ORIGINAL ARTICLE

Temporal associations between daily counts of fungal spores and asthma exacerbations

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Table 5 is available on our website.

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Background: Outdoor aeroallergens are one of a number of environmental factors thought to precipitate asthma exacerbations.

Aims: To investigate the short term associations between daily fungal spore concentrations and indicators of daily asthma exacerbations in a large urban population.

Methods: Daily counts of visits for asthma to family physicians and hospital accident and emergency (A&E) departments and emergency hospital admissions in London 1992–93 were compiled. Daily concentrations of fungal spores (30 species), daily average temperature, humidity, and concentrations of pollen and outdoor air pollution were also compiled. The analysis was restricted to the period when fungal spores were most prevalent (June to mid October). Non-parametric regression time series methods were used to assess associations controlling for seasonality, day of week, and meteorological factors. The sensitivity of the findings to the inclusion of pollen and air pollution into the models was also assessed.

Results: In children aged 0–14 years the relative risks for increases in the number of A&E visits and hospital admissions associated with changes in fungal spore concentrations from the lower to upper quartiles were 1.06 (95% CI 0.94 to 1.18) and 1.07 (0.97 to 1.19) respectively. The addition of pollen or air pollutants had little impact on the observed associations. A number of individual spore *taxa*, in particular *Alternaria*, *Epicoccum*, *Agrocybe*, *Mildews*, and both coloured and colourless Basidiomycetes and Ascomycetes, were associated with increases in the number of emergency visits and hospital admissions for asthma, although the precision of these estimates were low. No evidence was found for associations in adults.

Conclusions: Fungal spore concentrations may provoke or exacerbate asthma attacks in children resulting in visits to A&E departments and emergency hospital admissions. These findings were unlikely to be due to confounding by other environmental factors. The associations were comparable to those observed for ambient air pollution from similarly designed studies.

Outdoor fungal spores are one of a number of environmental factors thought to precipitate exacerbations of asthma.^{1,2} Skin prick tests using mould extracts have shown that some asthmatics are sensitised to fungal spores.³ Two types of time series studies have been used to assess the epidemiological evidence in support of these findings. Panel studies relate measures of fungal spore concentrations to symptom severity in a group or panel of subjects monitored over time whereas ecological time-series studies use daily indicators of asthma exacerbations in a population. Both sets of studies have contributed mixed evidence in support of an association.

Recent panel studies by Delfino⁴ and by Ostro⁵ have reported associations between fungal spore concentrations and increased symptom severity, decreased peak expiratory flow (PEF) and β -agonist inhaler use in adults, and increased incidence of shortness of breath, wheeze, and cough in asthmatic children respectively. Conversely, Jalaludin assessed PEF in a panel of school children and concluded that there was no evidence for an association with *Alternaria* spore concentrations.⁶

The small number of published ecological time series studies have used asthma attacks severe enough to warrant a visit to an emergency department or hospitalisation as the health endpoint. Some analyses used all asthma exacerbations whereas others have subdivided subjects by age. Furthermore, the large number of spore species and the numerous ways in which these can be grouped for analysis make it difficult to compare directly results between studies. Analyses also vary in terms of the period of the year studied

(summer *v* all year), the statistical methods used (correlation statistics; regression estimates), and the inclusion of other potential confounding factors such as air pollution.

Total fungal spore concentrations were examined in relation to asthma admissions and emergency room/department visits in studies in Canada,⁷ Western Australia,⁸ Cincinnati,⁹ and the Trent Region, UK¹⁰ with conflicting results. Some investigators grouped together spores according to their division—Deuteromycota, Basidiomycota, and Ascomycota—again with inconsistent findings.^{10–14}

Individual spore *taxa*, principally spores of *Alternaria*, *Cladosporium*, *Epicoccum*, *Didymella*, *Aspergillus*, and *Ganoderma*, have also been examined in a small number of these studies. Again, the findings for each spore *taxa* were not consistent across studies.^{7 10 13–15}

In this ecological time series study we aimed to investigate, in a systematic and comprehensive manner, the short term associations between a large number of fungal spore *taxa* and a range of indicators of asthma exacerbations subdivided by age. Asthma exacerbations were indicated by daily counts of emergency hospital admissions, visits to Accident and Emergency (A&E) departments and consultations with general practitioners (GPs). We were therefore able to examine the consistency of associations for different levels of severity of asthma exacerbations. The availability of

Abbreviations: GPRD, General Practice Research Database; HES, Hospital Episode Statistics; ICD-9, International Classification of Diseases, Ninth Revision; ONS, Office of National Statistics; PACF, partial autocorrelation function; PEF, peak expiratory flow

measurements of 30 individual spore *taxa* enabled a comprehensive examination of potential associations with asthma outcomes. Pollen counts, air pollution, and meteorological variables were all included in the analysis to assess the robustness of the findings for spores. Finally, we have used statistical methods commonly employed in time series studies of the short term effects of outdoor air pollution on health that are capable of detecting small, though statistically significant, associations between daily concentrations of air pollution and daily indicators of a population's health such as daily mortality.¹⁶

METHODS

Health outcome data

Daily counts of the number of GP consultations, visits to A&E departments, and number of hospitalisations for asthma in London were collected for the years 1992–94. Details of visits to a sample of between 45 and 47 GP surgeries across London were obtained from the Office of National Statistics (ONS) who managed the General Practice Research Database (GPRD) on behalf of the Department of Health. The GPRD was a nationwide compilation of details of consultations with, and prescriptions written by, participating GPs in England and Wales.

The numbers of subjects presenting at A&E departments with a self-diagnosis of asthma were collected from a sample of 12 A&E departments across Greater London. Daily numbers of emergency hospital admissions were obtained from the Hospital Episode Statistics (HES) system. The HES system, administered by the Department of Health, provides information on admitted patient care delivered by NHS hospitals (including private care delivered by the NHS) in England from 1989 to the present time. These data have been described in more detail in previous publications relating to this dataset.^{17–19} Visits to GP surgeries or hospital admissions for asthma were identified using the ICD-9 code 493 (International Classification of Diseases, Ninth Revision). Daily numbers of visits and admissions were constructed for ages 0–14 years and 15–64 years.

Aeroallergen data

The aeroallergen data were collected using a Burkard Volumetric seven day trap and in accordance with the guidelines of the British Aerobiology Federation.²⁰ This method involves drawing 10 litres of air per minute continuously on to a tape that has been coated with adhesive. Particles in the air stick to the tape that moves past the inlet at 2 mm per hour to give a time related sample. The aeroallergens are then identified and counted by a trained mycologist/palynologist and related to the volumes of air sampled to give concentrations per cubic metre of air averaged over 24 hours. The trap was located on an exposed roof 18 m above ground level in Islington, North London (51° 33 N, 0° 6 W). Fungal spore data were collected for the period 3 February 1992 to 20 December 1993 and pollen data were collected for the period 1 January 1992 to 31 July 1994.

Thirty different fungal spore *taxa* were identified. Daily total fungal spore and division totals for Deuteromycota, Basidiomycota, and Ascomycota spore concentrations were obtained by summing combinations of individual daily spore concentrations.

Pollen from 11 different plant species were also identified and counted. These included grass, nettle, and pollen from common tree species such as oak, hazel, and birch. Pollens were considered as potential confounders for the spore/asthma associations only and hence the health effects of individual pollen species were not investigated in this analysis.

