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The Influence of Air Pollution on Non-Infectious Hospitalizations for Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Time-Series from Serbia

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Abstract: The available data on the impact of air pollution on acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are inconsistent. We investigated the influence of air pollution on the number of severe AECOPD hospitalizations of non-infectious etiology in patients residing in Novi Sad, Serbia. In this time-series, we used a quasi-Poisson generalized linear model in conjunction with distributed lag non-linear models, after controlling for lag days, seasonal and long-term trends, and meteorological factors (air temperature and humidity), to estimate the relative risk (RR) of AECOPD hospitalization for each increase of 10 $\mu g/m^3$ in the air pollutant concentration. A total of 552 AECOPD hospitalizations were registered during 2017–2022. With each 10 $\mu g/m^3$ increase in the selected air pollutants' concentration, the cumulative RR (lags0–7) in single-predictor models for AECOPD admission were 1.52 (95% CI 0.98–2.35) for PM_{10}, 1.44 (95% CI 0.93–2.25) for $PM_{2.5}$, 1.13 (95% CI 0.87–1.47) for SO_2, and 0.99 (95% CI 0.69–1.42) for NO_2. Similar results were found in multi-predictor models as well as in group analyses between smokers and non-smokers. In conclusion, no significant associations between exposure to air pollutants and the daily AECOPD admissions were found. There is an obvious need for additional research on the topic.

Keywords: acute exacerbation of chronic obstructive pulmonary disease; air pollution; hospitalizations; particulate matter; sulfur dioxide; nitrogen dioxide; meteorological factors

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the world's leading public health issues, with high rates of morbidity and mortality and a significant social and economic burden [1]. Given the ongoing exposure to risk factors for COPD development (primarily smoking) and the globally prevalent issue of population aging, it is anticipated that the burden of this disease on all health systems will increase over the next few decades [2].

COPD's chronic and progressive course is marked by periods of remission interspersed with occasional acute exacerbations of COPD (AECOPD). According to the current Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guideline, AECOPD is defined as worsening dyspnea and/or cough with sputum production in the last 14 days, which may be accompanied by tachypnea and/or tachycardia, caused by infection, air pollution, or other agents that damage the respiratory tract, resulting in increased local inflammation of the respiratory tract and systemic inflammation [3]. Every AECOPD is a significant event in the course of COPD because it has a number of negative consequences for the patient, including accelerated deterioration of lung function, poor quality of life, frequent use of ambulatory medical facilities, frequent hospitalizations, and increased mortality [1]. In general, the economic burden of COPD is substantial, with a direct and indirect cost of EUR 38.6 billion spent on COPD management in the European Union in 2011, and around USD 60 billion in the United States, with the majority of costs spent on treating AECOPD [4]. Depending on its severity, AECOPD can be categorized as mild, for which only short-acting bronchodilators are required to treat aggravated symptoms and that can be treated on an outpatient basis; moderate, which can be treated in outpatient settings with short-acting bronchodilators, antibiotics, and/or oral corticosteroids; and severe, with the sudden and pronounced deterioration of respiratory symptoms necessitating hospitalization [5].

Even though AECOPD is most commonly caused by an infectious agent (respiratory viruses and bacteria), the influence of air pollution and meteorological factors on its development is being investigated with increasing interest. Although numerous toxic substances pollute the air, the contributions of short-term exposure to particulate matter (PM) with the size less than or equal to 2.5 μm ($PM_{2.5}$) or less than or equal to 10 μm (PM_{10}), as well as gaseous pollutants such as sulfur dioxide (SO_2) and nitrogen dioxide (NO_2), on the development of AECOPD have been investigated the most thus far. Numerous studies, typically originating from the countries with a higher burden of air pollution, such as China, Iran, Italy, Poland, Turkey, and South Korea, found a positive relationship between exposure to these air pollutants and AECOPD development, resulting in an increase in the number of emergency medical services interventions, outpatient visits to the physician, hospitalizations, and deaths [6–18]. There is also the possibility of synergistic action between various particulate and gaseous air pollutants, as well as other environmental factors (such as meteorological factors or infectious agents), which must all be considered in research evaluating the effects of these factors on AECOPD [19]. However, there have been studies in which the relationship between exposure to air pollution and the occurrence of AECOPD has not been established [20], indicating the need for further investigation on the subject.

Considering the inconsistency of the available data in the literature, the aim of this study was to investigate the influence of selected air pollutants on the number of severe AECOPD hospitalizations of non-infectious etiology in patients from the city of Novi Sad, Serbia, after controlling for lag days, seasonal and long-term trends, and meteorological factors.

2. Materials and Methods

2.1. Study Design

This research was conducted as a five-year time-series observational study (from 15 May 2017 until 15 May 2022). It analyzed the effects of selected ambient air pollutants (PM_{10}, $PM_{2.5}$, SO_2, and NO_2) on the number of non-infectious severe AECOPD (those requiring hospitalizations) in patients residing in Novi Sad, Serbia. A quasi-Poisson generalized linear model (GLM) was used to estimate the associations between the number of AECOPD admissions and the mean daily concentrations of selected air pollutants, while controlling for the effects of lag days, seasonal and long-term trends, day of the week, and meteorological factors (air temperature and relative air humidity).

2.2. Study Population

The study's population consisted of patients who were hospitalized at the Institute for Pulmonary Diseases of Vojvodina (IPDV) due to severe AECOPD over the aforementioned five-year period. IPDV is the university-affiliated tertiary referral pulmonary institute to which all patients with respiratory disease from Novi Sad gravitate. Novi Sad is the capital and administrative, economic, cultural, sporting, scientific, and tourist center of Vojvodina, the northernmost autonomous province of Serbia, and the second-largest city in Serbia, with more than 350,000 residents.

We analyzed the medical records of hospitalized patients and collected their basic socio-demographic and clinical data of interest. Since we wanted to exclude the effects of infectious agents on AECOPD onset, we decided to only analyze hospitalizations in which no clinical signs of infection were present. To confirm or rule out an infectious agent as the cause of the current severe AECOPD, data regarding the total number of leukocytes, neutrophils, and lymphocytes, as well as the levels of CRP (C-reactive protein) and fibrinogen, were gathered. The results of bacteriological sputum cultures and serological viral analyses were available for a limited number of AECOPD hospitalizations; all admissions for which these analyses indicated an acute infection were excluded from the study. Patients' sociodemographic features (gender, age, smoking status, comorbidities) and data regarding their previous medical history (elapsed time since COPD diagnosis, the total number of previous severe AECOPD) were collected as well. A detailed summary of the patient sampling is provided in Figure 1.

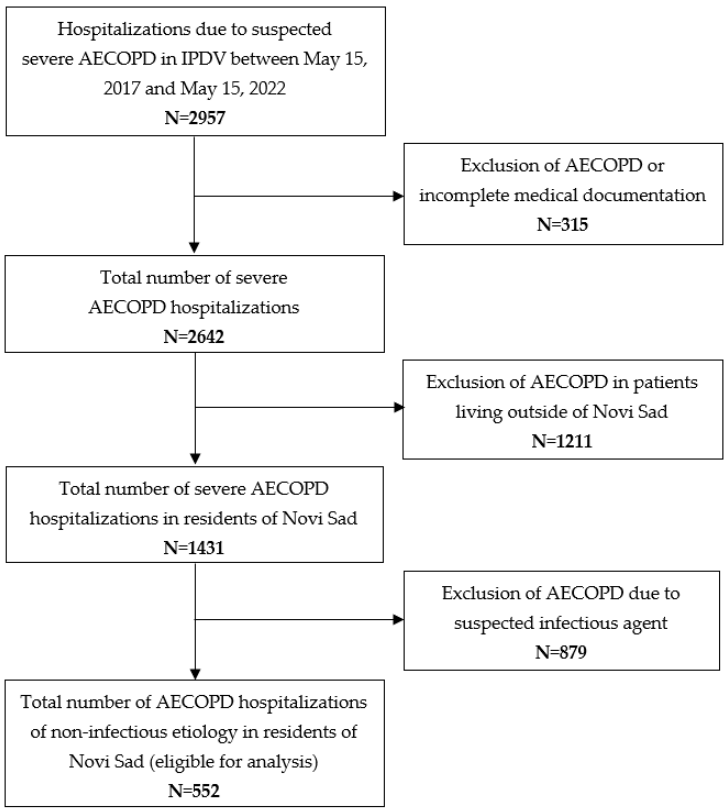


Figure 1. Flowchart of patient sampling.

The inclusion criteria for participation in this study were: aged over 40 years, residency in Novi Sad, a prior diagnosis of COPD, and actual hospitalization due to AECOPD with no clinical signs of infection. Patients with AECOPD suspected to be caused by an infectious agent and patients with incomplete medical documentation were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki, and approved by

the Institutional Review Board and Ethics Committee of IPDV (protocol code No. 113-III/1, date of approval 6 April 2021).

