

Immunodeficiency and other clinical immunology

Effects of environment on atopic status and respiratory disorders in children

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Background: We investigated whether living in areas with higher air pollution levels increases the prevalence of positive skin reactivity in children and the possible synergic effect of air pollution exposure and atopy on respiratory disorders.

Methods: This cross-sectional study was conducted in an urban area, in an industrialized area, and in a rural control area in the Latium region of Italy. A total of 2226 subjects, aged 7 to 11 years, were studied.

Results: The prevalence of children with positive skin test results did not vary significantly over the areas (urban area = 21.0%, industrialized area = 22.0%, rural area = 20.2%). Children living in polluted areas experienced significantly more cough and phlegm (odds ratio [OR] = 1.5), rhinitis (OR = 1.7), pneumonia (OR = 1.7), and early respiratory infections (OR = 1.4) than control subjects. The pattern of the odds ratios for atopy and air pollution suggested that the two factors were probably additive in affecting asthma and early respiratory infections (synergy index [SI] = 1.04 and 1.27, respectively), whereas they seemed to act synergically in regard to cough and phlegm (SI = 1.59), rhinitis (SI = 3.01), and pneumonia (SI = 2.75).

Conclusion: Environmental air pollution seems not to increase the prevalence of atopic status; it seems, however, to enhance the development of clinical symptoms among already sensitized subjects. (*J ALLERGY CLIN IMMUNOL* 1993;92:616-23.)

Key words: Asthma, atopy, environmental air pollution, epidemiology, synergism, respiratory health, children

Attention to the potential effects of environmental air pollution (EAP) on the respiratory health of children has been growing in recent years: an increased incidence of asthma,^{1, 2} bronchitis,³ and chronic cough⁴ has been observed for exposure to pollutants even below the standard international limits.^{5, 6} We have recently reported that children living in urban and industrialized

Abbreviations used

ATS:	American Thoracic Society
CI:	Confidence interval
CV:	Civitavecchia
EAP:	Environmental air pollution
ERI:	Early respiratory infection
OR:	Odds ratio
RM:	Rome city center
SO ₂ :	Sulfur dioxide
VT:	Province of Viterbo

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areas of Italy are more likely to have asthma and to have had pneumonia and respiratory infections during the first 2 years of life than children living in rural areas.⁷

Several questions remain open regarding the mechanisms by which EAP has deleterious effects on respiratory health; one of these questions

concerns the role of sensitive subgroups within the exposed population.⁸ Patients with asthma^{9, 10} and atopic subjects¹¹ seem to be more sensitive to pollutants; however, the reason that only some subjects with IgE-mediated reactivity to common environmental allergens have clinical symptoms is not fully understood. It could be hypothesized that EAP might also increase the number of these sensitive subjects; that is, it might increase the prevalence of atopy and bronchial hyperreactivity in the population. As a matter of fact, pollutants can induce allergic sensitization¹²⁻¹⁴ in animal studies, and a link between sulfur dioxide (SO₂)^{15, 16} and ozone^{17, 18} and bronchial hyperresponsiveness has been suggested. The prevalence of sensitive subgroups and the extent of their response to pollutants is of concern because susceptible individuals should be protected from adverse health effects.

In summary, two issues seem to be worth addressing, namely the possible relationship between outdoor pollution and IgE-mediated sensitization to environmental antigens and whether air pollutants increase the incidence of clinical symptoms in an already sensitized population. Therefore we analyzed data collected during a survey on respiratory disorders among schoolchildren⁷ to further evaluate the role of atopy on environmentally induced respiratory disorders. Two specific questions were addressed. (1) Is living in areas with higher exposure to EAP associated with an increased prevalence of positive skin reactivity to environmental allergens? (2) Is there synergism between EAP exposure and atopy in increasing the risk of having respiratory disorders?

