

Combined effects of aerobiological pollutants, chemical pollutants and meteorological conditions on asthma admissions and A & E attendances in Derbyshire UK, 1993–96.

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Summary

Background The effect of outdoor aeroallergen exposure in asthma may be enhanced by air pollutants, including ozone, nitrogen dioxide and particulates, and by certain weather conditions. It is not yet established whether these interactions are important in determining asthma morbidity at the population level.

Objective We have investigated the joint effects of aeroallergens, rainfall, thunderstorms and outdoor air pollutants on daily asthma admissions and Accident and Emergency (A & E) attendance using routinely collected data between 1993 and 1996 from Derby in central England.

Methods Daily counts during the aeroallergen season of grass and birch pollen, basidiospores, *Didymella*, *Alternaria* and *Cladosporium*, maximum 1 hour ozone and nitrogen dioxide and daily average black smoke measurements, all made in the vicinity of the city centre, were categorized in tertiles. Rainfall was classified as dry, light (≤ 2 mm) or heavy (> 2 mm). The modifying effect of outdoor pollutant levels, and rainfall or the occurrence of a thunderstorm, upon the effects of individual aeroallergens on asthma admissions and A & E attendance were investigated by fitting appropriate interactions in log linear autoregression models with adjustment for potential confounders.

Results We found a significant interaction between the effects of grass pollen and weather conditions upon A & E attendance, such that the increase with grass pollen count was most marked on days of light rainfall (adjusted rate ratio for ≥ 50 vs < 10 grains/m³ at lag 2 days = 2.1, 95% CI 1.4, 3.3). Asthma admissions increased with *Cladosporium* count. We found no statistically significant interactions between effects of any individual aeroallergen and outdoor air pollutant upon either measure of asthma morbidity.

Conclusions Rainfall and thunderstorms are important effect modifiers in the relation between grass pollen and measures of acute asthma morbidity. Interactions between ambient levels of aeroallergens and chemical pollutants in the Derby area do not play a major role in determining asthma admissions and A & E attendance.

Keywords: asthma morbidity, pollen, fungal spores, outdoor air pollutants, rainfall, thunderstorms, interactions

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Introduction

Outdoor air pollutants have been extensively investigated as potential causes of day-to-day variations in acute asthma morbidity, but the weight of evidence in relation to measured pollutants including nitrogen dioxide, ozone and particulates suggests that at current ambient levels any effects are small. However there is residual concern, [1,2] based on several pieces of empirical evidence, that exposure to high levels of some of these pollutants might nevertheless alter how an allergic asthmatic responds to the allergens in their environment. Molecular studies have suggested that the bioavailability of aeroallergen may be modulated by air pollutants [3,4]. *In vivo* studies have demonstrated an enhanced IgE production to allergen upon exposure to diesel exhaust particles [5]. Exposure to nitrogen dioxide, ozone and diesel particles have all been associated with increased airway responsiveness to allergen challenge in animal or chamber studies [6–10]. Collectively therefore these data suggest that the effects of various pollutants and aeroallergens might interact, but whether this occurs at ambient concentrations and pollutant aeroallergen mixtures, and how relatively important these interactions are to asthma morbidity at the individual or population level is unknown.

Few epidemiological studies have assessed jointly the effects of aerobiological and chemical pollutants upon acute asthma morbidity, and those which have collected data on both have generally not looked for evidence of interaction. Some have in fact found no direct effect of aeroallergens, notably pollen [11,12], but have largely disregarded the influence of rainfall and thunderstorms. Thunderstorms are associated with epidemics of acute asthma in which grass pollen appears to be important [13,14]. Rainfall may affect allergen particle size and respirability [15,16]. A specific hypothesis has emerged that pollen allergen may be transferred or exist in fine particles of various origins to more readily trigger attacks of asthma [4]. It is evident therefore that any study of the joint effects of allergens and pollutants needs to take into account rainfall and thunderstorms.

Derby is a city in central England with established monitoring of all of these variables. We have therefore used these data to investigate the joint effects of aeroallergens, rainfall, thunderstorms and outdoor air pollutant levels on measures of acute asthma morbidity in the local community numbering 400 000 population.

