

Chronic Exposure to Ambient Ozone and Lung Function in Young Adults

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Background: Tropospheric ozone (O₃) is an oxidant, outdoor air pollutant. Chronic exposure has been associated with decreased lung function in children and adolescents. This study investigated the effects of long-term exposure to O₃ on lung function in college freshmen.

Methods: We recruited University of California, Berkeley students (n = 255) who were lifelong residents of the Los Angeles and San Francisco Bay areas and who never smoked. Lifetime exposures to O₃, small particulate matter (PM₁₀), and nitrogen dioxide (NO₂) were based on spatial interpolation of compliance monitor measurements to all residences at which students lived. Spirometry was performed between February and May, times when students would not have had recent exposure to increased levels of O₃.

Results: Lifetime exposure to O₃ was associated with decreased levels of measures of small airways (<2 mm) function (FEF₇₅ and FEF_{25–75}). There was an interaction with the FEF_{25–75}/FVC ratio, a measure of intrinsic airway size. Subjects with a large ratio were less likely to have decreases in FEF₇₅ and FEF_{25–75} for a given estimated lifetime exposure to O₃. This association was not altered by history of chronic respiratory disease, allergy, second-hand exposure to environmental tobacco smoke, exposure to PM₁₀ and NO₂, or measurement errors in exposure assessment.

Conclusions: A history of increased level of lifetime exposure to ambient O₃ is associated with decreased function of airways in which O₃ deposition in the lungs is the greatest. Adolescents with

intrinsically smaller airways appear to be at greatest risk. Any environmental or genetic factors that lead to reduced airway size may lead to increased susceptibility to the adverse effects of ambient ozone.

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Tropospheric ozone (O₃) is an oxidant air pollutant formed from oxides of nitrogen and volatile organic compounds in the presence of sunlight.^{1,2} Approximately 115 million Americans live in areas that currently exceed the new 8-hour U.S. O₃ standard of 80 ppb (3-year average of 4th highest).³

Ozone is largely an outdoor pollutant, and personal exposures are much lower than ambient concentrations.⁴ Nonetheless, a variety of health outcomes have been associated with exposure to ambient O₃. Associations with short-term exposure have been reported for hospitalizations for respiratory illness,⁵ exacerbations of asthma⁶ and chronic obstructive pulmonary disease,⁷ total daily⁸ cardiovascular mortality (summertime levels⁹), decreases in lung function, and increased airway inflammation.^{10–14} Chronic exposure to high ambient O₃ environments has been associated with the onset of asthma^{15,16} and mortality from cardiovascular disease (summertime concentrations).¹⁷

Chronic exposure to high concentrations of ambient O₃ has been associated with decreased levels of 1-second forced expiratory volume (FEV₁), maximum midexpiratory flow (FEF_{25–75}), and forced expiratory flow after 75% of expired volume (FEF₇₅).^{18–21} Growth of FEV₁ and FEF_{25–75} during a 3-year period in first- and second-grade Austrian children was inversely associated with summertime O₃ concentrations. In contrast, a study of children (10–18 years) from 12 Southern California communities did not find an association between lung growth and annual average community-specific O₃ concentrations.²² However, the range of average concentrations across the 12 study communities was relatively small (factor of <2.5).

Previously, we reported that estimated lifetime exposure to ambient O₃ concentrations in adolescents reared in the Los Angeles and San Francisco Bay areas of California were

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associated with decreased levels of FEF_{25-75} and FEF_{75} .²⁰ Effects were comparable whether exposure was based on an entire lifetime (~18 years) or only on the first 6 years of life.²⁰ These data were consistent with studies in monkeys²³⁻²⁵ and human O_3 dosimetry²⁶ that indicate that the impact of O_3 on lung structure is at the level of the respiratory bronchioles and that measures that reflect small airway function take longer to recover than FEV_1 after controlled human exposure to O_3 .^{27,28} The present study was undertaken to corroborate the previous findings with a larger sample and a more complete assessment of confounding from exposure to other ambient pollutants and second-hand tobacco smoke.

METHODS

Design of Study

A convenience sample of freshman undergraduates between the ages of 16–19 years at the University of California, Berkeley (UCB) was recruited in 3 waves that began on 10 April 2000, 12 February 2001, and 6 February 2002. All waves ended in the first week of June. All students were from the Los Angeles area (LA—between latitudes 32° and 35° and longitudes 115.5° and 120.75°) or the San Francisco Bay area (SF—between latitudes 37° and 38.5° and longitudes 121.67° and 123°). (A map that shows locations is available with the online version of this article.) On the basis of sample size calculations, we sought to recruit approximately 200 subjects from LA and 100 from SF.

