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Original Research

HIV sero-positivity and risk factors for ischaemic and haemorrhagic stroke in hospitalised patients in Uganda: A prospective-case-control study

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ABSTRACT

Objectives: We examined HIV sero-positivity and risk factors in patients admitted with ischaemic stroke (IS) and haemorrhagic stroke (HS) in Kampala, Uganda.
Study design: We conducted a matched case-control study between December 2016 and December 2018 at St Francis Hospital, Nsambya.
Methods: The study population comprised of stroke cases (adults aged ≥18 years with IS or HS confirmed by neuroimaging) and controls (age- and sex-matched stroke-free adults aged ≥18 years who were recruited from the same hospital as the cases). A comprehensive assessment for sociodemographic, lifestyle and clinical factors was performed using the World Health Organization (WHO) STEP-wise approach to Surveillance (STEPS) for stroke risk factor surveillance. We used conditional logistic regression to identify risk factors associated with IS or HS.
Results: We enrolled 137 matched case-control pairs; 48 (35%) were men, and the mean ages were 62.4 years (SD ± 14.8) for cases and 61.1 years (SD ± 14.1) for controls. Of stroke patients, 86 (63%) had IS and 51 (37%) had HS. Overall, HIV sero-positivity was 10% among stroke cases versus 7% among controls. HIV sero-positivity was not significantly associated with stroke (unadjusted odds ratio [uOR] = 1.49, 95% confidence interval [CI] 0.59–3.78). A self-reported family history of diabetes mellitus was associated with an increased risk of all stroke (adjusted odds ratio [aOR] = 4.41, 95% CI 1.47–13.2), as well as for IS and HS separately (aOR = 3.66, 95% CI 1.09–12.4 and aOR = 4.99, 95% CI 1.02–24.4, respectively). High blood pressure (≥140/90 mmHg) was associated with an increased risk of all stroke (aOR = 12.3, 95% CI 42–44.1), and this was also true for IS and HS individually (aOR = 6.48, 95% CI 1.15–36.7 and aOR = 5.63, 95% CI 1.74–18.2, respectively).
Conclusions: No association was found between HIV sero-positivity and stroke occurrence among Ugandan stroke patients. Hypertension and a self-reported family history of diabetes mellitus were significant risk factors for both IS and HS. Interventions to reduce hypertension and diabetes mellitus in the Ugandan population are urgently required. Much larger studies are required to demonstrate if any association exists between HIV and stroke.

1. Introduction

Stroke remains one of the leading causes of morbidity and mortality worldwide [1]. Over 80% of stroke deaths occur in low- and middle-income countries (LMICs), including in sub-Saharan Africa (SSA) [2]. In Uganda, stroke accounts for 3.7% of all hospital admissions and is one of the top five causes of death in adults [1]. However, the relative contribution of haemorrhagic stroke (HS) and ischaemic stroke (IS) to the overall burden appears to vary considerably between populations, countries and regions [3]. The INTERSTROKE study, conducted in 22 countries, found that HS was highest in African countries at 34%, compared with high-income countries, where HS was 9% [3]. However, other studies conducted in SSA countries, such as Uganda and Zambia, have reported higher IS proportions of 69.3% and 65%, respectively,

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than HS [4,5].

HIV is a major public health concern worldwide [6]. SSA countries have the highest incidence, with nearly 70% of the global burden of HIV/AIDS [7]. In Uganda, HIV prevalence increased from 6.4% in 2004/05 to 7.3% in 2011, then decreased to 6.2% in 2016 [8–10]. HIV infection is an emerging vascular risk factor for stroke occurrence and it is now well recognised that it could potentially increase an individual's risk for stroke [11,12]. Between 1% and 5% of patients with HIV develop stroke, although a higher proportion (4–34%) have cerebral ischaemic lesions [13]. Potential causes of stroke in individuals with HIV include opportunistic infections, tumours, coagulopathies and direct HIV infection of the arterial wall [14].

Several epidemiological studies have identified risk factors for stroke in SSA [12,15]. More recently, HIV has been noted as a novel risk factor for stroke, with an increased risk of 5.61 (95% confidence interval [CI] 2.41–13.09; $p < 0{\cdot}0001$) compared with the general population [12]. Other previous studies in Malawi and South Africa have also suggested that HIV positivity is a significant independent risk factor for stroke [11,16]. However, some authors have suggested that the occurrence of stroke and HIV infection might often be coincidental [14].

The INTERSTROKE study demonstrated the frequency of the main risk factors for stroke worldwide, including SSA [3]. These are classified into non-modifiable factors, including older age, male gender and family history, and modifiable risk factors, including hypertension, diabetes mellitus (DM), obesity, dyslipidaemias, physical inactivity, low vegetable and fruit diet, heavy alcohol consumption and cigarette smoking [3,15]. The most common modifiable risk factor for stroke in SSA, including Uganda, remains hypertension [15]. Unfortunately, in SSA more than 70% of people are unaware of their hypertensive condition, and less than 3% have adequately controlled blood pressure (BP) [17]. In a community survey conducted in Uganda, the prevalence of uncontrolled hypertension was 20.2% [17]. In another rural Ugandan study, untreated hypertension, adjusted for age, ranged from 24.9% to 33% [18].

