Research Letter

Stroke-heart syndrome: mechanisms, risk factors, and adverse cardiovascular events

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New-onset cardiovascular complications following an ischaemic stroke, hereafter termed stroke-heart syndrome, are a major medical challenge of the 21st century, yet under-recognised and under researched.[1 2] Acutely, stroke-heart syndrome associates with poorer functional prognosis and increased mortality following stroke.[3] In the long-term, stroke-heart syndrome associates with significantly higher mortality compared to matched controls.[4] Although risk factors for stroke and cardiovascular disease are well documented,[5] and we have reasonable understanding of the likely underlying mechanisms of stroke-heart syndrome,[6] specific risk factors for stroke-heart syndrome and subsequent adverse events have not been investigated. Also, whether stroke-heart syndrome impacts males and females differently and whether there are sex-specific risk factors for poor outcomes is unknown. The aim of this study was to investigate the sex-specific incidence of stroke-heart syndrome and 5-year mortality, recurrent stroke and acute myocardial infarction (AMI) in males and females with different pre-existing risk factors.

This multi-centre cohort study utilised complete case, anonymised data within TriNetX, a global federated health research network with access to electronic medical records (EMRs) from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. As a federated network, research studies using TriNetX do not require ethical approval or patient informed consent as no identifiable information is received. The TriNetX network was searched on January 3, 2023 and de-identified datasets were analysed that included data from 2002-2023 with at least 5-years of follow-up (i.e. index event (incident ischaemic stroke) occurred at least five years ago). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eTable 1). More detailed information regarding the online database and methods used can be found within the supplementary file.

To gain access to TriNetX data, a request can be made (https://live.trinetx.com), but costs may be incurred, a data sharing agreement is necessary, and no patient identifiable information can be obtained.

Patients with incident acute ischaemic stroke, aged ≥18 years with at least 5-years follow-up (unless deceased during follow-up) were identified from the first instance of an International

Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code I63 (Cerebral infarction). A composite of newly diagnosed cardiovascular complications (within 4-weeks of ischaemic stroke) were identified via ICD-10-CM codes: I20-I25 (Ischaemic heart diseases) [i.e., ACS], I48 (Atrial fibrillation/flutter), I50 (Heart failure), I49.0 (Ventricular fibrillation/flutter) and I47.2 (ventricular tachycardia) [i.e., severe ventricular arrhythmias], and I51.81 (Takotsubo syndrome). The cohort was stratified by sex (female/male), age (≥75/<75 years), and modifiable risk factors (obesity [body mass index ≥30], hypertension [systolic blood pressure ≥140], T2DM [HbA1c >6.5%], and high LDL cholesterol [≥116 mg/dL]). The initial comparison compared patients with stroke-heart syndrome who were 1:1 matched with patients who experienced an ischaemic stroke only (i.e., without cardiac complications). The subsequent stratified cohort comparisons were 1:1 propensity score matched with a control cohort excluding the risk factor of interest. At the time of the search, 56 (primarily US-based) participating healthcare organisations provided data.

Following propensity score matching, Cox proportional hazards regression models reported hazard ratios (HR) with 95% confidence intervals (CIs) for 5-year incidence of all-cause mortality, recurrent stroke, and AMI, comparing stroke patients with new-onset cardiovascular complications (stroke-heart syndrome) with propensity matched controls (ischaemic stroke only or stroke-heart syndrome but without the pre-existing cardiovascular risk factor). Statistical significance was set at P<0.05.

Cohort characteristics. Of 682,203 patients with ischaemic stroke, 20% (n=135,834) presented with stroke-heart syndrome (49% (n=67,008) female and 50% (n=67,683) male). Following propensity score matching there were 269,210 patients in the overall analyses, 135,366 matched-males and 132,856 matched-females. Overall, the cohorts were well-matched for age, sex, ethnicity, included comorbidities, cardiovascular procedures, and cardiovascular medications (Supplement 3; Tables 2-4).