METHODS

Subject and data collection

Complete descriptions of the sample and the data collection have been reported elsewhere.^{7, 19} Briefly, we studied three areas of central Italy with different levels of air pollution: the Rome city Center (RM), polluted mostly by automobile exhaust and heating systems; Civitavecchia (CV), a nearby industrial town polluted by three oil-fired thermoelectric power plants; and three rural communities 130 km north of Rome in the province of Viterbo (VT), chosen as control. The annual median total SO₂ level over 24 hours was higher in CV (range of five monitors, 25 to 50 µg/m³) and in RM (range of five monitors, 39 to 97 µg/m³) than in VT (two monitors, 0 to 5 µg/m³). Annual median values of total suspended particulates were available only for CV (range of four monitors, 15 to 66 µg/m³) and for RM (range of five monitors, 86 to 248 µg/m³).

A total of 17 schools were randomly chosen from the list of the schools in the areas (3 for VT, 10 for RM, and 4 for CV) and 3092 children (978, 1137, and 977, respectively) from the second to the fifth grade (7 to 11 years old) were enrolled in the study. Data regarding symptoms or diseases were obtained from the parents through a self-administered questionnaire adapted from the American Thoracic Society (ATS)–Division of Lung Diseases instrument,²⁰ together with written consent for a medical examination and skin testing. For technical reasons, 303 fifth-grade children (79, 158, and 66 from VT, RM, and CV, respectively) could not undergo testing, leaving a final target sample of 2789 subjects. All of the children were examined, between February and June or between September and November of 1987, by 12 pulmonary medicine residents, who rotated weekly among the areas in pairs and were assisted by three professional nurses. Testing was performed in all communities during the same times of the year.

Skin prick tests were used to evaluate atopic status.²¹ Eight extracts of common allergens were tested (Bayrofarm, Milan, Italy): *Dermatophagoides pteronyssinus*, grass, mugwort, *Parietaria* species, cat fur, *Olea* species, trees, and *Alternaria* species. Histamine dihydrochloride (10 mg/ml) and diluent were used as positive and negative controls. After 15 minutes, the wheals greater than 4 mm² in diameter were outlined, and the markings were transferred to square millimeter paper by means of a tape. The wheal size was calculated by the product of the long axis by its perpendicular. Wheals of 4 mm² in diameter or greater were considered positive provided that the control solution produced no reaction and there was a positive reaction to histamine.

Variables and analysis

Atopic status was expressed both by a categorical index and by two ordinal indices. First, children with one or more positive test results were classified as atopic (skin +), and children without any skin reaction to allergen extracts were classified as nonatopic (skin –). Second, each subject was categorized on the basis of the number of positive reactions as nonatopic (no positive reaction), monoallergic (only one positive reaction), or polyallergic (two or more positive reactions). Lastly, in atopic children, the largest allergen wheal was chosen, and the ratio between allergen wheal and histamine wheal was coded on a 4-point scale (<0.5 = 1, 0.5 to 0.99 = 2, 1.0 to 1.99 = 3, 2.0 or more = 4).

The categories of respiratory symptoms and illnesses were derived from answers to the questionnaire: cough and phlegm apart from colds (ATS questions 14B and 15B), chest illness causing 3 days or more of restricted activities during the last year (ATS question 20A modified), history of pneumonia (ATS question 23F), early respiratory infections (ERIs) (defined as three episodes of bronchitis, or one episode of pneumonia or bronchi-

TABLE I. Percent distribution of selected characteristics of the child population by area of residence and by atopic status (Latium, Italy, 1987)

	Nonpolluted area (VT)		Polluted areas (CV and RM)	
	Skin –	Skin +	Skin –	Skin +
No. of subjects	598	151	1159	318
Male subjects	48.5	60.3	47.7	60.4
Age (mean $\pm$ SD)	9.30 $\pm$ 1.21	9.45 $\pm$ 1.13	9.35 $\pm$ 1.22	9.20 $\pm$ 1.396
Father's education				
< 6 yr	46.5	32.5	24.1	22.6
6-8 yr	33.8	34.4	32.5	32.4
9-13 yr	16.2	24.5	27.1	25.8
> 13 yr	1.5	6.0	12.7	16.4
Unknown	2.0	2.6	3.6	2.8
Passive smoking				
No	30.3	26.5	26.6	29.9
Yes	67.6	70.2	68.3	66.0
Unknown	2.2	3.3	5.1	4.1
Siblings: Yes	82.6	82.8	82.1	84.3
Responder to the questionnaire				
Mother	55.2	49.0	55.4	53.5
Father	14.5	21.2	19.2	24.2
Both parents	26.4	27.2	21.1	18.9
Others	1.7	2.0	2.2	2.2
Unknown	2.2	0.6	2.1	1.2

