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Ambient air pollution, lung function and airway responsiveness in children with asthma

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Abstract

Background—Although ambient air pollution has been linked to reduced lung function in healthy children, longitudinal analyses of pollution effects in asthma are lacking.

Objective—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 (NO_2) and sulfur dioxide (SO_2) levels in

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1,003 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 FVC %predicted, FEV_1/FVC and PC_{20}, adjusting for seasonality and confounders.

Results—Same-day and 1-week average CO levels were negatively associated with post-bronchodilator %predicted FEV_1 (change(95%CI) per IQR: −0.33(−0.49, −0.16), −0.41(−0.62, −0.21), respectively) and FVC (−0.19(−0.25, −0.07), −0.25(−0.43, −0.07)). Longer-term four-month averages of CO were negatively associated with prebronchodilator %predicted FEV_1 and FVC (−0.36(−0.62, −0.10), −0.21(−0.42, −0.01)). Four-month averaged CO and ozone levels were negatively associated with FEV_1/FVC ($p<0.05$). Increased four-month average NO_2 levels were associated with reduced post-bronchodilator FEV_1 and FVC %predicted. Long-term exposures to SO_2 were associated with reduced PC_{20} (%change(95%CI) per IQR:-6(-11,-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 may not protect but worsens the CO effects on PC_{20}. This clinical trial design evaluates modification of pollution effects by treatment without confounding by indication.

Keywords

asthma; ambient air pollution; airway hyperresponsiveness; inhaled corticosteroids; lung function

Introduction

Over the past thirty years evidence has accumulated demonstrating that ambient air pollution has adverse effects on the respiratory health of asthmatic and non-asthmatic 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 responsiveness (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 (ICS) 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 inhaled corticosteroids (ICS) may be more vulnerable to the adverse health effects of air pollution compared to those that are not on ICS.[13,14] These findings may reflect confounding by indication, since children with more symptomatic asthma may be more likely use an ICS. Only evaluation of pollution effects in the context of a clinical trial can test whether ICS increase or decrease susceptibility to air pollution.

The Childhood Asthma Management Program (CAMP) is such a randomized clinical trial involving eight 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 diagnosed with mild-to-moderate asthma.[15,16] Using the pre-randomization 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 and nitrogen dioxide having the strongest associations.

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

Methods

CAMP study design and methods have been described elsewhere.[16] Additionally, detail on all methods used in the present report is provided in an online data supplement. In summary, children enrolled in CAMP were 5–12 years of age and were hyperresponsive to methacholine at study entry. 1,041 Children entered the randomization phase and 311, 312, 418 children received budesonide, nedocromil, and placebo, respectively. All subjects were treated and followed for four years with visits at two and four months after randomization and at four-month intervals thereafter. Each parent or guardian signed a consent form and participants of 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 the bronchodilator administration, was conducted at randomization (RZ) and at follow up visits (n=13) according to the American Thoracic Society Standards. We considered both pre- and post-BD FEV_1 and FVC %predicted as outcomes in this current analysis as we investigated short- and long-term effects of air pollution. Additionally, the FEV_1/FVC % 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 fallen by 20% or more (PC_{20}).

Air Pollution Exposure Assessment

Monitoring data on 24-hour averages 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 %predicted and FEV_1/FVC%) and (log-transformed) PC_{20} and same day, 1-week and 4-month moving averages of pollution. 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 scale (IQR)).

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 (RZ) measurements and used ANOVA likelihood ratio to test effect differences across the 3 treatment groups.

We used SAS® software (version 9.2; SAS Institute Inc. 2008, Cary, NC USA) and IBM SPSS statistics (version 20; Armonk, NY USA: IBM Corp 2011) to manage all data. Statistical analysis was performed in IBM SPSS and R programming language (version 2.15.1; 2012-06-22).

Results

All subjects considered in this analysis were randomized into CAMP and followed up during the trial period. A total of 1,003 of the 1,041 total children (96.3%) children were studied. At study entry the mean (SD) age was 9 (2.1) and geometric mean (minmax) for PC_{20} was 1.1 (0.02-2.5) mg/ml. Table I shows the main characteristics of the participants. 82.5% of the children attended all visits during the 4 years of the trial (median number of completed visits=14 (range: 1-14)). Participants had a median of 14 (range: 1-14) pre-BD and 10 (range: 1-10) post-BD lung function measurements and 4 (range: 0-4) PC_{20} tests.

Pollution concentrations during December'93-June'99 are summarized by city in Table II. We report the number of observations, percentiles and IQR of daily concentrations of the 4 pollutants. Table E1 shows the IQR of the overall and the within-subject concentration of pollutants.

Correlations of 24-hour mean pollution concentrations are shown in Table E2. Overall, ozone was negatively correlated with the other 3 pollutants that were positively correlated with each other. The same pattern of correlation existed in the 8 separate cities (data shown in Table E3 in the online repository). These relationships are expected because ozone is a secondary pollutant of regional origin, whereas the other pollutants are primary and mostly associated with local sources.

