Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Online Supplement

Association of Improved Air Quality with Lung Development in Children

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Figure S1: Follow up periods for cohorts C, D, and E, including the years and average ages of follow-up.

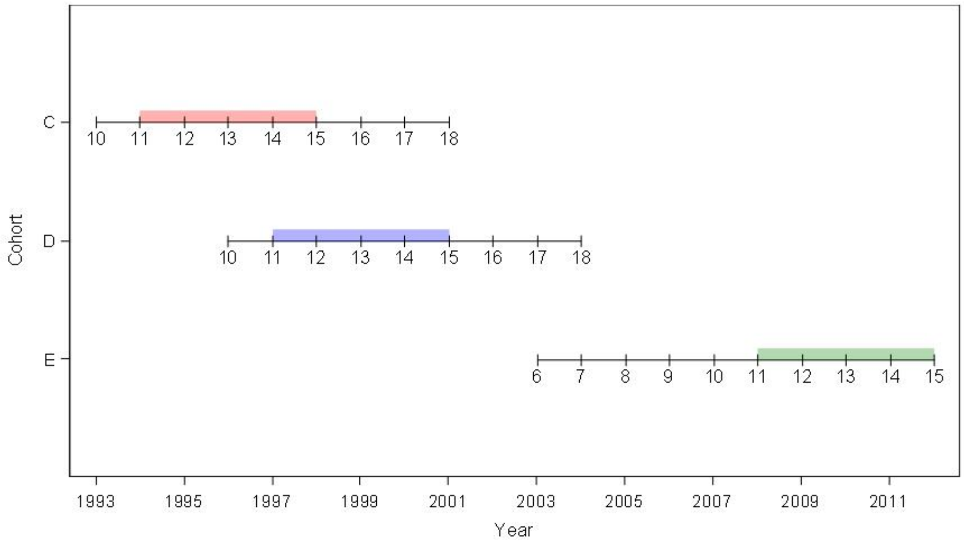


Figure S2: Locations of all CHS communities and the five specific communities (red dots) in which lung function measurements were obtained for all three cohorts

