The Influence of Weather on the Incidence of Primary Spontaneous Intracerebral Hemorrhage

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Background: Intracerebral hemorrhage has been associated with changes in various weather conditions. The primary aim of this study was to examine the collective influence of temperature, barometric pressure, and dew point temperature on the incidence of primary spontaneous intracerebral hemorrhage (sICH). *Methods:* Between January 2013 and December 2016, patients with sICH due to hypertension or amyloid angiopathy with a known time of onset were identified prospectively. Meteorological variables 6 hours prior to time of onset were obtained from the National Oceanic Atmospheric Administration via two weather stations. Using a Monte-Carlo simulation, random populations of meteorological conditions in a 6-hour time window during the same years were generated. The actual meteorological conditions 6-hours prior to sICH were compared to those from the randomly generated populations. The false discovery rate method was used to identify significant meteorological variables. *Results:* Time of onset was identified in 455 of 603 (75.5%) patients. Distribution curves for change in temperature, mean barometric pressure, and change in barometric pressure 6-hours prior to hemorrhage ictus were found to be significantly different from the random populations. (FDR approach $P < .05$). For a given change in temperature associated with intracerebral hemorrhage, mean barometric pressure was higher (1018 millibar (mb) versus 1016 mb, $P = .03$). Barometric pressure data was not influenced by variations in temperature. *Conclusions:* We concluded that barometric pressure primarily influences the incidence of intracerebral hemorrhage. The association described in the literature between temperature and intracerebral hemorrhage is likely confounded by variations in barometric pressure.

Key Words: Intracerebral hemorrhage—temperature—barometric pressure—dew point temperature

Introduction

The association between spontaneous intracerebral hemorrhage (sICH) and weather has been well described in the literature. Some studies have noted a seasonal pattern in sICH with events occurring more frequently during winter months.[1-4] Other studies have specifically looked at daily and monthly average temperatures and have found a higher prevalence of sICH during colder weather.[5-9] Finally, barometric pressure, humidity, and

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wind speed all have been examined in relation to sICH prevalence with conflicting results.[10]

Weather is often associated with simultaneous changes in numerous meteorological conditions, including temperature, barometric pressure, and dew point. Collectively, these key meteorological factors are the main determinants of season and impact precipitation in local regions. Thus, the current data on the association between weather and sICH can be confounded by examining only one meteorological factor. Therefore, the collective influence of these factors on the probability of sICH remains to be determined. Furthermore, the association of meteorological factors with sICH may be a chance event, rather than a true association. Thus, the probability that a unique change in weather is actually associated with sICH requires further investigation.

Given these gaps in the literature, the aims of this study were (1) to assess the probability that a particular meteorological change is more likely to occur during sICH as opposed to chance, (2) to understand the influence of temperature, barometric pressure, and dew point temperature collectively on the incidence of sICH, and (3) to examine the interaction between sICH clinical and imaging variables, and these meteorological parameters. Our hypothesis was that the association between sICH and weather is not a chance event. We further hypothesized that the association between colder temperatures and the higher incidence of sICH described in the literature is likely confounded by other meteorological variables.

Methods

Participants

This study was approved by the Rush University Medical Center (RUMC) Institutional Review Board and Ethics Committee. All patients with sICH were prospectively screened between January 1, 2013 and December 31, 2016. A diagnosis of primary sICH was made by consensus after review of the patient's initial non-contrast computed topography (CT) and/or CT angiogram. Selected patients underwent further diagnostic work-up with MRI/MRA and/or digital subtraction angiography to exclude occult vascular malformations. Primary sICH was defined as either due to hypertension or cerebral amyloid angiopathy using validated criteria.[11] Patients with sICH due to coagulopathy, vascular malformations, trauma, or tumors were excluded for purposes of this study.

The date and time of last known normal were prospectively ascertained from each patient via personal interview with either the patient or surrogate decision maker. Only patients with a known date and time of onset were included in the analysis ($n = 455$). Data including age and ethnicity were abstracted from the electronic medical record at the time of admission for each patient. Each sICH was classified according to location of the hematoma and probable etiology of the hemorrhage: hypertensive versus cerebral amyloid angiopathy (CAA) related. The location of the hematoma was divided into (1) deep versus lobar and (2) supratentorial versus infratentorial. Possible and probable CAA were identified using the Boston Criteria[11] and combined into one group. Given absence of tissue, no patient met criteria for definite CAA.

