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Exposure to air pollution and its effect on ischemic strokes (EP-PARTICLES study)

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It is well known that exceeded levels of particulate matter in the air and other air pollutants harmfully affect the cardiovascular system. Empirical analyses of the effects of these factors on stroke incidence and mortality are still limited. The main objective of our analyses was to determine the association between short-term exposure to air pollutants and stroke incidence in non-industrial areas, more specifically in north-eastern Poland. To achieve this aim, we used data from the National Health Fund on patients hospitalized for stroke between 2011 and 2020 in the largest city of the region described as the Green Lungs of Poland. The pollution levels and atmospheric conditions data were obtained from the Provincial Inspectorate for Environmental Protection and the Institute of Meteorology and Water Management. Using daily data on hospitalizations, atmospheric conditions, and pollution, as well as ordered logistic regression models the hypotheses on the impact of weather and air pollution conditions on ischemic strokes were tested. The study group included 4838 patients, 45.6% of whom were male; the average patient age was approximately 74 years. The average concentrations of $PM_{2.5}$ were 19.09 μg/m³, PM_{10} 26.66 μg/m³ and CO 0.35 μg/m³. Analyses showed that an increase in $PM_{2.5}$ and PM_{10} concentrations by 10 μg/m³ was associated with an increase in the incidence of stroke on the day of exposure (OR = 1.075, 95% CI 0.999–1.157, P = 0.053; OR = 1.056, 95% CI 1.004–1.110, P = 0.035) and the effect was even several times greater on the occurrence of a stroke event in general ($PM_{2.5}$: OR = 1.120, 95% CI 1.013–1.237, P = 0.026; PM_{10}: OR = 1.103, 95% CI 1.028–1.182, P = 0.006). Furthermore, a short-term (up to 3 days) effect of CO on stroke incidence was observed in the study area. An increase of 1 μg/m³ CO was associated with a lower incidence of stroke 2 days after the exposure (OR = 0.976, 95% CI 0.953–0.998, P = 0.037) and a higher incidence 3 days after the exposure (OR = 1.026, 95% CI 1.004–1.049, P = 0.022).

Following the latest WHO reports, the number of deaths caused by strokes has emerged since the year 2000 and in 2019 they were responsible for over 6 million deaths. Interestingly, dividing strokes into hemorrhagic and ischemic, a more significant increase was noted in the latter[1]. Although from 1990 to 2019 the contribution of ambient particulate matter with a diameter of < 2.5 μm ($PM_{2.5}$) pollution decreased from 32.5 to 20.1%, in 2019 air quality was the fourth leading risk factor contributing to stroke death and disability combined (DALYs)[2]. Regardless of the fact the exposure to air pollution gradually decreases in high-income countries, the problem is still relevant in Poland—a country with the highest particulate matter with a diameter of < 10 μm (PM_{10}) and $PM_{2.5}$ concentrations in the European Union (EU)[3,4]. Particulate matter was the sixth leading risk factor for all-cause mortality in Poland in 2019[3]. Although according to the World Bank, Poland is considered a high-income country, it still has to face post-transformation issues such as a high share of old cars[5,6]. Alleged pathomechanisms of detrimental effects of air pollution include endothelial dysfunction, generation of reactive oxygen species (ROS), and induction of systemic inflammation[7–9].

The incidence rates of strokes differ between seasons and days of the week. Many studies have reported that stroke incidence rates are the highest in winter and the lowest in summer[10,11]. Possible explanations might include the activation of the sympathetic nervous system during cold seasons, atrial fibrillation paroxysms in winter, and, finally, higher concentrations of air pollutants during heating seasons[12–14]. When analyzing weekly patterns of

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stroke occurrence, most studies are consistent with a phenomenon of Monday excess[15–17]. It comes in line with other research reporting more frequent occurrences of acute cardiovascular events such as myocardial infarction, aortic dissection, and takotsubo-syndrome on Mondays[16,18,19]. Nevertheless, the mechanisms and underlying factors remain blurred. Besides physiological mechanisms including Monday morning surge in blood pressure and increased double product, some hypotheses include differences in the socioeconomic status of patients[17,20–22].

Seasonal variations are inseparably connected with changing weather conditions. Many studies provided strong evidence of an association between stroke occurrence and ambient temperature[23–25]. Interestingly, it seems that change in temperature is more important than absolute temperature[25]. The detrimental influence of air pressure and humidity is controversial. Few studies granted evidence on the correlation between daily barometric pressure variation and daily stroke hospitalization, however, Cao et al. (2016) in their meta-analysis found no such relationship[26–28].

Considering the aforementioned inconsistencies, gaps in evidence, and lack of analysis from this part of Europe, there is a need for further research. The purpose of this study was to investigate temporal variations of stroke incidence in north-eastern Poland and its link with the short-term effect of air pollution in the years 2011–2020.

Materials and methods

Study population and data collection.   Data on stroke occurrence in the years 2011–2020 were collected from the National Health Fund. The data on air pollutants and weather conditions were obtained from Voivodeship Inspectorate for Environmental Protection in Bialystok and the Institute of Meteorology and Water Management. According to codes in the International Classification of Diseases-10th Revision, we extracted the data for ischemic stroke (ICD-10 I63). Patients were hospitalized in 5 hospitals in or nearby the city: University Clinical Hospital of Bialystok, Voivodeship Hospital in Bialystok, Hospital in Choroszcz, Hospital of the Ministry of Interior and Administration in Bialystok, and the City Hospital in Bialystok. The former three hospitals were responsible for over 99% of admissions. We included only Bialystok adult residents (>18 years old) admitted to the hospital with ischemic stroke diagnosis (ICD-10 I63) in the years 2011–2020. We excluded hospitalizations of patients transferred from another hospital and hospitalizations during a period without data on air pollutants concentration. We used the concentration of air pollutants (particulate matter with a diameter of 2.5 µm or less ($PM_{2.5}$), 10 µm or less (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), temperature, mean atmospheric pressure, and relative humidity. In the analysis, the exceedance of air pollution norms was determined based on the World Health Organization (WHO) guidelines concerning air quality. The 24-h concentrations recommended by the WHO are 45 µg/m³, 15 µg/m³, 40 µg/m³, 25 µg/m³, 4 mg/m³ for PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, respectively[29]. Days with missing data were excluded from the analysis.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Bioethics Committee of the Medical University of Białystok (approval number APK.002.81.2022). Additionally, it was registered in the database of clinical studies www.clinicaltrials.gov (accessed on 5 September 2022, identification number NCT05198492).

