Trigger factors for stroke in young adults: a case-crossover study

Ekker, M.S.; Verhoeven, J.I.; Rensink, K.M.L.; Schellekens, M.M.I.; Boot, E.M.; Alebeek, M.E. van; ... ; Leeuw, F.E. de

RESEARCH ARTICLE

Trigger Factors for Stroke in Young Adults

A Case-Crossover Study

Merel S. Ekker, MD, PhD, Jamie I. Verhoeven, MD,* Karlijn M.L. Rensink, Bsc,* Mijntje M.I. Schellekens, MD, Esther M. Boot, MD, Mayte E. van Alebeek, MD, PhD, Paul J.A.M. Brouwers, MD, PhD, Renate M. Arntz, MD, PhD, Gert W. van Dijk, MD, PhD, Rob A.R. Gons, MD, PhD, Inge W.M. van Uden, MD, PhD, Tom den Heijer, MD, PhD, Paul L.M. de Kort, MD, PhD, Karlijn F. de Laat, MD, PhD, Anouk G.W. van Norden, MD, PhD, Sarah E. Vermeer, MD, PhD, Marian van Zagten, MD, PhD, Robert J. van Oostenbrugge, MD, PhD, Marieke J.H. Wermer, MD, PhD, Paul J. Nederkoorn, MD, PhD, Henk Kerkhoff, MD, PhD, Fergus Rooyer, MD, Frank G. van Rooij, MD, PhD, Ido R. van den Wijngaard, MD, PhD, Catharina J. M. Klijn, MD, PhD, Anil M. Tuladhar, MD, PhD, and Frank-Erik de Leeuw, MD, PhD

Correspondence
Prof. Dr. de Leeuw
frankerik.deleeuw@radboudumc.nl

Neurology® 2023;100:e49-e61. doi:10.1212/WNL.0000000000201341

Abstract

Background and Objectives

Causes of stroke in young adults differ from those in the elderly individuals, and in a larger percentage, no cause can be determined. To gain more insight into the etiology of (cryptogenic) stroke in the young population, we investigated whether trigger factors, such as short-lasting exposure to toxins or infection, may play a role.

Methods

Patients aged 18–49 years with a first-ever ischemic stroke or intracerebral hemorrhage (ICH) in 17 participating centers in the Netherlands completed a questionnaire about exposure to 9 potential trigger factors in hazard periods and on a regular yearly basis. A case-crossover design was used to assess relative risks (RRs) with 95% confidence intervals (95% CIs) by the Mantel-Haenszel case-crossover method, for any stroke (ischemic stroke and ICH combined) and for different etiologic subgroups of ischemic stroke.

Results

One thousand one hundred forty-six patients completed the questionnaire (1,043 patients with an ischemic stroke and 103 with an ICH, median age 44.0 years, 52.6% men). For any stroke, an increased risk emerged within 1 hour of cola consumption (RR 2.0, 95% CI 1.5–2.8) and vigorous physical exercise (RR 2.6, 95% CI 2.2–3.0), within 2 hours after sexual activity (RR 2.4, 95% CI 1.6–3.5), within 4 hours after illicit drug use (RR 2.8, 95% CI 1.7–4.9), and within 24 hours after fever or flu-like disease (RR 14.1, 95% CI 10.5–31.2; RR 13.9, 95% CI 8.9–21.9). Four trigger factors increased the risk of other determined and cryptogenic ischemic stroke, 3 that of cardioembolic stroke, 2 that of large vessel atherosclerosis and likely atherothrombotic stroke combined and stroke with multiple causes, and none that of stroke due to small vessel disease.

Discussion

We identified cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever, and flu-like disease as potential trigger factors for stroke in the young population and found differences in the type and number of trigger factors associated with different etiologic subgroups of ischemic stroke. These findings might help in better understanding the pathophysiologic mechanisms of (cryptogenic) stroke in the young population.

*These authors contributed equally.

From the Department of Neurology (M.S.E., J.I.V., K.M.L.R., M.M.I.S., E.M.B., C.J.M.K., A.M.T., F.-E.L.), Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands; Department of Neurology (M.E.A., A.G.W.N.), Amphia Hospital, Breda, the Netherlands; Department of Neurology (P.J.A.M.B., R.M.A.), Medisch Spectrum Twente, Enschede, the Netherlands; Department of Neurology (G.W.D.), Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands; Department of Neurology (R.A.R.G., I.W.M.U.), Catharina Hospital, Eindhoven, the Netherlands; Department of Neurology (T.H.), Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands; Department of Neurology (P.L.M.K.), Elisabeth-TweeSteden Hospital, Tilburg; Department of Neurology (K.F.L.), Haga Hospital, the Hague, Netherlands; Department of Neurology (S.E.V.), Rijnstate Hospital, Arnhem, the Netherlands; Department of Neurology (M.Z.), Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands; Department of Neurology (R.J.O.), Maastricht University Medical Centre, Maastricht, the Netherlands; Department of Neurology (M.J.H.W.), Leiden University Medical Centre, Leiden, the Netherlands; Department of Neurology (P.J.N.), Amsterdam University Medical Centres, Location AMC, Amsterdam, the Netherlands; Department of Neurology (H.K.), Albert Schweitzer Hospital, Dordrecht, the Netherlands; Department of Neurology (F.R.), Zuyderland Hospital, Sittard-Geleen, the Netherlands; Department of Neurology (F.G.R.), Medical Centre Leeuwarden, Leeuwarden, the Netherlands; and Department of Neurology (I.R.W.), Haaglanden Medical Center, the Hague, the Netherlands.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AVM = arteriovenous malformation; **ICH** = intracerebral hemorrhage; **LSD** = lysergic acid diethylamide; **mRS** = modified ranking scale; **MET** = metabolic equivalent of task; **NIHSS** = National Institutes of Health Stroke Scale; **ODYSSEY** = Observational Dutch Young Symptomatic StrokE studY; **RR** = relative risk; **PAF** = population attributable fraction; **SAH** = subarachnoid hemorrhage; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment; **TIA** = transient ischemic attack.

Stroke affects approximately 2 million young individuals (aged 18–50 years) each year.[1-3] Stroke in young adults differs from stroke in elderly individuals.[4] The incidence of stroke in the young population is rising, whereas it is decreasing in the older population. In addition, the cause of an ischemic stroke in the young population remains undetermined in approximately 30% of the cases, making a causal treatment and the provision of adequate long-term prognosis difficult in these patients.[1,5-7] Intracerebral hemorrhage (ICH) at young age also differs from that in the older population because it more often has a macrovascular cause (e.g., an arteriovenous malformation [AVM]) and a higher percentage of patients in whom the cause is unknown.[8-12]

Therefore, it is likely that in young patients with stroke, other risk factors or factors that may convert risk factors into causes play a role. Trigger factors, such as exposure to toxins, caffeine, sexual activity, physical exercise, or infection, have been hypothesized to create a (short-lasting) prothrombotic state or cause an increase in blood pressure that may predispose to stroke.[13-15] Trigger factors differ from risk factors because risk factors are believed to be the start of a causal chain, accumulating to a cause of stroke, whereas trigger factors cause a short-term risk subsequent to the trigger. Several trigger factors have been identified for subarachnoid hemorrhage (SAH), ischemic stroke, and ICH.[13,14,16-18]

For young patients specifically, the role of these trigger factors has never been investigated. We therefore investigated whether potential trigger factors (alcohol consumption, cigarette smoking, coffee and cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever, and flu-like disease) maybe associated with stroke in young adults. We further hypothesized that differences exist in the strength of association between the various trigger factors per stroke subtype (ischemic stroke and ICH), per ischemic stroke etiology by TOAST classification, and per ICH etiology, since their underlying mechanisms are different. In addition, we hypothesized that trigger factors are associated with an increased risk of cryptogenic stroke.

