

Association of ozone exposure with asthma, allergic rhinitis, and allergic sensitization

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Background: Children are vulnerable to air pollution, which is known to be related to the recent increasing trend of allergic disease.

Objective: To investigate the effects of air pollution on respiratory allergic diseases in school children.

Methods: A prospective survey of parental responses to International Study of Asthma and Allergies in Childhood questionnaires, together with allergy evaluation, was conducted in 1743 school children selected from metropolitan cities and industrial areas during a 2-year period. Individual exposure to air pollution was estimated by using a geometric information system with the 5-year mean concentration of air pollutants.

Results: A total of 1,340 children (male:female ratio, 51.4:48.6) with a mean (SD) age of 6.84 (0.51) years were included in the analysis. Each child underwent allergy evaluation at the time of enrollment and at a 2-year follow-up. After 2 years, the 12-month prevalence of wheezing was significantly decreased, whereas the lifetime prevalence of allergic rhinitis showed a significant increase. Ozone exposure was significantly associated with the 12-month prevalence of wheeze (odds ratio per 5 ppb, 1.372; 95% confidence interval, 1.016-1.852). Ozone was also associated with allergic rhinitis in children who reside in industrial areas. In addition, significant positive associations between ozone and the rate of newly developed sensitization to outdoor allergen were found (P for trend = .007).

Conclusion: Exposure to ozone was associated with current wheeze and allergic rhinitis. An increased rate of newly developed sensitization to outdoor allergen by ozone may explain the association.

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INTRODUCTION

The prevalence of allergic disease has increased worldwide,^{1,2} a phenomenon that may be attributed to environmental effects.^{3,4} Among the environmental factors, air pollution is considered to be a major threat to childhood respiratory health.⁵ Children may be more vulnerable to air pollution because of their underdeveloped respiratory and immune systems,⁶ together with the fact that they inhale more air than adults per square meter.⁷

It is well known that ozone exacerbates allergic asthma⁸ and that exposure combined with exercise leads to decreases in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC), concurrent with increased airways resistance.⁹ Many studies have shown a potential association between exposure to traffic exhaust and allergic disease in children¹⁰⁻¹⁴; for example, exposure to a high level of air pollutants from traffic increases the prevalence of asthma symptoms and physician-diagnosed asthma.¹⁰ Exposure to diesel exhaust particle has been shown to lead to an increase in the total IgE level.¹¹ Living alongside busy roads is associated with an increased risk of allergic sensitization,^{12,13} and exposure of infants and school children to air pollution from traffic decreased their lung function.^{13,14} However, conflicting results also have been reported according to the patient's age, country, and study design.^{15,16} In particular, there is consid-

erable controversy regarding the link between air pollution and the development of allergic sensitization, whereas there is consistent evidence regarding the effect of air pollution on the development of respiratory symptoms.¹⁷ Moreover, few studies have been conducted in Asia.¹⁸ Therefore, the association between air pollution and allergic disease needs further evaluation. The objective of the present study was to evaluate the effect of air pollution, especially ozone, on the development of respiratory allergic diseases and allergic sensitization in Korean school children.

METHODS

Study Participants

From 2005 to 2006, we enrolled a total of 1,743 children from 16 elementary schools located in 2 different areas: 3 metropolitan cities and 4 industrial cities in Korea. Each industrial city had at least 1 national industrial complex, and nearby schools were invited to participate in the study. Parents of the participants were asked to respond to an International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to evaluate the presence of allergic diseases and risk factors. Respiratory and allergy evaluation, such as pulmonary function test, methacholine challenge test, and skin prick test, was performed as well. All participants were followed up 2 years later and underwent the same survey again in the same season.

Of 1,743 children, 403 children were lost to follow-up, with the most common reason being change to another school. Therefore, 1,340 children were included in this study (Figure 1). All children responded to the ISAAC questionnaire and underwent pulmonary and allergy evaluation twice at 2-year intervals. The cohort was composed of 689 boys and 651 girls, with a mean (SD) age of 6.84 (0.51) years at the time of enrollment.

The study protocol was approved by the institutional review boards of the University of Ulsan College of Medicine. Written consent was obtained from the parents of all participants after they were fully informed of the details of the study.

