

Original article

Air pollution and seasonal asthma during the pollen season.
A cohort study in Puertollano and Ciudad Real (Spain)

Background: Many studies have demonstrated a positive association between air pollutants and emergency visits for asthma. However, few studies have included pollen when analysing this relationship in mild–moderate asthmatic patients.

Objective: To determine the importance of the pollutants such as ozone (O₃), particles (PM₁₀), nitrogen dioxide (NO₂) and sulphur dioxide (SO₂) in the clinical course of mild–moderate pollen-allergic asthmatic patients from two Spanish towns in La Mancha: Puertollano (high pollution levels) and Ciudad Real (low pollution levels).

Methods: We used a Poisson regression model to study a cohort of 137 patients from Puertollano and Ciudad Real during two pollen seasons (2000–2001) and analysed the relationship between air pollutant and pollen levels and daily symptoms, the medication used and peak-flow measurements.

Results: The number of asthma symptoms and the mean values of the PM₁₀, SO₂ and NO₂ levels were higher in Puertollano than in Ciudad Real. In Puertollano, the risk of asthma increased by 6% with a 3-day lag for PM₁₀, by 8% with a 3-day lag for O₃, by 4% with a 1-day lag for SO₂ and by 15% with a 3-day lag for O₃ when its values exceeded the health threshold ($P < 0.05$).

Conclusions: The air pollution levels in Puertollano were associated with an increased risk of asthma symptoms in pollen-allergic asthmatic patients compared with a similar group from Ciudad Real.

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There has been a significant increase in the prevalence and severity of allergic diseases in the industrialized countries, with a higher incidence of allergic symptoms in urban environments than in rural areas, particularly with respect to pollen-induced symptoms. Furthermore, the changes caused by industrialization have led to a pronounced increase in the levels of pollution in cities. We have an example of this in Japan, where the diesel vehicle fleet increased 500 fold and the quantity of aromatic hydrocarbons derived from the diesel exhaust increased 1000 fold (1, 2). Many studies in the United States, Europe and Australia, have shown that the number of asthma-related visits to emergency departments and hospital admissions increase proportionally with the increase in certain pollutants [ozone (O₃), particles (PM₁₀), nitrogen dioxide (NO₂) and sulphur dioxide (SO₂)] (3–5). However, there are fewer studies which have evaluated other health indicators of lesser severity such as symptoms of asthma, spirometric changes and the use of asthma medication. These studies have enabled the relationship between pollutants and exacerbations to be observed in less severe (mild–moderate) asthma, which affects a broader spectrum of the population.

Similarly, several experimental and laboratory studies suggest a close relationship between pollens and environmental pollution. For example, exposure to ozone reduces to one half the dose of pollen necessary to produce a decrease of 15% in the forced expiratory volume (FEV₁) compared with noncontaminated air (6). Exposure to NO₂ and to particles (PM₁₀) (7, 8) increases the asthmatic response in subjects allergic to grass pollens. There are few epidemiological studies in which the relationship between pollutants, pollens and visits to emergency departments due to asthma crises has been analysed, and their results have been controversial; this may be because, as the study periods were not limited to the months of pollination, possible interactions between pollens and pollutants could be masked by the effects of the pollutants, which have a stable repercussion throughout the year (9, 10).

The objective of this study was to determine the role of pollutants on the clinical course of patients with mild–moderate, pollen-allergic asthma, living in two cities with different levels of pollution. To reduce the confounding factors between pollens and pollutants, the study was limited exclusively to the pollination season.

Material and methods

Study areas

Puertollano (population: 50 000, land area 224 sq.km) and Ciudad Real (population: 65 000, 286 sq.km) are two towns from Castilla-La Mancha, situated in the centre of Spain, in a flat region with a uniform vegetation. This area has a dry, continental climate and has extreme temperatures. The pollination period is short and intense, lasting about 6 weeks (the month of May and first half of June), with grass and olive being the most important allergenic pollens in the region (11). The socioeconomic activity is very different in the two cities. Puertollano is a highly industrialized city, with an oil refinery, a fertilizer factory and two thermal power stations. In contrast, Ciudad Real (38 km from Puertollano), the capital of the province, has principally administrative and service sector functions, lacking any industrial activity.