Students were eligible based on being a lifelong resident of LA or SF before enrollment at UCB, having a history of never smoking, no physical impairment that would hinder performance of spirometry, and no history of chronic respiratory disease. A history of asthma before age 12 years was permitted, provided that student had no symptoms and had not taken any medication at any time after age 12. Six students were in this category. Subjects were studied between February–May, when students from LA would not have been exposed to the high summertime O_3 concentrations.

The protocol for this study was approved by the Committee for the Protection of Human Subjects, University of California, Berkeley and the Committee on Human Research, University of California, San Francisco. Written, informed consent was obtained from all subjects, once eligibility was established.

Residential and Health Histories

Lifetime residential history was reconstructed with a standardized questionnaire. To verify all addresses and time periods, subjects and parents received the same questionnaire. We used a standardized questionnaire for subjects and parents to obtain information on birth history, past history of pneumonia and other lower respiratory tract illnesses, allergy history, history of symptoms related to asthma and physician

diagnosis of asthma, personal smoking history (tobacco and marijuana), second-hand exposure to tobacco smoke, and family history of chronic respiratory diseases. Discrepancies between subject and parental questionnaires were reconciled.

Testing Protocol

Height was measured with a wall-mounted stadiometer.²⁹ Weight was measured without shoes with a digital scale. Subjects completed a questionnaire to determine the occurrence of a respiratory illness within the previous 3 weeks and their use of caffeinated beverages within the previous 24 hours. Subjects who had symptoms of a lower respiratory illness at the time of testing were rescheduled after lower respiratory symptoms had abated.

Forced expiratory volume (FEV) measurements were obtained in the sitting position with nose clip, using a Collins Survey rolling seal spirometer. Data were saved directly to a computer (Plus software; Warren E. Collins, Co. Braintree, MA). Two modifications were made to the American Thoracic Society criteria³⁰: because of the young age of the subjects, tests that reached a plateau after 2 seconds in the absence of an abrupt termination were considered acceptable, and reproducibility criteria included peak expiratory flow rates (PEFR) within 10% of the maximum. Tracings were reviewed jointly by 2 investigators (J.B., I.T.). Forced vital capacity (FVC), FEV_1 , FEF_{25-75} , FEF_{75} were recorded, and the FEF_{25-75}/FVC ratio was calculated. This ratio estimates the reciprocal of the time constant of the lung³¹ and reflects intrinsic airway size.³²

Geocoding of Residences and Pollutant Data

A geocoding service, TeleAtlas (TeleAtlas, Menlo Park, CA), was used to assign latitude and longitude coordinates to residence locations. Of 543 residences, 94% were geocoded with the highest-quality match, 3% were geocoded to a zip code centroid, and another 3% were geocoded to lesser-quality matches.

We acquired air quality data from the California Air Resources Board (CD No. PTSD-02-017-CD), the Aerometric Information Retrieval System (AIRS), and from special requests to the Air Resources Board. Monthly mean measures of O_3 were derived from ambient air quality data that covered the lifetimes of all subjects. Averages were based on data from zip codes that corresponded to street addresses. We report only monthly 10 AM to 6 PM average ozone. Monthly 24-hour averages were obtained for NO_2 and particles with mass median aerodynamic diameter $\leq 10 \mu m$ (PM_{10}). Measurements for PM_{10} were not widely available before 1988. For these years, a factor of 0.57 was used to scale total suspended particulates (TSP) to estimate PM_{10} concentrations (derived for the years 1988–1992 from collocated PM_{10} and TSP data for California). Particulate matter with a mass median aerodynamic diameter $\leq 2.5 \mu m$ ($PM_{2.5}$) data were

not widely available until 1999; therefore, we did not study PM_{2.5}.

Monthly values were interpolated spatially from air quality-monitoring stations to the residence locations with inverse distance weighting and a maximum of 3 monitoring stations for each interpolation (maximum interpolation radius of 50 km). Quality codes were provided for each interpolation.

