



# THE ASSOCIATION OF AIR POLLUTANTS, METEOROLOGICAL PARAMETERS AND APPEARANCE OF VENOUS THROMBOEMBOLISM IN THE EMERGENCY DEPARTMENT: A RETROSPECTIVE STUDY

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**SUMMARY** – The aim of this retrospective study was to examine the association between air pollution and meteorological parameters with venous thromboembolism (VTE) in patients admitted to the Emergency Department of Sestre Milosrdnice University Hospital Center from December 2010 to November 2015. Analyzed data included daily patient admissions, surface air temperature, relative humidity, air pressure, and ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>) and particulate matter (PM<sub>10</sub>) concentrations across 1,826 days. Of the 1,381 admitted VTE patients, 1,068 had deep vein thrombosis (DVT) and 313 had pulmonary embolism (PE). DVT patients exhibited seasonal variations, peaking in winter and spring ( $P=0.034$ ). NO<sub>2</sub> and PM<sub>10</sub> concentrations were highest in winter and lowest in summer. Lower relative humidity correlated with VTE admissions in summer ( $P=0.033$ ), while higher relative humidity correlated with PE admissions in spring ( $P=0.005$ ). Elevated NO<sub>2</sub> was associated with VTE and DVT admissions overall. Higher PM<sub>10</sub> concentrations in spring correlated with VTE and DVT admissions. Air pollution, even within legal limits, is associated with the number of VTE patients.

**Keywords:** *air pollution; meteorological parameters; nitrogen dioxide; particulate matter; venous thromboembolism*

## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the most common and potentially preventable cardiovascular diseases worldwide, ranking third in prevalence after acute coronary syndrome and stroke<sup>1</sup>. Due to its clinical heterogeneity, ranging from asymptomatic cases to massive embolisms that can cause sudden death, VTE presents a significant

public health and economic challenge. In developed countries, the annual incidence varies between 104

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and 183 per 100,000 inhabitants<sup>2</sup>, while in Croatia, the number of newly diagnosed cases reaches approximately 6,500 annually<sup>3</sup>. The etiology of this disease is multifactorial, involving numerous genetic and acquired risk factors, with most patients having multiple factors contributing to disease development<sup>4</sup>.

Many studies have tried to find a link between VTE, weather conditions and air pollution, however the results are still mixed<sup>5</sup>. Seasonal patterns, particularly the peak in incidence during winter months, suggest a possible association with meteorological parameters, such as surface air temperature and atmospheric pressure, while the impact of air pollution, including particulate matter (PM<sub>10</sub>) and nitrogen dioxide (NO<sub>2</sub>) concentrations, have been studied as a potential trigger for vascular and thromboembolic events<sup>6,7</sup>.

The objective of this research was to determine the association between air pollution, weather and the incidence of VTE.

## Patients and methods

From December 2010 to November 2015, a total of 1,381 patients were admitted to the Emergency Department for VTE. All patients were diagnosed with DVT or PE according to the European Society of Cardiology guidelines, which align with the Croatian guidelines<sup>8,9</sup>. DVT was determined using a color doppler of the lower limb veins, whereas the diagnosis of PE was validated by computed tomography (CT) angiography of the pulmonary arteries. Individuals not living in the city of Zagreb were excluded from the study. Data was collected retrospectively using the hospital information system.

Information about the patients' age, sex and risk factors associated with VTE was collected. Specific information related to the risk of developing VTE was collected by checking the following parameters: active cancer, pregnancy, postpartum period, usage of oral contraceptives, major surgery within the previous month or orthopedic procedures, immobilization lasting over three days (due to trauma or acute illnesses), permanent immobility, thrombophilia, obesity, infections, high blood pressure, diabetes type 2, dyslipidemia, chronic obstructive pulmonary disease (COPD),

history of past VTE, liver diseases (cirrhosis, hepatitis B and C), autoimmune conditions and kidney impairment (glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>). Thrombophilia is defined as a condition characterized by an increased tendency for blood to clot, which can be either inherited or acquired, in accordance with the American Society of Hematology 2023 guidelines<sup>10</sup>.

Patients with significant risk factors for VTE were categorized into the group of provoked or secondary VTE. All remaining patients were classified as experiencing idiopathic, unprovoked VTE.

We defined the meteorological seasons as follows: winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November). Data on average daily surface air temperature (°C), relative humidity (%) and air pressure (hPa) were obtained from the Croatian Meteorological and Hydrological Service. We collected data on daily concentrations of ozone [O<sub>3</sub>, (µg/m<sup>3</sup>)], NO<sub>2</sub> (µg/m<sup>3</sup>) and PM<sub>10</sub> (µg/m<sup>3</sup>) from the Croatian Environment Agency's website<sup>11</sup>.

### Statistical analysis

Statistical data analysis was performed with the MedCalc software package. Categorical variables were presented as ratios or percentages and the normal distributions of numerical variables were examined. Meteorological parameters and concentrations of pollutants in the air were shown as mean values with corresponding standard deviations. To analyze the differences in patient admissions across seasons, the Kruskal-Wallis (KW) non-parametric test was used. Patient characteristics in relation to seasons were examined using the Chi-square test. The correlation between meteorological parameters and air pollutants was assessed using Pearson's correlation coefficient. To reduce the probability of an  $\alpha$  error in multiple correlations, the Bonferroni correction was applied. To investigate whether meteorological parameters and pollutant concentrations differed between days with patient admissions for VTE (positive days) and days without admissions (negative days), the t-test was employed. The analysis was conducted for the entire investigated period and across seasons, considering the type of incident: DVT and PE. The statistical significance of all analyzed parameters was considered at  $P < 0.05$ .

