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# Trigger Factors of Acute Stroke: A Case-Crossover Study

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***Abstract:*** *Compared to traditional chronic risk factors, our understanding of trigger factors for acute stroke remains relatively limited. This study aimed to identify common trigger factors associated with acute stroke onset and to determine whether exposure to these triggers differs across age groups. Using a case-crossover design, we compared each patient's exposures during the case period (hazard period) with their exposures during the control period. By analyzing the differences between trigger periods (acute exposure windows) and stable periods (baseline), we identified potential stroke triggers. Furthermore, we examined whether exposure patterns varied across different age groups. The study included 248 acute stroke patients (mean age 58.1±16.6 years; 141 males [56.8%]). Significant triggers included Valsalva maneuvers (OR=3.52, 95%CI=2.16-5.74), strenuous exercise (OR=2.47, 95%CI=1.56-3.92), sudden change of position (OR=2.93, 95%CI=1.82-4.74), temperature changes (OR=2.86, 95%CI=1.77-4.61), satiation (all levels), and anger intensity (all levels). Notably, no significant differences were observed in exposure to all investigated trigger factors across age groups. These findings provide novel insights into the pathophysiology of cerebral thrombosis and offer evidence-based guidance for targeted acute stroke prevention strategies.*

***Keywords:*** *Stroke; Trigger factor; Risk; Valsalva maneuvers; Strenuous exercise*

## 1. Introduction

Around the world, intensive research has been carried out on the long-term risk factors linked to acute strokes. Thanks to this research, we now have a comprehensive understanding of these factors. As our knowledge of these risk elements continues to expand, practical ways of categorizing the likelihood of an acute stroke have emerged. Prediction models accessible via the internet incorporate well-known risk factors like heart disease, high blood pressure, and diabetes. By using these models, we can estimate an individual's probability of experiencing an acute stroke over a multi-year period[1]. This enables focused adjustment of risk factors or application of therapeutic measures. Nevertheless, why does an individual with chronic hypertension and diabetes suffer an acute stroke today? Can the near-term risk of acute stroke be anticipated, or is it entirely unpredictable?

Multiple recent investigations have brought to light distinct diurnal, weekly, and seasonal trends in the occurrence of acute strokes. Ample evidence indicates that daily incidences of acute strokes reach their zenith not long after awakening in the morning and also around late afternoon. This not only underscores a temporal dimension to stroke occurrences but further emphasizes a circadian influence on cerebrovascular events[2-4]. The highest levels occur predominantly during the workweek, with Mondays being the most notable[5-9]. Our research team has previously validated the daily and weekly fluctuations in acute stroke incidence, which are closely tied to occupation-related patterns and lifestyle habits unique to various populations. While traditional risk factors elucidate the overall vulnerability to acute stroke via pathophysiological mechanisms, the temporal patterns of acute stroke onset clearly suggest that its occurrence is not random. Nevertheless, forecasting the precise timing of acute stroke events remains exceedingly challenging, even among high-risk populations, given existing preventive strategies.

The study aims to employ a case-crossover methodology to pinpoint the common triggers of acute stroke and examine whether exposure patterns differed across age groups. The findings are expected to

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deepen the understanding of short-term risk factors for acute stroke and offer valuable insights for the development of targeted prevention strategies.

## 2. Methods

### *2.1. Study Design and Participants*

For this case-crossover study, the pertinent data were retrieved from the medical information systems of two healthcare facilities: the University-Town Hospital of Chongqing Medical University and the Affiliated Rehabilitation Hospital of Chongqing Medical University. Ethical clearance was granted by the Ethics Committee of the University-Town Hospital of Chongqing Medical University, which acted as the principal institution for the project, and informed consent was appropriately secured.

