Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association

A Division of American Heart Association

Innovative Approaches Helpful to Enhance Knowledge on Weather-Related Stroke Events Over a Wide Geographical Area and a Large Population

Marco Morabito, Alfonso Crisci, Roberto Vallorani, Pietro Amedeo Modesti, Gian Franco Gensini and Simone Orlandini

Stroke 2011;42;593-600; originally published online Jan 27, 2011;
DOI: 10.1161/STROKEAHA.110.602037
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Innovative Approaches Helpful to Enhance Knowledge on Weather-Related Stroke Events Over a Wide Geographical Area and a Large Population

Marco Morabito, PhD; Alfonso Crisci, MA; Roberto Vallorani, MA; Pietro Amedeo Modesti, MD, PhD; Gian Franco Gensini, MD; Simone Orlandini, PhD

Background and Purpose—Results on the effect of weather on stroke occurrences are still confusing and controversial. The aim of this study was to retrospectively investigate in Tuscany (central Italy) the weather-related stroke events through the use of an innovative source of weather data (Reanalysis) together with an original statistical approach to quantify the prompt/delayed health effects of both cold and heat exposures.

Methods—Daily stroke hospitalizations and meteorologic data from the Reanalysis 2 Achieve were obtained for the period 1997 to 2007. Generalized linear and additive models and an innovative modeling approach, the constrained segmented distributed lag model, were applied.

Results—Both daily averages and day-to-day changes of air temperature and geopotential height (a measure that approximates the mean surface pressure) were selected as independent predictors of all stroke occurrences. In particular, a 5°C temperature decrease was associated with 16.5% increase of primary intracerebral hemorrhage of people ≥65 years of age. A general short-term cold effect on hospitalizations limited to 1 week after exposure was observed and, for the first time, a clear harvesting effect (deficit of hospitalization) for cold-related primary intracerebral hemorrhage was described. Day-to-day changes of meteorologic parameters disclosed characteristic U- and J-shaped relationships with stroke occurrences.

Conclusions—Thanks to the intrinsic characteristic of Reanalysis, these results might simply be implemented in an operative forecast system regarding weather-related stroke events with the aim to develop preventive health plans. **(*Stroke*. 2011;42:593-600.)**

Key Words: cerebrovascular disease ■ harvesting ■ hospitalizations ■ risk factors ■ reanalysis

Most of studies worldwide demonstrated significant relationships between weather and stroke events.[1–9] Nevertheless, as reported in a recent review,[10] authors often described discordant effects of both air temperature and atmospheric pressure.

Because it is well known that the temperature effect on overall stroke mortality reveals characteristic nonlinear relations,[3] also investigations dealing with hospitalizations should account for possible shape effects. Furthermore, the potential delayed effect of stroke events after temperature exposure has often been omitted with consequent incomplete study conclusions.

Another "typical" problem in epidemiological studies is the quality of weather/climatological data currently obtained from ground meteorologic stations. This approach limits the analyses on a restricted geographical area because most ground meteorologic variables (especially air temperature) suffer a limited spatial dependence starting from their measurement point and relying on land characteristics.

Atmospheric sciences have accurate and physically consistent tools that might solve this limitation: centralized homogenized data sets of gridded weather/climate data covering all globe surfaces and at different altitudes, briefly called "Reanalysis," provided by appropriate models that collect all available meteorologic observations.

Reanalysis products have played a major role in advancing climate science and are also being used in an increasing range of practical applications in sectors such as energy, agriculture, water resources, and insurance.[11,12] A few applications of Reanalysis to support epidemiological surveys already exist and particular attention was addressed to the evaluation of climate-related epidemic onset.[13,14] On the other hand, no such applications in environmental epidemiology of cerebrovascular diseases are reported in the scientific literature.

Received September 7, 2010; final revision received November 9, 2010; accepted November 30, 2010.

From the Interdepartmental Centre of Bioclimatology (M.M., P.A.M., G.F.G., S.O.), University of Florence, Firenze, Italy; the Institute of Biometeorology (A.C., R.V.), National Research Council, Firenze, Italy; Clinica Medica and Cardiologia (P.A.M., G.F.G.), University of Florence, Firenze, Italy; and Don Carlo Gnocchi Foundation, Centro S. Maria agli Ulivi, Onlus IRCCS, Pozzolatico, Italy (G.F.G., P.A.M.).

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.602037/DC1.

Correspondence to Marco Morabito, PhD, Interdepartmental Centre of Bioclimatology, University of Florence, Piazzale delle Cascine 18, 50144, Firenze, Italy. E-mail marco.morabito@unifi.it

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.602037**

Thanks to their intrinsic properties, Reanalysis data collected at a reasonable height asl allow the extension of environmental epidemiological surveys accounting for weather conditions over wide geographical areas, permitting large population-based studies.

The aim of this study was to retrospectively investigate the weather-related stroke events in a large sample of patients hospitalized in Tuscany (central Italy) during an 11-year period (1997 to 2007). For this purpose, the mentioned innovative source of weather data (Reanalysis) was used together with an original statistical approach accounting for the nonlinear effect of temperature and quantifying the prompt/delayed health effects of both cold and heat exposure.

