Air Pollution and Pulmonary Function in Asthmatic Children

Effects of Prenatal and Lifetime Exposures

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Background: Prenatal and early life periods represent critical windows for oxidant pollutant-induced lung remodeling. The objective of this study was to examine the association of prenatal and lifetime exposures to air pollutants with pulmonary function in a cohort of children with asthma.

Methods: Prenatal and lifetime exposure to several air pollutants was reconstructed for 232 children with asthma from the San Joaquin Valley of California, USA. Prenatal and lifetime residences were geocoded. We obtained data on monthly average ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and particulate matter with a median aerodynamic diameter <10 μm (PM_{10}) concentrations. Metrics were created for key developmental periods. Predictive models were developed for 8 pulmonary function measures. A newly-developed stepwise model selection procedure—the Deletion/Substitution/Addition algorithm—was implemented and results were compared with those obtained using traditional stepwise methods.

Results: Second-trimester exposure to NO_2 negatively affected forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), and first trimester exposure to PM_{10} negatively affected peak expiratory flow (PEF) rate. Exposure to CO in early years of life also had a negative effect on FEV_1/FVC and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75})/FVC. Second trimester exposure to PM_{10} and exposure to CO in the first 6 years of life had negative effects on forced expiratory flow at 25% of FVC. Prenatal, but not trimester-specific, exposure to CO was negatively associated with FEF_{25-75}. Effects were limited to subgroups, such as children who were African American, those diagnosed with asthma before the age of 2 years, and those exposed to maternal smoking during pregnancy.

Conclusion: Prenatal and early-life exposures to CO, PM_{10}, and NO_2 have a negative effect on pulmonary function in subgroups of asthmatic children.

(*Epidemiology* 2008;19: 550–557)

Numerous studies have demonstrated that short-term fluctuations in ambient air pollutants such as ozone (O_3), particulates with median aerodynamic diameter <10 μm (PM_{10}) and nitrogen dioxide (NO_2) are associated with increased acute respiratory symptoms and decreases in pulmonary function in children, especially in asthmatics.[1–3] Recent studies have reported negative effects of pollution on lung function in the first year of life[4] and among college freshman.[5] Given the heterogeneity of response to air pollution,[6–8] it is important to identify subgroups of children with asthma who are susceptible to air pollution-related effects.

The issue of prenatal exposure has assumed increasing importance, since ambient air pollution exposures of pregnant women have been shown to lead to adverse pregnancy outcomes and to respiratory morbidity and mortality in the first year of life.[9–12] Several of these studies found that exposures during the first trimester (a time of major lung and airway development) are associated with intrauterine growth retardation and preterm birth.[13,14] Early-life factors have been shown to be robust predictors of future health outcomes in multiple conditions and have effects that extend into adulthood. Pulmonary function measures have been shown to be useful predictors of mortality.[15] Consequently, the examination of the effects of early-life exposures on these outcomes may serve as useful early-warning signs of future morbidity and premature mortality.

This paper examines which prenatal and lifetime exposures to several ambient air pollutants were most predictive of current pulmonary function among a cohort of children aged 6–11 years with asthma.. We sought to identify characteristics of asthmatic children who are most responsive to these exposures.

Submitted 24 March 2007; accepted 5 December 2007; posted 27 May 2008.
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Supported by funding by the American Lung Association, National and East Bay of California Chapters and the California Air Resources Board (Contract 99-322).
Supplemental material for this article is available with the online version of the journal at www.epidem.com; click on "Article Plus."
***Editors' note**: Related articles appear on pages 588 and 561.*
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ISSN: 1044-3983/08/1904-0550
DOI: 10.1097/EDE.0b013e31816a9dcb

METHODS

Data for this study were collected within the context of the Fresno Asthmatic Children's Environment Study, a longitudinal epidemiologic study of 315 asthmatic children in Fresno, California. The focus of this paper is a separately funded substudy of 232 members of the cohort for whom prenatal and chronic exposure could be obtained.