Methods

Morbidity data

Derby is served by two acute Hospitals (Derby Royal Infirmary with attached Accident and Emergency (A & E)

unit, and Derby City Hospital). Asthma morbidity was assessed in terms of daily A & E attendances for the 4-year period from January 1993 to December 1996. Daily admissions to either Hospital were available from April 94 to December 96. Cases were identified using the international coding for diseases (ICD-9493 til March 95 and then ICD-10J45.9 & J46) and those with a main diagnosis of asthma were included. Only data for the 14 and over age group were included in these analyses.

Aerobiological pollutant ('aeroallergen') measurements

Of the daily aeroallergen counts available, we chose in this study to analyse grass and birch pollen [17], hyaline basidiospores (not including the ballistospores *Sporobolomyces* and *Tilletiopsis*) and coloured basidiospores [12], *Didymella* [18,19], *Alternaria* [12] and *Cladosporium* [20], which have been most consistently implicated in asthma. Measurements were made using a pollen/spore trap (Burkard Manufacturing Co Ltd, Rickmansworth, UK) sited 10 m above ground level in a Derby suburb 100 m above sea level and approximately 4 km south-west of the city centre. Daily slide or 7-day drum traps were used and analysed by standard methods [21].

Chemical pollutant ('pollutants') measurements

Measurements of ozone (O₃), nitrogen dioxide (NO₂) and black smoke were made by Derby City Council, data being collected from a city centre site since 1993, and black smoke from an urban background site approximately 1 mile away from 1994. An 8-port sampler giving 24 h averages was used for black smoke measurements. Black smoke was measured in accordance with the BS reflectance method (BS 1747 Part 2 1993). Ozone and NO₂ were measured as hourly averages by a UV absorption technique and chemiluminescence, respectively, using instrumentation granted Type Approval for use in the Department of the Environment Automatic Urban and Automatic Rural Networks. The maximum 1 hour NO₂ and O₃ values were computed for those days on which at least 75% of the one hour NO₂ values, and 75% of the hourly O₃ values between 6 am and 7 pm, were available, as in the project Air Pollution and Health: a European Approach (APHEA) studies [22].

Meteorological variables

Minimum and maximum temperature, relative humidity (wet and dry hygrometer), rainfall ('Snowdon' pattern rain gauge), and wind direction and speed ('Davis Instruments' anemometer) were measured daily 0.5 km from the site at which aeroallergens were measured. The occurrence of

thunderstorms was also recorded; thunderstorms occurred on 40 days during the study period.

Statistical analysis

Log linear autoregression models for time series of counts (described by Newson *et al.* [23]) were used for all primary analyses. Spearman Rank correlation analyses and simpler Poisson models allowing for overdispersion only, were used in initial exploration of the data, and to assess the associations between explanatory variables.

We first inspected the distribution of daily aeroallergen counts, and used this to define the aeroallergen season as days on which the count rose above zero for pollens and above the 75th percentile for spores (since spore counts rarely fell to zero but were negligible for approximately 75% of the year in most cases). We then expressed daily aeroallergen counts as four level factors; the bottom category identified days outside of the aeroallergen season, and the remaining three levels were based on tertile cut-offs during the aeroallergen season unless alternatives were implicated by published threshold levels (grass only). Black smoke, O₃, NO₂, and rainfall were also categorized as three level factors, taking tertile cut-offs (computed for those days which fell in one or more of the aeroallergen seasons). Rainfall was expressed as a three level factor with categories for dry days (0 mm rainfall), and for light (≤ 2 mm) and heavy (> 2 mm) rainfall.

The effects on asthma morbidity of aeroallergen measurements on the same day, lag 1 day, and lag 2 days were compared. The main effect of each aeroallergen was assessed as the trend in rate ratio for asthma morbidity across increasing tertiles within the aeroallergen season, and by comparing asthma morbidity in and out of the aeroallergen season. Regression models were fitted which incorporated appropriate interaction terms between the aeroallergen and the pollutant, rainfall and thunderstorm variables. The aeroallergen variable was fitted at the lag at which any direct effect was maximal; interactions with pollutants (categorized in tertiles) and meteorological measurements at the same lag, or with an additional 1 or 2 days lag were investigated. Complete admissions data were available for two and a half years during which time there was substantial missing smoke pollutant data, and interactions involving this pollutant have therefore been omitted from the analysis of the asthma admission outcome. There was also insufficient asthma admission data during the tree pollen season to assess the interactions involving birch. Categories for some other variables were combined to ensure sufficient numbers in each strata for interaction analysis. The significance of interactions was determined using the likelihood ratio statistic.