## Results

Zagreb's climate is defined as moderately warm and humid, showing seasonal variations with elevated surface air temperatures and reduced humidity in summer, while experiencing cooler, more humid winters (Table 1).

Concentrations of pollutants fluctuated over the year, showing peak levels of NO<sub>2</sub> and PM<sub>10</sub> during winter (Table 2). O<sub>3</sub> attained its highest levels in summer, as it develops from primary pollutants in the air when exposed to sunlight (Table 2). During winter, increased moisture in the air and cooler temperatures led to lower O<sub>3</sub> levels due to diminished photochemical reactions.

Meteorological parameters exhibited interdependence (Table 3), with relative humidity inversely related to temperature ( $r = -0.513$ ,  $P < 0.0001$ ), suggesting that humidity lowered as temperature rose. Air pressure showed a negative correlation with temperature ( $r = -0.239$ ,  $P < 0.0001$ ). Throughout the monitored timeframe, a slight negative correlation was noted between air pressure and relative humidity ( $r = -0.095$ ,  $P < 0.0001$ ).

Weather conditions had a major impact on pollution levels and seasonal trends (Table 3). All air pollutants apart from O<sub>3</sub> displayed positive correlations with one another, indicating that they have common emission sources.

During the study period, 1,381 patients with VTE were admitted. No VTE patients were admitted on 910 days, while one or more patients with this diagnosis were admitted on 916 days. The most common scenario was a single VTE admission, recorded on 589 days (64.30%). Two admissions per day occurred on 223 days (24.35%) and three or more admissions on 104 days (11.35%). Of the total number of patients, 209 (15%) had a recurrence of VTE.

Seasonal analysis revealed that the highest number of patients was admitted in spring (375 patients, 27.2%) and the lowest in summer months (306 patients, 22.2%) (Figure 1). Statistical analysis did not confirm a significant difference in admission numbers between seasons ( $P = 0.164$ ).

While acknowledging the controversy surrounding a post hoc power analysis, the following evaluation of study power was performed to assess the generalizability and statistical power of specific findings of PE

Table 1. The variation of meteorological parameters across the seasons in the City of Zagreb over five years.

	Temperature (°C)	Air humidity (%)	Air pressure (hPa)
Total	13.4 ± 8.5	67.8 ± 14.5	997.6 ± 7.2
Spring	13.5 ± 5.2	59.9 ± 13.3	996.3 ± 7.6
Summer	23.1 ± 3.8	60.1 ± 11.7	996 ± 3.9
Autumn	13.3 ± 5.7	74.9 ± 11.6	998.8 ± 6.9
Winter	3.4 ± 4.6	76.7 ± 11.7	999.3 ± 9.1

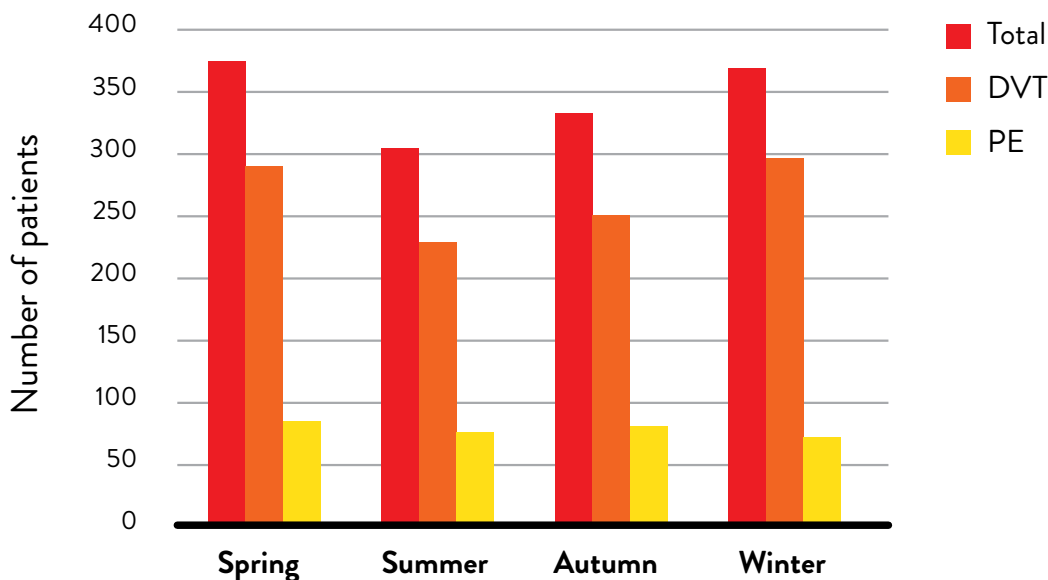
Table 2. Average daily concentrations of ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>) and particulate matter (PM<sub>10</sub>) in the City of Zagreb over a five-year period. Values are presented as mean and standard deviation (SD).

	O <sub>3</sub> (µg/m <sup>3</sup> ) Mean ± SD	NO <sub>2</sub> (µg/m <sup>3</sup> ) Mean ± SD	PM <sub>10</sub> (µg/m <sup>3</sup> ) Mean ± SD
Total	47.1±25.2	25.8±12.7	34.4±25.4
Spring	61.5±18.3	23.7±11.4	27.8±16.9
Summer	69.5±16.2	20.2±7.4	20.5±10.3
Autumn	31.6±16.3	26.2±10.5	36.5±27.4
Winter	25.2±15.3	32.9±16.1	53±31.2

Table 3. Correlation coefficients of air pollutants ( $\mu\text{g}/\text{m}^3$ ) and meteorological parameters in the City of Zagreb in the period from Dec 1, 2010 to Nov 30, 2015.

