

Association between Lifetime Ambient Ozone Exposure and Pulmonary Function in College Freshmen—Results of a Pilot Study¹

NINO KÜNZLI,^{*,†} FRED LURMANN,[‡] MARK SEGAL,[§] LONG NGO,[¶] JOHN BALMES,^{||} AND IRA B. TAGER^{*}

**Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley, California; †Institute for Social and Preventive Medicine, University of Basel, Switzerland; ‡Sonoma Technology, Inc., Sonoma, California; §Division of Epidemiology and Biostatistics, University of California, San Francisco, California; ¶Division of Biostatistics and Information Science, School of Public Health, University of California, Berkeley, California; and ||Division of Occupational and Environmental Medicine, University of California, San Francisco, California*

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Human health effects due to chronic exposure to ozone (O₃) have not been established due to problems with exposure assignment and the use of measures of lung function which may not reflect the site of O₃ toxicity in the lung. We investigated the feasibility of retrospective assessment of O₃ exposure-relevant covariates and derived lifetime “effective exposure” to ozone. Mid- and end-expiratory flows (FEF_{25–75%}, FEF_{75%}) were regressed against effective exposure and ecological lifetime exposure. A convenience sample of 130 UC Berkeley freshmen, ages 17–21, participated twice in the same tests (residential history, questionnaire, pulmonary function), 5–7 days apart. Students had to be life-long residents of Northern (SF) or Southern (LA) California. Monthly ambient O₃ concentrations (OZ) were assigned based on the lifetime residential history. An “effective time” (T) spent in OZ environments was derived for each residence and age stratum (0–2, 3–5, 6–11, 12+) with the use of questions about “total time spent outdoors” and time spent in “moderate” and/or “heavy” activity. Effective exposure was calculated over the lifetime (OZ × T) of each subject. Ozone metrics used were 8-hr averages (10 AM–6 PM) and “hours above 60 ppb.” FEF_{25–75%} and FEF_{75%} decreased with both effective exposure and ecologic assignment of O₃ exposure. For a 20 ppb increase (interquartile range) in 8-hr O₃, FEF_{75%} decreased 334 ml/sec (95%CI:11–657 ml/sec), which corresponds to 14% (1.0–28.3%) of the population mean FEF_{75%}. The corresponding effect on FEF_{25–75%} was –420 ml/sec (95%CI: +46 to –886, P =

0.08) or 7.2% of the mean. Use of time–activity data to define exposure had no impact on estimates. Negative confounding factors were region (SF vs LA), gender, and ethnicity. Lifetime 8-hr average O₃ concentrations ranged from 16 to 74 ppb with little overlap between regions. There was no evidence for different O₃ effects across regions. Effects were independent of lifetime mean PM₁₀, NO₂, temperature, or humidity. Effects on FEV1 tended to be negative whereas those for FVC, although negative in some models, were inconsistent and small. The strong relationship of lifetime ambient O₃ on mid- and end-expiratory flows of college freshmen and the lack of association with FEV1 and FVC are consistent with biologic models of chronic effects of O₃ in the small airways. Since the present study was designed as a pilot study, these findings have to be confirmed in a larger sample that is representative of the target population. ©1997 Academic Press

INTRODUCTION

Worldwide, millions of people regularly experience exposure to ambient ozone (O₃) concentrations well above air quality standards set to protect people from acute adverse health effects. Whereas a large body of experimental and epidemiologic research clearly has established health effects due to short-term increments in ambient ozone concentrations (19), long-term effects of lifetime exposure to greater than background levels of O₃ remain largely undefined. Moreover, the few epidemiologic studies that show long-term effects can be criticized on a number of grounds: (i) inadequate exposure assignments, (ii) uncontrolled confounding, (iii) selection bias due to subject drop-out, (iv) small numbers of study sites, (v) or/and the inability to separate effects of other pollutants (45, 26, 16, 37, 50).

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The main sources of data for the assessment of chronic effects of long-term ambient pollutant exposure are epidemiologic studies with ecologic exposure assignment, i.e., all subjects living within a geographical region are assigned the same exposure parameter that is derived from fixed-site monitors. Such a semiecologic design with extensive measurements of outcome and covariates on individuals but ecologic exposure assignment has a number of limitations: (i) lifetime exposure usually is not available and ambient concentrations during some arbitrarily defined time period are used instead [e.g., the last 12 or 24 months (45)]; (ii) no data on individual exposure or exposure-relevant factors are assessed; (iii) rather than the estimation of dose to the lung, which is the ultimate biologically relevant measure of exposure, such studies are constrained to use ambient O₃ concentration as "exposure." Obviously, it is not feasible to overcome these limitations in large-scale epidemiologic studies, and the relevance and impact of such inherent exposure misclassification on the assessment of long-term effects of ambient O₃ remain undefined. Under a broad range of conditions and assumptions, the exposure misclassification in such studies with ecologic assignment of ambient air pollution concentrations would be expected to yield underestimates of effects (52, 36). Given that the magnitude of chronic O₃ health effects at the level of the individual is likely to be relatively small, uncertainties in effect estimation will hamper etiologic inference and regulatory decisions (42).

The aims of our study were to: (i) investigate the feasibility of retrospective assessment of exposure-relevant covariates whose control could reduce exposure misclassification, and (ii) estimate the effects of lifetime O₃ exposure on lung function based on ecologic as well as more complex approaches to the assignment of "effective exposure." Since O₃ concentration profiles have typical daily and seasonal peak patterns, are relatively homogeneous over quite large regions, and are much lower indoors (31), we considered the following parameters as relevant to quantify individual effective exposure: ambient O₃ concentrations at each individual lifetime residence, time spent outdoors during the day, and levels of outdoor activity during summer seasons. The latter is a correlate of ventilation rate, which is a useful proxy for the intrapulmonary dose (5, 28). In a previous report (24), we have shown that the major elements for retrospective assessment of these parameters over the lifetime of our subjects were reasonably reproducible. This study was designed to: (i) estimate "effective lifetime exposure" and relate these derived exposure values to lung function mea-

asures, and (ii) compare these relationships to those between typical ecologic exposure assignment and pulmonary function.

We have chosen pulmonary function as an objective outcome measure (7) since it has important long-term relevance to health (47). Whereas research on short-term effects of O₃ has focused on volume measures (forced expiratory volume in total, FVC,² and in the first second, FEV1), we primarily focus on the relationship of O₃ with mid- and late-expiratory flow measures, FEF25–75% and FEF75%. These measures better reflect changes in small airways (21) and dosimetric modeling studies indicate the respiratory bronchiole to be the area of greatest O₃ deposition in humans (28). Toxicological studies on primates (19) and human autopsy data are consistent with the hypothesis that chronic respiratory bronchiolitis can result from long-term ozone exposure (46).