Previous research has shown that stroke subtypes have varying aetiologies, varying prognoses, and require different treatment and prevention strategies [19,20]. For example, in Zambia, HIV infection was independently associated with IS [4]. In the INTERSTROKE study, DM was not associated with stroke among Africans overall, but it was associated with both stroke types (with a higher effect size in IS than HS) in Nigeria and Ghana [3,15]. A systematic review found that hypertension was a key risk factor for stroke, but there were no statistically significant differences by stroke type [21]. Establishing the distinctive risk factors for each type of stroke has important implications for its management as well as primary and secondary prevention [22].

However, there remain insufficient data in SSA to reliably estimate the effect of various factors on the risk for IS and HS separately. In a recent systematic review [21], only five case-control studies were identified from SSA that reported information on risk factors for all stroke, and only one study reported data on IS and HS risk factors separately. Identification of locally preventable risk factors associated with different types of strokes remains an urgent issue and will help inform the Ugandan non-communicable disease (NCD) control programme to prioritise prevention/control strategies. In this hospital-based case-control study, we examine HIV sero-positivity and risk factors in patients admitted with IS and HS in Kampala, Uganda.

2. Methods

2.1. Study design and setting

We conducted a matched case-control study between December 2016 and December 2018 at Nsambya hospital, which is a large urban, private-not-for-profit hospital in Kampala, the capital city of Uganda. The hospital is situated approximately 5 km (3.1 miles) southeast of the central business district of Kampala. It is a tertiary referral hospital, receiving patients from all parts of the country. Most of the patients pay personal private fees for treatment, while others have insurance cover. Nsambya Hospital has an average of 19,000 admissions per year and treats an average of 300 out-patients per day.

2.2. Participants

A 'case' was defined as a patient who presented at Nsambya hospital within 7 days of the onset of symptoms during the study period. For inclusion, the patient had to meet the World Health Organization (WHO) stroke definition of rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting for more than 24 h or until death, with no apparent non-vascular cause [23] and with neuroimaging to confirm the stroke results.

A 'control' was defined as a patient attending the study hospital (where cases were recruited), who was in the same age range age (±5 years) as the stroke patient, but without any history or current clinical diagnosis of stroke.

The eligibility criteria for participation in the study as a case patient included [1]: being an adult aged ≥18 years old [2]; presenting within 7 days of the onset of symptoms; and [3] meeting the WHO stroke definition [23]. We excluded participants who were [1]: unable to consent or for whom consent could not be obtained from a caregiver [2]; unable to communicate and without a caregiver respondent; and [3] those who died within 24 h on the ward before neuroimaging was performed.

2.3. Selection and recruitment of cases

All consenting and confirmed cases of IS and HS by neuroimaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) were selected and recruited prospectively into the study. All cases were recruited consecutively until the required sample size was achieved. We used the standard WHO definition of stroke [23] and included both first-ever and recurrent stroke patients. To maximise recruitment and reduce selection bias, extensive awareness campaigns about the study were conducted within the hospital departments by the study team. Any possible cases of incident stroke patients in the outpatient department or emergency or medical wards were notified to the study team as soon as possible for assessment. Individuals with a clinical diagnosis of stroke were further evaluated by the study physicians and investigations performed. This prompt notification was particularly important to ensure that patients who were recovering from stroke were not missed for enrolment.

2.4. Selection and recruitment of controls

We recruited hospital-based controls, focusing on patients with conditions that were not related to stroke, other cardiovascular diseases or cancer (which may share some risk factors, such as smoking or HIV infection). Controls were approached at random (i.e. whoever seemed to be within the age/sex group of the cases), and one control patient was selected per case patient. If a control patient could not consent, another person was approached until sufficient controls were recruited. All participants were given an identification number to ensure that study procedures were performed anonymously. Control patients were recruited during the same study period as the case patients. Controls were matched by age (±5 years) and sex to minimise the potential confounding effect.

2.5. Study procedures

A modified questionnaire for the WHO STEP-wise approach to chronic disease risk factor surveillance (STEPS) and WHO STEP- wise approach to stroke surveillance [24] were used for data collection. The variables included non-modifiable risk factors (i.e. age, sex, socioeconomic status, and family history of stroke, hypertension and diabetes), modifiable risk factors (i.e. hypertension, DM, physical activity level, diet and alcohol use, smoking status, blood pressure) and other risk factors,

such as HIV infection, which were recorded for both cases and controls.

A medical examination was performed to determine systolic and diastolic arterial BP. BP measurements were taken on the left arm with the participant in the sitting position. Three sequential readings were taken, 3–5 min apart, and an average value was taken. A mean BP of ≥140/90 mm Hg was classified as hypertension. For case patients, the distinction between stroke subtypes (i.e. IS and HS) was based on CT scan or MRI findings. Neuroimaging was performed within 48 h of hospital admission. The images were reported by a radiologist and subsequently reviewed by a physician.