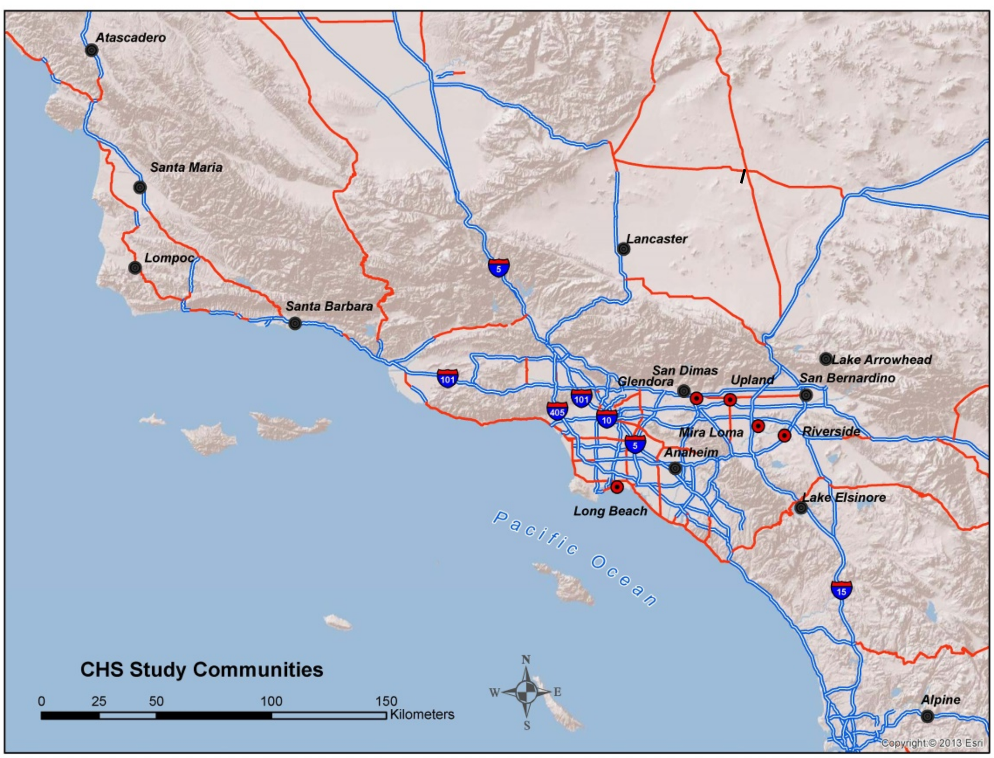


Figure S3: Levels of coarse particles (PM_{10} – $PM_{2.5}$). See Figure 1 for labeling details.

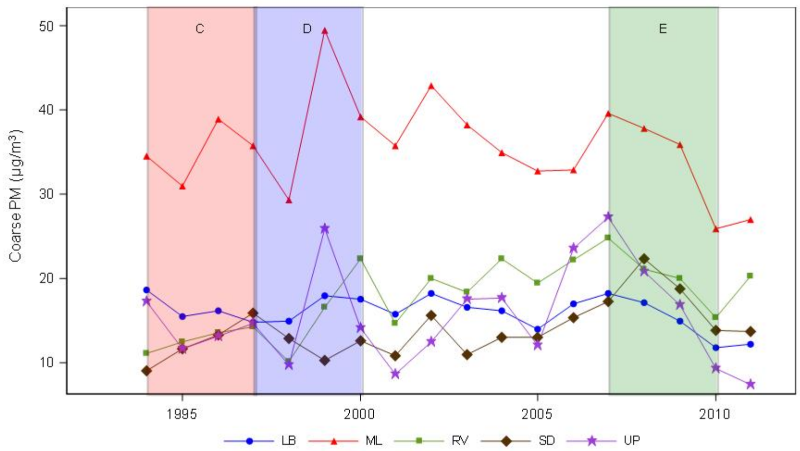
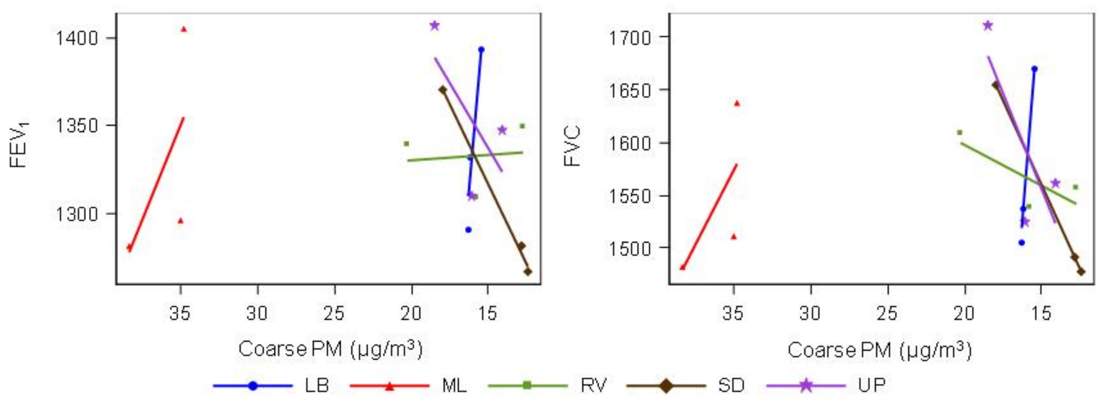


