

Does air pollution increase the effect of aeroallergens on hospitalization for asthma?

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Background: Clinical experiments demonstrate that the asthmatic response to an aeroallergen can be enhanced by prior exposure to an air pollutant.

Objective: We sought to compare the effects of ambient aeroallergens on hospitalization for asthma between high and low air pollution days in 11 large Canadian cities.

Methods: Daily time-series analysis was used, and results were adjusted for day of the week, temperature, barometric pressure, and relative humidity.

Results: The relative risk of admission for an interquartile increase in tree pollen levels was 1.124 (95% CI, 1.101-1.147) on days of lower values of fine particulate matter with a median aerodynamic diameter less than or equal to 2.5 μm (PM_{2.5}) compared with 1.179 (95% CI, 1.149-1.21) on days of higher PM_{2.5} values. Significant ($P \leq .05$) differences in the relative risks of admission between lower versus higher values of particulate matter with a median aerodynamic diameter less than or equal to 10 μm in diameter were 1.149 (95% CI, 1.118-1.181) versus 1.210 (95% CI, 1.161-1.261) for ascomycetes, 1.112 (95% CI, 1.085-1.14) versus 1.302 (95% CI, 1.242-1.364) for basidiomycetes, 1.159 (95% CI, 1.125-1.195) versus 1.149 (95% CI, 1.129-1.169) for deuteromycetes, and 1.061 (95% CI, 1.016-1.107) versus 1.117 (95% CI, 1.092-1.143) for weeds.

Conclusion: We identified an association between aeroallergens and hospitalizations for asthma, which was enhanced on days of higher air pollution. Minimizing exposure to air pollution might reduce allergic exacerbations of asthma. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Asthma, hospitalization, allergens, air pollution, epidemiology

Ambient aeroallergens have been associated with emergency department visits,¹ hospitalizations,^{2,3} and death⁴ caused by asthma. Ambient air pollution reduces lung function and has also been associated with an increased risk of hospitalization and death caused by asthma.⁵ Several clinical laboratory studies

Abbreviations used

PM₁₀: Particulate matter with a median aerodynamic diameter less than or equal to 10 μm in diameter
PM_{2.5}: Fine particulate matter with a median aerodynamic diameter less than or equal to 2.5 μm

demonstrated that the effect of allergen challenge on asthma was greater after prior exposure to an ambient air pollutant.⁶⁻¹¹

The clinical significance of this effect modification in the general population is uncertain. One study reported a positive interaction between air pollutants and aeroallergens, and another found no interaction.^{12,13}

To further investigate this, we determined the association between hospitalization for asthma and ambient aeroallergens across Canada stratified by days of higher versus lower air pollution. A very large database was necessary because the detection of interactive effects requires a much larger sample size than the detection of main effects.

METHODS

Hospitalizations for asthma

The primary outcome was the number of daily admissions in which the principal reason for hospitalization was asthma, which were coded 493 or J45 and J46 by using the International Classification of Disease, 9th or 10th revision (<http://www.who.int/classifications/icd/en/>). Data for the period from April 1, 1994, to March 31, 2007, were supplied by Statistics Canada, which collects information on virtually all asthma-related admissions in Canada and is made possible by the fact that acute care general medical hospitals in Canada are publicly funded.

Air pollution and meteorological data

Meteorological and air pollution data for each city were measured and supplied by Environment Canada and the National Air Pollution Monitoring System. Available climate data included 24-hour mean temperature, relative humidity, and maximum 24-hour changes in barometric pressure. Air pollution data were 24-hour concentrations of sulfur dioxide, nitrogen dioxide, carbon monoxide, and particulate matter of mean aerodynamic diameters of 10 and 2.5 μm (PM₁₀ and PM_{2.5}, respectively). One-hour maximum daily ozone concentrations were used.

