Topical Review

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Ambient Temperature and Stroke Risk

Evidence Supporting a Short-Term Effect at a Population Level From Acute Environmental Exposures

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These are times of increasing concern about the impact on global health of climate change and political turmoil on how to tackle global warming.[1,2] Global warming produces not only hotter summers and more frequent episodes of heat waves but also colder winters, especially in more temperate zones, with populations not accustomed to these unusual weather conditions.[3] These changes affect human physiology and have the potential of acutely influencing the occurrence of cardiovascular diseases, such as stroke, but the evidence has been until recently conflicting, a great number of which initially came from observational studies on season rather than temperature.[4–6]

In this review, we examine the current evidence on the association of acute ambient temperature changes and the risk of stroke morbidity and mortality by pathological subtypes.

Ambient Temperature as an Exposure Variable

Ambient temperature is defined as the temperature of the surrounding air, and as such, it is modified by humidity, so that in many studies, the exposure is a combination of temperature and humidity level or dew point temperature and may be expressed as thermo-hydrological index when humidity is controlled for.[7] Ambient temperature is usually measured at or near airport monitoring stations and thus may introduce bias on real indoor exposures and in urban to rural comparison.[8] The effect of ambient temperature on stroke has been studied in relation to daily or monthly mean, maximum, and minimum temperatures and temperature change or variation. It is suggested that mean ambient temperature is the best exposure measure because it can represent the exposure throughout the whole day and night and provide more easily interpretable results, although some authors state that all measurements of temperature have the same predictive ability on health outcomes.[9] Two methodological issues have been given special attention: temperature lag effect (exposure response association) and harvesting. Distributed lagged effects include both short-term and cumulative lagged effects, which seem to be different in cold or hot temperature exposures. Mortality displacement or harvesting occurs when the deaths of particularly frail individuals are brought forward by extreme temperatures, leading to a decrease in effect estimates for longer lag periods, in the case of stroke, this is especially important at older ages.[10] Air pollution can be a confounder or an effect modifier of the impact of ambient temperature on health, and so it is also frequently included in the models that aim at assessing its independent effect on stroke.[11] In fact, the association of short-term exposure to air pollution and stroke admissions or deaths have been reported both for ischemic and hemorrhagic stroke.[12,13] Particles (particulate matter with aerodynamic diameter <10 μm [PM_{10}] include ultrafine particles [$PM_{1.0}$], fine particles [$PM_{2.5}$], coarse particles [$PM_{10–2.5}$], gases [CO, NO_2, NO, SO_2], and ground-level ozone [O_3]) have been studied together with ambient temperature and other meteorologic parameters in the same populations.[14] Age and sex are also effect modifiers in this association.[8] Population acclimatization is another effect modifier, so it has been incorporated into studies of multiple locations, commonly by including the latitude of the population as a proxy for climate.[10]

Study Design

The majority of published studies have used 2 comparable designs: time series and case crossover. Time series refers to population or community studies during a determined time period. Incidence or mortality rates are compared in relation of exposure to ambient temperature collected at regular time intervals (daily, weekly, and monthly). Confounders and effect modifiers are included as the covariates to the regression models.[8] More recently, the case-crossover design has been increasingly used. It is a case–control design involving only cases when brief exposure, such as ambient temperature variations, causes a transient change in risk of an acute-onset disease as stroke. Controls are the same cases in periods without the exposure. The design resembles a retrospective nonrandomized crossover study but differs in having only 1 sample of the base population time. The average incidence rate ratio for a hypothesized effect period after the exposure

Received August 15, 2017; final revision received October 30, 2017; accepted November 9, 2017.

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(*Stroke*. 2018;49:255-261. DOI: 10.1161/STROKEAHA.117.017838.)

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.117.017838

is estimated. Self-matching of cases eliminates the threat of control-selection bias and increases efficiency.[15] The case-crossover study design has been refined from the original unidirectional to the bidirectional and most recently, to the time-stratified approach. The time-stratified approach limits the bias from selecting control periods only previously to the case period (unidirectional) or from not selecting control periods at random from the time at which the case occurred (bidirectional). Most commonly, control periods are selected within the same month and the same year that the case period occurred in the time-stratified approach to inherently minimize biases.[8]

