Title: Anger or Emotional Upset and Heavy Physical Exertion as Triggers of Stroke: The INTERSTROKE Study

Short Title: Triggers of Stroke

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Abstract

Aims: In INTERSTROKE, we explored the association of anger or emotional upset and heavy physical exertion with acute stroke, to determine the importance of triggers in a large, international population.

Methods & Results: INTERSTROKE was a case-control study of first stroke in 32 countries. Using 13,462 cases of acute stroke we adopted a case-crossover approach to determine whether a trigger within one hour of symptom onset (case period), vs. the same time on the previous day (control period), was associated with acute stroke. 9.2% (n=1,233) were angry or emotional upset and 5.3% (n=708) engaged in heavy physical exertion during the case period. Anger or emotional upset in the case period was associated with increased odds of all stroke (Odds Ratio (OR) 1.37, 99% Confidence Interval (CI), 1.15-1.64), ischemic stroke (OR 1.22, 99% CI, 1.00-1.49) and intracerebral hemorrhage (ICH) (OR 2.05, 99% CI 1.40-2.99). Heavy physical exertion in the case period was associated with increased odds of ICH (OR 1.62, 99% CI 1.03-2.55) but not with all stroke or ischemic stroke. There was no modifying effect by region, prior cardiovascular disease, risk factors, prevention medications, time or day of symptom onset. Compared with exposure to neither trigger during the control period, the odds of stroke associated with exposure to both triggers were not additive.

Conclusion: Acute anger or emotional upset was associated with the onset of all stroke, ischemic stroke and ICH, while acute heavy physical exertion was associated with ICH only.

Keywords: stroke, triggers, exertion, anger

Introduction

As stroke is a leading global cause of death and disability, stroke prevention is a global health priority[1, 2]. The INTERSTROKE study reported that ten potentially modifiable chronic risk factors are collectively associated with approximately 90% of the population attributable risk of stroke[3]. Despite multiple approaches to measuring cardiovascular risk burden, it remains difficult to predict when a stroke will occur[4]. Importantly, this risk burden predominantly reflects medium to long-term exposures (including hyperlipidaemia, obesity and smoking) rather than acute exposures with transient effects that may act as triggers of stroke[5]. This has been explored extensively for myocardial infarction, including our report on physical exertion, anger or emotional upset as triggers of acute events[6]. Although previous studies identified psychological stress[7, 8], life events[9], alcohol abuse, clinical infection, anger, coffee intake, sexual activity, trauma and surgery as potential triggers of stroke[10-12]. Few report on heavy physical exertion, anger or emotional upset and those studies had small sample sizes and were completed in one country or geographical region[13]. As with medium to long-term cardiovascular risk factors, the prevalence and relative importance of triggers may also vary by geographical region, justifying the need for international studies with standardized methodologies to explore this question. The INTERSTROKE study provides an ideal opportunity to explore the association between two potential triggers and acute stroke, including important effect modifiers, in a large, international population.

Methods

Population

INTERSTROKE is a large, international, case-control study carried out in 142 centres in 32 countries, whose methods have previously been described in detail[14]. In brief, cases were patients with acute first stroke (within 5 days of symptom onset and subsequent confirmed

neuroimaging within 1 week of presentation) who were recruited into INTERSTROKE and completed questionnaires within 72 hours of hospital admission. Age- and sex-matched controls (community-based or hospitals-based) were also recruited. In these analyses, we include only the cases of stroke, as the exposure to potential triggers was collected systematically in cases but not in controls.

Study Procedures

Research study staff performed a standardized physical examination on participants and administered a structured questionnaire. Participants with acute stroke were asked dichotomous questions, "Were you angry or emotionally upset?" and "Were you engaged in heavy physical exertion?" in the one hour before the onset of symptoms and during the corresponding one hour period on the previous day. Data were also collected for age, gender, smoking, usual physical activity, stress, education, medication use and cardiovascular risk factors. Hypertension was defined as a self-reported history of hypertension or blood pressure ≥140/90mmHg (including adjusted admission blood pressure, as previously reported[3]). Diabetes mellitus was defined as self-reported history of diabetes mellitus or HbA1c ≥6.5%. A history of atrial fibrillation prior to presentation was self-reported. Baseline physical activity, including work and leisure time, was categorised as sedentary (1-3 hours/week), mildly active (4 hours/week), moderately active (5hours/week) or strenuous (6 hours/week). Smoking status was defined as never, former or current smoking. Baseline level of stress, including work and home time, was dichotomised as none or some periods vs. several periods or permanent stress. Depression was defined as feeling sad, blue or depressed in the two weeks prior to stroke. Education was categorised as none, 1-8 years, 9-12 years or Trade School, College or University. Countries were grouped into seven geographical regions: (i) Western Europe, North America, Australia (Canada, Australia, Germany, Denmark, Sweden, United Kingdom and Ireland); (ii) Eastern Europe,

Central Europe, Middle East (Croatia, Poland, Turkey, Iran, United Arab Emirates, Russia and Saudi Arabia); (iii) China; (iv) South America (Argentina, Brazil, Chile, Colombia, Ecuador and Peru); (v) Southeast Asia (Thailand, Philippines and Malaysia); (vi) South Asia (India and Pakistan); (vii) Africa (South Africa, Mozambique, Uganda, Sudan and Nigeria). All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences (Hamilton, ON, Canada). The study was approved by appropriate ethics committees in all centres and/or countries; all participants, or their proxy, provided written informed consent on study enrollment; and the study was completed in line with ethical standards within each country.

Statistical Analysis

Categorical variables are presented as percentage (number) and continuous variables as mean (SD) or median (25th-75th percentiles), as appropriate. A case-crossover approach was used in which each participant acts as his/her own control[15]. The case period was defined as the one hour before the onset of stroke symptoms; the control period was defined as the corresponding one hour period on the day before symptom onset. Conditional logistic regression was used to estimate odds ratios (OR) and 99% confidence intervals (CIs) for anger or emotional upset and heavy physical exertion within the case period compared with the control period for all stroke, ischemic stroke and intracerebral hemorrhage (ICH). Because each participant acted as her or her own control, multivariable adjustment for baseline confounding factors was not required, but we did adjust for (i) the other triggering event because it varies with time, and (ii) an interaction between both triggers, as the interaction was statistically significant (p=0.004). Population-attributable risk (PAR) was calculated from the proportion of participants with exposure to the potential triggers in the case and control periods[16]; 99% CIs are also reported. The Breslow-Day test of homogeneity was used to explore if the

conditional relationship between triggers and acute stroke was consistent by the time and day of onset of stroke[17].

To explore if the associations differed significantly by conventional risk factors for stroke, analyses were stratified by the following pre-specified subgroups: age (<45, 45-65, >65 years), sex, smoking, diabetes mellitus, hypertension, atrial fibrillation, body mass index (BMI) (<25, 25-29.9, ≥30kg/m^2), angina and myocardial infarction. For anger or emotional upset, stratified analyses were also completed by baseline level of chronic stress, depression and level of education to explore if the associations differed by baseline psychosocial factors. For heavy physical exertion, stratified analyses were also completed by baseline level of physical activity to explore if the associations differed by usual level of activity as a proxy for physical fitness. Subgroup analyses are also presented for all stroke, ischemic stroke and ICH. For all stroke only, we also explored for differences in the observed associations by medications commonly used for the prevention of cardiovascular disease (aspirin, beta-blocker, ACE-i/ARB, lipid-lowering therapy and oral anticoagulant therapy), geographical region, the time and the day of the week of symptom onset. Differential effects between stratified analyses were considered significant if the p-value for the interaction term between the stratifying variable and the trigger was <0.01; this more conservative threshold was chosen to address multiple testing. A sensitivity analysis was restricted to those participants who completed all questionnaires themselves, thus excluding those cases of acute stroke in whom questionnaires were completed by proxies. All statistical analyses were performed with Stata/MP 16.1, except for population-attributable risk, for which R version 3.3.1 for Mac was used.

