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Impact of meteorological parameters and air pollution on emergency department visits for cardiovascular diseases in the city of Zagreb, Croatia

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The aim of this study was to investigate whether nitrogen dioxide (NO_2), ozone (O_3), and certain meteorological conditions had an impact on cardiovascular disease (CVD)-related emergency department (ED) visits in the metropolitan area of Zagreb. This retrospective, ecological study included 20,228 patients with a cardiovascular disease as their primary diagnosis who were examined in the EDs of two Croatian University Hospitals, Sisters of Charity and Holy Spirit, in the study period July 2008-June 2010. The median of daily CVD-related ED visits during the study period was 28 and was the highest during winter. A significant negative correlation was found between CVD-related emergency visits and air temperature measured no more than three days prior to the visit, and the highest negative correlation coefficient was measured two days earlier ($R=-0.266$, $p\leq0.001$). The number of CVD-related emergency visits significantly correlated with the average NO_2 concentration on the same day ($R=0.191$, $p<0.001$). The results of multiple stepwise regression analysis showed that the number of CVD-related emergency visits depended on air temperature, and NO_2 and O_3 concentrations. The higher the air temperatures, the lower the number of daily CVD-related emergency visits ($p<0.001$). An increase in NO_2 concentrations ($p=0.005$) and a decrease in O_3 concentrations of two days earlier ($p=0.006$) led to an increase in CVD-related ED visits. In conclusion, the decrease in O_3 concentrations and the increase in NO_2, even if below the legally binding thresholds, could be associated with an increase in CVD-related emergency visits and a similar effect was observed with lower temperature measured no more than three days prior to the visit.

KEY WORDS: *atmospheric humidity; atmospheric pressure; nitrogen dioxide; ozone; temperature*

In recent years, many studies and reviews have tried to identify and prove the effect of air pollution on cardiovascular diseases and explain the pathogenesis of this influence (1-4). Furthermore, several studies have shown that air pollution represents a great health risk even in developed countries with legally defined thresholds of air pollution (4-6). Cardiovascular diseases are the main mortality and morbidity cause both worldwide and in Croatia (5); it has been shown to an increasing extent that air pollution significantly contributes to worsened cardiovascular health (2-6). Zagreb, the capital of Croatia, is located in the northwest of the country, has a maritime temperate climate or oceanic climate (Cfb in the Köppen–Geiger climate classification system), and generally features four separate seasons with warm summers and cool (but not cold) winters and a relatively narrow annual temperature range. Around 1.2 million people live in a wider Zagreb metropolitan area, which accounts for more than 20 % of Croatia's population, making it the only metropolitan area in Croatia with a population of over one million and consequently an area with occasional higher levels of traffic-related pollution (7).

Nitrogen dioxide (NO_2) is both a primary and a secondary pollutant, as well as a strong respiratory irritant. Its main outdoor sources are motor vehicles and fossil-fuel power plants, whereas the most important indoor sources are gas heaters, stoves, and tobacco smoke (5, 6). Many studies and meta-analyses underlined the association between daily increases in NO_2 and cardiovascular and respiratory mortality and morbidity (1, 5, 6). Ozone (O_3) is a secondary pollutant created indirectly in the troposphere from its precursors, e.g. oxides of nitrogen and volatile organic compounds. In urban areas, the main sources of ozone precursors are combustion engines. A few studies have shown its association with hospital admissions for cardiovascular and respiratory diseases (8, 9). For many cardiovascular conditions, however, as few as 10 % of those examined in the emergency department (ED) were admitted to hospital (9-11) whereas the remaining 90 % were treated in the ED but were not hospitalised. Thus, the number of ED visits reflects the impact of air pollution on CVD

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population better than the number of hospitalised patients (10, 11).

The aim of this study was to investigate whether nitrogen dioxide, ozone, and certain meteorological conditions impacted CVD-related emergency visits in the metropolitan area of Zagreb over a period of two years. It is noteworthy to disclose that this study follows on a previously published similar study in which the impact of atmospheric air pollution by NO_2 and meteorological parameters on a number of patients examined in EDs was studied (12); however, this study also includes the impact of ozone and the population of the metropolitan area of Zagreb which is almost twice as large in comparison with the previous study, the data of which were gathered from one hospital only.

METHODS

In the study period between July 2008 and June 2010 77,532 patients were examined in the EDs of two hospitals: *Sisters of Charity* University Hospital Centre and *Holy Spirit* University Hospital. The study population included 20,228 patients with a cardiovascular disease as their primary diagnosis, classified as I00-I99 according to the 10th International Classification of Diseases (ICD-10). The data on patients' emergency department visits were extracted from the hospitals' electronic system, which is used in both hospitals' EDs. During the entire research period, this system was used to record the data on patients older than 18 years who were examined in EDs due to a cardiovascular disease. Patients without permanent residency in Zagreb and patients without a confirmed I00-I99 diagnosis were excluded from the study.

