scientific reports

OPEN

Modifiable Risk Factors for Stroke in Syria: A Nationwide Multi-centre Case-Control Study

Mhd Mustafa Albitar[1,4], Subhia Maya[1,4], Khaled Kalalib Al Ashabia[1], Ghassan Hamzeh[2] & Ameer Kakaje[1,3]✉

Stroke is the second-leading cause of death worldwide, including in Syria, and the third-leading cause of death and disability combined. With approximately 90% of strokes worldwide linked to modifiable risk factors, identifying and quantifying these factors within a specific population is essential for effective prevention. This is the first study to investigate primary risk factors for stroke in Syria. This study included the six primary stroke centres across four major cities in Syria. Data was collected through case files and a questionnaire answered by the cases or their proxies through personal interviews, as well as selected controls. A total of 411 cases were recruited, comprising 363 ischemic strokes (IS) and 48 haemorrhagic strokes, and with a matched ratio of 1:1 for age and sex. IS was significantly associated with multiple chronic conditions including atrial fibrillation AF [AOR 5.04 (2.64–9.62)], high body mass index (overweight [AOR 2.09 (1.28–3.40)], obesity [AOR 4.17 (2.32–7.50)]), hypercholesterolemia [AOR 2.10 (1.34–3.28], hypertension HTN [AOR 1.83 (1.23–2.73)], and diabetes mellitus DM [AOR 1.79 (1.18–2.71)]. Moreover, several lifestyle risk factors contributed to IS: Alcohol consumption [AOR 4.80 (1.72–13.41)], a diet lacking fruits and vegetables [AOR 2.04 (1.28–3.23)], and low physical activity PA [AOR 1.75 (1.01–2.86)]. Notably, over 40% of the population exhibited medication nonadherence. IS showed no significant association with cigarette smoking, heart failure (HF), ischemic heart disease (IHD), or a family history of stroke ($p > 0.05$). In contrast, haemorrhagic stroke was linked to higher BMI, HTN, DM, and AF ($p < 0.05$), but not to hypercholesterolemia, cigarette smoking, IHD, or HF ($p > 0.05$). This first nationwide multicentre case-controlled study in Syria identified critical modifiable risk factors for stroke, including hypertension, diabetes, atrial fibrillation, and obesity, with high rates of medication non-adherence, especially among hypertensive patients, complicating stroke risk. These findings underscore the urgent need for targeted health interventions promoting lifestyle modifications, medication adherence, and public health policies tailored to Syria's current resource-limited context to reduce the stroke burden and improve population health.

Keywords Stroke, Modifiable risk factors, Hypertension, Public health, Syria, Middle East

As of 2019, stroke has been identified as the second leading cause of death, and the third leading cause of death and disability combined[1]. Moreover, the Global Burden of Disease (GBD) 2016 study states that almost 25% of people around the world will have a stroke during their lifetime[2]. Furthermore, 25% of stroke survivors will have a recurrent stroke within five years[3]. The age-standardized incidence rate for all strokes per 100,000 is 136.5 to 167.5. In Syria, it is estimated to have an incidence rate of 175.8 to 196.2 per 100,000[1]. Females have been found to have a higher risk of developing a stroke during their lifetime[1,3], whereas strokes in men tend to be more severe[1].

Stroke remains a challenging and growing problem facing health systems worldwide[1], predominantly in low-income countries such as Syria, where age-standardized disability-adjusted life years (DALYs) are 3.7 fold higher than in high-income countries[1,4–6]. This is of particular concern, considering that almost 90% of strokes can be attributed to modifiable risk factors[1,5,7]. Furthermore, Bertram et al. (2018) reported that the countries most burdened with stroke and cardiovascular disease could, with additional funding, prevent millions of strokes and so multiply their initial investment by almost 11-fold[8].

[1]Faculty of Medicine, Damascus University, Damascus, Syrian Arab Republic. [2]Head of the Neurology Department, Al Assad University Hospital, Damascus, Syrian Arab Republic. [3]University Hospital Geelong, Barwon Health, Bellerine St, Geelong VIC 3220, Australia. [4]Mhd Mustafa Albitar, Subhia Maya and Khaled Kalalib Al Ashabia contributed equally to this work. ✉email: ameer.kakaje@hotmail.com

Globally, the main risk factors for ischemic stroke (IS) are hypertension (HTN), diabetes mellitus (DM), high cholesterol, ambient particulate matter pollution, and high body mass index (BMI)[1]. According to the INTERSTROKE study, the magnitude of the association between these risk factors and stroke varies regionally and between different populations[5]. As for haemorrhagic strokes, hypertension remains the main risk factor[1].

Stroke research is scarce in the Middle East compared to advanced economies; this is primarily notable in Syria, where there is scant research[9], albeit; stroke is the second leading non-commincable cause of death in Syria according to the Institute for Health Metrics and Evaluation which derives their data from the WHO Global Burden of Disease 2019[10]. Furthermore, in low income countries such as Syria, patient care is usually the responsibility of the patient's families due to a lack of structured rehabilitation post-stroke, which magnifies the burden[7].