Results

Of the 13,462 included participants with stroke, the mean age was 62.2 (13.6) years, 59.6% (n=8,021) were male, and there was representation from multiple ethnicities and regions

(Supplementary Table 1). The questionnaire was completed by the individual only in 41.4% (n=5,573), by a proxy only in 36.9% (n=4,967) and a combination of the individual and proxy in 21.7% (n=2,918).

Anger or Emotional Upset as a Trigger

Anger or emotional upset was reported by 9.2% (n=1,233) of participants during the case period and 8.3% (n=1,111) during the control period. We had missing data for six participants (<0.1%). Those who reported anger or emotional upset in the case period were more likely to be younger, male and to have higher levels of education, BMI and baseline stress. They were also more likely to have a history of diabetes, hypertension, angina, myocardial infarction or depression and less likely to be taking cardiovascular prevention medications (Supplementary Table 2). Compared with the control period, anger or emotional upset occurring during the case period was associated with increased odds of all stroke (OR 1.37, 99% CI 1.15-1.64 and PAR 2.5%, 99% CI 1.2-3.7), ischemic stroke (OR 1.22, 99% CI 1.00-1.49 and PAR 1.6%, 99% CI 0.0-3.2) and ICH (OR 2.05, 99% CI 1.40-2.99 and PAR 2.5%, 99% CI 1.8-5.8) (Figure 1, Supplementary Table 3). The odds of stroke occurring in those with anger or emotional upset in the case period were greater in those without a history of depression for all stroke ($p_{interaction}$ <0.001), ischemic stroke ($p_{interaction}$ <0.001) and ICH ($p_{interaction}$ 0.012). The odds of stroke occurring in those with anger or emotional upset were greater in those with lower levels of education for all stroke ($p_{interaction}$ <0.001) and ICH ($p_{interaction}$ 0.001), and in those without a history of diabetes for ICH ($p_{interaction}$ 0.002). There was no other effect modification by age group, gender, smoking, hypertension, atrial fibrillation, BMI, previous angina, previous myocardial infarction or baseline level of stress.

Heavy Physical Exertion as a Trigger

Heavy physical exertion was reported by 5.3% (n=708) of participants during the case period and 5.4% (n=725) during the control period. We had missing data for four participants (<0.1%). Those who reported heavy physical exertion in the case period were more likely to be younger, male, current smokers and not diabetic. They also were more likely to have higher levels of baseline physical activity and higher adjusted systolic blood pressure at the time of admission (Supplementary Table 3). Compared with the control period, heavy physical exertion occurring during the case period was not associated with all stroke (OR 1.02, 99% CI 0.82-1.27 and PAR 0.1%, 99% CI -1.0-1.1) or ischemic stroke (OR 0.89, 99% CI 0.69-1.14 and PAR -0.6%, 99% CI -2.0-0.5), but was associated with increased odds of ICH (OR 1.62, 99% CI 1.03-2.55 and PAR -0.9%, 99% CI -4.0-1.3) (Figure 2, Supplementary Table 5). The odds of all stroke occurring in those with heavy physical exertion in the case period were higher in females ($p_{interaction}$ 0.01), but there was no significant effect modification by age group, smoking, diabetes, hypertension, atrial fibrillation, previous angina, previous myocardial infarction, baseline atrial fibrillation or baseline level of physical activity. The odds of ICH were lowest in participants with BMI 25-29.9 ($p_{interaction}$ 0.001).

Effects of Both Triggers

Compared with exposure to neither trigger during the control period, the adjusted odds of stroke associated with exposure to both heavy physical exertion and anger or emotional upset occurring during the case period was not additive.

Effect Modification by Cardiovascular Medications

There were no significant modification of the associations between either anger or emotional upset and heavy physical exertion and all stroke when analyses were stratified by

baseline use of aspirin, beta-blockers, ACE-i/ARB, cholesterol lowering therapy or oral anticoagulants (Supplementary Table 6).

Effect Modification by Geographical Region and Timing of Stroke

In analyses stratified by geographical region, there was no significant effect modification for the association between all stroke and anger or emotional upset and heavy physical exertion in the case period (Figure 3, Supplementary Table 7). The conditional relationship between each trigger and all stroke was consistent by time and day of onset (p-value for homogeneity >0.05 for each comparison).

Ischemic Stroke Subtypes

For anger or emotional upset, the greatest magnitude of association was seen for those with 'other' (OR 2.53, 99% CI 1.30-4.90) ($p_{interaction}$ <0.001)(Table 1). There was no significant effect modification on analyses stratified by OCSP classification ($p_{interaction}$ 0.72). For heavy physical exertion, there were no significant effect modification on analyses stratified by etiological classification ($p_{interaction}$ 0.17) or OCSP classification ($p_{interaction}$ 0.43).

Sensitivity Analyses

Analyses restricted to participants who completed the questionnaires themselves showed similar results to our primary analyses. Anger or emotional upset in the case period was associated with increased odds of all stroke (OR 1.40, 99% CI 1.09-1.81), there was a weak and non-significant association with ischemic stroke (OR 1.25, 99% CI 0.95-1.63), but a strong and increased odds of ICH (OR 3.93, 99% CI 1.62-9.56) ($p_{interaction}$ 0.001). There was no association between heavy physical exertion in the case period and all stroke (OR 1.04, 99%

CI 0.77-1.40) or ischemic stroke (OR 0.94, 99% CI 0.68-1.29), but increased odds of ICH (OR 2.86, 99% CI 1.00-8.15)($p_{interaction}$ 0.009).

Discussion

In this large, international study we report that anger or emotional upset occurring in the one hour before stroke is relatively common and was associated with all stroke types, particularly for intracerebral hemorrhage. Heavy physical exertion was associated with increased odds of ICH only. No additive effects were seen in participants with both heavy physical exertion and anger or emotional upset in the one hour before stroke, and there were no significant differences by geographical region. Our findings are consistent with previous, although limited, research[13, 18], and extend findings to an international global population.

Although long-term exposure to established cardiovascular risk factors is associated with approximately 90% of the population-attributable risk of stroke (controlled for age and sex)[3], they do not explain circadian or seasonal variations in stroke incidence. Although multiple studies report on the role of potential triggering events of myocardial infarction[6, 19], less is known about potential triggering events of stroke. In the setting of already reduced perfusion, such as the presence of atherosclerotic plaque, exposure to the trigger may lead to a cardiovascular event[20]. However, the pathogenesis of ischemic stroke is more varied and less often due to atherosclerotic plaque, which may account for differences in pattern and magnitude of association for stroke, compared to acute myocardial infarction. In contrast, acute increases in blood pressure is a significant risk factor for ICH[12], and represents the most likely mechanism underlying the association with triggering events.

The case-crossover design is a powerful approach to study potential external triggers and effect modification as each individual serves as his or her own control, thereby controlling for many potential confounders. We did adjust for exposure to the other potential triggering

event, which may vary with time within the individual, unlike common risk factors such as hypertension and diabetes. We chose one hour as the case period as the transient effects of external triggers decrease significantly with time after exposure, modifying the likelihood that an association between external triggers and stroke would be found. Triggers, such as acute exposure to anger or emotional upset or heavy physical exertion, are thought to lead to sympathetic activation[21], catecholamine secretion[22], vasoconstriction and increased heart rate and blood pressure[12]. Given the importance of raised blood pressure as a risk factor for stroke, and variation in PAR between ischemic stroke and ICH[3], it is plausible that the effects of an external trigger may also differ by stroke type. While short-term increases in blood pressure may precipitate the onset of ICH[12], we speculate that short-term increases in heart rate may lead to an episode of atrial fibrillation leading to cardiac thrombus formation and a delayed onset of ischemic stroke (i.e. beyond one hour and outside our case period). Although we had limited numbers of participants with underlying atrial fibrillation before stroke and the interaction term was not statistically significant, our stratified analyses suggest increased odds of all stroke and ischemic stroke with heavy physical exertion in the case period, consistent with this hypothesis.