In all of these analyses, initial adjustment was made only

for a linear and quadratic long-term time trend, temperature (fitted as a double quadratic), humidity, thunderstorms, influenza epidemics (estimated as the weekly count in Royal College of General Practitioner returns for England and Wales) and day of the week. To establish whether the effect of an aeroallergen explained, or was explained by, other seasonal factors, further models were fitted with adjustment for a weighted moving average of asthma morbidity, with a filter appropriate to, and longer than the duration of aeroallergen peaks. Where an aeroallergen was strongly correlated with temperature or humidity, the effect of omitting the meteorological variable from the analysis was assessed, and where two allergens occurring in the same season were both significantly associated with morbidity, the effect of mutual adjustment was investigated.

Analyses were performed in SAS Version 6.12, primarily using the GENMOD and NLIN procedures. Statistical significance was inferred at a *P*-value of < 0.05 .

Results

The number of daily asthma-related A & E attendances and hospital admissions ranged, respectively, from 0 to 7 and 0–6, with means of 1.24 and 0.81. A & E attendants were of a younger age (mean 37, SD 20, 25th to 75th percentiles 21–52) than those admitted (mean 41, SD 19, percentiles 25–54).

Counts consistently above zero were observed for birch and grass pollen for only 2 and 4 months of the year, respectively, whilst the majority of fungal spores remained at a minimal but measurable level throughout, peaking for 2 to 3 months of the year (Table 1). Levels of O₃, NO₂ and black smoke were generally low although levels of O₃ and NO₂ did not exceed the World Health Organization standard on any day of the 4 years. Correlation analyses confirmed that grass pollen and *Cladosporium*, *Didymella* and *Alternaria* spore counts tended to be higher in warmer weather and basidiospores in more humid conditions (Table 2). *Didymella* and *Cladosporium* counts increased sharply with the occurrence of a thunderstorm, whereas grass pollen tended to be slightly reduced on the day of a thunderstorm, peaking in the days prior to the storm.

Asthma admissions and A & E attendances were both increased in association with thunderstorms, the maximum impact being seen on the same day with respect to A & E attendance (adjusted RR (95% CI) 1.3 [1.0,1.7]), whilst the rise in admissions tended to lag by one day (adjusted RR (95% CI) 1.7 [1.1,2.5]). Interactions with storms were accordingly analysed at these lags.

Grass and *Cladosporium* were the only aeroallergens studied for which increasing counts during the season were associated with a significant increase in either A & E attendances or admissions.

Table 1. Distribution of daily measurements of pollutant and aeroallergens

	Number of days data available	Min	Median (50th pct)	75th pct	Max	Number (%) days with count above zero	Season (months with over 50% of days above zero count (pollens) and 75th percentile (spores/pollutants))
<i>Pollen counts (m³)</i>							
Grass	1439	0	0	5	620	491 (34%)	May, Jun, Jul, Aug
Birch	1439	0	0	0	888	182 (13%)	Apr, May
<i>Spore counts (m³)</i>							
Basidiospores (hyaline)	1439	0	224	620	20064	1386 (94%)	Sep, Oct
Basidiospores (coloured)	1439	0	76	276	8364	1319 (92%)	Aug, Sep, Oct
<i>Didymella</i>	1439	0	16	85	10830	1089 (76%)	Jul, Aug, Sep
<i>Alternaria</i>	1439	0	4	28	4292	867 (60%)	Jul, Aug, Sep
<i>Cladosporium</i>	1439	0	668	3584	66248	1427 (99%)	Jun, Jul, Aug
<i>Pollutant</i>							
Maximum O ₃ p.p.b.	1309	0	19	26	88	1307 (100%)	None
Maximum NO ₂ p.p.b.	1242	8	27	36	95	1242 (100%)	None
Black smoke (µg/m ³)	1122	1	13	20	80	1122 (100%)	None

In this study, there was no significant effect of *Alternaria*, *Didymella* or hyaline basidiospores, either between days in and out of the aeroallergen seasons, or trends within the seasons, using either tertile cut-offs or alternative higher cut-offs. There was no statistical nor graphical evidence of effect modification by rainfall, thunderstorms or pollutant levels. Birch and coloured basidiospores both exhibited weak, but nonsignificant, trends with both A & E attendance and admissions, which persisted after controlling for the seasonal moving average. The weak effects of coloured basidiospores were no stronger during rainfall, nor in association with high levels of any one of the three

measured pollutants. There was no statistically significant interaction between the effects of birch pollen and rainfall (Fig. 1), or birch pollen and individual pollutants (Figs 2,3 and 4), but the effect of increasing birch count on A & E attendance was only apparent on wet days ($P=0.1$), and also tended to be marginally stronger when NO₂ was high.

