Short-term effects of air pollution on exacerbations of allergic asthma in Užice region, Serbia

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Abstract

Introduction: Many time-series studies have shown a positive association between air pollution and asthma exacerbation. However, till now only one study in Serbia has examined this relationship.

Aim: To examine the associations between air pollution and asthma emergency department (ED) visits in the Užice region, Serbia.

Material and methods: A time-stratified case-crossover design was applied to 424 ED visits for asthma exacerbation that occurred in the Užice region, Serbia, in 2012–2014. Data about ED visits were routinely collected in the Užice Health Centre. The daily average concentrations of particulate matter (PM$_{2.5}$ and PM$_{10}$), sulphur dioxide (SO$_2$), nitrogen dioxide (NO$_2$), and black carbon (BC) were measured by automatic ambient air quality monitoring stations. Odds ratios and their corresponding 95% confidence intervals were estimated using conditional logistic regression adjusted for the potential confounding influence of weather variables (temperature, humidity and air pressure).

Results: Statistically significant associations were observed between ED visits for asthma and 3-day lagged exposure to BC (OR = 3.23; 95% CI: 1.05–9.95), and between ED visits for asthma with coexisting allergic rhinitis and 0-day lag exposure to NO$_2$ (OR = 1.57; 95% CI: 0.94–2.65), 2-day lag exposure to SO$_2$ (OR = 1.97; 95% CI: 1.02–3.80), and 3-day lag exposure to PM$_{10}$ (OR = 2.38; 95% CI: 1.17–4.84).

Conclusions: Exposure to ambient air pollution in the Užice region increases the risk of ED visits for asthma, particularly during the heating season.

Key words: air pollution, allergic asthma, emergency department visits, case-crossover design, Serbia.

Introduction

The health effects of air pollution are increasingly recognized as a major public health concern. Previous studies that were carried out in major world cities proved the harmful effects of air pollutants on the course and prognosis of acute and chronic diseases among adults and children [1–3]. Estimates of the health impacts attributable to exposure to particulate matter (PM) with an aerodynamic diameter of 2.5 $\mu$m or less (PM$_{2.5}$), ozone (O$_3$), and nitrogen dioxide (NO$_2$) concentrations in 2015, were responsible for about 518700 premature deaths originating from long-term exposure in 41 European countries [4]. The epidemiological evidence relating short-term exposure with particulate matter with an aerodynamic diameter of 10 $\mu$m or less (PM$_{10}$), and related metrics: black smoke (BS), black carbon (BC) and total suspended particles, with health effects is substantial [5]. Recently published systematic review and meta-analysis of 110 time series studies have found evidence for adverse health effects of short-term exposure to PM$_{2.5}$ across a range of important health outcomes and diseases with
a considerable variation between different regions of the world [6].

Special attention is focused on the respiratory system, which is the first point of contact with air pollutants. The impact of air pollution on chronic respiratory diseases, such as chronic obstructive pulmonary disease and asthma, is well documented [7–9]. The harmful effects of principle air pollutants (PM, O₃, CO and NO₂) on the exacerbation of asthma, as well as respiratory morbidity and mortality in asthma patients are confirmed by epidemiological studies [10–12].

The global increase in the prevalence of allergic diseases is of great concern, especially in developing countries [13] and strong epidemiological evidence supports a relationship between air pollution and exacerbation of asthma and other allergic diseases [14].

Although the global problem of air pollution is recognized worldwide, there are only a few published studies on the effects of air pollution on human health in Serbia [15, 16].

Aim

The aim of this study was to assess the short-term effects of air pollutants (NO₂, SO₂, PM₁₀, PM₂.₅, and BC) concentrations on the exacerbation of the allergic bronchial asthma alone or asthma with coexisting allergic rhinitis (AR) in the Užice region, Serbia.