Association of pollution with level of lung function

Figure 1 presents the associations of pollution with post-BD FEV_1 and FVC %predicted. Same day and 1-week and 4-month moving averages of CO had the most consistent negative associations with %predicted post-BD FEV_1 (change (95%CI) per IQR: −0.3(−0.5,−0.2), −0.4(−0.6,−0.2), −0.6(−0.7,−0.1), respectively) and FVC (change (95%CI) per IQR: (−0.2(−0.3, −0.1), −0.3(−0.4, −0.1), −0.2(−0.4,−0.01), respectively). The 4-month average NO_2 was also negatively associated with post-BD FEV_1 and FVC %predicted (change (95%CI) per IQR: −0.2(−0.4, 0.01) and −0.2 (−0.4,−0.1), respectively). The evidence for negative effects on post-BD lung function was weaker for 4-month average exposure to ozone (all-months) compared to CO or NO_2. SO_2 was not associated with post-BD FEV_1 and FVC %predicted.

The city-wide estimates of the meta-analysis were similar to the estimates given by the model with adjustment for city and city by sine/cosine function of time interactions. Table E4 shows the city-specific and meta-analysis estimates for long-term exposures. Meta-analysis estimates of associations of post-BD FEV_1 and FVC %predicted with the 4-month average gas concentrations are comparable to all-cities model estimates in Figure 1.

Table E5 presents the associations of pollution with pre-BD FEV_1 (and FVC %predicted. Increases in the average CO levels in the 4-months prior to and including the day of the visit were associated with significant decreases in pre-BD FEV_1 (change(95%CI) per IQR: −0.4 (−0.62; −0.10) and FVC (change(95%CI) per IQR: −0.2 (−0.42, −0.01) %predicted. In contrast, compared to their associations with post-BD FEV_1, same day and 1-week averages had associations with pre-BD FEV_1 (change(95%CI) per IQR: −0.13(−0.29;0.02), −0.2(0.39,0)) and FVC (change(95%CI) per IQR: −0.12 (−0.24, 0.003), −0.15 (−0.30, 0.01)) %predicted that were the same order of magnitude, but somewhat smaller and somewhat weaker in significance. Increases in the NO_2 exposures were not associated with reduced pre-BD FEV_1 and FVC %predicted. Increase in 4-month SO_2 was associated with increases in pre-BD FVC %predicted (change(95%CI) per IQR: 0.23 (0.05,0.42).

Associations of long-term (4-month average) exposure with FEV_1/FVC% are shown in Figure 2. Reduced post-BD FEV_1/FVC was associated with increased 4-month averages of ozone and CO, but not with NO_2 or SO2 (change (95%CI) per IQR pollution increase: −0.4(−0.8,−0.1), −0.2(−0.3,−0.03), 0.03(−0.1,0.1), 0.03(−0.1,0.1), respectively). Similar associations were found with pre-BD FEV_1/FVC% (change(95%CI) per IQR: −0.3(−0.7,0.06), −0.2(−0.3,−0.02), −0.03(−0.1,0.1), −0.01(−0.1,0.1), respectively).

There was weak evidence of modification by treatment of pollution effect on lung function (Figure 3). Although there were differences in the magnitude of long-term pollution effect between placebo and budesonide or placebo and nedocromil (p-values for interactions ranging from 0.03 to 0.50), the overall likelihood ratio tests were not significant (ANOVA p>0.05; tables E6-E9 in the online repository).

Association of pollution with PC_{20}

Overall, the only pollutant that was significantly associated with PC_{20} was the 4-month average SO_2 level (%change (95%CI) per IQR: −6(−11,−1.5)). CO had a marginal overall effect on PC_{20} for all averaging periods (Figure 4). Compared to children on placebo, children on budesonide and nedocromil had a greater drop in PC_{20} with same day and 1-week average exposures to CO (ANOVA p= 0.04 and 0.08, respectively). This was more prominent for nedocromil. Treatment did not modify associations of $SO_2$with PC_{20}. Tables E10 and E11 in the online repository show the associations for all pollutants with PC_{20} and the results of interactions with treatment.

Associations of asthma outcomes with warm-month (May – September) ozone were not statistically significant (Table E12 in the online repository). Two-pollutant models showed similar pollutant-asthma outcomes associations as one-pollutant models (Table E13 in the online repository).

In our study, CO was the pollutant with the strongest and most significant associations with lung function and the only pollutant showing associations with both pre- and post-BD lung function with shorter (same day to 1-week)- and longer (4-month)-term exposures (Figure 1, and Table E5). Thus to evaluate whether the longer-term effects were independent of shorter-term effects we put either one-day or one-week averages in the same model with 4-month averages of CO. Since the same-day and 1-week average measurements are included in the original 4-month average estimate, this added to the correlation amongst the measures and introduced co-linearity into our model. To disentangle the shorter- and longer-term averages and their associations with our outcomes, we performed an additional analyses with newly created 4-month averages (ie., calculating the 4-month average leaving out the same day measurements, and calculating the 4-month average leaving out the 1-week average), adjusting for same day and 1-week average CO, respectively. The associations with pre-BD and post-BD lung function from models with single averaging periods, compared to those with shorter (one day or one week) plus longer (4-month) averaging periods are shown in Tables III and IV.

Discussion

Short-term adverse effects of pollution on children's pulmonary health have been extensively studied, meta-analyzed, and systematically reviewed. These studies provide strong evidence that short-term exposures to air pollution can increase airflow obstruction in asthmatic and non-asthmatic children,[20] and that long-term traffic pollution may increase incident asthma and reduce level of lung function in general populations of children.[2,21-24] There are fewer studies considering the effects of long-term exposures to pollution on lung function in asthmatic children,[1,2,20] and none that we know of evaluating long-term effects of pollution on lung function and AHR in asthmatic children in the context of a clinical trial.