Initially, 298 patients with acute stroke were recruited for the study, with data collected from January 1, 2024, to September 30, 2024. The study population comprised individuals who had their first-ever acute stroke and were at least 18 years old. Each participant received comprehensive cranial computed tomography and/or magnetic resonance imaging within 24 hours of symptom onset. The diagnosis of acute stroke was verified by a local neurologist and/or neurosurgeon, in accordance with the criteria specified in the relevant literature[10]. Furthermore, patients had to be conscious when initial neurological symptoms appeared and possess adequate mental status and cognitive function during interviews to accurately describe events prior to the stroke. Individuals with coexisting conditions like aneurysm, coagulopathy, intracranial tumor, vascular malformation, or a previous history of acute stroke were excluded. Other exclusion criteria included cases with ambiguous onset times and those who could not complete interviews or questionnaires for other reasons (Figure 1).

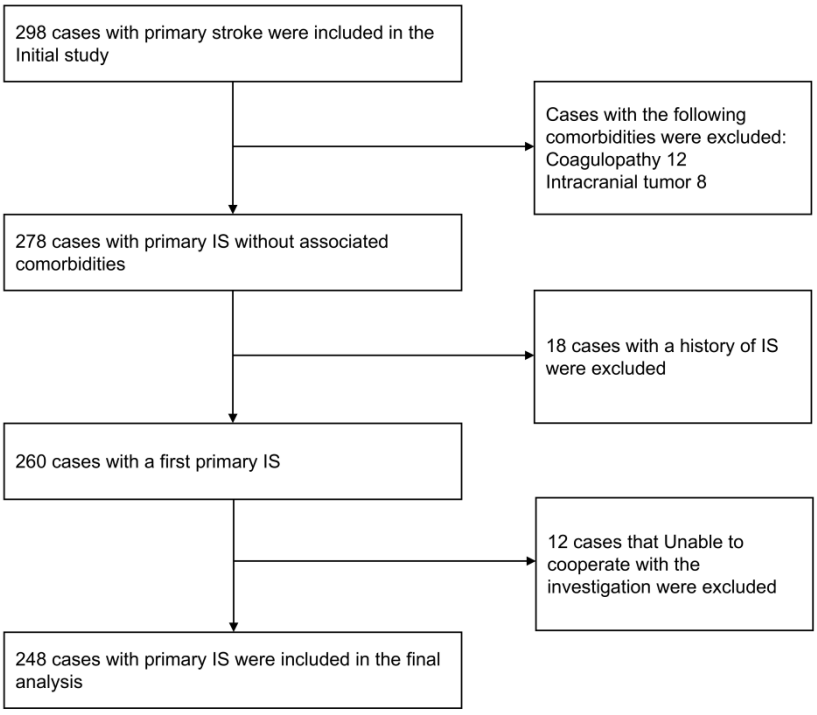


*Figure 1: Flow of participants through the screening process.*

### *2.2. Clinical Data*

Information was collected through face-to-face interviews using a specially designed questionnaire focusing on patients' mental and physical activities, as well as changes in environmental temperature (including meteorological data from local authorities and patient-reported differences between indoor and outdoor temperatures). Participants were divided into two age groups: younger (<60 years) and older (≥60 years). The period 0-2 hours before stroke onset was defined as the trigger phase (the primary exposure window for potential triggers), while the period 24-26 hours before was labeled as the stable phase. Patients were asked to recall and report any significant events during these two phases prior to

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acute stroke onset, including the exact timing and details of the circumstances. Potential trigger factors included anger, Valsalva maneuvers, sudden changes in position, strenuous exercise, alcohol consumption, satiation, and temperature fluctuations.

Potential triggers were identified by comparing exposure frequencies during the trigger and stable phases. Satiation was classified as follows: Level 1 (mild fullness with maintained appetite), Level 2 (moderate fullness without appetite), Level 3 (severe fullness with nausea/vomiting). Anger intensity was categorized as: Level 1 (slight anger), Level 2 (moderate anger), Level 3 (significant anger), Level 4 (extreme anger). A significant temperature change was defined as a decrease of 10°C or more within 24 hours.

