

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 (PC₂₀) 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 FEV₁ and forced vital capacity (FVC) percent predicted, FEV₁/FVC ratio, and PC₂₀, adjusting for seasonality and confounders.

Results: Same-day and 1-week average CO concentrations were negatively associated with postbronchodilator percent predicted FEV₁ (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 FEV₁ 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 FEV₁/FVC ratio ($P < .05$). Increased 4-month average nitrogen dioxide concentrations were associated with reduced postbronchodilator FEV₁ and FVC percent predicted. Long-term exposures to sulfur dioxide were associated with reduced PC₂₀ (percent change per interquartile range, -6% [95% CI, -11% to -1.5%]). Treatment augmented the negative short-term CO effect on PC₂₀. **Conclusions:** Air pollution adversely influences lung function and PC₂₀ in asthmatic children. Treatment with controller medications might not protect but rather worsens the effects of CO on PC₂₀. This clinical trial design evaluates modification of pollution effects by treatment without confounding by indication. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

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
 NO₂: Nitrogen dioxide
 SO₂: 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 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 (CO) and nitrogen dioxide (NO₂) 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, NO₂, and sulfur dioxide [SO₂]) 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 FEV₁ 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 FEV₁/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 FEV₁ had decreased by 20% or more (PC₂₀).

Air pollution exposure assessment

Monitoring data on 24-hour average concentrations of 4 gaseous pollutants (ozone, CO, NO₂, and SO₂) 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 (FEV₁ and FVC percent predicted and FEV₁/FVC ratio percentage) and (log-transformed) PC₂₀ 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 time¹⁹ 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 PC₂₀ 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).

TABLE I. Demographic characteristics (n = 1003)

City, no. (%)	
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)
St Louis	133 (13.3)
Toronto	101 (10.1)
Sex, no. (%)	
Male/female	602/401 (60/40)
Treatment group, no. (%)	
Placebo	407 (40.6)
Budesonide	298 (29.7)
Nedocromil	298 (29.7)
Ethnicity, no. (%)	
White	677 (67.5)
African American	137 (13.7)
Hispanic	97 (9.7)
Other	92 (9.2)
Annual income* $\geq$ \$30,000, no. (%)	
Yes/no	728/235 (76/24)
In utero smoking exposure, no. (%)	
Yes/no	114/854 (14/86)
Prebronchodilator lung function at randomization, mean (SD)	
FEV ₁ (% predicted)	93.8 (14.3)
FVC (% predicted)	104.0 (13.1)
FEV ₁ /FVC ratio (%)	79.7 (8.3)
Postbronchodilator lung function at randomization, mean (SD)	
FEV ₁ (% predicted)	103.0 (12.8)
FVC (% predicted)	106.5 (12.8)
FEV ₁ /FVC ratio (%)	85.5 (6.5)

*At baseline (1993-1995).

Participants had a median of 14 (range, 1-14) prebronchodilator and 10 (range, 1-10) postbronchodilator lung function measurements and 4 (range, 0-4) PC₂₀ tests.

Pollution concentrations during December 1993 to June 1999 are summarized by city and overall in Table II. We report the number of observations, percentiles, and IQRs of daily concentrations of the 4 pollutants. Table E1 in this article's Online Repository at www.jacionline.org shows the IQR of the overall and the within-subject pollutant concentrations.

Correlations of 24-hour mean pollution concentrations are shown in Table E2 in this article's Online Repository at www.jacionline.org. Overall, ozone concentrations were negatively correlated with those of the other 3 pollutants, which were positively correlated with each other. The same pattern of correlation existed in the 8 separate cities (data are shown in Table E3 in this article's Online Repository at www.jacionline.org). 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 lung function

Fig 1 presents the associations of pollution concentrations with postbronchodilator FEV₁ and FVC percent predicted. Same-day and 1-week and 4-month moving CO averages had the most consistent negative associations with percent predicted postbronchodilator FEV₁ (change per IQR, -0.3 [95% CI, -0.5 to -0.2], -0.4 [95% CI, -0.6 to -0.2], and -0.6 [95% CI, -0.7 to -0.1],

TABLE II. Distribution of 24-hour mean pollution concentrations by city and overall

Pollutant	City	No.		Percentiles					
		Valid	Missing	10th	25th	50th	75th	90th	IQR
Ozone (ppb)	ALB	1,336	358	13	19	28	36	43	17
	BAL	1,703	61	7	13	23	33	43	20
	BOS	1,660	62	7	13	21	30	38	17
	DEN	1,669	305	6	13	23	32	41	19
	SD	1,664	44	13	20	27	35	41	15
	SEA	1,071	833	7	11	17	22	28	11
	STL	1,667	195	7	12	22	32	41	20
	TOR	1,350	64	6	10	17	25	33	14
Total		12,120	1,922	8	14	22	31	39	18
CO (ppm $\times$ 10)	ALB	1,343	351	1	3	7	11	14	8
	BAL	1,719	45	3	5	7	11	15	6
	BOS	1,660	62	6	8	10	13	16	5
	DEN	1,684	290	4	5	8	12	17	7
	SD	1,664	44	4	5	8	11	17	6
	SEA	1,701	203	7	10	14	19	25	9
	STL	1,684	178	4	5	7	9	12	4
	TOR	1,350	64	2	6	10	12	15	6
Total		12,805	1,237	4	6	9	12	16	6
NO ₂ (ppb)	ALB	1,307	387	7	11	17	23	30	12
	BAL	1,719	45	14	18	24	29	36	11
	BOS	1,660	62	14	20	25	32	38	12
	DEN	1,577	397	10	20	29	36	44	17
	SD	1,664	44	10	13	19	26	34	13
	SEA	1,255	649	11	15	19	24	30	9
	STL	1,707	155	8	13	18	24	28	11
	TOR	1,350	64	13	19	25	32	39	13
Total		12,239	1,803	11	16	22	28	35	13
SO ₂ (ppb)	ALB	25	1,669	0	0	4	16	24	16
	BAL	1,719	45	2	4	6	9	14	6
	BOS	1,660	62	2	3	5	9	13	5
	DEN	1,571	403	1	2	4	7	10	4
	SD	1,454	254	1	2	2	3	5	1
	SEA	1,752	152	2	3	5	7	10	4
	STL	1,736	126	1	3	5	9	13	6
	TOR	1,347	67	0	2	4	6	9	4
Total		11,264	2,778	1	2	4	8	12	5

ALB, Albuquerque; BAL, Baltimore; BOS, Boston; DEN, Denver; SD, San Diego; SEA, Seattle; STL, St Louis; TOR, Toronto.

respectively) and FVC (change per IQR, -0.2 [95% CI, -0.3 to -0.1], -0.3 [95% CI, -0.4 to -0.1], and -0.2 [95% CI, -0.4 to -0.01], respectively). The 4-month average NO₂ concentration was also negatively associated with postbronchodilator FEV₁ and FVC percent predicted (change per IQR, -0.2 [95% CI, -0.4 to 0.01] and -0.2 [95% CI, -0.4 to -0.1], respectively). The evidence for negative effects on postbronchodilator lung function was weaker for 4-month average exposure to ozone (all months) compared with CO or NO₂. SO₂ concentrations were not associated with postbronchodilator FEV₁ and FVC percent 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 in this article's Online Repository at www.jacionline.org shows the city-specific and meta-analysis estimates for long-term exposures. Meta-analysis estimates of associations of postbronchodilator FEV₁ and FVC percent predicted with the 4-month average gas concentrations are comparable with all-cities model estimates in Fig 1.