Geographical Location and Weather Data

Rush University Medical Center (RUMC) is located in Chicago, Illinois. Ninety-five percent of sICH patients are transferred to RUMC for specialized care from surrounding community hospitals within a 50-mile radius while the remaining 5% are admitted directly from the RUMC emergency department. Geographically this catchment area, according to the Köppen-Geiger climate classification, experiences weather described as 'Dfa' which has cold winters and hot summers without a dry season.[12] Within the geographic area of this study, there are a few degrees of temperature variability based on proximity to Lake Michigan and urban heat island effects, but these were assumed constant for the purposes of this project. Weather variability during the winter season arises from large frontal systems that arrive along the westerly storm track. These tend to be large slow moving systems associated with significant changes in barometric pressure and snowfall. Summertime weather variability is associated with both frontal systems along the westerly storm track (similar to the winter) as well as southerly and southwesterly squall lines and local convective systems. In general, day to day variability in barometric pressure and temperature is between three to four times greater during the winter compared to summer.

Hourly temperature, sea level barometric pressure (SLP), and dew point data were obtained from the National Oceanic Atmospheric Administration weather stations at Midway and O'Hare International Airports. These airports are located 10.8 miles and 17.4 miles from RUMC, respectively and provided the most comprehensive weather data for our patient catchment area. To obtain the most representative condition, we averaged meteorological data between both locations. When data was missing from one station, we used data from the other station.

Statistical Analysis

Mean temperature, SLP, and dew point were calculated for the 6-hour period prior to each sICH event. Using the Robust Fit function in Matlab, a linear model was fitted to the 6 hours prior to sICH to also calculate the rate of change for these variables. Distribution curves for the six meteorological variables including mean temperature, rate of change of temperature (Δtemp), mean SLP, rate of change of SLP (ΔSLP), mean dew point, and rate of change of dew point (Δdew) were generated based on

normalized histograms from the population of 455 sICH events. The histogram and distribution curves were developed using the default automated binning algorithm within the Matlab software.

To assess whether the meteorological conditions associated with sICH events were chance events, we randomly selected a population of 455 6-hour periods of mean temperature, Δtemp, mean SLP, ΔSLP, mean dew point, and Δdew from all hourly weather data from 2013 to 2016. This process was repeated 2000 times to generate a large population of distribution curves using the Monte-Carlo method. These 2000 randomly generated distribution curves were derived from the same size population ($n = 455$) as the actual sICH population, and from the same weather data period allowing for a direct comparison between the actual sICH population versus the random population. The distribution of the actual sICH population was compared to the 2000 randomly selected population for each of the six meteorological variables using the Kolmogorov-Smirnov test to assess for statistical significance. The false discovery rate (FDR) method was applied for correction of multiple testing.

For statistically significant meteorological variables, we calculated the 99th percentile from the 2000 random population distribution curves and compared this to the actual sICH event distribution curve. sICH events above the 99th percentile were considered high probability to be associated with a particular meteorological parameter. Those below the 99th percentile were considered to be low probability. Univariate analysis was performed to compare differences in the high versus low probability groups for significant meteorological variables. Pearson correlation analysis was performed to examine the correlation among the meteorological variables within the high probability portions of the distribution curves.

Univariate analysis was performed to compare the age, location of the hematoma, and etiology of hemorrhage between the sICH events that occurred in the high and low probability ranges for significant meteorological variables. Continuous variables were compared using a *t*-test or Mann-Whitney U test as appropriate. Categorical variables were compared with chi-square test or Fisher's exact test.

Results

Patient Demographics and Weather Data

Among the 603 patients identified during the 3-year study period, 455 (75.5%) patients had an established date and time of last known normal. Mean age was 61 years (SD ± 14), 56% of patients were men, 59.1% were black, and 86.6% of patients were diagnosed as hypertensive. Most hemorrhages were supratentorial (83.1%) and deep (76.9%) (Table 1). The median ICH score was 1 (interquartile range: 1-3).