This retrospective ecological study aimed to evaluate the association (hourly, daily, and earlier days) between meteorological conditions, air pollutant levels, and cardiovascular patients referred to EDs during the study period. The number of CVD-related emergency visits was compared with meteorological conditions and NO_2 and O_3 air concentrations during the overall period of the study, as well as during seasons only. Seasons were determined by weather conditions and not by calendar division as follows: winter = December to February, spring = March to May, summer = June to August, autumn = September to November.

Environmental data

Air pollution data were taken from the State Network for Continuous Air Quality Monitoring. The concentration of NO_2 was measured daily with automatic analyser using the method of chemiluminescence at the monitoring stations Zagreb-1, Zagreb-2, and Zagreb-3 and were averaged. The concentrations of O_3 were measured only at Zagreb-1 due the fact that it is the only station measuring O_3 levels in Zagreb, using an automatic analyser based on the method of ultraviolet photometry (UV absorption at 254 nm). The measurements were performed at a height of 3 meters with the data integration frequency of one hour. The 8-hour and 24-hour averages were based on the hourly concentrations of NO_2 and O_3 and were analysed as such. Meteorological data: atmospheric temperature (ºC), atmospheric pressure (hPa), and relative atmospheric humidity (%) were based on the data collected at a Meteorological and Hydrological Service of Croatia's meteorological station that covers the area of Zagreb in which the population gravitating to the study EDs lives. The meteorological data were converted from hourly values to daily averages so as to compare them with CVD-related emergency visits.

Since this was a retrospective ecological study, written informed consent was not necessary according to local legislation. The study protocol complied with Good Clinical Practice as well as the Declaration of Helsinki and the Hospital Ethics Committee provided its approval of the study.

Statistical analysis

Descriptive statistics were presented as the mean±standard deviation and median with the interquartile range and the analysis focused on the correlation between CVD-related ED visits, air pollutants, and meteorological factors. The mean values of individual variables were tested by a nonparametric Mann-Whitney test, which included two samples, and a non-parametric analysis of Kruskal-Wallis ANOVA for multiple samples. Data distribution was analysed using logarithms for the variables whose distribution was not normal. The correlation between the number of patients and each of the meteorological variables and air pollutants was tested by non-parametric Spearman's rank correlation. The influence of a group of variables on the number of CVD-related emergency visits was tested by multiple stepwise regression analysis. A value of $p<0.05$ was considered statistically significant. Statistical analysis was done using the STATISTICA software, version 6.0 for Windows (Dell Software, StatSoft Inc., Tulsa, USA).

RESULTS

In the study period of two years, or 730 days, 77,532 patients were examined in the EDs of the two hospitals. According to the ICD-10 classification (I00-I99 diagnosis, which includes acute coronary syndrome, ischaemic heart disease, congestive heart failure, and arrhythmias), 20,228 patients were diagnosed with a cardiovascular disease. The median of the daily number of patients examined in EDs during the observation period was 107 and there were 28 CVD-related emergency visits. Table 1 shows the meteorological parameters, pollutant concentrations, and ED visits during the whole study period and seasons only.

Table 1 *Meteorological parameters, air pollutant concentrations, and number of cardiac patients' ED visits during the whole study period and during seasons*

	Entire study period	Spring	Summer	Autumn	Winter	Kruskal-Wallis ANOVA
	Median (25 %-75 %)	Median (25 %-75 %)	Median (25 %-75 %)	Median (25 %-75 %)	Median (25 %-75 %)	p value
Temperature (°C)	13.4 (-7.9–28.5)	13.8 (-1.2–26.5)	22.5 (13.3–28.5)	13.1 (1.0 – 25.4)	2.6 (-7.9–14.5)	p<0.001
Relative humidity (%)	68.9 (37.7–95.3)	60.7 (37.7–91.4)	61.5 (41.0–89.5)	73.5 (44.4–95.3)	78.9 (43.6–94.0)	p<0.001
Air pressure (hPa)	996 (966–1020)	997 (966–1009)	996 (984–1004)	998 (979–1013)	994 (971–1020)	p<0.001
NO_2 – hourly average (μg m^{-3})	22.3	19.9	20.0	25.7	24.2	p<0.001
NO_2 – daily average (μg m^{-3})	25.9	24.7	24.2	30.7	26.8	p<0.001
O_3 – hourly average (μg m^{-3})	41.5	59.4	60.3	29.4	25.0	p<0.001
O_3 – daily average (μg m^{-3})	48.0	57.7	59.5	36.5	27.1	p<0.001
Average daily number of cardiac patients examined in ED	28 (9-53)	28 (9-53)	24 (10-44)	29 (14-45)	30 (12-46)	p<0.001
Total number of cardiac patients examined in ED	20 228 (100)	5 294 (26.1)	4 455 (22.0)	5209 (25.8)	5270 (26.1)	p<0.001

