

Original article

The effects of allergens in outdoor air on both atopic and nonatopic subjects with airway disease

Background: Reports on air pollution and asthma exacerbations have been inconsistent, although effects of airborne allergen can be spectacular. With no generalized test for allergen in air, it is not known how far allergen is responsible for nonepidemic exacerbations of the disease.

Methods: Two hundred and ninety-seven patients using bronchodilators aged 18–64 years attending a London practice provided serum samples and were asked to report any acute respiratory events over the coming months. Small particles with a mean aerodynamic diameter $< 10 \mu\text{m}$ (PM_{10}) were collected using a high volume sampler on the roof of the practice. The ability of airborne particles to bind IgE from the patients was compared for particles sampled on the weekend before their reported exacerbation with particles sampled on the weekend 2 weeks before or after.

Results: Exacerbations were associated with a 25% increase in IgE binding to particles collected on the previous weekend compared with the control weekends (95% confidence interval: 10–43%; $P = 0.00089$). This increase was not higher in patients with positive skin tests or in those sensitized to grass or tree pollens.

Conclusions: Airborne allergen is an important cause of exacerbations even in those with 'intrinsic' asthma. It is important to identify the allergens responsible, as some of these may be controllable. Interpretation of associations of asthma exacerbations with other air pollutants is difficult in the light of these findings.

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Daily variations in levels of air pollution have been associated with changes in asthma morbidity. In London, variations in ozone levels have been associated with daily GP consultations for asthma (1), visits to accident and emergency rooms with respiratory complaints (2) and admissions for asthma (3) as well as total respiratory mortality. The data are, however, inconsistent. Neither of the two multicentre studies of acute air pollution effects using routine health data, Air Pollution and Health a European Approach (APHEA) I (4) nor APHEA II (5) found an association between hospital admissions from asthma and ozone levels. APHEA I found associations only with NO_2 and APHEA II with small particles. The study of GP consultations (1) also found an association with small particles but the Pollution Effects on Asthmatic Children in Europe (PEACE) study found no association between asthma exacerbations assessed through either symptoms or peak flow and PM_{10} (6) and only inconsistent associations with other pollutants (7). Some investigations of major air pollution episodes have specifically remarked on the lack of effect on patients with asthma, in marked contrast to patients with other chronic lung and cardiovascular diseases (8, 9).

In contrast, allergens have strong effects on sensitized individuals with asthma and are increased in the air at

times when pollution levels are also high. In the well documented epidemics of asthma in Barcelona, subsequently associated with release of soybean dust in the harbour area, the first associations published were with levels of oxides of nitrogen (10). The clue that this did not explain the epidemics came from the inconsistency of the association with periods of high general pollution levels unaccompanied by epidemics of asthma (11).

Some studies have attempted to test for the confounding effects of allergen by adjusting analyses for pollen counts and have shown weak main effects for pollens (3). This is, however, at best an incomplete method of assessing the effects of allergens as pollens are not themselves respirable particles, nor do they represent the full range of potential allergens in air.

In this study, we tested whether allergens in ambient air specific to individual subjects are associated with exacerbations of disease.

Methods

A clinical cohort of patients with obstructive airway disease was established and patients were asked to report exacerbations of disease. The analysis was as for a case-crossover design. The ability of

PM₁₀ to bind IgE from their serum was assessed using PM₁₀ collected on the weekend before their exacerbation and compared with PM₁₀ collected during a control weekend. The control weekend was randomly selected from that occurring either 2–3 weeks before or 2–3 weeks after a reported event for that patient.

