

# Sulfur dioxide and exacerbation of allergic respiratory diseases: A time-stratified case-crossover study

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**Background:** Strong epidemiological evidence suggests that air pollution plays a significant role in the exacerbation of allergic respiratory diseases. This study aimed to assess the potential relationship between daily levels of sulfur dioxide (SO<sub>2</sub>) and emergency department (ED) visits for allergic diseases. **Materials and Methods:** Data regarding ED visits for allergic respiratory diseases were routinely collected from the EDs in the Zlatibor district, and the General Hospital, Užice. The daily average concentrations of SO<sub>2</sub> were obtained from the regional automatic air quality monitoring stations. All data were collected from June 2012 to July 2014. A time-stratified case-crossover design was used. Crude odds ratios (ORs) and ORs adjusted for weather conditions were calculated using conditional logistic regression. **Results:** Statistically significant associations were seen between 0-day lagged exposure to SO<sub>2</sub> and ED visits for all allergic diseases (OR = 1.62; 95% confidence interval [CI]: 1.05–2.48; *P* = 0.028) and between 2-day lagged exposure to SO<sub>2</sub> and ED visits for asthma with allergic rhinitis (OR = 2.00; 95% CI: 1.03–3.88; *P* = 0.042). These results were adjusted for temperature, temperature<sup>2</sup>, and humidity. **Conclusion:** Our results suggest that short-term exposure to SO<sub>2</sub> conferred an increased risk of ED visits for allergic respiratory diseases, particularly for asthma with concomitant allergic rhinitis.

**Key words:** Air pollution, allergic respiratory diseases, emergency departments, sulfur dioxide

**How to cite this article:** Tomić-Spirić V, Kovačević G, Marinković J, Janković J, Ćirković A, Milošević Đerić A, *et al.* Sulfur dioxide and exacerbation of allergic respiratory diseases: A time-stratified case-crossover study. *J Res Med Sci* 2021;26:109.

## INTRODUCTION

The prevalence of allergic diseases is increasing worldwide.<sup>[1-3]</sup> It is estimated that more than 100 million workdays and school days are lost in Europe every year.<sup>[4]</sup>

Strong epidemiological evidence suggests that air pollution has an important role in the development of asthma and other allergic respiratory diseases, as well as in their exacerbation.<sup>[5-7]</sup> Numerous studies have demonstrated that short-term exposure to high

concentrations of the principal air pollutants (ozone, nitrogen oxides, carbon monoxide, sulfur oxides, and particulate matter [PM] - PM10 and PM2.5) may contribute to and exacerbate asthma.<sup>[8-11]</sup>

Sulfur dioxide (SO<sub>2</sub>) is an important air pollutant that can be a threat to human health, animal health, and plant life. Exposure to high concentrations of SO<sub>2</sub> may result in irritation and dysfunction of the respiratory tract. The most common clinical findings associated with SO<sub>2</sub> exposure are bronchospasm, pulmonary edema, pneumonitis, and acute airway obstruction.<sup>[12]</sup>

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DOI:

10.4103/jrms.JRMS\_6\_20

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**Submitted:** 19-Jan-2020; **Revised:** 13-Jul-2020; **Accepted:** 07-Jul-2021; **Published:** 29-Nov-2021

The recently published report “Air Pollution and Human Health: The Case of the Western Balkans” has shown that the population of the Western Balkans region to which Serbia belongs, is exposed to several times higher concentrations of air pollution in comparison to the national and EU guideline levels.<sup>[13]</sup> To the best of our knowledge, the relationship between outdoor air pollution and population health has not been explored sufficiently in the Western Balkans region.

Short-term exposure to SO<sub>2</sub> is largely related to the type and nature of local sources.<sup>[13]</sup> The emission of this pollutant is mostly related to the fossil fuel consumption, industrial processes, and volcanic activities.<sup>[12]</sup> In the Western Balkans region, the largest source of SO<sub>2</sub> in the air is the combustion of fossil fuels in thermal power plants, mostly in lignite power plants.<sup>[13]</sup> This region is characterized by energy poverty and a lack of awareness of the need to move to more sustainable and more environmentally friendly heating systems.<sup>[14]</sup>

It is well known that short-term exposure to elevated concentrations of SO<sub>2</sub> has effects on human health. For the first time in Serbia, we conducted a time-stratified case-crossover study to assess the relationship between the gaseous SO<sub>2</sub> pollutant and visits to emergency departments (EDs) due to worsening of allergic asthma and allergic rhinitis.

## MATERIALS AND METHODS

### Study design

A time-stratified case-crossover study was conducted in the Zlatibor district, western Serbia. The city of Užice is an administrative, economic, social, and cultural center of this part of Serbia, located in the valley of the river Đetinja, surrounded by three mountains: Zlatibor, Tara, and Zlatar. Sevojno, as one of two municipalities of Užice, is an industrial center with copper and aluminum mills, construction companies, and metal recycling facilities.