olitis during the first 2 years of life). Asthma was defined either by physician diagnosis (ATS question 29A) or by the presence of at least three of the following: wheeze with colds (ATS question 17A), wheeze apart from colds (ATS question 17B), dyspnea associated with wheeze (ATS question 18A), and wheeze after exercise. Lastly, a history of runny nose apart from colds was defined as rhinitis.

Prevalence odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the degree of association between the categorical index of atopic status and various respiratory conditions; logistic regression was used. Then we analyzed the relationships between area of residence and various respiratory disorders, as well as the separate and combined effects of the two exposures, (i.e., residence area and atopic status). Because the results for the two polluted areas did not differ to a great extent, data from the industrial and urban areas were pooled and compared with data from the nonpolluted area. The reference category was considered VT/skin– and adjusted ORs were computed for VT/skin+, (CV + RM)/skin–, and (CV + RM)/skin+ groups. The children's sex, age, passive parental smoking, father's education, presence of siblings, and respondent to the questionnaire were considered as potential confounders and included in all the logistic models.

Synergism, which is analogous to biologic interaction,

might be viewed as the response produced by simultaneous exposures to two etiologic agents, which exceeds (on an additive scale) the combined effects of the agents when acting independently. Antagonism, on the contrary, occurs when the combined effect from the two agents is lower than that caused by the two exposures separately. The index of synergy proposed by Rothman²² was used to evaluate the extent of synergism between the two factors, atopy and air pollution. This is calculated as the observed excess risk ratio from the combined exposures divided by the sum of the separate excess risks; simple additive effects yield an index of unity, whereas greater values indicate synergism, and lower values indicate antagonism.

Finally, the chi square test was used to evaluate contingency tables, and the Kruskal-Wallis test was used to analyze differences in atopy scores.

RESULTS

Skin test reactivity: Prevalence data by sex, season, residence area, and respiratory symptoms

Questionnaires were returned for 2648 children (94.9%), and skin tests were performed on 2226 (79.8%). There were 1126 male subjects. The consent rate for skin testing was lower in RM schools than in the other two study towns

TABLE II. Association between skin test reactivity and respiratory symptoms and disorders

	Skin –		Skin +		
	N (= 1757)	% (CI)	N (= 469)	% (CI)	OR (CI)
Cough & phlegm	99	5.6% (4.6-6.7)	46	9.8% (7-12.5)	1.9 (1.3-2.7)
Rhinitis	69	3.9% (3-4.8)	48	10.2% (7.5-13)	2.8 (1.9-4.2)
Chest illness	439	25.6% (23.5-27.7)	167	36.4% (32-41)	1.7 (1.3-2.1)
Pneumonia	71	4.1% (3.2-5)	32	6.9% (4.6-9.2)	1.5 (1.00-2.4)
Asthma	84	4.8% (3.8-5.8)	71	15.3% (12-18.6)	3.6 (2.6-5.1)
ERI	308	19.8% (17.8-21.8)	100	23.8% (19.7-28)	1.2 (0.93-1.6)

Odds ratios have been adjusted for sex, age, father's education, passive smoking, and number of siblings.

