

Air pollution interacts with past episodes of bronchiolitis in the development of asthma

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To cite this article: Kim BJ, Seo JH, Jung YH, Kim HY, Kwon JW, Kim HB, Lee SY, Park KS, Yu J, Kim HC, Leem JH, Lee JY, Sakong J, Kim SY, Lee CG, Kang DM, Ha M, Hong YC, Kwon HJ, Hong SJ. Air pollution interacts with past episodes of bronchiolitis in the development of asthma. *Allergy* 2013; DOI: 10.1111/all.12104.

Keywords

air pollution; airway hyper-responsiveness; asthma; bronchiolitis; pulmonary function.

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Accepted for publication 30 November 2012

DOI:10.1111/all.12104

Edited by: Thomas Bieber

Abstract

Background: Exposure to ambient air pollution and bronchiolitis are risk factors for asthma. The aim of this study was to investigate the effect of air pollution on the development of asthma in children with past episodes of bronchiolitis.

Methods: A prospective 2-year follow-up survey consisting of parental responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, and allergy evaluations were conducted in 1743 children with a mean age of 6.8 years. Recent 5-year exposure to air pollution was estimated using a geographic information system.

Results: Higher exposure to ozone was associated with airway hyper-responsiveness ($PC_{20} \leq 16$ mg/ml) at enrollment (odds ratio [OR] = 1.60, 95% CI [confidence interval] = 1.13–2.27) and with new episodes of wheezing during the 2-year period (OR = 1.92, 95% CI = 0.96–3.83). Past episodes of bronchiolitis were associated with both current wheezing and physician-diagnosed asthma. When the two factors were combined, the prevalence of bronchial hyper-reactivity (OR = 2.96, 95% CI = 1.41–6.24) and new wheezing (OR = 4.17, 95% CI = 0.89–19.66) as well as current wheezing and physician-diagnosed asthma was even greater (P for trend <0.05 for all). In children with both risk factors, lung function was significantly decreased, with atopic children being particularly vulnerable.

Conclusion: In children, the interaction between air pollution and past episodes of bronchiolitis resulted in a greater prevalence of asthma and pointed to an association with bronchial hyper-reactivity and decreased lung function. These results suggest mechanisms underlying the development of asthma.

The majority of children with asthma experience their first episode of wheezing in early childhood, usually in response to viral respiratory tract infections (1). Numerous epidemiologic studies have consistently shown that bronchiolitis is closely associated with childhood asthma (2–4). However, it is not known whether viral bronchiolitis contributes to the development of asthma or simply identifies infants who are at increased risk of asthma (5, 6).

Air pollution is associated with several adverse respiratory health outcomes in children and adults. Children may be particularly vulnerable to air pollution due to their underdeveloped respiratory and immune systems (7) and the fact that they inhale

more air per square meter of body surface than adults (8). Many studies have shown a potential association between exposure to traffic exhaust fumes and allergic diseases in children (9–13).

Therefore, we postulated that exposure to air pollution may place children who experience episodes of bronchiolitis in the early years of life at increased risk of asthma. However, little is known about the potential interaction between bronchiolitis and air pollution. In this study, we sought to investigate whether bronchiolitis and air pollution interact to influence the development of asthma in school children and to investigate the mechanisms underlying this effect.

Material and methods

Study population

This prospective cohort study was conducted as part of the first nationwide Children's Health and Environmental Research (CHEER) over 2 years in Korea. From 2005 to 2006, 3200 children from 16 elementary schools in seven cities located throughout Korea were enrolled 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. The response rate was 95.5%. Allergy evaluations such as pulmonary function, methacholine challenge, and skin prick tests were also performed in randomly selected children. The children were followed up 2 years later, and the same evaluations were conducted. After excluding children who had not undergone allergy evaluation, 1743 children were included in the data analysis based on the availability of a completed ISAAC questionnaire and an allergy evaluation at enrollment. The study population comprised 897 boys and 846 girls, with a mean age of 6.83 ± 0.52 years. Details of the subjects are described elsewhere (12).

