

The role of symptomatic colds in asthma exacerbations: Influence of outdoor allergens and air pollutants

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Background: Both air pollutants and respiratory viral infections have been recognized to be important triggers of asthma exacerbations, but the possible interaction of these has not been assessed in an epidemiologic study.

Objective: In this study, we aimed to assess the possible associations of symptomatic colds with outdoor allergens and air pollutants in exacerbating asthma.

Methods: A total of 57 adults and children with asthma participated in a 1-year study in Vancouver, British Columbia. Diary cards recording symptoms of asthma and colds, medication usage, and peak expiratory flow rates were completed twice daily. Outdoor air pollutant levels and levels of pollen and fungal spores were measured. Levels were examined for associations with exacerbations of asthma with symptoms of a cold, as compared with asthma exacerbations with no cold symptoms and colds in the absence of asthma exacerbations.

Results: Of 130 asthma exacerbations, 47% were associated with cold symptoms (accounting for 44% of episodes of colds). Asthma exacerbations with colds were associated with higher levels of sulfur dioxide, and nitric oxide during March to November in comparison with asthma exacerbations without cold symptoms ($P < .018$). Cold-symptom days overall were more common in winter and were significantly associated with lower temperatures, lower ozone levels, and higher sulfur dioxide, nitrogen dioxide, nitrogen oxide (NO and NO_x), and carbon monoxide levels.

Conclusions: Asthma exacerbations are commonly associated with cold symptoms. These episodes are associated with higher levels of sulfur dioxide and nitrogen oxides from March to November in comparison with asthma exacerbations without cold symptoms. (*J Allergy Clin Immunol* 2001;108:52-8.)

Key words: Asthma exacerbations, air pollutants, colds, viral respiratory infections

Respiratory viral infections have been reported to account for up to 80% to 85% of childhood asthma episodes.¹⁻⁶ They have been shown in adults to increase

Abbreviations used

AC: Asthma exacerbations with a symptomatic cold
ANC: Asthma exacerbation with no cold
CWNA: Cold with no asthma exacerbation
SO₂: Sulfur dioxide
NO: Nitric oxide
NO_x: Nitrogen oxide mix
NO₂: Nitrogen dioxide
O₃: Ozone
TSP: Total suspended particulates
COH: Coefficient of haze

airway responsiveness, even in subjects without clinical asthma.⁷ The effect is preferential in allergic subjects⁸ and in mice is associated with enhanced airway sensitization to allergen.⁹ Beasley et al¹⁰ identified a viral respiratory tract infection in 10% of 178 exacerbations of asthma in 31 adults and found a higher proportion (36%) of severe exacerbations to have such association. In a previous study of adults with asthma,¹¹ we similarly found that 9% of exacerbations were associated with symptomatic colds. A study of severe exacerbations of asthma in 33 patients presenting to an emergency room¹² also reported that 56% of the visits were associated with 1 or more symptoms suggestive of a viral syndrome (rhinorrhea in 38%, sore throat in 9%, and fever in 15%).

Our previous study demonstrated that symptomatic colds were more common among adults with asthma than among their nonasthmatic spouses,¹¹ particularly in the spring, summer, and fall. Although symptoms of a cold might in some cases be caused by allergic rhinitis rather than a viral infection, evidence suggesting that such episodes in children relate more to viral infections than to allergic responses comes from a case-control study of South African asthmatic children with and without acute exacerbations.¹³ There was a strong association of acute exacerbations with symptomatic colds but no association with changes in pollen or fungal spore counts or with known allergen exposure. Similar findings were reported in a Norwegian study of children with acute asthma exacerbations.⁴

Although viral culture and serology findings are not sensitive indicators of acute respiratory viral infections, Johnston et al⁶ found by combining the technique of reverse transcription-polymerase chain reaction with cul-

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ture that 80% to 85% of school-aged children with wheezing episodes tested positive for viruses, most commonly rhinovirus. It is therefore likely that most episodes of cold symptoms reflect true respiratory viral infections.

Environmental air pollutants also might contribute to acute asthma exacerbations. Increased levels of ambient ozone and sulfates,¹⁴ acid aerosols,¹⁵ and particulate air pollution,¹⁶ especially during the summer months, have been associated in Ontario with acute hospital admissions for asthma. In British Columbia, an increase in hospital emergency visits for asthma has been reported in September each year,¹⁷ possibly related to sulfate levels.