Table 1. *Clinical and radiographic characteristics of sICH cohort*

Characteristics	($N = 455$)
Age (years), mean (SD)	61 (14)
Male, *n*(%)	255 (56%)
Ethnicity, *n*(%)	
Black	269 (59.1)
White	102 (22.4)
Other	40 (0.08)
Hispanic/Latino	33 (0.07)
Asian	11 (0.02)
Location (%)	
Supratentorial versus infratentorial	378 (83.0%) versus 77 (16%)
Deep versus lobar	350 (76.0%) versus 105 (23%)
ICH etiology	
Hypertensive	394 (86.6%)
Possible/probable amyloid angiopathy	61 (13.4%)

Monte-Carlo Simulation

Figure 1 displays the distribution curve of actual sICH events compared to the distribution curve from the randomly generated population for the mean and change in temperature, SLP, and dew point. The distribution of actual sICH events was statistically significantly different (FDR corrected *P*-value < 0.05) from the 2000 randomly generated distributions curves for three meteorological parameters: (1) Δtemp (Fig 1A.2), (2) mean SLP (Fig 1B.1), and (3) Δ SLP (Fig 1B.2). There was no statistically significant difference for mean temperature, Δdew, and mean dew point. Therefore, these latter weather parameters were excluded from further analysis.

The probability of an sICH event was higher than the random population distribution when Δtemp was less than −0.9°C/hour or greater than 1.02°C/hour ($n = 81$, Fig 1A.2), when the mean SLP was between 999.5 millibar (mb) and 1006 mb ($n = 31$, Fig 1B.1), or when the Δ SLP was less than −0.67 mb/hour or greater than 0.36 mb/hour over 6 hours ($n = 131$, Fig 1B.2). Each of these higher probability groups occurred during rare and more extreme weather variability given their locations on the ends of the distribution curves. Respectively, the percentage of sICH patients in these higher probability ranges was 17.8% (Δtemp), 6.8% (mean SLP), and 28.8% (ΔSLP). There was a weak to moderate negative correlation between ΔSLP and Δtemp ($r = -0.25$ to -0.56). In univariate analysis, none of the clinical or imaging data assessed in Table 1 were found to be different between the high and low probability groups for Δtemp, mean SLP, or Δ SLP.

Univariate Analysis of Weather Parameters

For a given Δtemp, mean SLP was greater in the higher sICH probability range compared to the lower sICH