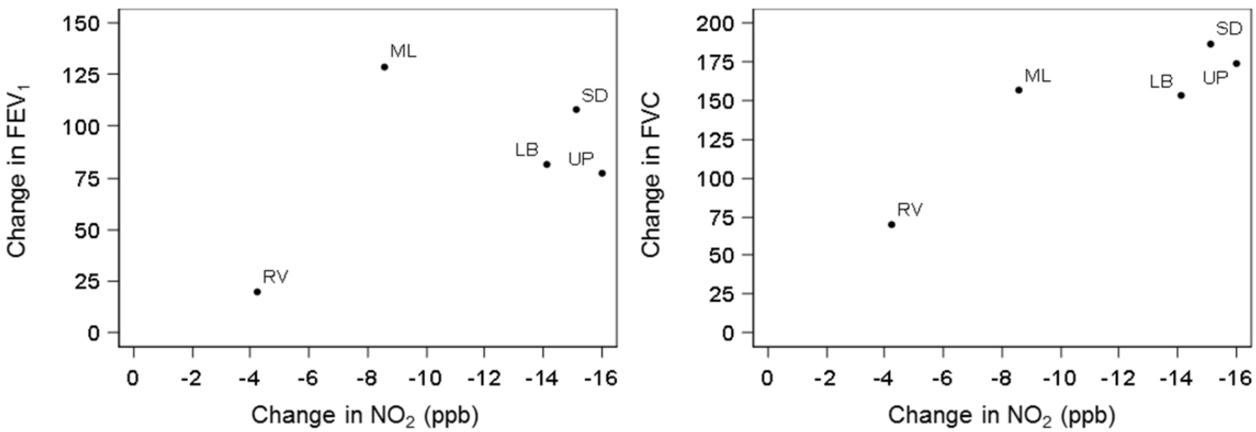
Figure S4: Community-average 4-year growth in FEV1 (a) and FVC (b) from age 11 to 15 versus the corresponding community-average levels of coarse particles.



Notes on Figures S3 and S4: Analysis of coarse particles

There was relatively little variability in the levels of coarse particles (PM_{10} – $PM_{2.5}$) over the study period (Figure S3), compared to that observed for PM_{10} and $PM_{2.5}$ (Figure 1). There was not a statistically significant association between the change in coarse particles over time and 4-yr growth of either FEV_1 (p=0.59) or FVC (p=0.18, Figure S4).

Figure S5: Predicted change in 4-yr lung function growth (vertical change in the trend lines of Figure 2) versus the change in average NO_2 over the study period (horizontal change in the trend lines of Figure 2) for each community
(LB=Long Beach, ML=Mira Loma, RV=Riverside, SD=San Dimas, UP=Upland)



Notes on Figure S5: The analysis of the magnitude of pollutant effect on lung function growth versus the magnitude of change in air quality

We investigated whether the expected gain in lung function over time within any one community was aligned with the magnitude of improvement in air quality within that community. Based on Figure 2, we abstracted the predicted change in lung function growth for each community over the study period as the vertical change in the corresponding trend line. Also based on Figure 2, we abstracted the community-specific changes in NO_2 over the study period, represented by the horizontal changes of each trend line. For example, over the study period, in Riverside the decline in NO_2 was 4.3 ppb with a corresponding estimated increase in FEV_1 growth of 19.8 ml (Figure 2), while in San Dimas the decline in NO_2 was larger (15.1 ppb) as was the estimated increase in FEV_1 growth (107.8 ml). Plotting the vertical changes versus horizontal changes from Figure 2 produces the figure above (Figure S5). We observe a trend in the exposure-response relationship for NO_2 with both FEV_1 and FVC. These plots suggest that if we did have a pure ‘control’ community, one with zero change in air quality over the study period, we might expect to observe little change in lung function growth.