Air pollution and meteorological data

Air pollution data were obtained from the Air Quality Data Archive website (<http://www.airquality.co.uk/archive/index.php>). Daily concentrations of PM₁₀ (particles with a median diameter of 10 microns or less), black smoke (BS), sulphur dioxide (SO₂), ozone (O₃), and nitrogen dioxide (NO₂) were downloaded for monitoring stations operational during the study period. Data from monitoring stations were not used if the data were incomplete (less than 75% of days with available measurements). Daily 24 hour average concentrations of PM₁₀, BS, and SO₂ and daily 8 hour and 1 hour average concentrations of O₃ and NO₂ respectively were used. The daily 8 hour and 1 hour concentrations of O₃ and NO₂ were highly correlated with their respective 24 hour measures (data not shown) and hence only the 8 and 1 hour measures were chosen for analysis. For the calculation of particle, SO₂, and NO₂ concentrations on any one given day, a minimum of 75% of the 24 hourly measures had to be available. For the daily O₃ measures, 6 from each 8 hour moving average were required. Days not satisfying these criteria were designated as missing. Where there was more than one monitor providing data for a pollutant, a simple "filling in" procedure was used to improve data completeness.²¹ The pollutant measures from all stations providing data were then averaged to provide single, city wide estimates of the daily levels of the pollutants.

Daily measures of temperature (maximum and minimum) and relative humidity (measured at 6am and 3pm) in central London (Holborn) were obtained from the Meteorological Office.

Statistical analysis

Poisson regression was used to model the dependencies of daily counts of asthma visits (to GP surgeries and A&E departments) and hospital admissions on daily spore concentrations. Other variables included in the models were terms to account for seasonality in the numbers of asthma events and for other potential confounding factors such as meteorological conditions, respiratory epidemics, and calendar factors—for example, day of week.

Time series of daily health events within a population are often serially correlated—this correlation deriving from associations with time varying factors rather than a direct relation between counts on successive days. Some of these time varying factors are known and measured—for example, daily average temperature—and others are unknown and unmeasured. To account for unmeasured confounders, non-linear functions of time are included in the models. These terms model the temporal (seasonal) pattern in the outcome series. Known, and measured, variables such as daily average temperature or daily levels of air pollution are included in the models as linear or non-linear terms as appropriate.

This approach to the analysis of time-series data in an epidemiological setting is commonly used in studies of the short term health effects of air pollution on daily indicators of mortality and morbidity. An example of this type of study is the APHEA 2 project (*Air pollution and health: a European approach*).²² The key elements of their approach, adopted for the present analysis, were (1) the use of non-parametric smoothing techniques within a generalised additive model framework; (2) use of the partial autocorrelation function (PACF) to guide selection of smoothing parameters to control for seasonality; (3) investigation of same day and lagged effects, linear or non-linear, of temperature and humidity; (4) control for day of week effects, bank holidays, and any other unusual events (for example, thunderstorms) using dummy variables.

Penalised splines were used to model seasonality in the outcome series.²³ Separate splines were used for time for each

year to allow for any discontinuity in the numbers of events from year to year. Knots were placed every seven days and the number of degrees of freedom used in the smoothing terms controlled using the smoothing parameter. Initial starting values for the smoothing parameters were chosen using the generalised cross validation method.²⁴ The smoothing parameters were then increased (and hence the number of degrees of freedom used decreased) until the sum of the absolute values of the sample partial autocorrelation function reached a minimum. In this way the serial correlation present in the outcome series is accounted for in the model but without the danger of overfitting the model.²² The analyses were carried out in R (R Foundation for Statistical Computing Version 1.9.0 Patched (27/04/2004), ISBN 3-900051-00-3).

The modelling procedure was carried out for each of the six health outcome series. As a result the “core” models for each time series were not necessarily the same. A four-level factor describing the total fungal spore concentrations by quartiles of the (seasonal) distribution was then fitted to each model. This approach enabled potential non-linear associations to be assessed. The initial analyses included the exposure on the same day as the health outcome, lag 0.

Associations between “family” subtotals and individual spore *taxa* and asthma visits and admissions were also investigated. Individual spore concentrations were either stratified by quartiles, dichotomised by the median (non-zero) values with a third level indicating zero concentrations or dichotomised as spores present/absent. Therefore the more prevalent spores were modelled using a four-level factor and the less prevalent ones using three- or two-level factors.

Sensitivity analyses

Sensitivity analyses to investigate associations at longer lags (associations between health outcome and previous days spore concentrations—lag 1 as well as lags 2 and 3) were carried out. We also investigated the robustness of the findings to the number of degrees of freedom used to model

seasonality in the time series. The sensitivity of the results to the inclusion of outdoor air pollution and grass and nettle pollen was also examined.

RESULTS

Figure 1 shows the daily number of asthma events together with the daily total fungal spore concentrations for the years 1992–93. The plots illustrate the seasonal variation in the number of asthma events, in particular the sharp increases in the younger age group at the start of the autumn. The plot of daily total spore concentrations over time for the two years indicates the clear seasonal pattern in fungal spore concentrations. To investigate this phenomenon further, days were grouped by quartiles of their daily total spore concentration and cross tabulated against month of year (data not shown). This revealed that the top two quartiles of spore concentrations occurred overwhelmingly during the months June to mid October, confirming the observed seasonal distribution. In order to prevent the possibility of any results being confounded by season the analysis for this paper concentrated on the 4.5 months between June and mid October in each of the two years. Table 1 gives descriptive statistics for the main outcome measures, spore and pollen counts, and other environmental variables for the period analysed, 31 May to 15 October 1992 and 1 June to 13 October 1993. PM₁₀ measures were unavailable on a substantial number of days during the analysis period and therefore were not considered further, BS was used as the indicator of particle pollution. Only grass and nettle pollens were prevalent during the months selected for analysis.

Table 2 and figure 2 show the results of the analysis of total spore concentrations quantified by quartile of the distribution. In children there was some weak evidence for an association between increases in hospital admissions for asthma and increases in levels of spore concentrations. The relative risks for quartiles (q) 2–4 were elevated compared to q1 (table 2). For A&E visits, the risks of visits with asthma on days when spore concentrations were high (q2–4) compared

Figure 1 Daily counts of visits to GP surgeries, A&E departments, and hospital admissions for asthma and total spore concentrations in London between 1992 and 1993.

Table 1 Summary statistics for health outcomes, fungal spore concentrations, and other environmental factors for the May to mid October 1992 and 1993