Creation of Lifetime Residential Histories and Summary of Activity Data

The time period for each residence was defined by a “from” date and a “to” date. The last “to” date represented the time that the student matriculated at UCB. We used population-based estimates of the age-stratum-specific median values for time typically spent out-of-doors by children and adolescents.^{20,33–35}

Assignment of Individual Exposures

The details and reliability of the exposure assignment method have been published.^{20,35,36} Briefly, we fit 2 basic models to estimate life-time pollutant exposure. The “time-outdoors” model included age-specific estimates of time spent outdoors at each residence obtained from an California Air Resources Board study.^{33,34} We used an indoor-outdoor O₃ ratio of 0.2 in this model. This model was fit only to estimate monthly average lifetime exposure to O₃. The “ecological” model omitted estimates of time spent outdoors and used only the residence-specific monthly average, interpolated pollutant concentrations. This model was used to estimate monthly average lifetime exposures to O₃, NO₂, PM₁₀ prior to 1988, and PM₁₀ concentrations from 1988 onward.

The “effective exposure” for a given residence was calculated as the average value across all monthly values for that residence.

$$EX_{ij} = (\sum EX_{ijkl})/D_{ij},$$

where EX_{ij} indicates “effective exposure” for the *i*th subject at the *j*th residence^{20,35}; $\sum EX_{ijkl}$ indicates the sum of monthly effective exposures; summation over *l* months; and D_{ij} indicates the duration that the *i*th subject lived at the *j*th residence.

The overall, effective lifetime exposure for the *i*th subject (EX_{*i*}) was calculated as a weighted average of the residence specific “effective exposures” (EX_{ij}).

$$EX_i = (\sum EX_{ij}(D_{ij})/(\sum D_{ij}),$$

summed over *j* residences.

Pulmonary Function Data

To generate the “base” lung function model, we fit sex-specific linear regressions of each lung function measure on age, height, and weight. Model fitting was conducted for each measure (mean of 2 or 3 acceptable/reproducible trials)

to determine the optimal model (based on Akaike’s Information Criterion). Models included tests of natural log transformations of the function measures and the square of height, as well as evaluation of smooth functions of weight and height. Models with and without smooth functions provided comparable fit; therefore, only models without smooths were used. In no case did age enter into the models. Model fit was evaluated with residual versus predicted plots and quantile-quantile plots.

Race-ethnicity (White, Asian, other [African-American, Hispanic, and Native American]) was added to each model. There were no consistent effects of this variable. Presence of any respiratory symptoms in the 3 weeks before testing or the use (type and amount) of caffeinated beverages had no association with any measure. There were no associations between any measure of pulmonary function and history of asthma before age 12 years, history of pneumonia, bronchitis, allergic conjunctivitis or rhinitis, or second-hand tobacco smoke exposure. The FEF_{25–75}/FVC ratio was associated with all function measures. It was not retained in the base model as a main effect; rather it was used as a stratification variable (interaction with lifetime exposure to O₃) to account for unmeasured differences related to race-ethnicity and to capture the effects of individual variability in intrinsic airway size on any observed effect of lifetime exposure to O₃.

Analysis of Effects of Lifetime Exposure on Lung Function

We first added the lifetime estimates of O₃ exposure to the base model along with an interaction term with FEF_{25–75}/FVC ratio as single interaction term or as quartiles of the interaction. Inferences were the same for both; therefore, we present results for the single interaction term. Similar regression analyses were conducted for PM₁₀ and NO₂.

We added terms for the lifetime exposure to PM₁₀ (separate terms for estimates before 1988 and from 1988 onward) and for NO₂. We then added a variable that indicated whether subjects were from LA or SF to account for any exposure and other confounders not otherwise measured. In no case did the region variable meaningfully change the coefficients for lifetime exposure to O₃ or the interaction with FEF_{25–75}/FVC.

We made separate corrections for measurement error due to the estimates of PM₁₀ exposure before 1988 based on linear regression with TSP and error in the estimates of lifetime exposure to O₃ (Appendix 1, available with the online version of this article). For this latter correction, we used within- and between-subject variance estimates from our published reliability study.³⁶ We could not estimate the joint effects or these sources of error, because we did not have estimates for the variance of the errors between the O₃ and the pre-1988 PM₁₀.

