

Original article

Epidemic asthma and the role of the fungal mold *Alternaria alternata*

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Background: After July 29, 2002, an epidemic of asthma admissions was associated with a thunderstorm in the United Kingdom.

Objective: We sought to study the cause of epidemics of asthma associated with thunderstorms.

Methods: We performed a case-control study of 26 patients presenting to Cambridge University Hospital with asthma after the thunderstorm. Control subjects were 31 patients with summer seasonal asthma. Subjects underwent skin tests and specific IgE serology to inhaled aeroallergens. Meteorologic and aerobiologic data correlated with asthma admissions were analyzed.

Results: Twenty-three of 26 cases had IgE sensitization to *Alternaria* species. Eleven of 31 control subjects gave a history of asthma exacerbation during thunderstorms. Ten of these 11 control subjects were sensitive to *Alternaria* species on skin testing, but *Alternaria* species sensitivity was only identified in 4 of the 20 remaining control subjects who did not report thunderstorm-related asthma symptoms. The odds ratio of having epidemic thunderstorm-related asthma if sensitive to *Alternaria* species was 9.31 (95% CI, 2.305-37.601; $P = .0008$) and 63.966 (95% CI, 3.577-1143.9; $P < .0001$) if sensitive to *Alternaria* species, *Cladosporium* species, or both. Poisson regression analysis showed that counts of broken *Alternaria* species and *Didymella* and *Cladosporium* species were significantly correlated with each other and with asthma admissions. The thunderstorm was associated with increased levels of *Alternaria*, *Cladosporium*, and *Didymella* species.

Conclusions: *Alternaria alternata* sensitivity is a compelling predictor of epidemic asthma in patients with seasonal asthma and grass pollen allergy and is likely to be the important factor in thunderstorm-related asthma.

Clinical implications: *Alternaria* species sensitization in asthmatic subjects with grass pollen sensitivity predicts susceptibility to thunderstorm-associated asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, thunderstorm, fungal spores, fungal molds, *Alternaria alternata*, broken *Alternaria*, *Didymella*, *Cladosporium*, grass pollen, epidemic, seasonal asthma

There was a sudden increase in asthma admissions in Cambridge, United Kingdom, associated with thunderstorms on July 29 and 30, 2002. Similar outbreaks were reported by hospitals in the same region in Bury St Edmunds, Huntingdon, Southend, and Chelmsford. Three patients were admitted to the Cambridge University Hospital intensive care unit requiring ventilation, and 1 possible victim was dead on arrival, the only asthma-related death in Cambridge in 2002.

Previous asthma epidemics have been reported in association with thunderstorms in Birmingham, United Kingdom, July 6 and 7, 1983¹; Nottingham, United Kingdom, June 20, 1984²; Melbourne, Australia, late spring 1984 and 1987 and November 29, 1989^{3,4}; London, United Kingdom, June 24, 1994⁵; and Wagga Wagga, Australia, October 30, 1997.⁶ These epidemics all occurred during the grass pollen season, and the patients were found to have hay fever or asthma with grass pollen allergy.⁷ The current assumption is that grass pollen sensitivity is responsible for outbreaks of thunderstorm-related asthma in sensitive individuals.^{5,8} However, epidemics of asthma in the United Kingdom are infrequent, even though thunderstorms and rainfall occur several times each year during the grass pollen season between May and June (Met Office data).

A recent study from Canada reported a strong association between emergency visits for asthma and thunderstorms that could not be explained by an increase in grass pollen counts but suggested that the mechanism might be through an increase in fungal spore counts.⁹ Sensitization to molds is a risk factor for severe and fatal asthma.¹⁰⁻¹² Targonski et al,¹² found the risk of asthma-related deaths more than doubled during days with high mold spore counts. A study by Newson et al¹³ indicated that asthma epidemics in the Trent region of the United Kingdom were about 10-fold more likely on days with high mold counts. *Alternaria* and *Cladosporium* species are widely distributed and, like *Didymella* species, grow on cereals and grasses. Approximate spore sizes are $9 \times 100 \mu\text{m}$ for *Alternaria* species, 2 to 10×3 to $35 \mu\text{m}$ for *Cladosporium* species, and 4 to 10×12 to $25 \mu\text{m}$

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Abbreviations used

ED: Emergency department
 GMT: Greenwich Mean Time
 SHA: Strategic Health Authority

for *Didymella* species. Fungal spores as aeroallergens increase to very high levels in late summer, and environmental levels have been found to be increased during thunderstorm-related outbreaks of asthma.⁹

The thunderstorm-related outbreak of asthma in eastern England occurred in late July, when grass pollen levels were decreasing. At this time, fungal spores increase rapidly to peak levels. Therefore we hypothesized that the reported sudden and severe increase in asthma morbidity was due to fungal spore exposure in susceptible allergic asthmatic subjects. We report the results of a case-control study conducted to investigate this outbreak and propose the likely mechanism for the cause of thunderstorm-related asthma.