2.3. Data on Air Pollution and Meteorological Factors

The study used a time-series of data on air pollution and certain meteorological factors (that were considered in multi pollutant models as a confounding factor). For the previously mentioned time frame, the average daily values of air temperature (°C), atmospheric pressure (mbar), relative air humidity (%), and wind speed (m/s) were collected, along with the average daily concentrations of PM_{10}, $PM_{2.5}$, SO_2, and NO_2 in $\mu g/m^3$.

Data on the average 24-h concentrations of the previously mentioned air pollutants were provided by the Institute for Public Health of Vojvodina, an authorized and accredited institution that performs daily measurements of the level of air pollutants in the environment at several measuring stations on the territory of the city of Novi Sad for local self-governments (Figure 2). A portion of the analyzed data was taken over by the Serbian Environmental Protection Agency (SEPA), which also conducts measurements at two representative measuring stations within the Novi Sad metropolitan area. All of this information is freely available to the public. The stations are positioned to measure two forms of air pollution: urban traffic (UT) and urban background (UB). For the purposes of this study, we analyzed data from stations measuring UB air pollution, which is an indicator of the basic air pollution in urban areas due to the integrated contribution of various close and distant sources of air pollution typical of the urban environment (energy, economic and residential facilities, traffic, agriculture, and regional contributions), regardless of the local hotspots.

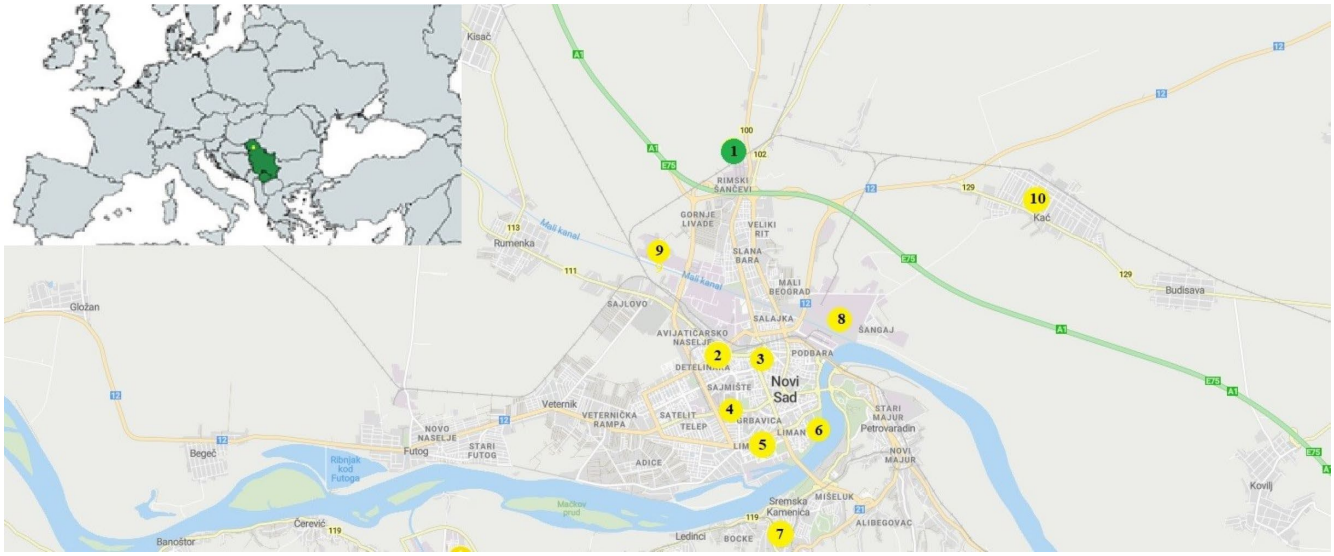


Figure 2. Network of stations for collecting data on meteorological factors and air pollution in the territory of Novi Sad: meteorological station: 1 (45°20′ N, 19°51′ E); air pollution stations: urban traffic–2 (45°15′ N, 19°49′ E), 3 (45°25′ N, 19°83′ E), 4 (45°24′ N, 19°81′ E); urban background—5 (45°14′ N, 19°50′ E), 6 (45°25′ N, 19°85′ E); suburban background—7 (45°13′ N, 19°50′ E); suburban industrial—8 (45°16′ N, 19°52′ E), 9 (45°29′ N, 19°78′ E); suburban traffic—10 (45°17′ N, 19°56′ E).

Data on the values of the investigated meteorological factors are also publicly available. They were obtained from the Republic Hydrometeorological Service of Serbia's website and were based on measured values from the city of Novi Sad's existing measuring station (Figure 2).

2.4. Statistical Analysis

A descriptive statistic was used to describe the socio-demographic characteristics and medical history of the patients, as well as the temporal distribution of AECOPD

hospitalizations and air pollutant concentrations. The data are represented by arithmetic means, standard deviations, and absolute and relative frequencies. Spearman's correlation coefficients were utilized for the analysis of the correlations between the air pollutant concentrations and the values of the meteorological factors.

The associations between air pollutant exposure and the number of severe AECOPD hospitalizations were evaluated using a quasi-Poisson GLM in conjunction with distributed lag non-linear models (DLNM) [21], given that this type of analysis allows the existence of a non-linear relationship between predictors and criteria (exposure–response relationship), but also relationships between time lags and criteria (lag–response relationship). Therefore, not only is the predictor included in the model, but also a matrix of predictor values by lags is created (cross-basis), which intersects the lag values and the predictor values, allowing for a different shape of the relationship and distributed lag effect at the same time [21]. In the majority of the models, the impact of lag was estimated as being linear. Regarding the influence of predictors on criteria, a linear relationship was optimal for all predictors and the criterion used (the number of AECOPD hospitalizations).

Although the linearity is dependent on the presumed relationship between the predictor and the criterion (based on theoretical assumptions and previous findings), it can also be empirically tested. In this regard, several models with different shapes of relationships between the predictors and a distributed lag effect on one side, and criteria on the other were examined. This included natural, cubic, penalized splines, and polynomial models, with different numbers of degrees of freedom (df). The models with the lowest values of quasi-BIC (Bayesian information criterion) were considered optimal. Quasi-BIC is an information criterion that is calculated when there is an excessive dispersion of the dependent variable, so a quasi-Poisson (regression) model is used in such instances. The formula used to calculate the quasi-BIC is as follows:

$$\text{Quasi-BIC} = -2\text{LL}/\hat{c} + K \times log(n), \quad (1)$$

where −2LL refers to −2* loglikelihood (which is incalculable in the case of a quasi-Poisson distribution, so −2LL obtained on the same model assuming a Poisson distribution is taken; hence this is quasi-BIC), $\hat{c}$ is the c-hat or overdispersion parameter that is extracted from the quasi-model, and *log(n)* is the natural logarithm of the sample size.

Four DLNM single predictor models were fitted. Each of these models included a natural cubic spline of time with 5 degrees of freedom (one for each study year) to account for seasonal and long-term effects. In addition, the day of the week (weekday or weekend) was included as a categorical variable in each model. Each model has a reference value for the predictor. The effect of changing the value of the predictor is observed in relation to that value. Regarding this, the usual method of analysis in studies of similar methodology was used, with 0 as the reference point, except for the predictor atmospheric pressure, where the reference value was 975 mbar. We opted for quasi-Poisson models to correct for overdispersion. The formulae used for single-predictor models are given below:

$$log(g[E(y_t)]) = \alpha + \beta \times \text{PM}_{10}(\text{UB})_{t,l} + \text{Day} + \text{ns}(\text{Date}, \text{df} = 5), \quad (2)$$

$$log(g[E(y_t)]) = \alpha + \beta \times \text{PM}_{2.5}(\text{UB})_{t,l} + \text{Day} + \text{ns}(\text{Date}, \text{df} = 5), \quad (3)$$

$$log(g[E(y_t)]) = \alpha + \beta \times \text{SO}_2(\text{UB})_{t,l} + \text{Day} + \text{ns}(\text{Date}, \text{df} = 5), \quad (4)$$

$$log(g[E(y_t)]) = \alpha + \beta \times \text{NO}_2(\text{UB})_{t,l} + \text{Day} + \text{ns}(\text{Date}, \text{df} = 5), \quad (5)$$

where *yt*—criteria (the dependent variable); *[E(yt)]*—expected number of AECOPD hospitalizations on a certain day *t*; *log*—link function; α—intercept; β—regression coefficient of the predictor; PM_{10}—average concentration of particulate matter with a size less than or equal to 10 μm in the urban background (UB) surrounding on day *t*; $PM_{2.5}$—average

concentration of particulate matter with a size less than or equal to 2.5 μm in the urban background (UB) surrounding on day *t*; SO_2—average concentration of sulfur dioxide in the urban background (UB) surrounding on day *t*; NO_2—average concentration of nitrogen dioxide in the urban background (UB) surrounding on day *t*; Day—predictor (workday or weekend on day *t*); ns(Date)—natural spline of dates to control seasonal factors; and df—degree of freedom.

