.54) | 2279(93.75) | <0.001 |
| Dyslipidemia, n (%) | 1316(54.13) | 2062(84.82) | <0.001 |
| Diabetes, n (%) | 287(11.81) | 1000(41.14) | <0.001 |
| Cardiac Disease, n (%) | 110(4.52) | 336(13.82) | <0.001 |
| HDL-Cholesterol, mg/dl, mean ± SD | 52.9±17.7 | 46.3 ± 18.2 | 0.211 |
| HDL-Cholesterol ≤ 18.54 mg/dl, n (%) | 480(19.74) | 816(33.57) | <0.001 |
| LDL-Cholesterol, mg/dl, mean ± SD | 120.3±44.6 | 121.0 ± 51.0 | <0.001 |
| LDL-Cholesterol ≥ 61.2 mg/dl, n (%) | 742(30.52) | 787(32.37) | 0.164 |
| LDL/HDL ratio, mean ± SD | 2.54±1.4 | 3.0 ± 1.8 | <0.001 |
| LDL/HDL ratio >2.96, n (%) | 599(24.64) | 785(32.29) | <0.001 |
| LDL/HDL ratio by thirds: | | | |
| *≤ 2.00* | 763(31.39) | 601(24.72) | <0.001 |
| *2.01 - 2.96* | 620(25.50) | 594(24.43) | |
| *≥ 2.97* | 599(24.64) | 1980(81.45) | |
| Total Cholesterol, mmol/l, mean ± SD | 194.7±49.1 | 190.3 ± 57.8 | <0.001 |
| Total Cholesterol ≥ 93.6 mg/dl, n(%) | 841(34.59) | 836(34.39) | 0.576 |
| Triglyceride, mg/dl, mean ± SD | 105.4±49.7 | 130.6 ±84.9 | <0.001 |
| Triglyceride ≥ 30.6 mg/dl, n (%) | 306(12.59) | 538(22.13) | <0.001 |
| Waist-to-hip Ratio, mean ± SD | 0.92 ±0.09 | 0.6 ± 0.5 | 0.294 |
| Waist-to-hip Ratio raised, n (%) | 1697(69.81) | 1884(77.50) | <0.001 |
| Waist-to-hip Ratio by thirds: | | | |
| *≤ .90* | 923(37.97) | 560(23.04) | <0.001 |
| *.91 - .96* | 729(29.99) | 811(33.36) | |
| *≥.97+* | 684(28.14) | 864(35.54) | |
| WHR[**], Lowest vs highest thirds, n (%) | 684(28.14) | 864(35.54) | <0.001 |

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|---|---|---|---|
| WHR**, 1st vs 2nd+3rd thirds, n (%) | 1413(58.12) | 1675(68.90) | <0.001 |
| BMI*** (kg/m2), mean ± SD | 26.2±6.0 | 26.7 ± 5.3 | 0.001 |
| BMI*** >30kg/m$^2$, n (%) | 506(20.81) | 430(17.69) | 0.664 |
| Physical Inactivity n (%) | 66(2.71) | 114(4.70) | <0.001 |
| Tobacco use in past 12 months, n (%) | 33(1.36) | 70(2.88) | <0.001 |
| Tobacco (any use), n (%) | 178(7.32) | 234(9.63) | 0.001 |
| Alcohol (current user), n (%) | 350(14.40) | 332(13.66) | 0.546 |
| Alcohol (any use), n (%) | 714(29.37) | 716(29.45) | 0.772 |
| Alcohol use categories: | | | |
| *Never Use* | 1694(69.68) | 1668(68.61) | <0.001 |
| *Ever Low Use* | 428(17.61) | 386(15.88) | |
| *Ever High Use* | 12(0.49) | 47(1.93) | |
| Stress, n (%) | 307(12.63) | 424(17.44) | <0.001 |
| Cancer, n (%) | 3(0.12) | 15(0.62) | <0.001 |
| Depression, n (%) | 140(5.76) | 177(7.32) | <0.001 |
| Family history of CVD, n (%) | 613(25.22) | 898(36.94) | <0.001 |
| Adding salt at table, n (%) | 200(8.23) | 145(5.96) | 0.007 |
| Low Vegetable Consumption, n (%) | 397(16.33) | 565(23.24) | <0.001 |
| Whole grains consumption, n (%) | 1995(82.06) | 1857(76.39) | 0.945 |
| Legumes consumption, n (%) | 1471(60.51) | 1471(60.51) | 1.00 |
| Fruit consumption, n (%) | 2005(82.48) | 1848(76.02) | 0.279 |
| Sugar consumption or otherwise, n (%) | 779(32.04) | 618(25.42) | 0.001 |
| Meat consumption or otherwise, n (%) | 1543(63.47) | 1587(65.28) | <0.001 |
| Fish consumption or otherwise, % | 2135(87.82) | 2001(82.31) | 0.834 |
| **Investigations** | | | |
| Electrocardiography | | 1467 (60.3) | |
| Echocardiography | | 1022 (42.0) | |
| Carotid Doppler | | 930 (38.3) | |
| Cranial CT scan | | 2431 (100.0) | |
| Previous stroke, n (%) | | 272(11.19) | |

