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ORIGINAL ARTICLE

The role of weather conditions and normal level of air pollution in appearance of stroke in the region of Southeast Europe

Marijana Knezovic[1] · Sanja Pintaric[2] · Marko Mornar Jelavic[3,4] · Vanja Basic Kes[1,3,5] · Visnja Nesek[5,6] · Sinisa Bogovic[7] · Bruno Cvetkovic[8] · Hrvoje Pintaric[1,3]

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Abstract

We investigated correlation between the normal level of air pollution, weather conditions and stroke occurrence in the region of Southeast Europe with a humid continental climate. This retrospective study included 1963 patients, 1712 (87.2%) with ischemic (IS) and 251 (12.8%) with hemorrhagic stroke (HS) admitted to emergency department. The number of patients, values of weather condition (meteorological parameters) [air temperature (°C), atmospheric pressure (kPa), relative humidity (%)] and concentrations of air pollutants [particulate matter (PM_{10}), nitrogen dioxide (NO_2), ozone (O_3)], were recorded and evaluated for each season (spring, summer, autumn, winter) during 2 years (July 2008–June 2010). The highest rate of IS was observed during spring (28.9%) ($p = 0.0002$) and HS in winter (33.9%) ($p = 0.0006$). We have found negative Spearman's correlations (after Bonferroni adjustment for the multiple correlations) of the number of males with values of relative humidity (%) (day 0, rho = − 0.15), the total number of strokes (day 2, rho = − 0.12), females (day 2, rho = − 0.12) and IS (day 2, rho = − 0.13) with concentrations of PM_{10} (μg/m^3), as well as negative correlations of the number of females (day 2, rho = − 0.12) and IS (day 2, rho = − 0.12) with concentrations of NO_2 (μg/m^3) (for all $p < 0.002$). In winter, the number of HS (day 0, rho = 0.25, $p = 0.001$) positively correlated with concentrations of O_3 (μg/m^3). The appearance of stroke has seasonal variations, with the highest rates during spring and winter. Positive correlation between the number of HS and values of O_3 requires an additional reduction of the legally permitted pollutants concentrations.

Keywords Stroke · Ozone · Particular matter · Nitrogen dioxide · Weather conditions

Introduction

Stroke is a major cause of mortality and disability in clinical practice. Its prevalence varies widely across the world, with the highest values in China, while in Europe, the peak prevalence was recorded in the eastern countries. These variations could be explained with genetic, as well as population differences in exposure to traditional cardiovascular risk factors (smoking, alcoholism, hypertension, diabetes, dyslipidemias, and obesity) [1]. Some role in pathogenesis of stroke has external environment, i.e., meteorological parameters and air pollutants, which may help to understand why cerebrovascular events occur at particular time. Studies have reported a seasonal peak of stroke incidence and mortality during winter and spring, and decrease during summer period [2]. A modest rise in serum levels of lipids, glucose, and fibrinogen has been recorded during winter, and reflects the presence of increased prothrombotic and proatherosclerotic factors [3]. Both positive and negative temperature

✉ Marko Mornar Jelavic
mjelavic@yahoo.com

1 University Hospital Center "Sestre milosrdnice", Zagreb, Croatia

2 First school of Economics, Zagreb, Croatia

3 School of Dental Medicine, University of Zagreb, Zagreb, Croatia

4 Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

5 School of Medicine, Josip Juraj Strossmayer, University of Osijek, Osijek, Croatia

6 University Hospital "Sveti Duh", Zagreb, Croatia

7 University Hospital Center Osijek, Osijek, Croatia

8 Teaching Institute of Public Health "dr.Andrija Stampar", Zagreb, Croatia

ranges have potentially important effects on cardiovascular mortality and morbidity [4–6]. Changes in barometric pressure may increase risk of intracranial hemorrhage [7]. Results of several studies obtained that correlation of stroke incidence with meteorological factors was more apparent in women than in men [2, 8]. It could be explained by less efficient thermoregulatory and sweating mechanisms and greater vascular sensitivity to outdoor temperature among women [9, 10].

