

Influence of particulate matter and meteorological conditions on multiple sclerosis relapse: a preliminary study in São Paulo, Brazil

Influência do material particulado e condições meteorológicas em surto de esclerose múltipla: um estudo preliminar em São Paulo, Brasil

Influencia de la materia particulada y condiciones meteorológicas en la esclerosis múltiple recaída: un estudio preliminar en Sao Paulo, Brasil

Fernanda Rodrigues **DINIZ**¹
Ana Lucia Frony **MACEDO**²
Marina Piacenti da **SILVA**^{1,3}

¹Department of Physics, Faculty of Sciences, UNESP Univ. State of São Paulo, 17033-360 Bauru-SP, Brazil

²Climatempo, Meteorological Company, 04011-061, São Paulo -SP, Brazil

³IPMet- UNESP Meteorological Center, Univ. State of São Paulo, 17033-360 Bauru -SP, Brazil

Abstract

Introduction: Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system, which in some cases may be characterized by recurrent relapses of inflammation that cause mild to severe neurological disability. Some studies around the world have associated the increase of systemic inflammatory responses and neuro-inflammation of patients with exposure to high levels of particulate matter (PM₁₀) and certain conditions of temperature and humidity. **Materials and methods:** The objective of this study was to verify the influence of the concentration of PM₁₀ and meteorological variables (air temperature and relative humidity) on the number of hospitalizations for MS in the city of São Paulo. Data from 2008 to 2016, which passed through descriptive statistics and inferences, were used as multiple linear regression models. **Results:** The models obtained indicated a positive relation ($p < 0.01$) in the number of hospitalizations with the increase of PM₁₀ and relative humidity, showing that 31.23% of hospital admissions can be explained by these variables. **Conclusion:** These results are important, since there are no other studies from Brazil that correlate meteorological and air quality variables with MS.

Descriptors: Air Pollution; Multiple Sclerosis; Linear Models.

Resumo

Introdução: A Esclerose Múltipla (EM) é uma doença crônica, inflamatória e desmielinizante do sistema nervoso central, que em alguns casos pode ser caracterizada por surtos recorrentes de inflamação que causam leve a grave deficiência neurológica. Alguns estudos em todo o mundo têm associado o aumento de respostas inflamatórias sistêmicas e neuroinflamação de pacientes quando expostos a altos níveis de material particulado (MP₁₀) e certas condições de temperatura e umidade. **Material e Método:** O objetivo deste estudo foi verificar a influência da concentração de material particulado (MP₁₀) e das variáveis meteorológicas (temperatura do ar e umidade relativa) sobre o número de internações por EM na cidade de São Paulo. Para isso foram utilizados dados destas no período de 2008 a 2016, os quais passaram por estatísticas descritivas e inferências, como modelos de regressão linear múltipla. **Resultados:** Os modelos obtidos indicaram relação positiva ($p < 0,01$) no número de internações com o aumento do material particulado MP₁₀ e umidade relativa, demonstrando que 31,23% das internações hospitalares podem ser explicadas por essas variáveis. **Conclusão:** Esses resultados são importantes, pois até agora, em nosso conhecimento, no Brasil não existem estudos que correlacionem as variáveis meteorológicas e de qualidade do ar com a Esclerose Múltipla.

Descritores: Poluição do Ar; Esclerose Múltipla; Modelos Lineares.

Resumen

Introducción: La esclerosis múltiple (EM) es una enfermedad del sistema crónica, inflamatoria y desmielinizante nervioso central, que en algunos casos puede ser caracterizada mediante recaídas recorrentes de inflamación causando leve a déficit neurológico grave. Algunos estudios de todo el mundo que han asociado el aumento de la respuesta inflamatoria sistémica y los pacientes neuro-inflamación cuando se expone a altos niveles de partículas (MP₁₀) y ciertas condiciones de temperatura y humedad. **Materiales y métodos:** El objetivo de este estudio fue investigar la influencia de la concentración de partículas (MP₁₀) y variables meteorológicas (humedad relativa del aire y temperatura) sobre el número de hospitalizaciones por MS en la ciudad de Sao Paulo. Para ello se utilizaron los datos de éstas 2008-2016, estos datos han pasado a través de las estadísticas descriptivas e inferencias, como varios modelos de regresión lineal. **Resultados:** Los modelos indican una relación positiva ($p < 0,01$) en el número de ingresos y el aumento de partículas MP₁₀ y la humedad relativa, lo que demuestra que 31,23% de los ingresos hospitalarios se puede explicar por estas variables. **Conclusión:** Estos resultados son importantes porque hasta ahora, a nuestro entender, en Brasil no existen estudios que correlacionan las variables meteorológicas y la calidad del aire con la esclerosis múltiple.