**Table II. Clustering of Modifiable Risk factors of Ischemic stroke and its pathophysiologic subtypes**

| Number of risk factors | All Ischemic stroke N=2431 | Small vessel disease N=1024 | Large-vessel atherosclerosis N=427 | Cardio-embolism N=258 | Undetermined etiology N=722 | P-value (Exact test) |
|---|---|---|---|---|---|---|
| 0 | 9(0.37%) | 6(0.59%) | 2(0.47%) | 0(0%) | 1(0.14%) | 0.336 |
| 1 | 42(1.763%) | 24(2.34%) | 12(2.81%) | 2(0.78%) | 5(0.69%) | 0.012 |
| 2 | 216(8.89%) | 98(9.57%) | 45(10.54) | 23(8.91%) | (6.93%) | 0.146 |
| 3 | 593(24.39%) | 245(23.93%) | 11(2.58/%) | 52(20.16%) | 185(25.62%) | 0.222 |
| 4 | 434(17.85%) | 174(16.99%) | 77(18.03) | 34(13.18%) | (20.64%) | 0.032 |
| 5 | 485(19.95%) | 207(20.21%) | 79(18.50%) | 54(20.93%) | 143(19.81%) | 0.827 |
| 6 | 214(80.80%) | 91(8.89%) | 27(6.32%) | (12.79%) | 63(8.73%) | 0.045 |
| 7 | 58(2.39%) | 23(2.25%) | 6(1.41%) | 13(5.04%) | 16(2.22%) | 0.023 |
| 8 | 16(0.66%) | 7(0.68%) | 4(0.94%) | 4(1.55%) | 1(0.14%) | 0.086 |
| 9 | 3(0.12%) | 1(0.10%) | 0(0%) | 1(0.39) | 1(0.14%) | 0.584 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 |

