Impact of Air Pollution on Daily Asthma Symptoms

Impacto da Poluição Atmosférica nos Sintomas Diários de Asma

ARTIGO ORIGINAL

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ABSTRACT

Introduction: The impact of air pollution on respiratory diseases, particularly in asthma, has been the subject of several studies. The impact of pollution on the daily symptoms of patients with asthma has been less studied. The aim of this study is to assess the association between the intensity of asthma symptoms and the variation of pollution levels.

Material and Methods: Patients with a diagnosis of asthma were instructed to record the intensity of their respiratory symptoms daily, expressed on a scale from 0 to 5, in the months of March and April 2018. The website of the Portuguese Environment Agency was consulted in order to obtain the daily levels of pollutants measured by the two local monitoring stations during the same period of time. Data was analyzed using a temporal causal model to study the association between pollutant levels – particulate matter, ozone, nitrogen dioxide and carbon monoxide – and the intensity of respiratory symptoms.

Results: From the 135 schedules delivered, 35 were correctly filled out and returned. The patient median age was 47.0 years, 18 being females. The best statistical model obtained identified ozone as the most relevant 'Granger cause' of asthma symptoms. Particulate matter, carbon monoxide and nitrogen also appeared as lower impact factors. The quality of the model was expressed by an R^2 of 0.92. The correlation between ozone values and asthma symptoms was more significant after five days. For the other identified factors there was a lag of four to five days.

Conclusion: In the place and period studied the air pollutants behaved as factors of variation in the intensity of asthma symptoms. The ozone level was the best predictive factor of symptom variation. Levels of particulate matter, carbon monoxide and nitrogen were identified as secondary markers. The time lag between the variables with the best correlation suggests there could be a delayed effect of pollutants on respiratory symptoms.

Keywords: Air Pollutants; Air Pollution; Asthma; Hypersensitivity

RESUMO

Introdução: O impacto da poluição atmosférica nas doenças respiratórias, nomeadamente na asma, tem sido objeto de numerosos estudos. A repercussão da poluição na sintomatologia diária dos doentes asmáticos tem sido menos estudada. Pretendemos estudar a relação entre a intensidade dos sintomas diários de asma e a variação dos níveis de poluição.

Material e Métodos: Foram selecionados doentes com diagnóstico de asma, sendo instruídos para anotar diariamente a intensidade dos seus sintomas respiratórios, expressa numa escala de 0 a 5, nos meses de março e abril de 2018. O *website* da Agência Portuguesa do Ambiente foi consultado e registaram-se os níveis diários de poluentes medidos pelas duas estações locais de monitorização durante o mesmo período. Os dados foram analisados utilizando um modelo causal temporal com a finalidade de relacionar os níveis de poluentes – partículas inaláveis com diâmetro menor que 10 µm, ozono, dióxido de nitrogénio e monóxido de carbono - com a intensidade dos sintomas de asma dos doentes.

Resultados: Dos 135 calendários entregues, 35 foram corretamente preenchidos e devolvidos. A mediana de idades dos doentes foi de 47,0 anos, sendo 18 do sexo feminino. O melhor modelo estatístico obtido identificou o ozono como a 'causa Granger' mais relevante para os sintomas de asma. A qualidade do modelo traduziu-se por um R^2 de 0,92. A correlação entre os valores de ozono e os valores dos sintomas de asma foi mais significativa após cinco dias. Para os outros fatores identificados verificou-se um desfasamento de quatro a cinco dias.

Conclusão: No período e local estudados, os poluentes atmosféricos comportaram-se como fatores de variação da intensidade dos sintomas de asma. O nível de ozono foi o melhor fator preditivo das variações da sintomatologia. Os níveis de partículas inaláveis, com diâmetro menor que 10 µm, de monóxido de carbono e de dióxido de nitrogénio foram identificados como marcadores secundários. O desfasamento temporal entre as variáveis com melhor correlação sugere um possível efeito retardado dos poluentes sobre os sintomas respiratórios.

