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CARDIOVASCULAR DISEASES AND AIR POLLUTION IN NOVI SAD, SERBIA

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Abstract

Objectives: A large body of evidence has documented that air pollutants have adverse effect on human health as well as on the environment. The aim of this study was to determine whether there was an association between outdoor concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) and a daily number of hospital admissions due to cardiovascular diseases (CVD) in Novi Sad, Serbia among patients aged above 18. **Material and Methods:** The investigation was carried out during over a 3-year period (from January 1, 2007 to December 31, 2009) in the area of Novi Sad. The number (N = 10 469) of daily CVD (ICD-10: I00-I99) hospital admissions was collected according to patients' addresses. Daily mean levels of NO_2 and SO_2, measured in the ambient air of Novi Sad via a network of fixed samplers, have been used to put forward outdoor air pollution. Associations between air pollutants and hospital admissions were firstly analyzed by the use of the linear regression in a single polluted model, and then trough a single and multi-polluted adjusted generalized linear Poisson model. **Results:** The single polluted model (without confounding factors) indicated that there was a linear increase in the number of hospital admissions due to CVD in relation to the linear increase in concentrations of SO_2 ($p = 0.015$; 95% confidence interval (95% CI): 0.144–1.329, $R^2 = 0.005$) and NO_2 ($p = 0.007$; 95% CI: 0.214–1.361, $R^2 = 0.007$). However, the single and multi-polluted adjusted models revealed that only NO_2 was associated with the CVD ($p = 0.016$, relative risk (RR) = 1.049, 95% CI: 1.009–1.091 and $p = 0.022$, RR = 1.047, 95% CI: 1.007–1.089, respectively). **Conclusions:** This study shows a significant positive association between hospital admissions due to CVD and outdoor NO_2 concentrations in the area of Novi Sad, Serbia.

Key words:
Ambient air pollution, Cardiovascular diseases, Patient admission, Effects of pollutants, Exposure-outcome relation

INTRODUCTION

In a huge number of references, adverse effects of air pollutants on respiratory diseases are well described [1–4]. However, in a recent period a number of papers suggest that air pollution may be associated with cardiovascular diseases [5–7]. According to Martins et al.'s opinion [8], the number of adverse health outcomes attributable to air pollutants is much larger for cardiovascular than for respiratory diseases and the elderly people are the ones who present the highest susceptibility.

Most of the observations across North America [9,10], Australia [11], China [12], Europe [13–15], Mediterranean area [16] and in some cities in south Serbia [17] have already examined the relationship between cardiovascular admissions and urban air pollution, but in the area of Novi Sad, Serbia, this relationship has not been assessed yet.

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A significant number of time-series studies [18–23] indicate predominant effects of particulates and carbon monoxide (CO) on CVD admissions. However, Burnet et al. [24] who examined association between air pollution and admissions due to CVD in Canada in a series of papers, report that this association could be explained by the effects of gases. Investigations conducted by Poloniecki et al. [13], Pönka et al. [25] or Morgan et al. [11] suggest independent effects of the nitrogen dioxide (NO_2) and sulphur dioxide (SO_2).

The aim of this study was to determine whether there was an association between outdoor concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) and the daily number of hospital admissions due to all cardiovascular diseases (CVD) in Novi Sad, Serbia, in the case of patients aged above 18.

MATERIAL AND METHODS

The investigation was carried out during the period from January 1, 2007 to December 31, 2009 in the area of Novi Sad. Novi Sad, the second largest city in Serbia, is located in the northern part of the country (Province of Vojvodina) and according to the data from 2009, it has a population of 285 756 inhabitants in a built-up area of approximately 60 km^2 [26].

