Trigger factors for spontaneous intracerebral hemorrhage: a case-crossover study

Etten, E.S. van; Kaushik, K.; Jolink, W.M.T.; Koemans, E.A.; Ekker, M.S.; Rasing, I.; ... ; Wermer, M.J.H.

Stroke

CLINICAL AND POPULATION SCIENCES

Trigger Factors for Spontaneous Intracerebral Hemorrhage: A Case-Crossover Study

Ellis S. van Etten, MD*; Kanishk Kaushik, MD*; Wilmar M.T. Jolink, MD, PhD; Emma A. Koemans, MD; Merel S. Ekker, MD; Ingeborg Rasing, MD; Sabine Voigt, BSc; Floris H.B.M. Schreuder, MD, PhD; Suzanne C. Cannegieter, MD, PhD; Gabriël J.E. Rinkel, MD, PhD; Willem M. Lijfering, MD, PhD; Catharina J.M. Klijn, MD, PhD; Marieke J.H. Wermer, MD, PhD

BACKGROUND: Whether certain activities can trigger spontaneous intracerebral hemorrhage (ICH) remains unknown. Insights into factors that trigger vessel rupture resulting in ICH improves knowledge on the pathophysiology of ICH. We assessed potential trigger factors and their risk for ICH onset.

METHODS: We included consecutive patients diagnosed with ICH between July 1, 2013, and December 31, 2019. We interviewed patients on their exposure to 12 potential trigger factors (eg, Valsalva maneuvers) in the (hazard) period soon before onset of ICH and their normal exposure to these trigger factors in the year before the ICH. We used the case-crossover design to calculate relative risks (RR) for potential trigger factors.

RESULTS: We interviewed 149 patients (mean age 64, 66% male) with ICH. Sixty-seven (45%) had a lobar hemorrhage, 60 (40%) had a deep hemorrhage, 19 (13%) had a cerebellar hemorrhage, and 3 (2%) had an intraventricular hemorrhage. For ICH in general, there was an increased risk within an hour after caffeine consumption (RR=2.5 [95% CI=1.8–3.6]), within an hour after coffee consumption alone (RR=4.8 [95% CI=3.3–6.9]), within an hour after lifting >25 kg (RR=6.6 [95% CI=2.2–19.9]), within an hour after minor head trauma (RR=10.1 [95% CI=1.7–60.2]), within an hour after sexual activity (RR=30.4 [95% CI=16.8–55.0]), within an hour after straining for defecation (RR=37.6 [95% CI=22.4–63.4]), and within an hour after vigorous exercise (RR=21.8 [95% CI=12.6–37.8]). Within 24 hours after flu-like disease or fever, the risk for ICH was also increased (RR=50.7 [95% CI=27.1–95.1]). Within an hour after Valsalva maneuvers, the RR for deep ICH was 3.5 (95% CI=1.7–6.9) and for lobar ICH the RR was 2.0 (95% CI=0.9–4.2).

CONCLUSIONS: We identified one infection and several blood pressure related trigger factors for ICH onset, providing new insights into the pathophysiology of vessel rupture resulting in ICH.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood pressure ■ caffeine ■ cerebral hemorrhage ■ risk ■ Valsalva maneuver

Spontaneous intracerebral hemorrhage (ICH) is the second most common cause of stroke.[1] With a median 30-day case fatality of 40%,[2] it is also the deadliest and most debilitating type of stroke. Established long-term risk factors for ICH include higher age, male sex, hypertension, diabetes, underweight, high alcohol intake, being black or from Hispanic origin, and apolipoprotein E genotype.[3–6] Most of these risk factors are involved only in the development of the underlying small vessel disease but not in the actual vessel rupture resulting in an ICH. Hypertension might be an exception, because it not only increases the underlying small vessel disease, but may also be involved in the actual rupture of the vessel.[7] ICH has been reported to

Correspondence to: Ellis S. van Etten, MD, Department of Neurology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, the Netherlands. Email e.s.van_etten@lumc.nl
*E.S. van Etten and K. Kaushik contributed equally.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.036233.
This manuscript was sent to Irene L. Katzan, Guest Editor, for review by expert referees, editorial decision, and final disposition.
For Sources of Funding and Disclosures, see page 1698.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

FETCH	Finding the Etiology in Spontaneous Cerebral Hemorrhage
ICH	intracerebral hemorrhage
RR	relative risk

occur during hypertensive crises,[8] after a sudden rise in blood pressure due to sudden emotional upset,[9] and while squatting.[10] Moreover, mean systolic blood pressure has been shown to be increased in the days and weeks before ICH.[11]

Rupture of intracranial aneurysms[12] and ischemic stroke[13] can be triggered by several trigger factors associated with acute, short-term surge in blood pressure, including caffeine consumption, emotional stress, vigorous physical exercise, sexual activity, and Valsalva maneuvers.[12,14] Moreover, systemic infection has been associated with triggering ischemic stroke.[15] Previous studies on trigger factors for ICH found an increased risk within hours after exposure to low ambient temperature.[16,17] Until now, trigger factors clearly related to short-term increase of blood pressure have likely been underreported. Whether certain blood pressure increasing factors like vigorous exercise or Valsalva maneuvers can actually trigger the acute vessel rupture resulting in ICH remains to be determined. Identifying trigger factors might improve our understanding of the final part of the cascade leading up to a vessel rupture causing ICH.

