

Influence of Ambient Fungal Spores on Emergency Visits for Asthma to a Regional Children's Hospital

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The impact of ambient aeroallergens on morbidity from childhood asthma is largely unknown. To address this issue, we studied the association between daily emergency department visits for asthma to a children's hospital, and daily concentrations of both pollen grains and fungal spores during a 5-yr period between 1993 and 1997. Air pollution and meteorological data accounted for in the analyses included ozone, nitrogen dioxide, sulfur dioxide, sulfates, temperature, barometric pressure, and relative humidity. The daily number of asthma visits ranged from 0 to 36 per day with an average of 7.5. Fungal spores, but not pollen grains, were associated with visits ($p < 0.05$). The percentage increase associated with each group, independent of the others, was 1.9% (SE 0.9) for deuteromycetes, 4.1% (1.6) for basidiomycetes, 2.8% (1.0) for ascomycetes, and 8.8% for these spores combined. In summary, fungal spores account for a significant proportion of the asthma exacerbations in children that prompt an emergency department visit.

The burden of illness in the population due to ambient fungus-induced asthma is unknown, although information to date would suggest an effect. Salvaggio and coworkers in 1971 reported a simple temporal correlation between Basidiospore concentrations and the seasonal outbreaks of asthma in New Orleans (1). More recently Targonski and coworkers reported that asthma-related deaths were more likely to occur on days with higher spore counts than days with lower spore counts (2). The relation may be causal or both may coincidentally increase during the same season. The purpose of the present study was to determine the influence of ambient spores on emergency department visits for asthma in children using time-series analytic techniques that filtered out unwanted (potentially confounding) seasonal trends and adjusted for day-of-the-week cycles in the data, and also changes in climate and air pollution.

METHODS

Study Population

The Children's Hospital of Eastern Ontario is the only children's hospital serving the Region of Ottawa, Ontario, which has a population of about 750,000. Since 1993, all emergency visits have been recorded in a database called the Epidemiology Patient Information System. In 1993, there were approximately 48,000 visits, of which 3,000 were for asthma. The present study included all patients presenting to the emergency department with a principal diagnosis of asthma between 1993 and 1997.

Exposure Data

Aeroallergen data (pollen grains and fungal spores) were collected using rotational implication sampling equipment operating at 2400

rpm set to collect 1 min from every 10-min period over a 24-h interval. The particles adhering to the silicon-coated sample rods were analyzed to determine the number of particles present per cubic meter of air sampled. The sampler was located at the Ottawa Airport, which is within 5 to 10 miles of the furthest reaches of the Ottawa area and about 4 miles from the Children's Hospital. Aeroallergen data were collected between March and October. The ground is frozen hard from November to February, and snow covered from December to February.

Daily meteorological data included maximum and minimum temperature, average barometric pressure, dew point temperature, and relative humidity. Available air pollution data included daily maximum for ozone (O_3), daily average of nitrogen dioxide (NO_2), daily average sulfur dioxide (SO_2), coefficient of haze (COH), and 24-h averaged sulfates measured every sixth day (SO_4). For the purposes of analysis, daily estimates of SO_4 were made using the measured values and daily total suspended particulates (TSP) as previously described (3). Air pollution and meteorological data were supplied by Environment Canada as part of the National Air Pollutions Network and climate archive.

Statistical Methods

Day-to-day changes in emergency visits for asthma were compared to day-to-day changes in the daily concentrations of aeroallergens. The existence of a correlation between asthma visits and fungal spores requires that the number of asthma visits increases along with the daily concentration of fungal spores. The expected delay (lag) between a high-aeroallergen day and the time for a patient to present to the emergency department in response to the exposure was unknown. To account for the uncertainty in the lag, we compared the day-to-day variation in asthma visits with fungal spore levels on the same day as well as 1, 2, 3, 4, and 5 d prior to the emergency visit. This is a standard approach in time-series analysis in air pollution research (4–7).

The proportion of the population visiting an emergency department for asthma on any given day is quite small (i.e., a few daily visits to hospitals in a population of several hundred thousand). The statistical model used assumed a Poisson distribution, independent events rarely occurring. Ordinary least-squares regression could not be used because it assumes a normal distribution in the outcome of interest (8).