HIV diagnosis was determined by two rapid tests in parallel (Unigold and Determine; Bioline, was used as a tiebreaker in situations of discrepant results, as per national guidelines [25]). Data on the confirmed HIV test result was recorded in the patient's file; if this was not available, the research team attempted to locate the information from laboratory records.

The bodyweight of many cases patients could not be determined with the equipment available due to their post-stroke disability and being bed ridden; thus, body mass index (BMI) was assessed using self-reported standardised pictorial images of women and men with known BMI values [26].

The modified-Rankin scale (mRS) [27] was used to measure the pre-stroke functional ability.

2.6. Definition of study measures

Participants were classified as hypertensive if their BP (mean of three measurements) was ≥140/90 mmHg or if there was a self-reported history of hypertension or history of receiving anti-hypertensive medications. DM was defined as a history of diabetes, use of drugs to control diabetes or a fasting blood glucose concentration >7.0 mmol/L, measured at first encounter. Smoking status was defined as never, former or current smoker. We defined current smokers as individuals who smoked any tobacco in the previous month and included those who had stopped within the preceding month. Former smokers were defined as those who had stopped >1 month earlier. Dietary history included regular intake of food items such as fruits and vegetables. Regular intake was defined as consuming five or more servings weekly. Alcohol use was assessed using a standardised WHO Alcohol Use Disorders Identification Test (AUDIT) [28]. Alcohol use was classified into three categories (i.e. harmless or low-risk drinkers: score 1–7; harmful or high-risk drinkers: score 8–19; and alcohol-dependent: score ≥20). A family history of stroke, hypertension and DM was defined as an immediate family member (parent, sibling or child) having a similar disease. Obesity was defined as a BMI of ≥30 kg/m^2. Pre-stroke functional status was assessed using the mRS: (i) mRS 0–2 was considered good; (ii) mRS 3 was fair; and (iii) mRS 4–5 indicated a poor outcome.

2.7. Sample size estimation

A sample size of 282 participants was required to assess the risk factors for both HS and IS stroke subtypes. Approximately 96 cases (and 96 controls) were needed for HS and 32 cases (and 32 controls) for IS. The sample was adjusted for a 10% rate of non-response. Sample estimates were based on the INTERSTROKE study [3], which assumes a proportion of hypertension in the controls with no history of stroke of 37% and a lower limit odds ratio (OR) for hypertension of 6.8 comparing cases of HS and 2.7 comparing cases of IS to controls. Correlation coefficients for exposure between matched cases and controls were estimated as 0.29 for HS and 0.36 for IS from the INTERSTROKE study. An 80% power and a two-sided level of significance of 0.05 was assumed.

2.8. Data analysis and quality assessment

Data were double entered in OpenClinica, cleaned and exported to STATA 15.0 (StataCorp, College Station, TX, USA) for analysis. We resolved discrepancies by checking the source documents for clarification for all possible confounders. Sociodemographic and clinical characteristics of the study participants were compared between cases and controls using the McNemar test for paired categorical outcomes. Using conditional logistic regression models, a crude analysis was conducted to determine the predictors of stroke by comparing cases to controls for each of the potential risk factors. Factors for which the association attained statistical significance on log-likelihood ratio test (LRT) [$p < 0.20$] were selected for the multivariable analysis. All the covariates that showed a strong relationship with outcome were also considered for multivariable analysis. We estimated the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) in the final models using conditional logistic regression modelling. We used the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) case-control reporting guidelines for methodological quality assessment [29].

2.9. Availability of data

The data collected in this study is suitable for sharing and procedures for accessing it are contained in the data sharing policy accessible from the Medical Research Council (MRC) website (https://www.mrcuganda.org/publications/data-sharing-policy).

3. Results

3.1. Recruitment profile

During the study period, 151 patients were screened; of these, 10 (7%) were excluded from analysis due to ineligibility (including, those who died within 24 h on the ward before CT scan was performed [n = 4]; those who had transient ischemic attacks [n = 4]; and those who presented 7 days after onset of symptoms [n=2]). In terms of control patients, 148 were screened and, of these, 7 (5%) were excluded (because they could not consent and their caregiver was not available at time of interview [n = 3] or because of a previous history of stroke [n = 4]). Thus, in total, 137 matched case-control pairs were enrolled and 4 unmatched pairs. The unmatched pairs (n = 4) were excluded from the final analysis (see Fig. 1).