The daily number of hospital admissions (N = 1093 days) due to all CVD (ICD-10: I00–I99) [27] was obtained from the Centre for Informatics and Biostatistics in health care of the IPHV according to addresses of the patients (if the patients were not residents of Novi Sad, they were not included in the analysis). In addition to the data on the daily number of hospital admissions during the observed period, data on the age of the hospitalized individuals were available. However, only the daily number of hospital admissions of individuals older than 18 years of age (with no upper age limit) was taken into consideration.

Daily mean levels of nitrogen dioxide (NO_2) and sulfur dioxide (SO_2), measured in the ambient air of Novi Sad via a network of fixed samplers, have been used to put forward outdoor air pollution. There were 10 fixed monitoring sites spread all over the city, although not all of them measured all air pollutants. NO_2 from 2 stations and SO_2 from 10 stations were measured in the period from 0:00 a.m. to 12:00 p.m. and determined as the 24 h-average values using the spectrophotometric and volumetric methods, respectively, in 1092 air samples [28]. Because of the laboratory limit value for the performed methodology (for $SO_2 < 2$ μg/m^3 and for $NO_2 < 4$ μg/m^3), concentrations of each measured gaseous air pollutant were categorized into 2 categories, as follows:

- SO_2 I category – concentrations < 2 μg/m^3,
- SO_2 II category – concentrations ≥ 2 μg/m^3,
- NO_2 I category – concentrations < 4 μg/m^3,
- NO_2 II category – concentrations ≥ 4 μg/m^3.

Such a division of data concerning air pollutants was necessary for data processing. Specifically speaking, in the examined 3-year period the values were below the limit of laboratory detection for SO_2 for over 63.4% of days and NO_2 over 55.1% was not noted as a numerical value, but exclusively as a nominal value < 2 μg/m^3, i.e. < 4 μg/m^3. Data on the daily mean air temperature and daily mean relative humidity were provided by the Republic Hydrometeorological Institute of Serbia [29].

Statistics

Beside descriptive statistics, the nature and strength of the association between NO_2 and SO_2 concentration and hospital admissions were analyzed using various analytical techniques. Spearman's rank correlation was performed for the inter-correlation check between the observed variables; the Chi^2 test and independent T-test were used for the seasonal change trend of NO_2, SO_2 and CVD admissions, respectively. After log transformation of the daily CVD admissions, the air pollutant exposure-outcome

relationship has been first examined using the univariate linear regression model for the whole observed period.

However, due to the potential impact of confounding factors (long term, season, days of the week, weather components) on the examined relationship, CVD admissions were then regressed throughout multiple linear regression models. For assessing the core model that explained the relationship between air pollutants and CVD, long term (day of the study), season (each year was divided into the summer season from March 21 to September 22 and the winter season from September 23 to March 20), days of the week, temperature and relative humidity were used. The contribution of each confounding factor to the model fitting was assessed by stepwise multiple regressions and then regarded in relation to the coefficient of F test according to the level of significance. The final model (without air pollutants) included: long term period as a linear term, days of the week as a dummy variable (working day coding with 0 and weekend day coding with 1) temperature as linear and quadratic terms, while relative humidity as a linear term and season as a dummy variable were not significant. Different shapes of functions were constructed in order to find the best fit of exposure-response relationship model. In order to check the adequacy of each model, spectral analysis, peridiograms, plots of residuals and QQ plots were used. To confirm that autocorrelation among regression residuals was not diagnosed, the Durbin-Watson test was used (a range between 1.5–2.5 was used to confirm the absence of autocorrelation) [30].

After establishing this core model, the significant association – detected using the single polluted model analysis, was evaluated by the generalized linear Poisson regression model [31,32] in relation to the daily number of hospital admissions due to CVD. Daily concentrations of each air pollutant were included in the model as dummy variables (I category of SO_2 and NO_2 was coded as 0, while II category of SO_2 and NO_2 was coded as 1). All the analyses were based on exposures on the day of admission. Relative risk (RR) with 95% confidence intervals (95% CI) for each air pollutant was obtained in the single polluted and multi-polluted models. The results are also presented as a percentage increase associated with a unit increase in the pollutant level by the formula:

$$100 \times (1 - \exp(\beta \text{ coefficient} \times 1) - 1) \quad (1)$$

where:

exp – exponential functions,

β – the estimated regression coefficient for pollutant.