Asthma visits show strong seasonal trends, lowest in the summer months and highest in autumn (Figure 1). Aeroallergens, air pollutants, viral epidemics, and climate also have strong seasonal trends. Therefore, any simple direct comparison between asthma and several exposure variables may demonstrate an association. To remove (filter) these potentially confounding long-term seasonal trends, locally weighted nonparametric regression and smoothing scatterplots (LOESS) were applied to each variable (9). A 90-d span minimized the autocorrelation within series.

Emergency department visits are higher on weekends and lower on weekdays. This day-of-the-week effect was also accounted for in the analysis.

Finally, the analysis was adjusted for day-to-day changes in meteorological variables and air pollution variables, which may influence day-to-day changes in asthma visits.

Asthma visits were related to aeroallergens using the following statistical model:

$$E(y_t) = f_y \exp\{\delta_1 S(w_t - f_w) + \delta_2 S(p_t - f_p) + \delta_3(x_t - f_x)\}$$

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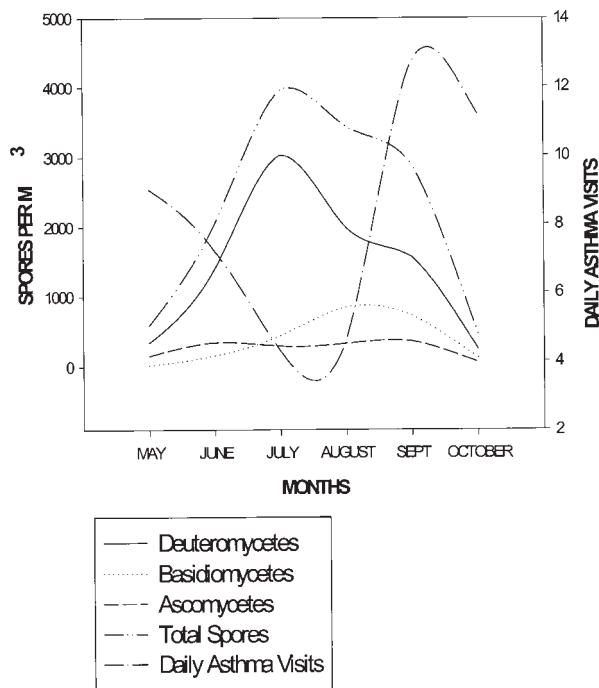


Figure 1. Seasonal pattern of daily counts for asthma, Deuteromycetes, Basidiomycetes, Ascomycetes, and total spores from May 1993 to October 1997 in Ottawa, Canada.

where $\{y_{it}\}_{i=1,Y,T}$ represent the number of asthma visits and $\{x_{it}\}_{i=1,Y,T}$ represent the spore concentrations on the t th of T d of observation. $f_y = E(y_{it}) = \exp\{\alpha \mathbf{d}_i + \delta_y \text{lo}(t)\}$ is the expected value of the asthma visit based on temporal trends and day-of-the-week effects on day t ; $f_w = E(w_{it}) = \exp\{\alpha \mathbf{d}_i + \delta_w \text{lo}(t)\}$ is the expected value of the weather variable based on temporal trends and day-of-the-week effects on day t ; $f_p = E(p_{it}) = \exp\{\alpha \mathbf{d}_i + \delta_p \text{lo}(t)\}$ is the expected value of the air pollution levels based on temporal trends and day-of-the-week effects on day t ; and $f_x = E(x_{it}) = \exp\{\alpha \mathbf{d}_i + \delta_x \text{lo}(t)\}$ is the expected value of the spores levels based on temporal trends and day-of-the-week effects on day t ; $\exp$ is the exponential function; α is a seven-dimensional parameter vector relating visits to the day of the week; $\mathbf{d}_i$ is a seven-dimensional vector that takes values of 1 to 7 for each day of the week; $\delta_y, \delta_w, \delta_p$, and δ_x are unknown parameters; lo is the nonparametric smooth representation of day of study to asthma visits (10), w_i is a weather variable recorded on day t , p_i is a pollution variable recorded on day t , and x_i is a spore variable recorded on day t . δ_1, δ_2 , and δ_3 are the vector of unknown parameters relating *prefiltered* (residuals after applying LOESS) weather, air pollution, and aeroallergen variables to emergency visits for asthma, respectively. S represents the smoothing spline fit in a generalized additive model (11), which related the nonlinear association between weather, air pollutants, and visits.