We aimed to study exposure to an array of potential trigger factors including infection, extreme temperature change, and several blood pressure increasing factors and their risk for developing ICH.

METHODS

Study Design, Setting, and Participants

We performed a case-crossover study among patients with acute ICH. We included consecutive ICH patients who were admitted to 3 university hospitals in the Netherlands: Leiden University Medical Center in Leiden, University Medical Center in Utrecht, and Radboud University Medical Center in Nijmegen and who were eligible for the FETCH study (Finding the Etiology in spontaneous Cerebral Hemorrhage). All patients who were ≥18 years of age, who presented with an ICH to one of the 3 hospitals between July 1, 2013, and December 31, 2019, and who had computed tomography-confirmed ICH were assessed for inclusion in this study. We excluded patients with an ICH secondary to trauma, a macrovascular cause, hemorrhagic transformation of an ischemic stroke, or tumor-associated hemorrhages. Patients who were unable to complete the questionnaire due to cognitive deficits, due to aphasia, who did not speak Dutch, who had a disturbance of consciousness, or who were missed because of transfer to another hospital were excluded. The FETCH study was approved by the Medical Ethics Review Committee of the University Medical Center in Utrecht, and informed consent was obtained. Patients who had a spontaneous ICH but who were not eligible for the FETCH study or who declined participation in the FETCH study, but who were still able and willing to complete a structured questionnaire were also included. The Medical Ethics Review Committee concluded that completing the questionnaire without participating in the FETCH study did not fall under the medical research on human subjects act (non-WMO). According to the AHA Journals' Guidelines, anonymized data are available by reasonable request to the first author. The STROBE checklist can be found in the Supplemental Material.

Trigger Factors

We constructed a questionnaire based on 2 previous studies for trigger factors for aneurysm rupture[12] and acute ischemic stroke.[18] To minimize recall bias, patients were interviewed within days or weeks after admission. If patients were unable to complete the questionnaire in one session, the interview was interrupted and continued at a later time. Time of ICH onset was defined as the time at which patients had noted symptoms. Baseline characteristics, including age, sex, anticoagulation use, and medical history, were obtained by reviewing hospital records. The location of the ICH was determined by evaluating the computed tomography images and the radiology report. ICH location was divided into deep, lobar, cerebellar, and intraventricular hemorrhage. ICH likely originating from the basal ganglia or thalamus were considered deep and ICH likely originating at the cortical and subcortical junction were considered lobar. Potential trigger factors included alcohol (all types, beer, wine, and liquor) and drug use (cocaine and marijuana), caffeine consumption (all types, coffee, caffeinated tea, and cola), cigarette smoking, vigorous exercise (metabolic equivalent of task ≥6, which corresponds to vigorous intensity activities like jogging or rope jumping), extreme temperature change (eg, visiting a sauna or taking an ice bath), flu-like disease or fever, minor head trauma (ie, bumping one's head before symptom onset, excluding evident traumatic hemorrhage), sexual activity, using sildenafil, strong emotions (eg, bursts of anger, experiencing strong positive or negative emotions, and startling), and Valsalva maneuvers (all types, coughing, sneezing, nose blowing, straining for defecation, and lifting >25 kg). For each of the potential trigger factors, patients were asked about exposure to each individual trigger factor in the previous year, time between ICH onset and their previous exposure, exposure shortly before ICH onset (observed exposure during the hazard period), and usual frequency of exposure (expected exposure). Data were checked for reliability, by asking for both time since previous exposure and exposure in the hazard period. The hazard period was defined for each potential trigger, based on the estimated duration effect, with a minimum induction time of zero. The hazard period was defined as 1 hour for caffeine consumption (coffee, cola, and caffeinated tea), smoking, emotions, extreme temperature changes, Valsalva maneuvers (coughing, sneezing, straining, and lifting ≥25 kg), sexual activity, exercise with a metabolic equivalent of task ≥6, and minor head trauma. The hazard period was 4 hours for use of cocaine, marijuana, or sildenafil. The hazard period was 24 hours for flu-like disease and fever. The hazard period for alcohol consumption was defined as 1 hour since alcohol absorption peaks at around 1

hour, and it is eliminated in about 6 hours, with the elimination rate decreasing with increased consumption.