Study region.   Białystok is the capital of Podlaskie Voivodeship, a region located in north-eastern Poland. It is inhabited by nearly 300,000 citizens, which makes it the 10th most populated city in Poland and the 2nd considering the population density. Close location to the four national parks, over 18% of the city area covered by forests, and the lack of heavy industry have an impact on the way the city is being perceived[30]. It is often referred to as the capital of the region known as the Green Lungs of Poland and is associated with the resistance to accepting the rush of modern lifestyle. In 2020 men accounted for 46.91% of the city's population, which resulted in a femininity ratio of 113, and 17.8% of citizens were over 65 years old[30]. With almost 80% of the share, area sources were the main sources of PM_{10} in the studied region in 2018[31].

Statistical analysis.   Due to the discrete nature of stroke incidences, discrete outcome models (such as logit and probit models) are usually used to link stroke hospital admissions to the observed risk factors[31]. As the daily number of stroke incidences is greater than two, the ordered nature between these levels is its inherent characteristic. Ordered outcome models have a potential advantage over unordered outcome models because they can account for the correlation among neighboring admissions levels by recognizing the ordered nature [for discussion or example see[32,33]. The assumptions of the ordered logit models were rigorously tested using the Wolfe-Gould test[34] and the test results indicate that the proportional odds assumption has not been violated[35].

Multivariate analysis was done using a generalized ordered logit model with the number of stroke incidences. The proportional odds ratios were estimated across the categories of the outcome variable—admissions for ischemic strokes in Białystok in 2011–2020. The exposure variables were each air pollutant at a lag of 0–7 days prior to admission. Also, the robustness analysis was performed allowing up to 30-day lags. Additionally, the logit model parameters were estimated for the robustness analyses, and the day on which at least one stroke incidence occurred was taken as the event.

The set of other explanatory variables included temperature, air pressure, relative humidity, day of the week, season (Spring, Summer, Autumn, Winter), year, and share of elderly (women aged over 60 and men over 65 years as a percentage of the total population). The weather variables were incorporated as a natural cubic spline with 4 df (3 equally-spaced knots), to control potential non-linear confounding effects[36,37]. Additionally, to avoid long-term bias we considered the time trend variable and indicator variables for the day of the week to account for intra-weekly variations in stroke incidences. In estimated equations, lag distributions for individual variables were included to get leveling off effect for seasonal and long-term trends[38,39].

	Ischemic stroke
Total, N	4838
CMR, (100,000 population/year)	162.9
SMR, (100,000 population/year)	174.6
Mean age, (SD)	74.3 (12.2)
Male, % (N)	45.6 (2207)
Daily mean (SD)	1.3 (1.2)
Daily median (minimum – maximum)	1 (0–8)
In-hospital mortality; %, (N)	16.8, (813)

Table 1. Ischemic stroke morbidity in Bialystok in the years 2010–2020. CMR, crude morbidity rate per 100,000 population per year; SD, standard deviation; SMR, standardized morbidity rate per 100,000 population per year.

	Ischemic stroke cases		
Season	N	%	P
Winter	1283	26.52	
Spring	1199	24.78	< 0.001
Summer	1138	23.52	
Autumn	1218	25.17	

Table 2. Seasonal variation in the frequency of ischemic stroke in the study population. Spring—months from March to the end of May, Summer—June to the end of August, Autumn—September to the end of November, Winter—December to the end of February.

Day of the week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	P
Ischemic stroke cases, N (%)	807 (16.68)	677 (13.99)	761 (15.73)	675 (13.95)	692 (14.30)	583 (12.05)	653 (13.29)	< 0.001
Dunn's pairwise comparison of stroke by day								
Tuesday	0.051							
Wednesday	0.8	0.11						
Thursday	0.03	0.64	0.72					
Friday	0.062	0.45	0.13	0.74				
Saturday	< 0.001	0.049	< 0.001	0.08	0.04			
Sunday	< 0.001	0.45	0.003	0.53	0.47	0.45		

Table 3. Weekly changes in the frequency of ischemic stroke occurrence in the study population. N; number.

Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI) in association with increases in exposures (per 10 μg/m³ increase in PMs and 1 mg/m³ in case of others). To control sample heterogeneity the estimates have been conducted in subsamples for the season, (age (65+ and 75+) and gender. All analyses were performed using MS Excel (Microsoft, 2020, version 16.40, Redmond, WA, USA) and Stata Statistical Software, (StataCorp, 2022, version 17, TX, USA).

Results

From 2010 to 2020 in Białystok, we recorded 4,838 ischemic stroke cases with a daily mean of 1.3 cases [Standard deviation (SD) = 1.2]. Out of the analyzed group, 45.6% of patients were male with a mean age of 74.3 years (SD = 12.2). The standardized morbidity rate (SMR) was 174.6 per 100,000 population/year and the crude morbidity rate was 162.9 per 100,000 population/year. In-hospital deaths accounted for 16.8% (N = 813) (Table 1).

Taking into account the seasonal distribution of ischemic stroke incidence we observed that the highest number of ischemic stroke cases occurred in the winter season 26.52% (N = 1238), and the lowest in spring 24.78% (N = 1199,), P < 0.001. Regarding the incidence of ischemic strokes throughout the week, the highest number of strokes occurred on Mondays 16.68% (N = 807) vs. Saturdays [12.05% (N = 583)] and Sundays [13.29% (N = 653)], P < 0.001 for pairwise comparsion, (Tables 2 and 3).