Meteorological parameters

The daily average of CVD-related emergency visits was the highest in winter season (Table 1). Moreover, non-parametric analysis (Spearman's correlation coefficient) showed that during the observation period CVD-related emergency visits significantly correlated to the air temperature measured no more than three days prior to the visit. The coefficient was negative, meaning that the lower the temperature the higher the number of CVD-related emergency visits. The highest negative correlation coefficient was found with the average temperature measured two days earlier (R=–0.266, p<0.001). The average relative air humidity of the same day positively correlated to CVD-related emergency visits (R=0.113, p=0.002). The average air pressure of the same day negatively correlated to the number of CVD-related emergency visits, but this correlation was not statistically significant (R=–0.056, p=0.131). Regarding the values of meteorological indicators by the observation period and by seasons, the lowest temperatures were recorded in winter with average 2.6 °C and the highest ones in summer (21.9 °C). The lowest atmospheric pressure was recorded in winter (994 hPa), and the highest in autumn (998 hPa) but without statistical significance, whereas the highest relative humidity was recorded in winter (80 %) and in autumn (75 %), with significant correlation between higher relative humidity and lower temperatures (Table 2).

The nitrogen-oxide (NO_2) effect

The highest daily values of air NO_2 were recorded in winter and the lowest in summer. During the two-year observation period, the hourly values of NO_2 concentrations never exceeded the legally binding threshold of 200 μg m^{-3} set by Croatian and EU legislation (EU Directive 2008/50/EC). The NO_2 threshold for the averaging time of one year is 40 μg m^{-3}, and it was not exceeded during the first year (1 July 2008 - 30 June 2009; 27.5 μg m^{-3}), nor during the second year (1 July 2009 - 30 June 2010; 27.1 μg m^{-3}) of the observed period. The number of CVD-related emergency visits significantly correlated to the average NO_2 concentration on the same day (R=0.191, p<0.001). NO_2 concentrations of previous days did not have a statistically significant effect on the number of CVD-related emergency visits (Table 3).

Table 2 *Correlations between meteorological parameters and air pollutant concentrations during the study period*

	Air temperature (°C)	Air pressure (hPa)	Relative humidity (%)	NO_2 (μg m^{-3})	O_3(μ gm^{-3})
Air temperature (°C)	-	-0.194*	-0.455*	0.010	0.657*
Air pressure (hPa)	-0.194*	-	0.000	-0.030	-0.127*
Relative humidity (%)	-0.455*	0.000	-	-0.031	-0.637*
NO_2 (μg m^{-3})	0.010	-0.030	-0.031	-	-0.384*
O_3 (μg m^{-3})	0.657*	-0.127*	-0.637*	-0.384*	-

** p value <0.05*

The ozone (O_3) effect

The highest hourly values of O_3 were recorded in summer (Table 1). The median hourly averages for the observation period amounted to 41.5 μg m^{-3}, and the highest were recorded in summer (60.3 μg m^{-3}). The highest daily averages were recorded in spring with the maximum of 126 μg m^{-3}, which is also the maximum for the whole observation period. The maximum eight-hour average concentration of O_3 for the two-year observation period was 160.4 μg m^{-3} and was recorded in summer. The medians of eight-hour moving averages were calculated, recording the highest values in spring and summer (59.4 and 59.6 μg m^{-3}).

The number of days with a maximum daily eight-hour mean of O_3 values higher than 120 μg m^{-3} (which is the target value according to the EU Directive 2008/50/EC) was specified. According to Croatian legislation, the maximum daily eight-hour moving average of O_3 concentrations should not exceed 120 μg m^{-3} on more than 25 calendar days, averaged over three years. During the two-year observation period, the number of days with ozone values above 120 μg m^{-3} was 38, out of which most were recorded in summer (24 days), whereas not a single day was recorded in winter. Considering the World Health Organization's (WHO) recommendation on the threshold of 100 μg m^{-3}, the number of days with eight-hour concentration averages above 100 μg m^{-3} was 166, out of which most were recorded in summer (81 days). During the observation period there was a statistically significant negative correlation between O_3 and relative humidity (R=-0.637, p<0.001) as well as air pressure (R=-0.127, p=0.001) (Table 2). The number of CVD-related emergency visits significantly negatively correlated to the average O_3 concentration on the same day, as well as up to three days earlier (Table 4). However, the correlation coefficient between the number of ED cardiac patients and the air temperature measured two days earlier was –0.266, whereas the correlation to O_3 concentrations measured two days earlier was significantly lower, amounting to –0.126. Meanwhile, the correlation coefficient between the temperature and O_3 amounted to 0.572 regarding the daily average, or even 0.737 regarding the maximum hourly O_3 values within a day.