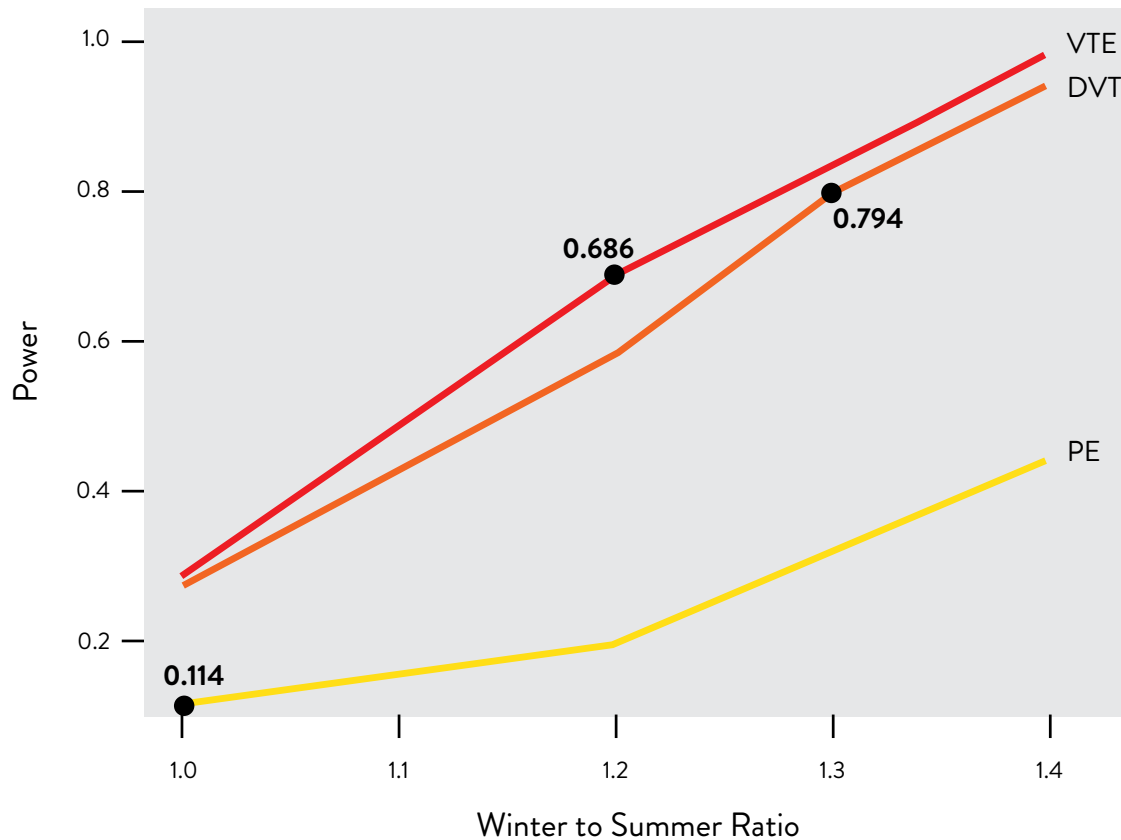
		Temperature (°C)	Humidity (%)	Pressure (hPa)	O <sub>3</sub> ( $\mu\text{g}/\text{m}^3$ )	NO <sub>2</sub> ( $\mu\text{g}/\text{m}^3$ )	PM <sub>10</sub> ( $\mu\text{g}/\text{m}^3$ )
Temperature (°C)	r	/	<b>-0.513</b>	<b>-0.239</b>	<b>0.661</b>	<b>-0.277</b>	<b>-0.417</b>
	P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	N		1826	1826	1806	1770	1826
Humidity (%)	r	<b>-0.513</b>	/	<b>-0.095</b>	<b>-0.649</b>	<b>0.053</b>	<b>0.19</b>
	P-value	<0.0001		<0.0001	<0.0001	0.0263	<0.0001
	N	1826		1826	1806	1770	1826
Pressure (hPa)	r	<b>-0.239</b>	<b>-0.095</b>	/	<b>-0.179</b>	<b>0.264</b>	<b>0.278</b>
	P-value	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
	N	1826	1826		1806	1770	1826
O <sub>3</sub> ( $\mu\text{g}/\text{m}^3$ )	r	<b>0.661</b>	<b>-0.649</b>	<b>-0.179</b>	/	<b>-0.445</b>	<b>-0.463</b>
	P-value	<0.0001	<0.0001	<0.0001		<0.0001	<0.0001
	N	1806	1806	1806		1758	1806
NO <sub>2</sub> ( $\mu\text{g}/\text{m}^3$ )	r	<b>-0.277</b>	0.053	<b>0.264</b>	<b>-0.445</b>	/	<b>0.691</b>
	P-value	<0.0001	0.0263	<0.0001	<0.0001		<0.0001
	N	1770	1770	1770	1758		1770
PM <sub>10</sub> ( $\mu\text{g}/\text{m}^3$ )	r	<b>-0.417</b>	<b>0.19</b>	<b>0.278</b>	<b>-0.463</b>	<b>0.691</b>	/
	P-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
	N	1826	1826	1826	1806	1770	

Figure 1. Patients with VTE, DVT and PE admitted to the Emergency Department over five years.



