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# Effects of ozone on consultations for asthma in children in Koper municipality: A time trend study

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**ABSTRACT**

Aiming at assessing the feasibility of linkage of existing health and environmental data in Slovenia in the case of the Koper Municipality in identifying the grounded need for public health action, the objective of the study was to assess the association between consultations on the primary health care level due to asthma and daily ozone concentrations. An ecological time-trend study with a single day as a unit of observation was performed in 2012. Periods from April 1 through October 31 were observed in 2010 and 2011. The study population was children, aged 0-12 years, who visited the Community Health Centre Koper for asthma. Logistic regression was used in analysis. The results showed statistically significant association between daily occurrence of at least one consultation for asthma and ozone daily maximum 8-hr average concentration 70 $\mu g/m^3$ or exceeded, lag 4 days (OR=4.77; p=0.042). There is an evidence of association between increased ozone levels and daily occurrence of any consultation for asthma in Koper Municipality. The study opened many challenges for future research. If they are resolved, evidence-based approach to public health activities in the field of environmental health in the region and in Slovenia would be strongly improved on this basis thereof.

**Key words:** ozone, asthma, ecological time-trend study, logistic regression, Koper Municipality

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## INTRODUCTION

Exposure to air pollution has been proven to be associated with a variety of adverse health effects. There is a strong evidence that especially increased air pollution with particulate matter ($PM_{10}$ and $PM_{2.5}$), and ozone ($O_3$), precipitates respiratory symptoms [1-5], and consequently emergency room visits and hospital admissions due to these symptoms [6-10]. Among the most susceptible population subgroups are children [3, 7, 11-17].

In Slovenia the highest $O_3$ concentrations occur in the western part, especially in the situations when the wind blows from the south or south-west direction, what reflects the transfer of $O_3$ across the border from Italy [18, 19]. Koper Municipality (KM) is a part of this region. It is located in the south-west (Figure 1a).

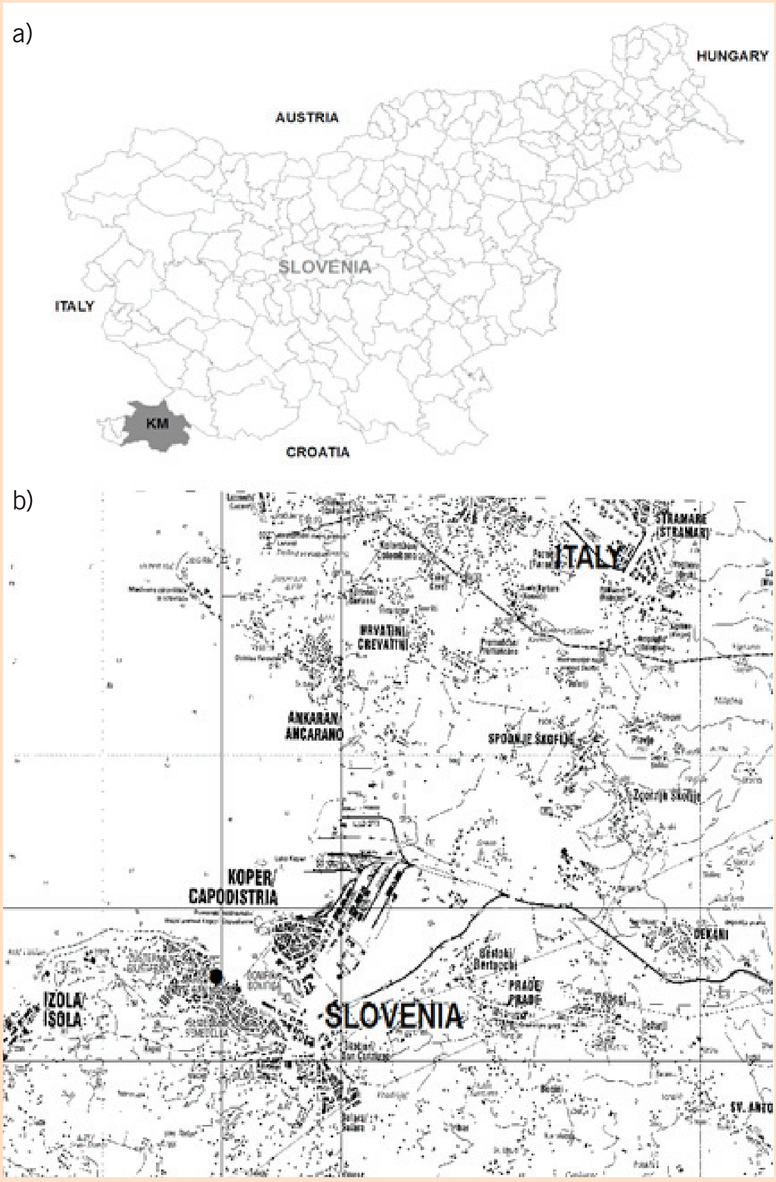


**Figure 1:**
The location of the Koper Municipality (KM) within Slovenia (a). Location of the Environment Agency of the Republic of Slovenia measuring station Markovec in the Koper Municipality (●) (b).