METHODS

The study was approved by the local research and ethics committee. Investigation was by means of case-control study of 26 case patients who presented to the hospital with acute asthma during the outbreak and 31 control subjects with seasonal asthma during the grass pollen season. Informed written or verbal consent was obtained from cases and control subjects.

Participants

Cases. Fifty-seven patients with a clinical diagnosis of asthma admitted to the medical admissions unit or seen in the emergency department (ED) at Cambridge University Hospital on July 29–31 after the thunderstorm were identified from the records by using the ED code RSO2 (for asthma). Subjects were sent a standard information sheet and questionnaire. Patients who did not reply were followed up with a telephone interview. In total, 26 responded to an invitation to participate in the study. Those who did not attend for clinical review, did not reply to the questionnaire, or were not contactable after discharge from the hospital were excluded from the study.

Control subjects. Control subjects were adult asthmatic patients older than 16 years consecutively attending the asthma and allergy clinic at Cambridge University Hospital. They were selected by nurses unaware of the study protocol if they gave a history of seasonal asthma during the grass pollen season before undergoing skin testing. Therefore details of the control subjects' allergic sensitization were not known before enrollment, in particular whether they had thunderstorm-related asthma. They were asked to complete the same questionnaire as the cases.

Specific allergen testing. Skin prick tests and specific IgE serology were undertaken to test for IgE-mediated sensitization to a number of allergens, including mixed grass pollen, tree pollen, *Alternaria alternata*, *Cladosporium cladosporioides*, *Aspergillus fumigatus*, and house dust mite (*Dermatophagoides pteronyssinus*; Allergy Therapeutics, Worthing, United Kingdom [UK]). Twenty-three of 26 cases had blood drawn for measurement of specific IgE serology, and 20 of 26 underwent allergy skin tests. Skin prick testing was performed by using standard methods, and a positive test response was identified as a wheal diameter of at least 3 mm greater than that elicited by the

negative control. A positive result from either skin prick tests or specific IgE serology was taken as evidence for specific allergen sensitization.

Questionnaire. The questionnaire contained 23 domains, requesting demographic details, asthma history (including precipitating factors), previous thunderstorm-related asthma symptoms, previous admissions for asthma, and courses of oral corticosteroids and contemporaneous treatment of asthma.

Asthma admission data. Numbers of asthmatic attendees during June through August of 1996 through 2005 were collected from the Cambridge University Hospital ED records, and asthma admissions to hospitals in the Norfolk, Suffolk, and Cambridgeshire Strategic Health Authority (SHA; configuration before July 2006) were obtained from the Hospital Episodes Statistics database by using the ICD10 codes for asthma (J45, J46). The pollen and fungal spore counts reported in this article were recorded at Derby, United Kingdom, and therefore we also extracted asthma admissions data from Hospital Episode Statistics for Trent SHA.

Pollen and fungal spore counts. Volumetric spore traps¹⁴ have been used to monitor pollen and spores at Derby, United Kingdom, since 1970. Daily slide or 7-day drum traps were used. Mounting and staining techniques and average daily concentrations per cubic meter of air for fungal spores and grass pollen were obtained by using standard methods.^{15,16} Daily counts of pollen and spores were recorded from June through August, and hourly counts were recorded from July 28 to August 3, 2002. Broken or damaged *Alternaria* species spores were expressed as a percentage of the total.

Air quality and meteorology. Ozone concentrations were downloaded from the UK National Air Quality Information Archive. Hourly concentrations during July 28 through 31, 2002, and daily concentrations during June through August 2002 to 2005 were extracted for Wicken Fen (near Cambridge) and Nottingham.