Air pollutants are a heterogeneous, complex mixture of gases, liquids, and particulate matter (PM), which are connected with an increased risk of cardiovascular events [11]. Furthermore, several studies have shown air pollution represents a great health risk even in developed countries with legally defined thresholds of air pollution [12–14]. Some studies have found, while the others excluded associations between air pollution and stroke admissions [15, 16].

Taken overall, existing studies lack consistency and further work is needed to clarify the nature of the link between weather, air pollution, and stroke incidence.

The aim of this study was to investigate correlation between the normal level of air pollution, weather conditions and stroke occurrence in the region of Southeast Europe, an area with a humid continental climate.

Patients and methods

Zagreb is the largest city of the Republic of Croatia, placed in Southeast Europe, with 1.2 million inhabitants (20% of the total Croatian population) [17].

We retrospectively analysed daily visits in emergency department (ED) of two hospitals in Zagreb (University Hospital Centre “Sestre milosrdnice” and University Hospital “Sveti Duh”), during a 2-year period (July 2008–June 2010). Only patients with ischemic (IS) or hemorrhagic stroke (HS) as a primary diagnosis and living in Zagreb were included.

According to the Köppen’s meteorological classification, the seasons were grouped as follows: winter = December–February, spring = March–May, summer = June–August, and autumn = September–November [18]. Daily average measures of meteorological parameters [air temperature (°C), atmospheric pressure (kPa), and relative humidity (%)] and air pollutants [PM_{10}, nitrogen dioxide (NO_2), and ozone (O_3)] were collected on the basis of hourly values reported by the Meteorological and Hydrological Service of Croatia and National Monitoring Station Zagreb-1 (Environmental Protection Agency).

Statistical analysis

Qualitative data are presented with absolute number (*N*) and percentage (%). To test the seasonal variations in stroke occurrence, a goodness-of-fit Chi-square test was used to compare the difference between the observed and expected number of strokes. Due to lack of evidence of seasonal distribution of stroke admission rate from the previous studies in our geographical area, the expected number of strokes is based on assumption of a homogeneous distribution of the number of admissions throughout seasons (the expected frequency of patients per seasons was defined as 25% of patients).

Quantitative data are presented with median and corresponding interquartile range; differences between two groups were tested by Mann–Whitney *U* test. Spearman’s Rank-Order Correlation analysis was used to determine the correlation of brain stroke admission rate with meteorological parameters and air pollutants. It was classified by Spearman’s rho values as very weak (0–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.0) correlations. The level of statistical significance was set at $p < 0.05$. For the multiple correlations, the statistical significance, after Bonferroni adjustment, was fixed at $p = 0.002$. Processing was done using the MedCalc 17.8.2 (MedCalc Software, Ostend, Belgium).

Results

The median daily values of meteorological parameters varied across seasons, while median concentrations of air pollutants were below the legally defined thresholds (Tables 1, 2). We obtained the following results:

1. Of the total of 1963 patients, there were 251 (12.8%) and 1712 (87.2%) cases with HS and IS, respectively (Fig. 1). Subjects with IS were older than those with HS [median aged 74 (18–104) vs 70 (23–95) years, $p < 0.001$]. The seasonal variation of stroke occurrence was confirmed by Chi-square test. We demonstrated that the peak stroke incidence was in spring ($N = 567$, 28.9%) ($p < 0.0001$). Among the stroke subtypes, the highest IS admission rate was observed in spring ($N = 495$, 28.9%) ($p = 0.0002$), while those with HS had the highest admission rate during winter months ($N = 85$, 33.9%), ($p = 0.0006$). Females (50.0%) were older [median aged 77 (22–104) vs 70 (18–95) years, $p = 0.001$]; we have found no significant gender differences in rates of HS and IS.