All patients aged 18–64 years registered with the Gallion's Reach Health Centre in Thamesmead, South East London, who had been diagnosed with asthma or bronchitis or had been prescribed at least one bronchodilator in the last 12 months were invited to take part in the study. Subjects were invited to the health centre where they had an initial examination, answered a questionnaire, had pre- and postbronchodilator lung function measurements (FEV1 and FVC), had skin prick tests to house dust mite (*Dermatophagoides pteronyssinus*), grasses (Group B2 pollens: oat grass, crested dog's tail, cocksfoot, rye grass, meadow grass, vernal grass, bent grass, brome, meadow foxtail, Timothy, meadow fescue and Yorkshire fog), cat fur, trees (Group 3 pollens: silver birch, beech, common oak, alder, ash, hazel, poplar, plane, elm willow), *Alternaria alternata* (Bencard; Allergy therapeutics, West Sussex, UK), *Aspergillus fumigatus* (Soluprick; ALK-Abello, Hungerford, UK), German cockroach (Allergopharma, Reinbek, Germany; obtained through Allerayde, Nottingham, UK) and latex (Stallergenes SA, Marseilles, France). Histamine dihydrochloride (10 mg/ml) (ALK-Abello) was used as a positive control and diluent as a negative control. Skin tests were undertaken by puncturing the skin with a lancet through the skin test solution on the volar aspect of the forearm and read at 15 min. Any wheal size > 0 mm was taken as a positive result provided there was no reaction to the diluent control. Atopy was defined as a positive reaction to any one of the allergens tested. All subjects gave a blood sample from which serum was stored at –20°C.

All members of the cohort were given a mini-Wright peak flow meter (Clement Clarke International Limited, London, UK) to take home and were asked to report to the study nurse any 'acute respiratory event' defined by the criteria in Table 1.

Airborne particles were collected of a range of aerodynamic diameters with a mean cut-off of 10 µm using a high volume PM₁₀ sampler [Model No 312A, Graseby Anderson (AEA Technology; Harwell Laboratories, Harwell, UK)] located on the roof of the Gallions Reach Health Centre with a flow rate of 1.2 m³/s. Filters were changed daily except at weekends when the samples were collected continuously from Friday to Monday. The air sampler collected approximately 50 mg of particulate matter per 24 h.

Allergen was extracted from the filters using methods similar to those used by Spieksma (12) for the investigation of grass pollen proteins on sub-micronic airborne particles, using GF50 glass fibre hydrophilic paper. 2 × 18 cm strips cut from the filters were extracted for 2 h on a roller mixer in 1 ml coating buffer (50 mM carbonate/bicarbonate buffer, pH 9.5) [Na₂CO₃ 1.59 g, NaHCO₃ 2.93 g, dissolved in 1 l deionized water]. Extracts from the filters were fixed directly to the plastic ELISA plates (Dynatech Laboratories, Chantilly, VA, USA). After coating overnight the plates were blocked for 1 h with beef serum albumin in phosphate buffered saline and incubated with serum from the patients. After washing,

the plates were further incubated with labelled goat IgG against human IgE (Vector Laboratories, Burlingame, CA, USA) and read. The ratio of IgE binding to the extracts and that binding to an extract from a blank filter was used in the analysis as a binding ratio.

Hourly PM₁₀ values were provided from the local Greenwich monitoring station.

The baseline characteristics of the subjects were assessed and the rate of reporting exacerbations estimated for each month following recruitment. Baseline characteristics were compared between those reporting an exacerbation and those not. Rates of exacerbation were reported by months since entering the study and by season.

IgE binding ratios were compared using the same patient's serum against particle extracts from PM₁₀ collected on event and control weekends. First, the natural logarithm of the IgE binding ratios was regressed against the event or control weekend as a binary predictor to estimate the geometric mean ratio of IgE to particulate binding ratios and confidence intervals. Second, the event-control status was regressed as the outcome variable against the binary logarithm of IgE binding ratio as a continuous predictor variable in a logistic regression to calculate confidence intervals for the odds ratio for an event per doubling of IgE binding ratio. This estimates the corresponding per-doubling relative risk. For both methods, confidence intervals were calculated using standard errors clustered by subject.