Clinical outcomes. Following propensity score matching, composite stroke-heart syndrome associated with significantly higher risk of 5-year mortality (HR 1.47, 95% CI 1.44-1.49, P<0.01), recurrent stroke (HR 1.12, 1.11-1.13, P<0.01), and AMI (HR 2.50, 2.43-2.58, P<0.01), compared to ischaemic stroke without cardiac complications. Overall, the HRs for these

outcomes were similar for females and males. When stratified by cardiovascular risk factors, all HRs tended to be higher compared to without the risk factor. This was particularly true for patients with stroke-heart syndrome and T2DM who had the highest risk of mortality for females (HR 1.70, 1.59-1.81, P<0.01) and males (HR 1.63, 1.53-1.73, P<0.01) as well as the highest risk of AMI for females (HR 2.91, 2.61-3.24, P<0.01) and males (HR 3.14, 2.86-3.46, P<0.01). Similarly, the highest risks for recurrent stroke were seen for patients with stroke-heart syndrome and hypertension for females (HR 1.82, 1.79-1.85, P<0.01) and males (HR 1.88, 1.85-1.92, P<0.01); T2DM for females (HR 1.67, 1.61-1.74, P<0.01) and males (HR 1.74, 1.68-1.81, P<0.01); and high LDL cholesterol for females (HR 1.60, 1.54-1.65, P<0.01) and males (HR 1.62, 1.56-1.68, P<0.01).