**Source of shape files:** DMNV25, GURS.

The results of outdoor air quality measurements in the KM in the past have shown that the burdening through $O_3$ is considerable [20-22]. On the other side, in the recent years the evidence on the relationship between respiratory diseases in children and air pollution in the KM accumulate [23, 24]. However, none of these studies has tried to link routine environmental and routine health data. There exist only one study which tried to link mortality data of the total population and air pollution with $O_3$ in the region [22].

Aiming at identifying the possibilities for targeted public health action, the objective of the study was to assess the association between consultations at the Community Health Centre Koper (CHCK) due to asthma symptoms and daily $O_3$ concentrations in children from the KM.

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## MATERIALS AND METHODS

### Study characteristics

The ecological time-trend study was conducted in 2012. The study population was children, aged 0–12 years, residing permanently (July 1, 2010: 5,965; July 1, 2011: 6,163) [25], or temporarily (as tourists) in the KM in the observed periods, who visited the CHCK for asthma symptoms. The data for the years 2010 and 2011 were analysed. Observation time was limited to the periods April 1 to October 31, when $O_3$ concentrations in the observed area are the highest. The unit of observation was a single day. Altogether, 428 days were observed. The study protocol was approved by the Ethical Committee of the Republic of Slovenia in 2012.

### Origin of data

Health data were obtained from health information systems of the CHCK. The information gathered was the number of children aged 0–12 years who for the first time visited CHCK due to asthma (including acute exacerbation of this chronic disease) by day in the observed periods.

Data on the concentration of air pollutants in the smallest possible time interval were obtained from the measuring station in Koper/Markovec (Figure 1b), which is part of the fixed stations of the national automated network for monitoring air quality of the Republic of Slovenia, operated by the Slovenian Environment Agency (SEA). The information on $O_3$, $PM_{10}$ and nitrogen dioxide ($NO_2$) concentrations (for all three 1-hr average in $\mu g/m^3$), air temperature (in °C) and relative humidity (as %) was obtained (Figure 1b).

### Data analysis

Observed outcome was basically the daily number of first consultations for asthma, which was later transformed to a binary indicator as to whether or not any first consultation for asthma occurred in a day, since the number of daily consultations was low.

As the explanatory factor only $O_3$ was considered, expressed as a daily maximum 8-hr average concentration. The 8-hr running averaged value for each hour was calculated as the average of the values for that hour and the 7 foregoing hours. The daily maximum value for a given calendar day was afterwards determined as the highest of the 24 possible 8-hour averages computed for that day. For the purposes of analysis additionally a binary indicator as to whether or not daily maximum 8-hr average achieved or exceeded the according to WHO 8-hour average baseline level for maximum 8-hour average of 70 $\mu g/m^3$ (the estimated background $O_3$ level) [26] was calculated. Lags of 0-5 days from exposure to the consultation day were examined to determine the amount of time between exposure and effect.

Some important covariates were considered as proposed in the literature [27]. Firstly, data on $PM_{10}$ and nitrogen dioxide ($NO_2$) were considered. Both were expressed as the average of the 24 hourly values covering the period from the midnight of the day-1 to the midnight of the day n. Lags of 0–5 days from exposure to consultation day were examined. Secondly, temperature and humidity were considered. Both were expressed as the average of the 24 hourly values covering the period from the midnight of the day-1 to the midnight of the day n. Finally, the seasonal factors were considered: the year of data collection, and the day of the week (workday or weekend day) and holiday indicators (yes, no). Meteorological and seasonal factors were used in analysis as background covariates [27].

Univariate relationship analysis was performed only as simple univariate correlation analysis between explanatory ($O_3$) and other pollution factors. The analysis was performed by using Pearson correlation method. Results are presented as a part of description of data.

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For statistical analyses SPSS for Windows, Version 18.0 (IBM Corporation, Armonk, NY, USA) was used.

