The Relationship between Air Pollution, Lung Function and Asthma in Adolescents

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Online Data Supplement

METHOD

Fourth, seventh, and tenth grade children were enrolled into the study in 1993 from 12 communities in southern California, (selected on the basis of different ambient pollution levels). In 1996, an additional fourth grade cohort from the same communities and schools was added to the study. The average participation rate of students in each classroom was 81%. At study entry parents or guardians of the children completed a questionnaire, which provided demographic information, characterized history of prior respiratory illness and its associated risk factors, and household characteristics. At study entry and in each subsequent year until high school graduation, children provided information on asthma symptoms, diagnoses of asthma and smoke exposure.

Study cohort

To provide a targeted age range in which to assess the effect of lung function on asthma risk from childhood through adolescence, this analysis was restricted to the two fourth grade cohorts (n=4,273). Lifetime history of asthma and wheezing at cohort entry was defined using questionnaire responses. Approximately 34% of the children had a history of asthma (n=681) or wheezing (n=763) at study entry. Children with any history of asthma/wheeze were excluded from the primary. To ensure a study population that was free of any previous history of wheeze or asthma, we also excluded children who did not have wheeze information (n=244) at study entry or had a history of serious childhood chest disease (i.e. chest surgery or cystic fibrosis) (n=7). Children who did not perform adequate lung function maneuvers at study entry (n=206) and subjects with less than one follow-up assessment (precluding incident asthma diagnoses, n=315) were excluded from the analysis of this study. These exclusions resulted in a total of 2,057 children classified as 'disease free' at baseline (Table 1).

Sociodemographic and medical history information

Ethnicity was defined as non-Hispanic white, Hispanic, African American, Asian, and mixed/other ethnicities. Selected aspects of children's early medical histories such as birth weight, preterm birth and duration of gestation and any special care at birth were collected at baseline from the parents. Parental history of asthma and allergy was collected at baseline. Family history of asthma and allergy was defined as any biological parent having been diagnosed with asthma. Parents also provided history of any allergies for their children. We categorized BMI into age- and sex-specific percentiles based on the Centers for Disease Control (CDC) BMI growth charts using one-month age intervals (11). Participants with BMI at or above the 85^{th} percentile were classified as overweight. Participation in team sports was used to assign children's physical activity levels.

Air-pollution data

Air-pollution–monitoring stations were established in each of the 12 communities in 1993. These stations have been measuring average hourly levels of ozone (O_3), nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}) since their establishment. Two-week integrated-filter samples for measuring acid vapor and the mass and chemical makeup of particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) were also collected. Acid vapor included both inorganic acids (nitric and hydrochloric) and organic acids (formic and acetic). For statistical analysis, we used total acid computed as the sum of nitric, formic and acetic acid levels. Hydrochloric acid was excluded from this sum, since levels were very low and close to the limit of detection. We also determined the levels of

elemental carbon and organic carbon using method 5040 of the National Institute for Occupational Safety and Health.[1] We computed annual averages on the basis of average levels in a 24-hour period in the case of PM_{10} and nitrogen dioxide, and a two-week period in the case of $PM_{2.5}$, elemental carbon, organic carbon and acid vapor. For ozone, we computed the annual average of the levels obtained from 10 a.m. to 6 p.m. (the eight-hour daytime average) and of the one-hour maximal levels. We also calculated long-term mean pollutant levels (from 1994 through 2003) for use in the statistical analysis of the lung-function outcomes. As relative position of the communities in respect to any given pollutant did not vary substantially between years, the long term average was the proper metric to be used in the analysis.