METHODS

Study Population and Protocol

The protocol for recruitment of subjects has been described previously (24). Briefly, a convenience sample of 274 freshmen at University of California Berkeley (UCB), ages 17–21, were recruited through on-campus advertisement. Students had to be lifelong residents of the Los Angeles Basin (LA) or the San Francisco Bay Area (SF). Students were excluded if they had any asthma after childhood, smoked more than 100 cigarettes in their lifetime, or smoked in the year prior to testing. Due to organizational constraints, some students participated in the questionnaire repeatability study (24), in the pulmonary function assessment, or in both parts. This report is restricted to the 130 subjects with test–retest data on both questionnaire and pulmonary function. Primarily, we present results from the first visit. To test the sensitivity of the major results, analyses were repeated using data from the second visit. All study procedures were implemented by a single technician. Students were evaluated in the study laboratory on two separate occasions 5–7 days apart at the same time of day. An identical protocol was used at each visit, including questionnaires (to evaluate residential history and exposure-

²Abbreviations used: CARB, California Air Resources Board; FEF25–75%, midexpiratory flow; FEF75%, flow at 75% of exhaled forced expiratory volume; FEV1, forced expiratory volume during the first second; FVC, forced vital expiratory capacity; LA, Southern California/Los Angeles Basin; MET, metabolic index of energy expenditure; SF, Northern California/San Francisco Bay Area; UCB, University of California Berkeley.

relevant factors) and pulmonary function measurement. The methods and procedures were approved by the Committee for the Protection of Human Subjects of UCB.

Exposure-Relevant Individual Parameters

Major elements of our exposure assignment described below were (i) location defined by the residential zip code area, (ii) time spent outdoors, and (iii) outdoor physical activity. Since these elements include components that relate to exposure (i) and to potential dose (ii, iii) we term our measure effective exposure.

As described previously (24), a residential history sheet requested detailed information about lifetime residences. From this we attempted to derive the exact residential location for each month of life. For each residence of more than 3 months in duration, the student was given a standardized self-completed questionnaire that solicited information on the following: home and neighborhood characteristics, schools attended, general and outdoor activity patterns, driving habits, and job history.

Time spent outdoors. For a given residence, an ordinal question asked about the relative time spent outdoors, compared to others of the same age (less/about the same/more than others). The question had to be answered separately for four age epochs: 0–2, 3–5, 6–11, and 12+ years old. To convert this categorical information into a time duration (e.g., hours per day), we used (24) published population data from the California Air Resources Board (CARB) time–activity study (22, 54). Median and quartile values, within each age group, were assigned for the three categories of answers (less/about the same/more than others) (24).

Outdoor activity. A series of questions, described elsewhere (24), asked about time spent at two levels of physical activity, “moderate” and “heavy,” which were described in an attached list with examples. Categorization was based on energy expenditure associated with an activity, as published in the physical activity literature (6). Moderate activities were those whose energy expenditure was between 3 and 5 METs (METabolic Unit = 3.5 ml of oxygen/kg/min = average energy expended when sitting quietly) (6, 12). Heavy activities were those that required >5 METs. These questions permitted the derivation of “hours per month” spent in moderate and heavy activity, respectively, for each student and residence (24).

Pulmonary Function

Pulmonary function was assessed with a SENSORMEDICS 2100 system which meets ATS standards (32). The device uses a mass flow anemometer to measure flow of molecules. The flow measurement is independent of temperature and pressure (38). Flow measures are integrated to obtain volume. Real-time visual display of the expiratory flow was provided. The volume characteristics of the instrument were checked twice daily with a 3-liter syringe. The nitrogen analyzer was calibrated daily in accordance to the manufacturer’s instruction. Subjects were tested in the seated position with nose clips.

Maximum expiratory flow–volume curves (MEFV) were obtained in accordance with ATS standards. In addition, acceptable curves were required to have a peak expiratory flow (PEF) within 10% of the maximum PEF (29). A maximum of eight attempts to obtain three tracings was permitted (8).

The same instrument was used to measure the slope of phase III of the nitrogen washout curve. Expiratory flow was controlled during the test by a real-time visual display with a line drawn at 300 and 600 ml/sec on a flow–time axis. After full expiration, subjects inhaled 100% oxygen in a single breath. While exhaling, the device continuously measured nitrogen concentrations. For an acceptable maneuver, the mean expiratory flow after the first 500 ml had to be between 300 and 600 ml. One exceedance above 600 ml was tolerated only if the transient volume was less than 300 ml. No more than two transients below 300 ml were accepted even if their volume was less than 300 ml. Furthermore, the expired vital capacity had to be within 5% of the best FVC obtained before. Again, three (and up to eight) N₂ washout maneuvers were required. Slope of phase III was calculated by an instrument algorithm as the best fit ordinary least squares regression line between the 750- and 1250-ml volume points.

Effective Ozone Exposure

Our concept of effective ozone exposure has two major elements: (i) an ambient ozone metric derived from fixed site monitors (OZ), and (ii) “exposure effective time” (*T*), i.e., time spent in the OZ environment. This ozone–time (OZ × *T*) product was termed effective exposure, since it contains elements of exposure as well as factors related to dose delivered to the lung.

Ozone concentration element. Ambient ozone concentration metrics were assigned to each month of

life for all residences. The centroid of each zip code defined residential location. For centroids located within 5 km of a monitor, the actual monitor readings were assigned. For more remote residences, interpolated values from the closest three monitors within 100 km were used by application of inverse distance squared weighting (20). From 1980 to the present, the closest monitor was within 20 km for more than 95% of the residences and always was within 40 km. For residences prior to 1980, the monitor network was less dense. Among 1976 residences—the average year of birth for our population—68% had the closest monitor with 20 km, and 98% were within 40 km.

For this presentation, mean 8-hr concentrations and number of hours above 60 ppb of O₃ were chosen as ozone metrics. To reasonably capture both concentration peaks and typical periods of high concentrations, we first considered the 8-hr window from 10 AM to 6 PM to derive the average 8-hr O₃ concentration (41) for each lifetime month living at a California residence [California Air Resources Board (CARB) monitor data]. The number of hours above 60 ppb was derived from the same data source.