The relationship between observed outcomes and explanatory factor adjusted to potential confounders was analysed by using logistic regression model [28, 29]. The modelling procedure was performed in two steps. In the first step, single pollutant models were defined by adding the single exposure variable (both indicators on $O_3$, and indicators on $PM_{10}$, and $NO_2$) to a set of background covariates (temperature, relative humidity, year of data collection, workday or weekend day, and holiday or not). These models were determined in order to obtain the best lag of exposure variable and covariates to be potentially included in the multi-pollutant model. In the process of determination, biological plausibility, e.g. the direction of relationship between the outcome and explanatory variable or covariate (only positive association was considered as plausible and acceptable), as well as statistical significance of this relationship, were considered. A p-value $\leq 0.05$ was considered as statistically significant, and a p-value $\leq 0.250$ was considered acceptable for entering a variable into the multi-pollutant model [28]. In the second step, a model that included best lags of all pollutants considered in the study ($O_3$, $PM_{10}$, $NO_2$), and a set of background covariates was defined. A stepwise method of selecting the variables to enter the final model was used [28].

## RESULTS

### Data description

Data on observed outcome were available for all 428 days of observation. In the year 2010 there were in total 163/214 (76.2 %) days with no consultations for asthma-related symptoms and 51/214 with any consultation, while in the year 2011 there were in total 187/214 (87.4 %) days with no consultations for asthma symptoms and 27/214 with any consultation. Maximal daily number of consultations was 3. Altogether there were 93 visits for asthma symptoms in the observed period (63 in 2010 and 30 in 2011).

$O_3$ daily maximum 8-hr average concentration (μg/m$^3$) was possible to calculate for total 423, $PM_{10}$ 24-hr average concentration (μg/m$^3$) for total 411, $NO_2$ 24-hr average concentration (μg/m$^3$) for total 411, 24-hr temperature average (˚C) for total 426, and 24-hr relative humidity average (%) for total 426 days of observation. Selected characteristics for these indicators are presented in Table 1.

**Table 1:**
Selected characteristics of the distribution of selected pollutants and meteorological factors in the Koper Municipality, Slovenia, from April 1 to October 31, in the years 2010 and 2011.

| Covariate | Year | N[1] | Mean | SD | Min | Max |
|---|---|---|---|---|---|---|
| $O_3$ daily maximum 8-hr average concentration (μg/m$^3$) | 2010 | 209 | 103.5 | 24.7 | 52.2 | 161.6 |
| | 2011 | 214 | 108.6 | 23.3 | 32.6 | 173.2 |
| $PM_{10}$ 24-hr average concentration (μg/m$^3$) | 2010 | 203 | 21.8 | 9.1 | 7.1 | 67.8 |
| | 2011 | 208 | 21.1 | 7.7 | 5.7 | 48.3 |
| $NO_2$ 24-hr average concentration (μg/m$^3$) | 2010 | 203 | 17.7 | 6.1 | 1.9 | 41.6 |
| | 2011 | 211 | 16.3 | 6.4 | 2.8 | 46.7 |
| Daily temperature average (˚C) | 2010 | 212 | 19.8 | 4.9 | 9 | 31 |
| | 2011 | 214 | 20.8 | 4.9 | 5 | 30 |
| Daily humidity average (%) | 2010 | 212 | 61.8 | 11.4 | 24 | 87 |
| | 2011 | 214 | 58.0 | 11.8 | 21 | 89 |

**Source:** Authors

Regarding the seasonal indicators, in each of observed years, there were in total 152/214 (71.0 %) workdays and 62/214 (29.0 %) weekend days in the observed period. In each of observed years, 2010 and 2011, there were in total 74/214 (34.6 %) holidays days and 140/214 (65.4 %) non-holidays days in the observed period. Additionally, in the year 2010 there were in total 188/209 (90.0 %) days in the observed period on which 8-hr average achieved or exceeded the WHO 8-hour average baseline level of 70 μg/m$^3$, while in 2011 there were 195/214 (91.1 %) such days.

Correlation analysis between daily 24-hr average concentration of $O_3$ (μg/m$^3$) and $PM_{10}$ 24-hr average concentrations (μg/m$^3$) showed only weak positive correlation (r=0.246; p≤0.001). Correlation analysis between daily 24-hr average concentration of $O_3$ (μg/m$^3$) and $NO_2$ 24-hr average concentrations (μg/m$^3$) showed only weak negative correlation (r=-0.234; p≤0.001). Correlation analysis between $PM_{10}$ 24-hr average concentrations (µg/m³) and $NO_2$ 24-hr average concentrations (µg/m³) showed moderate positive correlation (r=0.444; p≤0.001).