Descriptor: Contaminación del Aire; Esclerosis Múltiple; Modelos Lineales.

INTRODUCTION

Multiple sclerosis (MS) is a disease in which neuronal myelin is the target of an autoimmune process, characterized as an inflammatory, chronic disease of unknown etiology with consequent loss of neurological function^{1,2}. The more accepted pathogenic hypothesis is that MS may be the result of a particular combination of genetic predisposition and action of unknown environmental factors that, when present in the same individual, may lead to this dysfunction of the neurological system^{2,3,4}. The involvement of the neurological system can cause the patient with MS to suffer relapses. The main symptoms are muscle weakness,

lack of coordination, decreased unilateral visual acuity, double vision, dizziness, and sphincter dysfunction, among others⁵. Hospital admissions for MS typically occur because it relapses in patients, involving a new symptom or worsening of an old symptom for more than a day or several days⁶.

Not having a known and well-defined etiology, MS is investigated worldwide. Studies show that there are possible relationships between air pollution and hospital admissions for MS relapses, because particulate materials present in the atmosphere can increase the systemic

inflammatory response and neuro-inflammation^{3,7,8}. Among the particulate pollutants, particulate matter (PM₁₀) is a pollutant classified as inhalable particles considered harmful to human health because they can be deposited in the upper respiratory tract⁹. Besides PM₁₀, meteorological variables such as relative air humidity and temperature have also been considered possible factors contributing to relapses¹⁰.

To the best of our knowledge, there are no studies associating air pollution and meteorological factors with the occurrence of relapses of MS in Brazil. Therefore, the aim of this study was to evaluate the influence of meteorological parameters and PM₁₀ concentration on hospitalizations due to MS in São Paulo, Brazil, from January 2008 to March 2016.

MATERIAL AND METHOD

○ Meteorological data

The data used in this study refer to the city of São Paulo from January 2008 to March 2016. The meteorological variables are reanalyzed from NCEP/NCAR and were provided by the Climatempo[®] Company. Meteorological data correspond to the air temperature and relative humidity monthly averages. The monthly averages data of pollutant PM₁₀ were obtained from air quality system data of the Environmental São Paulo State Company (QUALAR-CETESB).

○ Hospital admissions data

Monthly data of hospital admissions for MS were obtained from the online system of the computer department of the Unified Health System in Brazil (DATASUS). The data available in this system involve the number of admissions by city, age, and gender. Although studies on the impact of pollution on population health recommend that daily values of meteorological variables should be used and that hospital admissions should be divided by age group¹¹, in this work the average monthly admissions were used, since MS has low prevalence in Brazil, with 15 cases per 100,000 inhabitants¹².

○ Statistical analysis

Descriptive analyses were performed of all variables in the study. The exponential smoothing method of *Holt-Winters* was used to smooth and eliminate any noise of the time series¹³. After the *Kolmogorov-Smirnov* test indicated normal distribution of data, the variables PM₁₀, relative humidity, air temperature, and hospital admissions due to MS were correlated using Pearson's model^{14,15}.

Although many studies that correlate air pollution and meteorological variables with diseases use the Poisson family of generalized linear models (MLG), in this study we used multiple linear regression^{3,16,17}. This model was chosen because the variables have a normal distribution and, according to the residue analysis, the model was adequate for our data^{11,13,17}. The objective of regression analysis is to measure the relation between an answer variable (*Y*) and a set of independent explanatory variables (*X*₁, *X*₂,...), as shown in equation 1¹⁸. In this equation, β's are the coefficients of regression, ρ is the number of explanatory variables, and *ε* is the residue.

$$Y = \beta_0 + \beta_1 X_1 + \dots + \beta_\rho X_\rho + \varepsilon \quad (1)$$

In the multiple linear regression model employed, the number of hospital admissions for MS was the dependent variable, and the explanatory variables were PM₁₀ concentration, air temperature, and relative humidity. For

the inclusion of variables in the model, we used the stepwise method. The stepwise model starts by inserting the independent variable that has the highest correlation with the response variable, and the criterion to add or remove a variable at any stage was expressed in terms of the partial F test. The value of α was 0.05 for input and 0.1 for output¹⁹. The statistical software used were SPSS version 13.0, Minitab 17, and Microsoft Office Excel 2007.

