

## ORIGINAL PAPER

# Decompensation of pollen-induced asthma in two towns with different pollution levels in La Mancha, Spain

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## Clinical and Experimental Allergy

### Summary

**Background** Allergic diseases have increased in industrialized countries and this increase is associated not only with genetic factors but also with lifestyle and environmental factors such as air pollution. Our hypothesis was that asthma in pollen-allergic patients from two towns with very different pollution levels in La Mancha (Spain) could be affected to a very different degree.

**Objective** Our objectives were to assess the risk factors associated with decompensation of pollen-induced asthma in the two towns and to perform a comparison between the patients from Puertollano (high pollution level) and Ciudad Real (low pollution level) with respect to daily symptoms, medication used and peak-flow measurements.

**Methods** We designed a cohort study with 137 patients (66 from Puertollano and 71 from Ciudad Real), conducted over 3 years (1999–2001) and including two pollen seasons. The two populations presented similar demographic and clinical characteristics. The variables studied included: area of residence, sex, age, smoking status, asthma symptoms and positive prick tests. Clinical decompensation was monitored by symptoms recorded on diary cards, twice daily peak-flow measurements and the use of protocolized medication.

**Results** There was a clinically relevant relationship between the place of residence and clinical decompensation. The risk of clinical decompensation in patients from Puertollano was up to three times higher than that of patients in Ciudad Real ( $P = 0.034$ ). Furthermore, patients from Puertollano and patients with moderate asthma presented more rapid decompensation compared with patients from Ciudad Real ( $P = 0.020$ ) and patients with mild asthma ( $P = 0.049$ ).

**Conclusion** In conclusion, pollen-allergic asthmatics in Puertollano present a poorer clinical course and become decompensated earlier than those from Ciudad Real and it could be due to air pollution.

**Keywords** air pollution, asthma, asthma exacerbations, pollen allergy, risk factors

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### Introduction

The prevalence of atopic diseases has increased significantly in developed countries over the past 30 years. Genetic factors are unlikely to explain these rapid increases. This rising prevalence has been associated with marked changes in both lifestyle and environmental quality (e.g. a shift in the population to urban centres, a larger number of vehicles on the roads) [1]. Among the potential environmental factors, exposure to ambient air pollution has been under intensive debate. Exacerba-

tions of asthma may be triggered by various air pollutants and allergen responses are enhanced by exposure to certain pollutants, although exposure to air pollution alone does not necessarily increase the incidence of allergic diseases [2].

There have been a number of studies on the short-term effects of air pollution on hospital admissions, showing severe episodes of asthma rather than transient disturbances of lung function [3–5]. Panel studies are a type of cohort study conducted over a brief period with multiple measurements on the same individuals. The daily

recording of symptoms, drug consumption and peak expiratory flow rates (PEFR) and their correlation with the concentration of pollutants enables episodes of mild-moderate asthma that do not require emergency treatment to be detected. The strength of epidemiological studies is that they measure the actual environmental exposure and effect in representative human populations and can be often generalized to the broader population without extrapolation.

For the present study we selected two cities in Castilla-La Mancha (Spain) which, due to their geographical proximity, shared the same types of pollens but which presented very different levels of pollution. The first was Puertollano, with an intense industrial activity generating a variety of primary and secondary pollutants that frequently exceed the maximum levels recommended by the European Environment Agency [6]. The other city was Ciudad Real, with a service-orientated economy, and a low level of pollution. Our hypothesis was that the pollen-allergic asthma patients in the two cities would present different degrees of affection of their asthma due to the environmental pollution. The objective of our study has therefore been to evaluate the risk factors associated with the clinical decompensation of allergic asthma in the two cities.

## Material and methods

### Study areas

Puertollano and Ciudad Real are two towns placed at tableland in the centre of Spain where cereal and olive cultivation is the most important agricultural income in these flat lands. Their pollen counts are similar because vegetation and weather is quite uniform so, we assumed that Puertollano and Ciudad Real pollen levels were the same. Puertollano, with 50 000 inhabitants, is situated 200 km south of Madrid and is the largest industrial nucleus of Castilla-La Mancha. Its industry includes the extraction and transformation of minerals and metals, an oil refinery, a fertilizer factory and two thermal power stations. Ciudad Real, 38 km from Puertollano, is a city of 65 000 inhabitants in which the principal activity is in the tertiary sector and in which there is no significant industrial activity.