Although A & E attendance and admissions for asthma tended to be lower on average during the *Cladosporium* season than during the remainder of the year, the admission rate rose significantly ($P=0.001$) with *Cladosporium* counts during the season (adjusted RR (95% CI) for top vs bottom tertile 2.1 [1.4, 2.3]), and was little changed by

Table 2. Correlations between daily aeroallergen counts, pollutants, and meteorological variables

	Max. temp.	Humidity	Rainfall	Thunderstorms	Windspeed	Max. O ₃	Max. NO ₂	Black smoke
Grass	<u>0.53</u>	-0.30	-0.18	-0.02	-0.01	0.07	-0.05	-0.06
Birch	-0.09	0.08	-0.10	-	-0.14	0.34	0.35	-0.10
Basidiospores (H)	-0.01	0.14	-0.16	0.10	-0.08	-0.19	0.08	0.12
Basidiospores (C)	-0.07	0.04	-0.16	-0.10	-0.12	-0.15	0.00	0.08
<i>Didymella</i>	0.20	0.00	0.15	0.20	-0.05	0.08	0.14	0.12
<i>Alternaria</i>	0.32	-0.19	-0.15	0.00	-0.08	0.17	0.11	-0.11
<i>Cladosporium</i>	<u>0.40</u>	-0.03	-0.01	0.13	-0.18	0.26	0.20	-0.06
Maximum O ₃	0.23	-0.31	-0.00	0.05	0.22			
maximum NO ₂	0.03	0.01	-0.07	0.08	-0.35			
Black smoke	-0.24	0.23	-0.11	0.05	<u>-0.45</u>			

Correlations involving aeroallergens restricted to days of the aeroallergen season (pollen counts above zero; spore counts above the 75th percentile). Correlations above 0.2 are in bold, above 0.4 are underlined.