Palavras-chave: Asma; Hipersensibilidade; Poluentes Atmosféricos; Poluição do Ar

INTRODUCTION

Outdoor air pollution is defined as the change in purity and air quality caused by the emission of chemical or biological substances released naturally or produced by anthropogenic sources.[1]

The contribution of human activities far exceeds natural sources, and several studies have shown that exposure to air pollution, in the short or long term, can have harmful consequences for health.[2-8]

Among the various pollutants present in the atmosphere, carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3) and particles smaller than 10 µm (PM10) are those with greatest evidence for health effects.[9-12] The evidence for a causal relationship of asthma with ambient pollution is still emerging, based on studies that have

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repeatedly shown associations of pollution with various asthma phenotypes and proxy markers, such as emergency room visits, school absenteeism, and steroid dependency.[13-15] In a Lancet Planetary Health publication, Pattanun Achakulwisut *et al*[16] estimated that 4.0 million (95% UI 1.8 – 5.2) new childhood asthma cases could be attributable to NO_2 pollution annually, accounting for 13% of the worldwide incidence. NO_2, mainly emitted by power generation, industrial and traffic sources, is an important constituent of particulate matter and ozone. There is increasing evidence that, independently, NO_2 can increase the symptoms of bronchitis and asthma, as well as facilitate respiratory infections and reduce lung function and growth.[17] Moreover, it may be responsible for premature death and increased morbidity associated with a broad spectrum of cardiovascular and respiratory conditions.[18,19]

Ozone in the lower atmosphere, to which humans are potentially exposed, is one of the major health risks associated with respiratory problems, such as asthma, reduced lung function and respiratory diseases. It is produced when carbon monoxide, methane or other volatile organic compounds (VOCs) are oxidized in the presence of nitrogen oxides (NOx) and sunlight.[20] One study in children reported higher propensity to develop asthma in areas with higher concentrations of ozone,[21] Li X *et al* report that maximal values of exposure measured daily in one or eight hour periods were more consistently associated with asthma exacerbations than 24 hour average exposure during the warm season[22] and Mengmeng Xua *et al* indicated that acute ozone exposure induces mitochondrial dysfunction and NLRP3 inflammasome activation, inducing airway inflammation and bronchial hyperresponsiveness.[23]

PM10 represents a particular health risk because it is able to enter the lungs and the bloodstream. Co-exposure to diesel and aeroallergens has been shown to increase levels of allergen-specific IgE, asthma severity, and bronchial hyperreactivity.[24,25] According to the World Health Organization (WHO), the acceptable daily exposure limit for PM10 is 50 µm/m^3. Annual mean values for PM10 should not exceed 20 µm/m,[3,26] or otherwise else ways the health impact associated with this pollutant could increase.

According to the WHO, some cities in Portugal, such as Albufeira, Almada, Aveiro, Barreiro, Coimbra, Estarreja, Faro, Loures, Marateca, Odivelas, Perafita, Portimão, Santiago do Cacém, Senhora da Hora, Setúbal and Sines are the cities with the highest levels of PM10 (exceeding 20 µm/m^3 annual average).[27]

Some studies demonstrate the ability of air pollutants to affect the course of asthmatic disease in different ways: acting as triggering stimuli; increasing pre-existing inflammation of the airways and/or modifying the response to aeroallergens or substances that act as irritants to the airways.[10,26]

The aim of this study is to study the impact of O_3, NO_2, CO and PM10 variations on intensity of asthma symptoms.

MATERIAL AND METHODS

Geographical area and monitoring stations

The Setúbal municipality occupies an area of 230.33 km^2.[28] The city of Setúbal lies in the eastern zone and accounts roughly for half of this area. The monitoring stations are implanted in the urban area and are separated from each other by a short distance, with Arcos being classified as a 'background' (i.e., not under the direct influence of traffic lanes or any nearby source of pollution) and Quebedo as a 'traffic' station (i.e., located close to high traffic routes allowing the evaluation of the maximum risk of population exposure to car traffic emissions) (Fig. 1).

Population

Among patients observed in the Immunoallergology Department of Setúbal Hospital in January and February 2018, those with asthma diagnosis and living in the city of Setúbal were invited to participate in the study, with their consent.

Patients with other pulmonary or cardiac diseases were excluded, as well as patients with history or clinical signs of respiratory infection during the study period or until 6 weeks before.

Only fully completed inquiries were considered.

Schedule

A calendar of March and April 2018 was given to each patient, and they were instructed to record the intensity of bronchial symptoms (shortness of breath, chest tightness, cough, wheezing) in each day, expressed on a visual analogue scale, graded 0 to 5: 0 - "no symptoms", 1 - "very few symptoms", 2 - "slight symptoms", 3 - "moderate symptoms", 4 - "severe symptoms", 5 - "unbearable symptoms".

In the case of children, the calendar was filled by their legal representative(s).