TABLE III. Association between residence area and respiratory symptoms and disorders

	Nonpolluted area (VT)		Polluted areas (CV and RM)		
	N (= 749)	% (CI)	N (= 1477)	% (CI)	OR (CI)
Cough & phlegm	36	4.8% (3.3-6.3)	109	7.4% (6-8.7)	1.5 (1.00-2.3)
Rhinitis	29	3.9% (2.5-5.3)	88	6% (4.8-7.2)	1.7 (1.05-2.7)
Chest illness	190	26% (22.8-29.2)	416	28.8% (26.5-31.2)	1.1 (0.85-1.3)
Pneumonia	23	3.1% (1.9-4.3)	80	5.5% (4.3-6.7)	1.7 (1.02-2.7)
Asthma	42	5.6% (4-7.3)	113	7.8% (6.4-9.1)	1.3 (0.95-1.9)
ERI	117	17.6% (14.7-20.5)	291	22.2% (20-24.5)	1.4 (1.1-1.8)

Odds ratios have been adjusted for sex, age, father's education, passive smoking, number of siblings, and responder to the questionnaire.

(VT = 83.3%, CV = 86.1%, RM = 70.6%). One or more positive skin reactions were detected in 469 subjects (21.1%), with 167 children (7.5%) showing reactivity to more than one allergen. *D. pteronyssinus* skin reactions were by far the most common (40.8%) followed by grass (15.8%), *Olea* species (8.8%), and *Parietaria* species (7.7%). Table I shows the percent distribution of selected characteristics of the children by area of residence and by atopic status. Boys were more likely to have positive skin test reactions than girls (overall: 25% vs 16.9%, OR = 1.65, CI = 1.34 to 2.03; one reaction: 16.9% vs 11.5%, OR = 1.62, CI = 1.26 to 2.09; two or more reactions: 8.3% vs 5.4%, OR = 1.71, CI = 1.2 to 2.4). No differences between atopic and nonatopic subjects were found in both areas with regard to age, passive smoking, presence of siblings, and responder to the questionnaire. Atopic subjects tended to belong to more educated families, as indicated by father's education.

The prevalence of subjects with positive skin test results was higher in winter (21.8%) and in spring (24.5%) than in autumn (17.1%, $\chi^2 = 9.96$, $p = 0.006$). There was a higher prevalence of two or more skin reactions in subjects tested in the

spring (9.7%) than in the other seasons (winter = 6.3%, autumn = 5.3%). Wheal size was also larger in the spring (Kruskal-Wallis test, $H = 8.7$, $p = 0.012$).

The prevalence of skin reactivity did not vary over the studied areas in regard to the number of children with positive test results (RM = 21.0%, CV = 22.0%, VT = 20.2%) ($\chi^2 = 0.82$, $p = \text{NS}$), the number of subjects with more than one positive reaction (RM = 6.9%, CV = 7.8%, VT = 5.7%) ($\chi^2 = 2.54$, $p = \text{NS}$), or the size of wheals among skin test reactors ($H = 0.77$, $p = \text{NS}$). The OR of the relationship between urban-industrial living and atopy (adjusted for sex, age, father's education, passive smoking, and siblings) was exactly 1.0 (95% CI = 0.79 to 1.27).

As expected, children with positive skin test results were more likely to have rhinitis (OR = 2.8, CI = 1.9 to 4.2) and asthma (OR = 3.6, CI = 2.6 to 5.1). Cough and phlegm apart from colds (OR = 1.9, CI = 1.3 to 2.7), chest illness (OR = 1.7, CI = 1.3 to 2.1), and pneumonia (OR = 1.5, CI = 1.0 to 2.4) were also more common in subjects with positive skin test results than in those with negative results (Table II).