In this unique asthma intervention trial, increases in the average long-term (4-month) concentrations of ozone, CO and NO_2 were all associated with reductions in lung function levels consistent with airflow obstruction, and with some decrease in vital capacity

represented by a drop in FVC. There are few air pollution studies including post-BD measurements with which to compare our findings. A recent study of subjects from the Manchester Asthma and Allergy Study (MAAS) birth cohort showed greater long-term pollution (NO_2 and PM_{10}) effect on post-BD FEV_1 %predicted compared to pre-BD FEV_1 %predicted.[25] Their findings motivated the hypothesis that the bronchodilator administration might reduce the influence of varying circadian and day-to-day bronchodilator tone on the measurement of FEV_1, potentially increasing the power of the study to show pollution influences on lung function. In our study, this may have been the case for shorter-term but not for longer-term cumulative averages of pollution exposure. Focusing on FEV_1 as an outcome, with one week and 4-month cumulative averages of CO in the same model, longer-term CO exposure was more consistently associated with lower pre-BD FEV_1 %predicted, and short-term CO exposure was more strongly/more consistently associated with lower post-BD lung function measures. Additional unmeasured short-term influences on pre-BD responses that were reversible by bronchodilator administration may have added noise and contributed to the variability in the pre-BD measurement, and this may have resulted in somewhat less robust associations of pollution exposures in the past week with pre-BD FEV_1. .

The within-subject variation of gaseous pollutants in our asthma trial was low (i.e., same day CO IQR=0.50 ppm), and while effects were statistically significant ($P<0.001$), given their small magnitude (for every 0.5 ppm increase in the same day CO concentration, there is a ~0.3 decrease in the average post-BD FEV_1 %predicted, which would be equivalent to a patient dropping from 103.0 to 102.7 average FEV_1 %predicted post-BD over a 4-year follow up), the lung function responses to pollution may not have short-term clinical relevance. Whether the small pollution-related changes in lung function that we observed have longer-term implications for lung growth and maximum attained lung function in these vulnerable asthmatic children remains to be assessed.

One study in adult asthmatics has reported associations of reduced lung function with short-term exposures to CO, but the mechanisms for this association is not known.[26] Endogenous hypoxic-induced CO is a mediator of vasodilation and bronchodilation and high doses of inhaled CO in mice decrease inflammation and AHR.[27-33] Exogenous CO at levels encountered by children in our cohort did not have beneficial effects.

Motor vehicles emissions are major sources of CO. These source produces many contaminants - such as fine particles and organic compounds - thus in this case it is likely that CO is a surrogate for other pollutants,[2,34,35] and that the observed associations might not be due to CO per se, but due to other pollutants in traffic emission mixtures. Similarly, NO_2 may be a marker for complex pollutant mixtures of pollutants emitted by the same sources or related through complex atmospheric reactions. Primary traffic-related pollutants such as elemental/black carbon or freshly emitted primary particles and secondary pollutants, including ozone, are often correlated with NO_2.[2,34,35] In the present study, air pollutant levels were correlated such that it was difficult to separate out the contributions of the individual pollutants. All effects estimates on asthma outcomes remained significant after controlling for co-pollutants/gases in multi-pollutant models.

Sarnat et al.[35] showed relatively strong associations of personal exposure of particles of ambient origin and ambient measurements, but considerably lower associations for gases. In particular, NO_2 primarily from traffic emissions, was more strongly associated with personal exposure to traffic particles. This suggests that ambient gases from traffic are associated with personal exposure to particles, and perhaps other compounds from traffic. Since CO is an antioxidant in the lung and not a plausible pollutant to reduce lung function we interpret it as a surrogate for particles and perhaps organic gases from traffic. The two pollutants associated with traffic sources—CO and NO_2—were most strongly and consistently associated with reduced level of lung function and more severe hyperresponsiveness in our children with asthma. Those were the same pollutants that influenced asthma exacerbations (i.e., more symptoms and use of relief medication) pre-randomization in this CAMP trial.[6] However, SO_2 which originates predominately from diesel combustion (diesel fuel content of sulfur was higher during 1990's) and non-traffic fossil fuels (e.g., coal burning power plants and domestic heating), was also associated with enhanced response to metacholine long-term. Most studies investigating the latter association are based on short-term exposures to diesel and they have shown that air pollution may enhance the responsiveness to metacholine as well as to inhaled allergens in sensitized subjects.[36-39] One animal study has suggested an increase in AHR with long-term sulfur dioxide exposure, supporting our findings for this pollutant.[40] However, our study is unique in the investigation of AHR and its relation with short-term as well as long-term in asthmatic children.

We also found a positive association of long-term exposure to SO_2 with pre-BD FVC. Again, experimental and epidemiological studies investigating lung function response to SO_2 focus on acute responses and this makes them difficult to be compared with our finding. Most epidemiologic findings show modest negative or null association of SO_2 with lung function.[41-43] Generally, it is suggested that after acute exposure to SO_2 the lung function returns to normal after some minutes to hours and that there is a great deal of inter-individual variation in response to SO_2.[44-46]