The limit of the daily mean given by the WHO guidelines for $PM_{2.5}$ was exceeded on 48% of days, 11.2% days for PM_{10}, and 5.5% days for NO_2. The daily mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and SO_2, were 19.1 μg/m³ (SD = 14.5, IQR = 14.3), 26.7 μg/m³ (SD = 17.7, IQR = 16.7), 13.9 μg/m³ (SD = 6.2, IQR = 7.6), and 3.0 μg/m³ (SD = 2.7, IQR = 2.8), respectively. The daily mean for SO_2 was not exceeded on any day during the observation

		NO₂ µg/m³	SO₂ µg/m³	PM₂.₅ µg/m³	PM₁₀ µg/m³	Temp. °C	RH %	Atm. P. hPa
All seasons	No. of daily observations, % (N)	98.4 (3594)	97.8 (3572)	95.5 (3488)	96.1 (3510)	100 (3653)	100 (3653)	100 (3653)
	Daily mean (SD)	13.9 (6.2)	3.0 (2.7)	19.1 (14.5)	26.7 (17.7)	8.1 (8.6)	80.1 (12.4)	1016.1 (8.6)
	Daily 1st quartile	9.5	1.2	9.6	15.5	1.8	71.8	1010.8
	Daily median	12.7	2.4	14.5	22.1	8	81.9	1015.9
	Daily 3rd quartile	17.1	4	24	32.2	15.2	90	1021.6
	Daily IQR	7.6	2.8	14.3	16.7	13.4	18.2	10.8
	Exceeded daily mean (WHO 2021 guidelines values), % (N)	5.5 (197)	0 (0)	48 (1661)	11.2 (393)	N/A	N/A	N/A
Autumn	Daily mean (SD)	15.08 (6.2)	5.4 (8.2)	30.87 (18.9)	22.39 (15.4)	3.4 (5.4)	89.2 (7.8)	1017.25 (9.7)
	Daily 1st quartile	10.46	1.58	17.43	11.83	0.1	85.6	1011
	Daily median	14.33	3.27	27.4	19.46	3.6	90.5	1017.55
	Daily 3rd quartile	18.8	5.33	38.86	30.71	7.1	94.8	1024.4
	Daily IQR	8.34	3.75	21.43	18.88	7	9.2	13.4
Spring	Daily mean (SD)	12.59 (5)	2.37 (1.5)	21.59 (9.8)	13.01 (6.3)	12.93 (5.4)	70.27 (11.8)	1014.88 (6.5)
	Daily 1st quartile	9.13	1.19	14.76	8.6	9	61.8	1010.5
	Daily median	11.73	2.08	19.84	11.38	13.35	69.8	1014.7
	Daily 3rd quartile	15.23	3.28	25.94	15.8	16.9	79	1019.5
	Daily IQR	6.1	2.09	11.18	7.2	7.9	17.2	9
Summer	Daily mean (SD)	12.61 (5.2)	3.41 (7.7)	20.72 (9.1)	10.4 (5.4)	16.54 (3.9)	78.36 (9.2)	1015.56 (5.8)
	Daily 1st quartile	8.92	1.11	14.06	6.67	13.9	72.45	1011.8
	Daily median	11.61	1.9	19	9.5	16.5	78.4	1015.5
	Daily 3rd quartile	15.16	2.95	25.46	13.33	19.3	84.8	1019.15
	Daily IQR	6.25	1.85	11.4	6.66	5.4	12.35	7.35
Winter	Daily mean (SD)	15.69 (7.5)	4.65 (3.7)	33.54 (24.3)	28.57 (19)	− 0.54 (5.6)	81.91 (12.1)	1016.67 (11.2)
	Daily 1st quartile	10.43	2.24	17.61	15.13	− 3	74.85	1008.9
	Daily median	14.2	3.93	26.73	23.67	0.5	84.5	1017
	Daily 3rd quartile	19.41	5.9	41.82	36.13	3.2	90.95	1024.4
	Daily IQR	8.98	3.67	24.21	21.01	6.2	16.1	15.5

Table 4. Statistics for daily concentrations of air pollutants and weather conditions in the period of 2011–2020. Atm. P., atmospheric pressure; IQR, interquartile range; N/A, not applicable; N/D, no data; NO₂, nitrogen dioxide; PM₂.₅, particulate matter with a diameter of 2.5 µm or less; PM₁₀ particulate matter with a diameter of 10 µm or less; RH, relative humidity; SD, standard deviation; SO₂, sulfur dioxide; Temp., temperature; WHO, World Health Organization.

Ischemic stroke	Days with exceeded daily limit values for NO₂ (N = 197)	Days without exceeded daily limit values for NO₂ (N = 3397)	P
Daily mean (SD), Median (1Q–3Q)	1.5 (1.3) 1 (1–2)	1.31 (1.2) 1 (0–2)	0.02
Ischemic stroke	**Days with exceeded daily limit values for PM₂.₅ (N = 1661)**	**Days without exceeded daily limit values for PM₂.₅ (N = 1827)**	**P**
Daily mean (SD), Median (1Q–3Q)	1.37 (1.2) 1 (0–2)	1.26 (1.2) 1 (0–2)	0.04
Ischemic stroke	**Days with exceeded daily limit values for PM₁₀ (N = 393)**	**Days without exceeded daily limit values for PM₁₀ (N = 3117)**	**P**
Daily mean (SD), Median (1Q–3Q)	1.45 (1.2) 1 (1–2)	1.31 (1.2) 1 (0–2)	0.6