Time element. Exposure effective time (T) spent in an oxidant environment was derived according to the following assumptions. First, our concept is restricted to the 10 AM–6 PM time window, i.e., a day consists of 8 hr of potential ozone exposure, ignoring the rest of the time. Given the typical O₃ concentration profile of morning rises, afternoon peaks, and little nighttime O₃ (31), this assumption is reasonable. Consequently, we assume that “time spent outdoors” (OUT_t) occurs always within this time window. As shown in the CARB data, this assumption reasonably reflects the typical outdoor time-activity patterns, mainly among children and adolescents (22). Second, given the clearly lower ozone concentrations indoors, our concept distinguished two microenvironments, indoor (IND) and outdoor (OUT). Thus, time spent indoors is equal to 8 hr minus total time spent outdoors [IND = (8 – OUT_t)]. Third, given the final purpose of effective exposure assignment, time spent indoors was weighted only one-fifth (0.2), to reflect a typical indoor/outdoor concentration ratio for O₃. Further sensitivity analyses assumed different indoor/outdoor (*i/o*) ratios, $F_{i/o}$ (0.5 and 0.8). Fourth, inclusion of individual data on time spent in moderate or heavy activity—again assumed to have occurred during the 8-hr window—was implemented using a weighting scheme to reflect the dependency of inhaled ozone dose on ventilation rates or level of activity. Specifically, time

spent in moderate (OUT_m) and heavy (OUT_h) was weighted twice and three times, respectively, as compared to the remaining time, considered to be at low activity. The weighting scheme directly reflects levels of energy expenditure (or ventilation) on which our definitions of moderate and heavy relied. Thus, to fully operationalize the total weighted time-equivalent (T_i) for the average day during the i th month of life, we calculated T_i as described by the following equation:

$$T = \text{OUT}_{it} + F_{i/o} (8 - \text{OUT}_{it}) + \text{OUT}_{im} + 2 \text{OUT}_{ih} \quad [1]$$

where OUT describes time spent outdoors with the subscript t for total time outdoors, i.e., including all levels of activity, m and h indicate moderate and heavy activity, and $F_{i/o}$ is the assigned *i/o* ratio.

Given a fixed outdoor ozone concentration (e.g., average monthly value), the following illustrates our assumptions: spending 5 hr indoors is assumed to have the same effect as 1 hr outdoors (in low activity); 1 hr of heavy activity outdoors yields the same amount of effective time outdoors as 2 hr moderate activity or as 3 hr low activity. A subject spending, in total, 4 hr outdoors, of which 2 hr was moderate and 0.5 hr in heavy activity, has the same value of effective time outdoors as a subject with a total of 3 hr outdoors, of which 2 hr was engaged in heavy activity, but no moderate activity at all (i.e., $4 + 2 + 2 \times 0.5 = 3 + 0 + 2 \times 2 = 7$ hr).

Monthly effective exposure. Effective exposure time, i.e., our weighted time measure (T_i), was next multiplied by the O₃ metric. In case of the monthly 8-hr average, this effective exposure corresponds to the ppb hours that a subject experienced every day, on average, for the entire month at a given residence. Thus, the effective exposure (EX) for the i th subject at the j th residence living in his/her k th age epoch during the l th month, is:

$$\text{EX}_{ijkl} = \text{OZ}_{ji} \times T_{ijkl} \quad [2]$$

OZ _{i} corresponds to the average 8-hr O₃ concentration during the l th month at the j th location derived from CARB ambient air-monitoring data, and T_{ijkl} is the subject–location–age epoch-specific value of the effective exposure time derived from Eq. [1].

For the metric “monthly hours above 60 ppb,” effective time outdoors had to be converted into a proportion, i.e., the fraction of total daily hours (8) “effectively spent outdoors” (e.g., 7 hr in the above ex-

ample, i.e., $7/8 = 0.88$). The monitor readings for the number of hours above 60 ppb on a given month were multiplied by this proportion. Thus, if the above subject lived 1 month at a location where monitor readings exceeded 60 ppb during 40 hr, the assigned value for that month would be 35 effective hours above 60 ppb.

Average monthly effective exposure for each residence. Based on the monthly measures of effective exposure, a summary measure for the total period living at a residence was calculated as the average value across all monthly values (per residence effective exposure),

$$EX_{ij} = \sum EX_{ijkl} / D_{ij} \quad [3]$$

where the numerator reflects the sum of all monthly effective values at the j th residence and D corresponds to the total duration (in months) the i th subject lived at the j th residence.

Lifetime effective exposure. In a last step, lifetime exposure summaries were derived, EX_i . This was the mean across all residence exposure values, weighted by the time lived at a residence.

$$EX_i = \sum EX_{ij} \times D_{ij} / \sum D_{ij} \quad [4]$$

This is the same as the overall average across all

lifetime monthly effective exposure values (EX_{ijkl}) for a subject.

Approaches for the assignment of effective exposure. Table 1 gives a summary of the model input factors used to derive effective exposure. Several approaches with differing levels of complexity were used. The definition of the time element of the five major approaches presented here were based on the following assumptions.

(i) The “main” approach (“time–activity model”) uses all elements of the concept described above. For “total time outdoors” (OUT_t), age-specific CARB median values were assigned for ages 0–2 (0.8 hr) and 3–5 (2.0 hr). For the two older age groups, CARB quartile values were used depending on the subjects’ answers to the ordinal questions on total time spent outdoors. Quartile values are given in Table 2. For hours spent in moderate and heavy activity, the residence-specific answers were used for ages 6 and older. For younger ages, we did not add any time spent in activity to the equation of effective time. For these ages, activities were rarely reported and, as mentioned for the question on total time outdoors, reliable measures are impossible to obtain for early life (24). The impact of assumptions with regard to i/o ratio was tested (0.2; 0.5; 0.8).

(ii) The “time outdoors” approach (Table 2, row 2) ignores individual time–activity information but directly applies the published age-group-specific CARB median value of total time spent outdoors.

TABLE 1
Input Factors Used to Derive Lifetime Effective Ozone Exposure

Input factor	Notation	Resolution	Derived from	Options
Ambient outdoor ozone	OZ	Per month over lifetime	Closest monitor station(s) ^a	Average 10 AM–6 PM concentration (AV8H) Monthly hours >60 ppb (10 AM–6 PM) (H060)
Indoor/outdoor ratio for ozone concentration	$F_{i/o}$	Per month over lifetime	Fixed fraction of ambient O ₃ (IND = $F_{i/o} \times OZ$)	(a) 0.2 (main value) (b) 0.5 (c) 0.8
Total time spent outdoors	OUT_t	Age-stratum-specific values ^b	CARB data ^c	Assigned age-stratum ^b specific values: Median CARB value Quartile CARB value, depending on answer to ordinal question on “time spent outdoors”
Time spent in moderate activity	OUT_m	Per residence	Questionnaire	Hours per month for age strata 6+ years
Time spent in heavy activity	OUT_h	Per residence	Questionnaire	Hours per month for age strata 6+ years

^a See text for criteria.

^b Age strata: 0–2, 3–5, 6–11, 12+ years.

^c CARB, California Air Resources Board Study on Activity patterns (55).

TABLE 2
Description of Four Approaches to Derive Lifetime Effective Ozone Exposure

Approach notation	Monthly ozone (OZ) ^a	$F_{i/o}$	Total time outdoors (OUT _t) age group specific values (hours per day) ^b				Activity (OUT _m /OUT _h)	
			0–2 years	3–5 years	6–11 years	12+ years	0–5 years	6+ years
(i) Time–activity model (main)	AV8H, H060	0.2/0.5/0.8	0.8	2.1	0.9/2.0/3.6 ^c	0/0.6/1.8 ^c	N/A ^d	Yes
(ii) Time outdoors	AV8H, H060	0.5	0.8	2.1	2.0	0.6	N/A	Yes
(iii) Ecologic	AV8H, H060	N/A	N/A	N/A	N/A	N/A	N/A	No
(iv) Ecologic, age 12 and older	AV8H, H060	N/A	N/A	N/A	N/A	N/A	N/A	No
(v) Ecologic, age <6 years	AV8H, H060	N/A	N/A	N/A	N/A	N/A	N/A	No

^a AV8H, 8-hr average; H060, hours above 60 ppb.