Aeroallergen data

Aeroallergens are collected by Aerobiology Research Laboratories using a standardized method that is the same for each city. Data were available for 11 of the largest Canadian cities ranging from the Atlantic to Pacific coasts. In each city rotational impaction methods were used to obtain 24-hour collections of aeroallergens (pollen grains and fungal spores). The particles adhering to the silicon grease-coated sample rods were analyzed to determine the

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number of particles present per 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%. Analysis was restricted to the period of time when levels of the aeroallergen of interest were consistently increased, which was arbitrarily defined. The period began with the presence of measurable allergen on 5 of 7 consecutive days and ended when no allergen was detected for 7 consecutive days. Concerning fungus, the major genera of the class basidiomycetes were *Coprinus*, *Boletus*, and *Ganoderma* species. The major genera of the class ascomycetes were *Leptosphaeria*, *Leptosphaeria* lookalikes, and *Oospora* (powdery mildews) species. The major genera of the class deuteromycetes (Fungi imperfecti) were *Cladosporium*, *Epicoecum*, and *Alternaria*.

Statistical methods

The allergen, climate, air pollution, and asthma admission variables were measured several hundred times over the course of the study, and each was expressed as a time series, methods that are typically used in air pollution research.¹⁴

We tested the log-linear association between aeroallergens and asthma hospitalizations using generalized linear models (S-PLUS, Professional Edition Version 6.2.1 for Microsoft Windows; Insightful Corp, Seattle, Wash), assuming a Poisson distribution for the hospitalization data.¹⁵ To model seasonal and other long-term trends in the data, we used natural cubic splines. For each sector, we tested many equally spaced intervals with knots every 15, 30, 60, 90, 120, 180, and 365 days of observation. The number of knots selected was determined by optimizing the Akaike information criterion goodness-of-fit test and the Bartlett test for autocorrelation¹⁶ and visually examining plots of residuals versus time to ensure that no pattern existed. Using stepwise backward and forward regression, we then tested the climate variables for inclusion using 3 *df*, one for the early half and one for the later half of the season holding the variable for time in the model. Of the 24-hour mean temperature, humidity, and barometric pressure, only temperature was significant on the day of admission and the 2 days before admission (lag 0,1,2). We also included an indicator variable for day of the week. The effect of aeroallergens on the day of admission and the 5 days before (lags 0,1,2,3,4,5) were tested, and the optimal lags were selected. Relative risks of hospitalization were presented for an interquartile (25th–75th) increase in air pollution stratified by the concentration of each air pollutant dichotomized as less than or equal to the median or greater than the median. A *z* test was used to test for differences in relative risks between higher and lower air pollution categories.

To pool data, we used a random-effects model¹⁷ with a random intercept to account for any inhomogeneity of results among the 11 cities. The effect estimates were weighted by the inverse sum of within and between-city variance. We combined the city-specific regression coefficients, β_j , by using the restricted maximum likelihood method. We assumed that

$$\hat{\beta}_j \sim N(\hat{\beta}, S_j + \gamma^2),$$

where $\hat{\beta}_j$ is the aeroallergen coefficient in city *j*, $\hat{\beta}$ is the pooled estimate from all of the cities, S_j is the estimated variance in city *j*, and γ^2 is the variance of the true aeroallergen effect between cities.

RESULTS

The combined population of the cities was 12,155,739 in the year 2000, the midpoint of the study (Table I). The average number of daily admissions for asthma was 28.67 during the 13 years of observation during the allergen season (ie, March through October). Mean daily air pollutant levels did not exceed US National Ambient Air Quality Guidelines concentrations (<http://www.epa.gov/air/criteria.html>, Fig 1). Variations were seen between cities with the largest PM₁₀ values, which ranged from about 12 to 27 $\mu\text{g}/\text{m}^3$ between March and October.