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

Air pollution data and exposure assessment

We calculated 5-year average (2001–2005) concentrations of air pollutants (ozone, carbon monoxide, nitric dioxide, sulfur dioxide, and particulate matter $<10 \mu\text{m}$ diameter) at the individual level using the Geostatistical Analyst extension of ArcGIS (ArcMap, version 9.3; ESRI Inc., Redlands, WA, USA) (Table S1). Cross-validation was performed for each pollutant using the root-mean-square standardized error (RMSE) to test the validity of the exposure estimating models. The RMSEs were close to 1 (range 1.02–1.31) for all air pollutants. Details are described elsewhere (12, 14, 15). Of the initial 1743 children, 361 were excluded from the estimation of exposure levels because they had moved to other addresses during the 5-year period or had failed to provide an adequate address. Study population was classified either into quartiles or into higher or lower exposure to each individual air pollutant based on the mean exposure value.

Questionnaires

The ISAAC questionnaire is a useful standardized method for determining the prevalence of allergic diseases. The modified Korean version of ISAAC was previously validated (16, 17). Children with a history of bronchiolitis were identified based on the question: 'Was your child ever diagnosed with bronchiolitis by a physician within the first 2 years of life?' Accordingly, 10.5% of the children had a history of bronchiolitis.

Allergy evaluation: skin prick, pulmonary function, and methacholine challenge test

Details are described elsewhere (12). Briefly, skin prick tests were performed for 16 common allergens (Allergopharma, Reinbek, Germany). Atopy was defined as the presence of one or more positive reactions. Data on lung function were collected at the children's school by trained field technicians using a portable

Micro Spirometer (Microspiro Hi-298; Chest Corporation, Tokyo, Japan) according to American Thoracic Society guidelines (18). Methacholine challenge tests were carried out using a modification of the method described originally by Chai et al. (19).

Statistics

To evaluate the single and combined effects of individual air pollutant and a history of bronchiolitis on asthma and airway hyper-responsiveness (AHR), the study population was classified into one of four groups for each individual air pollutant: higher exposure only, history of bronchiolitis only, none, or both. The risk of each group compared to the group with no risk factors for asthma and AHR ($\text{PC}_{20} \leq 16 \text{ mg/ml}$) was analyzed using multiple regression models. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). A linear regression model was used to analyze both the trends regarding the risk of children in the four groups for asthma and AHR and, after air pollution exposure was classified into quartiles, the association between air pollution and log PC_{20} . The interaction between higher exposure and history of bronchiolitis was analyzed using a general linear model. Age, sex, BMI, paternal and maternal history of allergy, maternal education, family income, place of residence, environmental tobacco smoke (ETS) at home, and pre-term birth were considered to be confounding factors and entered into covariates in all models. Additionally, to assess possible confounding effects by the other pollutants in the analyses, multi-pollutant models were calculated, simultaneously including all pollutants except the exposure of interest. *P* value <0.05 was considered statistically significant. All statistics were performed with SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population and prevalence of asthma

Of the 1743 children with a completed ISAAC questionnaire and allergy evaluation, 1340 children (76.9%) could be followed up 2 years later and underwent the same evaluation. There were no significant differences between the initial group and the follow-up group in terms of basic demographics (Table 1). In the latter, the log PC_{20} and atopic rate were increased significantly (Table 1). The lifetime and 12-month prevalence of wheezing episodes (current wheezing) at the start of the study were 26.0% and 13.2%, respectively, and the lifetime prevalence of physician-diagnosed asthma was 10.0%. Current wheezing had significantly decreased at the end of the 2-year follow-up, and during that time 12.1% of the children experienced new wheezing and 3.6% were newly diagnosed with asthma (Table S2).

Synergistic effect between air pollution exposure and a history of bronchiolitis on the prevalence of asthma

Children exposed to high levels of ozone did not have a significantly higher prevalence of asthma, while in children with a history of bronchiolitis, significant increases in the prevalence of asthma and related symptoms were determined (Table 2). However, for children with both risk factors, there was a significantly increasing trend toward a risk of asthma and related symptoms. In particular, children with both a greater exposure to ozone and history of bronchiolitis had a significantly higher prevalence of current asthma (both a positive response in the questionnaire regarding physician-diagnosed asthma and current wheezing)