To our knowledge, the possible association of air pollutants and respiratory viral infections in causing acute asthma exacerbations has not previously been assessed in an epidemiologic study. The present study was performed to assess possible associations between environmental factors such as air pollutants and symptomatic colds in the production of asthma exacerbations.

METHODS

Data were analyzed from a component of a 1-year prospective panel study of adults and children with asthma in Vancouver, British Columbia, and Winnipeg, Manitoba. The study assessed environmental exposures, symptomatic colds, personal host factors, characteristics of asthma, and variation in respiratory symptoms and pulmonary function. More detailed information on air pollution variables was obtained in Vancouver, and data from this site were used to examine the relationship between symptomatic colds with or without asthma exacerbations and air pollutant levels.

Vancouver, a city of approximately 1.5 million people, is located on the Pacific coast of Canada. It has mild winters (January mean, 3°C) and warmer summers (July mean, 17°C).¹⁸ There is a relatively early spring; tree pollen peaks in February and March and grass pollen in April (there is no ragweed pollen). The city has high levels of precipitation (1859 mm of rain annually) and high levels of total fungal spores in all seasons.

Patients with histories compatible with asthma and evidence of reversible airflow limitation or airway hyperresponsiveness were recruited into the study if they were aged 7 to 55 years of age and lived within 10 km of the study center. Patients with heart disease, patients with chronic lung disease (such as bronchiectasis and emphysema), and patients with occupational asthma were excluded. Adult patients were recruited from respiratory clinics and children from allergy clinics of the University of British Columbia.

At the onset of the study, patients came to the clinics for the initial interview and an entry questionnaire was completed. Allergy skin tests, lung function tests, and methacholine challenge tests were carried out. Each patient was instructed on how to complete the diary card, consisting of a daily record of their day and night symptoms, medication use, and peak flow rates, which were measured twice a day. After 2 weeks of practice to ensure adequate completion of the diaries, the patients started the 1-year panel study. They returned to the clinics every 3 months for interviews and spirometry.

Allergy skin tests were performed through use of the skin prick method with 13 common allergens (tree mixture, grass mixture, weed mixture, redroot pigweed, sorrel, English plantain, lamb's-quarters, mold mixture, feather mixture, cat dander, dog dander, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus*), together with a negative control (normal saline solution) and a positive control (histamine 1 mg/mL). The results were read at 15 min-

utes. A wheal diameter of 3 mm or greater than the negative control was considered a positive reaction. For this study, atopy was defined as the presence of 1 or more positive skin tests.

Environmental monitoring was carried out as follows:

- *Pollen and fungal spores.* A Burkard 7-day recording pollen and spore trap (Burkard Manufacturing, Hertfordshire, United Kingdom) was placed on the rooftop of the Children's Hospital in Vancouver (7 floors above ground level). The sampler draws 10 L of air per minute through a slit orifice, and airborne particulate matter is impacted on a rotating tape. The tape was covered with a mixture of Vaseline (Chesebrough-Ponds USA, Greenwich, Conn) and wax (9:1 ratio). After exposure, the tape was cut into daily segments and mounted on microscope slides. Glycerine jelly with basic fuchsin was used as the mounting media and stain. Pollen grains were microscopically enumerated along 12 transverse traverses (2-hour intervals) at a magnification of 512×; fungal spores were examined through use of a single longitudinal traverse at 640×. Counts were converted to average daily concentrations per cubic meter of air.
- *Air pollution data.* The Greater Vancouver Regional District has more than 40 monitoring stations in the Lower Mainland. The equipment and the methods of detection of particulates and gases are standardized across Canada. For each monitoring station and for each day of the follow-up period during the year, the hourly means, maximums, and minimums were obtained for the following indices of air quality: sulfur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), coefficient of haze (COH), nitric oxide (NO), and nitrogen oxide mix (NO_x). Total suspended particulate (TSP) levels were obtained every 6 days. SO₂ was measured by coulometry and ultraviolet fluorescence; NO₂, NO, and NO_x, by chemiluminescence; O₃, by chemiluminescence and ultraviolet photometry; COH, by light transmission through a paper tape through which air had been drawn and particles deposited; TSP, by gravimetry. The data for the period from the beginning of September 1991 to the end of March 1993 were used for analysis.
- *Climate.* The daily means, maximums, and minimums of temperature, humidity, wind velocity, and wind chill factor were obtained from the Atmospheric Environmental Service of Environment Canada.

