

Influence of outdoor aeroallergens on hospitalization for asthma in Canada

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Background: The risk of hospitalization for asthma caused by outdoor aeroallergens is largely unknown.

Objective: The objective of this study was to determine the association between changes in outdoor aeroallergens and hospitalizations for asthma from the Pacific coast to the Atlantic coast of Canada.

Methods: A daily time series analysis was done to test the association between daily changes in aeroallergens and daily changes in hospitalizations for asthma during a 7-year period between 1993 and 2000 in 10 of the largest cities in Canada. Results were adjusted for long-term trends, day of the week, climate, and air pollution.

Results: A daily increase, equivalent to the mean value of each allergen, was associated with the following percentage increase in asthma hospitalizations: 3.3% (95% CI, 2.3 to 4.1) for basidiomycetes, 3.1% (95% CI, 2.8 to 5.7) for ascomycetes, 3.2% (95% CI, 1.6 to 4.8) for deuteromycetes, 3.0% (95% CI, 1.1 to 4.9) for weeds, 2.9% (95% CI, 0.9 to 5.0) for trees, and 2.0% (95% CI, 1.1 to 2.8) for grasses. After accounting for the independent effects of trees and ozone, the combination of the 2 was associated with an additional 0.22% increase in admissions averaged across cities ($P < .05$).

Conclusion: These findings provide evidence for the hypothesis that aeroallergens are an important cause of severe asthma morbidity across Canada, and in some situations there might be a modest synergistic adverse effect of ozone and aeroallergens combined. (*J Allergy Clin Immunol* 2004;113:303-6.)

Key words: Asthma, fungus, pollen, air pollution, epidemiology

Clinical laboratory studies have demonstrated that aeroallergens can exacerbate asthma, an effect that might be potentiated by ozone.¹ The burden of illness in the population caused by aeroallergen-induced asthma is unknown, although information to date would suggest an effect. Salvaggio et al² in 1971 reported a simple temporal correlation between basidiospore concentrations and the seasonal outbreaks of asthma in New Orleans. Targonski et al³ reported that asthma-related deaths were more likely to occur on days with higher spore counts than on days with lower spore counts. The relationship might be causal, or

both might coincidentally increase during the same season. In 1995 to 1996 Health Canada commissioned a questionnaire survey of 28,000 students between 5 and 9 years of age from 9 health units across Canada. The reported prevalence of current hay fever or allergic rhinitis was 11.2%, and current asthma was reported in 13%. Of those with current asthma, asthma was reportedly triggered by plants, pollens, or grass in 58% and by mold or mildew in 33%. In Ottawa an association was found between daily changes in fungal spores and daily changes in emergency visits for asthma to a children's hospital. No associations with pollen could be detected. In contrast, Lierl and Hornung⁴ reported an association between asthma visits to the Cincinnati Children's Hospital, Ohio, and daily pollen counts but not fungal spores. The explanation for the different observations is unknown, but perhaps geographic differences in the outdoor aeroallergen mix importantly influence findings. The purpose of the present study was to determine the association between outdoor fungal spores and pollen grains on asthma morbidity across diverse geographic regions and to test for synergism between air pollution and aeroallergens.

To address these issues, we compared daily rates of hospital admissions for asthma with daily aeroallergen concentrations in 10 cities across Canada spanning the Atlantic to the Pacific coasts, which includes approximately one half of the country's population.

METHODS

Description of the study data

All Canadian cities with current and past daily information available for hospitalizations and aeroallergens and air pollutants were included. The study population consisted of all emergency hospitalizations for asthma between April 1, 1993 and March 31, 2000 in the cities of Saint John, Halifax, Ottawa, Toronto, London, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. The hospitalization data were provided by the Canadian Institute for Health Information, which collects information on virtually all asthma admissions in Canada, which is made possible by the fact that all acute care general medical hospitals in Canada are publicly funded. The International Classification of Diseases, 9th revision code was used. Cities in the Province of Quebec could not be included because their hospitalization data could not be included in the Canadian Institute for Health Information database that we accessed.