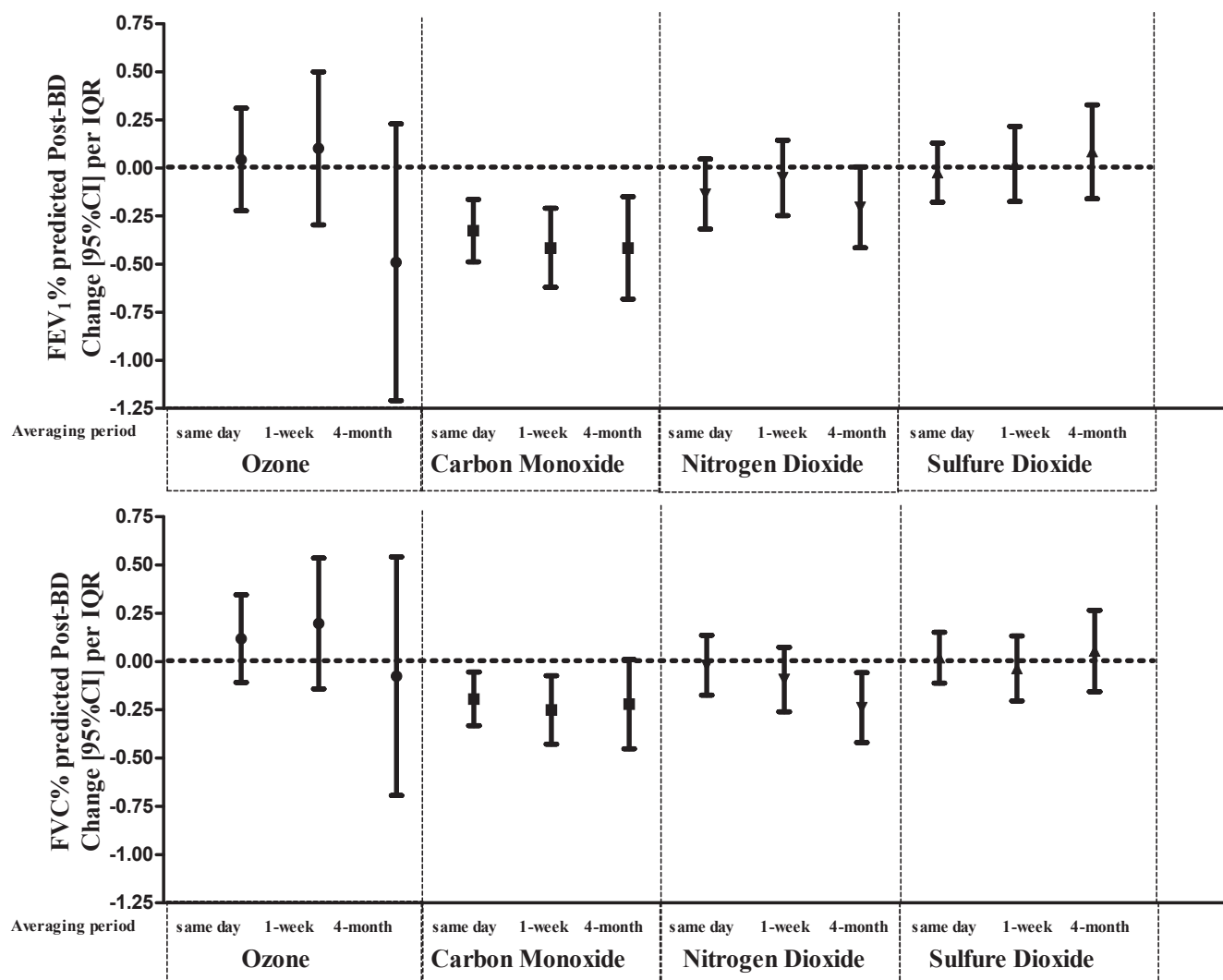


FIG 1. Same-day, 1-week, and 4-month moving averages of CO concentrations and 4-month average of NO₂ concentrations had negative associations with postbronchodilator FEV₁ (top) and FVC (bottom). The evidence for adverse effects on postbronchodilator lung function seems weak for 4-month average exposure to ozone (all months) compared with the traffic pollutants and there were not associations with SO₂. BD, Bronchodilator.

Table E5 in this article's Online Repository at www.jacionline.org presents the associations of pollution with prebronchodilator FEV₁ and FVC percent predicted. Increases in average CO concentrations in the 4 months before the visit and including the day of the visit were associated with significant decreases in prebronchodilator FEV₁ (change per IQR, -0.4 [95% CI, -0.62 to -0.10]) and FVC (change per IQR, -0.2 [95% CI, -0.42 to -0.01]) percent predicted. In contrast, compared with their associations with postbronchodilator FEV₁, same-day and 1-week averages had associations with prebronchodilator FEV₁ (change per IQR, -0.13 [95% CI, -0.29 to 0.02] and -0.2 [95% CI, 0.39 to 0]) and FVC (change per IQR, -0.12 [95% CI, -0.24 to 0.003] and -0.15 [95% CI, -0.30 to 0.01]) percent predicted that were the same order of magnitude but somewhat smaller and somewhat weaker in significance. Increases in NO₂ exposures were not associated with reduced prebronchodilator FEV₁ and FVC percent predicted. Increases in 4-month SO₂ concentrations was associated with increases in prebronchodilator FVC percent predicted (change per IQR, 0.23 [95% CI, 0.05-0.42]).

Associations of long-term (4-month average) exposure with FEV₁/FVC ratio percentage are shown in Fig 2. Reduced post-bronchodilator FEV₁/FVC ratio was associated with increased 4-month averages of ozone and CO concentrations but not with NO₂ or SO₂ concentrations (change per IQR pollution increase, -0.4 [95% CI, -0.8 to -0.1], -0.2 [95% CI, -0.3 to -0.03], 0.03 [95% CI, -0.1 to 0.1], and 0.03 [95% CI, -0.1 to 0.1], respectively). Similar associations were found with prebronchodilator FEV₁/FVC ratio percentage (change per IQR, -0.3 [95% CI, -0.7 to 0.06], -0.2 [95% CI, -0.3 to -0.02], -0.03 [95% CI, -0.1 to 0.1], and -0.01 [95% CI, -0.1 to 0.1], respectively).

There was weak evidence of modification by treatment of pollution effect on lung function (Fig 3). Although there were differences in the magnitude of the long-term pollution effect between placebo and budesonide or placebo and nedocromil (*P* values for interactions ranging from .03 to .50), the overall likelihood ratio test results were not significant (*P* > .05, ANOVA; see Tables E6-E9 in this article's Online Repository at www.jacionline.org).

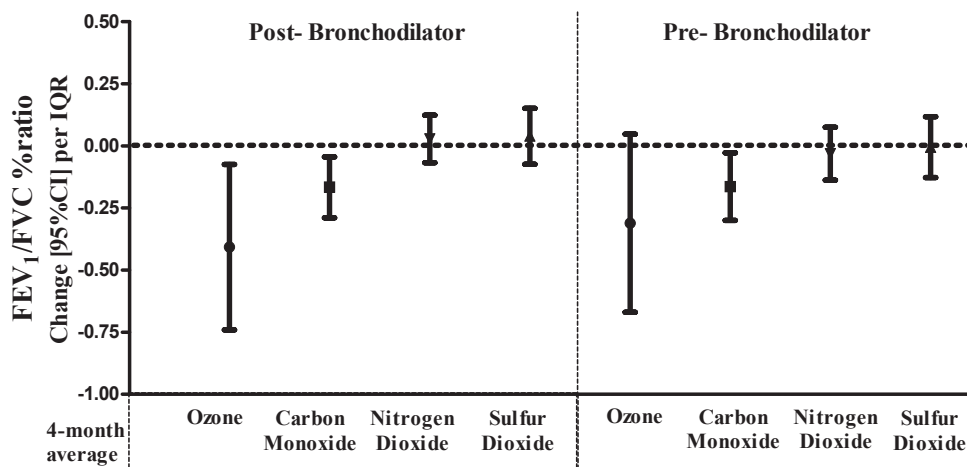


FIG 2. Reduced postbronchodilator FEV₁/FVC ratio (*left*) was associated with 4-month averages of ozone and CO concentrations but not with NO₂ or SO₂ concentrations. CO concentrations were also associated with the prebronchodilator ratio (*right*).

Association of pollution with PC₂₀

Overall, the only pollutant that was significantly associated with PC₂₀ was the 4-month average SO₂ concentration (change per IQR, -6% [95% CI, -11% to -1.5%]). CO had a marginal overall effect on PC₂₀ for all averaging periods (Fig 4). Compared with children receiving placebo, children receiving budesonide and nedocromil had a greater decrease in PC₂₀ with same-day and 1-week average CO exposures ($P = .04$ and $.08$, ANOVA, respectively). This was more prominent for nedocromil. Treatment did not modify associations of SO₂ concentrations with PC₂₀. Tables E10 and E11 in this article's Online Repository at www.jacionline.org show the associations for all pollutants with PC₂₀ and the results of interactions with treatment.

Associations of asthma outcomes with warm-month (May–September) ozone concentrations were not statistically significant (see Table E12 in this article's Online Repository at www.jacionline.org). Two-pollutant models showed similar pollutant–asthma outcome associations as 1-pollutant models (see Table E13 in this article's Online Repository at www.jacionline.org).

