Temperature and Precipitation Associate With Ischemic Stroke Outcomes in the United States

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Background**—**There is disagreement in the literature about the relationship between strokes and seasonal conditions. We sought to (1) describe seasonal patterns of stroke in the United States, and (2) determine the relationship between weather variables and stroke outcomes.

Methods and Results**—**We performed a cross-sectional study using Get With The Guidelines-Stroke data from 896 hospitals across the continental United States. We examined effects of season, climate region, and climate variables on stroke outcomes. We identified 457 638 patients admitted from 2011 to 2015 with ischemic stroke. There was a higher frequency of admissions in winter (116 862 in winter versus 113 689 in spring, 113 569 in summer, and 113 518 in fall; $P<0.0001$). Winter was associated with higher odds of in-hospital mortality (odds ratio [OR] 1.08 relative to spring, confidence interval [CI] 1.04–1.13, $P=0.0004$) and lower odds of discharge home (OR 0.92, CI 0.91–0.94, $P<0.0001$) or independent ambulation at discharge (OR 0.96, CI 0.94–0.98, $P=0.0006$). These differences were attenuated after adjusting for climate region and case mix and became inconsistent after controlling for weather variables. Temperature and precipitation were independently associated with outcome after multivariable analysis, with increases in temperature and precipitation associated with lower odds of mortality (OR 0.95, CI 0.93–0.97, $P<0.0001$ and OR 0.95, CI 0.90–1.00, $P=0.035$, respectively).

Conclusions**—**Admissions for ischemic stroke were more frequent in the winter. Warmer and wetter weather conditions were independently associated with better outcomes. Further studies should aim to identify sensitive populations and inform public health measures aimed at resource allocation, readiness, and adaptive strategies. **(*J Am Heart Assoc*. 2018;7:e010020. DOI: 10.1161/JAHA.118.010020.)**

Key Words: cerebrovascular disease • environment • epidemiology • ischemic stroke • seasonal variation

Stroke is recognized as a leading cause of morbidity and mortality, ranking as the second most common cause of death[1] and disability-adjusted life years[2] worldwide in 2015 estimates. It has also become recognized as a largely preventable disorder, of which an estimated 90% of the burden is attributable to modifiable risk factors that include metabolic, behavioral, and environmental conditions and exposures.[3] Among such exposures, the hypothesis that weather changes can affect physiologic conditions that either precipitate stroke or worsen stroke outcomes is a significant and broadly relevant public health concern.

Similar to acute coronary events,[4] stroke has been observed to demonstrate seasonal patterns in occurrence and outcome. Previous studies aimed at elucidating the link

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010020

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Clinical Perspective

What Is New?

- A relationship exists between stroke outcomes and weather during the week of stroke occurrence.

What Are the Clinical Implications?

- Stroke severity and/or recovery may be influenced by ambient weather variables.
- Understanding the observed relationship may lead to novel and improved stroke prevention and therapy.

between strokes and seasons, although performed worldwide, have been limited to either small studies of geographically and demographically isolated populations or broader studies confounded by variations in referral patterns and systems of acute stroke care. Additionally, there is some disagreement among study results, with a majority of the literature demonstrating evidence of higher stroke incidence in winter,[1,5–13] few studies finding higher incidence in spring,[14–17] few finding no seasonal association at all,[18–20] and others still finding a winter association strictly with mortality but not incidence.[21,22]

Using a nationwide stroke registry and meteorological data, we aimed to (1) describe seasonal patterns of stroke occurrence in the United States, and (2) determine the relationship between weather variables and stroke outcomes.