Pollution indices

The website of the Portuguese Environment Agency (APA) was consulted in order to extract data on the daily levels of pollutants measured by two monitoring stations, one 'background' and one 'traffic', from the same region and in the same period of time (March and April of 2018). The available data was the daily maximum values of O_3 at the 'background' station, the daily maximum values of NO_2 and CO at both stations, and the average daily PM10 in both stations.

Statistical treatment of data

Possible causal relationships between levels of pollutants and asthma symptomatology were analyzed, using an autoregressive time series model based on the concept of 'Granger causality', that provides a probabilistic approach for determining whether one time series is useful in forecasting another.

The scores recorded by the patients in each day were added together in order to obtain a day score. The resultant variable, the Sum of the Scores of Asthma Symptoms (SSAS), served as the dependent variable of our model. As

independent variables the PM10, O_3, NO_2, SO2, CO levels of both stations were used.

For correlation between variables Pearson's coefficient (r) was calculated.

Statistical analysis was performed using SPSS for Windows, version 23.0 [29].

The study was authorized by the Ethics Committee for Health of the Setúbal Hospital.

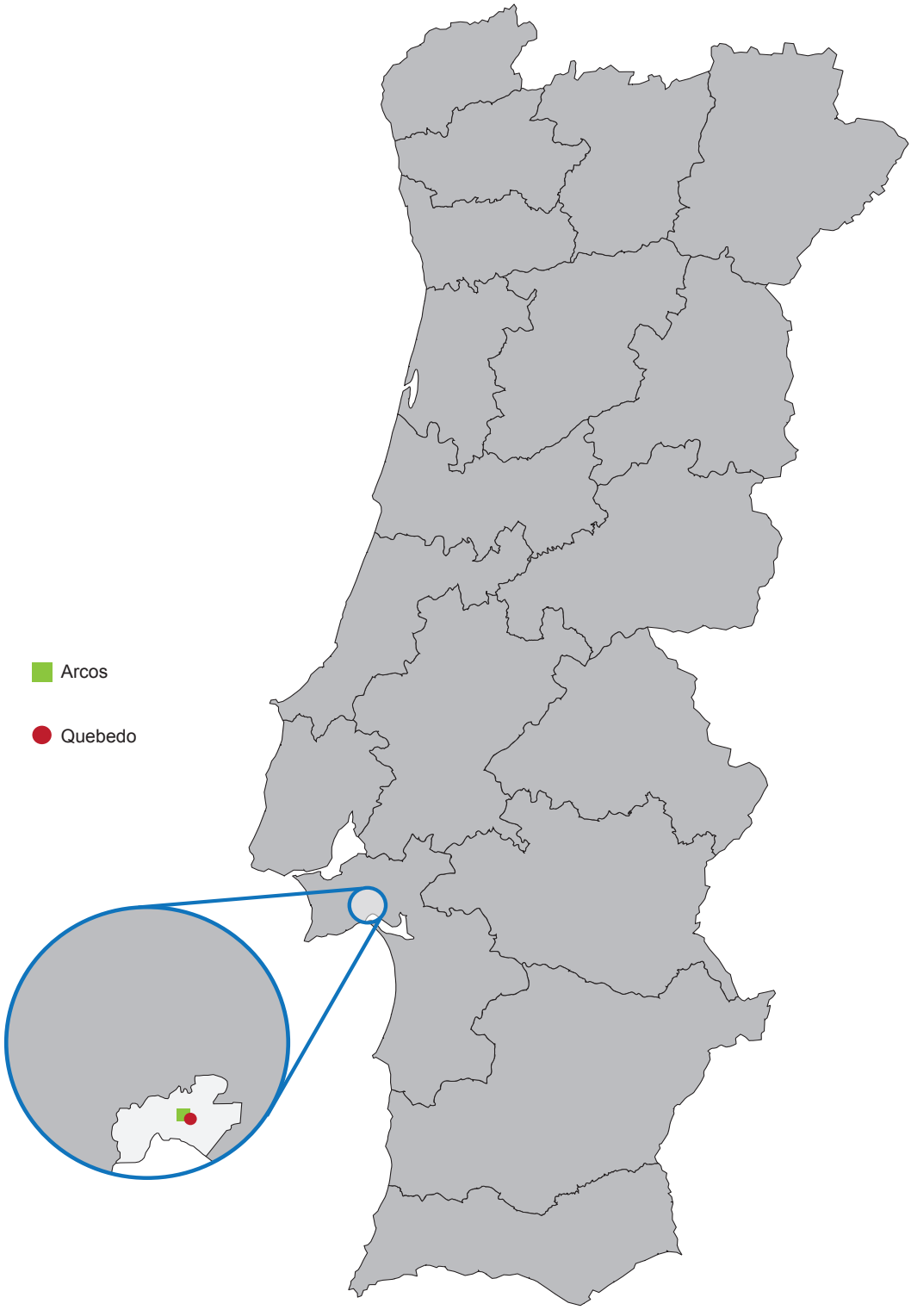

Figure 1 – Map of Portugal with the city of Setubal signposted on the right. On the left, the city of Setúbal, in white, with monitoring stations: green mark for Arcos and red mark for Quebedo.

Map of Portugal obtained in the site of Judicial Court of the Council of Setúbal. [accessed 2019 Aug 2]. Available from: https://comarcas.tribunais.org.pt/comarcas/apresentacao_mp.php?com=setubal.

Map of monitoring stations in the city of Setúbal obtained in the site of Lisbon and Tagus Valley Regional Coordination and Development Commission. [accessed 2019 Aug 2]. Available from: http://www.ccdr-lvt.pt/pt/avaliacao-da-qualidade-do-ar-na-rlvt/8085.htm.

Both maps were remade in vectorial format, using the above mentioned sources, by Acta Médica Portuguesa.

RESULTS

Of the 135 calendars delivered, 35 were correctly filled out and returned. The median age of patients was 47.0 years, ranging from 7 to 81 years, 18 being females (51.4%). Nine patients were younger than 18 years.