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 prebronchodilator and postbronchodilator lung function with shorter-term (same-day to 1-week) and longer-term (4-month) exposures (Fig 1 and see Table E5). Thus to evaluate whether the longer-term effects were independent of shorter-term effects, we put either 1-day or 1-week averages in the same model with 4-month CO averages. Because the same-day and 1-week average measurements are included in the original 4-month average estimate, this added to the correlation among the measures and introduced collinearity into our model. To disentangle the shorter- and longer-term averages and their associations with our outcomes, we performed additional analyses with newly created 4-month averages (ie, calculating the 4-month average by leaving out the same-day measurements and calculating the 4-month average by leaving out the 1-week average), adjusting for same-day and 1-week average CO concentrations, respectively. Associations with prebronchodilator and postbronchodilator lung function from models with single averaging periods compared with those with shorter (1-day or 1-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 nonasthmatic children²⁰ and that long-term traffic pollution can increase incident asthma and reduce lung function in general populations of children.^{2,21–24} There are fewer studies considering the effects of long-term pollution exposure on lung function in asthmatic children^{1,2,20} and none that we know of evaluating the 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 NO₂ were all associated with reductions in lung function consistent with airflow obstruction and with some decrease in vital capacity represented by a decrease in FVC. There are few air pollution studies including postbronchodilator measurements with which to compare our findings. A recent study of subjects from the Manchester Asthma and Allergy Study birth cohort showed a greater long-term pollution (NO₂ and particulate matter of up to 10 μ m in size) effect on postbronchodilator FEV₁ percent predicted compared with prebronchodilator FEV₁ percent predicted.²⁵ Their findings motivated the hypothesis that bronchodilator administration might reduce the influence of varying circadian and day-to-day bronchodilator tone on FEV₁ measurement, potentially increasing the power of the study to show pollution influences on lung function. In our study this might have been the case for shorter-term but not longer-term cumulative averages of pollution exposure. Focusing on FEV₁ as an outcome, with 1-week and 4-month cumulative averages of CO in the same model, longer-term CO exposure was more consistently associated with lower prebronchodilator FEV₁ percent predicted, and short-term CO exposure was more strongly/more consistently associated with lower postbronchodilator lung function measures. Additional unmeasured short-term influences on prebronchodilator responses that were reversible by using bronchodilator administration might have added noise and contributed to the variability in the prebronchodilator measurement, and this could have

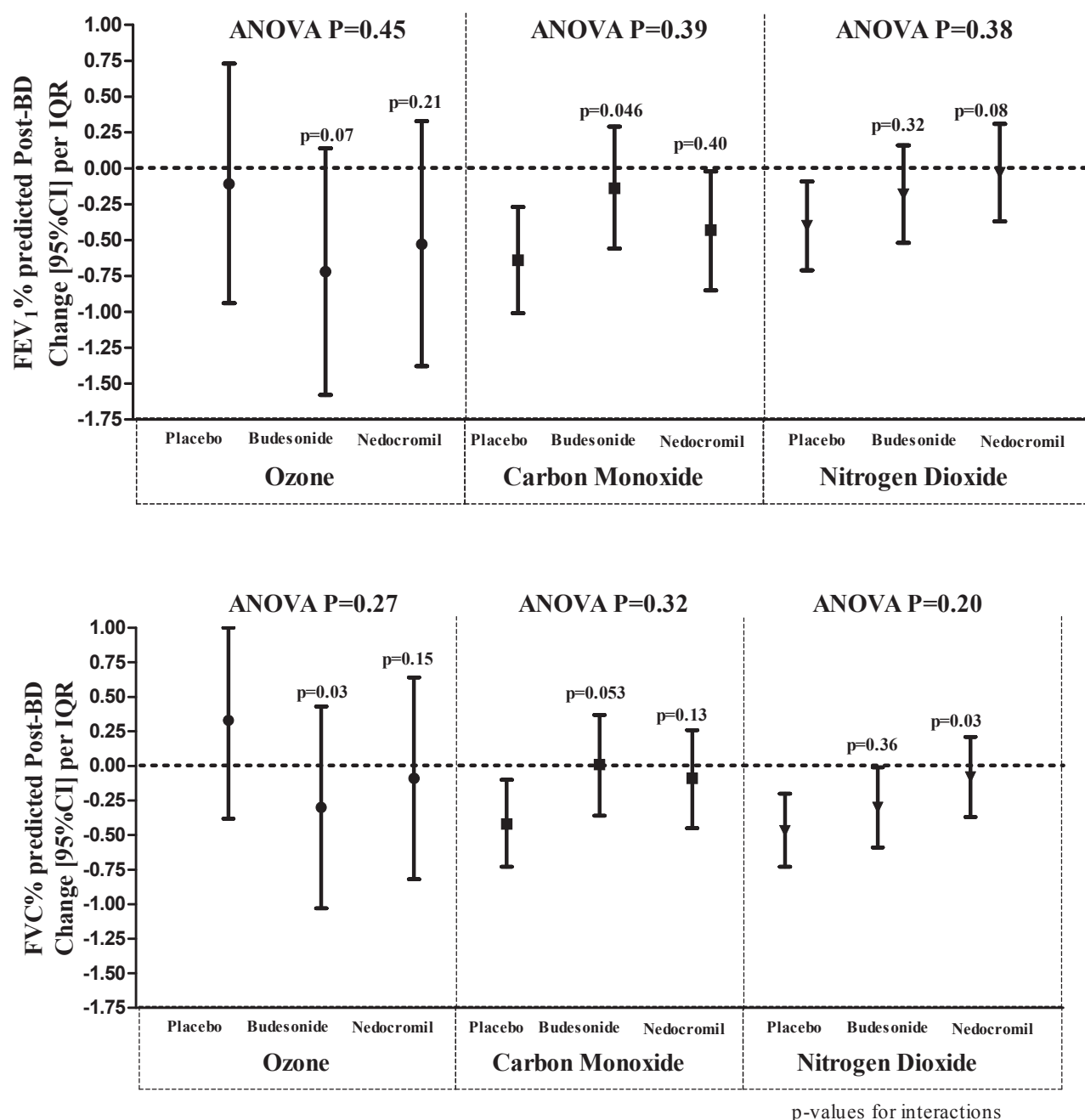


FIG 3. Long-term (4-month moving average) pollution effect modification by treatment. Although there were differences in the magnitude of long-term pollution effect between placebo and budesonide or placebo and nedocromil (*P* values for interactions), results of the overall likelihood ratio tests (ANOVA) were not significant.

resulted in somewhat less robust associations of pollution exposures in the past week with prebronchodilator FEV₁.

The within-subject variation of gaseous pollutants in our asthma trial was low (ie, same-day CO IQR, 0.50 ppm), and although effects were statistically significant (*P* < .001), given their small magnitude (ie, for every 0.5 ppm increase in the same-day CO concentration there is an approximately 0.3% decrease in the average postbronchodilator FEV₁ percent predicted, which would be equivalent to a patient's average FEV₁ percent predicted value decreasing from 103.0% to 102.7% after

bronchodilator over a 4-year follow-up), the lung function responses to pollution might 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 asthmatic patients has reported associations of reduced lung function with short-term CO exposures, but the mechanisms for this association are not known.²⁶ Endogenous hypoxic-induced CO is a mediator of vasodilation and