Methods

We performed a case-crossover study as part of the Observational Dutch Young Symptomatic StrokE studY (ODYSSEY), a Dutch multicenter prospective cohort study on the risk factors and prognosis of patients aged 18–49 years with a first-ever ischemic stroke or ICH. Details of the ODYSSEY have been previously described.[19] In short, our study comprises consecutive patients aged 18–49 years with first-ever symptomatic ischemic stroke with radiologic evidence of cerebral ischemia and with first-ever ICH. Patients with transient symptoms (duration of symptoms less than 24 hours) all had diffusion-weighted imaging positive lesions (DWI+) on MRI and as such were included as (minor) stroke according to the tissue-based definition.[20] Exclusion criteria were a traumatic ICH, SAH, and ICH due to ruptured aneurysm, ICH in a known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, or a history of a clinically symptomatic transient ischemic attack (TIA), ischemic stroke, or ICH.

Baseline Data Collection

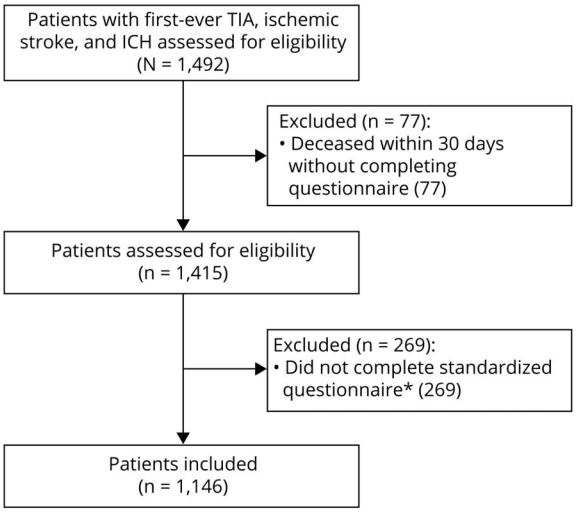
We systematically collected information including stroke characteristics and severity (National Institutes of Health Stroke Scale, NIHSS), acute treatment, diagnostic laboratory and cardiac tests, (vascular) risk factors, causes of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, modified ranking scale (mRS) at admission and discharge, and medication at discharge.

All patients completed a standardized structured questionnaire on level of education, marital status, employment, risk factors, and acute potential trigger factors including exposure and/or consumption within and outside predefined hazard periods. To minimize recall bias, patients were requested to complete the questionnaire as soon as possible after stroke, with or without assistance of their treating physicians or their family and/or acquaintance.

Trigger Factors

Trigger factors included alcohol consumption, cigarette smoking, caffein-containing coffee consumption, caffein-containing cola consumption, vigorous physical exercise, sexual activity, use of illicit drugs (cocaine, heroin, methadone, amphetamine, ecstasy, and D-lysergic acid diethylamide (LSD) were considered hard drugs; cannabis products and mushrooms containing psilocine were considered soft drugs),[21,22] and fever or flu-like disease, based on previous studies.[13,14,16,23-25] Exposure to a trigger factor in a predefined hazard period supposedly leads to a short-term increased risk compared with control hours of nonexposure. Questions were trigger factor specific, and patients were asked about their average exposure to each potential trigger factor in the previous year (usual frequency of exposure), time between onset of stroke and the last exposure, and exposure during a predefined hazard period. Hazard periods were predefined for all individual trigger factors, based on the estimated duration effect and previous literature, and were 1 hour for alcohol consumption, cigarette smoking, coffee consumption, cola consumption, and vigorous physical exercise, 2 hours for sexual activity, 4 hours for illicit drug use, and 24 hours for fever and flu-like disease. These

Figure 1 Patient Selection



*Patients that[1] had a very incomplete questionnaire,[2] refused to fill in the standardized questionnaire,[3] were unable to complete the questionnaire due to severe aphasia or cognitive impairment, or[4] had too large an interval between stroke onset and inclusion to reliably recall information requested in the questionnaire.

hazard periods were then compared with a patient's usual frequency of exposure to these triggers. For cigarette smoking, vigorous physical exercise, sexual activity, and fever or flu-like symptoms, patients were asked only whether they were exposed in the hazard period (yes/no). For alcohol consumption, coffee consumption, cola consumption, and illicit drug use, patients were also asked for the exact time interval between the last exposure and stroke onset.[13,14,16,23,26] To be able to compare our findings with some of the existing literature on trigger factors for ischemic stroke in an older population that used a hazard period of 2 hours,[14] we also assessed a 2-hour hazard period for alcohol consumption, coffee consumption, cola consumption, and illicit drug use (eTable 1, links.lww.com/WNL/C340). Illicit drug use was examined both combined and by subcategory (type of drugs, soft drugs vs hard drugs).[21,22]

Vigorous physical exercise (umbrella term) was examined separately for different grades of physical exercise. Each type of physical exercise was converted to a metabolic equivalent task [MET] by calculation of the ratio of the work metabolic rate to the resting metabolic rate. One MET is equivalent to the resting metabolic rate, for example, sitting quietly, and results in burning 1 kcal/kg/h. As an example, a patient with a weight of 70 kg performing a 1 MET activity (sitting) for 1 hour will use 70 kcal. We analyzed the following subcategories of vigorous physical exercise ([MET] ≥6): heavy exercise [MET] = 6, severe exercise [MET] = 7, extreme exercise [MET] = 8, and the combination of these 3 types of exercise, classified as vigorous physical exercise ([MET] ≥6). In addition, we assessed habitual exercisers (>500 [MET] minutes per week) vs rare exercisers (<500 [MET] minutes per week).[23,27] MET minutes were calculated by the number of minutes X the MET activity level, for example, 83.3 minutes of a MET 6 activity account for 500 MET minutes per week.

Data Analyses

We examined exposure to the various potential trigger factors using a case-crossover design, suitable for studying the effect of trigger factors within a hazard period compared with that in a control period.[14,15,28] Because each patient serves as their own control, confounding for chronic risk factors and participant characteristics will be minimized. Using the Mantel-Haenszel case-crossover method, a relative risk (RR) with 95% confidence interval (CI) was calculated for each potential trigger factor for any stroke (ischemic stroke and ICH combined) and for ischemic stroke and ICH separately, by calculating the ratio of the exposure in the hazard period and the expected yearly exposure frequency based on a patient's weekly or daily average frequency.[15] RRs should be interpreted as relative risks for a short-term period (trigger factors) and not as cumulative risks for the long-term. The p values were obtained by performing a conditional logistic regression analysis, which were adjusted for multiple comparisons using a Holm-Bonferroni post hoc analysis. All patients with certain unreliable answers were excluded (e.g., certain inconsistent answers and unmistakable untrue answers) before performing the analyses.