Back trajectories, giving the source of air over East Anglia on July 29 and 30, were provided by the Atmospheric Dispersion group at the Met Office. Recorded lightning strikes were extracted for the whole of July 2002, and data for July 28th through 31st were converted into strikes per hour per square kilometer for Cambridgeshire and Derbyshire. Hourly (for July 28–31, 2002) and daily (for June–August 2002) data for temperature, rainfall, wind speed and direction, maximum gust speed, and relative humidity for Cambridge and Watnall (Derbyshire) were extracted from Met Office databases.

Harvesting. Fortnightly national arable reports are compiled by ADAS, the former governmental advisory service that is now a consultancy and research organization (http://www.adas.co.uk/index.html?menu_pos=home). ADAS accessed the 2002 reports for agriculture and horticulture for East Anglia, specifically records of harvesting activity.

Statistical analysis

Comparisons between cases and control subjects were analyzed by using the statistical software package Graphpad (<http://www.graphpad.com>). Odds ratios were calculated, and 2-sided *P* values of less than .05 were considered significant. The Woolf approximation was used to calculate 95% CIs.

The associations between admissions in the Norfolk, Suffolk, and Cambridgeshire and Trent SHAs and meteorologic factors, pollen levels, percentage broken *Alternaria* species counts, and whole fungal spore counts were initially modeled with Poisson regression. However, to correct for extra-Poisson variation caused by daily counts, random-effects Poisson regression was used, with the days as random effects and other measurements as fixed covariates. S-PLUS (Insightful, Seattle, Wash) and WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) were used to estimate models. The mean daily counts were log transformed to fit a normal distribution. To model the serial structure of the data, in which measurements

TABLE I. Details of cases and control subjects

	Cases (n = 26)	Control subjects	
		All control subjects (n = 31)	Thunderstorm positive (n = 11)
Thunderstorm-related asthma	26	11	11
Female sex	11	17	6
Age (mean [range]) (y)	38.6 (18-67)	38.1 (16-60)	39.3 (16-58)
Previous asthma admissions	10	21	6
Oral steroids in the previous 5 y	16	23	10
Family history of atopy	14	18	10
Seasonal asthma symptoms	25	31	11
Symptoms starting before thunderstorm	18	10	10
Grass pollen sensitive*	22	28	8
<i>Alternaria</i> species sensitive*	23	14	10
<i>Cladosporium</i> species sensitive*	16	9	7
House dust mite sensitive*	13†	11	5
Tree pollen sensitive	10†	15	1
Cat allergen sensitive	10†	13	5

*As measured by means of skin prick testing, specific IgE serology, or both.

†From 20 subjects who had skin tests.

close together in time are more likely to be similar, an autoregressive model was used to relate the number of admissions on any day to the number of admissions on the previous day, as well as the covariates. Admissions in both regions were compared with the previous day's pollen and fungal spore counts to account for variation in the timing of intervening rainfall. Data are presented as frequencies or mean values unless otherwise stated.

RESULTS

Cases

Ninety-two patients older than 16 years attended the Cambridge University hospital ED with asthma between July 29 and August 5. Based on data for July from August 1999 from 2001, expected attendances would have been 8 to 9 patients over this period. Fifty-seven patients with asthma attended the hospital on July 29-31. Eight subjects younger than 18 years were excluded, 1 subject had left the country, and 22 did not attend follow-up or were not contactable and therefore were not included in the study (Table I).

Three of the 26 cases were admitted to the intensive care unit with severe asthma and required ventilation. Twenty-five of 26 cases provided a history of asthma symptoms or exacerbations only in summer. The remaining patient experienced asthma exacerbations in autumn. One of 26 presented with asthma for the first time. Eighteen gave a history of asthma since childhood, 24 had hay fever, and 17 gave a previous history of eczema. Eighteen of 26 cases reported asthma symptoms starting before rainfall. Only 7 of 26 cases were taking inhaled corticosteroids before the thunderstorm. After the thunderstorm, at follow-up in the asthma clinic, 25 of 26 were taking inhaled steroids.

Total IgE levels were increased at greater than 100 kU/L in 19 of 23 cases tested. Twenty-three of 26 cases were sensitive to *Alternaria* species, 16 of 26 were sensitive to *Cladosporium* species, and 22 of 26 had positive results to grass pollen on either skin prick testing or IgE serology (Table II).