VTE: venous thromboembolic disease; DVT: deep vein thrombosis; PE: pulmonary embolism.

Figure 2. Power of the Kruskal-Wallis test for VTE, DVT and PE admission rates, under three different scenarios regarding the Winter to Summer admission rate ratio (1, 1.2 and 1.4)



VTE: venous thromboembolic disease; DVT: deep vein thrombosis; PE: pulmonary embolism.

as compared to those of VTE and DVT, and also to provide useful suggestions regarding sample size and power for any possible future studies of VTE/DVT/PE-related emergency department admissions.

The power of the KW test to detect a seasonal effect on emergency department admission rates (for VTE, DVT and PE), given that some specified effect actually exists, was estimated using a Monte-Carlo method (with 10,000 replications), assuming that admissions data follow the Poisson distribution with seasonal means equal to the daily rates observed over the five-year period. Daily admission rates by season were computed from the data presented in Figure 2 and are shown in Table 4, along with the ratio of winter to

summer rates and power of the KW test for each of the three diagnoses. Although data was available for all four seasons, for the sake of simplicity only the ratio of winter to summer admission rates, which shows the greatest spread overall, was used in power evaluation.

As can be observed from Table 4, daily rates for VTE and DVT varied over the seasons with 20% and 28% higher rates, respectively, in winter than in summer, whereas PE admission rates were not only lower on average, but also showed only a minimal seasonal variation, with winter and summer rates being almost the same. Thus, the power of the KW test to detect seasonal effect for VTE and DV admissions was rather high (0.686 and 0.794, respectively), whereas it was

Table 4. Daily admission rates for DVT, VTE and PE by season, winter to summer rate ratio and the power of the Kruskal-Wallis test

Diagnosis	Spring	Summer	Autumn	Winter	Winter to Summer Ratio	Power
VTE	0.821	0.670	0.726	0.805	1.20	0.686
DVT	0.635	0.503	0.547	0.646	1.28	0.794
PE	0.186	0.166	0.179	0.160	0.96	0.114

VTE: venous thromboembolic disease; DVT: deep vein thrombosis; PE: pulmonary embolism.

Table 5. Demographic and clinical characteristics of patients with VTE\* Data available for 854 patients.

\*\* Kruskal-Wallis test.

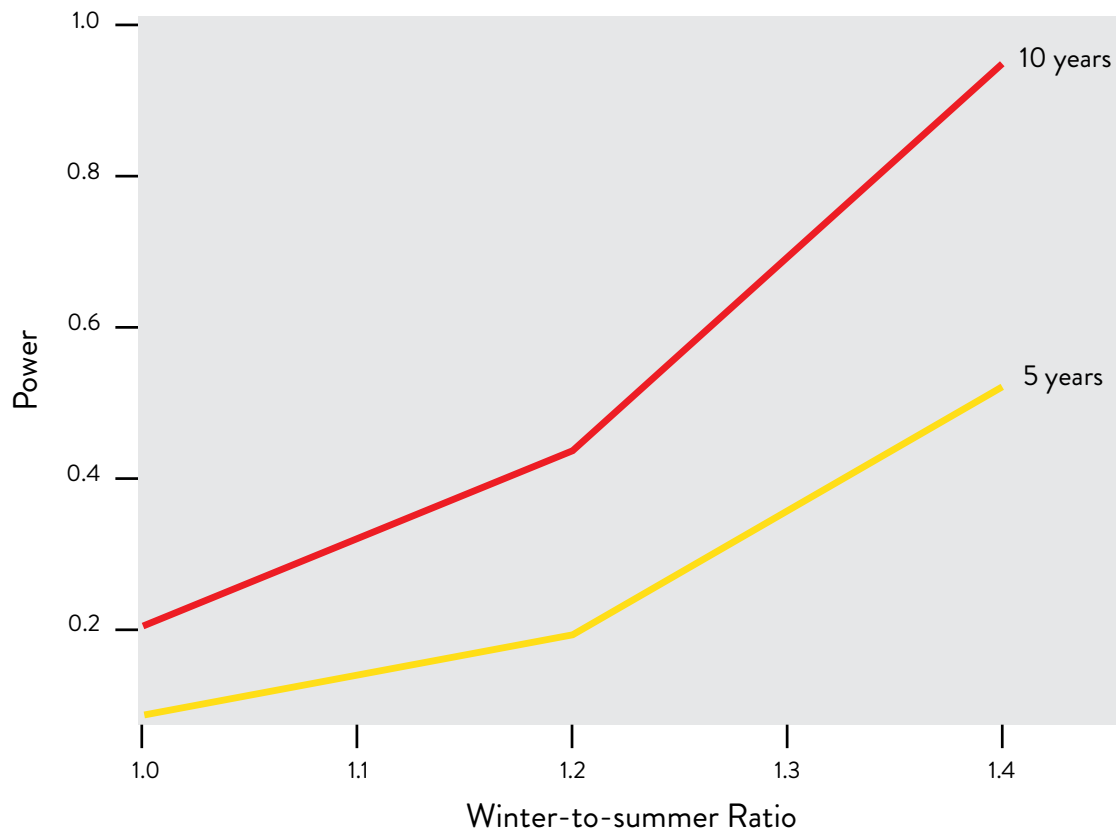
	Total	Spring	Summer	Autumn	Winter	P-value
Patient characteristics	1381 (100%)	375 (27.1%)	306 (22.2%)	332 (24%)	368 (26.6%)	0.331
Male/Female	675 (48.9%) / 706 (51.1%)	183/192	155/151	169/163	168/200	0.482
Age(year), median (range)**	68 (18-100)	68 (19-94)	65 (18-100)	68 (23-94)	71 (20-97)	<b>0.049</b>
Active cancer	328 (23.8%)	87 (26.5%)	77 (23.5%)	89 (27.1%)	75 (22.9%)	0.614
Pregnancy, oral contraceptives	28 (2%)	10 (35.7%)	7 (25%)	7 (25%)	4 (14.3%)	0.462
Major surgery	88 (6.4%)	28 (31.8%)	12 (13.6%)	26 (29.5%)	22 (25%)	0.075
Immobilization	118 (8.6%)	33 (28%)	25 (21.2%)	23 (19.5%)	37 (31.4%)	0.218
Immobility	100 (7.3%)	28 (28%)	22 (22%)	22 (22%)	28 (28%)	0.696
Thrombophilia	48 (3.5%)	9 (18.8%)	12 (25%)	12 (25%)	15 (31.2%)	0.682
BMI (kg/m <sup>2</sup> ), median (range) **	26.8 (15.21-51.42)	26.45 (18.36-49.38)	26.42 (17.47-40.14)	26.95 (17.58-51.42)	26.86 (15.21-42.25)	0.834
Arterial hypertension	793 (57.4%)	239 (30.1%)	145 (18.3%)	197 (24.8%)	212 (26.7%)	<b>0.0002</b>
Autoimmune conditions	44 (3.2%)	8 (18.2%)	8 (18.2%)	15 (34.1%)	13 (29.5%)	0.293
Diabetes	197 (14.3%)	53 (26.9%)	38 (19.3%)	53 (26.9%)	53 (26.9%)	0.649
Liver disease	19 (1.4%)	6 (31.6%)	3 (15.8%)	5 (26.3%)	5 (26.3%)	0.911
Smoker	205 (4.8%)	53 (25.9%)	50 (24.4%)	50 (24.4%)	52 (25.4%)	0.837
Recurrent VTE	209 (15.1%)	55 (26.3%)	46 (22%)	50 (23.9%)	58 (27.8%)	0.98
Hyperlipidemia	242 (17.5%)	68 (28.1%)	43 (17.8%)	66 (27.3%)	65 (26.9%)	0.269
KOPB	75 (5.4%)	15 (20%)	17 (22.7%)	20 (26.7%)	23 (30.7%)	0.529
Infection	272 (19.7%)	67 (24.6%)	76 (27.9%)	66 (24.3%)	63 (23.3%)	0.059
Kidney injury	90 (6.5%)	15 (16.7%)	20 (22.2%)	27 (30%)	28 (31.1%)	0.109

