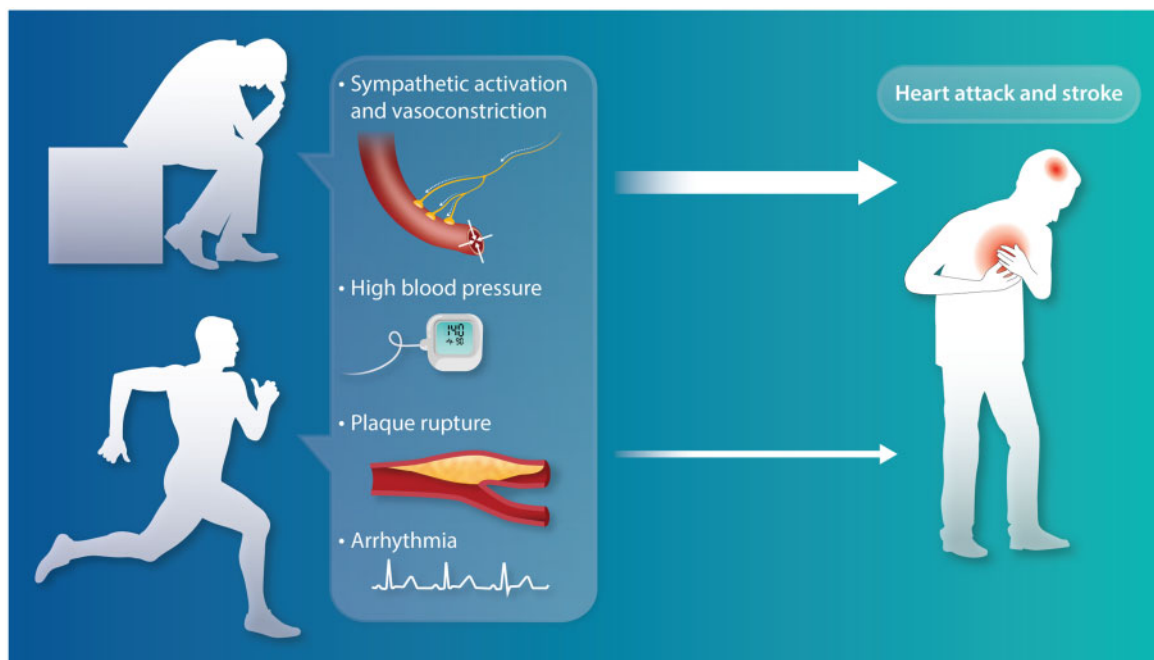


# Triggers of stroke: anger, emotional upset, and heavy physical exertion. New insights from the INTERSTROKE study

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This editorial refers to ‘Anger or emotional upset and heavy physical exertion as triggers of stroke: the INTERSTROKE study’, by A. Smyth *et al.*, <https://doi.org/10.1093/eurheartj/ehab738>.



**Graphical Abstract** Negative emotions and physical exertion may trigger stroke.

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'Could it be that my stroke was brought on by emotional stress?' This is a common question of stroke survivors directed to their physicians at follow-up. Stroke is a drastic event. Concerns about recurrent symptoms initiate the search for potential triggers—something one can control and change for good. A typical answer would be that indeed, extreme physical or emotional stress are risk factors for stroke, but their role as immediate triggers of stroke is unclear.

For heart disease, emotional and physical stress are known to provoke ischaemic events, particularly in vulnerable individuals.<sup>1</sup> Many of us know examples of how this observation has expanded into cultural narratives: such as in *The Godfather*, where Don Vito Corleone suffers a heart attack while playing with his grandson—physical exertion.<sup>2,3</sup> Pathophysiological arguments for emotional and physical factors inducing myocardial ischaemia include constriction of coronary arteries through sympathomimetic activation, or vessel obstruction due to prothrombotic activity, causing rupture of a pre-existing atherosclerotic plaque.<sup>1</sup> However, stroke aetiology is very heterogeneous.<sup>4</sup> To most stroke neurologists, with the exception of cervical artery dissection induced by trauma and indicated by a characteristic neck pain, triggers for stroke are less obvious. Therefore, while some studies have suggested that there may be physical or emotional triggers for stroke similar to myocardial infarction,<sup>5–7</sup> convincing evidence from large multinational cohorts has been lacking so far.

The study of Smyth *et al.*, published in this issue of the *European Heart Journal*, sheds new light on this important issue.<sup>8</sup> The authors present data from the INTERSTROKE study, spanning 32 countries and including 13 462 participants who had suffered a first ever ischaemic or haemorrhagic stroke. INTERSTROKE was designed to explore potentially modifiable risk factors for stroke and their importance for different populations worldwide. It reported that 10 potentially modifiable vascular risk factors collectively account for ~90% of the population's attributable risk of stroke.<sup>9</sup> In addition to chronic factors accumulating to contribute to risk over time, another goal of INTERSTROKE was to search for potential triggers of stroke: anger, emotional upset, or heavy physical exertion. During the first 72 h after stroke, participants (either independently or supported by their families) completed a questionnaire asking them if they had been 'angry or upset' or if they had 'engaged in heavy physical exercise' within the hour before stroke (case period) and during the same time on the day before (control period). Thus, in this case-crossover study, each participant served as her/his own control. An advantage of this approach is that it accounts for the fact that the perspective of what is upsetting or considered heavy exercise is very individual. The authors grouped strokes into 'ischaemic', 'haemorrhagic', or 'all strokes'. They adjusted their analyses of the potential triggers for a potential interaction between them. Since the patient group was large and risk factors as well as baseline clinical information were available, it was possible to stratify for age groups and traditional risk factors. Furthermore, triggers were placed into the individual context of pre-existing conditions: physical exertion stratified by level of individual baseline physical activity, and anger/emotional upset by pre-existing psychosocial factors, such as depression and presence of chronic stress.