1% relative increase corresponded to the relative risk of 1.01. A significance level of 5% (2 sided) was used. SPSS for Windows (version 17.0) was used for all data analyses.

RESULTS

Over the 3-year period (1093 days), in the study area there were 10 469 CVD admissions among persons aged between minimum 18 and maximum 102 years. The average age of the hospitalized persons equaled 64.24±13.19 years, while the mean daily number of CVD hospital admissions was 9 ($\bar{X}$ = 9.57±4.81), and it ranged from 0 to maximum 27 admissions during one day (Table 1). Troughout the whole study period, the average daily concentrations of SO_2 were 16.33 μg/m^3 with maximum 31 μg/m^3 (for the 36.6% of observed days), while for the NO_2 they were 19.93 μg/m^3 (for the 44.9% of observed days) with the maximum level of 137 μg/m^3. The average daily temperature and relative humidity were 12.51°C and 71.05%, respectively (Table 1).

The values of Spearman's correlations coefficients (Table 2) suggest the lack of relationship between concentration of SO_2, NO_2, temperature and relative humidity. Only temperature was positively associated with relative humidity ($r = 0.575$, $p < 0.000$).

Based on the season specific statistics, daily hospital admissions due to all CVD did not show seasonal change ($t = 0.724$; $p = 0.470$) throughout the whole observed period of time (Table 3), while seasonal variations

Table 1. Summary statistics of daily hospital admissions due to cardiovascular diseases (CVD), air pollution and weather variables trough the observed period i.e. 2007–2009

Variable (observed days)	$\bar{X}$	SD	Min.	Max
CVD hospital admissions (N = 1093)	9.57	4.81	0.00	27.00
Age of hospitalized patients	64.24	13.19	18.00	102.00
Temperature (N = 1093)	12.51	8.36	–12.00	29.70
Relative humidity (N = 1093)	71.05	14.39	21.00	99.00
SO_2* II category (N = 400)	16.33	4.33	2.00	31.00
NO_2* II category (N = 491)	19.93	18.36	4.00	137.00

* For the rest of the observed days, concentration of SO_2 and NO_2 were analyzed as SO_2 I category – concentrations of $SO_2 < 2$ μg/m^3 and NO_2 I category – concentrations of $NO_2 < 4$ μg/m^3, respectively.
SO_2 – sulfur dioxide; NO_2 – nitrogen dioxide.
$\bar{X}$ – mean; SD – standard deviation.
Min. – minimum; Max – maximum.

Table 2. Spearman's correlations coefficients among the key variables, Novi Sad, 2007–2009

Variable	SO_2		NO_2		Temperature		Air humidity	
	r	p	r	p	r	p	r	p
SO_2			–0.063	0.017	–0.082	0.028	–0.067	0.026
NO_2					–0.067	0.026	–0.048	0.170
Temperature							–0.575	0.000
Air humidity								

r – Spearman's coefficient.
Other abbreviations as in Table 1.

Table 3. Season – specific statistics for air pollutants and the daily number of hospital admissions due to cardiovascular diseases (CVD) over the years 2007–2009

Variables of interest	Winter season	Summer season	χ^2	p
SO_2 concentration – days (%)				
SO_2 I category	47.20	52.80	4.045	0.044
SO_2 II category	53.50	36.60		
NO_2 concentration – days (%)				
NO_2 I category	44.00	55.40	10.200	0.006
NO_2 II category	53.50	46.50		
			t	p
CVD admissions ($\bar{X}$±SD)	9.77±5.21	9.34±4.39	0.724	0.470

χ^2 – Chi square.
Other abbreviations as in Table 1.

of air pollutants were characterized by a significantly higher number of days with higher concentrations of SO_2 ($\chi^2 = 4.045$; $p = 0.044$) and NO_2 ($\chi^2 = 10.200$; $p = 0.006$) in the winter and smaller in the summer season (Table 3).