At the national level. This multi-centre case–control study aims to bridge the knowledge gap and to identify the main risk factors of stroke in Syria; to guide health policies in the country which will help reduce the burden of stroke mortality, morbidity, and productivity loss.

Methods

Study design and setting

This is a multicentre, age and sex-matched, and hospital-based case–control study. Cases were recruited from six public hospitals dispersed in four Syrian cities (Al Mouwasat University Hospital, Al Assad University Hospital, Al Mujtahid Hospital (Damascus Hospital) in Damascus, Aleppo University Hospital in Aleppo, Tishreen University Hospital in Lattakia, and Al Basil Specialized Hospital in Karam Al Looz in Homs) from 23/11/2021 to 13/9/2022. This study was approved by the Syrian Ministry of Higher Education and Scientific Research under reference number (5/011,026/4072) and by the Syrian Ministry of Health under reference number (1/18/145). Thus, all concerned hospitals were noted. Verbal consent was obtained from all participants or their proxies.

We included first-onset and recurrent strokes in patients 40 years or older. Our stroke diagnosis algorithm aligns with the diagnosis criteria by Yew and Cheng (2015)[11]. Patients with subarachnoid haemorrhages (SAH) and transient ischemic attacks (TIAs) were excluded.

Controls were individuals who visited or accompanied patients in surgical departments (mainly general and genitourinary surgery) and reported no active signs or history of TIA or stroke.

This study is in line with the STROBE checklist criteria[12].

Data collection

Data was collected through case file reviews and questionnaires answered by cases (or their proxies) and by identified control participants through face-to-face interviews conducted by doctors at respective hospitals. All other relevant investigations, such as brain imaging (non-contrast CT or MRI), electrocardiogram ECG, and echocardiography were accessed from case files. No investigations were performed for the control participants.

Statistical approach

Sample size and matching

The required sample size for this matched case–control study was calculated with α and β values of 0.05 and 0.1, respectively, using the prevalence of hypertension HTN and cigarette smoking in an earlier study in Syria[13] and the expected ORs according to the INTERSTROKE study in Eastern Europe, Central Europe, and the Middle East[5]. These parameters were entered at the University of Melbourne epidemiology calculator[14]. This resulted in a sample size of 217 cases vs. 217 controls when calculations were made according to cigarette smoking and 191 cases vs. 191 controls when calculations were made according to HTN. Hence, it was decided to gather a larger sample of 411 cases vs. 411 controls to compensate for any errors in our estimations of the correlation coefficient of 0.2. Of 411 cases, 48 had haemorrhagic stroke and 363 had an ischemic stroke.

Each case was matched with control for sex and age (± 5 years) with a ratio of 1:1; matching was extended (± 10 years) for cases older than 75 years. To check the efficiency of the matching process, Standardized Mean Difference (SMD) was calculated using the following formula: SMD = (mean1—mean2)/pooled SD, where mean1 and mean2 are the means of variables on which matching was based (sex and age) for the cases and controls, respectively, and pooled SD is the pooled standard deviation. In the outcomes, the SMD value for age was more than for sex. However, both SMD values were less than 0.2, indicating an acceptable matching approach. Thus, no further adjustment was needed for the matching process[15,16].

We categorized physical activity PA as low (Walking < 1.5 KM daily), moderate (Walking 20–30 min at least three times a week), and high (Walking > 30 min more than 3 times a week). Consanguinity was defined as when parents are first or second cousins. Walking less than 1.5 km Daily was considered poor physical activity. Hypercholesterolemia was defined as having total cholesterol level > 240 mg/dl in cases, and a history of hypercholesterolemia in controls. Fruit and vegetable consumption were self-reported and serving was defined as 100 g. A diet of less than 300 g/day of fruits and vegetables was considered lacking. Heart disease was self-reported by cases and controls, or diagnosed upon admission using ECG (arterial fibrillation AF) in cases. Heart disease HDs included atrial fibrillation AF, heart failure HF, heart valvular diseases HVDs, and ischemic heart disease IHD. BMI was self-reported, and its ranges were categorized into normal weight (BMI (18.5–24,9)), Overweight (BMI [25–29.9]), and Obesity (BMI (> 30)). BMI can be calculated with BMI = kg/m^2[17].

We confirm that this research has been conducted in accordance with the relevant guidelines and regulations set by our ethic committee which is in accordance with the global standard of research and with the Declaration of Helsinki.

