Clinical Neurology and Neurosurgery 176 (2019) 67–72

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Fine particulate air pollution and occurrence of spontaneous intracerebral hemorrhage in an area of low air pollution

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ARTICLE INFO

Keywords:
Air pollution
PM2.5
Intracerebral hemorrhage
Stroke

ABSTRACT

Objectives: The association between short-term ambient particulate matter ≤ 2.5 μm diameter (PM2.5) and spontaneous intracerebral hemorrhage (SICH) occurrence is unclear. We aimed to study the association of ambient PM2.5 with occurrence of SICH in an area of low air pollution in southern Portugal.
Patients and methods: PM2.5 levels from the 3 days before the SICH event (Lag 1, 2, 3) was compared with one control period (Lag 15–17) using a case-crossover analysis. Conditional logistic regression was used to estimate the odds ratio (OR) with 95% confidence interval (CI). Analysis was stratified by gender, age, functional neurological status, type of SICH, environmental factors (temperature, humidity, time of day and season).
Results: Three-hundred and eight patients were included (2010–2015); mean age 70.8 years, 62.8% were males. The mean values (μg/l) of PM2.5 were higher on the case days (Lag1 = 7.76, Lag2 = 7.64, Lag3 = 7.74) compared to control period (Lag14-17 = 6.77). For each 10 μg/l increase, the likelihood of SICH increased 5.7% (95% CI = 1.020-1.095. P = .002). The strength of the association was higher in patients younger than 70 years (OR = 1.064, 95% CI = 1.009–1.122); without prior to SICH neurological disability (OR = 1.061, 95% CI 1.022–1.101); with non-lobar type (OR = 1.054, 95% CI = 1.012–1.099). A circadian and circannual pattern was present with increased strength of the association when SICH occurred in the morning time (OR = 1,067, 95% CI = 1.012–1.125), in the fall (OR = 1.118, 95% CI = 1.031–1.213) and the in the winter (OR = 1.064, 95% CI = 1.002–1.129). The association was also potentiated at lower temperature values.
Conclusion: Short-term increases of PM2.5 are associated with occurrence of SICH in Algarve, a region of low ambient pollution. Patient and ambient level factors can influence the strength of this association.

1. Introduction

Air pollution is considered an emerging risk factor for stroke, with an estimated attributable contribution of 29.2% to the global stroke burden [1]. Ambient air pollution is a heterogeneous mixture of gases and particulate matter (PM) resulting from natural, industrial, and human related activities such as car traffic or indoor combustion of solid fuels [2]. Of the airborne particles, fine particulate matter of less than or equal to 2.5 μm in aerodynamic diameter (PM2.5), known to reach the blood stream, has been shown to better correlate with human health, including stroke incidence and mortality [3–5]. There is biological plausibility supporting the association between PM2.5 and cerebrovascular disease [6]. Induction of endothelial dysfunction, vasoconstriction, acute increased blood pressure, inflammation, dysautonomia and coagulation disturbances are among the implicated mechanisms [6,4]. Contrary to acute ischemic stroke (AIS), the

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https://doi.org/10.1016/j.clineuro.2018.11.022
Received 15 October 2018; Received in revised form 20 November 2018; Accepted 30 November 2018
Available online 01 December 2018