Statistical Analysis

We used a case-crossover design as it is very well suited to study the effect of an intermittent exposure (ie, trigger or trigger factor), with an immediate and transient effect on risk of developing a suddenly occurring outcome (in this case a ICH).[19] With this design, the relative risk (RR) with corresponding 95% CI can be estimated by calculating the ratio of the frequency of the exposure shortly before the ICH and the expected frequency using control information.[20–22] By using each case as its own control, this method eliminates bias and fixed confounding by chronic risk factors and subject characteristics.[19] The RR with a 95% CI were calculated for each trigger factor using the Mantel-Haenszel method for sparse data and using a conditional logistic regression analysis.[19,20,23,24] When patients were not exposed in the year before the ICH, they were excluded from the analysis of that particular trigger factor. Patients were considered always exposed when, based on the average frequency of exposure and the corresponding hazard period, there were no unexposed hours in the year before the ICH. Assuming a 20% to 80% exposure in the hazard period of the population, differing per triggering factor, a sample size of 150 would be sufficient to have 90% power and 2-tailed significance (α=0.05). This sample size would allow us to detect, for example, a RR of at least 2.3 for smoking, and a RR of at least 3.2 for physical exercise and alcohol consumption. To prevent reverse causation bias, unidirectional sampling was used for all analyses.[25] The population attributable fraction, defined as the proportion of the study population attributable to the exposure to a possible trigger,[12,26] was calculated for the different triggers that showed a statistically significant increased RR. Although this study was not specifically powered for analyzing RRs per ICH location, the RRs were calculated for patients with lobar and patients with deep ICH separately (excluding cerebellar and intraventricular hemorrhages). For this subanalysis, we calculated the RRs for trigger factors for which at least 90% of patients were exposed in the year previous to the hemorrhage to avoid analyzing trigger factors with very few numbers of exposure. To assess potential bias introduced by unreliable data, we performed 2 sensitivity analyses. For the first sensitivity analysis, we excluded patients with unreliable data (eg, when for an individual patient there was a discrepancy between the answer for time since last exposure and the answer for exposure in the hour before ICH onset, or when patients said that they never coughed in the year before the ICH which seems unlikely). For the second sensitivity analysis, we excluded patients who completed the questionnaire later than 2 weeks after ICH onset. We also performed a Holms-Bonferroni post hoc analysis for multiple hypothesis testing. Data analysis was performed using R (version 3.6.2). We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

RESULTS

We included 149 patients (mean age 64 years ±13 SD; 99 [66%] male) of a total of 1324 patients admitted to the 3 university hospitals. Patient selection is shown in the Figure. Of the 149 patients, 67 (45%) had a lobar ICH, 60 (40%) had a deep ICH, 19 (13%) had a cerebellar ICH, and 3 (2%) had an intraventricular hemorrhage. Baseline characteristics of the included patients are summarized in Table 1. The median duration between ICH onset and the interview was 6 days (interquartile range, 3 to 12 days).

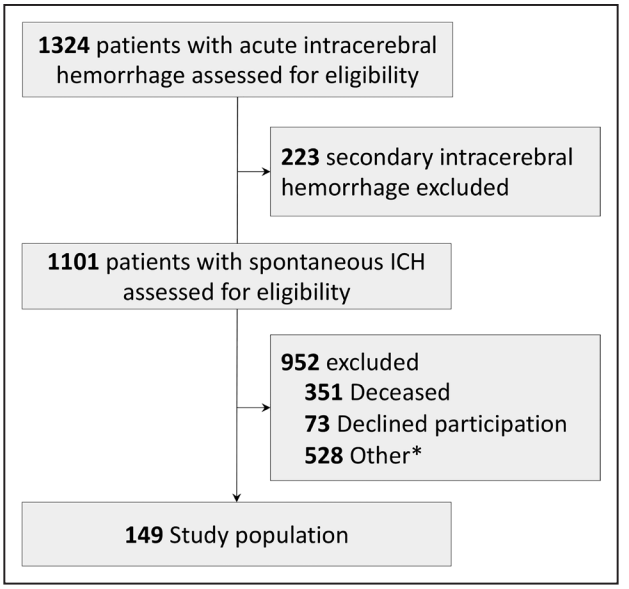

Figure. Patient selection for the 3 University Medical Centers combined.
ICH indicates intracerebral hemorrhage. *Other: this includes patients unable to complete the questionnaire due to cognitive deficits, due to aphasia, who did not speak Dutch, who had a disturbance of consciousness, or who were missed because of transfer to another hospital.