Statistical analysis
Data were analysed using the Statistical Package for Social Sciences version 26.0 (SPSS Inc., Chicago, IL, United States) and reported as frequencies and percentages (for categorical variables) and means and standard deviations (SD) (for continuous variables). Chi-square analyses were applied to compare cases and controls. A two-sided $P < 0.05$ was considered statistically significant. Univariate odds ratios (ORs) were calculated for each dichotomized risk factor that were statistically significant. Binary multivariable Enter logistic regression model was used to determine the adjusted ORs (AORs) with 95% confidence intervals. The population-attributable risk percentage (PAR%) is the proportion of disease incidence in exposed and non-exposed populations that can be attributed to exposure[18]. It was calculated from the adjusted OR and 95% confidence interval values using the following formula:

Prevalence of exposed cases × [(AOR–1)/AOR] × 100.[19].

Results
Overall, 573 cases and 744 controls comprised the study sample after case exclusions. All cases and controls had complete data, except for serum cholesterol levels, which were available for 293/573 cases. Cases were matched with stroke-free controls to determine potential stroke risk factors. This resulted in a sample of 411 matched cases for age and sex with a 1:1 ratio.

Ischemic stroke
This study analyzed 363 IS cases, with 164 (45.2%) being females and a mean age of 65.5 (±9.6) years. The distribution of cases included 61 (16.8%) cases from Al Mouwasat University Hospital, 19 (5.2%) from Al Assad University Hospital, and 28 (7.7%) from Al Mujtahid Hospital (Damascus Hospital) in Damascus, 139 (38.3%) from Aleppo University Hospital in Aleppo, 80 (22%) from Tishreen University Hospital in Lattakia, and 36 (9.9%) from Al Basil Specialized Hospital in Karam Al Looz in Homs.

Tables 1 and 2 demonstrate different variables and risk factors, comparing cases to controls using univariate analysis with Chi-square tests. Key findings indicated that higher BMI, lower physical activity, heavier cigarette smoking among smokers, alcohol consumption, a diet of fewer than three servings of vegetables and fruits, having a family history of stroke (particularly first degree), HTN, DM, hypercholesterolemia, AF, IHD, HF, HVD, and non-adherence to antihypertensive medications were all significantly associated with ischemic stroke ($p < 0.05$).

Table 3 provides odds ratios (ORs), adjusted odds ratios (AORs), and population-attributable risk (PAR%) for IS risk factors. Walking less than 1.5 km Daily was considered low physical activity. Significant findings from Tables 1 and 2 were included in the regression analysis, excluding heart valve disease (HVD) as a variable.

Variables		Cases n (%)	Controls n (%)	X^2	P-value
Lifestyle and family history					
BMI	18.5–24.9	78 (21.5)	136 (37.5)	40.09	**< 0.001***
	25–29.9	175 (48.2)	179 (49.3)		
	Above 30	110 (30.3)	48 (13.2)		
Physical activity†	Walk less than 1.5 km Daily	105 (28.9)	61 (16.8)	15.53	**< 0.001***
	Walk for 20–30 min. Three times a week at least	140 (38.6)	172 (47.4)		
	Walk more than 30 min more than three times a week	118 (32.5)	130 (35.8)		
Cigarette smoking	Yes	164 (45.2)	171 (47.1)	0.27	0.602
	No	199 (54.8)	192 (52.9)		
Pack-year scale	Less than 40	115 (70.1)	143 (83.6)	8.62	**< 0.01***
	More than 40	49 (29.9)	28 (16.4)		
Alcohol consumption	Yes	22 (6.1)	8 (2.2)	6.82	**< 0.01***
	No	341 (93.9)	355 (97.8)		
Daily servings of vegetables and fruits	More than three times	230 (63.4)	289 (79.6)	23.52	**< 0.001***
	Less than three times	133 (36.6)	74 (20.4)		
History of parental consanguinity	Yes	116 (32.0)	126 (34.7)	0.62	0.43
	No	247 (68.0)	237 (65.3)		
Family history of stroke	Yes	144 (39.7)	122 (33.6)	2.87	0.09
	No	219 (60.3)	241 (66.4)		
First-degree family history of stroke	Yes	82 (22.6)	57 (15.7)	5.56	**< 0.05***
	No	281 (77.4)	306 (84.3)		
First-degree family history of coronary heart diseases	Yes	98 (27.0)	57 (15.7)	13.79	**< 0.001***
	No	265 (73.0)	306 (84.3)		

Table 1. Prevalence of variables among cases and controls of ischemic stroke patients. Significant values are given in bold. †Walking less than 1.5 km Daily is considered poor physical activity.