As exposure to external triggers is common and clearly does not always lead to stroke, we sought to identify those most at risk from acute exposures. We found no significant effect modification for the association between triggering events and stroke, on stratification by multiple cardiovascular risk factors (including smoking, hypertension, atrial fibrillation, previous angina or myocardial infarction), common cardiovascular prevention medications, time or day of onset of symptoms of stroke. Although previous studies reported circadian variation in the time of onset of stroke, with a peak in the late morning[23, 24], we found no effect modification in the association between triggers and stroke by time of symptom onset. In addition, although the greatest proportion of strokes occurred on Monday, we also found no

effect modification in the association between triggers and stroke by day of symptom onset[24]. Our results from INTERSTROKE add to the literature on identify those most vulnerable to the effects of external triggers through risk factor stratification.

We did observe an increase in the odds of all stroke, ischemic stroke and ICH with anger or emotional upset during the case period in those without a history of depression and also in those with lower levels of education. Taken together, this suggests that those with higher levels of anger or psychological stress may have become acclimatized to the physiological responses to anger or emotional upset, which may blunt the physiological response to acute exposure to anger or upset[18]. Therefore, our findings highlight the importance of minimizing exposure to anger or emotional upset for the majority of the population.

Regular physical activity is known to play a role in the long-term prevention of cardiovascular disease. We did not observe any association between heavy physical exertion and acute stroke and no significant effect modification on analyses stratified by baseline level of physical activity. This contrasts against a previous study that reported moderate to extreme physical exertion as a potential trigger of subarachnoid hemorrhage[25], although the pathogenesis of stroke is different. Therefore, we continue to recommend regular physical activity for the prevention of cardiovascular disease, consistent with previous meta-analyses[26].

The main strengths of this study include the case-control design, ideal to explore the potential impacts of triggering events, and the large international nature of the cohort with first stroke. This also provides us with the ability to explore the role of effect modifiers because of the sample size. INTERSTROKE includes large numbers of individuals from all regions of the world and multiple ethnicities, making the results broadly applicable. INTERSTROKE also includes only participants with first stroke, thereby reducing the possibility that altered lifestyles or risk factors resulting from previous stroke would affect our estimates. In addition, sensitivity analyses yielded similar associations.

The main limitation of this study is recall bias. Although the case-crossover approach, where each participant acts as her or her own control, reduces the effect of differences in perception within participants, participants who experienced stroke may differentially recall the intensity of exposure and may recall exposures as more proximate to the symptom onset. In addition, proxies completed questionnaires on behalf on some participants, who were limited by functional impairment or disability (e.g. participants with anosognosia, amnesia or aphasia), further contributing to recall bias. However, sensitivity analyses restricted to participants that completed questionnaires themselves were similar to our primary results. Second, INTERSTROKE uses an observational design, meaning that we cannot establish causation. Third, exposure to potential triggering events was self-reported and objective scales were not used, as in some previous studies. As our comparison using the case-crossover approach is within individuals, it is unlikely that the lack of objective scales would significantly impact our findings as the participant is likely to interpret heavy physical exertion, anger or emotional upset consistently over time. In addition, our primary findings are consistent with studies of triggers of cardiovascular events, suggesting that our measurements of the exposures are equally valid. Fourth, although standardized methodology was used in all regions, risk factors were self-reported. However, this would likely result in an underestimation of the prevalence of risk factors and bias estimates toward the null. Similarly, because INTERSTROKE only includes those patients presenting with first stroke, these data cannot be applied to the impact of triggering events in a secondary prevention population.

Conclusions

We report that anger or emotional upset is common in the one hour before the onset of symptoms of stroke and was associated with all stroke types. In contrast, the evidence is less convincing to support heavy physical exertion as an external trigger for stroke. There was no

important effect modification by geographical region, time and day of onset of stroke, cardiovascular prevention medications and many cardiovascular risk factors.

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Disclosures

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Data Availability Statement

No new data were generated or analysed in support of this research.

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Figure 1. Association between Anger or Emotional Upset in Case Period and All Stroke, Ischemic Stroke and ICH*

*Adjusted for heavy physical exertion and interaction between heavy physical exertion and anger/emotional upset in case period.

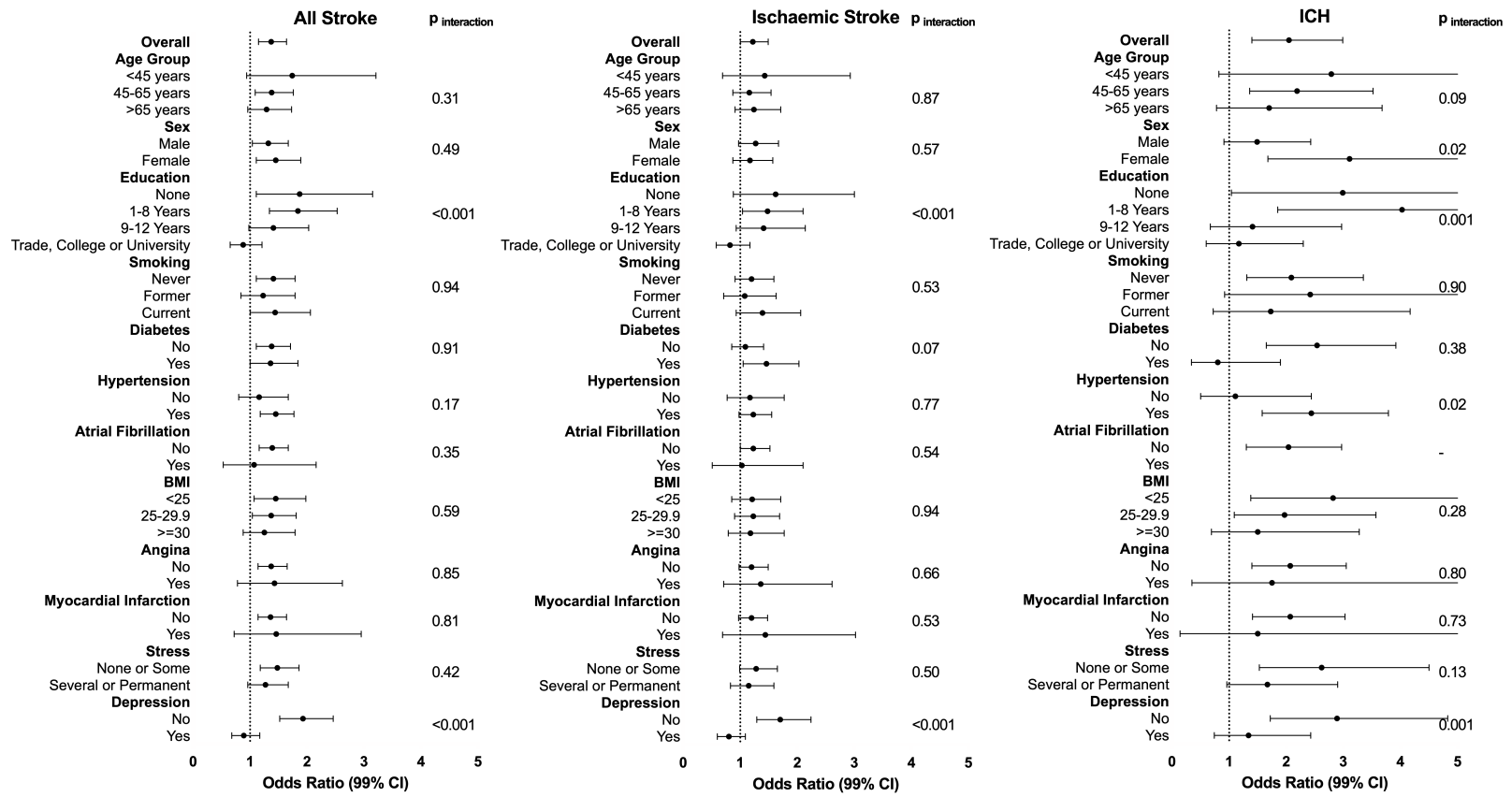


Figure 2. Association between Heavy Physical Exertion in Case Period and All Stroke, Ischemic Stroke and ICH*