Children and their families were recruited through community-based advertisements, school nurses and local physicians. Eligibility criteria included physician-diagnosed asthma, age 6–11 years at the time of the baseline interview, and having a primary residence within 20 km of the California Air Resources Board's Fresno First St. air monitoring site. Only asthmatic children who had been symptomatic or used medication or had a physician visit for asthma in the 12 months previous to enrollment were eligible. The original protocol consisted of an in-person office visit (baseline), followed by a series of home surveys, telephone calls, and office visits.

An in-person, baseline questionnaire was administered in English or Spanish. Baseline data were used to assign each child a severity score based on the criteria of the Global Initiative for Asthma asthma-severity classification scheme.[16] Spirometry was performed with a dry, rolling-seal spirometer (Spiroflow; P.K. Morgan Instruments, Andover, MA). Up to 8 attempts were allowed to obtain 3 acceptable tracings as described previously.[17] Measures included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$), and forced expiratory flow at 25% and 75% of vital capacity (FEF_{25} and FEF_{75}, respectively). Also considered were the ratio of FEV_1 to FVC (FEV_1/FVC), and the ratio of $FEF_{25–75}$ to FVC ($FEF_{25–75}$/FVC). The $FEF_{25–75}$/FVC ratio has the interpretation of the reciprocal of the time constant of the lung,[18] similar to Meade's $Vmax_{50}/(VC \times Pst(L)_{50})$ (ie, instantaneous flow at 50%, divided by vital capacity times elastic recoil pressure at 50% of vital capacity) and is reflective of intrinsic airway size.[19] The mean of the first 3 (but not less than 2) acceptable tracings was calculated.

Skin-prick allergen sensitivity tests to 14 antigens were performed with the MultiTest device (donated by Lincoln Laboratory, Decateur, IL), as described in eTable 1 (available with the online version of this article). Atopy was defined as one or more positive skin tests or a previous severe reaction to allergen skin testing.

Parents were asked to report the street address, city and state of all residences at which the mother lived during pregnancy or at which the child lived prior to enrollment in the study. Only addresses at which they lived for at least 3 months were recorded. Each address was geocoded with "EZ Locate Client" v.1.61, by Tele Atlas (www.geocode.com).

Pollutant concentrations were obtained from the Aerometric Information Retrieval System database supported by the US Environmental Protection Agency. Pollutants considered include O_3, NO_2, PM_{10}, and carbon monoxide (CO). Pollutant metrics were determined by time-averaging the raw database concentrations. The estimates were mapped to the residences or ZIP code centroids based on inverse distance weighting of the monthly average concentrations from the air monitoring stations (up to 3) located closest to the residence location. Residences were assigned a quality code, based on the distance to the nearest monitor(s). A code of 1 meant that at least 1 station used in the spatial interpolation was located within 5 km of the point of interest (residence location). Similarly, code 2 was used when the closest station was located, relative to the point of interest, between 5 and 50 km for O_3, NO_2, and PM_{10}, and between 5 and 25 km for CO. A code 3 was assigned when the closest station was located between 50 and 100 km for O_3, NO_2, and PM_{10}, and between 25 and 50 km for CO.

Based on the age range of this cohort, pollutant levels for the years 1989–2000 were obtained. For all pollutants, means of the monthly 24-hour averages were created, and, for several pollutants metrics, monthly means of maximum values within a day or the monthly means of multihour intervals were created. These monthly values were averaged separately across several important developmental time-periods.

The study protocol was approved by the Committee for the Protection of Human Subjects of the University of California, at Berkeley. Written informed consent was obtained from parents/legal guardians prior to enrollment.

Statistical Methods

We ran age-adjusted models for each of the pollutant metrics of interest from a regulatory standpoint (24-hour average for NO_2 and PM_{10} and 8-hour maximums for O_3 and CO) (eTable 2). We developed a common set of plausible confounders or effect modifiers based on previous studies of pulmonary function and air pollution (Table 1). Their associations with pulmonary function values are presented in eTable 3. Low birthweight, premature birth, atopy and asthma diagnosis before age 2 were found not be on the causal pathway between early life exposures and pulmonary function at age 6–11 (data not shown); therefore, we considered them as potential confounders.