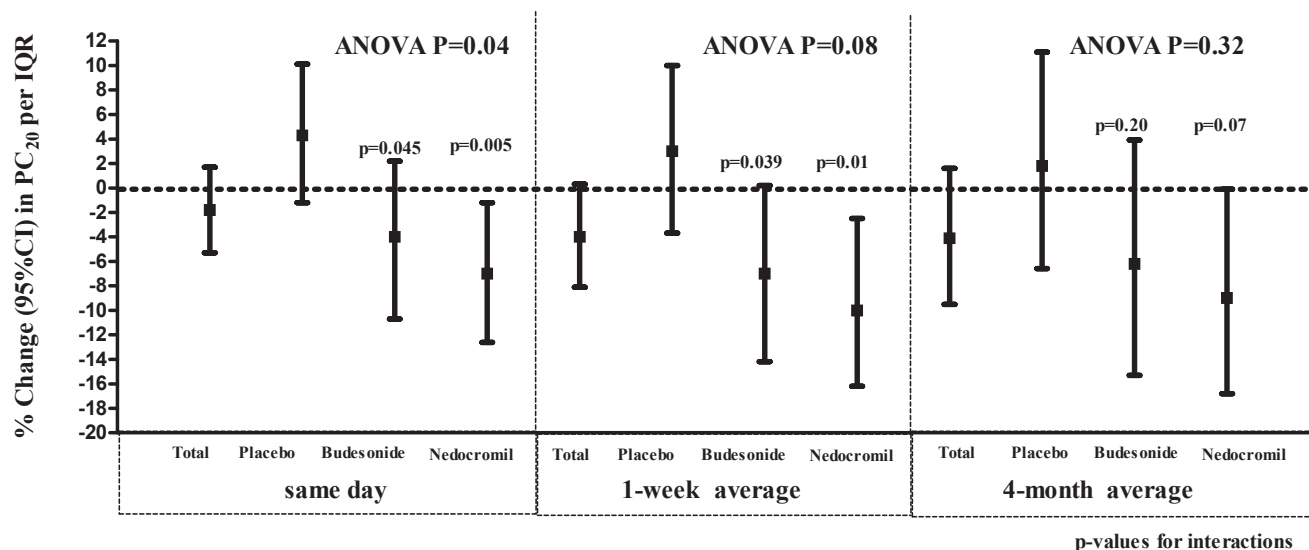


FIG 4. CO exposure had a marginal overall effect on PC₂₀ for all averaging periods. Compared with children receiving placebo, children receiving budesonide and nedocromil had a greater decrease in PC₂₀ with same-day (left) and 1-week (middle) average exposures to CO ($P = .04$ and $.08$, respectively, ANOVA).

TABLE III. Associations of CO concentration with FEV₁ percent predicted: models with single averaging periods are compared with models combining shorter (1-day or 1-week) and longer (4-month) averaging periods

CO	IQR (ppm × 10)	Prebronchodilator FEV ₁ (% predicted)				
		Model 1, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 3, change (95% CI) per IQR	Model 4, change (95% CI) per IQR	Model 5, change (95% CI) per IQR
Same day	5	−0.13 (−0.29 to 0.02), $P = .09$			−0.08 (−0.24 to 0.08), $P = .310$	
One-week average	4		−0.19 (−0.39 to 0.001), $P = .05$			−0.12 (−0.33 to 0.09), $P = .269$
Four-month average	3			−0.36 (−0.62 to −0.10), $P = .006$		
Four-month average excluding same day	3				−0.33 (−0.59 to −0.06), $P = .016$	
Four-month average excluding 1 week	3					−0.29 (−0.56 to −0.02), $P = .037$
CO	IQR (ppm × 10)	Postbronchodilator FEV ₁ (% predicted)				
		Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR
Same day	5	−0.33 (−0.49 to −0.16), $P < .001$			−0.28 (−0.45 to −0.11), $P = .001$	
One-week average	4		−0.41 (−0.62 to −0.21), $P < .001$			−0.36 (−0.58 to −0.14), $P = .002$
Four-month average	3			−0.42 (−0.68 to −0.15), $P = .002$		
Four-month average excluding same day	3				−0.29 (−0.56 to −0.01), $P = .043$	
Four-month average excluding 1 week	3					−0.20 (−0.4 to 0.08), $P = .17$

bronchodilation, and high doses of inhaled CO in mice decrease inflammation and AHR.²⁷⁻³³ Exogenous CO at concentrations encountered by children in our cohort did not have beneficial effects.

Motor vehicle emissions are major sources of CO. These sources produce many contaminants, such as fine particles and organic compounds, and thus in this case it is likely that CO is a surrogate for other pollutants^{2,34,35} and that the observed

TABLE IV. Associations of CO concentration with FVC percent predicted: models with single averaging periods are compared with models combining shorter (1-day or 1-week) and longer (4-month) averaging periods

CO	IQR (ppm × 10)	Prebronchodilator FVC (% predicted)				
		Model 1, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 3, change (95% CI) per IQR	Model 4, change (95% CI) per IQR	Model 5, change (95% CI) per IQR
Same day	5	−0.12 (−0.24 to 0.0), <i>P</i> = .054			−0.09 (−0.22 to 0.03), <i>P</i> = .142	−0.11 (−0.27 to 0.06), <i>P</i> = .15
One-week average	4		−0.15 (−0.3 to 0.01), <i>P</i> = .06			
Four-month average	3			−0.21 (−0.42 to −0.01), <i>P</i> = .042		
Four-month average excluding same day	3				−0.17 (−0.39 to 0.04), <i>P</i> = .108	
Four-month average excluding 1 week	3					−0.15 (−0.37 to −0.07), <i>P</i> = .180

CO	IQR (ppm × 10)	Postbronchodilator FVC (% predicted)				
		Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR	Model 2, change (95% CI) per IQR
Same day	5	−0.19 (−0.33 to −0.05), <i>P</i> = .006			−0.1 (−0.32 to −0.03), <i>P</i> = .02	
One-week average	4		−0.25 (−0.43 to −0.07), <i>P</i> = .006			−0.23 (−0.42 to −0.04), <i>P</i> = .019
Four-month average	3			−0.22 (−0.45 to 0.01), <i>P</i> = .061		
Four-month average excluding same day	3				−0.14 (−0.38 to 0.10), <i>P</i> = .244	
Four-month average excluding 1 week	3					−0.09 (−0.33 to 0.16), <i>P</i> = .49

associations might not be due to CO *per se* but rather to other pollutants in traffic emission mixtures. Similarly, NO₂ might be a marker for complex 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 NO₂ concentrations.^{2,34,35} In the present study air pollutant concentrations were correlated such that it was difficult to separate out the contributions of the individual pollutants. All effect estimates on asthma outcomes remained significant after controlling for copollutants/gases in multipollutant models.

Sarnat et al³⁵ showed relatively strong associations of personal exposure of particles of ambient origin and ambient measurements but considerably lower associations for gases. In particular, NO₂ 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. Because 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 2 pollutants associated with traffic sources, CO and NO₂, were most strongly and consistently associated with reduced lung function and more severe hyperresponsiveness in our asthmatic children. Those were the same pollutants that influenced asthma exacerbations (ie, more symptoms and use of relief medication) before randomization in this CAMP trial.⁶ However, SO₂, which

originates predominately from diesel combustion (diesel fuel content of sulfur was higher during the 1990s) and nontraffic fossil fuels (eg, 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 can enhance methacholine responsiveness, as well as inhaled allergen responsiveness, in sensitized subjects.³⁶⁻³⁹ One animal study has suggested an increase in AHR with long-term SO₂ exposure, supporting our findings for this pollutant.⁴⁰ However, our study is unique in the investigation of AHR and its relation with both short-term and long-term pollution exposure in asthmatic children.

We also found a positive association of long-term exposure to SO₂ with prebronchodilator FVC. Again, experimental and epidemiologic studies investigating lung function response to SO₂ focus on acute responses, and this makes comparison with our finding difficult. Most epidemiologic findings show modest negative or null association of the SO₂ concentration with lung function.⁴¹⁻⁴³ Generally, it is suggested that after acute exposure to SO₂, lung function returns to normal after some minutes to hours and that there is a great deal of interindividual variation in response to SO₂.⁴⁴⁻⁴⁶

Ozone is the most important tropospheric oxidant, which is formed through photochemical reactions involving NO₂ 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 effect if the children

exercise outdoors.⁴⁷⁻⁵⁰ We also show that longer exposure to ozone is associated with airflow obstruction, as indicated by a decrease in FEV₁/FVC ratio with an 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 the human lung with prolonged exposure.⁵¹⁻⁵³ The decrease in postbronchodilator FEV₁/FVC ratio might reflect the 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 receiving budesonide compared with those receiving placebo. The latter suggests a less clear relationship between exposure to ozone and airway inflammation. Two recent studies have suggested that children receiving ICSs 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 receiving ICSs 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-blind 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 receiving ICSs had greater exposure to ozone compared with placebo, either because they were more likely to spend more time outside and exercise more because of better asthma control^{15,18} or because they had greater minute ventilation because they were able to breathe more deeply when exercising.

In our study modification of the effects of CO on AHR by anti-inflammatory treatment suggests that use of controller medication might not protect asthmatic children from pollutant effects. The worsening of AHR with short-term exposure to CO was stronger for children receiving budesonide and nedocromil compared with 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 concentrations. Policy for pollution control and advice⁵⁵ to asthmatic children to avoid outdoor activities on days of high pollution concentrations remain the most powerful preventive measure.