### Results of uni-pollutant relationship analysis

The results of association between daily occurrence of any consultation for asthma symptoms and $O_3$ daily maximum 8-hr average concentration showed that in the lags 1, 3 and 4 that the higher $O_3$ daily maximum 8-hr average concentrations could be associated with a higher probability for daily occurrence of any consultation for asthma symptoms. However, in none of these lags the association was statistically significant (Table 2). Consequently, none of the lags was chosen to enter the multi-pollutant model, and no multi-pollutant model was defined at all. On the other side the results of association between daily occurrence of any consultation for asthma symptoms and $O_3$ daily maximum 8-hr average ≥70 µg/m³ showed a bit stronger association in the lag 4, since in this lag the association was borderline statistically significant (Table 2). Consequently, this lag was chosen to enter the multi-pollutant model.

**Table 2:**
Summary results of the logistic regression analysis of association between daily occurrence of any consultation for asthma symptoms and two ozone indicators for uni-pollutant models for lags 0-5.

| Explanatory factor/covariate | | N[1] | OR[2] | 95 % C.I.[3] limits for OR | | *p*-value |
|---|---|---|---|---|---|---|
| | | | | Lower | Upper | |
| $O_3$ daily maximum 8-hr average concentration, lag 0 | | 423 | 0.999 | 0.985 | 1.013 | 0.906 |
| $O_3$ daily maximum 8-hr average concentration, lag 1 | | 420 | 1.005 | 0.991 | 1.019 | 0.459 |
| $O_3$ daily maximum 8-hr average concentration, lag 2 | | 417 | 0.998 | 0.984 | 1.011 | 0.741 |
| $O_3$ daily maximum 8-hr average concentration, lag 3 | | 415 | 1.003 | 0.990 | 1.016 | 0.670 |
| $O_3$ daily maximum 8-hr average concentration, lag 4 | | 413 | 1.001 | 0.988 | 1.015 | 0.846 |
| $O_3$ daily maximum 8-hr average concentration, lag 5 | | 411 | 0.988 | 0.975 | 1.002 | 0.095 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 0 | No | 423 | 1.000 | | | |
| | Yes | | 0.687 | 0.262 | 1.797 | 0.444 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 1 | No | 420 | 1.000 | | | |
| | Yes | | 1.857 | 0.581 | 5.940 | 0.297 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 2 | No | 417 | 1.000 | | | |
| | Yes | | 1.211 | 0.408 | 3.596 | 0.730 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 3 | No | 415 | 1.000 | | | |
| | Yes | | 1.931 | 0.604 | 6.177 | 0.267 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 4 | No | 413 | 1.000 | | | |
| | Yes | | 3.571 | 0.775 | 16.447 | 0.102 |
| $O_3$ daily maximum 8-hr average concentration ≥70 µg/m³, lag 5 | No | 411 | 1.000 | | | |
| | Yes | | 0.625 | 0.213 | 1.833 | 0.392 |

**Source:** Authors

The results of association between daily occurrence of any consultation for asthma symptoms and $PM_{10}$ 24-hr average concentration showed that in lags 0-3 higher $PM_{10}$ concentrations were associated with a higher probability for daily occurrence of any consultation for asthma symptoms. In lags 0 and 2 it was statistically significant (Table 3). The

**Table 3:**
Summary results of the logistic regression analysis of association between daily occurrence of any consultation for asthma symptoms and selected pollutants for uni-pollutant models for lags 0-5.