TABLE IV. Separate and combined effects of atopy and residence area

	Nonpolluted area (VT)						Polluted areas (CV and RM)						Synergy index
	Skin –			Skin +			Skin –			Skin +			
	N (= 598)	%	OR (CI)	N (= 151)	%	OR (CI)	N (= 1159)	%	OR (CI)	N (= 318)	%	OR (CI)	
Cough & phlegm	26	4.3	1.0	10	6.6	1.6 (0.7-3.3)	73	6.3	1.4 (0.9-2.3)	36	11.3	2.6 (1.5-4.5)	1.59
Rhinitis	20	3.3	1.0	9	6	1.8 (0.7-4.2)	49	4.2	1.3 (0.7-2.3)	39	12.3	4.4 (2.4-7.9)	3.01
Chest illness	138	23.7	1.0	52	35.1	1.7 (1.2-2.5)	301	26.6	1.1 (0.8-1.4)	115	37	1.7 (1.3-2.4)	0.94
Pneumonia	17	2.9	1.0	6	4	1.4 (0.4-2.8)	54	4.8	1.5 (0.8-2.6)	26	8.3	2.5 (1.3-4.7)	2.75
Asthma	21	3.5	1.0	21	14	4.2 (2.2-7.9)	63	5.5	1.5 (0.95-2.5)	50	16	4.9 (2.8-8.4)	1.04
ERI	89	16.9	1.0	28	20.3	1.2 (0.7-1.9)	219	21.3	1.4 (1.0-1.85)	72	25.5	1.7 (1.2-2.4)	1.27

Odds ratios have been adjusted for sex, age, father's education, passive smoking, number of siblings, and responder to the questionnaire.

Adjusted odds ratios and 95% confidence intervals were calculated with nonatopic children living in the nonpolluted areas as the reference group.

Association between residence area and respiratory symptoms

With one exception, chest illness, the frequency of all outcome variables among schoolchildren from the polluted areas was higher than those from the nonpolluted area (Table III). These results, with the exception of rhinitis, are not completely independent of similar relationships previously reported,⁷ because data are from a subset of the published study.

Separate and combined effects of atopy and EAP

Children with positive skin test results who were living in the nonpolluted VT area were significantly more likely to have chest illnesses (OR = 1.7) and asthma (OR = 4.2) than children with negative results who were living in the same area (Table IV). Children with negative skin test results who were living in polluted (CV and RM) areas had more respiratory symptoms than children with negative results who were living in VT; they had significantly more ERIs (OR = 1.4), whereas the risks of having cough and phlegm, rhinitis, pneumonia, and asthma were all increased but did not reach statistical significance. When the effect of living in polluted areas was examined in children with positive skin test results (CV and RM/skin+), again with the VT/skin– group as reference, the ORs for cough and

phlegm (2.6), rhinitis (4.4), chest illness (1.7), pneumonia (2.5), asthma (4.9), and ERIs (1.7) were all significantly increased. For asthma and ERIs, the results were compatible with an additive effect of the two factors (synergy index = 1.04 and 1.27, respectively), whereas a synergy index greater than 1 was found in regard to each of the following: cough and phlegm, rhinitis, and pneumonia (Table IV), indicating that the combined effects of urban living and atopy were greater than the effect of either in isolation. However, in no case was the interaction term for a departure from the multiplicative model statistically significant.

DISCUSSION

We tested the hypothesis of an effect of EAP on the prevalence of skin test positivity and evaluated possible synergism of the two factors in determining respiratory disorders. We found that: (1) both atopy and living in polluted areas were closely related to respiratory symptoms and diseases; (2) the prevalence of skin reactivity seemed not to vary over the areas; (3) the effects of EAP and atopy were more or less additive with regard to asthma and ERIs, whereas synergism of the two exposures was observed for cough and phlegm, rhinitis, and pneumonia.

Several limitations of this study have already been indicated.⁷ They include the cross-sectional

design that precludes an appropriate evaluation of the temporal relationships among air pollution, inception of atopy, and development of respiratory symptoms. In addition, we studied only three areas; the actual exposure to air pollutants was not measured; and several confounders were considered, but some unmeasured factors, with an urban-rural gradient, could have been missed.