3.2. Participant demographic and clinical characteristics

We analysed 137 matched case-control pairs; 48 (35%) were male stroke patients, with mean ages of 62.4 years (SD ± 14.8) for cases and 61.1 years (SD ± 14.1) for controls. Of the case patients, 86 (63%) had IS and 51 (37%) had HS. The mean age of HS patients (61.5 ± 14.3 years) was significantly younger than IS patients (62.8 ± 15.0 years) [see Fig. 2]. More than half (n = 77; 51%) of all stroke cases were aged ≥60 years. The median time between the onset of symptoms and medical attention for IS patients was 2 days (interquartile range [IQR]: 1–4 days) compared with 1 day for HS patients (IQR: 1–5 days); this was not statistically significant (p = 0.936). Compared with controls, case patients had a significantly higher proportion of family members with DM (57.9% vs 42.1%) and recorded higher BPs (≥140/90 mmHg; 70.2% vs 29.8%). Other participant characteristics did not differ between control and case patients. Regarding the functional status, the pre-stroke mRS for all stroke patients before enrolment were 129 (94.1%) for mRS 0–2, 5 (3.7%) for mRS 3 and 3 (2.2%) for mRS 4–5 (see Table 1).

3.3. HIV sero-positivity

The overall proportion of HIV sero-positivity was 13 of 128 (10%) for stroke cases versus 9 of 128 (7.0%) for stroke-free controls (p = 0.702). The mean age of HIV sero-positive patients with stroke was 55 years (SD ± 12.9) versus years 57 years (SD ± 13.0) for control patients (p = 0.722). However, with regard to antiretroviral therapy (ART) initiation, there were no significant differences between HIV sero-positive stroke

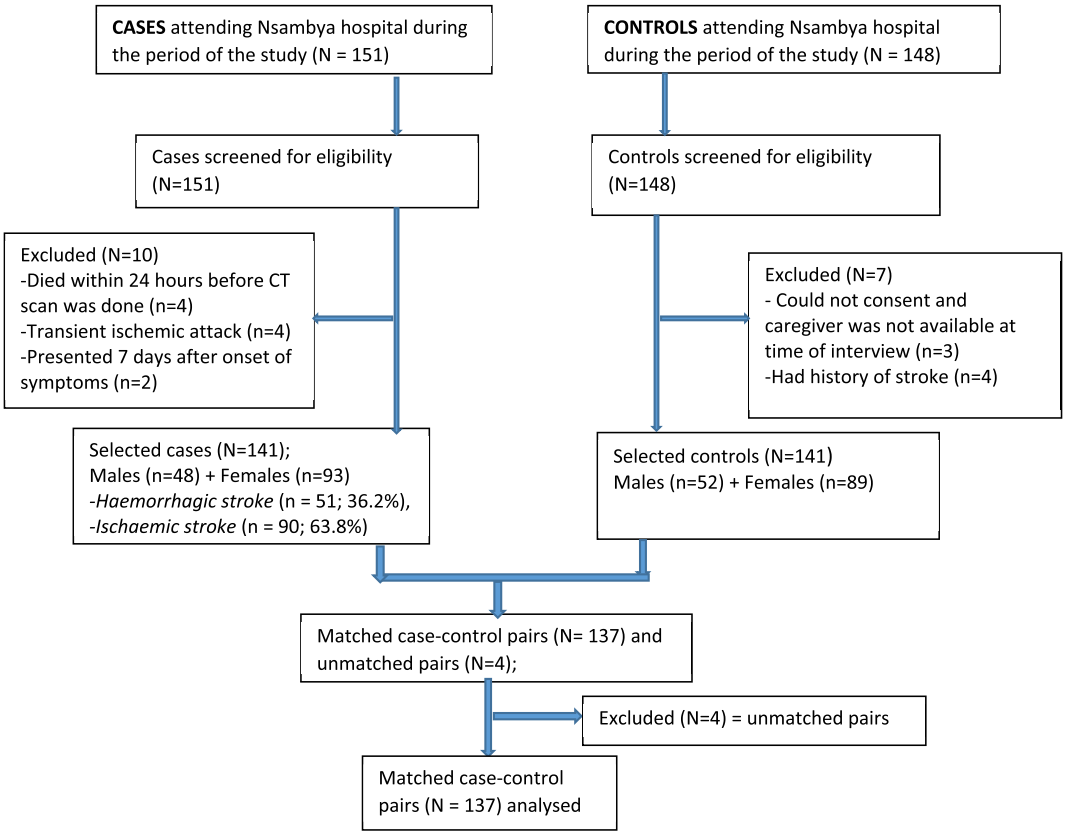

Fig. 1. Recruitment profile for stroke cases and controls at Nsambya hospital in Kampala, Uganda (2016–2018).