In the model, the O_3 measured in the 'background' station appears as the main impact factor in asthma symptoms, with a level of significance lower than 0.05 and a more significant correlation in Lag 5.

The model identified as factors of lower impact the CO (traffic station), NO_2 (background station) and PM10 (traffic station) with more significant correlations in Lag 5, 4 and 4 respectively. Fig. 2 shows the respective impact diagram.

Fig. 3 demonstrates the time evolution of the series studied expressed in Z scores, that is, each value corresponding to its distance from the mean in terms of standard deviation.

The R^2 of the model was 0.92 and the root mean square error was 0.05. Fig. 4 represents the expected and observed values of SSAS.

Considering the values from the two stations the Pearson's r for each pollutant were: NO_2 0.88, CO 0.65 and PM10 0.87.

The mean value of NO_2 was higher in the 'traffic' station; the values of CO and PM10 were similar in the two stations (Fig. 5). The averages of the variables included in the model were: SSAS 37.9 ± 7.7; O_3 97.3 µg/m^3 ± 8.9; NO_2 26.9 µg/m^3 ± 15.1; CO 0.23 mg/m^3 ± 0.07; PM10 19.7 µg/m^3 ± 7.9.

During the period studied every day had an air quality index classified as 'good', according to the Portuguese Environment Agency.

DISCUSSION

Ozone appeared as the main predictor of asthma symptoms in our model, with the most significant correlation between O_3 values and asthma symptoms after five days (Lag 5). For the other identified factors (PM10, CO, NO_2) there is a lag of four to five days (Lag 4 and 5). The late effect of pollutants on respiratory symptoms has already been described in the literature, and Bakonyi *et al*[19] reported a relationship of O_3 with respiratory diseases, which was only significant when the 3-day moving average of O_3 was used.

The model we present demonstrated good quality, with 92% of the variation of asthma symptoms explained by the variations of the identified factors (R^2 = 0.92) and a root mean square error, that is, a percentage difference between expected and observed values for the asthma symptoms of only 5%.

By using a statistical model based on the 'Granger causes' we are really looking for a relationship in which the values of a variable correlate with values of the target variable at a later time. In fact, this relationship is necessary but not enough to affirm a variable as the cause of another.