TABLE I. Population size and mean number of daily asthma admissions, temperature, and relative humidity for each of 11 Canadian cities between April 1, 1994, and March 31, 2007

City	Population (2000)	Asthma admissions (daily mean)	Temperature (daily mean °C)	Relative humidity (daily mean %)
Calgary	952,941	2.46	10.67	63.29
Edmonton	945,797	2.32	11.77	66.88
Halifax	366,309	1.34	12.75	80.21
Hamilton	678,639	1.20	15.42	75.34
London	449,750	0.75	15.60	73.14
Ottawa	822,804	1.38	15.36	67.55
St John	146,507	0.34	11.96	78.58
Toronto	4,761,231	12.10	16.11	67.40
Vancouver	2,040,295	3.98	14.81	78.02
Windsor	314,121	0.94	17.10	73.15
Winnipeg	677,345	1.86	13.27	64.24

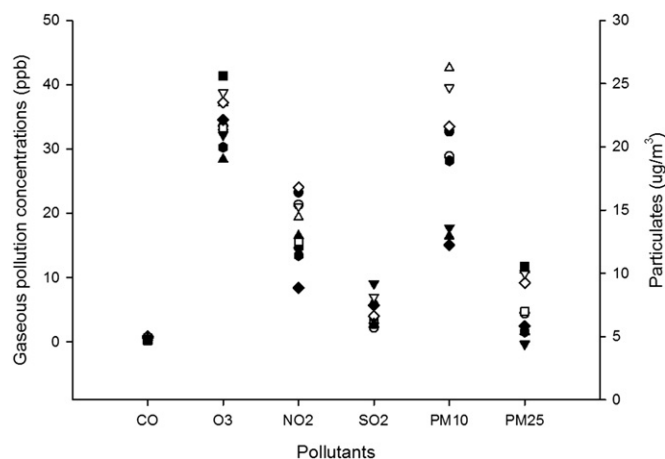


FIG 1. Air pollution concentrations for 11 Canadian cities between April 1, 1994, and March 31, 2007. CO, Carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; SO₂, sulfur dioxide. ●, Calgary; ○, Edmonton; ▼, Halifax; △, Hamilton; ■, London; □, Ottawa; ◆, St John; ◇, Toronto; ▲, Vancouver; ▽, Windsor; ●, Winnipeg.

Daily pollen counts averaged 15 grains/m³ for grass and weeds and about 30 grains/m³ for trees (Fig 2). Weed concentrations ranged from 2.13 grains/m³ in Halifax to 13.75 grains/m³ in Windsor. Tree concentrations ranged from 18.50 grains/m³ in Edmonton to 37.16 grains/m³ in Ottawa, and grass concentrations ranged from 4.08 grains/m³ in Halifax to 111.86 grains/m³ in Vancouver. Basidiomycete concentrations ranged from 266.78 grains/m³ in Calgary to 950.70 grains/m³ in Hamilton. Ascomycete concentrations ranged from 211.43 grains/m³ in Halifax to 697.45 grains/m³ in Hamilton. Deuteromycete concentrations ranged from 731.85 grains/m³ in Halifax to 2156 grains/m³ in Ottawa. Spore counts ranged from 300 to 2200 per cubic meter.

Each of the aeroallergens was associated with a significant increase in asthma admissions in the population independent of the concentration of air pollutants (Table II). However, the adverse effect of several aeroallergens was greater on days of higher versus lower air pollution. The aeroallergen effect sizes that were significantly different (*P* ≤ .05) between the higher and lower air pollution categories are presented in Table II. Several air pollutants increased the effect size of the fungi, basidiomycetes,