Definitions of asthma exacerbations and symptomatic colds

The present report was based on defining exacerbations from a review of each participant's 12-month diary (described above). An exacerbation was defined to have occurred if a change was recorded over a minimum of 2 days in at least 2 of the following variables: (1) an increase in asthma symptoms (each symptom was recorded in the diary on a severity scale of 0-3); (2) an increase in asthma medications (inhaled bronchodilators ± corticosteroid therapy); (3) a decrease in peak expiratory flow levels of at least 10% in comparison with the mean on the preceding 10 days at the same time of day.

We tested this definition on the 36 symptomatic instances judged to be exacerbations by the subjects in an associated case-control study that we have reported separately.¹⁹ Twenty-seven (93%) of the 29 who had adequate diary information would have been correctly classified and none of the 36 controls mistakenly classified.

For the present study, a symptomatic cold was defined as the concurrent presence on the diary record of at least 2 of the following 3 symptoms: fever, sore throat, and an increase or onset of nasal symptoms. These same criteria were used to define a cold in the case-control component of the study.¹⁹

TABLE I. Patient characteristics

No. of patients	57
Age (y)	26.8 ± 19
No. of children (age < 13 y)	35%
Male	49%
Current smokers	0%
Ex-smokers	16%
At least 1 positive allergy skin test	77%
Baseline inhaled bronchodilator use only	33%
Bronchodilator and inhaled steroids	67%
Mean daily inhaled steroid dose among users	775 µg
Oral steroids	0%
Asthma exacerbations with colds	61 (29%)
Asthma exacerbations with no cold	69 (33%)
Colds without asthma exacerbation	78 (38%)

TABLE II. Diary features of asthma exacerbations

Asthma exacerbations	With colds	Without colds	P value
Total	61	69	
No. of increased symptoms (cough, wheeze, dyspnea)			<.05
Three	59%	32%	
Two	25%	33%	
One	16%	29%	
Maximum symptom severity score increase, 2 or 3 on a scale range from 0-3	73%	39%	<.001
Bronchodilators			
Increased	75%	74%	NS
Mean daily increase among those who did increase (no. of puffs)	4.5	3.9	NS
Inhaled steroids			
Increased	38%	25%	NS
Mean amount of increase (µg)	335	412	NS
Oral steroids			
Increased or added	2%	1%	NS
Maximum mean (mg)	40	25	NS
Peak flow fall			
At least 20%	41%	38%	NS
Overall mean fall	22%	16%	NS

NS, Not significant.

Statistical analyses

Results were analyzed through use of the SAS statistical package (SAS Institute, Cary, NC) on a personal computer. The Student *t* test, general linear model, analysis of variance, and χ^2 test were used when appropriate.

Three groups of acute events were compared for subjects. One group included information related to days on which individuals had an asthmatic attack and a cold. Another group included information related to days on which individuals had only an asthma exacerbation (with no cold). The last group consisted of information related to days on which individuals had only a cold. In comparing the means between any 2 of these groups, one had to account for some individuals being in both groups and some individuals having more than 1 acute event within a group. To account for repeated observations per patient, a robust analysis was conducted with the patient being used as the sampling unit. Comparisons were made through use of a mean value of air pollutant per patient before colds and/or asthma exacerbations.

A difference in the sample means between any 2 groups consisted of 2 components: a paired difference that involved individuals who were in both groups and a nonpaired difference that involved individuals who were in only 1 of the 2 groups. The variance of each type of difference was calculated and used to estimate the SE of the weighted mean of the paired and unpaired differences. A *t* ratio the difference to its SE was calculated and declared significant if the associated *P* value was less than the Bonferroni value of 0.0183 when applied to analyses of air pollutant associations.

A similar analysis involved the comparison of the mean number of acute events per subject (ie, the mean number of colds versus colds with asthma exacerbations versus asthma exacerbations without colds). This analysis, which was based on the principle described above, was carried out for different categories defined by patient age, atopic status, and whether the event was concurrent with exposure to a seasonal allergen to which the subject had a positive allergy skin test result.

RESULTS

Features of the total group and of symptomatic colds and asthma exacerbations

Fifty-seven patients from Vancouver participated in the panel study and maintained regular diary records during the 1-year period. Their mean age was 27 years (Table I), 35% were children (aged 7 to 12 years), and 49% were male. None were current smokers, and 16% were ex-smokers. Seventy-seven percent were atopic. At the start of the study, 33% were taking only inhaled bronchodilators, 67% were also taking regular inhaled steroids (mean daily dose, 775 mg/day; range, 150-2000 mg/day) and none were taking oral corticosteroids.