Material and methods

Study area

The study was carried out over a 2-year period, from 1st July 2012 to 30th June 2014 in the Zlatibor District, Serbia (Figure 1 A). The main city of the region is Užice with 78,040 inhabitants [17], located in the latitude of 43°51' N and the longitude of 19°50' E. It is situated on both sides of the river Đetinja, with average elevation of 411 m above the sea level, surrounded by the Dinaric mountains Zlatibor, Tara and Zlatar. Besides the city of Užice (including Sevojno), two other surrounding municipalities, Čajetina with 14,745 inhabitants, and Kosjerić with 12,090 inhabitants [17] were included in this study. It is worth noting that there are three different climates in this region, from moderate-continental to mountain and high-mountain (sub-alpine and alpine) climate. While Užice and Sevojno are centres of heavy industry, the mountain Zlatibor, thanks to the specific continental and Mediterranean air currents, a so-called wind rose, is considered an air spa suitable for the treatment and recovery from many diseases, including asthma. Considering the above, the chosen geographical area is extremely interesting for the assessment of the relationship between air pollution and health.

The study was approved by the Užice Hospital Ethics Committee.

Study population

We obtained routinely collected data of emergency department (ED) visits for allergic asthma from the Užice Health Centre, either from the EDs (ambulances or home care) in Užice, Sevojno, and Kosjerić or from a general hospital in Užice. A medical doctor reviewed the ED records. The admission date, age, gender, place of residence, and ED diagnosis were considered for each patient. The inclusion criteria were: adults aged 18 years and older with the diagnosis of allergic asthma (International Classification of Diseases, 10th revision, code J45.0) or asthma with coexisting allergic rhinitis (AR). Patients who experienced worsening due to respiratory infections or asthma types other than allergic asthma were excluded from the study.

Air pollution, pollen and weather data

The daily average concentrations of air pollutants (SO₂, NO₂, PM₁₀, PM₂.₅, and BC) in micrograms per cubic meter (µg/m³) were measured by three automatic ambient air quality monitoring stations located in Užice, Sevojno, and Kosjerić (Figure 1 B). The concentrations were measured on the event day (0), on the previous day (–1), 2 days before (–2) and 3 days before (–3). Registered daily values of each air pollutant were average levels from all the stations, in order to assess the global environmental situation of the city and its surrounding.

The SO₂ concentration was determined by the spectrophotometric method, while the concentration of NO₂ was obtained by chemiluminescence detection. The PM monitor based on beta-ray attenuation was used to measure the concentrations of both PM₂.₅ and PM₁₀. The BCP (black carbon particles) concentration was measured with reflectometers.

The daily meteorological dataset (temperature, relative humidity, and surface air pressure), as well as air allergen data (daily tree, grass, and weed pollen concentrations) were obtained from the automatic meteorological station located at Zlatibor [18]. The following pollens were detected: Pinaceae, Betulaceae, Poaceae, Plantago spp., Urticaceae and Asteraceae.

Statistical analysis

A time-stratified case-crossover design was used to assess the risk of ED admissions for asthma alone and asthma with coexisting AR based on exposure to various air pollutants.

The degree of association between different environmental variables (air pollutants, pollens, temperature, humidity and air pressure) was tested by non-parametric Spearman’s rank correlation.

The multivariable conditional logistic regression models were applied as suitable for the explained design, aim and the type of data. Every seventh day before and after the event day was considered a control.
Lagged values were created for all models to assess an early effect: immediate (the event day, lag 0), and delayed (previous 3 days of exposure, lag 1, 2, and 3, respectively). The models were defined for each of the pollutants (NO$_2$, SO$_2$, PM$_{2.5}$, PM$_{10}$, BC) for lags 0, 1, 2, and 3, for patients with asthma alone and asthma with co-existing AR. To control potential confounding factors all models included daily weather variables (temperature, humidity and air pressure on lag 0). The results of the analyses were expressed as odds ratios (ORs) with their accompanying 95% confidence intervals (CIs). The ORs were calculated in relation to air pollution concentration based on the daily mean level of each air pollutant presented by the third quintile in the way when the first or fifth quintile was the referent category.

A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS statistical software (SPSS for Windows, release 21.0, SPSS, Chicago, IL).

**Results**

A total of 424 ED asthma visits (179 asthma alone and 245 asthma with AR) occurred during the study period (Table 1). Most of these visits (28.1%) concerned young adults aged 18–34 years. There were more visits among females (67.2%) and during the heating season (77.8%), while no statistically significant difference was seen between spring/summer and autumn/winter seasons.