All clinical information, including the patient's sex, age, onset time (hour-specific), health-related behaviors, past medical history, and location of hemorrhaging, was recorded. Alcohol consumption was defined as self-reported intake of alcohol more than three times per week. Smoking was defined as current regular use (regardless of amount). Hypertension was defined as a self-reported history of hypertension or a blood pressure of 140/90 mmHg or higher. Diabetes was defined as a self-reported history of diabetes mellitus or an HbA1c level of 6.5% or higher. Coronary heart disease was defined as a self-reported history of atherosclerotic plaque buildup within the coronary arteries, causing luminal stenosis (>50%) and subsequent myocardial ischemia. Hyperlipidemia was defined as a self-reported history of elevated plasma lipids, including total cholesterol (TC ≥5.2 mmol/L), low-density lipoprotein cholesterol (LDL-C ≥3.4 mmol/L), and triglycerides (TG ≥1.7 mmol/L).

### *2.3. Statistical Analyses*

To assess the influence of transient exposures on the risk of sudden-onset acute stroke, we adopted a case-crossover design, which is particularly well-suited for evaluating immediate and short-term effects. This approach enables the computation of odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) by comparing exposure frequencies during acute stroke hazard periods with those during stable control periods. By using each case as its own control, this design effectively eliminates selection bias and adjusts for confounding from chronic risk factors and fixed subject characteristics. Logistic regression analysis was used to calculate the ORs and 95% CIs for each trigger factor. A p-value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were conducted using IBM SPSS Statistics version 24.0.

## 3. Results

### *3.1. Baseline Characteristics*

This study included 248 first-ever acute stroke patients (mean age 58.1±16.6 years; 141 males [56.8%]), with 113 cases (45.6%) in the older age group (≥60 years). The cohort comprised 118 cerebral hemorrhage cases (47.5%) and 130 cerebral infarction cases (52.4%) (Table 1).

*Table 1: Baseline Characteristics.*

| | **Stroke patients (n=248)** |
|---|---|
| Male | 141 (56.8) |
| Age, years | 58.1 (16.6) |
| <60 | 135 (54.4) |
| ≥60 | 113 (45.6) |
| Stroke type | |
| Hemorrhage | 118 (47.5) |
| Infarction | 130 (52.4) |
| Medical history | |
| Hypertension | 115 (46.3) |
| Diabetes | 119 (47.9) |
| Coronary heart disease | 120 (48.3) |
| Hyperlipemia | 116 (46.7) |
| Smoking | 126 (50.8) |
| Alcohol consumption | 142 (57.2) |

Data are n (%) or mean (SD).

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### *3.2. Odds Ratios of Trigger Factors: Acute Phase vs. Stable Phase*

Acute stroke risk significantly increased within 2 hours after Valsalva maneuvers (OR=3.52, 95%CI=2.16-5.74), strenuous exercise (OR=2.47, 95%CI=1.56-3.92), sudden change of position (OR=2.93, 95%CI=1.82-4.74), temperature change (OR=2.86, 95%CI=1.77-4.61), satiation (all levels), and anger intensity (all levels) (Figure 2).

| Trigger factors | Events (0-2h/24-26h) | Odds Ratios (95% CI) | *P* |
|---|---|---|---|
| Valsalva maneuvers | 116/51 | 3.52 (2.16-5.74) | <0.001 |
| Strenuous exercise | 126/76 | 2.47 (1.56-3.92) | <0.001 |
| Sudden change of position | 119/51 | 2.93 (1.82-4.74) | <0.001 |
| Alcohol drinking | 116/103 | 1.02 (0.65-1.61) | 0.93 |
| Temperature change | 119/60 | 2.86 (1.77-4.61) | <0.001 |
| Satiation | | | |
| None | 38/56 | Reference | |
| Level 1 | 53/61 | 2.32 (1.14-4.70) | 0.02 |
| Level 2 | 70/65 | 2.90 (1.46-5.77) | 0.002 |
| Level 3 | 87/66 | 2.78 (1.44-5.39) | 0.002 |
| Anger | | | |
| None | 34/113 | Reference | |
| Level 1 | 42/56 | 3.42 (1.29-4.56) | 0.006 |
| Level 2 | 25/33 | 3.19 (1.52-6.72) | 0.002 |
| Level 3 | 72/32 | 6.58 (3.48-12.44) | <0.001 |
| Level 4 | 75/14 | 18.26 (8.46-39.40) | <0.001 |