Control subjects

Eleven of 31 control subjects with seasonal asthma gave a history of asthma exacerbations during thunderstorms. Five of these 11 described an exacerbation of asthma during the July 2002 thunderstorm and 6 during a thunderstorm in July 2003, 3 of 11 in both 2002 and 2003, and 3 of 11 during thunderstorms in other years. None of the control subjects were admitted in 2002 during these exacerbations, although 21 of 31 had previously been admitted with exacerbations of asthma, and 23 of 31 had required oral corticosteroids in the past 5 years. On skin prick testing, 10 of 11 were sensitive to *Alternaria* species, and 8 of 11 were grass pollen sensitive. Twenty-eight of 31 control subjects were grass pollen sensitive. Of the 3 control subjects not sensitive to grass pollen, 2 experienced typical symptoms of hay fever and were sensitive to *Alternaria* and *Aspergillus* species. The remaining control subjects were sensitive only to *Alternaria* species. Nine of 31 control subjects were sensitive to *Cladosporium* species, of which 7 gave a history of thunderstorm-related asthma (Table I).

Alternaria species sensitivity was a strong predictor of thunderstorm-related asthma in both the case and control groups (Table II).

Meteorology of July 29 and 30, 2002

In Cambridge, the summer of 2002 was generally wet, but during the week to July 29, there was little rain and relative humidity decreased from a high of 93% to around 60%, and daily maximum temperatures were above the long-term average. Ozone concentrations increased daily and on July 29 exceeded 180 $\mu\text{g}/\text{m}^3$, the high threshold as defined by the Department of Health Committee for the Medical Effects of Air Pollution (Department of Health Committee for the Medical Effects of Air Pollution; <http://www.advisorybodies.doh.gov.uk/comeap/>).

TABLE II. *Alternaria* species sensitivity, *Cladosporium* species sensitivity, or both in cases and control subjects and odds ratios for development of thunderstorm-related asthma based on sensitivities from skin prick tests and specific IgE serology

		Cases	Control subjects	Odds ratio (95% CI)	P value
<i>Alternaria</i> species	Positive	23	14	9.31 (2.31-37.6)	.0008
	Negative	3	17		
<i>Cladosporium</i> species	Positive	16	9	3.91 (1.29-11.84)	.017
	Negative	10	22		
<i>Cladosporium</i> or <i>Alternaria</i> species	Positive	26	14	63.966 (3.58-1143.9)	<.0001
	Negative	0	17		

Early on July 29, a line of converging air running southwest-northeast over southeast England, coupled with surface heating, saw the explosive development of thunderstorms from 10 AM Greenwich Mean Time (GMT) in Cambridgeshire, Essex, and East Midlands in the afternoon. In Cambridge, there was a storm during the evening of July 29, with lightning and rainfall at 8 PM GMT. Data for Watnall (between Derby and Nottingham) also showed evidence for a storm with associated cold dry outflow (data not shown). Analysis of trajectories showed that the air over Cambridge had been over Derby 6 hours earlier, and therefore pollen and spore counts are likely to be representative of levels in Cambridge. The main thunderstorm in East Anglia and the peak in asthma admissions occurred on July 30.

Pollen and spore counts

Threshold concentrations for triggering allergic symptoms are estimated to be 100 spores/m³ for *Alternaria* species and 3000 spores/m³ for *Cladosporium* species.¹⁷ There is no agreed threshold concentration for *Didymella* species, a 1-septate ascospore, but the count on July 30, 2002, was the highest in Derby since records began in 1970. The threshold level routinely used in the United Kingdom for allergic symptoms to grass pollen is 50 grains/m³ of air.¹⁸ Hourly data for July 28-30 (data not shown) showed that *Alternaria* species values were above the threshold for most of July 28 and 29 and until 6 PM GMT on July 30. Because the main pollen and spore counting was conducted in Derby, 60 miles east of Cambridge, we also obtained *Alternaria* species counts for Cambridge on July 29, and these were greater than 400/m³ (personal communication, Ursula Allitt). *Cladosporium* species values were above the threshold during July 28 and 29 and for most of July 30. *Didymella* species values were low on the 28th and 29th but increased dramatically at 1 AM GMT on July 30 and remained at exceptionally high levels until 5 AM GMT. Concentrations decreased from 9 AM to 4 PM GMT and then increased again, peaking at 6 PM GMT and remaining high throughout the rest of July 30 and 31, with the highest concentrations from 9 AM to 5 PM GMT. Other ascospores, including *Leptosphaeria* species, as well as *Didymella* species, were found in exceedingly high numbers on July 30 and 31, together with hyaline basidiospores, including *Sporobolomyces* and *Tilletiopsis* species. Grass

TABLE III. Percentage of broken or damaged *Alternaria* species spores, July 28-31, 2002

2002	<i>Alternaria</i> species spores per cubic meter of air	<i>Alternaria</i> species spores, % broken or damaged
July 28	400	49
July 29	655	25
July 30	240	23
July 31	5	0

pollen was intermittently above threshold values on July 28 and after 4 PM GMT on July 29 and 30.