Table 5. The comparison of the frequency of hospitalizations due to ischemic stroke on the days with and without exceeded daily norms recommended by the World Health Organization for nitrogen dioxide, particulate matter with a diameter of 10 µm or less, and particulate matter with a diameter of 2.5 µm or less. NO₂, nitrogen dioxide; PM₂.₅, particulate matter with a diameter of 2.5 µm or less; PM₁₀ particulate matter with a diameter of 10 µm or less; SD, standard deviation.
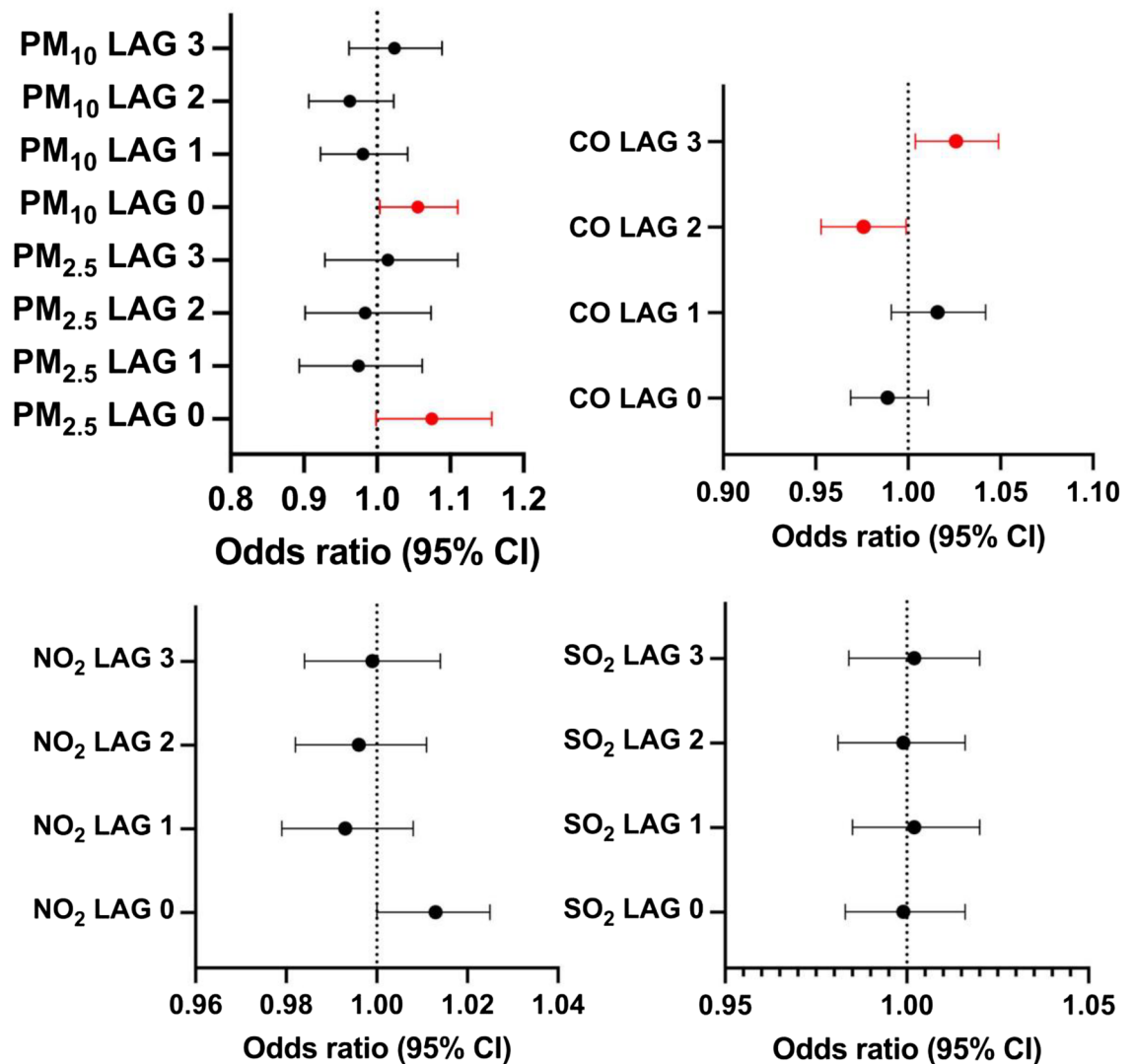
Figure 1. Overall associations between the exposure to short-term pollutants and ischemic stroke incidence.

time (Table 4). The frequency of hospitalizations due to ischemic stroke on the days with exceeded daily norms of $PM_{2.5}$ (1.37/day, N = 1661 vs. 1.26/day, N = 1827; P = 0.04) and NO_2 (1.5/day, N = 197 vs. 1.31/day, N = 3397; P = 0.02) was significantly higher than on days without exceeded limit values (Table 5).

The effect of air pollution on ischemic stroke incidence was noted on lag 0 for $PM_{2.5}$ with OR = 1.075 (95% CI 0.999–1.157, P = 0.053) as well as for PM_{10} with OR = 1.056 (95% CI 1.004–1.11, P = 0.04). Additionally, the effect of CO on lag 2 was associated with decreased number of strokes OR = 0.976 (95% CI 0.953–0.999, P = 0.04), whereas on lag 3 with increased stroke incidence OR = 1.026 (95% CI 1.004–1.049, P = 0.02) (Fig. 1).

The increase in concentration of $PM_{2.5}$ (1.109, 95% CI 1.002–1.227, P = 0.04), PM_{10} (1.089, 95% CI 1.010–1.174, P = 0.03) and NO_2 (1.028, 95% CI 1.006–1.050, P = 0.01) in winter season at lag 0 resulted in an increase in ischemic stroke incidence. This effect was also observed for CO in the summer season on lag 3 (OR = 1.037, 95% CI 1.008–1.067, P = 0.01). However, the opposite relation was noted for CO on lag 2 (OR = 0.957, 95% CI 0.924–0.990, P = 0.012) (Table 6).