Multiple stepwise regression analysis

The results of multiple stepwise regression analysis showed that the number of CVD-related emergency visits significantly depended on three variables: air temperature, NO_2 concentration, and O_3 concentration. The higher the air temperatures, the lower the number of CVD-related emergency visits (r=-0.09). The increase in O_3 concentrations was also associated with a decrease in CVD-related emergency visits (r=-0.190, p=0.006). Moreover, an increase in NO_2 concentrations was associated with an increase in CVD related emergency visits (r=0.055).

DISCUSSION

In this study, we investigated the impact of air pollutants together with meteorological parameters on the number of CVD-related emergency visits. Our data revealed that air pollutant levels and air temperature were associated with the number of CVD-related emergency visits. A significant increase in the daily number of CVD-related emergency visits was associated with increased NO_2 air concentrations lower O_3 concentrations on the same day, and lower air temperature measured no more than three days prior to the visit, with the highest negative correlation coefficient measured two days earlier.

The observed meteorological values were as expected, considering Zagreb's latitude and climate zone. According to our results, there was a negative correlation of air temperature and the number of CVD-related emergency visits throughout the whole observed period. Mean daily air temperature did not exceed 22.5 °C and most likely for that reason positive correlation was not found in the warmest part of the year. Moreover, the negative correlation coefficient in the warmest part of the year was undoubtedly the least pronounced. In many cities with Cfb climate, as in Zagreb, the mortality rate of cardiovascular disorders during winter

months is up to 25 % higher than in summer months, and air temperature fluctuations cause increased morbidity and mortality from cardiovascular diseases (13, 14). In the winter period, the longer the low temperature period the higher the risk, while in the warm part of the year increased air temperatures affect directly the risk of cardiovascular incidents (13-15). Numerous scientific studies have presented air temperature as the main parameter, with any accompanying air pollutant, which highly affects the risk of cardiovascular incidents (14-17), as confirmed by the results of our work.

Schwarz et al. (18) found that in 12 United States cities, covering a wide range of different geographical regions, the effects of relative humidity on ED cardiac visits were small, almost statistically insignificant, but the effects of low and high temperatures were high, especially with myocardial infarction. They concluded that the effects mainly occurred within a few days after exposure (usually two days) and ceased within ten days after exposure. The results of our study coincide with the results of their work, with an exception that the average relative humidity had a positive correlation coefficient with the number of ED visits of cardiac patients.

Although the levels of NO_2 have not exceeded the legally binding threshold values, there was a significant association between NO_2 concentration and the number of CVD-related emergency visits, especially in winter time when weather conditions favour the emergence of higher NO_2 concentrations. In our study, the strongest correlation was found with average daily values of NO_2 measured on the same day. This result shows that ambient NO_2 concentrations, which are below the legally binding limit values, strongly affect the number of CVD-related emergency visits, which was confirmed in several previous studies (19-21).

Several review studies (2, 9, 22) showed that O_3 was one of the most toxic compounds of mixed photochemical smog. Results of our study revealed a negative correlation between O_3 concentrations and CVD-related emergency visits, which is in line with previous studies (22-24). However, many studies showed destructive effects of this pollutant on the cardiovascular system. A study by Koken et al. (25) has proved in the city of Denver, which has a cold continental climate, a significant association of high temperatures and high O_3 values with CVD-related emergency visits, especially with acute myocardial infarction and cardiac arrhythmias. Similar to this, Shahi et al. (26) indicated that a growing number of cardiac patients examined in the emergency departments of the capital city of Tehran were recorded on the third day after two days of increased concentrations of ozone.

According to our findings, which are in agreement with most previous similar studies, health care systems need to be ready to control and treat diseases arising from air pollution. Data on the number of patients admitted is vital in ensuring suitable equipment and facilities proportionate to the number of admitted patients. On the other hand, because of the differences in pollutant levels of various geographical locations, the pattern of hospital admissions is noticeably different in days of greater pollution. Therefore, it is critical that health care systems of countries are informed about the pattern of hospital admissions and polluted days to have more accurate managing programmes for this crisis. Also, the need for improved legal regulations and lower upper legally binding threshold values of air pollution should be emphasised, because air pollution that is within the permitted legal levels is associated with the increase in CVD-related emergency visits, which was confirmed in our study, especially for NO_2.