TABLE 1. Description of Study Subjects

	Men (n = 108)	Women (n = 147)
Age (years); %		
18	52	63
19	44	36
≥20	4	1
Race/ethnicity; %		
White	37	27
Asian	49	54
Other	15	19
Residence*; %		
San Francisco area	39	44
Los Angeles	61	58
Duration of residence (years); mean ± SD	18.7 ± 2.0	18.4 ± 0.7
Respiratory history; %		
Inactive asthma [†] (n = 102, 145) [‡]	4	1
Lower respiratory illness before age 2 (n = 79, 124) [‡]	17	15
History of respiratory disease		
Bronchitis (n = 102, 138) [‡]	16	12
Pneumonia ever (n = 103, 138) [‡]	4	7
Hay Fever ever (n = 101, 136) [‡]	33	25
Family history of asthma/COPD (n = 100, 144) [‡]	26	35
History of exposure to second-hand exposure to tobacco smoke; % (n = 102, 139) [‡]	18	16
Estimated lifetime exposure to air pollutants [§] ; median (interquartile range, range)		
Ozone	36 (29–45, 19–64)	33 (26–44, 18–65)
8-hour average ppb “time outdoors” monthly ppb-hours	123 (97–169, 42–381)	112 (86–156, 35–362)
PM ₁₀ (4-hour average μg/m ³)		
Prior to 1987	73 (54–93, 34–117)	71 (53–93, 31–124)
1987 and later	36 (26–44, 18–68)	34 (26–44, 20–61)
Lifetime	48 (34–57, 21–80)	45 (34–58, 18–71)
NO ₂ (average ppb)	30 (22–40, 11–51)	27 (21–40, 8–50)
Pulmonary function measures; median (interquartile range, range) (n = 103, 145) [‡]		
FEV ₁ (liters)	4.31 (3.85–4.83, 2.86–6.00)	3.22 (2.91–3.48, 2.32–4.72)
FEF _{25–75} (liters/s)	4.55 (3.77–5.23, 3.14–8.37)	3.99 (3.10–4.48, 2.10–6.28)
FEF ₇₅ (liters/s)	2.23 (1.86–2.81, 1.19–5.67)	1.94 (1.59–2.35, 0.84–4.65)
FEV ₁ /FVC	85.8 (82.7–90.0, 72.3–98.0)	89.3 (86.0–92.5, 74.8–100.0)
FEF _{25–75} /FVC (s ⁻¹)	0.901 (0.783–1.051, 0.572–1.531)	1.076 (0.929–1.264, 0.578–1.975)
Coefficients of variation for pulmonary function; mean ± SD		
FEV ₁	1.5% ± 0.1%	1.4 ± 0.1%
FEF _{25–75}	3.2% ± 1.8%	3.0 ± 1.8%
FEF ₇₅	5.6 ± 3.7%	6.0 ± 3.7%
FEF _{25–75} /FVC	3.3 ± 1.7%	3.1 ± 1.9%

*See methods section for exact geographical definition.

[†]Physician diagnosis of asthma in childhood but no symptoms since age 12 years.

[‡]No. subjects (no. of men, no. of women) for whom data are available.

[§]All estimates derived from “ecological” model, except “time outdoors” model. See Methods section for description.

For ozone “time outdoors,” values of 591 and 511 ppb-hours are omitted because they are substantial outliers.

COPD, chronic obstructive pulmonary disease; ppb, parts per billion.

RESULTS

We enrolled 255 subjects of whom 58% were women. Approximately, 60% were life-long residents of the LA area (Table 1). Coefficients of variation for FEV₁, FEF₂₅₋₇₅, FEF₇₅, and FEF₂₅₋₇₅/FVC were consistent with our previously published data.³⁷

There were no meaningful differences between men and women with regard to the lifetime exposure estimates for any of the pollutants. Subjects who grew up in the LA area had higher median estimated lifetime exposure to O₃, PM₁₀ and NO₂ than did subjects from SF (as presented with the online version of this article). Distributions between these regions were overlapping, which resulted in a continuum of individual exposure terms across a broad range of individual estimated exposures.

We estimated the Spearman correlations between the lifetime exposure to O₃ (from the ecological model) and PM₁₀ prior to 1988, PM₁₀ from 1988 until enrollment at UCB, and NO₂; the correlations were 0.68, 0.81, and 0.57, respectively. Correlations between lifetime O₃ from ecological and main models and the mean O₃ levels 2, 3, 4, and 30 days prior to the time of lung function testing ranged between -0.03 and 0.01 (data not shown).