RESULTS

○ Descriptive statistics

Table 1 shows the characteristics of hospitalizations in the period according to the patients' age, gender, year, and month of hospitalization. The year 2008 had the most hospital admissions, followed by 2009, and the months with the highest incidence of hospitalizations were March and October.

Table 1. Distribution of cases of MS by sex, age group, year, and month of hospital admission from 2008 to 2016 in São Paulo

Variables	Number of admissions n=1,282 (100%)
Gender	
Female	945 (73.7%)
Male	337 (26.3%)
Age (years)	
≤ 30 years	434 (33.9%)
30–50 years	666 (51.9%)
≥ 50 years	182 (14.2%)
Year of admission	
2008	220 (17.2%)
2009	216 (16.8%)
2010	163 (12.7%)
2011	190 (14.2%)
2012	152 (11.9%)
2013	105 (8.2%)
2014	122 (9.5%)
2015	86 (6.7%)
2016	28 (2.2%)
Month of admission	
Jan	98 (7.6%)
Feb	116 (9.0%)
Mar	133 (10.4%)
Apr	97 (7.6%)
May	91 (7.1%)
Jun	87 (6.8%)
Jul	112 (8.7%)
Aug	115 (9.0%)
Sep	92 (7.2%)
Oct	123 (9.6%)
Nov	116 (9.0%)
Dec	102 (8.0%)

It is observed in Table 1 that the number of hospital admissions for MS females was 73.7% of the total, far greater compared to men (26.3%), and the same way that the number of admissions is higher among people aged between 30 and 50 years. These results are in agreement with other epidemiological studies worldwide, which have shown that the prevalence of MS is higher in women between 20 and 40 years old^{1,2,20}.

Figure 1 shows boxplots of meteorological variables, pollutant PM₁₀, and number of hospital admissions for MS in São Paulo by month (January to December). It is observed in Figure 1 that the meteorological variables present some seasonality, as expected, while the number of hospital admissions in the period presented great dispersion. Regarding the seasonal nature of variables throughout the year, the temperature and humidity are higher in summer (Dec–Feb) and lower in the winter (June–Aug). Additionally, the PM₁₀ shows higher concentrations in winter, probably due to higher occurrences of thermal inversion in São Paulo in this season²¹.

To evaluate the trend and seasonality of the variables, the time series were decomposed (Figure 2).

In Figure 2, the bars at the right-hand side are in the same range in user coordinates and indicate the relevance of each component to the series: relevance is inversely proportional to the size of the bar.

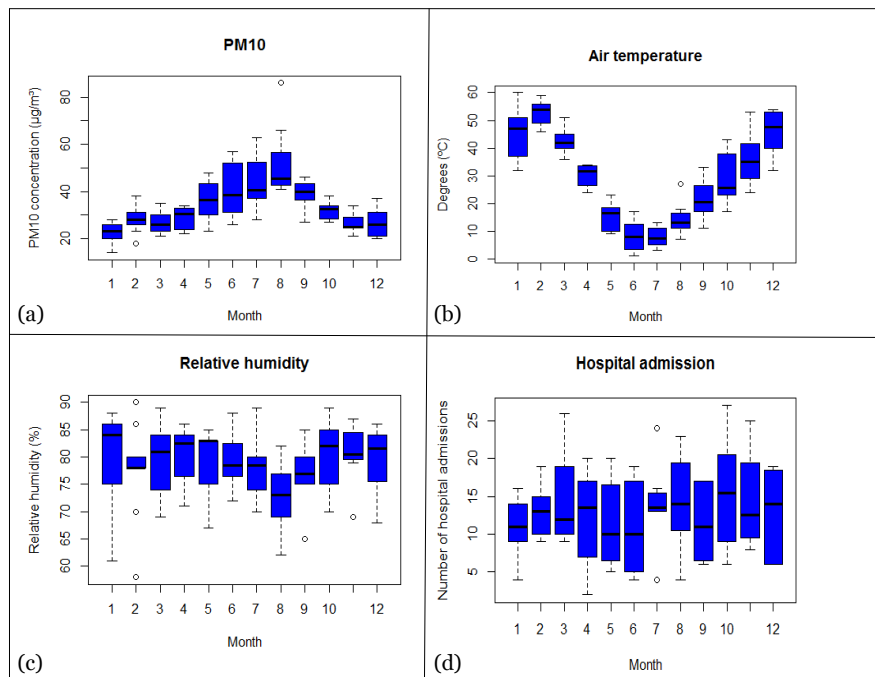


Figure 1: Temporal series of PM₁₀ concentration, air temperature, relative humidity, and hospitalizations for MS.