In fact, the proinflammatory effect of diesel exhaust particles on the respiratory epithelium level, which includes the release of cytokines involving Th17 cell differentiation observed in severe asthma, is documented in the literature.[32] Epidemiological studies in humans and animals suggest that atmospheric pollutants are involved in the pathogenesis of respiratory allergic diseases, both in terms of their development and exacerbations.[25]

Bakonyi *et al*[19] demonstrated a positive association between particulate pollutants, NO_2 and O_3, and respiratory diseases in children, by measuring daily levels of PM10, NO_2 and O_3 and assessing their association with daily am-

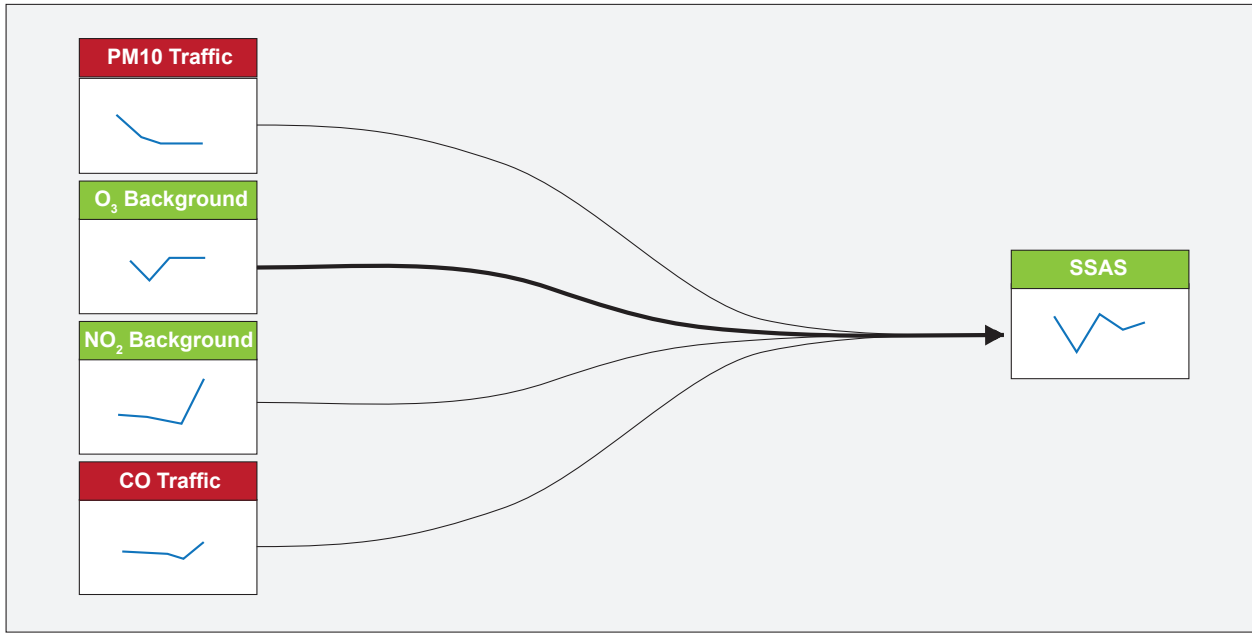

Figure 2 – Impact diagram of pollutants on the sum of the scores of asthma symptoms (SSAS). The thickness of the connection lines is proportional to the size of the impact. O_3 shows the highest impact.