To identify the smallest number of weather and pollutant variables required to predict visits we used a forward inclusion stepwise regression procedure to select a minimally sufficient set of pollutant predictors. The selection criteria was Akaike's Information Criteria (AIC), which is a function of the residual deviance and the model degrees of freedom.

Log-relative risks for a unit change in spores levels, δ_3 , and their corresponding standard errors were estimated using generalized additive models with S-PLUS (12). The percentage increase in visit rate corresponding to the mean spores levels is reported in addition to the statistical uncertainty in the parameter estimate given by the standard error. The ratio of the log-relative risk to the standard error (T value) is also reported.

RESULTS

Descriptive statistics for aeroallergens, air pollutants, and meteorological variables and emergency department visits are given in Table 1 for the months of May to September 1993 to

1997. The daily number of emergency department visits for asthma ranged from 0 to 36 per day with an average rate of 7.53. Emergency department visits and spore concentrations displayed both seasonal (Figure 1) and day-of-the-week cycles.

Of all the weather variables, relative humidity alone recorded on the date of visit was sufficient to explain day-to-day variations in emergency department visits for asthma based on a forward inclusion stepwise regression analysis using the AIC as the inclusion criteria. Similarly, ozone recorded on the day of the visit (lag = 0 days) was the most important air pollutant.

The percent increase in daily emergency department visits associated with an increase in the mean value of spore concentrations was determined under two models for relative humidity and ozone, including a linear representation for both filtered variables and an S-smoothed representation. The spore relative risk was insensitive to these adjustments for relative humidity and ozone. The percent increase in daily emergency department visits associated with an increase in the mean value of spore concentrations is given in Table 2. The possibility of a nonlinear association between emergency department visits and spores was tested by comparing the residual variation from the linear model to one using nonparametric smooth representation of spore concentrations (LOESS with a 50% span). Linear models adequately represented the concentrations-response relation (smallest p for linearity > 0.29).

The percent increases in daily emergency department visits for both spores and ozone examined simultaneously are given in Table 2. The spore effect was only slightly attenuated by co-adjustment for ozone. The greatest difference was observed for

TABLE 1
DESCRIPTIVE STATISTICS FOR DAILY AEROALLERGEN CONCENTRATIONS, AIR POLLUTANTS, WEATHER VARIABLES, AND DAILY NUMBER OF EMERGENCY DEPARTMENT VISITS FOR ASTHMA TO CHEO IN THE MAY TO SEPTEMBER PERIOD IN OTTAWA, 1993 TO 1997

	Mean	Percentiles		
		5	50	95
Fungal spores, spores/m ³				
Deuteromycetes				
<i>Alternaria</i>	40	0	16.0	154.7
<i>Cladosporium</i>	1,411	50.7	715.3	4,548.3
<i>Epicoccum</i>	11	0	4.2	42.6
<i>Penicillium/Aspergillus</i>	84	0	31	324.2
Total	1,672	85	873.1	4,990.7
Basidiomycetes				
<i>Ganoderma</i>	410	0	156.2	1,202.6
Total	551	0	249.1	1,525.4
Ascomycetes	297	11.7	168.8	983.8
Total spores	2,062	2.6	1,223.5	6,485.3
Pollen grains, grains/m ³				
Trees	61	39	60	88
Grasses	68	49	68	87
Ragweed	72	57	71	90
Air pollutants				
Ozone, ppb	32	15	30	58
NO ₂ , ppb	17	8	16	29
SO ₂ , ppb	1.9	0	1	6
COH*	0.17	0	0.2	0.4
SO ₄ , Mg/m ³	3.56	0.58	2.4	9.7
Meteorology				
Maximum temperature	23	13	24	31
Minimum temperature	12	3	12.5	19
Change in barometric pressure	0	-1.5	0.8	3.5
Dew point temperature	11	0.1	11.5	18.4
Relative humidity	67	45	67	88

* COH (coefficient of haze) units per 1,000 linear feet.

Epicoccum, ranging from 1.47 with no coadjustment to 0.2 with adjustment for ozone. However, the spore association with daily emergency department visits did not appear to be sensitive to coadjustment to the other pollutants (daily nitrogen oxide [NO₂], daily sulfur dioxide [SO₂], coefficient of haze [COH], and daily sulfate [SO₄]). The individual air pollutants were not significantly related to asthma admissions (results not shown).