By dividing the study group into patients above and below 75 years of age, the effect of NO_2 and CO was observed on lag 0 (OR = 1.015, 95% CI 1.001–1.029, p = 0.038 and OR = 0.974, 95% CI 0.952–0.997, P = 0.025, respectively) in the group of patients younger than 75 years old. Moreover, when comparing people younger and older than 65 years old, there is an association between an increase in the concentration of $PM_{2.5}$ and PM_{10} and stroke incidence in the latter group (OR = 1.091, 95% CI 1.013–1.176, P = 0.02 and OR = 1.068, 95% CI 1.015–1.125, P = 0.01, respectively). There was no significant impact of air pollution on stroke occurrence in people below 65 years old (Fig. 2).

By dividing the study group into women and men, the effect of PM_{10} was observed on lag 0 (OR = 1.065, 95% CI 1.009–1.123, P = 0.02) in the female patients. There was no significant impact of air pollution on stroke occurrence in the male population (Fig. 3).

Variables		Winter OR (95% CI)	P- value	Spring OR (95% CI)	P- value	Summer OR (95% CI)	P- value	Autumn OR (95% CI)	P- value
$PM_{2.5}$	LAG 0	1.109 (1.002–1.227)	0.045	1.091 (0.775–1.537)	0.617	1.218 (0.789–1.881)	0.373	1.055 (0.913–1.219)	0.467
	LAG 1	0.907 (0.807–1.021)	0.105	1.332 (0.934–1.900)	0.113	0.631 (0.389–1.024)	0.062	1.006 (0.852–1.189)	0.941
	LAG 2	1.019 (0.905–1.148)	0.755	0.652 (0.456–0.933)	0.019	0.863 (0.527–1.413)	0.558	1.008 (0.848–1.199)	0.924
	LAG 3	1.026 (0.906–1.163)	0.681	1.125 (0.821–1.541)	0.464	0.785 (0.476–1.295)	0.343	0.964 (0.812–1.145)	0.677
PM_{10}	LAG 0	1.089 (1.010–1.174)	0.026	1.094 (0.880–1.360)	0.420	1.020 (0.801–1.298)	0.873	1.041 (0.951–1.139)	0.381
	LAG 1	0.916 (0.836–1.004)	0.060	1.056 (0.843–1.322)	0.635	1.055 (0.799–1.392)	0.706	1.029 (0.927–1.141)	0.381
	LAG 2	1.048 (0.957–1.148)	0.309	0.818 (0.655–1.022)	0.077	0.839 (0.635–1.110)	0.219	1.029 (0.927–1.141)	0.595
	LAG 3	0.983 (0.893–1.081)	0.720	0.995 (0.804–1.233)	0.966	1.006 (0.750–1.348)	0.971	1.038 (0.932–1.156)	0.492
CO	LAG 0	2.303 (0.806–6.578)	0.119	0.908 (0.078–10.632)	0.939	0.995 (0.965–1.026)	0.741	0.970 (0.935–1.005)	0.096
	LAG 1	0.452 (0.126–1.616)	0.222	2.510 (0.150–42.033)	0.522	1.019 (0.981–1.059)	0.331	1.015 (0.976–1.057)	0.448
	LAG 2	1.118 (0.313–4.000)	0.864	0.141 (0.008–2.410)	0.176	0.957 (0.924–0.990)	0.012	0.997 (0.959–1.037)	0.885
	LAG 3	0.714 (0.187–2.724)	0.622	0.319 (0.021–4.830)	0.410	1.037 (1.008–1.067)	0.013	1.019 (0.979–1.061)	0.351
NO_2	LAG 0	1.028 (1.006–1.050)	0.013	0.998 (0.967–1.030)	0.897	1.016 (0.984–1.049)	0.330	0.838 (0.980–1.036)	0.611
	LAG 1	0.975 (0.951–1.000)	0.047	1.008 (0.976–1.042)	0.619	0.987 (0.951–1.025)	0.494	1.004 (0.973–1.037)	0.786
	LAG 2	1.012 (0.987–1.038)	0.359	0.987 (0.955–1.020)	0.428	0.998 (0.962–1.035)	0.899	0.988 (0.957–1.020)	0.457
	LAG 3	1.001 (0.976–1.027)	0.925	0.971 (0.940–1.004)	0.084	1.004 (0.968–1.041)	0.838	0.997 (0.966–1.030)	0.867
SO_2	LAG 0	1.028 (0.980–1.079)	0.260	0.877 (0.768–1.000)	0.050	1.006 (0.967–1.047)	0.768	1.000 (0.978–1.022)	0.990
	LAG 1	1.007 (0.955–1.060)	0.805	1.106 (0.953–1.284)	0.186	0.993 (0.953–1.035)	0.744	1.002 (0.980–1.025)	0.843
	LAG 2	0.988 (0.935–1.043)	0.662	0.999 (0.863–1.156)	0.991	1.020 (0.980–1.061)	0.333	0.998 (0.975–1.021)	0.840
	LAG 3	1.028 (0.974–1.085)	0.315	0.953 (0.826–1.100)	0.512	0.974 (0.933–1.018)	0.248	1.008 (0.984–1.033)	0.511

Table 6. Associations between the exposure to short-term pollutants and ischemic stroke incidence over the seasons. NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with a diameter of 2.5 μm or less; PM_{10} particulate matter with a diameter of 10 μm or less; SO_2, sulfur dioxide; CO, carbon monoxide.

Discussion

Our study is comprehensive and differs from others for several reasons. First, we analyze a non-industrial region with a predominance of the agriculture sector (considered as one of the cleanest regions in Poland). Second, we consider several types of air pollutants including $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO concentrations. Third, in our analyses, we pay attention to the heterogeneity of the studied group and the analyzed period—we estimate the impact of the mentioned pollutants on stroke incidences in subgroups by age, sex, and season of the year.