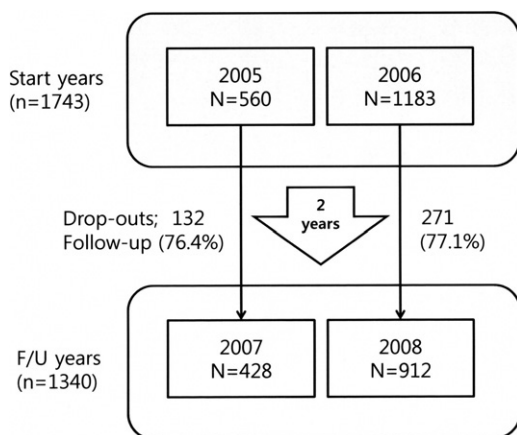


Figure 1. Follow-up of subjects.

Air Pollution Data and Exposure Assessment

Measurements of air pollutants were compiled from air monitoring data routinely collected at monitoring stations operated by the Department of Environment, Republic of Korea. From 11 to 27 monitoring stations were located in each of the 7 cities where the children were enrolled. Sulfur dioxide was measured by pulse UV fluorescence, nitrogen dioxide by the chemiluminescent method, carbon monoxide by the nondispersive infrared method, and particles measuring 10 μm or less (PM_{10}) by the β -ray absorption method. The hourly data available for gaseous pollutants and PM_{10} in each monitoring station were used to determine daily, monthly, and yearly averages.¹⁹ We calculated 5-year mean (2001-2005) concentrations of air pollutants at the individual level by the ordinary kriging method.²⁰ Kriging is a weighted combination of monitored values and uses spatial autocorrelation among data to determine the weights rather than assuming a function of inverse distance. Ordinary kriging was implemented with the Geostatistical Analyst extension of ArcGIS (ArcMap, version 9.3; ESRI Inc, Redlands, Washington). We also evaluated the quality of the predicted values from kriging using cross-validation. We assigned air pollutant concentrations for 5 years (2001-2005) for each individual based on location of the residence at the time of the baseline survey; the study population was assumed to be stable (did not move) during the exposure period.

Of 1,340 children, 45 were excluded from air pollution assessment because their residential addresses were incomplete. Therefore, 1,295 children were included in analyses regarding air pollution.

Questionnaires

ISAAC provides a useful standardized questionnaire for determining the prevalence of allergic diseases, and the modified Korean version of ISAAC was previously validated as a tool for assessing allergic symptoms and diagnoses in Korean children.^{21,22} The written questionnaire was composed of 3 parts. The first part consisted of general items, such as name, date of birth, sex, height, and weight. The second part focused on history of allergic disease, and the third part was about environmental factors pertinent to allergic diseases.

Serum Total IgE Levels and Skin Prick Tests

The concentration of total serum IgE was measured by fluorescent enzyme immunoassay using the AutoCAP System (Phadia AB, Uppsala, Sweden). Skin prick tests were performed for 16 common Korean inhalants and food allergens, together with negative and positive controls (Allergopharma, Reinbek, Germany). These allergens included the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, cat, dog, cockroach, the molds *Alternaria alternata* and *Aspergillus fumigatus*, grass, tree mix (I), tree mix (II), mugwort, ragweed, egg, milk, peanut, and soybean. Of these allergens, grass, tree mix (I), tree mix (II), mugwort, and ragweed were regarded as outdoor allergens. A mean wheal diameter of at least 3 mm greater than the negative control was considered to be a

