## **ORIGINAL ARTICLE**

## Effect of environmental temperature variation on cerebrovascular disease

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## ABSTRACT

**Introduction:** cerebrovascular disease is a neurological emergency that requires immediate diagnosis and therapeutic intervention, sometimes influenced by changes in weather and climate.

**Objective:** to describe the relationship between temperature and atmospheric pressure with admissions and deaths due to cerebrovascular disease.

Methods: a cross-sectional descriptive study was developed in the "Mártires del 9 de abril" Hospital of the Sagua la Grande Municipality in the period between 1993 and 2017. The universe of hospitalized patients with this diagnosis was 3719; we worked with the population, no sample was selected. The review of individual medical records was performed with the aim of collecting data of interest related to the variables under study. The prognosis of admissions and deaths was modeled using the Objective Regression Regression methodology.

Results: a statistical description of these two variables was made. The mean number of admissions was 148.7 cases, with a standard deviation of 24.9. The mean number of deaths was 35.7 with a standard deviation of 13.2.

**Conclusions:** as the minimum temperature increases, admissions and deaths increase, so this impact is related to climate change. In the case of admissions, as atmospheric pressure increases, the number of admissions decreases.

**Key words:** cerebrovascular disease; climate effects; climate impact; income; deaths

#### **RESUMEN**

Introducción: la enfermedad cerebrovascular es una urgencia neurológica que requiere un diagnóstico y una intervención terapéutica inmediatos, en ocasiones se encuentra influenciada por los cambios del tiempo y el clima.

**Objetivo:** describir la relación entre temperatura y presión atmosférica con los ingresos y fallecidos por enfermedad cerebrovascular.

**Métodos:** se desarrolló un estudio descriptivo transversal en el Hospital "Mártires del 9 de abril" del Municipio de Sagua la Grande en el período comprendido entre 1993 y 2017. El universo de pacientes hospitalizados con este diagnóstico fue de 3719; se trabajó con la población, no se seleccionó muestra. Se realizó la revisión de las historias clínicas individuales con el objetivo de recoger los datos de interés relacionados con las variables en estudio. Para el pronóstico de los ingresos como para el de los fallecidos se modeló utilizando la metodología de la Regresión Objetiva Regresiva.

**Resultados:** se realizó una descripción estadística de estas dos variables. La media de los ingresos fue de 148,7 casos, con una desviación estándar de 24,9. Los fallecidos tuvieron como media 35,7 con una desviación estándar de 13,2.

**Conclusiones:** a medida que aumenta la temperatura mínima aumentan los ingresos y los fallecidos, por lo que este impacto está relacionado con el cambio climático. En el caso de los ingresos a medida que la presión atmosférica aumenta la cantidad de ingresos disminuye.

**Palabras clave:** enfermedad cerebrovascular; efectos del clima; impacto climático; ingresos; fallecidos

## **INTRODUCTION**

Cerebrovascular disease (CVD) is a syndrome that includes a group of heterogeneous diseases with a common point: an alteration in the vasculature of the central nervous system leading to an imbalance between oxygen supply and oxygen requirements and resulting in focal dysfunction of the brain tissue; on the other hand, it refers to the nature of the lesion and is classified into two major groups: ischemic and hemorrhagic.<sup>(1)</sup>

In studies carried out in Europe, Russia, Australia and the United States, the worldwide incidence of CVD was estimated at 300 to 500 x 105 inhabitants per year, between 45 and 84 years of age. Every 10 years, the incidence increases significantly above 35 years of age and triples to 3000 x 105 inhabitants in individuals over 85 years of age. The incidence of cases/year in the United States is 531 to 730 000, in Germany 127 000, in Italy 112 000, in the United Kingdom 101 000, in Spain 89 000, in France 78 000, in Poland 60 000 and in Japan 55 000. In Brazil, the crude CVD mortality rate has increased over the last three decades;<sup>(2)</sup> in Peru, the authors report that about 90% of strokes are associated with modifiable risk factors in which prevention is essential.<sup>(3)</sup>