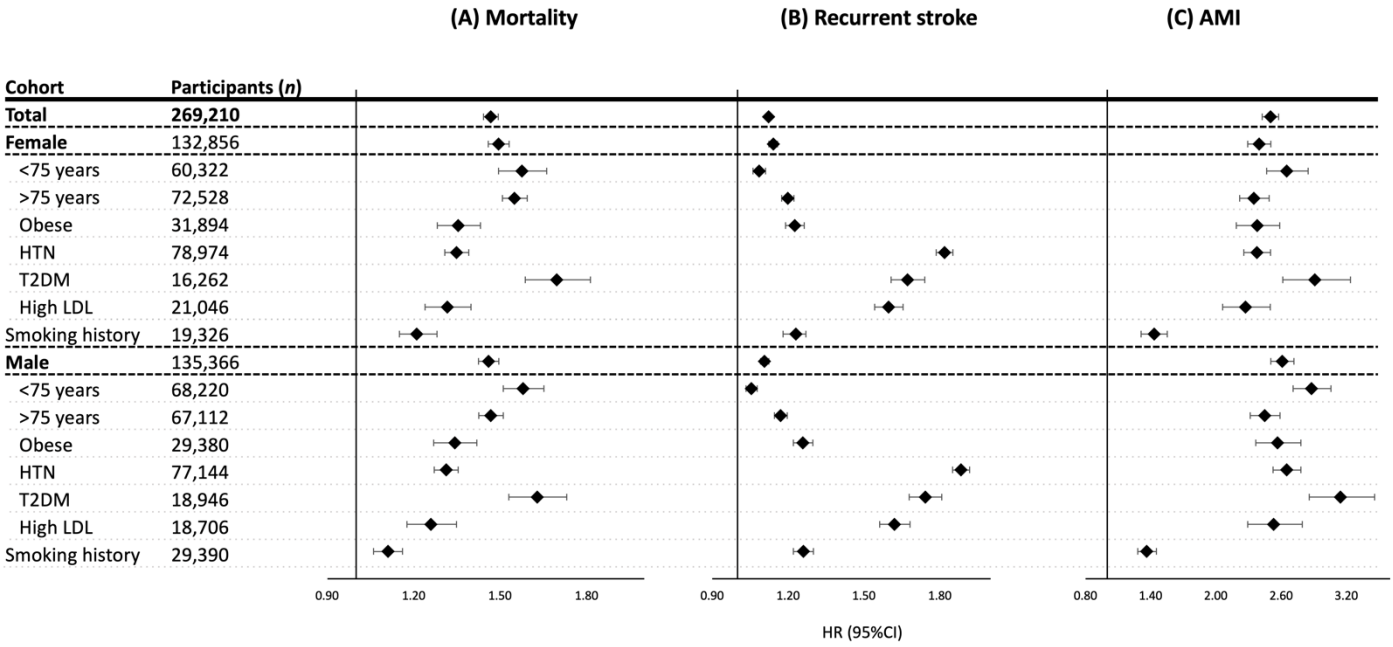

Figure 1. Forest plots presenting hazard ratios and 95% confidence intervals for mortality (A), recurrent stroke (B), and acute myocardial infarction (C) comparing patients with stroke-heart syndrome to propensity score matched patients without stroke-heart syndrome (total cohort, female, and male comparisons) following incident ischaemic stroke. The analyses stratified by cardiovascular risk factors (age, obesity, hypertension, diabetes, LDL, smoking) include patients with stroke-heart syndrome comparing those with and without the risk factor of interest. Sample size represents exposure and control cohort.
AMI; acute myocardial infarction HTN; hypertension, LDL; low-density lipoprotein;
T2DM; type 2 diabetes mellitus,

Table 1. Incidence of each investigated risk factor with stroke-heart syndrome and associated 5-year event rates for mortality, recurrent stroke, and acute myocardial infarction, following propensity score matching.

Cohort	% (n) with risk factor and SHS (i.e., incidence)	HR (95% CI) for mortality	HR (95% CI) for recurrent stroke	HR (95% CI) for AMI
Total*	135,834	1.47 (1.44, 1.49)	1.12 (1.11, 1.13)	2.50 (2.43, 2.58)
Female*	67,008	1.49 (1.46, 1.53)	1.14 (1.12, 1.16)	2.40 (2.29, 2.50)
Male*	67,683	1.46 (1.42, 1.50)	1.11 (1.09, 1.12)	2.61 (2.50, 2.72)
Females <75 years[#]	30,161	1.58 (1.49, 1.66)	1.09, 1.06, 1.11)	2.65 (2.47, 2.85)
Males <75 years[#]	34,110	1.58 (1.51, 1.65)	1.05 (1.03, 1.08)	2.88 (2.71, 3.06)
Females ≥75 years[#]	36,264	1.55 (1.51, 1.59)	1.20 (1.17, 1.22)	2.35 (2.22, 2.49)
Males ≥75 years[#]	33,556	1.47 (1.43, 1.51)	1.17 (1.15, 1.20)	2.45 (2.31, 2.59)
Females with obesity[#]	15,947	1.35 (1.28, 1.43)	1.23 (1.19, 1.26)	2.38 (2.19, 2.59)
Males with obesity[#]	14,690	1.34 (1.27, 1.42)	1.26 (1.22, 1.30)	2.56 (2.37, 2.78)
Females with HTN[#]	39,487	1.35 (1.31, 1.39)	1.82 (1.79, 1.85)	2.37 (2.26, 2.50)
Males with HTN[#]	38,572	1.31 (1.27, 1.35)	1.88 (1.85, 1.92)	2.65 (2.52, 2.78)
Females with T2DM[#]	8,131	1.70 (1.59, 1.81)	1.67 (1.61, 1.74)	2.91 (2.61, 3.24)
Males with T2DM[#]	9,473	1.63 (1.53, 1.73)	1.74 (1.68, 1.81)	3.14 (2.86, 3.46)
Females with high LDL[#]	10,523	1.32 (1.24, 1.40)	1.60 (1.54, 1.65)	2.27 (2.06, 2.50)
Males with high LDL[#]	9,353	1.26 (1.18, 1.35)	1.62 (1.56, 1.68)	2.53 (2.29, 2.79)
Females with smoking history[#]	9,663	1.21 (1.15, 1.28)	1.23 (1.18, 1.27)	1.43 (1.31. 1.55)

Males with smoking history[#]	14,695	1.11 (1.06, 1.16)	1.26 (1.22, 1.30)	1.36 (1.28, 1.45)

AMI; acute myocardial infarction, CI; confidence interval, HR; hazard ratio, HTN; hypertension, LDL; low density lipoprotein, SHS; stroke-heart syndrome, T2DM; type 2 diabetes mellitus, 95% CI; 95% confidence interval.