Ozone is the most important tropospheric oxidant which is formed through photochemical reactions involving NO_2 and hydrocarbons. Cumulative exposure is a function of both the rate and duration of exposure and it has been shown that effects of pollution on children's health have greater impact if the children exercise outdoors.[47-50] We also show that longer exposure to ozone is associated with airflow obstruction, indicated by decrease in FEV_1/FVC with increase in 4-month average ozone concentration. Ozone and other air pollutants initiate intracellular oxidative stress and are linked to chronic damage and effects on to the human lung with prolonged exposure.[51-53] The decrease in post-BD FEV_1/FVC may reflect airway wall remodeling process related to repeated exposures to ozone and other pollutants.[54] For ozone, associations of reduced lung function with pollution also tended to be stronger for children on budesonide compared to placebo. The latter suggests a less clear relationship between exposure to ozone and airway inflammation. Two recent studies have suggested that children on ICS were more vulnerable to the adverse effects of ozone and other air pollutants.[13,14] The authors speculated that the observed associations might be explained by the fact that children on ICS are more likely to have worse asthma and that confounding by indication might exist. The design of our trial prevents confounding by indication because of the double-blinded randomized distribution of treatment to children of

similar asthma severity. Although the evidence for the interaction of ICS treatment on ozone mediated effects is weak, it is plausible that the children on the ICS had greater exposure to ozone compared to placebo, either because they were more likely to spend more time outside and exercise more due to better control of their asthma,[15,18] or because they had greater minute ventilation because they were able to breathe more deeply when exercising.

In our study, modification of CO effects on AHR by anti-inflammatory treatment suggests that use of controller medication may not protect asthmatic children from pollutant effects. The worsening of AHR with short-term exposure to CO was stronger for children on budesonide and nedocromil compared to placebo, a finding that needs further investigation. Nevertheless, a public health interpretation of this finding is that controller medication use should not be assumed to be sufficient as a preventive measure on days with high pollution levels. Policy for pollution control and advice[55] to asthmatic children to avoid outdoor activities on days of high pollution levels remain the most powerful preventive measure.

The present report provides a unique contribution in that it can be considered a meta-analysis of eight large, within-city panel studies. Yet, it does not suffer from many of the challenges associated with meta-analyses in the published literature (e.g., between-study heterogeneity and obvious publication bias). The large and geographically diverse panel of children participating in CAMP trial was followed from December 1993 to June 1999, on average for 4 years. This allowed us to examine the health effects of ambient concentrations of CO, NO_2, SO_2 and ozone across seasons and geographic regions and results from this study may be applicable to a broad population.

Many studies investigating the long-term effects of pollution have focused on traffic-related exposures and used surrogate measures such as distance to major roads, road density or vehicle density.[2,20,21,23,56,57] In this study we measured daily pollutant concentrations to predict long-term (4-month (but also acute (same day) and intermediate (1-week)) effects on asthma severity in children. We acknowledge that exposure is at the zip/postal code rather than the residence level. However, we limited exposure misclassification bias in two ways: 1) by using zip/postal code level concentrations of pollution instead of averaging monitor-specific concentrations by city; and 2) by restricting the period of interested to the period of the trial for which the great majority of the participants attended all visits. In addition, we investigated pollutants that tend to be regional and we also focus on long-term exposure which is less prone to misclassification. Recent evidence supports the value of further investigating, where feasible, whether pollution effects vary by gender.[58] Unfortunately, this is outside of the scope of our manuscript and we lack sufficient power for assessment of a three-way interaction (pollution by treatment group by gender).

We conclude that exposure to gaseous pollutants adversely influences level of lung function and AHR in asthmatic children, and treatment use worsens the short-term effects of CO on AHR. The longitudinal evaluation of children treated with daily asthma therapy in a clinical trial enabled us to separate the modification of pollution effects by treatment without confounding by indication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We dedicate this manuscript to the memory of our friend and colleague Dr. Gail G. Shapiro who passed away unexpectedly during the development of this study. Dr. Shapiro dedicated her life to understanding the causes of childhood asthma and determining the best treatments for asthma. She is deeply missed by her colleagues, patients, and the asthma community.

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Abbreviations

AHR	airway responsiveness
BD	bronchodilator
CAMP	Childhood Asthma Management Program
CO	Carbon monoxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICS	Inhaled corticosteroids
IQR	Interquartile range
NO_2	Nitrogen dioxide
PC_{20}	Metacholine concentration causing a 20% reduction in FEV_1
RZ	Randomization
SD	Standard deviation
SO_2	Sulfur dioxide

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Clinical Implications

Exposure to gaseous pollutants adversely influences lung function and airway hyperresponsiveness levels in asthmatic children. Anti-inflammatory treatment use may worsen the negative short-term effects of some pollutants on airway hyperresponsiveness.

Capsule Summary

Gaseous pollutants adversely influence lung function and airway hyperresponsiveness.

The longitudinal evaluation of children on daily asthma therapy in a clinical trial enabled us to separate the modification of pollution effects by treatment without confounding by indication.

