

*Original Research*

# The Relationship Between Short-Term Exposure to PM<sub>10</sub> and Emergency Room Visits in Urban Area Near Copper Smelter

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## Abstract

A large number of studies have examined the effect of air pollution on mortality and morbidity. However, the most of those studies have investigated associations between air pollution and only one or two specific diseases such as cardiovascular, pulmonary and mental diseases or pregnancy-related problems. This study aimed at exploring the risk effect of particulate matter air pollution on the emergency room visits for all these diseases in the city of Bor, Serbia. The data on daily emergency room visits between April 2014 and December 2018 as well as daily measurements of PM<sub>10</sub> from 4 stations were collected. The Generalized-Additive Model (GAM) with quasi-Poisson regression was applied to assess the connection between daily PM<sub>10</sub> and emergency room visits for each outcome. Calendar time, temperature and relative humidity were incorporated as confounding variables. Each 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> at lag 0:3 day was associated with 0.33% (95% CI: 0.11, 0.54) and 1.22 % (95% CI: 0.73, 1.71) increments in admission for cerebrovascular diseases and pregnancy-related problems, respectively.

**Keywords:** air pollution, PM<sub>10</sub>, Generalized-Additive Model, human health

## Introduction

It is a well-known fact that the emission of gases from copper smelters [1] with increased content of SO<sub>2</sub> and PM<sub>10</sub> which contain the toxic elements: As, Cd, Pb, Ni and Hg has a negative impact on human health [2], cause cancer, respiratory and cardiovascular diseases [3], and increases mortality [4]. The WHO estimated that exposure to ambient PM pollution

accounted for 4.2 million premature deaths globally in 2016, including 0.5 million in Europe [5]. Particulate matter (PM) presents a complex mixture of organic and inorganic substances and can have a different composition, which depends on the emission source. PM comes from various sources including motor vehicles, road dust, industrial and agricultural combustion, wood burning, forest fires, pollens and molds, volcanic emissions and sea spray. The varying contribution of these sources is different worldwide. To protect human health the EU introduced two limitations for particulate matter: the PM<sub>10</sub> daily mean value may not exceed 50 µg/m<sup>3</sup> for more than 35 times

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in a year and the  $PM_{10}$  annual mean value may not exceed  $40 \mu\text{g}/\text{m}^3$  [6].

Increased pollution, especially in developing countries, is a serious problem a population may face. Many studies have proven the connectedness between the high concentration of pollutants in the ambient air and the consequences it has for human health in these areas. For quite some time now, researchers have been trying to find out how air pollution affects an increased rate of premature mortality [7], the occurrence of acute myocardial infarction [8], respiratory diseases [9], hypertension [10], mental disorders [11] and an increased number of miscarriages [12].

### $PM_{10}$ and Respiratory Diseases

Most pollutants enter the body through the respiratory system, which is why the consequences of poor quality of the air on the respiratory system are the most visible [13]. Various studies have shown that exposure to particulate matter (PM) concentrations is associated with asthma [14], COPD [15], acute bronchitis and allergic rhinitis [16].

### $PM_{10}$ and Cardiovascular Diseases

The biological mechanisms that connect air pollution with heart disease include the direct effects of pollutants on the cardiovascular system [17], blood and pulmonary receptors, and indirect effects through pulmonary oxidative stress and inflammatory reactions. These direct effects of air pollution are an acceptable explanation for sudden cardiovascular reactions (occurrence within a few hours), such as myocardial infarction. Less acute (i.e. occurring in a period from a few hours to a few days) and chronic indirect effects may occur through pulmonary oxidative stress/inflammation caused by inhaled contaminants. A large number of studies have reported a relation between  $PM_{10}$  and cardiovascular morbidity. Some of them explored the effects on broad categories of cardiovascular diseases [18, 19], and few studies have looked at the relationship between  $PM_{10}$  and specific cardiovascular diseases at the same time [20, 21].