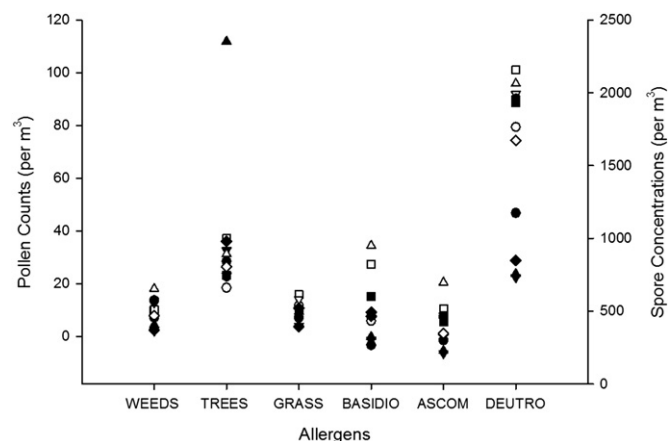


FIG 2. Seasonal mean concentrations of aeroallergens. *ASCOM*, Ascomycetes; *BASIDIO*, basidiomycetes; *DEUTRO*, deuteromycetes. ●, Calgary; ○, Edmonton; ▼, Halifax; △, Hamilton; ■, London; □, Ottawa; ◆, St John; ◇, Toronto; ▲, Vancouver; ▽, Windsor; ●, Winnipeg.

ascomycetes, and deuteromycetes. Particulate matter, especially PM_{10} , increased the effect size of all the aeroallergen groups. Significant ($P \leq .05$) differences in relative risks of admission for lower versus higher PM_{10} values were 1.149 (95% CI, 1.118-1.181) versus 1.210 (95% CI, 1.161-1.261) for ascomycetes, 1.112 (95% CI, 1.085-1.14) versus 1.302 (95% CI, 1.242-1.364) for basidiomycetes, 1.159 (95% CI, 1.125-1.195) versus 1.149 (95% CI, 1.129-1.169) for deuteromycetes, and 1.061 (95% CI, 1.016-1.107) versus 1.117 (95% CI, 1.092-1.143) for weeds. The relative risk of admission for an interquartile increase in tree pollen was 1.124 (95% CI, 1.101-1.147) on days of lower $PM_{2.5}$ values compared with 1.179 (95% CI, 1.149-1.21) on days of higher $PM_{2.5}$ values.

DISCUSSION

Significance of aeroallergens

Urban ambient air pollution and aeroallergens independently aggravate pre-existing asthma,¹⁻⁵ and there is laboratory evidence of interactive effects.⁶⁻¹¹ The purpose of the present study was to determine whether there are significant interactive effects in a real-world community setting. In 1991, Molino et al⁶ demonstrated that prior inhalation of ozone at concentrations that did not cause bronchoconstriction enhanced the response to inhaled grass or ragweed pollen in sensitized subjects with asthma. The concentration of methacholine that provoked a 15% reduction in FEV_1 was 0.013 mg/mL with ambient air followed by allergen compared with 0.0056 mg/mL with 0.12 ppm of ozone followed by allergen. Many other controlled clinical laboratory studies have also demonstrated interactive effects of aeroallergens and air pollutants on asthmatic subjects.⁷⁻¹¹

In contrast to the large number of clinical studies, there is little information on the significance of an aeroallergen-air pollutant interaction in the general population. In 2004, we reported that in Canada a daily increase in tree pollen concentrations equivalent to the magnitude of its mean value increased hospitalizations for asthma by 2.9% (95% CI, 0.9% to 5.0%) for tree pollen. After accounting for the independent effects of tree pollen and ozone, their combination was associated with an additional 0.22% increase in admissions ($P < .05$). Studying interactive effects

TABLE II. Pooled estimate among 11 cities of percentage change in daily hospitalization (95% CI) with an increase in allergen concentrations equal to their pooled interquartile ranges stratified by air pollution concentration

	Air pollutant	RR of asthma hospitalization for an IQR increase in aeroallergen concentration	
		Lower air pollutant concentration	Higher air pollutant concentration
Ascomycetes	CO	1.11 (1.096-1.124)	1.153 (1.137-1.169)
	PM_{10}	1.149 (1.118-1.181)	1.210 (1.161-1.261)
Basidiomycetes	CO	1.107 (1.092-1.121)	1.167 (1.15-1.183)
	NO_2	1.09 (1.074-1.107)	1.179 (1.16-1.198)
	SO_2	1.073 (1.051-1.094)	1.204 (1.152-1.26)
	PM_{10}	1.112 (1.085-1.14)	1.302 (1.242-1.364)
Deuteromycetes	CO	1.116 (1.102-1.13)	1.156 (1.14-1.172)
	NO_2	1.116 (1.099-1.134)	1.175 (1.157-1.193)
	SO_2	1.117 (1.101-1.133)	1.149 (1.129-1.169)
Trees	PM_{10}	1.159 (1.125-1.195)	1.299 (1.193-1.414)
	$PM_{2.5}$	1.124 (1.101-1.147)	1.179 (1.149-1.21)
Weeds	PM_{10}	1.061 (1.016-1.107)	1.117 (1.092-1.143)

Only the associations in which there was a significant difference between days with lower versus higher air pollution are presented.