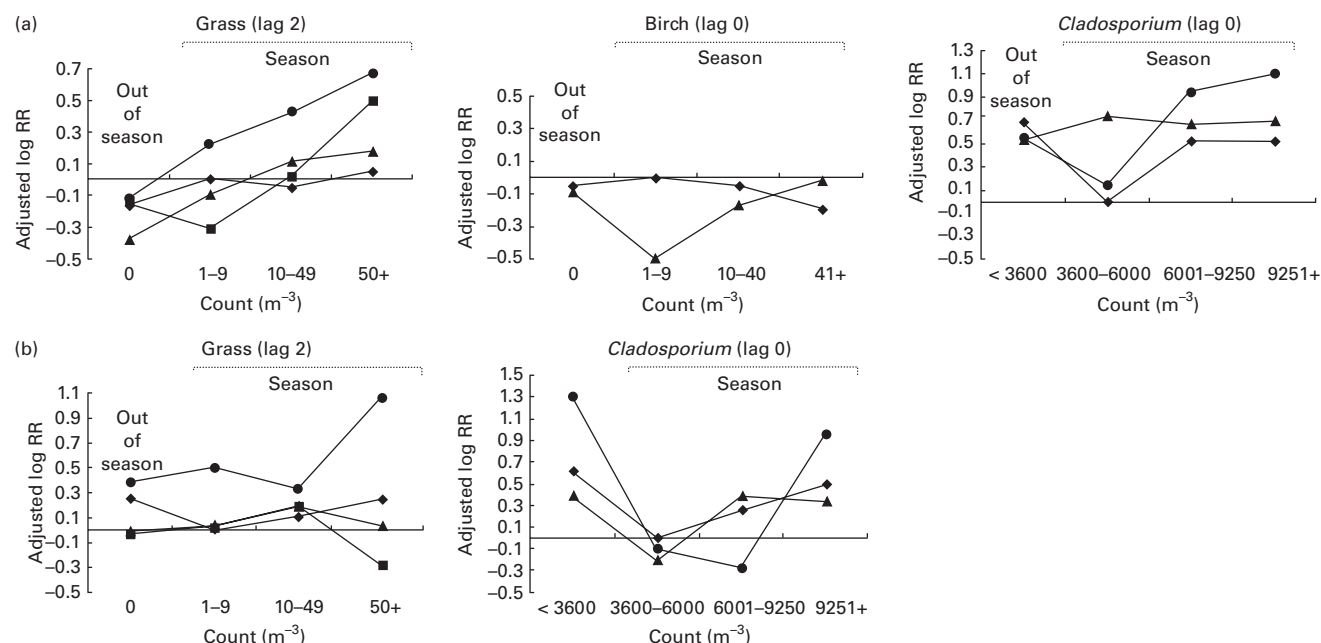


Fig. 1. Estimated log rate ratios for asthma (a) A & E attendance and (b) admission according to level of pollen (grass and birch) and *Cladosporium* (in four categories; out of season, and tertiles during season) and weather conditions (dry, light, heavy rainfall or thunderstorm). Rate ratios are adjusted for long-term time trends, temperature, humidity, influenza epidemics, and day of the week, and are given relative to a baseline of dry days at the lowest tertile of aeroallergen count during the season. (◆) No rain, no storm; (■) light rainfall; (▲) heavy/any (birch, *Cladosporidium*) rainfall; (●) thunderstorm. Baseline is at lowest tertile and dry conditions.

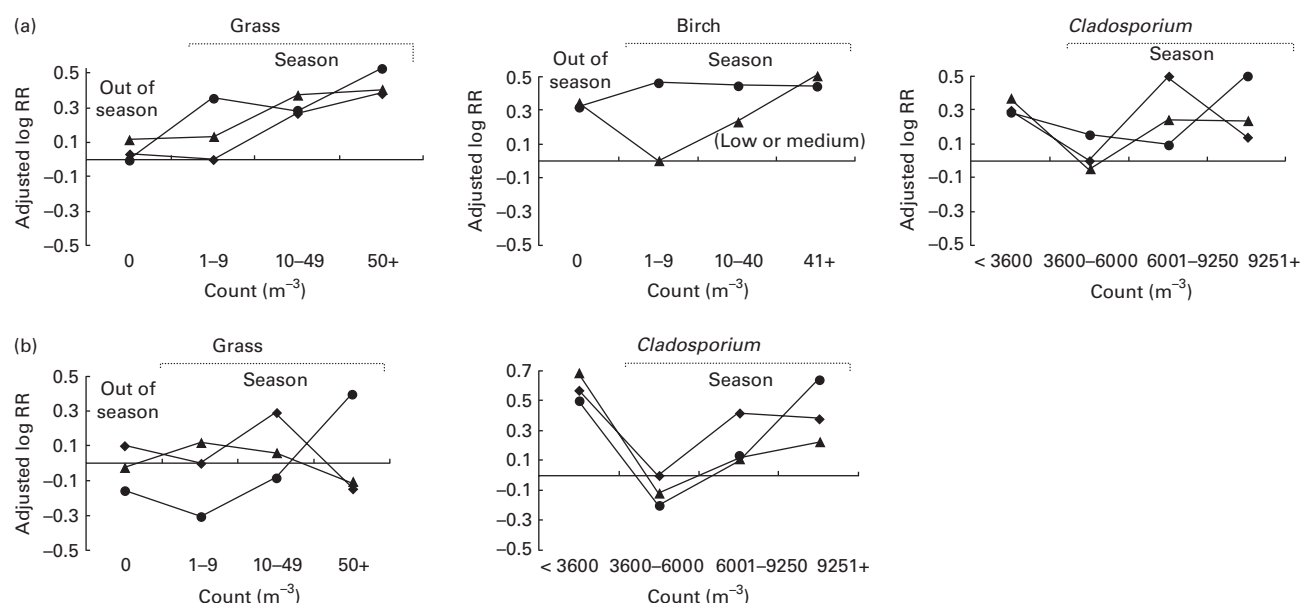


Fig. 2. Estimated log rate ratios for asthma (a) A & E attendance and (b) admission according to level of pollen (grass and birch) or *Cladosporium* (in four categories; out of season, and tertiles during season) and ozone concentration (in tertiles). Rate ratios are adjusted for long-term time trends, temperature, humidity, influenza epidemics, and day of the week, and are given relative to a baseline of lowest tertile of ozone and of aeroallergen count during the season. (◆) Low ozone (< 15 p.p.b.); (▲) medium ozone; (●) high ozone (> 24 p.p.b.). Baseline: low count and low ozone.