Table 1 Average daily values of meteorological parameters during a 2-year study period (July 2008–June 2010)

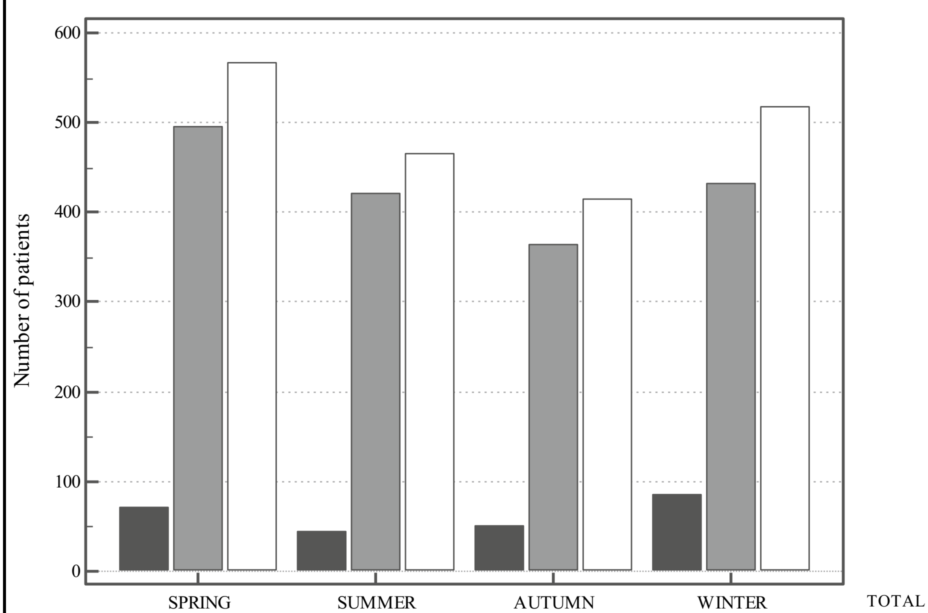
	Days	Temperature (°C) median (range)	Relative humidity (%) median (range)	Air pressure (hPa) median (range)
Total	730	13.4 (− 7.9 to 28.5)	68.9 (37.7 to 95.3)	996 (966 to 1020)
Spring	184	13.8 (− 1.2 to 26.5)	60.7 (37.7 to 91.4)	997 (966 to 1009)
Summer	184	22.5 (13.3 to 28.5)	61.5 (41.0 to 89.5)	996 (984 to 1004)
Autumn	182	13.1 (1.0 to 25.4)	73.5 (44.4 to 95.3)	998 (979 to 1013)
Winter	180	2.6 (− 7.9 to 14.5)	78.9 (43.6 to 94.0)	994 (971 to 1020)
Kruskal–Wallis ANOVA		$p = 0.000$	$p = 0.000$	$p = 0.000$

Statistical significance with $p < 0.05$

Table 2 Average daily values (below legally defined thresholds) of air pollution parameters during a 2-year study period (July 2008–June 2010)

	Days	PM_{10} (μg/m^3) median (range)	Days	NO_2 (μg/m^3) median (range)	Days	O_3 (μg/m^3) median (range)
Total	720	25.7 (4.6 to 146.6)	692	25.9 (1.7 to 89.7)	646	47.1 (4.7 to 135.4)
Spring	184	22.2 (5.5 to 61.2)	184	24.7 (2.0 to 59.3)	184	56.6 (13.7 to 127.6)
Summer	181	20.4 (5.5 to 83.6)	180	24.2 (5.5 to 41.7)	164	59.4 (16.6 to 135.4)
Autumn	182	31.5 (4.6 to 93.8)	148	30.7 (3.7 to 53.2)	128	36.5 (9.1 to 80.3)
Winter	173	37.1 (9.6 to 146.6)	180	26.8 (1.7 to 89.7)	170	27.5 (4.7 to 70.5)
Kruskal–Wallis ANOVA		$p = 0.000$		$p = 0.000$		$p = 0.001$