Aeroallergen data (pollen grains and fungal spores) had been collected by using rotational impaction sampling located in each city. The particles adhering to the silicon grease-coated sample rods were analyzed to determine the number of particles present per

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2003.11.016

TABLE I. Asthma admission counts, population size, air pollution concentrations, and climate for each of 10 Canadian cities between April 1, 1993, and March 31, 2000

	No. of asthma admissions	Population (× 10 ⁵)	O ₃ ppb	NO ₂ ppb	SO ₂ ppb	CO ppm	Mean temperature (°C)	24-hr change in barometric pressure (× 10 ⁻⁵)	% Relative humidity
Calgary	7,780	7.68	20.9	18.9	3.1	0.6	13.1	21.2	19.2
Edmonton	6,214	6.16	20.5	17.9	2.2	0.5	12.9	-35.4	19.2
Halifax	2,650	1.80	20.2	16.3	7.3	0.6	16.5	-105.5	24.2
London	1,903	1.25	32.7	15.2	3.8	0.5	17.4	222.2	26.1
Ottawa	5,435	9.39	20.6	17.0	2.9	0.5	17.8	220.69	25.6
Saint John	1,199	1.02	22.4	8.8	9.4	0.8	14.4	-41.27	21.7
Toronto	21,493	23.85	24.9	25.1	4.2	0.9	18.3	68.6	26.4
Vancouver	5,667	18.32	16.2	17.2	3.6	0.7	13.8	54.16	18.8
Windsor	1,922	1.98	27.2	22.7	7.6	0.7	18.3	130.93	26.1
Winnipeg	5,803	6.88	22.7	11.4	NA	0.5	16.4	-171.63	25.0
Totals	60,066	78.33	—	—	—	—	—	—	—

TABLE II. The seasonal mean concentrations (95% CIs in parentheses) of aeroallergens during their season by city

City	Aeroallergens					
	Basidiomycetes (spores/m ³)	Ascomycetes (spores/m ³)	Deuteromycetes (spores/m ³)	Weeds (grains/m ³)	Trees (spores/m ³)	Grass (spores/m ³)
Calgary	193.9 (4.2-695.8)	256.2 (4.2-929.8)	1144.5 (60.5-3686.8)	13.7 (0-31.1)	58.4 (1.0-210.8)	18.2 (0-38.5)
Edmonton	296.1 (4.4-1067.2)	350.8 (9.0-1331.1)	1543.7 (75.1-5525.2)	12.8 (0-37.8)	83.2 (1.0-374.6)	13.3 (0-52.2)
Halifax	262.7 (3.9-1083.5)	164.5 (4.2-614.8)	609.7 (12.7-2003.6)	3.3 (0-9.7)	83.4 (0-425.7)	11.2 (0-37.2)
London	525.5 (7.5-1854.8)	192.6 (9.2-663.0)	1729.5 (52.9-5195.1)	50.0 (1.0-212.8)	125.9 (0-500.4)	12.2 (0-46.3)
Ottawa	696.2 (7.8-2280.0)	345.1 (7.9-1162.7)	1666.5 (16.9-5538.4)	58.0 (1.0-214.4)	121.2 (1.0-461.1)	18.3 (0-74.3)
Saint John	384.3 (4.2-1478.4)	251.7 (4.2-931.2)	700.7 (21.9-2264.5)	3.7 (0-10.0)	143.4 (1.0-680.4)	7.8 (0-25.9)
Toronto	376.7 (12.7-1203.8)	230.0 (7.9-717.8)	1293.8 (31.6-4471.6)	35.1 (0-149.1)	131.5 (1.0-479.2)	15.6 (0-49.7)
Vancouver	247.9 (12.7-827.9)	149.3 (8.4-515.4)	592.9 (31.8-1873.9)	5.3 (0-16.2)	182.1 (1.1-882.4)	14.0 (0-48.2)
Windsor	445.3 (7.8-1439.9)	481.1 (11-1741.9)	1747.9 (38-5240.8)	69.0 (1.1-290.2)	188.7 (1.1-753.8)	18.7 (0.8-63.6)
Winnipeg	363.2 (8.4-1114.5)	286.4 (8.4-930.1)	1664.4 (39-5354.7)	21.9 (0-73.1)	131.5 (1.0-543.9)	15.5 (0-41.7)

cubic meter of air sampled. This method had been previously tested for reliability by performing counts on 15 randomly chosen fields magnified both 20 and 40 times on each rod. At each magnification, the correlation coefficient between the 2 rods was at least 95%. Aeroallergens had been collected in the same fashion in each city supervised by the same company, Aerobiology Associates. During the period of observation the fungal data had been identified by microscopic morphology and grouped according to class and genus. The major genera of the class Basidiomycetes were *Coprinus*, *Botrytis* and *Ganoderma*. The major genera of the class Ascomycetes were *Leptosphaeria*, *Leptosphaeria* look-alikes, and *Oospora* (powdery mildews). The major genera of the class Deuteromycetes (Fungi Imperfecti) were *Cladosporium*, *Penicillium/Aspergillus*, and *Alternaria*.⁵