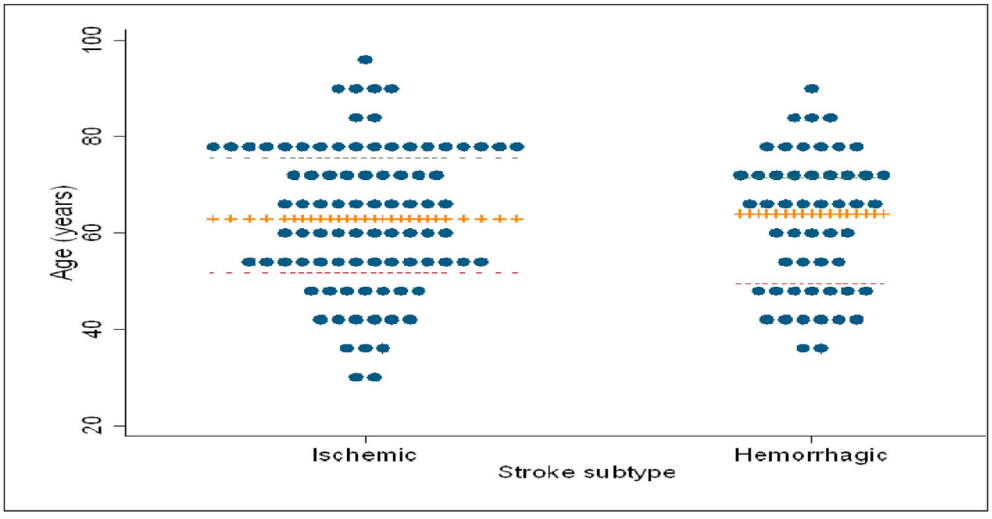

Fig. 2. Dot plot showing age for ischaemic and haemorrhagic stroke patients in Kampala, Uganda (2016–2018).

cases and stroke-free controls. The proportion of HIV sero-positivity among HS patients was 5 of 47 (10.6%) compared with 8 of 84 (9.5%) among IS patients, which was also not statistically different (p = 0.801) (Table 1).

3.4. Risk factor association with all stroke and stroke type

Table 2 shows the results of univariate and multivariate analyses. In the univariate analysis, a family history of DM (uOR = 2.50, 95% CI 1.45–4.32) and a BP ≥ 140/90 (uOR = 4.82, 95% CI 2.52–9.22) were associated with all stroke. HIV sero-positivity and excessive alcohol use were not significantly associated with stroke (uOR = 1.49, 95% CI 0.59–3.78 and uOR = 1.07, 95% CI 0.64–1.77, respectively) (see Table 2).

In the adjusted (multivariable) analysis, a self-reported family history of DM was associated with an increased risk of all stroke (aOR = 4.41, 95% CI 1.47–13.2), as well as for IS and HS separately (aOR = 3.66, 95% CI 1.09–12.4 and aOR = 4.99, 95% CI 1.02–24.4, respectively). High BP (≥140/90 mmHg) was associated with an increased risk for all stroke (aOR = 12.3, 95% CI 3.42–44.1.0), and this was also true for IS and HS individually (aOR = 6.48, 95% CI 1.15–36.7 and aOR = 5.63, 95% CI 1.74–18.2, respectively) (Table 2).

Table 1
Participant characteristics by case-control status and stroke type in Kampala, Uganda (2016–2018).