For each predictor (exposure), we calculated the relative risk (RR) of AECOPD hospitalizations (response) for each 10 $\mu g/m^3$ increase in the air pollutant concentration. The reference value of the predictor against which the RRs were calculated in these analyses was a concentration of 0 $\mu g/m^3$ for the selected air pollutants. If the RR for a predictor is less than 1, it indicates that the predictor level reduces the criterion value. If the RR is greater than 1, it means that a certain level of the predictor increases the criterion value. If the RR is 1, then it means that there is no association between the predictor and the criterion. However, to be able to say that a change in the predictor significantly increases or decreases the value of the outcome, the 95% confidence interval RR must not include 1, i.e., the lower and upper limits of the confidence interval must be either both greater than 1 or both less than 1. Firstly, single-predictor models with different lag days (single-day lag models—from lag0 to lag7 and cumulative-day lag models—lags0–1 to lags0–7) were applied to determine the possibility of lagged effects, since some time is usually needed for air pollutants to induce negative health effects on the respiratory system. For instance, lag0 relates to the daily mean concentration of air pollutants on the day of AECOPD admission, lag1 to the concentration on the day before, and so on. Similarly, lags0–1 represents the average concentration of air pollutants on the current and previous day, while lags0–7 represents the average air pollutant concentration of the current and seven days prior to AECOPD admission. To evaluate the stability of the effects of air pollutants on AECOPD admissions, multi-predictor models were utilized to estimate the effects of confounding air pollutants and meteorological variables. The formula used for multi-predictor models is given below:

$$log(g[E(y_t)]) = \alpha + \beta \times PM_{2.5}(UB)_{t,l} + \beta \times SO_2(UB)_{t,l} + \beta \times Temp._{t,l} + \beta \times Hum._{t,l} + Day + ns(Date, df = 5), \quad (6)$$

where *yt*—criteria (the dependent variable); *[E(yt)]*—the expected number of AECOPD hospitalizations on a certain day *t*; *log*—link function; α—intercept; β—regression coefficient of the predictor; $PM_{2.5}$—average concentration of particulate matter with a size less than or equal to 2.5 μm in the urban background (UB) surrounding on day *t*; SO_2—average concentration of sulfur dioxide in the urban background (UB) surrounding on day *t*; Temp.—average daily air temperature on day *t*; Hum.—average daily relative air humidity on day *t;* Day—predictor (workday or weekend on day *t*); ns(Date)—natural spline of dates to control seasonal factors; df—degree of freedom. As can be seen, only predictors that were considered significant in single-predictor models ($PM_{2.5}$ and SO_2) were included in the multi-predictor models were included

A value of $p < 0.05$ was considered statistically significant for all tests. All analyses were conducted within the R: A language and environment for statistical computing, version 3.0.2 (RC Team, Vienna, Austria, R foundation for Statistical Computing, 2019) utilizing the "dlnm" package [21].

3. Results

3.1. Descriptive Statistics

Out of a total of 2957 hospitalizations due to AECOPD during the aforementioned five-year period, after excluding those who did not meet the inclusion criteria for our study, a total of 552 AECOPD hospitalizations (18.67%) were further analyzed. A basic sociodemographic analysis of this sample is given in Table 1, including the data regarding past medical history related to COPD.

Table 1. Sociodemographic analysis and patients' medical history.

		Number of Patients (%)
Gender	Male	228 (41.3)
	Female	324 (58.7)
Age	Under 65	176 (31.88)
	65 or older	376 (68.12)
Smoking status	Active smokers	239 (44%)
	Former smokers	228 (41.9%)
	Non-smokers	76 (14%)
Comorbidities	Cardiovascular diseases	446 (80.8)
	Other respiratory diseases	50 (9.06)
	Diabetes mellitus	71 (12.86)
	Other endocrinological diseases	94 (17.03)
	Depression	68 (12.32%)
	Other psychiatric diseases	21 (3.8%)
	Neurological diseases	69 (12.5)
	Gastrointestinal diseases	87 (15.76)
	Malignancy	89 (16.12%)
	Urogenital diseases	45 (8.15)
	Other	66 (11.96%)
COPD history	Mean years since COPD diagnosis	9.33 (±7.31, range 0–45)
	Previous hospitalizations due to AECOPD	3.4 (±5.78, range 0–41)

Legend: COPD—chronic obstructive pulmonary disease; AECOPD—acute exacerbation of chronic obstructive pulmonary disease.

The average number of AECOPD admissions was 0.3 per day, 9.09 per month, or 110.58 per year over the observed period. The daily average concentrations of selected air pollutants ($PM_{10,}$ $PM_{2.5}$, SO_2 and NO_2) were 28.8 (1.46–219.00), 19.81 (1.00–149.00), 10.22 (0.28–50.83), and 14.54 $\mu g/m^3$ (1.82–78.00), respectively. Figure 3 depicts the time-series distribution of the selected air pollutants and the number of AECOPD admissions over the observed period.

3.2. Correlations between Air Pollutants and Meteorological Factors

The coefficients of correlation between the average daily concentrations of the selected air pollutants and the values of the selected meteorological factors are presented in Table 2. Spearman's rank correlation coefficient was used to compute the correlations (since the variables do not have a normal distribution). As shown in Table 2, correlations do exist, but they are mostly weak ($p < 0.30$). Moderate correlations with metrological factors (air temperature and humidity) were observed for NO_2, which should be taken into account when building the model. It can also be seen that both PM_{10} and $PM_{2.5}$ are highly correlated with each other, which suggests that they are likely to reduce one another's strength in the same model.

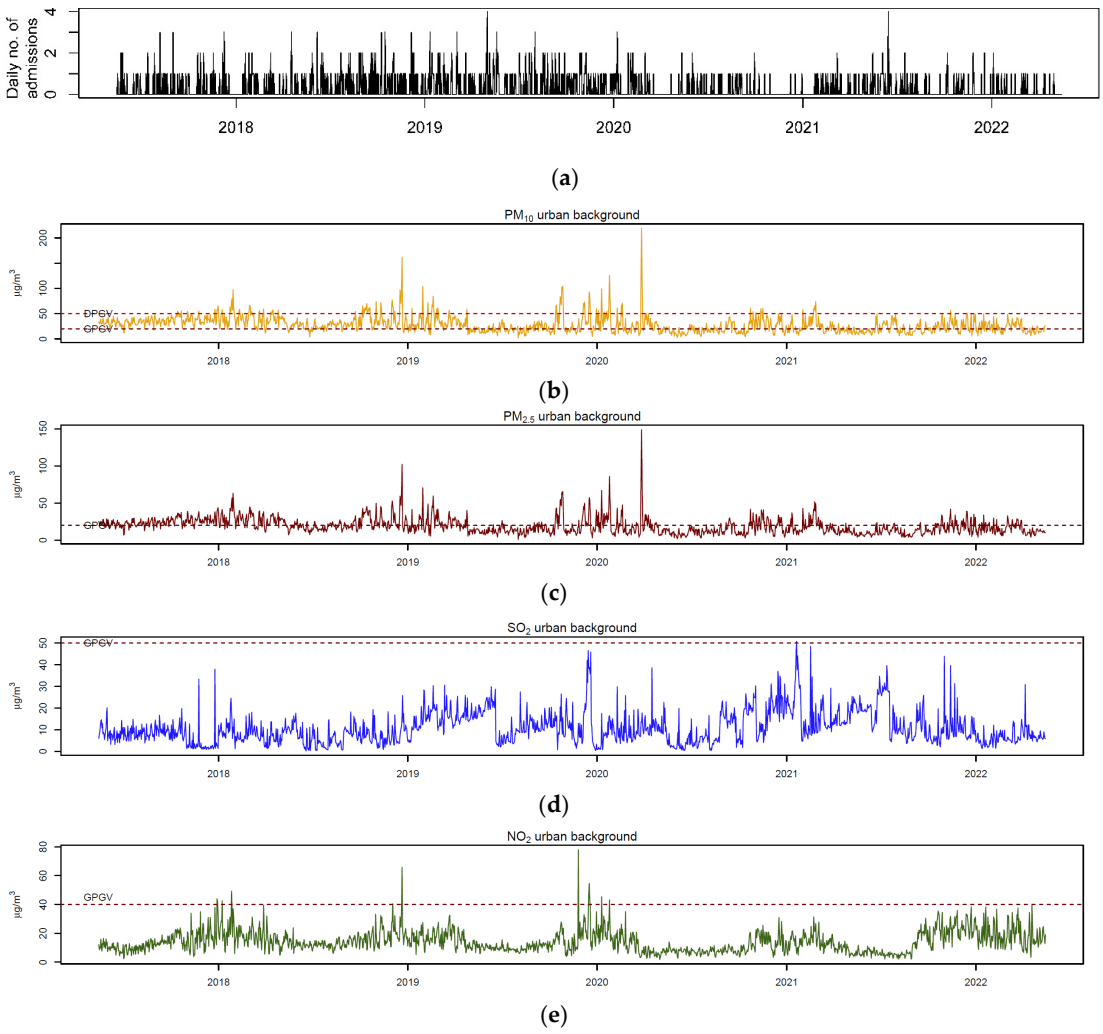


Figure 3. Time-series: (**a**) daily number of AECOPD hospital admissions—vertical axis refers to daily number of AECOPD admissions, horizontal axis to time; (**b**) average daily PM_{10} concentrations; (**c**) average daily $PM_{2.5}$ concentrations; (**d**) average daily SO_2 concentrations; (**e**) average daily NO_2 concentrations. For air pollutants, the dashed line indicates the daily (red) and annual (dark red) recommended values according to the Directive 2008/50/EC of the European Parliament and of the Council.