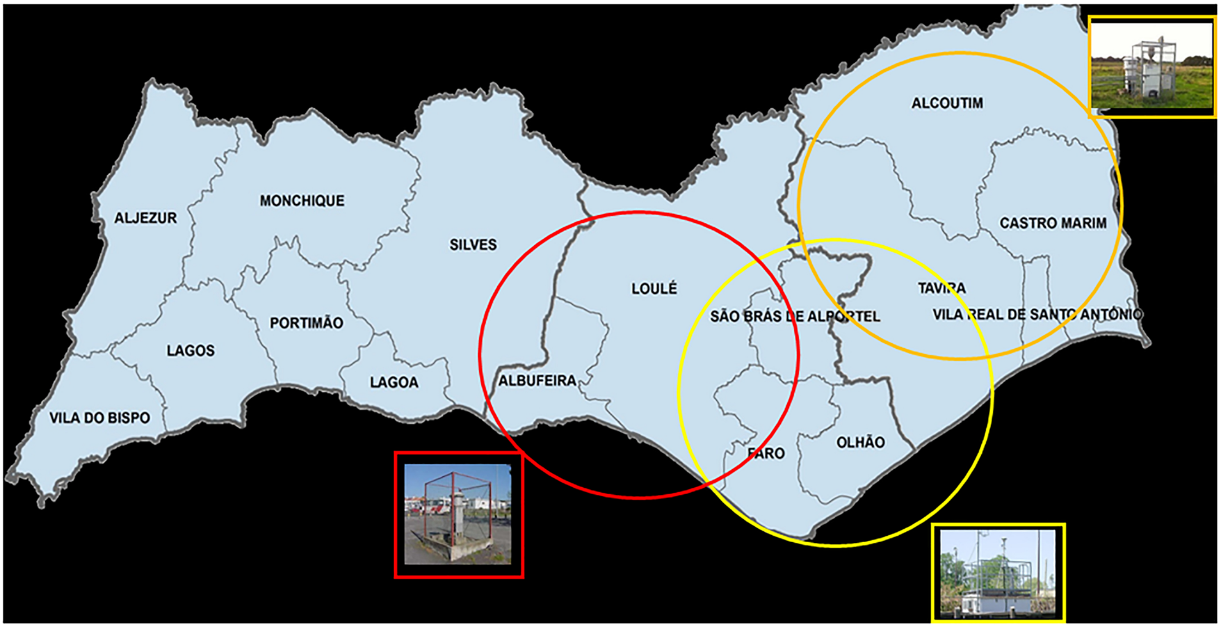

Fig. 1. The map of Algarve with the three background air ambient monitoring stations from the subregion of Central and Sotavento: located in Loulé (red circle); in Faro (yellow circle) and in Alcoutim (orange circle) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

literature on the associations between short-term changes in ambient PM2.5 levels and spontaneous intracerebral hemorrhage (SICH) occurrence is sparse and inconsistent [4,5]. Without having a threshold or exposure-response relationship, day-to-day changes of PM2.5 concentration increased the risk of all-cause mortality in areas of low levels of ambient pollution [7]. This further enhances the need to expand the data on the association between ambient PM2.5 levels and stroke, particularly of hemorrhagic type. The current study aimed to estimate the short-term changes in ambient PM2.5 levels on the occurrence of SICH in a region with low level of ambient air pollution in southern Portugal.

2. Material and methods

2.1. Study area and population

Algarve is the southernmost region of continental Portugal with an area of 4997 km^2 and 451,006 inhabitants. The region has a four seasons temperate Mediterranean climate [8]. The Algarve University Hospitalar Center is the sole regional tertiary hospital qualified to treat stroke in the region. Details of case identification and data collection are described elsewhere [9]. Briefly, we performed daily screening of admitted and discharged patients from the emergency department, SU, neurology, internal medicine, and neurosurgical wards, and weekly screening of all urgent or emergent brain images using the institutional electronic clinical registry and the electronic medical imaging database, respectively, were performed for case identification (2010 to 2015). An electronic generated list of patients with ICH (International Classification of Diseases^{-9} [ICD-9] codes 431 and 432) per year was used for completeness verification. Only patients with presumable small vessel related ICH (lobar and deep located) from the subregion of Central and Sotavento Algarve were included. The baseline individual data including specific timing of stroke occurrence, day, hour or time of the day was extracted from the individual electronic clinical charts.

2.2. Meteorological and air pollution data

Daily and hourly PM2.5 measurements was provided by the Commission for Coordination and Regional Development of the Algarve (CCDR Algarve) which centrally stores data from the regional network of fixed-site ground stations. For this study, 3 background stations from the subregion of Central and Sotavento Algarve were considered (Fig. 1). Daily values were of PM2.5 were considered when at least ≥ 75% of hourly measurements on a particular day were available. Daily meteorological data, temperature (minimum, maximum, medium) and humidity for each of the municipalities were obtained from the Portuguese Meteorological Bureau.

2.3. Exposure assessment

The mandatory individual postcode, which is automatically linked to the electronic clinical chart, was used to identify the patient residence. To reduce exposure misclassification, for each patient, PM2.5 measurements from the closest meteorological station were considered. Only patients living at a maximum of 40 km from any station were included [10].