Table S1: Demographic Characteristics

Variable	All N=2,120	Cohort C N=669	Cohort D N=588	Cohort E N=863	P-value*
Age at baseline†	11.0 (0.5)	10.9 (0.5)	10.9 (0.4)	11.3 (0.6)	<0.001
Height (cm)†					
Age 11	145.9 (6.9)	145.7 (6.8)	145.8 (6.8)	146.0 (7.1)	0.73
Age 13	158.0 (7.3)	157.7 (7.4)	157.8 (7.4)	158.2 (7.2)	0.44
Age 15	165.6 (6.9)	165.5 (6.9)	165.8 (7.1)	165.6 (6.7)	0.85
Male					
No	1105 (52.1%)	344 (51.4%)	298 (50.7%)	463 (53.7%)	0.49
Yes	1015 (47.9%)	325 (48.6%)	290 (49.3%)	400 (46.3%)	
Race					
Asian	157 (7.8%)	61 (9.4%)	47 (8.0%)	49 (6.3%)	<0.001
Black	126 (6.3%)	60 (9.2%)	43 (7.4%)	23 (3.0%)	
Mixed	229 (11.4%)	47 (7.2%)	57 (9.7%)	125 (16.1%)	
Other	469 (23.4%)	130 (20.0%)	115 (19.7%)	224 (28.9%)	
White	1027 (51.1%)	351 (54.1%)	323 (55.2%)	353 (45.6%)	
Hispanic ethnicity					
Yes	870 (42.1%)	204 (31.0%)	193 (32.9%)	473 (57.6%)	<0.001
No	1196 (57.9%)	455 (69.0%)	393 (67.1%)	348 (42.4%)	
Asthma at baseline					
No	1646 (82.2%)	536 (86.3%)	465 (82.9%)	645 (78.7%)	<0.001
Yes	356 (17.8%)	85 (13.7%)	96 (17.1%)	175 (21.3%)	
Education					
Did not finish HS	300 (14.8%)	107 (16.5%)	61 (10.7%)	132 (16.3%)	0.0105
HS diploma/some college	1167 (57.6%)	372 (57.4%)	352 (62.0%)	443 (54.6%)	
College diploma or greater	560 (27.6%)	169 (26.1%)	155 (27.3%)	236 (29.1%)	
Insurance					
No	252 (12.3%)	110 (16.9%)	78 (13.5%)	64 (7.9%)	<0.001
Yes	1790 (87.7%)	540 (83.1%)	501 (86.5%)	749 (92.1%)	
In-utero smoke exposure					
No	1793 (88.2%)	532 (82.7%)	494 (86.4%)	767 (93.7%)	<0.001
Yes	241 (11.8%)	111 (17.3%)	78 (13.6%)	52 (6.3%)	
Passive tobacco smoke exposure					
No	1555 (77.9%)	477 (73.7%)	411 (73.7%)	667 (84.2%)	<0.001
Yes	442 (22.1%)	170 (26.3%)	147 (26.3%)	125 (15.8%)	
Smoked >100 cigarettes by age 15					
No	2077 (98.0%)	643 (96.1%)	573 (97.4%)	861 (99.8%)	<0.001
Yes	43 (2.0%)	26 (3.9%)	15 (2.6%)	2 (0.2%)	
Pests					
No	483 (25.3%)	137 (22.8%)	100 (18.6%)	246 (31.9%)	<0.001
Yes	1428 (74.7%)	464 (77.2%)	438 (81.4%)	526 (68.1%)	
Pets					
No	627 (30.4%)	172 (25.7%)	110 (18.7%)	345 (42.8%)	<0.001
Yes	1437 (69.6%)	497 (74.3%)	478 (81.3%)	462 (57.2%)	
Dogs					
No	1114 (54.0%)	319 (47.7%)	260 (44.2%)	535 (66.3%)	<0.001
Yes	950 (46.0%)	350 (52.3%)	328 (55.8%)	272 (33.7%)	
Cats					
No	1457 (70.6%)	444 (66.4%)	360 (61.2%)	653 (80.9%)	<0.001
Yes	607 (29.4%)	225 (33.6%)	228 (38.8%)	154 (19.1%)	
Carpet					
No	125 (6.1%)	29 (4.5%)	21 (3.6%)	75 (9.2%)	<0.001
Yes	1917 (93.9%)	621 (95.5%)	558 (96.4%)	738 (90.8%)	
Mildew/Mold					
No	1484 (75.4%)	484 (75.7%)	428 (75.5%)	572 (75.1%)	0.96
Yes	484 (24.6%)	155 (24.3%)	139 (24.5%)	190 (24.9%)	
Water damage					
No	1733 (85.2%)	552 (84.9%)	494 (85.8%)	687 (84.9%)	0.89
Yes	302 (14.8%)	98 (15.1%)	82 (14.2%)	122 (15.1%)	
Gas stove					
No	322 (15.7%)	102 (15.6%)	109 (18.8%)	111 (13.7%)	0.038
Yes	1723 (84.3%)	552 (84.4%)	472 (81.2%)	699 (86.3%)	
Air conditioning					
No	425 (20.6%)	156 (23.7%)	143 (24.6%)	126 (15.3%)	<0.001
Yes	1640 (79.4%)	503 (76.3%)	439 (75.4%)	698 (84.7%)	
Date of home construction					
1960s to 1970s	692 (32.6%)	215 (32.1%)	184 (31.3%)	293 (34.0%)	0.11
1980 or later	604 (28.5%)	199 (29.7%)	167 (28.4%)	238 (27.6%)	
Before 1960	440 (20.8%)	146 (21.8%)	137 (23.3%)	157 (18.2%)	
Do not know/Missing	384 (18.1%)	109 (16.3%)	100 (17.0%)	175 (20.3%)	