The study participants were adults aged 18 years and older who lived in Užice, Sevojno, Čajetina, and Kosjerić, and who visited an ED or were hospitalized with a diagnosis of asthma or allergic rhinitis during the time period from July 01, 2012, to June 30, 2014. According to the 2011 Serbian Census, estimates of the number of adult residents were 78,040, 14,745, and 12,090 for Užice (including Sevojno), Čajetina, and Kosjerić, respectively.<sup>[15]</sup>

### Health data

Data on allergic respiratory diseases were obtained retrospectively from ED visits in Užice, Sevojno, and Kosjerić and from the General Hospital in Užice. Patients' age, sex, diagnosis, and date of the visit were recorded. Criteria for inclusion in the study were adults 18 years of

age and over, diagnosed with allergic rhinitis (International Classification of Diseases [ICD], 10<sup>th</sup> revision, code J.30.4), allergic asthma (ICD, 10<sup>th</sup> revision, code J.45.0), or asthma with allergic rhinitis. We excluded all ED visits due to nonallergic asthma, as well as visits due to exacerbation of allergic respiratory diseases caused by infection.

### Environmental data

The concentrations of SO<sub>2</sub> (µg/m<sup>3</sup>) were obtained on a daily basis from the regional automatic ambient air quality monitoring stations placed in Užice, Sevojno, and Kosjerić. The daily values of concentration were calculated by averaging over all these stations. The SO<sub>2</sub> concentration was measured by a simple and sensitive spectrophotometric method.

The weather data such as temperature (°C), relative humidity (%), and air pressure (mbar) were obtained from the automatic weather station at Zlatibor.<sup>[16]</sup>

The study was approved by the Ethics Committee of the Health Center Užice (no.: 0303/8785).

### Statistical analysis

A time-stratified case-crossover analysis as an alternative to the Poisson time series regression model was applied to analyze the potential risk of ED visits for respiratory allergic diseases related to short-term exposure to SO<sub>2</sub>. This design represents a special type of matching in which cases serve as their own controls. We compared the time just preceding the acute event (“case” time) with every 7<sup>th</sup> day before and after the event day (“control” time). The advantage of case-crossover design is that characteristics such as gender and age that might confound the association are controlled for.<sup>[17]</sup>

Categorical variables were presented by absolute numbers and percentages, while mean and interquartile range (IQR) were used for continuous variables. Age was presented as mean and also as categorical variable (<65 and ≥65 years).

The association between SO<sub>2</sub> and weather characteristics, such as temperature, humidity, and air pressure was assessed by Spearman's rank correlation, applicable for nonnormal data. For the assessment of normality, the Kolmogorov–Smirnov test was used. Three models of conditional logistic regression analyses (one unadjusted and two adjusted for the potentially confounding influences of the meteorological conditions) were applied for all allergic respiratory diseases, and each allergic disease separately (dependent variables) by including the SO<sub>2</sub> exposure estimates as an independent variable. We included different lag periods (lag 0, 1, 2, and 3) to detect the event day (lag 0) and events in the previous 3 days of exposure (lag 1, 2, and 3, respectively). The cumulative effect of exposure was also calculated. The confounders for the

first adjusted model were temperature, humidity, and air pressure on the same day as SO<sub>2</sub> exposure estimates, while temperature, temperature<sup>2</sup>, and humidity on the previous day were confounders in the second adjusted model.

The results of the analyses were presented as the odds ratios (ORs) and their 95% confidence intervals (CIs). We calculated the ORs for the daily mean level of SO<sub>2</sub> concentration presented by the IQR.

A *P* < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

During the study period, we observed 523 ED visits for allergic respiratory diseases. There were more women than men (62.5% vs. 37.5%). The mean age of the patients was 45.95 ± 17.24 years (mean ± standard deviation), and most of them (84.1%) had <65 years of age. More than three-thirds of all ED visits (76.3%) occurred during the heating season. The distribution of 245 asthmatic patients with allergic rhinitis who visited ED in the same period, according to sex, age, and the heating season was similar [Table 1]. Thirty-two (6.1%) of all patients were hospitalized.

Daily concentrations of SO<sub>2</sub> and weather characteristics during the study period are presented in Table 2.

Mean daily concentrations of SO<sub>2</sub> did not exceed permitted limit values for the EU (125 µg/m<sup>3</sup> for 24 h) and were higher during the winter season so-called “heating season” with a comparison to the summer season so-called “nonheating season” (18.37 ± 9.35 vs. 16.54 ± 7.97).