Identification was done according to daily air pollution, and meteorologic data were supplied by Environment Canada as part of the National Air Pollutions Network and climate archive. Meteorologic data included maximum and minimum temperatures, average barometric pressure, dew point temperature, and relative humidity. Air pollution data included the 1-hour daily maximum concentration of ozone (O₃), daily average of nitrogen dioxide (NO₂), daily average sulfur dioxide (SO₂), and coefficient of haze. Analyses were restricted to the months of the year when the pollen or spore under study was present. There is no uniform definition for when a season begins or ends. We arbitrarily defined it as follows. For each city and each aeroallergen grouping, the season began when there were 5 of 7 consecutive days with measurable aeroallergen concentrations, and the season ended with no detectable aeroallergen for 7 consecutive days.

Statistical methods

We used Generalized Additive Models (GAM)1 with stringent convergence criteria ($\epsilon < 10^{-14}$) in Spls Software 2 (Insightful Corporation, Seattle, Wash) to determine the daily variations in hospital admissions for asthma and their relationship to daily vari-

ations in aeroallergen concentrations. For each city separately, the effect of potentially confounding long-term trends, such as could be caused by viral epidemics and other unknown factors, were accounted for by using fully parametric natural cubic splines with 3 knots per year. The degrees of freedom and number of knots were determined by Akaike Information Criteria.⁶ These methods of analysis are commonly used in air pollution research.^{6,7} The allergen, climate, air pollution, and asthma admission variables had been measured several hundred times during the course of the study, and each variable was expressed as a time series. To remove any patterns in the time series that might cause an artifactual association between variables, each series was filtered. Each time-series model included indicator variables for the day of the week and were adjusted for temporal trends by using natural spline functions to day of study with knot for each of 30, 90, 180, 270, and 365 days of observation. We then selected a model with the number of knots that either minimized the Akaike Information Criteria⁸ or maximized the evidence that the model residuals did not display any type of structure, including serial correlation, by using Bartlett's test. Serial correlation structure in the residuals was examined after fitting models with natural spline functions. The above steps were implemented separately for each city. We then used Generalized Additive Models (GAM)1 with stringent convergence criteria ($\epsilon < 10^{-14}$) in Spls Software 2 to determine the association between the filtered aeroallergens and filtered asthma admissions⁹ (S-Plus 6.1 or Windows users manual).¹⁰ Day-of-the-week and daily changes in meteorologic variables and air pollution variables were also accounted for by using backwards stepwise regression, with a threshold of P less than .05 for inclusion by using Akaike Information Criteria. Lags between 0 and 5 days were explored. A linear association between daily aeroallergen concentrations and daily hospitalizations for asthma visit rates was assumed on the logarithmic scale, consistent with the Poisson variation.

The association of primary interest was expressed by the per-

TABLE III. Percent increase in emergency department visits for asthma associated with a spore concentration increase equal in magnitude to its mean presented by city (95% CIs in parentheses)