Methods

Patient Data Analysis

This study was carried in Tuscany (central Italy), an area of approximately 22 990 km^2 and 3.5 million inhabitants.

Health outcome stroke data were provided during an 11-year period (1997 to 2007) by the Hospitalization Registry of the Tuscany Region. Patients with a primary discharge diagnosis coded by professional nosologists as stroke according to the International Classification of Diseases, 9th Revision, Clinical Modification (codes 430 to 438), together with the date of impatient discharge, gender, and birthday, were selected from all regional medical institutions.

Only data of people residing in Tuscany were considered. Stroke subtypes were categorized as subarachnoid hemorrhagic stroke (SHS; code 430), primary intracerebral hemorrhage (PIH; codes 431 to 432), ischemic stroke (IS; codes 433 to 435), and other stroke (codes 436 to 438).[15] Hospitalizations were stratified by age (<65 years; ≥ 65 years).

Weather Data

Daily average air temperature (T_{850hPa}) and geopotential height (Hgt_{850hPa}) were selected from the grid point located over Tuscany at 850-hPa atmospheric pressure level from the NCEP-DOE Reanalysis 2 Achieve.[16] The 850-hPa pressure level represents 1 of the lowest atmospheric layer generally considered in meteorology to evaluate ground weather characteristics. T_{850hPa} (°C) and Hgt_{850hPa} (m) represent reliable proxy of the average surface temperature and sea level pressure.

Hgt_{850hPa} represents the height where the isobaric measure corresponds to 850 hPa. The average altitude of Hgt_{850hPa} for the Italian latitudinal range is approximately 1500 m, but this value can change depending on the air mass characteristics moving in the atmosphere over the Earth's surface: an increasing/decreasing Hgt_{850hPa} indicates an increasing/decreasing sea level atmospheric pressure corresponding to high/low atmospheric pressure, respectively.

Statistical Analysis

All statistical analyses were made by R statistical software Version 2.8.1.

Variations of stroke hospitalizations among years, seasons, and days of the week were investigated by nonparametric analyses (Kruskal-Wallis and Wilcoxon test).

Weather-related stroke hospitalizations were initially investigated through generalized linear models[17] with Poisson link. Meteorologic input data were assessed by averaging T_{850hPa} and Hgt_{850hPa} measured on a specific day with the value measured the previous one (lag 0 to 1) and also day-to-day changes of meteorologic variables (ΔT_{850hPa} and ΔHgt_{850hPa}) were calculated. Temporal variables (years, seasons, and days of the week), public holidays, and summer population reduction due to holidays were considered as categorical factors. Daily hospitalizations were the dependent variables. Model selection was made by the step Akaike Information Criterion function ("MASS" R-package).

Generalized additive models[18] with a Poisson link were successively used to estimate smoothed shapes of exposure–response curves between stroke hospitalizations using predictors previously selected by the generalized linear model/step Akaike Information Criterion analyses. Break points,[19] corresponding to critical thresholds of weather variables were then identified.

With the aim to account the prompt or delayed effects on stroke hospitalizations of low/high temperatures and to quantify the possible "harvesting" effect, an innovative modeling approach named "constrained segmented distributed lag model"[20] was adopted. A maximum of 60 days was considered as a sufficient length of time to estimate all possible short-term excess/deficit due to either heat or cold exposure. A specific R-package, "modTempEff," was used.[20] Results are summarized showing the peak lag specific risks of cold/heat for a 1°C decrease/increase of T_{850hPa} below/above the previous identified temperature critical thresholds. Furthermore, a graphical representation of the distributed lag (DL) curves for cold and heat is also shown.

Results

Descriptive Statistic

Descriptive statistic is shown in the supplemental materials (available at http://stroke.ahajournals.org.). Highly significant fluctuations ($P<0.001$) of total stroke hospitalizations were observed among years, seasons, and days of the week. A progressive increase in hospitalizations going from 1997 to 2006, followed by a slight decrease in 2007 (respect to 2006), was observed. Minimum peaks of hospitalizations were observed during summer and on Sunday, whereas the maximum occurred on Monday.

Relationships Between Meteorologic Variables and Stroke

The generalized linear model/step Akaike Information Criterion procedure selected all meteorologic variables as independent predictors of all stroke events (Table 1).

Significant negative associations between T_{850hPa} and all stroke hospitalizations and particularly PIH ($P<0.001$) were observed with the greatest effect in people ≥ 65 years of age; a 5°C decrease of T_{850hPa} was related to 1.9% and 16.5% increase of all stroke and PIH, respectively. These associations were essentially linear and a steeper line in subjects ≥ 65 years of age hospitalized for PIH (Figure 1A) than for all stroke (Figure 1B) was observed.

Negative associations were also found when the Hgt_{850hPa} was considered (Table 1), but lower magnitudes than T_{850hPa} were noticed. Significant associations were observed when all stroke, IS, and other stroke were considered with a prevalent effect in people ≥ 65 years of age. These associations were nonlinear and with well-defined estimated break points. The steepest curve was evidenced when hospitalization for IS of subjects ≥ 65 years of age were considered (Figure 1C).