*Comparison of stroke-heart syndrome vs ischaemic stroke only.

[#]Comparison of stroke-heart syndrome with cardiovascular risk factor vs stroke-heart syndrome without cardiovascular risk factor.

In this multi-centre cohort study of 682,203 patients with first ischaemic stroke, stroke-heart syndrome had 20% incidence and associated with significantly higher risk of mortality, recurrent stroke, and AMI compared to patients with ischaemic stroke but without new onset cardiac complications. Incidence was similar for males and females but highest among those aged ≥75 years and those with hypertension. Although overall, the risk for 5-year mortality, recurrent stroke, and AMI were similar for females and males, the risk tended to be higher for those with certain modifiable risk factors (i.e., hypertension, T2DM, and high LDL).

Prior work has shown that major adverse cardiovascular events following ischaemic stroke are comparable for males and females and occur in people without known pre-existing risk factors.[7] Interestingly, a higher mortality and lower health related quality of life, seen following ischaemic stroke for females compared to males, is attenuated after correction for age, stroke severity, and pre-morbid function.[8 9] Therefore, no clear sex-based differences in outcomes following stroke-heart syndrome seems in agreement with prior work in ischaemic stroke cohorts. Our finding of higher adverse event risk following stroke-heart syndrome for all investigated (pre-existing) cardiovascular risk factors does, however, emphasise the importance of cardiovascular health in patients with cardiac involvement following stroke.

It is important to note when interpreting these findings that distinguishing stroke–heart syndrome from (otherwise unknown) concomitant or preceding cardiovascular complications is challenging, and reverse causation may have impacted the results. Nonetheless, these results highlight the importance of a broad and comprehensive cardiovascular health focus to promote secondary prevention following stroke.[10] One example of a comprehensive cardiovascular health approach is the American Heart Associations' 'Life's Essential 8'.[9] When maintaining ideal cardiovascular health (diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure), there was a lower lifetime risk of coronary heart disease. Further, the American Heart Association's recent primary care agenda[11] emphasised modifiable risk factors for cognitive decline including depression, hypertension, physical inactivity, diabetes, obesity, hyperlipidaemia, poor diet, smoking, social isolation, excessive alcohol use, sleep disorders, and hearing loss. This focus on both heart and brain health is topical and supported by the present study's findings.

Collectively, this highlights a need for a comprehensive cardiovascular health rehabilitation pathway for those with multimorbid brain-heart conditions, such as stroke-heart syndrome.[10] Further research is therefore warranted which (prospectively) investigates integrated and comprehensive cardiovascular health rehabilitation for patients with stroke-heart syndrome.

Overall, the incidence of new-onset cardiac complications following ischaemic stroke (stroke-heart syndrome) was 20% and comparable for females and males. Stroke-heart syndrome associated with higher 5-year risk of mortality, recurrent stroke, and AMI compared to matched patients with ischaemic stroke but without cardiac complications. Risk was similar for males and females. However, of those with stroke-heart syndrome, the highest risk of poor prognosis was in those with additional modifiable risk factors, particularly hypertension, type 2 diabetes mellitus, and high LDL cholesterol.

Authors contributions

Authorship: BB contributed to the conception and design of the work. BB and SH contributed to the acquisition, analysis, and interpretation of data for the work. BB drafted the manuscript. SH, DAL, AH, GYHL critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data availability

To gain access to TriNetX data, a request can be made (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained.

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