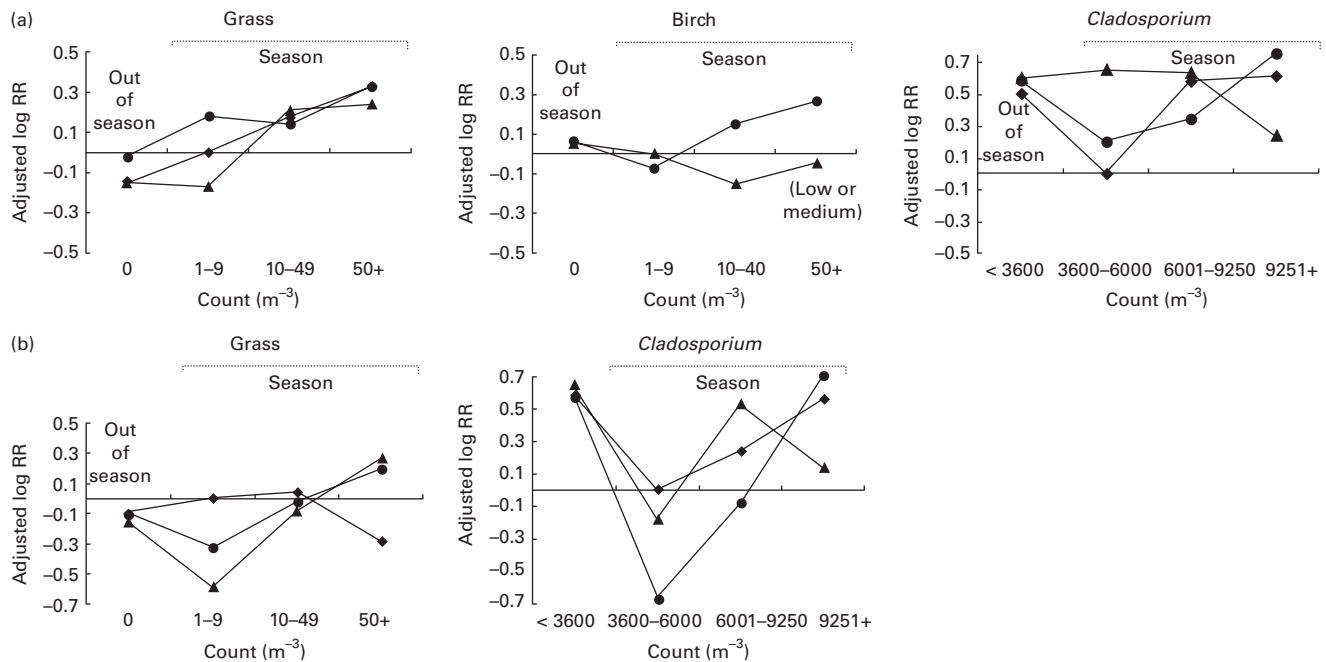


Fig. 3. Estimated log rate ratios for asthma (a) A & E attendance and (b) admission according to level of pollen (grass and birch) or *Cladosporium* (in four categories; out of season, and tertiles during season) and nitrogen dioxide concentration (in tertiles). Rate ratios are adjusted for long-term time trends, temperature, humidity, influenza epidemics, and day of the week, and are given relative to a baseline of lowest tertile of nitrogen dioxide and of aeroallergen count during the season. (◆) Low NO₂ (< 24 p.p.b.); (▲) medium NO₂; (●) high NO₂ (> 33 p.p.b.). Baseline: low count and low NO₂.

additional adjustment for the seasonal moving average, or for grass pollen counts. A similar association was apparent for A & E attendance, but the trend was slightly weaker and only significant before adjustment for hot temperature (adjusted RR (95% CI) 1.5 [1.1, 2.1]). For both outcomes an effect of *Cladosporium* was only apparent for counts on the same day (lag 0), and was no greater on wet days (Fig. 1), marginally, though not significantly greater on stormy days (Fig. 1d), and there was little evidence that the effect was modified by pollutant conditions (Fig. 2–4).