Methodology

In this comprehensive review, we chose to summarize the data available from published systematic reviews and meta-analysis on the effect of acute exposure to ambient temperature on stroke risk. We used the following search terms: cerebrovascular disease, stroke, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, ambient temperature, low temperature, hot temperature, meteorologic factors, systematic reviews, and meta-analysis. We searched PUBMED, OVID-MEDLINE, and SCOPUS. Because the last systematic review found included articles only until December 2015, we included other articles published after this date, using the same search terms without systematic review as search term. We selected articles if they were cohort population based or case series from consecutive hospital admissions and if they presented estimates with 95% confidence intervals (CIs) of the association of acute hot or cold temperature exposure with total stroke or by pathological subtype (ischemic stroke [IS], intracerebral hemorrhage [ICH], or subarachnoid hemorrhage [SAH]), adjusted by confounders. We defined acute as daily exposure although some studies present monthly exposures to temperature variations. We did not make a separate assessment of the strength of the evidence from each article because most of the data came from systematic reviews.

Effect of Ambient Temperature on All Strokes

Published data support a significant association between acute ambient temperature changes and overall stroke risk. Lian et al[16] in a systematic review and meta-analysis of ambient temperature and overall stroke, which included 2 070 923 events in 20 original time series or case-crossover studies published until 2014 presenting data on stroke incidence or mortality as a result of exposure to ambient temperature, reported that an increase of 1°C increased the risk by 1.13% (0.58–1.68) and that a decrease in 1°C increased the risk by 1.2% (0.84–1.57). This association was stronger in those ≥65 years of age and heterogeneous between sexes; in men, the risk increased in hot days, whereas in women, the risk increased in colder temperatures. Lag effect was also found to be different between increasing or decreasing temperatures, being shorter with temperatures the day before or same day in hot days and 2 to 4 days after exposure in cold days. The results differed if the measured outcome was mortality or incidence. An increase of 1°C was associated with 1.5% (0.9–2.2) increase in stroke mortality, whereas a decrease of 1°C was associated with a 1.2% (0.9–1.5) increase in stroke mortality. No association was found between higher temperatures and incidence of overall stroke, whereas lower temperatures increased incidence risk by 0.9% (0.3–1.6). Zorrilla-Vaca et al,[17] in a recent systematic review and meta-analysis investigating the association of low mean ambient temperature and stroke incidence that included 19 736 patients in 26 studies, showed that lower temperatures were significantly associated with higher risk of stroke (adjusted pooled effect size [ES], 0.03; P=0.003). This association was heterogeneous (I2=98.5%; P<0.001) because of geographic latitude, average temperature, and percentage of men. The lag effect of cold temperature seems especially evident in mortality risk because it may have an effect ≤2 weeks. A study in 8 large cities in China found that the relative risks (RRs) of extreme cold (first percentile of temperature) and cold (10th percentile of temperature) temperatures over lags 0 to 14 days were 1.39 (1.18–1.64) and 1.11 (1.06–1.17), compared with the 25th percentile of temperature. Contrarily, the effect of hot temperature was found to be more immediate in stroke mortality with an RR of 1.06 (1.02–1.10) for extreme hot temperature (99th percentile of temperature) and 1.14 (1.05–1.24) for hot temperature (90th percentile of temperature), compared with the 75th percentile of temperature over lags 0 to 3 days.[18] Another recent study in 12 counties in the Hubei province, China, showed a J-shaped effect of temperature on the risk of stroke mortality. Cold spells increased deaths with a 2-to-3 day delay (odds ratio [OR], 1.180; 95% CI, 1.043–1.336), whereas on heat-wave days, the risk increased less (OR, 1.114; 95% CI, 1.012–1.227), and the lag was 0 to 2 days.[19]

Effect of Ambient Temperature on IS

In a systematic review and meta-analysis of population, community-based or hospital registries aimed at determining whether ambient temperature was associated with hospital admission for stroke; Wang et al included 21 studies and a total of 476 511 patients. In the case of IS (8 studies, 290 154 patients), the authors reported that they found no significant association between ambient temperature and IS admissions or between minimum or maximum ambient temperatures and IS admissions. Three of 4 studies reported a significant increase risk of IS in women associated with low mean ambient temperature, and 4 studies showed that increasing age was associated with a stronger risk of IS in lower temperatures. The authors reported that 2 studies found a significant association between large changes in mean ambient temperature and IS admission, with an increase between 1.5% and 2.1% for every degree Celsius raise in mean temperature.[20] One study performed in Korea showed that higher mean temperatures were associated with a higher incidence of IS, especially in the older age (≥65) group and in men.[14] Zorrilla-Vaca et al[17] in their systematic review showed no significant association of mean low temperature on IS (adjusted pooled ES, 0.03; 95% CI, 0.06–0.01; P=0.132). Contrary to these findings, Lian et al[16] in their systematic review on the short-term effect of ambient temperature on the risk of stroke reported that both hot and cold temperatures were associated with IS: pooled ES, 1.03 (95% CI,