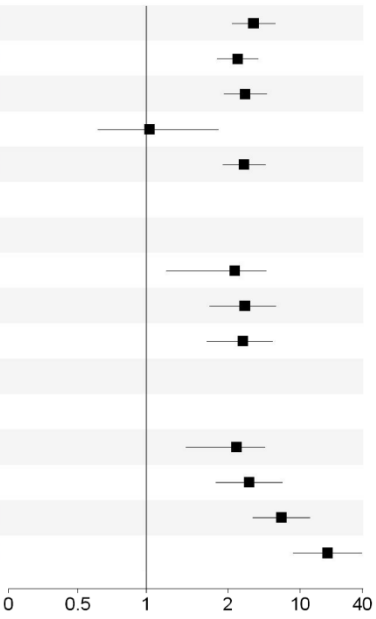


*Figure 2: Trigger factors odds ratios during acute stroke active phase versus stable phase.*

### *3.3. Trigger Factor ORs by Age Group*

Importantly, no significant differences in exposure to investigated triggers were found between age groups (Figure 3).

| Trigger factors | Events (≥60/<60 ys) | Odds Ratios (95% CI) | *P* |
|---|---|---|---|
| Valsalva maneuvers | 78/89 | 1.03 (0.70-1.51) | 0.886 |
| Strenuous exercise | 89/113 | 0.91 (0.63-1.31) | 0.606 |
| Sudden change of position | 79/91 | 1.04 (0.70-1.53) | 0.856 |
| Alcohol drinking | 96/123 | 0.89 (0.62-1.28) | 0.534 |
| Temperature change | 87/92 | 1.24 (0.85-1.81) | 0.263 |
| Satiation | | | |
| None | 48/46 | Reference | |
| Level 1 | 43/71 | 0.60 (0.34-1.05) | 0.074 |
| Level 2 | 63/72 | 0.87 (0.51-1.48) | 0.594 |
| Level 3 | 72/81 | 0.86 (0.51-1.45) | 0.575 |
| Anger | | | |
| None | 65/82 | Reference | |
| Level 1 | 48/50 | 1.16 (0.69-1.96) | 0.578 |
| Level 2 | 27/31 | 1.08 (0.58-2.02) | 0.799 |
| Level 3 | 46/58 | 0.96 (0.57-1.63) | 0.886 |
| Level 4 | 40/49 | 0.96 (0.55-1.66) | 0.872 |

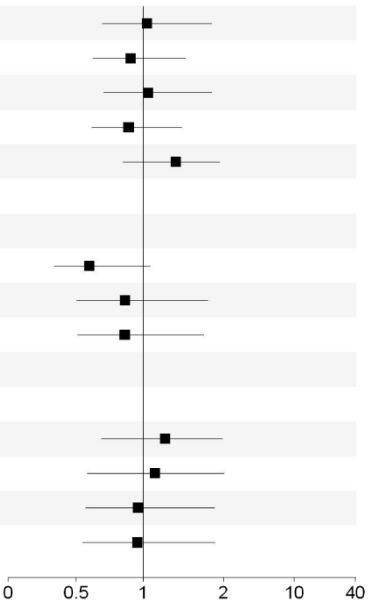


*Figure 3: Trigger factors odds ratios for acute stroke active phase in different age groups.*

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## 4. Discussion

We identified several trigger factors associated with acute stroke onset, but found no significant age-related differences in exposure to these triggers.