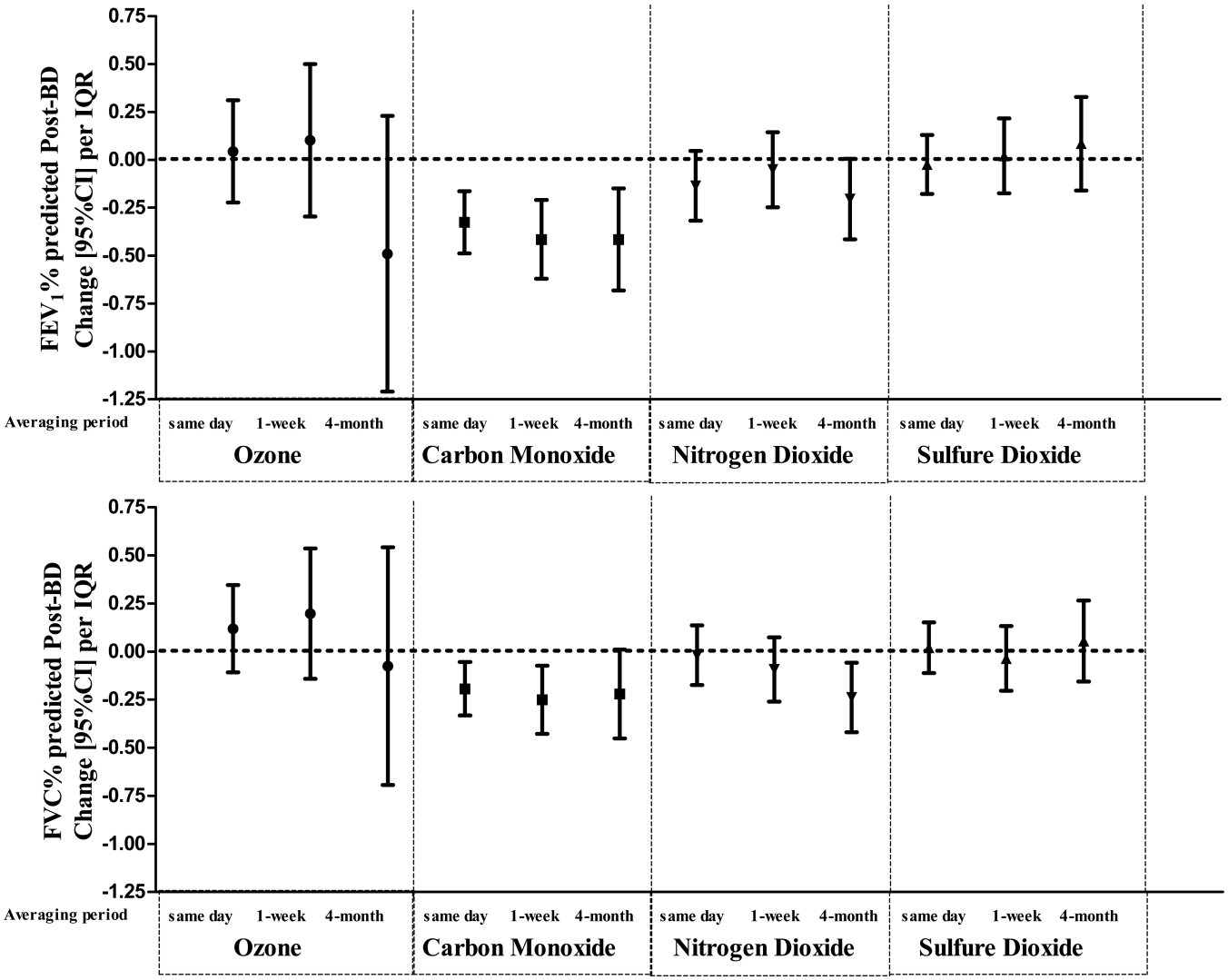

Figure 1.

Same day and 1-week and 4-month moving averages of carbon monoxide and 4-month average of nitrogen dioxide had negative associations with post-BD FEV_1 (top graphs panel) and FVC (bottom graphs panel). The evidence for adverse effects on post-BD lung function seems weak for 4-month average exposure to ozone (all-months) compared to the traffic pollutants and there were not associations with sulfur dioxide.