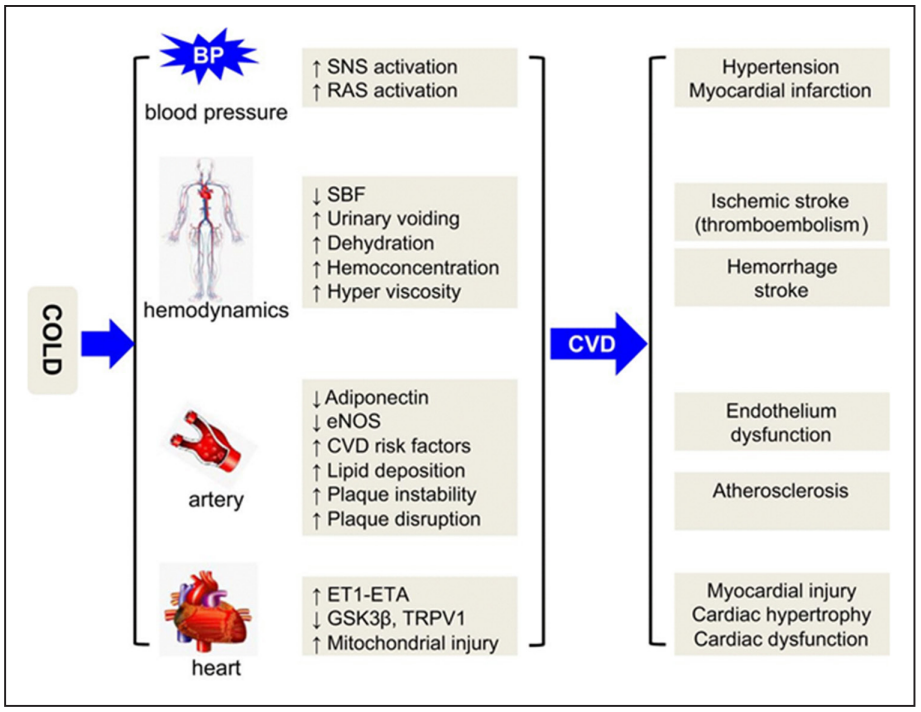

Figure 1. Summary of hypothesized mechanisms by which cold exposures induce cardiovascular disorders. Cold-air exposure activated both sympathetic nervous system (SNS) and renin–angiotensin system (RAS), which also interact with each other, thereby elevating the blood pressure (BP), leading to hypertension and CVD, such as myocardial infarctions. Skin blood flow (SBF) next decreased in response to cold exposure because of the vasoconstriction accompanied by increased urine voiding leads to dehydration, increasing the risk of hemorrhagic and ischemic stroke by causing hemoconcentration and hyperviscosity. In addition, endothelium dysfunction, evidenced by endothelial NO synthase (eNOS) inhibition, could be induced by cold exposure, which may be in relation to cold-inhibited adiponectin expression in the vascular system. As well, CVD risk factors were higher after cold exposure, contributing to atherosclerosis by enhancing lipid deposition, plaque instability, and plaque disruption. Finally, plasma endothelin (ET)-1 levels increased during cold exposure, induced hypophosphorylation of GSK3 (glycogen synthase kinase 3), and downregulation of temperature-sensor protein TRPV1 (transient receptor potential vanilloid) by activation of ETA (endothelin A) receptor, triggering mitochondria dysfunction and resulting in myocardial injury, cardiac hypertrophy, and cardiac dysfunction. Reprinted from Liu et al[24] (page H1804) with permission. Copyright © 2015, the American Physiology Society.