Variables		Cases n (%)	Controls n (%)	X^2	P-value
Hypertension (HTN)	Yes	211 (58.1)	137 (37.7)	30.22	**< 0.001***
	No	152 (41.9)	226 (62.3)		
Hypertensive medication adherence	Yes	102 (48.3)	87 (63.5)	7.70	**< 0.01***
	No	109 (51.7)	50 (36.5)		
Diabetes mellitus (DM)	Yes	153 (42.1)	103 (28.4)	15.09	**< 0.001***
	No	210 (57.9)	260 (71.6)		
Diabatic medication adherence	Yes	83 (53.5)	60 (57.7)	0.43	0.511
	No	72 (46.5)	44 (42.3)		
Hypercholesterolemia	Yes	70 (34.0)	63 (17.8)	18.68	**< 0.001***
	No	136 (66.0)	290 (82.2)		
Heart diseases (HDs)	Yes	180 (49.6)	64 (17.6)	83.07	**< 0.001***
	No	183 (50.4)	299 (82.4)		
Heart diseases medication adherence	Yes	113 (62.8)	45 (70.3)	1.71	0.278
	No	67 (37.2)	19 (29.7)		
Atrial fibrillation (AF)	Yes	80 (22.0)	18 (5.0)	45.35	**< 0.001***
	No	283 (78.0)	345 (95.0)		
Ischemic heart disease (IHD)	Yes	55 (15.2)	27 (7.4)	10.78	**< 0.01***
	No	308 (84.8)	363 (92.6)		
Heart Failure (HF)	Yes	36 (9.9)	11 (3.0)	14.22	**< 0.001***
	No	327 (90.1)	352 (97.0)		
Heart valve diseases (HVDs)	Yes	28 (7.7)	8 (2.2)	11.69	**< 0.01***
	No	335 (92.3)	355 (97.8)		
Smoking + HTN	Yes	106 (29.2)	62 (17.4)	14.26	**< 0.001***
	No	257 (70.8)	300 (82.6)		
Smoking + DM	Yes	73 (20.1)	39 (10.7)	12.20	**< 0.001***
	No	290 (79.9)	324 (89.3)		
HTN + DM	Yes	92 (25.3)	40 (11.0)	25.04	**< 0.001***
	No	271 (74.7)	323 (89.0)		
HDs + HTN + DM	Yes	57 (15.7)	12 (3.3)	32.43	**< 0.001***
	No	306 (84.3)	351 (96.7)		
Low physical activity + DM	Yes	54 (14.9)	19 (5.2)	18.66	**< 0.001***
	No	309 (85.1)	344 (94.8)		

Table 2. Demonstrating chronic diseases and medication adherence of IS patients. Significant values are given in bold.

Risk factor	ORs (95% CI)	AORs (95% CI)	PARs% (95% CI) according to AORs
BMI			
Normal	–	–	–
Overweight	1.70 (1.20–2.41)	**2.09 (1.28–3.40)**	25.14 (10.54–34.02)
Obese	4.00 (2.58–6.20)	**4.17 (2.32–7.50)**	23.03 (17.24–26.26)
Low physical activity	2.02 (1.41–2.88)	**1.75 (1.01- 2.86)**	12.39 (0.29–18.80)
Alcohol	2.86 (1.26–6.52)	**4.80 (1.72–13.41)**	4.83 (2.55–5.65)
Not having three daily servings of vegetables and fruits or more	2.26 (1.62–3.15)	**2.04 (1.28–3.23)**	18.66 (8.01–25.27)
First degree family history of stroke	1.57 (1.08–2.28)	1.17 (0.70–1.97)	3.28 (− 9.69–11.13)
First-degree family history of coronary heart diseases	1.99 (1.38–2.86)	1.29 (0.78–2.15)	6.07 (− 7.62–14.44)
IHD	2.22 (1.37–3.61)	1.93 (1.00–3.72)	7.32 (0–11.14)
HF	3.52 (1.76–7.04)	2.15 (0.87–5.27)	5.30 (− 1.48–8.02)
AF	5.41 (3.17–9.25)	**5.04 (2.64–9.62)**	17.63 (13.67–19.71)
HTN	2.29 (1.70 – 3.08)	**1.83 (1.23—2.73)**	26.35 (10.86–36.82)
DM	1.84 (1.35–2.51)	**1.79 (1.18–2.71)**	18.58 (6.42–26.56)
Hypercholesterolemia	2.37 (1.59–3.52)	**2.10 (1.34–3.28)**	17.81 (8.63–23.63)

Table 3. Odds ratios (ORs), adjusted odds ratios (AORs), and population attributable risk (PARs%) for risk factors of IS patients. Significant values are given in bold.