Statistical significance with $p < 0.05$



	SPRING	SUMMER	AUTUMN	WINTER	TOTAL
HS	72 (28.7%)	44 (17.5%)	50 (19.9%)	85 (33.9%)	251 (12.8%)
IS	495 (28.9%)	421 (24.6%)	364 (21.3%)	432 (25.2%)	1712 (87.2 %)
TOTAL	567 (28.9%)	465 (23.7%)	414(21.1%)	517 (26.3%)	

Fig. 1 Number of patients with stroke during a 2-year study period (July 2008–June 2010)

2. As it is presented in Tables 3 and 4, we have found negative correlations of the number of males with values of relative humidity (%) (day 0, rho = − 0.15), the total number of strokes (day 2, rho = − 0.12), females (day 2, rho = − 0.12) and IS (day 2, rho = − 0.13) with concentrations of PM_{10} (μg/m^3), as well as negative correlations

Table 3 Spearman's Rank-Order Correlation analysis (rho) of meteorological parameters during a 2-year study period (July 2008–June 2010)

	Total	Females	Males	IS	HS
Temperature (°C) day 0					
rho	− 0.05	− 0.08	− 0.01	− 0.02	− 0.10
95% CI	− 0.12 to 0.02	− 0.15 to − 0.01	− 0.08 to 0.06	− 0.09 to 0.06	− 0.17 to − 0.02
p	0.684	0.034	0.836	0.687	0.011
Days	730	730	730	730	730
Temperature (°C) day 1					
rho	− 0.07	− 0.09	− 0.02	− 0.03	− 0.09
95% CI	− 0.14 to 0.01	− 0.16 to − 0.02	− 0.09 to 0.05	− 0.11 to 0.04	− 0.16 to − 0.02
p	0.071	0.014	0.625	0.372	0.013
Days	730	730	730	730	730
Temperature (°C) day 2					
rho	− 0.06	− 0.08	− 0.02	− 0.03	− 0.09
95% CI	− 0.13 to 0.01	− 0.15 to − 0.01	− 0.09 to 0.06	− 0.11 to 0.04	− 0.16 to − 0.02
p	0.085	0.024	0.652	0.360	0.013
Days	730	730	730	730	730
Temperature (°C) day 3					
rho	− 0.04	− 0.04	− 0.02	− 0.01	− 0.09
95% CI	− 0.11 to 0.03	− 0.12 to 0.03	− 0.10 to 0.05	− 0.08 to 0.07	− 0.16 to − 0.02
p	0.297	0.236	0.588	0.861	0.011
Days	730	730	730	730	730
Relative humidity (%) day 0					
rho	− 0.10	0.00	− 0.15	− 0.10	− 0.02
95% CI	− 0.17 to − 0.03	− 0.07 to 0.07	− 0.22 to − 0.07	− 0.17 to − 0.03	− 0.09 to 0.05
p	0.010	0.950	**0.002**	0.010	0.550
Days	730	730	730	730	730
Relative humidity (%) day 1					
rho	− 0.06	0.02	− 0.10	− 0.07	0.02
95% CI	− 0.13 to 0.01	− 0.05 to 0.09	− 0.17 to − 0.03	− 0.14 to 0.01	− 0.06 to 0.09
p	0.106	0.579	0.010	0.067	0.682
Days	730	730	730	730	730
Relative humidity (%) day 2					
rho	− 0.02	0.04	− 0.08	− 0.02	0.00
95% CI	− 0.09 to 0.05	− 0.03 to 0.11	− 0.15 to − 0.00	− 0.09 to 0.06	− 0.07 to 0.07
p	0.578	0.280	0.044	0.673	0.960
Days	730	730	730	730	730
Relative humidity (%) day 3					
rho	− 0.02	0.03	− 0.06	− 0.02	0.00
95% CI	− 0.10 to 0.05	− 0.04 to 0.11	− 0.14 to 0.01	− 0.09 to 0.05	− 0.07 to 0.08
p	0.603	0.366	0.102	0.626	0.909
Days	730	730	730	730	730
Atmospheric pressure (hPa) day 0					
rho	0.04	0.01	0.06	0.04	0.03
95% CI	− 0.04 to 0.11	− 0.06 to 0.08	− 0.02 to 0.13	− 0.04 to 0.11	− 0.05 to 0.10
p	0.293	0.818	0.119	0.330	0.489
Days	730	730	730	730	730