0.35–1.72) for hot temperature, and pooled ES, 0.71 (95% CI, 0.40–1.02) for cold temperature. In the case of cold temperature, this effect was independent of season.[21,22] A retrospective case-series study performed in 1763 consecutive adult patients hospitalized admitted with neurologist-confirmed IS between April 1, 1999, and October 31, 2008, and residing in the metropolitan region of Boston, Mass, showed that IS peaked in the 10 to 24 hours after the decrease in apparent temperature to decline after this and that it significantly increased in more humid days (incidence rate ratio, 1.11; 95% CI, 1.00–1.23).[22] In another study of consecutive adults with strokes hospitalized from January 1, 2004, to December 31, 2013, in Seoul, IS was associated with higher mean monthly temperatures independently of other meteorologic variables, such as humidity, PM_{10}, and NO_2 (OR, 1.006; 95% CI, 1.002–1.011).[14] A more recent study conducted in 7 emergency hospitals in the Hiroshima prefecture, Japan, from January 2012 to December 2013, reported that among 3935 consecutive hospitalized patients with stroke, the frequency of IS increased when the mean daily thermohydrological index varied either cooler or warmer from a previous day to the onset day (RR extreme cold, 1.19 [95% CI, 1.05–1.34]; RR warmth, 1.16 [95% CI, 1.04–1.30]; and RR extreme warmth, 1.16 [95% CI, 1.03–1.31]).[7] In relation to IS subtypes by etiology, a retrospective case-series study on 4310 patients admitted to Nippon Medical School Chiba Hokusoh Hospital, just 46.7 km from Tokyo and only 16.1 km away from Tokyo Narita Airport, reported an increase in the frequency of admission of atherothrombotic, lacunar, and cardioembolic IS when the difference between the mean temperatures of a day and of the previous week decreased by 1°C (P=0.0121, 0.0151, and 0.0079, respectively). Conversely, a 1°C change in maximum ambient temperature significantly increased the number of admissions of patients with atherothrombotic and cardioembolic IS but not lacunar infarction (P=0.0291, and 0.0130, respectively).[23]

Effect of Ambient Temperature on ICH

In 6 of 11 studies analyzed by Wang et al in their systematic review, an increase in admission of ICH in colder days was reported, whereas only 4 studies found an increase in the risk associated with a higher mean ambient temperature. All studies found a higher association at increasing age. In 4 studies, ICH was associated with temperature fluctuations, independently if the exposure occurred 1 or 30 days before the event. Particularly interesting are the findings of a study in Taiwan—a country—where according to the authors, the population does not usually use heating at temperatures around 10°C, so that ambient temperature measured outdoors could better reflect indoor ambient temperature exposures. This cross-sectional