Adjusted for anger/emotional upset and interaction between heavy physical exertion and anger/emotional upset in case period

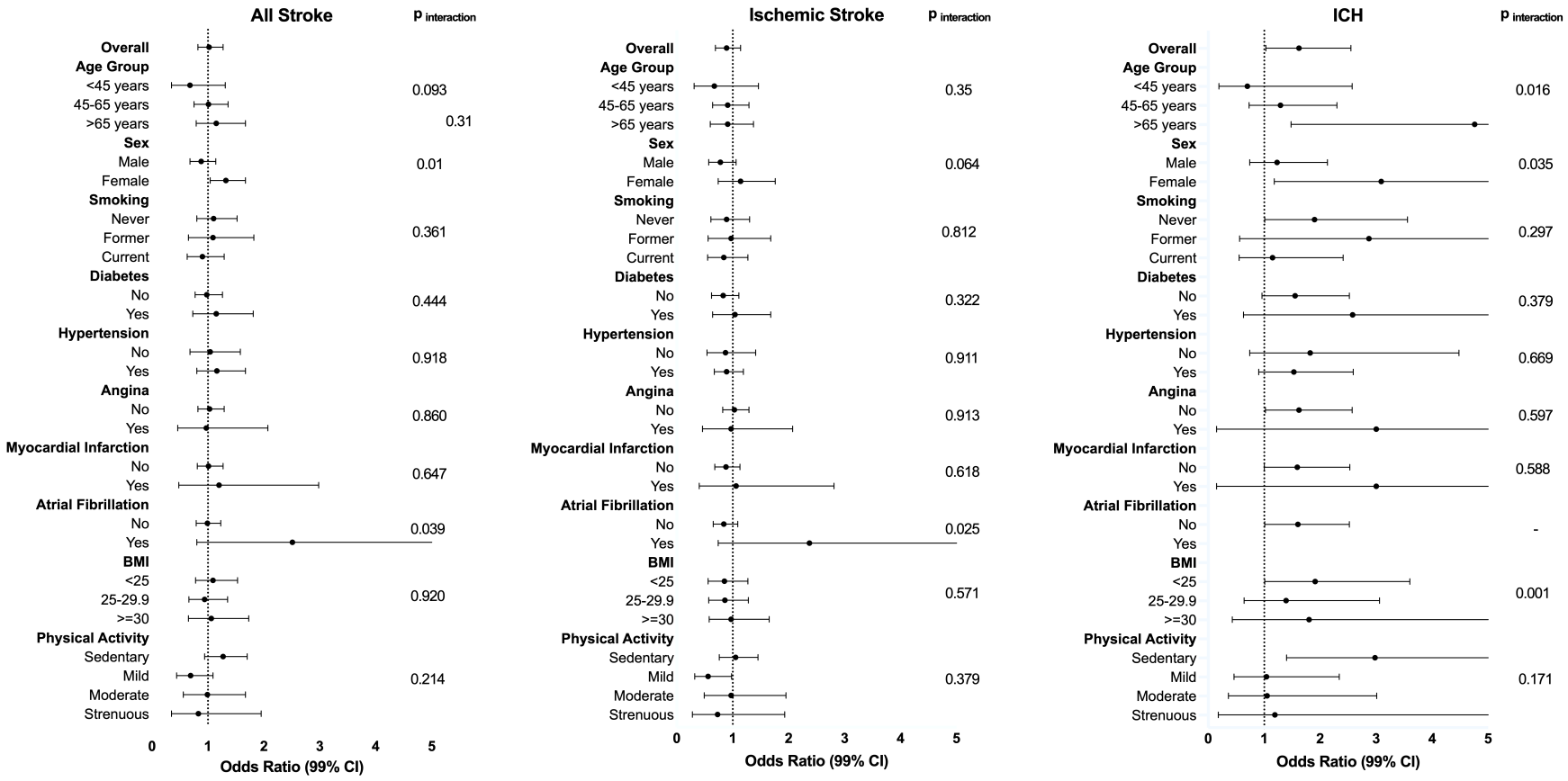
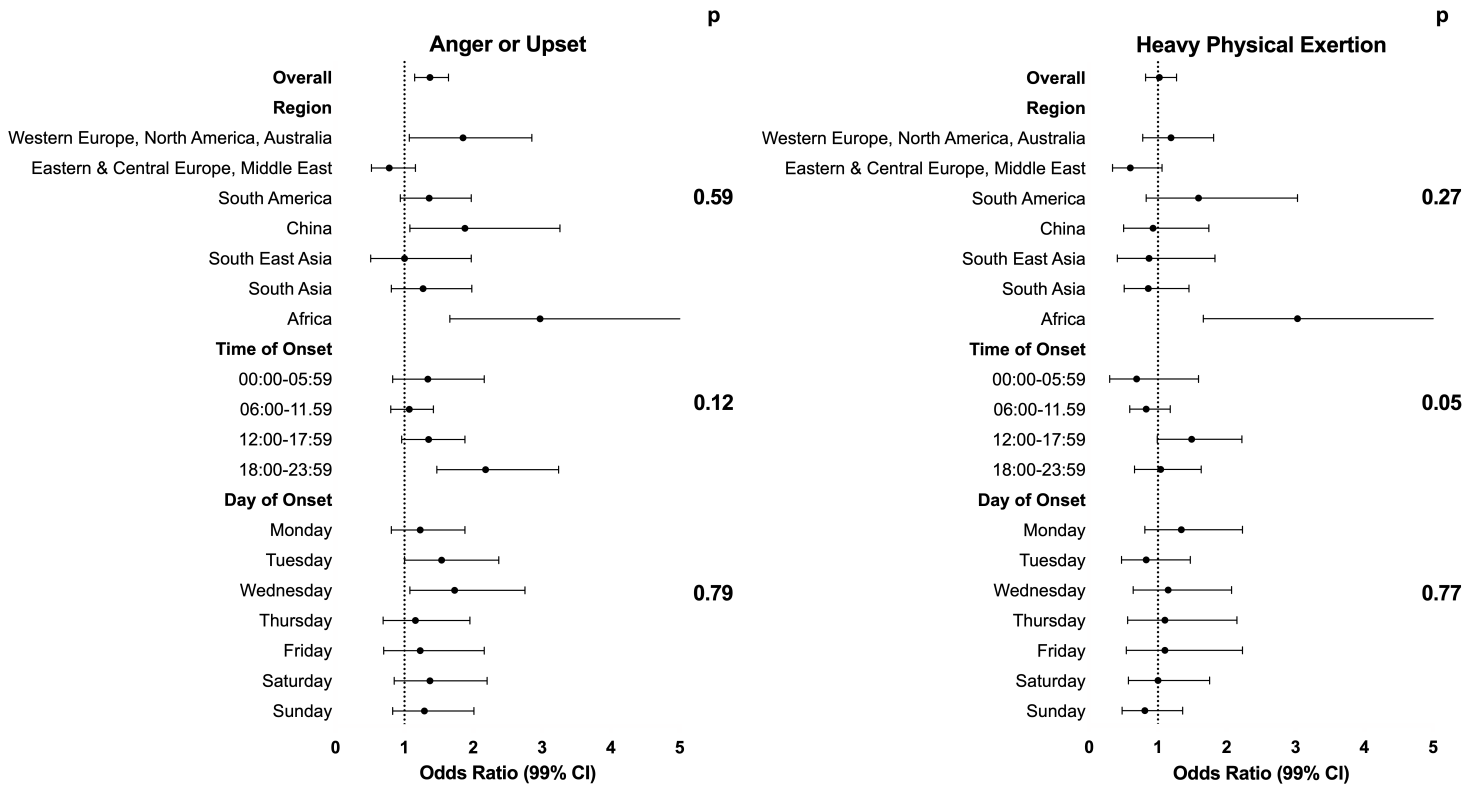


