sclerosis

Article

Impacts of Air Pollution and Thermal Discomfort in Hospitalizations for Multiple Sclerosis in Sao Paulo, Brazil

Fernanda Rodrigues Diniz [1,2,*], Fábio L. T. Gonçalves [1], Carolina Letícia Zilli Vieira [3] and Marina Piacenti-Silva [2]

1 Institute of Astronomy, Geophysics and Atmospheric Sciences, USP University of São Paulo, Sao Paulo 05508-090, Brazil; fabio.goncalves@iag.usp.br
2 Department of Physics and Meteorology, School of Sciences, São Paulo State University–UNESP, Bauru, Sao Paulo 17033-360, Brazil; marina.piacenti@unesp.br
3 Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA; cazilli@hsph.harvard.edu
* Correspondence: fernanda_diniz2@live.com; Tel.: +55-1198477-6332

Abstract: Multiple sclerosis (MS) is an autoimmune, neurological, and demyelinating disease of unknown etiology. Neuroinflammation caused by the disease has been associated with air pollution as well as bioclimatic conditions. The aim of this study was to investigate the impacts of air pollution and human thermal discomfort on hospitalizations for multiple sclerosis in Sao Paulo, Brazil, from 2008 to 2015. Generalized Additive Model for Location Scale and Shape (GAMLSS) with Zero Inflated Poisson was used to relate multiple sclerosis hospitalizations in three age groups (less than 30 years old, between 30 and 50 years old, and more than 50 years old) and gender (female and male) with atmospheric pollutants PM_{10}, SO_2, NO_2, NO, and NO_x and thermal discomfort. The results showed that the exposure to an increase of 1 $\mu g/m^3$ in SO_2 concentration is highly associated with a 10% increase of the risk of MS hospitalization (95% CI: 2–21%) in female patients and a 7.5% (95% CI: 1.5–16%) increase in male patients. PM_{10} and NO were associated with increased MS risk only for female patients, mainly aged between 30 and 50 years old (2% and 1% increase in hospitalizations, respectively). The cold discomfort was also associated with MS hospitalization, mainly in males (2% increase in hospitalizations; 95% IC: 1–3%). These results are important, since there are few studies that relate air pollution and thermal discomfort with hospitalizations for multiple sclerosis in Brazil.

Keywords: multiple sclerosis; air pollutants; thermal discomfort

check for updates

Citation: Diniz, F.R.; Gonçalves, F.L.T.; Zilli Vieira, C.L.; Piacenti-Silva, M. Impacts of Air Pollution and Thermal Discomfort in Hospitalizations for Multiple Sclerosis in Sao Paulo, Brazil. *Sclerosis* **2023**, *1*, 113–123. https://doi.org/10.3390/sclerosis1030012

Academic Editors: Bradley Turner and Sara Gil-Perotin

Received: 20 April 2023
Revised: 6 July 2023
Accepted: 22 September 2023
Published: 26 September 2023

1. Introduction

In recent years, there have been significant advances in knowledge about the effects of air pollutants on human health [1,2]. Most of the studies show a significant impact of air pollution on respiratory and cardiovascular diseases [3,4]. However, recent studies demonstrate the relationship between air pollution exposures and neuroinflammatory responses, which may be related to the development of diseases of the central nervous system such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis [5–9]. This study was conducted to investigate possible associations between air pollution and thermal discomfort and multiple sclerosis hospitalizations.

Multiple sclerosis is a major neurological disability disease characterized by chronic inflammation and demyelinating disease, in which the myelin sheath is the target of an autoimmune process with consequent loss of neurological function [8,10]. Although the etiology of MS is still unknown, the most accepted pathogenic hypothesis is that MS is the result of the conjunction of a certain genetic predisposition and unknown environmental factors that can promote a dysfunction of the immune system, possibly by developing autoimmune activity [8,10]. According to epidemiological studies, MS has a higher prevalence in females [8].

Studies in multiple countries have shown that there are possible links between atmospheric pollution and hospitalizations for MS relapses, since exposures to certain pollutants present in the atmosphere may increase the systemic inflammatory response and neuroinflammation [6–13]. In Italy, a study found significant relationships in the occurrence of MS relapses due to exposure to PM_{10} [14]. A similar study was carried out in São Paulo city, Brazil, in which significant relationships were also found between MS relapses and PM_{10} [5]. In addition to PM_{10}, other pollutants may be related to MS relapses, such as sulfur dioxide (SO_2), nitrogen oxides (NO_x), and nitrogen dioxide (NO_2) [6,9,13]. The first epidemiological study on MS in Brazil was conducted in São Paulo city in 1990, indicating a prevalence of 4.27/100,000 inhabitants (5.59/100.000 women and 2.89/100.000 men), an index considered low when compared to countries in the northern hemisphere [11]. In 2008, a study reported a prevalence of MS in São Paulo city of 15/100,000 inhabitants, showing that the MS prevalence increased almost four times in the city between 1990 to 2008 [12].

Studies also show that patients with MS are more sensitive to variations in temperature and humidity. In these patients, increased body temperature can cause fatigue, lack of vitality, emotional distress, and dependence and life restrictions in general [15,16]. In addition to fatigue, the increase in body temperature may trigger the onset of neurological symptoms, so the quantification of the thermal comfort of the study region is of paramount importance [15,16].

We are aware of only one previous study in Sao Paulo, Brazil, that related an air pollutant with multiple sclerosis relapses; however, in that study, only PM_{10} was taken into consideration [5]. In this context, the objective of the current study was to investigate the associations between multiple atmospheric pollutants, including particulate matter less than 10 µm (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), nitrogen monoxide (NO), oxides of nitrogen (NO_x), and sulfur dioxide (SO_2). Separately, we investigated the relation between human thermal discomfort and sclerosis hospitalizations in São Paulo city between January 2008 and December 2015.