Table 2 provides summary statistics for air pollutants, pollens and weather variables. During the study period, concentrations of NO$_2$ and SO$_2$ remained below the permitted daily limit values (85 µg/m$^3$ for NO$_2$ and 125 µg/m$^3$ for SO$_2$), whilst daily concentrations of PM$_{10}$ and BC exceeded permitted limit values (50 µg/m$^3$ for PM$_{10}$ and 50 µg/m$^3$ for BC) proposed by the national Regulation on monitoring conditions and air quality requirements.

Correlations between air pollutants, pollens and weather conditions are shown in Table 3. Air pollutants were all positively correlated with each other ($p = 0.24–0.83$). The highest correlation was seen between PM$_{10}$ and PM$_{2.5}$ ($p = 0.83$), and between PM$_{10}$ and BC ($p = 0.75$). NO$_2$ was moderately correlated with particulates ($p = 0.37–0.46$). There was a weak correlation between SO$_2$ and the other air pollutants ($p = 0.24–0.33$). All pollens were weak-moderately and positively correlated between each
other ($\rho = 0.15–0.62$), and were negatively correlated with air pollutants ($\rho$ ranged from –0.17 to –0.52).

Estimated adjusted odds ratios with 95% CI for ED visits for asthma alone and asthma with allergic rhinitis based on 1–3-day lagged exposure to air pollution are displayed in Table 4.

### Table 1. Number (%) of emergency department visits for asthma by age groups, sex and season in the Užice region, Serbia (2012–2014)

| Characteristic | Asthma alone | Asthma with AR | Total |
|----------------|--------------|----------------|-------|
| Total visits   | 179 (100)    | 245 (100)      | 424 (100) |
| Age group:     |              |                |       |
| 18–34          | 44 (24.6)    | 75 (30.6)      | 119 (28.1) |
| 35–44          | 26 (14.5)    | 52 (21.2)      | 78 (18.4) |
| 45–54          | 32 (17.9)    | 47 (19.2)      | 79 (18.6) |
| 55–64          | 36 (20.1)    | 42 (17.1)      | 78 (18.4) |
| ≥ 65           | 41 (22.9)    | 29 (11.8)      | 70 (16.5) |
| Gender:        |              |                |       |
| Males          | 52 (29.1)    | 87 (35.5)      | 139 (32.8) |
| Females        | 127 (70.9)   | 158 (64.5)     | 285 (67.2) |
| Season:        |              |                |       |
| Spring/summer  | 90 (50.3)    | 116 (47.3)     | 206 (48.6) |
| Autumn/winter  | 89 (49.7)    | 129 (52.7)     | 218 (51.4) |
| Heating season*:| 36 (20.1)    | 58 (23.7)      | 94 (22.2) |
| No             | 143 (79.9)   | 187 (76.3)     | 330 (77.8) |

AR – allergic rhinitis. *6 months’ period, from 15th October to 15th April.

Statistically significant associations were observed between ED visits for asthma and 3-day lagged exposure to BC (OR= 3.23; 95% CI: 1.05–9.95), and between ED visits for asthma with coexisting AR and 0-day lag exposure to NO$_2$ (OR = 1.57; 95% CI: 0.94–2.65), 2-day lag exposure to SO$_2$ (OR = 1.97; 95% CI: 1.02–3.80) and 3-day lag exposure to PM$_{10}$ (OR = 2.38; 95% CI: 1.17–4.84).

### Discussion

The present study analysed the impact of air pollution on ED visits for allergic asthma in the adult population of the Užice region. The results suggest a positive association between ambient exposure to PM$_{10}$, BC, SO$_2$ and NO$_2$ pollutants and ED visits for asthma. The highest association was with BC and PM$_{10}$. The most immediate effects were seen for NO$_2$, associated with the reporting-day pollutant level.

PM, a complex, heterogeneous mixture whose composition changes in time and space, and depends on emissions from various sources, atmospheric chemistry and weather conditions, includes “fine particles” which are 2.5 $\mu$m in diameter or less (PM$_{2.5}$) and “coarse particles” which have diameters between 2.5 and 10 $\mu$m (PM$_{10}$) [19]. Many epidemiological studies have shown short-term harmful health effects of PM [5]. However, it is likely that not every PM component is equally important in causing health effects [20]. Combustion-related particles, known as black carbon (BC) particles, are thought to be more harmful to health than PM that is not generated by combustion [20]. Historical studies are based on BS, but more recent studies use absorbance (Abs), BC or elemental carbon (EC) as exposure indicators [21]. The highest association in the current study occurred with