Figure 3. Associations between Potential Triggers and All Stroke, stratified by geographical region, time of onset and day of onset*

*Adjusted for anger/emotional upset and interaction between heavy physical exertion and anger/emotional upset in case period; P for interaction for analyses stratified by region, p for homogeneity for analyses stratified by time of onset and day of onset of stroke



Graphical Abstract

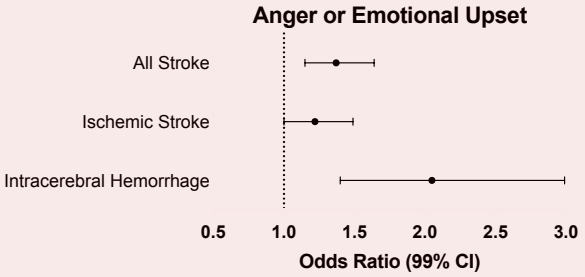
ANGER OR EMOTIONAL UPSET AND HEAVY PHYSICAL EXERTION AS TRIGGERS OF STROKE

INTERSTROKE CASE CONTROL STUDY OF 13,462 CASE OF ACUTE STROKE FROM 32 COUNTRIES

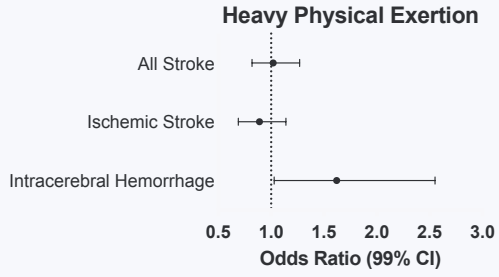
ANGRY OR EMOTIONALLY UPSET? → **1 HOUR BEFORE** STROKE SYMPTOMS

HEAVY PHYSICAL EXERTION? → 1 HOUR ON **DAY BEFORE** SYMPTOMS

CASE-CROSSOVER APPROACH (PARTICIPANT ACTS AS OWN CONTROL)



GREATER ODDS WITHOUT DEPRESSION
GREATER ODDS WITH LOW EDUCATION
NO DIFFERENCE BY AGE, SEX OR RISK FACTORS



GREATER ODDS IN FEMALES
LOWER ODDS WITH NORMAL BMI
NO DIFFERENCE BY AGE, RISK FACTORS OR BASELINE PHYSICAL ACTIVITY

NO INCREASE WITH EXPOSURE TO BOTH TRIGGERS

NO DIFFERENCE BY CARDIOVASCULAR MEDICATIONS

CONSISTENT BY GEOGRAPHICAL **REGION**

CONSISTENT BY TIME & DAY OF ONSET OF STROKE SYMPTOMS

STRENGTHS
INTERNATIONAL COHORT, LARGE NUMBER OF FIRST STROKES, BROAD RANGE OF ETHNICITIES

LIMITATIONS
RECALL BIAS, ASSOCIATION NOT CAUSATION, SELF-REPORTED EXPOSURES

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Characteristics of Cohort

Characteristic		
Age, years, mean (SD)		62.2 (13.6)
Sex, % (n)	Male	59.6% (8,021)
	Female	40.4% (5,441)
Ethnicity, % (n)	European	21.8% (2,937)
	Chinese	29.9% (4,016)
	South Asian	22.5% (3,032)
	Other Asian	5.2% (704)
	Latin American or Aboriginal	10.4% (1,400)
	Black African	3.7% (504)
	Other	6.5% (869)
Education, % (n)	None	16.0% (2,156)
	1-8 years	39.7% (4,933)
	9-12 years	26.3% (3,541)
	Trade School, College or University	21.0% (2,830)
Smoking, % (n)	Never	55.8% (7,502)
	Former	13.9% (1,875)
	Current	30.3% (4,078)
Diabetes, % (n)		28.1% (3,776)
Hypertension, % (n)		72.6% (9,775)
Atrial Fibrillation, % (n)		4.8% (642)
Global Stress, %(n)	None/Some periods	79.4% (10,605)
	Several/Permanent	20.6% (2,745)
Depression		18.4% (2,456)
BMI	<25	48.7% (6,437)
	25-29.9	34.7% (4,588)
	≥30	16.6% (2,188)
Medications, % (n)	ACE-i/ARB	20.6% (2,775)
	Aspirin	15.7% (2,111)
	Beta Blocker	13.9% (1,876)
	Cholesterol-lowering therapy	11.5% (1,545)
	Oral Anticoagulants	2.1% (279)
Previous CVD, % (n)	Myocardial Infarction	4.8% (641)
	Angina	5.9% (789)
Physical Activity, % (n)	Sedentary	76.4% (10,278)
	Mild Exercise	13.3% (1,790)
	Moderate Active	7.6% (1,021)
	Strenuous Exercise	2.7% (365)
Time of Onset of Stroke, % (n)	00:00-05:59	12.0% (1,609)
	06:00-11:59	41.9% (5,617)
	12:00-17:59	25.8% (3,459)
	18:00-23:59	20.2% (2,710)

Supplementary Table 1 (continued). Characteristics of Cohort

Characteristic		
Day of Onset of Stroke, % (n)	Monday	16.9% (2,275)
	Tuesday	16.1% (2,160)
	Wednesday	14.6% (1,965)
	Thursday	11.4% (1,529)
	Friday	11.6% (1,562)
	Saturday	13.6% (1,832)
	Sunday	15.9% (2,139)

Supplementary Table 2. Cohort Characteristics by Anger or Emotional Upset during the case period

		No Anger or Emotional Upset (n=12,223)	Anger or Emotional Upset (n=1,233)	p value
Age Group	<45 years	88.6% (1,160)	11.4% (150)	<0.001
	45-65 years	89.8% (5,969)	10.2% (682)	
	>65 years	92.8% (4,864)	7.2% (376)	
Sex	Female	91.7% (7,354)	8.3% (664)	<0.001
	Male	89.5% (4,869)	10.5% (569)	
Smoking Status	Never Smoker	90.8% (6,808)	9.2% (691)	0.004
	Former Smoker	89.1% (1,670)	10.9% (205)	
	Current Smoker	91.8% (3,742)	8.2% (336)	
Diabetes	No	91.5% (8,852)	8.5% (824)	<0.001
	Yes	89.3% (3,369)	10.7% (405)	
Hypertension	No	92.0% (3,392)	8.0% (294)	0.003
	Yes	90.4% (8,831)	9.6% (939)	
Systolic Blood Pressure	Time of Admission	158.8 (23.0)	159.3 (31.5)	0.58
	Morning after Admission	145.7 (23.6)	146.0 (25.5)	0.58
	Time of Interview	141.2 (21.5)	142.3 (23.7)	0.08
Atrial Fibrillation	No	90.9% (11,641)	9.1% (1,172)	0.76
	Yes	90.5% (581)	9.5% (61)	
BMI	<25	93.4% (6,012)	6.6% (423)	<0.001
	25-29.9	90.0% (4,129)	10.0% (459)	
	≥30	86.8% (1,898)	13.2% (289)	
Angina	No	91.1% (11,538)	8.9% (1,128)	<0.001
	Yes	86.7% (684)	13.3% (105)	
Myocardial Infarction	No	91.1% (11,672)	8.9% (1,143)	<0.001
	Yes	85.9% (550)	14.1% (90)	
Global Stress	None / Some Periods	93.9% (9,961)	6.1% (643)	<0.001
	Several Periods / Permanent	78.8% (2,163)	21.2% (582)	
Depression	No	93.3% (10,194)	6.7% (731)	<0.001
	Yes	79.8% (1,960)	20.2% (495)	
Education	None	92.7% (1,998)	7.3% (158)	<0.001
	1-8 Years	91.6% (4,520)	8.4% (413)	
	9-12 Years	92.0% (3,254)	8.0% (284)	
	Trade, College or University	86.7% (2,451)	13.3% (3773)	
Aspirin	No	91.3% (10,362)	8.7% (984)	<0.001
	Yes	88.2% (1,860)	11.8% (249)	
Beta Blocker	No	91.5% (10,588)	8.5% (989)	<0.001
	Yes	87.0% (1,632)	13.0% (243)	
ACE-i/ARB	No	91.6% (9,791)	8.4% (893)	<0.001
	Yes	87.7% (2,432)	12.3% (340)	
Cholesterol Lowering Therapy	No	91.1% (10,854)	8.9% (1,059)	0.002
	Yes	88.7% (1,369)	11.3% (174)	
Oral Anticoagulants	No	91.0% (11,986)	9.0% (1,190)	<0.001
	Yes	84.6% (236)	15.4% (43)	