Table 3 (continued)

	Total	Females	Males	IS	HS
Atmospheric pressure (hPa) day 1					
rho	0.06	− 0.01	0.09	0.06	0.00
95% CI	− 0.01 to 0.13	− 0.08 to 0.07	0.02 to 0.17	− 0.01 to 0.14	− 0.07 to 0.07
p	0.103	0.951	0.013	0.088	0.947
Days	730	730	730	730	730
Atmospheric pressure (hPa) day 2					
rho	0.02	− 0.04	0.07	0.02	0.00
95% CI	− 0.05 to 0.09	− 0.11 to 0.03	− 0.01 to 0.14	− 0.05 to 0.10	− 0.07 to 0.08
p	0.560	0.307	0.078	0.544	0.905
Days	730	730	730	730	730
Atmospheric pressure (hPa) day 3					
rho	− 0.01	− 0.05	0.03	− 0.01	0.00
95% CI	− 0.08 to 0.67	− 0.12 to 0.03	− 0.04 to 0.10	− 0.08 to 0.06	− 0.07 to 0.07
p	0.834	0.216	0.399	0.797	0.984
Days	730	730	730	730	730

Statistical significance after Bonferroni adjustement with $p < 0.002$

HS hemorrhagic stroke, *IS* ischemic stroke

of the number of females (day 2, rho = − 0.12) and IS (day 2, rho = − 0.12) with concentrations of NO_2 (μg/m^3) (for all $p < 0.002$);

3. In winter, the number of HS (day 0, rho = 0.25, confidence interval [0.11–0.39], $p = 0.001$) was in positive correlations with concentrations of O_3 (μg/m^3) particles.

Discussion

According to our knowledge, this is the first study which investigates the role of weather conditions and air pollution on the appearance of stroke in the region with a humid continental climate. We want to emphasize that concentrations of air pollutants were below legally defined thresholds during the whole study period. Across studies, findings are inconsistent, complex, and often contradictory.

Stroke continues to be a leading cause of morbidity and mortality, with clearly identified physiological and lifestyle risk factors. Weather conditions may also be connected to stroke, and multiple meteorological variables have been examined as possible influences on stroke occurrence [19].

Weather conditions may be involved in several pathophysiological mechanisms, which were not completely explained [19]. For example, high temperature leads to endothelial dysfunction, dehydration, and increased blood viscosity, with consequent higher risk of adverse vascular events. Cerebral ischemia is worsened by elevated body temperature in both laboratory animals and human stroke patients [19]. In addition, as we already mentioned in "Introduction" section, results of several studies obtained that correlation of stroke incidence with meteorological factors was more apparent in women than in men [2, 8]. It could be explained by less efficient thermoregulatory and sweating mechanisms and greater vascular sensitivity to outdoor temperature among women [9, 10].

Several authors reported every 1 °C increase in mean temperature during the preceding 24 h was associated with a 2.1% rise in hospital admissions for IS [20]. Furthermore, low temperature the day before and at the day of stroke has been found to be a significant risk factor for intracerebral hemorrhage (ICH) [21]. An average 5 °C fall in mean temperature was associated with a 7% elevation in hospital admissions, especially females [8, 22]. Ohwaki et al. reported that days on which hypertensive ICH occurred had significantly lower minimum temperatures compared with the previous day, while the others excluded any influence of temperature on stroke [21–23]. In this study, we also have found no significant correlation between the number of strokes and air temperature.

According to the literature data, the number of patients with stroke positively correlated with atmospheric pressure [23]. Other studies reported risk of IS increased almost fourfold when air pressure fell more than 3 hPa from the previous day, and increased emergency admissions due to ICH were observed for every 1 hPa drop in air pressure from the day prior to the event [23, 24]. Finally, several authors reported no relationship between air pressure and the incidence of particular stroke subtypes [21, 25], which is in consistence with our results.