Population attributable fractions (PAFs), which indicate the fraction of a certain disease in a population that is attributable to exposure to a particular factor, were calculated for the trigger factors for which the RR remained significant after the Holm-Bonferroni test.[13,29] The PAFs can be used as an assessment tool for the health effect of exposure in a (study) population. It is calculated based on the RR and prevalence of exposure. The prevalence of exposure (p_e) is calculated as follows: the mean number of exposures per year/number of hazard periods per year. The PAF is then calculated through the following formula: $pe((RR-1)/(pe(RR-1)+1))$.[13,29]

To minimize potential recall bias or bias introduced by potential unreliable data, we performed 2 sensitivity analyses. First, all patients who completed the questionnaire later than 30 days after stroke onset based on the completed questionnaire or inclusion date were excluded, after which analyses were performed again. Second, we converted the usual frequency for all trigger factors (except for fever and flu-like disease) to 16 hours per day, assuming most exposure to trigger factors to take place during waking hours and not during an average of 8 hours of sleep.[13,15,23] To explore possible different mechanisms of trigger factors and unveil potential mechanisms of cryptogenic strokes specifically, we stratified our analysis for cause of stroke according to the TOAST classification. For intracerebral hemorrhage, we investigated patients with a macrovascular underlying cause and all "other" causes separately.

Data were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Data were analyzed using SPSS software version

Table 1 Baseline Characteristics

	Overall	Ischemic stroke <24 h	Ischemic stroke >24 h	ICH
Demographics				
18–49 y, N (%)	1,146 (100)	80 (7.0)	963 (84.0)	103 (9.0)
Median age (IQR)	44.0 (37.8–47.4)	43.3 (36.6–46.3)	44.2 (38.4–47.6)	43.1 (34.5–46.7)
Men, N (%)	603 (52.6)	45 (56.3)	501 (52.0)	57 (55.3)
Stroke characteristics				
Median NIHSS at admission, median (range)	1.0 (0–42)	0.0 (0–8)	3.0 (0–42)	2.0 (0–20)
Vascular risk factors, frequency (%)				
Smoking	549 (47.9)	29 (36.3)	492 (51.1)	28 (27.2)
Hypertension	437 (38.1)	22 (27.5)	364 (37.8)	51 (49.5)
Diabetes mellitus	107 (9.3)	4 (5.0)	100 (10.4)	3 (2.9)
Hypercholesterolemia	718 (62.7)	47 (58.8)	645 (67.0)	26 (25.2)
Alcohol	78 (6.7)	6 (7.5)	68 (7.1)	3 (2.9)
BMI >25 kg/m^2	555 (48.4)	29 (36.3)	488 (50.7)	38 (36.9)
TOAST classification, frequency (%)				
Large artery atherosclerosis	41 (3.6)	5 (6.3)	36 (3.7)	n.a.
Likely atherothrombotic stroke	131 (12.5)	5 (6.3)	126 (13.1)	n.a.
Small vessel disease	133 (12.7)	6 (7.5)	127 (13.2)	n.a.
Cardioembolic	180 (17.2)	19 (23.8)	161 (16.7)	n.a.
Other determined cause	225 (21.6)	17(21.3)	208 (21.6)	n.a.
Multiple causes	65 (6.2)	6 (7.6)	59 (6.1)	n.a.
Cryptogenic	268 (25.7)	22 (27.5)	246 (25.5)	n.a.
ICH etiology				
Hypertensive	n.a.	n.a.	n.a.	40 (38.8)
AVM	n.a.	n.a.	n.a.	13 (12.6)
Cavernoma	n.a.	n.a.	n.a.	10 (9.7)
Other causes[a]	n.a.	n.a.	n.a.	15 (14.6)
Unknown	n.a.	n.a.	n.a.	25 (24.3)
ICH localization, frequency (%)				
Lobar	n.a.	n.a.	n.a.	34 (33.0)
Basal ganglia	n.a.	n.a.	n.a.	38 (27.2)
Thalamus	n.a.	n.a.	n.a.	6 (5.8)
Cerebellar	n.a.	n.a.	n.a.	8 (7.8)
Brainstem	n.a.	n.a.	n.a.	13 (12.6)

Abbreviations: n.a = not applicable; ICH = intracerebral hemorrhage; IQR = interquartile range; NIHSS = The National Institutes of Health Stroke Scale; AVM = arteriovenous malformation.
[a] Other causes were as follows: dural arteriovenous fistula,[2] coagulopathy due to coagulation disorder,[2] illicit drug use (cocaine),[1] Posterior Reversible Encephalopathy Syndrome (PRES),[1] vasculitis,[1] diffuse intravasal coagulation during pregnancy,[1] multiple venous emboli in patient with Eisenmenger syndrome,[1] predisposition disorder of right hemisphere with mental retardation.[1]

Table 2 Relative Risk With 95% Confidence Intervals for Trigger Factors for Any Stroke

Trigger factor	Patients exposed in previous year	Patients exposed in hazard period	Patients not included (not exposed[a], missing data[b])	RR (95% CI)
Alcohol consumption	411	24	735 (444, 291)	1.3 (0.9–2.0)
Cigarette smoking	356	182	790 (670, 120)	0.6 (0.5–0.6)
Coffee consumption	659	118	487 (267, 220)	1.0 (0.8–1.2)
Cola consumption	346	39	800 (443, 357)	2.0 (1.5–2.8)[c]
Vigorous physical exercise [MET≥6]	804	186	342 (334, 8)	2.6 (2.2–3.0)[c]
Regular[d]	384	109	762 (757, 5)	1.6 (1.3–1.9)[c]
Irregular[d]	420	77	726 (723, 3)	10.2 (7.9–13.1)[c]
Heavy exercise [MET = 6]	767	144	368 (358, 10)	2.9 (2.4–3.4)[c]
Severe exercise [MET = 7]	476	54	670 (655, 15)	2.6 (2.0–3.5)[c]
Extreme exercise [MET = 8]	257	38	889 (884, 5)	4.5 (3.2–6.4)[c]
Sexual activity	641	26	505 (498, 7)	2.3 (1.5–3.4)[c]
Illicit drug use	69	16	1,077 (995, 82)	2.8 (1.7–4.9)[c]
Soft drugs only	19	4	1,127 (1,102, 25)	2.1 (0.7–6.48)
Hard drugs only	15	3	1,131 (1,128, 3)	5.9 (1.5–22.9)
Hard drugs ± soft drugs	35	9	1,093 (1,111, 18)	2.7 (1.4–5.5)
Fever	279	19	867 (861, 6)	14.1 (8.5–23.5)[c]
Flu-like disease	407	20	739 (736, 3)	13.9 (8.9–21.9)[c]

Abbreviations: RR = relative risk; CI = confidence interval; MET = metabolic equivalent of task.
[a] Patients who were not exposed in the previous year.
[b] Lack of necessary data per trigger factor, for example, due to patients who did not answer specific questions about their usual frequency.
[c] RR and 95% CI remained significant after correction for multiple hypothesis testing by the Holm-Bonferroni test.
[d] Regular (habitual) exercisers (>500 [MET] minutes per week, irregular (rare) exercisers (<500 [MET] minutes per week.

22 (IBM), R version 3.6.2 (R Project for Statistical Computing), and Microsoft Office Excel 2007.

Standard Protocol Approvals, Registrations, and Patient Consents

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). All patients signed informed consent.

Data Availability

The raw and anonymized data used in this study can be made available to other researchers on request. Written proposals can be addressed to the corresponding author and will be assessed by the ODYSSEY investigators for appropriateness of use, and a data sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

Results

Baseline Results

Of 1,492 patients who participated in the ODYSSEY, 1,146 patients (76.8%) completed the trigger factor questionnaire (Figure 1). Ischemic stroke was found in 1,043 patients (91.0%) and ICH in 103 (9.0%). The median age was 44.0 years (interquartile range, IQR, 37.8–47.4 years), and 603 patients were men (52.6%). Of all 1,043 patients with ischemic stroke, 80 patients (7.7%) had transient symptoms (duration less than 24 hours). Baseline characteristics of the included patients are summarized in Table 1. The median duration between stroke onset and inclusion was 7 days (IQR 3–29 days). The median duration between stroke onset and completing the standardized questionnaire was 9 days (IQR 3–33 days).