*Risk factor combinations (score 1 or 0) for hypertension, dyslipidemia, diabetes mellitus, obesity, cardiac disease, smoking, alcohol use, perceived stress, depression, low vegetable consumption, physical inactivity and meat consumption.*
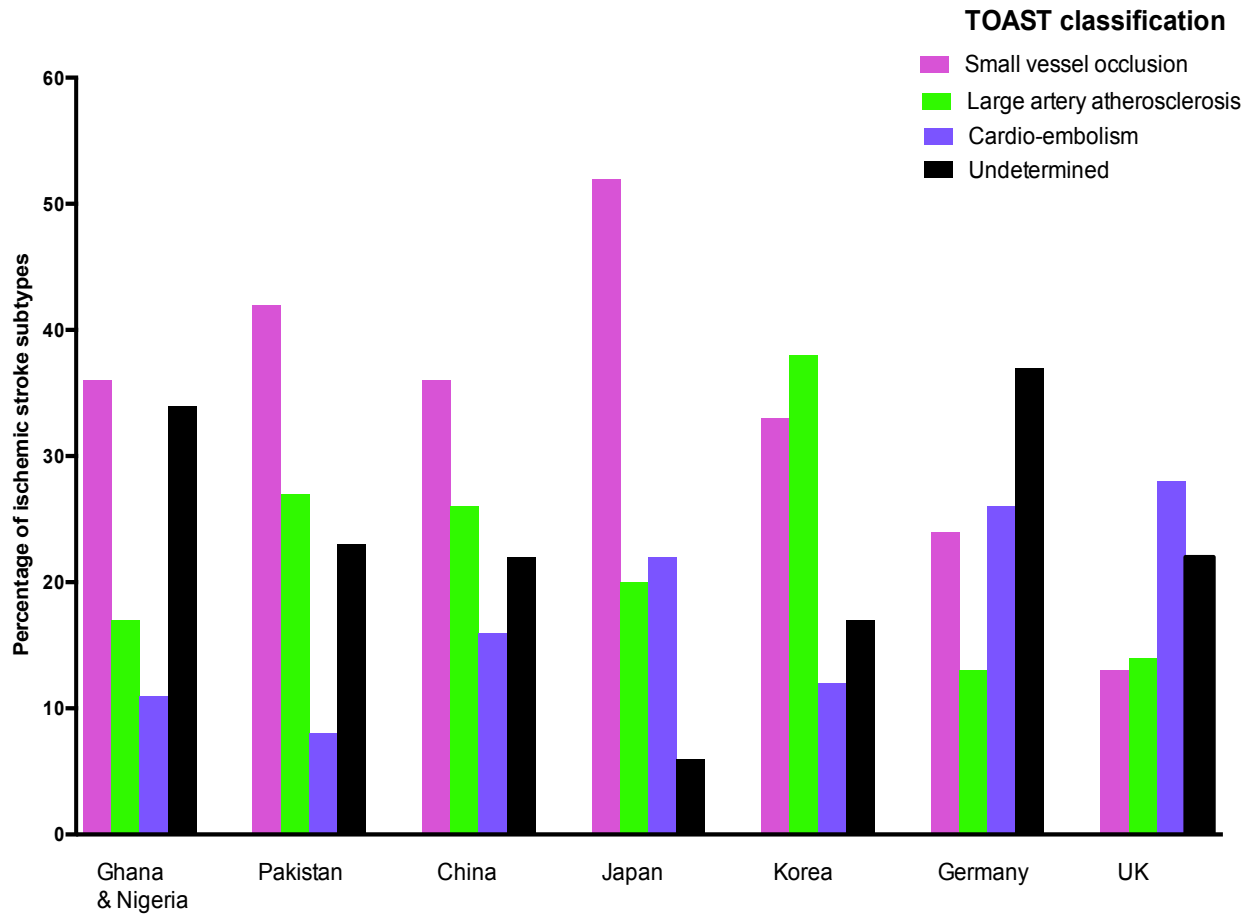
**Supplementary Figure I. Comparison of ischemic stroke subtypes in West Africa, Asian** (Pakistan, China, Japan, Korea) **and Western (**Germany and UK) **countries.**

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**STROBE Statement**—Checklist of items that should be included in reports of case-control studies

| | Item No | Recommendation | Please insert check where included or N/A where not applicable |
|---|---|---|---|
| Title and abstract | 1 | (a) Phenotypic Characterization of Ischemic Stroke Subtypes among West Africans | |
| | | (b) **Objective:** To identify the qualitative and quantitative contributions of conventional risk factors for occurrence of ischemic stroke and its key pathophysiologic subtypes among West Africans. | |

**Methods:** The Stroke Investigative Research and Educational Network (SIREN) is a multicenter, case-control study involving 15 sites in Ghana and Nigeria. Cases include adults aged ≥18 years with ischemic stroke who were etiologically subtyped using the A-S-C-O-D classification into Atherosclerosis, Small-vessel occlusion, Cardiac pathology, Other causes and dissection. Controls were age-and-gender matched stroke-free adults. Detailed evaluations for vascular, lifestyle and psychosocial factors were performed. We used conditional logistic regression to estimate adjusted odds ratios (aOR) with 95% Confidence Interval.

**Results:** There were 2,431 ischemic stroke case and stroke-free control pairs with respective mean ages of $62.2 \pm 14.0$ versus $60.9 \pm 13.7$ years. There were 1,024(42.1%) small vessel occlusions, 427(17.6%) large-artery atherosclerosis, 258(10.6%) cardio-embolic, 3(0.1%) carotid dissections and 719(29.6%) undetermined/other causes. The aOR (95%CI) for the 8 dominant risk factors for ischemic stroke were hypertension 10.34(6.91,15.45), dyslipidemia 5.16(3.78,7.03), diabetes mellitus 3.44(2.60,4.56), low green vegetable consumption 1.89(1.45,2.46), red meat consumption 1.89(1.45,2.46), cardiac disease 1.88(1.22,2.90), monthly income \$100+1.72(1.24,2.39) and psychosocial stress 1.62(1.18,2.21). Hypertension, dyslipidemia, diabetes were confluent factors shared by small-vessel, large-vessel and cardio-embolic subtypes. Each stroke case and stroke-free control pair had an average of $5.3 \pm 1.5$ and $3.2 \pm 1.0$ adverse cardio-metabolic risk factors respectively (p<0.0001).