Table 1. Characteristics of the Study Participants

Characteristic	Study participants (n = 1340)
Male:female ratio	51.4:48.6
Age, mean (SD), y	6.84 (0.51)
Grade, No. (%)	
1	1,222/1,340 (91.2)
2	118/1,340 (8.8)
BMI, mean (SD)	16.69 (2.34)
Paternal history of allergic disease, No. (%)	71/1,160 (6.1)
Maternal history of allergic disease, No. (%)	67/1,157 (5.8)
Paternal educational level, No. (%)	
≤12 years	598/1,238 (48.3)
>12 years	640/1,238 (51.7)
Maternal educational level, No. (%)	
≤12 years	742/1,223 (60.7)
>12 years	481/1,223 (39.3)
Family income, No. (%)	
<\$3,000 (US)	809/1,224 (66.1)
≥\$3,000 (US)	415/1,224 (33.9)
Address, No. (%)	
Metropolitan cities	620/1,340 (46.3)
Industrial areas	720/1,340 (53.7)
Prematurity, No. (%n)	64/1,219 (5.3)
Breastfeeding >3 mo, No. (%)	467/1,206 (38.7)
Smoking during pregnancy, No. (%)	3/1,231 (0.2)
ETS home, No. (%)	356/1,228 (29.0)
Dog ownership, No. (%)	219/1,250 (17.5)
Cat ownership, No. (%)	56/1,236 (4.5)
Bronchiolitis within first 2 years of life, No. (%)	129/1,236 (10.4)

Abbreviations: BMI, body mass index; ETS, environmental tobacco smoke.

positive result. Atopy was defined as the presence of 1 or more positive reactions via the skin prick test.

Pulmonary Function Test

Data on children's lung function were collected by trained field technicians who visited the schools. Baseline spirometry was performed on each study participant according to American Thoracic Society guidelines²³ using a portable microspirometer (Microspiro HI-298; Chest Corporation, Tokyo, Japan). We measured FVC, FEV₁, and the mean forced expiratory flow during the middle half of FVC (FEF_{25%-75%}).

Methacholine Challenge Test

Methacholine challenge tests were performed using a modification of the method described originally by Chai et al.²⁴ Spirometric measurements (FEV₁ and FVC) were made using a computerized spirometer (Microspiro-HI 298) in accordance with the recommendations of the American Thoracic Society. The time course of the preceding inspiration was standardized, and the FVC maneuver was continued until a pause in the FEV₁ curve was obvious by visual inspection. Methacholine (Sigma Diagnostics, St. Louis, Missouri) solutions were prepared at different concentrations (0.625, 1.25, 2.5, 5, 12.5, and 25 mg/mL) in buffered saline solution (pH 7.4). A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Maryland) was used to generate an aerosol from a nebulizer (DeVilbiss 646; DeVilbiss Health Care, Somerset, Pennsylvania). Each participant inhaled 5 inspiratory capacity breaths of buffered saline solution and increasing concentrations of methacholine at 5-minute intervals. The procedure was terminated when the FEV₁ decreased by more than 20% of its saline solution. The response to the methacholine challenge was expressed as the concentration that caused a decrease in FEV₁ of 20% from baseline (PC₂₀).

Statistical Analysis

The associations between air pollution and the prevalence of respiratory allergic diseases were analyzed using multiple logistic regression, and the results are presented as odds ratios (ORs) and 95% confidential intervals (CIs). The association between air pollution and the level of total IgE and number of sensitizations was analyzed with linear regression. Air pollution exposure was classified into quartiles according to histogram and used as categorical variables. All statistical analyses were performed with SPSS statistical software version 15.0 for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

Study Population and Prevalence of Allergic Diseases

Of the 1,340 children in the study, 620 (46.3%) resided in metropolitan cities and 720 (53.7%) resided in industrial areas. The characteristics of the study population are summarized in Table 1. The levels of allergic markers, such as atopy, airway hyperresponsiveness, and total IgE, were measured at the time of enrollment and 2 years later. The log PC₂₀ and the atopy rate increased significantly during the 2-year period

Table 2. Five-Year Mean Concentrations of Air Pollutants at the Individual Level in 1,295 Patients

Pollutant	Minimum	10th	25th	50th	Mean	75th	90th	Maximum
Nitrogen dioxide, ppb	13.49	13.48	18.50	28.21	25.87	33.10	36.65	37.02
Ozone, ppb	14.35	14.40	16.17	20.75	21.39	26.82	28.22	28.79
Sulfur dioxide, ppb	4.09	4.19	5.03	5.87	6.99	8.90	11.12	13.69
Carbon monoxide, ppm	4.89	4.89	5.61	6.37	6.37	7.11	7.75	7.76
PM ₁₀ , µg/m ³	38.98	44.82	49.89	67.08	59.86	68.61	69.33	71.94

Abbreviation: PM₁₀, particles measuring 10 µm or less.