Trigger Factors for Any Stroke

For any stroke (ischemic stroke and ICH combined), an increased risk emerged within 1 hour of cola consumption (RR 2.0, 95% CI 1.5–2.8) and vigorous physical exercise (RR 2.6, 95% CI 2.2–3.0), within 2 hours after sexual activity (RR 2.4, 95% CI 1.6–3.5), within 4 hours after illicit drug use (RR 2.8, 95% CI 1.7–4.9), and within 24 hours after fever or flu-like disease (RR 14.1, 95% CI 10.5–31.2; RR 13.9, 95% CI 8.9–21.9; Table 2). No increased risk was found after exposure of alcohol or coffee consumption. Cigarette smoking decreased the risk of any stroke within 1 hour. Regular exercisers showed a lower relative risk (RR 1.6, 95% CI

Table 3 Relative Risk With 95% Confidence Intervals for 2 Sensitivity Analyses on Trigger Factors for Any Stroke

Trigger factor	RR (95% CI)	Patients excluded (>30 days interval)	RR (95% CI) sensitivity 1[a]	RR (95% CI) sensitivity 2[b]
Alcohol consumption	1.3 (0.9–2.0)	117	1.2 (0.8–2.0)	0.9 (0.6–1.3)
Cigarette smoking	0.6 (0.5–0.6)	67	0.6 (0.5–0.7)	[c]
Coffee consumption	1.0 (0.8–1.2)	170	0.9 (0.7–1.2)	0.6 (0.5–0.7)
Cola consumption	2.0 (1.5–2.8)[d]	77	1.8 (1.2–2.6)[d]	1.3 (0.9–1.8)
Vigorous physical exercise [MET≥6]	2.6 (2.2–3.0)[d]	224	2.6 (2.1–3.1)[d]	1.6 (1.4–1.8)[d]
Heavy exercise [MET = 6]	2.9 (2.4–3.4)[d]	214	2.7 (2.1–3.3)[d]	1.8 (1.5–2.1)[d]
Severe exercise [MET = 7]	2.6 (2.0–3.5)[d]	145	2.6 (1.9–3.6)[d]	1.7 (1.3–1.2)[d]
Extreme exercise [MET = 8]	4.5 (3.2–6.4)[d]	75	4.8 (3.2–7.2)[d]	2.9 (2.0–4.0)[d]
Sexual activity	2.4 (1.6–3.5)[d]	178	2.8 (1.8–4.3)[d]	1.5 (1.0–2.2)
Illicit drug use	2.8 (1.7–4.9)[d]	12	3.7 (2.1–6.8)[d]	1.8 (1.1–3.0)
Fever	14.1 (8.5–23.5)[d]	68	18.1 (10.5–31.2)[d]	—
Flu-like disease	13.9 (8.9–21.9)[d]	112	18.4 (11.6–29.3)[d]	—

Abbreviations: RR = relative risk; CI = confidence interval; MET = metabolic equivalent of task.
[a] Exclusion of patients that completed the questionnaire >30 d after onset of stroke.
[b] Usual frequency was calculated with 16 hours awake time and 8 h of sleep, assuming exposure to all trigger factors except fever and flu-like disease more likely to be during waking hours.
[c] No reliable RR with 95% CI could be calculated because of the very high usual frequency that exceeded the number of hours a year necessary to calculate a usual frequency.
[d] RR and 95% CI remained significant after correction for multiple hypothesis testing by the Holm-Bonferroni test.

1.3–1.9) than the group who did not exercise regularly (RR 10.2, 95% CI 7.9–13.1) (Table 2). The analysis of subcategories of illicit drug use did not show a significant difference in the risk of developing stroke after the use of soft or hard drugs (Table 2).

When patients who completed the questionnaire later than 30 days after stroke onset (sensitivity analysis 1) or who had unreliable answers (sensitivity analysis 2) were excluded, results remained similar. When we reduced the maximum duration of exposure to 16 hours per day, RRs for all trigger factors were lower (Table 3).

PAFs are summarized in eTable 2, links.lww.com/WNL/C341. We found the highest PAF for vigorous physical exercise (12.4%) and the lowest for illicit drug use (0.3%).

Trigger Factors Stratified by Ischemic Stroke or ICH

Vigorous physical exercise and sexual activity increased the risk for both ischemic stroke and ICH during the hazard period, whereas cola consumption, illicit drug use, fever, or flu-like disease increased only the risk for ischemic stroke (Table 4, eFigure 1, links.lww.com/WNL/C338).

Trigger Factors for Different Causes of Ischemic Stroke

We found 4 trigger factors for cryptogenic stroke, vigorous physical exercise (RR 3.2, 95% CI 2.3–4.3) (including the subcategories of heavy exercise (RR 3.7, 95% CI 2.7–5.1), severe exercise (RR 3.3, 95% CI 1.9–5.7), and extreme exercise (RR 3.2, 95% CI 1.7–6.2)), illicit drug use (RR 4.0, 95% CI 1.7–9.7), fever (RR 7.9, 95% CI 2.5–25.5), and flu-like disease (RR 10.4, 95% CI 3.9–28.1, Table 5 and eFigure 2, links.lww.com/WNL/C339). For large artery disease and likely atherothrombotic stroke combined, we found only fever and flu-like disease to be trigger factors. No trigger factors were found for stroke due to small vessel disease. Three trigger factors (vigorous physical exercise, including the subcategories of heavy exercise, severe exercise, and extreme exercise, fever, and flu-like disease) showed an increased RR for developing a cardioembolic stroke. Four trigger factors (cola consumption, vigorous physical exercise, including the subcategories of heavy exercise, severe exercise, and extreme exercise, fever, and flu-like disease) were found to increase the risk for a stroke with other determined cause. Two trigger factors (vigorous physical exercise, including the subcategories of heavy exercise, severe exercise and extreme exercise, and fever) were found to increase the risk for stroke due to multiple causes.

Trigger Factors for Causes of Intracerebral Hemorrhage

Table 6 summarizes the results for the macrovascular causes and "other causes" in ICH. In the macrovascular category, heavy exercise (RR 19.2, 95% CI 3.8–97.7) and extreme exercise (RR 83.2, 95% CI 5.2–1,336.3) were trigger factors. For the category with all "other causes," cola consumption, vigorous exercise, severe exercise, extreme exercise, and sexual activity seemed to increase the risk of developing an ICH after

Table 4 Relative Risk With 95% Confidence Intervals for Trigger Factors Stratified by Ischemic Stroke and Intracerebral Hemorrhage