Materials and Methods

The Get With The Guidelines (GWTG)-Stroke program was developed by the American Heart Association and American Stroke Association as a national quality improvement initiative to address gaps in acute stroke care and adherence to guideline recommendations. Because data were collected for clinical care and quality improvement rather than primarily for research, the American Heart Association (the steward of the data according to contracts between the American Heart Association and participating hospitals) cannot provide the data, statistical analysis code, or other study materials to other researchers. Details of the design and conduct of GWTG-Stroke have previously been described.[23,24] In brief, participating sites are trained to collect patient-level data on consecutive acute stroke and transient ischemic attack patients, which include clinical and demographic characteristics, diagnostic testing, treatments, adherence to quality measures, in-hospital outcomes, and discharge dispositions. Chart reviews of prospectively and retrospectively identified patients are performed by trained auditors to confirm eligibility, and the high accuracy and reliability of abstracted data has previously been demonstrated.[25] Deidentified data are collected using a web-based patient management tool (Outcome, A Quintiles Company, Cambridge, MA). The Duke Clinical Research Institute serves as the data analysis center, analyzing aggregate deidentified data for research purposes. Participating sites receive either human research approval to enroll cases in GWTG-Stroke without requiring individual patient consent under the common rule, or a waiver of authorization and exemption from subsequent review by their Institutional Review Board.

Design

We performed a cross-sectional study of patients admitted for the first time with ischemic stroke to GWTG-Stroke sites across the continental United States.

Subjects

We included adult (aged >18 years) patients admitted for the first time with out-of-hospital ischemic strokes to fully participating GWTG sites, defined as sites with continuous participation throughout the study period with ≥1 submitted stroke admission each quarter.

Exposure

Seasons were separated into spring (March 23–June 21), summer (June 22–September 21), fall (September 22–December 21), and winter (December 22–March 22). Climate data were obtained from the National Climatic Data Center of the National Oceanic and Atmospheric Administration. Daily climate records from all weather stations in each of 9 climate regions defined by the National Climatic Data Center (Figure 1) were obtained from the Global Historical Climatology Network. These included temperature and precipitation on the day of admission as well as averages over the 7 days preceding admission. Precipitation measurements did not include snowfall. GWTG-Stroke sites were linked by latitude and longitude coordinates to the nearest weather stations as reported in the Historical Observing Metadata Repository (HOMR).

Outcome

The primary outcome was in-hospital mortality of any cause. The secondary outcomes were discharge disposition to home and independent ambulatory status upon discharge.

Covariates

Data were collected on potentially confounding patient factors and hospital factors. These included age, sex, race/

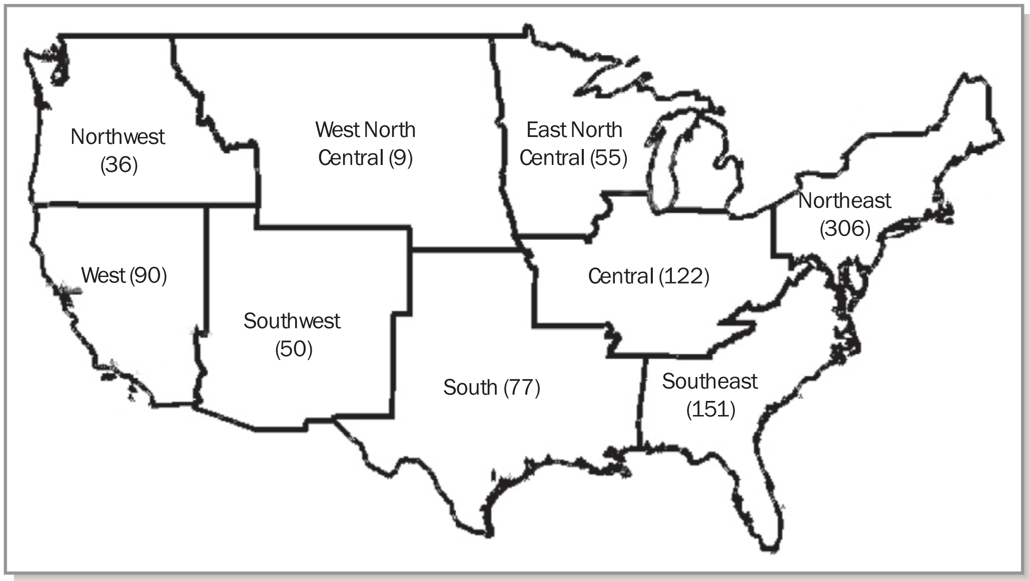

Figure 1. Climate regions of the United States, as defined by the National Climatic Data Center. The number of included Get With The Guidelines sites in each region are labeled.

ethnicity, medical history of atrial fibrillation/flutter, coronary artery disease or prior myocardial infarction, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, smoking, National Institutes of Health Stroke Scale (NIHSS) score, hospital type (teaching or non-teaching), number of beds, rural location, The Joint Commission primary stroke center status, annual hospital ischemic stroke volume, and annual thrombolytic administration volume.