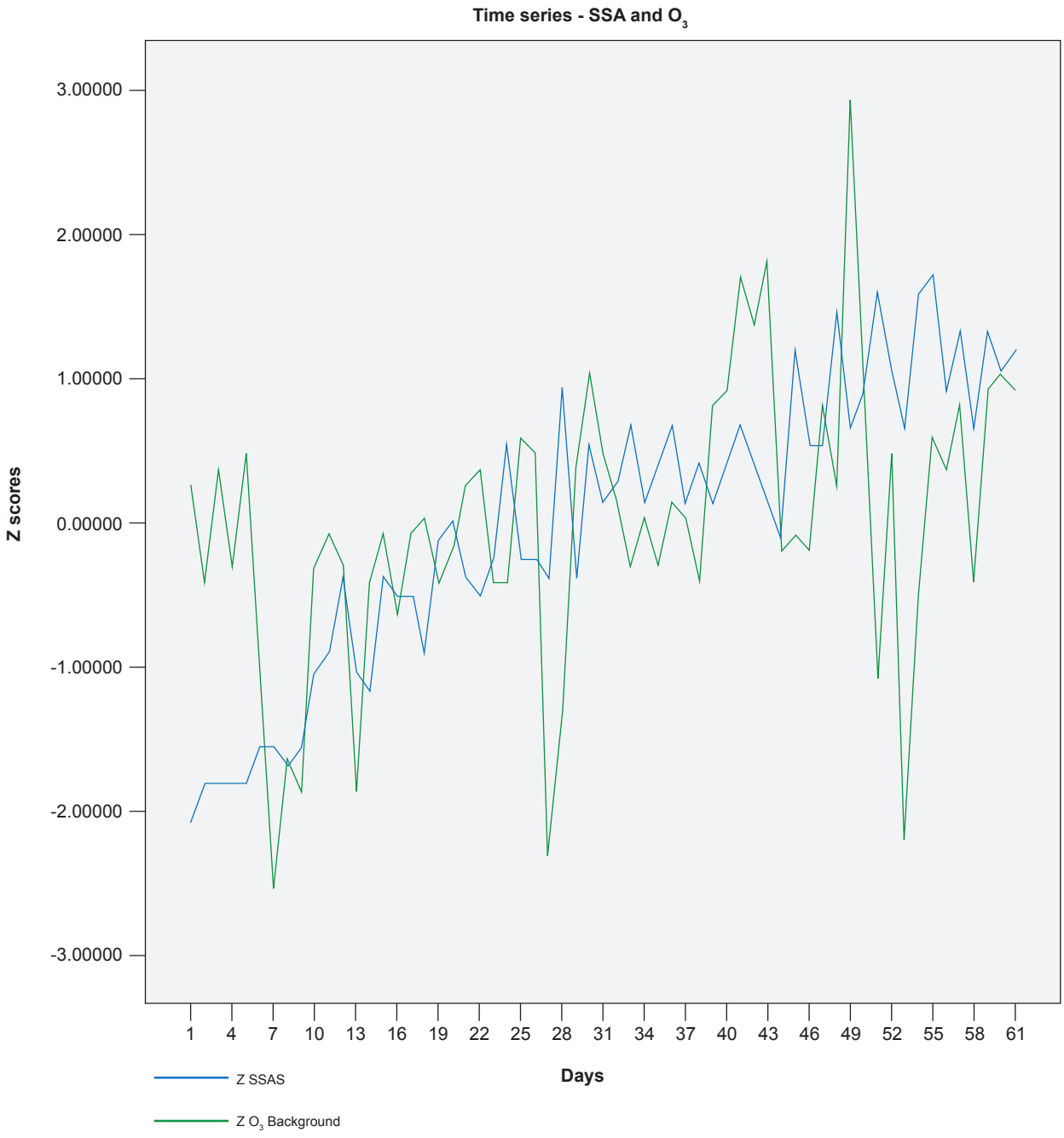

Figure 3 – Evolution lines of the sum of the scores of Asthma symptoms (in blue) and ozone (in green), values expressed as z scores. It is possible to observe an almost parallel variation of z scores of SSAS and O_3.

bulatory visits for respiratory disease (ICD-9 between 460 and 519). Although Bakonyi *et al* did not specifically correlate asthmatic disease with the levels of air pollutants, they were able to verify that the levels of pollution interfered in the respiratory morbidity of the child population of the city of Curitiba.

As for Portugal, only a few articles have focused on the impact of pollution on asthma and none of them concerns our region, Setúbal. Besides, these studies disclosed associations between pollutant levels and emergency room visits for acute effects,[30] or with causes of death by region for long term outcomes.[31] Our study presents an original approach, allowing an insight into the effects of low-level pollutant exposure on chronic mild symptoms evaluating the daily symptom variation rather than severe asthma events.

The months of March and April were selected to avoid the seasonality of respiratory infections, as well as high levels of atmospheric pollens, thus reducing the effect of confounding factors.

By aiming to obtain a daily symptom index for a two-month period we chose a very simple way of recording consisting of filling a calendar with a global assessment of symptoms according to a visual analogue scale, with the aim of minimizing dropouts. Even so, the study demanded