	TIA and ischemic stroke				Intracerebral hemorrhage			
Trigger factor	Patients exposed in previous year	Patients exposed in hazard period	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed in previous year	Patients exposed in hazard period	Patients not included (not exposed, missing data[a])	RR (95% CI)
Alcohol consumption	374	20	669 (407, 262)	1.2 (0.8–1.9)	37	4	66 (66, 0)	3.4 (1.2–9.5)
Cigarette smoking	335	174	708 (593, 115)	0.6 (0.5–0.6)	21	8	82 (77, 5)	0.6 (0.5–0.7)
Coffee consumption	606	108	437 (236, 201)	1.0 (0.8–1.2)	53	10	50 (31, 19)	1.1 (0.5–2.2)
Cola consumption	321	35	437 (400, 37)	1.9 (1.4–2.7)[b]	25	4	78 (43, 35)	4.1 (1.0–16.6)
Vigorous physical exercise [MET≥6]	732	167	311 (311, 0)	2.5 (2.1–3.0)[b]	72	19	31 (30, 1)	3.6 (2.1–6.1)[b]
Heavy exercise [MET = 6]	699	132	344 (325, 19)	2.9 (2.4–3.4)[b]	68	12	35 (33, 2)	2.8 (1.6–5.1)
Severe exercise [MET = 7]	445	50	598 (586, 12)	2.5 (1.9–3.4)[b]	31	4	72 (69, 3)	5.8 (1.6–20.3)[b]
Extreme exercise [MET = 8]	238	32	805 (801, 4)	4.0 (2.8–5.8)[b]	19	6	84 (83, 1)	18.1 (3.9–84.6)[b]
Sexual activity	586	20	457 (451, 6)	1.9 (1.2–3.0)[b]	55	7	47 (46, 1)	5.6 (2.4–13.6)[b]
Illicit drug use	67	15	976 (903, 73)	2.7 (1.6–4.7)[b]	2	1	101 (92, 9)	7.4 (0.5–118.7)
Fever	257	18	786 (780, 6)	15.1 (9.0–25.5)[b]	22	1	81 (81, 0)	6.3 (0.6–62.8)
Flu-like disease	372	20	671 (633, 38)	15.2 (9.7–23.8)[b]	35	0	68 (68, 0)	[c]

Abbreviations: RR = relative risk; CI = confidence interval; MET = metabolic equivalent of task.
[a] Data could be missing due to patients who did not answer specific questions about their usual frequency.
[b] RR and 95% CI remained significant after correction for multiple hypothesis testing by the Holm-Bonferroni test.
[c] Not a single patient with ICH was exposed to flu-like disease during the hazard period; therefore, no RR could be calculated.

exposure. Owing to a small sample size, RRs could not be calculated in the "macrovascular" group for the trigger factors cola consumption, severe exercise, illicit drug use, fever, or for flu-like disease in both the "macrovascular" and "other" groups.

Discussion

We found cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever, and flu-like disease as possible trigger factors for stroke overall, and for ischemic stroke in young adults, with the highest RR for fever and flu-like disease. For ICH, cola consumption, vigorous physical exercise, and sexual activity were trigger factors, but not illicit drug use, fever, and flu-like disease. Trigger factors differed according to etiologic groups of ischemic stroke. i (4) trigger factors for stroke with other determined cause and for cryptogenic strokes. Vigorous physical exercise showed the highest PAF.

Several plausible biological explanations exist on how trigger factors increase the risk of stroke. First, some trigger factors, such as caffeine consumption,[30,31] certain types of drugs,[32] sexual activity,[33] and vigorous physical exercise[23] transiently increase blood pressure. An increased blood pressure may result in increased shear stress on the arterial vessel wall, potentially resulting in the disruption of the endothelial cell surface. This can consequently increase the risk of thrombotic occlusion, especially in combination with a hypercoagulable state reportedly to be induced by strenuous physical exercise.[23,34,35] Conversely, a sudden rise in blood pressure might trigger rupture of a vessel wall, resulting in an ICH.[13,16] In addition, some drug types are known to cause vasospasms without a blood rise, which can also lead to stroke.[36]

Second, fever and flu-like disease may result in an increased stroke risk because it can lead to systemic inflammation with endothelial

Table 5 Relative Risk With 95% Confidence Intervals for Trigger Factors Stratified by Etiology According to TOAST Classification for Ischemic Stroke

	Large vessel atherosclerosis + likely atherothrombotic stroke (N = 172)			Small vessel disease (N = 133)			Cardioembolic stroke (N = 180)		
Trigger factor	Patients exposed in previous year (exposed in hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)
Alcohol consumption	48 (3)	124 (83, 41)	1.2 (0.4–3.8)	52 (1)	81 (49, 32)	0.4 (0.1–2.5)	74 (3)	106 (61, 45)	1.0 (0.3–3.0)
Cigarette smoking	77 (36)	95 (63, 32)	[b]	51 (32)	82 (66, 16)	[b]	42 (24)	138 (130, 8)	0.9 (0.5–1.6)
Coffee consumption	97 (17)	75 (32, 43)	0.9 (0.5–1.5)	79 (14)	54 (28, 26)	0.8 (0.5–1.4)	115 (21)	65 (37, 28)	1.3 (0.8–2.1)
Cola consumption	55 (4)	117 (55, 62)	0.9 (0.3–2.4)	40 (2)	93 (55, 38)	0.7 (0.2–2.3)	53 (6)	127 (68, 59)	2.8 (1.2–6.8)
Vigorous physical exercise [MET≥6]	112 (20)	60 (59, 1)	1.6 (1.0–2.6)	88 (14)	45 (43, 2)	1.2 (0.7–2.0)	137 (32)	43 (43, 0)	2.9 (2.0–4.2)[c]
Heavy exercise [MET = 6]	110 (17)	62 (60, 2)	1.8 (1.1–3.0)	84 (11)	49 (41, 8)	1.6 (0.9–3.0)	134 (28)	46 (44, 2)	3.1 (2.1–4.5)[c]
Severe exercise [MET = 7]	53 (6)	119 (117, 2)	2.1 (0.9–4.8)	57 (4)	76 (73, 3)	1.0 (0.4–2.5)	94 (10)	86 (86, 0)	3.6 (1.8–7.1)[c]
Extreme exercise [MET = 8]	30 (6)	142 (142, 0)	7.1 (2.5–20.2)[c]	27 (2)	106 (105, 1)	1.9 (0.4–8.8)	49 (6)	131 (131, 0)	4.0 (1.6–10.5)[c]
Sexual activity	85 (5)	87 (86, 1)	2.9 (1.3–6.5)	78 (2)	55 (54, 1)	1.4 (0.3–5.6)	114 (4)	66 (65, 1)	2.2 (0.8–5.8)
Illicit drug use	10 (1)	162 (133, 29)	1.1 (0.2–8.1)	13 (4)	120 (113, 7)	4.8 (1.4–16.5)	12 (1)	168 (161, 7)	1.0 (0.1–8.4)
Fever	33 (3)	139 (138, 1)	18.8 (5.8–61.0)[c]	25 (0)	108 (108, 0)	—	55 (6)	125 (125, 0)	29.1 (12.3–68.4)[c]
Flu-like disease	61 (6)	111 (111, 0)	24.8 (10.8–56.9)[c]	45 (1)	88 (88, 0)	7.1 (1.0–51.6)	68 (5)	112 (111, 1)	22.2 (8.8–55.8)[c]

	Other determined stroke (N = 225)			Multiple causes (N = 65)			Cryptogenic stroke (N = 268)		
Trigger factor	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)
Alcohol consumption	83 (6)	142 (90, 50)	1.7 (0.8–3.6)	15 (0)	50 (29, 21)	—	102 (7)	166 (95, 71)	1.8 (0.8–4.0)
Cigarette smoking	65 (32)	160 (132, 28)	0.9 (0.5–1.6)	30 (18)	35 (27, 8)	0.8 (0.4–1.4)	70 (32)	198 (174, 24)	0.5 (0.4–0.8)
Coffee consumption	125 (21)	100 (60, 40)	0.9 (0.5–1.4)	37 (9)	28 (18, 10)	1.2 (0.5–2.5)	154 (26)	114 (60, 54)	1.0 (0.7–1.5)
Cola consumption	71 (14)	154 (82, 72)	4.9 (2.6–9.3)[c]	25 (3)	40 (21, 19)	1.3 (0.5–3.9)	78 (7)	190 (118, 72)	2.0 (0.9–4.4)
Vigorous physical exercise [MET≥6]	154 (40)	71 (70, 1)	3.4 (2.4–4.9)[c]	46 (10)	19 (18, 1)	2.8 (1.6–5.2)[c]	196 (51)	72 (70, 2)	3.2 (2.3–4.3)[c]