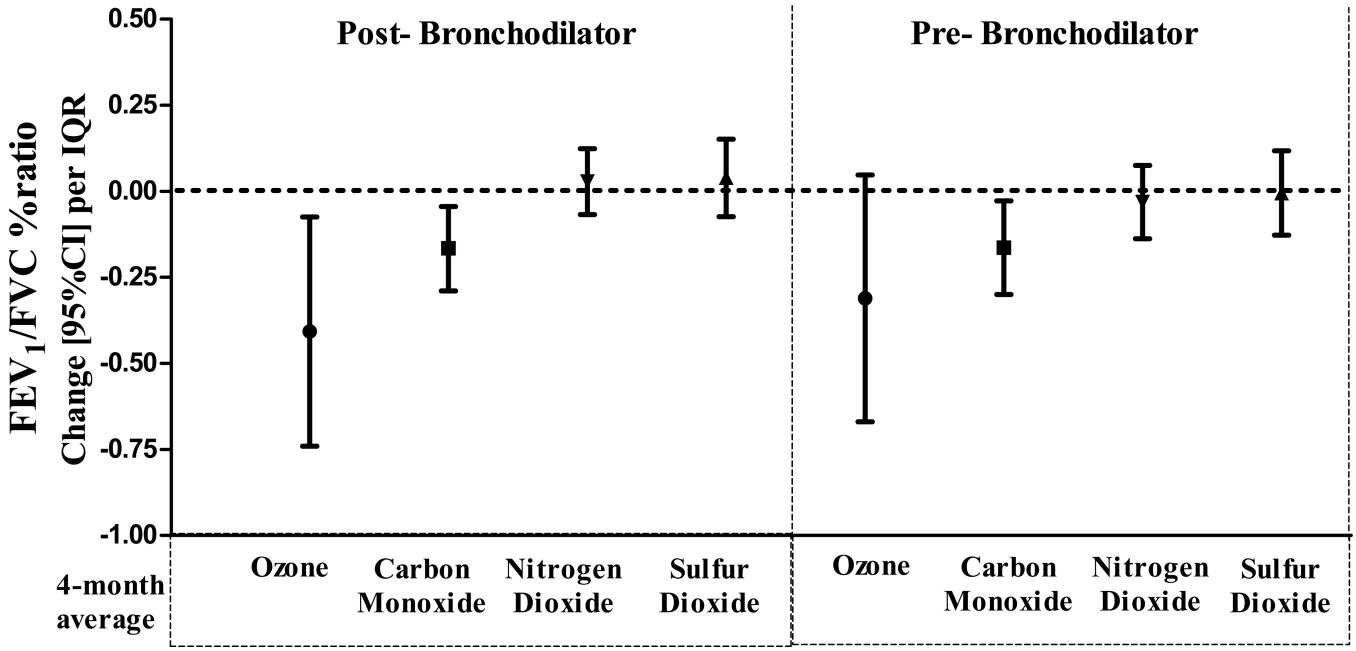

Figure 2.

Reduced post-bronchodilator (BD) FEV_1 /FVC (left graph panel) was associated with 4-month averages of ozone and carbon monoxide, but not with nitrogen dioxide or sulfur dioxide. Carbon monoxide also associated with pre-BD ratio (right graph panel).

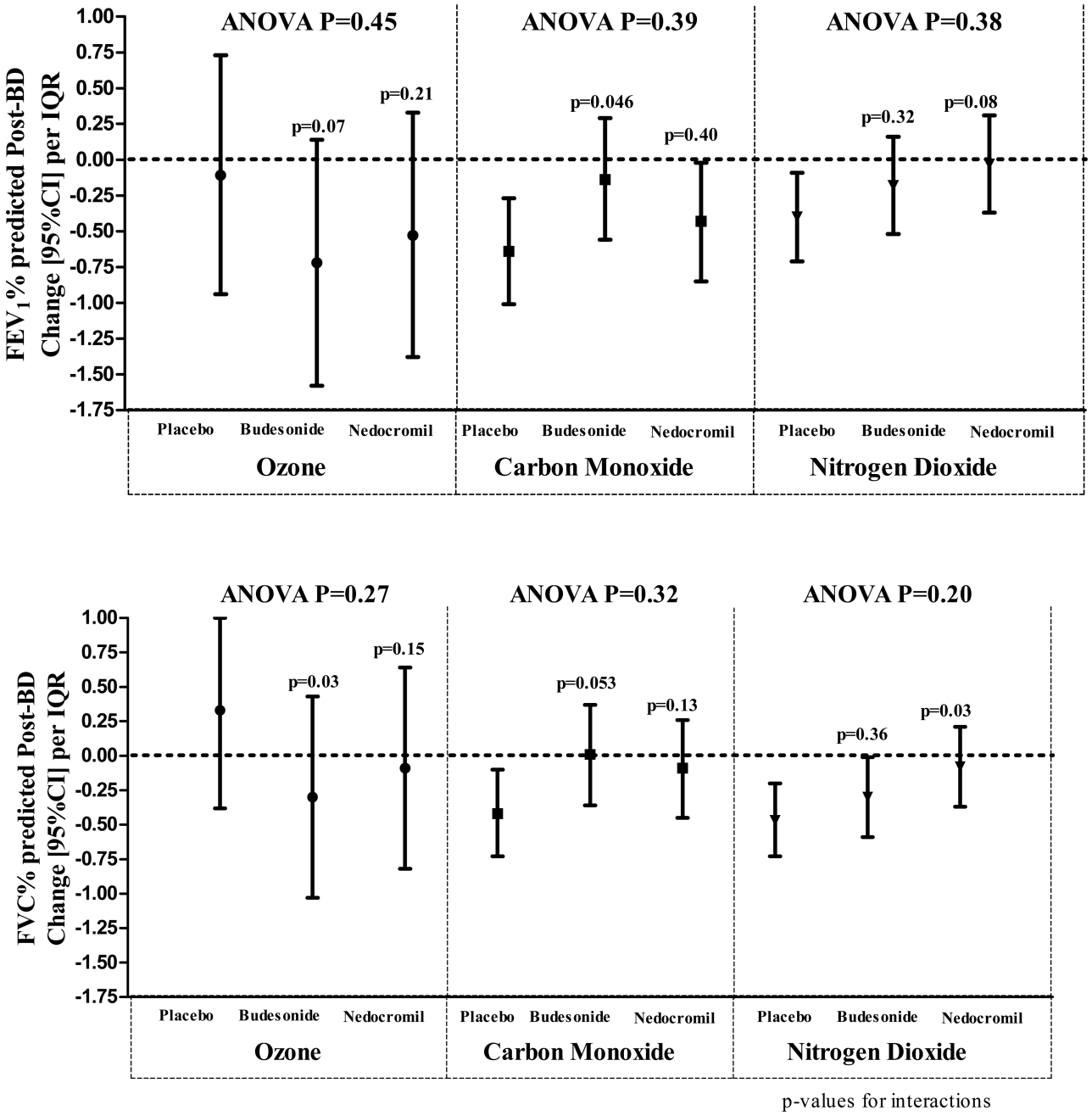

Figure 3.

shows long-term (4-month moving average) pollution effect modification by treatment. Although there were differences in the magnitude of long-term pollution effect between placebo and budesonide or placebo and nedocromil (p-values for interactions), the overall likelihood ratio tests (ANOVA) were not significant.