Data on all cardiovascular diseases and daily SO_2 and NO_2 concentrations obtained in the single linear regression show that NO_2 and SO_2 were significant predictors of hospital admissions, with a 95% CI for the NO_2 of 0.214–1.361 ($p = 0.007$) and for the SO_2 of 0.144–1.329 ($p = 0.015$). Coefficient of determination (R^2) for SO_2 in the single polluted model was 0.005, while for NO_2 it was 0.007 (Table 4).

Adjusted Poisson regression model (Table 5) indicated that only concentrations of NO_2 were significantly associated with the daily number of hospital admissions due to CVD. In the single polluted model, just like in the multiple polluted model, RR for NO_2 was 1.049 (95% CI: 1.009–1.091) and 1.047 (95% CI: 1.007–1.089), respectively.

DISSCUSION

This is the first study examining effects of gaseous air pollution on all CVD hospital admissions in Novi Sad, Serbia. As we expected, the levels of gaseous pollution in the area of Novi Sad were moderate. The average daily values of SO_2 and NO_2 troughout the whole period of investigation were bellow the National Standard [33] and WHO recommendations [34,35].

A seasonal variation of NO_2 and SO_2 concentrations revealed a noticeable winter peak. Similar results were reported by other authors [36,37]. The higher number of days with concentration of $SO_2 > 2$ μg/m^3 during the

Table 4. Association between the monitored components of air pollution and the daily hospital admissions due to cardiovascular diseases throughout the 3-year period – results of the single linear regression model without confounding

Pollutants	β coefficients	R^2	F	p	95% CI for β	
					lower bound	upper bound
SO_2	0.736	0.005	5.945	0.015	0.144	1.329
NO_2	0.787	0.007	7.259	0.007	0.214	1.361

β – regression coefficients.
F – Fisher value.
CI – confidence interval.
Other abbreviations as in Table 1.

Table 5. Adjusted Poisson regression model[a] – association between the gaseous air pollution and cardiovascular diseases admissions in 2007–2009 period, Novi Sad

Pollutants	β coefficients	RR	p value	95% CI for β	
				lower bound	upper bound
SO_2 II category*	–0.039	0.962	0.262	0.900	1.029
NO_2 II category*	0.048	1.049	0.016	1.009	1.091
SO_2 II category**	–0.029	0.972	0.409	0.908	1.040
NO_2 II category**	0.046	1.047	0.022	1.007	1.089

[a] Model adjusted for long term, weekend and temperature.
Category of SO_2 and NO_2 is regarded as the reference category in: * single polluted model and ** multi-polluted model.
RR – relative risk; β – regression coefficients.

winter season could be related to the increased combustion of fuel used for domestic heating [38]. Zhao et al. [39] suggest that seasonal variability of NO_2 may result mainly from seasonal changes in chemical loss of NOx, which is very high in the summer and very low during the winter. Also, the increased atmospheric stability in the winter period may lead to a built up concentration of ambient air pollutants [40,41]. Attempting to investigate the role of SO_2, NO_2, particulate matter, temperature, relative humidity and wind speed in respiratory admissions (COPD, asthma and emphysema) Agarwal et al. [42] show that winter months have greater exposure risk as pollutants often get trapped in the lower layers of atmosphere resulting in high concentrations. However, there is no seasonal pattern for the date of daily hospital admissions for all cardiovascular diseases. Although we do expect similar change like with the gaseous air pollution, this could be explained by the influence of some other confounding factors which we have not taken into consideration. Research conducted by Kovats and colleagues confirm phenomena similar to ours in London [43]. However, in Spain, Valencia, cardiovascular admission series presented a seasonal trend with higher numbers in the coldest months [15].