The main findings of our work show that air pollution affects the incidence of ischemic strokes with the greatest effect in the winter season. The main pollutants affecting the number of hospitalizations were PMs as well as NO_2 and CO. Considering the occurrence of strokes over a week, the highest number occurred at the beginning of the week.

Chronobiology is a trending field of science that examines how natural rhythms affect our lives. Seasonal and weekly fluctuations have a serious influence on human health, which was demonstrated multiple times[10,11,22,40]. Our study revealed significant seasonal variation in the occurrence and mortality rate of ischemic stroke. Most recent studies have shown an association between cold season and greater hospital admission and mortality due to acute ischemic stroke, which comes in line with our results[10,11]. On the other hand, Bahonar et al.[42] and Raj et al.[43] demonstrated no considerable seasonal fluctuation in Isfahan, Iran and New Delhi, India, respectively. However, these two aforementioned studies were performed in warm climates with relatively high temperatures during the cold season, suggesting that these conclusions may not be easily extrapolated to temperate climate countries. There are many ischemic stroke risk factors with seasonal predominance such as hypertension and atrial fibrillation. According to many studies, average blood pressure is significantly higher in the winter season
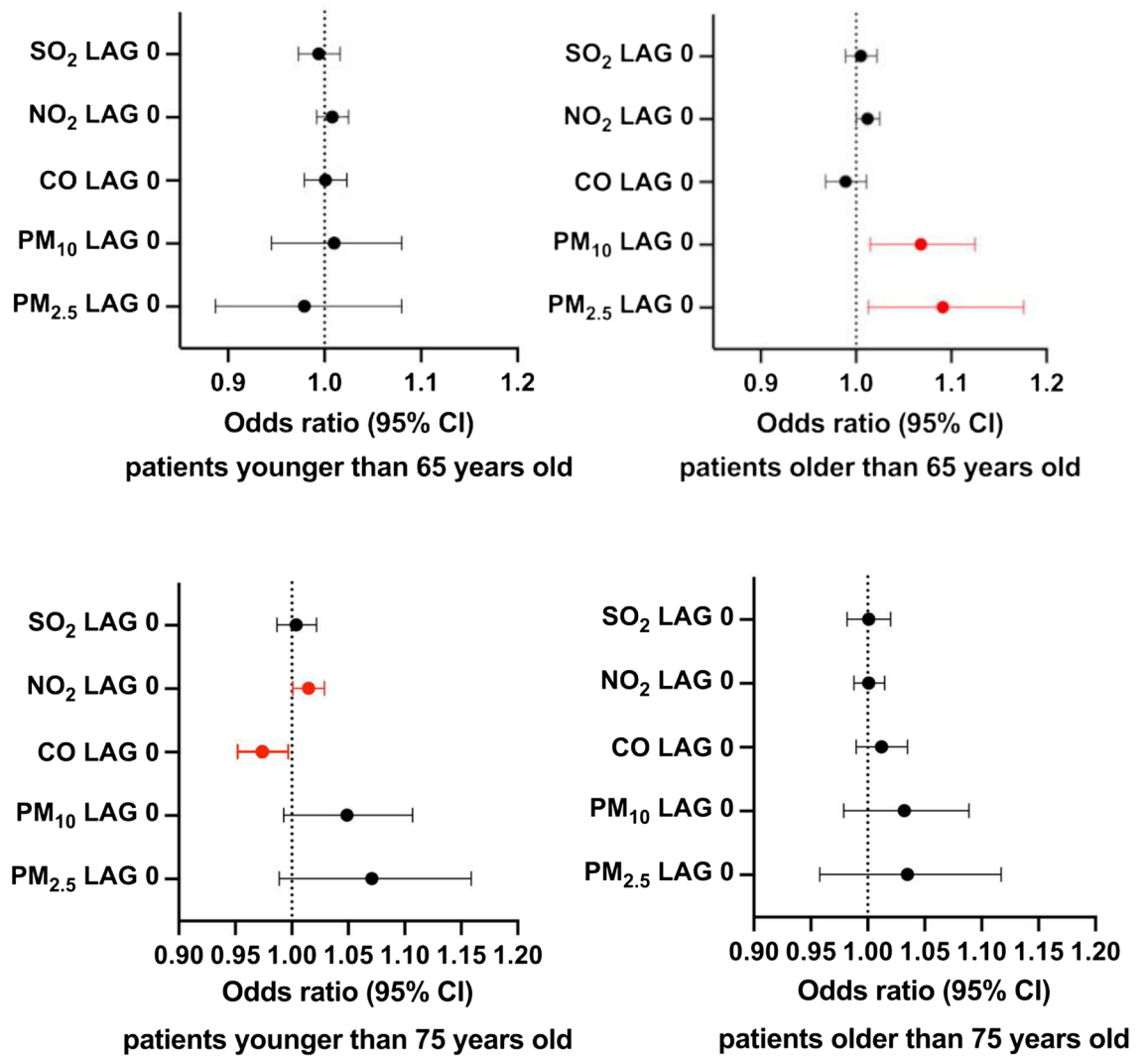
Figure 2. Associations between the exposure to short-term pollutants and ischemic stroke incidence in the study group divided by age.
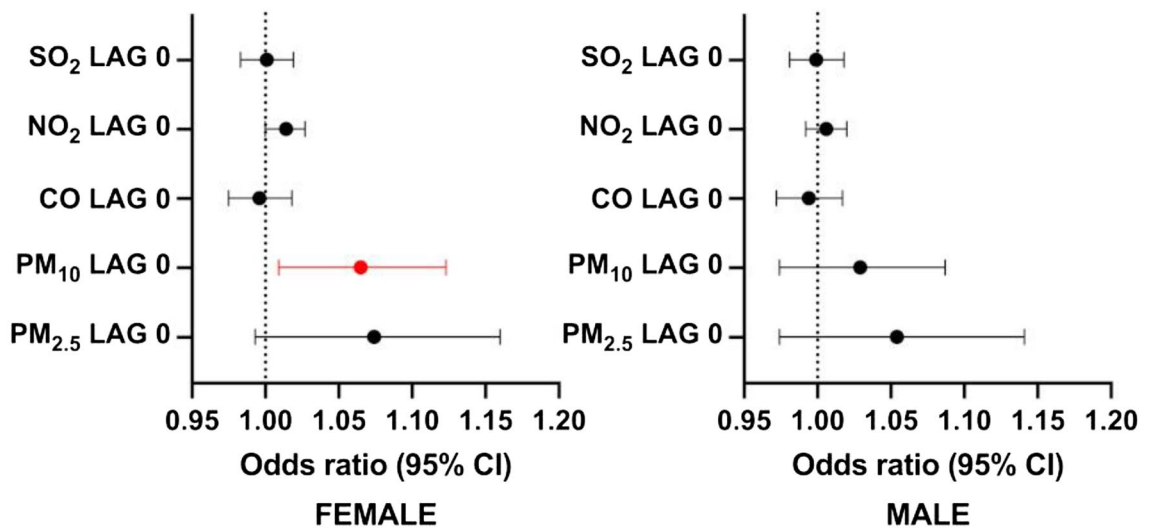