Harvesting

National arable reports show that winter barley was harvested as normal, from mid-end July, whereas harvesting of winter wheat was delayed by rain, until mid-end August. Combine harvesting results in fragmentation of *Alternaria* species spores (Table III). Farmers received forecasts of the thunderstorms of July 29 and 30, 2002, and would have increased harvesting activity in response.

The previous day's broken *Alternaria*, *Didymella*, and *Cladosporium* species counts were highly correlated with each other and significantly associated with asthma admissions (Table IV and Fig 1). An increase in broken *Alternaria* species count of 10/m³ increased the number of asthma admissions by 2.21 times. The previous day's broken *Alternaria* species value remained just as significantly associated with asthma admissions when the previous day's *Didymella* species value and rainfall were included in the model (data not shown). Conversely, the previous day's grass pollen count was negatively associated with asthma admissions, with a 13% reduction in asthma admission rate per 100 pollen grain increase per cubic meter. The autoregressive models did not improve model fit, and results are therefore not reported.

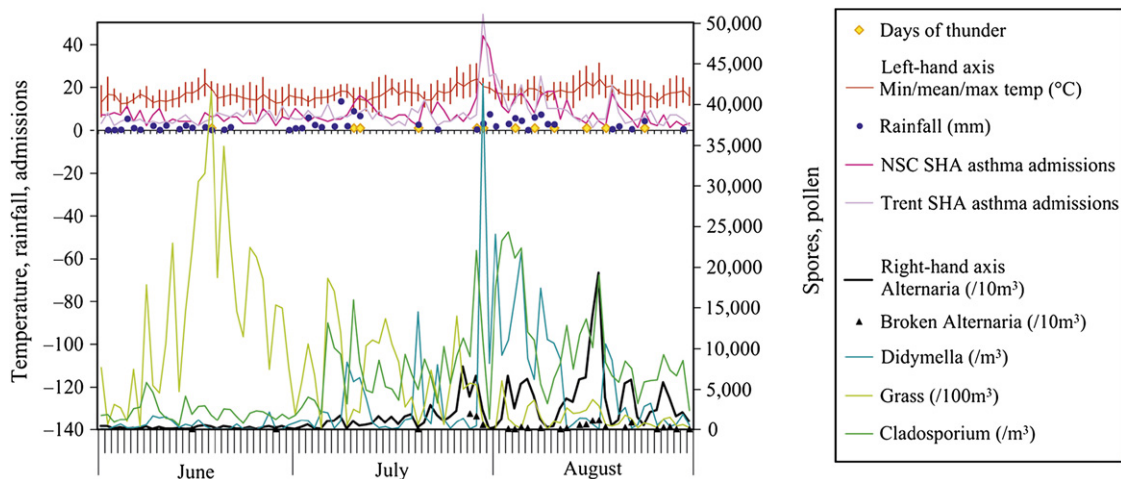
DISCUSSION

The fungal spores of *Alternaria* and *Cladosporium* species are known to cause allergic sensitization and seasonal asthma symptoms. In the United Kingdom in July and August (at the end of the grass pollen season),

TABLE IV. Results of random-effects Poisson regression analyses on relative asthma admission rates with 95% CIs