### Patients

We selected a cohort of asthma patients referred to the Allergy clinics of Puertollano and Ciudad Real during 1999 and 2000 for suspected seasonal asthma. The study was conducted over 3 years (1999–2001) including two pollen seasons (1st May to 15th June) for the years 2000 and 2001. Every individual patient was only studied during one season. The inclusion criteria were: (a) mild-moderate seasonal asthma of at least 2 years duration according to

the International Consensus report on Diagnosis and Treatment of Asthma in Bethesda, Maryland 1992 [7]; (b) sensitization to grass and olive pollen; (c) resident for at least 5 years in the city under study; and (d) between 14 and 49 years of age. We rejected patients presenting any of the following exclusion criteria: (a) use of specific immunotherapy over the previous 2 years; (b) severe seasonal asthma; (c) perennial asthma; (d) sensitization to other allergens different from pollens; (e) severe associated organic disease, psychiatric disease or drug addiction. Written informed consent was obtained from all adult participants and written parental consent for children; the study was approved by the Institutional Review Board.

### Skin prick and laboratory tests

Skin prick testing was performed on all selected patients using a standard aeroallergen battery including mites, pollens, fungi, and cat and dog dander. Histamine chlorhydrate at 10 mg/mL and phenolated glycerol saline solution were used, respectively, as the positive and negative controls.

### Diary cards

Patients recorded three different variables each day during the study period (1st May to 15th June): (1) subjective symptoms of asthma, recorded at the end of the day, on a scale of 0–3: (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = intense symptoms); (2) peak-flow measurement using the Mini-Wright meter in the morning at night, always recording the best of three consecutive measurements; and (3) drug consumption according to the following protocol: non-decompensated group: budesonide 400 mcg/day and terbutaline as required were allowed; and the decompensated group: fluticasone 1000 mcg/day, salmeterol 100 mcg/day and terbutaline as required. Oral steroids could be added.

### Clinical decompensation

Based on the modified Bousquet et al. [8] criteria, we grouped the patients into four levels: (a) level 1: no symptoms of asthma, no drug consumption and no changes in the PEFR; (b) level 2: symptoms that did not require any increase in the permitted medication (short-acting bronchodilators as required and 400 mcg/day of inhaled corticosteroids); PEFR = 60–80% of the predicted value with <30% diurnal variation; (c) level 3: asthma symptoms that required long-acting bronchodilators and >400 mcg/day of inhaled corticosteroids; PEFR <60% of the predicted value with <30% diurnal variation; (d) level 4: as level 3 but with a diurnal variation of the PEFR >30%. The patients in levels 3 and 4 were considered to be decompensated and were evaluated by one of the study doctors.

### Statistical analysis

Odds ratios (OR) was used to determine risk factors for clinical decompensation. The variables included in the analyses were the area of residence (Ciudad Real vs. Puertollano), sex (male vs. female), age (younger vs. older than 25 years), smoking status (never vs. ever), asthma symptoms (mild vs. moderate) and positive prick tests (to a single pollen vs. several pollens). Adjusted ORs were obtained using logistic regression. Finally, the time to decompensation was analysed using the Kaplan–Meier method, assessing the effect of each risk factor on the time to decompensation using a Cox's regression model, simultaneously readjusting for all variables. The statistical analyses were performed using the Stata statistical package, version 8.0 (StataCorp., College Station, TX, 2003).

### Results

We selected 166 patients of which a total of 137 patients completed the study, 71 from Ciudad Real and 66 from Puertollano. We lost 14 patients; six of them before starting the study and eight of them during the study. We did not find differential drop-out between the two cities. The patients from each town presented similar demographic and clinical 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). The distribution of specific allergen sensitivities was equal in both towns (Table 2).

Table 3 shows the crude ORs for clinical decompensation and the adjusted ORs after adjusting simultaneously for all variables in a multivariate logistic regression model. Patients from Puertollano presented almost twice the risk of developing clinical decompensation than patients from Ciudad Real [OR = 1.95, (95% confidence interval (CI): 0.75–5.24)]. This increase in the risk rose to threefold [OR = 3.14, (1.09–9.04)] after simultaneously adjusting for all variables in the multivariate logistic regression model and this difference was statistically significant ( $P=0.034$ ). Females presented a higher risk of decompensation than males [OR = 2.64 (0.94–7.41)], showing marginal significance in both the crude ( $P=0.062$ ) and adjusted ( $P=0.064$ ) analyses. There were no differences by age, smoking status or positive prick tests. The risk of decompensation was three times higher in patients with moderate asthma than in mild asthmatics [OR = 3.61, (0.97–13.39)], but once again this only showed marginal significance ( $P=0.055$ ) after adjusting for all variables in the logistic regression model.