The present report provides a unique contribution in that it can be considered a meta-analysis of 8 large, within-city panel studies. Yet it does not suffer from many of the challenges associated with meta-analyses in the published literature (eg, between-study heterogeneity and obvious publication bias). The large and geographically diverse panel of children participating in the 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, NO₂, SO₂, and ozone across seasons and geographic regions, and results from this study might 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 2 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 interest 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 sex.⁵⁸ Unfortunately, this is outside the scope of our article, and we lack sufficient power for assessment of a 3-way interaction (pollution by treatment group by sex).

We conclude that exposure to gaseous pollutants adversely influences 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.

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.

Clinical implications: Exposure to gaseous pollutants adversely influences lung function and AHR levels in asthmatic children. Anti-inflammatory treatment use might worsen the negative short-term effects of some pollutants on AHR.

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Materials and Methods

The Childhood Asthma Management Program (CAMP): is a multi-center, double-blinded clinical trial involving eight clinical centers 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 asthma. Details of the CAMP study design and methods have been described elsewhere.^{E1} In summary, children enrolled in CAMP were 5–12 years of age at the initial interview, and completed a 5-16 week pre-randomization screening period (1993-1995). All participants had mild-to-moderate asthma with increased airway responsiveness to methacholine (a provocation concentration causing a 20% reduction in FEV₁ [PC₂₀] ≤ 12.5 mg/ml) 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 follow-up visits at CAMP centers 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 administration of two puffs of albuterol, was conducted at randomization (RZ) and at follow up visits (n=13) according to the American Thoracic Society Standards. The focus of the trial on long-term effects of

the treatments on lung function was reflected in the choice of post-bronchodilator FEV₁ percentage of predicted (post-BD FEV₁ % predicted) as the primary outcome measure.^{E2} This decision was based in part, on the assumption that bronchodilator administration would reduce the influence of varying circadian and day-to-day bronchial tone on the measurement of FEV₁, thereby reducing the variability in FEV₁, and potentially increasing the power of the study to show a significant difference in the FEV₁ growth between the treatment groups. However, to date, it has not been established that use of the post- compared to the pre-bronchodilator FEV₁ is associated with a lower variance of change in FEV₁ in patients with obstructive diseases or that there is less month-to-month variability than in the pre-bronchodilator measurements.^{E3} We considered both pre- and post-BD measurement as outcomes in this current analysis as we intended to investigate both short- and long-term effects of air pollution, and some investigators have posited that post-BD lung function is more likely to reflect long-term effects of environmental exposure, while pre-bronchodilator responses may be more influenced by short term exposures. We also acknowledge that post-BD measures have been recommended for assessment of the severity of obstructive diseases. FEV₁/FVC ratio was also used as another measure of airflow obstruction.

Using the Wright nebulizer-tidal breathing technique a methacholine challenge was performed annually during the treatment phase, at least 4 hours after the last use of a short-acting bronchodilator and at least 24 hours after the last use of a long-acting bronchodilator. After a control diluent challenge, nine doubling doses of methacholine were nebulized for 2 minutes each at 5-minute intervals. Spirometry was performed 90 seconds after each challenge until FEV₁ had fallen by 20% or more. Methacholine

challenge was not performed within 28 days of an upper respiratory tract infection or the use of prednisone for exacerbations of asthma.

Air Pollution Exposure Assessment

Data on concentrations of 4 gaseous pollutants (ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide) were obtained from the Aerometric Information Retrieval System (www.epa.gov/air/data/index.html) for US cities and from the Ontario Ministry of the Environment (www.ene.gov.on.ca/environment; Air Quality Assessment and Reporting Unit) for Toronto. For each metropolitan area, multiple monitors were used to measure ambient pollution concentrations. Monitor-specific concentrations were 24-hour averages for ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide. In most cases, for US participants we were able to link ZIP codes of their address at study entry to US Census 2000 ZIP Code Tabulation Areas to identify the latitudes and longitudes of the centroids of those areas. In a few cases ZIP Code centroid coordinates were obtained from www.zip-codes.com. Coordinates for Canadian postal codes were obtained from www.batchgeo.com. 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). If none of the monitors within 50 km radius was operating the air pollution concentration of that day was set as missing.

Exclusion criteria

Participants were excluded if we were unable to assign their ZIP or postal codes to latitudes and longitudes or if we verified that the centroid of the ZIP or postal code in

which they lived was greater than 50 km from the nearest pollutant monitor. For the Canadian participants, a few monitors northwest of Toronto became operational after 2000 and subjects living in postal codes near those monitors were excluded. In total 38 subjects of the 1041 trial participants (3.7%) were excluded.

Statistical Analysis

We examined the relation of level of lung function (FEV_1 and FVC % predicted and FEV_1/FVC ratio) and (log-transformed) PC_{20} with ZIP-code level measures of concentrations of ozone (ppb), carbon monoxide (ppmx10), nitrogen dioxide (ppb) and sulfur dioxide (ppb). 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.^{E4} We examined the associations of our outcomes with same day, 1-week and 4-month moving averages of pollution, to assess associations of short-term and longer-term estimated pollution exposures with our 4-monthly (or for PC_{20} , annually) measured outcomes. The moving averages were created by averaging the daily pollution concentrations for the periods of interest on and preceding the clinic visit for lung function and/or PC_{20} measurement. For any given averaging period, we required that 75% of the daily pollution data were available.

We aimed to investigate short- and long-term effects of gaseous pollutants on lung function level. The rationale for choosing the 4-month moving averages was that in the CAMP trial spirometry was performed every 4 months as indicated in the methods section (4-month interval between follow up visits). We were also interested in short-

term effects but in order to limit the number of tests we restricted the analyses to the acute (i.e., same day exposure) and intermediate (1-week moving average) exposures. One and two-pollutant models (ozone –nitrogen dioxide; ozone-carbon monoxide; and carbon monoxide-nitrogen dioxide) were performed.

We fit a linear mixed model - with random intercepts for each subject - to estimate the associations between pulmonary outcomes and ambient air pollutant concentrations. Number of days from randomization was used as the time trend in the model. Potential for confounding by a number of factors was considered carefully, basing choice of covariates on prior CAMP experience^{E5,E6}: For lung function, we controlled for gender, ethnicity, *in utero* smoking exposure, annual family income (dichotomized at \$30K per annum at baseline (1993-1995)), treatment group and treatment by time interaction, and for PC₂₀, in addition, we controlled for IgE levels, height and history of parental asthma. We ran the model for PC₂₀ with and without adjusting for pre-BD FEV₁.

Confounding due to seasonal factors is a primary consideration in air pollution epidemiology, and we adjusted for “season” by using sine and cosine functions of time^{E7} and their interactions with city. In addition, we decomposed daily ambient pollution concentrations into between- and within-subject exposures. Specifically, subject *i*'s exposure to pollutant x_1 on day *t* was decomposed as follows: The between-subject component, is subject *i*'s average exposure during the time in which he or she was observed, and the within-subject component, is the deviation from the average on day *t*. The between-subject effect of exposure is the degree to which an outcome is associated with differences in the air pollutants across participants. This effect estimate is potentially confounded by time-independent factors (e.g., gender).

Within-subject effect is the degree to which an outcome is associated with differences in the air pollutants when comparing across daily (or hourly) measurements within the same phase for the same participant. This component of the exposure-outcome relationship is likely to be far less confounded by season or by covariates that vary primarily across individual (e.g. in utero smoking exposure, etc) than between-subject effects,^{E8} and they are more comparable to the parameters estimated in a traditional panel study, where all subjects are observed over a single time period. For further discussion regarding the decomposition of time-varying exposures into between- and within-subject components, see the papers by Sheppard^{E8} and Neuhaus and Kalbfleisch.^{E9} We report estimates of within-subject exposure effects.

To assess potential effect modification of the pollution-asthma outcomes associations by treatment we included an interaction term, i.e., pollutant concentration by treatment into the models while excluding the baseline (RZ) measurements.

To compare the magnitude of effects across different pollutants, effect estimates were scaled to interquartile range IQR increases in within-subject pollutant concentrations determined from the distribution of all measurements. Two tailed p-values of <0.05 were considered statistically significant and p-values between 0.05 and 0.09 of borderline significance.

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).