City	Aeroallergens					
	Basidiomycetes (spores/m ³)	Ascomycetes (spores/m ³)	Deuteromycetes (spores/m ³)	Weeds (grains/m ³)	Trees (grains/m ³)	Grass (grains/m ³)
Calgary	2.2 (0.2-4.1)	1.1 (-1.2 to 3.5)	4.2 (1.2-7.5)	0.1 (-0.1 to 0.7)	1.4 (0.02-3.11)	0.2 (-0.0 to 0.5)
Edmonton	3.3 (-0.3 to 7.2)	4.5 (1.6-7.6)	4.6 (0.8-8.5)	1.2 (0.2-2.1)	1.5 (0.1-2.7)	1.6 (0.4-2.8)
Halifax	4.6 (1.2-8.9)	2.5 (0.5-4.6)	4.2 (-2.3 to 11)	2.1 (-1.0 to 5.3)	4.8 (2.7-6.9)	3.19 (1.5-4.9)
London	6.7 (4.0-9.5)	6.3 (3.5-9.2)	6.8 (0.1-12.2)	3.5 (1.7-5.3)	4.8 (0.1-8.2)	5.8 (3.2-8.5)
Ottawa	2.9 (0.6-5.3)	2.5 (0.3-4.8)	3.7 (0.9-6.4)	0.3 (-1.7 to 0.7)	0.2 (-0.1 to 0.8)	0.2 (-0.1 to 0.4)
Saint John	5.3 (-0.2 to 11.1)	3.3 (-0.0 to 6.8)	9.3 (1.2-17.8)	3.0 (0.5-5.7)	1.7 (-0.9 to 4.3)	0.0 (0.0-0.0)
Toronto	2.74 (1.3-4.3)	2.5 (0.9-4.2)	1.5 (-0.3 to 3.4)	2.7 (1.7-3.7)	0.7 (0.2-1.6)	0.3 (0.2-0.8)
Vancouver	0.9 (-2.8 to 4.7)	3.5 (0.7-3.4)	4.0 (0.5-7.7)	0.6 (0.5-0.8)	1.8 (-0.4 to 3.9)	0.7 (0.2-1.2)
Windsor	5.9 (3.3-8.5)	5.6 (2.9-8.4)	2.5 (-5.7 to 11.4)	3.3 (0.6-6.1)	3.5 (1.9-5.2)	6.5 (4.1-8.8)
Winnipeg	3.0 (0.9-5.2)	3.0 (0.6-5.4)	3.1 (0.5-5.8)	3.3 (1.5-5.1)	1.8 (0.1-3.5)	0.2 (-0.1 to 0.5)

Models accounted for long-term temporal trends, day-of-week effects, and weather variables.

centage increase in the number of daily hospitalizations for asthma corresponding to an increase in concentrations of pollen grains and fungal spores equivalent to their mean values, $100 * (1 - \exp(Bx))$ where B is the log relative rate in hospitalizations for a unit change in concentration (x). Uncertainty is represented by $100 * (1 - \exp(sx))$ where s is the standard error of B.

RESULTS

The results are based on 60,066 asthma admissions to 108 hospitals from 10 cities with an estimated population of 7.83 million people (Table I). Across cities, O₃, NO₂, and CO varied 2-fold, SO₂ 3-fold, and temperature and humidity by 50%. Descriptive statistics for pollen grains and fungal spores are presented in Table II. There was significant variation in aeroallergen concentrations and climate across cities, with the greatest difference seen in weeds. Ragweed is infrequent on both the Atlantic and Pacific coasts. For the long-range transported air pollutant ozone, mean values varied by less than 50%, whereas for point source pollutants such as SO₂, the variation was greater. Mean temperatures varied 2-fold. The associations between aeroallergens and asthma are presented for each city in Table III. For all associations between aeroallergens and asthma admissions, adjustment for air pollutants did not affect the results by more than 1% absolute difference, except for grass in Windsor where the percent increase in admissions was 6.5% adjusted for temporal trends, day of week, and weather, but this decreased to 5.2% when air pollutants were added to the model. Therefore, only the values unadjusted for air pollution are presented. There were consistently positive associations between asthma and aeroallergens in each city, and the majority were statistically significant. Within an aeroallergen group, the CIs for each city overlapped one another for the most part. Age stratification at the approximate 50th percentile (13 years or younger vs older than 13 years) did not change the direction of the association between aeroallergens and hospitalizations.