Variable	Min	1st Qu	Median	3rd Qu	Max	Mean	SD	NA
Outcome (n/day)								
GP visits, 0–14 y	0	5	13	18.8	38	13.2	8.9	0
GP visits, 15–64 y	0	6	22	28	46	19.1	12.1	0
AE visits, 0–14 y	3	10	14	21	49	16.2	8.5	0
AE visits, 15–64 y	4	9	12	15	39	12.3	4.8	0
Admissions, 0–14 y	3	13	18	27	80	22.6	13.8	0
Admissions, 15–64 y	3	10	13	17	35	13.8	5.1	0
Fungal spores (spores/m ³)								
Total spores	38.9	2493.8	3701.7	5805.4	16119.4	4425.0	2801.0	0
Deuteromycota	38.9	1283.0	1969.0	3104.0	12130.0	2529.0	2056.0	0
<i>Alternaria</i>	0	19.4	58.3	155.6	1419.0	127.4	209.4	0
<i>Aspergillus</i>	0	58.3	233.3	622.2	7136.0	586.7	1049.1	0
<i>Cladosporium</i>	0	743.8	1244.0	2056.0	6942.0	1536.0	1204.5	0
<i>Drechslera</i>	0	0	0	19.4	466.7	12.4	38.7	0
<i>Epicoccum</i>	0	0	19.4	58.3	350.0	35.8	44.2	0
<i>Periconia</i>	0	0	0	24.3	175.0	20.5	33.8	0
<i>Stemphylium</i>	0	0	0	19.4	369.4	16.6	36.9	0
Other coloured	0	19.4	58.3	116.7	622.2	88.4	94.9	0
Other hyaline	0	0	38.9	77.8	486.1	61.5	80.4	0
<i>Torulla</i>	0	0	0	24.3	233.3	21.0	37.3	0
<i>Botrytis</i>	0	0	0	38.9	291.7	23.1	38.5	0
Basidiomycota	0	466.7	935.8	1594.0	6499.0	1242.0	1087.6	0
<i>Coprinus</i>	0	38.9	81.7	209.0	1167.0	165.3	216.8	0
<i>Ganoderma</i>	0	19.4	38.9	77.8	252.8	53.2	46.5	0
<i>Agrocybe</i>	0	19.4	58.3	155.6	2217.0	187.2	371.8	0
Rusts	0	0	0	19.4	330.6	13.2	29.9	0
Smuts	0	0	19.4	151.7	2372.0	176.3	374.5	0
Other coloured	0	19.4	58.3	175.0	1517.0	124.6	179.2	0
Other hyaline	0	0	0	0	199.3	9.8	31.3	0
<i>Tilletiopsis</i>	0	0	0	58.3	1633.0	110.2	262.6	0
<i>Sporobolomycetes</i>	0	0	175.0	466.7	4531.0	402.2	642.8	0
Ascomycota	0	103.3	272.2	777.8	4769.0	630.2	829.9	0
<i>Leptosphaeria</i>	0	19.4	77.8	175.0	1031.0	137.8	184.1	0
<i>Pleospora</i>	0	0	0	0	116.7	3.6	12.4	0
1-Septate	0	0	0	0	466.7	10.3	37.5	0
<i>Xylaria</i>	0	0	19.4	38.9	350.0	29.4	40.5	0
Mildews	0	0	0	23.3	427.8	22.2	44.9	0
<i>Didymella</i>	0	0	50.1	291.7	4122.0	343.3	650.5	0
Other coloured	0	0	17.5	38.9	374.3	24.3	39.8	0
Other hyaline	0	0	19.4	58.3	583.3	52.4	91.3	0
Filiform	0	0	0	0	116.7	6.8	17.2	0
<i>Myxomycetes</i>	0	0	0	19.4	252.8	13.4	28.4	0
Pollens (grains/m ³)								
Hazel	0	0	0	0	1	0	0.1	0
Birch	0	0	0	0	2	0	0.2	0
Alder	0	0	0	0	0	0	0	0
Oak	0	0	0	0	2	0	0.4	0
Nettle	0	1	3	9.8	73	7.0	10.0	0
Grass	0	0	2	13	135	13.1	24.6	0
Plantain	0	0	0	0	6	0.3	0.9	0
Lime	0	0	0	0	6	0.2	0.6	0
Dock	0	0	0	0	6	0.3	0.8	0
Chestnut	0	0	0	0	6	0.2	0.8	0
Willow	0	0	0	0	3	0.1	0.3	0
Pollutants								
PM ₁₀ (µg/m ³)	9.1	18.7	23.8	31.7	99.8	27.2	12.8	23
BS (µg/m ³)	2.3	7.3	9.9	13.5	34.0	10.6	5.0	0
O ₃ 8 hour (ppb)	1.4	11.4	16.5	22.8	79.9	18.8	11.2	1
NO ₂ 1 hour (ppb)	22.1	36.4	45.0	56.5	113.7	49.5	17.7	0
SO ₂ (ppb)	3.2	5.5	7.1	9.3	32.2	8.1	4.2	0
Meteorology								
Temperature (°C)	7.2	14.7	16.5	18.2	23.1	16.4	2.8	0
Humidity (%)	41.0	60.0	67.5	77.8	92.0	68.7	10.7	0

Min, minimum; Max, maximum; SD, standard deviation; Qu, quartile; NA, number of days, from 687, on which data were unavailable.

to low (q1) were of comparable magnitude. A similar pattern of response to A&E visits and admissions was observed for GP consultations except that for days with the highest spore concentration there appeared to be no difference in the risk of a visit with a complaint of asthma compared to days in the lowest quartile. In adults there appeared to be no evidence of an association between the outcome measures and the spore concentrations.

The number of degrees of freedom used to model seasonality in the asthma consultations, visits, and admissions in children

were 14.4, 14.3, and 12 representing approximately 1.6/1.6/1.5 degrees of freedom per month respectively. In adults the corresponding totals were 5, 6.6, and 10.3. The results may have been sensitive to the number of degrees of freedom used to model seasonality—fluctuations in the number of daily asthma events may have been attributed to spore concentrations when in fact they should have been attributed to normal seasonal variation. To examine the potential for this, an additional set of models were constructed using the generalised cross validation method to select degrees of freedom. This method tends to

Table 2 Relative risks for increases in visits to GP surgeries, A&E departments, and admission to hospital for asthma associated with increases in fungal spore concentrations including pollutants (black smoke (BS), ozone (O₃), nitrogen dioxide (NO₂), and sulphur dioxide (SO₂)) and grass and nettle pollen in two “pollutant” models