Table 3. Five-Year Mean (SD) Concentrations of Air Pollutants at the Individual Level by Residential Area in 1,295 Children

Pollutant	Metropolitan cities	Industrial areas	P value
Nitrogen dioxide, ppb	29.64 (6.06)	22.50 (6.84)	<.001
Ozone, ppb	17.70 (2.67)	24.68 (3.66)	<.001
Sulfur dioxide, ppb	5.23 (0.93)	8.56 (2.23)	<.001
Carbon monoxide, ppm	7.07 (0.40)	5.74 (0.88)	<.001
PM ₁₀ , $\mu\text{g}/\text{m}^3$	63.05 (8.26)	57.01 (11.56)	<.001

Abbreviation: PM₁₀, particles measuring 10 μm or less.

(e-Table 1). The lifetime and 12-month prevalences of wheezing were 26.1% and 12.9%, respectively, and the lifetime prevalence of asthma diagnosis was 10.1%. The lifetime and 12-month prevalences of allergic rhinitis symptoms were 47.0% and 42.6%, respectively, and the lifetime prevalence of allergic rhinitis was 26.4%. After the 2-year period, the 12-month prevalence of wheezing was significantly decreased, whereas the lifetime prevalence of allergic rhinitis showed a significant increase (e-Table 2). This trend suggests an allergic march in children.

Air Pollutants and Asthma

The 5-year means of air pollutants before the enrollment were 25.87 ppb of nitrogen dioxide, 21.39 ppb of ozone, 6.99 ppb of sulfur dioxide, 0.63 ppm of carbon monoxide, and 59.86 $\mu\text{g}/\text{m}^3$ of PM₁₀ (Table 2). Outdoor air pollution differed between industrial and metropolitan areas, with the levels of ozone and sulfur dioxide higher in industrial areas but the levels of the other pollutants (nitrogen dioxide, carbon monoxide, and PM₁₀) higher in metropolitan cities. These differences are likely to reflect differences in the type of pollutants emitted from traffic and factories (Table 3).

Using a geometric information system, each participant's individual exposure level was estimated according to their residential address and the local 5-year means of air pollutants. Each individual in the study population was categorized into 1 of 4 groups based on the extent of their exposure to pollutants. Categorical analyses in quartiles revealed an association of ozone and the prevalence of 12-month wheezing (OR per 5 ppb, 1.372; 95% CI, 1.016-1.852) (Table 4).

Table 4. Asthma-Related Prevalence at the Time of Enrollment^a

	No. (%) of participants by ozone concentration, ppb				OR (95% CI) for ozone per 5 ppb ^b
	≤15	15-20	20-25	>25	
Wheeze, ever	33/156 (21.2)	70/264 (26.5)	146/531 (27.5)	86/333 (25.8)	1.224 (0.977-1.534)
Wheeze, past 1 year	17/156 (10.9)	29/264 (11.0)	74/531 (13.9)	46/333 (13.8)	1.372 (1.016-1.852)
Asthma diagnosis, ever	12/155 (7.7)	29/264 (11.0)	57/528 (10.8)	31/333 (9.3)	1.246 (0.890-1.745)
Asthma treatment, past 1 year	5/156 (3.2)	9/264 (3.4)	30/531 (5.6)	16/333 (4.8)	1.536 (0.912-2.588)

Abbreviations: CI, confidence interval; OR, odds ratio.

^a When children were exposed to the higher level of ozone, they showed an increased prevalence of current wheezing (wheeze, past 1 year).

^b Adjusted for sex, age, body mass index, paternal and maternal allergy history, paternal education, family income, place of residence, breastfeeding, environmental tobacco smoke home, keeping of dog and cat, preterm birth, bronchiolitis within first 2 years of life, eosinophil count, log total IgE, log concentration that caused a decrease in forced expiratory volume in 1 second of 20% from baseline, and sensitization.

Air Pollutants and Allergic Rhinitis

The incidence of allergic rhinitis was not significantly associated with air pollutants. However, when residential area was considered, a significant positive association between ozone and the presence of allergic rhinitis appeared in the study participants from the industrial area (Table 5), where the concentration of ozone was higher.