Statistical Analysis

Baseline characteristics, comorbidities, hospital characteristics, and discharge outcomes were described overall and by season using proportions for categorical variables and medians with 25th and 75th percentiles for continuous variables. Differences in the frequency distributions of these characteristics between seasons were compared using Pearson's Chi-square or Fisher's exact tests (where applicable) for categorical row variables and Kruskal–Wallis tests for continuous row variables.

Multivariable regression analysis was performed to assess the effect of season (with reference to spring), climate region (with reference to Northeast), and climate variables (7-day average minimum and maximum temperatures, 7-day average precipitation) on outcomes. Logistic regression with generalized estimating equations (GEEs) was used to account for the clustering of patients within different sites.

We used a nested series of models to investigate the relationships between season, climate region, patient and hospital characteristics, stroke severity, and weather variables. First, we compared the results of models that adjusted for all patient and hospital level covariates and climate region, to see if season-related differences were accounted for by differences in case mix. Next, we adjusted for stroke severity, defined as the National Institutes of Health Stroke Scale (NIHSS) score. Finally, we added variables for precipitation and temperature. Separate models were fitted for the climate variables precipitation, 7-day average minimum temperature, and 7-day average maximum temperature.

Multiple imputation was used to handle missing data on patient baseline characteristics including NIHSS. Hospital-level variables and climate variables were not imputed. Rates of missing variables are summarized in Table S1.

All P values were 2-sided and statistical significance was defined as $P<0.05$. SAS version 9.4 was used for all statistical analyses.

Results

From an initial data set of 1 184 818 patients admitted to fully participating sites between March 23, 2011 and March 22, 2015 with ischemic stroke, 7112 patients admitted in Alaska, Hawaii, or with missing state information were excluded. Alaska and Hawaii have <6 sites participating in GWTG-Stroke and thus state-level analyses were not permitted under the GWTG contract. 216 318 patients who transferred between facilities, left against medical advice, or had missing discharge destinations were excluded; 480 706 patients with prior stroke or transient ischemic attack and 23 044 patients with in-hospital stroke were excluded. This led to a final study population of 457 638 ischemic stroke

Table 1. Baseline Characteristics of Ischemic Stroke Patients on Admission, by Season

Variables	Spring	Summer	Fall	Winter	*P* Value*
Admissions (%)	113 689 (24.8)	113 569 (24.8)	113 518 (24.8)	116 862 (25.5)	<0.0001
Female (%)	57 988 (51.0)	57 781 (50.9)	58 542 (51.6)	59 525 (50.9)	0.003
Mean age (SD)	72 (14.8)	71 (14.9)	72 (14.8)	72 (14.8)	<0.0001
Race (%)					0.06
White	79 500 (70.0)	79 201 (69.9)	79 543 (70.2)	81 822 (70.2)	
Black	18 871 (16.6)	18 871 (16.6)	18 642 (16.5)	19 138 (16.4)	
Hispanic	8024 (7.1)	8109 (7.2)	7977 (7.0)	8044 (6.9)	
Asian	3207 (2.8)	3290 (2.9)	3226 (2.9)	3533 (3.0)	
Other	3907 (3.4)	3917 (3.5)	3932 (3.5)	4086 (3.5)	
Missing	180 (0.2)	181 (0.2)	198 (0.2)	239 (0.2)	
Insurance (%)					<0.0001
Self-pay	6931 (7.2)	7147 (7.3)	6670 (6.9)	6575 (6.6)	
Medicare	36 877 (38.0)	36 597 (37.5)	36 379 (37.5)	37 597 (37.9)	
Medicaid	9643 (10.0)	10 062 (10.3)	9699 (10.0)	9865 (10.0)	
Other	43 479 (44.9)	43 902 (44.9)	44 215 (45.6)	45 078 (45.5)	
Missing	16 759 (14.7)	15 861 (14.0)	16 555 (14.6)	17 747 (15.2)	
Arrival by emergency medical services (%)	58 353 (56.3)	58 548 (56.3)	61 168 (57.6)	63 627 (58.4)	<0.0001
Mean minutes to arrival	498	499	497	511	<0.0001
Mean NIHSS	6.1	6.0	6.2	6.2	<0.0001
Independently ambulatory on admission (%)	31 185 (44.3)	31 028 (44.6)	29 895 (43.4)	29 901 (42.8)	<0.0001
Atrial fibrillation/flutter (%)	19 311 (17.0)	18 863 (16.6)	19 894 (17.5)	20 632 (17.7)	<0.0001
Prosthetic heart valve (%)	1284 (1.1)	1257 (1.1)	1257 (1.1)	1296 (1.1)	0.95
Coronary artery disease (%)	24 953 (22.0)	24 645 (21.7)	24 850 (21.9)	25 472 (21.8)	0.50
Carotid stenosis (%)	2844 (2.5)	2668 (2.4)	2783 (2.5)	2929 (2.5)	0.05
Diabetes mellitus (%)	35 256 (31.0)	35 175 (31.0)	34 980 (30.8)	36 398 (31.2)	0.39
Peripheral vascular disease (%)	4560 (4.0)	4327 (3.8)	4408 (3.9)	4715 (4.0)	0.02
Hypertension (%)	83 766 (73.7)	83 056 (73.1)	83 588 (73.6)	86 054 (73.6)	0.01
Smoker (%)	21 257 (18.7)	21 852 (19.2)	20 734 (18.3)	21 123 (18.1)	<0.0001
Dyslipidemia (%)	47 378 (41.7)	46 840 (41.2)	47 123 (41.5)	48 613 (41.6)	0.18
Heart failure (%)	9259 (8.1)	9195 (8.1)	9324 (8.2)	9736 (8.3)	0.19