only 0.114 for PE admissions, which is commensurate with the findings (i.e., *P*-values for the KW test) presented in this study.

To further evaluate the impact of mean daily admission rates and their seasonal variation on power, for each of the three diagnoses, power was estimated under three different scenarios regarding seasonal variation, with the winter to summer admission rate ratio set to 1, 1.2 and 1.4 (with spring and autumn rates held at the same level), as displayed in Figure 2. Given a very low mean admission rate for PE, the power of detecting seasonal variation would be approximately 0.44 even if the actual winter admission rates were 40% higher than summer admission rates.

Finally, the question arose of what impact would extending the observation period from 5 to 10 years have on the power of detecting seasonal variation in PE admissions where one actually exists. The results, displayed in Figure 3, demonstrate that under all three scenarios regarding the winter to summer rate ratio, doubling the observation period yields a substantial increase in power. However, power of close to 0.80 is achieved only under the assumption that winter rates were 40% higher than summer rates. In other words, to detect a seasonal variation in PE admissions (if one exists), either a higher number of admissions would have to be available (e.g., from a larger number of emergency departments), or the observation period would have to be extended.

Figure 3. Power of the Kruskal-Wallis test for PE admission rates, under three different scenarios regarding the winter to summer admission rate ratio (1, 1.2 and 1.4) and two different scenarios regarding the observation period (5 years and 10 years)



PE: pulmonary embolism

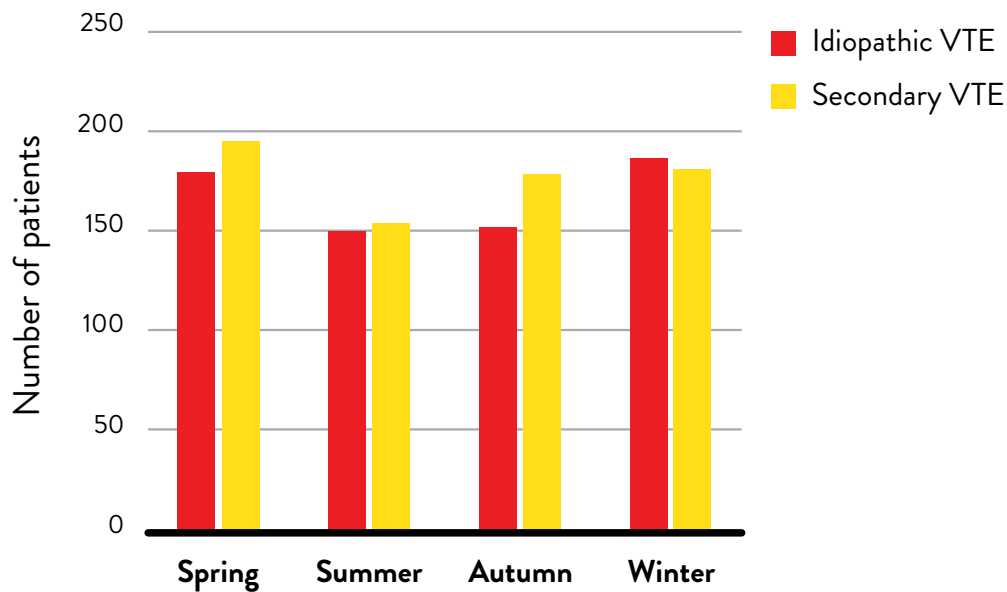
Table 6. Comparison of air temperature (°C), relative humidity (%) and air pressure (hPa) across seasons between VTE-positive and VTE-negative days in the City of Zagreb over a five-year period. The analysis was performed using the *t*-test and the results are presented as the mean and standard deviation for the observed period. Statistically significant values are highlighted in bold.