In Cuba, in 2020, there were 10 821 deaths, with a crude rate of 90.4 x 100 000 inhabitants, and an adjusted rate of 39.7 x 100 000 inhabitants. In the province of Villa Clara, in that year, the total number of deaths from this cause was 668, for a crude rate of 85.9 x 100 000 inhabitants (Anuario Estadístico de Salud, 2021).<sup>(4)</sup>

Stroke is caused by risk factors that, when affecting a patient, trigger it;<sup>(5)</sup> triggering or predisposing factors are those that, when affecting vulnerable patients who present several risk factors, are capable of starting or provoking a disease crisis. One component of the physical environment (environment) that potentially influences diseases of the circulatory system is local meteorological

variables. This influence is both direct and indirect and can act either positively or negatively.

One of the diseases that, according to multiple research results, is also influenced by changes in weather and climate, are cerebrovascular diseases.<sup>(6)</sup>

Temperature and its variation cannot be categorized as risk factors, but as triggering factors capable of causing a stroke in patients with risk factors and low adaptive capacity. Elderly patients are, for this reason, the most vulnerable group.<sup>(7,8)</sup>

In relation to cardiovascular morbidity and mortality some investigators have reported higher incidence of myocardial infarction and cerebral vascular events during the cold winter months in countries with extreme climates, but also in other regions with warmer temperatures.<sup>(9)</sup>

Seasonal variation in CVD reflects a complex interaction between individual susceptibility, both physiological and behavioral, and a wide range of environmental factors, most notably temperature.

Low temperatures activate the sympathetic nervous system and increase the secretion of catecholamine, a hormone responsible for increasing heart rate and thus cardiac output. This causes a change in blood composition and increases blood pressure, cholesterol, and fibrinogen in the blood, a protein responsible for clot formation.<sup>(10)</sup>

It is necessary to investigate the effects of variations in environmental temperature on human health, which are seen with greater incidence due to climate change and have a direct impact on cerebrovascular disease.

The aim of this study is to describe the relationship between temperature and atmospheric pressure with admissions and deaths due to cerebrovascular disease.

## **METHODS**

A cross-sectional descriptive study was developed in the "Martires del 9 de abril" University Hospital in the Municipality of Sagua la Grande, Villa Clara Province, in the period between 1993 and 2017.

The universe of hospitalized patients with a diagnosis of CVD was 3 719; we worked with the population, no sample was selected (in a first stage 700 patients, in a second stage 1 656 and in a third stage 1 363).

The study employed theoretical and empirical methods that, with elements of qualitative and quantitative approaches, allowed the research to be carried out. Theoretical methods

- Analysis-synthesis: allowed the analysis of theoretical sources and basic contents to go deeper into cerebrovascular disease (CVD) and its relationship with meteorological variables, in addition to being used in the interpretation of the diagnostic results, the elaboration of the proposal and the arrival at partial and final conclusions.
- Induction-deduction: it favored reflection on the definitions considered in the construction of the theoretical framework, establishing the relationship between the particular and the general.

- Historical-logical: it allowed the historical study of the different concepts and definitions of CVD, the historical evolution of research relating health, meteorological variables, the periodization of the different trends in the world, Latin America and Cuba and their location in a timeline.

Empirical methods

 Document analysis: a review of the individual medical records of each patient was carried out in order to collect the data of interest related to the variable under study. The author elaborated a data collection model to collect the information in the three stages of the research.

For the prognosis of admissions and deaths, we used the Objective Regressive Regression (ORR) methodology and created, in a first step, dichotomous variables DS, DI and NoC in which:

NoC- number of base cases,

DS=1 if NoC is odd, DI=0 if NoC is even, when DI=1, DS=0 and vice versa.

Subsequently, the module corresponding to the Regression analysis of the statistical package SPSS version 19.0 (IBM Company, 2010) was executed, specifically the ENTER method, by which the predicted variable and the ERROR are obtained.

Then the autocorrelations of the variable ERROR were obtained, paying attention to the maximums of the significant partial autocorrelations PACF. The new variables were then calculated according to the significant Lag of the PACF. Finally, these regressed variables were included in the new regression in a process of successive approximations until a white noise in the regression errors was obtained.