^b CARB, California Air Resources Board Study on Activity patterns (55).

^c Assignment depending on answer to question on total time outdoors, median or quartile values.

^d See text for explanation.

Thus, this approach requires no questionnaire data regarding total time outdoors and moderate or heavy activity, but relies instead on the availability of relevant population data.

(iii) The “ecologic approach” (Table 2, row 3) derived lifetime exposure based on the residence-specific, fixed-site monitor data only. No time–activity data were used, nor were any assumptions made about time spent indoors versus outdoors. This approach is similar to studies published so far but requires ambient monitor data for all lifetime residences, as do approaches (i) and (ii).

(iv) The “ecologic, ≥12 years” approach (Table 2, row 4) is similar to (iii). In this case, however, only monitor averages for ages 12 and older were implemented. Thus, only the most recent residential and exposure history—the last 5–6 years prior to coming to UC Berkeley—is reflected in this measure. This approach is applicable if only a few years of monitor data were available, and it is comparable to semiecologic studies published so far, using concentration averages across some recent few years.

(v) The “ecologic, <6 years” is similar to (iv) but derives monitor data over the first 6 years of life only. Such early lifetime exposure may be of major relevance for the development of the lung.

Statistical Analyses

Effects of effective lifetime ozone exposure on pulmonary function were evaluated by linear regression. Lung function values from the maneuver with the highest sum of FVC + FEV1 were used as the dependent variables (8). Before being entered into the regression, effective exposure values (EX_i) were first standardized for each individual (EX_i′) according to the formula:

$$EX_i' = (EX_i - EX) / SD_{EX} \quad [5]$$

where EX is the mean value across all EX_i and SD_{EX} is the corresponding standard deviation. Coefficients for EX_i′, therefore, indicate the change in lung function per standard deviation of effective exposure. The main model included dummy variables for gender, region (SF versus LA), ethnicity (Asian/White/others), height, and a region*sex interaction term. Given the narrow age range in our selected population, age was not a significant predictor of lung function. Interaction terms for exposure with gender, region, and/or ethnicity were tested but were not found to be significant. All analyses fulfilled the Gaussian distribution assumptions for residuals which were homoscedastic, and transformation of lung function values, often a requirement in adult populations, was not required in this population. Analyses were done with the SAS/STAT Statistical Software (43) on a personal computer.

RESULTS

Table 3 presents population characteristics for the student subsample ($N = 130$) with both questionnaire and pulmonary function participation on two occasions 5–7 days apart. Gender and ethnic distribution differed across regions with a high participation of students with Asian background among those raised in the SF Bay Area (67% versus 39% in LA). For males and females, group mean pulmonary function values tended to be higher in LA than in SF except for the flow parameters for males.

As explained under Methods, effective exposure time was a major element of our exposure assignment. Table 4 presents summary statistics for the lifetime average effective exposure time in hours per

TABLE 3
Demographic Characteristics and Mean Lung Function Values for the Study Population

Characteristic	SF bay area (<i>N</i> = 89) [<i>N</i> (%)]	LA basin (<i>N</i> = 41) [<i>N</i> (%)]	Total (<i>N</i> = 130) [<i>N</i> (%)]
Gender			
Female	35 (39)	18 (44)	53 (41)
Male	54 (61)	23 (56)	77 (59)
Ethnicity			
Asian	60 (67)	16 (39)	76 (58)
Caucasian	23 (26)	17 (41)	40 (31)
Others	6 (7)	8 (20)	14 (11)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	18.5 (0.7)	18.8 (1.0)	18.6 (0.8)
Height (cm)			
Female	162.1 (9.9)	164.1 (10.9)	162.7 (10.2)
Male	174.2 (7.4)	177.6 (7.0)	175.2 (7.4)
Weight (kg)			
Female	60.8 (12.9)	63.2 (10.1)	61.6 (12.0)
Male	69.9 (9.7)	72.5 (9.8)	70.7 (9.7)
Female			
FVC (liter)	3.54 (0.5)	3.84 (0.56)*	3.64 (0.54)
FEV1 (liter)	3.13 (0.44)	3.31 (0.41)	3.19 (0.43)
FEF25–75% (liter/sec)	3.76 (0.87)	3.92 (0.87)	3.81 (0.87)
FEF75% (liter/sec)	2.04 (0.65)	2.12 (0.68)	2.06 (0.66)
N ₂ -slope	0.99 (0.51)	0.96 (0.37)	0.98 (0.46)
Male			
FVC (liter)	4.87 (0.77)	5.09 (0.82)	4.94 (0.78)
FEV1 (liter)	4.19 (0.62)	4.29 (0.72)	4.22 (0.65)
FEF25–75% (liter/sec)	4.73 (1.1)	4.58 (1.12)	4.68 (1.10)
FEF75% (liter/sec)	2.50 (0.71)	2.48 (0.76)	2.49 (0.72)
N ₂ -slope	0.97 (0.20)	0.86 (0.36)	0.94 (0.41)

* *P* = 0.05 for *t* test, SF versus LA.

day. There was no significant difference across study regions. As expected, assumptions about indoor/outdoor ratio have a strong impact on the absolute value, given the relatively short time subjects spend outdoors (see CARB data indicated in Table 3). Assuming an *i/o* ratio ($F_{i/o}$) of 0.2, the lifetime median value was 4.5 effective exposure hours per day (see Table 4), based on the main time–activity approach. Ignoring any individual activity data [approach (ii)] the corresponding time value was 2.7 hr ($F_{i/o} = 0.2$). Comparing approach (i) with (ii) demonstrates the relative impact on estimates of effective exposure time of the partitioning and weighing scheme applied to total time outdoors and moderate and heavy activity: in the main time–activity model, about 40% of the effective time value was driven by including moderate and heavy activity with their corresponding weights (4.5 versus 2.7 hr). As a consequence, the same pattern emerges for absolute values of derived effective exposure (Tables 2 and 4).