2.4. Study design and statistical analysis

This design was developed as a variant of the case–control design to study the effects of transient exposures on acute events [11]. The case period was defined as the last three days before the SICH event (Lag 1,2,3), which was compared with one control period (Lag 15–17). The lag of 1,2 and 3 relates to the PM2.5 concentrations on 1, 2 and 3 calendar day prior to SICH occurrence (Fig. 2). Short-term changes in this specific lag period were shown to correlate with risk of stroke in several studies [3].

For the control period, we used the average PM2.5 concentration [12] of the day 1516 and 17 to reduce exclusion of cases due to missing data. Conditional logistic regression analysis was performed to estimate the association between stroke occurrence and ambient PM2.5. Stratified analyses using the average PM2.5 concentrations (Lag1-3) were performed to examine whether the associations differed in consideration individual factors (gender, age, functional neurological status, type of SICH) and environmental factors (temperature, humidity, time of day and season). Any case with at least two of the three Lag days for a given patient had PM2.5 concentrations available in ≥ 75% of the day was analyzed.

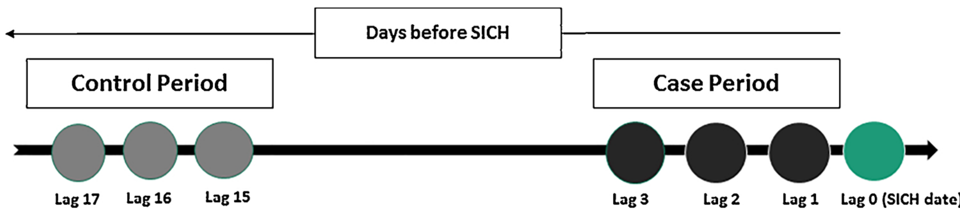

Fig. 2. Schematic representation of the cross-over design of the study. For each case of spontaneous intracerebral hemorrhage (SICH) there is a case period (the 3 immediate days or lag days prior to the stroke onset) and the control period (day 15, 16 and 17 prior to the stroke onset).

Table 1
Baseline characteristics of the study population and timing of spontaneous intracerebral hemorrhage occurrence.

	No. people (%)
Age	
≤ 70	166 (45.1 %)
> 70	202 (54.9)
Sex	
Male	231 (62.8)
Female	137 (37.2)
Modified Rankin scale	
≤ 2	330 (89.9)
≥ 3	37 (10.1)
Type of SICH	
lobar	105 (28.5)
Non lobar	263 (71.5)
Circadian period at SICH onset	
Morning	155 (42.1)
Afternoon	102 (27.7)
Night	89 (24.2)
Unknown	22 (6)
Season at SICH onset	
Winter	117 (31.8%)
Spring	96 (26.1%)
Summer	73 (19.8%)
Autumn	82 (22.3%)

SICH: Spontaneous Intracerebral Hemorrhage.

Table 2
Absolute PM2.5 values in the case and control period.

	Mean	SD	Minimum	Maximum
Case period				
Mean	7,90	5,57	0,308	20,947
Lag 1	7.76	6,07	0,015	23,989
Lag 2	7.64	5,78	0,092	21,293
Lag 3	7.74	6,08	0,004	23,383
Control period	6.77	5,63	0,083	18,950

SD : Standard deviation.

3. Results

We included 78.1% (368) of the 471 SICH cases that occurred during the study period. Patients were excluded (n = 103) because of absence of PM2.5 data (41/39.8%), incomplete SICH information (8/7.6%) and living 40 km away from any of the monitoring stations (54/52.4%). The mean age of was 70.8 years (SD: 12.6), range 29–99 years. The baseline characteristics of the enrolled subjects are described in Table 1. The majority were males (62.8%); independent (89.9%) ; with non-lobar or deep SICH (71.5%); and had stroke onset in morning (42.1%) and winter (31.8%). Taking in account the mean values from the case period, the crude odds of occurring SICH was increased by 5.7% (OR = 1057. 95%CI = 1,020-1,095. P = .002) when the PM2.5 concentration increased by 10 µg/l from the control period. Table 2 shows that the mean values of PM2.5 concentrations were higher on any of the case period days as compared to average control period. The differences of the mean P2.5 concentrations for any of the case days and the entire case period to the control period was statistically significant (Table 3). Table 4 resumes effect modification of clinical and meteorological variables on the association between PM2.5 and SIHC occurrence and Fig. 3 the variables with statistically significant associations. The magnitude of the association was higher in patients ≤ 70 years; without pre-stroke functional impairment; when SICH occurred in the morning, winter, and at lower values of minimum and maximum temperature; and at higher temperature amplitude. The association was statistically significant only for non-lobar type of SICH.