We have previously shown that the average levels of study pollutants of the 12 communities of this study varied substantially between the communities, but there was little year-to-year (1994-2001) variation in levels within any one community(2). Similar to our earlier report, average level of O_3 was not correlated with any of the other pollutants though a significant correlation was observed between all other study pollutants during the period 1994-2003 (Table E1). Thus, $PM_{2.5}$, NO_2, acid vapor, PM_{10} and elemental and organic carbon are a correlated non-ozone 'package' of pollutants with a similar pattern relative to each other across the 12 communities. The annual ranking of the communities into 'high' (six communities) and 'low' (six communities) based on annual average of ozone or any of the non-ozone 'package' of pollutants remained consistent throughout the calendar years between 1994 and 2003. Communities defined as 'high' or 'low' based on any of the non-ozone 'package' of pollutants were the same for all of the correlated pollutants. Thus the communities stratified into 'high' and 'low' based on the $PM_{2.5}$ level should be considered 'high' and 'low' for all of the non-ozone pollutants. However, we have defined them as high/low $PM_{2.5}$ because $PM_{2.5}$ showed the strongest effect in statistical associations between lung function and new onset asthma (Figure 1).

Table E1. Correlation of mean air-pollution levels from 1994 through 2003 across the 12 communities*

Pollutant	NO_2	Acid Vapor	PM_{10}	$PM_{2.5}$	Elemental Carbon	Organic Carbon
				R values		
Ozone (10a.m.-6p.m.)	-0.10	0.36	0.17	0.15	-0.04	0.12
NO_2		0.86	0.67	0.81	0.94	0.64
Acid Vapor†			0.79	0.86	0.88	0.75
PM_{10}				0.95	0.85	0.97
$PM_{2.5}$					0.92	0.90
Elemental Carbon						0.88

* Unless otherwise noted, values are the 24 hour average pollution levels. NO_2 denotes nitrogen dioxide and $PM_{2.5}$ and PM_{10} particulate matter with an aerodynamic diameter of less than 2.5 μm and less than 10 μm, respectively. All pairwise correlations were significant except between ozone and other pollutants.

† Acid vapor is the sum of nitric, formic and acetic acid.

Lung function measurement

To determine the predicted lung function values, i.e., FVC, FEV_1 and $FEF_{25-75,}$ we fitted a gender-specific linear regression model for log-transformed observed lung function values with the known predictors from previous literature.[2,3] The selection of the best prediction model

was based on the attained R^2. The best model for predicting lung function included race ("White", "Hispanic", "African-American", "Asian", "Mixed" or "Others"), log values for height, body-mass index, the square of body-mass index, any exercise or respiratory tract illness on the day of the test, exposure to secondhand tobacco smoke and indicator variables for field technician and spirometer. The predicted model attained R^2 value of 0.80 or better for FVC and FEV_1 in both sexes but was much lower for FEF_{25-75}, 0.44 for girls and 0.54 for boys. An R^2 value above 0.60 or 0.80 could be attained for FEF_{25-75} if the prediction model also included observed FVC or FEV_1 values. Previous publications also have noted similar low R^2 values for FEF_{25-75} [4,5] when the prediction model does not include any lung function terms. The percent predicted lung function was computed by dividing the observed lung function measurement by the predicted values and was expressed in percentage (%). A percent predicted value of less than 100% meant that the child's observed lung function was lower than the expected value. The percent predicted lung function values were similar in both sexes at study entry (Table E2). The percent predicted values and ratios in this study were similar to earlier published reports.[3, 4] The FEV_1/FVC values ranged from 64-100% with less than 8% of children having baseline value less than 80%. The FEF_{25-75} values ranged from 31.7% to 212.8% though 5%-95% of the data ranged from 68.4%-140.1%.