		VTE			DVT			PE		
		negative (N=910)	positive (N=916)	P-value	negative (N=910)	positive (N=916)	P-value	negative (N=910)	positive (N=916)	P-value
Temperature (°C)	Total	13.6±8.5	13.2±8.5	0.361	13.6±8.5	13.1±8.5	0.217	13.4±8.5	13.3±8.5	0.751
	Spring	13.7±5.2	13.5±5.2	0.675	13.5±5.2	13.6±5.2	0.922	13.6±5.2	13.1±5.3	0.416
	Summer	23.1±3.7	23.2±3.8	0.681	23.1±3.8	23.1±3.8	0.973	23.1±3.7	23.3±4.1	0.658
	Autumn	13.5±5.7	13.1±5.8	0.373	13.4±5.6	13.2±5.9	0.709	13.4±5.8	12.7±5.3	0.305
	Winter	3.2±4.8	3.6±4.3	0.334	3.2±4.7	3.7±4.4	0.247	3.4±4.6	3.2±4.4	0.738
Humidity (%)	Total	68.0±14.4	67.7±14.5	0.648	68.1±14.3	67.5±14.7	0.347	67.7±14.6	68.9±13.9	0.171
	Spring	59.4±13.2	60.4±13.4	0.410	60.1±13.1	59.7±13.5	0.778	59.2±13.3	63.9±12.9	<b>0.005</b>
	Summer	61.2±12.2	58.9±11.0	<b>0.033</b>	60.9±12.1	58.8±11.0	0.057	60.3±11.7	59.0±11.8	0.414
	Autumn	75.0±11.2	74.9±12.1	0.88	75.2±11.3	74.6±12.2	0.986	74.8±11.7	75.9±11.2	0.416
	Winter	76.5±11.9	76.9±11.5	0.703	76.6±11.8	76.9±11.7	0.808	76.6±11.9	77.3±10.6	0.655
Pressure (hPa)	Total	997.4±7.2	997.8±7.3	0.330	997.4±7.3	997.8±7.2	0.230	997.7±7.2	997.2±7.3	0.296
	Spring	996.3±7.7	996.4±7.5	0.817	996.2±7.5	996.6±7.5	0.639	996.6±7.7	995.3±6.9	0.185
	Summer	995.8±4.1	996.1±3.8	0.360	995.8±4.1	996.2±3.9	0.248	996.0±3.9	995.9±4.0	0.900
	Autumn	998.5±6.5	999.2±7.2	0.256	998.5±6.9	999.4±6.9	0.286	998.7±6.7	999.2±7.6	0.650
	Winter	999.3±9.3	999.4±8.9	0.925	999.3±9.6	999.4±9.1	0.912	999.5±9.1	998.4±9.3	0.362

Table 7. Comparison of air pollutants ( $\mu\text{g}/\text{m}^3$ ) across seasons between VTE-positive and VTE-negative days in the City of Zagreb over a five-year period. The analysis was performed using the *t*-test and the results are presented as the mean and standard deviation for the observed period. Statistically significant values are highlighted in bold.