The summarized results of all cities combined are presented in Table IV. A daily increase, equivalent to the mean value of each allergen, was associated with the following percentage increases in asthma hospitalizations: 3.3% (95% CI, 2.3 to 4.1) for basidiomycetes, 3.1% (95% CI, 2.8 to 5.7) for ascomycetes, 3.2% (95% CI, 1.6

TABLE IV. Percent increase (95% CIs in parentheses) in emergency department visits associated with an aeroallergen increase equal in magnitude to its mean

Aeroallergen (particle/m ³)	Mean	Percent increase
Basidiomycetes	380	3.27 (2.3-4.10)
Ascomycetes	271	3.07 (2.79-5.66)
Deuteromycetes	1269	3.20 (1.63-4.79)
Weeds	33	3.03 (1.10-4.90)
Trees	125	2.87 (0.87-4.97)
Grass	14	1.95 (1.08-2.83)

to 4.8) for deuteromycetes, 3.0% (95% CI, 1.1 to 4.9) for weeds, 2.9% (95% CI, 0.9 to 5.0) for trees, and 2.0% (95% CI, 1.1 to 2.8) for grasses.

With the main effects of ozone and aeroallergen held in the model, statistically significant interaction terms were found for the following: (1) basidiomycetes in Ottawa, Vancouver, and Windsor; (2) deuteromycetes in Halifax, Ottawa, and Windsor; (3) weeds in London, Saint John, and Windsor; (4) trees in Calgary, Edmonton, Halifax, and Vancouver; and (5) grass in Halifax. Averaged over all cities, only the interaction term for ozone and trees was significant at *P* less than .05; the combination of the 2 was associated with a 0.22% further increase in admissions, *P* less than .05.

DISCUSSION

In major cities from the Atlantic to Pacific coasts, daily increases in outdoor aeroallergens were associated with daily increases in hospital admissions for asthma. For a given proportionate increase, fungal spores tended to have a greater influence than pollens. Differences in effect sizes between cities were relatively small, given the relatively larger differences in geography and climate. The results cannot necessarily be extrapolated to more southern climates, but many of these aeroallergens are found throughout North America and Europe, basidiospores for example.^{11,12} Apart from population-based studies, smaller studies with clinical measurements also support a causal association between asthma exacerbations. O'Hollaren et al¹³ reported an approximate 200-fold increased risk of severe asthma exacerbations in those sensitized to *Alternaria alternata*. The prevalence of skin test positivity to *A alternata* was 91% in 11 patients admitted to hospital

with respiratory arrest from asthma compared with 31% in 99 patients with asthma but without a history of respiratory arrest. In Montreal, Delfino et al¹⁴ detected reductions in peak flow associated with fungi but not pollen.

Our findings are relatively resistant to confounding. The existence of a correlation requires that the daily number of hospitalizations for asthma changes with the daily concentration of fungal spores for 7 years. The major risk factors for asthma would not be expected to confound our findings because 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.^{15,16}

In the present study, statistically significant pollen effects were detected in about half of the cities, although the direction was positive in all cities. Delfino et al¹⁷ and Epton et al¹⁸ did not detect associations between pollen counts and symptoms, inhaler use, or peak flows. Lierl and Hornung⁴ did find an association between asthma visits to the Cincinnati Children's Hospital, Ohio, and daily concentrations of pollen grains but not fungal spores. One explanation for apparent differences in pollen effects between cities might be that effect sizes are relatively small, requiring a very large number of observations to obtain conventional levels of statistical significance. Differences in effect sizes might also result from geographical differences in the species mix with different allergenic potentials. Finally, differences in climate might influence the potency of pollen. It has been shown that dampness and light rainfall might cause the relatively large pollen grains to rupture, releasing hundreds of allergenic starch granules of respirable size. Schappi et al^{19,20} measured concentrations of grass group 5 allergens in the atmosphere and reported that the proportion of total allergen and respirable particles was 37% on dry days and 57% during light rain. Lewis et al²¹ reported that grass pollen influenced emergency department visits for asthma most markedly on days of light rainfall, and no effects were found on dry days.

Possible reasons why fungal spores had a larger and more consistent effect than pollens include a potentially higher allergenicity averaged over the general population, the much greater concentration of outdoor spores than pollen grains, and the larger diameter of intact grains compared with the smaller spores, which are of a more respirable size.

The synergism between the observed effects of ozone and some aeroallergens, especially with tree pollen, is of modest size, but it is consistent with previous laboratory studies of controlled exposure of asthmatic subjects.^{1,22,23} Our observation supports those of Lierl and Hornung,⁴ who reported a synergistic association between coarse particulate matter pollution and pollen counts. The interactive effects were not consistent across all cities in our study, suggesting that the effect might be very small or perhaps specific to certain environments.