Trigger Factors for ICH in General

For all ICH combined showed in Table 2, the risk for developing an ICH was 2.5 times higher in the hour after caffeine consumption (95% CI=1.8–3.6, Table 2) compared with the hours not consuming caffeine. This increased risk was mainly driven by coffee consumption (RR=4.8 [95% CI=3.3–6.9]). Minor head trauma (RR=10.1 [95% CI=1.7–60.2]), sexual activity (RR=30.4 [95% CI=16.8–55.0]), strong emotions (RR=5.7 [95% CI=2.2–14.6]), Valsalva maneuvers (RR=2.3 [95% CI=1.4–3.6]), and vigorous exercise (RR=21.8 [95% CI=12.6–37.8]) also increased the risk of ICH onset in the hour after exposure to these trigger factors. Within 24 hours after flu-like disease or fever the risk for ICH was also increased (RR=50.7 [95% CI=27.1–95.1]). After correcting for multiple hypothesis testing, caffeine consumption (all types combined and coffee), flu-like disease or fever, minor head trauma, sexual activity, 2 Valsalva maneuvers (straining for defecation and heavy lifting), and vigorous exercise showed a statistically significant increased risk for ICH (Table 2). Population attributable fractions were 27.7% for caffeine (all types), 33.9% for coffee alone, 18.2% for vigorous exercise, 17.0% for straining

Table 1. Baseline Characteristics

Variables	ICH patients, n=149
Age	64±13
Men	99 (66%)
Site intracerebral hemorrhage	
Lobar	67 (45%)
Deep	60 (40%)
Cerebellar	19 (13%)
Intraventricular	3 (2%)
Past medical history	
Hypertension	79 (53%)
Hypercholesterolemia	44 (30%)
Previous ICH	10 (7%)
Diabetes	23 (15%)
Cardiac disease	32 (22%)
Atrial fibrillation	26 (17%)
Anticoagulation use	
Vitamin K antagonists	23 (15%)
NOAC	6 (4%)
LMWH	2 (1%)
Cigarette smoking*	
Never	61 (41%)
Past	58 (39%)
Current <20 cigarettes/d	21 (14%)
Current ≥20 cigarettes/d	6 (4%)
Alcohol, units/wk*	
0	45 (30%)
≤14	83 (56%)
>14	17 (12%)

Values are displayed as mean±SD, or n (%). ICH indicates intracerebral hemorrhage; LMWH, low molecular weight heparin; and NOAC, non-vitamin K antagonist oral coagulants.

*2% missing values.

for defecation, 13.6% for flu-like disease or fever, 9.1% for sexual activity, 6.0% for heavy lifting, and 1.2% for minor head trauma (Table 3). Smoking, alcohol consumption, and temperature change did not show an increased risk for triggering an ICH (Table 2). The small number of patients who answered to have used marijuana (n=4) or cocaine (n=1) or had used sildenafil (n=4) precluded analysis of these potential triggers. The sensitivity analyses excluding unreliable data or data from patients who completed the questionnaire later than 2 weeks showed similar results (Table 4).

Trigger Factors for Deep and Lobar ICH

When looking at lobar (n=67) and deep ICH (n=60) separately, at least 90% of patients were exposed to caffeine consumption and Valsalva maneuvers (all maneuvers combined) in the year previous to the ICH. Valsalva maneuvers seemed to have an increased risk for ICH onset in deep ICH (RR=3.5 [95% CI=1.7–6.9]). In lobar ICH patients, the risk for ICH within an hour after Valsalva maneuvers was not significantly increased (RR=2.0 [95% CI=0.9–4.2]). The risk for ICH onset after caffeine consumption was similar for deep ICH (RR=2.5 [95% CI=1.4–4.4]) and lobar ICH (RR=2.8 [95% CI=1.7–4.8]).

DISCUSSION

We found that caffeine consumption, minor head trauma, sexual activity, 2 Valsalva maneuvers (straining for defecation and lifting >25 kg), and vigorous exercise were associated with developing a ICH within 1 hour after exposure. Flu-like disease or a fever was associated with development an ICH within 24 hours after exposure. The largest population attributable fraction was for coffee consumption.

Several blood pressure increasing factors were associated with a higher risk of ICH onset, including caffeine consumption, sexual activity, Valsalva maneuvers, and vigorous exercise. The observed increased risk of caffeine consumption for vessel rupture causing ICH, that seemed mainly driven by drinking coffee, is in concordance and of similar magnitude as in previous research on rupture of intracranial aneurysms (RR=1.7 [95% CI=1.2–2.4]).[12,27] Caffeine as a trigger factor for ICH can be explained biologically by 2 pathways. First, it has been shown that shortly after caffeine consumption, blood pressure increases,[28] potentially triggering the onset of an ICH. Second, coffee consumption has been associated with changes in hemostatic factors. In a study on venous thrombosis, coffee consumers had lower coagulation factor VIII levels and a lower risk of thrombosis than nonconsumers.[29] A possible explanation could be that the anti-inflammatory properties of coffee and their effect on endothelial cells and thrombocytes lowers the level of the von Willebrand Factor which is in complex with factor VIII.[30] Although changes in hemostatic factors do not directly cause bleeding but rather turn a small bleed caused by the underlying small vessel disease into a large bleed, this might trigger ICH in patients with underlying small vessel disease. For straining, vigorous exercise, sexual activity, and heavy lifting, an increase in blood pressure also seems the likely pathophysiological process causing onset of ICH. Sudden increase of blood pressure due to squatting has been shown to be associated with onset of ICH.[10] The observed association of exercise as a trigger factor has previously also been demonstrated for rupture of intracranial aneurysms.[12]