NIHSS indicates National Institutes of Health Stroke Scale.
**P* values indicate differences in frequency distributions across levels that include levels not shown here, such as 25th percentile, 75th percentile, median, standard deviation, minimum, and maximum.

patients (mean aged 71 years [SD 15], female n=233 836 [51%]) from 896 GWTG sites.

Baseline characteristics are shown in Table 1. There were differences in the frequency distributions across seasons for age, insurance, arrival mode and hours, onset to arrival time, NIHSS, ambulatory status, atrial fibrillation/flutter, and smoking, though the absolute differences were small (Table 1). Climate variables showed both meaningful and statistically significant differences across seasons, as shown in Table 2. Among hospital level variables, only climate region showed strong differences across seasons ($P<0.001$). Teaching hospital status and The Joint Commission Primary Stroke Center status were statistically different across seasons (P=0.02 and 0.04, respectively) though with small absolute differences in frequency. A map illustrating the climate regions and the number of GWTG-Stroke hospitals in each region is displayed in Figure 1.

Among the 457 638 ischemic stroke patients, 116 862 had strokes occurring in the winter season, as compared with 113 689 in spring, 113 569 in summer, and 113 518 in fall ($P<0.0001$). The results of multivariable regression analysis of the association of season and weather variables with

Table 2. Climate Variables (7-Day Average Before Admission*), by Season

Variables	Spring	Summer	Fall	Winter	*P* Value†
Mean precipitation, mm	3.19	3.26	2.59	2.34	<0.0001
Mean snowfall, mm	0.72	0.00	1.60	7.80	<0.0001
Minimum temperature, °C	11.00	18.70	7.10	−0.20	<0.0001
Maximum temperature, °C	22.30	29.60	17.40	10.10	<0.0001

*Climate data measured on the day of admission, not shown here, showed similar distributions to those averaged over 7 days.
†*P* values indicate differences in frequency distributions across levels that include levels not shown here, such as 25th percentile, 75th percentile, median, standard deviation, minimum, and maximum.

outcomes are summarized in Table 3, along with the nested series of models used to investigate the relationship between seasons and outcomes. In unadjusted analyses, winter season was associated with worse outcomes, and summer was associated with better outcomes. However, overall differences were small, and adjusting for climate region and case mix, attenuated the observed season-related differences. Additional adjustment for stroke severity had little effect. After adding weather variables (precipitation and temperature), the association with season became small and inconsistent. However, precipitation and temperature showed significant associations with outcome which were