2. Materials and Methods

2.1. Study Design

This study is an ecological observational study that is defined by the level at which data are analysed, at the population or group level [17]. The purpose of this study is to study the relationship between exposure risk factors (air pollution and thermal discomfort) and disease (MS hospitalizations) [17]. Hospitalizations for multiple sclerosis were selected according to the International Classification of Diseases (ICD-10-GM code G35). Hospitalizations of all multiple sclerosis phenotypes (G35) were analyzed collectively and correlated with environmental factors in the city of São Paulo. Thus, this study is limited to the association of pollution and thermal comfort with all multiple sclerosis hospitalizations, without distinguishing the phenotype of the disease or the multiple hospitalizations by the same patient.

2.2. Data

2.2.1. Hospitalizations

The daily multiple sclerosis hospitalization information (ICD-10 Code: G35) in São Paulo city was obtained from the department of the Unified Health System (DATASUS). The period of daily data collection was between January 2008 and December 2015. Studies of the impact of air pollution on population health recommend that daily values of variables be used and that hospitalizations be divided by age group [17]. For this reason the data were aggregated by gender (male and female) and age (under 30 years old, between 30 and 50 years old, and over 50 years old). These age groups were chosen since the prevalence of MS is higher in young adults [12]. This study includes people with multiple hospitalizations, who were counted each time there was hospitalization.

2.2.2. Pollutants and Metorological Variables

The PM_{10}, O_3, NO, NO_2, NO_x, and SO_2 pollutant data were obtained from the Environmental Company of São Paulo State (CETESB). The daily averages of air pollution were measured at 12 monitoring stations located in São Paulo city from January 2008 to December 2015. These pollutants were chosen because previous studies linked them to multiple sclerosis or other neurological diseases [8,9,13,14]. The daily data of the meteorological variables were obtained from the Mirante de Santana station of the monitoring network of National Institute of Meteorology (INMET). The meteorological parameters were mean air temperature and mean relative humidity.

2.3. Human Thermal Discomfort Index (HDI)

The method used to obtain the human thermal discomfort index (HDI) was based on the formula bellow [18]:

$$\mathrm{HDI} = 0.99\mathrm{T_a} + 0.36\mathrm{T_d} + 41.5 \tag{1}$$

where HDI is the index of human thermal discomfort, T_a is the mean air temperature in degrees Celsius (°C), and T_d is the dew point temperature in degrees Celsius (°C). T_d was calculated using Equation (2) [19]:

$$\mathrm{T_d} = \frac{\mathrm{B_1} \times \left[\mathrm{Ln}\left(\frac{\mathrm{U_r}}{100}\right) + \left(\frac{\mathrm{A_1} \times \mathrm{T_a}}{\mathrm{B_1} + \mathrm{T_a}}\right)\right]}{\mathrm{A_1} - \mathrm{Ln}\left(\frac{\mathrm{U_r}}{100}\right) - \left(\frac{\mathrm{A_1} \times \mathrm{T_a}}{\mathrm{B_1} + \mathrm{T_a}}\right)} \tag{2}$$

where Ur is the relative humidity of the air in percent (%), B_1 = 243.04, and A_1 = 17.625.

According to [18], for HDI values greater than 80, the thermal condition is heat stress; for HDI between 75 and 80, the condition is heat discomfort; the HDI range between 60 and 75 represents the comfortable range; for HDI values between 55 and 60, the condition is cold discomfort; and, finally, for HDI values less than 55, the thermal condition is cold stress. Table 1 shows the average conditions for HDI classification.

Table 1. Average conditions for HDI classification between 2008 and 2015.

Relative Humidity (%)	Air Temperature (°C)	HDI	Classification HDI
72.25	10.12	<55	Cold Stress
77.45	13.06	55–60	Cold Discomfort
74.18	21.21	60–75	Comfortable
69.02	26.82	75–80	Heat Discomfort
67.60	32.06	>80	Heat Stress

2.4. Statistical Analysis

First, we performed descriptive analysis of the study variables, including MS hospitalizations, pollutants, and HDI information. In the case of pollutants, the daily mean concentrations of each pollutant during the study period were analyzed, identifying the period of the year in which there are high concentrations. As for the HDI, the most frequent thermal comfort conditions were also identified in São Paulo city. In order to identify the most appropriate statistical model, we used the Kolmogorov Smirnov test to verify the distribution of the study variables.

The response variables were total multiple sclerosis hospitalizations, by age group (under 30 years old, between 30 and 50 years old, and over 50 years old) and by gender (female and male); and the explanatory variables were the pollutants and HDI. The models were adjusted for days of the week and holidays because fewer hospitalizations usually occur on weekends and holidays. We categorized days of the week ranging from 1 to 7 (1 Sunday and 7 Saturday), and holidays ranging from 0 to 1, in which 1 represented holidays and 0 represented no holiday [17]. To adjust for seasonality, we used a function called the cubic spline, which is a function that smoothes the time series [17,20]. We used

Generalized Additive Model for Localization Scale and Shape (GAMLSS) with Zero Inflated Poisson (ZIP) distribution. This distribution was chosen because MS hospitalizations in São Paulo city do not occur every day, with most of the days in the series of hospitalizations equal to zero.