As shown, ozone exposure parameters were largely different across regions due to the distinct

environmental characteristics, e.g., the ambient ecologic lifetime average in Northern California students ranged from 16 to 33 ppb. The corresponding range among Southern California students was 25–74 ppb. The 95th percentile for SF (32 ppb) corresponded to the 5th percentile for LA. On average, SF students experienced median monthly ambient 8-hr ozone concentrations of 22.5 ppb. The corresponding median among LA students was 51.5 ppb (see Table 4, ecologic approach). Implementation of the outdoor time element [approach (ii)] resulted in an estimated median of 59.9 (SF) and 138.3 ppb-hr (LA), respectively, for daily effective exposure over the lifetime of individuals. The main approach yields a population median of 94 and 228 ppb-hr, respectively ($F_{i/o} = 0.2$). Assuming $F_{i/o} = 0.5$ gave about 50% higher median values (142 and 328 ppb-hr), and $F_{i/o} = 0.8$ about 90% higher median values (186 and 421 ppb-hr). Figure 1 plots ecologic means versus the values derived from the time–activity approach for the 8-hr metric. The overall correlation is strong ($r = 0.88$), but lower within regions (0.75 and 0.56

TABLE 4

Distribution (Median and Interquartile Range, IQR) of Derived Lifetime Effective Exposure Time, Effective Ozone Exposure (Daily ppb-hr and Monthly Number of Hours above 60 ppb), and Ecologic Lifetime Environmental Conditions for Different Approaches, by Region of Residence

Lifetime parameter	Approach	$F_{1/0}$	SF bay area ($N = 89$) [median (IQR)]	LA basin ($N = 41$) [median (IQR)]	Total ($N = 130$) [median (IQR)]
Effective exposure time (hours per day)	(i) (Main)	0.2	4.5 (3.5–5.3)	4.6 (3.9–5.5)	4.5 (3.7–5.4)
	(i)	0.5	6.3 (5.5–7.2)	6.4 (5.8–7.3)	6.3 (5.6–7.2)
	(i)	0.8	8.2 (7.5–9.2)	8.1 (7.7–9.0)	8.2 (7.5–9.2)
	(ii) (Time outdoors)	0.2	2.7 (2.66–2.71)	2.7 (2.65–2.70)	2.7 (2.65–2.71)
Effective ozone exposure 8-hr average ppb-hr	(i) (Main)	0.2	93.6 (77–124)	228.1 (205–272)	123.1 (88–207)
	(i)	0.5	142.2 (111–176)	327.8 (291–368)	172.5 (125–291)
	(i)	0.8	186.1 (145–231)	421.2 (392–460)	226.5 (160–384)
	(ii) (Time outdoors)	0.2	59.9 (47–75)	138.3 (108–159)	74.7 (50–105)
	(iii) (Ecologic)	—	22.5 (17–28)	51.5 (40–60)	27.5 (19–39)
Monthly hr >60 ppb	(i) (Main)	0.2	2.1 (0.7–4.8)	35.5 (27–44)	4.5 (1.0–26)
	(i)	0.5	3.0 (0.8–7.6)	54.1 (38–62)	6.8 (1–36)
	(i)	0.8	3.8 (1.1–10.4)	72.3 (48–83)	9.3 (2–43)
	(ii) (Time outdoors)	0.2	1.1 (0.4–3.1)	24.1 (17–29)	2.9 (0.6–11.3)
	(iii) (Ecologic)	—	3.2 (1.1–9.0)	70.2 (52–87)	8.5 (1.7–34)
Average PM_{10} ($\mu g/m^3$)	Ecologic ^a	—	31.2 (30–32)	51.1 (46–54)	31.7 (30–45)
Average NO_2 ($\mu g/m^3$)	Ecologic	—	25.0 (23–26)	45.4 (41–48)	25.8 (24–40)
Average temperature ($^{\circ}F$)	Ecologic	—	57.8 (57–59)	63.3 (63–64)	58.8 (58–63)
Average rel. humidity (%)	Ecologic	—	73.2 (68–74)	68.5 (67–70)	70.3 (67–74)

^a Same derivation as (iii) for ozone.

for SF and LA, respectively). In fact, with increasing ambient concentrations, discrepancies across values from these two approaches increase. The regional pattern for lifetime PM_{10} and NO_2 averages was similar to the one described for O_3 with LA having higher values than the SF region. The range, how-

ever, was clearly less distinct for these pollutants, and there was very little variability across the assigned PM_{10} values within SF.

Effect estimates for lifetime O_3 exposure defined from hours above 60 ppb and 8-hr averages are given in Table 5. Both “small airway” flow measures

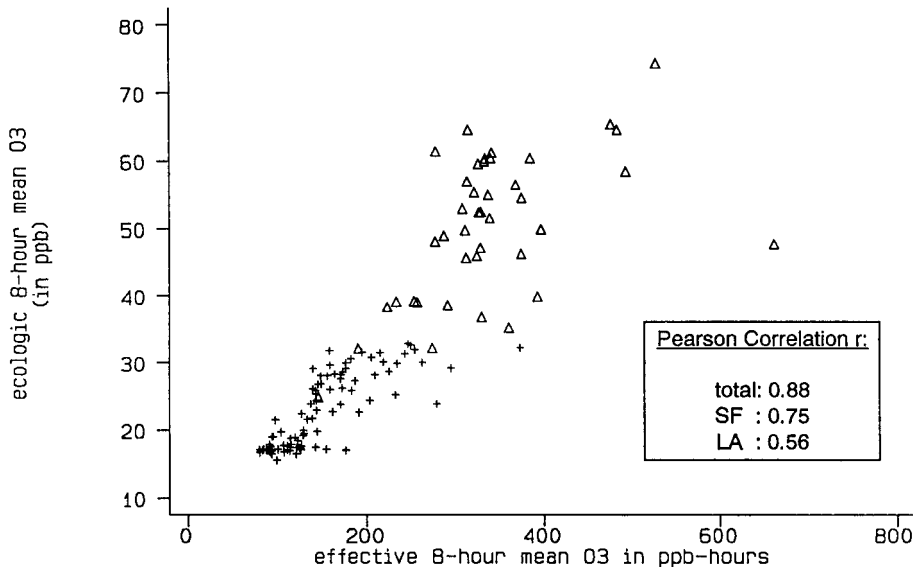


FIG. 1. Lifetime effective exposure of all subjects ($N = 130$) based on the time-activity approach (effective 8-hr mean), plotted against the ecologic ambient 8-hr averages across all lifetime residences of students raised in San Francisco (+) and Los Angeles (Δ).

TABLE 5

Change in Pulmonary Function (and Standard Error) per Standard Deviation of Lifetime Effective Ozone Exposure for Two Metrics and Five Approaches ($F_{i/o} = 0.2$)^a