Table 3. Association of Outcomes With Season and Weather Variables

Variables	Model: Unadjusted OR (95% CI)	Unadjusted *P* Value	Adjusted for Patient and Hospital OR (95% CI)	*P* Value	Adjusted for Patient, Hospital, NIHSS* OR (95% CI)	*P* Value	Adjusted for Patient and Hospital, NIHSS,* Weather OR (95% CI)	*P* Value
Outcome: mortality								
Spring (ref)	1.00	…	1.00	…	1.00	…	1.00	…
Summer	0.95 (0.91–0.99)	0.015	0.95 (0.91–0.99)	0.023	0.95 (0.91–0.99)	0.013	1.01 (0.95–1.07)	0.814
Fall	1.03 (0.99–1.08)	0.136	1.00 (0.96–1.05)	0.824	1.00 (0.96–1.04)	0.999	0.93 (0.88–0.98)	0.008
Winter	1.08 (1.04–1.13)	0.0004	1.04 (1.00–1.08)	0.072	1.04 (1.00–1.08)	0.058	0.89 (0.83–0.95)	0.0004
Precipitation	0.95 (0.91–0.99)	0.010	…	…	…	…	0.95 (0.90–1.00)	0.035
Min Temp†	0.96 (0.95–0.97)	<0.0001	…	…	…	…	0.95 (0.93–0.97)	<0.001
Outcome: discharge home								
Spring (ref)	1.00	…	1.00	…	1.00	…	1.00	…
Summer	1.02 (1.01–1.04)	0.004	1.02 (1.00–1.04)	0.019	1.01 (0.99–1.03)	0.280	1.00 (0.97–1.03)	0.817
Fall	0.96 (0.94–0.97)	<0.0001	0.98 (0.96–1.00)	0.030	0.96 (0.94–0.98)	0.0004	1.00 (0.98–1.03)	0.746
Winter	0.92 (0.91–0.94)	<0.0001	0.95 (0.93–0.97)	<0.0001	0.93 (0.91–0.95)	<0.0001	1.00 (0.97–1.04)	0.984
Precipitation‡	1.01 (0.99–1.03)	0.205	…	…	…	…	1.01 (0.99–1.02)	0.318
Min Temp†‡	1.03 (1.03–1.03)	<0.0001	…	…	…	…	1.02 (1.01–1.04)	<0.001
Outcome: independent ambulation at discharge								
Spring (ref)	1.00	…	1.00	…	1.00	…	1.00	…
Summer	1.05 (1.03–1.07)	<0.0001	1.05 (1.03–1.08)	<0.001	1.04 (1.02–1.07)	0.001	1.04 (0.99–1.10)	0.096
Fall	1.00 (0.98–1.03)	0.891	1.03 (1.01–1.06)	0.013	1.02 (0.99–1.05)	0.114	1.06 (1.03–1.10)	0.001
Winter	0.96 (0.94–0.98)	0.0006	0.99 (0.97–1.02)	0.615	0.97 (0.94–1.00)	0.044	1.03 (0.97–1.09)	0.385
Precipitation‡	1.00 (0.99–1.02)	0.636	…	…	…	…	1.03 (0.99–1.06)	0.117
Min Temp†‡	1.02 (1.01–1.03)	<0.0001	…	…	…	…	1.01 (0.99–1.03)	0.382

CI indicates confidence interval; Min Temp, minimum temperature; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.
*Models where NIHSS was imputed (not shown) showed similar results as the complete case analysis (shown).
†Models where daily maximum temperature was substituted for daily minimum temperature gave similar results.
‡Precipitation: per additional 10 mm; Minimum temperature: per additional 5°C.