Concerning the potential effect of day-to-day changes of meteorologic variables on stroke hospitalizations, ΔHgt_{850hPa} was selected as a weak significant positive predictor of all stroke ($P=0.056$), other stroke, and people ≥ 65 years of age admitted for PIH. In these latter cases, a characteristic "U-shaped" relationship was observed (Figure 1D): the minimum hospitalization was observed when small negative ΔHgt_{850hPa} occurred; starting from this point, hospitalizations gradually increase as the ΔHgt_{850hPa} progressively decreased or increased.

Table 1. Generalized Linear Models: Estimate (±SE) and Statistical Probability Are Indicated for Selected Predictors*

Stroke	Meteorological Variables			
	T_{850hPa}	Hgt_{850hPa}	ΔHgt_{850hPa}	ΔT_{850hPa}
All stroke				
Total	−0.019 (±0.005)§	−0.009 (±0.004)†	0.006 (±0.003)	0.012 (±0.003)§
<65 years of age				
≥65 years of age	−0.021 (±0.006)§	−0.010 (±0.004)‡	0.005 (±0.003)	0.013 (±0.003)§
SHS				
Total				−0.019 (±0.012)
<65 years of age				
≥65 years of age				−0.023 (±0.008)‡
PIH				
Total	−0.139 (±0.015)§			−0.013 (±0.009)
<65 years of age	−0.054 (±0.011)§			−0.022 (±0.011)†
≥65 years of age	−0.140 (±0.016)§		0.014 (±0.010)	
IS				
Total		−0.017 (±0.005)§		0.019 (±0.005)§
<65 years of age				
≥65 years of age		−0.018 (±0.005)§		0.021 (±0.005)§
Other stroke				
Total		−0.008 (±0.005)	0.006 (±0.004)	0.015 (±0.004)§
<65 years of age				
≥65 years of age		−0.011 (±0.005)†		0.016 (±0.005)§

*Analyses were controlled for categorical variables: years, seasons, days of the week, celebrations, summer decrement of population. Blank area indicates that the meteorological variable was not selected as a model predictor after Akaike Information Criterion minimal selection.

†$P<0.05$.

‡$P<0.01$.

§$P<0.001$.

The generalized linear model/step Akaike Information Criterion also selected the ΔT_{850hPa} as a significant predictor of stroke hospitalizations. Highly significant positive relationships were observed for all stroke, IS, and other stroke, especially when people ≥65 years of age were considered; ΔT_{850hPa} increase of 5°C was associated with an increase of 1.2%, 1.5%, and 2.6% of all stroke, IS, and other stroke, respectively. A "J-shaped" association (Figure 2A), characterized by a sudden marked increased risk of hospitalization when the ΔT_{850hPa} exceeded +5°C, was observed; the estimated break point was higher in all strokes (Figure 2B) than in people ≥65 years of age (Figure 2C). A sudden increase of hospitalizations also occurred when ΔT_{850hPa} exceeded −5°C (Figure 2A) but in this case after reductions of hospitalizations for extreme negative ΔT_{850hPa} values were observed.

On the other hand, opposite ΔT_{850hPa} estimated values were observed when SHS and PIH were considered (Table 1): ΔT_{850hPa} was selected as a negative significant predictor of both people ≥65 years and <65 years of age hospitalized for SHS and PIH, respectively. In these cases, prevalent linear associations were observed; ΔT_{850hPa} decrease of 5°C was associated to an increase of 8.2% and 11.5% of SHS and PIH hospitalization, respectively.

Constrained Segmented DL Model

The average estimated T_{850hPa} thresholds (Table 2) where stroke hospitalizations were at their minimum were 8°C for the total number of stroke and people <65 years of age and 10°C for people ≥65 years of age corresponding to average ground level temperatures of 13°C and 16°C, respectively, during the period under study.

The lag at which the cold effect on hospitalization was greatest (peak lag) was limited to 7 days after exposure. A prompt cold effect (lag 0 to 2) on PIH hospitalization was observed (Table 2), also associated with the greatest cold effect among all outcomes and in particular for people ≥65 years of age. The estimated DL curve of cold effect on PIH (Figure 3A) clearly showed a short-term "harvesting" effect across lag 3 to 6. The harvesting effect occurs when a positive association at short lags (positive lag-specific DL coefficients) is followed by negative associations at longer lags (negative lag-specific DL coefficients), which should suggest a "deficit" of hospitalization. Then DL coefficients tended to zero at longer lags (Figure 3A).