Air Pollutants and Allergic Markers for Atopy

To investigate the association between air pollutants and atopic biomarkers, the relationship between ozone and IgE or sensitization to outdoor allergens was analyzed. A significant association was found between ozone and total IgE level. Children exposed to higher levels of ozone had increased levels of total IgE (P for trend = .03) (Figure 2). However, the significance disappeared after adjusting for residential area.

The rate of newly developed sensitization to outdoor allergens during the 2-year study period showed a significant association with the level of ozone after adjusting for confounding factors (Figure 3), whereas new sensitization to indoor allergen was not significantly associated with any of the air pollutants (data not shown).

DISCUSSION

The present study conducted nationwide in Korea revealed that higher exposure to ozone was associated with 12-month prevalence of wheeze (OR per 5 ppb, 1.372; 95% CI, 1.016-1.852) and with the prevalence of allergic rhinitis. In addition, an increased rate of newly developed sensitization to outdoor allergens during the 2-year period was also found in children exposed to the higher levels of ozone. These findings suggest that ozone may be associated with respiratory allergic symptoms by promoting the new development of pollen sensitization.

According to a recent meta-analysis, traffic exhaust contributes to the development of respiratory symptoms in healthy children, but potential effects of traffic exhaust on the development of allergic sensitization in children remain controversial.¹⁷ The present study showed a significant association between newly developed allergen sensitization and exposure to ozone. The association with ozone was only for outdoor allergens, including grass, tree, and weeds pollen, a

Table 5. Adjusted Odds Ratios (95% Confidence Intervals) for Ozone and Allergic Rhinitis by Residential Area

Ozone per 5 ppb ^a	Metropolitan cities	Industrial areas
Symptom ever	1.007 (0.764-1.328)	1.360 (1.011-1.829)
12-Month symptom	1.042 (0.792-1.372)	1.469 (1.079-1.999)
Diagnosis ever	0.943 (0.693-1.281)	1.720 (1.220-2.425)
12-Month treatment	0.867 (0.627-1.200)	1.778 (1.222-2.586)

^aAdjusted for sex, age, body mass index, paternal and maternal allergy history, paternal education, family income, place of residence, breastfeeding, environmental tobacco smoke home, keeping of dog and cat, preterm birth, bronchiolitis within first 2 years of life, eosinophil count, log total IgE, log concentration that caused a decrease in forced expiratory volume in 1 second of 20% from baseline, and sensitization.

finding that is consistent with previous studies.^{12,13} The reason that the association with ozone is restricted to outdoor allergens may reflect the postulated mechanism in which this pollutant acts as an adjuvant to promote allergic sensitization, an effect that is more likely to occur outdoors, where the ozone concentration is higher. Particulate matter and nitrogen dioxide were associated with the development of allergic sensitization in previous studies; however, ozone was significant in the present study. Total IgE concentration showed a similar association with exposure to ozone, although this was not significant after adjusting for residential area. This finding suggests that air pollution may promote IgE production as reported in previous studies.¹¹ We measured additional biological markers, such as PC₂₀, total eosinophil count, and FEV₁, but no significant associations were found.

We used the 5-year mean concentration of traffic air pollutants to estimate the exposure level because this reflects the long-term exposure of an individual. However, the 5-year mean

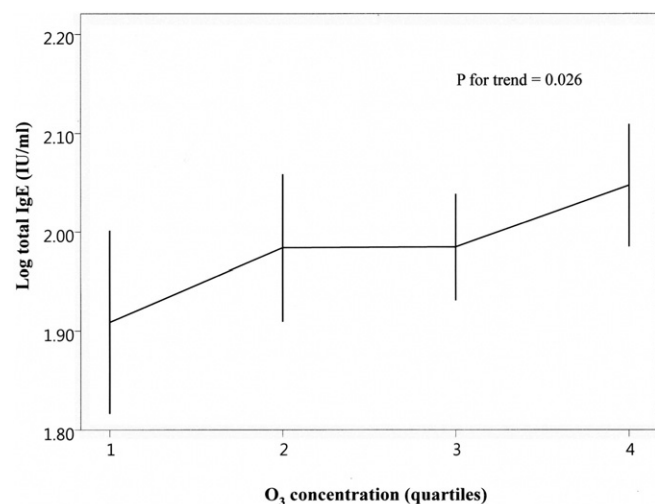


Figure 2. Association (odds ratios) between Residential Level of Ozone and Total IgE. (P for trend adjusted for sex, age, parental history of allergy, maternal education. For ozone, <15 ppb, 15–20 ppb, 20–25 ppb, >25 ppb).