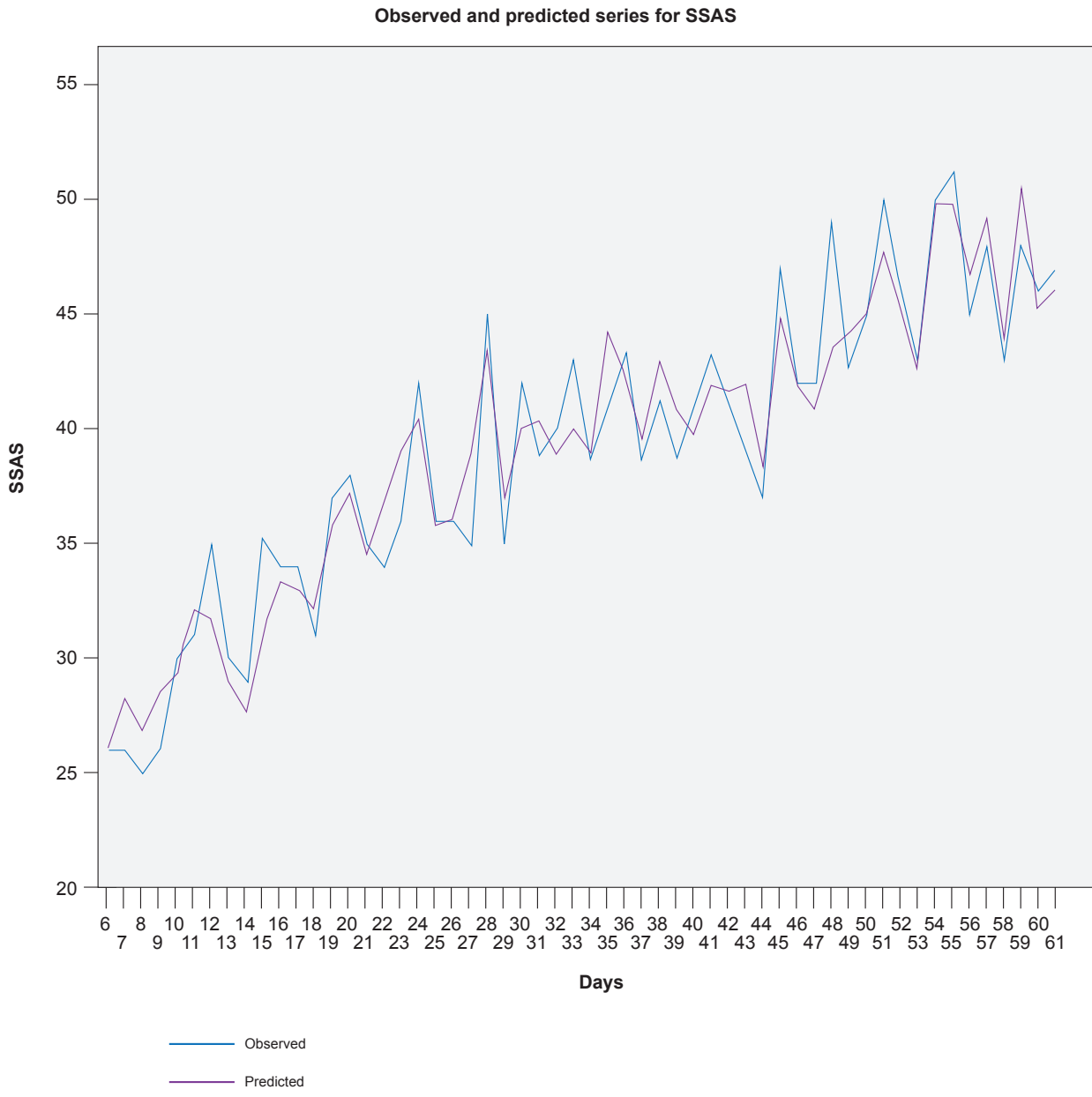

Figure 4 – Evolution of the observed and expected series concerning the sum of the scores of asthma symptoms (SSAS). It is possible to observe the overlap between the two lines, reflecting the good model quality.

a high level of patient collaboration which reflected on the small sample size. This implied some limitations with the analysis, with other potential, demographic, socioeconomic or clinical factors not being considered. However, it was compensated to some extent by the fact that all the accepted inquiries were fully completed.

The pollutants that were analyzed were necessarily restricted to those provided by the APA website, and it was not possible to include others mentioned in the literature that are implicated in respiratory symptoms. This also was a limitation of our study.

It should be noted that our results suggest an association between pollution and the daily fluctuations of asthma symptoms, which do not necessarily correspond to significant exacerbations of the disease. We also underline that this relationship was identified at a time in which the air quality index was always classified as 'good', suggesting that even acceptable levels of pollutants may have some effect on asthma symptoms.