Variable	Case-control status			Ishaemic stroke		Heamorrhagic stroke	
	Case (n=137) [n (%)]	Control (n=137) [n (%)]	p-value[a]	Case (n=86) [n (%)]	Control (n=86) [n (%)]	Case (n=51) [n (%)]	Control (n=51) [n (%)]
Age (years) [mean (±SD)]	62.4 (14.8)	61.1 (14.1)	0.494	62.8 (15.0)	61.4 (15.2)	61.5 (14.3)	60.6 (14.3)
Age (years) (n=274)			0.808				
- < 60	60 (49)	62 (51)		36 (47)	40 (53)	24 (52)	22 (48)
- ≥ 60	77 (51)	75 (49)		50 (52)	46 (48)	27 (48)	29 (52)
Gender, male **(n=274)**	48 (50)	48 (50)	–	31 (50)	31 (50)	17 (50)	17 (50)
Education level (n=274)			0.275				
-No education	18 (60)	12 (40)		12 (71)	5 [29]	6 (46)	7 (54)
-Primary	56 (53)	50 (47)		34 (52)	32 (48)	22 (55)	18 [45]
-Secondary & above	63 (46)	75 (54)		40 [45]	49 (55)	23 (47)	26 (53)
Self-reported history of HTN (n=260)			0.106				
- Yes	76 (55)	63 (45)		48 (57.8)	35 (42.2)	28 (50)	28 (50)
- No	54 [45]	67 (55)		33 (41.8)	46 (58.2)	21 (50)	21 (50)
Self-reported history of DM (n=268)			0.757				
- Yes	25 (48)	27 (52)		19 (59.4)	13 (40.6)	6 [30]	14 (70)
- No	109 (50)	107 (50)		65 (47.8)	71 (52.2)	44 (55)	36 [45]
Family history of stroke (n=264)							
- Yes	39 (44.8)	48 (55.2)	0.402	28 (48.2)	30 (51.7)	11 (37.9)	18 (62.1)
- No	80 (51.6)	75 (48.4)		47 (49)	49 (51)	33 (55.9)	26 (44.1)
- Don't know	13 (59.1)	9 (40.9)		9 (64.3)	5 (35.7)	4 (50)	4 (50)
Family history of DM (n=266)			<0.001				
- Yes	99 (57.9)	72 (42.1)		64 (58.7)	45 (41.3)	35 (56.5)	27 (43.5)
- No	34 (35.8)	61 (64.2)		21 (34.4)	40 (65.6)	13 (38.2)	21 (61.7)
Family history of HTN (n=268)			0.440				
- Yes	89 (47.6)	98 (52.4)		54 (45.4)	65 (54.6)	35 (51.5)	33 (48.5)
- No	33 (54.1)	28 (45.9)		23 (60.5)	15 (39.5)	10 (43.5)	13 (56.5)
- Don't know	12 (60)	8 (40)		8 (61.5)	5 (38.5)	4 (57.1)	3 (42.8)
Current smoking (n=268)							
- Yes	27 (61.4)	17 (38.6)	0.099	17 (68.0)	8 (32.0)	10 (52.6)	9 (47.4)
- No	107 (47.8)	117 (52.2)		68 (46.9)	77 (53.1)	39 (49.4)	40 (50.6)
Alcohol use (n=274)			0.782				
-Low risk drinkers	101 (49.5)	103 (50.4)		69 (51.1)	66 (48.9)	32 (46.4)	37 (53.6)
-Harmful/high risk	36 (51.4)	34 (48.6)		17 (45.9)	20 (54.1)	19 (57.6)	14 (42.4)
Blood pressure ≥ 140/90 (n=260)			<0.001				
- Yes	73 (70.2)	31 (29.8)		41 (69.5)	18 (30.5)	32 (71.1)	13 (28.8)
- No	57 (36.5)	99 (63.5)		39 (38.6)	62 (61.4)	18 (32.7)	37 (67.3)
Taking anti-HTN drugs (n = 272)			0.145				
- Yes	71 (54.6)	59 (45.4)		46 (58.2)	33 (41.7)	25 (49.0)	26 (51)
- No	65 (45.8)	77 (54.2)		39 (42.9)	52 (57.1)	26 (51)	25 (49)
Taking anti-DM drugs (n=254)			0.200				
- Yes	20 (41.8)	28 (58.3)		17 (56.7)	13 (43.3)	3 [7]	15 (83)
- No	107 (51.9)	99 (48.1)		64 (48.5)	71 (51.5)	43 (58.1)	31 (41.9)
Taking aspirin (n=266)			0.161				
- Yes	23 (60.5)	15 (39.5)		13 (54.2)	11 (45.8)	12 (14.2)	2 [4]
- No	110 (48.2)	118 (51.8)		69 (49.3)	71 (50.7)	49 (55.7)	39 (44.3)
Regular fruit diet (n=246)			0.089				
- 0–4 days	8 (50.9)	78 (49.1)		52 (51.5)	49 (48.5)	29 (50)	29 (50)
- 5–7 days	27 (41.5)	38 (58.5)		16 (42.1)	22 (57.9)	11 (40.7)	16 (59.3)
- Don't know	15 (68.2)	7 (31.8)		8 (61.5)	5 (38.5)	7 (77.8)	2 (22.2)
Regular vegetable diet (n=240)			0.690				
- 0-4	73 (50.3)	72 (49.7)		45 (50.0)	45 (50.0)	28 (50.9)	27 (49.1)
- 5-7	37 (47.4)	41 (52.6)		25 (51.0)	24 (49.0)	12 (41.4)	17 (58.6)
- Don't know	10 (58.8)	7 (41.2)		4 (44.4)	5 (55.6)	6 (75.0)	2 (25.0)
Obese (n=274)			0.468				
- Yes	28 (45.9)	33 (54.1)		20 (51.2)	10 (48.7)	8 (36.4)	14 (63.6)
- No	109 (51.2)	104 (48.8)		66 (49.6)	67 (50.3)	43 (53.8)	37 (46.2)
HIV status (n=256)			0.702				
- Positive	13 (59.1)	9 (40.9)		8 (61.5)	5 (38.4)	5 (55.6)	4 (44.4)
- Negative	68 (49.3)	70 (50.7)		44 (48.4)	7 (51.6)	24 (51.1)	23 (48.9)
- Don't know	47 (49.0)	49 (51.0)		29 (50.0)	29 (50.0)	18 (47.4)	20 (52.6)
On ART treatment (n = 222)			0.722				
- Yes	6 (50)	6 (50)		4 (50.0)	4 (50.0)	2 (50)	2 (50)
- No	105 (50)	105 (50)		66 (50.0)	66 (50.0)	39 (50)	39 (50)
Pre-stroke functional status (n=137)[b]							
-mRS 0–2	129 (94.1)			63 (90)		48 (100)	
-mRS 3	5 (3.7)			4 [6]		0 (0)	
–mRS 4–5	3 (2.2)			3 [4]		0 (0)	
Median time between onset of symptoms and medical attention [days (IQR)] (n=137)[t]	2 [1–4]			2 [1–4]		1 [1–5]	

ART; antiretroviral therapy; DM, diabetes mellitus; HTN, hypertension.
[a] P-values are Chi-square for categorical and T-test for continuous variables.
[b] Question applied only to case patients.

Table 2
Risk factor association with all stroke and stroke type in Kampala, Uganda (2016–2018).