Figure 1 shows the survival functions for the number of days to become decompensated. Patients from Puertollano and patients with moderate asthma became decompensated faster compared with patients from Ciudad Real

**Table 1.** Description area of residence, air pollution levels and characteristics of the study sample

|                                | Ciudad Real   | Puertollano   |
|--------------------------------|---------------|---------------|
| Population                     | 65 000        | 50 000        |
| Land area (sq km)              | 286           | 224           |
| Pollen counts                  | Mean (SD)     | Mean (SD)     |
| Daily levels of <i>Poaceae</i> | 84.9 (113.3)  | 84.9 (113.3)  |
| Daily levels of <i>Olea</i>    | 100.1 (143.2) | 100.1 (143.2) |
| Air pollution levels           | Mean (SD)     | Mean (SD)     |
| PM <sub>10</sub>               | 81.6 (48.6)   | 100.4 (58.3)  |
| SO <sub>2</sub>                | 6.0 (3.4)     | 97.7 (159.8)  |
| NO <sub>2</sub>                | 32.7 (12.2)   | 55.4 (27.4)   |
| O <sub>3</sub>                 | 129.3 (22.4)  | 111.3 (43.4)  |
| Study sample                   | <i>n</i> (%)  | <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)      |
| Asthma symptoms*               |               |               |
| Mild                           | 3 (4.3)       | 30 (45.4)     |
| Moderate                       | 67 (95.7)     | 36 (54.6)     |
| Total                          | 71 (51.8)     | 66 (48.2)     |

\*Some figures do not add to totals due to non-response.

**Table 2.** Distribution of specific allergen sensitivities in Puertollano, Ciudad Real and both

|                                          | Both towns<br><i>N</i> = 137 | Puertollano<br><i>N</i> = 66 | Ciudad Real<br><i>N</i> = 71 |
|------------------------------------------|------------------------------|------------------------------|------------------------------|
| Only allergic to one pollen <i>n</i> (%) | 10 (7.3%)                    | 7 (10.6%)                    | 4 (5.6%)                     |
| Allergic to various pollens <i>n</i> (%) | 118 (86%)                    | 59 (89%)                     | 59 (83.1%)                   |
| Allergic to grass <i>n</i> (%)           | 93 (67.9%)                   | 61 (92.4%)                   | 32 (45.1%)                   |
| Allergic to olive <i>n</i> (%)           | 98 (72.5%)                   | 65 (98.5%)                   | 33 (46.5%)                   |

( $P=0.020$ ) and patients with mild asthma ( $P=0.049$ ). We also found that females become decompensated earlier than males, although this result was only marginally significant ( $P=0.064$ ). Finally, we found no differences in the survival functions by age, smoking status or positive prick tests.

### Discussion

Clinical decompensation in pollen-allergic asthma patients in two cities in Castilla-La Mancha was more marked in Puertollano than in Ciudad Real. The proximity

Table 3. Crude and adjusted\* odds ratios (OR) and 95% confidence interval (95% CI) for decompensation risk factors

|                        | Crude analysis    |         | Adjusted analysis* |         |
|------------------------|-------------------|---------|--------------------|---------|
|                        | OR (95% CI)       | P-value | OR (95% CI)        | P-value |
| Area                   |                   |         |                    |         |
| Ciudad Real            | 1                 |         | 1                  |         |
| Puertollano            | 1.95 (0.75; 5.24) | 0.129   | 3.14 (1.09; 9.04)  | 0.034   |
| Sex                    |                   |         |                    |         |
| Male                   | 1                 |         | 1                  |         |
| Female                 | 2.30 (0.88; 6.37) | 0.062   | 2.64 (0.94; 7.41)  | 0.064   |
| Age (years)            |                   |         |                    |         |
| <25                    | 1                 |         | 1                  |         |
| ≥25                    | 0.64 (0.24; 0.16) | 0.312   | 0.80 (0.30; 2.10)  | 0.647   |
| Smoking status         |                   |         |                    |         |
| Never                  | 1                 |         | 1                  |         |
| Ever                   | 2.12 (0.64; 6.38) | 0.142   | 1.84 (0.58; 5.87)  | 0.303   |
| Asthma symptoms        |                   |         |                    |         |
| Mild                   | 1                 |         | 1                  |         |
| Moderate               | 1.97 (0.59; 8.48) | 0.240   | 3.61 (0.97; 13.39) | 0.055   |
| Positive prick test to |                   |         |                    |         |
| A single pollen        | 1                 |         | 1                  |         |
| Several pollens        | 0.32 (0.07; 1.72) | 0.089   | 0.74 (0.14; 3.86)  | 0.721   |

\*From a logistic regression model adjusted by all variables simultaneously.

of the two cities meant that they were very similar not only in climatic and environmental aspects (similar exposure to pollen allergens), but also from an economic and socio-cultural point of view. The principal distinguishing factor was therefore the different levels of pollutants between Puertollano (an industrial city) and Ciudad Real.