Continued

Table 5 Relative Risk With 95% Confidence Intervals for Trigger Factors Stratified by Etiology According to TOAST Classification for Ischemic Stroke *(continued)*

	Other determined stroke (N = 225)			Multiple causes (N = 65)			Cryptogenic stroke (N = 268)		
Trigger factor	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)
Heavy exercise [MET = 6]	143 (26)	82 (78, 4)	3.2 (2.1–4.9)[c]	44 (8)	21 (20, 1)	4.6 (2.0–10.7)[c]	185 (42)	83 (81, 2)	3.7 (2.7–5.1)[c]
Severe exercise [MET = 7]	95 (12)	130 (127, 3)	2.6 (1.5–4.4)[c]	25 (5)	40 (40, 0)	3.8 (1.4–10.4)[c]	121 (13)	147 (143, 4)	3.3 (1.9–5.7)[c]
Extreme exercise [MET = 8]	48 (6)	177 (175, 2)	4.7 (2.0–10.8)[c]	14 (4)	51 (51, 0)	4.6 (1.7–12.6)[c]	70 (8)	198 (197, 1)	3.2 (1.7–6.2)[c]
Sexual activity	112 (5)	113 (101, 12)	2.4 (0.9–6.4)	40 (0)	25 (25, 0)	—	147 (4)	121 (120, 1)	1.5 (0.6–4.1)
Illicit drug use	14 (4)	211 (195, 16)	4.3 (1.3–14.0)	7 (0)	58 (55, 3)	—	11 (5)	257 (236, 21)	4.0 (1.7–9.7)[c]
Fever	58 (4)	167 (165, 2)	13.1 (3.4–51.0)[c]	13 (2)	52 (50, 2)	48.4 (10.2–230.3)[c]	74 (3)	194 (193, 1)	7.9 (2.5–25.5)[c]
Flu-like disease	78 (4)	147 (146, 1)	15.5 (5.6–42.9)[c]	21 (0)	44 (43, 1)	—	100 (4)	168 (168, 0)	10.4 (3.9–28.1)[c]

Abbreviations: RR = relative risk; CI = confidence interval; MET = metabolic equivalent of task.
[a] Data could be missing due to patients that did not answer specific questions about their usual frequency.
[b] No reliable RR with 95% CI could be calculated because of the very high usual frequency that exceeded the number of hours a year necessary to calculate a usual frequency.
[c] RR and 95% CI remained significant after correction for multiple hypothesis testing by the Holm-Bonferroni test.

dysfunction, a prothrombotic condition and increased platelet activation and aggregation.[16,26,37,38] Our finding of fever and flu-like disease to be trigger factors is in line with previous literature investigating trigger factors in an older population.[16,26] Given the observation that the1-year cumulative incidence of infection is much higher than the incidence of stroke at young age,[1-3,39] future research should identify when and which environmental, genetic, or other factors predispose young people to ischemic stroke. The ongoing case control SECRETO study may potentially shed light on these mechanisms.[40]

In contrast to previous studies in older populations, coffee consumption was not identified as a trigger factor for any type of stroke in our young population.[13,16,24] A possible explanation may be that the effect of a sudden blood pressure surge differs between old and young people, with the elderly individuals more often having long-standing hypertension, atherosclerosis, and reduced vessel wall elasticity.[41,42]

In line with previous literature, we did not find cigarette smoking as a trigger factor and even found a negative relative risk. The main difference we found regarding coffee consumption and cigarette smoking compared with the significant trigger factors in our study was the high usual daily frequency of cigarette smoking and coffee consumption, vs less frequent occurrence of triggers such as (extreme) exercise, sexual activity, illicit drug use, and fever or flu-like disease. To date, there is only 1 study that found cigarette smoking to be a trigger factor; however, this was a case-control study investigating patients with a subarachnoid hemorrhage (SAH) with controls from the general population, in which patients with SAH smoked much more compared with the controls. One can therefore speculate that a regular high consumption of coffee and very frequent habituation of cigarette smoking may lead to tolerance of the hemodynamic effects of caffeine and nicotine.[13,43,44]

Our study may provide etiologic clues especially for young patients with stroke without an identifiable cause. Vigorous physical exercise and the different bouts of exercise, illicit drug use, fever, and flu-like disease may all result in a temporary rise in blood pressure or a prothrombotic condition.[13,23,26,30-35,37,38] However, this study alone is not enough to validate the causality of trigger factors in young patients with cryptogenic stroke. To obtain further support for a role of trigger factors in (cryptogenic) stroke, these patients could be followed up for recurrent stroke and their relation with the earlier identified trigger factor. In addition, more objective measurements of blood pressure and other vital functions during some of the trigger factors can be obtained with the use of "wearable electronic devices," for example, smartwatches and comparable applications.[45] This would also help to look at individual differences in reaction to triggers, which could be further studied with individual measurements and blood tests before and afterward.

Table 6 Relative Risk With 95% Confidence Intervals for Trigger Factors Stratified by Etiology for Intracerebral Hemorrhage

	Macrovascular[a] (N = 25)			Other (N = 78)		
Trigger factor	Patients exposed in previous year (exposed in hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)	Patients exposed (year, hazard period)	Patients not included (not exposed, missing data[a])	RR (95% CI)
Alcohol consumption	12 (1)	13 (4, 9)	1.8 (0.3–12.8)	25 (3)	53 (33, 20)	4.7 (1.4–16.3)[b]
Cigarette smoking	2 (1)	23 (23, 0)	16.0 (0.0–6,598.3)	19 (7)	59 (55, 4)	0.5 (0.5–0.6)
Coffee consumption	12 (3)	13 (7, 6)	1.7 (0.5–6.0)	41 (7)	37 (24, 13)	0.9 (0.4–2.2)
Cola consumption	3 (0)	22 (11, 11)	—	22 (4)	56 (32, 24)	5.1 (1.2–22.0)[b]
Vigorous physical exercise [MET≥6]	17 (5)	8 (8, 0)	17.6 (4.5–69.1)	55 (14)	23 (22, 1)	2.7 (1.5–5.0)[b]
Heavy exercise [MET = 6]	17 (4)	8 (8, 0)	19.2 (3.8–97.7)[b]	51 (8)	27 (25, 2)	2.0 (1.0–4.0)
Severe exercise [MET = 7]	8 (0)	17 (17, 0)	—	23 (4)	55 (53, 2)	6.7 (1.9–24.5)[b]
Extreme exercise [MET = 8]	3 (1)	22 (22, 0)	83.2 (5.2–1,336.3)[b]	16 (5)	62 (61, 1)	15.2 (2.7–86.0)[b]
Sexual activity	16 (1)	9 (9, 0)	4.1 (0.5–33.0)	39 (5)	39 (38, 1)	6.1 (2.3–16.2[b]
Illicit drug use	0 (0)	25 (22, 3)	—	2 (1)	76 (71, 5)	7.4 (0.5–118.7)
Fever	3 (0)	22 (22, 0)	—	19 (1)	59 (59, 0)	6.6 (0.7–67.4)
Flu-like disease	2 (0)	23 (23, 0)	—	33 (0)	45 (45, 0)	—

[a] Macrovascular causes contain patients with arteriovenous malformations (AVM), cavernous malformation and dural arteriovenous fistula.
[b] RR and 95% CI remained significant after correction for multiple hypothesis testing by the Holm-Bonferroni test.