The data correspond to the years from 1993 to 2017 and belong to a Hospital in Sagua La Grande, Villa Clara, Cuba. The climatic variables correspond to the same period from the Sagua la Grande Meteorological Station (latitude: 22°13' N, longitude: 80°02' W).

The Research Ethics Committee of the institution analyzed and endorsed its development and the Provincial Scientific Council accepted the research project.

## RESULTS

# Statistical description of the variables annual deaths and admissions for cerebrovascular diseases

Table 1 shows the descriptive statistics for the mean number of admissions and deaths per year due to cerebrovascular disease in Sagua la Grande. There is a higher number of admissions (mean is 148.7 cases, with a standard deviation around the mean values of 24.9); decedents have mean 35.7, with a standard deviation of 13.2. There are 25 years in total, from 1993 to 2017.

**Table 1.** Descriptive statistics of the number of admissions and deaths due to cerebrovascular diseases

	Minimum	Maximum	Average	Standard deviation
Income	109	201	148.76	24.887
Deceased	21	71	35.72	13.234

#### Description of a ROR model for income. Impact of climate

The model explains 99.5% of the variance explained, with an error of 18 cases (Table 2). The Durbin Watson statistic is close to two, so it could be considered that there is no more information to add in the residuals.

Model	R	R square <sup>b</sup>	R-squared corrected	Standard error of estimation	Durbin-Watson
1	.995ª	.989	.986	17.946	1.586

Table 2. Summary of the ROR model for the income variable

<sup>a</sup> Predictor variables: LAG4PatmSagua, Step23, DI, NoC, LAG4TminSagua

<sup>b</sup> For regression through the origin (the model without an intersection term) R-squared measures the proportion of the variability of the dependent variable explained by regression through the origin

Dependent variable: income

Fisher's F is significant at 99%, with a value of 295.55 p<0.001, so it is a valid model

Table 3 shows the parameters of the model. All the variables are significant: there is a tendency for the annual income to decrease as the minimum temperature increases, four months back the number of income increases and the expert criterion given above is corroborated. As the minimum temperature increases by 1°C, income increases in 36 cases.

Model	Non-standardized coefficients B Standard error		Typified coefficients Beta	t	Sig.		
DI	-6.869	8.165	031	841	.413		
NoC	-1.384	.698	147	-1.982	.065		
LAG4TminSagua	36.132	10.670	4.781	3.386	.004		
Step23	-2.316	19.769	003	117	.908		
LAG4PatmSagua	546	.215	-3.635	-2.534	.022		

#### **Table 3.** Income ROR model coefficients

Dependent variable: income Linear regression through the origin

As for the results for the variable number of admissions for cerebrovascular disease, Figure 1 shows the model with its prognosis, values that are very similar at first glance. If the trend continues, the number of admissions would decrease. Both the model containing the minimum temperature<sup>(14)</sup> and the one containing the atmospheric pressure obtain equal results; however, as the atmospheric pressure increases by 2hPa the number of admissions decreases in one case.

## **Description of a ROR model for deceased persons. Climate impact**

Table 4 shows the parameters of the model. All variables are significant except the trend (NoC) which, although negative, is not significant, is case 23, which was not significant, but was left in the sample for statistical indications. The minimum temperature regressed on four years (LAG4TminSagua) and the maximum temperature regressed on two (lag2TmaxSagua) enter the model. As both maximum and minimum temperatures increase, the number of fatalities increases. When the minimum temperature increases by 1°C, fatalities increase by nine

cases, while when the maximum temperature increases by  $1^{\rm o}{\rm C},$  fatalities increase by 11.6 cases.