CONCLUSION

All the air pollutants studied behaved as factors of variation of the intensity of asthma symptoms in the place and period that were examined. During this period the O_3 level was the best predictive factor of symptom variability. Levels of PM10, CO and NO_2 were identified as secondary markers. We also verified that the time lag between the variables with the best correlation suggests there could be a delayed effect of the pollutants on the respiratory symptoms, and even levels of pollution which are considered acceptable

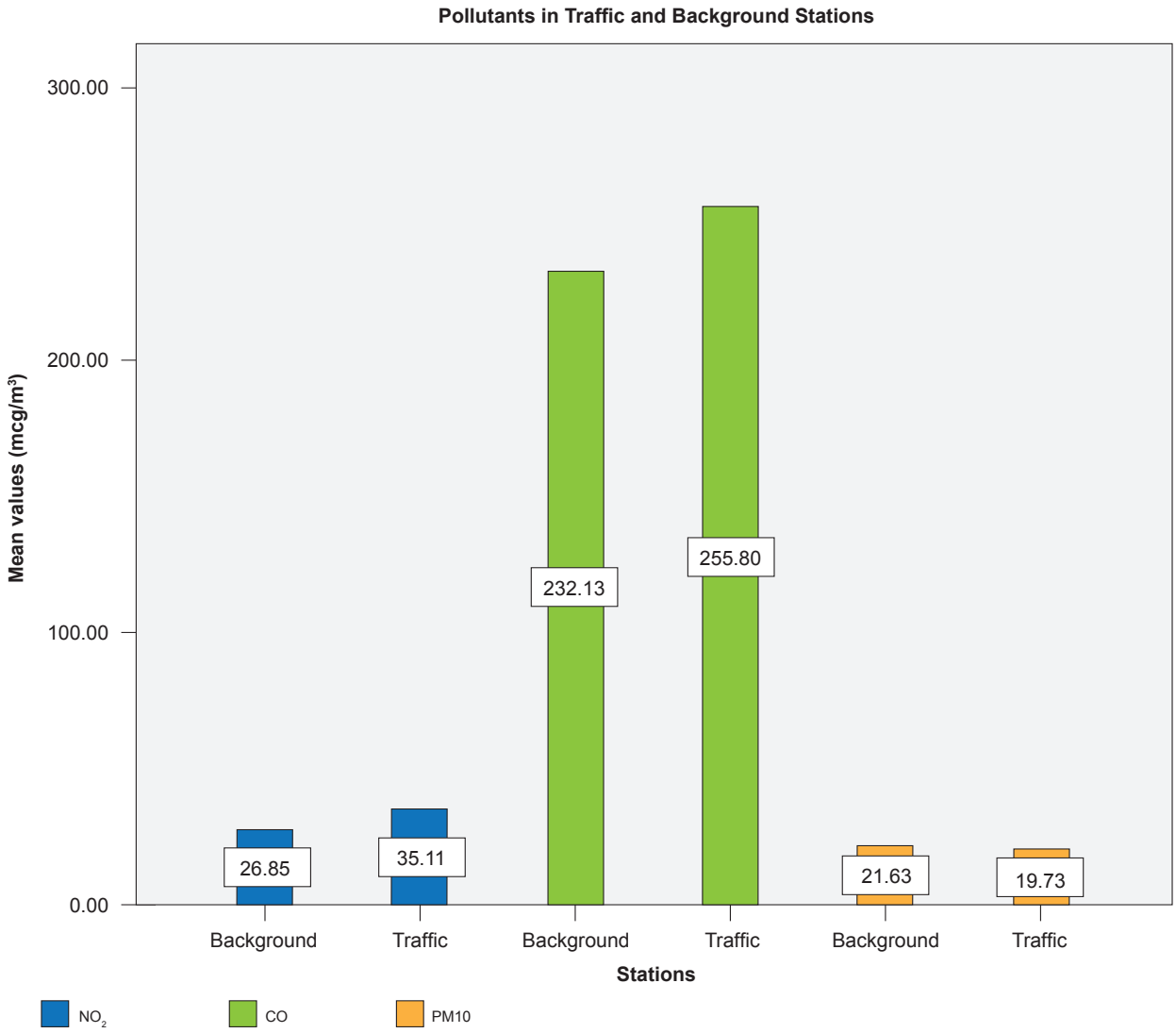

Figure 5 – Average of pollutant levels recorded at the two monitoring stations

may have repercussions on asthma symptoms.

A better understanding of the pollutant-related effects on asthma at a global level is crucial in order to implement policy initiatives aimed at addressing the improvement of asthma outcomes.

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AUTHORS CONTRIBUTION

SF, BKC: Data aquisition, conception of the paper, draft and critical review.

MM: Critical review, approval of the vinal version of the manuscritp.

LC: Data aquisition, analysis of the leaflets.

ET: Statistic analysis, draft and critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

None of the authors has conflict of interests to declare.

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