Grass pollen counts were significantly associated only with A & E attendance, which was generally higher during the grass pollen season. The main effect of increasing grass pollen counts was not statistically significant, though reached borderline significance ($P = 0.06$) before controlling for high temperature, to which grass pollen count was strongly related. However, there was a significant interaction between the effects of grass pollen and weather conditions ($P = 0.02$), such that A & E attendance was unrelated to grass pollen count on dry days, but increased with grass

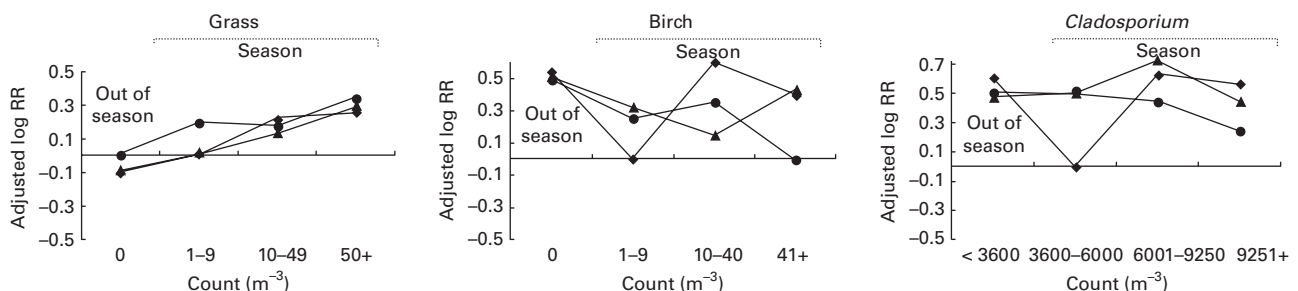


Fig. 4. Estimated log rate ratios for asthma A & E attendance according to level of pollen (grass and birch) or *Cladosporium* (in four categories; out of season, and tertiles during season) and black smoke concentration (in tertiles). Rate ratios are adjusted for long-term time trends, temperature, humidity, influenza epidemics, and day of the week, and are given relative to a baseline of lowest tertile of black smoke and of aeroallergen count during the season. (◆) Low smoke (< 8 µg/m³); (▲) medium smoke; (●) high smoke (> 17 µg/m³). Baseline: low count and low black smoke.

pollen count on wet or stormy days, most markedly on days of light rainfall (adjusted OR for (50 vs < 10 grains/m³ 2.1 (95% CI 1.4, 3.3) (Fig. 1), this relationship being apparent even with adjustment for a moving average. The effect was strongest when pollen counts were analysed at lag 2 days, though apparent at alternative lags, and was slightly stronger when we used a top cut-off of 50 grains per cubic metre (a published 'threshold' [24]) rather than the top tertile of 30 grains/m³. There was no graphical nor statistical evidence that the overall effect of grass (Fig. 2–4), or the effect on wet or stormy days (data not shown), was modified by the level of any of O₃, NO₂ or smoke pollution.

There was no significant association of asthma admissions with grass pollen counts, and though admissions were higher when a high grass pollen count at lag 2 days preceded stormy conditions, this occurred on only 8 days during the two and a half years in which admission data were available and was not statistically significant. There was also a tendency for the effect of grass pollen on admissions to be more marked when preceded by high ozone, and weaker when preceded by low nitrogen dioxide but neither of these interactions reached conventional statistical significance (both $P = 0.1$).

Discussion

In this study, we have examined a large number of potential interactions between effects of three individual outdoor air pollutants and seven aeroallergens upon two measures of asthma morbidity in this UK population. We found weak and nonsignificant interactions between birch and NO₂, and between grass and both O₃ and NO₂ in relation to A & E attendance and hospital admissions, respectively. These interactions did not indicate substantially higher levels of morbidity when the highest levels of chemical pollutant and aeroallergen coincided. There was no suggestion of any further interactions between aeroallergens and pollutants. Our analyses confirmed that an effect of grass on one measure of asthma morbidity was dependent upon rainfall, but we found no hint of interactions between grass and any of ozone, nitrogen dioxide or black smoke in determining morbidity, even when restricted to days with rainfall.