Outcome	Total spores		+ BS		+ O ₃		+ NO ₂		+ SO ₂		+ Grass		+ Nettle	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Children														
GP visits														
Q1	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2	1.05	(0.95 to 1.17)	1.06	(0.95 to 1.17)	1.07	(0.97 to 1.19)	1.05	(0.95 to 1.17)	1.05	(0.95 to 1.17)	1.06	(0.96 to 1.17)	1.06	(0.96 to 1.17)
Q3	1.08	(0.96 to 1.21)	1.08	(0.97 to 1.21)	1.09	(0.97 to 1.22)	1.08	(0.96 to 1.21)	1.08	(0.96 to 1.20)	1.08	(0.97 to 1.20)	1.08	(0.97 to 1.20)
Q4	0.98	(0.86 to 1.11)	0.98	(0.87 to 1.11)	0.97	(0.86 to 1.10)	0.98	(0.86 to 1.11)	0.97	(0.86 to 1.10)	0.98	(0.87 to 1.11)	0.98	(0.87 to 1.11)
AE visits														
Q1	1.00		1.00		1.00		0.00		1.00		1.00		1.00	
Q2	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.16)	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.15)
Q3	1.06	(0.95 to 1.17)	1.05	(0.95 to 1.17)	1.06	(0.95 to 1.18)	1.06	(0.95 to 1.18)	1.06	(0.96 to 1.18)	1.05	(0.95 to 1.17)	1.05	(0.95 to 1.17)
Q4	1.06	(0.94 to 1.18)	1.06	(0.94 to 1.18)	1.06	(0.94 to 1.18)	1.07	(0.95 to 1.20)	1.06	(0.95 to 1.19)	1.05	(0.94 to 1.18)	1.05	(0.94 to 1.18)
Admissions														
Q1	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2	1.01	(0.92 to 1.11)	1.01	(0.92 to 1.11)	1.01	(0.92 to 1.11)	1.01	(0.92 to 1.11)	1.01	(0.92 to 1.11)	1.00	(0.92 to 1.10)	1.00	(0.92 to 1.10)
Q3	1.04	(0.95 to 1.15)	1.04	(0.95 to 1.15)	1.04	(0.94 to 1.15)	1.05	(0.95 to 1.15)	1.05	(0.95 to 1.16)	1.04	(0.95 to 1.14)	1.04	(0.95 to 1.14)
Q4	1.07	(0.97 to 1.19)	1.08	(0.97 to 1.20)	1.07	(0.97 to 1.20)	1.08	(0.97 to 1.20)	1.08	(0.97 to 1.20)	1.07	(0.97 to 1.19)	1.07	(0.97 to 1.19)
Adults														
GP visits														
Q1	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2	1.02	(0.94 to 1.11)	1.02	(0.93 to 1.11)	1.01	(0.93 to 1.11)	1.02	(0.93 to 1.11)	1.02	(0.94 to 1.11)	1.01	(0.93 to 1.10)	1.01	(0.93 to 1.10)
Q3	1.03	(0.94 to 1.12)	1.02	(0.93 to 1.11)	1.03	(0.94 to 1.12)	1.03	(0.94 to 1.13)	1.03	(0.94 to 1.13)	1.03	(0.94 to 1.12)	1.03	(0.94 to 1.12)
Q4	1.01	(0.92 to 1.11)	1.03	(0.94 to 1.12)	1.01	(0.92 to 1.11)	1.01	(0.91 to 1.11)	1.01	(0.92 to 1.11)	1.01	(0.92 to 1.10)	1.01	(0.92 to 1.10)
AE visits														
Q1	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2	0.95	(0.86 to 1.05)	0.95	(0.86 to 1.05)	0.95	(0.86 to 1.05)	0.95	(0.86 to 1.05)	0.95	(0.86 to 1.05)	0.94	(0.86 to 1.04)	0.94	(0.86 to 1.04)
Q3	0.96	(0.87 to 1.07)	0.95	(0.86 to 1.05)	0.97	(0.87 to 1.08)	0.96	(0.86 to 1.07)	0.97	(0.87 to 1.07)	0.96	(0.87 to 1.07)	0.96	(0.87 to 1.07)
Q4	0.96	(0.86 to 1.08)	0.96	(0.87 to 1.07)	0.96	(0.86 to 1.07)	0.96	(0.85 to 1.07)	0.97	(0.86 to 1.08)	0.96	(0.86 to 1.07)	0.96	(0.86 to 1.07)
Admissions														
Q1	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2	1.00	(0.91 to 1.11)	1.01	(0.91 to 1.12)	1.00	(0.90 to 1.10)	1.01	(0.91 to 1.11)	1.00	(0.91 to 1.11)	1.01	(0.92 to 1.12)	1.01	(0.92 to 1.12)
Q3	1.04	(0.93 to 1.15)	1.01	(0.91 to 1.12)	1.04	(0.94 to 1.16)	1.04	(0.94 to 1.16)	1.04	(0.93 to 1.15)	1.04	(0.94 to 1.15)	1.04	(0.94 to 1.15)
Q4	0.99	(0.88 to 1.11)	1.04	(0.94 to 1.16)	0.99	(0.88 to 1.12)	1.00	(0.89 to 1.13)	0.99	(0.88 to 1.12)	0.99	(0.88 to 1.11)	0.99	(0.88 to 1.11)

The baseline is the lower quartile (Q1).

Figure 2 Log relative risk of the health outcome associated with a change in spore concentration from the lowest quartile (Q1) to the 2nd, 3rd, and 4th quartiles (Q2–Q4). Point estimates and 95% confidence intervals are shown.

overparameterise the models when the outcomes are serially correlated.²⁵ The degrees of freedom chosen using this automated method were 18.7, 22.6, and 21.9 in children and 8.9, 19.4, and 19.9 in the models for adults (data not shown). The patterns of associations derived from these models largely follow those observed in the models constructed using the PACF criterion. This suggested that the associations observed in the main analysis were unlikely to be confounded by inappropriate seasonal control.

Further sets of models were run using lagged values for the spore concentrations. These analyses were designed to investigate the possibility that the different health endpoints were affected by spore concentrations on different time frames—that is, a visit to a GP surgery following exposure to high spore concentrations may have taken longer to occur than an emergency admission to hospital. Lags between exposure and outcome of 1, 2, and 3 days were investigated. The results suggested that the associations were generally weaker for lags 1 and 2 and by lag 3 the associations observed in children had disappeared (data not shown).

Table 2 also shows the associations between the six outcome/age groups and quartiles of spore concentration with and without adjustment for air pollutants, BS, O₃, NO₂, and SO₂. The magnitude and direction of the associations remained largely unaltered following the inclusion of air pollution measures into the statistical models. Similarly, the addition of grass and nettle pollen did not alter the findings for total spore concentrations alone.

Subtotals for the three spore divisions were added in turn to the models for the three outcomes. The results of these analyses are presented in table 3. Increases in hospital admissions were associated with increases in spore concentrations for the groups Deuteromycota, and Basidiomycota (q2–q4 compared to q1) and with spore concentrations in q3–4 compared to q1 for Ascomycota. Associations with the three subtotals and A&E visits were less consistent although in some quartiles the increases in A&E visits were large and statistically significant. There was little evidence for associations with GP visits and any of the three spore subtotals. Unlike total spore concentrations, the spore group subtotals showed some associations with visits and admissions in adults, although these associations tended to be for one or two quartiles of their distribution only rather than for all three quartiles. Furthermore, none of the subgroups showed any evidence of a trend in the effect estimates across their range of concentrations.

Individual spore concentrations were added in turn to the models for children for the three outcomes. The results of

these analyses are presented in table 4. Increases in many individual spores showed associations with one or more of the health outcomes studied. The spores most strongly and consistently associated with A&E visits and hospital admissions were *Alternaria*, *Epicoccum*, *Botrytis*, *Agroclybe*, *Smuts*, coloured and hyaline Basidiospores, mildews, and other coloured Ascomycetes. The only spore associated with all three outcomes was *Coprinus*. A number of spores were associated with only one outcome.

DISCUSSION

We have shown that during the months June to mid October, when spores were most prevalent, increases in total spore concentrations were associated with increases in visits to A&E departments and hospitalisations for asthma in children. The statistical significance of these associations was weak. The evidence for associations with visits to GP surgeries was less clear. The associations with total spore concentrations observed in children were robust to the inclusion of outdoor air pollution and grass and nettle pollens in the models and were also insensitive to increases in the level of adjustment for seasonal control. When spore concentrations were grouped by type, the magnitude of associations with A&E visits and admissions in children were increased compared to those for total spores. A number of individual spore *taxa* were found to be associated with asthma admissions and visits to A&E departments. We found no evidence of associations between total fungal spore concentrations and asthma exacerbations in adults.

In this study we have examined associations between three health endpoints, subdivided by age, and a large number of spore *taxa*. We also chose to model the relationships between spore concentrations and health outcomes using ordinal variables, as we have assumed no a priori knowledge about the shapes of the concentration-response relationships. Hence there were a large number of estimates to interpret. We have therefore concentrated upon the size and direction of the associations rather than their statistical significance in drawing conclusions. One advantage of studying a large population was that the counts of the health events were relatively large compared to some time series studies. However, the identification and counting of individual spore *taxa* is labour intensive and so only data for two years were available reducing the power of the study.