### $PM_{10}$ and Psychic Disorders

In recent years, studies have found that air quality may affect the occurrence of certain mental disorders, such as schizophrenia. It has been proven that genetic and environmental factors contribute to schizophrenia [22]. Given that there are indications that only 7% of the risk for schizophrenia can be attributed to genes [23], it is easy to conclude that environmental factors play a crucial role in this case. Suspended particle pollution is considered to be one of the most important factors. Recent studies conducted in China have shown a serious relationship between exposure to  $PM_{10}$  concentrations and daily hospital admission for schizophrenia

[24-28]. There are various explanations for how air pollution, specifically  $PM_{10}$ , actually affects the occurrence of schizophrenia. One of the explanations says that  $PM_{10}$  activates microglia, produces inflammatory factors, and then causes the onset of schizophrenia [26]. In addition, there is an assumption that exposure to heavy metals, such as lead and cadmium, which are an integral part of particulate matter, may be one of the causes of schizophrenia and other mental disorders [29, 30].

### $PM_{10}$ and Pregnancy-Related Diseases

The developing fetus is particularly susceptible to environmental pollutants, including air pollution. In developing embryos, the placenta serves as a barrier against many dangerous substances from the environment, but it cannot protect against all components of air pollution. In addition, recent studies have found a link between exposure to outdoor air pollution during the entire pregnancy [31, 32] and higher rates of miscarriages or stillbirths [33], as well as many other adverse pregnancy outcomes [34].

Therefore, this time-series analysis aims to explore the impacts of air pollution on hospital admissions for respiratory, cardiovascular and mental diseases and pregnancy-related problems and at pointing out how increased pollution impacts the health of the population.

## Material and Methods

### Study Area

The problem of air pollution in the city of Bor has been present for decades now. One of the European largest and oldest copper mines is located in the city of Bor. Mining in Bor City started in 1902, when a significant copper ore deposit was discovered. The exploitation and urbanization of this part of Serbia, which was previously rural has been ongoing since then [35]. The copper smelter is located in the immediate vicinity of the city, whose population counts approximately 40000 inhabitants. The local population is exposed to pollutants such as sulfur dioxide and  $PM_{10}$  with a high percentage of arsenic, lead, cadmium, mercury and nickel [36]. Since 2010, the suspended  $PM_{10}$  particles in the ambient air and their physical and chemical characterization have been the subject matter of several research studies in the Bor urban area [37-40]. One of the first air quality assessments included attempts to identify the emission sources using statistical methods and identify the most polluted locations in the city [36]. The copper smelting plant was identified as the primary source of pollution. In the meantime, a new copper smelting plant and a sulfuric acid plant were opened in 2016, which was supposed to improve air quality in the city and reduce

the concentration of pollutants, which unfortunately has not happened to date.

### Data Collection

Based on a similar research study conducted in Beijing [20], and for the purposes of this study, the data about the number of patients were collected from the local emergency room in Bor, Serbia. The same was used to examine the risk of the pollution caused by the copper smelter for human health in order to make recommendations on how the quality of the life of the local population might be improved. The data about the number of patients with a specific diagnosis were collected on a daily basis. The daily average PM<sub>10</sub> and sulfur dioxide (SO<sub>2</sub>) were obtained from the Bor Municipality's website. The daily mean temperature and relative humidity were obtained from the Mining and Metallurgy Institute in Bor and the Serbian Agency for Environmental Protection websites, respectively. The analysis included the patients with cardiovascular, respiratory, mental and pregnancy-related problems who asked for help from the emergency room during the day. Since medical data are not publicly available, only the data about the number of the patients were allowed to use. In contrast, the authors needed approval from the special ethics commission for the additional data such as patient gender and age. Although there is an initiative in Serbia to make such data publicly available, these data are still protected and only presented in the form of reports at country's level. According to the authors' knowledge, this is the first analysis in this part of Europe that examines the impact of pollution on the occurrence of certain diseases. For the needs of the research study, the data about the number of patients and the diagnoses were obtained from the electronic database of the Emergency Room in Bor. The diagnoses are primary, classified based on the International Classification of Diseases (ICD-10). The cardiovascular outcomes included cerebrovascular events (I60-I69), ischemic heart disease (I20-I25), other heart diseases (I44-I49), and heart failure (I50). The respiratory outcomes included upper respiratory tract infection (common cold (J00), inflammation (J02-J06)), chronic lung obstruction (J44.103, J44.901) and asthma (J45-46). The mental diseases included schizophrenia (F20) and pregnancy-related diseases (O20).