Some of the pollutants in the Fresno area are temporally correlated, as are pollutant metrics for different time periods (eg, lifetime vs. first 3 years of life). Strong correlation indicates there is a lack of information in the data to draw conclusions about the effect of individual pollutant metrics, which may lead to spurious findings. Therefore, rather than trying to model the effect of *each* pollutant metric on each outcome, we used methods to identify which pollutant metrics were most predictive of pulmonary function. In this exploratory analysis, a large series of metrics was considered

TABLE 1. Characteristics of the Fresno Asthmatic Children's Environment Study Subjects With Prenatal and Chronic Exposure Information Available (n = 232)

Demographic variables	
Age at baseline (yrs); mean (SD)	8.56 (1.7)
Race; %	
Black	14
Hispanic	38
White	45
Other	3
Sex (male); %	57
Family income <$30,000/yr; %	43
Current exposures; %	
Smoker in home	15
Lives within 4 blocks of major roadway	78
Current anthropometric measurements; mean (SD)	
Height (in)	51.6 (4.6)
Weight (lb)	71.9 (26.5)
Pulmonary function at baseline; mean (SD)	
FVC (L)	1.95 (0.51)
FEV_1 (L/s)	1.61 (0.43)
PEF (L/s)	3.88 (1.16)
$FEF_{25–75}$ (L/s)	1.77 (0.66)
FEV_1/FVC	0.82 (0.07)
$FEF_{25–75}$/FVC	0.91 (0.28)
FEF_{25} (L/s)	3.32 (1.11)
FEF_{75} (L/s)	0.83 (0.35)
Birth/prenatal characteristics; %	
Low birth weight (<5.5 lb)	6
Premature birth (<37 wks gestation)	12
Mothers age at child's birth (yrs)	
≤18	6
≥35	14
First-born child	48
Mother smoked when pregnant	9
Breastfed (any)	72
Birthplace	
California	93
Fresno or Clovis	76
Pollutant season of birth	
Winter (Oct–Jan)	28
Spring (Feb–May)	41
Summer (June–Sept)	31
Health history; %	
Parental report of rhinitis	31
Parental report of eczema	18
Severe asthma (modified GINA score)	20
Atopic by skin test/previous severe reaction	62
Asthma diagnosed by age 2 yrs	39
Residential history provided; mean (range)	
% of pregnancy	87 (11–100)
% of life	97 (12–100)

simultaneously to identify variables that provided the best predictive model for each pulmonary function outcome. The Deletion/Substitution/Addition (DSA) routine[20] uses the L2 loss function criterion (ie, minimizes the residues between observed and expected based on cross-validated model estimates). In this procedure, candidate predictors of the outcome, given all pollutant metrics and covariates (confounders and effect modifiers), are defined with polynomial generalized linear models generated with the algorithm (see below) under user-specified constraints. The space of candidate predictors is parameterized with 3 variables: the number of terms, the order of interactions, and sum of powers in each term. Models were restricted to size = 10, interaction = 2, and sum of powers = 3. To reduce the number of candidate confounders and modifiers (>100), a candidate-reduction step was implemented. Univariate regression analyses of the explanatory variables on each candidate variable were run and the *P* values that correspond with the test of the null hypothesis were used to rank the candidate variables. The model selection procedure relies on cross-validation and, thus, random splits of the data. For a given call, the data splits correspond to the aggregation of *k* independent 5-fold splits of the data. The value for *k* was set to 10. During this process, models that are influenced by outliers will not hold up in the cross-validation process and will not be chosen as the "best model." They are not likely to be reported in any stable way over the 10 repetitions. Additional details about the Deletion/Substitution/Addition routine are presented in the appendix (available with the online version of this article).

Standard errors were obtained for the semi-parametric model selected with this routine, using the GEE package in the software package R,[21] the estimate of standard errors assumed an independence correlation structure. Note that this approach ignores the extra variability of our estimates introduced by the model-selection procedure, and thus possibly underestimates the variance.