Supplementary Table 2 (continued). Cohort Characteristics by Anger or Emotional Upset during the case period

		No Anger or Emotional Upset (n=12,223)	Anger or Emotional Upset (n=1,233)	p value
Region	Western Europe, North America, Australia	91.2% (1,745)	8.8% (168)	<0.001
	Eastern & Central Europe, Middle East	85.3% (1,189)	14.7% (205)	
	South America	84.9% (1,248)	15.1% (222)	
	China	96.5% (3,849)	3.5% (138)	
	Southeast Asia	91.6% (783)	8.4% (72)	
	South Asia	90.9% (2,604)	9.1% (260)	
	Africa	82.7% (805)	17.3% (168)	
Time of Onset	00:00 – 06:00	90.4% (1,454)	9.6% (154)	<0.001
	06:00 – 12:00	92.6% (5,197)	7.4% (416)	
	12:00 – 18:00	89.9% (3,111)	10.1% (348)	
	18:00 – 24:00	88.6% (2,401)	11.4% (308)	
Day of Week of Onset	Monday	90.4% (2,056)	9.6% (218)	0.76
	Tuesday	90.9% (1,962)	9.1% (196)	
	Wednesday	91.1% (1,790)	8.9% (174)	
	Thursday	91.2% (1,394)	8.8% (134)	
	Friday	90.5% (1,414)	9.5% (148)	
	Saturday	91.6% (1,678)	8.4% (154)	
	Sunday	90.2% (1,927)	9.8% (209)	

Supplementary Table 3. Association between Anger or Emotional Upset in Case Period and All Stroke, Ischemic Stroke and ICH

	All Stroke			Ischemic Stroke			ICH		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	9.2% (1,233)	1.37 (1.15-1.64)	-	8.8% (922)	1.22 (1.00-1.49)	-	10.2% (311)	2.05 (1.40-2.99)	-
Age Group									
<45	11.5% (150)	1.74 (0.94-3.21)	0.313	12.0% (112)	1.43 (0.69-2.93)	0.870	10.0% (38)	2.79 (0.82-9.51)	0.094
45-65	10.3% (682)	1.38 (1.09-1.76)		9.8% (482)	1.16 (0.87-1.54)		11.5% (200)	2.19 (1.36-3.52)	
>65	7.2% (376)	1.29 (0.96-1.73)		7.1% (309)	1.24 (0.91-1.71)		7.5% (67)	1.70 (0.78-3.68)	
Sex									
Male	8.3% (664)	1.32 (1.04-1.67)	0.486	8.0% (496)	1.27 (0.97-1.67)	0.573	9.2% (168)	1.49 (0.91-2.43)	0.016
Female	10.5% (569)	1.45 (1.11-1.89)		10.1% (426)	1.17 (0.87-1.57)		11.7% (143)	3.11 (1.68-5.78)	
Education									
None	7.3% (158)	1.87 (1.11-3.15)	<0.001	7.0% (112)	1.62 (0.88-3.00)	<0.001	8.3% (46)	2.99 (1.04-8.59)	0.001
1-8 Years	8.4% (413)	1.84 (1.34-2.53)		8.2% (305)	1.48 (1.04-2.10)		8.8% (108)	4.03 (1.85-8.78)	
9-12 Years	8.0% (284)	1.41 (0.98-2.03)		7.6% (211)	1.41 (0.93-2.14)		9.6% (73)	1.41 (0.67-2.97)	
Trade, College or University	13.3% (377)	0.88 (0.65-1.21)		12.7% (293)	0.82 (0.58-1.17)		16.3% (84)	1.17 (0.60-2.30)	
Smoking									
Never	9.2% (691)	1.41 (1.11-1.79)	0.940	8.8% (495)	1.20 (0.91-1.59)	0.532	10.5% (196)	2.09 (1.31-3.35)	0.895
Former	10.9% (205)	1.23 (0.84-1.79)		10.0% (159)	1.08 (0.71-1.63)		16.0% (46)	2.42 (0.92-6.37)	
Current	8.2% (336)	1.44 (1.00-2.06)		8.4% (267)	1.39 (0.93-2.06)		7.7% (69)	1.73 (0.72-4.17)	
Diabetes									
No	8.5% (824)	1.38 (1.11-1.71)	0.909	8.0% (579)	1.09 (0.85-1.41)	0.074	9.9% (245)	2.54 (1.65-3.92)	0.002
Yes	10.7% (405)	1.36 (1.00-1.84)		10.6% (339)	1.46 (1.05-2.03)		11.2% (66)	0.80 (0.34-1.90)	
Hypertension									
No	8.0% (294)	1.16 (0.80-1.67)	0.167	8.3% (243)	1.17 (0.77-1.77)	0.771	6.6% (51)	1.11 (0.50-2.44)	0.024
Yes	9.6% (939)	1.45 (1.18-1.77)		9.1% (679)	1.23 (0.98-1.55)		11.4% (260)	2.44 (1.58-3.79)	
Atrial Fibrillation									
No	9.2% (1,172)	1.39 (1.16-1.67)	0.354	8.9% (866)	1.23 (1.00-1.52)	0.540	10.1% (306)	2.04 (1.30-2.97)	-
Yes	9.5% (61)	1.07 (0.53-2.16)		9.2% (56)	1.03 (0.51-2.10)		14.7% (5)	-	
Angina									
No	8.9% (1,128)	1.37 (1.14-1.65)	0.850	8.6% (829)	1.20 (0.98-1.49)	0.656	10.0% (299)	2.07 (1.40-3.05)	0.797
Yes	13.3% (105)	1.43 (0.78-2.62)		12.9% (93)	1.36 (0.71-2.61)		17.4% (12)	1.75 (0.35-8.80)	

*Adjusted for heavy physical exertion and interaction between heavy physical exertion and anger/emotional upset in case period.

Supplementary Table 3 (continued). Association between Anger or Emotional Upset in Case Period and All Stroke, Ischemic Stroke and ICH

	All Stroke			Ischemic Stroke			ICH		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	9.2% (1,233)	1.37 (1.15-1.64)	-	8.8% (922)	1.22 (1.00-1.49)	-	10.2% (311)	2.05 (1.40-2.99)	-
Myocardial Infarction									
No	8.9% (1,143)	1.36 (1.14-1.64)	0.811	8.6% (840)	1.20 (0.97-1.48)	0.531	10.1% (303)	2.07 (1.41-3.03)	0.729
Yes	14.1% (90)	1.46 (0.72-2.95)		13.8% (82)	1.44 (0.69-3.02)		17.8% (8)	1.50 (0.14-15.75)	
BMI									
<25	6.6% (423)	1.45 (1.07-1.98)	0.591	6.7% (317)	1.21 (0.85-1.71)	0.940	6.3% (106)	2.82 (1.38-5.73)	0.281
25-29.9	10.0% (459)	1.37 (1.04-1.81)		9.3% (340)	1.23 (0.90-1.69)		12.8% (119)	1.97 (1.09-3.57)	
>=30	13.2% (289)	1.25 (0.88-1.79)		12.6% (226)	1.18 (0.79-1.77)		16.2% (63)	1.50 (0.69-3.28)	
Stress									
None or Some	6.1% (643)	1.48 (1.18-1.86)	0.415	6.0% (494)	1.28 (0.99-1.65)	0.504	6.3% (149)	2.62 (1.53-4.50)	0.133
Several or Permanent	21.2% (582)	1.27 (0.96-1.67)		20.0% (421)	1.15 (0.83-1.59)		25.4% (161)	1.67 (0.96-2.90)	
Depression									
No	6.7% (731)	1.93 (1.52-2.46)	<0.001	6.4% (537)	1.70 (1.29-2.24)	<0.001	7.6% (194)	2.89 (1.72-4.83)	0.012
Yes	20.2% (495)	0.89 (0.68-1.17)		19.1% (381)	0.80 (0.60-1.09)		24.7% (114)	1.34 (0.74-2.43)	