The seasonal trend of monthly mean concentrations of SO<sub>2</sub> during the 2-year study period is presented in Figure 1.

**Table 1: Characteristics of emergency department visits for allergic respiratory diseases in the Zlatibor district, Serbia**

Variables	Allergic respiratory diseases (n=523), n (%) <sup>*</sup>	Asthma with allergic rhinitis (n=245), n (%)
Sex		
Males	196 (37.5)	87 (35.5)
Females	327 (62.5)	158 (64.5)
Age (years±SD)	45.95±17.24	44.71±16.03
<65	440 (84.1)	216 (88.2)
≥65	83 (15.9)	29 (11.8)
Heating season <sup>†</sup>	404 (76.3)	187 (76.3)
Nonheating season	119 (22.8)	58 (23.7)

<sup>\*</sup>Allergic rhinitis, asthma, and asthma with allergic rhinitis; <sup>†</sup>15<sup>th</sup> October to 15<sup>th</sup> April. SD=Standard deviation

The levels of SO<sub>2</sub> were elevated during the heating season although did not exceed the limit values and low during the nonheating season.

Statistically significant negative correlation in the present study was found between temperature and SO<sub>2</sub> ( $y = 22.9 - 0.43x$ ; coefficient correlation  $\rho = -0.44$ ), while statistically significant positive correlation was seen between humidity and SO<sub>2</sub> ( $y = 49.18 + 0.51x$ ;  $\rho = 0.29$ ). Higher concentration of SO<sub>2</sub> during winter months might be associated with reduced dilution efficiency by diffusion of air flow, increased combustion of fuel from biomass for heating, as well as with inversion of temperature resulting in smog occasions.

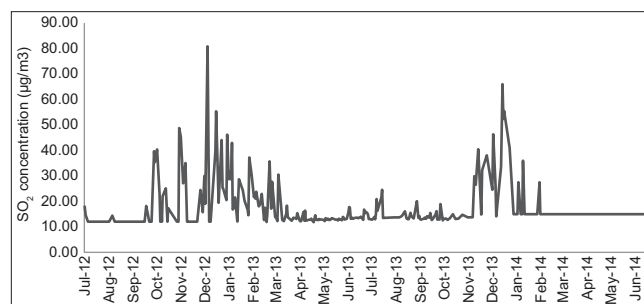
Crude and adjusted ORs with their 95% CI for ED visits due to worsening of respiratory allergic diseases in relation to short exposure of SO<sub>2</sub> are shown in Table 3.

We observed statistically significant associations between 0-day lagged exposure to SO<sub>2</sub> and ED visits for all allergic diseases ([crude OR = 1.53; 95% CI: 1.01–2.31; *P* = 0.044]; OR adjusted for temperature, temperature<sup>2</sup>, and humidity [OR = 1.62; 95% CI: 1.05–2.48; *P* = 0.028]). Statistically significant associations were also found between 2-day lagged exposure to SO<sub>2</sub> and ED visits for asthma with allergic rhinitis ([crude OR = 1.97; 95% CI: 1.03–3.77; *P* = 0.041]; OR adjusted for temperature, temperature<sup>2</sup>, and humidity [OR = 2.00; 95% CI: 1.03–3.88; *P* = 0.042]).

## DISCUSSION

It is well known that short-term SO<sub>2</sub> exposure depends on the prevailing meteorological conditions. According to our results, the levels of SO<sub>2</sub> in the Zlatibor district were elevated during the heating season although did not exceed the limit values and low during the nonheating season. Similar results were reported in other studies.<sup>[18,19]</sup>

Like Polish authors, we observed seasonal variation of SO<sub>2</sub> concentration as a consequence of different atmospheric conditions in summer and winter months, changing weather on a particular day, and human-induced activity.<sup>[19]</sup>



**Figure 1: Seasonal trend of monthly mean concentrations of sulfur dioxide in the Zlatibor district, Serbia (2012 – 2014)**