A completely different situation was observed for the heat effect. In this case, a delayed heat effect on hospitalizations was observed; the greatest heat peak lag was only observed 2 (PIH; Figure 3B), 3 (SHS), or more weeks after the heat exposure. The magnitude of the heat effect was in most cases

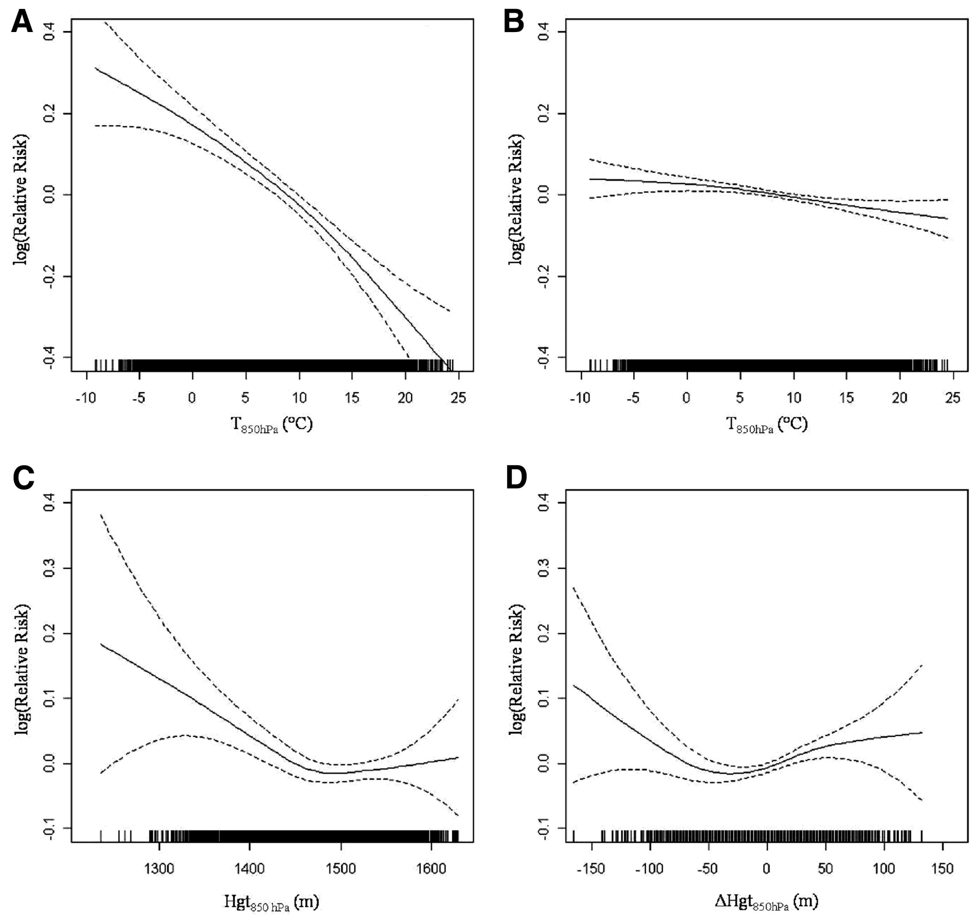

Figure 1. Relationship between smoothing plots of air temperature (T_{850hPa}), geopotential height (Hgt_{850hPa}), and day-to-day change of geopotential height (ΔHgt_{850hPa}), against subjects ≥65 years of age hospitalized for primary intracerebral hemorrhage (A, D), all stroke (B), and IS (C). The geopotential height considered in this study represents the height at which the isobaric measure corresponds to 850 hPa (averagely 1500 m asl). An increasing/decreasing Hgt_{850hPa} indicates an increasing/decreasing sea level atmospheric pressure, corresponding to high/low atmospheric pressure, respectively.

very weak and often significantly lower than that observed for the cold effect (Table 2).

Discussion

This study provides helpful results to clarify several discordances among previous studies and supports a recent review,[10] which reported that the influence of climate/weather on cerebrovascular risk is biologically plausible.

One of the major contribution to this study derives by the use of an innovative source of meteorologic data (Reanalysis). Thanks to the main characteristics of the Reanalysis (reduced spatial meteorologic variability, data are uniform, homogeneous, and continuous), it was possible to perform this study over a wide geographical area.

The main findings are:

(1) Both daily averages and day-to-day changes of T_{850hPa} and Hgt_{850hPa} were selected as independent predictors of all stroke occurrences with a prevalent effect on people ≥65 years of age.

(2) Differences in weather-related hospitalizations for specific stroke subtypes were observed:

- T_{850hPa} decrease was linearly associated with PIH increases.
- Hgt_{850hPa} decrease was nonlinearly associated with IS and other stroke increases.
- ΔHgt_{850hPa} disclosed characteristic "U-shaped" relationships with PIH and other stroke.
- ΔT_{850hPa} revealed "J-shaped" associations with IS and other stroke but also showed negative linear relationships with SHS and PIH.

(3) A short-term cold effect on hospitalizations limited to 1 week after exposure was observed; on the other hand, delayed and very weak heat effects were observed.