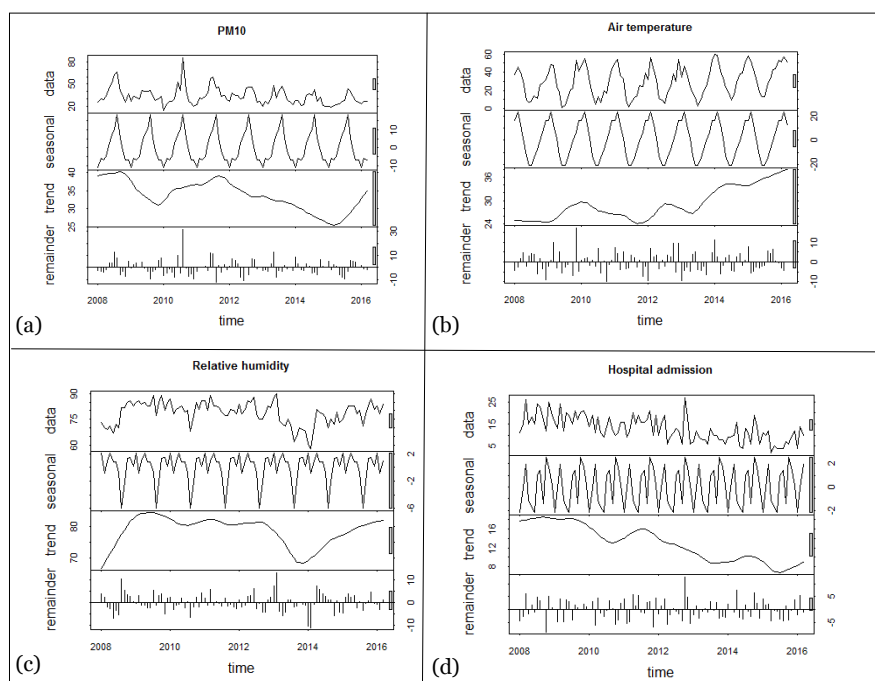


Figure 2: Decomposition of temporal series of PM₁₀ concentration, air temperature, relative humidity, and hospitalizations for MS

Figure 2 demonstrates that PM₁₀ concentration has shown a declining trend, probably due to the Brazilian law in 2008 requiring the use of catalytic converters in vehicles, reducing the emission of PM₁₀ in the atmosphere²². Air temperature has a positive trend. The relative humidity has one period with values below average, justified by the fact that the years 2013/2014 were the driest registered since 1995 in São Paulo²³. It is observed that hospital admissions have a negative tendency in the studied period, just as the PM₁₀. The seasonal component appears in all series; however, as expected, this component is more relevant to explain the temperature behavior. The remainder component (irregularities) is quite relevant in all series.

There are no studies that report the cause of the decrease in hospitalizations; however, since hospitalizations and PM₁₀ have the same trend in the study period, it can be inferred that these two variables are related in some way. To investigate a possible relation between them, Table 2 presents the results obtained from the Pearson correlation test among the meteorological variables (Temp.= air temperature; Humid.= relative humidity), PM₁₀, and the number of hospital admissions (total, by age and gender).