One aspect of the collection of the A&E data is worthy of note. A visit to an A&E department represented simply the attendance of a member of the public at a hospital emergency department with a self-diagnosis of asthma. Although a

Table 3 Relative risks for increases in visits to GP surgeries, A&E departments, and admission to hospital for asthma associated with increases in fungal spore concentrations

Outcome	Total spores		Deuteromycota		Basidiomycota		Ascomycota	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Children GP visits	Q1	1.00	1.00		1.00		1.00	
	Q2	1.05 (0.95 to 1.17)	1.00	(0.90 to 1.10)	0.93	(0.83 to 1.04)	0.97	(0.87 to 1.09)
	Q3	1.08 (0.96 to 1.21)	0.97	(0.87 to 1.09)	1.09	(0.97 to 1.22)	1.08	(0.97 to 1.21)
	Q4	0.98 (0.86 to 1.11)	0.97	(0.86 to 1.10)	1.01	(0.90 to 1.14)	0.93	(0.83 to 1.05)
AE visits	Q1	1.00	1.00		1.00		1.00	
	Q2	1.04 (0.94 to 1.15)	1.00	(0.91 to 1.11)	0.99	(0.89 to 1.11)	1.02	(0.91 to 1.14)
	Q3	1.06 (0.95 to 1.17)	1.03	(0.93 to 1.15)	1.14	(1.02 to 1.27)	1.01	(0.90 to 1.14)
	Q4	1.06 (0.94 to 1.18)	1.00	(0.89 to 1.13)	1.07	(0.96 to 1.20)	1.15	(1.02 to 1.29)
Admissions	Q1	1.00	1.00		1.00		1.00	
	Q2	1.01 (0.92 to 1.10)	1.04	(0.95 to 1.14)	1.07	(0.97 to 1.18)	0.98	(0.89 to 1.09)
	Q3	1.04 (0.95 to 1.15)	1.05	(0.96 to 1.15)	1.16	(1.04 to 1.28)	1.06	(0.95 to 1.18)
	Q4	1.07 (0.97 to 1.19)	1.05	(0.94 to 1.18)	1.10	(0.99 to 1.23)	1.07	(0.96 to 1.20)
Adults GP visits	Q1	1.00	1.00		1.00		1.00	
	Q2	1.02 (0.94 to 1.11)	1.01	(0.93 to 1.10)	1.06	(0.97 to 1.16)	1.02	(0.93 to 1.11)
	Q3	1.03 (0.94 to 1.12)	0.98	(0.90 to 1.08)	1.12	(1.03 to 1.23)	1.03	(0.95 to 1.13)
	Q4	1.01 (0.92 to 1.11)	1.07	(0.98 to 1.18)	1.07	(0.97 to 1.17)	0.98	(0.89 to 1.08)
AE visits	Q1	1.00	1.00		1.00		1.00	
	Q2	0.95 (0.86 to 1.05)	0.94	(0.85 to 1.04)	1.06	(0.96 to 1.17)	1.08	(0.97 to 1.20)
	Q3	0.96 (0.87 to 1.07)	1.03	(0.93 to 1.15)	1.02	(0.91 to 1.13)	1.02	(0.91 to 1.15)
	Q4	0.96 (0.86 to 1.08)	1.03	(0.92 to 1.16)	0.99	(0.89 to 1.11)	1.03	(0.91 to 1.15)
Admissions	Q1	1.00	1.00		1.00		1.00	
	Q2	1.00 (0.91 to 1.11)	0.98	(0.88 to 1.08)	1.03	(0.93 to 1.14)	1.12	(1.00 to 1.25)
	Q3	1.04 (0.93 to 1.15)	1.06	(0.95 to 1.18)	1.01	(0.91 to 1.13)	1.07	(0.95 to 1.20)
	Q4	0.99 (0.88 to 1.11)	1.01	(0.90 to 1.14)	1.02	(0.91 to 1.15)	1.01	(0.89 to 1.14)

Q1–4, quartiles of fungal spore concentrations; Q1, baseline.

patient's own assessment of their health problems may have been affected by patterns in self-diagnosis and their awareness of asthma as a disease, it seems unlikely that these would have changed substantially during the relatively short study period and in a manner likely to have introduced bias in the estimates of the health effects of fungal spores. Furthermore, any trends in self-diagnosis resulting in a systematic change in the average number of daily visits attributed to asthma would have been modelled as long term trends in the daily asthma counts and hence accounted for in the analysis.

One potential limitation of this study was that spore counts were made at a single trap located 18 m above ground level in central London and used as the measurement of exposure for the whole study population. Unfortunately, data from other locations were not available to assess the spatial variation in spores. Previous research has shown that the results from a standard network monitoring site were representative of the general patterns of spore concentrations within a radius of 50 km.^{26–27} Fungal spores differ in their sizes and dispersal features according to *taxa* but those that are dispersed by the wind tend to be released in large numbers and spread over a large area.

Another potential problem with this study was the possibility of confounding by other seasonal or other environmental factors. Seasonal patterns in asthma exacerbations were particularly evident in children and are thought to be related to the increase in acute bronchitis and spread of respiratory infections as children return to school.^{28–31} Some other environmental risk factors such as ozone are also highly seasonal and could confound any associations between asthma exacerbations and fungal spores. We have tried however to limit these potential sources of confounding in a number of ways. Firstly, as the fungal spore counts were highly seasonal, peaking during the months June to October, we restricted our analysis to the main spore season. Secondly,

by carefully selecting model terms and carrying out sensitivity analyses we were able to assess the robustness of the observed associations to alternative model specifications. One potential disadvantage of restricting the analysis to the spore season might be that the relatively small number of *atopic* asthmatics sensitive to fungal spores³ would be prepared for the spore season and either start, or increase, their medication in advance of the season beginning. This could suggest that an all-year analysis might reveal associations that an analysis of the spore season would not. However, we felt that the benefit of reducing the potential for seasonal confounding outweighed any potential gain from an all-year analysis. This approach has been taken in a number of studies^{7 8 13 32} although not all.^{10 11 14}

The sizes of the associations between total spore counts and the three health indicators for children were broadly comparable, but there were differences in the pattern of responses across the health outcomes. For GP visits the associations in the second and third quartiles were elevated compared to the lowest quartile but not in the fourth quartile. For hospital admissions the associations increased in size as the spore concentrations increased. For A&E visits, associations in quartiles 2–4 were all elevated by similar amounts compared to quartile 1. One possible explanation for this pattern of responses was that the more severe asthma exacerbations, resulting in an emergency hospital admission, were provoked by the higher spore concentrations. Furthermore, it is possible that these more severe cases were unlikely to have involved a visit to a GP surgery, the patient attending A&E directly from where they were admitted to hospital. This hypothesis might also explain the lower risk ratios in the highest quartile for GP consultations. However, it was not possible to test this hypothesis with these unlinked data and we are not aware of any other studies that have examined associations across a range of health outcomes.