In accordance with the aim of this study, we have found statistically significant, positive associations between the daily hospital admissions due to all CVD for the patients aged above 18 and the measured levels of gaseous pollutants.

The coefficient of determination indicated that only 0.7% and 0.5% of the variation in admissions could be explained by NO_2 and SO_2 (respectively). According to some other results [44], it is a very small predictable percent.

These results have to be considered with caution because they did not include some important factors like long term fluctuations, seasonal variations or day of the week, which may contribute to some associations between air pollution and CVD diseases [45]. Also, the studies suggest that differences in temperature and humidity might influence the composition of air pollution mix and therefore, might play a part in its effect on human health [46,47].

In the Poisson regression model with air pollutants and all significant confounding variables (long term, weekend and temperature) taken into account, the effects attributable to NO_2 and SO_2 change slightly – only NO_2 shows independently significant association with admissions due to CVD, while SO_2 remains insignificant. According to partial regression coefficients of the NO_2 and corresponding RR of hospital admissions in the single and multi-polluted models, each increase in the concentration of NO_2 by 1 $\mu g/m^3$ in the days when NO_2 concentration was > 4 $\mu g/m^3$ compared to the days when NO_2 concentration was < 4 $\mu g/m^3$ contributed to increasing the daily number of CVD admissions by 4.9% and 4.7%, respectively.

The obtained results suggest that NO_2 plays a dominant role in the higher risk of hospitalization due to cardiovascular diseases in the days when there are low concentrations of NO_2, in the case of our study – average of 19.93 $\mu g/m^3$, compared to the days when the concentrations of NO_2 were almost minimal (< 4 $\mu g/m^3$). The fact that negative health effects of air pollutants can be observed even if the air pollutants concentrations are below the values prescribed by the WHO [48,49,50] was confirmed by some authors [51].

Direct comparison of these results with the results of other studies is very complicated, on the one hand, due to the use of different health outcomes and, on the other hand, due to different methodological approach.

Association between air pollution and hospital admissions was analyzed using linear regression models, logistic regression model or variations to the Poisson model [12,52,53]. Pablo et al. [44] pointed that the results generated by the models differ and there is no sound justification for the use of one model over another. Despite the widely differing methodology approach, similar results to ours are shown in other studies [54,55]. In one study in Poland [56], authors got the results similar to ours and

they suggested that it was rather the effect of $PM_{2.5}$ which was strongly correlated with NO_2. Using data on hospital admissions due to cardiovascular diseases in London and ambient NO_2 levels, Poloniecki et al. [13] estimate that daily average NO_2 levels, ranging from 7.8 ppb (14.66 μg/m^3) to 196 ppb (368.48 μg/m^3), with a median of 34.3 ppb (64.48 μg/m^3), are associated with hospital admissions due to acute myocardial infarction (winter only), arrhythmia and combined circulatory disease with a 2.7%, 2.7% and 2.4% increase per 29 ppb (54.52 μg/m^3) increment in 24-hour NO_2 respectively. A case crossover study in Taipei, Taiwan, has also investigated the association between NO_2 level and hospital admissions due to cardiovascular diseases for the period 1997–2001. A statistically significant association was found in the case of warm and cold days. Associations were also observed for particles (PM_{10}), ozone (O_3), sulfur dioxide (SO_2) and carbon monoxide (CO) [57]. Similarly to our research, in most of the studies there where increases in daily NO_2 concentrations that have been associated with increased admissions due to specific cardiac conditions [24,58,59] and the concentrations had the strongest association with admissions on the same day. Wong et al found a significant increase (1.3%) in hospital admissions due to all CVD in Hong Kong, China in relation to the increase in the NO_2 level by 10 μg/m^3 [12]. As we have already mentioned, a direct comparison of our results with the previously stated ones is somewhat limited because of the applied categorization of the investigated pollutants. Namely, the obtained percentage of the increase in RR on average (4.9% and 4.7%) and the increase in NO_2 concentration by 1 g/m^3 which seems to be fairly comparable to other studies, refer exclusively to the days when the NO_2 concentration was less than 2 μg/m^3, and not to the entire tested period as it was done in other studies. However, some of the authors reported no significant associations between NO_2 levels and CVD admissions in all age groups [15] or ages between 5 and 64 years [12].