Figure 3. Associations between the exposure to short-term pollutants and ischemic stroke incidence in the study group divided by sex.

due to low temperature causing vasoconstriction and increased vascular resistance[44,45]. Many analyses from different countries have shown that sympathetic nervous system stimulation and the aforementioned higher blood pressure during the cold season lead to a greater occurrence of atrial fibrillation[13].

Our work showed that not only seasonal fluctuation matters but also weekly variation plays a huge role in ischemic stroke occurrence. In line with other publications, our results revealed that the frequency of stroke increased at the beginning of the week and decreased over the weekends[22]. To this day there is still a lack of research to explain this phenomenon. It may be related to the beginning of the week being a period with higher blood pressure and greater psychological stress compared to other days. Murakami et al.[21] suggested morning blood pressure surge was the greatest on Mondays. On the other hand, some of the latest studies argue that incidents with similar pathomechanisms such as acute coronary syndromes might peak on other days of the week[40]. It may be due to the fact that over time more people are working from home with a much less rigid framework of a working week. In addition, as we demonstrated, short-term exposure to air pollution may be an important trigger for ischemic stroke. Reis et al.[46] suggested that exposure to NO_2 and $PM_{2.5}$ varies considerably accounting for home and workplace locations with higher concentrations in the latter. Recently World Health Organization introduced new 2021 Air Quality Guidelines (2021) with more demanding thresholds[36]. The frequency of hospitalizations due to ischemic stroke on the days with exceeded daily norms of $PM_{2.5}$ and NO_2 was significantly higher than on days without exceeded limit values, whereas stroke occurrence was similar on the days with and without exceeded daily norms of PM_{10}.

In our analysis, 54.4% of stroke events were experienced by women. That is a common pattern in Western countries due to longer life expectancy and older age at the time of stroke onset in the female population[47,48]. This can also be attributed to the loss of the protective effect of estrogen in postmenopausal elderly women[49]. However, most studies from Asia, especially China, demonstrate that men have a higher prevalence of stroke, reaching even up to 65.5% of all stroke events[50,51]. We believe it may be related to smoking and particularly disproportion between male and female smokers in Western and Asian countries. In China, 49.7% of men and only 3.5% of women smoke cigarettes, while in Poland there are 31.8% male and 24.4% female smokers[52]. Men are 14-times more likely to smoke tobacco products than women in China, whereas this difference is not that noticeable in Poland, since the smoking men-to-women ratio is only 1.3.

Our study region—Bialystok—is a non-heavily industrialized area, but a high prevalence of detached houses and coal combustion being still a popular way of household heating leads to high concentrations of PMs, especially in the cold season[53]. This may explain the seasonal results of our analysis as the effect of PMs and NO_2 was more pronounced in the winter season. In addition, the effect of pollutants on stroke incidence has been studied in different subgroups of patients[54,55]. Zhao et al.[41] showed that among patients with hypertension, the effects of $PM_{2.5}$ and PM_{10} were greater during the cold season. This seasonal trend was also confirmed in an overall group of patients with stroke[56]. On the other hand, in a study performed in Tianjin, a higher risk of ischemic stroke was observed between April and September[27].

The air pollution problem is no longer only a concern for metropolitan areas, as was once commonly believed, where we have an extensive monitoring system, and where the awareness of residents is steadily increasing. It is becoming clear that seemingly pollution-free smaller agglomerations and peripheral cities are also struggling with smog[57]. Low environmental awareness often combined with low socioeconomic status consequently leads to suboptimal ecological choices that affect the health and lives of the inhabitants of these areas. Once we are aware of this, we can notice that not enough research on the influence of air pollution on human health is performed in smaller cities, since most of the studies take place in big agglomerations[58,59].

Even though the analyzed area is often described as the Green Lungs of Poland, the $PM_{2.5}$ daily mean limit given by the WHO guidelines was exceeded on a considerable number of days, as we mentioned before. We found that a 10 μg/m^3 increase in PM_{10} concentration was associated with a significant increase in stroke incidence on the day of exposure, however, no significant association for $PM_{2.5}$ was found. Moreover, the possibility of a day without stroke was 9% for a decrease of 10 μg/m^3 in $PM_{2.5}$ and PM_{10} concentration. In a study on 248 Chinese cities, authors observed that a 10 μg/m^3 increase in $PM_{2.5}$ was significantly associated with hospital admissions due to ischemic stroke[60]. Hu et al.[56] in a time-series study noted a 1.06% increase in stroke hospitalizations with every 10 μg/m^3 increase in $PM_{2.5}$. Several studies show associations between both particulate matters ($PM_{2.5}$ and PM_{10}) and ischemic stroke[61,62]. On the other hand, Dong et al.[63] reported no significant associations between particulate matters and daily ischemic stroke counts.