Subjects

We designed a cohort study of 3 years duration (1999–2001), covering two pollination seasons (2000–2001). The project was undertaken in four stages, with the participation of the Allergy Units of Puertollano and Ciudad Real. Stage one, patient inclusion, ran from October to March, 1999–2000. Each individual patient was only studied for one season. We included only mild–moderate seasonal asthmatics allergic to grass and/or olive pollen and who had resided in the study town for over 5 years. The second stage was performed during the month of April, giving the patients the case report form (CRF) and the peak expiratory flow rate (PEFR) measurement device. The third stage corresponded to the active collection of information. During this stage, the patients recorded the intensity of their symptoms, the use of medication and the daily peak-flow values in the CRF; the concentrations of pollens and pollutants were also quantified on a daily basis. Finally, in stage four, study closure, the CRFs were collected. Written informed consent was obtained from all participants; the study was approved by the Institutional Review Board.

Skin prick tests

Skin prick testing was performed on all selected patients using a standard battery of aeroallergens (ALK-Abello S.A., Madrid, Spain) according to the method described by the Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology (12). We included mites, Gramineae, Oleaceae, Chenopodiaceae, Plantaginaceae, Compositae, Fungi, and cat and dog dander. Only patients with sensitization to grass and/or olive pollen were selected.

Diary cards

In the month of April, all patients were given the CRFs and a Mini-Wright Peak Flow meter (Clement Clarke International Ltd., Birmingham, UK), and they were instructed on how to record all data during the pollination period:

- Subjective symptoms of asthma, recorded at the end of the day, on a scale of 0 to 3: (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms).
- Mini-Wright peak-flow measurement in the morning and at night, always recording the best of three consecutive measurements.

- Drug consumption: terbutaline as required (1 point per 500 µg dose), budesonide 400 µg/day (2 points), salmeterol 100 µg/day (3 points) and fluticasone 1000 µg/day (4 points). Oral steroids (6 points) could be added.

Aerobiological study

From 1st May to 15th June, the daily pollen concentration was measured in Ciudad Real using a Hirst-type Burkard 7-day volumetric spore trap (Burkard Manufacturing Ltd., London, UK). As Puertollano and Ciudad Real are only 38 km apart and the vegetation and altitude are similar in the two areas, the pollen values obtained were considered to be applicable to both cities. This assumption is based on data collected in another town in the province (Alcázar de San Juan), at a distance of 70 km from Ciudad Real. Over three consecutive years (1998–2000), another Burkard collector was installed in this city, and the data obtained on the concentrations of grass and olive pollens were similar to those of Ciudad Real (unpublished data). Allergen exposure was determined using the total daytime pollen counts collected every day during the study period.

Measurement of pollutants

The Environmental Quality Department of Castilla-La Mancha provided us with data from the Puertollano Surveillance Network (60 000 inhabitants), which has four measuring stations, and a mobile unit was installed in Ciudad Real (70 000 inhabitants) for the 45 days of the active collection of information. Levels of SO₂, NO₂, PM₁₀ and ozone were determined hourly in µg/m³. The pollutants studied were measured using the same methodology in both towns: AF21M SO₂ analyser (Environnement, S.A., France), AC31M nitrogen oxide analyser NO–NO₂ (Environnement), MPSI 100 suspended particle analyser (Environnement), and DASIBI 1008 ozone analyser (DASIBI, Cologno Monzese, Italy). For the analysis, we used the 24-h maximum of the hourly average levels of ozone, NO₂, SO₂ and PM₁₀. We also used the daily 1-h maximum ozone levels at any monitoring site to assess the 'ozone exceedances' (days of population alert for concentrations over 180 µg/m³) (13).

Temperature, relative humidity and barometric pressure measurements were recorded daily in Puertollano and Ciudad Real.

Statistical analysis

Poisson regression models with correction for overdispersion were used to evaluate the effects of the atmospheric pollutants and the pollen levels on the daily number of symptoms; linear and quadratic tendency terms were included to control the confounding seasonal effect. The effects of the atmospheric pollutants and the pollen levels for the day in question and the delayed effects up to 4 days were evaluated in multipollutant models for each city. From these models, we finally selected the lag-time that gave the strongest association for each air pollutant and pollen level.

Results

A total of 152 patients were identified as eligible for inclusion in the current analysis; seven patients withdrew in Puertollano and eight patients in Ciudad Real leaving a

final study population of 137 patients, 66 in Puertollano and 71 in Ciudad Real. The patients from each town presented similar demographic characteristics (Table 1), although a difference was observed in the male: female ratio ($P = 0.008$), with a higher proportion of males in Ciudad Real than in Puertollano (62% and 39.4% respectively).