Valsalva maneuvers cause a temporary increase in intracranial pressure (ICP) by raising intrathoracic pressure, which impacts the cerebrovascular system in multiple ways. First, the heightened intrathoracic pressure is directly conveyed to the intracranial venous system, impairing cerebral venous return. This leads to an accumulation of cerebral blood volume and a subsequent rise in ICP[11]. Second, during the Valsalva maneuver, phase II (the hypotensive phase) and phase IV (the blood pressure rebound phase) can trigger significant blood pressure fluctuations through sympathetic activation. In phase II, reduced venous return causes a drop in cardiac output and mean arterial pressure, prompting the sympathetic nervous system to activate in an effort to stabilize blood pressure. In phase IV, both cardiac output and peripheral vascular resistance increase simultaneously, causing rapid blood pressure recovery to baseline or even higher levels[12]. This hemodynamic instability is especially dangerous for individuals with hypertension or vascular structural abnormalities, as it may lead to thrombus formation[13]. From a hemodynamic standpoint, the ICP elevation and blood pressure oscillations caused by Valsalva maneuvers greatly exacerbate the disruption of vascular wall compliance, thereby increasing the risk of vascular endothelial injury[14].

The condition following meals, especially those high in fat and carbohydrates, leads to sharp increases in blood glucose and lipid levels. These changes set off oxidative stress and inflammatory reactions that undermine the function of the vascular endothelium. Research has shown that the spike in blood glucose after eating (postprandial hyperglycemia) disrupts the ability of blood vessels to widen in response to endothelium-dependent signals. This disruption happens because the protein kinase pathway is activated, and advanced glycation end-products build up, both of which reduce the availability of nitric oxide[15]. Moreover, the increase in low-density lipoprotein cholesterol after meals makes it more prone to oxidative modification, which in turn speeds up the formation of atherosclerotic plaques and destabilizes existing plaques[16].

Sudden changes in body position, like quickly moving from lying down to standing up, are connected to a higher risk of acute stroke. This link happens because of problems with the body's automatic control system and changes in the pressure that keeps blood flowing to the brain. When you change positions, sensors in your neck (carotid sinus baroreceptors) usually tell your heart and blood vessels to quickly adjust to keep blood flowing to your brain. But in older people or those with issues in their automatic control system, these sensors might not work as well. This can slow down blood pressure adjustments and might cause temporary spikes in blood pressure[17, 18]. In addition, long-term high blood pressure (chronic hypertension) changes how the brain regulates its blood flow. It makes the brain's ability to adjust to changes in blood pressure less effective. This means that when blood pressure suddenly drops, people with chronic hypertension are more likely to experience a lack of blood flow to the brain (cerebral ischemia)[19].

When a person feels angry, it triggers the body's stress response system, specifically the hypothalamic-pituitary-adrenal (HPA) axis. This activation quickly causes the release of adrenaline and norepinephrine, hormones that can raise the top number of your blood pressure (systolic blood pressure) within just a few minutes[20]. Studies have shown that heightened activity in the amygdala during anger can directly influence cardiovascular control centers via the locus coeruleus-noradrenergic pathway[21].

Changes in temperature have a more significant effect on stroke incidence and mortality compared to specific temperature values. When the temperature drops quickly, the body responds by narrowing blood vessels to reduce heat loss and maintain its core temperature. This process, known as thermoregulatory vasoconstriction, leads to an increase in blood pressure throughout the body. This sudden rise in blood pressure can put extra stress on the walls of blood vessels, especially in people who already have high blood pressure or hardening of the arteries. This extra stress can cause plaques in the blood vessels to break apart, leading to blockages and increasing the risk of stroke[22].

This study has several important strengths and corresponding limitations. We used a case-crossover design, which effectively reduced the impact of individual confounders by using self-matching techniques. This approach allowed us to systematically analyze the daily changes in acute stroke triggers for the first time, helping to develop preventive measures specific to different times of the day. Also, by including emotional intensity grading, we were able to show dose-response relationships, making the findings more useful for clinical practice. However, there could be recall bias, which might affect the accuracy of the exposure data, especially for emotional intensity and exercise-related details. Moreover,

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the study's regional sampling limits the ability to generalize the results to other populations.

This study identifies Valsalva maneuvers, strenuous exercise, sudden change of position, temperature change, satiation, and anger as key short-term triggers for acute stroke. Notably, no substantial age-related differences were observed in exposure to any of these identified triggers. These findings provide novel insights into stroke pathophysiology and underscore the importance of prevention strategies incorporating behavioral modifications across all age groups.

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