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On the Causal Paths Underlying the Relation between Atmospheric Temperature and Acute Stroke

To the Editor:

We thank Al Mamun et al[1] for their interest in our work[2] and for giving us the opportunity to further discuss the causal relations potentially underlying the triggering of stroke events by atmospheric temperature. In general, we agree with their arguments regarding the interplay between several orders of factors, which we explore below offering a framework for future research. At the same time, we explain why this does not directly implicate with the analysis and interpretation of our data.

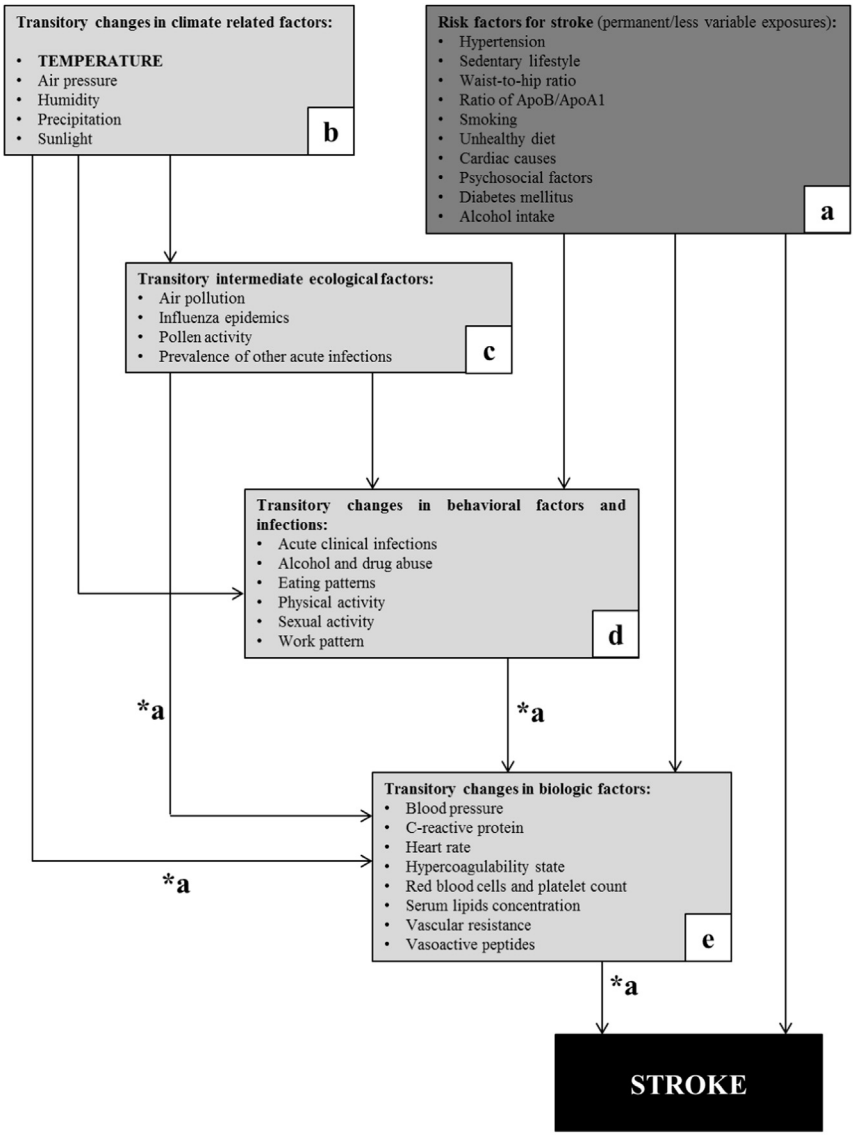
Although over 90% of stroke events are attributable to 10 well-identified risk factors,[3] these exposures (Fig 1, box a) are relatively stable throughout time, contributing to a higher background risk of stroke but not explaining why an event occurs to a certain individual at a specific time. Other conditions or circumstances, including day-to-day variation in atmospheric temperature, intense physical activity, heavy eating, alcohol and drug abuse, acute clinical infections, etc. (Fig 1, boxes b and d), are transitory exposures potentially triggering an acute stroke event,[4,5] through a cascade of effects that remains poorly understood.