Each of these statistical parameters was measured for the full set of event and control weeks for each subject and also for three subsets of subject-weeks. These subsets corresponded to (1) atopic subjects who gave a positive skin prick test for at least one of the seven antigens tested, (2) subjects giving a positive skin prick test for grass or tree pollen, and (3) subjects allergic to grass or tree pollen and reporting an episode in the months from April to August.

All analyses were performed using Stata (StataCorp 2005, Stata Statistical Software: Release 9.0; Stata Corporation, College Station, TX, USA).

Ethical permission for the study was obtained from the Local Research Ethics Committee at Greenwich Hospital. The purpose of the study was explained to the patients and they gave written consent.

Results

The clinic's patient database contained approximately 11 000 adult patients aged 18–64 of whom approximately 850 patients were eligible for the study. Of these, 297 participants agreed to take part in the study.

Table 2 shows that more women than men were included in the study with 42% having never smoked and 36% still smoking. Inhaled steroids had been taken in the previous 12 months by 74% of those in the study. Skin sensitivity to allergen was demonstrated in 55% of the sample and the commonest allergen was grass (35%).

The analysis is based on 94 episodes of acute respiratory symptoms reported to the nurse by 60 patients. Episodes were more likely to be reported in the months immediately after the initial examination, 60% (61) of reported episodes occurring in the first 3 months.

Table 3 shows that episodes were most commonly reported by those who were over 55 years old, but there was no clear association with sex, smoking history or use of inhaled corticosteroids in the previous 12 months. Nor

Table 1. Definition of an 'acute respiratory event'

'Yes' answer to any one of the following:

1. Symptoms of chest tightness, shortness of breath, wheezing, coughing or phlegm started or got worse
2. Waking with any of the above symptoms
3. Need to increase medication for breathing
4. Need to cut down on usual activities because of any of the above symptoms
5. Peak flow level fallen (if monitoring routinely carried out)

Table 2. Baseline characteristics of the 297 subjects included in the cohort

	Frequency	Percent
Sex		
Male	103	34.7
Female	194	65.3
Age group (last birthday)		
18–24	24	8.1
25–34	77	25.9
35–44	64	21.6
45–54	71	23.9
55–65	61	20.5
Current smoking status		
Never	125	42.1
Ex	66	22.2
Current	106	35.7
Inhaled steroids in previous 12 months		
Nonuser	77	25.9
User	220	74.1
Sensitization (<i>n</i> = 294)		
Cat	85	28.9
House dust mite	87	29.6
Grass pollen	102	34.7
Aspergillus	14	4.8
Cockroach	13	4.4
Latex	7	2.4
Alternaria	23	7.8
Tree pollen	50	17.0
Grass or tree pollen	118	40.1
Any allergen	162	55.1