Table 1 Characteristics of the subjects

Variable	At enrollment (<i>n</i> = 1743)	Two-year follow-up (<i>n</i> = 1340)	<i>P</i> value
Sex (M : F)	51.5:48.5 (897:846)	51.3:48.7 (686:650)	N-S
Age (years)	6.83 ± 0.52	8.83 ± 0.50	<0.01
Grade			
1 > 3	91.7% (1598/1743)	91.2% (1222/1340)	N-S
2 > 4	8.3% (145/1743)	8.8% (118/1340)	
BMI	16.69 ± 2.46	17.97 ± 3.01	<0.01
Paternal history of allergic disease	5.7% (85/1499)	6.1% (71/1160)	N-S
Maternal history of allergic disease	9.5% (142/1499)	9.1% (106/1159)	N-S
Maternal education			
≤ 12 years	59.1% (936/1588)	60.7% (742/1223)	N-S
>12 years	41.1% (652/1588)	39.3% (481/1223)	
Family income			
<3000 USD	65.0% (1031/1587)	66.1% (809/1224)	N-S
≥ 3000 USD	35.0% (556/1587)	33.9% (415/1224)	
Address			
Metropolitan area	44.9% (783/1743)	46.3% (620/1340)	N-S
Industrial area	55.1% (960/1743)	53.7% (720/1340)	
Prematurity, % (<i>n</i>)	5.1% (81/1583)	5.3% (64/1219)	N-S
Breast feeding >3 months, % (<i>n</i>)	39.4% (618/1567)	38.7% (467/1206)	N-S
Smoking during pregnancy, % (<i>n</i>)	0.3% (5/1599)	0.2% (3/1231)	N-S
ETS at home, % (<i>n</i>)	43.4% (692/1594)	44.3% (544/1228)	N-S
Bronchiolitis within first 2 years of life, % (<i>n</i>)	10.5% (168/1600)	10.4% (129/1236)	N-S
Atopy	29.3% (509/1740)	40.2% (538/1337)	<0.01
PC ₂₀ ≤ 16 mg/ml	35.1% (595/1688)	17.5% (233/1335)	<0.01
Log PC ₂₀	1.33 ± 0.49	1.53 ± 0.35	<0.01

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

(OR = 7.54 (2.67–21.32), *P* for interaction <0.01) (Table 2). The results for carbon monoxide and nitrous dioxide exposure were similar to those obtained for ozone (Table 2). Main effects analyses also showed the absence of significant association between any of the pollutants and the prevalence of asthma, while for bronchiolitis, these associations were significant (Table S3).

Synergistic effect between air pollution exposure and a history of bronchiolitis on asthma development during the 2-year follow-up period

Children with high ozone levels had an increased prevalence of new episodes of wheezing during the 2-year period and of AHR at enrollment (Table 3), while children with a history of bronchiolitis did not. These higher prevalences increased even further in children who had both risk factors (*P* for trend <0.01) (Table 3). The synergistic effect may become significant if the number of children within each group is increased. Carbon monoxide showed a similar pattern to that of ozone (Table 3), while the results for nitrogen dioxide, sulfur dioxide, and particulate matter were not consistent (data not shown). In addition, the main effects of air pollutions and bronchiolitis were similar to those described above except that a history of bronchiolitis became significant for newly diagnosed asthma (Table S4).

Air pollutants and biomarkers (atopy, pulmonary function test, and AHR)

Neither past history of bronchiolitis nor greater exposure to air pollution was associated with atopy (data not shown). However, greater exposure to ozone was significantly associated with decreased lung function, including predictive values for FVC, FEV₁, FEF_{25–75%}, and PC₂₀. The effect of ozone was augmented

by a history of bronchiolitis (Table 4). Categorical analyses of quartiles revealed a significant negative association between ozone and log PC₂₀ (OR for PC₂₀ ≤ 16 mg/ml per 5 ppb = 1.25, 95% CI = 1.09–1.43). When children were stratified according to atopic state at enrollment, atopic children had a lower log PC₂₀ (Fig. 1). Children with more risk factors had a significantly lower log PC₂₀, but the effect was significant only in atopic children (*P* for trend = 0.01) (Fig. 2). This result suggests that the interaction between the effects of air pollution and a history of bronchiolitis are altered by the presence of atopy.

Discussion

The results of this prospective cohort study conducted over a period of 2 years in Korea suggest that in children a greater exposure to air pollution and a history of bronchiolitis may interact synergistically to affect the development of asthma, with the underlying mechanism possibly related to increased AHR and decreased pulmonary function. In addition, children exposed to high ozone levels tended to have decreased pulmonary function and PC₂₀ values, while in atopic children, there was a tendency toward a lower PC₂₀ than in nonatopic children. To the best of our knowledge, this is the first report describing a potential synergistic effect in children of air pollution and a history of bronchiolitis in the development of asthma.