Some studies have shown associations between SO_2 exposure and all CVD admissions [60,61], however our study did not confirm these results in the adjusted model. Few studies using data on CVD admissions in total population and the daily level of SO_2 published results of epidemiological investigations similar to ours [57,62]. On the other hand, Biggeri et al. [63] in their investigation trough the 6 Italian cities (Turin, Milano, Bologna, Firenze, Rome, and Palermo), in the 1995–1999 period, show association between SO_2 level and hospital admission due to CVD in total population. Hospital admissions increase by 2.8% in response to the increase in the concentration of pollution by 10 μg/m^3. Sunyer et al. [14] also confirm the increase of hospital admissions due to all CVD in total population in Birmingham, London, Milan, Netherlands, Paris, Rome, and Stockholm. According to our results indicating a highly significant negative correlation between SO_2 and humidity, one of the variables that can help to explain the non-significant association between SO_2 and CVD admissions could be the level of air humidity. Similarly, as reported in APHEA – II study, the association of SO_2 with cardiovascular admissions (both at all ages and over 65 years) was stronger in the case of lower levels of humidity (the percentage increase in all cardiovascular admissions at all ages was 1.67, 95% CI: 0.65–2.71, per 10 μg/m^3 of SO_2 in the case of the lowest levels of humidity and 0.81, 95% CI: 0.43–1.19 in the case of the highest ones) [14]. Also, our results suggest that association with CVD admissions became non-significant after adjusting for NO_2, temperature and other confounding variables. Similarly, in the European APHEA II project [14] it was found that association with all cardiovascular admissions (both at all ages and above 65 years) got weaker and became non-significant after adjusting for CO, NO_2, black smoke, and PM_{10} concentration.

Responsibility of the gaseous air pollution for cardiovascular diseases has been observed in experimental [64] and epidemiological studies [65,66]. Although we did not

examine potential effects of gaseous air pollution on circulatory system, the strength of our study is of significant public health interest to a large number of people exposed to air pollution in the area of Novi Sad. However, more investigations with the detailed data on the characteristics of factors such as sex, smoking habits, comorbid conditions or personal exposure to air pollutants, which were not taken into consideration because of the incomplete database, are needed to confirm or refute these findings. Still, some studies have concluded that hospital databases provide more reliable information on adverse effects of air pollution when broad diagnostic classes are used such as health indicators of the air quality [67]. It should be noted that, we used data on outdoor air pollution concentrations of SO_2 and NO_2 measured at fixed-point monitors, which did not represent precise exposure estimates. Some of the earlier studies [68,69] indicate that such ambient concentrations may be poor surrogates for actual exposure to air pollution. Another limitation of this study could be the quality of using routinely collected health data in relation to exposure-outcome, without the possibility to separate urgent admissions due to CVD from the total number of CVD admissions. Delfino [67] has also pointed that the use of administrative data has several limitations (use of non-urgent admissions or delays in hospital admission from emergency rooms). Still, the results obtained in this study could constitute the baseline for further analytic epidemiological – environmental research.

Apart from the above limitation of the study, we can conclude that the levels of gaseous pollution throughout the period 2007–2009 in the area of Novi Sad were moderate, with a noticeable winter peak. Daily hospital admissions due to all cardiovascular diseases in population aged above 18, without seasonal change, were significantly positively associated with the measured gaseous air pollutants in Serbia. Apart from air pollutants, daily temperature and other contributing factors like long term fluctuations or day of the week, play a significant role in its association.

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