| Explanatory factor/covariate | N[1] | OR[2] | 95 % C.I.[3] limits for OR | | p-value |
|---|---|---|---|---|---|
| | | | lower | upper | |
| $PM_{10}$ 24-hr average concentration, lag 0 | 424 | 1.031 | 1.001 | 1.063 | 0.045 |
| $PM_{10}$ 24-hr average concentration, lag 1 | 421 | 1.031 | 0.999 | 1.064 | 0.056 |
| $PM_{10}$ 24-hr average concentration, lag 2 | 418 | 1.033 | 1.002 | 1.065 | 0.038 |
| $PM_{10}$ 24-hr average concentration, lag 3 | 416 | 1.005 | 0.975 | 1.036 | 0.749 |
| $PM_{10}$ 24-hr average concentration, lag 4 | 414 | 0.997 | 0.966 | 1.029 | 0.851 |
| $PM_{10}$ 24-hr average concentration, lag 5 | 412 | 0.997 | 0.966 | 1.028 | 0.830 |
| $NO_2$ 24-hr average concentration, lag 0 | 414 | 1.033 | 0.990 | 1.077 | 0.139 |
| $NO_2$ 24-hr average concentration, lag 1 | 412 | 1.030 | 0.986 | 1.075 | 0.185 |
| $NO_2$ 24-hr average concentration, lag 2 | 410 | 1.022 | 0.980 | 1.064 | 0.309 |
| $NO_2$ 24-hr average concentration, lag 3 | 409 | 1.006 | 0.964 | 1.050 | 0.783 |
| $NO_2$ 24-hr average concentration, lag 4 | 408 | 0.996 | 0.955 | 1.038 | 0.838 |
| $NO_2$ 24-hr average concentration, lag 5 | 407 | 1.023 | 0.981 | 1.066 | 0.288 |

**Source:** Authors

association was slightly stronger in lag 2. However, since this difference was not big, and biologically more plausible is lag 0, this lag was chosen to enter the multi-pollutant model. The results of association between daily occurrence of any consultation for asthma symptoms and $NO_2$ 24-hr average concentration showed that in all lags except in the lag 4 higher $NO_2$ concentrations could be associated with a higher probability for daily occurrence of any consultation for asthma symptoms. However, only in lags 0 and 1 the association was borderline statistically significant (Table 3). It was slightly stronger in lag 0. Consequently, this lag was chosen to enter the multi-pollutant model.

## Results of multi-pollutant relationship analysis

The results of multi-pollutant relationship analysis are presented in the Table 4. In the model, in which all statistically non-significant variables were omitted by the procedure itself, the association between daily occurrence of any consultation for asthma symptoms and $O_3$ daily maximum 8-hr average concentration 70 $\mu g/m^3$ or exceeded, lag 4, was statistically significant. The results indicated that on the days on which $O_3$ daily maximum 8-hr average was $\geq 70$ $\mu g/m^3$ the odds for any consultation for asthma symptoms were 4.77-times higher than on other days. In $PM_{10}$ 24-hr average, lag 0, the association was also statistically significant (Table 4).

**Table 4:**
Results of the logistic regression analysis (stepwise method) of association between daily occurrence of any consultation for asthma symptoms and ozone concentration, controlled for selected covariates (N=388).

| Explanatory factor/covariate | | OR[1] | 95 % C.I. limits for OR | | p-value |
|---|---|---|---|---|---|
| | | | lower | upper | |
| $O_3$ daily maximum 8-hr average concentration ≥70 μg/m³, lag 4 | No | 1.000 | | | |
| | Yes | 4.769 | 1.057 | 21.520 | 0.042 |
| $PM_{10}$ 24-hr average concentration, lag 0 | | 1.036 | 1.005 | 1.068 | 0.024 |
| Year | 2010 | 1.000 | | | |
| | 2011 | 0.412 | 0.236 | 0.719 | 0.002 |
| Work day | No | 1.000 | | | |
| | Yes | 5.021 | 2.075 | 12.150 | <0.001 |
| Holiday | No | 1.000 | | | |
| | Yes | 0.485 | 0.258 | 0.910 | 0.024 |

**Source:** Authors

## DISCUSSION

The most important results of our study showed that the association between increased $O_3$ concentrations and daily occurrence of any consultation for asthma symptoms in KM can be confirmed. They are comparable to the results of the study of Myers et al. [7], which is one of the studies most similar to our study in terms of the methodology employed (logistic regression was employed for modelling of the daily occurrence of any consultation for asthma symptoms). The results were also similar – $O_3$ (lagged two days) was statistically significantly associated with increased odds of at least one asthma medical visit per day. Our results are also similar to the results of a study performed by Ji et al. [10]. In their meta-analysis was reported that it was evident that number of consultations for asthma in children in emergency department was statistically significantly associated with $O_3$ levels. The results of our study indicate that problems in children with asthma in the KM occurred already when daily maximum 8-hr average was ≥ 70 μg/m³. This is consistent with WHO Air quality guidelines [26] and indicates that the attention we should be paid to adverse effects of $O_3$ in lower concentrations than are actual threshold values (8-hr average target value of 120 μg/m³).