The association between bronchiolitis in early childhood and subsequent development of asthma is well known. During bronchiolitis, lower respiratory viral infections may induce a bronchial inflammatory cascade, causing the bronchiolitis to persist even after the virus has been eradicated. This may result in atopy or AHR such that children are more susceptible to asthma (20, 21). Thus, early insult to the respiratory tract can lead to lasting AHR and thereby affect respiratory health later in life. The

Table 2 Synergistic effect between exposure to each air pollutant and a history of bronchiolitis on the prevalence of asthma

Risk factor	Group	Lifetime wheezing	Current wheezing	Physician-diagnosed asthma	Current asthma*
Ozone and bronchiolitis	None (n = 825)	1.00 (24.5%)	1.00 (12.6%)	1.00 (8.7%)	1.00 (4.7%)
	Higher exposure only (n = 369)	0.67 (0.44–1.00) (19.6%)	0.72 (0.42–1.23) (10.1%)	0.80 (0.42–1.53) (7.4%)	0.98 (0.41–2.34) (4.1%)
	Bronchiolitis only (n = 93)	4.67 (2.87–7.63) (60.2%)	1.94 (1.08–3.50) (23.7%)	2.86 (1.55–5.28) (23.7%)	1.51 (0.58–3.95) (8.6%)
	Both (n = 48)	3.49 (1.62–7.51) (54.2%)	2.73 (1.14–6.56) (29.2%)	3.81 (1.53–9.46) (29.2%)	7.54 (2.67–21.32)† (20.8%)
	P for trend	<0.01	0.02	<0.01	<0.01
Carbon monoxide and bronchiolitis	None (n = 834)	1.00 (24.7%)	1.00 (12.7%)	1.00 (8.8%)	1.00 (4.8%)
	Higher exposure ^a only (n = 358)	0.66 (0.43–0.99) (19.0%)	0.71 (0.41–1.23) (9.8%)	0.84 (0.44–1.60) (7.3%)	1.04 (0.44–2.46) (3.9%)
	Bronchiolitis only (n = 94)	4.48 (2.76–7.27) (59.6%)	1.89 (1.05–3.40) (23.4%)	2.83 (1.54–5.23) (23.4%)	1.50 (0.57–3.89) (8.5%)
	Both (n = 47)	3.89 (1.78–8.49) (55.3%)	2.99 (1.24–7.25)† (29.8%)	4.10 (1.64–10.27) (29.8%)	8.30 (2.91–23.69)† (21.3%)
	P for trend	<0.01	0.01	<0.01	<0.01
Nitric dioxide and bronchiolitis	None (n = 542)	1.00 (24.9%)	1.00 (13.7%)	1.00 (8.7%)	1.00 (5.4%)
	Higher exposure only (n = 650)	0.93 (0.43–2.02) (21.4%)	0.70 (0.25–1.95) (10.3%)	1.41 (0.44–4.56) (8.0%)	1.08 (0.23–5.04) (3.9%)
	Bronchiolitis only (n = 47)	2.98 (1.47–6.03) (55.3%)	1.23 (0.51–3.02) (21.3%)	5.75 (2.53–13.06) (34.0%)	3.30 (1.18–9.18) (14.9%)
	Both (n = 94)	6.93 (2.16–22.22) (59.6%)	5.70 (1.39–23.44) (27.7%)	7.06 (1.28–38.88) (21.3%)	7.92 (0.97–64.80) (11.7%)
	P for trend	<0.01	<0.01	<0.01	0.01

The results are presented as the odds ratios and 95% confidence intervals, adjusted for age, sex, BMI, paternal and maternal allergy history, maternal education, family income, place of residence, breast feeding, ETS at home, preterm birth, and air pollutants. Exposure level is higher than the mean value for each air pollutant.

*Physician-diagnosed asthma plus current wheezing.

†P for the interaction between high O₃ or CO and bronchiolitis < 0.01.

‡P for the interaction between high CO and bronchiolitis = 0.10.