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1 **Online repository**

2 **Table E1. Interquartile ranges (25th to 75th percentile) of pollution concentrations**

IQR	Overall	Within- subject
O ₃ same day	18	15
O ₃ 1-week m.a	16	14
O ₃ 4-month m.a	13	11
CO same day	6	5
CO 1-week m.a	6	4
CO 4-month m.a	6	3
NO ₂ same day	13	10
NO ₂ 1-week m.a	10	7
NO ₂ 4-month m.a	8	4
SO ₂ same day	5	4
SO ₂ 1-week m.a	4	3
SO ₂ 4-month m.a	3	2

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4 O₃: ozone (ppb); CO: carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); IQR: interquartile range, ppb: part
5 per billion; ppm: parts per million; m.a: moving average

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17 **Table E2. Correlations of 24-hour mean pollution concentrations**

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		O ₃	CO	NO ₂	SO ₂
Spearman's rho	O ₃	1	-0.4*	-0.3*	-0.2*
	CO	-0.4*	1	0.4*	0.2*
	NO ₂	-0.3*	0.4*	1	0.4*
	SO ₂	-0.2*	0.2*	0.4*	1

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20 O₃: ozone (ppb); CO: carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb)

21 * correlation is significant at p<0.05 (2-tailed)

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27 **Table E3. City-specific correlation of 24-hour mean pollution concentrations**

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CITY CENTER			NO ₂	O ₃	SO ₂	CO
ALB	Spearman's rho	NO ₂	1.000	-0.488*	NA	0.446*
		O ₃	-0.488*	1.000	NA	-0.473*
		SO ₂	NA	NA	NA	NA
		CO	0.446*	-0.473*	NA	1.000
BAL	Spearman's rho	NO ₂	1.000	-0.160*	0.379*	0.387*
		O ₃	-0.160*	1.000	-0.311*	-0.352*
		SO ₂	0.379*	-0.311*	1.000	0.295*
		CO	0.387*	-0.352*	0.295*	1.000
BOSTON	Spearman's rho	NO ₂	1.000	-0.218*	0.378*	0.346*
		O ₃	-0.218*	1.000	-0.414*	-0.315*
		SO ₂	0.378*	-0.414*	1.000	0.273*

		CO	0.346*	-0.315*	0.273*	1.000
DEN	Spearman's rho	NO ₂	1.000	-0.301*	0.469*	0.416*
		O ₃	-0.301*	1.000	-0.187*	-0.512*
		SO ₂	0.469*	-0.187*	1.000	0.343*
		CO	0.416*	-0.512*	0.343*	1.000
SD	Spearman's rho	NO ₂	1.000	-0.527*	0.150*	0.743*
		O ₃	-0.527*	1.000	-0.092*	-0.446*
		SO ₂	0.150*	-0.092*	1.000	0.188*
		CO	0.743*	-0.446*	0.188*	1.000
SEA	Spearman's rho	NO ₂	1.000	-0.170*	0.321*	0.512*
		O ₃	-0.170*	1.000	-.053	-0.284*
		SO ₂	0.321*	-.053	1.000	0.203*
		CO	0.512*	-0.284*	0.203*	1.000
STL	Spearman's rho	NO ₂	1.000	-0.247*	0.532*	0.535*

TOR	Spearman's rho	O ₃	-0.247*	1.000	-0.145*	-0.223*
		SO ₂	0.532*	-0.145*	1.000	0.302*
		CO	0.535*	-0.223*	0.302*	1.000
		NO ₂	1.000	-0.339*	0.462*	0.533*
		O ₃	-0.339*	1.000	-0.208*	-0.296*
		SO ₂	0.462*	-0.208*	1.000	0.324*
		CO	0.533*	-0.296*	0.324*	1.000

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30 ALB: Albuquerque0. BAL: Baltimore0. BOS: Boston0. DEN: Denver0. SD: San Diego0. SEA: Seattle0. STL: Saint Louis0. TOR: Toronto0.

31 O₃: ozone (ppb); CO: carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); ppb: part per billion; ppm: parts per
 32 million

33 ***P-value<0.05**

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37 **Table E4: City-specific and city-wide (meta-analysis) associations of within-subject 4-month average pollution concentration with post-**
 38 **BD FEV₁ and FVC %predicted**

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4-month average	City	IQR	post-BD FEV ₁ %predicted	post-BD FVC %predicted
			Change	Change
O₃ (ppb)	ALB	12	-1.69	-1.78*
	BAL	15	0.31	1.04
	BOS	12	-1.02	-0.65
	DEN	12	0.61	1.85*
	SD	10	-1.13	-0.14
	SEA	4	-1.35	-1.20
	STL	14	-2.37	-0.52
	TOR	10	0.74	-0.03
	Meta-analysis[#]	11	-0.64**	-0.21
CO (ppmx10)	ALB	4	-0.35	-0.05
	BAL	3	-0.76	-0.02
	BOS	2	-0.10	0.10

	DEN	3	-1.64*	-1.57*
	SD	5	0.18	-0.19
	SEA	4	-0.14	-0.32
	STL	1	0.25	0.24
	TOR	4	-0.49	-0.09
	Meta-analysis[#]	3	-0.37*	-0.17
NO₂ (ppb)	ALB	6	-0.03	-0.43
	BAL	4	-0.04	-0.05
	BOS	4	-0.81*	-0.83*
	DEN	6	-0.78**	-0.77*
	SD	7	0.03	0.26
	SEA	3	0.37	0.06
	STL	2	-0.23	-0.06
	TOR	3	-0.26	0.07
	Meta-analysis[#]	4	-0.24*	-0.23*
SO₂ (ppb)	ALB	NA	NA	NA
	BAL	3	0.06	-0.03
	BOS	5	-0.49	-0.23

	DEN	1	0.55	0.30
	SD	1	0.08	-0.16
	SEA	2	0.14	0.13
	STL	2	0.30	0.39
	TOR	2	-0.08	-0.06
	Meta-analysis[#]	2	0.08	0.09

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41 ALB: Albuquerque, BAL: Baltimore, BOS: Boston, DEN: Denver, SD: San Diego, SEA: Seattle, STL: Saint Louis, TOR: Toronto, O₃: ozone
42 (ppb); CO: carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); N: number of observations; IQR: interquartile
43 range, ppb: part per billion; ppm: parts per million; IQR: Interquartile range, ppb: parts per billion; ppm: parts per million; FEV₁: forced
44 expiratory volume in 1 second; FVC: forced vital capacity; BD: bronchodilator; CI: confidence interval; NA: not applicable

45 [#]Fixed effects are used. When index of heterogeneity is > 50% the random effects are used

46 * p<0.05

47 ** 0.05≤p<0.1

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50 **Table E5: Associations of within-subject pollution with pre-BD FEV₁ and FVC %predicted**

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Within-subject	IQR	Pre-BD FEV ₁ %predicted			Pre-BD FVC %predicted		
		N	Change	(95%CI)	N	Change	(95%CI)
O ₃ same day	15	11394	-0.02	(-0.270; 0.24)	11393	0.09	(-0.110; 0.30)
O ₃ 1-week m.a	14	11377	-0.15	(-0.530; 0.24)	11376	0.03	(-0.270; 0.33)
O ₃ 4-month m.a	11	11140	-0.50	(-1.170; 0.17)	11139	-0.25	(-0.780; 0.28)
CO same day	5	12044	-0.13**	(-0.290; 0.02)	12043	-0.12**	(-0.240; 0.003)
CO 1-week m.a	4	12047	-0.2**	(-0.390; 0.00)	12046	-0.15**	(-0.300; 0.01)
CO 4-month m.a	3	12048	-0.4*	(-0.620; -0.10)	12047	-0.2*	(-0.420; -0.01)
NO ₂ same day	10	11523	-0.07	(-0.250; 0.10)	11522	-0.003	(-0.14; 0.14)
NO ₂ 1-week m.a	7	11494	-0.04	(-0.230; 0.15)	11493	0.02	(-0.13; 0.16)
NO ₂ 4-month m.a	4	11502	-0.1	(-0.310; 0.09)	11501	-0.1	(-0.23; 0.09)
SO ₂ same day	4	10530	0.10	(-0.050; 0.25)	10529	0.06	(-0.060; 0.17)
SO ₂ 1-week m.a	3	10537	0.14	(-0.040; 0.33)	10536	0.12	(-0.030; 0.26)
SO ₂ 4-month m.a	2	10540	0.15	(-0.080; 0.39)	10539	0.23*	(0.050; 0.42)