### Table 2. Daily concentrations of air pollutants, pollen levels and weather variables in the Užice region, Serbia (2012–2014)

| Pollutant                  | Median | IQR | Min. | Percentiles |
|----------------------------|--------|-----|------|-------------|
|                            |        |     |      | 20% | 40% | 60% | 80% | Max. |
| NO$_2$ 24 h [µg/m$^3$]     | 6.93   | 8.37| 1.58 | 3.34 | 5.17 | 8.52 | 13.23 | 78.25 |
| SO$_2$ 24 h [µg/m$^3$]     | 15.00  | 4.49| 11.51| 12.84 | 14.08 | 15.00 | 19.40 | 80.78 |
| PM$_{2.5}$ 24 h [µg/m$^3$] | 27.08  | 25.67| 9.33 | 16.48 | 22.11 | 31.73 | 45.50 | 414.42 |
| PM$_{10}$ 24 h [µg/m$^3$]  | 34.32  | 32.38| 9.90 | 19.07 | 28.13 | 42.15 | 58.69 | 327.36 |
| BC 24 h [µg/m$^3$]         | 21.66  | 38.67| 4.00 | 8.33  | 16.33 | 29.00 | 54.67 | 308.67 |
| Tree pollens [grains/m$^3$]| 0.00   | 3.00| 0.00 | 0.00  | 0.00  | 1.00  | 4.00  | 503.00 |
| Grass pollens [grains/m$^3$]| 0.00   | 0.00| 0.00 | 0.00  | 0.00  | 0.00  | 0.00  | 243.00 |
| Weed pollens [grains/m$^3$]| 0.00   | 2.00| 0.00 | 0.00  | 0.00  | 0.00  | 5.00  | 370.00 |
| Temperature [°C]           | 16.20  | 15.27| –6.67| 5.80  | 13.02 | 18.79 | 24.23 | 36.23 |

IQR – interquartile range, NO$_2$ – nitrogen dioxide, SO$_2$ – sulphur dioxide, PM$_{2.5}$ – particulate matter with an aerodynamic diameter of 2.5 $\mu$m or less, PM$_{10}$ – particulate matter with an aerodynamic diameter of 10 $\mu$m or less, BC – black carbon.
Table 3. Matrix of correlation coefficients* between air pollutants, pollen levels and weather variables in the Užice region, Serbia (2012–2014)

| Variable       | NO₂ | SO₂ | PM₂.₅ | PM₁₀ | BC | Tree pollens | Grass pollens | Weed pollens | Temperature | Humidity |
|----------------|-----|-----|-------|------|----|---------------|---------------|--------------|-------------|----------|
| NO₂            | 1.00|     |       |      |    |               |               |              |             |          |
| SO₂            | 0.24| 1.00|       |      |    |               |               |              |             |          |
| PM₂.₅          | 0.37| 0.28| 1.00  |      |    |               |               |              |             |          |
| PM₁₀           | 0.39| 0.31| 0.83  | 1.00 |    |               |               |              |             |          |
| BC             | 0.46| 0.33| 0.68  | 0.75 | 1.00|               |               |              |             |          |
| Tree pollens   | –0.20| –0.18| –0.37 | –0.39| –0.27| 1.00          |               |              |             |          |
| Grass pollens  | –0.25| –0.17| –0.41 | –0.45| –0.47| 0.30          | 0.30          |              |             |          |
| Weed pollens   | –0.30| –0.27| –0.35 | –0.52| 0.15| 0.62          | 1.00          |              |             |          |
| Temperature    | –0.39| –0.44| –0.56 | –0.54| –0.67| 0.25          | 0.47          | 0.60         | 1.00        |          |
| Humidity       | 0.29 | 0.29| 0.33  | 0.28 | 0.41| –0.31         | –0.35         | –0.42        | –0.77       | 1.00     |

*Spearman correlation coefficients. All values are statistically significant. NO₂ – nitrogen dioxide, SO₂ – sulphur dioxide, PM₂.₅ – particulate matter with an aerodynamic diameter of 2.5 μm or less, PM₁₀ – particulate matter with an aerodynamic diameter of 10 μm or less, BC – black carbon.