4. Discussion

Despite the satisfactory levels of airborne PM2.5 registered in the region, below the currently considered safe levels of 15 µg/l [13] or 25 µg/l [14] maximum annual average, short-time rises of the pollutant increased the occurrence of SICH. The association between short-term pollution and occurrence of stroke has been shown also in places were air pollution is below the recommended levels [15,16]. In some [17–20] but not all [21,22] studies in the last decade, short-term PM2.5 rises were found to increased risk of SICH occurrence. Several factors may account for this inconsistency. $PM_{2.5}$ is a dynamic complex mixture of particles such as nitrate, sulfate, organic carbon, ammonium, metals, trace elements and others. Its source varies from industrial combustion, sea salt, soil, traffic-related and wood burning [13]. There is evidence

Table 3
Mean differences of PM2.5 (µg/l) concentrations between case days and control period.

Comparison			95% CI of the Difference		
	Mean difference	SD	Lower	Upper	P
Lag 1 versus control period	1.381	3.678	0.797	1.964	< 0.001
Lag 2 versus control period	1.288	3.871	0.674	1.902	< 0.001
Lag 3 versus control period	1.865	4.196	1.200	2.531	< 0.001
Mean Lag1-3 versus control period	1.511	3.274	0.992	1.631	< 0.001

CI: Confidence interval; SD: Standard deviation.

Table 4

Association between short-term increases of PM2.5 and spontaneous intracerebral hemorrhage occurrence adjusted for clinico-demographic, radiological, circadian, circannual and environmental factors.

Adjusted for	Odds ratio#	(95% CI)		P Value
Age group				
≤ 70	1.064	1.009	1.122	* 0.022
> 70	1.051	1.002	1.103	* 0.043
Gender				
Female	1.002	0.991	1.026	0.917
Male	1.017	0.897	1.069	0.063
Type of spontaneous intracerebral hemorrhage				
Lobar	1.065	0.992	1.143	0.081
Non lobar	1.054	1.012	1.099	* 0.012
Modified Rankin Scale				
≤ 2	1.061	1.022	1.101	* 0.002
≥ 3	1.023	0.910	1.150	0.700
Circadian				
Morning	1.067	1.012	1.125	* 0.016
Afternoon	1.060	0.991	1.135	0.092
Night	1.028	0.956	1.106	0.458
Season				
Winter	1.064	1.002	1.129	* 0.044
Spring	1.009	0.933	1.092	0.817
Summer	1.048	0.966	1.136	0.263
Autumn	1.118	1.031	1.213	*0.007
Minimum temperature (degree Celsius)				
Lag 1. Tº ≤ 8.5	1.063	1.004	1.126	* 0.037
Lag 1. Tº 8.5 to 14	1.053	0.984	1.127	0.132
Lag 1. Tº > 14	1.055	0.991	1.124	0.092
Lag 2. Tº ≤ 8.5	1.063	1.004	1.126	* 0.036
Lag 2. Tº 8.5 to 14	1.046	0.980	1.116	0.174
Lag 2. Tº > 14	1.061	0.995	1.133	0.073
Lag 3. Tº ≤ 8.5	1.058	1.000	1.120	0.051
Lag 3. Tº 8.5 to 14	1.055	0.987	1.128	0.118
Lag 3. Tº > 14	1.060	0.994	1.131	0.076
Maximum temperature (degree Celsius)				
Lag 1. Tº ≤ 17.5	1.062	1.004	1.124	* 0.035
Lag 1. Tº 17.5 to 23.5	1.065	0.994	1.141	0.072
Lag 1. Tº > 23.5	1.047	0.982	1.117	0.160
Lag 2. Tº ≤ 17.5	1.061	1.003	1.122	* 0.040
Lag 2. Tº 17.5 to 23.5	1.071	0.999	1.148	0.055
Lag 2. Tº > 23.5	1.044	0.980	1.112	0.183
Lag 3. Tº ≤ 17.5	1.063	1.004	1.124	* 0.035
Lag 3. Tº 17.5 to 23.5	1.054	0.985	1.128	0.125
Lag 3. Tº > 23.5	1.054	0.989	1.124	0.105
Temperature amplitude				
Lag 1. Tº ≤ 8.5	1.050	0.987	1.118	0.122
Lag 1. Tº 8.5 to 11.5	1.054	0.994	1.119	0.079
Lag 1. Tº > 11.5	1.067	1.001	1.138	* 0.048
Lag 2. Tº ≤ 8.5	1.064	0.999	1.132	0.052
Lag 2. Tº 8.5 to 11.5	1.038	0.980	1.100	0.204
Lag 2. Tº > 11.5	1.077	1.006	1.152	* 0.033
Lag 3. Tº ≤ 8.5	1.054	0.993	1.120	0.084
Lag 3. Tº 8.5 to 11.5	1.048	0.987	1.113	0.123
Lag 3. Tº > 11.5	1.072	1.003	1.146	* 0.041
Humidity (%)				
Lag 1. Up to 65	1.050	0.978	1.127	0.175
Lag 1. 65 to 77	1.059	0.914	1.149	0.057
Lag 1. > 77	1.044	0.988	1.104	0.124
Lag 2. Up to 65	1.053	0.988	1.122	0.113
Lag 2. 65 to 77	1.052	0.987	1.121	0.120
Lag 2. > 77	1.015	0.006	1.329	0.236
Lag 3. Up to 65	1.052	0.986	1.123	0.123
Lag 3. 65 to 77	1.046	0.984	1.112	0.147
Lag 3. > 77	1.072	1.002	1.339	0.124