Table 3. Associations of confounders with study events in 297 subjects

	Unadjusted rate ratio (95% CI)	<i>P</i>	Mutually adjusted rate ratio (95% CI)	<i>P</i>
Sex				
Male	1.43 (0.76, 2.67)	0.26	1.34 (0.75, 2.39)	0.33
Female	1.00 (ref.)		1.00 (ref.)	
Age group (last birthday)				
18–24	0.12 (0.03, 0.50)	0.007	0.13 (0.03, 0.54)	0.01
25–34	0.35 (0.17, 0.72)		0.39 (0.19, 0.80)	
35–44	0.35 (0.16, 0.78)		0.37 (0.17, 0.81)	
45–54	0.44 (0.21, 0.93)		0.47 (0.23, 0.94)	
55–65	1.00 (ref.)		1.00 (ref.)	
Current smoking status				
Never	1.00 (ref.)	0.14	1.00 (ref.)	0.57
Ex	1.77 (0.83, 3.79)		1.20 (0.56, 2.55)	
Current	1.73 (0.94, 3.20)		1.38 (0.76, 2.49)	
Inhaled steroids in previous 12 months				
Nonuser	1.00 (ref.)		1.00 (ref.)	
User	1.14 (0.61, 2.11)	0.68	1.00 (0.57, 1.76)	0.99
Positive skin test				
Cat	0.68 (0.37, 1.25)	0.22	1.03 (0.55, 1.95)	0.92
House dust mite	0.82 (0.43, 1.58)	0.56	1.01 (0.51, 1.98)	0.98
Grass pollen	0.65 (0.37, 1.16)	0.15	0.80 (0.46, 1.38)	0.42
Aspergillus	0.40 (0.06, 2.74)	0.35	0.50 (0.07, 3.70)	0.49
Cockroach	0.66 (0.16, 2.66)	0.56	0.63 (0.14, 2.83)	0.54
Latex	0.00 (–, –)	–	0.00 (–, –)	–
Alternaria	1.15 (0.52, 2.57)	0.73	1.37 (0.58, 3.24)	0.47
Tree pollen	0.85 (0.44, 1.64)	0.63	1.03 (0.54, 1.98)	0.93
Grass or tree pollen	0.69 (0.40, 1.20)	0.19	0.86 (0.51, 1.45)	0.57
Any allergen	0.74 (0.41, 1.32)	0.31	1.04 (0.56, 1.95)	0.9

Table 4. Geometric mean case/control ratio of IgE binding ratios

Study events	Subjects	Filters	Ratio (95% CI)	<i>P</i>
All subjects and seasons	60	188	1.25 (1.10, 1.43)	0.0008
Atopic subjects	32	88	1.23 (0.99, 1.52)	0.06
Subjects allergic to grass or tree pollen	23	62	1.26 (1.07, 1.48)	0.007
Grass or tree pollen allergics in summer	17	40	1.14 (0.88, 1.47)	0.29

Table 5. Odds ratio for case status per doubling of IgE binding ratio

Study events	Subjects	Filters	OR (95% CI)	<i>P</i>
All subjects and seasons	60	188	2.03 (1.27, 3.25)	0.003
Atopic subjects	32	88	1.77 (0.90, 3.46)	0.096
Subjects allergic to grass or tree pollen	23	62	3.19 (1.35, 7.53)	0.008
Grass or tree pollen allergics in summer	17	40	1.66 (0.73, 3.78)	0.23

was there any association with sensitivity to any of the allergens tested.

Taking all subjects together, the binding of patient serum IgE to PM₁₀ was 25% greater in the weekend before the episode than in the control weekends (*P* = 0.00089) (Table 4). This was equivalent to a doubling of the risk of an episode if the binding ratio doubled (*P* = 0.0032) (Table 5). There was no evidence that this effect was more pronounced in those who reacted to the skin prick tests, and although there was a slightly increased risk for those who were sensitized to pollens, this increase was not significant and the effect was not specific to the summer months when pollens are common.

The median of hourly PM₁₀ measurements taken at Greenwich during the study period was 16.1 mg/m³ (interquartile range 12.0–22.4). Only 286 (1.62%) of the 17 651 hourly PM₁₀ measurements were above the 24 h standard of 50 mg/m³ and the maximum recorded value was 220.7 mg/m³. There was no discernable association between episodes and PM₁₀ values.

Discussion

This study has shown that those experiencing exacerbations of airway disease are more likely to have IgE against small particulate air pollution at the time of the exacerbation than at control times 2–3 weeks before or after the exacerbation. This is strong evidence that airborne allergen in outside air contributes to exacerbations of airway disease. This effect was not, however, confined to those who had evidence of allergy on skin testing.

In designing the study, we deliberately kept the definitions broad because it is hard to distinguish clearly between asthma and other airway diseases in middle and later life and labels are often unhelpful and because we felt that the most important distinction was between atopic and nonatopic disease in the context of this

project. Within the limits of language used, we would argue, however, that these results refer to asthma.

The distinction between intrinsic and extrinsic asthma based on whether there were positive skin tests to allergen was made by Rackemann in 1947 and has been in use since (13).