The third finding was the number of patients (males) negatively correlated with relative humidity. Decreases in humidity on the day of and/or day before stroke have been

Table 4 Spearman's Rank-Order Correlation analysis (*rho)* of air pollution parameters during a 2-year study period (July 2008–June 2010)

	Total	Females	Males	IS	HS
PM_{10} (μg/m^3) day 0					
rho	− 0.02	− 0.05	0.02	− 0.03	0.02
95% CI	− 0.09 to 0.06	− 0.12 to 0.03	− 0.05 to 0.09	− 0.10 to 0.05	− 0.05 to 0.10
p	0.695	0.226	0.549	0.497	0.515
Days	720	720	720	720	720
PM_{10} (μg/m^3) day 1					
rho	− 0.06	− 0.07	− 0.01	− 0.08	0.03
95% CI	− 0.13 to 0.01	− 0.14 to 0.00	− 0.09 to 0.06	− 0.16 to − 0.01	− 0.04 to 0.11
p	0.092	0.063	0.739	0.027	0.369
Days	720	720	720	720	720
PM_{10} (μg/m^3) day 2					
rho	− 0.12	− 0.12	− 0.04	− 0.13	0.00
95% CI	− 0.19 to − 0.05	− 0.19 to − 0.05	− 0.11 to 0.04	− 0.20 to − 0.06	− 0.07 to 0.07
p	**0.001**	**0.001**	0.315	**0.001**	0.995
Days	720	720	720	720	720
PM_{10} (μg/m^3) day 3					
rho	− 0.07	− 0.06	− 0.03	− 0.07	− 0.02
95% CI	− 0.14 to 0.01	− 0.13 to 0.01	− 0.11 to 0.04	− 0.14 to 0.00	− 0.09 to 0.05
p	0.068	0.102	0.376	0.053	0.601
Days	720	720	720	720	720
NO_2 (μg/m^3) day 0					
rho	− 0.01	− 0.01	0.01	− 0,01	− 0.01
95% CI	− 0.09 to 0.06	− 0.09 to 0.06	− 0.07 to 0.08	− 0.08 to 0.06	− 0.08 to 0.07
p	0.707	0.760	0.896	0.802	0.814
Days	692	692	692	692	692
NO_2 (μg/m^3) day 1					
rho	− 0.06	− 0.07	− 0.01	− 0.07	0.02
95% CI	− 0.13 to 0.01	− 0.14 to 0.00	− 0.09 to 0.06	− 0.15 to 0.00	− 0.05 to 0.10
p	0.110	0.063	0.782	0.050	0.532
Days	694	694	694	694	694
NO_2 (μg/m^3) day 2					
rho	− 0.09	− 0.12	0.00	− 0.12	0.05
95% CI	− 0.16 to − 0.01	− 0.19 to − 0.04	− 0.08 to 0.08	− 0.19 to − 0.05	− 0.02 to 0.13
p	0.018	**0.002**	0.990	**0.001**	0.170
Days	694	694	694	694	694
NO_2 (μg/m^3) day 3					
rho	− 0.04	− 0.04	− 0.02	− 0.06	0.02
95% CI	− 0.11 to 0.03	− 0.11 to 0.04	− 0.09 to 0.05	− 0.13 to 0.02	− 0.05 to 0.10
p	0.303	0.333	0.595	0.139	0.563
Days	694	694	694	694	694
O_3 (μg/m^3) day 0					
rho	0.01	− 0.04	0.05	0.00	0.02
95% CI	− 0.07 to 0.08	− 0.12 to 0.04	− 0.03 to 0.13	− 0.08 to 0.08	− 0.06 to 0.10
p	0.836	0.323	0.193	0.991	0.608
Days	646	646	646	646	646

Table 4 (continued)