		VTE			DVT			PE		
		Negative (N=910)	Positive (N=916)	P-value	Negative (N=910)	Positive (N=916)	P-value	Negative (N=910)	Positive (N=916)	P-value
$\text{O}_3$ ( $\mu\text{g}/\text{m}^3$ )	Total	48.0±25.1	46.2±25.3	0.121	47.8±25.0	46.1±25.3	0.168	47.4±25.2	45.7±25.2	0.579
	Spring	62.3±18.9	60.4±17.7	0.180	62.3±18.5	60.4±18.0	0.259	61.9±18.5	59.3±16.9	0.274
	Summer	69.7±16.3	69.3±16.3	0.853	69.7±16.4	69.3±16.0	0.804	69.3±16.1	70.5±17.4	0.585
	Autumn	32.1±16.2	30.6±16.4	0.130	32.1±16.0	30.6±16.9	0.327	32.1±16.6	29.1±14.4	0.152
	Winter	26.0±15.7	24.2±14.8	0.082	26.0±15.3	24.2±15.2	0.229	25.6±15.7	22.6±12.2	0.151
$\text{NO}_2$ ( $\mu\text{g}/\text{m}^3$ )	Total	24.7±12.0	26.9±13.2	<b>0.0002</b>	24.8±11.9	27.2±13.6	<b>0.0001</b>	25.8±12.9	26.0±11.3	0.753
	Spring	22.4±11.4	24.9±11.4	<b>0.026</b>	22.7±11.2	24.9±11.7	0.050	23.5±11.6	24.5±10.8	0.507
	Summer	19.8±7.1	20.7±7.6	0.222	19.9±7.2	20.8±7.6	0.218	20.2±7.4	20.3±7.5	0.918
	Autumn	25.4±10.2	27.2±7.6	0.071	25.5±10.3	27.5±10.7	0.055	26.2±10.5	26.5±10.5	0.811
	Winter	31.4±15.2	34.4±16.8	0.048	31.5±14.9	34.8±17.4	<b>0.035</b>	33.0±16.7	33.1±12.5	0.961
$\text{PM}_{10}$ ( $\mu\text{g}/\text{m}^3$ )	Total	33.4±25.7	35.3±26.2	0.127	33.5±25.7	35.6±26.3	0.084	34.3±26.1	34.7±25.2	0.791
	Spring	26.1±14.8	29.4±18.5	<b>0.034</b>	25.8±14.9	30.4±19.0	<b>0.004</b>	28.0±16.7	26.9±18.0	0.607
	Summer	19.8±9.7	21. ±10.9	0.129	20.1±9.8	21.2±11.1	0.269	20.4±10.5	21.2±9.5	0.526
	Autumn	36.6±28.2	36.4±26.6	0.935	36.9±28.2	35.9±26.1	0.711	36.3±27.8	37.5±25.7	0.730
	Winter	52.4±31.0	53.6±31.5	0.68	52.8±30.9	53.3±31.7	0.869	52.7±31.5	54.7±29.6	0.626

Figure 4. Graphical representation of admissions of VTE patients according to the presence or absence of known risk factors at the Emergency Department over five years.



VTE: venous thromboembolic disease

The analysis of clinical and demographic characteristics did not reveal significant differences between patients admitted in different seasons, except regarding the presence of arterial hypertension and patient age (Table 5). Additionally, seasonal variability in patient age was observed, with younger patients more frequently admitted during summer ( $P=0.049$ ) (Table 5).

A total of 710 patients (51.4%) had major risk factors for VTE, including active malignancy, pregnancy, the postpartum period, the use of oral contraceptives, immobilization (longer than 3 days), major surgery in the last month or orthopedic surgery and permanent immobility (Table 5). The remaining 671 patients (48.6%) did not have major risk factors. Etiological analysis (idiopathic vs. provoked VTE) did not show significant differences in distribution across seasons ( $P=0.640$ ) (Figure 4).

Research results on the association between meteorological parameters and air pollution with

patient admissions for VTE showed seasonal variability, which varied within specific VTE subgroups. Temperature and air pressure did not differ between days with and without admissions, neither overall nor within subgroups and seasons (Table 6). Lower relative humidity values were recorded on summer days with VTE admissions ( $P=0.033$ ), while higher values were observed on spring days with PE admissions ( $P=0.005$ ) (Table 6).

O<sub>3</sub> concentrations did not differ between days with and without VTE admissions, nor across subgroups or seasons (Table 6). Significant differences were noted in NO<sub>2</sub> concentrations, with higher levels on days with positive VTE cases ( $P=0.0002$ ), especially in spring ( $P=0.026$ ) and winter ( $P=0.048$ ). Higher NO<sub>2</sub> levels were also observed on positive DVT days ( $P=0.0001$ ), particularly in winter ( $P=0.035$ ). Additionally, higher PM<sub>10</sub> concentrations were recorded on days with VTE admissions ( $P=0.034$ ) and DVT admissions ( $P=0.004$ ).

## Discussion

This study examined seasonal trends and the possible effects of weather conditions and air pollution on the incidence of VTE in the urban setting of Zagreb, characterized by a moderately warm and humid climate. While no significant seasonal variations were detected in the overall admissions for VTE, the analysis showed trends associated with DVT, indicating an increased patient count in the winter-spring period ( $P=0.034$ ). Earlier studies investigating seasonal changes in VTE have produced mixed outcomes. However, the majority of studies indicate a peak in patient incidence during winter months<sup>12,13</sup>.

We did not observe a link between surface air temperature and air pressure and the admission of patients with VTE. Earlier research indicates that lower surface air temperatures create conditions that increase the risk of thrombosis, including sympathetic-mediated reactions like peripheral vasoconstriction, shivering, elevated heart rate and blood pressure, procoagulant blood composition, increased infections, elevated cholesterol levels and lower vitamin D levels<sup>13-15</sup>. Findings regarding the association between atmospheric pressure and VTE are inconsistent<sup>16-18</sup>; nonetheless, experimental research has demonstrated that lower air pressure results in higher platelet aggregation<sup>19</sup>.

Interestingly, there was an association between low relative air humidity and increased numbers of patients admitted for VTE during summer, indicating a potential influence of dehydration and hemoconcentration on thrombosis development. On the other hand, there was a positive correlation between relative humidity and the number of patients with PE ( $P = 0.005$ ) during spring. Previous research shows differing results concerning the influence of air humidity on VTE<sup>20</sup>. The specific mechanism by which air humidity impacts human health is yet to be determined.

Studies analyzing the association between air pollution and VTE are scarce and results are inconclusive<sup>21,22</sup>. This may be due to differences in pollution levels, geographic and climate conditions, measurement methods and confounding factors, such as lifestyle and social conditions. The inhalation of polluted air leads to increased heart rate, elevated blood pressure, a rise in fibrinogen concentration and coagulation factors, arterial vasoconstriction, increased inflammatory

mediators and endothelial dysfunction, ultimately resulting in thrombotic events<sup>23</sup>.