Table 4. Adjusted odds ratios with 95% confidence intervals for the relationship between exposure to outdoor air pollution and emergency department visits for asthma in the Užice region, Serbia (2012−2014)

| Asthma | Lags | NO₂ | SO₂ | PM₂.₅ | PM₁₀ | BC |
|--------|------|-----|-----|-------|------|----|
| Alone  | 0-day lag | 1.23 (0.66–2.29) | 0.83 (0.34–1.99) | 1.28 (0.58–2.85) | 1.01 (0.53–1.93) | 1.35 (0.44–4.18) |
|        | 1-day lag | 1.30 (0.68–2.47) | 1.07 (0.46–2.48) | 1.39 (0.62–3.14) | 1.00 (0.49–2.03) | 1.19 (0.41–3.44) |
|        | 2-day lag | 0.70 (0.37–1.35) | 1.01 (0.42–2.45) | 1.30 (0.56–2.98) | 0.71 (0.33–1.50) | 2.46 (0.78–7.75) |
|        | 3-day lag | 1.00 (0.53–1.91) | 0.57 (0.23–1.40) | 1.76 (0.74–4.18) | 0.92 (0.45–1.87) | 3.23 (1.05–9.95) |
| With AR| 0-day lag | 1.57 (0.94–2.65) | 0.84 (0.40–1.75) | 1.01 (0.52–1.95) | 1.38 (0.75–2.54) | 0.60 (0.29–1.26) |
|        | 1-day lag | 1.34 (0.79–2.29) | 0.74 (0.37–1.50) | 0.87 (0.44–1.71) | 1.44 (0.77–2.69) | 0.84 (0.40–1.77) |
|        | 2-day lag | 1.08 (0.63–1.84) | 1.97 (1.02–3.80) | 0.82 (0.41–1.64) | 1.63 (0.84–3.17) | 0.83 (0.40–1.72) |
|        | 3-day lag | 1.52 (0.89–2.59) | 0.97 (0.47–1.99) | 1.14 (0.56–2.32) | 2.38 (1.17–4.84) | 0.96 (0.46–2.02) |

NO₂ – nitrogen dioxide, SO₂ – sulphur dioxide, PM₂.₅ – particulate matter with an aerodynamic diameter of 2.5 μm or less, PM₁₀ – particulate matter with an aerodynamic diameter of 10 μm or less, BC – black carbon. Odds ratios were calculated for the third quintile of selected air pollutants and were adjusted for temperature, humidity and air pressure on the same day. Referent value for PM₂.₅ and BC was first quintile, while referent value for NO₂, SO₂ and PM₁₀ was fifth quintile. All significant values are in bold.

BC. We found that concentration of BC in the third quintile increased the risk for asthma exacerbation on lag-3, for more than three times (OR= 3.23; 95% CI: 1.05–9.95). The large concentration of BC that exceeds permitted daily limit values, in the Užice region, is a result of household heating during the cold season because most of the heating houses use coal or oil. Previous studies have reported positive associations between BC and ED visits and hospital admissions for asthma [22–24].

PM₁₀ is one of the top air pollutants in Serbia, with all air quality monitoring stations in the country registering exceedances of the permitted daily limit value of 50 μg per cubic meter (μg/m³) [25]. We observed a significant association between 3-day lag exposure to PM₁₀ and ED visits for asthma with coexisting AR (OR = 2.38; 95% CI: 1.17–4.84), which is in accordance with most previous studies of short-term health effects [26–31].

In contrast, several other studies have failed to observe a statistically significant association [24, 32, 33].

According to a large systematic review and meta-analysis of 110 peer-reviewed time series studies, Atkinson et al. [6] pointed to adverse associations between short-term exposure to daily concentrations of PM₂.₅ and daily mortality and hospital admissions for cardiovascular and respiratory diseases. Zheng et al. [30] and Orellano et al. [34] in their systematic reviews and meta-analyses of 87 and 22 studies respectively, found a significant association between exposure to PM₂.₅ and asthma exacerbations. However we failed to find any statistically significant association between exposure to PM₂.₅ and asthma ED visits, which is in accordance with a Canadian study conducted by Lavigne et al. [35].