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53 O₃: ozone (ppb); CO: carbon monoxide (ppm x10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of
54 observations; IQR: Interquartile range. ppb: parts per billion; ppm: parts per million; FEV₁: forced expiratory volume in 1 second; FVC: forced
55 vital capacity; BD: bronchodilator; CI: confidence interval

56 * p<0.05

57 ** 0.05≤p<0.1

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68 **E6. Treatment group modification of within-subject pollution effect on Pre-BD FEV₁ %predicted**

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			Placebo			Budesonide			Nedocromil		
Within-subject	N	IQR	Coefficient	95%CI		Coefficient	95%CI		Coefficient	95%CI	
O ₃ same day	10531	15	0.02	-0.33	0.37	0.03	-0.37	0.43	-0.13	-0.52	0.26
O ₃ 1-week m.a	10531	14	-0.12	-0.59	0.36	0.15	-0.36	0.66	-0.18	-0.68	0.32
O ₃ 4-month m.a	10515	11	-0.48	-1.23	0.28	-0.20	-0.97	0.57	-0.63	-1.39	0.14
CO same day	10299	5	-0.03	-0.26	0.20	-0.24	-0.52	0.03	-0.19	-0.47	0.08
CO 1-week m.a	11141	4	-0.16	-0.44	0.12	-0.33	-0.65	-0.01	-0.23	-0.54	0.09
CO 4-month m.a	11142	3	-0.45	-0.79	-0.10	-0.29	-0.68	0.09	-0.36	-0.74	0.02
NO ₂ same day	11143	10	-0.06	-0.33	0.21	-0.19	-0.52	0.13	0.04	-0.27	0.34
NO ₂ 1-week m.a	11144	7	0.03	-0.24	0.31	-0.28	-0.60	0.05	0.02	-0.29	0.34
NO ₂ 4-month m.a	10740	4	-0.10	-0.38	0.18	-0.28	-0.60	0.03	-0.03	-0.34	0.28
SO ₂ same day	10734	4	0.12	-0.10	0.34	0.15	-0.12	0.42	-0.04	-0.30	0.22

SO ₂ 1-week m.a	10707	3	0.29	0.04	0.55	0.04	-0.27	0.34	-0.02	-0.33	0.28
SO ₂ 4-month m.a	10709	2	0.21	-0.08	0.51	0.02	-0.32	0.37	0.14	-0.20	0.48

O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of observations; IQR: Interquartile range0. ppm: parts per million; FEV₁: forced expiratory volume in 1 second; BD: bronchodilator; CI: confidence interval

* P-value for placebo vs budesonide or placebo vs nedocromil <0.10

83 E7. Treatment group modification of within-subject pollution effect on Post-BD FEV₁ %predicted

Within-subject	N	IQR	Placebo			Budesonide			Nedocromil		
			Coefficient	95%CI		Coefficient	95%CI		Coefficient	95%CI	
O ₃ same day	7325	15	0.12	-0.26	0.49	-0.06	-0.50	0.37	0.12	-0.31	0.55
O ₃ 1-week m.a	7311	14	0.25	-0.26	0.76	0.23	-0.34	0.80	0.24	-0.31	0.80
O ₃ 4-month m.a	7184	11	-0.11	-0.94	0.73	-0.72*	-1.58	0.14	-0.53	-1.38	0.33
CO same day	7741	5	-0.23	-0.49	0.03	-0.35	-0.65	-0.06	-0.34	-0.63	-0.05
CO 1-week m.a	7741	4	-0.37	-0.68	-0.07	-0.47	-0.82	-0.12	-0.49	-0.84	-0.14
CO 4-month m.a	7742	3	-0.64	-1.01	-0.27	-0.14*	-0.56	0.29	-0.43	-0.85	-0.02
NO ₂ same day	7439	10	-0.14	-0.43	0.15	-0.16	-0.51	0.19	0.05	-0.28	0.38
NO ₂ 1-week m.a	7418	7	-0.02	-0.32	0.28	-0.21	-0.57	0.15	0.05	-0.29	0.39
NO ₂ 4-month m.a	7414	4	-0.40	-0.71	-0.09	-0.18	-0.52	0.16	-0.03*	-0.37	0.31
SO ₂ same day	6760	4	0.08	-0.16	0.32	0.00	-0.29	0.30	-0.15	-0.43	0.13
SO ₂ 1-week m.a	6761	3	0.21	-0.06	0.49	-0.05	-0.40	0.30	-0.04	-0.37	0.29

SO ₂ 4-month m.a	6764	2	0.09	-0.22	0.41	0.17	-0.22	0.55	0.17	-0.20	0.54
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86 O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of

87 observations; IQR: Interquartile range0. ppm: parts per million; FEV₁: forced expiratory volume in 1 second; BD: bronchodilator; CI:

88 confidence interval

89 * P-value for placebo vs budesonide or placebo vs nedocromil <0.10

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98 **E8. Treatment group modification of within-subject pollution effect on Pre-BD FVC %predicted**

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Within-subject	N	IQR	Placebo			Budesonide			Nedocromil		
			Coefficient	95%CI		Coefficient	95%CI		Coefficient	95%CI	
O ₃ same day	7325	15	0.23	-0.04	0.50	-0.02	-0.33	0.29	-0.02	-0.32	0.28
O ₃ 1-week m.a	7311	14	0.18	-0.19	0.55	0.11	-0.29	0.51	0.04	-0.35	0.42
O ₃ 4-month m.a	7184	11	-0.08	-0.67	0.51	0.03	-0.57	0.63	-0.27	-0.87	0.33
CO same day	7741	5	-0.07	-0.25	0.11	-0.23	-0.45	-0.01	-0.06	-0.27	0.16
CO 1-week m.a	7741	4	-0.15	-0.37	0.07	-0.21	-0.46	0.04	-0.16	-0.41	0.09
CO 4-month m.a	7742	3	-0.30	-0.58	-0.03	-0.18	-0.49	0.13	-0.18	-0.48	0.12
NO ₂ same day	7439	10	0.00	-0.21	0.22	-0.20	-0.45	0.05	0.15	-0.09	0.39
NO ₂ 1-week m.a	7418	7	0.05	-0.17	0.26	-0.21	-0.47	0.04	0.07	-0.18	0.31
NO ₂ 4-month m.a	7414	4	-0.18	-0.40	0.04	-0.29	-0.54	-0.04	0.07	-0.18	0.31
SO ₂ same day	6760	4	0.02	-0.16	0.19	0.08	-0.13	0.29	0.04	-0.17	0.24

SO ₂ 1-week m.a	6761	3	0.12	-0.08	0.32	0.06	-0.19	0.30	0.12	-0.11	0.36
SO ₂ 4-month m.a	6764	2	0.21	-0.02	0.45	0.05	-0.23	0.32	0.23	-0.03	0.50

O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of observations; IQR: Interquartile range0. ppm: parts per million; FVC : forced vital capacity; BD: bronchodilator; CI: confidence interval

* P-value for placebo vs budesonide or placebo vs nedocromil <0.10

113 **E9. Treatment group modification of within-subject pollution effect on Post-BD FVC %predicted**

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Within-subject	N	IQR	Placebo			Budesonide			Nedocromil		
			Coefficient	95%CI		Coefficient	95%CI		Coefficient	95%CI	
O ₃ same day	7325	15	0.24	-0.07	0.56	-0.12	-0.49	0.26	0.17	-0.19	0.54
O ₃ 1-week m.a	7311	14	0.41	-0.02	0.84	0.14	-0.34	0.62	0.36	-0.11	0.83
O ₃ 4-month m.a	7184	11	0.33	-0.38	1.04	-0.30*	-1.03	0.43	-0.09	-0.82	0.64
CO same day	7741	5	-0.15	-0.37	0.07	-0.23	-0.48	0.02	-0.18	-0.43	0.07
CO 1-week m.a	7741	4	-0.26	-0.52	0.00	-0.26	-0.56	0.04	-0.30	-0.59	0.00
CO 4-month m.a	7742	3	-0.42	-0.73	-0.10	0.01*	-0.36	0.37	-0.09	-0.45	0.26
NO ₂ same day	7439	10	-0.05	-0.30	0.20	-0.13	-0.43	0.16	0.07	-0.21	0.35
NO ₂ 1-week m.a	7418	7	-0.09	-0.35	0.16	-0.26	-0.57	0.04	-0.07	-0.36	0.22
NO ₂ 4-month m.a	7414	4	-0.47	-0.73	-0.20	-0.30	-0.59	-0.01	-0.08*	-0.37	0.21
SO ₂ same day	6760	4	0.07	-0.13	0.28	0.01	-0.24	0.27	-0.04	-0.28	0.20