Experimental studies have demonstrated that exposure to pollutants, particularly particulate matter and ozone, may enhance airway response to environmental allergens in susceptible individuals [9, 10]. In time-series studies there is still little information on this subject. Galan et al. [3], in Madrid, demonstrated an association between air pollution and asthma-related hospital emergencies and this effect was independent of airborne pollen concentrations. Likewise, Anderson et al. [11] investigated the interaction between pollens, pollutants and daily hospital admissions for asthma in London. They concluded that the pollutants showed a significant association with asthma crises, but that there was no convincing evidence that the effects of air pollutants and airborne pollens interact in causing hospital admission. In Finland, Rossi et al. [12] also reported a positive relationship between the total suspended particle concentration and asthma-related emergencies, but no association was observed between attacks of asthma and airborne pollen levels. Their studies are of long duration (36, 60 and 12 months, respectively), in contrast to our model of 6 weeks duration, limited to the pollen season. Perhaps in these cases, the presence of pollutants throughout the year could have hidden the

effect that the pollen could have had on the asthma patients, despite their high concentrations of grass pollen in London and birch pollen in Finland.

On the other hand, Lierl and Hornung [13], in Cincinnati, did find an association between exacerbations of asthma severe enough to require visits to the hospital and elevated concentrations of airborne pollen and small particles. Their study was limited to the months of April to October. However, we consider our model to be the most appropriate for evaluating the relationship between pollens and pollutants as all the patients were allergic to pollens and the observation period was limited to the period of high pollen counts in the province of Ciudad Real.

Decompensation occurred faster in the patients in Puertollano than in Ciudad Real, possibly due to environmental factors in Puertollano that accelerate this deterioration. Furthermore, the patients with moderate asthma became decompensated more rapidly than those with mild asthma. These results were similar to the series by Gent et al. [14] and Forsberg et al. [15] Asthma severity divides the patients into two levels of vulnerability to air pollution. Subjects with severe asthma were at a significantly increased risk of experiencing respiratory symptoms.

In conclusion, the pollen-allergic asthma patients in Puertollano presented a higher risk of clinical decompensation than those of Ciudad Real. Future studies in Puertollano may be able to determine the effect of the different pollutants on the poorer clinical course of asthma patients in this city.