**Conclusion:** Traditional vascular risk factors demonstrate important differential effect sizes with pathophysiologic, clinical and preventative implications on the occurrence of ischemic stroke among indigenous West Africans.

| **Introduction** | | | |
|---|---|---|---|
| Background/rationale | 2 | The qualitative and quantitative contributions of the various traditional medical and lifestyle risk factorsto the occurrence of key pathophysiologic subtypes of ischemic stroke among indigenous Africans, has not been comprehensively explored. | |

| Objectives | 3 | To identify the qualitative and quantitative contributions of conventional risk factors for occurrence of ischemic stroke and its key pathophysiologic subtypes among West Africans. |
|---|---|---|
| **Methods** | | |
| Study design | 4 | A multi-center Case-control study design. Cases were stroke patients presenting within hospitals at study sites. Controls were stroke-free subjects recruited mainly from the communities from the catchment areas of stroke cases. |
| Setting | 5 | <ul><li>Study was conducted at 15 sites in Ghana and Nigeria. Study centers were tertiary referral hospitals.</li><li>Study recruitment commenced in August 2014 to June 2018.</li></ul> |
| Participants | 6 | <ul><li>Stroke cases included consecutive consenting Ischemic strokes (in unconscious/aphasic subjects, consent from next of kin was obtained) adults aged >18 years with first clinical stroke within 8 days of current symptom onset or 'last seen without deficit' with neuroimaging confirmation with CT or MRI scan within 10 days of symptom onset.</li><li>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 (QVSFS).</li></ul>(b) Case-control study—For matched studies, give matching criteria and the number of controls per case<ul><li>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 its risk factors.</li><li>Case : Control matching was 1:1</li></ul> |

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| Variables | 7 | We collected basic demographic and lifestyle data including ethnicity of the subjects and their parents, socioeconomic status, cardiovascular risk profile and dietary patterns. We used validated instruments to assess physical activity, stress, depression, cigarette smoking, and alcohol use. Using a uniform SOP across all study sites, we collected blood samples for HbA1c and early morning samples after overnight fast in cases (post-acute phase when fasting is feasible) and controls for fasting blood glucose, and fasting lipid profile [total cholesterol (TC), Low Density Lipoprotein-cholesterol (LDL-C), High Density Lipoprotein-cholesterol (HDL-C) and triglyceride (TG)]. |
| Data sources/ measurement | 8* | **Definition of risk factors** |

- Hypertension: Blood pressure (average of three measurements used) was recorded at baseline and daily for 7 days or until death. A cutoff of ≥140/ 90 mmHg for up to 72 hours after stroke, a history of hypertension, or use of antihypertensive drugs before stroke or >72 hours 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. Definition of hypertension in controls was self-reported history of hypertension or use of antihypertensive drugs or average BP at first clinical encounter ≥140/90mmHg.

- Diabetes mellitus was defined based on history of diabetes mellitus, use of medications for DM, an HBA1c >6.5% or a fasting blood glucose (FBG) levels > 7.0mmol/l at 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.

- Dyslipidemia was defined as fasting TC ≥5.2mmol/L, HDL-C ≤1.03mmol/l, TG ≥ 1.7mmol/l or LDL-C ≥ 3.4mmol/l according to NCEP guidelines or use of statin prior to stroke onset. Based on 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) 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, valvular heart diseases.

- Obesity: We assessed both waist-to-hip ratio (WHR) and body-mass index. Subjects were classified individually either using the WHO guidelines using cutoffs of 0.90 (men) and 0.85 (women) for WHR or 30kg/m$^2$ for BMI (Obesity).

- 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 4hours or more per week.

- 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 while 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 unit of alcohol = 8g of alcohol).

- Smoking status was defined as current smoker (individuals who smoked any tobacco in the past 12 months) or never/former smoker.