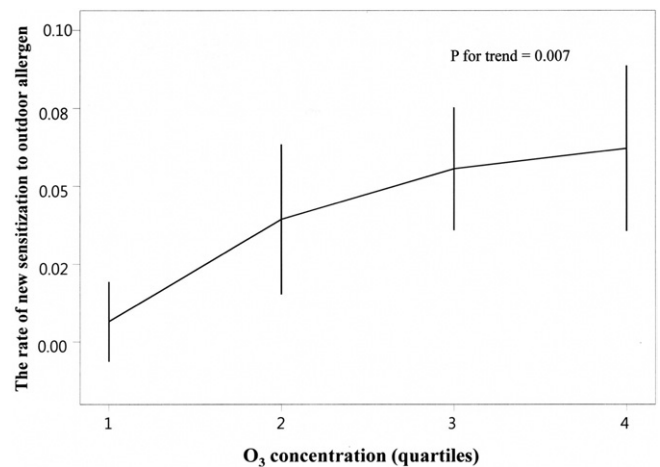


Figure 3. Association between Residential Level of Ozone and the rate of Newly Developed Sensitization to Outdoor Allergens during the 2-Year Study Period. (Outdoor allergens were as follows; grass, tree mix (I), tree mix (II), mugwort, ragweed. P for trend adjusted for sex, age, parental history of allergy, maternal education. For ozone, <15 ppb, 15–20 ppb, 20–25 ppb, >25 ppb).

does not reflect periodic (seasonal or daily) fluctuation, which may also be important in the development of asthma and allergic rhinitis. Therefore, future study may achieve greater sensitivity by using more precise measures of air pollution.

The central mechanism underlying the harmful effect of air pollution is oxidative stress. The reactive oxidative species produced in response to air pollution can overwhelm the redox system, working in a balance of biological prooxidant and antioxidant processes, and damage the cell wall lipid, protein, and DNA, thereby leading to airway inflammation and airway hyperreactivity.²⁵ Therefore, dietary and genetic factors that influence the redox system may modulate the effects of air pollution on allergic diseases. A diet rich in antioxidant was found to be associated with a low prevalence of allergic disease.²⁶ According to glutathione-S-transferase M1 and glutathione-S-transferase P1 polymorphism coding the glutathione S transferase enzyme genotype, the response to air pollution was different.²⁷ The positive effect of antioxidant supplementation was predominantly found only in children genetically susceptible to the effects of oxidants.²⁸ This is an example of gene and environmental interaction. Inconsistent results from many studies regarding the association of air pollution with allergic diseases can be caused by the gene-environmental interaction. Therefore, more comprehensive studies that investigate genetic polymorphisms in the redox system and dietary factors are necessary to learn the exact effect of air pollutant on allergic disease.

The present study has several limitations. It was conducted prospectively, but the study participants were not enrolled in early life. It might result in reverse causality induced by avoidance behavior due to the child's disease. It was also hard to determine the effect of air pollution on the child during early life, which is considered a critical period for the development of allergic diseases. Two years may not be long enough to evaluate

changes induced by air pollutants, and the follow-up rate was relatively low at 77%. Genetic polymorphism and dietary factors were not considered in the analysis. However, this nationwide study enrolled more than 1,000 children; therefore, the data can be considered representative of an Asian country. We obtained a greater than 95% response rate to the ISAAC questionnaire, which, together with additional biologic markers measured on almost every study participant, allowed a highly reliable assessment of allergic phenotype. Besides the traditional confounding factors, in terms of allergy, several additional important factors, such as sensitization and airway hyperresponsiveness, were included in the analysis under the assumption that they would provide a more precise assessment of the effect of air pollution on asthma and allergic rhinitis. Therefore, despite several limitations in the present study, the results provide firm evidence supporting an association between air pollution and allergic disease. To the best of our knowledge, this is the first report showing an association between ozone and allergic disease and sensitization in Asian children.