Table 2. Correlation coefficients between air pollutant concentrations and meteorological factors.

	PM_{10}	**$PM_{2.5}$**	**SO_2**	**NO_2**	**AP**	**Temp.**	**Hum.**	**WS**
PM_{10}		0.97 **	0.02	0.49 **	0.22 **	−0.16 **	0.03	−0.21 **
$PM_{2.5}$	0.97 **		0.00	0.52 **	0.23 **	−0.22 **	0.07	−0.20 **
SO_2	0.02	0.00		−0.07	−0.18 **	0.03	−0.13 **	−0.02
NO_2	0.49 **	0.52 **	−0.07 **		0.33 **	−0.52 **	0.34 **	−0.16 **
AP	0.22 **	0,23 **	−0.18 **	0.33 **		−0.33 **	−0.01	−0.13 **
Temp.	−0.16 **	−0.22 **	0.03	−0.52 **	−0.33 **		−0.58 **	−0.17 **
Hum.	0.03	0.07 **	−0.13 **	0.34 **	−0.01	−0.58 **		−0.03
WS	−0.21 **	−0.20 **	−0.02	−0.16 **	−0.13 **	−0.17 **	−0.03	

Legend: PM_{10}—average concentration of particulate matter with a size less than or equal to 10 µm in the surrounding urban background (UB); $PM_{2.5}$—average concentration of particulate matter with a size less than or equal to 2.5 µm in the surrounding urban background (UB); SO_2—average concentration of sulfur dioxide in urban background (UB) surrounding; NO_2—average concentration of nitrogen dioxide in the surrounding urban background (UB); AP—atmospheric pressure; Temp.—air temperature; Hum.—relative air humidity; WS—wind speed; ** $p < 0.01$.

3.3. Influence of Air Pollution on AECOPD Hospitalizations (Single-Predictor and Multi-Predictor Models)

In the single-predictor models, we calculated the cumulative RR (lags0–7) for each 10 μg/m^3 increase in air pollutant concentration on the number of AECOPD hospitalizations and found no significant difference for any of the selected air pollutants: for PM_{10} RR 1.52 (95% CI 0.98–2.35), for $PM_{2.5}$ RR 1.44 (95% CI 0.93–2.25), for SO_2 RR 1.13 (95% CI 0.87–1.47), and for NO_2 RR 0.99 (95% CI 0.69–1.42). A more detailed analysis of the effect of increasing concentrations of air pollutants on AECOPD hospitalizations is given in Table 3.

Table 3. RR of AECOPD hospitalization for each 10 μg/m^3 increase in selected air pollutants (single-predictor models).

Concentration (in μg/m^3)	RR (95% CI RR)			
	PM_{10} UB	**$PM_{2.5}$ UB**	**SO_2 UB**	**NO_2 UB**
10	0.97 (0.89–1.06)	0.95 (0.84–1.07)	0.91 (0.76–1.09)	0.91 (0.76–1.08)
20	0.94 (0.80–1.12)	0.90 (0.70–1.16)	0.83 (0.57–1.19)	0.82 (0.57–1.17)
30	0.92 (0.71–1.18)	0.85 (0.59–1.24)	0.75 (0.43–1.31)	0.74 (0.44–1.27)
40	0.89 (0.64–1.25)	0.81 (0.49–1.33)	0.68 (0.33–1.43)	0.67 (0.33–1.37)
50	0.86 (0.57–1.32)	0.77 (0.41–1.43)	0.62 (0.25–1.56)	0.61 (0.25–1.48)
60	0.84 (0.51–1.39)	0.73 (0.34–1.54)		0.55 (0.19–1.60)
70	0.82 (0.45–1.47)	0.69 (0.29–1.66)		0.50 (0.14–1.74)
80	0.79 (0.40–1.55)	0.66 (0.24–1.78)		
90	0.77 (0.36–1.64)	0.62 (0.20–1.92)		
100	0.75 (0.32–1.73)	0.59 (0.17–2.06)		
110	0.73 (0.29–1.83)	0.56 (0.14–2.21)		
120	0.71 (0.26–1.93)	0.53 (0.12–2.38)		
130	0.68 (0.23–2.04)	0.50 (0.10–2.56)		
140	0.67 (0.20–2.16)	0.48 (0.08–2.75)		
150	0.65 (0.18–2.28)			
160	0.63 (0.16–2.41)			
170	0.61 (0.15–2.55)			
180	0.59 (0.13–2.69)			
190	0.57 (0.12–2.84)			
200	0.56 (0.10–3.00)			
210	0.54 (0.09–3.17)			

Legend: PM_{10}—average concentration of particulate matter with a size less than or equal to 10 μm in the surrounding urban background (UB); $PM_{2.5}$—average concentration of particulate matter with a size less than or equal to 2.5 μm in the surrounding urban background (UB); SO_2—average concentration of sulfur dioxide in the surrounding urban background (UB); NO_2—average concentration of nitrogen dioxide in the surrounding urban background (UB); RR—relative risk; CI—confidence interval; $p < 0.05$.

When assessing the single-lag models (from lag0 to lag7), no significant effects were found for PM_{10} and NO_2 (even though higher, but statistically non-significant RRs were observed in later lags, from lag5 to lag7), as well as regarding cumulative lag effects (lags0–1 to lags0–7). For $PM_{2.5}$ higher, but statistically non-significant RRs were also observed in higher lags (lag5 to lag7), while we found a "protective effect" (RR below 1) on AECOPD hospitalizations in the initial lag, which is stronger for concentrations of $PM_{2.5} \geq 50$ μg/m^3 (the strongest "protective effect" was observed for 50 μg/m^3 on lag0; RR 0.80 (95% CI 0.65–0.99), as well as the "protective" cumulative effects of concentrations ≥70 μg/m^3 on lags0–2 (RR 0.50, 95% CI 0.25–0.99) and concentrations ≥40 μg/m^3 on lags0–1 (RR 0.74, 95% CI 0.55–0.99). Over time, the RR becomes elevated (faster at higher concentrations) (Figure 4a). Similarly, significant daily "protective effects" in single-lag models (lag0 to lag2) were also observed for all SO_2 concentrations (RR 0.96, 95% CI 0.92–0.99 for 10 μg/m^3 at lag2), as well as regarding cumulative lags0–5 (RR 0.86, 95% CI 0.76–0.98 for 10 μg/m^3 at lags01). Given that in lags5–7, RR becomes elevated, these effects are suppressed, and in the end, no significant overall effect is obtained (Figure 4b). Supplementary Tables S1 and S2 display the observed lag effects for $PM_{2.5}$ and SO_2 in more detail.