We thank Lee Coates, Medical Laboratory Technologist, Aerobiology Research Laboratories, Ottawa, Ontario, Canada, and the data managers and supervisors at the Canadian Institute of Health Information.

REFERENCES

- Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, et al. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. *Lancet* 1991;338:199-203.
- Salvaggio J, Seabury J, Schoenhardt EA. New Orleans asthma. V. Relationship between Charity Hospital asthma admission rates, semiquantitative pollen and fungal spore counts, and total particulate aerometric sampling data. *J Allergy Clin Immunol* 1971;48:96-114.
- Targonski PV, Persky VW, Ramekrishnan V. Respiratory pathophysiological responses: effect of environmental molds on risk of death from asthma during the pollen season. *J Allergy Clin Immunol* 1995;95:955-61.
- Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 2003;90:28-33.
- de Hoog GS, Guarro J, Gené J, Figueras MJ. Atlas of clinical fungi. 2nd ed. Utrecht: Centraalbureau voor Schimmelcultures; 2000. p. 1-20.
- Burnett RT, Smith-Doiron M, Stieb D, Raizenne ME, Brooks JR, Dales RE, et al. Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. *Am J Epidemiol* 2001;153:444-52.
- Hoek G, Schwartz JD, Gros R, Eilers P. Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, The Netherlands. *J Arch Environ Health* 1997;52:455-63.
- Akaike H. A new look at the statistical model identification. *IEEE Trans Automatic Control* 1974;19:716-22.
- Hastie T, Tibshirani R. Generalized additive models. London: Chapman and Hall; 1990.
- McCallagh P, Nelder JA. Generalized linear models. 2nd ed. London: Chapman and Hall; 1989.
- Lopez M, Voigtlander JR, Lehrer SB, Salvaggio JE. Bronchoprovocation studies in basidiospore-sensitive allergic subjects with asthma. *J Allergy Clin Immunol* 1989;84:246.
- Lehrer SB, Hughes JM, Altman LC, Bousquet J, Davies RJ, Gell L, et al. Prevalence of basidiomycete allergy in the USA and Europe and its relationship to allergic respiratory symptoms. *Allergy* 1994;49:460-5.
- O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324:359-63.
- Delfino RJ, Murphy-Moulton AM, Burnett RT, Brook JR, Becklake MR. Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. *Am J Respir Crit Care Med* 1997;155:568-76.
- Platts-Mills T. Major risk factors according to age: the relevance of indoor allergens to the increase in asthma. In: Neff HE, Boena-Cagnani CE, Habbri L, Holgate S, O'Bryne TO, editors. *Asthma: a link between environment, immunology and the airways*. Seattle: Hogrefe & Huber Publishers; 1999.
- von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000;105:9-19.
- Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, Koutrakis P. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. *Am J Respir Crit Care Med* 1996;154:633-41.
- Epton MJ, Martin IR, Graham P, Healy PE, Smith H, Balasubramaniam R, et al. Climate and aeroallergen levels in asthma: a 12 month prospective study. *Thorax* 1997;52:528-34.
- Schappi GF, Taylor PE, Staff IA, Rolland JM, Suphioglu C. Immunologic significance of respirable atmospheric starch granules containing major birch allergen Bet v 1 (abstract). *Allergy* 1999;54:478-83.
- Schappi GF, Taylor PE, Pain MC, Cameron PA, Dent AW, Staff IA, et al. Concentrations of major grass group 5 allergens in pollen grains and atmospheric particles: implications for hay fever and allergic asthma sufferers sensitized to grass pollen allergens. *Clin Exp Allergy* 1999;29:633-41.
- Lewis SA, Corden JM, Forster GE, Newlands M. Combined effects of aerobiological pollutants, chemical pollutants and meteorological conditions on asthma admissions and A & E attendances in Derbyshire UK, 1993-96. *Clin Exp Allergy* 2000;30:1724-32.
- Jenkins HS, Devalia JL, Mister RL, Bevan AM, Rusznak C, Davies RJ. The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time-dependent effects. *Am J Respir Crit Care Med* 1999;160:33-9.
- Vagaggini B, Taccola M, Cianchetti S, Carnevali S, Bartoli ML, Bacci E, et al. Ozone exposure increases eosinophilic airway response induced by previous allergen challenge. *Am J Respir Crit Care Med* 2002;166:1073-7.