Our study was unique in plotting measures of asthma morbidity stratified by pollutant and aeroallergen levels. However it was a small study over a short time scale yielding limited statistical power to test for interactive effects. We were analysing data from an area with relatively low ambient pollutant concentrations, and we had a relatively crude measure of particulate pollution measured at a single outdoor site, which is likely to represent an imprecise approximation of individual exposure. Our data set was also insufficient to allow us to analyse direct effects, or any modification by pollutant exposure, of extreme aeroallergen

counts such as might occur in response to specific conditions like thunderstorms. Thus we cannot preclude the possibility that certain combinations of pollutants and aeroallergens are associated with increases in hospital admissions or A & E events. Whilst our study has the advantage of using two different measures of asthma morbidity, these outcomes still reflect the morbidity of a small proportion of the asthmatic population; we have not investigated influences upon primary care (general practitioner attendance) or upon the degree of symptoms and use of medication in the wider community. However, the interactions which were suggested by our study were relatively inconsequential, with substantially less influence on the number of acute asthma cases than other natural phenomena including thunderstorms, rainfall and the day of the week. This is consistent with a previous study finding little evidence of interaction between pollens and pollution in determining hospital admissions in London [25].

In the course of this study, we assessed the direct effects of some of the major aeroallergens implicated in asthma. We found grass pollen and *Cladosporium* had statistically significant effects upon asthma morbidity. We used aeroallergen measurements from one site only, but these have been previously demonstrated to reflect the symptom pattern [26] and, it is presumed therefore, the exposure pattern for a wide area, encompassing the population served by the two hospitals we have studied. Other studies have implicated *Cladosporium* in autumnal asthma [20]. In our study, the effect of *Cladosporium* was relatively inconsistent, being significant only for admissions, and only when analysed with no lag. *Cladosporium* counts peak during thunderstorms, but the time period of our study was too short to assess the effect of these extreme *Cladosporium* counts. Nevertheless, when we fitted the interaction between grass and weather, it was apparent that the effect of thunderstorms upon both asthma outcomes was substantially reduced out of the grass pollen season. This suggests that grass is relatively more important in the phenomena of thunderstorm asthma.

Unlike *Cladosporium*, A & E attendance was associated with increasing grass pollen counts during rainy periods of the grass pollen season at each lag investigated. However, the effect was strongest when analysed using grass pollen counts two days before, and rainfall the day prior to the index day. This, and the stronger effect in light than heavy rainfall is consistent with the proposed mechanisms for effect modification by rainfall. Grass pollen grains are too large to gain access to the lower airways, but rupture upon contact with water, releasing numerous starch granules containing Lol p 5 [28], the major grass allergen, which is then available in greater quantities in particles of a respirable size [15] with potential to trigger an asthmatic response. Very similar processes have been described for

birch pollen [16], and there was a suggestion in our analyses that the effect of birch, too, may be stronger during rainfall. However, the birch pollen season is short, and the data available for these analyses consequently limited. That we did not see an interaction between grass and rainfall upon asthma admissions may also be due to the relatively smaller amount of data on this clinical end point, but might also reflect differences in the population and the pathology of the disease being measured; admissions were more common in the elderly and more strongly associated with viral epidemics than were the number of A & E attendants. Nevertheless, both asthma outcomes were most common in association with high grass pollen counts and thunderstorms. Rainfall did not seem to entirely explain this observation, even for A & E attendance, which suggests either that we have not used an adequate marker of total grass allergen exposure during a thunderstorm, or that there are other, as yet undetermined, factors involved.

We conclude that if outdoor levels of ozone or nitrogen dioxide amplify the response of an allergic asthmatic to outdoor aeroallergens, these effects are relatively minor determinants of levels of acute asthma morbidity in this community. There was also no effect modification by black smoke exposure, but further study is implicated using less crude measures of particulate pollution, and specifically of diesel exhaust particles. Above all, our findings suggest that future studies should be of a sufficient size to be able to account for weather conditions in studying interactions with outdoor aeroallergens. Specifically, our data suggests that rainfall and thunderstorms are important effect modifiers in the relation between grass and asthma morbidity.

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