**Table 2: Sulfur dioxide concentrations and weather variables in the Zlatibor district, Serbia**

Variable	Mean±SD	Minimum	25%	50%	75%	Maximum	IQR
SO <sub>2</sub> 24 h (µg/m <sup>3</sup> )	17.95±9.08	11.51	13.05	15.00	17.54	80.78	4.49
Temperature (°C)	15.41±9.24	-6.67	7.57	16.20	22.80	36.23	15.03
Humidity (%)	57.91±19.91	11.53	40.10	58.30	74.53	98.80	34.43
Air pressure (mbar)	962.21±6.67	936.33	958.27	962.90	966.73	982.33	8.47
Heating season*							
SO <sub>2</sub> 24 h (µg/m <sup>3</sup> )	18.37±9.35	11.51	13.08	15.00	18.42	77.77	5.35
Temperature (°C)	14.77±9.24	-6.67	7.00	15.20	22.33	36.23	15.33
Humidity (%)	58.68±19.92	11.53	41.02	59.14	74.68	98.80	33.66
Air pressure (mbar)	961.19±6.85	936.33	958.03	962.73	966.93	982.33	8.90
Nonheating season							
SO <sub>2</sub> 24 h (µg/m <sup>3</sup> )	16.54±7.97	11.86	12.99	14.93	15.07	80.78	2.07
Temperature (°C)	17.60±8.93	-2.10	11.27	18.90	24.23	35.90	13.08
Humidity (%)	55.33±19.67	11.53	38.83	50.93	74.27	96.80	35.43
Air pressure (mbar)	962.26±6.03	941.33	958.75	963.07	966.03	979.80	7.28

\*6-month period in the year, from 15<sup>th</sup> October to 15<sup>th</sup> April. SO<sub>2</sub>=Sulfur dioxide; SD=Standard deviation; IQR=Interquartile range

**Table 3: Odds ratios for the relationship between exposure to sulfur dioxide and emergency department visits for allergic rhinitis and asthma in the Zlatibor district, Serbia**

ED visits	Lags	OR* (95% CI)	OR† (95% CI)	OR‡ (95% CI)
Allergic respiratory diseases	Lag (0)	1.53 (1.01–2.31), <i>P</i> =0.044	1.53 (1.00–2.34), <i>P</i> =0.049	1.62 (1.05–2.48), <i>P</i> =0.028
Asthma with allergic rhinitis	Lag (-2)	1.97 (1.03–3.77), <i>P</i> =0.041	1.97 (1.02–3.80), <i>P</i> =0.044	2.00 (1.03–3.88), <i>P</i> =0.042

\*Crude; †Adjusted for temperature, humidity and air pressure on the same day; ‡Adjusted for temperature, temperature<sup>2</sup> and humidity on the previous day. ED=Emergency department; OR=Odds ratio; CI=Confidence interval

Our results that statistically significant associations were found between exposure to SO<sub>2</sub> and ED visits for allergic diseases are in agreement with previously published studies in adults<sup>[18,20,21]</sup> and children.<sup>[22–28]</sup> However, several authors failed to detect any association between SO<sub>2</sub> and asthma ED visits/hospitalizations.<sup>[29,30]</sup>

Zheng *et al.* in a large meta-analysis of 65 available studies showed that SO<sub>2</sub> was associated with significantly increased risks of ED visits and hospitalizations due to asthma: relative risk (95% CI); 1.011 (1.007, 1.015); *I*<sup>2</sup> test = 77.1%; population attributable fractions (95% CI): 1.1 (0.7, 1.5).<sup>[8]</sup> In a recently published time-stratified case-crossover study in Chengdu, China, Chen *et al.* found that after adjustment for weather conditions, IQR increase in SO<sub>2</sub> of 13 µg/m<sup>3</sup> was associated with an increase of 18.8% in emergency ambulance dispatches for asthma.<sup>[18]</sup> The observed effect of the SO<sub>2</sub> on asthma ED visits/hospitalization is biologically plausible. It has been observed that SO<sub>2</sub> stimulates airway inflammation and eosinophilia and induces bronchospasm and airway fibrosis in asthma.<sup>[31]</sup> It has been shown that SO<sub>2</sub> and its derivatives could increase epidermal growth factor (EGF), EGF receptor, intercellular adhesion molecule-1, and cyclooxygenase-2 expression in human bronchial epithelial cells (BEP2D), through transcription and translation processes that may explain inflammation and overproduction of mucus in asthma exacerbation.<sup>[32]</sup>

The main strengths of the present study are a novel population reviewed, applied time-stratified case-crossover

design as an appropriate method for the assessment of brief changes in risk related to short-term exposure of SO<sub>2</sub>, and risk adjustments for the potential confounding influence of weather condition.

However, we are aware of some limitations of this study. First, the exposure to SO<sub>2</sub> pollutant for each individual was estimated on the basis of regional measurements of SO<sub>2</sub> pollution from fixed-site monitoring stations. Second, the possible confounding influence of other air pollutants and aeroallergens on the risk estimation was not taken into account. Third, our study results may not be generalizable to the entire Serbian population. Further studies with data on larger populations from different settings would be necessary to confirm our findings.

## CONCLUSION

Our results confirm a significant association between short-term exposure to SO<sub>2</sub> and increased risk of ED visits for allergic respiratory diseases, particularly for individuals with asthma with coexisting allergic rhinitis, in the Zlatibor district. Further studies considering the possible confounding influence of other air pollutants and aeroallergens on the risk estimation are needed.

## Acknowledgments

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant No. 200110. The manuscript has been read and approved

by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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