The GAMLSS model was proposed to overcome the limitations of Generalized Linear Models (GLMs) and Generalized Additive Models (GAMs) [21]. Equation (3) presents the algebraic form of the models used in this study.

$$\begin{aligned} Log\,|E(Y_i)| = {} & \beta_0 + \beta_1 cs(PM_{10}) + \beta_2 cs(O_3) + \beta_3 cs(NO) + \beta_4 cs(NO_2) + \beta_5 cs(NO_x) + \beta_6 cs(SO_2) \\ & + \beta_7\, cs\left(HDI_{Comfortable}\right) + \beta_8 cs\left(HDI_{Heat}\right) + \beta_9 cs(HDI_{Cold}) + \beta_{10} cs(HDI_{Heat\ stress}) \\ & + \beta_{11} cs(HDI_{Cold\ stress}) + \beta_{12} DOW + \beta_{13} H + \beta_{14} cs(Time) \end{aligned} \quad (3)$$

where Y_i is the MS hospitalization count, assuming a Zero Inflated Poisson distribution (for hospitalizations separated by age and gender). The *β's* are coefficients generated by the models, *cs* is the cubic spline function, *DOW* represents the days of the week, *H* represents the holidays, and *Time* represents the variation in time.

All variables that appear in Equation (3) were initially included in the models; however, using a stepwise method, we only included the significant variables.

Based on the β coefficients obtained by the models, it was possible to calculate the relative risk of total MS hospitalization (i.e., for all age groups and genders), for each age group (under 30 years old, between 30 and 50 years old, and over 50 years old) and for each gender (female and male) due to exposure to each pollutant and thermal discomfort interval. Relative risks were calculated with a 95% confidence interval.

3. Results

3.1. MS Hospitalizations

Table 2 shows the number of MS hospitalizations in the study period according to the patient's age, gender, and year of hospitalization.

Table 2. Characteristics of MS hospitalizations in the study period.

Variables	Number of Hospitalizations
Gender	
Female	1792
Male	698
Age	
≤30 years	420
30–50 years	1523
≥50 years	547
Year	
2008	565
2009	440
2010	266
2011	400
2012	269
2013	175
2014	215
2015	160
Total	2490

Table 2 shows that the number of MS hospitalizations of the female gender is approximately 70% of the total, and thus much larger compared to the male gender; furthermore, the number of hospitalizations is highest in the age group between 30 and 50 years old. These results are in agreement with other epidemiological studies, which found MS mainly affects young women [11].

3.2. Pollutants

Figure 1 shows the time series of the six pollutants, as well as the trend line (blue) of each of these pollutants from 2008 to 2015 and the air quality standard established by the World Health Organization (WHO).

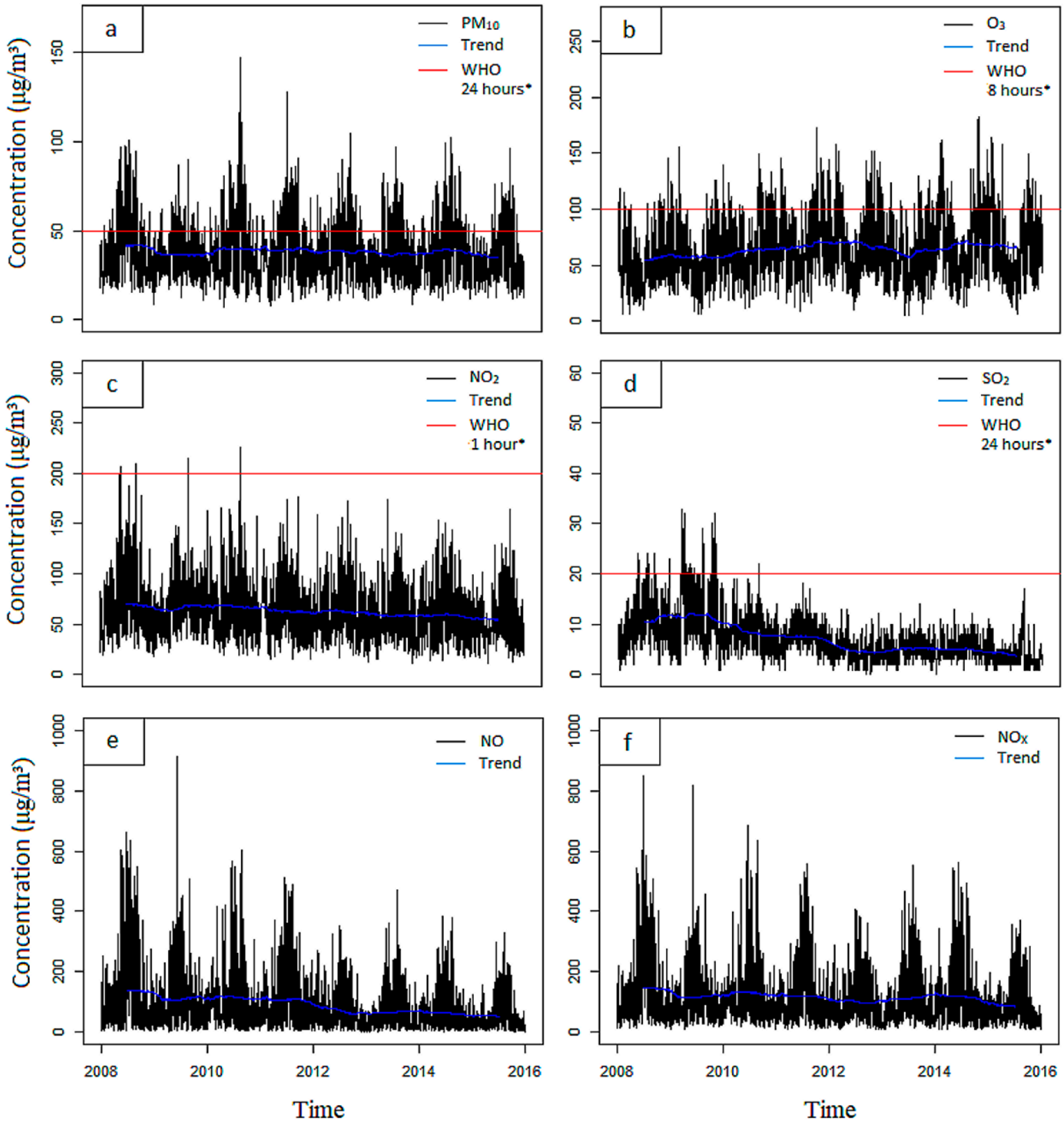

Figure 1. Time series from 2008 to 2015 of concentrations of pollutants: (**a**) PM_{10}, (**b**) O_3, (**c**) NO_2, (**d**) SO_2, (**e**) NO, and (**f**) NO_x. The blue line represents the concentration trend of each pollutant and the red line represents the quality standard established by the WHO for each of the pollutants. (*) Time-weighted average for each of the pollutants.