† Values for age and height are the mean (standard deviation).

* p-value comparing mean age and height and proportions of remaining variables across the three cohorts. The test for height includes adjustment for sex, race, and Hispanic ethnicity

Table S2: Mean pollutant levels corresponding to the colored bands in Figure 1

Pollutant	Cohort	Years	Long Beach	Mira Loma	Riverside	San Dimas	Upland
NO_2 (ppb)	C	1994-1997	34.4	23.3	24.7	36.6	39.4
	D	1997-2000	32.9 (-4.5%)	25.3 (8.5%)	25.7 (4.0%)	32.4 (-11.6%)	36.2 (-8.1%)
	E	2007-2010	20.3 (-41.0%)	16.7 (-28.3%)	21.4 (-13.2%)	21.5 (-41.3%)	23.4 (-40.7%)
O_3 (10a-6p, ppb)	C	1994-1997	28.6	56.2	61.9	52	48.8
	D	1997-2000	28.8 (0.7%)	49.3 (-12.3%)	54.1 (-12.5%)	41.4 (-20.5%)	40.9 (-16.1%)
	E	2007-2010	31.4 (10.0%)	48.4 (-13.9%)	54.5 (-11.9%)	46.6 (-10.5%)	47.5 (-2.6%)
PM_{10} ($\mu g/m^3$)	C	1994-1997	37.5	66.5	42.1	36.9	42.9
	D	1997-2000	35.9 (-4.2%)	66.0 (-0.7%)	41.5 (-1.4%)	32.5 (-12.0%)	39.9 (-7.1%)
	E	2007-2010	28.4 (-24.2%)	52.6 (-20.8%)	33.4 (-20.7%)	29.9 (-19.1%)	34.7 (-19.2%)
$PM_{2.5}$ ($\mu g/m^3$)	C	1994-1997	21.3	31.5	29.3	24.5	28.7
	D	1997-2000	19.7 (-7.5%)	27.6 (-12.2%)	25.7 (-12.2%)	19.6 (-19.9%)	23.8 (-17.2%)
	E	2007-2010	13.0 (-38.9%)	17.8 (-43.3%)	13.1 (-55.3%)	11.9 (-51.6%)	16.1 (-43.9%)

Mean pollutant level over the indicated 4-yr period in each community (values in parentheses are the percent change compared to Cohort C)

Table S3: Mean lung function level and growth in girls and boys

	Girls			Boys		
	Age			Age		
Outcome	11 years	15 years	4-yr growth	11 years	15 years	4-yr growth
FEV_1 (ml)	2,274	3,150	876	2,311	3,831	1,520
FVC (ml)	2,581	3,573	992	2,708	4,483	1,774

Table S4: Sensitivity analysis of the effect of decreased NO2 levels on 4-year lung function growth