Our study has several strengths. First, we add novelty to the existing literature by investigating young adults with stroke specifically in a unique sample of more than 1,000 young adults with stroke, which allowed for subanalyses regarding both stroke type and etiology of ischemic stroke. Second, the case-crossover design allowed us to limit confounding by patient-specific characteristics, such as age, sex, comorbidity, and vascular risk factors. Third, the large sample size of our cohort, with patients prospectively included in both academic and general hospitals in the Netherlands in different regions, provides a reliable representation of a stroke population consisting of young adults. Fourth, results largely remained in sensitivity analyses, suggesting that recall bias and bias due to unreliable data did not have a large influence on our results. Fifth, due to our sample size, we were able to investigate categories of specific trigger factors separately, such as grades of physical exercise, fever, and flu-like disease.[13,14,16] Reporting RRs stratified by the severity of physical exercise might be of additional value because circulating levels of catecholamines and hence platelet activation are supposedly related to the relative intensity of physical exercise.[34]

There are also limitations that need to be addressed. Survival and selection bias might have been introduced because patients with a more severe stroke who died before being able to complete the questionnaire or who had too severe symptoms or cognitive deficits were not included. This might have affected the generalizability of our results. However, it is unlikely that trigger factors influence the severity of stroke.[16] Given that trigger factors are believed to only cause a short-lasting relative risk, potentially leading to stroke, there is no pathophysiologic plausible explanation that they would be related to larger emboli and thus more severe stroke, though formal evidence is lacking. Second, recall bias might have occurred, given the detailed questions that patients were asked about their activities and exposure previous to such a serious life-event as stroke, although in the sensitivity analyses, this did not seem to be an important factor. Third, we had a small sample of patients with ICH and exposure to illicit drug use. Fourth, we were not able to distinguish between

different types of cola consumption (e.g., regular cola, diet cola, etc). We did not gather information on caffein-containing energy drinks. Fifth, the number of missing data on the trigger factors assessed varied. On one hand, a lot of patients have filled in "unknown" to 1 or more questions about the last exposure, usual exposure, or amount of exposure to a certain trigger factor, leading to exclusion for that specific analysis. On the other hand, missing data may have been caused by incomplete answering questions because patients felt it inappropriate to reveal personal private details. This may have led to an underestimation of some of these trigger factors and to smaller subgroups per trigger factor, which may have influenced the width of the 95% CIs.

Clinical Importance

Trigger factors might not have the same effect on every individual. More insight into the personalized effect of trigger factors would provide more insight in why certain people are affected by a trigger factor and why other people are not, possibly leading to new information into stroke mechanisms and eventually tailor-made preventive advice. One could think of several explanations for varying effects on individuals of the trigger factors that turned out relevant in our study. For example, caffeine consumption and exercise are believed to create a lower risk for individuals who are frequently exposed in comparison with those who are not.[23,24] For illicit drug use, the individual variety of pharmacokinetic interactions could lead to a different outcome per individual. In addition, other individual characteristics or comorbidities can contribute to the role a trigger factor might play. For example, while the systemic inflammatory effects of fever and flu-like disease may serve as a trigger for both ischemic stroke and ICH, some viral infections such as COVID-19, are known for the risk of venous thrombosis.[46] This will allegedly not increase the risk for arterial stroke, unless, for example, an individual also has a patent foramen ovale (PFO).[47]

To conclude, fever and flu-like disease are the strongest trigger factors for stroke in young adults, followed by cola consumption, vigorous physical activity exercise, sexual activity, and illicit drug use. Future research should focus on how and when trigger factors are converted into risk factors in which patients to clarify etiology in the substantial group of (cryptogenic) stroke in young patients and provide more personalized prevention.

Study Funding

Professor Dr. F.E. de Leeuw has received a VIDI grant (016-126-351) and the Clinical established investigator Dutch Heart Foundation grant (2014 T060); Dr. A.M. Tuladhar is a junior staff member of the Dutch Heart Foundation (grant number 2016T044); Professor Dr. M.J.H. Wermer has received a VIDI grant (9171337) of the ZonMw/NWO and the Clinical established investigator Dutch Heart Foundation grant (2016T86); Professor Dr. C.J.M. Klijn reports grants the Dutch Heart Foundation, CVON2015–01: CONTRAST, and the support of the Brain Foundation Netherlands (HA2015 · 01·06), outside the submitted work.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* January 22, 2022. Accepted in final form August 17, 2022. Submitted and externally peer reviewed. The handling editor was Brad Worrall, MD, MSc, FAAN.

Appendix Authors

Name	Location	Contribution
Merel S. Ekker, MD, PhD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Jamie Inge Verhoeven, MD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Karlijn M.L. Rensink, BSc	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Mijntje M.I. Schellekens, MD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Esther M. Boot, MD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Mayte E. van Alebeek, MD, PhD	Department of Neurology, Amphia Hospital, Breda, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design
Paul J.A.M. Brouwers, MD, PhD	Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Renate M. Arntz, MD, PhD	Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix (continued)

Name	Location	Contribution
Gert W. van Dijk, MD, PhD	Department of Neurology, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Rob A.R. Gons, MD, PhD	Department of Neurology, Catharina Hospital, Eindhoven, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Inge W.M. van Uden, MD, PhD	Department of Neurology, Catharina Hospital, Eindhoven, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Tom den Heijer, MD, PhD	Department of Neurology, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Paul L.M. de Kort, MD, PhD	Department of Neurology, Elisabeth-TweeSteden Hospital, Tilburg	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Karlijn F. de Laat, MD, PhD	Department of Neurology, Haga Hospital, the Hague, Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Anouk G.W. van Norden, MD, PhD	Department of Neurology, Amphia Hospital, Breda, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Sarah E. Vermeer, MD, PhD	Department of Neurology, Rijnstate Hospital, Arnhem, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Marian van Zagten, MD, PhD	Department of Neurology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Robert J. van Oostenbrugge, MD, PhD	Department of Neurology, Maastricht University Medical Centre, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Marieke J.H. Wermer, MD, PhD	Department of Neurology, Leiden University Medical Centre, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Paul J. Nederkoorn, MD, PhD	Department of Neurology, Amsterdam University Medical Centres, Location AMC, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Henk Kerkhoff, MD, PhD	Department of Neurology, Albert Schweitzer Hospital, Dordrecht, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Fergus Rooyer, MD	Department of Neurology, Zuyderland Hospital, Sittard-Geleen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Frank G. van Rooij, MD, PhD	Department of Neurology, Medical Centre Leeuwarden, Leeuwarden, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Ido R. van den Wijngaard, MD, PhD	Department of Neurology, Haaglanden Medical Center, the Hague, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Catharina J.M. Klijn, MD, PhD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Anil M. Tuladhar, MD, PhD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Frank-Erik de Leeuw, MD, PhD	Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and BehaviourNijmegen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Ekker MS, Verhoeven JI, Vaartjes I, van Nieuwenhuizen KM, Klijn CJM, de Leeuw FE. Stroke incidence in young adults according to age, subtype, sex, and time trends. *Neurology.* 2019;92(21):e2444–e2454.
2. Ekker MS, Jacob MA, van Dongen MME, et al. Global Outcome Assessment Life-long after stroke in young adults initiative-the GOAL initiative: study protocol and rationale of a multicentre retrospective individual patient data meta-analysis. *BMJ Open.* 2019;9(11):e031144.
3. Feigin VL, Roth GA, Naghavi M, et al; Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 2016;15(9):913-924.
4. van Alebeek ME, Arntz RM, Ekker MS, et al. Risk factors and mechanisms of stroke in young adults: the FUTURE study. *J Cereb Blood flow Metab.* 2018;38(9):1631-1641.
5. Waje-Andreassen U, Thomassen L, Jusufovic M, et al. Ischaemic stroke at a young age is a serious event–final results of a population-based long-term follow-up in Western Norway. *Eur J Neurol.* 2013;20(5):818-823.
6. Ferro JM, Massaro AR, Mas JL. Aetiological diagnosis of ischaemic stroke in young adults. *Lancet Neurol.* 2010;9(11):1085-1096.
7. Arboix A, Cendrós V, Besa M, et al. Trends in risk factors, stroke subtypes and outcome. Nineteen-year data from the Sagrat Cor Hospital of Barcelona stroke registry. *Cerebrovasc Dis (Basel, Switzerland).* 2008;26(5):509-516.