Variables		Cases n (%)	Controls n (%)	X^2	P-value
BMI	18.5–24.9	4 (8.3)	19 (39.6)	12.87	**< 0.01***
	25–29.9	27 (56.3)	18 (37.5)		
	Above 30	17 (35.4)	11 (22.9)		
Physical activity	Walk less than 1.5 km daily	7 (14.6)	8 (16.7)	2.16	0.339
	Walk for 20–30 min. Three times a week at least	24 (50.0)	17 (35.4)		
	Walk more than 30 min more than three times a week	17 (35.4)	23 (47.9)		
Alcohol consumption	Yes	2 (4.2)	0 (0.0)	2.04	0.153
	No	46 (95.8)	48 (100)		
Cigarette smoking	Yes	22 (45.8)	19 (39.6)	0.38	0.536
	No	26 (54.2)	29 (60.4)		
History of parental consanguinity	Yes	17 (35.4)	14 (19.2)	0.43	0.413
	No	31 (64.6)	34 (70.8)		
First-degree family history of stroke	Yes	12 (25.0)	12 (25.0)	0.00	1
	No	36 (75.0)	36 (75.0)		
First-degree family history of coronary heart diseases	Yes	15 (31.2)	7 (14.6)	3.77	0.052
	No	33 (68.8)	41 (85.4)		
Hypertension (HTN)	Yes	32 (66.7)	15 (31.2)	12.05	**< 0.01***
	No	16 (33.3)	33 (68.8)		
Diabetes mellitus (DM)	Yes	23 (47.9)	11 (22.9)	6.56	**< 0.05***
	No	25 (52.1)	37 (77.1)		
Hypercholesterolemia	Yes	3 (17.6)	6 (14.0)	0.13	0.718
	No	14 (82.4)	37 (86)		
Atrial fibrillation (AF)	Yes	9 (18.8)	0 (0.0)	9.93	**< 0.01***
	No	39 (81.2)	48 (100)		
Ischemic heart disease (IHD)	Yes	7 (14.6)	6 (12.5)	0.09	0.765
	No	41 (85.4)	42 (87.5)		
Heart Failure (HF)	Yes	4 (8.3)	2 (4.2)	0.71	0.399
	No	44 (91.7)	46 (95.8)		

Table 4. showing haemorrhagic stroke risk factors using chi-squares. Significant values are given in bold.

Patients with AF exhibited a markedly elevated risk of developing stroke with an AOR of 5.04 (2.64–9.62). Obesity was associated with a four-fold increase in developing ischemic strokes. Furthermore, ischemic patients were found to be 55% more likely to have HTN compared to controls (prevalence: 58.1% vs. 37.7%, PAR: 26.35%). As for DM, the prevalence was nearly 50% higher in IS cases than controls (153 (42.1%) vs. 103 (28.4%), PAR: 18.58%), with all comparisons yielding a p value of < 0.001.

Haemorrhagic stroke

This study included 48 haemorrhagic stroke cases, with 22 (45.8%) female and a mean age of 65.5 years (± 8.0). HTN was observed in cases twice as frequently as controls (66.7% vs. 31.2%), while DM prevalence doubled (47.9% vs. 22.9%). Key risk factors significantly associated with hemorrhagic strokes included higher BMI, HTN, DM, and AF ($p < 0.05$). (Table 4).

Discussion

To the best of our knowledge, this is the first nationwide case–control study that addresses stroke risk factors in the Syrian population inside Syria.

Ischemic stroke

Based on population-attributable risks (PAR), several IS risk factors were identified in the Syrian population: HTN, high BMI, a diet with fewer than three servings of fruits and vegetables daily, DM, hypercholesterolemia, AF, low PA, and alcohol consumption. This is consistent with GBD estimations for the Middle East and North Africa (MENA) region[1].

In our study, a significant proportion of participants reported nonadherence to their medications:46.6% for hypertension, 46.1% for diabetes, and 34.7% for heart-related medication. This can be due to the low socioeconomic status of the Syrian population, as more than 80% of the population lives under the poverty line[20]. Moreover, this potentially reflects low health literacy among the population. This is a major public health issue as these three medical conditions were significantly statistically associated with stroke.

Of heart diseases, AF exhibited the strongest association with IS (AOR 5.04). Furthermore, the prevalence of AF among ischemic cases was 22%, notably higher than rates reported in other Middle Eastern countries

(9–13%), although that reference study did not differentiate between stroke subtypes[21]. Notably these rates are lower than rates of other ischemic stroke reported in Lebanon (27%)[22] (30.1%)[23].

The previous controversies about heart failure (HF) as an independent risk factor for stroke are now reducing as evidence builds that identifies it as a risk factor for all stroke subtypes[24]. Our study found an increased risk of IS in patients with HF and IHD using bivariate analysis. However, when adjusting for the multiple comorbidities with regression including AF, this association ceased to be statistically significant, with AOR rates at 2.15 (0.87–5.27) and 1.93 (1.00–3.72), respectively.

Hypertension (HTN) is the most prominent risk factor for cardiovascular diseases[25]. The AOR of developing IS in hypertensive patients was estimated to be 1.83 (1.23–2.73) in our study. This number aligns with INTERSTROKE's estimations for Eastern Europe, Central Europe, and the Middle East 2.11 (1.52–2.95) and with another case–control study from Saudi Arabia AOR 2.12 (1.74–2.57) while lower than estimations from Lebanon AOR of 2.74 (1.05–7.18). Even though the Saudi Arabian study did not differentiate between stroke subtypes, IS constituted 90% of their cases[5,23,26].