Several sets of analyses were conducted using the Deletion/Substitution/Addition routine. First, for descriptive purposes, the list of candidate variables for each pulmonary function outcome model was restricted to the characteristics listed in Table 1 (ie, no pollutant metrics). Next, a more extensive analysis expanded the list of candidate variables to include pollutant-specific metrics for the entire pregnancy, each trimester, the first 3 years of life, the first 6 years of life, and the entire lifetime. Additional analyses were run that restricted the list of possible pollutant metrics to those that summarize the entire prenatal and entire lifetime intervals. In these last 2 sets of analyses, a single pollutant or combination of pollutants could have entered the best model.

The Deletion/Substitution/Addition algorithm is relatively new; therefore, for comparison purposes, the more traditional step-wise regression also was performed with SAS software (SAS Institute, Cary, NC). In this approach, vari-

ables are added 1 by 1 to the model; and the F statistic for a variable to be added must be significant ($P < 0.05$) at the user-specified entry level.

RESULTS

The characteristics of the subgroups included in this analysis are displayed in Table 1. A comparison of the pulmonary function values by characteristics is in eTable 3. The 6 children (3%) who were born in Mexico were not included in the prenatal analysis, due to our inability to obtain prenatal exposure information from Mexico. At the time of the baseline interview, only 20% of mothers were living in the home they had lived when pregnant with the enrolled child.

The distributions of pollutant metrics used for regulatory purposes are presented in Figure 1. As expected, the trimester-specific metrics are more variable than those for the entire prenatal or year-long metrics. Correlations between pairs of these pollutants are presented in Table 2. Only the entire pregnancy and lifetime measures are presented. In general, the strongest correlations are seen between NO_2 and CO, which are both negatively correlated with O_3.

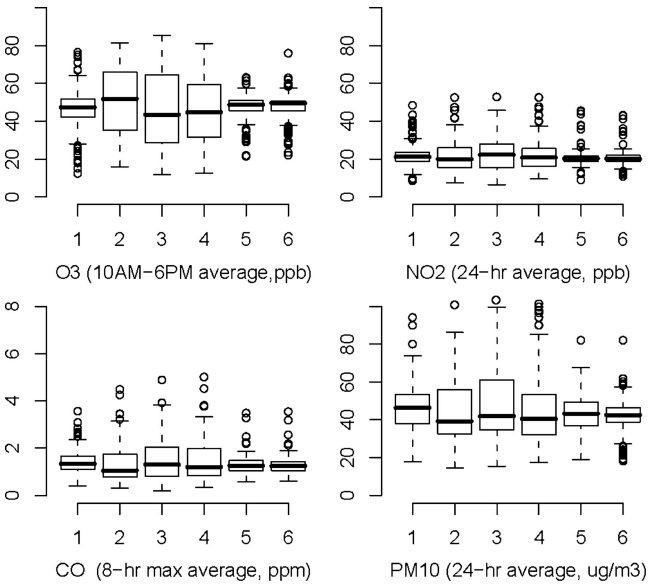

FIGURE 1. Distribution of pollutant metrics used for regulatory purposes. Timeframes: 1, entire prenatal period; 2, 1st trimester; 3, 2nd trimester; 4, 3rd trimester; 5, entire lifetime; 6, age 0–3 years; 7, age 0–6 years.

The results of the set of models that did not consider any pollutants in the candidate list are displayed in eTable 4. Table 3 displays the findings from the primary model selection process that included metrics for each trimester, the entire pregnancy, the first 3 and 6 years of life, and lifetime (birth through enrollment in the original study). In general, the effect sizes ranged from declines of 0% to 7.8% in the mean pulmonary function measure per interquartile-range (IQR) increase in the mean pollutant concentration. The list of variables selected for each model can be found in the table. As expected, height was selected in each model, with the exception of the ratio outcomes. For brevity, only the pollutant metrics selected are discussed below. The best model for FVC included a negative interaction between NO_2 during the second trimester and African American race. The best model for FEV_1 included a negative term for NO_2 in the second trimester (cubed). The best model for PEF included a negative interaction between first trimester exposure to PM_{10} and mothers' smoking status when pregnant. The best model for $FEF_{25–75}$ included a positive (but not significant) effect of exposure to CO during the first trimester. For the FEV_1/FVC ratio, a negative effect of CO during the first 3 years of life (squared) was chosen. The best model for $FEF_{25–75}$/FVC identified a negative effect of CO during the first 6 years of life among children diagnosed with asthma before the age of 2 years. The best model for FEF_{25} included a negative interaction between exposure to PM_{10} during the second trimester and mother's smoking status during pregnancy, as well as a negative interaction between CO in the first 6 years of life and a diagnosis of asthma before the age of 2 years. No pollutant effect was identified for FEF_{75}.