In summary, this study revealed that ozone exposure was significantly associated with the 12-month prevalence of wheeze and with all prevalences of allergic rhinitis. In addition, a significant association was found between ozone and newly developed sensitization to outdoor allergen during the 2-year study period. These findings suggest that ozone is a significant risk factor for respiratory allergic diseases and that mechanism may be related to sensitization to outdoor allergens.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.anai.2011.05.025.

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e-Table 1. Results of Allergic and Respiratory Screening During the 2-Year Study Period

Variable	Start years (2005-2006)	Follow-up years (2007-2008)	P value ^a
Male:female ratio	51.4:48.6		
Age, mean (SD), y	6.84 (0.51)	8.83 (0.50)	<.001
BMI	16.68 (2.34)	17.98 (3.02)	<.001
Eosinophil count, mean (SD), %	3.71 (2.56)	3.86 (2.82)	.04
Eosinophil counts ($\geq 4\%$), No. (%)	460/1,335 (34.5)	478/1,309 (36.5)	
Log total IgE, mean (SD), IU/mL	1.99 (0.61)	2.00 (0.62)	.95
Total IgE ≥ 100 IU/mL, No. (%)	639/1,331 (48.0)	644/1,297 (49.7)	
Total IgE ≥ 300 IU/mL, No. (%)	288/1,331 (21.6)	296/1,297 (22.8)	
Log PC ₂₀ , mean (SD), mg/mL	1.34 (0.48)	1.53 (0.35)	<.001
PC ₂₀ ≤ 8 , No. (%)	265/1,297 (20.4)	129/1,335 (9.7)	
PC ₂₀ ≤ 16 , No. (%)	441/1,297 (34.0)	233/1,335 (17.5)	
FVC, mean (SD)	1.52 (0.24)	1.90 (0.29)	<.001
FVC predicted, mean (SD), %	100.12 (12.99)	95.16 (12.32)	<.001
FEV ₁ , mean (SD)	1.38 (0.21)	1.72 (0.25)	<.001
FEV ₁ predicted, mean (SD), %	106.09 (13.64)	101.59 (12.90)	<.001
FEF _{25%-75%} , mean (SD)	1.74 (0.39)	1.79 (0.55)	.002
FEF _{25%-75%} predicted, mean (SD), %	98.39 (22.44)		
Atopy, No. (%)	395/1,337 (29.5)	535/1,337 (40.0)	<.001
Sensitizations, No. (%)			
1	133/1,337 (9.9)	144/1,337 (10.8)	
2	195/1,337 (14.6)	256/1,337 (19.1)	
3	46/1,337 (3.4)	92/1,337 (6.9)	
≥ 4	21/1,337 (1.6)	43/1,337 (3.2)	

Abbreviations: BMI, body mass index; FEF_{25%-75%}, mean forced expiratory flow during the middle half of FVC; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PC₂₀, concentration that caused a decrease in FEV₁ of 20% from baseline.

^a Paired *t* test for continuous variable.

e-Table 2. Prevalence of Allergic Diseases During the 2-Year Study Period in 1,340 Study Participants

Variable	Start years (2005-2006)	Follow-up years (2007-2008)	P value ^a
Wheeze, ever, No. (%)	336/1,285 (26.1)	305/1,324 (23.0)	.06
Wheeze, past 1 year, No. (%)	166/1,285 (12.9)	123/1,324 (9.3)	.003
Asthma diagnosis, ever, No. (%)	129/1,281 (10.1)	130/1,319 (9.9)	.86
Asthma treatment, past 1 year, No. (%)	60/1,285 (4.7)	50/1,324 (3.8)	.26
AR symptom, ever, No. (%)	596/1,268 (47.0)	670/1,316 (50.9)	.05
AR symptom, past 1 year, No. (%)	540/1,268 (42.6)	603/1,316 (45.8)	.10
AR diagnosis, ever, No. (%)	335/1,268 (26.4)	398/1,316 (30.2)	.03
AR treatment, past 1 year, No. (%)	271/1,268 (21.4)	304/1,314 (23.1)	.28

Abbreviation: AR, allergic rhinitis.

^a There was no significant difference in prevalence between inner-city and industrial areas.