It is reasonable to hypothesize that the temporal variability of stroke events cannot be attributed to a single cause, but it is an expression of interacting multifactorial causes, in which changeable and unchangeable stroke risk factors as well as environmental factors are involved. In particular, age per se is an important independent risk factor for stroke. In a recent European large population-based study,[21] the authors evidenced that some important stroke risk factors such as the prevalence of hypertension, diabetes mellitus, coronary heart disease, and, in man, atrial fibrillation decreased in subjects >70 to 80 years of age. Notwithstanding in the present study, the weather was selected as a significant predictor of stroke events, especially in the elderly population, suggesting an

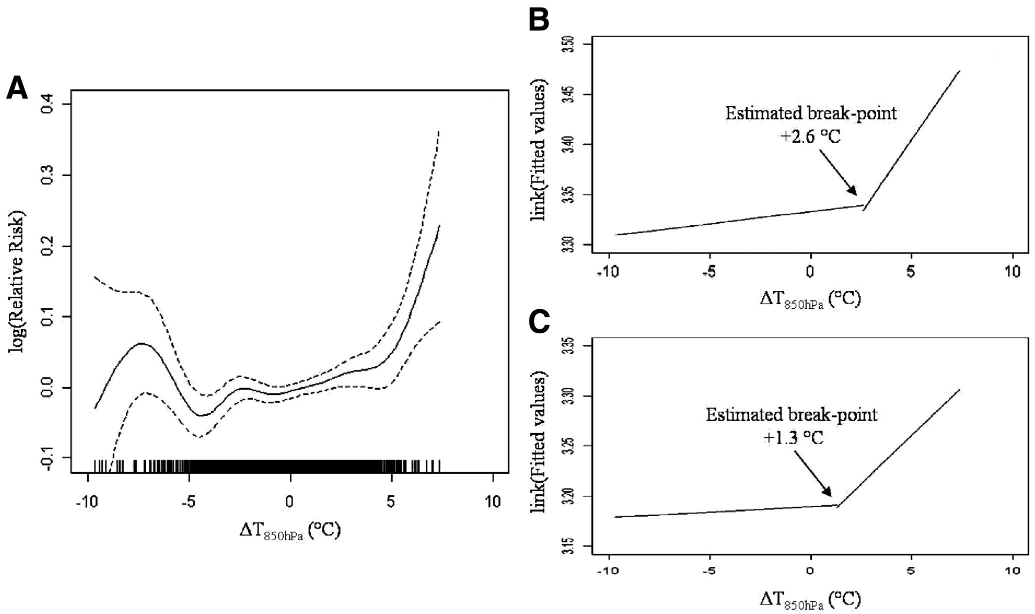

Figure 2. The relationship between the smoothing plot of day-to-day change of air temperature (ΔT_{850hPa}) against all stroke hospitalizations (A). Estimated break points (critical thresholds) in all stroke (B) and in people ≥65 years of age (C).

aggravating effect of the environment on stroke occurrences. On the other hand, the prevalence of traditional cardiovascular risk factors, including smoking, alcohol, and obesity, evidenced in patients <60 years of age,[21] might play a major role on risk of stroke in younger subjects.

Effect of Air Temperature

The association between T_{850hPa} decrease and PIH emphasized in this study agrees with previous findings in different population and geographical areas of Asia,[2,9] Europe,[1,7] and North America.[22] Despite elevated blood pressure and in-

Table 2. The Constrained Segmented DL Model

Outcome	Estimated T_{850hPa} Thresholds, °C	Percent Change in Hospitalization per 1°C Decrease/Increase of T_{850hPa} Below/Above the Threshold (95% CI) — Cold Effect: Peak Lag	Cold Effect: Effect at Peak Lag	Heat Effect: Peak Lag	Heat Effect: Effect at Peak Lag
All stroke					
Total	9.5	4	0.10 (0.06–0.15)	60	0.03 (0.01–0.05)
<65 years of age	8.2	7	0.12 (0.03–0.22)	20	0.02 (0.00–0.05)
≥65 years of age	17.1	2	0.15 (0.07–0.23)	60	0.00 (0.00–0.01)
SHS					
Total	7.8	7	0.24 (0.00–0.47)	22	0.02 (−0.06–0.10)
<65 years of age	6.0	7	0.00 (0.00–0.00)	20	0.00 (0.00–0.00)
≥65 years of age	8.0	7	0.19 (−0.01–0.39)	29	0.00 (0.00–0.00)
PIH					
Total	5.4	0	1.34 (0.87–1.80)	15	0.02 (0.00–0.04)
<65 years of age	2.9	0	0.77 (0.16–1.37)	16	0.00 (0.00–0.00)
≥65 years of age	13.4	0	1.45 (0.98–1.90)	15	0.02 (0.00–0.04)
IS					
Total	2.9	5	0.20 (0.02–0.39)	60	0.04 (0.04–0.05)
<65 years of age	6.2	6	0.13 (0.02–0.24)	48	0.15 (0.07–0.23)
≥65 years of age	1.4	5	0.21 (0.06–0.36)	60	0.04 (0.01–0.06)
Other stroke					
Total	13.6	3	0.22 (0.12–0.31)	60	0.00 (0.00–0.00)
<65 years of age	18.4	4	0.02 (−0.08–0.03)	52	0.00 (0.00–0.00)
≥65 years of age	11.3	3	0.28 (0.17–0.39)	38	0.26 (0.07–0.45)

