Ambient air pollution, lung function, and airway responsiveness in asthmatic children

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Background: Although ambient air pollution has been linked to reduced lung function in healthy children, longitudinal analyses of pollution effects in asthmatic patients are lacking.
Objective: We sought to investigate pollution effects in a longitudinal asthma study and effect modification by controller medications.
Methods: We examined associations of lung function and methacholine responsiveness (PC_{20}) with ozone, carbon monoxide (CO), nitrogen dioxide, and sulfur dioxide concentrations in 1003 asthmatic children participating in a 4-year clinical trial. We further investigated whether budesonide and nedocromil modified pollution effects. Daily pollutant concentrations were linked to ZIP/postal code of residence. Linear mixed models tested associations of within-subject pollutant concentrations with FEV_1 and forced vital capacity (FVC) percent predicted, FEV_1/FVC ratio, and PC_{20}, adjusting for seasonality and confounders.
Results: Same-day and 1-week average CO concentrations were negatively associated with postbronchodilator percent predicted FEV_1 (change per interquartile range, −0.33 [95% CI, −0.49 to −0.16] and −0.41 [95% CI, −0.62 to −0.21], respectively) and FVC (−0.19 [95% CI, −0.25 to −0.07] and −0.25 [95% CI, −0.43 to −0.07], respectively). Longer-term 4-month CO averages were negatively associated with prebronchodilator percent predicted FEV_1 and FVC (−0.36 [95% CI, −0.62 to −0.10] and −0.21 [95% CI, −0.42 to −0.01], respectively). Four-month averaged CO and ozone concentrations were negatively associated with FEV_1/FVC ratio ($P < .05$). Increased 4-month average nitrogen dioxide concentrations were associated with reduced postbronchodilator FEV_1 and FVC percent predicted. Long-term exposures to sulfur dioxide were associated with reduced PC_{20} (percent change per interquartile range, −6% [95% CI, −11% to −1.5%]). Treatment augmented the negative short-term CO effect on PC_{20}.
Conclusions: Air pollution adversely influences lung function and PC_{20} in asthmatic children. Treatment with controller medications might not protect but rather worsens the effects of CO on PC_{20}. This clinical trial design evaluates modification of pollution effects by treatment without confounding by indication. (J Allergy Clin Immunol 2016;137:390-9.)

Key words: *Asthma, ambient air pollution, airway hyperresponsiveness, inhaled corticosteroids, lung function*

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Abbreviations used
AHR: Airway responsiveness
CAMP: Childhood Asthma Management Program
CO: Carbon monoxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
IQR: Interquartile range
NO_2: Nitrogen dioxide
SO_2: Sulfur dioxide

Over the past 30 years, evidence has accumulated demonstrating that ambient air pollution has adverse effects on the respiratory health of asthmatic and nonasthmatic children.[1-4] In observational studies of asthmatic children, higher short-term exposures to air pollution have been associated with more symptoms, increased need for reliever medication, hospital admissions, lung function decrements, and airflow obstruction.[5-9]

Although ambient air pollution has been linked to reduced lung function in healthy children, longitudinal analyses of air pollution effects in asthma are lacking. For instance, there are no clinical trials that assessed associations of long-term pollution with lung function, airflow obstruction, and airway hyperresponsiveness (AHR) and modification of putative pollution effects by controller medications. Pollutants induce adverse effects by affecting oxidant signaling pathways and airway inflammation.[10,11] Inhaled corticosteroids (ICSs) have been shown to reduce oxidative stress and improve airway function and asthma symptoms.[8,12] However, recent observational studies suggest that asthmatic children using ICSs might be more vulnerable to the adverse health effects of air pollution compared with those who are not receiving ICSs.[13,14] These findings might reflect confounding by indication because children with more symptomatic asthma might be more likely to use an ICS. Only evaluation of pollution effects in the context of a clinical trial can test whether an ICS will increase or decrease susceptibility to air pollution.