Table 3 Synergistic effect between exposure to each air pollutant and a history of bronchiolitis on the development of asthma and airway hyper-responsiveness (AHR) during the 2-year study period

Risk factor	Group	New wheezing	Newly diagnosed asthma	PC ₂₀ ≤ 16 mg/ml	New AHR*
Ozone and bronchiolitis	None (n = 825)	1.00 (9.0%)	1.00 (3.0%)	1.00 (29.2%)	1.00 (9.6%)
	Higher exposure only (n = 369)	1.92 (0.96–3.83) (15.2%)	0.78 (0.25–2.45) (3.1%)	1.60 (1.13–2.27) (45.3%)	0.87 (0.35–2.17) (5.7%)
	Bronchiolitis only (n = 93)	2.00 (0.61–6.49) (12.9%)	1.93 (0.55–6.78) (6.8%)	1.30 (0.79–2.15) (36.0%)	0.75 (0.24–2.32) (8.5%)
	Both (n = 48)	4.17 (0.89–19.66) (27.8%)	3.06 (0.47–19.76) (11.5%)	2.96 (1.41–6.24) (57.1%)	– (0%)
	P for trend	<0.01	0.10	<0.01	0.25
Carbon monoxide and bronchiolitis	None (n = 834)	1.00 (9.0%)	1.00 (3.0%)	1.00 (29.5%)	1.00 (9.8%)
	Higher exposure only (n = 358) ^a	1.99 (1.00–3.95) (15.4%)	0.83 (0.26–2.60) (3.2%)	1.55 (1.10–2.20) (45.3%)	0.77 (0.30–1.97) (5.2%)
	Bronchiolitis only (n = 94)	2.01 (0.62–6.55) (12.9%)	1.95 (0.56–6.84) (6.8%)	1.36 (0.83–2.22) (36.7%)	0.74 (0.24–2.30) (8.5%)
	Both (n = 47)	4.28 (0.91–20.12) (27.8%)	3.11 (0.48–20.84) (12.5%)	2.76 (1.30–5.85) (56.3%)	– (0%)
	P for trend	<0.01	0.09	<0.01	0.73
Nitric dioxide and bronchiolitis	None (n = 542)	1.00 (9.7%)	1.00 (3.2%)	1.00 (28.6%)	1.00 (9.1%)
	Higher exposure only (n = 650) ^a	1.22 (0.35–4.23) (11.9%)	1.26 (0.10–15.50) (3.0%)	1.71 (0.87–3.35) (39.2%)	1.24 (0.26–5.86) (8.1%)
	Bronchiolitis only (n = 47)	3.35 (0.69–16.34) (18.8%)	4.09 (0.77–21.68) (13.0%)	2.61 (1.28–5.32) (47.8%)	– (0%)
	Both (n = 94)	17.45 (0.78–39.84) (18.2%)	5.80 (0.22–154.71) (6.5%)	0.92 (0.64–5.71) (41.3%)	0.60 (0.05–7.03) (8.9%)
	P for trend	0.12	0.08	0.04	0.61

The results are presented as the odds ratios and 95% confidence intervals, adjusted for age, sex, BMI, paternal and maternal allergy history, maternal education, family income, place of residence, breast feeding, ETS at home, preterm birth, and air pollutants. Exposure level is higher than the mean value for each air pollutant.

^aNew airway hyper-responsiveness: PC₂₀ > 16 mg/ml at enrollment and PC₂₀ ≤ 16 mg/ml at follow-up.

Table 4 Comparison of pulmonary function tests and PC₂₀ based on ozone exposure and a history of bronchiolitis

At enrollment	FVC pred (%)	FEV ₁ pred (%)	FEF _{25–75%} pred (%)	PC ₂₀ (mg/ml)
None	100.50 ± 95.32	107.08 ± 13.32	102.03 ± 21.70	35.71 ± 19.46
Higher exposure to ozone only	100.22 ± 12.42	105.22 ± 13.41[†]	94.36 ± 22.69[†]	27.75 ± 21.41[†]
Bronchiolitis only	98.51 ± 13.58	104.48 ± 13.50	96.88 ± 25.25	32.86 ± 21.13
Both	95.32 ± 12.86^{*†}	99.77 ± 13.92^{*†}	85.97 ± 21.66^{*†}	24.90 ± 20.45[†]

The results are presented as the mean ± standard deviation. Exposure level is higher than the mean value.

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF_{25–75%}, mean forced expiratory flow during the middle half of FVC.