Model	FEV_1 growth, age 11 to 15		FVC growth, age 11 to 15	
	Difference	P-value	Difference	P-value
Base model (NO_2)*	91.4 (47.9, 134.9)	<0.001	168.9 (127.0, 210.7)	<0.001
Additional Adjustments				
Base + education	90.7 (47.6, 133.9)	<0.001	168.4 (126.8, 210.0)	<0.001
Base + insurance	89.1 (45.6, 132.7)	<0.001	166.5 (127.4, 205.7)	<0.001
Base + in-utero smoke	90.7 (47.3, 134.1)	<0.001	168.6 (126.8, 210.5)	<0.001
Base + passive smoke exposure	90.6 (47.4, 133.7)	<0.001	168.5 (126.8, 210.2)	<0.001
Base + active tobacco smoking	90.9 (47.5, 134.4)	<0.001	167.8 (126.9, 208.7)	<0.001
Base + acute O_3	94.0 (51.9, 136.0)	<0.001	169.7 (128.4, 210.9)	<0.001
Base + asthma	92.6 (49.3, 136.0)	<0.001	168.1 (126.4, 209.9)	<0.001
Base + pests	89.2 (46.4, 131.9)	<0.001	169.2 (127.2, 211.2)	<0.001
Base + pets	87.4 (44.1, 130.7)	<0.001	167.4 (125.1, 209.6)	<0.001
Base + dog	90.7 (46.3, 135.1)	<0.001	169.9 (126.9, 213.0)	<0.001
Base + cat	88.7 (45.2, 132.1)	<0.001	165.8 (124.5, 207.1)	<0.001
Base + carpet	88.6 (45.8, 131.5)	<0.001	167.8 (126.1, 209.5)	<0.001
Base + mildew/mold	91.2 (47.4, 135.0)	<0.001	168.6 (126.7, 210.6)	<0.001
Base + water damage	91.2 (47.8, 134.7)	<0.001	168.7 (127.0, 210.4)	<0.001
Base + gas stove	92.0 (48.4, 135.6)	<0.001	170.0 (128.0, 212.0)	<0.001
Base + air conditioning	90.7 (47.3, 134.2)	<0.001	168.4 (126.9, 209.9)	<0.001
Base + date of home construction	91.8 (48.1, 135.5)	<0.001	168.7 (126.9, 210.4)	<0.001
Subgroups				
Girls only	70.9 (29.3, 112.5)	<0.001	113.0 (71.4, 154.6)	<0.001
Boys only	112.4 (43.1, 181.8)	0.002	236.3 (165.4, 307.2)	<0.001
Non-hispanic white	84.2 (21.3, 147.1)	0.0087	168.8 (109.3, 228.4)	<0.001
Hispanic white	104.4 (42.8, 165.9)	0.0009	179.0 (107.3, 250.7)	<0.001
Non-asthmatics only	82.2 (35.1, 129.4)	<0.001	139.2 (97.0, 181.4)	<0.001
Asthmatics only	150.8 (43.2, 258.5)	0.006	306.9 (195.0, 418.9)	<0.001
Complete data at ages 11 and 15	87.8 (45.3, 130.2)	<0.001	161.7 (122.0, 201.3)	<0.001

* Base model is equivalent to the effect estimates shown for NO_2 in Table 1

Table S5: Estimated difference in 4-yr height growth for average decreases in ambient pollutant levels

Pollutant	Level at age 11			Level at age 15			Growth, age 11 to 15		
	Difference		P-value	Difference		P-value	Difference		P-value
NO_2	0.26	(-0.65, 1.16)	0.58	-0.13	(-0.91, 0.66)	0.75	-0.39	(-1.12, 0.34)	0.29
O_3 (10-6)	0.18	(-0.39, 0.74)	0.55	0.18	(-0.30, 0.67)	0.46	0.01	(-0.44, 0.46)	0.97
PM_{10}	0.16	(-0.54, 0.86)	0.66	-0.07	(-0.68, 0.53)	0.81	-0.24	(-0.81, 0.34)	0.42
$PM_{2.5}$	0.07	(-0.73, 0.87)	0.87	-0.06	(-0.75, 0.62)	0.85	-0.14	(-0.83, 0.56)	0.70