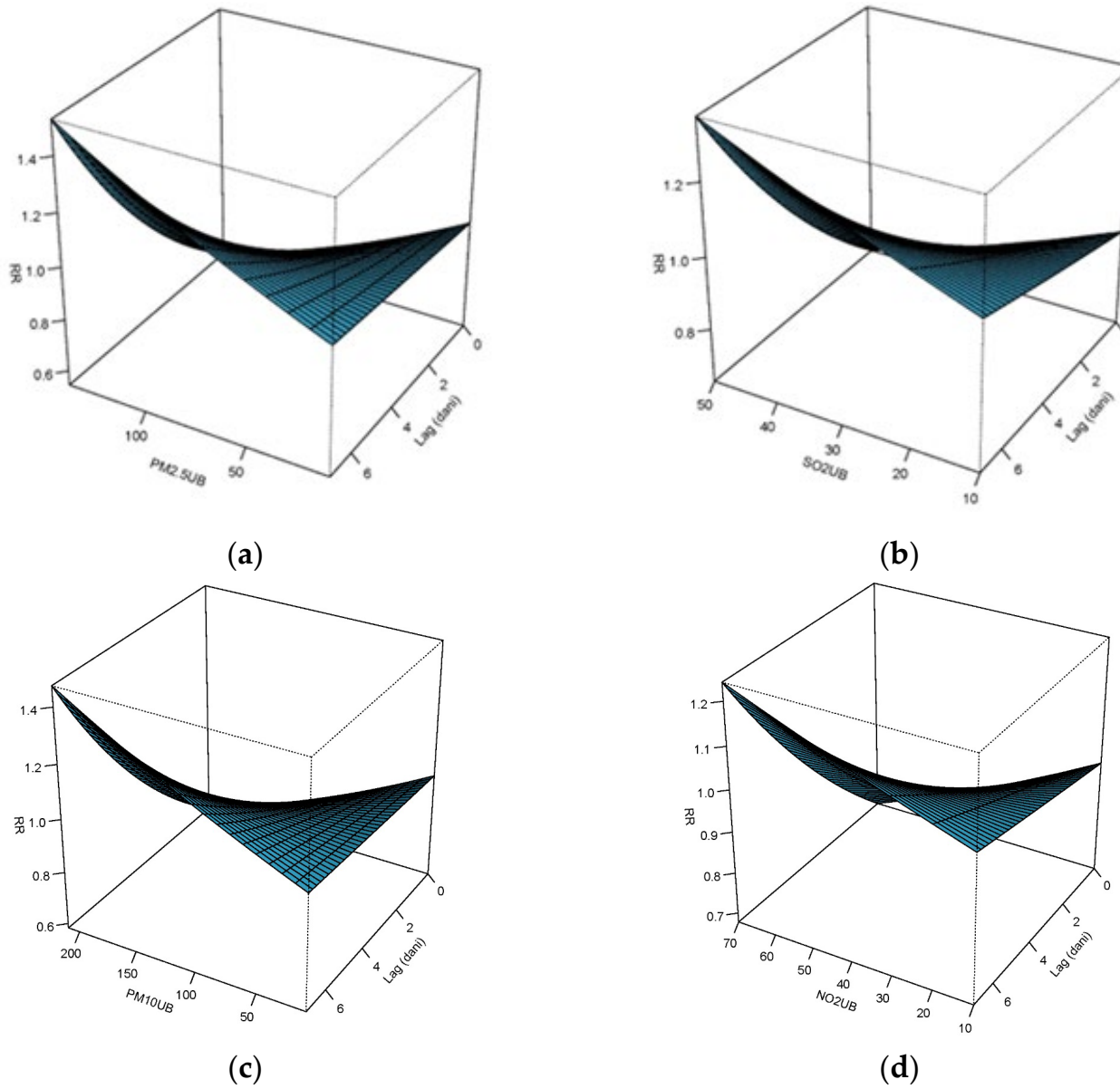
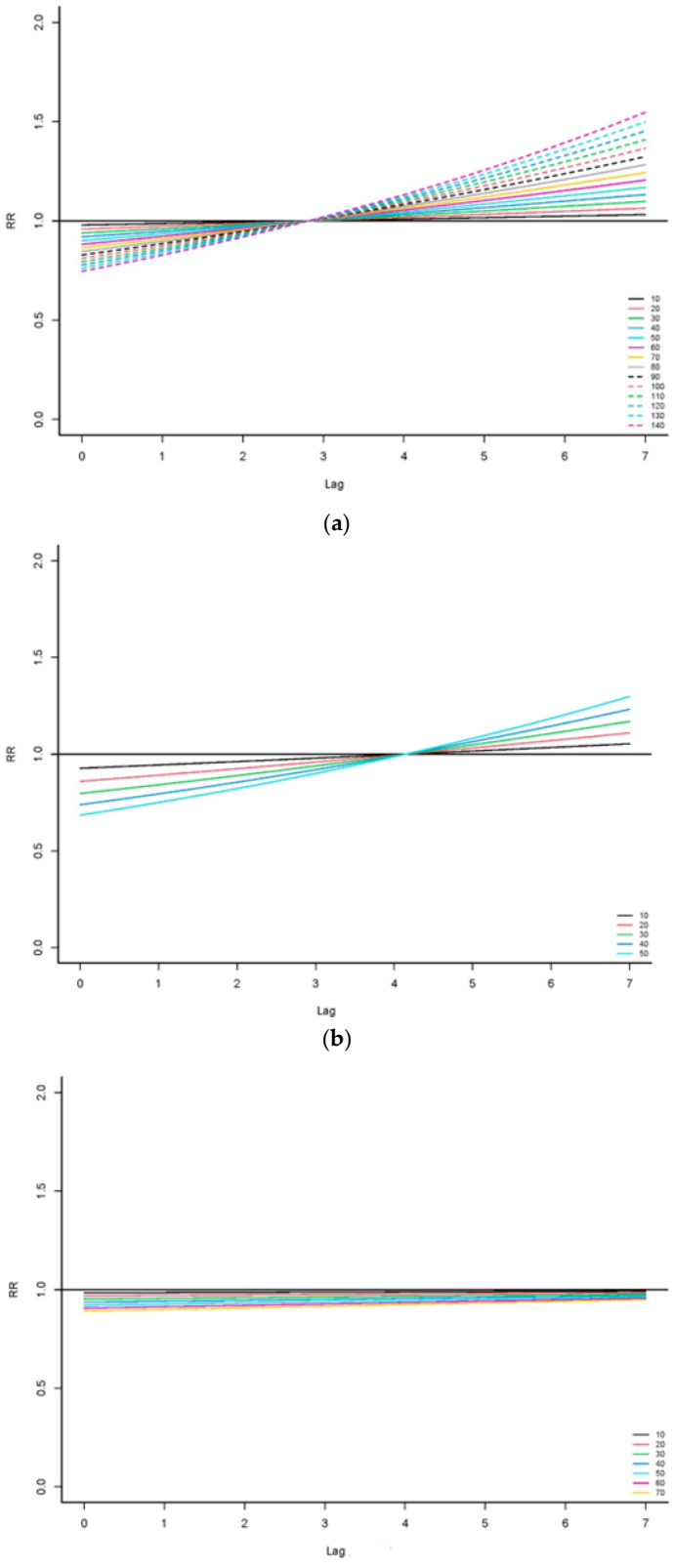


Figure 4. Lag effects of air pollutants on AECOPD hospitalization: (**a**) $PM_{2.5}$UB; (**b**) SO_2UB; (**c**) PM_{10}UB; (**d**) NO_2. On these bi-dimensional figures, RR is represented on the vertical axis, with the minimal value of 0. On the first horizontal axis, the concentrations of air pollutants are disposed (lower concentration on the right, higher on the left), while on the other horizontal axis, lags are presented (lower lag on the right, higher on the left).

Similar results were obtained in the multi-predictor models. The calculated cumulative RR for hospitalization due to AECOPD for each 10 $\mu g/m^3$ increase in air pollutant concentration was 1.36 for $PM_{2.5}$ (95% CI 0.36–5.11), 0.75 for SO_2 (95% CI 0.43–1.33), and 0.69 for NO_2 (95% CI 0.20–2.35). A more detailed analysis of the impact of lag effects in the multi-predictor models did not show statistically significant differences for either single-lag or cumulative-lag models (Figure 5).



(**a**)

(**b**)

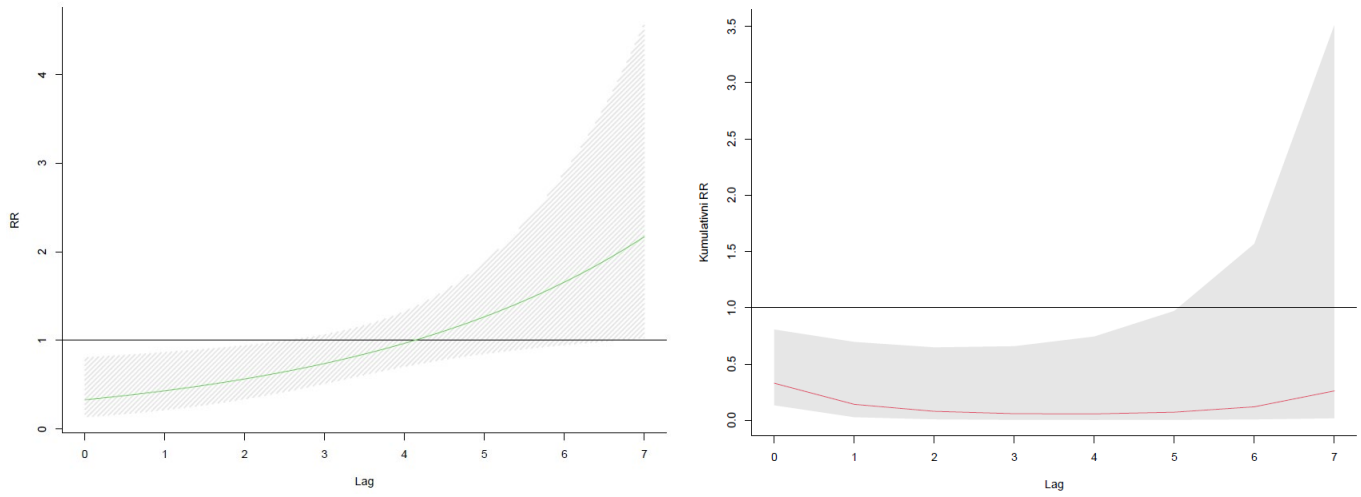
(**c**)

Figure 5. Lag effects of air pollutants on AECOPD hospitalization on multi-predictor models: (**a**) $PM_{2.5}$UB; (**b**) SO_2UB; (**c**) NO_2. RR is represented on the vertical axis, lag days on the horizontal axis, and colored curves represent different concentrations of air pollutants. No statistically significant association can be observed.