Of the 139 episodes of colds defined from diary records, 88% consisted of nose and throat symptoms, 12% consisted of fever with nose or throat symptoms, and 18% involved all 3 symptoms. Forty-four percent of colds were associated with asthma exacerbations. In 52% of the asthma exacerbations associated with colds, the colds were manifested by all 3 cold symptoms.

There were 130 asthma exacerbations, 47% associated with colds. Asthma exacerbations with colds were associated with more asthma symptoms (*P* < .05) and more severe symptoms (*P* < .001) than asthma exacerbations with no colds (Table II). However, medication increases and peak flow declines were similar for exacerbations with and without colds (Table II). Duration of asthma exacerbations could not be reliably determined from the diary records because there was no uniform management of exacerbations.

Of the 139 episodes of symptomatic colds, 61 (44%) immediately preceded or occurred at the onset of asthma exacerbations. When colds were associated with asthma exacerbations, the cold preceded the exacerbation by a mean of 1.73 days, most often starting on the same day (44% of episodes) or 1 day before (21% of episodes). In addition, there were 69 asthma exacerbations with no associated cold; this was 53% of all asthma exacerbations.

The per-patient number of exacerbations with a cold ranged from 0 through 11 (mean, 1.07); 51% of patients had at least 1 exacerbation. Sixty-three percent of

TABLE III. Characteristics of symptomatic colds and asthma exacerbations occurring separately and combined (in 57 subjects)

Subject grouping	No. of subjects	No. of colds/asthma exacerbations			P value
		AC (n = 61)	ANC (n = 69)	CWNA (n = 78)	
Children (age < 13 y)	20	34	35	45	NS
Older subjects	37	27	34	33	NS
Atopic subjects	44	54	56	66	NS
Nonatopic subjects	13	7	13	12	NS
Subjects with concurrent relevant seasonal allergen exposure		20	31	40	NS
Subjects without concurrent relevant seasonal allergen exposure		41	38	38	NS
Children with relevant seasonal allergen exposure		8	14	21	NS
Older subjects with relevant seasonal allergen exposure		12	17	19	*
Type of acute event by season of episodes (%)					NS
Spring (March-May)		27	27	29	—
Summer (June-August)		11	22	20	—
Autumn (September-November)		25	24	22	—
Winter (December-February)		37	27	28	—

AC, Asthma exacerbation with a cold; ANC, asthma exacerbation with no cold; CWNA, cold with no asthma exacerbation; NS, not significant.

*P value < .001 for comparison between AC and CWNA, accounting for the presence of individual subjects in 1 or more exacerbation group and the occurrence of more than 1 acute event in some subjects in each group.

patients had at least 1 exacerbation without a cold, the range being 0-14 (mean, 1.21 per patient). The per-patient number of colds with no associated asthma exacerbation ranged from 0 through 18 (mean, 1.37); there was at least 1 cold without asthma in 56% of patients. Thus colds as defined by the diary card information were common in this population and were associated with almost 50% of asthma exacerbations.

Relationship of colds to outdoor environmental measures

Levels of ambient outdoor pollutants, pollen, fungal spores, and climatic variables were compared for days in which at least 1 patient recorded cold symptoms and days in which no patient recorded cold symptoms. Days in which cold symptoms were recorded had significantly higher mean levels of SO₂ (5.3 ± 4.7 [mean ± SD] vs 4.7 ± 4.2 ppb; *P* = .0002), NO₂ (24.9 ± 11.3 vs 23.5 ± 11 ppb; *P* = .0003), NO (42 ± 45.5 vs 38.1 ± 45.1 ppb; *P* = .006), NO_x (67 ± 54.7 vs 61.7 ± 53.8 ppb; *P* = .003), and CO (1.11 ± 0.72 vs 1.01 ± 0.69 ppm; *P* = .0001), significantly lower mean levels of O₃ (13.8 ± 11.6 vs 14.7 ± 11.1 ppb; *P* = .01) and significantly lower daytime temperatures (11.3 ± 5.8°C vs 11.8 ± 6.3°C; *P* = .008).

Colds or allergic rhinitis?