Figure 1a shows the time series of PM_{10}, whose WHO air quality standard is 50 $\mu g/m^3$ in 24 h. In this way it is possible to observe that, in many days in São Paulo city, the PM_{10} concentration exceeds the WHO standard, and the tendency of this pollutant in the atmosphere is to decrease over time. The high concentrations of this pollutant, as well as those of NO_2, NO, NO_x, and SO_2, are observed in winter periods. Figure 1b shows the daily concentrations of O_3. In many days, daily O_3 concentrations were higher than the WHO-specified standard for 8 h (100 $\mu g/m^3$). Ozone is an oxidative pollutant that can cause eye and nose irritation, and it has the highest concentrations in summer periods. The NO_2 concentrations remained below the WHO standard of 200 $\mu g/m^3$ in 1 h (Figure 1c). Between 2008 and 2011, there were some days when NO_2 levels surpassed the WHO standard. Overall, there has been a decrease in NO_2 over time. The same is observed for SO_2 (Figure 1d) where there were many exceedances of the WHO standard at 20 $\mu g/m^3$ at the beginning of the period between 2008 and 2010, but with a clear decrease in SO_2 in São Paulo city. For NO and NO_x pollutants (Figure 1e,f), there is no air quality standard stipulated by WHO; however, similar to PM10 and SO_2, these two pollutants have been observed at varying concentrations in the atmosphere.

3.3. Human Thermal Discomfort Index (HDI)

Figure 2 shows the number of days in the period from 2008 to 2015 where there were conditions of cold stress, cold discomfort, comfortable days, heat discomfort, and heat stress.

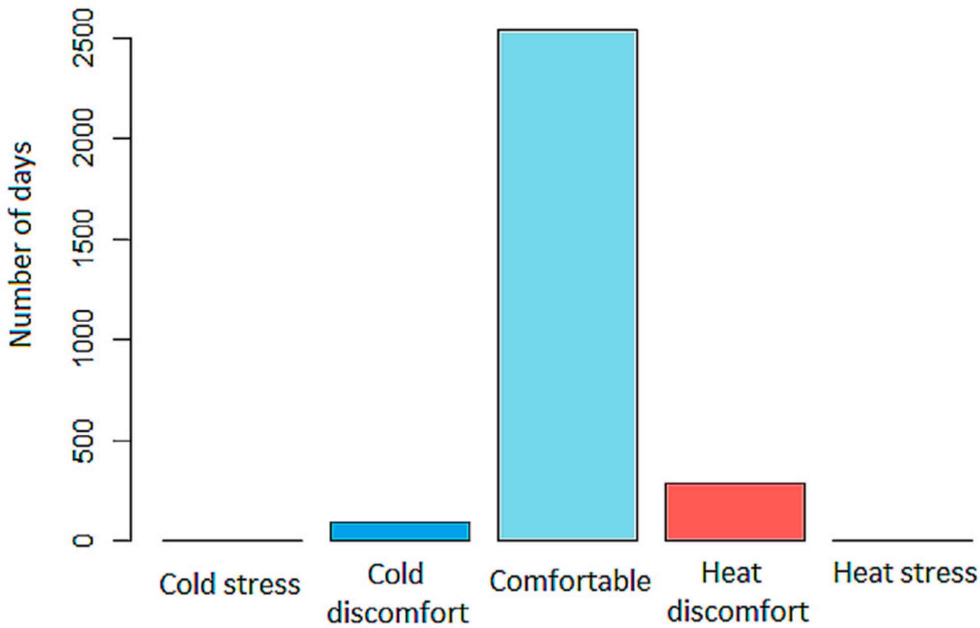

Figure 2. Number of days with comfort conditions established by the HDI in the period from 2008 to 2015.

In São Paulo city, the HDI showed comfortable conditions in most of the days in the period from 2008 to 2015 (2534 days), with only 92 days in which cold discomfort was observed in the winter months and 287 days in which heat discomfort was observed during the summers in the city. There were no days with stress conditions due to cold or heat.

3.4. Relation between Pollutants and HDI with MS

To relate the concentrations of the pollutants and the HDI to the MS hospitalizations, the GAMLSS statistical model was used with a Zero Inflated Poisson distribution. Table 3 shows the GAMLSS models results, presenting the β coefficients and the statistical significance (*p*-value).

Table 3. GAMLSS model results.