When only summary metrics for the entire pregnancy or lifetime were considered, the results were similar; effect sizes ranged from no effect to decreases of 15% in the mean pulmonary function measure per IQR increase in the pollutant concentration (eTable 4). Stepwise procedures (eg, PROC REG in SAS) do not consider all interactions and nonlinear terms unless specifically included in the model statement.

TABLE 2. Correlations Between Regulatory Pollutant Metrics for Prenatal and Lifetime Intervals

	Lifetime				Prenatal			
Lifetime	CO (8-h maximum)	NO_2 (24-h average)	O_3 (8-h maximum)	PM_{10} (24-h average)	CO (8-h maximum)	NO_2 (24-h average)	O_3 (8-h maximum)	PM_{10} (24-h average)
CO (8-h maximum)	1	0.68	−0.40	0.05	0.52	0.37	−0.16	−0.05
NO_2 (24-h average)	—	1	−0.40	0.30	0.36	0.51	−0.16	0.12
O_3 (8-h maximum)	—	—	1	0.39	−0.01	−0.07	0.26	0.22
PM_{10} (24-h average)	—	—	—	1	.23	0.17	0.11	0.42

TABLE 3. Best Predictive Model When Entire Prenatal, Trimester-Specific, First 3 and 6 Years, and Lifetime Metrics Were Considered

Outcome	Intercept and Other Terms in Model	Pollutant Coefficients	SE for Pollutant Coefficient	Adjusted R-Square	Effect Size per IQR Increase in Pollutant
FVC	−2.8013 + 0.0932 × height	−0.0077 (NO_2 [daily max, 2nd tri] × black race)	0.0011	0.7442	−7.1%
FEV_1	−1.8450 + 6.98e − 04 × $height^2$ −0.3150 × black race	−1.837e − 06 × NO_2 (6 AM–6 PM avg, 2nd tri)[3]	0.000001	0.6627	−1.2%
PEF	1.584 + 0.0001 × $height^2$ × age	−0.0112 (PM_{10}, 24 h avg, 1st tri × mother smoked when pregnant)	0.0029	0.6391	−7.8%
$FEF_{25–75}$	0.7214 + 0.1275 × age −0.3450 × diagnosed with asthma <2 yrs old	+0.0215 × CO (24 h avg, 1st tri)[3]	0.0113	0.2540	0.9%
FEV_1/FVC	0.8762 − 0.103 × atopy −0.0402 × diagnosed with asthma <2 yrs old	−0.0073 × CO (daily max, age 0–3)[2]	0.0016	0.1335	−2.5%
$FEF_{25–75}$/FVC	1.0179 − 0.1393 (ever used steroid × atopy)	−0.2179 (CO [24 h avg, age 0–6] × diagnosed with asthma <2 yrs old)	0.0446	0.1302	−4.8%
FEF_{25}	1.2239 + 0.0053 × (height × age)	−0.0076 × (PM_{10} [24 h avg, 2nd tri] × mother smoked when pregnant)	0.0033	0.4939	−5.6%
		−0.8717 (CO [24-h avg, age 0–6]^2 × diagnosed with asthma <2 yrs old)	0.015	—	−6.7%
FEF_{75}	0.5290 + 0.0000032 × $height^3$ −0.1231× ever used steriods −0.1450 × black race −0.1143 × diagnosed with asthma <2 yrs old) −0.0557 × low income	—	—	0.2109	—

Therefore, for the comparison of the model selection procedures, all interaction and nonlinear terms that were identified by the Deletion/Substitution/Addition procedure (ie, for FVC, NO_2 during the second trimester × African American race) were calculated and included as candidates for that outcome in the more traditional step-wise approach (Table 4). For FVC, for example, both model selection results included the height and a negative interaction for NO_2 during the second trimester and African American race. The stepwise model selection process also included negative terms for 2nd trimester exposure to CO and current inhaled steroid use, as well as a positive term for PM_{10} during the first 3 years of life.