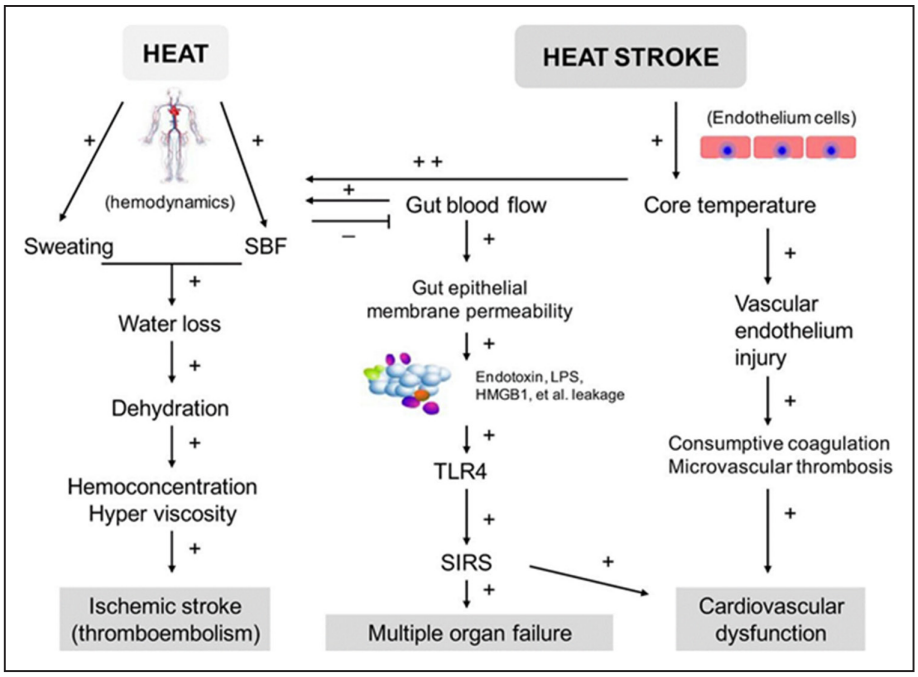

Figure 2. Summary of hypothesized mechanisms by which heat and heat stroke induce cardiovascular disorders. Increased skin blood flow (SBF) and sweating in response to heat exposure lead to water loss and dehydration. The accompanied hemoconcentration and hyperviscosity may cause thromboembolism, leading to increased risk of ischemic stroke. In presence of heat stroke, increased core temperature redistributed the blood flow to the skin to facilitate heat loss and limit hyperthermia. Accordingly, gut blood flow decreases and the prolonged reduction in gut blood flow would cause increase in the gut epithelial membrane permeability, allowing bacteria, its toxic cell wall component lipopolysaccharide (LPS), or HMGB1 (high mobility group box 1) to leak from the gut lumen into the systemic circulation. TLR4 (toll-like receptor 4) recognizes these molecules, stimulating the innate and adaptive immune systems and causing systemic inflammatory response syndrome (SIRS). Together with it, the hyperthermia-impaired vascular endothelium induces occlusion of arterioles and capillaries (microvascular thrombosis) or excessive bleeding (consumptive coagulation), leading to multiorgan system failure, including cardiovascular dysfunction. +, activation; ++, aggravation; –, inhibition. Reprinted from Liu et al[24] (page H1805) with permission.

case-only study showed a significant association between ICH incidence and monthly mean low temperature (under 17°C), as well as monthly mean ambient temperature variations, especially extreme cold in the previous 72 hours.[24] In a case-crossover prospective study among 593 patients in Maputo, Mozambique, acute decreasing temperature >2.4°C in any consecutive days in the previous week was a trigger factor for first ever stroke (adjusted OR, 1.28; 95% CI, 1.05–1.56), particularly ICH (adjusted OR, 1.50; 95% CI, 1.07–2.09).[25] In the systematic review by Zorrilla-Vaca et al,[13] the association between ICH and low temperature was investigated in 8 studies, including 1495 patients, and was borderline significant (adjusted pooled ES, 0.05; 95% CI, 0.10–0.00; P=0.057), and no association was found in this study between ICH and high temperature. More recently, a study of consecutive patients with hemorrhagic stroke in Seoul, which investigated simultaneously the effect of meteorologic factors and air pollutants on ICH and SAH admissions, showed that mean monthly temperature was correlated with ICH but not independently associated in a Poisson model after controlling for factors such as humidity, insolation, atmospheric pressure, NO_2, O_3, and PM_{10}, except in those >60 years of age.[26] In the Hiroshima study, ICH incidence decreased on extremely high temperature days (RR, 0.72; 95% CI, 0.54–0.95) and increased when the thermo-hydrological index was extremely cold in the 4 days before the onset day (RR, 1.33; 95% CI, 1.03–1.71).[7]

Effect of Ambient Temperature on SAH

Wang et al reported inconsistent results for an association between mean ambient temperature and SAH. They pooled data from 2 of 5 studies and with a combined OR of 1.00 (95% CI, 0.98–1.01). According to the authors, 2 studies reported an association between temperature change during the previous 24 hours and 1 reported that variations in temperature were associated with increased SAH risk.[20] Zorrilla-Vaca et al[17] included 325 patients with SAH in 2 studies and found a significant association with low temperature (adjusted pooled ES, 0.03; 95% CI, 0.04–0.01; P<0.001). A systematic review of seasonal and meteorologic determinants of aneurysmal SAH, which included 48 articles and 72 694 patients, showed that the incidence of SAH was lower in summer than in winter (RR, 0.89; 95% CI, 0.83–0.96), but no association with temperature was found.[27] Similarly, no independent association was reported in the study in Seoul between mean temperature and SAH admissions.[26]

Mechanisms

The proposed mechanisms by which ambient temperature increases stroke risk differs in cold or hot temperature exposure. In cold weather conditions, it has been linked mainly to increase blood pressure, peripheral vasoconstriction, increase platelet count, and increased blood viscosity mostly associated with increased sympathetic activity (Figure 1).[28] Although this

Table. Systematic Reviews and Meta-Analysis of the Effect of Ambient Temperature on Stroke Risk