### Statistical Analysis

Some studies have examined the relationship between individual pollutants and their consequences for health [41, 42]. Given that air pollution occurs as a result of mixing pollutants in the gaseous, liquid and solid states, the results obtained using a single pollutant model would quickly be eliminated by adding other pollutants to the model. For this reason, and in order to obtain a complete and realistic picture, many researchers recommend that multi-pollutant models

should be used when studying the effect of pollution on human health [43]. GAM (Generalized Additive model) is one of the most commonly used methods that allow a simultaneous inclusion of two or more pollutants.

For this reason, GAM was used to assess the relationship between the PM<sub>10</sub> variation (Lags 0, 1, 2 and 3) and the daily number of the patients for each particular diagnosis. At lag 0, GAM was used to detect connection between air pollution and disease on a given day. Similarly, the mean concentration of air pollution at lag 1, 2 and 3 refer to one, two or three days before and the number of patients on the current day. Overall cumulative exposure to PM<sub>10</sub> on the current day and the previous three days (lag 0:3), was also estimated.

GAM is a flexible model for estimating the unknown non-linear relationship between air pollution and the variable refers to the daily number of the subjects of the diseases [44, 45]. GAM was used in this study with the quasi-Poisson distribution because the daily counts of the patients have overdispersion. Several covariates were adjusted with the penalized spline function. The generalized cross-validation (GCV) score was used to find the optimum degrees of freedom (df) [46]. For the calendar time the optimal df was 7 per year, for the mean temperature the optimal df was 3 and for the relative humidity the optimal df was 3 as well. Beside the single lag model, the distributed lag model, where the multiple lags (lag 0:3) of air pollution are simultaneously included in the model, was applied. The algorithm flow is shown in Fig. 1. In the one-pollutant model, PM<sub>10</sub> was separately included in GAM. In the two-pollutant model, SO<sub>2</sub> simultaneously joined PM<sub>10</sub> in GAM.

Model I (the one-pollutant model):

$$\log(\mu_t) = \alpha + \beta_{t-1}(\text{PM10}_{t-1}) + s(\text{Time}, \text{df} = 7) + s(\text{T}, \text{df} = 3) + s(\text{RH}, \text{df} = 3) \quad (1)$$

where the  $\log(\mu_t)$  referred to the daily number of the diseases,  $t$  was the first day and  $l$  was the lag days.  $\beta_{t-1}(\text{PM10}_{t-1})$  represented the one-way pollution model for PM<sub>10</sub>,  $\beta_{t-1}$  was the regression coefficient and PM<sub>10,t-1</sub> was the mean concentration of PM<sub>10</sub>. The time was the calendar time. T stood for temperature and RH was relative humidity.  $\alpha$  was an intercept and  $s$  was the penalized cubic spline function.

All the results were expressed as the percentage changes (PC (%)) in the daily subject visits for each outcome for a 10 µg/m<sup>3</sup> increment of the PM<sub>10</sub> concentrations and its 95% confidential intervals [20]. PC% was calculated as follows:

$$PC (\%) = [\exp(10 * \beta_{t-1}) - 1] * 100 \quad (2)$$

Statistical analysis was performed using the R software (<https://www.r-project.org>). To fit the GAM

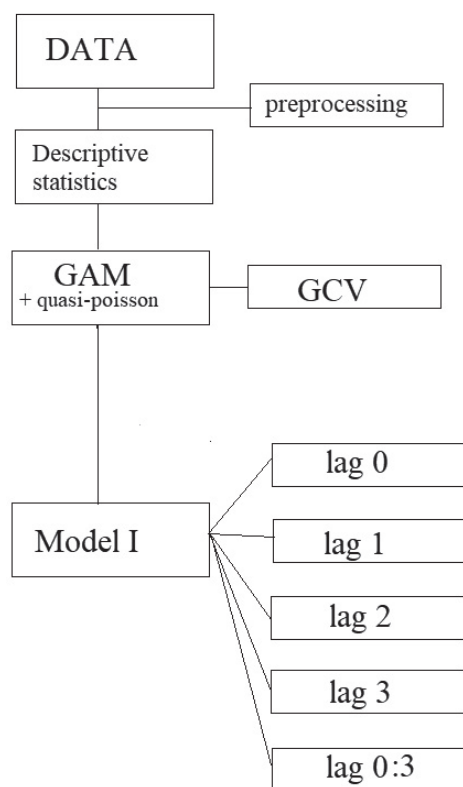


Fig. 1. Basic algorithm of Generalized-Additive Model.

model the ‘mgcv’ package was used.  $p < 0.05$  was considered statistically significant.