*Adjusted for heavy physical exertion and interaction between heavy physical exertion and anger/emotional upset in case period

Supplementary Table 4. Cohort Characteristics by Heavy Physical Exertion in case period

		No Heavy Physical Exertion (n=12,750)	Heavy Physical Exertion (n=708)	p value
Age Group	<45 years	93.4% (1,223)	6.6% (87)	<0.001
	45-65 years	93.8% (6,241)	6.2% (410)	
	>65 years	96.2% (5,045)	3.8% (197)	
Sex	Female	96.0% (5,219)	4.0% (219)	<0.001
	Male	93.9% (7,531)	6.1% (489)	
Smoking Status	Never Smoker	95.7% (7,181)	4.3% (320)	<0.001
	Former Smoker	93.9% (1,761)	6.1% (114)	
	Current Smoker	93.3% (3,804)	6.7% (274)	
Diabetes	No	94.3% (9,129)	5.7% (548)	0.001
	Yes	95.8% (3,615)	4.3% (160)	
Hypertension	No	94.5% (3,485)	5.5% (201)	0.54
	Yes	94.8% (9,265)	5.2% (507)	
Systolic Blood Pressure	Time of Admission	158.7 (30.1)	161.9 (30.8)	0.005
	Morning after Admission	145.6 (23.7)	147.3 (24.8)	0.08
	Time of Interview	141.2 (21.7)	142.7 (22.4)	0.07
Atrial Fibrillation	No	94.7% (12,136)	5.3% (679)	0.39
	Yes	95.5% (613)	4.5% (29)	
BMI	<25	95.2% (6,127)	4.8% (309)	0.05
	25-29.9	94.3% (4,328)	5.7% (260)	
	≥30	94.1% (2,058)	5.9% (129)	
Angina	No	94.7% (12,002)	5.3% (666)	0.94
	Yes	94.7% (747)	5.3% (42)	
Myocardial Infarction	No	94.7% (12,135)	5.3% (681)	0.22
	Yes	95.8% (614)	4.2% (27)	
Physical Activity	Sedentary	96.7% (9,939)	3.3% (338)	<0.001
	Mildly Active	89.2% (1,597)	10.8% (193)	
	Moderately Active	87.5% (893)	12.5% (128)	
	Strenuous	86.6% (316)	13.4% (49)	
Aspirin	No	94.7% (10,746)	5.3% (601)	0.67
	Yes	94.9% (2,003)	5.1% (107)	
Beta Blocker	No	94.7% (10,963)	5.3% (615)	0.52
	Yes	95.0% (1,783)	5.0% (93)	
ACE-i/ARB	No	94.8% (10,133)	5.2% (553)	0.38
	Yes	94.4% (2,617)	5.6% (155)	
Cholesterol Lowering Therapy	No	94.8% (11,293)	5.2% (621)	0.48
	Yes	94.4% (1,457)	5.6% (87)	
Oral Anticoagulants	No	94.7% (12,486)	5.3% (692)	0.72
	Yes	94.3% (263)	5.7% (16)	

Supplementary Table 4 (continued). Cohort Characteristics by Heavy Physical Exertion in case period

		No Heavy Physical Exertion (n=12,750)	Heavy Physical Exertion (n=708)	p value
Region	Western Europe, North America, Australia	92.8% (1,777)	7.2% (137)	<0.001
	Eastern & Central Europe, Middle East	93.3% (1,300)	6.7% (94)	
	South America	94.7% (1,392)	5.3% (78)	
	China	96.4% (3,844)	3.6% (143)	
	Southeast Asia	90.8% (776)	9.2% (79)	
	South Asia	96.2% (2,756)	3.8% (109)	
	Africa	93.0% (905)	7.0% (68)	
Time of Onset	00:00 – 06:00	97.4% (1,567)	2.6% (42)	<0.001
	06:00 – 12:00	95.4% (5,357)	4.6% (257)	
	12:00 – 18:00	92.9% (3,212)	7.1% (247)	
	18:00 – 24:00	94.1% (2,549)	5.9% (160)	
Day of Onset	Monday	93.9% (2,135)	6.1% (139)	0.49
	Tuesday	94.9% (2,049)	5.1% (110)	
	Wednesday	95.0% (1,865)	5.0% (99)	
	Thursday	94.7% (1,447)	5.3% (81)	
	Friday	95.3% (1,489)	4.7% (73)	
	Saturday	94.5% (1,731)	5.5% (101)	
	Sunday	95.1% (2,034)	4.9% (105)	

Supplementary Table 5. Association between Heavy Physical Exertion in Case Period and All Stroke, Ischemic Stroke and ICH

	All Stroke			Ischemic Stroke			ICH		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	5.3% (708)	1.02 (0.82-1.27)	-	4.6% (477)	0.89 (0.69-1.14)	-	7.6% (231)	1.62 (1.03-2.55)	-
Age Group									
<45	6.6% (87)	0.68 (0.35-1.31)	0.093	6.4% (60)	0.67 (0.31-1.46)	0.350	7.1% (27)	0.70 (0.19-2.57)	0.016
45-65	6.2% (410)	1.01 (0.75-1.36)		5.4% (263)	0.91 (0.64-1.29)		8.4% (147)	1.29 (0.73-2.30)	
>65	3.8% (197)	1.15 (0.79-1.67)		3.4% (146)	0.91 (0.60-1.37)		5.7% (51)	4.76 (1.48-15.31)	
Sex									
Male	6.1% (489)	0.88 (0.68-1.14)	0.010	5.1% (318)	0.78 (0.57-1.06)	0.064	9.3% (171)	1.26 (0.74-2.13)	0.035
Female	4.0% (219)	1.32 (1.04-1.67)		3.8% (159)	1.14 (0.74-1.76)		4.9% (60)	3.09 (1.18-8.09)	
Smoking									
Never	4.3% (320)	1.10 (0.8-1.52)	0.361	3.7% (208)	0.89 (0.61-1.30)	0.812	6.0% (112)	1.90 (1.01-3.56)	0.297
Former	6.1% (114)	1.09 (0.65-1.82)		5.4% (86)	0.97 (0.56-1.68)		9.8% (28)	2.87 (0.56-14.69)	
Current	6.7% (274)	0.90 (0.63-1.29)		5.8% (183)	0.84 (0.55-1.27)		10.1% (91)	1.15 (0.55-2.41)	
Diabetes									
No	5.7% (548)	0.98 (0.77-1.26)	0.444	4.9% (353)	0.83 (0.62-1.11)	0.322	7.9% (195)	1.55 (0.96-2.52)	0.379
Yes	4.2% (160)	1.15 (0.73-1.81)		3.9% (124)	1.04 (0.64-1.68)		6.1% (36)	2.58 (0.63-10.52)	
Hypertension									
No	5.5% (201)	1.04 (0.68-1.58)	0.918	4.5% (130)	0.87 (0.54-1.41)	0.911	9.2% (71)	1.82 (0.74-4.48)	0.669
Yes	5.2% (507)	1.16 (0.80-1.67)		4.6% (347)	0.89 (0.67-1.19)		7.0% (160)	1.53 (0.90-2.59)	
Angina									
No	5.3% (666)	1.03 (0.82-1.29)	0.860	4.6% (441)	0.88 (0.68-1.15)	0.913	7.5% (225)	1.62 (1.02-2.57)	0.597
Yes	5.3% (42)	0.97 (0.46-2.07)		5.0% (36)	0.91 (0.41-2.03)		8.7% (6)	3.00 (0.15-58.79)	
Myocardial Infarction									
No	5.3% (681)	1.01 (0.81-1.27)	0.647	4.6% (454)	0.88 (0.68-1.13)	0.618	7.5% (227)	1.59 (1.00-2.53)	0.588
Yes	4.2% (27)	1.20 (0.48-2.98)		3.9% (23)	1.06 (0.40-2.81)		8.9% (4)	3.00 (0.15-58.73)	
Atrial Fibrillation									
No	5.3% (679)	0.99 (0.79-1.23)	0.039	4.6% (452)	0.84 (0.65-1.09)	0.025	7.5% (227)	1.60 (1.01-2.52)	-
Yes	4.5% (29)	2.51 (0.80-7.93)		4.1% (25)	2.37 (0.74-7.55)		11.8% (4)	-	