Response Variables	Explanatory Variables	β	Std. Error	T Value	*p*-Value
Hospitalization: Total	Intercept	1.0823	0.391463	2.77	0.00573
	SO_2	0.0818	0.004617	13.49	0.00000
	NO	0.0035	0.000601	5.98	0.00000
	Nox	−0.0020	0.002586	2.96	0.00312
	PM_{10}	0.0093	0.000699	−2.21	0.02698
	NO_2	−0.0058	0.001529	−3.37	0.00076
	Cold	0.0198	0.005562	−3.53	0.00043
	Heat	−0.0050	0.009499	−2.04	0.04118
Hospitalization: Age < 30 years	Intercept	−0.7063667	0.924210	−0.76	0.44476
	SO_2	0.0721	0.011181	5.96	0.00000
	NO	0.0042	0.000367	11.30	0.00000
	Cold	0.0050	0.001849	−2.03	0.04218
	Heat	−0.0240	0.002224	2.62	0.00888
Hospitalization: Age between 30 and 50 years	Intercept	1.1536203	0.527950	2.19	0.02896
	PM_{10}	0.0116	0.003080	4.51	0.00001
	O_3	−0.0095	0.002377	−5.57	0.00000
	SO_2	0.0901	0.005656	14.36	0.00000
	NO	0.0035	0.000805	3.14	0.00171
	Nox	−0.0063	0.000890	−5.36	0.00000
	Cold	0.0005	0.000787	−2.72	0.00649
	Heat	−0.0002	0.000110	−4.68	0.00000
Hospitalization: Age > 50 years	Intercept	−2.2591229	0.195089	−11.58	0.00000
	SO_2	0.0488	0.009691	4.98	0.00000
	NO	0.0038	0.000338	10.58	0.00000
Hospitalization: Female gender	Intercept	−1.1601294	0.658319	−1.76	0.07813
	PM10	0.0218	0.003927	5.54	0.00000
	SO_2	0.0925	0.006960	8.74	0.00000
	NO_2	−0.0045	0.002200	−2.69	0.00711
	NO	0.0033	0.000413	8.08	0.00000
	O_3	−0.0069	0.001664	−2.38	0.01733
	Cold	0.0070	0.001979	−1.77	0.07645
	Heat	0.0001	0.000021	2.04	0.04104
Hospitalization: Male gender	Intercept	−5.6264	0.973510	−5.78	0.00000
	SO_2	0.0715	0.010040	8.65	0.00000
	Cold	0.0198	0.001323	2.88	0.00405
	Heat	−0.0020	0.000028	3.30	0.00098

As Table 3 shows, only significant explanatory variables ($p < 0.05$) remained in the models. For the model representing total hospitalizations as a response variable, almost all pollutants had a significant relationship with MS hospitalizations, except ozone (Table 3). SO_2 showed a positive relationship with the response variables in all models (positive β value), which means that when SO_2 increases by 1 $\mu g/m^3$, hospitalizations increase according to the β value. PM_{10} showed significant ($p < 0.05$) associations with the response variables representing hospitalizations of female patients aged 30 to 50 years, as well as total hospitalizations (Table 3). The NO pollutant also presented a positive and significant relationship with almost all the response variables that represent MS hospitalizations in São Paulo city, except for male hospitalizations. The pollutants NO_2, NO_x, and O_3 were negatively associated with MS hospitalizations. The thermal discomfort indices classified as cold discomfort and heat discomfort were significant in almost all models, except for the response variable representing the MS hospitalizations of patients over 50 years old. Cold discomfort was positively associated with hospitalizations, which means that cold discomfort may be linked to an increase of the number of hospitalizations. There was an association between heat discomfort and decreased MS hospitalizations.

Using the relative risk graph, it is possible to compare the impact of pollutants and the HDI on the number of MS hospitalizations in the different age groups and gender. Figure 3 shows the relative risk of MS hospitalization due to exposure to the six pollutants PM_{10}, O_3, NO_2, SO_2, NO, and NO_x, and HDI, besides the discomfort due to cold and heat.