The prevalence of HTN in all controls (37%) was slightly higher than estimations made by the PURE study in low-income countries and the Middle East, which were 32.14% and 33%, respectively[25,27]. The prevalence of HTN in the Syrian population needs to be studied and more formalized diagnosis is needed to evaluate the actual burden of HTN, as no new data is available after the conflict in Syria. Medication availability and awareness about the importance of adherence may also have been influenced by the conflict. Our results highlight this, as non-adherent hypertensive patients were more likely to develop ischemic strokes, which is also reported in South Korea. Uncontrolled HTN not only increases stroke risk but also contributes to the development of heart diseases [28,29]. Therefore, this issue must be tackled with absolute urgency and should not be underestimated by patients, as even modest control of hypertension can decrease stroke risk by 40%[30].

DM is a global health threat strongly associated with stroke[1]. This is particularly seen in Saudi Arabia and other countries in the Middle East, as it is the second-most reported risk factor[26,31]. The data obtained in our study (AOR 1.79 (1.34–3.28)) broadly aligns with regional trends. According to Hamzeh et al. (2019), 41.2% of Syrian diabetic patients do not know that DM is a risk factor for Stroke, and 10.8% think it is not[32]. This low awareness contributes to our high DM medication non-adherence in both cases and controls. Therefore, unless an effective program is adopted, the health burden associated with diabetes in Syria, including stroke, is anticipated to increase.

The link between high blood cholesterol and a higher risk of stroke is still debatable, as several studies showed no or a weak relationship[33]. Our study found an increased stroke risk with hypercholesterolemia, which was also reported in Saudi Arabia[26], and the Asia Pacific region[34]. These findings call for more thorough investigations to determine the correlation between detailed lipid profile components and stroke in Syria and possibly the Middle East.

Our study suggests a decline in the prevalence of obesity in Syria over the past 12 years, dropping from 43.2% in 2011[13]. This decline could be linked to the country's conflict and economic conditions, obesity remains a significant stroke risk factor.

Though the importance of a healthy diet has been linked with stroke prevention, most clinicians tend to underestimate its effect[23]. According to our study, a diet containing three or fewer servings of fruit and vegetables daily doubles the risk of developing IS AOR 2.04 (1.28–3.23). This preventative effect has been established in multiple cohort studies and might be explained by their high content of micronutrients especially Potassium, which was shown to reduce blood pressure, decreasing the risk of stroke[35].

Although cigarette smoking is considered a significant risk factor for IS globally and regionally[1,31], our results showed no statistical significance in this area. The similarly high prevalence of smoking among IS cases (45.2%) and controls (47.1%) may indicate a public health epidemic of elevated smoking behaviours. This epidemic of smoking behaviours spans the borders of three East Mediterranean countries, as the prevalence rate for current cigarette smoking was 35.1% in Lebanon, 32.0% in Jordan, and 28.2% in Palestine[36]. However, we did not include shisha smoking in our study.

Haemorrhagic stroke

Our study demonstrates that a higher BMI is associated with an increased risk of haemorrhagic stroke. However, some studies suggest a protective effect of higher BMI in women[37] and an increased risk in men[38]. Due to our sample size limitations, we were unable to analyse these gender differences in depth.

HTN is the most common risk factor for haemorrhagic strokes[39]. Our study showed a significant association ($p < 0.05$) as 66.7% of cases had HTN compared to only 31.2% of controls. Cigarette smoking and alcohol consumption are recognized as major risk factors for haemorrhagic strokes, as is diabetes mellitus, which has been linked to microbleeds[39]. Our study only found an association with DM from the factors mentioned above. Interestingly, some studies have suggested that lower total cholesterol levels could be linked to an increased risk of haemorrhagic strokes[33,39]. However, our findings did not support this association, indicating that the relationship between cholesterol levels and haemorrhagic stroke may be more complex than previously considered. Additionally, we identified an association between atrial fibrillation (AF) and hemorrhagic stroke. This relationship may be attributed to the use of anticoagulants in AF patients, which can heighten the risk of bleeding events.

Strengths and limitations

Thia study has several limitations. Firstly, the use of a self-report questionnaire to gather information may introduce recall bias, especially in severe stroke cases where proxies were interviewed on behalf of the patients. BMI was calculated according to patients', proxies', and controls' answers, which might have impacted our responses. Additionally, the case–control design employed is susceptible to bias due to differences in how risk factors were measured between cases and controls. This was particularly evident in the assessment of heart diseases and hypercholesterolemia, as we were unable to conduct ECG, echocardiography, or serum-cholesterol tests in the control group. Moreover, not all cases were able to undergo serum-cholesterol tests due to limited funding and resources in Syrian hospitals, which have been greatly affected by the economic situation post-war.