Figure 1. Actual value and forecast for annual revenues

Model		Unstandardized coefficients		Typified coefficients	t	Sig.
		В	Error típico	Beta		
1	DS	-484.927	138.669	-10.043	-3.497	.003
	DI	-487.745	138.044	-9.631	-3.533	.003
	NoC	397	.380	184	-1.047	.312
	LAG4TminSagua	9.072	5.109	5.233	1.776	.096
	Step23	-12.375	9.526	077	-1.299	.214
	LAG2TmaxSagua	11.588	3,703	9.825	3.129	.007

Table 4. Coefficients of the ROR model of deceased persons

Dependent variable: deceased; Linear regression through the origin

## DISCUSSION

Weather conditions influence people directly and indirectly, and are recognized as a precipitating factor for human health because they have the capacity to produce specific effects on the physiology of vulnerable or meteorologically labile individuals. The predisposing effects of meteorological conditions on human health capable of producing significant increases in daily morbidity and mortality from various chronic and communicable diseases are referred to as meteorotropic effects.

The magnitude and extent of the risk associated with meteorotropic effects depends on the hazard posed by the predisposing meteorological conditions, which act as an external factor, as well as on the vulnerability of the exposed individuals, which is determined for two different options:<sup>(11)</sup>

- a) Individual vulnerabilities associated with poorly modifiable risk factors such as age, sex, height, weight, body mass index and circadian rhythm characteristics. If reliable data on the presence of comorbidities and personal practice of unhealthy habits (smoking, alcoholism, drugs) are available, the personalized assessment of vulnerabilities can be adequately expanded;
- b) Collective or regional vulnerability calculated by considering the overall excess mortality rate as the indicator for a selected territory.

### **ROR model description for income. Impact of climate**

The model explains that all the variables are significant and there is a tendency for the annual income to decrease; as the minimum temperature increases four months ago, the number of incomes increases. This corroborates the expert criterion given above. With an increase of 1°C in the minimum temperature, admissions increase by 40.52 cases.

Throughout their lives, human beings maintain their body temperature within very narrow limits of variation and are protected at all costs. To maintain internal temperature within these limits, humans have developed highly effective physiological and, in some cases, specialized responses to acute heat stress. The purpose of these responses is to facilitate the conservation, production, or elimination of body heat.<sup>(12)</sup>

High temperatures cause excessive sweating which reduces plasma volume and causes blood pressure to drop. The sudden rise in temperature also causes an increase in the viscosity of the blood concentration of cholesterol and the amount of erythrocytes and platelets.<sup>(13)</sup>

The increase in blood viscosity and the slowing of blood circulation are the main pathophysiological aspects that link the increase in temperature with cerebrovascular disease and, particularly, with those of ischemic etiology.

## Description of a ROR model for the deceased. Impact of climate

The model explains that all variables are significant. The minimum temperature regressed in four years (LAG4TminSagua) and the maximum temperature regressed in two years (lag2TmaxSagua) are included in the model. Table 4 shows the model with its forecast; these values have a great coincidence at first sight. If the trend continues, the number of deaths would decrease.

As both maximum and minimum temperatures increase, the number of deaths increases. When the minimum temperature increases by 1°C, the number of deaths increases by nine cases, while when the maximum temperature increases by 1°C, the number of deaths increases by 11.6 cases.

The critical point in the pathophysiology of ischemic cerebrovascular disease is the decrease in cerebral blood flow (CBF). Meteorological variables such as temperature can cause an increase in viscosity and slowing of circulation, which in a patient with previous circulatory deterioration due to arteriosclerosis can favor thrombus formation and trigger the crisis. We cannot fail to mention the effects of low temperatures that could increase circulation and blood pressure, fracture pre-existing atheroma plaques and provoke thrombotic effects or, based on their incidence in the cardiovascular system, provoke arrhythmias or worsen existing ones, thus favoring the formation of emboli.