There are several reasons that may account for these findings. Firstly, patients with respiratory diseases as well as mothers of children with chronic respiratory diseases in Slovenia are well-informed as to how to react in relation to their disease. A 4-day delay after exposure to high $O_3$ levels to the observed effect could be due to the fact that mothers of asthmatic children, particularly those who have been experiencing the disease of their child for some time, are able to manage their child's disease on their own. Only when the condition fails to improve they decide to consult a doctor. Since preventive notification of the population on the air pollution in Slovenia is also well-managed, as daily air pollu-

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tion levels are daily monitored by SEA, which promptly notifies the public, the mothers have additional information enabling them to react accordingly. Secondly, the children with a chronic respiratory disease have been already prescribed a therapy and the effects of air pollution with $O_3$ are less expressed. Thirdly, the Regional Institute of Public Health Koper (RIPHK) constantly provides information on adverse effects of the air pollution with $O_3$ in the region. The final reason could be the exposure misclassification since there is only one measuring station for monitoring air quality located in the region.

Our study has some limitations. Firstly, in the entire coastal region only one fixed air pollution measuring station is located, making detection of any differences between individual areas in the KM impossible. However, the air pollution may vary considerably between micro-locations [21]. The solution would be to evaluate exposure to polluted air by mathematical modelling [30, 31], and the study upgraded with a geographical analysis taking into account places of residence of children who sought medical attention for asthma or other respiratory diseases in the observation period. Secondly, we were able to use only the health data starting from 2010 because before 2010 the CHCK had used the old software which did not allow for a display of information needed for the analysis in our study. Consequently, we were limited to a very short observation period. Together with a small population this meant a relatively low frequency of the endpoint. However, the general problem in Slovenia with health data for the use in ecological research is the lack of uniform software for recording health data [32]. The final limitation might be that children without permanent residence in the KM coming to the doctor due to current health aggravation were included in the analysis. Particularly during summer months, there are many tourists staying in the KM, including many children. However, we established that 70% of children seeking medical assistance in CHCK came from the KM. We decided for this inclusion during the study, as the number of consultations for asthma was small from the aspect of analytical methods. On the other side, the study has also several strengths. Firstly, the results of the study themselves, which already in such a short time-series indicated positive association between observed phenomena, are the most important strength. Secondly, the present study provides important information for further work in the field of health promotion in the region. Finally, all methodological issues arisen during the study represent a new challenge for further work, particularly in the field of studying the association between environmental and health data on a population level, since the results and particularly the process itself provide information as to what should be improved if such studies are to be carried out in Slovenia in the future.

The present study brought several challenges for future research in the field, the most important being how to evaluate exposure more geographically precisely. This could be done only by mathematical modelling. Definite challenge would be to develop the methodology for studying the relationship between atmospheric pollution by $O_3$ and health phenomena in population on the level of small spatial units on such a complex terrain as

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is in the coastal area of Slovenia (mountainous region, coastal meteorology and weak winds that maintain sustainable high $O_3$ concentrations). Development of such a methodology would be of a huge importance for the planning and implementation of public health activities aimed at areas where there is a high concentration of vulnerable population. In doing so, attention should be paid to both, local residents and tourists. Swedish Environmental Research Institute has drawn attention to the problem of $O_3$ pollution in the southern Europe where the most serious problems occurred in densely-populated areas, often near the coasts, already over a decade ago [33]. The highest concentrations happened to occur in the most attractive tourist areas. This was especially the case in Athens and its surroundings, in parts of the coast of eastern Spain, and the Po valley in northern Italy [33], which is located in the immediate vicinity of Slovenija. Erlih and Eržen [23] concluded in their survey that transfer of $O_3$ air pollution from the industrial north of Italy seems to be the main cause of pollution with $O_3$ in the KM. The fact is that the highest $O_3$ concentrations occur in the coastal region in the summer when this region is on the western outskirts area of higher air pressure. In such situations the prevailing winds are weak west and south-west winds [18]. This hypothesis is supported by the results of other studies in Slovenia [34] and Italy [35]. In KM, such an area with a high concentration of vulnerable population (children and adolescents under 15), is the area of Debeli rtič Health Resort. More than 10,000 children are accommodated there in a season, among them a lot with chronic respiratory disease.

We can conclude that an increased number of consultations for asthma in children in the KM is associated with increased concentrations of $O_3$. Yet these conclusions must be evaluated in the light of the limitations of the study. Despite these limitations, we believe that this study brings new insights on how to manage the problem of $O_3$ in the coastal area of Slovenia. Our study also opened new challenges for future research. If they are resolved, evidence-based approach to public health activities in the field of environmental health in Slovenia would be strongly improved on this basis thereof.

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