In Table 2, it may be observed that the daily number of symptoms was higher in Puertollano (mean = 25.1) than in Ciudad Real (mean = 23.2). Peak-flow measurements did not show significant differences in the two cities. With respect to the concentration of pollutants, the mean PM_{10} in Puertollano was higher than in Ciudad Real (100.4 vs 81.6 $\mu\text{g}/\text{m}^3$). The mean NO_2 and SO_2 concentrations were also higher in Puertollano (55.4 and 97.7 $\mu\text{g}/\text{m}^3$ respectively) than in Ciudad Real (32.7 and 6.0 $\mu\text{g}/\text{m}^3$ respectively). The ozone levels were similar in the two cities, but the number of days on which the health threshold was

exceeded was much higher in Puertollano than in Ciudad Real (11 days vs 2 days).

Table 3 shows a positive linear correlation between the PM_{10} and the NO_2 levels only in Puertollano ($r = 0.67$), as was also found for the SO_2 and O_3 ($r = 0.54$). A positive correlation was observed between the Poaceae and Oleaceae levels ($r = 0.53$).

The results of the Poisson regression models for each city are presented in Table 4. These show a percentage increase in the number of symptoms for an increment in the interquartile range of the levels of atmospheric pollution and types of pollen. In Puertollano, statistically significant ($P < 0.05$) percentage increases were observed in the risk, close to 6% for PM_{10} at a 3-day lag, over 8% for the O_3 levels, and of 4% at a 1-day lag for SO_2 . Likewise, the days on which the O_3 threshold was exceeded carried a risk of 15% compared with the days on which this threshold was not exceeded. In contrast, in Ciudad Real, a statistically significant increase of 4% in the effect, with a 3-day lag, was only observed for *Olea europaea* pollen.

Table 1. Demographic characteristics of the study sample

Study sample	Ciudad Real <i>n</i> (%)	Puertollano <i>n</i> (%)
Sex		
Male	44 (62.0)	26 (39.4)
Female	27 (38.0)	40 (60.6)
Age* (years)		
<25	31 (44.9)	27 (40.9)
≥25	38 (55.1)	39 (59.1)
Smoking status*		
Never	56 (80.0)	55 (85.9)
Ever	14 (20.0)	9 (14.1)
Total	71 (51.8)	66 (48.2)

*Some figures do not add to totals due to nonresponse.

Table 3. Matrix of linear correlation coefficients between air pollutants and pollen levels in Ciudad Real and Puertollano

	Ciudad Real					Puertollano				
	PM_{10}	SO_2	NO_2	O_3	Poaceae	PM_{10}	SO_2	NO_2	O_3	Poaceae
SO_2	0.12					0.26				
NO_2	-0.07	0.24				0.67	0.36			
O_3	0.06	-0.02	0.03			0.22	0.54	0.36		
Poaceae	0.04	-0.14	-0.16	0.11		0.08	0.01	-0.01	0.19	
Olea	0.03	-0.26	-0.10	0.39	0.53	0.19	0.36	0.14	0.36	0.53

Table 2. Descriptive analysis of the number of symptoms, atmospheric pollutants and pollen levels in Ciudad Real and Puertollano

			Percentile distribution						
		Mean (SD)	Minimum	P10	P25	P50	P75	P90	Maximum
Ciudad Real									
No. of symptoms		23.2 (8.7)	5.0	11.0	16.0	24.0	30.0	34.0	47.0
Daily levels of	PM_{10}	81.6 (48.6)	31.0	45.0	53.7	72.0	87.5	119.0	399.0
	SO_2	6.0 (3.4)	2.0	3.0	4.0	5.5	7.0	10.0	26.0
	NO_2	32.7 (12.2)	8.0	19.0	23.0	31.5	43.0	50.0	67.0
	O_3	129.3 (22.4)	89.0	99.0	112.0	127.0	143.0	158.0	199.0
Exceedances of	O_3 [n (%)]	2 (2.1%)							
Puertollano									
No. of symptoms		25.1 (9.1)	3.0	12.0	18.0	28.0	31.0	35.0	42.0
Daily levels of	PM_{10}	100.4 (58.3)	32.0	44.5	59.0	84.5	128.2	180.0	346.0
	SO_2	97.7 (159.8)	2.0	5.0	8.0	37.5	135.0	249.3	1019.0
	NO_2	55.4 (27.4)	3.0	26.0	37.0	54.0	67.0	85.0	189.0
	O_3	111.3 (43.4)	43.0	67.0	81.0	109.5	127.7	153.0	271.0
Exceedances of	O_3 [n (%)]	11 (11.7%)							
Pollen									
Daily levels of	Poaceae	84.9 (113.3)	1.0	4.0	9.0	42.0	108.0	244.0	559.0
	Olea	100.1 (143.2)	0.0	2.0	7.0	38.5	108.0	339.0	596.0