Temperature and its variation cannot be catalogued as risk factors, but as triggering factors capable of causing a stroke in patients with risk factors and low adaptive capacity. Elderly patients are, for this reason, the most vulnerable group.<sup>(14)</sup>

Seasonal variation in CVD reflects a complex interaction between individual susceptibility, both physiological and behavioral, and a wide range of environmental factors, among which temperature and environmental pollution stand out. With respect to environmental temperature, increases in morbidity and mortality from CVD have been described in both winter and summer, several associated with cold and heat waves; similarly, temperature transitions and variability can also trigger the occurrence of the disease.<sup>(15)</sup>

Intracerebral hemorrhage (ICH) is the most common type of hemorrhagic stroke and occurs when a blood vessel in the brain ruptures and spills blood into the surrounding brain tissue. Chronic hypertension is the most notable risk factor for ICH and is responsible for almost 60% of cases. Proliferation of smooth muscle cells in arterioles occurs with constant hypertension and over time; these cells die and the tunica media is replaced by collagen, causing the vessels, with decreased tone and distensibility, to eventually undergo aneurysmal dilatation. These microaneurysms (Charcot-Bouchard aneurysms) are susceptible to rupture and result in cerebral hemorrhage.<sup>(16)</sup>

Rupture of cerebral blood vessels constitutes the cause of hemorrhagic cerebrovascular events. Temperature, and particularly its decrease, can cause an increase in blood pressure in a context of thermal stress with activation of the sympathetic system; thus it is related to the pathophysiology of this disease.

The development of Gerontology in recent years suggests that in the process of atherosclerosis important intrinsic biological events occur, which are influenced and modified by the environment, which needs a long time to clinically manifest atherosclerosis.<sup>(17)</sup>

## CONCLUSIONS

Meteorological variables act as precipitating factors for both ischemic and hemorrhagic CVD. As the temperature rises, the number of admissions increases. As both maximum and minimum temperatures increase, the number of deaths increases.

## **BIBLIOGRAPHIC REFERENCES**

- García Alfonso C, Martínez Reyes AE, García V, Ricaurte Fajardo A, Torres I, Coral Casas J. Actualización en diagnóstico y tratamiento del ataque cerebrovascular isquémico agudo. Univ Med [Internet]. 2019 [cited 05/03/2023];60(3):1-17. Available at: <u>https://revistas.javeriana.edu.co/index.php/vnimedica/article/view/24640</u>. <u>https://doi.org/10.11144/Javeriana.umed60-3.actu</u>
- Sera García R, Sera Blanco RA, García Díaz M. Mortalidad por diabetes mellitus, enfermedad cardiovascular y cerebrovascular en Cuba durante el quinquenio 2012-2016. Medimay [Internet]. 2018 [cited 05/03/2023];25(1):50-61. Available at: <u>https://revcmhabana.sld.cu/index.php/rcmh/article/view/1192/1512</u>
- Málaga G, De La Cruz Saldaña T, Busta Flores P, Carbajal A, Santiago Mariaca K. La enfermedad cerebrovascular en el Perú: estado actual y perspectivas de investigación clínica. Acta Méd Peru [Internet]. 2018 [cited 05/03/2023];35(1):51-54. Available at: <u>http://www.scielo.org.pe/scielo.php?script=sci\_arttext&pid=S1728-</u> 59172018000100008&lng=es&nrm=iso&tlng=es
- Ministerio de Salud Pública. Dirección de Registros Médicos y Estadísticas de Salud. Anuario Estadístico de Salud 2020 [Internet]. La Habana: Minsap; 2021 [cited 05/03/2023]. Available at: <u>http://files.sld.cu/bvscuba/files/2021/08/Anuario-Estadístico-Espa%C3%B1ol-2020-Definitivo.pdf</u>
- Sepúlveda Contreras J. Caracterización de pacientes con accidente cerebrovascular ingresados en un hospital de baja complejidad en Chile. Univ Salud [Internet]. 2021 [cited 05/03/2023];23(1):8-12. Available at: <u>http://www.scielo.org.co/scielo.php?script=sci\_arttext&pid=S0124-</u> <u>71072021000100008&lng=en. https://doi.org/10.22267/rus.212301.208</u>
- Alcalá Briones RD. Correlación entre los factores meteorológicos (temperatura, humedad y presión atmosférica) y la incidencia mensual de la ruptura de aneurismas intracraneales [thesis]. Nuevo León: Universidad Autónoma de Nuevo León; 2021 [cited 05/03/2023]. Available at: <u>http://eprints.uanl.mx/id/eprint/20481</u>
- Lavados PM, Olavarría VV, Hoffmeister L. Ambient temperature and stroke risk: evidence supporting a short-term effect at a population level from acute environmental exposures. Stroke [Internet]. 2018 [cited 05/03/2023];49(1):255–261. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/29229725/</u>. <u>https://doi.org/10.1161/STROKEAHA.117.017838</u>
- Seung-Hoon L, editors. Stroke Revisited: Hemorrhagic Stroke [Internet]. Singapore: Springer Singapore; 2018 [cited 05/03/2023]. Available at: <u>https://link.springer.com/book/10.1007/978-981-10-1427-7</u>. <u>https://doi.org/10.1007/978-981-10-1427-7</u>
- Albaladejo Blanco C, Cerna Arévalo C, Montellà Jordana N. Variabilidad estacional de la presión arterial: diferencias verano-invierno detectadas por monitorización ambulatoria. Hipertens Riesgo Vasc [Internet]. 2019 [cited 05/03/2023];36(2):110-113. Available at: <u>https://www.elsevier.es/es-revista-hipertension-riesgo-vascular-67articulo-variabilidad-estacional-presion-arterial-diferencias-S1889183719300054</u>. <u>https://doi.org/10.1016/j.hipert.2019.01.002</u>
- Fundación Española del Corazón. El frío aumenta la presión arterial, el colesterol y los coágulos sanguíneos. Madrid: Fundación Española del Corazón [Internet]. [cited 05/03/2023]. Available at: <u>https://fundaciondelcorazon.com/prensa/notas-deprensa/2714-frio-aumenta-presion-arterial-colesterol</u>