Table 4 Associations between individual spore *taxa* of division Deuteromycota and children's asthma consultations, A&E visits, and hospital admissions

Spore/outcome		GP		AE		HA	
		RR	95% CI	RR	95% CI	RR	95% CI
<i>Alternaria</i>	Q1	1.00		1.00		1.00	
	Q2	1.01	(0.90 to 1.13)	1.10	(0.99 to 1.22)	1.08	(0.99 to 1.19)
	Q3	1.05	(0.94 to 1.18)	1.09	(0.97 to 1.22)	1.09	(0.99 to 1.21)
	Q4	0.98	(0.85 to 1.13)	1.08	(0.94 to 1.24)	1.08	(0.96 to 1.23)
<i>Aspergillus</i>	Q1	1.00		1.00			
	Q2	0.98	(0.89 to 1.09)	0.92	(0.84 to 1.02)	0.99	(0.90 to 1.08)
	Q3	0.99	(0.88 to 1.10)	1.00	(0.90 to 1.12)	1.07	(0.97 to 1.17)
	Q4	0.97	(0.85 to 1.11)	1.01	(0.90 to 1.13)	1.05	(0.95 to 1.17)
<i>Cladosporium</i>	Q1	1.00		1.00			
	Q2	1.00	(0.89 to 1.13)	1.07	(0.96 to 1.20)	0.95	(0.86 to 1.05)
	Q3	1.01	(0.90 to 1.14)	1.03	(0.92 to 1.15)	1.04	(0.95 to 1.15)
	Q4	0.97	(0.85 to 1.10)	1.11	(0.98 to 1.25)	0.98	(0.88 to 1.10)
<i>Drechslera</i>	N	1.00		1.00		1.00	
	Y	1.01	(0.93 to 1.10)	1.01	(0.93 to 1.09)	1.06	(0.99 to 1.14)
<i>Epicoccum</i>	O	1.00		1.00		1.00	
	<M	1.02	(0.93 to 1.13)	1.07	(0.98 to 1.17)	1.11	(1.03 to 1.21)
	>M	1.01	(0.91 to 1.13)	1.07	(0.96 to 1.18)	1.09	(0.99 to 1.19)
<i>Periconia</i>	N	1.00		1.00		1.00	
	Y	0.97	(0.89 to 1.06)	1.03	(0.96 to 1.11)	0.99	(0.93 to 1.07)
<i>Stemphylium</i>	N	1.00		1.00		1.00	
	Y	1.06	(0.98 to 1.15)	0.99	(0.91 to 1.06)	1.02	(0.95 to 1.09)
Other coloured	Q1	1.00		1.00		1.00	
	Q2	0.93	(0.83 to 1.04)	0.98	(0.87 to 1.09)	1.08	(0.98 to 1.20)
	Q3	0.95	(0.85 to 1.06)	1.00	(0.89 to 1.11)	1.06	(0.96 to 1.17)
	Q4	0.88	(0.77 to 1.01)	0.99	(0.87 to 1.12)	1.12	(1.00 to 1.26)
Other hyaline	O	1.00		1.00		1.00	
	<M	1.10	(1.00 to 1.22)	1.05	(0.95 to 1.16)	0.97	(0.89 to 1.07)
	>M	1.08	(0.99 to 1.19)	1.06	(0.97 to 1.16)	0.97	(0.89 to 1.05)
<i>Torulla</i>	N	1.00		1.00		1.00	
	Y	0.95	(0.88 to 1.03)	1.01	(0.93 to 1.08)	0.96	(0.90 to 1.03)
<i>Botrytis</i>	N	1.00		1.00		1.00	
	Y	0.92	(0.85 to 0.99)	1.06	(0.98 to 1.15)	1.12	(1.04 to 1.20)
<i>Coprinus</i>	Q1	1.00		1.00		1.00	
	Q2	1.09	(0.97 to 1.23)	1.04	(0.93 to 1.17)	1.06	(0.95 to 1.18)
	Q3	1.10	(0.98 to 1.24)	1.05	(0.94 to 1.17)	1.10	(0.99 to 1.22)
	Q4	1.08	(0.93 to 1.26)	1.05	(0.91 to 1.21)	1.12	(0.98 to 1.28)
<i>Ganoderma</i>	Q1	1.00		1.00		1.00	
	Q2	1.01	(0.91 to 1.12)	1.02	(0.92 to 1.12)	1.05	(0.96 to 1.15)
	Q3	1.01	(0.90 to 1.13)	0.96	(0.86 to 1.07)	1.10	(1.00 to 1.22)
	Q4	1.09	(0.96 to 1.23)	0.98	(0.87 to 1.11)	1.06	(0.95 to 1.18)
<i>Agrocybe</i>	Q1	1.00		1.00		1.00	
	Q2	0.94	(0.84 to 1.06)	0.95	(0.84 to 1.07)	1.00	(0.90 to 1.12)
	Q3	0.85	(0.76 to 0.96)	1.01	(0.90 to 1.15)	1.09	(0.97 to 1.23)
	Q4	0.80	(0.67 to 0.97)	1.10	(0.93 to 1.31)	1.29	(1.10 to 1.51)
Rusts	N	1.00		1.00		1.00	
	Y	1.04	(0.95 to 1.13)	1.00	(0.93 to 1.08)	0.99	(0.92 to 1.06)
Smuts	O	1.00		1.00		1.00	
	<M	0.98	(0.89 to 1.07)	1.08	(0.99 to 1.18)	1.03	(0.95 to 1.11)
	>M	0.96	(0.84 to 1.10)	1.08	(0.95 to 1.22)	1.06	(0.94 to 1.18)
Other coloured	Q1	1.00		1.00		1.00	
	Q2	1.00	(0.89 to 1.12)	1.06	(0.94 to 1.19)	0.96	(0.86 to 1.07)
	Q3	0.92	(0.82 to 1.02)	1.06	(0.95 to 1.19)	1.09	(0.98 to 1.21)
	Q4	0.96	(0.83 to 1.09)	1.10	(0.96 to 1.25)	1.09	(0.96 to 1.23)
Other hyaline	N	1.00		1.00		1.00	
	Y	1.07	(0.96 to 1.18)	1.07	(0.97 to 1.17)	1.04	(0.96 to 1.13)
<i>Tilletiopsis</i>	N	1.00		1.00		1.00	
	Y	1.01	(0.93 to 1.10)	1.04	(0.96 to 1.13)	0.99	(0.92 to 1.07)
<i>Sporobolomyces</i>	O	1.00		1.00		1.00	
	<M	0.98	(0.89 to 1.08)	1.06	(0.97 to 1.15)	1.05	(0.96 to 1.14)
	>M	1.02	(0.92 to 1.12)	1.11	(1.01 to 1.22)	1.03	(0.94 to 1.13)
Leptosphaeria	Q1	1.00		1.00		1.00	
	Q2	0.99	(0.89 to 1.09)	1.10	(0.99 to 1.22)	0.98	(0.89 to 1.09)
	Q3	1.08	(0.96 to 1.22)	1.10	(0.98 to 1.24)	0.98	(0.88 to 1.09)
	Q4	0.93	(0.83 to 1.05)	1.10	(0.98 to 1.24)	0.97	(0.87 to 1.08)
Pleospora	N	1.00		1.00		1.00	
	Y	0.95	(0.85 to 1.07)	1.12	(1.01 to 1.25)	0.94	(0.85 to 1.04)
1-Septate	N	1.00		1.00		1.00	
	Y	1.01	(0.92 to 1.11)	1.05	(0.96 to 1.14)	0.98	(0.90 to 1.06)
Xylaria	O	1.00		1.00		1.00	
	<M	1.07	(0.98 to 1.16)	0.97	(0.89 to 1.05)	0.98	(0.91 to 1.05)
	>M	1.03	(0.92 to 1.14)	0.97	(0.87 to 1.07)	0.96	(0.88 to 1.05)
Mildews	N	1.00		1.00		1.00	
	Y	0.96	(0.88 to 1.04)	1.08	(1.00 to 1.16)	1.10	(1.02 to 1.18)
Didymella	O	1.00		1.00		1.00	
	<M	1.00	(0.92 to 1.10)	1.06	(0.98 to 1.16)	1.03	(0.95 to 1.11)
	>M	1.03	(0.93 to 1.14)	1.08	(0.98 to 1.19)	1.02	(0.94 to 1.12)