However, although 'intrinsic' asthma has been found more often among women and patients with a later onset and more severe disease, it has been difficult to show any major differences in pathology (14, 15). The findings reported here show that many patients who would be normally defined as having intrinsic asthma do have an increased response to allergens in ambient air at the time of their exacerbations. Our definition of atopy in this study was very sensitive. Definition of atopy as any skin response to allergen greater than the control reaction is a very low threshold for clinical practice, and the range of allergens was broad enough to encompass most common allergic responses in the UK. That people who were skin test negative to a broad panel of allergens still responded to air borne allergen suggests that there is some difficulty in excluding extrinsic asthma by use of common skin tests.

The nature of the allergens responsible for these effects is unknown. Increases in pollen counts have been associated with asthma admissions in London (3) and with emergency room visits in California (16), and it is recognized that allergen fragments from pollens can be found in the respirable fraction of particles from ambient air (12, 17–19). We cannot assess in this study the relative contribution of pollen allergen as the effects of pollen allergen have been controlled for by the strong matching of event and control periods by season. It is plausible that pollen allergens are responsible for some increase in exacerbations during the pollen season among pollen allergic patients, although the effect in this cohort was relatively small and not significant (data not shown). It is, however, very unlikely that pollen allergens are responsible for the main effects reported here. Pollen allergic subjects were not at greater risk in this study, the events were not confined to the pollen season and pollen exposure has been largely matched for.

Of the common outdoor allergens, the next most common would be moulds. Mould spores have been associated with increased mortality from asthma (20) and respiratory arrest (21), and other severe episodes (22), with increases in episodes of asthma requiring either admission (23) or visits to emergency rooms (24, 25) and with severity of asthma as judged by symptoms or peak flow rates (26, 27). Sensitivity to moulds has also been associated with severe asthma (28, 29). We performed

skin tests against *Aspergillus* and *Alternaria* and those sensitized to these allergens were not specifically associated with sensitivity to allergen in PM_{10} at the time of their exacerbation. This certainly does not exclude mould allergens as an explanation. Mould allergens are represented by a much wider range of allergens than we tested for and are notoriously variable depending on the growing conditions of the mould. Newson noted an increase in asthma admissions associated with increased fungal spore counts, but no association with any specific taxon (23). Dales reported increases in hospitalization for asthma in Canada associated with basidiomycetes, ascomycetes and deuteromycetes, as well as weed, tree and grass pollen counts (30).

In Denver, there were reports of latex allergen in outdoor air (31). We performed skin tests against latex allergen and only seven patients (2%) were positive. These few people were not overrepresented in the group experiencing exacerbations associated with allergen in PM_{10} .

Finally, allergens from industrial and commercial sources have been responsible for some major outbreaks and these have included soy bean (11) and castor bean (32, 33) allergens from processing plants or silos. We cannot exclude such allergens from involvement in the exacerbations reported here and these are potentially of particular importance because they are more susceptible to control measures.

We have considered the possibility that the binding that we observed in this study is nonspecific binding of IgE to a component of particulate air pollution that is not itself an allergen. This is very unlikely for two reasons. First, there is very little association between levels of PM_{10} and exacerbations of airway disease, and adjusting for these in the current analyses made no difference to the results as would be expected in such a small study and with such generally low levels of PM_{10} . Second, the component of air pollution that was being bound to IgE has to be both strongly bound to IgE and a much more potent cause of exacerbations of airway disease than PM_{10} itself. This combination of characteristics is unlikely other than for allergen.

The large effect of allergens in apparently unsensitized individuals and not confined to common pollens and moulds suggests caution in interpreting associations between asthma exacerbations and other air pollutants and might explain why the reports are so inconsistent. It does not, however, alter the recommendations relating to control of these other pollutants. Current air quality standards are largely based on increases in cardiovascular risks, which are not altered by these observations.

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