In our study, we additionally wanted to determine whether there was age- and sex-dependent difference in stroke incidence. We found that females were more susceptible to exceeded PM_{10} concentrations on the day of exposure which is in line with the case-crossover analysis by Wang et al.[64]. Similar results were obtained for $PM_{2.5}$ short-term exposure[56]. As for the age, people over the age of 65 were more vulnerable to the effects of increased concentrations of $PM_{2.5}$ as well as PM_{10} on the day of exposure. On the contrary, Qi et al.[27] results suggest younger age is associated with a higher risk of pollution-triggered ischemic stroke, which is interesting considering that none of the pollutants analyzed in our study showed an impact on the group of patients under 65 years old.

Reports revealed that with 37.9%, Poland is the country with the highest share of old passenger cars (20 years or older) in the EU[6]. These older automobiles tend to have greater emissions of gaseous air pollutants such as NO_2, SO_2, and CO. We observed that a 10 μg/m^3 increase in NO_2 concentration was associated with greater stroke incidence on the day of exposure for people under 75 years old (OR 1.015 95% CI 1.001–1.029 p = 0.038), both sexes during the winter season (OR 1.028 95% CI 1.006–1.050 p = 0.013) and also females regardless of age and season (OR 1.014 95% CI 1.000–1.027 p = 0.043). Most of the conducted analyses are coherent with each other, showing an association between short-term exposure to NO_2 and ischemic stroke occurrence[63,64]. Moreover, Byrne et al.[61] found that an increase in NO_2 concentration was associated with a rise in hospitalizations due to stroke in winter. On the other hand, Sun et al.[65] demonstrated no significant impact of NO_2 on ischemic stroke. There is still not enough research on air pollutants' influence on human health depending on age group, gender,

and seasons. As our results have shown, we believe people in their early retirement days (younger than 75 years old) are far more mobile, spend more time outdoors, and therefore are more exposed to ambient air pollution. On the other hand, older people (older than 75 years old) tend to spend more and more time indoors each year due to various sicknesses and a lack of energy, therefore are less likely to experience exposure to air pollutants such as NO_2. In our study, we noted that a 10 µg/m³ increase in CO concentration had opposite effects on LAG 2 (OR 0.976, 95% CI 0.953–0.999, p = 0.037) and LAG 3 (OR 1.026 95% CI 1.004–1.049 p = 0.022), especially LAG 2 (OR 0.957, 95% CI 0.924–0.990, p = 0.012) and LAG 3 (OR 1.037, 95% CI 1.008–1.067, p = 0.013) in summer season. We have three hypotheses regarding this occurrence. It was shown multiple times in experimental studies that carbon monoxide has a neuroprotective effect by suppressing neuroinflammation and alleviating blood–brain barrier disruption, activation of the Nrf2 pathway, improving mitochondrial biogenesis, etc.[66]. Moreover, Zeynalov et al.[67] presented that appropriate CO levels protected the brain from transient focal ischemia after 90 min and reperfusion injury after 48 h in mice subjected to occlusion of the middle cerebral artery. Firstly, even though carbon monoxide has a harmful effect on human health, exposure to this particular air pollutant in appropriate concentrations might prove beneficial and decrease ischemic stroke incidence. Secondly, it can also be explained by a phenomenon similar to the "harvesting effect". Shah et al.[68] in their meta-analysis demonstrated an increase in stroke incidence on the day of exposure to CO, however, 2 days after exposure we observed a significant decrease in hospitalizations in our study. A short period of excess ischemic stroke incidence might cause a period of ischemic stroke deficit. Lastly, we assume that not only mean CO concentration have an impact on stroke incidence but also fluctuations in concentrations may have an influence on stroke occurrence. Contrary to many other studies, in our work, short-term exposure to SO_2 had no significant impact on stroke incidence[68,69].

Numerous studies have been conducted on the influence of air pollutants on the occurrence of ischemic stroke and there is contrasting evidence regarding the influence of individual air pollutants[68,70]. However, in our study group, several observations not previously found collectively in a single analysis emerged. Such different results of the influence of different pollutants can be partly explained by the difference in the studied regions and populations, which has a direct influence on the smog composition. The size of the study population and the period of the analysis is also not without significance.

Any study proving the harmful effects on human health should prompt the government to implement systemic changes that could significantly reduce the incidence of morbidity in the future. Promoting pro-environmental choices among residents and making them aware of the harmful effects of smog on human health and life is also significant. At this point, the fastest clinical course of action is to educate vulnerable groups and implement preventive behaviors in their lives, since the benefits of something as simple as taking a walk outside can be overshadowed by the negative effects of pollution exposure[71].

Several strengths of our study should be noted. A large sample of patients with ischemic stroke was analyzed, additionally, the period of the analysis is noteworthy. Data on the occurrence of ischemic stroke were obtained from the main hospitals in Bialystok admitting and treating stroke patients. The analysis of a substantial number of pollutants, not only particulate matter, is also a major advantage (Supplementary Information).

Limitations

Our study has several limitations. First, pollution data from the analyzed city came from only two existing monitoring stations. Second, since the residence was used to link with the exposure to air pollution there could be some exposure misclassification given that the address of residence may not always reflect the level of exposure of an individual.

Conclusions

The stroke occurrence associated with air pollution was significantly greater in the winter season. The highest and the lowest frequencies of stroke incidence occurred at the beginning of the week and on weekends, respectively. Exceeded daily $PM_{2.5}$ and NO_2 concentration norms were associated with more admissions due to stroke. In the studied region besides PMs, the short-term influence of CO on stroke occurrence was observed. The effect was noted up to 3 days after exposure. Systemic changes are crucial and preventive measures should be undertaken for vulnerable groups, especially during wintertime.

Data availability

The data that support the findings of this study are available from the corresponding author on request.

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