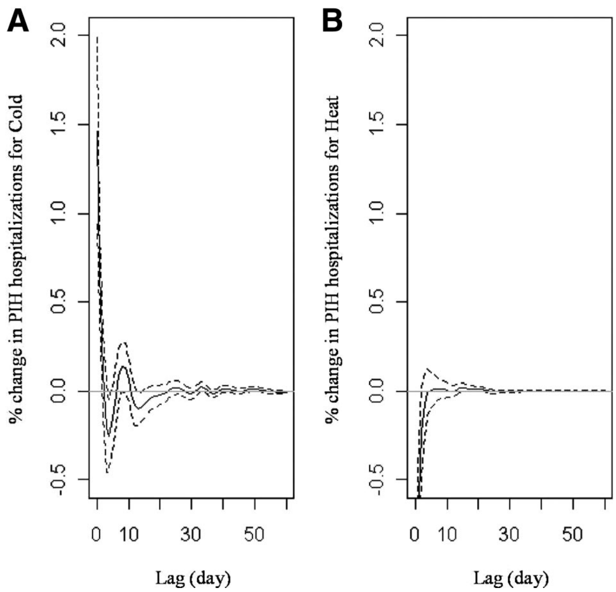

Figure 3. Estimated distributed lag curves of cold (A) and heat (B) effect on subjects ≥65 years of age hospitalized for PIH.

creased blood lipids associated with low temperatures[23,24] that might be hypothesized as possible contributing mechanisms of PIH, several authors[9] evidenced that the relationship between low temperature and intracerebral hemorrhage was also significant after adjustment for blood pressure and total cholesterol. For this reason, it is also plausible that other biological reactions to cold conditions might contribute to explain the underlying pathophysiology responsible for this relationship. Other authors[25] recently investigated the potential rule played by short-term temperature changes and found that a variation of 3°C within 24 hours before the ictus increased the incidence of stroke. This value was found similar to the estimated break points (critical thresholds) identified in this study, in which a characteristic "J-shaped" association between ΔT_{850hPa} and all stroke hospitalizations was observed; a lower critical ΔT_{850hPa} threshold in subjects ≥65 years of age (1.3°C) than in the total sample (2.6°C) was observed. This means that elderly people might experience a stroke event in advance when day-to-day increases of air temperature occur. The marked increase of stroke hospitalizations observed when the ΔT_{850hPa} exceeded 5°C (Figure 2) might appear contradictory with the significant increase of all stroke observed in this study when the T_{850hPa} decreases. This apparent contradiction is solved knowing that most of ΔT_{850hPa} increases exceeding 5°C (94% of days) occurred during the coldest months of the year (October to March) and never during warmer months (June to September). This means that stroke increased when substantial increase of ΔT_{850hPa} started from a relatively low daily average temperature value, typical of the coldest months of the year. These day-to-day temperature changes may be associated with behavioral changes that in turn might influence the risk of stroke hospitalization.[26] This hypothesis is supported by another study[27] that demonstrated that the highest winter blood pressure followed a sudden day-to-day air mass change: from anticyclonic weather (settled, cloudless and cold weather) to a cyclonic one (unstable, cloudy, and mild weather). In this condition, the thermal perception of people might be especially worsened if subjects are surprised in outdoor environment with inappropriate clothing. Correct clothing behavior was indeed reported to contribute in preventing the excess winter mortality.[3]

Furthermore, it is already known that, especially when cold conditions are considered, the temperature effect on mortality is not limited to the same-day exposure but it shows a well-observed DL effect.[28] The application in the present study of a new modeling approach, which accounts for the nonlinear effect of temperature and the DL of heat and cold exposures, allowed to demonstrate the deeper cold effect on stroke hospitalizations than the heat effect. Several authors[28] showed a sustained and distributed cold effect on mortality across a 60-day period in other cities. On the other hand, in the present study, the cold effect on stroke hospitalizations was less distributed and limited to 1 week after exposure. The reason of this discrepancy is probably because most patients with stroke die several days or months after hospitalization.

Moreover, hospitalizations for PIH revealed the highest temperature dependence among stroke subtypes showing a prompt cold effect (lag 0 to 2) followed by a short-term harvesting effect. This phenomenon has been previously described in studies concerning the heat effect on mortality[28] and at our knowledge this is the first time that the harvesting effect is also described for cold-related hospitalizations. This short-term "deficit" of hospitalizations across lag 3 to 6 suggests that several frail people vulnerable to cold effects (such as those with pre-existing cardiovascular risk factors) may be expected to be hospitalized anyway within a short-term period.

Effect of Atmospheric Pressure

Only few scientific evidences on the potential influence of atmospheric pressure on stroke have been reported.[4,6] Nevertheless, the observed significant increase of IS when the Hgt_{850hPa} decreased (meaning a sea level decrease of atmospheric pressure) was in accordance with a Russian study.[4] These authors also concluded that any decrease in air pressure represents an important predictor of all stroke. The "U-shaped" relationship of ΔHgt_{850hPa} with stroke events disclosed in this study supports findings from a recent European study[6] and help to clarify discordances among previous research. At the moment, the physiological mechanisms to describe the relationship between atmospheric pressure and stroke are still unexplained and only theoretical hypotheses have been proposed.[10]

Strengths and Limitations of the Study

The main strength of this study was the use of Reanalysis data derived by modeling different sources of measured meteorologic data. A good agreement between observed surface meteorologic variables and National Oceanic and Atmospheric Administration Reanalysis data has clearly been shown.[29] The Reanalysis approach might allow several useful advantages in environmental epidemiology: (1) great weather space–temporal data availability all over the

Globe starting from 1979; (2) data are uniform because assessed by using the same methodology, which reflects the state-of-the-art analysis/forecast system to perform data assimilation; and (3) data are homogeneous, continuous, and without any lack.