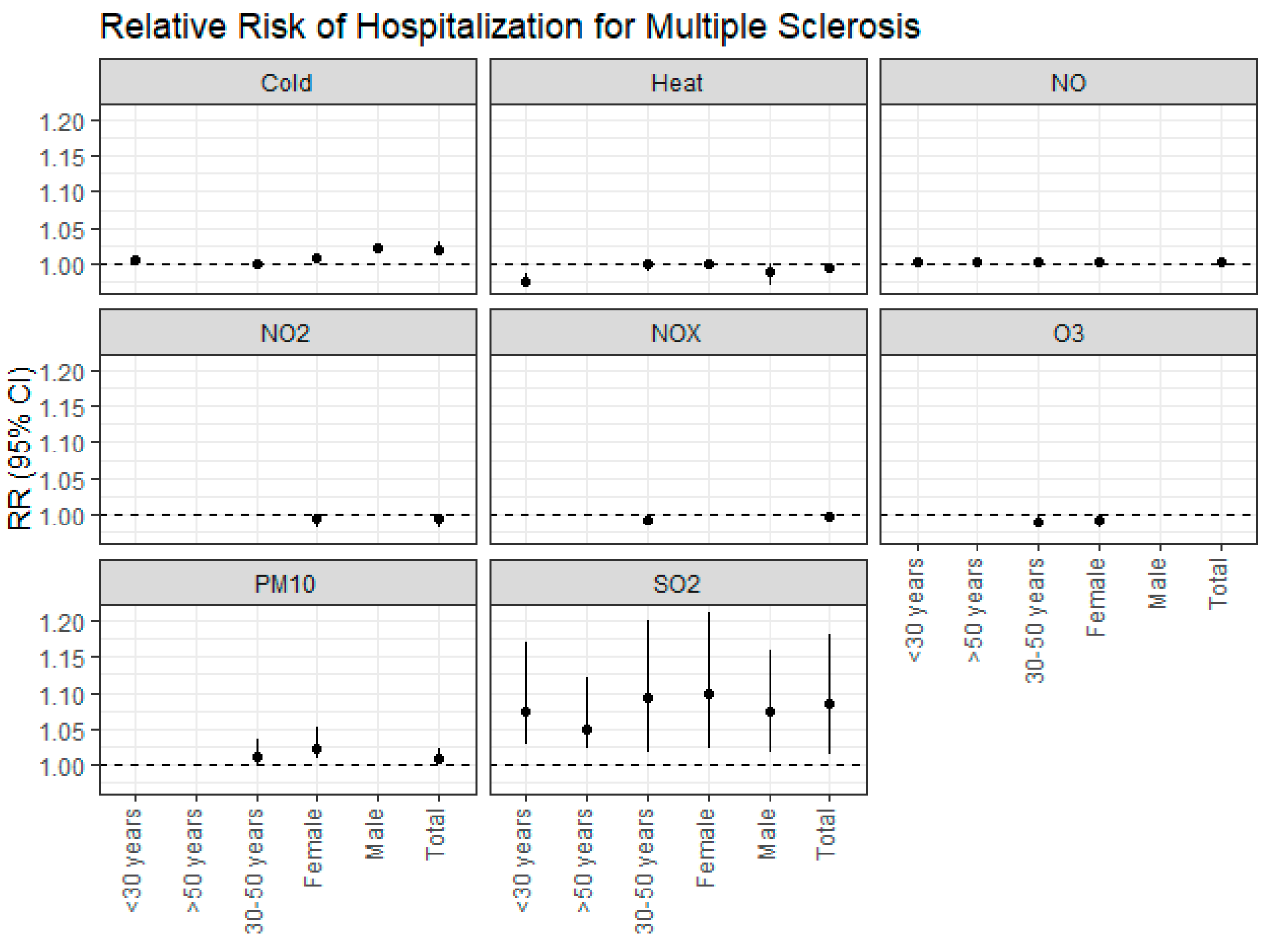

Figure 3. Relative risk of hospitalization for MS in the city of São Paulo due to thermal discomfort and an increase of 1 $\mu g/m^3$ of pollutants SO_2, PM_{10}, NO, NO_2, O_3, and NO_x (95%CI).

Of all the pollutants under study, SO_2 has the highest risk factor for MS hospitalization in São Paulo city for all age groups and genders (Figure 3). The risk of total MS hospitalization related to SO_2 concentrations was 1.085 (95% CI: 1.013–1.18). For patients under 30 years old, the risk of hospitalization is 1.075 (95% CI: 1.028–1.17); for 30 to 50 years old, the risk of hospitalization for exposure to SO_2 increases to 1.094 (95% CI: 1.016–1.20); and the risk is slightly lower in patients over 50 years old, being 1.05 (95% CI: 1.023–1.12). SO_2 has a higher risk factor in female patients than in male, and the relative risk for female patients is 1.10 (95% CI: 1.023–1.21) and for male patients it is 1.074 (95% CI: 1.018–1.16).

PM_{10} also presented a high risk factor for hospitalization of MS patients. However, this pollutant was significant only for the models of total hospitalizations, age between 30 and 50 years, and female gender, where the risks of hospitalization due to exposure to this pollutant were 1.009 (95% CI: 1.005–1.023), 1.011 (95% CI: 1.001–1.035), and 1.022 (95% CI: 1.008–1.051), respectively. The NO pollutant is also associated with hospitalization risk for patients with MS; however, these risks are much smaller when compared to those for PM_{10} and SO_2. Exposure to NO was associated with MS risk in all ages and female gender, including 1.003 (95% CI: 1.001–1.008) for total hospitalizations, 1.004 (95% CI: 1.0007–1.009) for patients under 30 years old, 1.003 (95% CI: 1.001–1.008) for patients between 30 and

50 years old, 1.003 (95% CI: 1.0007–1.0008) for patients over 50 years old, and 1.003 (95% CI: 1.0008–1.007) for female patients.

The pollutants O_3, NO_2, and NO_x were not associated with risk of MS hospitalization in any age group or gender (Figure 3). Cold discomfort was associated with increased risk of total hospitalizations for patients under 30 years old, female and male. The highest risk of MS hospitalization due to cold discomfort was observed in male patients, with a risk of 1.022 (95% CI: 1.018–1.022). The total hospitalizations without distinguishing age and gender were associated with a risk of 1.02 (95% CI: 1.012–1.029); furthermore, there was a risk of hospitalization of 1.007 (95% CI: 1.005–1.012) in women, and a risk of hospitalization of 1.005 (95% CI: 1–1.009) in patients under 30 years old. There were no significant associations between heat and risk of hospitalization of MS patients.

4. Discussion

Our findings showed that MS hospitalizations in São Paulo city were more common in women and patients between 30 and 50 years old. The cause of the decrease in hospitalizations over time is unknown; however, it is believed that the change in treatment with different drugs, such as the use of vitamin D, may be reducing MS hospitalizations. The role of environmental conditions may also be linked to the MS incidence.

In this study, there were significant associations between MS hospitalizations and exposure to pollutants SO_2, PM_{10}, and NO, as well as cold discomfort. Sulfur dioxide was the pollutant that showed the strongest associations with MS hospitalization, with a 21% risk in female patients. Sulfur dioxide (SO_2) is a yellowish, soluble, and irritating gas considered to be an acidic pollutant, for which high concentrations in the atmosphere have been linked to adverse human health outcomes, especially in mixtures with other pollutants.

Recent studies show that exposure to sulfur dioxide is associated with MS [13,22,23]. A study in Tehran, Iran, found an association between SO_2 concentrations and MS relapses. Another study found that regions with high concentrations of SO_2 are a significant risk factor for the increase in cases of children with multiple sclerosis [22]. An experimental study testing the chronic sulfur dioxide exposure in rats showed signs of neuroinflammation and memory loss [23].

In this study, PM_{10} exposure was associated with a risk of hospitalization up to 5% in female patients. This pollutant is classified as inhalable particles with diameters of less than 10 µm, which are capable of being deposited in the upper respiratory tract and have been shown to be harmful to human health. Studies have shown relations between PM_{10} and neuroinflammatory responses, as occurs with multiple sclerosis. A study in Italy showed that high concentrations of PM_{10} are a risk factor of up to 46% for the occurrence of MS relapses [14]. Diniz et al. [5] showed that there is a significant correlation between PM_{10} and MS relapses in São Paulo city. PM_{10} concentrations in São Paulo city frequently surpass the WHO standard levels.