- For psychosocial risk factors, we adapted measures of psychosocial stress and depression in the INTERSTROKE study. Psychosocial stress combined measures of stress at home/work (e.g., 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.

  - Family history of cardiovascular risk/diseases was defined based on self-reported history of any of hypertension, diabetes, dyslipidemia, stroke, cardiac disease or obesity in participants' father, mother, sibling or second degree relative.

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|---|---|---|
| Bias | 9 | Selection and Referral biases were approached by: |

Selection and Referral biases were approached by:
- maintaining a Log/Registry of all patients admitted to a hospital with acute stroke by screening all stroke admissions 3 times a week,

- use of surrogate respondents (defined above) for patients unable to communicate because of severe stroke or aphasia.

- Broadening patient recruitment to include patients admitted to hospital, seen in emergency room and ambulatory clinics.

- Community engagement outreaches were conducted across sites periodically to sensitize members of the community and encourage stroke patients to present in SIREN hospitals.

Diagnostic investigation bias was approached by developing a diagnostic algorithm and conducted regular training workshops to ensure similar level of investigations across sites. All our study sites were tertiary centers. Each site has a team comprising of neurologists, cardiologists, neuro-sonologists, neuroradiologists, and laboratory scientists.

Recall bias result when the presence or absence of a medical condition may influence patients' or caregiver's ability to recall events. Where possible, objective evidence of risk factors by physical or laboratory measurements were performed.

Interviewer Bias may result from knowledge of case or control status. This may influence the manner that questions are asked or indirectly influence interviewee response. To overcome this potential bias, interviewers were trained to obtain information in a standardized fashion.

| | | |
|---|---|---|
| Study size | 10 | Prevalence of stroke in Africa is up to 315 per 100,000 population. Given the current prevalence and incidence rate of stroke in Africa, a sample size of 2000 cases and 2000 controls will provide sufficient sample size for the intended study to get a power of 80% for detecting an effect size of odds ratio at least 1.4, allowing for several types of exposures (categorical, count or continuous). |
| Quantitative | 11 | Quantitative variables were averaged and compared between cases and controls |

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| variables | | where appropriate. |
| Statistical methods | 12 | Bivariate associations between risk factors and ischemic stroke (including pathophysiologic subtypes) were assessed using McNemar and chi-square test for paired categorical outcomes. Furthermore, we determined the adjusted associations between the risk factors and ischemic stroke and stratified by its subtypes using conditional logistic regression with adjustment for potential confounders that were not used in the matching (except baseline age which was included as a residual confounder due to the non-exact age matching). Covariates were included in the adjusted models based on careful literature review, our clinical understanding of ischemic stroke risk, and empirical evidence (significant associations observed in bivariate analyses). The final adjusted models were assessed for collinearity using variance inflation factor (VIF) and goodness of fit using residual analysis. Odds ratio (OR) and 95% confidence intervals in the final models were estimated. The adjusted Population Attributable Risks (PARs) of ischemic stroke (and subtypes) with their respective 95%CI for each exposure variable included in the best-fitted adjusted models were estimated using the AF R-package[17] with the variance estimated via the delta method. Composite PARs for the risk factors for ischemic stroke and its etiologic subtypes were calculated using the ATTRIBRISK R package with its 95% CI computed via the bootstrap method.[20] All statistical tests of hypotheses were two-sided at 5% significance level. Statistical analyses and graphics were produced with SAS 9.4 and R statistical program (version 3.4.2) |
| Participants | 13* | (a) 4,050 stroke cases were approached, 3,270 were enrolled, 2,431 had Ischemic stroke |
| | | (b) 3,000 controls were approached, 2,944 were enrolled, 2,431 matched with Ischemic stroke cases |
| | | (c) 1,056 cases were excluded due to stroke mimics, lack of cranial CT scan, unwillingness to participate in the study. |
| | | (d) 56 controls were excluded because previous history of stroke. |
| Descriptive data | 14* | (a) Of the 3,285 stroke cases in the SIREN cohort, 2431 (74.0%) had Ischemic stroke. The mean ages of stroke cases was 62.2 ± 14.0 versus 60.9 ± 13.7 years among controls. |
| Outcome data | 15* | There were 1,024(42.1%) small vessel occlusions, 427(17.6%) large-artery atherosclerosis, 258(10.6%) cardio-embolic, 3(0.1%) carotid dissections and 719(29.6%) undetermined/other causes. |
| Main results | 16 | The aOR (95%CI) for the 8 dominant risk factors for ischemic stroke were hypertension 10.34(6.91,15.45), dyslipidemia 5.16(3.78,7.03), diabetes mellitus 3.44(2.60,4.56), low green vegetable consumption 1.89(1.45,2.46), red meat consumption 1.89(1.45,2.46), cardiac disease 1.88(1.22,2.90), monthly income $100+1.72(1.24,2.39) and psychosocial stress 1.62(1.18,2.21). Hypertension, dyslipidemia, diabetes were confluent factors shared by small-vessel, large-vessel and cardio-embolic subtypes. Each stroke case and stroke-free control pair had an average of 5.3 ± 1.5 and 3.2 ± 1.0 adverse cardio-metabolic risk factors respectively (p<0.0001). |
| | | Each stroke case and stroke-free control pair had an average of 5.3 ± 1.5 and 3.2 ± 1.0 adverse cardio-metabolic risk factors respectively (p<0.0001). |
| Other analyses | 17 | N/A |
| Discussion | | |
| Key results | 18 | The higher preponderance of SVO and lower frequency of cardio-embolic stroke in our study is in accord with data from other developing countries such as Pakistan[22] and China[23] but contrasts with data from high-income countries such as Germany[13] and the United Kingdom (UK) [24]. Data from this study and those of |