Ambient air pollution, lung function and asthma

To assess the effect of ambient air pollution on the relationship between lung function and new asthma, we needed to consider the possible effect of the communities as all children within a community had the same exposure levels. To address this issue we fitted two stage models to this time dependent data.[6] Letting $\lambda(t)$ be the expected hazard rate for asthma in this population and $\lambda_{bs/sex\text{-}age}(t)$ be the sex- and age-specific baseline hazard, then the first stage proportional hazard model[24] has the following form:

Stage 1: $\lambda(t) = \lambda_{bs/sex\text{-}age}(t) \exp\{b_{cLF}Z + \gamma W\}$ ……(1)

where, b_{cLF} corresponds to 12 community-specific slopes of lung function on asthma risk. This model is further adjusted for different individual level covariates, W (such as race/ ethnicity). The first stage model is followed by an ecologic regression model in the form:

$b_{cLF} = \delta_0 + \delta X_c + \eta_c$ ……(2)

The parameter δ_0, the mean of the within-community slopes b_{cLF}, serves as an aggregated effect estimate of lung function across communities. However, our parameter of interest is δ, which characterizes the modifying effect of the long-term average pollution levels (X_c) on the relationship between lung function and asthma. Note that the second stage model (2) accounts for heterogeneity in the community specific slopes via η_c. The second stage "ecologic" regression is weighted by the inverses of the variances of b_{cLF}.

Using this framework, we fitted separate models for seven pollutants; O_3 (10 a.m.–6 p.m. daily average ozone), and averages of PM_{10}, $PM_{2.5}$, NO_2, acid vapor (sum of nitric, formic and acetic acid), and elemental and organic carbon. The averages were based on available daily (or bi-weekly) pollutant levels from 1994 to 2003. The effect of ambient pollution on the relationship between lung function and new onset asthma was graphically presented by plotting the pollutant on the X-axis and community specific hazard ratio over the 10th-90^{th} percentile range of lung function on the Y-axis. The exponential regression line is drawn through the predicted values derived from the stage two equations.

Table E2: Descriptive statistics of lung functions at study entry (age 7-9 years) for Children's Health Study participants without any history of physician-diagnosed asthma.

Sex	N	Variable	Mean (%)	Standard Dev (%)	Median (%)	Lower Quartile (%)	Upper Quartile (%)	Minimum (%)	Maximum (%)
Girls	1095	FVC	100.6	10.7	100.5	94.1	107.4	50.4	138.6
		FEV_1	100.6	11.0	100.8	93.7	108.1	35.6	136.6
		FEV_1/FVC	89.3	5.3	89.3	86.2	92.3	64.2	100.0
		FEF_{25-75}	102.8	23.4	101.9	87.3	117.5	31.6	212.8
		FEF_{25-75}/FVC	110.6	26.1	109.1	91.4	127.2	37.1	217.3
Boys	962	FVC	100.5	9.8	100.5	93.6	107.1	60.9	135.0
		FEV_1	100.5	10.2	100.3	93.9	106.8	68.9	141.8
		FEV_1/FVC	87.4	5.0	87.4	84.4	90.3	64.0	100.0
		FEF_{25-75}	102.3	21.5	100.7	87.1	116.5	36.6	178.5
		FEF_{25-75}/FVC	101.2	23.3	99.4	85.0	114.1	36.2	202.1

Table E3: Comparison of selected characteristics of Children's Health Study participants between those with (n=2,057) and without (n=521) sufficient lung function assessment

	N (2057)	%	N (521)	%	P-value
Age at Entry					
7-9 Years	1441	70.0	326	62.6	0.38
10 Years	557	27.1	164	31.5	
11-12 Years	59	2.9	31	5.9	
Race/ethnicity					
Non-Hispanic white	1094	53.2	249	47.8	0.04
Hispanic	651	31.7	170	32.6	
African-American	110	5.4	40	7.7	
Asian	101	4.9	16	3.1	
Mixed	63	3.1	19	3.6	
Other/unknown	38	1.9	27	5.2	
Gender					
Female	1095	53.2	282	54.1	0.86
Male	962	46.8	239	45.9	
Parental history of asthma	273	13.3	76	14.6	0.41
History of allergy	371	18.0	88	16.9	0.92
History of allergic rhinitis	322	15.7	102	19.7	0.61
Humidifier use	497	24.2	107	20.5	0.60
Maternal Smoking during pregnancy	293	14.2	93	17.8	0.63
Postnatal maternal smoking	189	9.2	82	15.7	0.17
Household second-hand smoking	357	17.4	132	25.3	0.17
Pests in home	1455	70.7	343	65.8	0.51
Dogs in home	1134	55.1	235	45.1	0.04
Pets in home	1562	75.9	352	67.6	0.07
Health insurance	1661	80.8	92	17.7	0.39
Parental Income*					
≤14,999	307	17.5	127	29.6	0.05
15,000-49,999	749	42.7	188	43.8	
>50,000	697	39.8	114	26.6	
Parental Education*					
Less than high school	295	14.9	100	20.1	0.26
High school or greater	1678	85.1	397	79.9	
Cohort					
1993	1046	50.9	291	55.9	0.19
1996	1011	49.1	230	44.1	