Estimated differences in height growth (in cm) are scaled to the median of the 5 community-specific declines in each air pollutant, specifically to 14.1 ppb in NO_2, 5.5 ppb in O_3 (10 am - 6 pm), 8.7 $\mu g/m^3$ in PM_{10}, and 12.6 $\mu g/m^3$ in $PM_{2.5}$

Notes on Table S5: The analysis of height growth

We analyzed the association between height growth and changes in air quality to determine whether the pollution-related associations we observed with lung function growth might be due to a more general time trend in physiological development. We used the same spline-based approach as was used for lung function (see "Statistical Modeling" in this supplement) to model the relationship between height and air quality. This model included adjustments for sex, race, Hispanic ethnicity, and study community. As shown above, neither height growth nor mean height at age 11 or 15 is significantly associated with the change in any of the pollutants.

Table S6: Correlation coefficients among changes in community-specific mean pollutant levels from 1994-1997 to 2007-2010

Pollutant	O_3	PM_{10}	$PM_{2.5}$
NO_2	0.02	0.82	0.82
O_3		0.33	0.39
PM_{10}			0.93

Table S7: Cross sectional analysis of lung function at age 15 to examine sensitivity to the use of different spirometers

Outcome	Pollutant	Cohort E: Measured Lung Function[a]		Cohort E: Modeled Lung Function[b]	
		Difference	P-value	Difference	P-value
FEV_1	NO_2	200.0 (142.7, 257.3)	<0.001	209.3 (153.7, 265.0)	<0.001
	O_3 (10-6)	-12.4 (-48.1, 23.3)	0.49	-10.2 (-44.9, 24.6)	0.57
	PM_{10}	120.8 (75.7, 166.0)	<0.001	130.3 (86.4, 174.2)	<0.001
	$PM_{2.5}$	132.9 (82.4, 183.4)	<0.001	143.6 (94.6, 192.7)	<0.001
FVC	NO_2	293.0 (231.5, 354.6)	<0.001	342.0 (282.3, 401.7)	<0.001
	O_3 (10-6)	-13.7 (-52.7, 25.2)	0.49	20.2 (-18.0, 58.3)	0.30
	PM_{10}	180.8 (132.0, 229.6)	<0.001	245.7 (198.6, 292.8)	<0.001
	$PM_{2.5}$	218.1 (163.7, 272.4)	<0.001	306.9 (254.7, 359.0)	<0.001

a Measured values using the ScreenStar spirometer for Cohort E (Spiroflow spirometer used for Cohorts C and D)

b Modeled values used for Cohort E, based on a prediction model for Spiroflow-spirometer measurements as a function of ScreenStar-sprirometer values. Measured values from the Spiroflow were used for Cohorts C and D.

Notes on Table S7: Sensitivity analysis related to the use of different spirometers

For Cohorts C and D, PF testing was performed using rolling-seal spirometers (Spiroflow Model 132; P.K. Morgan Ltd., Gillingham, UK), while in Cohort E, PF testing was performed using pressure transducer-based spirometers (Screenstar, Morgan Scientific, Haverhill, Massachusetts, USA). Sensitivity analyses were conducted to assess whether the use of different spirometers (“Spiroflow” in Cohorts C and D, “Screenstar” in Cohort E) might have influenced pollution effect estimates. In a prior study, we measured FEV_1 and FVC on 59 children aged 17.3 to 19.5 years using both spirometers. These data were used to build two prediction models for Spiroflow FEV_1 and FVC, respectively, as a function of the corresponding Screenstar values. That model was developed on older teenagers, and thus we applied it to the last year of observation in Cohort E (mean age 15) to obtain predicted Spiroflow-based FEV_1 and FVC. Using the age-15 cross-sectional data for all three cohorts, we estimated the effect of declines in air pollution on mean FEV_1 and FVC, first using the Screenstar measurements for Cohort E and then using the Spiroflow predictions for Cohort E (above Table S7). Statistically significant associations were observed for both FEV_1 and FVC with NO_2, PM_{10}, and $PM_{2.5}$ (all with P<0.001) regardless of the reference spirometer for cohort E. This suggests that use of Screenstar measurements in Cohort E for the primary analyses did not lead to any systematic biases in the pollution effects reported elsewhere in this paper.