# SUPPLEMENTARY MATERIAL

others support a growing notion that the relative frequency distribution of ischemic stroke subtypes follows geographic or ecological trends with racial or genetic underpinnings. In support of the latter, SVOs was twice more common among Africans in UK[24] and US [25] ischemic stroke cohorts than Caucasians who had a greater propensity towards cardio-embolic and large-artery atherosclerotic diseases. Indeed, in a unique tri-population study, SVO was more prevalent in indigenous Africans (47%), followed by African Americans (35%) and then European Americans (21%).[26] The genetic architecture of the different ischemic stroke subtypes is now the pursuit of several research groups and consortia.[5-7]

| Limitations | 19 | Case-control studies such as ours are limited in establishing causality but rather seek to demonstrate associations and quantify effect sizes of risk factors. <ul><li>Our estimates of DM should be cautiously interpreted given that only fasting blood glucose was used to diagnose DM in control subjects, while HbA1c, and/or FBS were combined in stroke cases.</li><li>The burden of cardiac diseases may have been underestimated due to limited ECG and echocardiographic evaluations for subjects.</li><li>A significant number of our stroke subjects had severe strokes at the time of recruitment, necessitating a proxy evaluation of lifestyle and behavioral history. However, 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 subjects with direct evaluation.</li><li>Due to the high proportion of critically ill stroke patients, not all of them could undergo exhaustive investigations to determine the etiology of ischemic and hemorrhagic strokes before their demise.</li></ul> |
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| Interpretation | 20 | Small vessel occlusion is the dominant ischemic stroke subtype among West Africans. Traditional vascular risk factors demonstrate important differential effect sizes with pathophysiologic, clinical and preventative implications on the occurrence of ischemic stroke among indigenous West African populations. Strategic and sustained efforts targeting multiple cardio-metabolic factors at both individual and population levels may yield the greatest dividends for primary and secondary prevention of stroke among indigenous Africans. |
| Generalisability | 21 | Implementation of interventions targeting these leading risk factors at the population level should substantially curtail the burden of stroke among West Africans. |
| Funding | 22 | NIH Grant U54 HG007479 under the H3Africa initiative and R01NS107900. The study funders had no role in study design, data collection, analysis, interpretation, or writing of the report. |