A further limitation is represented in the challenge we faced in matching cases aged 80 and older. This was due to the methodology used for control selection, as there were very few older companions available for patients in hospitals.

Nonetheless, the multicentre setting portrays a more realistic and generalizable image of the Syrian population, especially since the centres were spread over four major cities. The selection of controls as patients' companions from departments other than neurology (mainly general and genitourinary surgery) was to avoid associations with vascular risk factors as much as possible. This method appears to have reasonably estimated the prevalence of risk factors. For example, the Prevalence of HTN in our controls was 37.7% which corresponds with two studies in Syria which found it to be 40.6%[40] and 45.6%[13], while hypercholesterolemia is prevalent in 17.8% of our controls compared to 21.9% in a 2011 study[13].

Conclusion

Notably, hypertensive medication non-adherence poses a challenge to clinicians and health policymakers and increases the burdens of stroke and other cardiac complications that could have been avoided with proper management. This issue requires health policy actions to prevent further morbidity and mortality, especially when considering the dire economic situation in the country. Simple recommendations could significantly improve stroke outcomes in Syria, including promoting a healthy lifestyle, ensuring strict medication adherence, and implementing routine screenings for stroke risk factors.

The scarcity of studies in Syria hinders public efforts aiming to ameliorate the significant health issue. As such, more research is required to guide public health efforts to mitigate these modifiable risk factors for this severe and life threatening condition.

Data availability

The data used and analyzed during the current study are available from the corresponding author upon reasonable request.

Received: 17 June 2024; Accepted: 16 December 2024
Published online: 02 January 2025

References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol.* **20**(10), 795–820 (2021).
2. Feigin, V. L. et al. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N. Engl. J. Med.* **379**(25), 2429–2437 (2018).
3. Akyea, R. K. et al. Sex, age, and socioeconomic differences in nonfatal stroke incidence and subsequent major adverse outcomes. *Stroke* **52**(2), 396–405 (2021).
4. World Bank. List of Economies July 2021. https://www.acpe-accredit.org/pdf/ISP/WorldBankData-CountryClassifications.pdf. (2021) (Accessed March 2023).
5. O'Donnell, M. J. et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* **388**(10046), 761–775 (2016).
6. Jaberinezhad, M. et al. The burden of stroke and its attributable risk factors in the Middle East and North Africa region, 1990–2019. *Sci. Rep.* **12**(1), 2700 (2022).
7. Campbell, B. C. V. & Khatri, P. Stroke. *Lancet* **396**(10244), 129–142 (2020).
8. Bertram, M. Y. et al. Investing in non-communicable diseases: an estimation of the return on investment for prevention and treatment services. *Lancet* **391**(10134), 2071–2078 (2018).
9. Salhab, H. A., Salameh, P., Hajj, H. & Hosseini, H. Stroke in the Arab world: A bibliometric analysis of research activity (2002–2016). *ENeurologicalSci* **13**, 40–45 (2018).
10. Institute for Health Metrics and Evaluation. Top 10 causes of death and disability (DALYs) in 2021 and percent change 2011–2021, all ages combined. Seattle: IHME; 2021. https://www.healthdata.org/research-analysis/health-by-location/profiles/syria?language=41.
11. Yew, K. S. & Cheng, E. M. Diagnosis of acute stroke. *Am. Fam. Phys.* **91**(8), 528–536 (2015).
12. von Elm, E. et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* **61**(4), 344–349 (2008).
13. Al Ali, R., Rastam, S., Fouad, F. M., Mzayek, F. & Maziak, W. Modifiable cardiovascular risk factors among adults in Aleppo, Syria. *Int. J. Public Health* **56**(6), 653–662 (2011).
14. Stevenson M NT, Heuer C, Marshall J, Sanchez J, Thornton R, Reiczigel J, Robison-Cox J, Sebastiani P, Solymos P, Yoshida K, Firestone S. epiR: An R package for the analysis of epidemiological data. R package version 0.9–69. https://shiny.vet.unimelb.edu.au/epi/sample.size.mccs/. (2015). (Accessed March 2023).
15. Cohen, J. *Statistical Power Analysis for the behavioural Sciences* 2nd edn. (Routledge, 1988).
16. Austin, P. C. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar. Behav. Res.* **46**(3), 399–424 (2011).
17. Nuttall, F. Q. Body mass index. *Nutr. Today* **50**(3), 117–128 (2015).
18. Askari, M. & Namayandeh, S. M. The difference between the population attributable risk (PAR) and the potentioal impact fraction (PIF). *Iran. J. Public Health* **49**(10), 2018–2019 (2020).
19. Rockhill, B., Newman, B. & Weinberg, C. Use and misuse of population attributable fractions. *Am. J. Public Health* **88**(1), 15–19 (1998).
20. Kakaje, A. et al. Mental disorder and PTSD in Syria during wartime: a nationwide crisis. *BMC Psychiatry* https://doi.org/10.1186/s12888-020-03002-3 (2021).
21. Salam, A. M., Kaddoura, R., Salih, V. & Asopa, S. Atrial fibrillation in Middle Eastern Arabs and South Asians: a scoping review. *Rev. Cardiovasc. Med.* **22**(4), 1185–1196 (2021).
22. Malek, E. G. et al. TOAST classification and risk factors of ischemic stroke in Lebanon. *Acta Neurol. Scand.* **141**(4), 294–300 (2020).