Atopic patients recorded more colds with and without asthma exacerbations than did nonatopic patients (mean, 1.23 vs 0.54 for colds with exacerbations and 1.50 vs 0.92 for colds without asthma exacerbations); however, the number of nonatopic individuals in this study was small. The proportion of exacerbations with colds that occurred during a relevant allergy season (as determined by the patient's skin test response and outdoor pollen or fungal spore levels at the time of symptoms) was smaller than the proportion of each of these events alone during relevant allergy seasons. This suggests that some episodes of apparent colds without asthma exacerbations

were actually symptoms of pollen-induced allergic rhinitis, though overall, colds occurred mainly in the winter and spring months (Table III) and were associated with temperature and pollutant measures consistent with a nonsummer distribution (as shown above).

With respect to seasonal distribution, the 3 groups of acute symptoms were similar. Colds and exacerbations of asthma all showed a trend to increased prevalence in the late fall and winter and spring months.

Relationships of asthma exacerbations and colds with air pollutants

The outdoor environmental pollutant levels were averaged per patient for 1, 3, and 5 days before each acute event (colds with and without asthma exacerbations and asthma exacerbations without a cold) and compared for these 3 types of acute event. There was a statistically significant association for asthma exacerbations with colds and levels of SO₂, NO, and NO_x, which were significantly higher for a 3-day mean before exacerbations with colds than for a 3-day mean before exacerbations without colds (*P* < .01) during warmer months (March-November). This was not evident in the cooler months and was not evident for 1 day before the acute event (or 3 days after the onset [data not shown]). Assessment of children and adults separately through use of mean per patient values for colds and or asthma exacerbations showed the relation of colds with asthma exacerbation to be significant for preceding SO₂ in children and for preceding NO and NO_x in adults (*P* < .05). Each individual subject could have more than 1 type of acute event; 13 subjects had colds with and colds without asthma exacerbations, 7 had asthma exacerbations with and without colds, and 13 had asthma exacerbations without a cold and colds without asthma exacerbations. Therefore, further analyses were performed to correct for this (as described in the Methods section). These analyses showed that asthma exacerbations with a cold continued to be statistically significant-

TABLE IV. Vancouver mean pollutant levels 1, 3, or 5 days before a day of an acute episode, March–November

Pollutant (March–November)	Pollutant level (ppb)					
	Exacerbation group			P value		
	AC (n = 20)	ANC (n = 28)	CWNA (n = 27)	AC vs ANC	AC vs CWNA	ANC vs CWNA
SO ₂						
1-day mean	4.58	3.54	5.23	.190	.825	.222
3-day mean	4.94	3.04	4.68	.018*	.595	.016*
5-day mean	5.00	3.45	4.65	.031	.513	.023
NO						
1-day mean	31.35	19.64	32.07	.092	.643	.081
3-day mean	34.68	18.95	28.32	.015*	.371	.006*
5-day mean	36.67	20.70	27.28	.014*	.074	.003*
NO _x						
1-day mean	53.64	39.82	52.27	.108	.969	.059
3-day mean	57.96	28.60	51.74	.202	.604	.003*
5-day mean	60.06	41.28	50.65	.024	.194	.001*
NO ₂						
1-day mean	31.35	19.64	32.07	.128	.334	.067
3-day mean	23.19	19.58	23.03	.061	.963	.016*
5-day mean	23.27	20.53	23.65	.217	.999	.012*
Ozone						
1-day mean	16.19	20.55	15.23	.153	.848	.038
3-day mean	16.01	19.35	16.50	.300	.426	.218
5-day mean	15.51	19.84	17.05	.256	.140	.369

Averaged per patient for episodes of colds and asthma exacerbations—ie, for each patient a maximum of 1 value per acute grouping for each pollutant per time period.

*P value less than the Bonferroni value of .0183 is significant.

ly associated with preceding 3-day mean levels of SO₂ and NO and 5-day mean levels of NO versus asthma exacerbations without a cold (Table IV). In addition, there was a significant association between colds without asthma exacerbations versus asthma exacerbations without a cold and 3- and 5-day preceding levels of NO, NO_x, and NO₂.

Relationship of colds and/or asthma exacerbations with other environmental factors

There was no significant difference in numbers of acute patient episodes with respect to any of the other environmental factors—ie, temperature, humidity, TSP, COH, O₃, and fungal spore and pollen counts.

DISCUSSION

This study is consistent with other studies showing that symptomatic colds are important triggers of asthma in children and in adults. During this 1-year study of symptoms as recorded on diary cards, symptomatic colds were associated with 46.9% of asthma exacerbations.