\*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

| Suspected Stroke cases approached, n =7,000 | | Controls approached, n =3,000 |
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| Excluded because of no head CT scan, n =2,950 | | Excluded because of incomplete data or stroke symptoms, n= 592 |
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| Stroke cases with CT scan, n =4,050 | | Eligible controls of analysis n = 2,944 |
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| Excluded because stroke symptoms lasted >10 days before head CT scan was taken, n = 765 | | Excluded because of pairing with hemorrhagic stroke cases or inexact age/sex matching, n=513 |
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| Stroke cases with CT scan within 10 days of onset, n =3,285 | |
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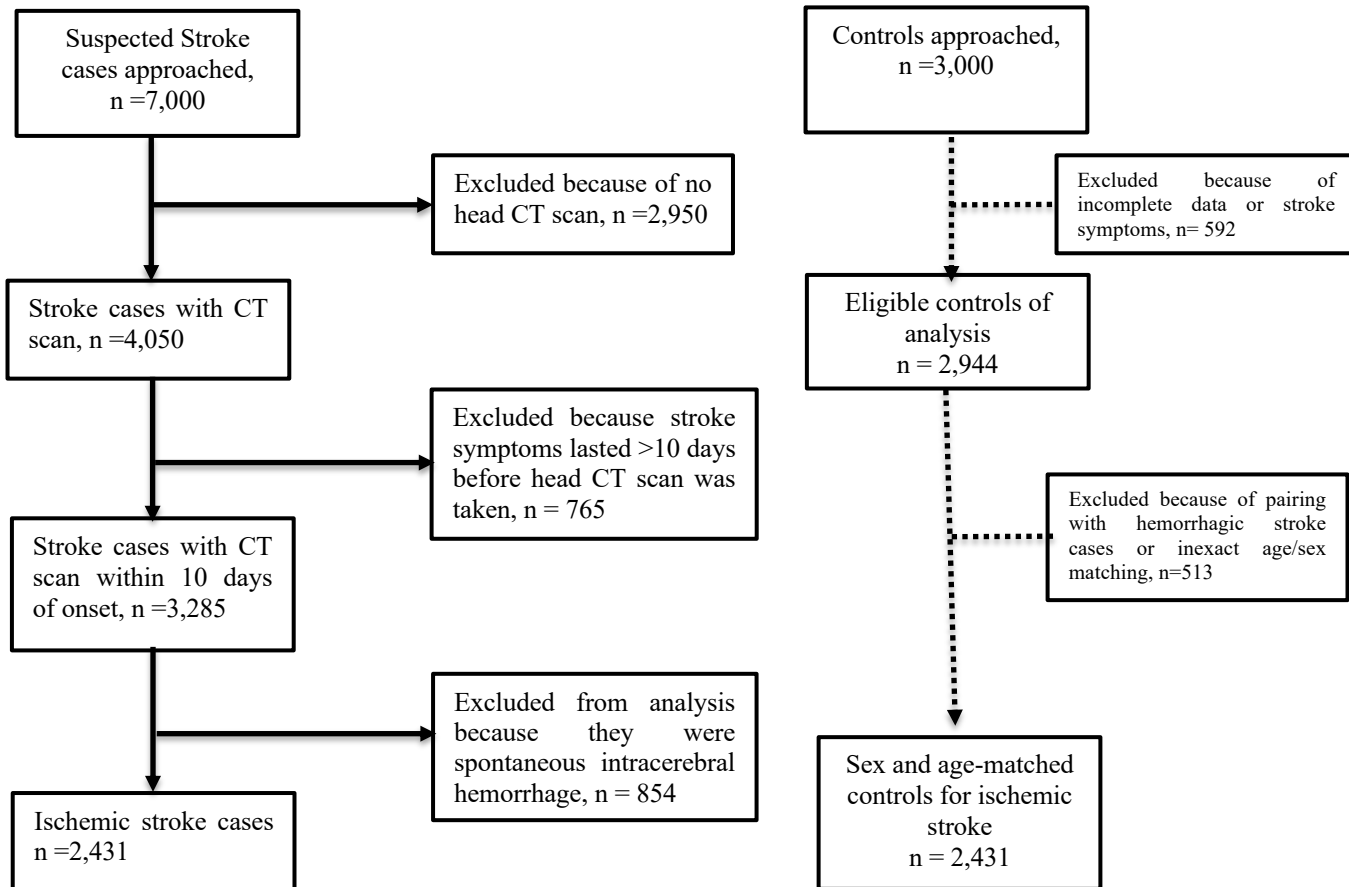| Excluded from analysis because they were spontaneous intracerebral hemorrhage, n = 854 | | Sex and age-matched controls for ischemic stroke n = 2,431 |
|---|---|---|

| Ischemic stroke cases n =2,431 | |
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Figure II. Flow chart of stroke cases and controls included in the analysis