SO ₂ 1-week m.a	6761	3	-0.03	-0.27	0.21	-0.04	-0.34	0.26	0.00	-0.28	0.29
SO ₂ 4-month m.a	6764	2	-0.04	-0.31	0.23	0.06	-0.26	0.39	0.14	-0.18	0.45

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117 O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); N: number of observations; IQR:

118 Interquartile range0. ppm: parts per million; FVC : forced vital capacity; BD: bronchodilator; CI: confidence interval

119 * P-value for placebo vs budesonide or placebo vs nedocromil <0.10

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128 **E10. Association of within-subject pollution with metacholine concentration causing a 20% reduction in FEV₁**

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Within-subject	N	IQR	PC ₂₀		
			%Change	95%CI	
O ₃ same day	2880	15	-1.5	-7.7	5.2
O ₃ 1-week m.a	2878	14	-3.8	-12.8	6.1
O ₃ 4-month m.a	2809	11	3.6	-11.7	21.7
CO same day	3039	5	-1.8	-5.3	1.7
CO 1-week m.a	3040	4	-4.0*	-8.1	0.3
CO 4-month m.a	3040	3	-4.1	-9.5	1.6
NO ₂ same day	2959	10	-1.0	-4.9	3.2
NO ₂ 1-week m.a	2946	7	-1.2	-5.3	3.0
NO ₂ 4-month m.a	2955	4	-0.9	-5.2	3.7

SO ₂ same day	2660	4	-2.1	-5.2	1.1
SO ₂ 1-week m.a	2661	3	-3.4	-7.3	0.7
SO ₂ 4-month m.a	2661	2	-6.0*	-10.9	-1.5

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131 O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of
 132 observations; IQR: Interquartile range. ppm: parts per million; PC20: Metacholine provocation concentration (mg/dl) causing a 20% reduction
 133 in FEV₁; bronchodilator; CI: confidence interval

134 * p<0.05

135 * 0.05<=p<0.1

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142 **E11. Treatment group modification of within-subject pollution effect on metacholine concentration causing a 20% reduction in FEV₁**

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Within-subject	N	IQR	Placebo			Budesonide			Nedocromil		
			%Change	95%CI		%Change	95%CI		%Change	95%CI	
O ₃ same day	2880	15	-6.9	-15.5	2.5	0.6	-9.8	12.2	3.2	-7.0	14.5
O ₃ 1-week m.a	2878	14	-7.3	-18.9	6.0	5.0	-8.9	21.0	-8.7	-21.0	5.6
O ₃ 4-month m.a	2809	11	-3.3	-20.4	17.5	4.7	-14.6	28.5	11.3	-9.3	36.6
CO same day	3039	5	4.3	-1.2	10.1	-4.6*	-10.7	2.2	-7.0*	-12.6	-1.2
CO 1-week m.a	3040	4	3.0	-3.7	10.0	-7.2*	-14.2	0.2	-10.0*	-16.2	-2.5
CO 4-month m.a	3040	3	1.8	-6.6	11.1	-6.2	-15.3	3.9	-9.0*	-16.8	-0.1
NO ₂ same day	2959	10	2.2	-4.3	9.1	-3.2	-10.1	4.3	-2.6	-9.4	4.7
NO ₂ 1-week m.a	2946	7	3.9	-2.6	10.9	-5.1*	-12	2.4	-4.1	-11.1	3.4
NO ₂ 4-month m.a	2955	4	2.6	-4.1	9.6	-3.6	-11.0	4.4	-2.8	-9.9	4.9
SO ₂ same day	2660	4	0.1	-4.8	5.2	-2.0	-7.6	3.8	-5.3	-10.8	0.5

SO ₂ 1-week m.a	2661	3	-1.6	-7.5	4.7	-1.4	-8.2	5.9	-7.9	-14.4	-0.9
SO ₂ 4-month m.a	2661	2	-6.9	-13.1	-0.2	-5.1	-13.1	3.7	-6.7	-14.4	1.8

O₃: ozone (ppb); carbon monoxide (ppm x 10); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); m.a: moving average; N: number of observations; IQR: Interquartile range. ppm: parts per million; PC20: Metacholine dose Metacholine provocation concentration (mg/dl) causing a 20% reduction in FEV₁; BD: bronchodilator; CI: confidence interval

* P-value for placebo vs budesonide or placebo vs nedocromil <0.10

157 **E12a-c. Associations of warm-months (May-September) within-subject Ozone with lung function and PC₂₀:**

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12a.		Pre-BD FEV1 %predicted				Post-BD FEV1 %predicted			
Within-subject	IQR (ppb)	N	Change	95%CI		N	Change	95%CI	
O ₃ same day	13	5199	-0.036	-0.341	0.270	4036	-0.016	-0.298	0.266
O ₃ 1-day lag	13	5199	-0.030	-0.343	0.284	4036	0.011	-0.282	0.305
O ₃ 1-week m.a	9	5197	-0.021	-0.393	0.351	4035	0.035	-0.311	0.381

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12b.		Pre-BD FVC %predicted				Post-BD FVC %predicted			
Within-subject	IQR (ppb)	N	Change	95%CI		N	Change	95%CI	
O ₃ same day	13	5199	0.046	-0.198	0.291	4036	0.040	-0.205	0.285
O ₃ 1-day lag	13	5199	-0.007	-0.258	0.243	4036	-0.034	-0.289	0.221
O ₃ 1-week m.a	9	5197	0.061	-0.237	0.358	4035	-0.002	-0.302	0.299

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12c.			PC20		
Within-subject	IQR (ppb)	N	%Change	95%CI	
O ₃ same day	13	1067	0.959	0.887	1.036
O ₃ 1-day lag	13	1067	0.997	0.921	1.080
O ₃ 1-week m.a	9	1067	0.965	0.878	1.061

O₃: ozone (ppb); m.a: moving average; N: number of observations; IQR: Interquartile range
 volume in 1 second; FVC : forced vital capacity; PC20: Metacholine dose (mg/ml) at which 20% drop in forced expiratory volume in 1 second is achieved; BD: bronchodilator; CI: confidence interval

* P interaction<0.05

* 0.05<= P interaction<0.1

172 **Table E13. Comparison of between one- and two-pollutant model analysis of associations of 4-month average pollution with asthma**
 173 **outcomes**
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	4-month average	One-pollutant model		Two-pollutant model	
		change per IQR	p value	change per IQR	p value
FEV ₁ % predicted post BD	ozone	-0.49	0.18	-0.50	0.17
	nitrogen dioxide	-0.20	0.06	-0.23	0.04
FEV ₁ % predicted post BD	carbon monoxide	-0.42	0.002	-0.40	0.004
	nitrogen dioxide	-0.20	0.06	-0.17	0.13
FEV ₁ % predicted post BD	carbon monoxide	-0.42	0.002	-0.52	<0.001
	ozone	-0.49	0.18	-0.71	0.05
FVC % predicted post BD	ozone	-0.08	0.80	-0.14	0.66
	nitrogen dioxide	-0.24	0.01	-0.23	0.01
FVC % predicted post BD	carbon monoxide	-0.21	0.06	-0.28	0.02

	ozone	-0.08	0.80	-0.20	0.53
FVC % predicted post BD	carbon monoxide	-0.21	0.06	-0.21	0.09
	nitrogen dioxide	-0.24	0.01	-0.22	0.02
PC ₂₀ (%change)	ozone	3.65	0.66	2.73	0.74
	nitrogen dioxide	-0.85	0.71	-0.77	0.74
PC ₂₀ (%change)	carbon monoxide	-4.11	0.16	-3.01	0.23
	ozone	3.65	0.66	2.15	0.79
PC ₂₀ (%change)	carbon monoxide	-4.11	0.16	-3.01	0.26
	nitrogen dioxide	-0.85	0.71	-0.46	0.84

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177 IQR: Interquartile range0. ppm: parts per million; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; PC20: Metacholine

178 dose (mg/ml) at which 20% drop in forced expiratory volume in 1 second is achieved; BD: bronchodilator; CI: confidence interval

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