CO, Carbon monoxide; IQR, interquartile range; NO_2 , nitrogen dioxide; RR, relative risk; SO_2 , sulfur dioxide.

had not been the primary purpose of the study, but an interaction term was significant.¹² However, another Canadian study found that the effect of ozone and particulate air pollution on emergency admissions for asthma was not influenced by ambient aeroallergen concentrations.¹³ However, this study was based on data from 1 metropolitan city in Canada, resulting in much less power than the present study to detect interactive effects.

Theories to explain an aeroallergen-air pollution interaction

It has been hypothesized that damage to the airways by air pollutants might increase mucosal permeability and thereby penetration of allergens.¹⁸ Metal components of fine particulate air pollution might enhance the allergic response. Fine particles with higher concentrations of metals increased the airway response to ovalbumin in sensitized mice, whereas lower $PM_{2.5}$ concentrations did not.¹⁹ Diesel exhaust particles have been shown to enhance the production of IgE specific to ovalbumin in sensitized mice. This can be inhibited by antioxidants, suggesting that the adjuvant effect of the particles is mediated by reactive oxygen species.²⁰ Diesel exhaust particles might also facilitate transportation of pollen antigens to the small airways.²¹ Disruption of pollen grains by diesel exhaust particles was observed by using scanning electron microscopy. This could possibly facilitate the release of allergens, enhancing the allergic response.²² Through inhibiting ciliary beat frequency,²³ diesel exhaust particles might reduce allergen clearance and prolong the allergic response.

Limitations of the study

It is not possible to measure personal exposure to air pollutants and aeroallergens in a large population. The error in attributing exposure would likely be random in nature and underestimate the observed effect of these variables. Allergic characterization of

subjects is not feasible in a large population study, and skin test reagents are not widely available for many outdoor allergens, such as the basidiomycetes group. With time-series analysis, it is unnecessary to characterize the allergic sensitivity of the subjects. The increase in asthma admissions on days of high aeroallergen levels must be by persons with asthma who are sensitive to the allergens, unless there exists a confounding factor.

Although all allergens were observed to increase hospitalization for asthma, not all allergen–air pollutant interactions were found to be significant. Lack of power might be the most likely reason for the lack of statistical significance for some allergen–pollutant combinations. Although we had 13 years of daily observations, the tree pollen season is only 2 to 3 months a year, and fungi are present for 5 to 7 months. The sample size is further reduced by dividing the allergen period into 2 groups defined by level of air pollution (higher vs lower). We compare the effects of lower versus higher air pollution and not zero versus higher air pollution. Also, peak periods of allergens do not necessarily correspond to peak periods of air pollution. Levels of ozone and particulates are highest in July and August, whereas levels of tree pollen are maximal in April, May, and June. Weeds and fungi tend to be highest in August and September, when sulfur dioxide and nitrogen dioxide levels are lowest.

Summary

We observed that there is an increased risk of asthma hospitalization associated with ambient aeroallergens on days of higher air pollution. Decreasing air pollution levels might reduce the morbidity from allergic asthma exacerbations in the general population.

We thank Environment Canada for providing meteorologic and air pollution data.

Key messages

- Aeroallergens are risk factors for asthma severe enough to precipitate hospitalization.
- The presence of air pollution appears to increase the morbidity from aeroallergens.
- Decreasing air pollution levels might reduce the severity of allergic asthma exacerbations in the general population.

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