	Total	Females	Males	IS	HS
O_3 (μg/m^3) day 1					
rho	0.04	0.00	0.04	0.04	− 0.02
95% CI	− 0.04 to 0.12	− 0.08 to 0.08	− 0.03 to 0.12	− 0.04 to 0.12	− 0.10 to 0.06
p	0.335	0.967	0.248	0.281	0.654
Days	646	646	646	646	646
O_3 (μg/m^3) day 2					
rho	0.03	0.01	0.03	0.06	− 0.07
95% CI	− 0.05 to 0.11	− 0.06 to 0.09	− 0.04 to 0.12	− 0.02 to 0.13	− 0.13 to 0.02
p	0.391	0.753	0.376	0.148	0.155
Days	646	646	646	646	646
O_3 (μg/m^3) day 3					
rho	0.06	0.05	0.04	0.07	− 0.01
95% CI	− 0.02 to 0.14	− 0.02 to 0.13	− 0.04 to 0.11	− 0.01 to 0.15	− 0.09 to 0.07
p	0.120	0.166	0.342	0.070	0.769
Days	646	646	646	646	646

Statistical significance after Bonfferoni adjustement with $p < 0.002$

HS hemorrhagic stroke, *IS* ischemic stroke

significantly linked to IS, transient ischemic attack [21] and subarachnoid hemorrhage (SAH) [26]. Another researches have shown no direct relationship between humidity and stroke, including IS [21, 23, 27, 28] and ICH [22, 23, 27, 29].

Chronic inhalation of air pollutants may cause chronic pulmonary and systemic oxidative stress and inflammation, with endothelial dysfunction, vasoconstriction, and atherosclerosis at the vasculature level, and coagulation with thrombosis at the blood tissue level [30]. These processes are critical for the onset of cerebrovascular events, such as stroke, especially IS.

Studies of short-term air pollution exposure (up to lag of 7 days) and hospitalization for any stroke have reported associations between PM_{10} [31–34], NO_2 [33, 35–37], and O_3 [38–40] and IS. A majority of studies did not observe associations between air pollutants and HS, with a few exceptions [33, 41–44]. A few studies reported stronger associations between O_3 and IS in men than women [38, 39, 45]. Air pollution on warm days was more strongly associated with HS and IS in some countries, and both HS and IS in Taiwan [33, 35, 40].

Shah et al. performed meta-analysis based on 94 studies in 28 countries [46]. They reported HS was less common then IS. In terms of the same day exposures, they found small positive associations between the risk of hospitalization or mortality for stroke and each of $PM_{2.5}$, $PM_{10,}$ and NO_2. In terms of stroke subtypes, they found positive associations between IS and exposure to $PM_{2.5}$ and NO_2, and between HS and exposure to NO_2.

Butland et al. analysed 1758 incident strokes (1311 were ischemic and 256 were hemorrhagic) [47]. They found no association between all stroke or IS and the same day exposure to $PM_{2.5}$, PM_{10}, $O_{3,}$ and NO_2. For HS, they found a negative association with PM_{10} suggestive of a 14.6% fall in risk per 10 mg/m^3 increase in pollutant.

We have found the values of PM_{10} and NO_2 negatively correlated with the number of patients (total), females and IS. In winter, the number of HS positively correlated with O_3. For negative correlations between the number of strokes and concentrations of air pollutants, we have no reasonable explanation. These unique or rare findings of our study are similar with previously mentioned investigation of Butland et al., in which authors got unexplained negative association of stroke and PM_{10} [47].

Some limitations of our study include small number of HS. In addition, our study design did not include other stroke subtypes, because we primarily evaluated stroke admissions from ED medical records, and classification stroke by subtypes requires more specific diagnostic tools that are not obtained in ED.

In conclusion, the appearance of stroke in the region with a humid continental climate has seasonal variations, with the highest prevalence during spring and winter. Positive correlation between the number of HS and values of O_3 (μg/m^3) requires an additional reduction of the legally permitted pollutants concentrations. Our results may provide useful data for the future planning of public health measures to minimize the influence of weather conditions and air pollutants on population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study has approval of the appropriate institutional Ethics committee.

Informed consent For this type of study, formal consent is not required.

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