## Results and Discussion

### Baseline Characteristics

The descriptive statistics were presented by the mean, the standard deviation (SD), the minimum (min), the maximum (max), the 25<sup>th</sup> percentile, the 50<sup>th</sup> percentile (the median) and the 75<sup>th</sup> percentile of the variables that represented environment and morbidity data (Table 1). From 2014 to 2018 year, the total number of all the patients who had visited the emergency room was 13842, of whom a total of 8316 (60.08%) were those with all cardiovascular diseases, 5165 (37.31%) were the patients with all respiratory diseases, 237 (1.71%) were those with psychic disorders and 124 (0.9%) were the patients with pregnancy problems. The mean daily concentrations of air pollutants were  $40.53 \mu\text{g}/\text{m}^3$  and  $115.1 \mu\text{g}/\text{m}^3$  for  $\text{PM}_{10}$  and  $\text{SO}_2$ , respectively.

The distribution of the daily  $\text{PM}_{10}$  and  $\text{SO}_2$  concentrations from 2014 to 2018 is presented in Fig. 2. The figure shows the presence of the exceedances of the limited values for both pollutants

Table 1. Summary statistics of environment and morbidity data during 2014–2018.

	mean±SD	Min	25 <sup>th</sup> percentile	50 <sup>th</sup> percentile	75 <sup>th</sup> percentile	Max
Air pollutant concentrations						
$\text{PM}_{10}$ ( $\mu\text{g}/\text{m}^3$ )	40.53±29.3	0.91	18.23	33.27	54.53	168.60
$\text{SO}_2$ ( $\mu\text{g}/\text{m}^3$ )	115.1±122.2	2	46	89	147	2125
Meteorological variables						
Mean temperature (°C)	11.55±5.2	-12.7	4.78	11.70	18.91	37.10
Relative humidity (%) Daily number of patients	75.81±14.4	15.0	66	76	86.7	100
All cardiovascular						
Ischemic heart disease	2.4±1.81	0	1	2	3	10
Other heart diseases	1.56±1.45	0	1	1	2	7
Cerebrovascular diseases	0.56±0.77	0	0	0	1	4
Heart failure	0.02±0.75	0	0	0	0	1
All respiratory						
Inflammation	1.38±1.97	0	0	1	2	15
Asthma	1.27±1.19	0	0	1	2	5
Common cold	0.04±0.18	0	0	0	0	1
Chronic lung obstruction	0.13±0.42	0	0	0	0	3
Other						
Psychic disorders	0.13±0.37	0	0	0	0	2
Pregnancy related diseases	0.07±0.28	0	0	0	0	2