In the case of ICH following within an hour after minor head trauma, the mechanistic pathway seems less straightforward. Pain could cause a sudden rise in blood pressure through activation of the sympathetic nervous system.[31] However, although we excluded evident traumatic ICH, also the minor head trauma might still have triggered ICH through the direct traumatic disruptions of the cerebral vessels and damage to the blood brain barrier. Furthermore, besides direct injury, secondary

Table 2. RR and 95% CI for Trigger Factors for ICH

Trigger factors	No. exposed in previous year	No. exposed in hazard period	No. not included (not exposed, missing data)	RR (95% CI)
Alcohol				
All types	118	3	(29, 2)	0.3 (0.1–1.1)
Beer	62	1	(86, 1)	0.1 (0.0–2.4)
Wine	87	0	(62, 0)	…
Liquor	43	2	(105, 1)	2.9 (0.6–13.6)
Caffeine				
All types	142	54	(6, 1)	2.5 (1.8–3.6)*
Coffee	131	42	(15, 3)	4.8 (3.3–6.9)*
Tea	87	11	(59, 3)	7.0 (4.2–11.7)
Cola	70	5	(77, 2)	8.9 (4.6–17.3)
Cigarette smoking	33	9	(116, 0)	0.7 (0.3–1.9)
Exercise, MET ≥6	82	16	(66, 1)	21.8 (12.6–37.8)*
Valsalva maneuvers				
All types	137	29	(12, 0)	2.3 (1.4–3.6)
Coughing	95	8	(49, 5)	12.4 (7.8–19.8)
Sneezing	115	5	(30, 4)	5.0 (2.9–8.7)
Nose blowing	93	7	(50, 6)	56.4 (29.9–106.2)
Straining for defecation	59	5	(86, 4)	37.6 (22.4–63.4)*
Lifting >25 kg	58	6	(91, 0)	6.6 (2.2–19.9)*
Temperature change	23	1	(126, 0)	13.2 (1.5–113.4)
Flu-like disease or fever	60	16	(89, 0)	50.7 (27.1–95.1)*
Minor head trauma	36	2	(113, 0)	10.1 (1.7–60.2)*
Strong emotions	60	7	(89, 0)	5.7 (2.2–14.6)
Sexual activity	70	5	(78, 1)	30.4 (16.8–55.0)

Example: the RR for all types of caffeine was 2.5, this was calculated using data from 142 patients who drank caffeine containing beverages in the year before the ICH, of which none of the patients were always exposed and 54 were exposed to drinking caffeine in the hour before the ICH (hazard period). Six patients did not drink caffeine in the year before the ICH (not exposed) and 1 patient had missing data. The few patients who answered to have used marijuana (n=4) or cocaine (n=1) or had used sildenafil (n=4) precluded analysis of these potential triggers. MET ≥6 corresponds to vigorous intensity activities. ICH indicates intracerebral hemorrhage; MET, metabolic equivalent of task; and RR, relative risk.

*After correcting for multiple testing, these relative risks remained statistically significantly increased.

coagulopathy has also been described in patients with traumatic brain injury.[32] Whether the mechanisms seen in patients with traumatic brain injury can be applied to minor head trauma remains uncertain.

An ICH might be triggered by flu-like disease or fever through endothelial dysfunction, thrombophilia, and coagulopathy following systemic inflammation.[15,33] Although our estimate for the risk of ICH triggered by flu-like disease or fever was imprecise, this association has been demonstrated in previous studies.[34,35] A case-crossover study investigating the occurrence of sepsis or septicemia during different time windows before stroke onset, showed that the risk for ICH was increased (odds ratio=16.0 [95% CI=11.8–21.8]) with sepsis or septicemia during the 30 days before stroke onset.[34] Similarly, a population-based longitudinal study in Taiwan showed that patients with septicemia had an increased risk for ICH within 6 months (hazard ratio=1.82 [95% CI=1.35–2.46]).[35] In both studies, the increased risk gradually declined over time. Furthermore, it is worth mentioning that there is increasing evidence for an association between a SARS-CoV-2 infection and ICH.[36]

It is important to note that the reported RRs for these trigger factors represent a short-term increased risk in the short exposure (hazard) period and that they do not represent a cumulative risk over a longer period of time. A steep increase of blood pressure has previously been described in the days and weeks before ICH.[11] In addition, our data suggest that a sudden, short lasting increase in blood pressure in the hour before an ICH provokes rupture of a vessel. In most instances of ICH, patients have underlying small vessel disease, such as hypertensive (atherosclerotic) arteriopathy or cerebral amyloid angiopathy.[37] In these patients at increased risk for ICH, these trigger factors that are normally innocent and routine actions, can now be the last step in a longer cascade leading up to an ICH. In that sense, the increased risks of these trigger factors provide insights into the pathophysiological mechanisms triggering vessel rupture in ICH.