The independent effects of the spore groups were evaluated by adding all three to a model using stepwise forward regression. The percentage increase in asthma visits associated with each group independent of (adjusted for) the others was 1.94% (SE 0.9) for Deuteromycetes, 4.10% (1.63) for Basidiomycetes, 2.77% (1.0) for Ascomycetes, and 8.8% for all these spores combined (all $p < 0.05$). The effect of "total spores" disappeared when the former three families were also entered into the model.

In contrast to fungal spores, we were unable to detect an association between emergency asthma visits and weeds, grasses, or trees. The percentage increases in asthma adjusted for humidity and ozone were 1.85% (SE 1.23), 0.4% (SE 0.82), and 0.44% (SE 0.89), respectively ($p > 0.10$).

DISCUSSION

Summary of Significant Findings

Being population based, this study addresses the burden of illness in Ottawa, Canada, children due to aeroallergen-induced asthma. Fungal spores accounted for about 8.8% of emergency visits for asthma by children. Basidiomycetes had the strongest effect, at 3.5%. The effect was approximately equal in magnitude but not correlated with ozone, the pollutant with the largest effect on respiratory morbidity. Deuteromycetes, Basidiomycetes, and Ascomycetes appeared to have independent effects. Grass, tree, and ragweed pollen had no detectable effect.

Strength of Evidence Supporting a Causal Relation

Given the method of analysis used, it is unlikely that the association is due to an unmeasured confounding factor. Perhaps the most important would be viral infections that increase in the late summer/early autumn when basidiospore concentrations also increase, and that are the major cause of asthma ex-

acerbations in children (13). However, the present analysis filters out such seasonal trends and compares daily changes in spore counts to daily changes in asthma visits. The major risk factors for asthma would not be expected to confound our findings as they do not change day to day in concert with aeroallergen levels. These factors include socioeconomic and demographic characteristics, indoor exposure to environmental tobacco smoke, and antigens from dust mites, pets, and cockroaches. For further discussion of the risk factors for allergy and asthma, the reader is referred to recent reviews (14, 15).

The biological plausibility of a spore effect on emergency visits for asthma is provided by several small studies of subjects selected on the basis of having asthma and positive skin prick tests to fungi. In these subjects early and late asthmatic reactions were induced by spore extracts of Basidiomycetes, *Cladosporium*, and *Penicillium* (16, 17). Lopez and coworkers demonstrated that among those with asthma who are sensitized to Basidiospore extracts, inhalation of Basidiospore extract may provoke early and late asthmatic reactions (17). These observations establish the link between allergy to fungi and asthma. Reed stated that "Although molds can cause asthma, it is not clear how often they do" (18). Perzanowski and coworkers reported on populations of schoolchildren (19). Of those with bronchial hyperreactivity, the prevalence of immunoglobulin E (IgE) antibodies to *Alternaria* allergens was 62% in Los Alamos (New Mexico) and 19% in Albermarle (Virginia). These results indicate that allergy to fungi is not uncommon and that there are regional variations. Halonen and coworkers point out that asthma is often associated with multiple allergies (20). Therefore *Alternaria* sensitivity may reflect a causative agent and/or may be an indicator of several important allergic sensitivities. For example, Persanowski reported that patients sensitized to *Cladosporium* were usually sensitized to *Alternaria*. Our results compliment these studies by showing that there are independent clinical effects of different spores as measured by important asthma exacerbations.

Comparison with Previous Studies

Targonski and coworkers reported that from March to October, deaths from asthma were more likely to occur on days

TABLE 2
PERCENT INCREASE IN EMERGENCY DEPARTMENT VISITS FOR ASTHMA TO THE CHILDRENS' HOSPITAL OF EASTERN ONTARIO, CANADA, ASSOCIATED WITH A SPORE CONCENTRATION INCREASE EQUAL IN MAGNITUDE TO ITS MEAN, MAY TO OCTOBER 1993 TO 1997