The Childhood Asthma Management Program (CAMP) is such a randomized clinical trial involving 8 cities in North America (Albuquerque, New Mexico; Baltimore, Maryland; Boston, Massachusetts; Denver, Colorado; San Diego, California; Seattle, Washington; St Louis, Missouri; and Toronto-Ontario, Canada). Its main goal was to evaluate the long-term effectiveness and safety of daily inhaled anti-inflammatory medication in children given a diagnosis of mild-to-moderate asthma.[15,16] Using the prerandomization observational data from this trial, we reported that short-term air pollution exposures increased asthma symptoms and use of relief medication,[6] with carbon monoxide (CO) and nitrogen dioxide (NO_2) having the strongest associations.

The current article investigates in the same CAMP study whether short- and long-term exposures to 4 of the US Environmental Protection Agency's criteria air pollutants (ozone, CO, NO_2, and sulfur dioxide [SO_2]) are associated with lung function and AHR in asthmatic children. In addition, we investigate whether anti-inflammatory treatment with an ICS or nedocromil modifies the effects of pollution on asthma outcomes.

METHODS

The CAMP study design and methods have been described elsewhere.[16] Additionally, details on all the methods used in the present report are provided in the Methods section in this article's Online Repository at www.jacionline.org. In summary, children enrolled in CAMP were 5 to 12 years of age and hyperresponsive to methacholine at study entry. One thousand forty-one children entered the randomization phase, and 311, 312, and 418 children received budesonide, nedocromil, and placebo, respectively. All subjects were treated and followed for 4 years, with visits at 2 and 4 months after randomization and at 4-month intervals thereafter. Each parent or guardian signed a consent form, and participants 7 years of age and older signed an assent form approved by each clinical center's institutional review board.

Outcomes measures

Spirometry before and after bronchodilator administration was conducted at randomization and follow-up visits (n = 13), according to American Thoracic Society Standards. We considered both prebronchodilator and postbronchodilator FEV_1 and forced vital capacity (FVC) percent predicted values as outcomes in this current analysis as we investigated short- and long-term effects of air pollution. Additionally, the FEV_1/FVC percentage ratio was used as another measure of airflow obstruction. Using the Wright nebulizer/tidal breathing technique, a methacholine challenge was performed annually during the treatment phase. Spirometry was performed 90 seconds after each challenge until FEV_1 had decreased by 20% or more (PC_{20}).

Air pollution exposure assessment

Monitoring data on 24-hour average concentrations of 4 gaseous pollutants (ozone, CO, NO_2, and SO_2) were obtained for each metropolitan area. The ZIP or postal code centroid coordinates were used to link participants to daily concentrations from the nearest monitor within 50 km that did not have missing data on that day (December 1993 through June 1999).

Statistical analysis

We fitted a linear mixed model with random intercepts for each subject to estimate the associations between lung function (FEV_1 and FVC percent predicted and FEV_1/FVC ratio percentage) and (log-transformed) PC_{20} and same-day, 1-week, and 4-month moving averages of pollution. The number of days from randomization was the time trend of the model. Potential for confounding factors was considered carefully, basing choice of covariates on prior CAMP experience.[17,18] To estimate associations across all cities, we constructed a model including city as a covariate but also compared estimates of this model with study-wide estimates from meta-analyzing city-stratified models. We adjusted for "season" by using sine and cosine functions of time[19] and their interactions with city. In addition, we decomposed daily pollution concentrations into between- and within-subject exposures. We report estimates of within-subject exposure effects (on interquartile range [IQR] scale).

To assess potential effect modification of the pollution-outcomes associations by treatment, we included a pollutant concentration by treatment interaction into the models while excluding the baseline (randomization) measurements and used the ANOVA likelihood ratio to test effect differences across the 3 treatment groups.

We used SAS software (version 9.2; SAS Institute, Cary, NC) and IBM SPSS statistical software (version 20; IBM, Armonk, NY) to manage all data. Statistical analysis was performed with IBM SPSS and R programming language software (version 2.15.1).

RESULTS

All subjects considered in this analysis were randomized into CAMP and followed up during the trial period. A total of 1003 (96.3%) of the 1041 total children were studied. At study entry, the mean age was 9 years (SD, 2.1 years), and the geometric mean for PC_{20} was 1.1 mg/mL (minimum-maximum, 0.02-2.5 mg/mL). Table I shows the main characteristics of the participants. In total, 82.5% of the children attended all visits during the 4 years of the trial (median number of completed visits, 14; range, 1-14).

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