23. Maalouf, E., Hallit, S., Salameh, P. & Hosseini, H. Eating behaviours, lifestyle, and ischemic stroke: A Lebanese case-control study. *Int. J. Environ. Res. Public Health* **20**(2), 1487 (2023).
24. Kim, W. & Kim, E. J. Heart failure as a risk factor for stroke. *J. Stroke* **20**(1), 33–45 (2018).
25. Chow, C. K. et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* **310**(9), 959–968 (2013).
26. Alhazzani, A. A., Mahfouz, A. A., Abolyazid, A. Y. & Awadalla, N. J. Risk factors of the first-time stroke in the southwest of Saudi Arabia: A case-control study. *Brain Sci.* **11**(2), 222 (2021).
27. Yusufali, A. M. et al. Prevalence, awareness, treatment and control of hypertension in four Middle East countries. *J. Hypertens.* **35**(7), 1457–1464 (2017).
28. Lee, H. J., Jang, S. I. & Park, E. C. Effect of adherence to antihypertensive medication on stroke incidence in patients with hypertension: a population-based retrospective cohort study. *BMJ Open* **7**(6), e014486 (2017).
29. Ahuja R, Ayala C, Tong X, Wall HK, J Fang. Public awareness of health-related risks from uncontrolled hypertension. https://www.cdc.gov/pcd/issues/2018/17_0362.htm#:~:text=Uncontrolled%20hypertension%20increases%20the%20risk,decline%20(1%E2%80%933. (2018) (Accessed March 2023).
30. Soler, E. P. & Ruiz, V. C. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. *Curr. Cardiol. Rev.* **6**(3), 138–149 (2010).
31. El-Hajj, M., Salameh, P., Rachidi, S. & Hosseini, H. The epidemiology of stroke in the Middle East. *Eur. Stroke J.* **1**(3), 180–198 (2016).
32. Hamzeh, A. et al. Awareness of diabetes and diabetic retinopathy among a group of diabetic patients in main public hospitals in Damascus, Syria during the Syrian crisis. *BMC Health Serv. Res.* **19**(1), 549 (2019).
33. Goldstein, L. B., Seshadri, S. & Sacco, R. L. 16 - Risk Factors and Prevention. In *Stroke* 7th edn (eds Grotta, J. C. et al. et al.) 187-206.e6 (Elsevier, 2022).
34. Zhang, X. et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int. J. Epidemiol.* **32**(4), 563–572 (2003).
35. He, F. J., Nowson, C. A. & MacGregor, G. A. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* **367**(9507), 320–326 (2006).
36. Nakkash, R. et al. Prevalence of cigarette and waterpipe tobacco smoking among adults in three Eastern Mediterranean countries: a cross-sectional household survey. *BMJ Open* **12**(3), e055201 (2022).
37. Kroll, M. E. et al. Adiposity and ischemic and haemorrhagic stroke. *Neurology* **87**(14), 1473–1481 (2016).
38. Shiozawa, M. et al. Association of body mass index with ischemic and haemorrhagic stroke. *Nutrients* **13**(7), 2343 (2021).
39. Unnithan AKA, Das JM, Mehta P. Haemorrhagic Stroke. In: StatPearls. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK559173/. (Accessed 30 May 2024). (2024).
40. Maziak, W. et al. Cardiovascular health among adults in Syria: a model from developing countries. *Ann. Epidemiol.* **17**(9), 713–720 (2007).

Acknowledgements
We would like to acknowledge Dr. Mhd Homam Safiah for his essential help in statistics and data analysis, Dr. Reem Abdulhameed for her collaboration in data collection, and all the doctors who helped in data collection in all medical centres and are the backbone of the Syrian health system.

Author contributions
Mhd Mustafa Albitar, Subhia Maya, Khaled Kalalib Al Ashabi are all co-first authors and have contributed equally to the study design, data collection, and drafting. Ameer Kakaje is the corresponding and senior author and has contributed to drafting and editing, data analysis and curation. Ghassan Hamzeh has contributed in study design and supervision. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Consent
This study was approved by the Ministry of Higher Education and Scientific Research under reference number (5/011026/4072) and by the Ministry of Health under reference number (1/18/145). Thus, all concerned hospitals were noted. Verbal consent was obtained from all participants or their proxies.

Additional information
Correspondence and requests for materials should be addressed to A.K.

Reprints and permissions information is available at www.nature.com/reprints.