In the single-predictor models, we calculated the cumulative RR (lags0–7) for each 10 μg/m^3 increase in the air pollutant concentration on the number of AECOPD hospitalizations for active smokers and non-smokers (Table 4). During this analysis, no statistically significant association was found between the cumulative exposure to each of the selected air pollutants and the number of AECOPD hospitalizations in either of the two groups of patients. A more detailed analysis of the time lags revealed that only in lag7 was the exposure to high concentrations of $PM_{2.5}$ shown to be associated with an increased number of AECOPD admissions among smokers, with a more pronounced effect at higher concentrations of $PM_{2.5}$ (Figure 6).

Table 4. Cumulative RR (lags0–7) with 95% CI in parentheses of AECOPD hospitalization for each 10 μg/m^3 increase in selected air pollutants (single-predictor and multi-predictor models).

Variable		PM_{10}	$PM_{2.5}$	SO_2	NO_2
		Single-predictor models			
Smoking status	Smokers	0.52 (0.13–2.07)	0.49 (0.12–1.96)	1.02 (0.46–2.24)	0.47 (0.16–1.37)
	Non-smokers	0.87 (0.26–2.94)	0.79 (0.23–2.72)	0.59 (0.28–1.24)	0.83 (0.33–2.11)
		Multi-predictor models			
	Smokers	-	1.55 (0.23–10.41)	1.04 (0.46–2.34)	0.63 (0.11–3.59)
	Non-smokers	-	1.02 (0.17–6.13)	0.58 (0.27–1.26)	0.86 (0.18–4.15)



(**a**) (**b**)

Figure 6. Effects of higher concentrations of $PM_{2.5}$ on RR for AECOPD hospitalizations among active smokers: (**a**) lag association curve for $PM_{2.5}$ concentration of 140 μg/m^3. This figure shows that although in the initial lags (lag0 to lag3), the RR gradually increases, it is always below 1, while in lag4 to lag6, the RR would be above 1, but without statistical significance. Only in lag7 is statistical significance observed between the exposure to high concentrations of $PM_{2.5}$ and the number of AECOPD hospitalizations (RR 2.17 (1.03–4.58)); (**b**) cumulative association for $PM_{2.5}$ concentration of 140 μg/m^3. This figure shows that there is no significant cumulative effect in lags0–7 (RR 0.26 (0.02–3.51)).

4. Discussion

In this single-center time-series conducted over a five-year period (2017–2022) among residents of Novi Sad, Serbia, who were hospitalized due to AECOPD of non-infectious etiology, we found no statistically significant RR for AECOPD admissions for every 10 μg/m^3 increase in the selected air pollutant concentrations (PM_{10}, $PM_{2.5}$, SO_2, and NO_2), despite

the fact that in the majority of the models utilized, the associations were positive in direction (RR over 1). Furthermore, higher concentrations of $PM_{2.5}$ ($\geq$50 $\mu g/m^3$) were found to be associated with a decrease in the number of AECOPD hospitalizations at early lags (lags0–2), with similar results for SO_2. There was no statistically significant increase in AECOPD admissions for every 10 $\mu g/m^3$ increase in the chosen air pollutant concentrations in either active smokers or nonsmokers.

Numerous studies conducted thus far have demonstrated a positive correlation between short-term exposure to air pollution and morbidity and mortality due to AECOPD, although no conclusive causal relationship has been established. Various studies employ distinct methodologies and statistical analyses, consider different numbers of lag days, and are carried out across various geographical areas, with different concentrations of air pollutants to which patients are exposed, which also contain different chemical constituents. Numerous other associated factors may influence the effects of air pollution on AECOPD development, such as interactions between single air pollutants or with meteorological factors, different individual exposures, and associated viral or bacterial infections, all of which may contribute to the obtaining of diverse, sometimes completely contradictory results, making it difficult to compare and comprehend the obtained data.

One of the pioneering projects from the end of the 20th century (the APHEA project) revealed a positive correlation between short-term exposure to elevated concentrations of certain particulate and gaseous ambient air pollutants, and an increased risk of hospitalization and mortality due to AECOPD [22]. Since then, there has been a growing emphasis on investigating the effects of air pollution on adverse respiratory effects. Searching the PubMed database using the keywords "COPD" and "air pollution" yields approximately 2500 research articles investigating the impact of air pollution on COPD, with nearly 200 papers published annually over the past five years.

In the beginning, PM_{10} was the most frequently investigated pollutant and was correlated with AECOPD, but in recent years, $PM_{2.5}$ have received increasing attention, as they penetrate the deepest into the respiratory tract (due to their size) as well as due to their chemical compounds, making them even more hazardous to the development of AECOPD. Thus, according to a 2020 meta-analysis of 18 studies [23], an increase in $PM_{2.5}$ concentration was associated with a 2.5% increase in the number of AECOPD hospitalizations (OR of 1.025, 95% CI 1.018–1.032). Another meta-analysis analyzing only studies conducted in Chinese cities [24] found a correlation between short-term exposure to $PM_{2.5}$ and the number of AECOPD hospitalizations (OR 1.033, 95% CI: 1.021–1.046 for each concentration increase of 10 $\mu g/m^3$), and a similar effect was observed for PM_{10} (OR 1.029, 95% CI: 1.018–1.041). In a 2013 meta-analysis that analyzed the results of 31 studies [25], it was determined that an increase in PM_{10} concentration by 10 $\mu g/m^3$ was associated with a 2.7% increase in the number of AECOPD hospitalizations (OR 1.027, 95% CI: 1.019–1.036). Gaseous pollutants were found to be associated with an increase in AECOPD-related hospitalizations as well. A recently published meta-analysis from 2022 [26] revealed a positive correlation between the number of AECOPD admissions and exposure to SO_2 (RR 1.016, 95% CI: 1.012–1.021 for each increase in the concentration of 10 $\mu g/m^3$) and NO_2 (RR 1.016, 95% CI: 1.012–1.120 for each increase in the concentration of 10 $\mu g/m^3$), while in another meta-analysis from 2017, a 10 $\mu g/m^3$ increase in SO_2 and NO_2 was associated with 2.1% and 4.2% increased risk of AECOPD-related hospitalizations [6]. More recent studies that found a positive relationship between short-term exposure to air pollutants and AECOPD admissions are listed in Table 5.

Table 5. Selected studies demonstrating a positive association between air pollutant exposure and number of AECOPD hospitalizations.