^{*}*P* < 0.05 compared with children exposed to high levels of ozone only.

[†]*P* < 0.05 compared with children with no risk factors.

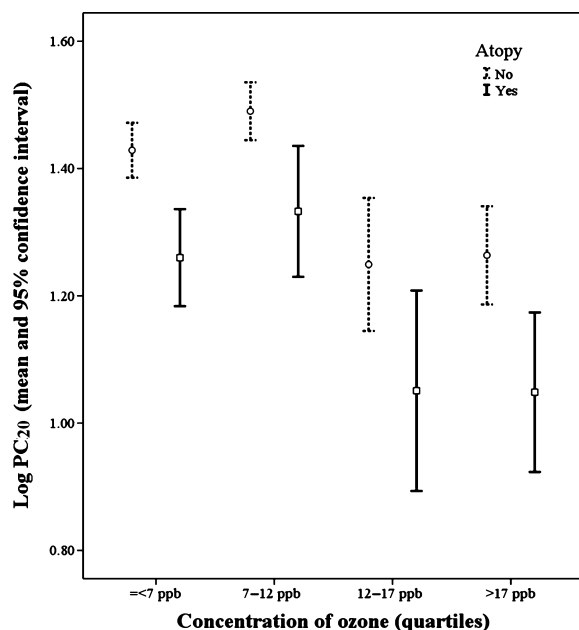


Figure 1 Log PC₂₀ and 95% confidence intervals according to ozone exposure and atopic state. Children exposed to high levels of ozone tended to have a lower Log PC₂₀. Those with atopy tend to have a lower PC₂₀ than nonatopic children.

results of the present study are consistent with those earlier finding, in that bronchiolitis during early childhood was shown to be associated with current wheezing, lifetime wheezing, and physician-diagnosed asthma in 6-year-old children. In addition, we identified an association between air pollution and AHR that was further strengthened by a past history of bronchiolitis. Higher ozone exposure was also significantly associated with decreased lung function, especially regarding FEF_{25–75%} as an index of airway obstruction and PC₂₀. The effect of air pollution was enhanced by a history of bronchiolitis even though past episodes of bronchiolitis alone did not affect lung function. A possible explanation for these observations is that reactive oxidative species produced in response to air pollution can overwhelm the redox system to damage the cell wall lipids, protein, and DNA, leading to airway inflammation and AHR (22). Pro-inflammatory effects in the airways also have been demonstrated following acute inhalation of diesel exhaust particles in healthy volunteers (23). An experimental murine study showed that air pollution can inhibit IFN- γ production, thereby enhancing Th2 cytokine-mediated inflammation (24). Based on these observations, we speculate that air pollution increases AHR through oxidative

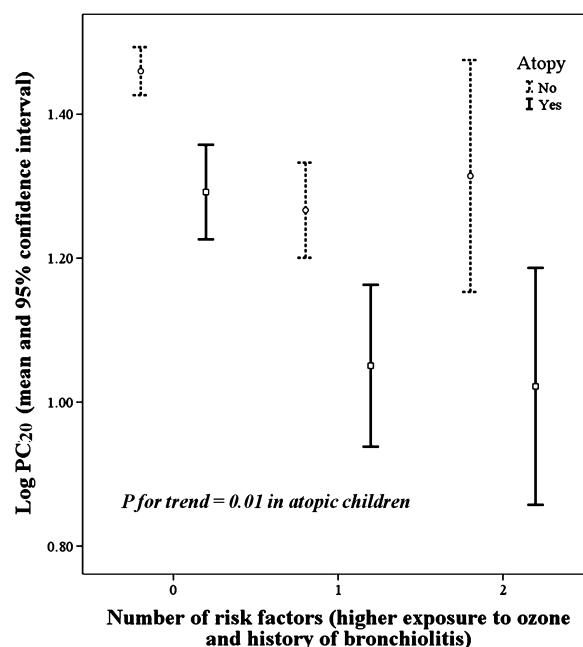


Figure 2 Log PC₂₀ and 95% confidence intervals according to the number of risk factors (higher exposure to ozone and past history of bronchiolitis). In atopic children, as the number of risk factors increased, there was a trend toward greater airway hyper-responsiveness. (*P* for trend = 0.01 for atopic children, adjusted for age, sex, BMI, paternal and maternal allergy history, maternal education, family income, place of residence, breast feeding, ETS at home, preterm birth, and air pollutants). Nonatopic children did not show this trend.