NO was also shown to be associated with MS hospitalizations in São Paulo city; however, this risk was only about 1%. NO is a soluble and lipophilic gas synthesized by endothelial cells, macrophages, and neuron clusters in the brain, promoting effects such as muscle relaxation, vasodilation, and bronchodilation [24]. However, NO may potentially contribute to the pathogenesis of MS and to the various facets of the disorder, such as inflammation, oligodendrocyte lesion, changes in synaptic transmission, axonal degeneration, and neural death [24]. Although previous studies have shown relationships between MS and the pollutants NO_2, NO_x, and O_3, in the present study these pollutants did not show a significant association with MS hospitalizations in São Paulo city.

Our results show that cold discomfort was also linked to MS hospitalizations. Unlike the air pollutants, the risk of MS hospitalization in conditions of cold discomfort was higher in men than in women, and was approximately 2.2%. In the literature, heat has been proven to be a major factor for patient discomfort, often generating fatigue [15]. However, some studies [15,16] showed that patients with multiple sclerosis tend to feel more comfortable in environments above 23 °C and a small number of people feel comfortable in environments below 23 °C, but this may also depend on factors such as gender and age. Another explanation related to cold discomfort and MS hospitalization is that during the winter in Sao Paulo city, there are the highest concentrations of pollutants such as SO_2, PM_{10}, and NO, which may be linked to the cold discomfort itself. Cold discomfort can also lead to a lack of vitamin D due to low solar radiation associated with winter periods and decreased sun exposure during cold weather [25]. Lack of vitamin D is a widely studied MS risk factor and its decrease during cold periods may contribute to MS hospitalizations [25].

Our findings are limited to demonstrating a strong association between increased concentrations of SO2, PM10, and NO, as well as cold discomfort, and the rise in the total number of multiple sclerosis hospitalizations (ICD-10-GM: G35) in the city of São Paulo. In other words, we did not take into consideration the distinction of the results by disease phenotype or the recurrence of hospitalizations by the same patient over time. For future studies, it would be interesting to verify how pollutants are associated with disease progression and to further investigate the spatial concentration of hospitalizations and SO_2 concentrations, especially in different socioeconomic contexts. We found that although SO_2 concentrations do not exceed WHO limits in the city of São Paulo, they are highly associated with increased hospitalizations for MS. Therefore, the policies on the adverse effects of SO_2 should be reviewed, since lower concentrations of this pollutant may somehow already be harmful to health.

5. Conclusions

The results obtained in this study confirm that air pollution, in particular SO_2, PM_{10}, and NO pollutants, as well as cold discomfort conditions, in São Paulo city, are associated with increased multiple sclerosis hospitalizations. This study may help improve the patient advice to minimize outdoor activity during days with high levels of pollutants, including SO_2, PM_{10}, and NO. Residents may prefer to live far from urban polluted areas. It should be noted that there are few studies that have correlated meteorological variables, including thermal comfort and air quality, with multiple sclerosis. In addition, this study may provide new insights for the investigation of the pathogenic mechanisms of multiple sclerosis.

Author Contributions: Conceptualization, F.R.D.; methodology, F.R.D. and M.P.-S.; data curation, F.R.D.; statistical analysis, F.R.D.; writing—original draft preparation, F.R.D., M.P.-S. and C.L.Z.V.; writing—review and editing, F.R.D., F.L.T.G., M.P.-S. and C.L.Z.V.; visualization, F.R.D. and F.L.T.G.; supervision, M.P.-S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Sao Paulo Research Foundation—FAPESP (Process 2019/09879-1 and 2015/22864-2).

Institutional Review Board Statement: Approval for the study was not required in accordance with Brazil Platform. This study does not involve humans, it is a non-human intervention study. The type of study is ecological observational. To carry out the study, we used a database with information on hospitalizations and the human thermal discomfort index was calculated from climatic data.

Acknowledgments: The authors would like to thank the funding agency FAPESP (Process 2015/18613-4 and 2015/22864-2) for support in this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Manisalidi, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* **2020**, *8*, 14. [CrossRef] [PubMed]
2. Keswani, A.; Akselrod, H.; Anenberg, S.C. Health and Clinical Impacts of Air Pollution and Linkages with Climate Change. *NEJM Evid.* **2022**, *1*, 1–13. [CrossRef]
3. Bălă, G.P.; Râjnoveanu, R.M.; Tudorache, E.; Motișan, R.; Oancea, C. Air pollution exposure—The (in)visible risk factor for respiratory diseases. *Environ. Sci. Pollut. Res.* **2021**, *28*, 19615–19628. [CrossRef]
4. Al-Kindi, S.G.; Brook, R.D.; Biswal, S.; Rajagopalan, S. Environmental determinants of cardiovascular disease: Lessons learned from air pollution. *Nat. Rev. Cardiol.* **2020**, *17*, 656–672. [CrossRef] [PubMed]