Study/ Country	No. of AECOPD	Time Period	Study Design	Lag Days [a]	Air Pollutant	OR/RR/PC (95% CI) [b]	Confounding Factors
Song et al., [8] 2022; China	4766	January 2015–December 2018	Time-series	0–7	$PM_{2.5}$	OR 1.114 (1.055 to 1.176)	Temperature, humidity, other air pollutants, time, holiday, day of the week
Dąbrowiecki et al., [9] 2023; Poland	26,948	1 January 2011 – 31 December 2018	Case-crossover	0–21	PM_{10} $PM_{2.5}$ SO_2 NO_2	RR 1.028 (1.008 to 1.049) RR 1.030 (1.006 to 1.055) RR 1.145 (1.038 to 1.262) RR 1.032 (0.988 to 1.078) [d]	Temperature, humidity, atmospheric pressure, time, city, day of the week
Zhou et al., [10] 2021; China	4980	1 January 2016–31 December 2020	Time-series	6 6 6 9	PM_{10} $PM_{2.5}$ SO_2 NO_2	PC 1.3% (0.3 to 2.4) PC 2.8% (1.0 to 4.7) PC ~3.2% (−0.7 to 7.1) [d] PC 3.6% (1.2 to 6.2)	Seasonal and long-term trends, air pollutants
Gao et al., [11] 2019; China	73,076	1 January 2013–28 February 2017	Time-series	0–7 0–6 0–1 0–6	PM_{10} $PM_{2.5}$ SO_2 NO_2	PC 0.92% (0.55 to 1.30) PC 0.82% (0.38 to 1.26) PC 2.07% (1.0 to 3.15) PC 3.03% (1.82 to 4.26)	Temperature, humidity, seasonal and long-term trends
Sun et al., [12] 2019; China	4761	1 January 2015–31 December 2017	Time-series	0	$PM_{2.5}$	PC 1.05% (0.14 to 1.96)	Temperature, humidity, other air pollutants, time, holiday, day of the week
Raji et al., [13] 2020; Iran	4534	March 2008–March 2018	Time-series	2 4	$PM_{2.5}$ NO_2	RR 1.003 (1.001 to 1.005) RR 1.049 (1.017 to 1.124) (only in females)	Temperature, humidity, trend, seasonality, weekdays, holidays
Jin et al., [14] 2022; China	40,002	2014—2015	Case-crossover	0–5	$PM_{2.5}$	OR 1.016 (1.006 to 1.027)	Temperature, humidity, holiday
Pini et al., [15] 2021; Italy	431	January 2014–January 2016	Time-series	0–5 0–5	PM_{10} $PM_{2.5}$	RR 1.07 (1.01 to 1.14) RR 1.11 (1.04 to 1.18)	Medium and long-term temporal trends, holidays, influenza, humidity, temperature
Mercan et al., [16] 2020; Turkey	23,830	1 August 2016–1 August 2019	Time-series	0 0	PM_{10} SO_2	RR 1.029 (1.022 to 1.035) RR 1.065 (1.056 to 1.075)	Temperature, humidity, atmospheric pressure, holiday, day of the week,
Peng et al., [17] 2022; China	665,541	1 January 2008–31 July 2020	Time-series	1	PM_{10} $PM_{2.5}$	PC 0.361% (0.151 to 0.572) PC 1.167% (0.820 to 1.515)	Temperature, humidity, seasonality, weekdays, holidays
Han et al., [18] 2021; China	85,301	January 2007–February 2018	Case-crossover	6 0–7 0–4 5	PM_{10} $PM_{2.5}$ SO_2 NO_2	OR 1.01 (1.00 to 1.01) [c] OR 1.11 (1.10 to 1.13) [c] OR 1.65 (1.53 to 1.79) [c] OR 1.05 (1.04 to 1.05) [c]	Temperature, humidity, atmospheric pressure

Legend: AECOPD–acute exacerbation of chronic obstructive pulmonary disease; RR–risk ratio; OR–odds ratio; PC—percent change; CI—confidence interval; PM_{10}—particulate matter with a size less than or equal to 10 μm; $PM_{2.5}$—particulate matter with a size less than or equal to 2.5 μm; SO_2—sulfur dioxide; NO_2 –nitrogen dioxide; [a]—strongest effects are displayed; [b]—measured with each 10 $\mu g/m^3$ increase in air pollutant concentration; [c]—per unit increase in air pollutant concentration; [d]—not statistically significant.

In contrast to gaseous air pollutants, which may have an immediate effect, some studies indicate that there may be a lag effect for PM to manifest their harmful effects [10]. This is partially explained by the direct bronchoconstrictor effect of gaseous air pollutants, especially SO_2, which can cause sudden dyspnea and worsening of the underlying disease. Moreover, the delayed effect of PM is explained by their indirect effects on AECOPD, such as the stimulation of mucus secretion in the airways, the downregulation of the expression of antimicrobial peptides on the surface of the respiratory epithelium, which predisposes patients to the occurrence of infection-mediated AECOPD, as well as the intensification of inflammation in the airways due to the stimulation of the activity of alveolar macrophages [9]. However, there are studies in which such effects of time lags have not been demonstrated [12], all of which speak to the need for additional research on the temporal effects of air pollutants on AECOPD.

In addition, the analysis of different studies indicates that the estimated effect of exposure to air pollution on the increase in hospitalizations varies in magnitude. Thus, in one meta-analysis that included studies from European and North American countries, it was determined that an increase in $PM_{2.5}$ concentration was associated with a 3.1% increase in AECOPD hospitalizations [27]. In a meta-analysis of Chinese studies, this proportion was 2.5% [23], whereas it was lower in other Asian studies (0.82% in a Chinese study [11] and 0.99% in a Taiwanese study [28]). A potential explanation for these findings is the difference in the average daily concentrations of air pollutants, given that relatively higher levels of air pollutants in Asian countries could reduce sensitivity to a unit change in exposure, as demonstrated by the concentration-response curves [12].

We hypothesized at the outset of the study, based on a review of the relevant literature, that there would be a positive association between exposure to air pollution and the number of AECOPD hospitalizations. In our study, however, no statistically significant association between AECOPD admissions and any of the examined air pollutants was established, either in the single-predictor or in the multi-predictor models, while the protective effects of elevated $PM_{2.5}$ and SO_2 concentrations on hospital admissions due to AECOPD in the early lags were also determined. There are several potential explanations for these results, some of which represent the limitations of our study.

First, it is important to note that the daily average concentrations of the selected air pollutants (PM_{10}, $PM_{2.5}$, SO_2, and NO_2) in our study were relatively low (the average values for the whole time period were 28.8, 19.81, 10.22, and 14.54 $\mu g/m^3$, respectively) and without significant deviations from the standards recommended by the WHO and the European Council, which could explain a portion of the results. These findings are in contrast to the majority of the studies published in recent years that found a positive correlation between air pollution and AECOPD (see Table 5), as the majority of these studies originated from countries with high air pollution levels, such as China. Nonetheless, studies conducted in regions where the air pollutant concentrations were within WHO-recommended levels demonstrated an increased risk of AECOPD associated with air pollution exposure [17,29,30], indicating that factors other than just air pollutant concentration may play a role in the onset of AECOPD. In addition, our research included a relatively small sample of AECOPD hospitalizations (552) from a single center, which can significantly reduce the power of the statistical analyses used and may have led to overlooking certain associations between air pollution and AECOPD. Currently, the majority of studies employing a methodology similar to ours are conducted in populous East Asian nations where the incidence of COPD is much higher. Moreover, in our study, we analyzed only severe AECOPD (those leading to hospitalizations), whereas mild and moderate cases, which can be treated ambulatorily, were not included, which may have underestimated the effects of air pollution on the development of AECOPD in general. The inability to account for certain behavioral determinants, such as the use of air conditioning or time spent outdoors, the fact that some of the patients may work outside the city and are exposed to different level of air pollution, which can influence an individual's exposure to air pollution and the development of AECOPD, may have also impacted the results. In this study, we relied on

air pollution data from stationary monitoring stations that record the daily variation in the air pollutant concentration and assumed that the mean daily concentration represents the population's exposure, as is the case for the vast majority of time-series. However, this may not necessarily reflect the individual exposure, introducing bias into the evaluation of the effects of air pollution on AECOPD.

To the best of our knowledge, this is the first study to distinguish between AECOPD caused by an infectious agent and that without an infectious cause. Some studies have clearly demonstrated a synergistic effect between exposure to air pollution and respiratory viral infections [31]. Air pollution can damage the respiratory epithelium and increase inflammation in the airways, thereby predisposing patients with COPD to a variety of respiratory infections that may exacerbate their symptoms. Thus, one study from South Korea demonstrated a direct correlation between elevated PM levels and an increase in the detection rate of respiratory viruses, whereas no such correlation was observed for bacterial pathogens [32]. As we analyzed only non-infectious AECOPD hospitalizations, it is possible that the absence of this air pollution-viral infection relationship contributed to the results obtained.

The effect of higher $PM_{2.5}$ concentrations and all SO_2 concentrations in the initial lags on the decreased incidence of AECOPD admissions is another intriguing finding of our study. Similar protective effects were observed in a study conducted in Berlin, but only for NO_2 and on lag day 1 [20]. Such outcomes can be explained in numerous ways. It is possible that the patients, having received information about the elevated concentrations of air pollutants, reduced their exposure to them by avoiding prolonged exposure or by using personal protective equipment such as face masks. The presence of the so-called Harvest effect, which implies that the highest number of AECOPD hospitalizations occur on the day of maximum air pollutant concentration, decreasing the number of patients requiring hospitalization the following day [20], must be considered, as well as the possibility that a certain number of patients at risk of severe AECOPD died before they could be hospitalized [33].

Reviewing the literature, we came across a considerable number of studies in which, similar to ours, no association between exposure to air pollution and an increase in AECOPD hospitalizations was established (Table 6), although it must be noted that the majority of these studies were conducted in the first decade of the 21st century. According to a study conducted in Birmingham, England [34], for every 15 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations, the number of hospitalizations due to AECOPD decreased by 3.9% (95% CI: −9.0–1.6%). An Italian study also found no association between $PM_{2.5}$ exposure and increased AECOPD admissions [33], with similar effects observed for PM_{10} in a study by Faustini et al. [35]. A recent German study [20] revealed a statistically significant increase in AECOPD hospitalizations for every 10 $\mu g/m^3$ increase in NO_2 concentrations. However, such an effect was not obtained for particulate air pollution (PM_{10} and $PM_{2.5}$) or for ozone (in single-pollutant models, increased ozone concentrations were associated with a decreased risk of AECOPD admission). In one multicenter European study, it was determined that even long-term exposure to PM has no effect on the prevalence of COPD [36].