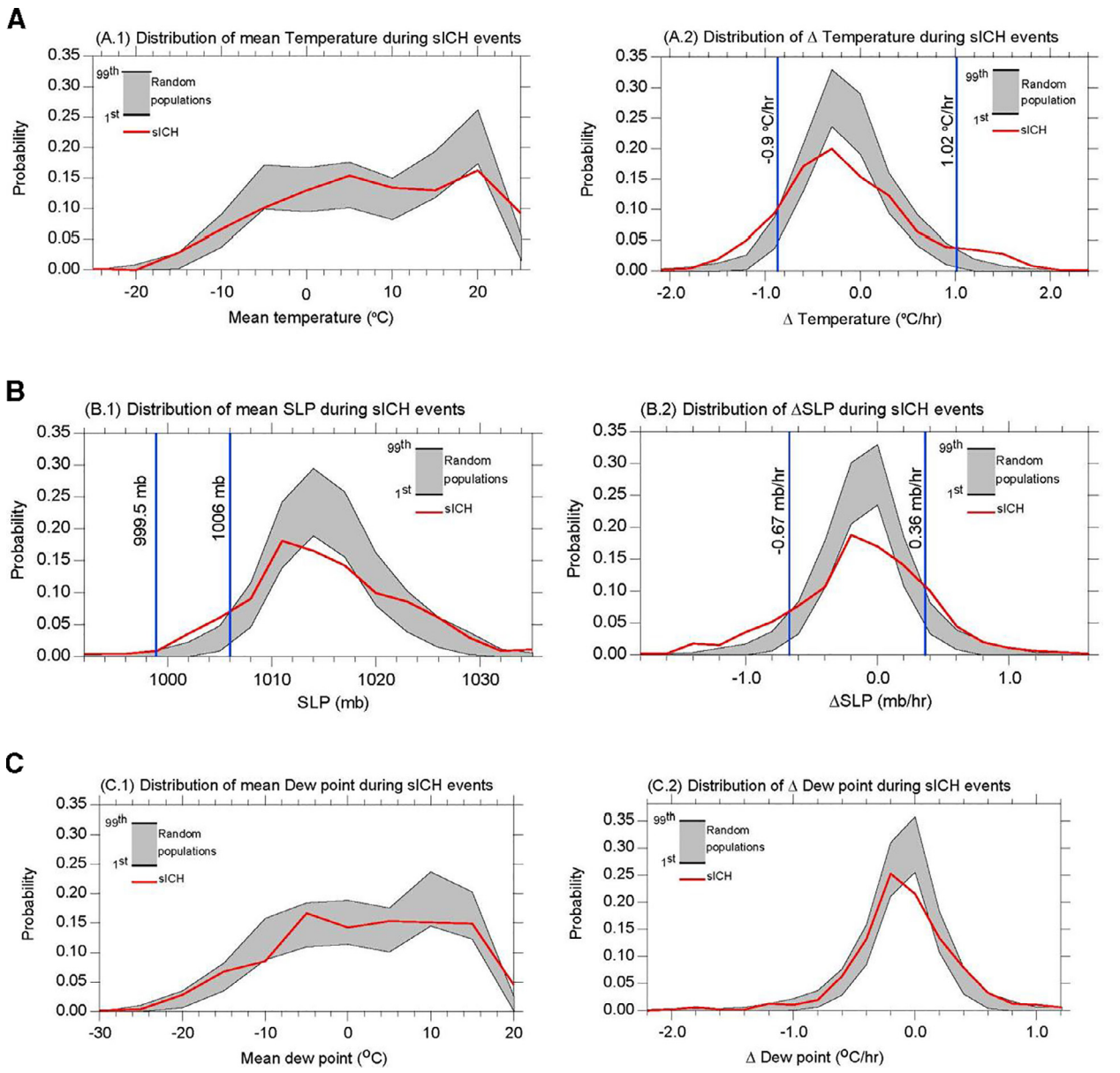

Figure 1. *Comparison of the probability of actual sICH events to the Monte-Carlo random population distribution curves for meteorological parameters. The probability of actual sICH events (red curve) compared to the 99th percentile of random populations derived from the Monte-Carlo simulation (upper black line) was significant (P < .05) for Δtemp (A.2), mean SLP (B.1), and ΔSLP (B.2). For these meteorological parameters, the vertical blue lines outline the cutoff where the probability of sICH events is greater than the 99th percentile of random populations.* Abbreviations*: mb, millibar; sICH, spontaneous intracerebral hemorrhage. (Color version of figure is available online.)*

probability range (1018 mb ± 7.45 versus 1016 ± 7.67 mb, $P = .03$) (Table 2). For a given mean and ΔSLP, there was no statistical difference between the low and high probability groups for the other meteorological parameters, notably temperature (Tables 3 and 4).

Discussion

The results of this study support our hypothesis suggesting that the influence of weather on the incidence of sICH is not a chance event. Furthermore, our data found that differences in barometric pressure may confound the influence temperature has on the incidence of sICH. For example, wintertime is associated both with the coldest mean temperatures and the greatest variation in barometric pressure.

Colder temperatures have been hypothesized to lead to higher sICH prevalence through their effects on systemic blood pressure (BP). Exposure to significant decreases in temperature can cause elevation in acute BP. The mechanism for this elevation is mediated thru various pathways involving the sympathetic nervous system and the hypothalamic pituitary adrenal axis. Shivering, vasoconstriction of cutaneous vessels to preserve heat, and the

Table 2. *Differences in weather parameters for high and low sICH probability ranges for a given change in temperature*

	High probability range ($N = 81$)	Low probability range ($N = 374$)	P-value
Mean SLP (mb), mean (SD)	1018. 0 (7.4471)	1016.0 (7.6702)	**0.03**
Change in SLP (mb/h), mean (SD)	−0.0102 (0.4886)	−0.0150 (0.5170)	0.9

Abbreviation: mb, millibar.