Variable (previous day's count)	Norfolk/Suffolk/Cambridgeshire RAAR (95% CI)	Trent RAAR (95% CI)	Combined RAAR (95% CI)
Grass pollen (per 100 increase/m ³)	0.85 (0.72-1.01), <i>P</i> = .0688	0.86 (0.73-1.02), <i>P</i> = .0819	0.87 (0.75-0.99), <i>P</i> = .0434
<i>Alternaria</i> species (per 1000 increase/m ³)	0.99 (0.58-1.62), <i>P</i> = .9474	1.17 (0.71-1.87), <i>P</i> = .5353	1.05 (0.68-1.61), <i>P</i> = .8259
Broken <i>Alternaria</i> species (per 10 increase/m ³)	2.36 (1.54-3.66), <i>P</i> < .0001	2.10 (1.34-3.28), <i>P</i> = .0011	2.21 (1.51-3.27), <i>P</i> < .0001
<i>Didymella</i> species (per 10,000 increase/m ³)	1.68 (1.43-2.01), <i>P</i> < .0001	1.60 (1.34-1.90), <i>P</i> < .0001	1.65 (1.42-1.90), <i>P</i> < .0001
<i>Cladosporium</i> species (per 10,000 increase/m ³)	1.47 (1.15-1.86), <i>P</i> = .0015	1.53 (1.22-1.92), <i>P</i> = .0002	1.47 (1.20-1.79), <i>P</i> = .0002

RAAR, Poisson regression analyses on relative asthma admission rates.

**FIG 1.** Graphic representation of asthma admissions, Cambridge meteorology and Derbyshire aerobiology from June-August 2002.

environmental levels of these spores increase rapidly, and allergic sensitization correlates with the severity of asthma symptoms.¹¹ In sensitive individuals inhalation of *Alternaria* species spores results in an asthmatic response, followed by an increase in bronchial hyperresponsiveness.¹⁹ Sensitivity to *Alternaria* species is associated with a more severe phenotype of asthma and is reported in patients who either died or experienced a near-fatal episode of asthma.¹⁰ Asthma deaths attributed to fungal spore allergy are associated with increased *Alternaria* species levels. In Chicago a 2-fold increase in asthma deaths was reported on days with high fungal spore counts but not high grass or ragweed pollen levels.¹² Seasonal peaks in asthma deaths have also been reported in August in the eastern region of the United Kingdom,²⁰ in Scotland,²¹ and in September and October in Ontario, Canada.²² Three of our cases with thunderstorm-related asthma presented with life-threatening asthma. One was hypoxic with pulseless electrical activity and pressures of 60 mm H₂O when intubated. The only asthma-related death in Cambridgeshire in 2002 occurred on July 29 on the day of the storm.

Previous studies of asthma exacerbations associated with thunderstorms have shown that the majority occur in allergic asthmatic subjects sensitive to grass pollen.⁸ Our data support this view, with 22 of 26 cases sensitive to grass pollen with a high incidence of seasonal asthma and hay fever. However, not all patients with seasonal asthma or grass pollen sensitivity and hay fever have asthma symptoms during thunderstorms, and not all thunderstorms during the height of the grass pollen season in June are associated with epidemic asthma. In 2002, thunder and rainfall occurred in June at the height of the grass pollen season and in early July, when grass pollen levels were still increased.

During the period of interest for our study, grass pollen levels were well below the peaks seen a few weeks earlier. Therefore to identify the difference between subjects with seasonal asthma who have thunderstorm-related asthma compared with those who do not, we chose a control group of consecutive asthmatic patients who gave a clinical history of predominantly seasonal asthma before the results of skin testing were known. As expected, all of our 31 control subjects were atopic, and the majority were

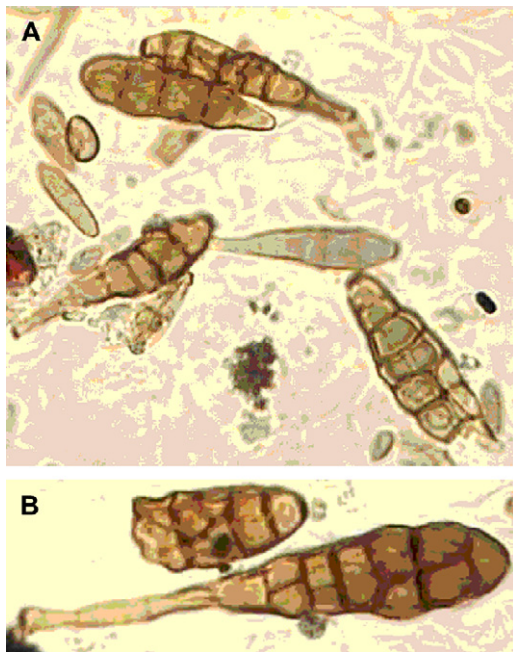


FIG 2. A, *Alternaria alternata* spores. B, Broken *Alternaria* spore adjacent to an intact spore.