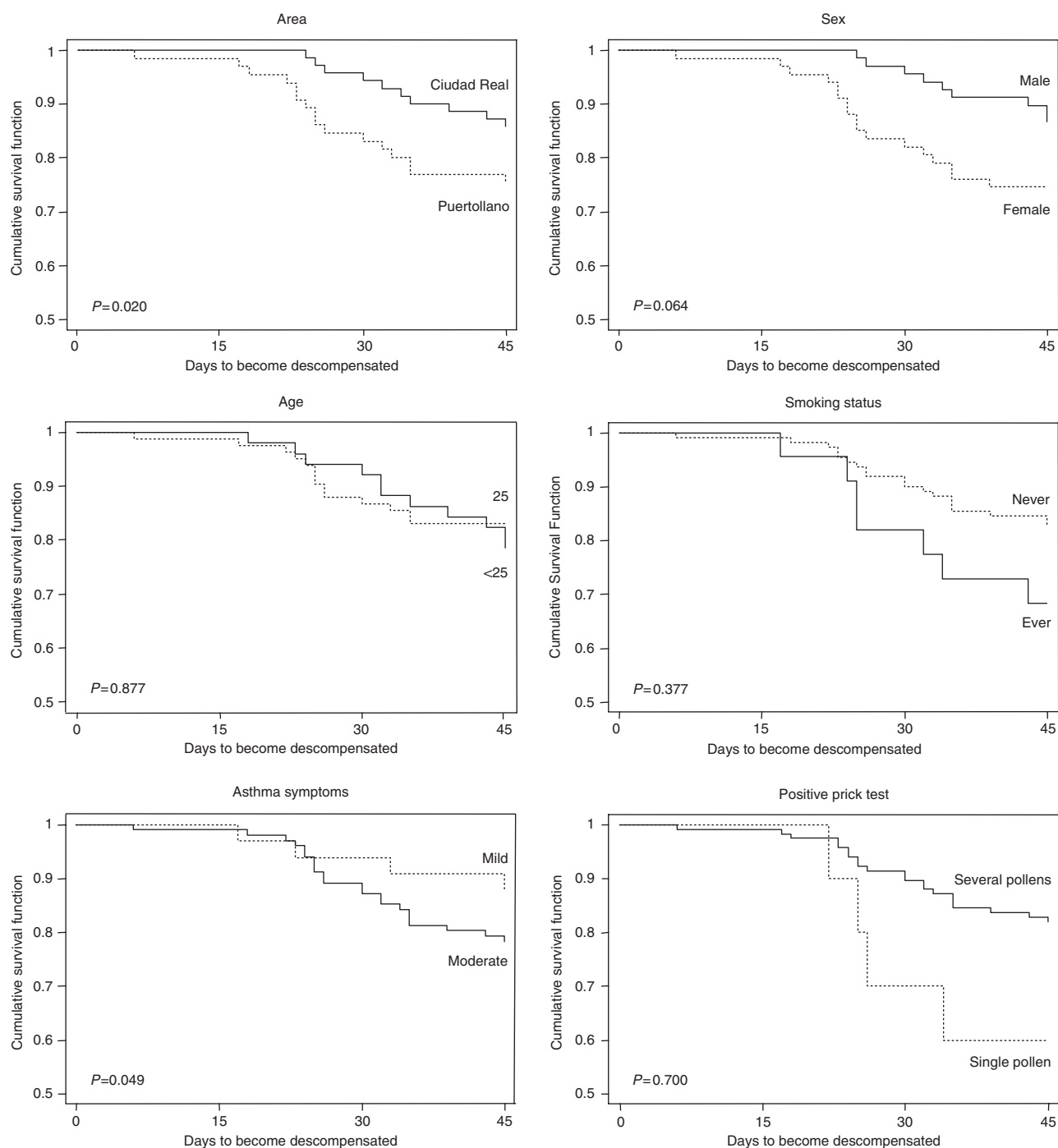


Fig. 1. Survival functions to become decompensated<sup>#</sup>.

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## References

- 1 von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000; **105**:9–19.
- 2 Díaz-Sánchez D. Pollution and the immune response: atopic diseases – are we too dirty or too clean? *Immunology* 2000; **101**:11–8.
- 3 Galan I, Tobias A, Banegas JR, Aránguez B. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J* 2003; **22**:802–8.
- 4 Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis* 1993; **147**:826–31.
- 5 Atkinson RW, Anderson HR, Strachan DP, Bland JM, Bremner SA, Ponce de Leon A. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. *Eur Respir J* 1999; **13**:257–65.
- 6 Fiala J, Cernikovský L, de Leeuw F, Livorova H. Air pollution by ozone in Europe in summer 2002. EEA Topic Report 6/2002, European Environment Agency, Copenhagen, Denmark.
- 7 Sheffer AL, Bousquet J, Busse W *et al.* International Consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992; **5**:601–41.
- 8 Bousquet J, Hejjaoui A, Clauzel AM *et al.* Specific immunotherapy with standardized *Dermatophagoides pteronyssinus* extract. *J Allergy Clin Immunol* 1988; **82**:971–7.
- 9 Jörres R, Nowak D, Magnussen H. Effects of ozone exposure on airway responsiveness to inhaled allergens in subjects with allergic asthma or rhinitis. *Am J Respir Crit Care Med* 1996; **153**:56–64.
- 10 Higgins BG, Francis HC, Yates C *et al.* Environmental exposure to air pollution and allergens and peak flow changes. *Eur Respir J* 2000; **16**:61–6.
- 11 Anderson HR, Ponce-de-Leon A, Bland JM, Bower JS, Emberlin J, Strachan DP. Air pollution, pollens, and daily admissions for asthma in London 1987–92. *Thorax* 1998; **53**:842–8.
- 12 Rossi OVJ, Kinnula VL, Tienari J, Huhti E. Association of severe asthma attacks with weather, pollen, and air pollution. *Thorax* 1993; **48**:244–8.
- 13 Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbation. *Ann Allergy Asthma Immunol* 2003; **90**:28–33.
- 14 Gent J, Triche E, Holford T *et al.* Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA* 2003; **290**:1859–67.
- 15 Forsberg B, Stjernberg N, Linné R, Segerstedt B, Wall S. Daily air pollution levels and acute asthma in southern Sweden. *Eur Respir J* 1998; **12**:900–5.