Lifetime ozone exposure metric/ and approach	Exposure SD (min/max)	FVC coeff. (SE)	FEV1 coeff. (SE)	FEF25–75 coeff. (SE)	FEF75% coeff. (SE)	N2-slope coeff. (SE)
Hrs. >60 ppb (unit:hours/month)						
(i) Time–activity	18.8 (2/85)	0.0 (0.1)	–0.092 (0.085)	–0.326 (0.168)**	–0.252 (0.117)*	0.033 (0.075)
(ii) Time outdoors	10.5 (2/35)	–0.167 (0.111)	–0.195 (0.096)*	–0.361 (0.192)**	–0.242 (0.134)**	0.017 (0.086)
(iii) Ecologic	30.8 (1/104)	–0.148 (0.112)	–0.179 (0.096)**	–0.348 (0.193)**	–0.241 (0.134)**	0.008 (0.086)
(iv) Ecologic, ages ≥12	28.3 (0.2/110)	+0.004 (0.09)	–0.048 (0.08)	–0.196 (0.156)	–0.190 (0.108)**	–0.045 (0.067)
(v) Ecologic, ages <6	4.3 (1/14)	–0.137 (0.116)	–0.196 (0.099)**	–0.416 (0.200)*	–0.262 (0.139)**	+0.06 (0.08)
10 AM–6 PM ppb-hr/day						
(i) Time–activity	89.6 (45/583)	+0.066 (0.074)	–0.030 (0.065)	–0.224 (0.128)**	–0.190 (0.089)*	–0.052 (0.056)
(ii) Time outdoors	40.8 (40–199)	–0.039 (0.102)	–0.105 (0.087)	–0.320 (0.174)**	–0.243 (0.121)*	–0.079 (0.079)
(iii) Ecologic (ppb)	14.8 (16/74)	–0.02 (0.103)	–0.092 (0.089)	–0.311 (0.176)**	–0.247 (0.122)*	–0.089 (0.079)
(iv) Ecologic, last residence (ppb)	12.7 (17/74)	+0.109 (0.09)	+0.003 (0.08)	–0.236 (0.153)	–0.253 (0.105)*	–0.100 (0.067)
(v) Ecologic, ages <6	18.1 (14/75)	–0.024 (0.105)	–0.115 (0.091)	–0.360 (0.180)**	–0.260 (0.125)*	–0.015 (0.08)

^a PFT = $a + b$ (standardized exposure) + c (height) + d (ethnicity) + e (sex) + f (region) + g (sex*region).

* $P \leq 0.10$.

** $P \leq 0.05$.

(FEF25–75% and FEF75%) were significantly lower with increasing O₃ exposure, a consistent finding across all approaches. In contrast, results for FVC were all nonsignificant and those for FEV1 showed inconsistent relationships. Coefficients for analyses restricted to effective exposure measures for the time period age 12 and older were lower than for lifetime hours >60 ppb while those for analyses restricted to the first 6 years of life were higher. A similar pattern was observed for ppb-hr for FEF25–75% but was less obvious for FEF75%. With the slope of phase III of the nitrogen washout measure as the dependent variable, none of the estimates were significantly different from zero.

To test the sensitivity of the effect estimation on major input parameters, lifetime effective exposure values were derived assuming different i/o ratios. As shown in the first three rows of Table 6, point estimates and precision remained very similar. Next, answers given on visit 2 rather than visit 1 were used. As previously shown (24), all input variables (i.e., residential history), to derive ambient O₃ parameters and time–activity data, were sources of reporting error between the two visits. Results based

on visit 2 data, however, were again little changed (Table 6).

The lower part of Table 6 indicates the change in effect estimates due to covariates included in the model. As shown for FEF75%, in all models—including the unadjusted univariate assessment—coefficients for exposure were negative. The same observation was made for FEF25–75% (not shown). For volume measures, however, this pattern was less consistent. In all cases, unadjusted results were considerably confounded by other covariates, as shown in Table 6. Region of residence was a strong negative confounder with mean levels of lung function being higher in LA than in SF (see Table 3). The same pattern of negative confounding was observed for gender and to a lesser extent for ethnicity. In fact, these two factors—both important predictors for lung function—were distributed differently across regions.

Other pollutants and climate factors were considered as potential confounders (see Table 6). Assignment of these lifetime values were based on the same ecologic procedure used in the derivation of ozone values [approach (iii)]. Adjustment for PM₁₀

TABLE 6

Sensitivity of Coefficients (Change in FEV1 and FEF75% per Standard Deviation of Effective Hours with Ozone >60 ppb) on Assumptions Regarding Indoor/Outdoor Ratio, Data Set, and Covariates Included in Linear Regression Model^a

Sensitivity tested for	FEV1 (liter)			FEF75% (liter/sec)		
	Coeff.	SE	r^2	Coeff.	SE	r^2
$F_{i/o}$ (main model, ^b visit 1)						
0.2 (default model)	-0.092	0.085	0.61	-0.252	0.117**	0.18
0.5	-0.118	0.092	0.61	-0.271	0.127**	0.16
0.8	-0.132	0.095	0.61	-0.274	0.127**	0.18
Visit 2 data, main model, $F_{i/o} = 0.2^b$	-0.144	0.090	0.63	-0.324	0.126**	0.23
Covariates in model ($F_{i/o} = 0.2$, visit 1)						
No covariates (crude estimate)	+0.022	0.067	0.001	-0.064	0.064	0.01
Region, height	-0.001	0.096	0.46	-0.212	0.114*	0.16
Sex, region	-0.072	0.096	0.45	-0.246	0.116**	0.12
Sex, region, ethnicity	-0.147	0.091	0.54	-0.289	0.117**	0.15
Sex, height	+0.01	0.044	0.57	-0.075	0.060	0.15
Sex, region, height	-0.033	0.086	0.57	-0.221	0.114*	0.17
Sex, ethnicity	-0.036	0.046	0.60	-0.101	0.063	0.16
Main model ^b + PM ₁₀	-0.083	0.085	0.61	-0.237	0.117**	0.20
Main model + NO ₂	-0.096	0.086	0.61	-0.257	0.118**	0.18
Main model + PM ₁₀ , NO ₂ , temp., humidity	-0.100	0.090	0.62	-0.173	0.124	0.22

^a All models based on main approach (time-activity) of lifetime exposure assignment.

^b "Main model" included; reg, region (SF/LA); eth, ethnicity (Asian/white/other); ht, height; s*r, sex*region interaction.

* $P \leq 0.10$.

** $P < 0.05$.

had little impact on ozone effect point estimates, although O₃ and PM₁₀ lifetime values were highly correlated in the total sample ($r = 0.78$). Within LA, these two pollutants were uncorrelated ($r = 0.16$). The correlation in the SF area was positive ($r =$

0.33). PM₁₀ itself was unrelated to pulmonary function.

Another way to present the observed association of ozone with lung function is given in Fig. 2. Residuals of the regression of FEF75% against all co-

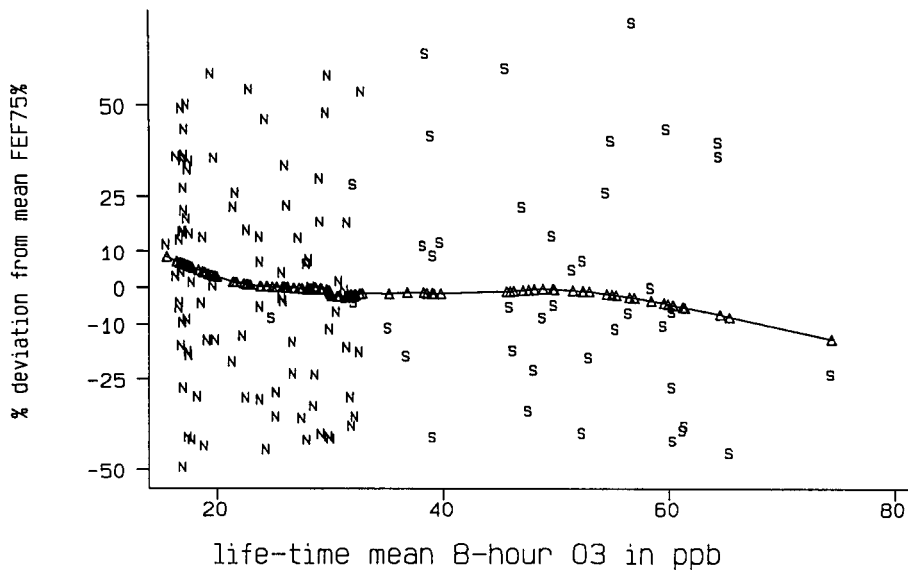


FIG. 2. Adjusted deviation (height, sex, region, ethnicity) in percent compared to population mean FEF75% versus lifetime ambient 8-hr mean exposure and LOWESS, smoothing curve using 80% of the data at each point. N (for North California), S (for South California), Los Angeles; triangles, smoothed data.