Anger and emotional upset during the case period were reported by 9.2% of participants, while heavy physical exertion was reported

by 5.3%. Younger age, male sex, higher body mass index (BMI), higher education, and higher levels of baseline stress and depression were more common among those stroke patients with reported anger and emotional upset as potential triggers. Stroke patients indicating heavy physical exertion during the case period were more likely to be younger, more often male, current smokers, and not suffering from diabetes. Their baseline level of physical activity was higher, as was their systolic blood pressure on admission. These group differences are very interesting *per se*. While the association of negative emotions with stress or depression is in line with our knowledge about stress and cardiovascular disease, the association of higher education in participants reporting anger and emotional upset warrants further investigation.<sup>10</sup> Notably, these group differences were adjusted for in the analyses of associations between the two types of triggers (emotional vs. physical) on the different types of stroke (ischaemic, haemorrhagic, and all). As a result, the authors found that anger and emotional upset during the case period were associated with all strokes, ischaemic stroke, and haemorrhagic stroke. Heavy physical exertion during the case period was only associated with haemorrhagic stroke [odds ratio (OR) 1.62, 99% confidence interval (CI) 1.03–2.55]. Intriguingly, the odds of suffering a stroke after a potential emotional trigger were greater in patients without prior depression and with lower educational status. The odds of suffering a stroke after heavy exercise were greatest in women and lowest in patients with normal BMI (*Graphical Abstract*).

The novel data obtained in a large multinational cohort convincingly show that anger and emotional upset are common before stroke, and that their experience is associated with an increased risk of suffering a stroke immediately afterwards, suggesting that they could be stroke triggers. Heavy physical exertion was associated with haemorrhagic stroke only. No clear causality can be drawn from these results. However, it is plausible to speculate that increased sympathetic tone and catecholamine excretion contribute to stroke due to vasoconstriction or cardiac arrhythmia in cases of feelings of upset. In the case of heavy physical exertion, acute increases in blood pressure may increase the risk for brain haemorrhage. Smyth *et al.* had performed a similar analysis previously in data from the INTERHEART study.<sup>3</sup> It is noteworthy that in these acute myocardial infarction (AMI) patients, both physical activity and anger or emotional upset during the case period were associated with an increased odds of AMI, which was overall higher than that of stroke in INTERSTROKE (OR 3.05, 99% CI 2.29–4.07).

What does this study contribute to the field? Definitely, anger and emotional upset should be avoided, and physical exertion should not exceed the limits of individual capacity. Although INTERSTROKE was conducted in patients with first-ever ischaemic stroke, it is likely that this advice is even more important for secondary stroke prevention, which will have to be addressed in future studies. Furthermore, the study provides strong support for the recent concept of negative emotions and stress in the pathophysiology of cardiovascular disease. For the stroke survivor asking 'Could it be that my stroke was brought on by emotional stress?' the answer would be 'Yes, this is possible.' Future research, possibly supported by stress indicators from wearable devices, will identify more potential triggers of stroke and delineate who is at particular risk.

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## References

- Edmondson D, Newman JD, Whang W, Davidson KW. Emotional triggers in myocardial infarction: do they matter? *Eur Heart J* 2013;**34**:300–306.
- Coppola FF. *The Godfather*. Hollywood: Paramount Pictures; 1972.
- Smyth A, O'Donnell M, Lamelas P, Teo K, Rangarajan S, Yusuf S; INTERHEART Investigators. Physical activity and anger or emotional upset as triggers of acute myocardial infarction: the INTERHEART study. *Circulation* 2016;**134**:1059–1067.
- Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, Donnan GA. Ischaemic stroke. *Nat Rev Dis Primers* 2019;**5**:70.
- Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology* 2004;**63**:2006–2010.
- Guiraud V, Amor MB, Mas JL, Touze E. Triggers of ischemic stroke: a systematic review. *Stroke* 2010;**41**:2669–2677.
- Mostofsky E, Penner EA, Mittleman MA. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. *Eur Heart J* 2014;**35**:1404–1410.
- Smyth A, O'Donnell M, Hankey GJ, Rangarajan S, Lopez-Jaramillo P, Xavier D, Zhang H, Canavan M, Damasceno A, Langhorne P, Avezum A, Pogossova N, Oguz A, Yusuf S; on behalf of the INTERSTROKE investigators. Anger or emotional upset and heavy physical exertion as triggers of stroke: the INTERSTROKE study. *Eur Heart J* 2022;**43**:202–209.
- O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogossova N, Weimar C, Iqbal R, Diaz R, Yusuf K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S; INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;**388**:761–775.
- Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol* 2018;**15**:215–229.