Table 4. Effects of the levels of pollen and atmospheric pollutants on the number of symptoms in Ciudad Real and Puertollano

		Ciudad Real				Puertollano			
		(Lag)	IQR	%	(95% CI)	(Lag)	IQR	%	(95% CI)
Air pollutants									
Daily levels of	PM ₁₀	(1)	33	0.6%	(-2.0, 3.3)	(3)	69	5.6%	(0.2, 11.7)*
	SO ₂	(1)	3	1.9%	(-1.7, 5.6)	(1)	127	4.0%	(1.0, 7.1)*
	NO ₂	(4)	20	2.5%	(-3.1, 8.4)	(3)	30	-2.4%	(-7.7, 3.3)
	O ₃	(4)	31	0.9%	(-5.6, 7.9)	(3)	48	8.5%	(2.2, 15.2)*
Exceedances of	O ₃	(0)		9.4%	(-10.7, 34.0)	(0)		15.3%	(3.7, 28.2)*
Pollen									
Daily levels of	Poaceae	(0)	99	0.8%	(-2.6, 4.2)	(2)	99	-0.4%	(-4.0, 3.4)
	Olea	(3)	101	4.1%	(1.0, 7.4)*	(4)	101	1.7%	(-1.2, 4.7)

* $P < 0.05$.

Discussion

The results of this study suggest that pollen-allergic asthmatic patients living in a more polluted region (Puertollano) present more symptoms of seasonal asthma than those living in a city with a low level of pollution (Ciudad Real). The poorer clinical course of the patients in Puertollano was significantly related to the environmental pollution (ozone, PM₁₀, NO₂, SO₂), evidenced by a greater severity of symptoms and a higher consumption of medication. Majority of publications on the effects of environmental pollution on the respiratory tract have included a number of different respiratory pathologies in the same study (chronic bronchitis, respiratory tract infections, exacerbations of asthma) (14, 15). Furthermore, the effects of pollution have often been evaluated using the relationship between the levels of pollutants and asthma-related hospital admissions or visits to emergency departments (3, 4, 16), leading to this association being more evident in the patients with severe asthma than in those with mild asthma (17, 18). In addition, studies in asthmatics have not usually distinguished between atopic and nonatopic aetiologies. The novelty of our study consists of selecting a homogeneous group of patients with mild-moderate pollen-allergic asthma. This restrictive selection criterion has allowed us to make comparisons unaffected by the dispersion factor created by the multiple aetiologies of asthma.

The interest in knowing the interaction between pollens and environmental pollution arose two decades ago with the study by Ishizaki et al. (2), who demonstrated the relationship between pollutants and a higher prevalence of pollinosis in areas close to motorways, compared with rural areas (with similar exposure to *Cryptonia japonica* pollen). However, it was the epidemiological studies by von Mutius et al. (19), comparing Munich (West Germany) and Leipzig (East Germany), that revealed the association between various pollutants and different pathologies. A predominance of asthma and atopy was found in Munich due to the pollution secondary to road traffic, whereas bronchitis was more common in Leipzig

due to the burning of fossil fuels as a source of energy. Five years later, with the new western lifestyle in Leipzig, there has been an increase of between 2.3% and 5.1% in the prevalence of pollinosis (20). Bates et al. (21) in Vancouver, Segala et al. (4) in Paris and Anderson et al. (10) in London associated SO₂ with visits to the emergency departments. In contrast, studies performed in Madrid (9), Rome (22) and Valencia (23) found no relationship between SO₂ and the hospital admissions for asthma. In Puertollano, the SO₂ concentrations reached very high levels, increasing the symptoms of allergic asthma by 4%. In contrast to other pollutants, this repercussion occurred with a delay of only 1 day, which could be explained by the direct effect of SO₂ on the smooth muscle or via sensory afferent nerve fibres that cause reflex bronchoconstriction (24).