All these characteristics allow large population-based studies over wide geographical areas. Moreover, because Reanalysis data are interpolated onto a system of grids and are ready for operative forecast systems, results can simply be implemented for biometeorological/epidemiological purposes.

This study has also several potential limitations. It is expected that there is misclassification of the outcome because of inaccurate discharge diagnosis codes. However, accuracy and reliability of International Classification of Diseases, 9th Revision codes for identifying stroke in Italian healthcare databases have been previously evaluated[15,30] and agreement was substantial for the whole code group 430 to 438 and for specific stroke subtypes. Furthermore, it was not known the exact time of onset of stroke and data on nonhospitalized cases and those who died before admission were not available for the analyses.

The potential impacts of other environmental variables such as atmospheric pollutions as well as airborne allergens were not considered in this study. Although these variables are strongly interrelated with weather conditions, their individual effect might potentially contribute to increase the risk of stroke admissions.[5] The very weak heat effect on stroke occurrences evidenced in this study might hide a pollution effect and in particular the potential short-term effect of ozone air pollution.[31] However, heterogeneity of the pollution effect and sometimes conflicting results have been noted.[32,33] In Tuscany, both environmental pollutions and airborne allergens data are discontinuously monitored, generally covering limited geographical areas (the main urban areas). For these reasons, these data are not associated with Reanalysis data applied in this study. Further investigations might be performed over limited geographical areas and for short time periods also taking into consideration the potential contribution of other atmospheric (ie, pollution and pollens) and meteorologic (ie, humidity and wind) variables or even the microclimate nearest to the subject, which should represent the real individual exposure that does not necessarily correspond to the environmental meteorologic conditions.

Another limitation is that other potential confounders such as influenza epidemics or other respiratory infections were not directly considered in this study. Infections are strongly related to the season with a prevalence at our latitude during winter.[34] Despite in the current study that the analyses were controlled for several temporal variables such as the season, residual confounding by short-term respiratory epidemics remains a possibility.

Conclusions

This study highlights the influence of meteorologic conditions on stroke occurrences and provides further information helpful to enhance knowledge on this complex and still controversial phenomenon. Weather has a different impact on specific stroke subtypes, confirming the fact that stroke is a heterogeneous condition. Characteristic U- and J-shaped weather associations with stroke events and, for the first time, a clear short-term harvesting effect for cold-related PIH hospitalizations were described. Because all these findings have been obtained by using an innovative source of meteorologic data (Reanalysis) directly interpolated onto a grid of a weather forecast system, results from epidemiological studies can simply be implemented in operative forecast systems for biometeorological purposes. The development of public health strategies to minimize the weather-related stroke risk represents a strategic preventive health plan.

Acknowledgments

We thank the National Oceanic and Atmospheric Administration/Outstanding Accomplishments in Research/Earth System Research Laboratory Physical Sciences Division, Boulder, CO, for providing NCEP_Reanalysis 2 data (www.esrl.noaa.gov/psd/).

Sources of Funding

This study was supported and granted by the National Strategic Programme "Environment and Health" (Ministero della Salute-Ricerca Finalizzata 2006 ex art 12 D.Lgs 502/92) and by the Regional MeteoSalute Project, Regional Health System of Tuscany.

Disclosures

None.

References

1. Capon A, Demeurisse G, Zheng L. Seasonal variation of cerebral hemorrhage in 236 consecutive cases in Brussels. *Stroke*. 1992;23:24–27.
2. Chen ZY, Chang SF, Su CL. Weather and stroke in a subtropical area: Ilan, Taiwan. *Stroke*. 1995;26:569–572.
3. The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. *Lancet*. 1997;349:1341–1346.
4. Feigin VL, Nikitin YP, Bots ML, Vinogradova TE, Grobbee DE. A population-based study of the associations of stroke occurrence with weather parameters in Siberia, Russia (1982–92). *Eur J Neurol*. 2000;7:171–178.
5. Low RB, Bielory L, Qureshi AI, Dunn V, Stuhlmiller DF, Dickey DA. The relation of stroke admissions to recent weather, airborne allergens, air pollution, seasons, upper respiratory infections, and asthma incidence, September 11, 2001, and day of the week. *Stroke*. 2006;37:951–957.
6. Jimenez-Conde J, Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Subirana I, Roquer J. Weather as a trigger of stroke. Daily meteorological factors and incidence of stroke subtypes. *Cerebrovasc Dis*. 2008;26:348–354.
7. Saloheimo P, Tetri S, Juvela S, Pyhtinen J, Hillbom M. Seasonal variation of intracerebral haemorrhage in subjects with untreated hypertension. *Acta Neurol Scand*. 2009;120:59–63.
8. Giua A, Abbas MA, Murgia N, Corea F. Climate and stroke: a controversial association. *Int J Biometeorol*. 2010;54:1–3.
9. Matsumoto M, Ishikawa S, Kajii E. Cumulative effects of weather on stroke incidence: a multi-community cohort study in Japan. *J Epidemiol*. 2010;20:136–142.
10. McArthur K, Dawson J, Walters M. What is it with the weather and stroke? *Expert Rev Neurother*. 2010;10:243–249.
11. Schwartz MN, George RL. On the Use of Reanalysis Data for Wind Resource Assessment. NREL/CP-500-25610. Golden, CO: National Renewable Energy Laboratory; 1998. Available at: www.nrel.gov/docs/fy99osti/25610.pdf. Accessed November 9 2010.
12. Challinor AJ, Wheeler TR, Slingo JM, Crauford PQ, Grimes D. Simulation of crop yields using ERA-40: limits to skill and nonstationarity in weather-yield relationships. *J Appl Meteor*. 2005;44:516–531.
13. Rhodes CJ, Hollingsworth TD. Variational data assimilation with epidemic models. *J Theor Biol*. 2009;258:591–602.