Table 4 Continued

Spore/outcome		GP		AE		HA	
		RR	95% CI	RR	95% CI	RR	95% CI
Other coloured	0	1.00		1.00		1.00	
	<M	0.94	(0.86 to 1.04)	1.04	(0.95 to 1.13)	1.06	(0.98 to 1.15)
	>M	0.97	(0.87 to 1.07)	1.05	(0.96 to 1.16)	1.08	(0.99 to 1.18)
Other hyaline	0	1.00		1.00		1.00	
	<M	1.01	(0.92 to 1.10)	1.01	(0.92 to 1.10)	0.96	(0.88 to 1.04)
	>M	0.96	(0.87 to 1.07)	1.00	(0.90 to 1.11)	1.09	(1.00 to 1.20)
Filioform	N	1.00		1.00		1.00	
	Y	0.99	(0.91 to 1.09)	0.96	(0.88 to 1.05)	1.07	(0.99 to 1.15)
Myxomycetes	N	1.00		1.00		1.00	
	Y	1.03	(0.95 to 1.11)	1.07	(0.99 to 1.15)	1.00	(0.93 to 1.07)

Q1–Q4, 1st to 4th quartile; Q1, baseline; 0, <M, >M, concentrations zero and below and above median (on non-zero days); Y, N, spores present and not present.

In table 5 (see <http://www.occenvmed.com/supplemental>) we have summarised the findings of published ecological time series studies of the effects of fungal spores on asthma hospitalisations and emergency room visits (to our knowledge there were no studies of fungal spores in relation to visits to general practitioners). The table lists the outcomes studied, the spores (or combination of spores) investigated and their main findings.

Only Newson and colleagues investigated associations between total spore concentrations and asthma admissions in children. They found no evidence of an association and their method of analysis did not give an estimate of the effect size for comparison with our own.¹⁰ Results from the two studies are consistent, however, in reporting no associations between total spore counts and asthma hospitalisations in adults. It is not clear in the present study why the observed associations tended to be concentrated in children rather than adults. Associations between total spores and visits to emergency departments for asthma have been studied by Dales and Lierl.^{9, 11} Dales, using a comparable time series method to this study, reported a significant increase in the number of asthma visits by children of 2.2% evaluated at the mean spore concentration (2062 spores/m³). The figure from our study was a 7% increase in visits for a change in spore concentrations from the 1st to 3rd quartiles (2493–5805 spores/m³). Conversely, Lierl, analysing only the months when spores were most prevalent in Cincinnati (April to October), found no evidence of an association despite testing the associations at lags 0, 1, 2, and 3.

A number of studies have investigated spore concentrations in the three main divisions—Deuteromycota, Basidiomycota, and Ascomycota. Dales examined associations between asthma admissions and A&E visits and spore concentrations from the three subdivisions in 10 Canadian cities and in Ontario respectively.^{7, 11} Associations were strongest between admissions and the three spore groups, less so for A&E visits—a finding comparable with our results. However, Newson reported no associations between admissions and any of the three subgroup totals.¹⁰ Similarly, findings from studies by Rosas (all-age asthma admissions) and Stieb (all-age emergency department visits) reported mixed results.^{12, 13}

Newson and colleagues did find associations between individual spore taxa (dichotomised at 90th percentile) and asthma admissions in children aged 0–14 years unlikely to be due to chance given the large number of analyses. These spores were hyaline Basidiospores, *Didymella*, *Leptosphaeria*, *Botrytis*, and other Ascomycetes. In the present study hyaline Basidiospores, *Didymella*, *Botrytis* and other Ascomycetes were all positively associated with admissions for asthma. However, *Leptosphaeria* was only associated with increased A&E visits, not admissions.

Dales and co-workers have studied individual spore taxa in relation to asthma emergency department visits⁷ and admissions for asthma¹¹ in Canada. They concluded that concentrations of *Alternaria*, *Cladosporium*, *Epicoccum*, *Aspergillus*, and *Ganoderma* were all associated with increased attendances to hospital emergency departments in children, although not all achieved statistical significance at the 5% level. Our findings supported their conclusions for *Alternaria*, *Cladosporium*, and *Epicoccum* in terms of increased visit numbers but without achieving statistical significance. We found no evidence for an association between asthma visits and concentrations of *Aspergillus* and *Ganoderma*. For admissions (all ages), spore counts from all three genera studied (Deuteromycetes comprising *Alternaria*, *Aspergillus*, and *Cladosporium*; Basidiomycetes comprising *Coprinus*, *Botrytis*, and *Ganoderma*; and Ascomycetes comprising *Leptosphaeria* and *Oospora* (powdery mildews)) were associated with increased asthma admissions. As table 4 of our study shows, these spores were found also to be associated with increased admissions for asthma in children (except for *Cladosporium* and *Leptosphaeria*, both of which were associated with A&E visits but not admissions—a somewhat conflicting result).

Another contemporary study conducted by Stieb and colleagues in 2000 examined numerous specific spore taxa as well as pollen and air pollution measures over a five year period in Saint John, Canada.¹³ They concluded that *Alternaria* and *Cladosporium*, measured in the summer months, were positively and significantly associated with increased visits to emergency departments for asthma. They also concluded that these associations were independent of concurrent air pollution concentrations. *Epicoccum* and *Ganoderma* were found to be negatively and significantly associated with asthma ED visits.

The GP and A&E visits and emergency hospital admissions for asthma used in the present analysis were also studied in relation to air pollution.^{17–19} For GP consultations in children, the percentage change in mean number of asthma visits for 10th–90th percentile increases in the pollutants studied ranged from –8.6% for ozone, 3.8% for PM₁₀ to 6.1% for NO₂. For children's A&E visits and hospital admissions the percentage changes for ozone, PM₁₀ and NO₂ were –5%, 7.4%, 9.0% and –6.2%, 3.3%, 2.1% respectively. Roughly comparable figures from this study for total spores and A&E visits and admissions in children were 6% and 7%. These results suggest that the short term health effects of fungal spores are of a similar magnitude (comparing 10th to 90th percentiles) as those of air pollution. We have not presented the results of an analysis of possible interactions between air pollution and spores since they will be the subject of a separate paper.

In this study we have presented the epidemiological evidence for an association between numbers of asthma

Main messages

- Fungal spore concentrations may provoke asthma attacks in children that result in visits to A&E departments and emergency admission to hospital. These findings were unlikely to be due to confounding by meteorological factors, pollen, or air pollution.
- These associations were comparable to those observed for ambient air pollution from similarly designed studies.

Policy implications

- Fungal spores may be responsible for some increases in the frequency and/or severity of asthma symptoms.
- Doctors and patients may need to consider exposure to fungal spores as a potential trigger for asthma and consider appropriate medication use as a precautionary measure.

exacerbations in the population and outdoor fungal spores. The question arises as to whether these associations are causal? It is likely that the proportions of daily asthma events (hospitalisations, etc) attributable to aeroallergen exposure are likely to be small. However, analyses of asthma epidemics occurring during thunderstorms^{33–38} and the unloading of soya beans in Barcelona³⁹ suggest that aeroallergens can play a significant role in precipitating asthma attacks. Furthermore, studies have linked the magnitude of the effects of fungal spores to asthma severity in subjects.^{40–41} This study does not throw any light on the possible mechanisms involved but does suggest that such associations are observable on “non-epidemic” days.