Table 2. Coefficients of Pearson correlation test

	PM ₁₀	Temp.	Humid.	Total	≤ 30 years	30-50 years	≥ 50 anos	Female
Temp.	-0.833**							
Humid.	-0.113	-0.016						
Total	0.513**	-0.440**	0.163					
≤ 30 years	0.521**	-0.463**	-0.155	0.723**				
30-50 years	0.268**	-237*	0.283**	0.869**	0.388**			
≥ 50 years	0.184	-0.146	0.265*	0.535**	0.213*	0.335*		
Female	0.477**	-0.405**	0.042	0.906**	0.753**	0.732**	0.514**	
Male	0.199*	-0.188	0.288**	0.676**	0.358**	0.698**	0.378**	0.334**

* Correlation is significant at the 0.05 level
 ** Correlation is significant at the 0.01 level

The correlations among the concentration of PM₁₀, the total number of hospital admissions, and almost all subgroups (age and gender) were positive, with $p < 0.01$, indicating that the higher the concentration of PM₁₀, the higher the number of hospitalizations. Regarding the meteorological variables, the air temperature showed a negative correlation with hospitalizations and the relative humidity a positive correlation with admissions of patients between 30 and 50 years and of male gender. These results agree with others studies, such as that of Angelici et al.¹⁶, which demonstrated a positive relation between PM₁₀ and MS admissions in Lombardy, Italy, and that of Gregory et al.³, which showed a positive relation between PM₁₀ and female patient admissions.

○ Adjustments of the multiple linear regression model with the stepwise method

Before the development of multiple linear regression, residual analysis was performed to verify the adjustment of hospitalization data and PM₁₀ to the model, since residuals should follow a normal distribution for the model^{11,17,24}. The independent temperature and humidity variables were also added to improve predictability. Even if the main interest is in the effect of PM₁₀ on hospitalizations for MS, it is advisable to include the other variables capable of affecting hospitalizations²⁴. For the multiple linear regression models, the variables were the total number of hospitalizations and hospitalizations by age group (≤ 30 years, between 30 and 50 years, and ≥ 50 years) and by gender (female and male). Figure 3a shows the probability of normality of fit errors. The closer the residuals are distributed, the better the model fits the data. As shown in Figure 3a, all data are well adjusted to the models, since the residuals have normal distribution.

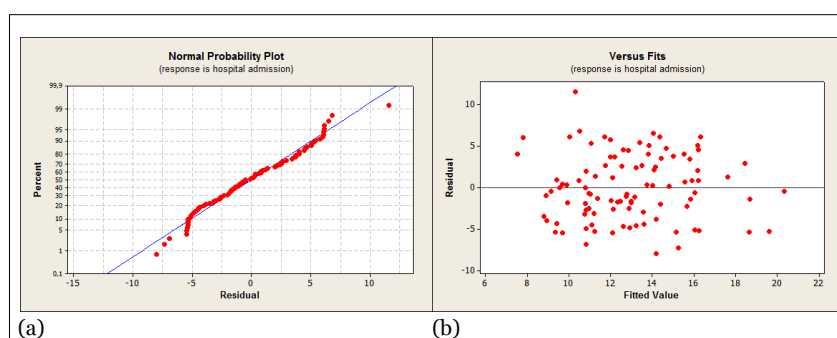


Figure 3: a) Normal probability plot to general admission; b) Residual versus fitted value to general admission

Figure 3b shows residuals as a function of adjusted values. Residuals are distributed randomly around the zero mean, with no specific pattern, which justifies that the multiple linear regression models are adequate to the data^{17,25}.

○ **Regression models**

Table 3 shows the results of the six multiple linear regression models, in which R^2 indicates the coefficient of determination of each model, the coefficients β indicate the relation of the independent variables with the responses variables, S.E is the standard error of β , the T-Value is the value of the Student's test, p is the level of significance, and VIF is the inflation of variance, which measures the collinearity of the independent variables. In this case, since VIF is equal to 1, the independent variables are not correlated.

Table 3. Results of the multiple linear regression models

Models	Term	β	S.E	T- Value	P	VIF
1 - Admission total $R^2= 31.23\%$	Constant	-9.41	5.30	-1.78	0.08	
	PM ₁₀	0.28	0.04	6.32	0.00	1.01
	Humidity	0.16	0.06	2.63	0.01	1.01
2 - Female admissions $R^2=22.7\%$	Constant	2.18	1.42	1.53	0.13	
	PM ₁₀	0.21	0.04	5.35	0.00	1.00
3 - Male admissions $R^2= 13.76\%$	Constant	-5.68	2.43	-2.34	0.02	
	PM ₁₀	0.05	0.02	2.46	0.02	1.01
	Humidity	0.09	0.03	3.30	0.00	1.01
4 - Admissions < 30 years $R^2=27.15\%$	Constant	-0.61	0.86	-0.71	0.48	
	PM ₁₀	0.14	0.02	6.01	0.00	1.00
5 - Admissions 30–50 years $R^2= 17.88\%$	Constant	-7.37	3.42	-2.16	0.03	
	PM ₁₀	0.10	0.03	3.40	0.00	1.01
	Humidity	0.14	0.04	3.42	0.00	1.01
6 - Admissions > 50 years $R^2= 11.71\%$	Constant	-3.78	1.64	-2.31	0,02	
	PM ₁₀	0.03	0.01	2.25	0,03	1.01
	Humidity	0.06	0.02	3.01	0.00	1.01