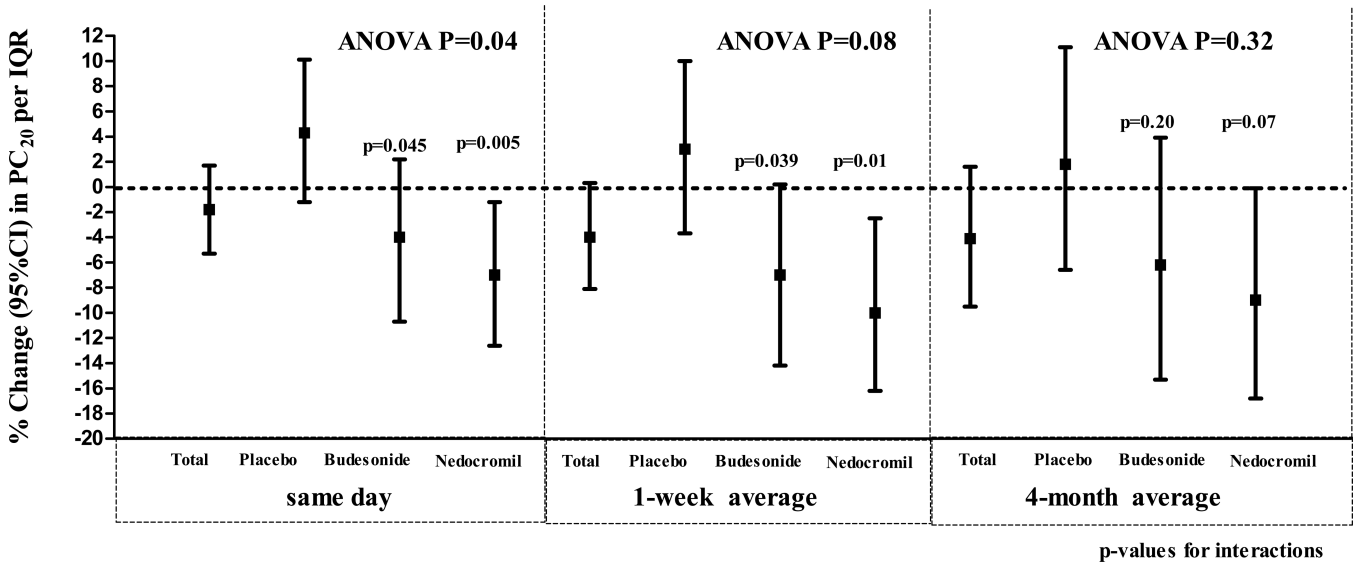

Figure 4.

Carbon monoxide had a marginal overall effect on PC_{20} for all averaging periods. Compared to children on placebo, children on budesonide and nedocromil had a greater drop in PC_{20} with same day (left graph panel) and 1-week (middle graph panel) average exposures to carbon monoxide (ANOVA p= 0.04 and 0.08, respectively).

Table I

Demographic characteristics

N= 1003	
City; n (%)	
Albuquerque	121 (12.1)
Baltimore	126 (12.6)
Boston	123 (12.3)
Denver	141 (14.1)
San Diego	122 (12.2)
Seattle	136 (13.6)
Saint Louis	133 (13.3)
Toronto	101 (10.1)
Sex; n (%)	
Males/Females	602/401 (60/40)
Treatment Group; n (%)	
Placebo	407 (40.6)
Budesonide	298 (29.7)
Nedocromil	298 (29.7)
Ethnicity; n (%)	
Caucasians	677 (67.5)
African-Americans	137 (13.7)
Hispanics	97 (9.7)
Other	92 (9.2)
$Annual Income =>30K USD; n (%)	
Yes/No	728/235 (76/24)
In utero smoking exposure; n (%)	
Yes/No	114/854 (14/86)
Pre bronchodilator lung function at randomization; mean (SD)	
FEV_1 % predicted	**93.8 (14.3)**
FVC % predicted	**104.0 (13.1)**
FEV_1/FVC %	**79.7 (8.3)**
Post bronchodilator lung function at randomization; mean (SD)	
FEV_1 % predicted	103.0 (12.8)
FVC % predicted	106.5 (12.8)
FEV_1/FVC %	85.5 (6.5)

FEV_1 : forced expiratory volume in 1 second; FVC: forced vital capacity; SD: standard deviation

$ =>30K USD: equal or more than 30,000 United State Dollars at baseline (1993-1995)