In concordance with other research<sup>24,25</sup>, we observed seasonal fluctuations in air pollutant levels, with the greatest levels of NO<sub>2</sub> and PM<sub>10</sub> observed in winter months, whereas O<sub>3</sub> levels were highest in summer. Higher winter levels of NO<sub>2</sub> and PM<sub>10</sub> in Zagreb can be attributed to elevated emissions from major energy facilities, vehicle traffic and traditional small combustion appliances (stoves, boilers, water heaters, fireplaces, heating oil and natural gas). A positive correlation exists among these pollutants in every season, indicating their shared sources of emission. A further source of particulate matter in the atmosphere is the combination of road surfaces with deicing substances (salt) and anti-slip materials (sand) they are treated with in winter, leading to the formation of dust. During winter, the reduction of NO<sub>2</sub> in reactions that form photochemical O<sub>3</sub> is lessened because of decreased sunlight in the colder season<sup>26</sup>. Meteorological factors like nocturnal cooling and the influx of cold air frequently lead to temperature inversions that confine pollution close to the surface. In contrast, during summer, levels of these pollutants decrease because elevated temperatures promote the mixing of air with clean air and aid in the dispersion of pollutants<sup>27</sup>. O<sub>3</sub> is a secondary pollutant created by photochemical reactions driven by sunlight from other pollutants, with these reactions being the most intense during the summer months when sunny days and solar radiation levels peak<sup>28</sup>.

This study found no correlation between O<sub>3</sub> levels and the incidence of VTE, regardless of incident type or season. Elevated levels of NO<sub>2</sub> were noted on days when patients with VTE and DVT were admitted, and seasonal analysis indicated this correlation only during winter and spring (Table 7). During spring, increased levels of PM<sub>10</sub> were linked to hospital admissions of patients suffering from VTE and DVT (Table 7).

Existing research connects elevated levels of air pollutants to a greater occurrence of VTE<sup>29</sup>, while also highlighting the significance of personal exposure assessment and the substantial geographic variability in pollution concentrations (pollution within regulated limits versus significantly degraded air quality). The European Union air quality standards define the upper limit of the annual average of NO<sub>2</sub> as 40 µg/m<sup>3</sup> and the same applies to PM<sub>10</sub><sup>30</sup>.

It is important to highlight that the urban lifestyle and habits of Zagreb's population, including reduced outdoor activity during extreme weather conditions and the use of air conditioning, may have diminished the potential impact of meteorological and pollution factors on the occurrence of VTE. The limitations of this study include its retrospective design, a relatively small number of patients with PE and the use of monitoring stations to estimate personal exposure, which may lead to an underestimation or overestimation of actual exposure. Additionally, it is not possible to determine the exact time of symptom onset or the role of external conditions at the time of disease occurrence, further complicating the interpretation of results. Considering these limitations, future prospective studies could strengthen evidence for causality by, for example, collecting more granular data on individual exposure and physiological responses.

Research on the influence of weather patterns and air pollution on the number of emergency department patients is becoming increasingly popular, as it could be used to predict daily emergency admissions, thereby contributing to improved organization and quality of care. Furthermore, chronobiological data could be used to identify at-risk patient groups in the population and critical time periods during the day, month and year, enabling the implementation of preventive measures, such as increased physical activity, a modification of other behavioral patterns and ultimately the application of anticoagulant therapy.

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## Sažetak

## UTJECAJ ONEČIŠĆENJA ZRAKA I METEOROLOŠKIH PARAMETARA NA BROJ BOLESNIKA S VENSKOM TROMBOEMBOLIJOM U CENTRU ZA HITNI PRIJEM: RETROSPEKTIVNA STUDIJA

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Cilj ove retrospektivne studije bio je ispitati povezanost između onečišćenja zraka i meteoroloških parametara s venskom tromboembolijom (VTE) kod bolesnika primljenih u Objedinjeni hitni bolnički prijem Kliničkog bolničkog centra Sestre Milosrdnice u razdoblju od prosinca 2010. do studenog 2015. Analizirani podaci uključivali su dnevne prijeme bolesnika, temperaturu zraka na površini, relativnu vlažnost, tlak zraka te koncentracije ozona ( $O_3$ ), dušikovog dioksida ( $NO_2$ ) i krutih čestica ( $PM_{10}$ ) tijekom 1826 dana. Od 1381 primljenog bolesnika s VTE-om, 1068 imalo je duboku vensku trombozu (DVT), a 313 plućnu emboliju (PE). Bolesnici s DVT-om pokazivali su sezonske varijacije, s vrhuncem zimi i u proljeće ( $P=0,034$ ). Koncentracije  $NO_2$  i  $PM_{10}$  bile su najviše zimi, a najniže ljeti. Niža relativna vlažnost korelirala je s prijemima za VTE ljeti ( $P=0,033$ ), dok je viša relativna vlažnost korelirala s prijemima za PE u proljeće ( $P=0,005$ ). Povišeni  $NO_2$  bio je povezan s prijemima za VTE i DVT općenito. Više koncentracije  $PM_{10}$  u proljeće korelirale su s prijemima zbog VTE i DVT. Onečišćenje zraka, čak i unutar zakonskih ograničenja, povezano je s porastom broja bolesnika s venskom tromboembolijom.

*Ključne riječi: onečišćujuće tvari zraka; meteorološki parametri; dušikov dioksid; krute čestice; venska tromboembolija*