Statistical Modeling

We used a mixed-effect linear spline model to investigate the relationship between longitudinal measurements of lung function and change in air quality. The use of a spline model was necessary in order to properly depict the non-linear growth trajectory of lung function during adolescence. Linear splines are piecewise linear functions that are joined smoothly at a pre-specified number of breakpoints, known as knots.[1] Such modeling approaches have been used for lung function trajectories in the Harvard six cities study[2] and the Southern California Children's Health Study[3-7].

To describe the model, let Y_{ij} denote the lung function measurement on subject i at visit j and let T_{ij} denote the corresponding age at which the measurement was recorded. We define $T_{ij}^* = (T_{ij} - T_0)/R$ to be age centered at age T_0 and standardized to range R, which allows us, for example, to focus on mean lung function at age T_0 (e.g. age 15) and growth in lung function over range R (e.g. 4 years from 11 to 15). Let Z_{km} denote the multi-year mean level of a given pollutant (e.g. NO_2 or $PM_{2.5}$, as shown in Table S2) for cohort k in community m. Let $\mathbf{X_{ij}}$ denote a vector of adjustment covariates, which includes both time-dependent (e.g. height, BMI) and time-independent (e.g. community, sex, race) variables. The model relating longitudinal lung function measurements to age, pollution, and covariates has the form:

$$Y_{ij} = \alpha_0 + \alpha_1 T_{ij}^* + \beta_0 Z_{km} + \beta_1 Z_{km} T_{ij}^* + \underline{\delta} S(T_{ij}^*) + \underline{\gamma}\mathbf{X_{ij}} + \mathbf{e_{km}} + \mathbf{e_i} + e_{ij}$$

The parameters of primary interest are β_1, which quantifies how air pollution for cohort k in community m affects lung function growth over age range R, and β_0, which quantifies how air pollution affects mean lung function at age T_0. The function $S(T_{ij}^*)$ parameterizes the spline, with knots at ages 12, 14, and 16. A fixed effect for community is included as part of the adjustment covariates to focus health-effect estimates and inferences on temporal changes in air pollution (rather than cross-community comparisons). Random effects for both level and growth are included at the cohort/community level ($\mathbf{e_{km}}$) and individual level ($\mathbf{e_i}$), with an overall residual (e_{ij}) that captures deviations of each observed lung function measurement from the fitted model. The HPMIXED procedure in SAS (Version 9.4, SAS Institute Inc., Cary, NC) was used to fit the models.

References for Statistical Modeling

1. DeBoor C. A Practical Guide to Splines. New York: Springer-Verlag; 1974.
2. Wang X, Dockery D, Wypij D, et al. Pulmonary function growth velocity in children 6 to 18 years of age. Am Rev Respir Dis 1993;148:1502-8.
3. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-67.
4. Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet 2007;369:571-7.
5. Berhane K, Gauderman W, Stram D, Thomas D. Statistical issues in studies of the long term effects of air pollution: The southern California Children's Health Study (with discussion). Stat Sci 2005;19:414-49.
6. Berhane K, McConnell R, Gilliland F, et al. Sex-specific effects of asthma on pulmonary function in children. Am J Respir Crit Care Med 2000;162:1723-30.
7. Berhane K, Molitor NT. A Bayesian approach to functional-based multilevel modeling of longitudinal data: applications to environmental epidemiology. Biostatistics 2008;9:686-99.