Table II

Distribution of 24-hour mean pollution concentrations by city

Pollutant	City	N		Percentiles					IQR
		Valid	Missing	10	25	50	75	90	
O_3 (ppb)	**ALB**	1336	358	13	19	28	36	43	17
	BAL	1703	61	7	13	23	33	43	20
	BOS	1660	62	7	13	21	30	38	17
	DEN	1669	305	6	13	23	32	41	19
	SD	1664	44	13	20	27	35	41	15
	SEA	1071	833	7	11	17	22	28	11
	STL	1667	195	7	12	22	32	41	20
	TOR	1350	64	6	10	17	25	33	14
	TOTAL	**12120**	**1922**	**8**	**14**	**22**	**31**	**39**	**18**
CO (ppm×10)	**ALB**	1343	351	1	3	7	11	14	8
	BAL	1719	45	3	5	7	11	15	6
	BOS	1660	62	6	8	10	13	16	5
	DEN	1684	290	4	5	8	12	17	7
	SD	1664	44	4	5	8	11	17	6
	SEA	1701	203	7	10	14	19	25	9
	STL	1684	178	4	5	7	9	12	4
	TOR	1350	64	2	6	10	12	15	6
	TOTAL	**12805**	**1237**	**4**	**6**	**9**	**12**	**16**	**6**
NO_2 (ppb)	**ALB**	1307	387	7	11	17	23	30	12
	BAL	1719	45	14	18	24	29	36	11
	BOS	1660	62	14	20	25	32	38	12
	DEN	1577	397	10	20	29	36	44	17
	SD	1664	44	10	13	19	26	34	13
	SEA	1255	649	11	15	19	24	30	9
	STL	1707	155	8	13	18	24	28	11
	TOR	1350	64	13	19	25	32	39	13
	TOTAL	**12239**	**1803**	**11**	**16**	**22**	**28**	**35**	**13**
SO_2 (ppb)	**ALB**	25	1669	0	0	4	16	24	16
	BAL	1719	45	2	4	6	9	14	6
	BOS	1660	62	2	3	5	9	13	5
	DEN	1571	403	1	2	4	7	10	4
	SD	1454	254	1	2	2	3	5	1
	SEA	1752	152	2	3	5	7	10	4
	STL	1736	126	1	3	5	9	13	6
	TOR	1347	67	0	2	4	6	9	4
	TOTAL	**11264**	**2778**	**1**	**2**	**4**	**8**	**12**	**5**

ALB: Albuquerque, BAL: Baltimore, BOS: Boston, DEN: Denver, SD: San Diego, SEA: Seattle, STL: Saint Louis, TOR: Toronto, O_3: ozone (ppb); CO: carbon monoxide (ppm × 10); NO_2: nitrogen dioxide (ppb); SO_2: sulfur dioxide (ppb); N: number of observations; IQR: interquartile range, ppb: part per billion; ppm: parts per million

Table III

Associations of carbon monoxide with FEV_1 % predicted: models with single averaging periods are compared to models combining shorter (one day or one week) and longer (4-month) averaging periods

Carbon Monoxide	IQR (ppm ×10)	Pre bronchodilator FEV_1 % predicted				
		MODEL 1 Change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 3 change (95%CI) per IQR P-value	MODEL 4 change (95%CI) per IQR P-value	MODEL 5 change (95%CI) per IQR P-value
Same day	**5**	−0.13 (−0.29, 0.02) P=0.09			−0.08 (−0.24, 0.08) P=0.310	
1 week average	**4**		−0.19 (−0.39, 0.001) P=0.05			−0.12 (−0.33, 0.09) P=0.269
4 month average	**3**			−0.36 (−0.62, −0.10) P=0.006		
4 month average excluding same day	**3**				−0.33 (−0.59, −0.06) P=0.016	
4 month average excluding 1 week	**3**					−0.29 (−0.56,−0.02) P=0.037

Carbon Monoxide	IQR (ppm ×10)	Post bronchodilator FEV_1 %predicted				
		MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value
Same day	**5**	−0.33 (−0.49, −0.16) P<0.001			−0.28 (−0.45, −0.11) P=0.001	
1 week average	**4**		−0.41 (−0.62, −0.21) P<0.001			−0.36 (−0.58, −0.14) P=0.002
4 month average	**3**			−0.42 (−0.68, −0.15) P=0.002		
4 month average excluding same day	**3**				−0.29 (−0.56, −0.01) P=0.043	
4 month average excluding 1 week	**3**					−0.20 (−0.4, 0.08) P=0.17

FEV_1: forced expiratory volume in 1 second, IQR: interquartile range, ppm: parts per million, CI: confidence interval

Table IV

Associations of carbon monoxide with FVC % predicted: models with single averaging periods are compared to models combining shorter (one day or one week) and longer (4-month) averaging periods

Carbon Monoxide	IQR (ppm ×10)	Pre bronchodilator FVC % predicted				
		MODEL 1 Change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 3 change (95%CI) per IQR P-value	MODEL 4 change (95%CI) per IQR P-value	MODEL 5 change (95%CI) per IQR P-value
Same day	**5**	−0.12 (−0.24, 0.0) P=0.054			−0.09 (−0.22,0.03) P=0.142	−0.11 (−0.27, 0.06) P=0.15
1 week average	**4**		−0.15 (−0.3, 0.01) P=0.06			
4 month average	**3**			−0.21 (−0.42, −0.01) P=0.042		
4 month average excluding same day	**3**				− 0.17 (−0.39, 0.04) P=0.108	
4 month average excluding 1 week	**3**					−0.15 (−0.37, −0.07) P=0.180

Carbon Monoxide	IQR (ppm ×10)	Post bronchodilator FVC % predicted				
		MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value	MODEL 2 change (95%CI) per IQR P-value
Same day	**5**	−0.19 (−0.33, −0.05) P=0.006			−0.17 (−0.32, −0.03) P=0.02	
1 week average	**4**		−0.25 (−0.43, −0.07) P=0.006			−0.23 (−0.42, −0.04) P=0.019
4 month average	**3**			−0.22 (−0.45, 0.01) P=0.061		
4 month average excluding same day	**3**				−0.14 (−0.38, 0.10) P=0.244	
4 month average excluding 1 week	**3**					−0.09 (−0.33, 0.16) P=0.49

FVC: forced vital capacity, IQR: interquartile range, ppm: parts per million, CI: confidence interval