Table 3. *Differences in weather parameters for high and low sICH probability ranges for a given mean SLP*

	High probability range ($N = 31$)	Low probability range ($N = 424$)	P-value
Change in SLP (mb), mean (SD)	−0.1363 (0.4218)	−0.00489 (0.5170)	0.17
Change in temperature (˚C/hr), mean (SD)	0.00403 (0.5526)	0.0196 (0.7239)	0.90

Abbreviation: mb, millibar.

Table 4. *Differences in weather parameters for high and low sICH probability ranges for a given change in SLP*

	High probability range ($N = 131$)	Low probability range ($N = 324$)	P-value
Mean SLP (mb), mean (SD)	1016.3 (9.5344)	1016.3 (6.8824)	0.97
Change in temperature (˚C/h), mean (SD)	0.0646 (0.6280)	−0.00014 (0.7447)	0.35

Abbreviation: mb, millibar.

mammalian diving reflex can lead to increase in cardiac output, systemic vascular resistance, and BP.[13] Sudden extreme temperature changes, such as can occur with the famous "Ice-Bucket Challenge," have been implicated as a cause for sICH in some patients.[14] The relationship between outdoor temperature and BP has been examined in several large epidemiologic cohorts.[15-18] Collectively, these studies found an inverse relationship between BP and temperature. For every 10°C reduction in temperature, systolic BP and diastolic BP were noted to be higher by 1.5 to 8.0 mm Hg and 1.1 to 2.9 mm Hg, respectively. It is unclear whether these relatively small degrees of BP change in an already hypertensive patient would translate to an increased risk for sICH.

However, outdoor activity patterns in North America, particularly within this studied geographic area, suggest that patients spend less than 2% of total daily time exposed to outdoor temperatures.[19] In extreme outdoor temperatures, exposure to the weather is likely further limited. Therefore, the influence of ambient outdoor temperature and seasons on BP through reflexive and autonomic pathways may be minimal when indoor temperature is controlled. In addition, any minimal time spent outdoors during extreme weather conditions is optimized by personal attire and/or alterations in transportation mode to maintain one's preferred temperature. Gradual changes in seasonal temperature may allow for a more proactive and preventative approach by individuals to control personal temperature.

In a large study involving 500,000 men and women in China, there was minimal variation in systolic BP among individuals living in northern urban China compared to rural regions.[17] This was believed to be secondary to the widespread availably of central heating in more developed urban areas allowing for individualized control of personal temperature. In normotensive males, the presence of indoor climate control at work blunted seasonal variation on blood pressure.[20] Control of personal temperature, led to a more direct relationship between blood pressure and indoor temperature, as opposed to outdoor temperature.[21]

We found that increase and decrease in outdoor temperature of greater than 6°C (10.8°F) were associative with a higher probability of sICH. Rapid changes in temperature beyond which normal homeostatic mechanisms are able to adjust may lead to poor blood pressure control and a higher risk for sICH. The changes in temperature associated with the higher probability of sICH in our study were rare and extreme weather events. Therefore, these aberrant weather conditions may disrupt normal homeostatic mechanisms. Alternatively, acute alterations in temperature may lead to behavioral changes that cause patients to be less likely to seek medical attention for symptoms that may signal a new stroke. In contrast to prior studies, we found that increases in temperature were associated with an increased probability of sICH. Elevations in temperature have also been found to be associated with increase in nighttime and early morning BP.[21] Frequent BP and core body temperature monitoring may provide a better understanding of an underlying relationship.

In our study, we found a higher barometric pressure in the higher probability Δtemp group (Table 2). Within this study's geographic area, wintertime average temperature and sea level barometric pressure (SLP) is ∼−2°C and 1019 mb, respectively. Summertime average temperature

and SLP is ~24°C and 1015 mb, respectively. Therefore, the mean barometric pressure in the Δtemp higher probability group (Table 2) more closely approximates the wintertime averages compared to summertime averages normally seen in our geographic area. We did not find that mean temperature influenced the incidence of sICH. The overall analysis suggests that barometric pressure confounds and may be a more significant factor in the incidence of sICH than temperature.