There were consistent inverse associations between increasing lifetime exposure to O₃ and FEF₇₅ and FEF₂₅₋₇₅ for men and women (Table 2). Comparable regressions with lifetime exposure to PM₁₀ and NO₂ showed similar results (Table 3). The results indicate that the adverse impact of increased lifetime exposure to O₃, PM₁₀ and NO₂ are de-

TABLE 3. Sex-Specific Effects of Estimated Lifetime Mean 8-Hour Exposure to PM₁₀ and NO₂, based on Ecological Models

Lung Function	Parameter Estimates (Standard Error)	
	Men	Women
LnFEF ₇₅		
Lifetime total PM ₁₀	-0.009 (0.0009)	-0.010 (0.0007)
Interaction PM ₁₀ × FEF ₂₅₋₇₅ /FVC	+0.009 (0.007)	+0.008 (0.0005)
Adjusted R ² for model	0.62	0.67
LnFEF ₇₅		
Lifetime mean 8-hour NO ₂	-0.029 (0.003)	-0.032 (0.002)
Interaction NO ₂ × FEF ₂₅₋₇₅ /FVC	+0.030 (0.003)	+0.025 (0.002)
Adjusted R ² for model	0.62	0.62

Units for parameter estimates: for total PM₁₀, μg/m³ and for interaction, μg/m³*s⁻¹; for NO₂, ppb. Each model includes height² as determined by optimal base models. See footnote to Table 2 for interpretation of parameters on the log scale. Standard error of the estimates given in parentheses.

creased with increasing FEF₂₅₋₇₅/FVC ratio. When PM₁₀ (alone or with NO₂) was added to the O₃ ecological model for FEF₇₅ (Table 4, columns labeled “none”), there was no

TABLE 2. Sex-Specific Effects of Estimated Lifetime Mean 8-Hour Exposure to Ozone

Lung Function Measure	Parameter Estimates (Standard Error)			
	Men		Women	
	Ecological Model	Time Outdoors Model	Ecological Model	Time Outdoors Model
FEV ₁				
Mean 8-hour O ₃	-0.011 (0.006)	-0.002 (0.001)	-0.011 (0.004)	-0.003 (0.0009)
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.007 (0.007)	+0.003 (0.001)	0.007 (0.003)	0.002 (0.0008)
Adjusted R ² for model	0.40	0.41	0.41	0.41
LnFEF ₇₅				
Mean 8-hour O ₃	-0.027 (0.002)	-0.006 (-11.75)	-0.029 (0.002)	-0.006 (0.0005)
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.026 (0.002)	+0.006 (12.30)	0.024 (0.002)	0.006 (0.0004)
Adjusted R ² for model	0.64	0.64	0.64	0.57
LnFEF ₂₅₋₇₅				
Mean 8-hour O ₃	-0.020 (0.002)	-0.004 (-12.48)	-0.23 (0.002)	-0.005 (0.0004)
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.020 (0.002)	+0.005 (13.57)	0.020 (0.001)	0.005 (0.0003)
Adjusted R ² for model	0.67	0.68	0.64	0.62

Units for parameter estimates: for O₃, ppb for ecological model and pph-hours for “time outdoors” model; for interaction, ppb (ppb-hours)*sec⁻¹. Standard error of the estimates given in parentheses. Each model includes height (or height²) and weight as determined by optimal base models. Parameters on the log scale can be interpreted as percent change per unit change in lifetime mean exposure and unit change in the FEF₂₅₋₇₅/FVC: (e^{-2β} - 1). For example, the parameter estimate for O₃ alone represents a 2.7% decrease (e^{-0.27} - 1) = (0.972 - 1) = -2.7%, per 1 ppb decrease in lifetime mean exposure.

TABLE 4. Effects of Measurement Error on the Estimated Effects of Lifetime Mean Eight-Hour Exposure to Ozone on FEF₇₅, based on Ecological Model