#Calculated for each 10 μg/l increase of PM2.5; CI: confidence interval; * indicates $p < 0.05$; Tº: temperature.

that the specific nature of the constituents of PM2.5 may have different toxicity properties [6,23] and influence differently the occurrence of hemorrhagic stroke independently of the overall PM2.5 levels [24]. Unfortunately data on specific PM2.5 subcomponents in the region is not available. The type of study design, the interaction with several covariates such as meteorological factors, socio-demographic conditions, clinical status, accuracy of air pollutants measurements, misclassification of type of stroke or exposure and time of onset also account from the disparities of the results found in literature [10,25–27]. Moreover, within the same place, air pollution exposure and inhalation doses differs depending on the mode of transport, with higher exposures for commuters using motorized transport [27]. By using a case-crossover study we were able to reduce the effect of time-stable confounders such as socio-demographic variables or individual susceptibility factors or any kind of microenvironments [11]. In addition, the availability of detailed patient-specific data that were extracted from the medical charts including timing of stroke onset, specific area of residence was obtained from the clinical charts reducing the effect of misclassification of exposure and time of onset, that potentially occur in studies based on administrative data [10,25]. Cerebrovascular hemodynamics is altered by minor rises of PM2.5 concentrations in the elderly [28]. In our study however, the magnitude of the impact of increases of PM2.5 was higher in the younger group. This may due to older people spending most of their time indoors. However, confounding effect is to be considered because subjects with non-lobar SICH, which are younger, also had an increase magnitude of the effect of PM2.5. Short-term exposure to specific air pollutants, including PM2.5, can cause clinically significant acute elevations of blood pressure [29,30]. Therefore, it is reasonable to consider that in susceptible individuals, with underlying hypertension related chronic deep small vessel disease, short–term elevations of PM2.5 could precipitate rupture of the vessels or deep located SICH. On the other hand, because of its poor association with hypertension, short-term increases of PM2.5 would not markedly increase the occurrence of lobar SICH.

As in previous studies, the magnitude of the association between PM2.5 and SICH occurrence increased at lower ambient temperature [18,19], during the coolest seasons [31]. Synergism between drops of temperature and increased levels of PM2.5 is a possible explanation, but seasonal differences in exposure or air pollution mixture is a possibility [31,23]. This study has some limitations to be considered. Factors such as composition of PM2.5, indoor exposure data including housing conditions (air filtration, addition sources of PM2.5 such as the heating system) that might alter the association between specific compositions of PM2.5 were not considered.

A substantial part of patients (21.9%) were excluded from the analysis, mostly because of living 40 km away from the closest monitoring station or because of the unavailability of PM2.5 data. However, patients who lived away from monitoring stations were excluded to improve the spatial precision of the measurement of the association between the levels of the pollutant and the occurrence of SICH. Moreover, the PM2.5 measurement failures occurred randomly and independently of the occurrence of SICH. It is therefore unlikely that this limitation influenced significantly the study results.