DISCUSSION

In multivariable analyses, negative effects on pulmonary function were found for exposure to PM_{10}, NO_2, and CO during key neonatal and early life developmental periods. Most of the effects were limited to subgroups of the population with characteristics typically associated with a greater prevalence or severity of asthma. Specifically, children who are African American, were diagnosed with asthma at an early age, exposed to maternal smoking during pregnancy or had a history of atopy or steroid use were the most responsive to the pollutants. The study findings highlight the importance of characterization of exposures during important developmental periods, such as specific trimesters or years of life, which may be useful to identify possible mechanisms by which pollutants exert their effect and to identify critical periods for intervention.

When the adjusted R-square values from the variables in the models chosen by the Deletion/Substitution/Addition procedure were compared with those from the traditional stepwise procedure, the results sere similar. More important, the overall conclusions are similar—prenatal and early-life exposure to CO and NO_2 were negatively associated with lung function at age 6–11 years. However, our new procedure identified nonlinear effects for many of the associations. For several outcomes, multiple pollutants were included in the model selected. These findings highlight the need for flexible model-selection strategies (such as this one) that consider all relevant interactions and nonlinear terms and copollutants. Important interactions would have been missed and null effects may have been assumed when, in fact, key subgroups appear to be substantially more susceptible.

There are several other advantages to this newer model selection method. The Deletion/Substitution/Addition procedure uses cross-validation to identify the best model. SAS fits the model on the entire dataset and does not use the cross-validation; it is therefore more susceptible to over-fitting the model. The traditional stepwise selection tended to pick a larger model, and one with several pollutants. Often these pollutants had opposite signs, which may have counter intu-

TABLE 4. Model Selected by Traditional Stepwise Selection

	Coefficient	Standard Error
FVC (adjusted R-square = 0.7504)		
Intercept	−2.8619	0.2452
Inhaled steroid use	−0.1295	0.0435
CO (24-h average, 2nd trimester)	−0.0878	0.0415
PM_{10} (24-h average, age 0–3 yrs)	0.0121	0.0037
Height	0.0869	0.0055
NO_2 (1 h-max, 2nd trimester) × African American race interaction	−0.0066	0.0013
FEV_1 (adjusted R-square = 0.6941)		
Intercept	−1.8072	0.2318
Asthma diagnosis at <2 yrs	−0.1233	0.0403
Eczema	−0.1845	0.0619
Inhaled steroid use	−0.0834	0.0398
African American race	−0.2401	0.0526
NO_2 (6 AM–6 PM average, 2nd trimester)	−0.0071	0.0024
PM_{10} (24-h average, age 0–3 yrs)	0.0102	0.0034
Height	0.0633	0.0050
PEF (adjusted R-square = 0.6340)		
Intercept	−5.5549	0.6998
Asthma diagnosis at <2 yrs	−0.2595	0.1225
PM_{10} (24-h average, age 0–3 yrs)	0.0303	0.0103
Height	0.1615	0.0151
PM_{10} (24-h average 1st trimester) × mother smoked while pregnant interaction	−0.0102	0.0039
$FEF_{25–75}$ (adjusted R-square = 0.2786)		
Intercept	1.16510	0.3318
Asthma diagnosis at <2 yrs	−0.35514	0.0959
Eczema	−0.39476	0.1474
CO (24-h average, lifetime)	−0.94454	0.3975
Height (squared)	0.00054	0.0107
$FEF_{25–75}$/FVC (adjusted R-square = 0.0827)		
Intercept	0.9680	0.0335
Asthma diagnosis at <2 yrs	−0.0348	0.0123
History of steroid use	−0.0272	0.0122
CO (8-h max, lifetime)	−0.1090	0.0303
FEV_1/FVC (adjusted R-square = 0.1276)		
Intercept	1.6161	0.2761
History of steroid use	−0.1360	0.0455
CO (8-h max, prenata1)	0.1711	0.0653
O_3 (10 AM–6 PM average, lifetime)	−0.0254	0.0069
CO (1-h max, lifetime)	−0.3242	0.0919
O_3 (24-h average, age 0–3 yrs)	0.0345	0.0086
CO (24-h average, age 0–3 yrs) × asthma diagnosis at <2 yrs interaction	−0.1814	0.0599
FEF_{25} (adjusted R-square = 0.4823)		
Intercept	−4.0815	0.8082
History of eczema	−0.5145	0.2162
African American race	−0.3768	0.1871
NO_2 (1-h max, age 0–3 yrs)	0.0344	0.0142
Height	0.1251	0.0165
CO (24-h average, age 0–6 yrs)^2 × asthma diagnosis at <2 yrs interaction	−1.0460	0.1953
FEF_{75} (adjusted R-square = 0.1844)		
Intercept	0.9639	0.1573
Asthma diagnosis at <2 yrs	−0.1448	0.0546
History of steroid	−0.1453	0.0535
CO (8-h max, lifetime)	−0.4214	0.1423
Height (cubed)	0.000003	0.0008