Model for LnFEF ₇₅	Men				Women				
	Measurement Error Correction		Measurement Error Correction		Measurement Error Correction		Measurement Error Correction		
	None	PM ₁₀ Before 1987	8-Hour Mean O ₃	None	PM ₁₀ Before 1987	8-Hour Mean O ₃	None	PM ₁₀ Before 1987	8-Hour Mean O ₃
Model 1									
Mean 8-hour O ₃	-0.029 (0.002)	Not applicable	-0.031 (0.002)	-0.026 (0.002)	Not applicable	-0.027 (0.002)	-0.026 (0.002)	Not applicable	-0.027 (0.002)
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.029 (0.002)		+0.031 (0.002)	+0.023 (0.001)		+0.024 (0.002)	+0.024 (0.002)		+0.024 (0.002)
Model 2									
Mean 8-hour O ₃	-0.031 (0.003)	-0.027 (0.007)	-0.030 (0.003)	-0.024 (0.003)	-0.24 (0.007)	-0.025 (0.003)	-0.025 (0.003)		-0.025 (0.003)
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.026 (0.002)	NC	+0.029 (0.003)	+0.025 (0.002)	NC	+0.026 (0.002)	+0.026 (0.002)	NC	+0.026 (0.002)
PM ₁₀ before 1988	-8.7 × 10 ⁻⁴ (0.001)	-0.006 (0.010)	-0.004 (0.002)	+1.5 × 10 ⁻⁴ (0.001)	+9.7 × 10 ⁻⁴ (0.009)	+1.5 × 10 ⁻⁴ (0.001)	+1.5 × 10 ⁻⁴ (0.001)		+1.5 × 10 ⁻⁴ (0.001)
PM ₁₀ 1988 and later	+0.006 (0.003)	NC	+0.003 (0.004)	-0.007 (0.003)	NC	-0.007 (0.003)	-0.007 (0.003)	NC	-0.007 (0.003)
Model 3									
Mean 8-hour O ₃	-0.030 (0.003)	Not performed	Not performed	-0.025 (0.003)	Not performed	Not performed	-0.025 (0.003)	Not performed	Not performed
Interaction O ₃ × FEF ₂₅₋₇₅ /FVC	+0.026 (0.002)			+0.025 (0.002)			+0.025 (0.002)		
PM ₁₀ before 1988	-0.001 (0.002)			+0.001 (0.002)			-0.004 (-0.004)		
PM ₁₀ 1988 and later	+0.005 (0.004)			-0.004 (-0.004)			-0.004 (-0.004)		
NO ₂	+0.002 (0.003)			-0.004 (0.002)			-0.004 (0.002)		

See Table 2 footnote for details.
 NC, no correction required to these coefficients.

meaningful change in the regression parameters for either lifetime exposure to O₃ or the interaction term. The main effect parameter estimates for PM₁₀ and NO₂ were reduced substantially. The addition of FVC to the models, to account for difference in lung volumes, increased the magnitude and precision of the coefficients for O₃ and the interaction terms, with little impact on the relative associations with PM₁₀ and NO₂ (data not shown). When models were fit without the interaction term, the O₃ coefficients for FEF₂₅₋₇₅ and FEF₇₅ for men were in the negative direct but weak; for women, the coefficient for FEF₂₅₋₇₅ was weakly positive (data not shown).

Figure 1 illustrates the modification of O₃ effect by FEF₂₅₋₇₅/FVC ratio. Men whose FEF₂₄₋₇₅/FVC ratio was in the upper quartile of the male ratio distribution showed no relation between increasing lifetime exposure for O₃ and FEF₇₅, whereas those whose ratio was in the lowest quartile showed a progressive percentage decrease in FEF₇₅ with increasing lifetime exposure (Fig. 1A). Similar relationships are shown for women (Fig. 1B). For the 17-ppb difference in lifetime exposure to O₃ (difference in median lifetime exposure to O₃ for students raised in LA vs. SF), the “no-effect” FEF₂₄₋₇₅/FVC ratio is 1.17 for men and 1.04 for women (Fig. 1). For a man whose FEF₂₄₋₇₅/FVC ratio is at the 25th percentile (0.783), the estimated effect of this 17 ppb difference is a 15% reduction in FEF₇₅. For a women at the comparable percentile (0.929), the estimated reduction is 3%. Adjustment for the measurement errors due to estimation of PM₁₀ from TSP up to 1988 and those related to the within-subject variation in the estimation of lifetime exposure to ozone did not change the results (Table 4).

There was a suggestion that the estimates based on ages 6 years and older are somewhat larger than those based on ages birth to 6 years; the confidence intervals (CI) for the O₃ main effect and interaction terms overlap (eg, among men, the CI for O₃ main effect was -0.019 to 0.031 for ages 0-5 and -0.023 to -0.039 for ages 6 and older).

DISCUSSION

Estimated lifetime exposure to ambient concentrations of ozone in adolescents (ages 18-20 years) is associated with reduced levels of lung function measures that reflect the function of the small airways. We have shown that the ratio of FEF₂₅₋₇₅/FVC, a measure that reflects airway size,³² is an important physiological marker for susceptibility to effects of long-term exposure to O₃ on lung function in adolescents; failure to include this measure in the analysis resulted in much less consistent results. The observation that FEF₂₅₋₇₅/FVC is heritable, and that it is decreased in healthy nonsmoking and smoking first-degree relatives of persons with early-onset chronic obstructive pulmonary disease,³⁸ supports the importance of this ratio as a marker for susceptibility to oxidant environmental exposures.