Variable	All stroke		Ischaemic stroke	Haemorrhagic stroke
	uOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Education level				
-No education[a]	Ref	Ref	Ref	ref
-Primary	0.73 (0.32–1.68)	0.79 (0.10–6.03)	0.19 (0.02–2.36)	2.40 (0.47–12.2)
-Secondary & above	0.53 (0.23–1.23)	0.62 (0.08–4.67)	0.15 (0.01–2.88)	1.65 (0.32–8.59)
Self -reported history of HTN				
- No[a]	Ref	Ref	Ref	Ref
- Yes	1.61 (0.96–2.71)	1.42 (0.42–4.73)	0.78 (0.11–5.78)	1.42 (0.31–6.55)
HIV sero-positivity				
Negative	Ref			
Positive	1.49 (0.59–3.78)	–	–	–
Don't know	0.99 (0.58–1.69)	–	–	–
Alcohol use				
-Low risk drinkers	Ref			
-Harmful/ high risk	1.07 (0.64–1.77)	–	–	–
Family history of DM				
- No[a]	Ref	Ref	Ref	Ref
- Yes	**2.50 (1.45–4.32)**	**4.41 (1.47–13.2)**	**4.99 (1.02–24.4)**	**3.66 (1.09–12.4)**
Family history of HTN				
- No[a]	Ref			
- Yes	0.77 (0.42–1.43)	–	–	–
- Don't know	1.23 (0.41–3.75)	–	–	–
Smoking				
- No[a]	Ref	Ref	Ref	Ref
- Yes	1.91 (0.92–3.96)	0.74 (0.18–3.11)	1.82 (0.13–26.3)	0.58 (0.14–2.42)
BP ≥ 140/90				
- No[a]	Ref	Ref	Ref	Ref
- Yes	**4.82 (2.52–9.22)**	**12.3 (3.42–44.1)**	**6.48 (1.15–36.7)**	**5.63 (1.74–18.2)**
Anti-HTN intake				
- No[a]	Ref	Ref	Ref	Ref
- Yes	1.38 (0.87–2.17)	1.37 (0.41–4.62)	2.44 (0.38–15.5)	0.99 (0.25–4.00)
Regular fruit diet				
- 0–4 days[a]	Ref	Ref		
- 5–7 days	0.69 (0.40–1.22)	0.64 (0.22–1.86)	–	
- Don't know	1.98 (0.80–4.91)	5.72 (0.90–13.6)	–	

Bold values indicate a significant association.
aOR, adjusted odds ratio; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; uOR, unadjusted odds ratio.
[a] = Reference category.

4. Discussion

4.1. Summary of the main findings

In this case-control study, risk factors have been identified, including a family history of diabetes and high BP (≥140/90 mmHg), that are associated with both HS and IS among individuals in Uganda. Overall, the patients presenting with stroke in this study had a much higher prevalence of vascular risk factors, particularly hypertension and diabetes, than the general population in Uganda. Our study provides essential information on the importance of the most common, potentially preventable, risk factors and builds on previous epidemiological studies from SSA and other parts of the world [3,15]. These findings are important in guiding the selection of interventions used to target modifiable risk factors for the prevention of cardiovascular disease, including stroke, in Uganda.

4.2. Interpretations

Similar to other findings in SSA [30], in this study, we did not find any association between HIV sero-positivity and stroke occurrence. In contrast, a study in Malawi found that HIV infection was significantly associated with stroke [11]. In fact, other reports show that, in addition to opportunistic infections, such as varicella-zoster virus, HIV infection is known to cause endothelial dysfunction, resulting in accelerated atherosclerosis and small vessel disease [14]. There is however a suggestion that HIV sero-positivity and stroke co-occurrence may be coincidental [14]. Although our study was underpowered to fully address the influence of HIV on stroke occurrence, it is important that further studies investigate this potential association. Results of future studies will better inform decision makers and shape subsequent interventions in SSA, given that HIV/AIDS continues to be a major public health problem in this region.

Consistent with previous studies [5,15], our findings show that hypertension (BP ≥ 140/90 mmHg) was the most important independent risk factor for all stroke and a highly significant predictor of both stroke subtypes. In the INTERSTROKE study [3], a history of hypertension was a significant risk factor for all stroke. However, recent studies show that the gradient of the relationship between hypertension and HS is steeper than that for IS [15]. Hypertension is a well documented risk factor for both stroke types in SSA and elsewhere, and in most cases, it is either uncontrolled or poorly controlled [3,12]. In this study, it is a concern that only a few of the hypertensive stroke cases were receiving antihypertensive treatment. This may be a result of poor public awareness, poor access to healthcare and perhaps poor healthcare practices, or low levels of adherence to treatment.