In this study we found a positive association between exposure to NO₂, one of the main air pollutants which is...
typically associated with vehicle emissions, and ED visits for asthma with coexisting AR (OR = 1.57; 95% CI: 0.94–2.65). The harmful effects of NO2 exposure on asthma exacerbation were reported by several studies [12, 22, 24, 28, 33, 34, 36]. Modig et al. [37] found a positive association between asthma onset (OR per 10 μg/m3 1.46, 95% CI: 1.07–1.99) and incident asthma in adults (OR per 10 μg/m3 1.54, 95% CI: 1.00–2.36) and the levels of NO2, which remained statistically significant after adjusting for potential confounders. Several authors [22, 31] found a strong correlation between emergency admissions for asthma and NO2, and SO2 pollutants and ED visits for allergic asthma in the Užice region, Serbia. Since most inhabitants in Užice, Kosjerić, and Sevojno use coal for heating, the introduction of a gas pipeline would reduce the concentration of combustion pollutants such as BC and SO2, which could decrease the number of asthma exacerbations. According to WHO recommendations [5], particulate air pollution can be reduced using stricter air quality standards and limits for emissions from various sources, reducing energy consumption, especially that based on combustion sources, changing modes of transport, land use planning, as well as individual behavioural changes (e.g. using cleaner modes of transport and household energy sources). Reasonable efforts to reduce ambient pollution levels and aeroallergen exposures offer the expectation to reduce asthma morbidity and asthma exacerbation in the Užice region.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Elliot AJ, Smith S, Dobney A, et al. Monitoring the effect of air pollution episodes on health care consultations and ambulance call-outs in England during March/April 2014: a retrospective observational analysis. Environ Pollut 2016; 14: 903-11.
2. Weber SA, Insaf TZ, Hall ES, et al. Assessing the impact of fine particulate matter (PM2.5) on respiratory-cardiovascular chronic diseases in the New York City Metropolitan area using Hierarchical Bayesian Model estimates. Environ Res 2016; 151: 399-409.
3. Xu Q, Li X, Wang S, et al. Fine particulate air pollution and hospital emergency room visits for respiratory disease in urban areas in Beijing, China, in 2013. PLoS One 2016; 11: e0153099.
4. European Environment Agency. Air quality in Europe 2018 report. EEA, Copenhagen, Denmark. Available from https://wvvveea.europa.eu/publications/air-quality-in-europe-2018.
5. WHO. Health effects of particulate matter. Policy implications for countries in eastern Europe, Caucasus and central Asia. Copenhagen: World Health Organization Regional Office for Europe, 2013. Available from http://www.euro.who.int/__data/assets/pdf_file/0006/189051/Health-effects-of-particulate-matter-final-Eng.pdf.
6. Atkinson RW, Kang S, Anderson HR, et al. Epidemiological time series studies of PM2.5 and daily mortality and hospital
10. Schildcrout JS, Sheppard L, Lumley T, et al. Ambient air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. Am J Epidemiol 2006; 164: 505-17.

11. Samoli E, Nastos PT, Paliatsos AG, et al. Acute effects of air pollution on children with respiratory symptoms: a systematic review and meta-analysis. Environ Health Perspect 2010; 118: 449-57.

12. Altzibar JM, Tamayo-Uria I, De Castro V, et al. Epidemiology of asthma exacerbations and their relation with environmental factors in the Basque Country. Clin Exp Allergy 2015; 45: 1099-108.

13. Leung TF, Ko FW, Wong GW. Roles of pollution in the prevalence and exacerbations of allergic diseases in Asia. J Allergy Clin Immunol 2012; 129: 42-7.

14. Lee SY, Chang YS, Cho SH. Allergic diseases and air pollution. Asia Pac Allergy 2013; 3: 145-54.

15. Stevanović I, Jovašević-Stojanović M, Jović Stošić J. Associations between ambient air pollution, meteorological conditions and exacerbations of asthma and chronic obstructive pulmonary disease in adult citizens of the town of Smederevo. Vojnosanit Pregl 2016; 73: 152-8.

16. Stanković A, Nikolić M. Long-term ambient air pollution exposure and risk of high blood pressure among citizens in Nis, Serbia. Clin Exp Hypertens 2016; 38: 119-24.

17. Census of Population, Households and Dwellings in the Republic of Serbia 2011: Comparative Overview of the Number of Population in 1948, 1953, 1961, 1971, 1981, 1991, 2002 and 2011, Data by settlements. Statistical Office of Republic of Serbia, Belgrade 2014. p. 178.