In conclusion this study shows that small rises in PM2.5 levels increases the occurrence of SICH in a low polluted area. There is a need for clarification of the underlying mechanisms of the association between SICH and PM2.5. Finally, our study reinforces the growing evidence that no safe level of exposure to PM2.5 exists and individuals may have different cerebrovascular or systemic susceptibility.

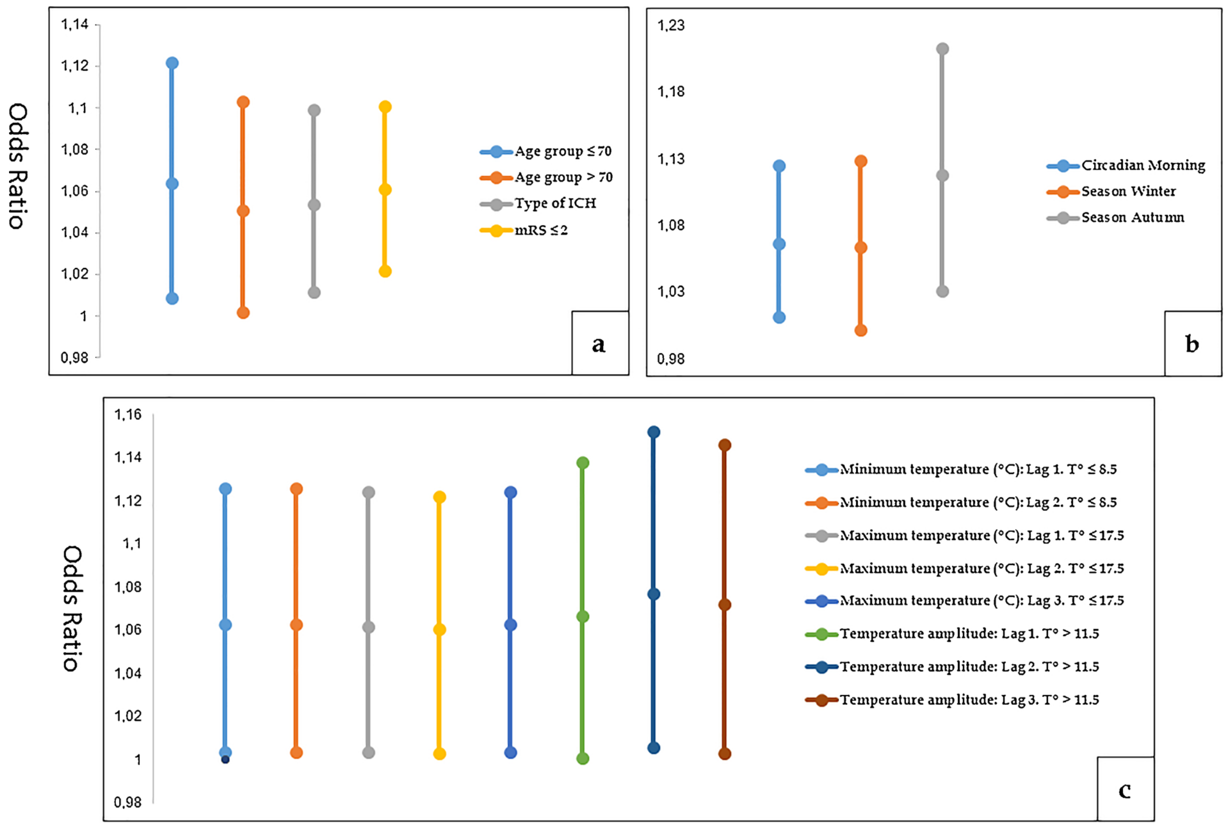

Fig. 3. Association between short-term increases of PM2.5 and spontaneous intracerebral hemorrhage occurrence adjusted for clinico-demographic (a), circadian and circanuallity pattern (b) and meteorological factors (c).

Sources of funding

The study was financially supported by Portuguese Stroke Association (2017 research grant).

Acknowledgments

The authors acknowledge the Portuguese Meteorological Institute and the Commission for Coordination and Regional Development of the Algarve (CCDR Algarve) for providing the data used in this research and Dra. Ana Cristina Guerreiro (Departamento de Saúde Pública e Planeamento of Algarve) for the valuable insights.

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