stress and that bronchiolitis increases the susceptibility to the effects of air pollution by altering the airway mucosal barrier. Moreover, AHR was further increased when children were atopic, even though atopy was not significantly related to air pollution or past bronchiolitis. Therefore, it seems that atopy makes children vulnerable to the effects of air pollution. Finally, children with a history of bronchiolitis who were exposed to high ozone levels had significantly decreased lung function, which may influence the development of asthma as well. While the interactions between early respiratory infection and other familial or environmental factors were evaluated in previous reports, ours is the first study to examine the interaction between air pollution and bronchiolitis.

In examining this interaction, we used the 5-year average concentration of air pollutants to estimate the exposure level because it reflects the long-term exposure of an individual. It should be noted, however, that the 5-year average does not reflect periodic

(seasonal or daily) fluctuations, which may also be important in the development of asthma. To account for individual air pollution exposure levels, we categorized children into one of either two or four groups to investigate the interaction between exposure and a history of bronchiolitis. Although exposure to air pollution was continuous, the exposure data tended to cluster according to the school in which the children were enrolled. Therefore, categorical analyses were more suitable and decreased the potential influence of errors in measuring individual exposure levels.

The present study has several limitations. The history of bronchiolitis was obtained from the parental questionnaire and could suffer from recall bias. Some of the children described as having bronchiolitis may instead have been asthmatic. Also, 2 years may not have been long enough to evaluate changes induced by air pollutants, and the follow-up rate was relatively low (77%). This short follow-up period may explain why only an increasing trend toward new wheezing was obtained when analyzed with respect to the combination of air pollution and bronchiolitis, even though this relationship became more significant in single pollutant models [OR = 1.91 (1.03–3.55) for high ozone levels, OR = 4.97 (1.12–22.02) for the combination] (data not shown). This was also the case for newly diagnosed asthma, which was determined in only 3.6% during the 2-year period. Therefore, a longer follow-up would be valuable in testing whether newly diagnosed asthma is also associated with the interaction between air pollution and bronchiolitis. An additional consideration is that genetic polymorphisms and dietary factors known to affect oxidative stress were not considered in the analysis. Nonetheless, as the present prospective study was conducted nationwide and enrolled more than 1000 children, the data can be considered as representative of Korea. The response rate to the ISAAC questionnaire was >95%, and additional biomarkers were measured for almost every child. These data allowed a reliable analysis of the effects of air pollution and a past history of bronchiolitis.

In summary, this study revealed that there may be a synergistic effect between air pollution (ozone, carbon monoxide, and nitric dioxide) and bronchiolitis in the development of childhood asthma. The underlying mechanism may involve increased AHR and decreased lung function. In addition, atopy may make children more vulnerable to the effects of air pollution on AHR. Together, these findings suggest that environmental control may improve respiratory health in children with atopy or bronchiolitis.

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Author contributions

B. J. Kim involved in the data generation/analysis and interpretation of data/preparation of main manuscript. J. H. Seo, Y. H. Jung, H. Y. Kim, J. W. Kwon, H. B. Kim, S. Y. Lee, K. S. Park, and J. Yu performed the data generation/analysis and interpretation of data. H. C. Kim, J. H. Leem, and J. Y. Lee involved in the data generation (air pollution)/analysis and interpretation of data/preparation of manuscript (methods for air pollution data and exposure assessment). J. H. Leem, J. Sakong, S. Y. Kim, C. G. Lee, D. M. Kang, M. Ha, and Y. C. Hong contributed to the regional PI of each city; study design/data generation/analysis and interpretation of data. H. J. Kwon contributed to the CHEER study PI/study design/data generation. S. J. Hong involved in the Study PI/study design/data generation/analysis and interpretation of data/preparation of main manuscript.

Conflict of interest

All the authors have nothing to disclose.

Acknowledgments

This study was supported by a 'Children's Health and Environment Research' grant from the Ministry of Environment, Republic of Korea.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Five-year average concentration of air pollutants estimated by residential address ($n = 1382$).

Table S2. Prevalence of asthma during the 2-year study period.

Table S3. Main effects of air pollutants and a history of bronchiolitis on the prevalence of asthma.