*Adjusted for anger/emotional upset and interaction between heavy physical exertion and anger/emotional upset in case period

Supplementary Table 5 (continued). Association between Heavy Physical Exertion in Case Period and All Stroke, Ischemic Stroke and ICH

	All Stroke			Ischemic Stroke			ICH		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	5.3% (708)	1.02 (0.82-1.27)	-	4.6% (477)	0.89 (0.69-1.14)	-	7.6% (231)	1.62 (1.03-2.55)	-
BMI									
<25	4.8% (309)	1.09 (0.78-1.53)	0.920	4.0% (189)	0.85 (0.56-1.27)	0.571	7.2% (120)	1.91 (1.01-3.60)	0.001
25-29.9	5.7% (260)	0.94 (0.66-1.35)		5.0% (181)	0.86 (0.57-1.28)		8.5% (79)	1.39 (0.64-3.06)	
>=30	5.9% (129)	1.06 (0.65-1.73)		5.6% (101)	0.97 (0.58-1.65)		7.2% (28)	1.80 (0.43-7.57)	
Physical Activity									
Sedentary	3.3% (338)	1.27 (0.94-1.70)	0.214	3.0% (243)	1.05 (0.76-1.45)	0.379	4.4% (95)	2.98 (1.40-6.34)	0.171
Mild	10.8% (193)	0.69 (0.44-1.09)		9.5% (120)	0.56 (0.32-0.98)		13.7% (73)	1.04 (0.46-2.34)	
Moderate	12.5% (128)	0.99 (0.56-1.76)		10.2% (78)	0.97 (0.49-1.92)		19.6% (50)	1.05 (0.36-3.01)	
Strenuous	13.4% (49)	0.83 (0.35-1.95)		13.0% (36)	0.73 (0.28-1.93)		14.6% (13)	1.19 (0.18-7.85)	

*Adjusted for anger/emotional upset and interaction between heavy physical exertion and anger/emotional upset in case period

Supplementary Table 6. Associations between Triggers and All Stroke by Cardiovascular Prevention Medications

	Anger or Emotional Upset			Heavy Physical Exertion		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	9.2% (1,233)	1.37 (1.15-1.64)	-	5.3% (708)	1.02 (0.82-1.27)	-
Aspirin						
No	8.7% (984)	1.40 (1.15-1.71)	0.592	5.3% (601)	0.99 (0.78-1.26)	0.461
Yes	11.8% (249)	1.28 (0.88-1.86)		5.1% (107)	1.18 (0.69-2.01)	
Beta Blockers						
No	8.5% (989)	1.36 (1.12-1.65)	0.767	5.3% (615)	0.98 (0.78-1.24)	0.270
Yes	13.0% (243)	1.43 (0.94-2.18)		5.0% (93)	1.28 (0.72-2.29)	
ACE-i/ARB						
No	8.4% (893)	1.35 (1.09-1.66)	0.670	5.2% (553)	0.99 (0.78-1.27)	0.580
Yes	12.3% (340)	1.43 (1.03-2.00)		5.6% (155)	1.11 (0.71-1.73)	
Cholesterol Lowering						
No	8.9% (1,059)	1.34 (1.11-1.61)	0.286	5.2% (621)	0.98 (0.77-1.23)	0.166
Yes	11.3% (174)	1.66 (1.02-2.70)		5.6% (87)	1.39 (0.75-2.56)	
Oral Anticoagulants						
No	9.0% (1,190)	1.34 (1.12-1.60)	0.028	5.3% (692)	1.02 (0.82-1.27)	0.933
Yes	15.4% (43)	4.08 (1.11-14.94)		5.7% (16)	1.07 (0.26-4.36)	

*Adjusted for other trigger (heavy physical exertion or anger/emotional upset) and interaction between heavy physical exertion and anger/emotional upset in case period

Supplementary Table 7. Associations between Triggers and All Stroke by Geographical Region, Time and Day of Onset

	Anger or Emotional Upset			Heavy Physical Exertion		
	Prevalence	**OR (99% CI)***	**p_{int}**	**Prevalence**	**OR (99% CI)***	**p_{int}**
Overall	9.2% (1,233)	1.37 (1.15-1.64)	-	5.3% (708)	1.02 (0.82-1.27)	-
Region						
Western Europe, North America, Australia	8.8% (168)	1.85 (1.07-2.85)	0.59	7.2% (137)	1.19 (0.78-1.81)	0.27
Eastern & Central Europe, Middle East	14.7% (205)	0.78 (0.52-1.16)		6.7% (94)	0.60 (0.34-1.06)	
South America	15.1% (222)	1.36 (0.94-1.97)		5.3% (78)	1.59 (0.83-3.03)	
China	3.5% (138)	1.88 (1.08-3.26)		3.6% (143)	0.93 (0.50-1.74)	
Southeast Asia	8.4% (72)	1.00 (0.51-1.97)		9.2% (79)	0.87 (0.41-1.83)	
South Asia	9.1% (260)	1.27 (0.81-1.98)		3.8% (109)	0.86 (0.51-1.45)	
Africa	17.3% (168)	2.97 (1.66-5.34)		7.0% (68)	3.03 (1.66-5.34)	
Time of Onset						
00:00-05:59	9.6% (154)	1.34 (0.83-2.16)	0.12	2.6% (42)	0.69 (0.30-1.59)	0.05
06:00-11:59	7.4% (416)	1.07 (0.80-1.42)		4.6% (257)	0.83 (0.59-1.18)	
12:00-17:59	10.1% (348)	1.35 (0.96-1.88)		7.1% (247)	1.49 (0.99-2.22)	
18:00-23:59	11.4% (308)	2.18 (1.47-3.24)		5.9% (160)	1.04 (0.66-1.63)	
Day of Onset						
Monday	9.6% (218)	1.23 (0.81-1.88)	0.79	6.1% (139)	1.34 (0.81-2.23)	0.77
Tuesday	9.1% (196)	1.54 (1.00-2.37)		5.1% (110)	0.83 (0.47-1.46)	
Wednesday	8.9% (174)	1.73 (1.08-2.75)		5.0% (99)	1.15 (0.64-2.07)	
Thursday	8.8% (134)	1.16 (0.69-1.95)		5.3% (81)	1.10 (0.56-2.15)	
Friday	9.5% (148)	1.23 (0.70-2.16)		4.7% (73)	1.10 (0.54-2.23)	
Saturday	8.4% (154)	1.37 (0.85-2.20)		5.5% (101)	1.00 (0.57-1.75)	
Sunday	9.8% (209)	1.29 (0.83-2.01)		4.9% (105)	0.81 (0.48-1.36)	

*Adjusted for anger/emotional upset and interaction between heavy physical exertion and anger/emotional upset in case period; P for interaction for analyses stratified by region, p for homogeneity for analyses stratified by time of onset and day of onset of stroke

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