- 11. Lecha Estela LB. Pronósticos Biometeorológicos [Internet]. La Habana: CITMATEL; 2019 [cited 05/03/2023]. p. 210. Available at: https://www.libreriavirtualcuba.com/pronosticos-biometeorologicos
- Ikefuti PV, Barrozo LV, Braga ALF. Mean air temperature as a risk factor for stroke mortality in São Paulo, Brazil. Int J Biometeorol [Internet]. 2018 [cited 05/03/2023];62(8):1535–1542. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/29802502/</u>. <u>https://doi.org/10.1007/s00484-018-1554-y</u>
- Sauchay Romero L, Rivero Valencia A, Ortiz Bultó PL. Mortalidad por accidentes cerebro vasculares e influencia de la variabilidad climática en el occidente de Cuba, 2001-2005. Rev Cubana Meteorol [Internet]. 2017 [cited 05/03/2023];23(1):43-56. Available at: <u>http://rcm.insmet.cu/index.php/rcm/article/view/228</u>
- 14. Chen R, Yin P, Wang L, Liu C, Niu Y, Wang W, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. BMJ [Internet]. 2018 [cited 05/03/2023];363:k4306. Available at: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6207921/</u>. <u>https://doi.org/10.1136/bmj.k4306</u>
- Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. Eur Heart J [Internet]. 2017 [cited 05/03/2023];38(13):955-960. Available at: <u>https://academic.oup.com/eurheartj/article/38/13/955/3056909</u>. <u>https://doi.org/10.1093/eurheartj/ehw151</u>
- 16. González Hernández A, Rodríguez Hernández N, Hernández Tamayo AJ. Caracterización de pacientes con hemorragia intraparenquimatosa espontánea. Univ Méd Pinareña [Internet]. 2019 [cited 05/03/2023];15(2):205-213. Available at: <u>https://revgaleno.sld.cu/index.php/ump/article/view/341</u>
- 17. Licea Puig M. Aterosclerosis y diabetes mellitus. Revisión bibliográfica. Rev Cubana Med [Internet]. 1986 [cited 05/03/2023];25(12):1149-1176. Available at: <u>https://revmedicina.sld.cu/index.php/med/article/view/3041</u>

## **CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

## **AUTHORS' CONTRIBUTION**

JLAF: conceptualization, formal analysis, data curation, research, visualization, writing the original draft, writing (review and editing). NHM: conceptualization, formal analysis, data curation. ROR, RFD: data curation, research. LMBM, LGG: research.