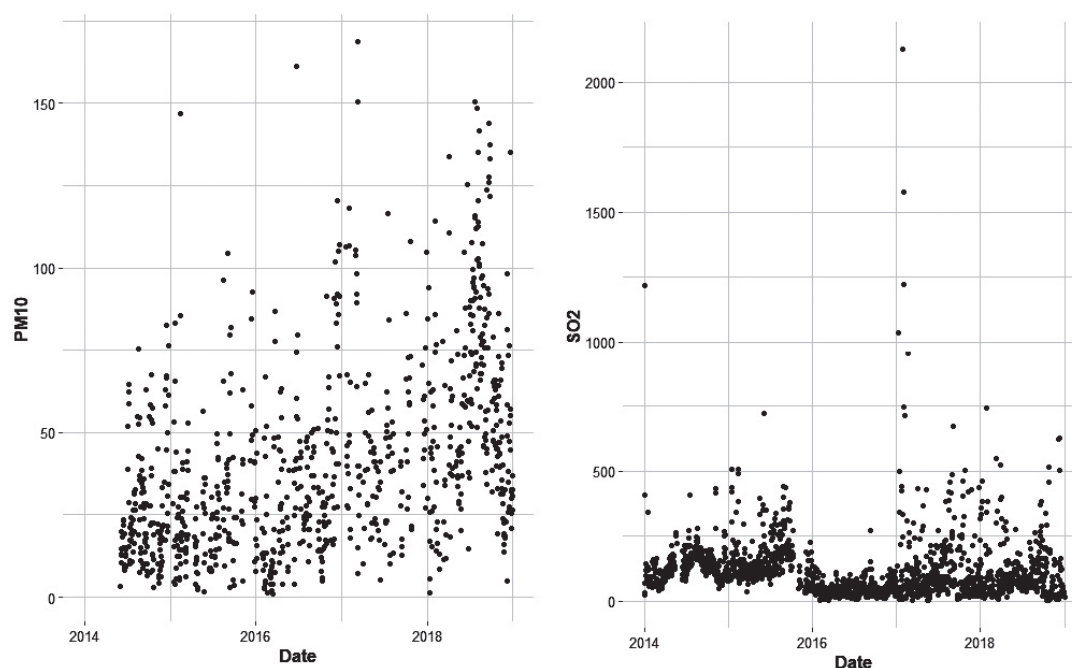


Fig. 2. The time-series plots of the PM<sub>10</sub> and SO<sub>2</sub> concentrations between 2014 and 2018.

during the observed period. The mean daily limited values of the PM<sub>10</sub> concentration were exceeded 272 times during the observed period, with the highest daily average value of 168 µg/m<sup>3</sup>. The mean daily concentrations of SO<sub>2</sub> were exceeded 66 times during the study period, with the maximum daily average values exceeding 2000 µg/m<sup>3</sup>.

### The Association between Pollution and Morbidity

The estimates obtained from the one pollutant model are given in Table 2.

According to the single pollutant model, each 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> (lag 3) is associated with the 0.24% (95% CI: 0.04, 0.44) increase in the output visits for the subjects with cerebrovascular diseases.

Table 2. Percentage changes with 95% CI in daily emergency room admission for all diseases associated with a 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> concentrations for the different lag structures.

Disease	Lag 0 day	Lag 1 day	Lag 2 day	Lag 3 day	Lag 0-3 days
All cardiovascular	-0.009 (-0.64,0.62)	-0.021 (-0.65,0.61)	-0.059 (-0.69,0.57)	-0.053 (-0.68,0.57)	-0.035 (-0.58,0.51)
Ischemic heart disease	-0.013 (-0.69,0.66)	-0.044 (-0.73,0.64)	-0.083 (-0.76,0.59)	0.230 (0.11,0.51)	<b>0.070 (0.03,0.13)</b>
Heart failure	0.508 (-1.23,1.77)	-0.203 (-1.52,1.15)	-0.270 (-1.63,1.12)	-1.462 (-3.28,0.92)	-0.034 (-0.81,0.74)
Other heart diseases	0.010 (-0.70,0.72)	-0.061 (-0.78,0.66)	-0.024 (-0.73,0.68)	-0.011 (-0.72,0.69)	-0.010 (-0.59,0.57)
Cerebrovascular diseases	-0.021 (-0.86,0.81)	0.026 (-0.79,0.85)	-0.249 (-0.59,0.59)	<b>0.240 (0.04,0.44)</b>	<b>0.330 (0.11,0.54)</b>
All respiratory	-0.033 (-0.74,0.67)	-0.084 (-0.78,0.62)	-0.103 (-0.79,0.59)	-0.087 (-0.79,0.61)	-0.036 (-0.61,0.54)
Inflammation	-0.236 (-0.56,0.58)	-0.235 (-0.55,0.58)	<b>0.230 (0.08,0.51)</b>	0.008 (-0.78,0.81)	-0.072 (-0.69,0.55)
Common cold	-0.425 (-1.52,1.19)	-0.836 (-2.29,1.15)	-1.208 (-2.55,0.67)	-1.285 (-2.42,0.88)	-0.422 (-1.14,0.81)
Asthma	0.140 (-0.60,0.88)	0.110 (-0.62,0.84)	0.007 (-0.73,0.74)	-0.133 (-0.88,0.61)	0.004 (-0.58,0.59)
Chronic lung obstruction	0.193 (-0.62,1.01)	-0.455 (-1.37,0.97)	-0.668 (-1.08,0.76)	-0.561 (-1.45,0.83)	-0.199 (-0.53,0.63)
Psychic disorders	-0.217 (-0.98,0.55)	0.238 (-0.89,0.87)	-0.080 (-0.75,0.59)	-0.130 (-0.79,0.54)	-0.056 (-0.83,0.72)
Pregnancy-related diseases	0.009 (-0.95,0.97)	0.369 (-0.51,1.25)	1.220 (0.73,1.54)	<b>1.084 (-0.17,1.34)</b>	<b>1.220 (0.73,1.71)</b>