14. Shaman J, Pitzer VE, Viboud C, Grenfell BT, Lipsitch M. Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biol*. 2010;8:e1000316.
15. Leone MA, Gaviani P, Ciccone G. Inter-coder agreement for ICD-9-CM coding of stroke. *Neurol Sci*. 2006;27:445–448.
16. Kanamitsu M, Ebisuzaki W, Woollen J, Yang SK, Hnilo JJ, Fiorino M, Potter GL. NCEP-DEO AMIP-II Reanalysis (R-2). *Bul of the Atmos Met Soc*. 2002:1631–1643.
17. McCullagh P, Nelder JA. *Generalized Linear Models,* 2nd ed. London: Chapman and Hall; 1989.
18. Hastie T, Tibshirani R. Generalized additive models in medical research. *Stat Methods Med Res*. 1995;4:187–196.
19. Muggeo VM. Estimating regression models with unknown break-points. *Stat Med*. 2003;22:3055–3071.
20. Muggeo VM. Analyzing temperature effects on mortality within the R environment: The constrained segmented distributed lag parameterization. *J Stat Softw*. 2010;32:1–17.
21. Andersen KK, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40 102 patients with first-ever ischemic stroke. A Nationwide Danish Study. *Stroke*. 2010;41:2768–2774.
22. Ramirez-Lassepas M, Haus E, Lakatua DJ, Sackett L, Swoyer J. Seasonal (circannual) periodicity of spontaneous intracerebral hemorrhage in Minnesota. *Ann Neurol*. 1980;8:539–541.
23. Modesti PA, Morabito M, Bertolozzi I, Massetti L, Panci G, Lumachi C, Giglio A, Bilo G, Caldara G, Lonati L, Orlandini S, Maracchi G, Mancia G, Gensini GF, Parati G. Weather-related changes in 24-hour blood pressure profile: effects of age and implications for hypertension management. *Hypertension*. 2006;47:155–161.
24. Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. *Clin Sci (Lond)*. 1994;86:43–48.
25. Coelho FM, Santos BF, Cendoroglo Neto M, Lisboa LF, Cypriano AS, Lopes TO, Miranda MJ, Avila AM, Alonso JB, Pinto HS. Temperature variation in the 24 hours before the initial symptoms of stroke. *Arq Neuropsiquiatr*. 2010;68:242–245.
26. Ebi KL, Exuzides KA, Lau E, Kelsh M, Barnston A. Weather changes associated with hospitalizations for cardiovascular diseases and stroke in California, 1983–1998. *Int J Biometeorol*. 2004;49:48–58.
27. Morabito M, Crisci A, Orlandini S, Maracchi G, Gensini GF, Modesti PA. A synoptic approach to weather conditions discloses a relationship with ambulatory blood pressure in hypertensives. *Am J Hypertens*. 2008;21:748–752.
28. Muggeo VM, Hajat S. Modelling the non-linear multiple-lag effects of ambient temperature on mortality in Santiago and Palermo: a constrained segmented distributed lag approach. *Occup Environ Med*. 2009;66:584–591.
29. Kalnay E, Cai M. Impact of urbanization and land-use change on climate. *Nature*. 2003;423:528–531.
30. Leone M, Capponi A, Varrasi C, Tarletti R, Monaco F. Accuracy of the ICD-9 codes for identifying TIA and stroke in an Italian automated data base. *Neurol Sci*. 2004;25:281–288.
31. Henrotin JB, Besancenot JP, Bejot Y, Giroud M. Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France. *Occup Environ Med*. 2007;64:439–445.
32. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke*. 2005;36:2549–2553.
33. Oudin A, Strömberg U, Jakobsson K, Stroh E, Björk J. Estimation of short-term effects of air pollution on stroke hospital admissions in Southern Sweden. *Neuroepidemiology*. 2010;34:131–142.
34. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. *Stroke*. 2003;34:2518–2532.