variates of the main model, except effective exposure, expressed as a percentage of the mean FEF75% are plotted against the lifetime average 8-hr ozone values. The curve describes a nonparametric, locally weighted smoothing line (LOWESS) using 80% of the data at each point (49). Consistent with the parametric analyses, the graph does not give evidence for different slopes between regions and visualizes the problem of the two very distinct regions with regard to O₃ exposure.

The use of standardized coefficients permits comparison across approaches but obscures absolute effects. To enhance interpretation, we give an example of unstandardized results for the lifetime ecologic 8-hr average concentration. Given the lifetime interquartile range of 20 ppb ozone [approach (iii)], a mean decrease in FEF75% of 0.334 liter/sec (0.011–0.657) can be estimated for a lifetime of 19 years. This corresponds to a 14.4% (1.0–28.3%) decrease compared to the overall mean value of FEF75% in this population (2.319 liter/sec). The corresponding effects for FEF25–75% were –0.420 liter/sec (+0.046 to –0.886 liter/sec) or 7.2% (+1.1 to –20.5%) of the mean (4.326 liter/sec).

DISCUSSION

This is the first study that relates lifetime cumulative exposure to ambient concentrations of ozone to small airway pulmonary function parameters. Despite the limited sample size of this feasibility study, our point estimates for effective O₃ exposure were significant for FEF25–75% and FEF75% and robust to various methods for the specification of exposure. Among these 17- to 21-year-old, never-smoking California students, FEF75% decreased by 167 ml/sec for a 10 ppb increment in lifetime ambient 8-hr mean O₃ exposure. These mid- and end-expiratory flow measures are considered early indicators for pathologic changes that might ultimately progress to chronic obstructive lung disease (10, 34, 15, 56). This disease model is based primarily on research that relates to cigarette smoking, but its relevance is supported by data in animals in which the primary site of O₃ injury in the lung is the centriacinar region (31, 11, 46). The negative results with regard to FVC and FEV1, which are better indicators for dysfunction in the large airways, further supports the model and underlies the importance of the assessment of long-term O₃ effects on pulmonary flows rather than FVC or FEV1.

Several issues are relevant for the interpretation of these results. As shown in Table 6, univariate analyses did not significantly show the observed as-

sociations between flow measures and exposure. The relationship was confounded mainly by region, but by gender and ethnicity as well. In our data, the heterogeneity in ethnicity and gender distribution across region was considerable. Given the important and complex relation of these factors to lung function, it would be preferable to have large enough populations within gender and ethnicity strata rather than to rely on statistical adjustment. The study had limited power to test for different response functions across gender. A nonsignificant interaction term suggested stronger O₃ effects on flows among male students (not shown).

The strong impact of controlling for study region might reflect two elements: first, control for residual confounding of ethnicity and gender, and second, some other unmeasured factors that differ across region. Uncontrolled regional factors have been suggested in other studies. Kinney (27), in an approach similar to that reported here, studied a small sample of military cadets from a number of locations in 16 U.S. states and three regions. Locations were eligible based on the ambient ozone profiles with “low” (second-highest 1-hr value < 140 ppb) and “high” (>180 ppb) areas. A preliminary report showed lower FEF25–75% among those coming from high O₃ sites. However, this pattern seemed consistent only for two out of three large U.S. regions. We were very limited in the ability to test for differences with regard to the shape of the effect function across region or to test for thresholds of effects as suggested by Schwartz (at 40–50 ppb 7-hr annual mean values) (45). In our regression models, the exposure–region interaction term did not clearly suggest different exposure functions ($P = 0.2$ for the interaction) and the direction of the coefficients would have indicated larger effects for Northern California than for the LA Basin. This inference is further supported by the residual analyses in Fig. 2.

All these limitations are due mainly to the small sample size and the choice of a convenience sample—both consequent to this being a feasibility study. Students were healthy nonsmokers, but further control for self-selection processes was not attempted.

Our estimates for ozone exposure effects on FEF25–75% and FEF75% were not considerably confounded by other environmental conditions which are of major concern for validity in all other studies regarding long-term effects of O₃ on lung function reported thus far. Inclusion of lifetime average values of PM₁₀, NO₂, temperature, or humidity, derived according to the same principles as described for ecologic O₃ measures, had only minor im-

pact on O_3 coefficients. All these factors were significantly correlated with effective ozone exposure. However, addition of all factors at the same time to the main model did not remove the observed association with O_3 (Table 6). It is of note that coefficients for PM_{10} were not significantly different from zero for any of the pulmonary function tests. In contrast to these results, particulate pollution has been shown to be associated with a broad and coherent range of health outcomes, including lung function (35). In our study, random error in particulate exposure assignment was likely to be larger than that for O_3 , for which the monitor network was denser over the 20-year period considered herein. In 1990, there were 24 and 31 O_3 monitors but only 14 and 16 PM_{10} monitors in the SF and LA regions, respectively. Furthermore, in contrast to O_3 , the two areas experienced less distinct distributions of particulate pollution, with virtually no dispersion within the SF region. For PM_{10} the third quartile value of LA was only 1.8 times higher than the first quartile of SF. For ambient 8-hr O_3 values, this range differed by a factor of 3.5. Thus, the exposure variance of PM_{10} is limited and effects on pulmonary function are unlikely to be detected in our small sample.

All lung function measurements were performed on the UC Berkeley campus in Berkeley, California, which is a low oxidant city in the SF Bay Area. Students participated mostly during the semester and were unlikely to have spent their time at LA homes shortly prior to examination. Thus, acute and sub-acute carryover effects of local air pollution are an unlikely explanation for our findings.

For volume measures, FVC and FEV1, results were not only less precise and smaller in magnitude but also quite sensitive to the method of specification of exposure. Since FEV1 reflects both large- and small-airway physiology, these results are not surprising given the data on O_3 pathophysiology cited previously (11). This statement is supported by the explanatory power which was more than 10 times smaller for FEV1 as compared to FEF75% (Table 6) despite the larger measurement variability of the latter. In contrast to the UCLA results (17), we did not find any association of ambient O_3 with the slope of phase III of the nitrogen washout. This measure has a larger within-subject variability than the other parameters reported, limiting the statistical power. Furthermore, comparison with the study of Detels *et al.* (16) has to be done with caution due to differences in devices and N_2 washout procedures.