In addition to hypertension, a family history of diabetes had a strong association for both HS and IS in this study. This is consistent with earlier studies conducted in SSA and elsewhere in the developed world [31,32]. Previous epidemiological studies have documented a three-to five-fold increase of cardiovascular disease in diabetic individuals compared with non-diabetic individuals [3,21,33]. Multiple indirect or direct pathways that result in accelerated atherosclerosis have been proposed to explain the effects of elevated glucose levels on the cardiovascular system [34,35]. However, the relationship between the high prevalence of family history of diabetes and cardiovascular disease could also be due to shared genetic factors, shared environmental factors or both [31]. Given the rising burden of non-communicable disease in SSA, the findings of the present study, combined with existing evidence [31], indicate that understanding the genetic basis for the interactions between risk factors and stoke can inform targeted prevention efforts, as part of a broader approach with surveillance, prevention, acute care and rehabilitation.

Similar to previous studies from SSA, this case-control study also showed higher numbers of IS than HS [5,15]. However, other studies in Rwanda [36] and Ethiopia [37] have reported conflicting findings, observing higher HS prevalence compared with IS. The distribution of stroke types is known to differ between populations, with HS making up a greater proportion of all strokes in SSA [3]. It has been reported that higher rates of HS in SSA are related to a greater prevalence of hypertension [38]. Although our study was underpowered to fully address this, the recorded differences in prevalence rates could, in part, explain the global variations in the incidence of IS and HS [39]. Additionally, the variation in prevalence rates could also be due to the widely different age compositions of the populations studied.

Most of the patients in the current study were aged ≥60 years, and a female dominance was observed in both IS and HS. However, the current study participants were much older than those in previous studies from SSA [40], but lower than the typical age of stroke patients in the

developed world [41]. Our results show that stroke occurs at a relatively younger age in Uganda compared to developed countries [42], a finding that is consistent with earlier reports in SSA [36]. Both the age and gender distribution of our case patients differs greatly from previous studies conducted in developed and many developing countries [37,43]. Earlier reports have shown that women tend to live longer than men, who die of other comorbidities, and, as a result, women often outnumber men in stroke prevalence figures [44]. It is equally likely that the results in the current study reflect patterns of referral to hospital. In Tanzania, only a small proportion of stroke patients are admitted to hospital [12]. Perhaps, men simply don't want to go to hospital, whereas women do? This highlights the biases associated with hospital-based studies in SSA.

4.3. Study limitations

First, as stroke patient recruitment was from a private hospital and based on neuroimaging, our data may have a selection bias; milder strokes cases and patients who died in the community would be excluded. A study in East Africa used a similar approach to capture these cases and they described similar risk factor profiles to those found in the current study (12). Thus, the selection bias may lead to an overestimation or and underestimation of some effects.

Second, although controls from the community would have been ideal, hospital-based control patients were easier to recruit and generally belonged to the same population as hospital-based case patients. Relatedly, the value of hospital-based controls is that the cases and controls have the same likelihood of getting to hospital – in this regard, they are matched. Furthermore, all cases were defined prospectively with accepted criteria and all controls were carefully clinically screened to eliminate individuals who may have had a subclinical disease.

Third, retrospective recall of events is often difficult and can lead to recall bias, especially if the events were a long time ago. However, we used some well validated tools to mitigate this. Fourth, the absence of an association between important risk factors and HS and IS could be due to insufficient power. Hence, larger, prospective, population-based studies are required. Owing to the relatively small number of patients with the ability to pay for some investigations, such as electrocardiogram (ECG), echocardiography (ECHO) and serum lipid profiles, important risk factors, like atrial fibrillation and serum lipids, could not be investigated in the current study. Future research is warranted to investigate the lipid profile association with stroke in Uganda. Also, the bodyweight of many stroke patients could not be determined with the equipment available due to their post-stroke disability and being bed ridden. From the literature, the method used in this study of assigning weight-based descriptors to individuals has a greater likelihood of patients misperceiving their weight [45].

Finally, participant recruitment was from one urban health facility, which has implications for generalisability of the results. While the hospital is urban and receives patients from all parts of the country, our study sample may not be a true representation of the characteristics of the urban populations in Uganda. Hence, the results may not be generalisable to all urban settings in Uganda and thus future research should include other urban facilities in the country.

5. Conclusions

This study found no association between HIV sero-positivity and stroke occurrence among Ugandan stroke patients. However, hypertension and a self-reported family history of DM appeared to be significant risk factors for both HS and IS. With the increasing burden of stroke in SSA populations, including Uganda, interventions to reduce cardiovascular risk factors should be implemented as a priority. At the individual patient level, there should be a better effort at diagnosing and controlling both DM and hypertension. Much larger studies may be required to demonstrate if any association exists between HIV and stroke.

Ethical approval

Ethical approval was obtained from the Uganda Virus Research Institute Research and Ethics Committee and the Uganda National Council for Science and Technology (reference number HS364). Written informed consent was obtained from the research participants before performing any study procedures. To maintain participant confidentiality, all study data were collected using only numerical unique identifiers.

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Authors' contributions

GN conceived and designed the study, OK and GN performed the statistical analysis, GN wrote the manuscript; MA, TM, MN, PS, JBMD, PC, LY, ED, JS; and RN oversaw the overall execution of the manuscript writing; RN oversaw the critical revisions of the manuscript. All authors read and approved the final manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of competing interest

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