Results demonstrate that all models indicated a positive relation in the number of hospitalizations and PM₁₀ concentration, as shown by the β coefficients in Table 3. In addition to the PM₁₀, most of the models showed a positive relationship of hospitalizations with relative air humidity. Air temperature was removed from the models because it did not have a significant representation ($p > 0.05$). This probably can be explained by the fact that high relative humidity and high particulate pollution occur in opposite temperature conditions (summer and winter, respectively). The best model was considered as a response to the number of total admissions, which obtained a higher coefficient of determination (R^2), indicating that 31.23% of the number of hospitalizations can be explained by PM₁₀ and relative humidity.

DISCUSSION

PM₁₀ is one of the most harmful pollutants to human health, and many studies try to understand its effects on health, especially in cases of respiratory and cardiovascular diseases²⁶⁻²⁸. In addition to respiratory and cardiovascular diseases, recent studies have shown that air pollution may have an influence on neurodegenerative diseases, such as Parkinson's disease, Alzheimer's, and MS^{3,16,29}. Among the various pollutants, particulate materials and heavy metals are prominent in the impact of neurodegenerative diseases, due to the fact that these pollutants contribute to the neuroinflammatory response^{3,5}.

MS, the focus of this study, is a disease of unknown etiology, making studies even more difficult and complex but necessary to discover the origin of the disease. Not only the origin of MS but also the progression of the disease is a mystery. Patients with a recurrent type of MS are most affected by relapses of MS, which mostly cause hospital admissions and sometimes new neurological lesions^{2,6}.

In this study, we investigated MS hospitalizations in the city of São Paulo over a period of eight years (2008–2016). During this period, there were a total of 1,282

hospitalizations, in which the majority included women between 30 and 50 years of age. This study was limited only to hospitalizations by the Unified Health System (UHS), which means that it does not represent all MS hospitalizations in the city of São Paulo, which in many cases occur in private hospitals.

Despite this limitation, we obtained good results from the relationships between MS hospitalizations and PM₁₀ for the city of São Paulo. For all age groups and genres, concentrations of PM₁₀ were shown to contribute to the increase in hospitalizations ($p < 0.01$). Our study is in agreement with the results obtained by Angelici et al.¹⁶ and Gregory et al.³ which showed a relationship between the increase in PM₁₀ concentrations and the increase in admissions in Lombardy, Italy, and Tehran, Iran, respectively. In addition to PM₁₀, our study also showed a positive relation ($p < 0.01$) of hospitalizations with relative air humidity. In the study of Salvi et al.¹⁰ the authors also pointed out the relationships between the seasonality of MS hospitalizations and the seasonality of relative air humidity in Italy. Other studies show that high relative humidity causes increased fatigue in patients with MS^{30,31}.

Our study focused only on the pollutant PM₁₀, due to the fact that there is more literature on MS and this pollutant, mainly and only from other countries. However, we should not rule out the possibility that other pollutants may also contribute significantly to the occurrence of MS relapses, as well as the contribution of meteorological variables, since air pollution always acts in conjunction with atmospheric conditions, which should not be neglected.

CONCLUSION

Our results showed that the higher the relative humidity and PM₁₀ concentrations, the greater the number of hospitalizations for MS. The models indicated a higher PM₁₀ ratio with female hospitalizations of the age group below 30 years. The results obtained in this work confirm for the city of São Paulo the hypothesis that air pollution, as well as some atmospheric conditions, may play an important role in the occurrence of MS relapses. These results are important, since up to now in Brazil there are no studies concerning meteorological or air quality variables with such disease. In addition, they may open new viewpoints to investigate the pathogenic mechanisms of MS.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

CORRESPONDING AUTHOR

Marina Piacenti da Silva
marinapsilva@fc.unesp.br

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