Table 3. RR, Prevalence, and Population Attributable Fraction Associated With Trigger Factors

Trigger factors	RR (95% CI)	Proportion of study population exposed (%)	Prevalence (%)	PAF
Caffeine				
All types	2.5 (1.8–3.6)	95%	25.2%	27.7%
Coffee	4.8 (3.3–6.9)	88%	13.6%	33.9%
Valsalva maneuver				
Straining for defecation	37.6 (22.4–63.4)	40%	0.6%	17.0%
Heavy lifting >25 kg	6.6 (2.2–19.9)	39%	1.1%	6.0%
Exercise, MET ≥6	21.8 (12.6–37.8)	55%	1.1%	18.2%
Flu-like disease or fever	50.7 (27.1–95.1)	40%	0.3%	13.6%
Minor head trauma	10.1 (1.7–60.2)	24%	0.1%	1.2%
Sexual activity	30.4 (16.8–55.0)	47%	0.3%	9.1%

MET indicates metabolic equivalent of task; PAF, population attributable fraction; and RR, relative risk.

Although this study was not sufficiently powered to assess the difference in RR between lobar (often associated with cerebral amyloid angiopathy) and deep ICH (often associated with hypertensive arteriopathy), Valsalva maneuvers seemed to increase the risk for deep ICH onset more strongly than lobar ICH. This might be due to the fact that superficial perforating arterioles are less susceptible to increased blood pressure than perforation arterioles in the basal ganglia.[38]

Table 4. RR and 95% CI for Spontaneous Intracerebral Hemorrhage for Trigger Factors Excluding (1) Unreliable Data and (2) Patients That Were Interviewed Later Than 14 Days After Intracerebral Hemorrhage Onset

Trigger factors	% Unreliable data in main analysis	RR (95% CI)	% Interviewed >14 d in main analysis	RR (95% CI)
Alcohol				
All types	15	0.4 (0.1–1.4)	14	0.3 (0.1–2.1)
Beer	19	0.1 (0.0–3.1)	16	0.2 (0.0–7.2)
Wine	…	…	15	…
Liquor	12	3.6 (0.7–17.1)	12	2.6 (0.3–22.6)
Caffeine				
All types	6	2.7 (1.9–3.9)	15	2.5 (1.5–4.0)
Coffee	6	3.0 (2.0–4.4)	17	4.5 (2.7–7.4)
Tea	18	2.1 (1.1–4.1)	14	6.0 (2.9–12.2)
Cola	30	3.0 (1.1–8.5)	19	13.8 (6.2–30.4)
Cigarette smoking	18	0.7 (0.3–1.9)	15	0.4 (0.1–1.9)
Exercise, MET ≥6	19	13.7 (7.4–25.4)	18	12.5 (5.8–27.3)
Valsalva maneuvers				
All types	43	2.2 (1.4–3.5)	15	2.3 (1.3–3.9)
Coughing	38	2.5 (1.1–5.5)	19	11.2 (6.2–20.1)
Sneezing	39	1.1 (0.4–3.0)	17	4.2 (2.0–8.8)
Nose blowing	33	3.3 (1.4–8.1)	14	14.2 (8.1–24.8)
Straining for defecation	36	8.6 (3.1–23.5)	17	42.2 (17.4–102.6)
Lifting >25 kg	14	6.6 (2.2–20.1)	19	6.4 (1.8–22.2)
Temperature change	13	13.3 (1.6–114.5)	22	16.9 (1.8–157.6)
Flu-like disease or fever	22	65.0 (34.0–124.3)	20	59.0 (24.4–142.5)
Head trauma	25	10.5 (1.7–64.3)	17	…
Strong emotions	23	2.7 (0.9–8.5)	20	4.5 (1.2–16.8)
Sexual activity	24	11.7 (4.6–30.0)	20	9.3 (2.2–40.2)

MET ≥6 corresponds indicates no events in hazard period to vigorous intensity activities. MET indicates metabolic equivalent of task; and RR, relative risk.

Careful recommendations on modifiable risks factors could be given, such as limiting excessive coffee consumption or earlier treatment of constipation. However, avoiding these triggers altogether does not seem reasonable nor desirable. Considering an incidence rate of an ICH of 24.6 per 100 000 person-years,[2] and the high number coffee consumptions during a person's lifetime, the number of coffee consumptions persons would need to avoid to prevent a single ICH would be gigantic.[39]