The statistically significant estimates are highlighted in bold.

Table 3. Percentage changes with 95% CI in daily emergency room admission for all diseases associated with a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$  concentrations for the different lag structures in two-pollutant model.

Disease	Lag 0 day	Lag 1 day	Lag 2 day	Lag 3 day	Lag 0-3 days
All cardiovascular	0.077 (0.01,0.15)	0.046 (0.03,0.17)	-0.004 (0.02,0.11)	0.070 (0.02,0.28)	0.510 (0.02,0.29)
Ischemic heart disease	0.015 (-0.21,0.24)	-0.047 (-0.28,0.19)	-0.091 (-0.31,0.14)	-0.032 (-0.27,0.20)	-0.056 (-0.14,0.03)
Heart failure	0.597 (-1.83,3.08)	-0.025 (-2.38,2.38)	-0.227 (-2.94,2.56)	-1.497 (-4.48,1.58)	0.152 (-0.95,1.27)
Other heart diseases	-0.005 (-0.28,0.27)	-0.081 (-0.36,0.19)	-0.048 (-0.32,0.22)	-0.03 (-0.29,0.24)	-0.024 (-0.13,0.08)
Cerebrovascular diseases	-0.002 (-0.43,0.42)	0.034 (-0.39,0.46)	-0.271 (-0.72,0.18)	0.140 (0.08,0.28)	0.180 (0.09,0.35)
All respiratory	0.039 (0.07,0.11)	0.068 (0.02,0.14)	0.005 (0.01,0.13)	0.105 (0.01,0.39)	<b>0.150 (0.05,0.35)</b>
Inflammation	-0.238 (-0.65,0.18)	-0.244 (-0.64,0.17)	-0.145 (-0.53,0.24)	<b>0.160 (0.06,0.26)</b>	<b>0.180 (0.07,0.29)</b>
Common cold	-0.521 (-2.55,1.55)	-0.881 (-3.34,1.64)	-1.257 (-3.61,1.15)	-1.382 (-3.60,0.89)	-0.406 (-1.43,0.63)
Asthma	0.070 (-0.24,0.38)	0.089 (-0.19,0.37)	0.023 (-0.25,0.29)	-0.148 (-0.46,0.17)	-0.008 (-0.10,0.08)
Chronic lung obstruction	0.089 (-1.01,1.19)	-0.481 (-1.71,0.76)	-0.676 (-1.88,0.55)	-0.577 (-1.73,0.59)	-0.269 (-0.73,0.19)
Psychic disorders	-0.095 (-0.99,0.81)	0.163 (-0.67,1.00)	-0.055 (-0.89,0.79)	-0.195 (-1.02,0.63)	-0.068 (-0.37,0.23)
Pregnancy-related diseases	0.011 (-1.22,1.26)	0.357 (-0.81,1.54)	<b>0.100 (0.07,2.06)</b>	<b>0.110 (0.05,0.23)</b>	<b>0.150 (0.05,0.38)</b>

The statistically significant estimates are highlighted in bold.

Also, the increase in  $\text{PM}_{10}$  (lag 0:3 - accumulative) is associated with the 0.33% (95% CI: 0.11, 0.54) increase in admission for cerebrovascular diseases. Besides, the increase in  $\text{PM}_{10}$  (lag 0:3 - accumulative) is associated with the 0.07% (95% CI: 0.03, 0.13) increase in the subjects with ischemic heart disease. The largest increase in the number of the subjects with pregnancy-related problems found for  $\text{PM}_{10}$  on day 4 (Accumulative) was 1.22 % (95% CI: 0.73, 1.71).