Author, Year	Inception Month and Year	Type of Studies	No. of Included Studies	No. of Patients or Events	Pathological Subtypes	Low Temperature			High Temperature		
						Mortality and Morbidity Combined	Mortality	Incidence	Mortality and Morbidity Combined	Mortality	Incidence
Lian et al, 2015[16]	September 2014	All studies	20	2 070 923	All strokes	Increased risk	Increased risk	Increased risk	Increased risk	Increased risk	Increased risk
					Ischemic	Increased risk			Increased risk		
					ICH	Increased risk			Decreased risk		
					SAH						
Wang et al, 2016[20]	October 2015	Population, community, or hospital registries with consecutive recruitment for at least 1 y	21	476 511	All strokes						
					Ischemic			Increased risk			No increased risk
					ICH			Increased risk			No increased risk
					SAH			No association			No increased risk
Zorrilla-Vaca et al, 2016[17]	December 2015	All studies	26	19 736	All strokes	Increased risk					
					Ischemic	No increased risk					
					ICH	Increased risk					
					SAH	Increased risk					

ICH indicates intracerebal hemorrhage; and SAH, subarachnoid hemorrhage.

mechanism does not fully explain the observed long-time lag between exposure to cold and ICH in many studies and the fact that no association between admission blood pressure and low temperature in patients with ICH nor with their previous history of hypertension was reported in 1 study.[20] In high ambient temperature, the proposed mechanisms involved in higher stroke risks are increased sweating and skin blood flow, producing dehydration, increased blood viscosity, hemoconcentration, and elevated cholesterol levels (Figure 2).[29]

Prevention

Prevention strategies should consider individual patient vulnerabilities, such as increasing age and geographic location. Both cold and hot temperature exposure increase stroke risk in the elderly through various mechanisms, such as impaired ability to thermoregulate, premorbid conditions, such as diabetes mellitus, and medications that modify blood pressure, circulation, and perspiration rates.[9] A decrease in the perception of warmth or cold can complicate the capacity of the elderly to identify when they are experiencing thirst or cold temperature and decrease their ability to adapt. Populations not usually exposed to cold weather are at higher risk of stroke in bitter winters, and those not accustomed to hot summers are at increased risk of stroke in hot spells.[9] To adapt to these changing weather conditions and decrease the impact on health, in the case of cold weather, 2 strategies have been proposed at individual, building, and neighborhood scale: the no-regrets policy and the resilience, which include exercise, home weatherization, and district heating, as well as clothing, home energy assistance programs, and warming centers.[9] In the case of heat waves, heat health warning systems, increased use of air conditioning and cooling centers, and increasing reflectivity and canopy in urban areas are proposed strategies.[30]

Implications for Future Research

There are several implications for future research in this field both in epidemiology and pathophysiology and eventually in interventions evaluation.

Temperature changes and its impact on incidence and prognosis should be included in future prospective population-based or community stroke studies, and specific prospective studies should be designed to answer some of the controversies on the presence and strength of the association of ambient temperature and stroke, particularly in the case of hot temperature in which

results have been more conflicting. Research could also focus on studying prospectively the possible underlaying mechanisms of hot and cold temperature in the 3 main pathological subtypes of stroke. Furthermore, studies may be specifically designed to measure the impact of preventive interventions proposed to decrease the effect of temperature on stroke.

Limitations and Pitfalls

A limitation of this review is that even though we based this article mostly on the results of systematic reviews that included population-based data or consecutive patient admission, we cannot rule out the possibility of bias because none was truly a population community-based study of stroke incidence and prognosis meeting the suggested gold standard criteria of stroke incidence studies, which simultaneously investigated the effect of hot or cold temperature on the risk.[31] Another limitation is that methodologies were not homogeneous, and some difference in risk could be because of study design, particularly because older studies used time series and newer ones used case-crossover design. Unfortunately, there were no sensitivity analyses according to study design in the meta-analysis included. Finally, the outcomes studied (hospital admissions and mortality) not only differed but are based on administrative data and subject to possible misclassification and selection bias.

Conclusions

The current evidence supports an acute effect of ambient temperature on stroke risk (Table). The effect is nonlinear, with increased risk in both cold and hot temperatures. Hot temperatures seem to have a more immediate effect, particularly in increasing the risk of IS; cold temperatures have a longer lag effect and increase more the risk of ICH. Whatever the exposure or the outcome, older ages are at increased risk. Sex does not respond equally to ambient temperatures: women are at increased risk of stroke at colder temperatures, whereas men at hotter. Geographical location is an important confounding variable in the risk to due acclimatization.

Disclosures

None.

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KEY WORDS: cold temperature ■ hot temperature ■ intracerebral hemorrhage ■ stroke ■ subarachnoid hemorrhage