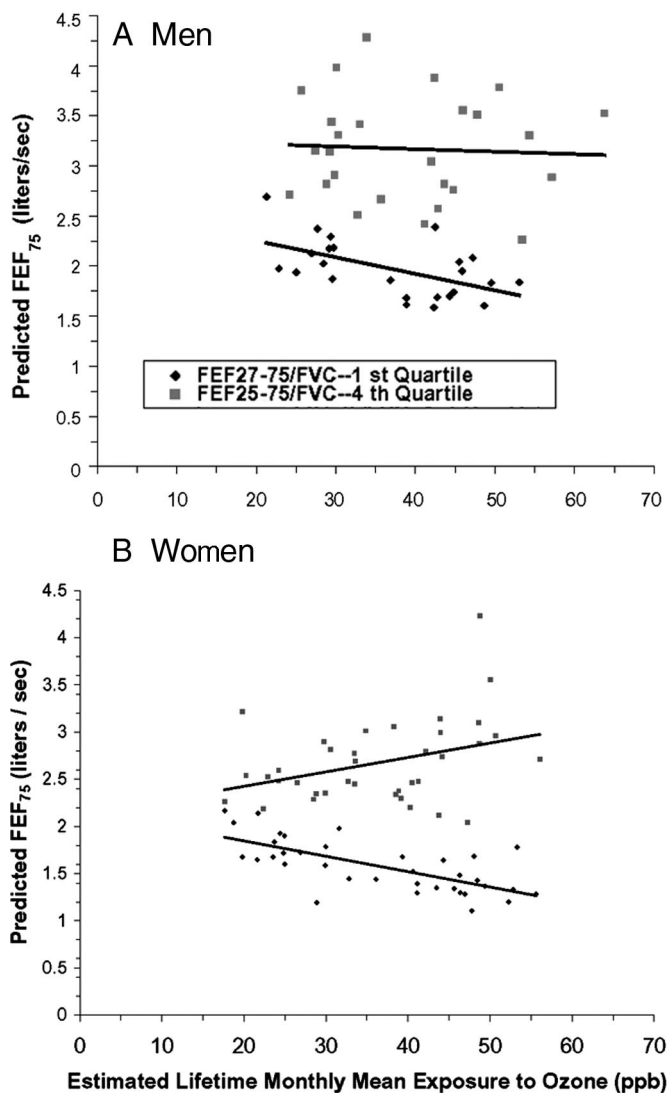


FIGURE 1. Effect of level of FEF_{25-75}/FVC ratio on the association between estimated lifetime exposure to O_3 and predicted FEF_{75} (based on models in last row of Table 4) for men (A) and women (B). Lower cluster of data points represents predicted values for subjects in the lowest quartile of the FEF_{25-75}/FVC ratio distribution. Upper cluster of data points represents predicted values for subjects in the highest quartile of the FEF_{25-75}/FVC ratio distribution. Lines are for visualization only and not based on the models in Table 4.

Although the overall results did not suggest a strong difference in the association between men and women, the level of the FEF_{25-75}/FVC ratio at which “no effect” would be expected was lower for women than for men (1.04 and 1.17, respectively). This observation suggests that men may be more sensitive to the effects of long-term ozone exposure than women. Compared with those in the highest quartile of FEF_{25-75}/FVC , men and women in the lowest quartile had

estimated reductions of 38% and 37%, respectively, in their predicted FEF_{75} (based on medians for each quartile) for comparable estimated lifetime O_3 exposures (median 38 ppb/mo). Thus, the results are unclear on this issue.

We have dealt with a number of factors that could have led to spurious associations with lifetime exposures to O_3 . We restricted the study to subjects who were lifetime never-smokers without history of chronic respiratory diseases. Self-reported race/ethnicity was not associated with measures of lung function, and the use of the FEF_{25-75}/FVC ratio and of FVC controlled for potential differences in race that are related to small airways and lung volume. Second-hand exposure to tobacco smoke also was not associated with any measure of lung function. Inclusion of exposure estimates for PM_{10} and NO_2 did not change the parameter estimates for O_3 , nor did the inclusion of an indicator variable to control for unmeasured effects due to residence in LA versus SF. Finally, there was no correlation between estimated lifetime exposure to O_3 and average ambient O_3 concentrations in the 2, 3, 4 and 30 days prior to spirometry, and most of the subjects performed spirometry after having been in Berkeley for several months, during a time when concentrations of O_3 , PM_{10} and NO_2 are low (average 8-hour maximum ozone = 30 ppb, 24-hour NO_2 = 12 ppb, and 24-hour PM_{10} = 17 $\mu g/m^3$ in August–October).