Table S4. Main effects of air pollutants and a history of bronchiolitis on the development of asthma and AHR during the 2-year study period.

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Supplementary Table 1. Five-year average concentration of air pollutants estimated by residential address (n = 1382)

Pollutant	Min	10th	25th	50th	Mean	75th	90th	Max
Nitrogen dioxide (ppb)	13.15	14.26	18.57	28.14	25.90	31.18	34.65	39.60
Ozone (ppb)	3.74	4.53	5.30	8.01	10.32	14.76	20.03	29.66
Sulfur dioxide (ppb)	3.74	4.53	5.17	6.17	6.72	8.01	9.37	13.62
Carbon monoxide (ppm)	0.14	0.18	0.23	0.30	0.41	0.70	0.77	0.97
PM ₁₀ (µg/m ³)*	40.74	48.11	49.86	61.32	58.78	66.92	68.96	74.14

*particulate matter less than 10 µm in diameter.

Supplementary Table 2. Prevalence of asthma during the 2-year study period

Variable	At enrollment (n = 1743)	Two years later (n = 1340)	P value
Lifetime wheezing, % (n)	26.0% (433/1664)	23.0% (305/1324)	0.06
Current wheezing (wheezing within 1 year), % (n)	13.2% (220/1664)	9.3% (123/1324)	<0.01
Physician-diagnosed asthma, % (n)	10.0% (166/1660)	9.9% (130/1319)	0.90
Current asthma*	5.2% (90/1663)	4.3% (57/1319)	0.17
Current asthma treatment (asthma treatment within 1 year), % (n)	4.6% (76/1664)	3.8% (50/1324)	0.29
New wheezing [#]	–	12.1% (115/954)	
Newly diagnosed asthma [†]	–	3.6% (41/1153)	

*Current asthma: physician-diagnosed asthma plus current wheezing.

[#]New onset of wheezing during the 2-year study period.

[†]Newly diagnosed with asthma by a physician during the 2-year study period.

Supplementary Table 3. Main effects of air pollutants and a history of bronchiolitis on the prevalence of asthma

Risk factors	Lifetime wheezing	Current wheezing	Physician-diagnosed asthma	Cu
Bronchiolitis	4.69 (3.11–7.08)	2.22 (1.37–3.61)	3.45 (2.08–5.71)	2.8
O ₃ (per 5 ppb)	0.87 (0.74–1.02)	0.93 (0.76–1.33)	1.04 (0.83–1.30)	1.2
CO (per 0.2 ppm)	0.90 (0.78–1.04)	0.95 (0.79–1.15)	1.03 (0.83–1.27)	1.2
NO ₂ (per 5 ppb)	0.96 (0.71–1.30)	0.89 (0.60–1.33)	0.79 (0.51–1.23)	0.6

Odds ratios and 95% confidence intervals were assessed using logistic regression.

Age, sex, BMI, paternal and maternal allergy history, maternal education, family income, place of residence, breast feeding, ETS at home, preterm birth, bronchiolitis, and air pollutants were included in the logistic regression models.

*Physician-diagnosed asthma plus current wheezing.

Supplementary Table 4. Main effects of air pollutants and a history of bronchiolitis on the development of asthma and AHR during the 2-year study period.

Risk factors	New wheezing	Newly diagnosed asthma	PC ₂₀ ≤16 mg/ml	Ne
Bronchiolitis	2.06 (0.83–5.10)	2.89 (1.04–8.02)	1.46 (0.97–2.20)	0.6
O ₃ (per 5 ppb)	1.41 (1.08–1.85)	0.94 (0.61–1.46)	1.24 (1.08–1.42)	0.8
CO (per 0.2 ppm)	1.28 (1.00–1.64)	1.02 (0.68–1.54)	1.19 (1.05–1.35)	0.8
NO ₂ (per 5 ppb)	0.98 (0.57–1.69)	1.03 (0.45–2.38)	1.25 (0.95–1.64)	1.1

The results are presented as the odds ratios and 95% confidence intervals determined using logistic regression.

Age, sex, BMI, paternal and maternal allergy history, maternal education, family income, place of residence, breast feeding, ETS at home, preterm birth, bronchiolitis, and air pollutants were included in logistic regression models.

* PC₂₀>16 mg/ml at enrollment and PC₂₀≤16 mg/ml at follow-up.