	Days Lagged*	Correlation with Oxone	Model Specification†		
			Spore Only	Spore and Ozone	Ozone
Deuteromycetes					
Total	2	0.0125	1.79 (0.8) [‡]	1.81 (0.8) [§]	1.60 (3.54)
<i>Alternaria</i>	2	-0.0288	1.67 (0.96)	1.74 (1.04)	1.67 (3.53)
<i>Cladosporium</i>	2	0.0057	1.64 (0.74) [§]	1.19 (0.78)	1.73 (3.54)
<i>Epicoccum</i>	2	-0.0728	1.47 (0.96)	0.2 (1.05)	4.0 (4.5)
<i>Penicillium/Aspergillus</i>	2	0.0456	1.75 (0.87) [§]	2.34 (1.08) [§]	2.59 (7.56)
Basidiomycetes					
Total	3	0.0168	3.75 (1.66) [§]	3.41 (1.68) [§]	4.45 (3.98)
<i>Ganoderma</i>	3	0.009	3.3 (1.5) [§]	3.13 (1.5) [§]	4.34 (3.82)
Ascomycetes	0	0.068	2.86 (0.96) [§]	2.96 (0.96) [§]	1.42 (3.55)
Total spores	2	-0.029	2.18 (0.89) [§]	2.15 (0.89) [§]	3.71 (3.37)

* Number of days between emergency department visit and high spore levels prior to visit.

† All models accounted for long-term temporal trends, day-of-the-week effects, and relative humidity. The "spore only" model includes the individual spore whereas the "spore and ozone" model includes the spore of interest and ozone.

‡ Standard error of percentage increase in daily emergency department visits attributable to change in daily mean spore concentration.

§ T ratio is larger than 2 ($p < 0.05$).

|| Standard error of percentage increase in daily emergency department visits attributable to change in daily mean ozone concentration.

with higher total spore counts (2). Perhaps the most often quoted study is that of Salvaggio and coworkers, who in 1971 reported a simple temporal correlation between Basidiospore concentrations and the seasonal outbreaks of asthma in New Orleans (1), but in a 1981 review, Salvaggio and Aukrust concluded that a cause-and-effect relation remained unproven (21). The relation between spores and hospital admissions was demonstrated by overlaying the spore count and the number of hospital visits; the two curves rose together during the autumn. There are three possible explanations for the extremely large magnitude of effect suggested by the graphic analysis. First, spores could be the cause of a several-fold increase in admissions for asthma. Second, another potent cause of asthma exacerbations may be present in the autumn at the same time as Basidiospores peaked. This possibility is likely, given that viral infections are the major cause of asthma exacerbations among children. Johnston and coworkers demonstrated that 85% of severe exacerbations were caused by viral infections, 75% of which were rhinovirus, which has an autumn peak (13). Our analysis controlled for seasonal trends, such as viral epidemics, and found that spores caused about 8.8% of visits for asthma. Thus, the present study confirmed the association between Basidiospores and important asthma exacerbations reported by Salvaggio and coworkers, although we suggest that the magnitude of effect is more modest and does not account for the autumn peak in asthma visits. Peak flow studies in subjects with asthma also support a more modest effect of spores. Among fourth and fifth grade students, Neas and coworkers reported that approximate 1% decrements in morning peak flow were associated with *Cladosporium* and *Epicoccum* but there was no measurable effect of *Ganoderma*, the latter being the predominant basidiospore (22).

We found no significant effect of pollen. In support of this finding, Delfino and coworkers and Epton and coworkers, reported associations between spores and both asthma symptoms and inhaler use (23, 24) and neither found an association between pollen counts and symptoms, inhaler use, or peak flows (23, 24). Thus, both clinical panel studies and the present community-based study suggest a distinct difference in the potency of aeroallergens to exacerbate asthma, with spores having a much greater magnitude of effect than pollens. Although pollens may be an important cause of allergic conjunctivitis and rhinitis, they do not account for significant asthma morbidity in the Ottawa community where pollen levels are average when compared with other regions of Canada. This finding does not deny the existence of asthma inducible by pollen grains, but in our community perspective, any possible pollen effect was considerably smaller than that of spores.

The reported associations between ambient fungus and asthma also have implications for research into the adverse health effects of residential fungus contamination. We found an association between emergency visits for asthma and outdoor *Aspergillus/Penicillium* yet the indoor concentrations of this fungus may be several times higher than outdoors (25). Homes can be sinks/traps for several species of outdoor-sourced mould spores. Li and Kendrick reported levels of *Cladosporium* of about 4,000 spores/m³ indoors and 6,000 spores/m³ outdoors during August (25). Although, only two-thirds of outdoor levels, indoor *Cladosporium* exposure may be a risk factor for asthma given that people spend about 90% of their time indoors (25).

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