itive interpretations due to the colinearity among the pollutants. In addition, the Deletion/Substitution/Addition approach can compare models based on different samples sizes, unlike methods such as the Akaike's Information Criteria, which can only compare across same sample size or nested models. These results lead us to feel that traditional step-wise method should not be considered the "gold standard" and that the cross-validation methods are superior.

The large number of exposures and modifiers examined may raise concerns about multiple testing. Given that this was the first study to examine this research question and is exploratory (given the small sample size), our approach erred on the side of too many, rather than too few, comparisons. For example, when our model-selection procedure is allowed to "choose" between a metric that covers the entire prenatal period and a metric that covers only the 2nd trimester, the cross-validation process revealed that the model with the 2nd trimester metric was superior. This more specific and biologically more plausible finding would not be revealed if only summary (or fewer) metrics were considered. The same argument applies to the inclusion of modifiers such as race. For FVC, the model with the interaction between African American race and NO_2 was chosen over a model that also included main effects for each term, which suggests that the effect may be limited to, or at least substantially greater among, African American children.

Finally, the "state of the art" with respect to the research question warrants the detailed exploration undertaken. Current approaches to the multipollutant complexity of the ambient environment have been constrained by model-fitting choices. Moreover, they have required some "guessing" as to the proper form of the model without a thorough investigation of the strength of the guess. On theoretical grounds, the Deletion/Substitution/Addition method identified the "best fit" (ie, smallest cross-validated loss function) for the form and complexity. When combined with subject matter knowledge, this allows for the exploration of the sensitivity of results to a range of model specifications and presents results that are maximally robust with respect to these issues.

In contrast to previous findings,[5] we did not find a negative effect of exposure to O_3 among this cohort. As shown in Table 2, NO_2 and O_3 concentrations are negatively correlated ($r = -0.4$), while NO_2 and CO concentrations are

highly positively correlated ($r = 0.7$) in Fresno. NO_2 and CO are markers for pollutants generated by urban combustion sources, primarily mobile sources in Fresno. Most of the residences are located in the urban and suburban areas that have elevated NO_2 and moderate O_3 concentrations. Few participants lived in the downwind areas (eg, near Parlier, CA) that have high O_3 and low NO_2 and CO concentrations. The absence of rural downwind exposures in our study population probably explains the lack of O_3 association with the outcome. The NO_2 and CO associations are stronger than the O_3 association in this urban setting, where substantial scavenging of O_3 by fresh NO emissions occurs.

Our data suggest that first and second trimester pollutant exposures (PM_{10} and NO_2, specifically) had a negative effect on pulmonary function at age 6–11 years. An important consideration in the determination of the effects of various environmental exposures on respiratory health in children is the state of development of the lungs and the immune system at the time of exposure. The lungs begin to develop at 6 weeks of gestation and continue through distinct phases of progression. The airways and blood vessels are in place by 26 weeks' gestation. The proliferation of alveoli occurs primarily from 26 weeks through birth, and continues during extrauterine life until approximately 8 years of age, although most alveoli are formed by age 2 years. In utero exposure to tobacco products has been shown to have effects on measures of airway function and not on lung volumes, which suggests that there is a vulnerable period with respect to respiratory tract development in the first and early second trimesters.[22] Since tobacco smoke contains many compounds found in ambient air (NO_2, CO, fine particulate, polycyclic aromatic hydrocarbon), it is reasonable to hypothesize that ambient pollutant exposures also alter the development of the fetal respiratory tract through similar mechanisms.