When adjusting for the other pollutant ( $\text{SO}_2$ ) in the two-pollutant model, the estimated effects of  $\text{PM}_{10}$  on cerebrovascular and pregnancy related diseases remained statistically significant as it was in the single-pollutant model (Table 3).

In the present study, positive associations were found between  $\text{PM}_{10}$  and the emergency visits for cerebrovascular diseases and pregnancy associated diseases. Similar findings had been reported in previous studies [31, 47]. The results were slightly affected by the other pollutant ( $\text{SO}_2$ ) when estimated in the two-pollutant model, but association remained positive.

The relationship between  $\text{PM}_{10}$  and hospital visits due to cerebrovascular diseases had been very well studied [48, 49]. In their research study, Feng et al. [20] found a positive relationship between emergency admissions and cerebrovascular diseases. The results showed that, each 10  $\mu\text{g}/\text{m}^3$  increase in day 4 (Accumulative) moving average  $\text{PM}_{10}$  was associated with a significant 0.36% (95% CI: 0.11%, 0.61%) increase in hospital admission of cerebrovascular diseases. Zhang et al. [21] reported in their paper that the relative risks of cerebrovascular disease visits were consistently above 1.000, suggesting that the influence of  $\text{PM}_{10}$  on this disease lasted for more than 6 days.

A significant positive relationship was also found between  $\text{PM}_{10}$  and pregnancy related diseases. The biological mechanisms behind particulate matter and spontaneous abortion and stillbirth have not been understood well. While many pathways between PM and spontaneous abortion and stillbirth have been proposed, none has been proven. The largest number of the heavy metals (which are an integral part of  $\text{PM}_{10}$ ) cross the placental barrier and exhibit fetotoxic effects (a decrease in fetal weight, damage to the immune system, and a chromosome aberration with the appearance of various malformations) and the occurrence of miscarriages [50]. In this study it was found that a day by day exposure to high levels of  $\text{PM}_{10}$  is associated with an increased risk of adverse pregnancy outcomes. Similar findings were reported by Moridi et al. [51] and Gaskins et al. [52]. On the other hand, some studies conducted in China [53] and Iran [54] did not find any association between a short term exposure to  $\text{PM}_{10}$  and the risk of pregnancy loss.

Unlike other similar research studies, this study failed to confirm positive statistically significant relationship between  $\text{PM}_{10}$  and schizophrenia [27, 28]. A possible explanation for said would be that damage to the central nervous system (a memory loss, personality changes, encephalopathy, etc.) more frequently occurs as a consequence of chronic exposure to air pollution and after continuous exposure to small concentrations [55]. However, chronic clinical manifestations may occur even after short-term acute exposure to very high concentrations, which probably accounts for the results obtained in the previous studies.

Surprisingly, no positive relationship was found between  $\text{PM}_{10}$  and all respiratory diseases.

After adjusting for  $\text{SO}_2$ , however, the relationship became positive at all the lags and significant at lag 0:3 - accumulative (0.15 (95% CI: (0.05%, 0.35%)). In order to give a logical explanation for that, it is very important from the point of view of health that PM should be classified by the particle size, because their respirability, physical and partly chemical activity depend on their sizes. Particles with a diameter less than 10 micrometres ( $\text{PM}_{10}$ ) are deposited and stick to the moist mucous membrane, from where they are mostly coughed up. On the other hand,  $\text{SO}_2$  is a gas considered to be quite a serious irritant to the upper respiratory tract. Due to its good solubility in water, and therefore in mucous membranes, it is one of the irritants of the upper respiratory tract and makes local effects. It is sulfuric acid anhydride and causes chemical inflammation by reducing the defense mechanisms of the respiratory tract – lung clearance, thus facilitating the deposition and penetration of larger particles.