*Numbers don’t add up to 2057 due to presence of missing data.

Table E4: Cumulative incidence rate, person years of follow-up and number of newly diagnosed cases of asthma, by lung function categories.

Lung Function	Person Years	New Asthmatics	Cumulative Incidence Rate (per 1000 person year)
FVC(%Predicted)*			
<=90	1942.0	28	14.4
90-110	8656.6	157	18.1
>110	2437.5	25	10.2
FEV_1(%Predicted)			
<=90	1858.6	36	19.4
90-110	8776.1	150	17.1
>110	2425.3	25	10.3
FEF_{25-75} (%Predicted)			
80-100	5987.8	122	20.4
100-120	4071.3	62	15.2
>=120	2844.1	27	9.5
Total	13130.6	212	16.1

*Percent predicted is calculated as the percentage of observed lung function values over predicted.

Table E5: Association of lung function categories at study entry with new onset asthma among CHS children, adjusted relative risk (HR) and 95% confidence intervals (95% CI)*

Lung Function	Model 1		Model 2		Model 3		Model 4	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
FVC%	0.87	(0.60-1.27)	0.81	(0.51-1.28)	0.90	(0.61-1.32)	0.95	(0.67-1.34)
FEV%	0.64	(0.44-0.94)†	0.57	(0.37-0.87)†	0.63	(0.43-0.92)†	0.67	(0.47-0.96) †
FEF_{25-75}%	0.53	(0.35-0.79)‡	0.47	(0.29-0.75)‡	0.46	(0.30-0.70)‡	0.50	(0.34-0.72) ‡

*All Cox models are adjusted for race/ethnicity and communities with separate baseline hazards for gender and age at entry.
† P-val<0.05
‡P-val<0.005
Model 1: The asthma definition is restricted to children with inhaler use.
Model 2: The analysis is restricted to children less than 10 years of age at study entry.
Model 3: The analysis is restricted to 5^{th} to 95^{th} percentile of lung function.
Model 4: The analysis is adjusted for preterm birth, birth weight, maternal smoking during pregnancy, family history of asthma and ambient $PM_{2.5}$.

Table E6: Risk of new onset asthma for FEV_1 scaled to 10^{th}-90^{th} percentile range, stratified by community specific annual average $PM_{2.5}$ level*

Model	Low $PM_{2.5}$		High $PM_{2.5}$		P-value
	HR	95%CI	HR	95%CI	
Model 1	0.44	(0.28-0.70) †	1.10	(0.68-1.78)	0.05
Model 2	0.41	(0.14-0.69) †	1.07	(0.62-1.87)	0.05
Model 3	0.38	(0.21-0.71) †	0.85	(0.47-1.55)	0.04
Model 4	0.41	(0.25-0.67) †	1.05	(0.63-1.75)	0.02

*All Cox models are adjusted for race/ethnicity and communities with separate baseline hazards for gender and age at entry.

† P-val<0.0001

Model 1: The asthma definition is restricted to children with inhaler use.

Model 2: The analysis is restricted to children less than 10 years of age at study entry.

Model 3: The analysis is restricted to 5^{th} to 95^{th} percentile of lung function.

Model 4: The analysis is adjusted for preterm birth, birth weight, maternal smoking during pregnancy and family history of asthma.

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