Decrease in ambient temperature with or without precipitation can influence atmospheric barometric pressure. This meteorological phenomenon may give rise to an apparent increase in sICH prevalence during colder temperatures. Furthermore, whereas temperature can be artificially regulated indoors, barometric pressure remains nearly constant whether indoors or outdoors.[22] Changes in atmospheric barometric pressure have been associated with an increased prevalence in migraines and aneurysmal subarachnoid hemorrhages.[23-27] Even in pressurized cabins on commercial flights, drops in barometric pressure are believed to be the trigger for flight-associated headaches.[28] Although the physiological mechanism for these associations remain unclear, blood pressure elevation during drops in barometric pressure have been described in animal models and the clinical setting.

In rat models, reduction of atmospheric pressure by 40 mb in controlled climatic chambers led to increased neuronal activity in the spinal trigeminal nucleus caudalis. Only neuron units receiving afferent input from the cornea were receptive to lowering of barometric pressure. Concurrent with this change in pressure was an increase in mean arterial pressure and a delayed decrease in heart rate.[29] The authors hypothesized whether changes in barometric pressure can influence intra-ocular pressure, and thus activate the V1 distribution of the trigeminal nerve with isolated corneal afferent input. The change in BP and HR noted in this study mimics the mammalian diving reflex that occurs with colder temperature. Other trigeminocardiac reflexes, unrelated to temperature, can produce decrease in HR with elevations in BP.[30]

BP elevation is a well described response in some individuals climbing to higher altitudes (>1500 m).[31] Decreases in barometric pressure with higher altitudes can reduce the partial pressure of oxygen in arterial blood. This can not only cause compensatory vasodilation of the cerebral vasculature, but also increases cardiac output and blood pressure via chemoreceptors in the carotid bodies. Conversely, mild decreases in altitude (<100 m) with increased oxygen tension have been associated with reductions in BP.[32] Mild changes in atmospheric pressure have been found to impact peripheral arterial distensibility, specifically in young hypertensive men.[33] This effect was lost with aging and presumably stiffening of peripheral vasculature.

In our study, the mean SLP associative with sICH is equivalent to a 30-40 m increase in altitude from baseline. Most of the sICH events occurred during reduction in barometric pressure, while a small subset occurred with an increase. However, in study by Honig et al a smaller decrease in barometric pressure of 0.238 to 0.736 mb was associated with deep hypertensive versus CAA-related sICH.[34] Most studies have not examined the influence of barometric pressure in studying the association between temperature and sICH. Furthermore, it is unclear whether small changes in barometric pressure at sea level impact blood pressure and blood arterial oxygen tension.

The analytical approach used in this study uniquely clarifies the relationship between sICH and weather that has prevailed in the literature. The association between weather and sICH prevalence may be confounded by a multitude of variables. By using the Monte-Carlo simulation, we are able to better estimate the influence of each weather parameter on sICH given that only small proportion of sICH events appears to be associated with changes in climate. Furthermore, dramatic changes in weather can occur over a short period of time. Therefore, the use of average daily, weekly, or monthly weather parameters is limited and may produce misleading conclusions. Finally, we examined three main weather parameters simultaneously to look for confounders; examination of only one weather parameter may lead to bias.

Our study has several limitations. First, patients from only one referral center were evaluated, which may lead to selection bias with respect to the severity of sICH. However, our median sICH score (median = 1) suggests that most hemorrhages were mild in severity and would be similar to patients cared for at non-university based facilities. Second, we examined one geographic area using two weather stations which limits the generalizability of our data. Replication of our methodology in other geographic regions would provide supporting evidence of our data. Finally, other environmental factors such as pollutants, ambient CO_2 levels, and noise levels have been associated with blood pressure changes, cardiovascular events, and may confound our results.

Conclusions

The influence of weather on the incidence of sICH in not a chance event and occurs in a small percentage of patients during rare and extreme weather conditions. Our results suggest that barometric pressure has a greater influence on sICH incidence than temperature. Although changes in temperature are associated with sICH, its effects may be modulated by barometric pressure. Further study is required to understand how changes in barometric pressure affect systemic and cerebrovascular physiology.

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