grass pollen sensitive. Eleven of our 31 control subjects also gave a history of thunderstorm-related asthma, and 10 of the 11 were sensitive to *Alternaria* species. There were only 3 control subjects who were not grass pollen sensitive; all 3 had positive skin test responses to *Alternaria* species and experienced exacerbations of asthma during thunderstorms. It was likely therefore that this group of 11 control subjects had a similar but milder phenotype of epidemic asthma during thunderstorms. Patients with hay fever have bronchial hyperresponsiveness during the grass pollen season, irrespective of whether they have asthma symptoms.²³ The rapid increase in fungal spore levels overlaps the end of the grass pollen season, thereby preventing the natural recovery of bronchial hyperresponsiveness in asthmatic subjects allergic to spores at the end of the grass pollen season.²³ Therefore although grass pollen sensitivity is not an absolute prerequisite for thunderstorm-related asthma, by causing bronchial hyperresponsiveness, it acts as a cofactor in patients with hay fever and *Alternaria* species allergy by lowering the threshold at which severe acute asthma takes place.

Our results suggest that epidemic thunderstorm-related asthma toward the end of the grass pollen season is most strongly associated with fungal spore sensitivity and particularly with *Alternaria* species. During the week leading up to July 29, weather conditions were ideal for *Alternaria* and *Cladosporium* species, resulting in levels that exceeded the critical threshold.¹⁷ On the 3 days after July 29, there was a 10- to 20-fold increase in the expected number of emergency attendances for acute asthma associated with an increase of both broken and whole

A. alternata spore counts before and during the storm (Fig 2). *Didymella exitialis* shares many antigens with *Alternaria* species, and the very high levels of *Didymella* species released after the rain might have also contributed to some of our asthma attendances. Unfortunately, it was not possible to test this theory because *Didymella* species was not available to us as a standardized extract for skin testing. However, previous experienced investigators found that *Didymella* species sensitization was exceptionally uncommon, and therefore routine testing to this fungal mold was discontinued many years ago (personal communication, William Frankland). In a similar study 20 years ago, Packe and Ayres¹ reported using skin prick test solutions for sensitization to *D. exitialis*. Their results argue against an important role for *Didymella* species, *Sporobolomyces* species, or both. Our results also suggest cross-sensitization between fungal spores. Sixteen of 23 cases and 7 of 11 control subjects with thunderstorm-related asthma exhibited *Cladosporium* species sensitivity. Only 1 of the 33 cases or control subjects who experienced thunderstorm-related asthma was not sensitized to *Alternaria* or *Cladosporium* species, clearly demonstrating the impressive value of skin testing to *Alternaria* and *Cladosporium* species in identifying cases of thunderstorm-related asthma.

Farming practice contributes to the increase in fungal spore levels before thunderstorms. *Alternaria*, *Cladosporium*, and *Didymella* species grow on cereals. Hyde and Williams²⁴ suggested that *Alternaria* species spores are present in large numbers, especially during harvesting, and can be inhaled whole or as fragments. Corden and Millington²⁵ frequently observed bursts of *Alternaria* species spores during grass mowing and harvesting and microscopic evidence of *Alternaria* species spores broken into fragments, presumably caused by mechanized harvesting. We found that from July 28-30, 2002, approximately a quarter of the spores were damaged or broken, releasing submicronic *Alternaria* species particles that more easily access the lower respiratory tract. Over many years of microscopic examination of the air flora, *Alternaria* species is the only fungal spore that has been found broken. Friesen et al²⁶ observed that harvesting liberated immense numbers of fungal spores, many carried large distances by wind currents. Furthermore, in response to a Met Office forecast of heavy rain or thunderstorm, cereal farmers in the United Kingdom will bring forward harvesting to save their crop. This leads to increased concentrations of airborne *Cladosporium* species and both broken and complete spores of *Alternaria* species. Using hospital asthma admission data separately for the Trent and the Norfolk, Suffolk, and Cambridgeshire SHAs for the 3 months of June through August 2002, we were able to demonstrate a clear correlation between admission rates for asthma and levels of broken *Alternaria* species and *Didymella* and *Cladosporium* species. However, unbroken *Alternaria* species counts did not correlate with asthma admissions, supporting the hypothesis that a number of factors are required before epidemic asthma occurs during thunderstorms. Over the 3-month period,

an increase in the broken *Alternaria* species count of 10/m³ was associated with a 2.21-fold increase in asthma admissions. Correcting for *Didymella* species and rainfall did not diminish the effect of broken *Alternaria* species counts on asthma admission rates. A little surprisingly, grass pollen counts were negatively associated with asthma admissions, with a 13% reduction in asthma admissions per 100 pollen grain increase per cubic meter. The statistical analysis from June through August incorporated the peak grass pollen season, and we therefore conclude that grass pollen is unlikely to be an independent causative factor in thunderstorm asthma.