18. National network of automatic stations for air quality monitoring. Available from: http://www.amskvsjepa.gov.rs/?lng=en

19. WHO Air Quality Guidelines. Global Update 2005. Copenhagen: World Health Organization Regional Office for Europe, 2006. Available from http://www.euro.who.int/__data/assets/pdf_file/0005/78638/90038.pdf

20. WHO. Health Relevance of Particulate Matter from Various Sources. Report on a WHO Workshop. Copenhagen: World Health Organization Regional Office for Europe, 2007. Available from http://www.euro.who.int/__data/assets/pdf_file/0007/778658/E90672.pdf

21. Olstrup H, Johannson C, Forsberg B. The use of carbonaceous particle exposure metrics in health impact calculations. Int J Environ Res Public Health 2016; 13: E249.

22. Castellsague J, Sunyer J, Sáez M, Antó JM. Short-term association between air pollution and emergency room visits for asthma in Barcelona. Thorax 1995; 50: 1051-6.

23. Walters S, Griffiths RK, Ayres JG. Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulphur dioxide and smoke. Thorax 1994; 49: 133-40.

24. Sunyer J, Spix C, Quénéh P, et al. Urban air pollution and emergency admissions for asthma in four European cities: the APHEA Project. Thorax 1997; 52: 760-5.

25. Serbian Environmental Protection Agency (SEPA). Annual Report on the Environment: Excessive air pollution registered in Belgrade, other Serbian cities in 2017. Available from https://balkangreenenergynews.com/sepa-report-excessive-air-pollution-registered-in-belgrade-other-serbian-cities-in-2017/

26. Schwartz J, Slater D, Larson TV, et al. Particulate air pollution and hospital emergency room visits for asthma in Seattle. Am Rev Respir Dis 1993; 147: 826-31.

27. Rossi OV, Kinnula VL, Tienari I, Huhti E. Association of severe asthma attacks with weather, pollen, and air pollution. Thorax 1993; 48: 244-8.

28. Atkinson RW, Anderson HR, Strachan DP, et al. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J 1999; 13: 257-65.

29. Galán I, Tobias A, Banegas JR, Aránguez E. Short-term effects of air pollution on daily asthma emergency room admissions. Eur Respir J 2003; 22: 802-8.

30. Zheng XY, Ding H, Jiang LN, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis. PLoS One 2015; 10: e0138346.

31. Moghtaderi M, Zarei M, Farjadian S, Shamsizadeh S. Prediction of the impact of air pollution on rates of hospitalization for asthma in Shiraz based on air pollution indices in 2007-2012. Open J Air Pollution 2016; 5: 37-43.

32. Chen L, Omaye ST. Air pollution and health effects in Northern Nevada. Rev Environ Health 2001; 16: 133-49.

33. Tonias JM, Ballester F, Rivera ML. Association between hospital emergency visits for asthma and air pollution in Valencia, Spain, Occup Environ Med 1998; 55: 541-7.

34. Orellano P, Quarta N, Reynoso J, et al. Effects of outdoor air pollution on asthma exacerbations in children and adults: systemic review and multilevel meta-analysis. PLoS One 2017; 12: e0174050.

35. Lavigne E, Villeneuve PJ, Cakmak S. Air pollution and emergency department visits for asthma in Windsor, Canada. Can J Public Health 2012; 103: 4-8.

36. Simpson R, Williams G, Petroeschvsky A, et al. The short-term effects of air pollution on hospital admissions in four Australian cities. Aust N Z J Public Health 2005; 29: 213-21.

37. Modig L, Torén K, Janson C, et al. Vehicle exhaust outside the home and onset of asthma among adults. Eur Respir J 2009; 33: 1261-7.

38. Zhang S, Li G, Tian L, et al. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: a systematic review and meta-analysis. Environ Res 2016; 148: 15-23.

39. Bates DV, Baker-Anderson M, Sizto R. Asthma attack periodicity: a study of hospital emergency visits in Vancouver. Environ Res 1990; 51: 51-70.

40. Gharehchahi E, Mahvi AH, Amini H, et al. Health impact assessment of air pollution in Shiraz, Iran a two-part study. J Environ Health Sci Eng 2013; 11: 1.