The close relationship between skin test positivity and asthma or rhinitis is well known.²³ Moreover, children with positive skin test results in our study were more likely to have had cough and phlegm, pneumonia, and chest illness (Table II). Atopic subjects may have abnormal cellular immunity,²⁴ and defense mechanisms of the bronchial tree, such as mucociliary clearance,²⁵ may be impaired. Thus an increased susceptibility to infections could be present. On the other hand, viral infections per se can enhance allergic sensitization,²⁶ and an alteration in the interactions between helper and suppressor lymphocytes has been hypothesized.²⁷

Children living in polluted areas were more ill than children living in unpolluted areas, which is similar to results we have previously reported.⁷ Rhinitis, which was not previously analyzed, was found in the present study to be increased in CV and RM. This confirmed results of recent studies^{28, 29} that showed an increase in prevalence of rhinitis in subjects living in urban-industrial areas.

There are scanty data on the effect of environmental air pollution on the prevalence of atopy in children. Berciano et al.³⁰ found higher mean values of serum IgE in children living in polluted areas but only in those without a family history of atopy. Other studies have shown that children living in polluted areas are more likely to be reactors² or to have a different pattern of allergic sensitization.³¹ We did not find any difference in the prevalence of skin positivity between children living in VT and children living in CV and RM. A bias could have been introduced by the lower compliance rate observed in RM than in VT and CV. However, this is unlikely to have significantly distorted the results because no difference was observed between VT and CV when RM was excluded from the analysis.

Experimental animal studies have demonstrated that both SO₂¹² and particulates¹⁴ have an adjuvant activity for IgE production. There is evidence that heredity,³² perinatal environmental factors,³³ and infections in the first years of life³⁴ play a key role in influencing the development of atopy. Thus an increase of IgE caused by pollut-

ant exposure is conceivable, but it could be difficult to detect, given the strong influence of other factors³⁵ in atopy development. Furthermore, the age range of our sample can be a potential confounder; it is possible that effects of air pollution on the development of sensitization would be seen if younger children were investigated.

We did not have sufficient power to distinguish clearly between multiplicative and additive models in our study, as is often the case even with large epidemiologic investigations.³⁶ The pattern of ORs, however, suggested that atopy potentiates the effect of EAP for at least some respiratory outcomes.

Recently, an increased response to allergen has been found in patients with atopic asthma exposed to allergen after inhalation of ozone.³⁷ It is similarly well known that SO₂ and ozone can enhance bronchial reactivity in patients with asthma,^{15, 18} probably by inducing epithelial inflammation of the airways.¹⁶ The synergic mechanisms by which EAP and atopy act in increasing the prevalence of rhinitis, cough and phlegm, and pneumonia is less easy to explain. An increase in respiratory symptoms in atopic children living in a polluted area¹¹ has been previously observed. In the attempt to explain our results it should also be considered that pollutants can increase the growth of infectious organisms,³⁸ impair the pulmonary clearance of infectious agents,³⁹ and affect mucociliary clearance.⁴⁰

Recently, a thorough study of the effect of ozone on allergic sensitization and the cellular immune system has been reported by Zwicky et al.⁴¹ Although no difference was found in levels of serum IgE, abnormalities of cellular immunity were detected in children exposed to ozone as compared with children living in the control area. In exposed children the absolute and relative numbers of T helper cells decreased and those of T suppressor cells increased, resulting in a low helper to suppressor ratio. Thus it is likely that atopic subjects, who may have abnormal cellular immunity as an expression of the atopic status itself,²⁴ or perhaps as a result of environmental exposure,⁴¹ become more susceptible to infections when exposed to pollutants than do nonatopic subjects. Another possible explanation is that airway responsiveness, which is closely related to allergic sensitization, modifies the relationship between air pollution and respiratory symptoms; it is likely that atopic subjects with increased bronchial responsiveness are prone to experience respiratory symptoms when exposed to pollutants.

Longitudinal observations may better clarify the issue.

In conclusion, we were unable to provide evidence that air pollution exposure increases the prevalence of atopic status. However, EAP has a greater effect on the respiratory health of atopic subjects than on that of nonatopic individuals. The former sensitive group should be taken into account when safe limits of air pollutants are defined. Further studies with biologic markers such as leukocyte counts, serum IgE, and lymphocyte subpopulations are needed to better clarify the mechanisms underlying the interaction between atopy and EAP.

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