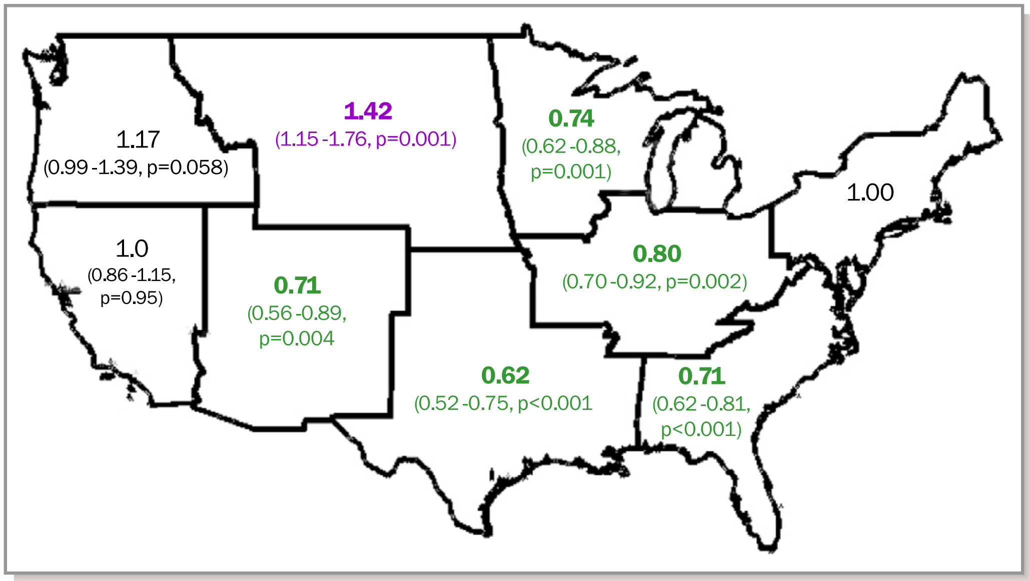

Figure 2. Odds ratios for mortality in each climate region relative to the Northeast, calculated from the model that adjusted for patient and hospital characteristics and National Institute of Health Stroke Severity score, not weather.

independent of other factors: a 5° increase in minimum temperature had odds ratio (OR) 0.95 for in-hospital mortality (confidence interval [CI] 0.93–0.97, P<0.0001) and OR 1.02 for discharge home (CI 1.01–1.04, P<0.0001). An increase in precipitation of 10 mm had OR 0.95 for in-hospital mortality (CI 0.90–1.00, P=0.035). In general terms, warmer and wetter weather conditions were associated with better outcomes.

Significant associations were also found between climate regions and outcomes, most robustly reflected in the primary outcome in-hospital mortality, as summarized in Figure 2. Odds ratios for climate regions were calculated with reference to the Northeast, with the following regions demonstrating relatively lower odds of mortality: Southeast, Central, East North Central, South, and Southwest regions. The West North Central region showed higher odds of mortality relative to the Northeast.

Discussion

We found that there were more frequent stroke admissions in the winter season compared with other seasons. A purely season-related impact on stroke outcomes was not found to be significant after adjustment for climate region and case mix, however specific weather variables such as temperature and precipitation were found to be independently associated with outcomes, in that warmer and wetter weather conditions around the time of admission were associated with better outcomes.

The trends we found are generally consistent with prior studies, including a recent study using nationwide administrative data that found an association between lower average temperatures and stroke hospitalizations. This particular study also examined diurnal temperature fluctuations and found an association between larger fluctuations and stroke hospitalization rates.[26] Our results are also consistent with those of many small regional studies which have examined cohorts around the world from cities in Italy to cities in Japan. Most of these have found cold temperatures to have a short-term association with elevation in the risk of stroke occurrence, with the risk period ranging from 1 to 2 days in some studies to 1 week in others.[1,27–31] One study that examined a registry of stroke and transient ischemic attack patients during the 1980's in the Lehigh Valley, in Northeastern United States, found a significant negative correlation between temperature and ischemic stroke, though with a 2-month lag.[32]

There are several possible biologic mechanisms by which cold temperatures could precipitate stroke. There has been a cooling effect described that coincides with decreasing plasma volume and increasing plasma viscosity with increased platelet, cholesterol, and fibrinogen concentrations without concomitant increases in protein C, thus concentrating risk factors for arterial thrombosis.[33,34] Other work has demonstrated higher leukocyte counts, higher hematocrits, and higher blood pressures on stroke admissions in the winter coinciding with seasonal variability.[12] Higher blood pressures in winter and colder temperatures have been widely reported.[35–37] Various cardiovascular risk factors have been assessed for seasonal occurrence as well, with 1 study of over 200 000 patients in 15 countries finding higher levels of many risk factors in winter, which included body mass index, waist circumference, blood pressure, triglycerides and cholesterol, and blood glucose.[38]