Limitations

Although the study period was rather short, there were no exceptional events that could have influenced the results. The study was based on a population as large as 1.2 million

Table 3 *Cardiovascular disease related-emergency visits over a period of 692 days correlated with nitrogen-dioxide (NO_2) concentrations*

	Correlation coefficient R	p value
maximum hourly NO_2 concentration	0.072	0.057
average daily NO_2 concentration	0.191	<0.001
average daily NO_2concentration 1 day earlier	0.034	0.378
average daily NO_2 concentration 2 days earlier	-0.037	0.329
average daily NO_2 concentration 3 days earlier	-0.009	0.804

Table 4 *Cardiovascular disease-related emergency visits over a period of 646 days correlated with ozone (O_3) concentrations*

	Correlation coefficient R	p value
maximum hourly O_3 concentration	-0.183	<0.001
average daily O_3 concentration	-0.191	<0.001
average daily O_3 concentration 1 day earlier	-0.132	0.0007
average daily O_3 concentration 2 days earlier	-0.126	0.0014
average daily O_3 concentration 3 days earlier	-0.108	0.0061

inhabitants, among which daily CVD-related emergency visits were quite frequent and reached the number of 28, which ensured the statistical power of the analysis. However, the results of the study should be considered in the light of certain limitations. The O_3 data was taken from only one monitoring station, which may lead to the misclassification of exposure level. However, this misclassification is non-differential and should bias the effect estimates towards the null. Moreover, as with every ecological study, there is a lack of precise exposure estimates at individual level and misclassification of exposure due to different daily activity patterns and local mobility of each patient and the deduction of cause-effect relations should be done with caution. Additionally, there are large scale factors that may influence CVD rates and CVD-related emergency visits which were not taken into account.

In conclusion, to the authors' knowledge this was the first study in Croatia that investigated the influence of air pollution, including nitrogen dioxide (NO_2) and ozone (O_3), and certain meteorological parameters on emergency department visits of patients with cardiovascular diseases.

The authors report no conflict of interest.

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Utjecaj meteoroloških parametara i onečišćenja zraka na preglede u Hitnoj službi zbog kardiovaskularnih bolesti u gradu Zagrebu, Hrvatska

Cilj istraživanja bio je ispitati imaju li dušikov dioksid (NO_2), ozon (O_3) i određene meteorološke prilike utjecaja na broj pregleda u Hitnoj službi (HS) zbog kardiovaskularnih bolesti (KVB) u gradu Zagrebu. U ovu retrospektivnu, ekološku studiju bilo je uključeno 20.228 bolesnika s primarnom dijagnozom jedne od kardiovaskularnih bolesti, pregledanih u HS-u dviju kliničkih bolnica: Sestre milosrdnice i „Sveti Duh“, u promatranom razdoblju od srpnja 2008. do lipnja 2010. Medijan dnevnih pregleda u HS-u zbog KVB-a tijekom promatranog razdoblja bio je 28, a najviše tijekom zime. Značajna negativna korelacija utvrđena je između broja pregleda u HS-u zbog KVB-a i temperature zraka do tri dana ranije, s najvećim negativnim koeficijentom korelacije dva dana ranije (R=-0,266, p=0,000). Broj pregleda u HS-u zbog KVB-a značajno korelira s prosječnim koncentracijama NO_2 na isti dan (R=0,191, p=0,000). Rezultati stupnjevite regresijske analize pokazali su da broj pregleda u HS-u zbog KVB-a ovisi o temperaturi zraka i koncentraciji NO_2 i O_3. Što je viša temperatura zraka, to je manji broj pregleda u HS-u zbog KVB-a (p=0,000), a slično vrijedi i za koncentraciju ozona (p=0,006). Povećanje koncentracije NO_2 povezano je s povećanjem broja pregleda u HS-u zbog KVB-a (p=0,005). Zaključno se može ustvrditi da povećanje koncentracije NO_2 može biti povezano s povećanjem broja pregleda u HS-u zbog KVB-a, čak ako su navedene koncentracije unutar pravnoobvezujućih razina, sa sličnim utjecajem niže temperature zraka do tri dana ranije.

KLJUČNE RIJEČI: *atmosferski tlak; atmosferska vlaga; dušikov dioksid; ozon; temperatura*