The proportion of asthma exacerbations related to symptomatic colds was greater during the late fall, winter, and spring months. The possibility that some of these symptomatic colds truly were manifestations of allergic rhinitis has been considered, especially for episodes of increased nasal symptoms and sore throat without fever, inasmuch as PCRs or other laboratory confirmations of a viral etiology were

not obtained in this study. Asthma exacerbations with colds were not associated with pollen or fungal spore levels, making it unlikely that many of these episodes resulted from seasonal allergic responses, though some episodes might have been due to seasonal allergic rhinitis and some to nonseasonal allergic responses.

We found an association from March to November in Vancouver between higher levels of SO₂ and NO for 3 days before asthma exacerbations with a cold in comparison with the levels of these pollutants before asthma exacerbations without a cold. The same pollutants, as well as NO₂ and NO_x, were associated with symptomatic colds without asthma exacerbations in comparison with asthma exacerbations without a cold, suggesting that the relationship was with the symptomatic colds. The lack of a significant difference in the pollutant levels between these episodes during the winter months, when pollutant levels were generally higher, might relate to reduced personal exposure to outdoor agents in winter. In addition, there was probably greater exposure in winter to indoor nitrogen oxides and other pollutants (69% of patients had gas heating and 12% had gas stoves), which might have masked any association with outdoor pollutants.

Acute asthma exacerbations have previously been associated with increased levels of outdoor air pollutants—SO₂, sulfates, particulates, NO_x, and O₃.^{13–17,20} In addition, indoor NO₂ exposure has been associated with lower morning peak flow levels in children with asthma.²¹ However, those reports did not assess concurrent viral respiratory infections in triggering asthma exacerbations.

An interaction between air pollutants and viral respiratory infections has been suspected on the basis of demonstrated reductions in mucociliary clearance times with increasing concentrations of exposure to O₃ in an animal study²² and with other air pollutants, such as sulfuric acid and cigarette smoke,²³ in human beings. Possible effects of pollutants such as O₃ on immune mechanisms²⁴ have also been suggested. NO is known to induce vasodilation in the nose and lower respiratory tract^{25,26} and potentially might exacerbate symptoms on this basis.

It is possible that the apparent association seen between symptomatic colds with asthma exacerbations and air pollutants was due to a coincidental seasonal rise. It has been demonstrated that there is a seasonal pattern to some viral respiratory infections; in North America, for example, respiratory syncytial virus and influenza virus infections generally tend to peak in winter or early spring, rhinovirus infections in spring and early autumn, and parainfluenza later in the autumn.²⁷⁻²⁹ In addition, there is a seasonal fluctuation in some outdoor air pollutant levels—notably O₃ and NO_x, which are interdependent. O₃ levels are higher in the summer months because of formation from NO_x, volatile organic compounds, increased sunlight, and oxygen. NO will act as a scavenger of O₃, forming NO₂ and other components of NO_x, whereas nitrogen oxides—especially NO₂—in the summer are partially converted to O₃. There is increased rural production of NO_x in the summer months, and this contributes to increased rural levels of O₃ at this time. Similarly, though SO₂ might be produced to a similar degree throughout the year, levels can fluctuate with varying oxidation to sulfuric acid and sulfates, which increases in the summer months in North America.³⁰

Our lack of association of pollutants with colds versus asthma exacerbations with or without colds during the winter months could also suggest an interaction of pollutants with only selected viruses in enhancing the asthmatic response. For example, this might have occurred with rhinovirus and parainfluenza virus, which are more prevalent during the spring and autumn seasons, rather than with influenza viruses, which are present in the winter months, when levels of these air pollutants are actually higher. Future studies using PCRs to identify specific viral infections in a study such as this might clarify any specific viral interaction.

Several possible mechanisms might explain an interrelationship between respiratory viral infections and these outdoor air pollutants. Animal studies have shown that nitrogen oxides can damage ciliated respiratory cells and depress airway mucociliary clearance of particles and infectious agents. Susceptibility to respiratory infection increased in animals even after exposure to ambient and near-ambient concentrations of NO₂.³¹⁻³³

At a cellular level, exposure of human bronchial epithelial cell cultures to NO₂ has resulted in an increased release of IL-8, TNF- α , GM-CSF, RANTES, and soluble intercellular adhesion molecule-1.³⁴⁻³⁶ Such an increase, particularly in the last of these, might be a factor facilitating respiratory viral infection in exposed

individuals and might explain our observed associations.

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