Aside from identifying an elevated stroke frequency in the winter, perhaps the more important finding of this study is the association between weather and stroke outcomes. Weather-related differences in outcomes may be a consequence of other comorbidities that likewise demonstrate seasonal variation. United States census data from the 1930's to 1980's revealed sharp rises in both respiratory disease and stroke mortality in the winter; stroke mortality was independently associated with both respiratory disease mortality and temperature.[39] It has also been suggested that winter mortality may be increased in populations with less preparedness,[40] which could manifest on the individual level as cold protective measures or on the systems level as adaptive response implementation and resource allocation. Understanding the contributing factors to winter mortality in stroke patients could inform such response and resource preparedness on population levels.

There is limited prior research into the relationship between precipitation and stroke outcomes. Prior studies that included weather variables other than temperature have examined them as contributors to risk of stroke occurrence, and resulted in mixed data, finding either no effect[41] or an increased risk of stroke incidence with higher rainfall.[30] A study in Boston, Massachusetts found that on days with higher levels of relative humidity, the association between ischemic stroke risk and ambient temperature was stronger.[29] Interestingly, another study that examined the risks conferred by weather patterns on aneurysmal subarachnoid hemorrhage outcomes did find a similar effect, in that greater precipitation was associated with significantly reduced in-hospital mortality. The authors of that study postulated that associated low sunlight and/or increased depression could alter emotional stress and care seeking behaviors in a way that could affect outcome. In secondary analysis, precipitation and temperature were associated with outcome in a model independent of climate region or season, thus raising the possibility that the findings reflect interaction between the 2 variables. In many regions, wetter weather is associated with warmer weather, and it may be that temperature still mediates most of the protective effect observed. Or, perhaps similarly to the findings in the aforementioned study,[29] the effect of precipitation may be strengthening that of temperature. Finally, the observation that cardiovascular mortality can be attributable to air pollution[42] also raises the possibility of pollution as a third variable, as inverse relationships between precipitation and air pollution have been observed.[43]

Our study examines a phenomenon that has been of worldwide interest for decades, widely reported, but with inconsistencies in dedicated studies. Our use of data from a national quality initiative in the United States, as one country with multiple climates, offers more breadth than regional studies and reduced systems variability compared with multinational studies. However, it also has several important limitations. Because GWTG-Stroke is a database of stroke hospitalizations, true incidences could not be determined in the context of the entire population and seasonal variation could only be described by the differences in frequency of stroke admissions across seasons. As a consequence of large samples, small variations in frequency distributions for all variables were easily detected and statistically significant; the meaningfulness of each detected pattern relative to others is thus uncertain. Although GWTG-Stroke enrolls hospitals across the nation, the representation of fully participating sites between regions created by climate zones did vary, thus limiting generalizability. Climate data also reflected ambient conditions on the day-of and week-of stroke for each patient's climate region, but may not have reflected individual exposures. Finally, unmeasured confounding variables likely contributed to some of our findings on primary and secondary analyses, given the breadth of interactions between climate, geography, and regional population factors in addition to interacting meteorological conditions.

Summary

Warmer and wetter weather were independently associated with mortality and discharge disposition among patients hospitalized with ischemic stroke in the United States. Further study of the mechanism of this effect is needed, as well as further characterization of the populations most vulnerable to the risks conferred by weather changes. Understanding the mechanisms underlying the observed associations may help to identify sensitive populations and inform public health measures aimed at resource allocation, readiness, and adaptive strategies for sensitive populations.

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SUPPLEMENTAL MATERIAL

Table S1. Missing Rates of Adjustment Variables.

Variable	Missing Rate (%)
Age	0.0
Sex	0.0
Race/Ethnicity	0.2
Medical History Variables	0.0
NIHSS Score	20.4
Precipitation	12.1
Minimum Temperature	18.1
Maximum Temperature	18.1
Hospital Type	0.4
Number of Beds	0.4
Rural Location	0.0
TJC Primary Stroke Center	0.0
Annual Ischemic Stroke Volume	0.0
Annual IVtPA Volume	0.0