In utero exposure to tobacco smoke is known to be associated with low birth weight[23] and with lower lung function later in childhood[24,25] and the occurrence of asthma.[26] In utero exposures to maternal smoking have been found to be associated with decreased pulmonary function in infants[27,28] and children of school age, especially for small airway flows.[25] Data from the NHANES3 study indicate that high cotinine levels in children aged 4–11 years were associated with 2% declines in FEV_1 and 6% declines in $FEF_{25–75}$.[29] These effect sizes are quite similar to those seen for an IQR increase in the pollutants examined in this analysis.

There are limitations to this study and our analytic approach. Our findings are based solely on asthmatic children and may not apply to children without asthma. When exposure assignment is based on ambient central monitors, misclassification is always a concern. Most pollutants, however, do not vary a great deal within geographic areas of this size, and therefore, central monitors are likely to be a good representation of outdoor exposures. Children of this age do not attend schools that are far enough from their homes to warrant the use of a different monitor. It is possible that the observed significant negative health findings are confounded or due to chance. This is unlikely, given the wide range of confounders and modifiers considered, and the consistency with which these effects were identified across a range of outcomes, time periods and with extensive cross-validation and model selection strategies. The Deletion/Substitution/Addition approach automatically tests for interactions between all candidate covariates that could be problematic if biologically irrelevant covariates are identified. All of the interactions reported here, however, are biologically plausible, given an extensive literature on risk factors for asthma severity and susceptibility to environmental exposures.

These findings are based on observational data, and, as such, are subject to bias due to observed and unobserved confounding. Consequently, the effects observed cannot necessarily be interpreted as causal. However, given the broad range and parameterizations of confounders and modifiers that were considered in the model selection, it is likely that most key confounders have been addressed.

These findings are important for several reasons. There is an expanding literature regarding the harmful effects of prenatal exposures on children's health. Our data provide support for the concept that effects of prenatal exposures can be seen among school-aged children. As has been shown in the literature regarding passive smoke exposure, it is difficult to disentangle the effect of prenatal and postnatal exposures. Our models suggest that each time period of exposure may contribute independently to different dimensions of school-age children's pulmonary function. For 4 of the 8 pulmonary-function measures, prenatal exposures were more influential than early-lifetime metrics, while, in contrast, the ratio measures (FEV_1/FVC and $FEF_{25–75}$/FVC) were most influenced by postnatal exposures. This may reflect the fact that airway development and final alveolarization occur at different stages and, therefore, exposure during these phases affects different dimensions of lung health. The effect sizes for prenatal exposures are comparable to those for tobacco exposure during pregnancy. The large number of pregnant women and young children exposed to these pollutants, however, may increase the magnitude of the resulting public health burden. If these effects remain in adulthood, children exposed in early-life may be at greater risk for serious and debilitating respiratory disease.

We identified clinically meaningful health effects of prenatal and early life pollutant exposures. The Deletion/Substitution/Addition procedure identified interactions, nonlinear effects, and copollutant effects that were not as readily identified with a more traditional analytic approach. These findings suggest that prenatal and early-life exposures to NO_2, CO, and PM_{10} adversely affect the pulmonary function of asthmatic children through preadolescence, and that the

timing of the exposure may be more important than overall dose. Most effects were limited to subgroups of the population with characteristics typically associated with asthma severity. Evaluation of population subgroups at greater risk for adverse respiratory responses to air pollution is important for the estimation of the public health burden imposed by air pollution. Identification of susceptible groups may provide useful scientific information about the mechanisms for air pollution-related health effects.

ACKNOWLEDGMENTS

We recognize the important work of Lucas Carlton for geocoding the addresses. We also acknowledge the contributions of the entire FACES staff.

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