In the current study, the strongest effects of  $\text{PM}_{10}$  were observed with a delay of 2 or 3 days. Such lag effects of particulate matter on human health could be explained by the fact that small daily doses of the pollutant do not cause immediate damage when they do not exceed the maximum allowable concentration. However, the concentration of free radicals in blood and extracellular fluid depends on the concentration of pollutants on the one hand and on the capacity of the free radical defense mechanism on the other. At the lower concentrations of free radicals (a lower pollutant concentration), the antioxidant defensive system (NADH, NADPH, glutathione, glutathione peroxidase, catalase, superoxide dismutase, and ascorbic acid) block the influence of free radicals by creating a new harmless compound instead of toxins. With greater formation of free radicals (due to cumulative exposure to pollution), however, defense mechanisms can be exhausted and defeated, in which case, pathological cumulative effects will occur, which may cause the onset or progression of certain diseases.

To our knowledge, this study is the first one to investigate the effects of  $\text{PM}_{10}$  air pollution on cardiovascular (total and specific), respiratory (total and specific), pregnancy and mental morbidity at the high pollution episodes that have been occurred in Bor (Serbia) over the last decades. Unfortunately, the environmental picture in Bor has not been very favorable for very long time [56, 57]. The trend continues. The  $\text{PM}_{10}$  and  $\text{SO}_2$  concentrations continue to exceed the daily allowed limit values almost every day [58].

## Conclusions

This study once again confirms that short-term exposure to air pollution, especially to high concentrations of  $\text{PM}_{10}$ , has a very negative impact on human health. The most important results of this study

are: (1) there is a direct and significant association between  $\text{PM}_{10}$  levels and emergency admissions for cerebrovascular and pregnancy diseases; 2). the contribution of other pollutants (in this case  $\text{SO}_2$ ) is very important and must be considered. The results obtained in this study confirm to a certain extent some of the results obtained in previous studies. However, the differences in physicochemical characteristics of the measured  $\text{PM}_{10}$ , as well as the socio-demographic characteristics of the examined population, and their lifestyle may explain varied results found in different research.

Based on the research results of this article, the following conclusions and suggestions can be provided:

- First, they are very important from the perspective of the local population' health protection, especially of specific categories, like pregnant women and chronic patients. Based on our findings, we would recommend to reduce their outdoor activities during elevated concentrations of pollutants.
- Second, this study again highlights the importance of monitoring and controlling the emission sources, especially large ones, like in this case. To mitigate the consequences of air pollution, strict emission control techniques and multi-sectoral collaborations are required.
- Third, the results of this study could be used to assist authorities in taking preventative measures in the long run.

This study has several strengths. Firstly, this study aims to examine the overall effects of  $\text{PM}_{10}$  on an increased number of emergency visits for cardiovascular, respiratory, pregnancy-related and mental illnesses. Secondly, the data concerning the pollutant concentrations from all the four local monitoring stations were used, which can mitigate measurement errors compared to using the data from just one monitoring station. Thirdly and ultimately, the most important is the fact that this is the first study to explore the impact of pollution on human health in this highly polluted region.

Of course, this study also has some important limitations. The first limitation is reflected in the fact that air monitoring station data were used in this study to represent an individual exposure to air pollution not taking into account indoor air pollution and the mobility of human activity. The second limitation pertains to the fact that the number of patients only included those who visited the emergency room during the study period. One of the rules adhered to at the Bor Medical Center, which the Emergency Room is just a part of, however, reads that not all noncritical patients go to the emergency department if they have a medical problem between 8 am and 8 pm, in which case such patients have to go to their chosen doctor, so they were not included in this study if they came to the Medical Centre between 8 am and 8 pm. The third limitation reflects in the fact that the results show that the health effects of  $\text{PM}_{10}$  were also affected by the other pollutant ( $\text{SO}_2$ ).

Considering this fact, further studies are needed to reveal the potential mechanism of pollutant interactions. Unfortunately, more information of other pollutants, such as O<sub>3</sub>, NO<sub>2</sub>, CO and PM<sub>2.5</sub>, were not available for the study period. The fourth limitation, and maybe the most important one, is that it was impossible to include the demographic data, such as gender and age.

By including the complete database in future research and additional data such as patient gender, age and concentration of other pollutants, a complete impression will be gained of the extent to which such increased concentrations actually may and do affect certain categories of residents and based on which a plan how to protect the health of the population has to be proposed.

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### Conflict of Interest

The authors declare no conflict of interest.

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