5. Diniz, F.R.; Frony-Macedo, A.L.; Piacenti-Silva, M. Influence of particulate matter and meteorological conditions on multiple sclerosis relapse: A preliminary study in São Paulo, Brazil. *Arch. Health Investig.* **2017**, *6*, 394–398. [CrossRef]
6. Ponzano, M.; Schiavetti, I.; Bergamaschi, R.; Pisoni, E.; Bellavia, A.; Mallucci, G.; Carmisciano, L.; Inglese, M.; Cordioli, C.; Marfia, G.A.; et al. The impact of PM2.5, PM10 and NO_2 on COVID-19 severity in a sample of patients with multiple sclerosis: A case-control study. *Mult. Scler. Relat. Disord.* **2022**, *68*, 104243. [CrossRef]
7. Abbaszadeh, S.; Tabary, M.; Aryannejad, A.; Abolhasani, R.; Araghi, F.; Khaheshi, I.; Azimi, A. Air pollution and multiple sclerosis: A comprehensive review. *Neurol. Sci.* **2021**, *42*, 4063–4072. [CrossRef]
8. Cortese, A.; Lova, L.; Comoli, P.; Volpe, E.; Villa, S.; Mallucci, G.; La Salvia, S.; Romani, A.; Franciotta, D.; Bollati, V.; et al. Air pollution as a contributor to the inflammatory activity of multiple sclerosis. *J. Neuroinflamm.* **2020**, *17*, 334. [CrossRef]
9. Jeanjean, M.; Bind, M.A.; Roux, J.; Ongagna, J.C.; Sèze, J.; Bard, D.; Leray, E. Ozone, NO_2 and PM10 are associated with the occurrence of multiple sclerosis relapses. Evidence from seasonal multi-pollutant analyses. *Environ. Res.* **2018**, *163*, 43–52. [CrossRef]
10. Moreira, M.A.; Felipe, E.; Mendes, M.F.; Tilbery, C.P. Esclerose Múltipla: Estudo descritivo de suas formas clínicas em 302 casos. *Arq. Neuro-Psiquiatr.* **2000**, *58*, 460–466. [CrossRef]
11. Callegaro, D.; Goldbaum, M.; Morais, L.; Tilbery, M.K.; Moreira, A.; Gabbai, A.A.; Scaff, M. The prevalence of multiple sclerosis in the city of São Paulo, Brazil, 1997. *Acta Neurol. Scand.* **2001**, *104*, 208–213. [CrossRef] [PubMed]
12. Cristiano, E.; Patrucco, L.; Rojas, J.L. A systematic review of the epidemiology of multiple sclerosis in South America. *Eur. J. Neurol.* **2008**, *15*, 1273–1278. [CrossRef] [PubMed]
13. Heydarpour, P.; Amini, H.; Khoshkish, S.; Seidkhani, H.; Sahraian, M.A.; Yunesian, M. Potential Impact of Air Pollution on Multiple Sclerosis in Tehran, Iran. *Neuroepidemiology* **2014**, *43*, 233–238. [CrossRef] [PubMed]
14. Angelici, L.; Piola, M.; Cavalleri, T.; Randi, G.; Cortini, F.; Bergamaschi, R.; Baccarelli, A.A.; Bertazzi, P.A.; Pesatori, A.C.; Bollati, V. Effects of particulate matter exposure on multiple sclerosis hospital admission in Lombardy region, Italy. *Environ. Res.* **2016**, *145*, 68–73. [CrossRef]
15. Petajan, J.H.; White, A.T. Recommendations of physical activity in patients with multiple sclerosis. *Sports Med.* **1999**, *27*, 179–191. [CrossRef]
16. Christogianni, A.; O'Garro, J.; Bibb, R.; Filtness, A.; Filingeri, D. Heat and cold sensitivity in multiple sclerosis: A patient-centred perspective on triggers, symptoms, and thermal resilience practices. *Mult. Scler. Relat. Disord.* **2022**, *67*, 104075. [CrossRef]
17. Tadano, Y.S.; Ugaya, C.M.L.; Franco, A.T. Método de regressão de Poisson: Metodologia para avaliação do impacto da poluição atmosférica na saúde populacional. *Ambiente Soc.* **2009**, *12*, 241–255. [CrossRef]
18. Ono, H.S.P.; Kawamura, T. Sensible Climates in Monsoon Asia. *Int. J. Biometeorol.* **1991**, *35*, 39–47. [CrossRef]
19. Lawrence, M.G. The Relationship between Relative Humidity and the Dewpoint Temperature in Moist Air. *Bull. Am. Meteorol. Soc.* **2005**, *86*, 225–233. [CrossRef]
20. Gasparrini, A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. *J. Stat. Softw.* **2011**, *43*, 1–20. [CrossRef]
21. Rigby, R.A.; Stasinopoulos, D.M. Generalized additive models for location, scale and shape. *J. R. Stat. Soc. Ser. C (Appl. Stat.)* **2005**, *54*, 507–554. [CrossRef]
22. Lavery, A.M.; Waubant, E.; Casper, T.C.; Roalstad, S.; Candee, M.; Rose, J.W.; Belman, A.; Weinstock-Guttman, B.; Aaen, G.; Tillema, J.-M.; et al. Urban air quality and associations with pediatric multiple sclerosis. *Ann. Clin. Transl. Neurol.* **2018**, *5*, 1146–1153. [CrossRef] [PubMed]
23. Yao, G.; Yue, H.; Yun, Y.; Sang, N. Chronic SO_2 inhalation above environmental standard impairs neuronal behavior and represses glutamate receptor gene expression and memory-related kinase activation via neuroinflammation in rats. *Environ. Res.* **2015**, *137*, 85–93. [CrossRef] [PubMed]
24. Encinas, J.M.; Manganas, L.; Enikolopov, G. Nitric Oxide and Multiple Sclerosis. *Curr. Neurol. And Neurosci. Rep.* **2005**, *5*, 232–238. [CrossRef]
25. Disanto, G.; Handel, A.E.; Morahan, J.M.; Deluca, G.C.; Kimball, S.M.; Hypponen, E.; Giovannoni, G.; Ebers, G.C.; Ramagopalan, S.V. Vitamin D and multiple sclerosis hospital admissions in Scotland. *QJM Int. J. Med.* **2011**, *104*, 1001–1003. [CrossRef]