8. Ruíz-Sandoval JL, Cantú C, Barinagarrementeria F. Intracerebral hemorrhage in young people: analysis of risk factors, location, causes, and prognosis. *Stroke.* 1999; 30(3):537-541.
9. Hostettler IC, Seiffge DJ, Werring DJ. Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Rev Neurother.* 2019;19(7):679-694.
10. van Asch CJJ, Velthuis BK, Rinkel GJE, et al; DIAGRAM Investigators. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ (Clinical research ed).* 2015;351:h5762.
11. Koivunen R-J, Satopää J, Meretoja A, et al. Incidence, risk factors, etiology, severity and short-term outcome of non-traumatic intracerebral hemorrhage in young adults. *Eur J Neurol.* 2015;22(1):123-132.
12. Yang NR, Kim JH, Ahn JH, Oh JK, Chang IB, Song JH. Is nontraumatic intracerebral hemorrhage different between young and elderly patients?. *Neurosurg Rev.* 2020; 43(2):781-791.
13. Vlak MHM, Rinkel GJE, 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(7):1878-1882.
14. Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology* 2004;63(11):2006-2010.
15. Zhang Z. Case-crossover design and its implementation in R. *Ann translational Med.* 2016;4(18):341.
16. Etten ESK K, Jolink WMT, Koemans EA, et al. Trigger Factors for Spontaneous Intracerebral Hemorrhage: A Case-Crossover Study. *Stroke*; 2021.
17. Ghiasmand M, Moghadamnia MT, Pourshaikhian M, Kazemnejad Lili E. Acute triggers of myocardial infarction: a case-crossover study. *Egypt Heart J.* 2017;69(4): 223-228.
18. Guiraud V, Amor MB, Mas JL, Touzé E. Triggers of ischemic stroke: a systematic review. *Stroke.* 2010;41(11):2669-2677.
19. Arntz RM, van Alebeek ME, Synhaeve NE, et al. Observational Dutch Young Symptomatic StrokE studY (ODYSSEY): study rationale and protocol of a multicentre prospective cohort study. *BMC Neurol.* 2014;14:55.
20. Easton JD, Saver JL, Albers GW, et al. American Heart Association, American Stroke Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Interdisciplinary Council on Peripheral, Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart association/American stroke association stroke council; council on cardiovascular surgery and anesthesia; council on cardiovascular radiology and intervention; council on cardiovascular nursing; and the interdisciplinary council on peripheral vascular disease. The American academy of neurology affirms the value of this statement as an educational tool for neurologists. *Stroke.* 2009;40(6):2276-2293.
21. *Opium Law, Class I and II Drugs.* Updated July 1, 2021. [online]. Available at: government.nl/topics/drugs/difference-between-hard-and-soft-drugs. Accessed August 18, 2021.
22. Lee JP, Antin TMJ. How do researchers categorize drugs, and how do drug users categorize them? *Contemp Drug Probl.* 2012;38(3):387-428.
23. 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(3):330-336.
24. Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA. Coffee and acute ischemic stroke onset: the Stroke Onset Study. *Neurology.* 2010;75(18): 1583-1588.
25. Mostofsky E, Burger MR, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA. Alcohol and acute ischemic stroke onset: the stroke onset study. *Stroke.* 2010;41(9): 1845-1849.
26. 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(10):3156-3168.
27. Kaminsky LA, Montoye AHK. Physical activity and health: what is the best dose? *J Am Heart Assoc.* 2014;3(5):e001430.
28. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health.* 2000;21:193-221.
29. Mansournia MA, Altman DG. Population attributable fraction. *BMJ.* 2018;360:k757.
30. Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *Eur J Clin Nutr.* 1999;53(11):831-839.
31. 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(1):137-141.
32. Fonseca AC, Ferro JM. Drug abuse and stroke. *Curr Neurol Neurosci Rep.* 2013;13(2): 325.
33. Foreman PM, Griessenauer CJ, Selim MH, et al. Sexual activity as a trigger for intracranial hemorrhage. *Acta Neurochir (Wien).* 2016;158(1):189-195.
34. Thompson PD, Franklin BA, Balady GJ, et al, American Heart Association Council on Nutrition, Physical Activity, and Metabolism, American Heart Association Council on Clinical Cardiology, American College of Sports Medicine. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart association council on nutrition, physical activity, and metabolism and the council on clinical cardiology. *Circulation.* 2007;115(17):2358-2368.
35. Lee KW, Lip GYH. Effects of lifestyle on hemostasis, fibrinolysis, and platelet reactivity: a systematic review. *Arch Intern Med.* 2003;163(19): 2368-2392.
36. Neiman J, Haapaniemi HM, Hillbom M. Neurological complications of drug abuse: pathophysiological mechanisms. *Eur J Neurol.* 2000;7(6):595-606.
37. Elkind MSV. Why now? Moving from stroke risk factors to stroke triggers. *Curr Opin Neurol.* 2007;20(1):51-57.
38. D' Atri LP, Schattner M. Platelet toll-like receptors in thromboinflammation. *Front Biosci (Landmark Ed).* 2017;22(11):1867-1883.
39. World Health O. *Global Influenza Strategy 2019-2030*: World Health Organization; 2019.
40. Putaala J, Martinez-Majander N, Saeed S, et al. Searching for explanations for cryptogenic stroke in the young: revealing the triggers, causes, and outcome (SECRETO): rationale and design. *Eur Stroke J.* 2017;2:116-125.
41. Lee HY, Oh BH. Aging and arterial stiffness. *Circ J.* 2010;74(11):2257-2262.
42. Mozaffarian D, Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation.* 2015;131(4):e29-e322.
43. Robertson D, Frölich JC, Carr RK, et al. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *N Engl J Med.* 1978;298(4):181-186.
44. Ammon HP, Bieck PR, Mandalaz D, Verspohl EJ. Adaptation of blood pressure to continuous heavy coffee drinking in young volunteers. A double-blind crossover study. *Br J Clin Pharmacol.* 1983;15(6):701-706.
45. Beukenhorst AL, Parkes MJ, Cook L, et al. Collecting symptoms and sensor data with consumer smartwatches (the knee OsteoArthritis, linking activity and pain study): protocol for a longitudinal, observational feasibility study. *JMIR Res Protoc.* 2019;8(1):e10238.
46. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *Br J Haematol.* 2020;189(5):846-847.
47. Palleri D, Guidarini M, Mariucci E, et al. Patent foramen ovale related cryptogenic stroke during COVID-19 disease in three patients: a case series. *J Stroke Cerebrovasc Dis.* 2021;30(12):106115.