Table 6. Selected studies demonstrating a negative association between air pollutant exposure and number of AECOPD hospitalizations/emergency department visits.

Study/ Country	No. of AECOPD	Time Period	Study Design	Lag Days [a]	Air Pollutant	OR/RR/PC (95% CI)	Confounding Factors
Hoffmann et al., [20] 2022; Germany	8645	1 January 2005–31 December 2015	Time-series	0	PM_{10} $PM_{2.5}$ NO_2	N/A (0.988 to 1.032) [b] N/A (0.966 to 1.019) [b] RR 1.123 (1.081 to 1.168) [b,*]	Seasonal and long-term trends, temperature, humidity, wind speed
Stieb et al., [37] 2009; Canada	40,491 (ED visits)	1990s–early 2000s	Time-series	0	PM_{10} $PM_{2.5}$ SO_2 NO_2	PC −0.6 (−3.3 to 2.2) per 20.6 μg/m^3 increase PC −1.8 (−6.1 to 2.7) per 8.2 μg/m^3 increase PC −1.9 (−4.3 to 0.6) per 5.1 ppb increase PC 0.1 (−5.6 to 6.2) per 18.4 ppb increase	Temporal cycles, temperature, humidity, day of the week, holidays
Slaughter et al., [38] 2005; USA	1.1 cases/day	January 1995–December 2000	Time-series	1	PM_{10} $PM_{2.5}$	RR 0.99 (0.91 to 1.08) [b] RR 0.98 (0.90 to 1.07) [b]	Seasonal and long-term trends, time, temperature, humidity, day of the week
Peel et al., [39] 2005; USA	7.42 cases/day (ED visits)	1 January 1993–31 August 2000	Time-series	0–3	PM_{10} NO_2 SO_2	RR 1.018 (0.994 to 1.043) [b] RR 1.035 (1.006 to 1.065) * per 20 ppb increase RR 1.016 (0.985 to 1.049) per 20 ppb increase	Seasonal and long-term trends, time, temperature, dew point, day of the week, holiday, hospital entry and exit
Faustini et al., [35] 2005; Italy	38,577	1 January 2001–31 December 2005	Case-crossover	0	PM_{10} NO_2	PC 0.67 (−0.02 to 1.35) [b] PC 1.20 (0.17 to 2.23) [b,*]	Temperature, atmospheric pressure, seasonal and long-term trends, holidays, influenza epidemics
Belleudi et al., [33] 2010; Italy	15,087	10 April 2001–31 December 2005	Case-crossover	0	PM_{10} $PM_{2.5}$	PC 0.40 (−1.41 to 2.25) for 14 μg/m^3 PC 1.88 (−0.27 to 4.09) for 10 μg/m^3	Seasonal trends, temperature, barometric pressure, holidays
Anderson et al., [34] 2001; UK	N/A	October 1994–December 1996	Time-series	0	PM_{10} $PM_{2.5}$ SO_2 NO_2	PC −1.8 (−6.9 to 3.5) [c] PC −3.9 (−9.0 to 1.6) [c] PC −4.2 (−8.9 to 0.8) [c] PC 2.5 (2.1 to 7.3) [c]	Long-term time trends, seasonal patterns, influenza epidemic, day of the week, temperature, humidity

Legend: AECOPD–acute exacerbation of chronic obstructive pulmonary disease; RR–risk ratio; OR–odds ratio; PC–percent change; CI–confidence interval; ED–emergency department; PM_{10} –particulate matter with a size less than or equal to 10 μm; $PM_{2.5}$–particulate matter with a size less than or equal to 2.5 μm; SO_2–sulfur dioxide; NO_2–nitrogen dioxide; N/A–not available; [a]–strongest effects are displayed; [b]–measured with each 10 μg/m^3 increase in air pollutant concentration; [c]–per 10–90th percentile increment in air pollutant concentration; *–statistically significant.

There are few studies on the effects of air pollution on AECOPD originating from Serbia, and even among those available, the results obtained are inconsistent, reflecting a similar situation on a global scale. In a study conducted in Smederevo, a Serbian city with higher concentrations of air pollutants due to the presence of an iron factory, it was determined that in 2011 the incidence of moderate and severe AECOPD was unrelated to exposure to particulate air pollution (PM_{10} and $PM_{2.5}$) [40]. Another study from the end of the first decade of the 21st century, also conducted in Novi Sad and employing a similar methodology as in our study, concluded that there is no statistically significant association between exposure to SO_2 and NO_2 and the number of AECOPD hospitalizations [41]. In a 2019 study conducted in Niš, Serbia, there was no influence of SO_2 exposure on the increased number of emergency room admissions for AECOPD, even after controlling for black smoke, for which there was a small, but significant association [42]. A different study from Niš found an increase in AECOPD admissions by 0.7% for every 10 $\mu g/m^3$ increase in the daily NO_2 concentration; however, given the low calculated RR of 1.007 (95% CI 1.000–1.015), this association cannot be considered positive [43]. In a 2016 project of the City Health Administration of Novi Sad, data on environmental air pollutants (PM_{10}, SO_2, and NO_2) and the number of daily hospitalizations due to AECOPD (including infectious and non-infectious agents) were analyzed [44]. There was a statistically significant positive association between increasing SO_2 concentrations and the daily number of AECOPD admissions (RR 1.054, 95% CI 1.020–1.088), but no such effect was observed for NO_2 (RR 0.995, 95% CI 0.995–1.007), similar to the results of our study.

Considering that cigarette smoking is the leading risk factor for the development of COPD [2], we wanted to investigate whether there were differences in exposure to air pollution and the number of AECOPD hospitalizations between active smokers and non-smokers. After statistical analysis, it was determined that neither the single-predictor nor the multi-predictor models demonstrated a statistically significant association between exposure to air pollution and the number of AECOPD admissions in any of the aforementioned patient groups. Data on the smoking status of patients are lacking in a large number of studies employing a similar methodology to ours, since data are usually collected automatically, typically obtaining the diagnosis code of the observed health outcome and basic socio-demographic data, such as gender and age. In a recent study by Song et al. [8], exposure to high concentrations of $PM_{2.5}$ increased the risk of developing AECOPD, and that effect was presented in both smokers (the cumulative RR (lags0–7) was 1.113 (95% CI: 1.042–1.187)) and non-smokers (the cumulative RR was 1.122 (95% CI: 1.040–1.210)). Although the directions of the correlation are different, neither our study nor the aforementioned study found a difference between smokers and non-smokers in terms of the risk of AEHOBP onset and exposure to air pollution, indicating that further research is required to examine the interaction between tobacco smoke and air pollution.

5. Conclusions

Numerous recent studies have found an association between air pollution exposure and the incidence of AECOPD hospitalizations. In our study, however, neither the single-predictor nor the multi-predictor models revealed any statistically significant association between AECOPD admissions and any of the examined air pollutants, calculated at every 10 $\mu g/m^3$ increase in the selected air pollutant concentrations. In addition, elevated $PM_{2.5}$ and SO_2 concentrations were associated with a reduction in AECOPD-related hospital admissions in the early lags. The smoking status of patients did not influence their susceptibility to develop AECOPD due to air pollution exposure.

Our findings not only contribute to the body of knowledge regarding the effect of air pollution on the incidence of AECOPD, but also confirm the need for additional research in this area, since the results of different studies, including ours, are not coherent enough. It is necessary to repeatedly conduct studies employing a similar methodology in different geographic regions, even if similar results are obtained, to establish a conclusive causal relationship between air pollution and AECOPD onset. Future research should focus

on analyzing data from multiple centers, and we encourage other scientists to examine infectious and non-infectious AECOPD separately.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/atmos14040730/s1. Table S1: Lag effects (single-lags and cumulative lags) of increasing $PM_{2.5}$ concentrations on the RR for AECOPD hospitalizations; Table S2: Lag effects (single-lags and cumulative lags) of increasing SO_2 concentrations on the RR for AECOPD hospitalizations.

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Data Availability Statement: Data on the values of the considered meteorological factors for the city of Novi Sad, Serbia, are publicly available from the Republic Hydrometeorological Service of Serbia's website (https://www.hidmet.gov.rs/index_eng.php (accessed on 15 August 2022)), while publicly available data on air pollutant concentrations can be retrieved from the Serbian Environmental Protection Agency's website (http://www.sepa.gov.rs/ (accessed on 18 August 2022)). The data presented in this study are available upon request from the corresponding author.

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