In an experimental setting, Díaz-Sánchez et al. (25) have shown that the maximum effect of PM₁₀ occurs with a 3-day lag, associated with the late phase of the bronchial inflammatory response. In our study, the concentration of PM₁₀ was higher in Puertollano than in Ciudad Real; after a lag of 3 days, there was a 6% increase in the risk of asthma in the Puertollano group. Our results are consistent with other reports such as those published by Schwartz et al. (3) in Seattle, Galan et al. (9) in Madrid and Lipsett et al. (26) in Santa Clara.

Ozone shows a positive association with hospital admissions for asthma in epidemiological studies carried out in Valencia (21), Atlanta (16) and Mexico (27). Other studies, performed in Europe (APHEA project) (28) and Canada (21), did not find this association, probably due to the low levels of ozone during the study period. In Puertollano, the ozone presented a very peculiar behaviour. This secondary pollutant, generated by the action of sunlight on NO₂ in the presence of hydrocarbons and transported by the wind, is usually detected at a certain distance from the focus of emissions (29). However, in Puertollano, the ozone remained in the city, and frequently exceeded the levels recommended by the European Environment Agency. During the 90 study days (45 each year), a total of 18 ozone exceedances

(> 180 µg/m³ of air) were detected, five in the year 2000 and 13 in 2001 (29% of the days analysed). These episodes of pollution had a clear effect on the clinical course of the patients in Puertollano, causing an increase of over 15% in the symptoms and use of medication compared to the days on which this threshold was not exceeded. As occurs with the particles, the effect of the ozone also occurs with a 3-day lag. The exacerbation of asthma with exceedances of ozone has been reported by Cody et al. (30) in New Jersey (34 exceedances, 27% of the days analysed) and Romieu et al. (27) in Mexico (49 exceedances, 28%). In contrast, Bates et al. (21) in Canada, did not find this association, probably because there were only two exceedances per year.

It is common to find a relationship between the pollen concentration and the daily number of cases of asthma in the general population (10, 31), although a direct correlation is not always present as pollinic antigens derived from other parts of the plant or from the osmotic rupture of the pollen grains themselves also induce symptoms (32, 33). In our series, we have detected this relationship only with *O. europaea* pollen in Ciudad Real. This discordance may be due to the fact that we used a cohort of patients diagnosed with asthma and receiving anti-inflammatory treatment with inhaled corticosteroids, which could modify their clinical response. In our study, the variable to be explained is the total number of symptoms in the asthma group; here, the pollen does have an effect but does not increase the symptoms significantly. Furthermore, the proximity of the two populations (38 km) in a flat region with uniform vegetation, allows it to be assumed that the pollen concentrations are similar in Ciudad Real (where the Buckard collector was installed) and Puertollano. The association found for the *O. europaea* pollen in Ciudad Real is probably because the lower concentration of pollutants in this city compared with that in Puertollano means that the effect of the pollens becomes more visible.

Our study has certain limitations. First, the intensity of seasonal allergic asthma depends on the concentration of

airborne pollens which, in our area, is very variable and can vary by threefold from one year to another. The asthma suffered by a specific patient may thus be moderate-intense one year and mild the following year. Furthermore, there may have been a negative relationship between the PEF values and the concentration of pollutants (5), an aspect we have not been able to demonstrate in our study. The stable lung function values that we have found in our patients could be due to the fact that they were allowed to use inhaled corticosteroids and β-agonists, which probably prevented decompensation of the PEF. We have not determined the internal pollution (within the home), as the initial survey of the patients indicated that the presence of gas fires or cookers and smoking was similar in the two patient groups. Other pollutants, such as benzene and volatile organic compounds, could have been included together with the classical pollutants, but we did not have the appropriate technology available for their measurement.

In conclusion, taking in consideration the limitations of this study, environmental pollution appears to lead to a poorer clinical course of pollen-allergic asthma in the patients in Puertollano. As the most significant relationship occurs with ozone, it would be advisable to reduce the levels of this pollutant, and also to increase public awareness of the alert situations. In this way, by taking appropriate preventive measures, the risk for asthmatic patients could be reduced.

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