Previous studies have demonstrated increased airborne levels of *Alternaria* species during thunderstorms⁹ and of other fungal spores during epidemic asthma, although a direct causal effect has not been established.¹ Girgis et al⁷ showed that 61% of patients with thunderstorm-related asthma were sensitized to *Cladosporium* species compared with 35% of control subjects but were unable to show that *Alternaria* species sensitization was increased. However, their control subjects included all patients who had attended for asthma in the 4 months preceding the outbreak, and therefore this group was more likely to have been adequately treated for asthma, reducing the likelihood of thunderstorm-related asthma. In neither study were there adequate data on environmental levels of grass pollen or fungal spores at the time of the asthma outbreak. Ozone causes bronchial hyperresponsiveness,²⁷ and levels of ozone were very high before the thunderstorm on July 29. Taylor and Jonsson²⁸ have proposed a mechanism by which updraughts entrain pollen grains into the high humidity of a cloud base, where the grains rupture, and downdraughts transport the fragments to ground level in dry cold outflows extending about 5 km ahead of the rainfall. It is likely that the same mechanism applies to fungal spores. This process would explain why many of our cases had symptoms before rainfall and many claim the ability to foretell the imminent arrival of a thunderstorm by a worsening of their asthma. Large-scale thunderstorms with associated outflows occur on average less than twice per annum in the United Kingdom, and even fewer during the day when the population is exposed to aeroallergens. This might explain why asthma epidemics occur infrequently. Other reported factors associated with a sudden increase in asthma symptoms include a preceding dry spell followed by winds that cause a sudden increase in allergens, an increase in lightning strikes,⁶ and a sudden decrease in temperature with an increase in humidity.²⁹ The vast majority of asthmatic subjects who have symptoms during thunderstorms are atopic, and therefore the primary mechanism is allergen-induced acute bronchospasm. Our data suggest that the most important mechanisms associated with large thunderstorms are fragmentation of *Alternaria* species spores into easily respirable allergenic fragments, a high concentration of fungal spores, and its transportation over large distances. Other associated factors, such as ozone and a sudden reduction in temperature, might contribute to bronchial hyperresponsiveness.

In population studies, hay fever affects 23% of the population.³⁰ *Alternaria* species sensitivity ranges from 3.3% in a large study of Italian children, 5.5% in a cohort of Isle of Wight children, and up to 12.9% in a nationwide US survey of both adults and children, with evidence for a 3-fold increase in sensitization rates between 1980 and 1994.³¹⁻³³ Our results indicate that approximately one third of control subjects with seasonal asthma are sensitized to *Alternaria* species. The 88% (23/26) *Alternaria* species sensitization in our case population and 91% (10/11) in our control population with thunderstorm-related asthma suggests clinical significance, strongly supporting an important role for *Alternaria* species as a potent allergen for seasonal allergic asthma, which cannot be ignored. We propose that *Alternaria* species sensitivity results in thunderstorm-related epidemic asthma in sensitized asthmatic subjects. A prolonged grass pollen season leads to bronchial hyperresponsiveness in subjects doubly sensitized to grass pollen and *Alternaria* species, and a large-scale thunderstorm occurring at the time of harvesting with high fungal spore counts and fragmented *Alternaria* species levels combine to trigger symptoms. Vulnerable groups of asthmatic subjects can be identified from previous asthma exacerbations and should undergo appropriate skin tests. Collaboration between the Met Office and aeroallergen-counting centers should allow prediction of future epidemics and warn at-risk groups in time. It is likely also that epidemic asthma will occur more frequently in future seasons if the trend over the last 35 years for an earlier and lengthening *Alternaria* species season continues.²⁵ The next challenge will be to assess whether prophylactic therapy with high-dose inhaled or oral corticosteroids or specific immunotherapy to *Alternaria* species can prevent these potentially life-threatening attacks of asthma.

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