The epidemiological evidence from time series studies of the health effects of fungal spores is sparse by comparison to that for air pollution. The large number of spore *taxa* available for study together with the many different outcomes, defined by disease, age, and severity (admission, visit, etc), mean that it is difficult to build a coherent picture from the published literature. In our study of London during the summer months over a two year period we have found a pattern of results that are comparable with the findings from some studies but not others. Although the precision of the effect estimates from our study is low there is evidence to suggest that exposure to fungal spores in the outdoor environment may trigger or exacerbate asthma attacks leading to visits to emergency departments or hospitalisation. Furthermore, these estimates are comparable, if not larger, in size to those obtained from similarly designed studies of the health effects of air pollution. The public health significance of fungal spores in precipitating severe asthma attacks may have been underestimated.

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REFERENCES

- 1 Strachan DP. The role of environmental factors in asthma. *Br Med Bull* 2000;**56**:865–82.
- 2 Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;**49**:171–4.
- 3 Hendrick DJ, Davies RJ, D'Souza MF, et al. An analysis of skin prick reactions in 656 asthmatic patients. *Thorax* 1993;**30**:2–8.
- 4 Delfino RJ, Zeiger RS, Seltzer JM, et al. The effect of outdoor fungal spore concentrations on daily asthma severity. *Environ Health Perspect* 1997;**105**:622–35.
- 5 Ostro B, Lipsett M, Mann J, et al. Air pollution and exacerbation of asthma in African-American children in Los Angeles. *Epidemiol* 2001;**12**:200–8.
- 6 Jalaludin BB, Chey T, O'Toole BI, et al. Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. *Int J Epidemiol* 2000;**29**:549–57.
- 7 Dales RE, Cakmak S, Burnett RT, et al. Influence of ambient fungal spores on Emergency visits for asthma to a Regional children's hospital. *Am J Respir Crit Care Med* 2000;**162**:2087–90.
- 8 Hobday JD, Stewart AL. The relationship between daily asthma attendance, weather parameters, spore count and pollen count. *Aust N Z J Med* 1973;**3**:552–6.
- 9 Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 2003;**90**:28–33.
- 10 Newson R, Strachan D, Corden J, et al. Fungal and other spore counts as predictors of asthma admissions for asthma in the Trent region. *Occup Environ Med* 2000;**57**:786–92.
- 11 Dales RE, Cakmak S, Judek S, et al. Influence of outdoor aeroallergens on hospitalisation for asthma in Canada. *J Allergy Clin Immunol* 2004;**113**:303–6.
- 12 Rosas I, McCartney HA, Payne RW, et al. Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. *Allergy* 1998;**53**:394–401.
- 13 Stieb DM, Beveridge RC, Brook JR, et al. Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. *J Expos Anal Environ Epidemiol* 2000;**10**:461–77.
- 14 Lewis SA, Corden JM, Forster GE, et al. Combined effects of aerobiological pollutants, chemical pollutants and meteorological conditions on asthma admissions and A&E attendances in Derbyshire UK, 1993–1996. *Clin Experiment Allergy* 2000;**30**:1724–32.
- 15 Garty BZ, Kosman E, Ganor E, et al. Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. *Ann Allergy Asthma Immunol* 1998;**81**:563–70.
- 16 Katsouyanni K, Touloumi G, Samoli E, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: Results from 29 European cities within the APHEA2 project. *Epidemiol* 2001;**12**:521–31.
- 17 Hajat S, Haines A, Goubet SA, et al. Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. *Thorax* 1999;**54**:597–605.
- 18 Atkinson RW, Anderson HR, Strachan DP, et al. 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.
- 19 Atkinson RW, Bremner SA, Anderson HR, et al. Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. *Arch Environ Health* 1999;**54**:398–411.
- 20 Emberlin JC. Sampling Pollens. *J Aerosol Sci* 1997;**28**:365–70.
- 21 Buck SF. A method of estimation of missing values in multivariate data suitable for use with an electronic computer. *J R Stat Soc (B)* 1960;**22**:302–6.
- 22 Touloumi G, Atkinson R, Le Tertre A, et al. Analysis of health outcome time series data in epidemiological studies. *Environmetrics* 2004;**15**:101–17.
- 23 Wood SN, Augustin NH. GAMS with integrated model selection using penalised regression splines and applications in environmental modelling. *Ecol Model* 2002;**157**:157–77.
- 24 Green PJ, Silverman BW. *Nonparametric regression and generalised linear models*. London: Chapman and Hall, 1994.
- 25 Hart JD. Kernel regression estimation with time series errors. *J R Stat Soc (B)* 1991;**53**:173–87.
- 26 Eversmeyer MG, Kramer CL. Vertical concentrations of fungal spores above wheat fields. *Grana* 1987;**26**:97–102.
- 27 Hirst JM, Stedman OJ, Hurst GW. Long distance spore transport. Vertical sections of spore clouds over the sea. *J Gen Microbiology* 1967;**48**:357–77.
- 28 Storr J, Lenney W. School holidays and admission with asthma. *Arch Dis Child* 1989;**64**:103–7.
- 29 Ayres JG. Trends in asthma and hay fever in general practice in the United Kingdom. 1976–83. *Thorax* 1986;**41**:111–16.
- 30 Johnston SL, Pattemore PK, Sanderson G, et al. Community study of the role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;**310**:1225–9.
- 31 Khot A, Burn R, Evans N, et al. Seasonal variation and time trends in childhood asthma in England and Wales 1975–1981. *BMJ* 1984;**289**:235–7.

- 32 Jones GN, Sletten C, Mandry C, et al. Ozone level effect on respiratory illness: an investigation of emergency department visits. *South Med J* 1995;**88**:1049–56.
- 33 Bellomo R, Gigliotti P, Treloar A, et al. Two consecutive thunderstorm associated epidemics of asthma in the city of Melbourne. The possible role of rye grass pollen. *Med J Aust* 1992;**156**:834–7.
- 34 Celenza A, Fothergill J Kupek E, et al. Thunderstorm associated asthma: a detailed analysis of environmental factors. *BMJ* 1996;**312**:604–7.
- 35 Hajat S, Goubet SA, Haines A. Thunderstorm-associated asthma: The effect on GP consultations. *Br J Gen Pract* 1997;**47**:639–41.
- 36 Packe GE, Ayres JG. Asthma outbreak during a thunderstorm. *Lancet* 1985;**2**:199–204.
- 37 Venables KM, Allitt U, Collier CG, et al. Thunderstorm-related asthma—the epidemic of 24/25 June 1994. *Clin Exp Allergy* 1997;**27**:725–36.
- 38 Wallis DN, Webb J, Brooke D, et al. A major outbreak of asthma associated with a thunderstorm: experience of accident and emergency departments and patients' characteristics. *BMJ* 1996;**312**:601–4.
- 39 Anto JM, Sunyer J. Asthma collaborative group of Barcelona. A point source asthma outbreak. *Lancet* 1986;**327**:900–3.
- 40 O'Driscoll BR, Hopkinson LC, Denning DW. Mould sensitisation is common amongst patients with severe asthma requiring multiple hospital admissions. *BMC Pulmonary Medicine* 2005;**5**:1–10.
- 41 Denning DW, O'Driscoll BR, Hogaboam CM, et al. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;**27**:615–26.

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