We assessed the potential effect of 2 sources of measurement error (use of questionnaire responses to estimate exposure to O_3 and estimation of PM_{10} from TSP prior to 1988). Neither measurement error correction had a meaningful effect on the magnitude of the association with O_3 (Table 4). Thus, it seems unlikely that measurement error contributed substantially to the associations that we observed for O_3 .

We cannot state with certainty that O_3 alone is responsible for the associations observed. However, in California, the O_3 and $PM_{2.5}$ seasons (the latter a result largely of combustion sources) do not overlap to any great extent,^{39,40} in contrast to the considerable overlap on the eastern part of the United States.⁴¹ Associations between $PM_{2.5}$ and lung function have been observed in short-term exposure studies,^{10–14} but few data are available for the long-term exposures noted here. In contrast to $PM_{2.5}$, the coarse PM ($PM_{10-2.5}$) does overlap with the end of the O_3 season in California.⁴² $PM_{10-2.5}$ contains small amounts of material from combustion sources but, more importantly, it is a source of iron, a transition metal that participates in the generation of reactive oxygen species⁴³ and endotoxin.⁴⁴ The latter are potent stimulators of inflammation in the lung.⁴⁵ Finally, in California, NO_2 levels tend to increase towards the end of the O_3 season. Although NO_2 has not been associated with changes in lung function, NO_2 is an oxidant with pulmonary deposition similar to that of O_3 .⁴⁶ However, controlled exposure studies in humans suggest that NO_2 may not be as toxic as O_3 , as measured by depletion of antioxidant activity and

increases in inflammatory markers in respiratory tract lining fluid.^{47–49} Thus, our data are best interpreted as an expression of the oxidant environments to which the subjects were exposed over their lifetimes, as well as to effects specific to the oxidant properties of O₃ itself.

That our data do reflect, at least in part, some effects that are specific to O₃ relates also to the functional abnormalities observed. Primate models of cyclical, chronic exposures to O₃^{23–25} have established clearly that airway remodeling occurs at the level of the respiratory bronchiole as a consequence of these exposures. Controlled O₃-exposure studies in humans suggest that a similar process could be occurring.²⁸ Based on pathologic correlations with measures of lung function in humans,⁵⁰ we expect that measures such as FEF₇₅ (and to a lesser extent FEF_{25–75}), which primarily reflect the function of small airways (<2 mm in diameter),⁵¹ would show the most consistent associations with lifetime exposure, as is the case with our data; this argument is strengthened further by the importance of the interaction between lifetime exposure and the FEF_{25–75}/FVC ratio, which is a more direct surrogate for intrinsic airway size.^{31,32}

Our observation on the similarity of the estimated exposure associations from birth through age 5 years and after the first 6 years of life suggest that the observed effects may have been driven by exposures very early in life. However, the correlations between exposures during these 2 age periods (range, 0.88–0.92 for ecological models) limit the certainty around this inference. Evidence does suggest that abnormalities of small airways are associated with early life exposures, such as in utero tobacco smoke exposure,⁵² and these abnormalities appear to persist into childhood.⁵³ Levels of ambient air pollution have been associated with adverse birth outcomes that are similar to those observed for women who smoke, ie, low-birth-weight, small-for-gestational-age infants.⁵⁴ Because ambient air pollution, such as cigarette smoke, is a potent inducer of oxidative stress,⁵⁵ it is reasonable to expect that events very early in development and infancy could have lasting effect on lung function. The consequent reduction in the size of small airways of such exposures is thought to be related, in part, to increased risk of wheezing in childhood and to the association between second-hand smoke exposure and asthma in children.⁵⁶ Thus, reduced small airway size, as reflected by the FEF_{25–75}/FVC ratio may also be a marker of sensitivity to oxidant damage early in life and a risk marker for altered lung function during periods of growth and development.

We cannot account fully for the differences between the implications of our study and the failure of several longitudinal studies to observe decreases in lung growth related to O₃ exposure.^{22,57} The studies differ substantially in design, methods of exposure assignment, and populations studied and, in the case of the Austrian studies,^{21,57} in pollutant environments. The failure of these studies to consider the

FEF_{25–75}/FVC ratio as a marker of susceptibility also could account for some of the differences.

In summary, we have observed an association between long-term exposure to ambient ozone in adolescents who have lived all of their lives in 1 of 2 regions of California and decreased measures of small airways function. The associations are independent of any effects related to PM and NO₂. Our data further suggest that the associations observed may have their origins in early life and that underlying abnormality of small airways is a physiological marker for sensitivity to strongly oxidant environments.

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