A strength of our study is the fact that we avoided case specific fixed confounders (like age, sex, and chronic comorbidity) by using a case-crossover design, that we interviewed patients shortly after admission, and that we looked at trigger factors for deep and lobar ICH separately. Our study also has limitations. Patients with severe hemorrhage could not participate in this study, although their ICH might have been triggered by one of the above mentioned trigger factors. The inclusion of a relatively small proportion of the total number of admitted ICH patients who were also in a relatively good clinical condition might affect the generalizability of our results. This might have introduced survival bias, although it is unlikely that some triggers favor a more severe ICH. Conducting a prospective population-based study keeping track of potential trigger factors throughout the follow-up period before the event occurs, could avoid such bias. However, in this type of population-based design large numbers of participants would have to record their activities almost continuously which makes it unfeasible. Second, we cannot eliminate the occurrence of recall bias and some answers to the questionnaires may have been unreliable (eg, answers about sexual activity or illicit drug use or unintentional, inconsistent answers about other triggers), which could have introduced incorrect data. However, the sensitivity analysis removing the unreliable answers showed comparable results. Third, exposure to certain triggers is only present during specific times of day. For example, coffee consumption occurs less at night. Introducing additional assumptions to correct for circadian rhythm or time-trend analysis for any of the triggers would, however, overfit our analysis to the study population. Finally, it seems likely that the dose of caffeine influences the risk of ICH. Although this study did not look into the dose of caffeine consumptions, future studies could explore the association between caffeine dose and ICH onset.

The present study shows that flu-like disease and fever and several blood pressure increasing activities are associated with onset of ICH which supports the hypothesis that infection and a sudden and short increase in blood pressure might trigger ICH.

ARTICLE INFORMATION

Received June 11, 2021; final revision received July 26, 2021; accepted October 19, 2021.

Affiliations

Department of Neurology (E.S.v.E., K.K., E.A.K., I.R., S.V., M.J.H.W.), Department of Epidemiology (S.C.C., W.M.L.), Einthoven Laboratory for Experimental Vascular Medicine (S.C.C., W.M.L.), and Department of Internal Medicine, Section Thrombosis and Hemostasis (S.C.C.), Leiden University Medical Center, the Netherlands. Department of Neurology and Neurosurgery, University Medical Center Utrecht Brain Center, Utrecht University, the Netherlands (W.M.T.J., G.J.E.R., C.J.M.K.). Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Centre for Neuroscience, Radboud University Medical Center, Nijmegen, the Netherlands (M.S.E., F.H.B.M.S., C.J.M.K.).

Sources of Funding

This study was supported by a personal grant to Dr Wermer from the Dutch Heart Foundation (Clinical Established Investigator grant 2016T86). The FETCH study (Finding the Etiology in Spontaneous Cerebral Hemorrhage) was supported by personal grants to Dr Klijn from the Dutch Heart Foundation (grant no. 2012 T077) and The Netherlands Organization for Health Research and Development (Aspasia grant no. 015.008.048).

Disclosures

Dr Wermer reports independent support from the Netherlands Organization for Scientific Research (Vidi grant 9171337 and Aspasia grant) and Dr Schreuder reports independent support from the Dutch Heart Foundation (Senior Clinical Scientist grant 2019T060). The other authors report no conflicts.

REFERENCES

1. Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. *JAMA*. 2019;321:1295–1303. doi: 10.1001/jama.2019.2413
2. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167–176. doi: 10.1016/S1474-4422(09)70340-0
3. Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, Jimenez-Conde J, Hansen BM, Fernandez-Cadenas I, Cortellini L, et al; International Stroke Genetics Consortium. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. *Ann Neurol*. 2010;68:934–943. doi: 10.1002/ana.22134
4. Caceres JA, Goldstein JN. Intracranial hemorrhage. *Emerg Med Clin North Am*. 2012;30:771–794. doi: 10.1016/j.emc.2012.06.003
5. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke*. 2003;34:2060–2065. doi: 10.1161/01.STR.0000080678.09344.8D
6. Jolink WMT, Wiegertjes K, Rinkel GJE, Algra A, de Leeuw FE, Klijn CJM. Location-specific risk factors for intracerebral hemorrhage: systematic review and meta-analysis. *Neurology*. 2020;95:e1807–e1818. doi: 10.1212/WNL.0000000000010418
7. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373:1632–1644. doi: 10.1016/S0140-6736(09)60371-8
8. Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V. Hypertension crisis. *Blood Press*. 2010;19:328–336. doi: 10.3109/08037051.2010.488052
9. Lammie GA, Lindley R, Keir S, Wiggam MI. Stress-related primary intracerebral hemorrhage: autopsy clues to underlying mechanism. *Stroke*. 2000;31:1426–1428. doi: 10.1161/01.str.31.6.1426
10. Chakrabarti SD, Ganguly R, Chatterjee SK, Chakravarty A. Is squatting a triggering factor for stroke in Indians? *Acta Neurol Scand*. 2002;105:124–127. doi: 10.1034/j.1600-0404.2002.1o196.x
11. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, Mehta Z, Rothwell PM. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *Lancet Neurol*. 2014;13:374–384. doi: 10.1016/S1474-4422(14)70031-6
12. Vlak MH, Rinkel GJ, Greebe P, van der Bom JG, Algra A. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. *Stroke*. 2011;42:1878–1882. doi: 10.1161/STROKEAHA.110.606558
13. Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology*. 2004;63:2006–2010. doi: 10.1212/01.wnl.0000145842.25520.a2
14. Schievink WI, Karemaker JM, Hageman LM, van der Werf DJ. Circumstances surrounding aneurysmal subarachnoid hemorrhage. *Surg Neurol*. 1989;32:266–272. doi: 10.1016/0090-3019(89)90228-0

15. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a stroke risk factor and determinant of outcome after stroke. *Stroke*. 2020;51:3156–3168. doi: 10.1161/STROKEAHA.120.030429
16. Zheng D, Arima H, Sato S, Gasparrini A, Heeley E, Delcourt C, Lo S, Huang Y, Wang J, Stapf C, et al; INTERACT2 investigators. Low ambient temperature and intracerebral hemorrhage: the INTERACT2 study. *PLoS One*. 2016;11:e0149040. doi: 10.1371/journal.pone.0149040
17. Jimenez-Conde J, Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Subirana I, Roquer J. Weather as a trigger of stroke. *Cerebrovasc Dis*. 2008;26:348–354.
18. Mostofsky E, Laier E, Levitan EB, Rosamond WD, Schlaug G, Mittleman MA. Physical activity and onset of acute ischemic stroke: the stroke onset study. *Am J Epidemiol*. 2011;173:330–336. doi: 10.1093/aje/kwq369
19. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193–221. doi: 10.1146/annurev.publhealth.21.1.193
20. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153. doi: 10.1093/oxfordjournals.aje.a115853
21. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman R, Benson H, Muller JE. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset study investigators. *Circulation*. 1995;92:1720–1725. doi: 10.1161/01.cir.92.7.1720
22. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142:91–98. doi: 10.1093/oxfordjournals.aje.a117550
23. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.
24. Zhang Z. Case-crossover design and its implementation in R. *Ann Transl Med*. 2016;4:341. doi: 10.21037/atm.2016.05.42
25. Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. *Int J Epidemiol*. 2014;43:1645–1655. doi: 10.1093/ije/dyu081
26. Mansournia MA, Altman DG. Population attributable fraction. *BMJ*. 2018;360:k757. doi: 10.1136/bmj.k757
27. Anderson C, Ni Mhurchu C, Scott D, Bennett D, Jamrozik K, Hankey G; Australasian Cooperative Research on Subarachnoid Hemorrhage Study Group. Triggers of subarachnoid hemorrhage: role of physical exertion, smoking, and alcohol in the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke*. 2003;34:1771–1776. doi: 10.1161/01.STR.0000077015.90334.A7
28. Hartley TR, Sung BH, Pincomb GA, Whitsett TL, Wilson MF, Lovallo WR. Hypertension risk status and effect of caffeine on blood pressure. *Hypertension*. 2000;36:137–141. doi: 10.1161/01.hyp.36.1.137
29. Roach RE, Siegerink B, le Cessie S, Rosendaal FR, Cannegieter SC, Lijfering WM. Coffee consumption is associated with a reduced risk of venous thrombosis that is mediated through hemostatic factor levels. *J Thromb Haemost*. 2012;10:2519–2525. doi: 10.1111/jth.12034
30. Reis A, Perez-Gregorio R, Mateus N, de Freitas V. Interactions of dietary polyphenols with epithelial lipids: advances from membrane and cell models in the study of polyphenol absorption, transport and delivery to the epithelium. *Crit Rev Food Sci Nutr*. 2020:1–24.
31. Burton AR, Fazalbhoy A, Macefield VG. Sympathetic responses to noxious stimulation of muscle and skin. *Front Neurol*. 2016;7:109. doi: 10.3389/fneur.2016.00109
32. Maegele M, Aversa J, Marsee MK, McCauley R, Chitta SH, Vyakaranam S, Walsh M. Changes in coagulation following brain injury. *Semin Thromb Hemost*. 2020;46:155–166. doi: 10.1055/s-0040-1702178
33. Fattahi F, Zetoune FS, Ward PA. Complement as a major inducer of harmful events in infectious sepsis. *Shock*. 2020;54:595–605. doi: 10.1097/SHK.0000000000001531
34. Boehme AK, Ranawat P, Luna J, Kamel H, Elkind MS. Risk of acute stroke after hospitalization for sepsis: a case-crossover study. *Stroke*. 2017;48:574–580. doi: 10.1161/STROKEAHA.116.016162
35. Lee JT, Chung WT, Lin JD, Peng GS, Muo CH, Lin CC, Wen CP, Wang IK, Tseng CH, Kao CH, et al. Increased risk of stroke after septicaemia: a population-based longitudinal study in Taiwan. *PLoS One*. 2014;9:e89386. doi: 10.1371/journal.pone.0089386
36. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, Molina-Nuevo JD, García-García J, Lozano-Setién E, Alcahut-Rodriguez C, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain*. 2020;143:3089–3103. doi: 10.1093/brain/awaa239
37. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701. doi: 10.1016/S1474-4422(10)70104-6
38. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497. doi: 10.1016/S1474-4422(13)70060-7
39. Macleod MR, White PM. Not tonight, darling, I might get a headache. *Stroke*. 2011;42:1807–1808. doi: 10.1161/STROKEAHA.111.617787