So far, evidence suggests that transitory changes in atmospheric temperature (Fig 1, box b) can trigger an acute stroke event by influencing biological factors, like blood pressure and heart rate, serum concentration of lipids and vasoactive peptides, platelet aggregation, etc. (Fig 1, box e), that lead to an acute event (b → e → stroke). However, the relation between temperature variation and changes in biological factors may also be indirect as different weather conditions can promote changes in the individual's lifestyle patterns or the occurrence of infections (Fig 1, box d), which in turn are also associated with the biologic mechanisms (Fig 1, box e) underlying the triggering of stroke (b → d → e → stroke). Paths involving transitory variations in intermediate ecological factors, such as air pollution, pollen activity or the frequency of acute infections (Fig 1, box c), may also have to be considered (b → c → d → e → stroke or b → c → e → stroke).[6-10]

Beyond the role of conventional risk factors in the pathophysiology of stroke (a → stroke), their presence could influence how temperature directly or indirectly affects human homeostasis,[6] acting as effect modifiers (variables that differentially modify the observed effect of a risk factor on disease status),[11] meaning that the magnitude of the association between atmospheric temperature and stroke may be different according to the presence or absence of a certain risk factor (represented by "*a" in Fig 1).

The quantification of the direct and indirect effects of temperature as a trigger for acute stroke and the potential differences according to the presence of different risk factors has, in general, not been addressed in previous research. We agree with Al Mamun et al[1] that these are relevant research questions and deserve the attention of the scientific community as this knowledge may ultimately lead to the adaptation of therapeutic and preventive measures according to individual characteristics.[12] However, these objectives are challenging and methodologically demanding, given the difficulties in assessing transitory exposures and the large number of potential factors involved, and the fact that documenting effect–modification requires very large sample sizes.

In our study,[2] we examined different hazard periods and were able to estimate the overall effect of temperature as a trigger of acute stroke in a subtropical climate setting; the results were adjusted to humidity, precipitation, and mean temperature and stratified according to age, sex, and stroke subtype. We believe our findings contribute for a better understanding of this phenomenon, despite the ample scope for further exploring the underlying mechanisms, and offer health services the opportunity to predict periods of higher affluence to the hospital because of stroke according to variations in the atmospheric temperature. These are relevant implications of our study that do not depend on further clarification of the mechanisms involved.



Box a (dark grey) represents permanent/less variable exposures (risk factors)
Boxes b, c, d and e (light grey) represent transitory exposures (triggers)
*a represents the potential effect modification that risk factors (box a) exert on the relationship between transitory exposures and stroke or the immediate biologic factors leading to stroke

Figure 1. *Simplified diagram of the causal relations between climate-related factors and stroke.*

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http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.07.001

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Effect of Tissue Plasminogen Activator Dose and Interval on Stroke Severity

The recent study by Sahlas et al[1] in the *Journal of Stroke and Cerebrovascular Diseases* concluded that "the estimation of a patient's weight in the acute setting can lead to overcalculation of the tissue plasminogen activator dose, which is associated with poorer functional outcomes." However, this conclusion is not well supported by their study[1] because the most severe ischemic stroke cases were the ones that were most likely not weighed, and this severity could have led to the increased mortality that was found[2] and the majority of unweighed patients were actually given an underdose that was associated with better discharge outcomes, as explained below.

First, the authors stated that patients were "routinely weighed if medically stable," which suggests that those who were not weighed were more critical. This was supported by the data, in which the National Institutes of Health Stroke Scale scores were 36.4% higher for unweighed patients than for unweighed patients at the time of admission. Consequently, the differences in stroke severity at admission can explain the differences in outcomes of the medical care at discharge. Although this is a key factor to consider, the authors do not discuss this issue. They also do not discuss other comorbidities that may have contributed to worse outcomes. Therefore, the study conclusion that poor estimates of patient weight for the purpose of calculating the dose of tissue plasminogen activator increases discharge mortality is not supported by data in their study.

Second, in contrast to the main conclusion of the study, if the intervening variable of stroke severity is ignored, the study presents evidence that poor weight estimates may be beneficial. Patients who were given an underdose of tissue plasminogen activator had the same modified Rankin Scale score at discharge with 0% mortality as those patients who were given an accurate dose and had 7% discharge mortality. Thus, the conclusion that incorrect weight estimates led to worse outcomes is contradicted by this evidence.

Finally, it is also worth noting that the time interval between stroke onset and infusion of tissue plasminogen activator, a known cause of poor outcomes,[2] was not provided. Given the importance of this interval in predicting functional outcomes and discharge mortality and its presumed availability during the study, the omission of such data is a weakness.

The study has many strengths, including a focused and important hypothesis, excellent literature review, good sample size, excellent statistical analysis methods, and much valuable blood chemistry data. Despite these strengths, their findings can be explained by either stroke severity or interval from stroke onset to activator infusion. This indicates that the study's conclusion that inaccurate patient weight estimation and subsequent misdosing are associated with poorer outcomes is not sufficiently supported to be implemented in emergency department or surgical units at this time.