Interpretable studies on long-term effects of ambient O_3 exposure on pulmonary function are sparse,

and the potential to compare our results with other data is limited. Our results are consistent with an analysis of NHANES II spirometry data from 4300 people, age 6–24, across 48 U.S. cities. Although ambient monitoring data from up to only 2 years prior to measurements were used to assign exposure, Schwartz reported highly significantly negative coefficients for NO_2 , TSP, and the annual 7-hr average O_3 concentration in relation to FVC, FEV1, and peak flow (45). This large population across 48 areas is the most powerful study published so far that relates to chronic effects of ozone on lung function. A major limitation, however, stems from the unknown correlation between pollutants which could be tested one-by-one only. The high number of regions and reasonably broad range of exposure makes this study a unique example of a valid strategy to reduce inherent limitations of studies with ecologic exposure assignment. In fact, all other studies rely on a small number of sites, e.g., two or three, ecologic exposure assignment, and rather limited ranges of exposure. The large UCLA study on air pollution and chronic bronchitis reported higher prevalence of reduced lung function in a “high oxidant” area, based on cross-sectional data (17) and significantly increased annual change in ΔN_2 (nitrogen washout) derived from the 5-year follow-up (17). The two sites (17, 16) and three sites (40) compared, respectively, differed not only by oxidant levels but also by other important pollutants, socio-demographic factors, and participation patterns. These were serious sources of uncontrolled confounding. The inability to disentangle oxidant effects from those of other pollutants is a central problem in other two-site comparisons that report significant associations between reduced pulmonary function and ambient O_3 (50, 25, 51) or “no association” (30, 14). A Canadian study (50), despite including children from 10 communities, basically made comparisons across two levels of exposure. Ontario children had, on average, a 1.7 and 1.3% lower FVC and FEV1, respectively, compared to a Saskatchewan sample. Such an effect could not be observed for flow measures. Annual mean O_3 concentrations were 24 and 31 ppb. Austrian data (44) across the three study zones were not interpretable (higher prevalence of impaired FEF75% in the high O_3 zone but no effects on the mean lung function values). Furthermore, the low-ozone zone was characterized by high particulate pollution, a confounding problem which cannot be resolved in such a design.

Other large studies, such as the 6-city study (53), the 24-city study (48), and the Swiss Study on Air Pollution and Lung Disease in Adults [SAPALDIA

(3)], did not report associations of pulmonary function and long-term exposure to O_3 and might be interpreted as negative studies with regard to chronic effects of O_3 (4). In terms of O_3 exposure distributions, however, these apparently large studies have to be considered "few-site" semiecologic studies with all of the limitations mentioned above. For example, annual mean values of O_3 across the 6-city study ranged from 20 to 28 ppb with basically two clusters, 20–22 and 27–28 ppb (18). The situation is very similar to that of SAPALDIA, with a range of only 15–32 ppb across 8 sites, again clustered on two levels.

Our study made a major effort to improve individual lifetime exposure assignments. In contrast to typical semiecologic studies, we did not choose some finite number of areas from which to select subjects but included participants from two large regions that consisted of a large number of cities, i.e., zip code areas, with a dense monitor network. Thus, despite relying on fixed-site monitor data, each subject carried his or her individual residential history for which individual exposure profiles were derived. Our data suggest that lifetime measures are more strongly related to flows at mid and low lung volumes than exposure measures based on the last 5–6 years of residence only (Table 5). This finding might be due to chance, or it may indicate the potential importance of exposure misclassification in studies with limited exposure data. Similarly, the higher effect estimates for early lifetime "effective exposure" might suggest that this period in life is particularly important for health consequences of exposures to ambient O_3 . Further research is clearly needed to confirm this interpretation.

The geographic diversity and the broad range of exposure further amplified the analytic power of this study. Studies published to date have lacked either one or both of these two design advantages and never considered time–activity patterns. As a consequence, exposure misclassification may have been sufficiently large in these studies to have severely reduced the efficiency of effect assessment. As shown in the SAPALDIA diary data, time spent outdoors varies considerably between and within study sites (23), rendering the average monitor concentration a poor measure of ozone exposure, unless the exposure range across areas is large. The only study so far with an extensive approach to the definition of lifetime cumulative exposure to air pollution is the Seventh Day Adventist study (AHSMOG), which has published long-term effects of particles but not oxidants on chronic obstructive lung disease incidence. Ambient mean ozone concentrations ranged from 11 to 24 ppb from the lowest to the highest decile (2).

Unfortunately, this study did not assess lung function until 1993 and no results are published to date. Several studies have reported discrepant findings for effects on lung function versus symptoms (50, 44, 17). We could argue that chronic symptoms may be considered later manifestations of the disease process compared to changes in small-airway function. Furthermore, lung function tests are more objective measures of respiratory health than symptoms (7).

A third design feature of our study relates to the attempt to consider time–activity patterns in the derivation of lifetime oxidant exposure. Time spent outdoors should be considered an important exposure-relevant factor, given some ambient O_3 concentration. In fact, the AHSMOG study (2) noted that coefficients of air pollutant effects on disease morbidity were twice as large after adjustment for time spent indoors. Interestingly, use of time–activity data had very little impact on our point estimates (standardized coefficients) of effect. Thus, time–activity patterns may be unnecessary for the assessment of lifetime oxidant exposure. The consistency across approaches (Tables 2 and 5), however, is likely an effect of improved power of our design due to the broad range of exposure and the use of individual exposure histories, applied to all approaches, and ought not to be generalized to all study designs. Studies lacking either or both of these design features might benefit from some estimates of time–activity patterns. As shown (24), the factors used to derive effective exposure can be assessed with reasonable precision. Furthermore, despite similar relative results with different approaches, the choice of exposure derivation in terms of all factors (O_3 metric, exposure assignment approach, *i/o* ratio) is very influential on absolute values of effective exposure, thus on the absolute effects. For example, the time–activity 8-hr mean exposure measure ranged over six standard deviations, whereas the ecologic one was less spread (i.e., over only four standard deviations). Whereas one standard deviation of the 8-hr measures was 54–73% of the median value, it was 3.6–4.2 times larger than the median for "hours >60 ppb" measures (Tables 4 and 5). As shown in Fig. 1, ecologically and time–activity-based values were highly correlated ($r = 0.88$) over the total range but showed considerable scatter within smaller ranges of exposure. Differences due to the adoption of a time–activity approach instead of the ecologic assignment increased with increasing ambient concentrations. Classification of subjects might, in some cases, depend considerably on the choice of effective exposure measure. This has regulatory implications. Depending on time–activity pat-

terns and other factors usually not controlled (e.g., *i/o* ratio), effective exposure—and thus the effects—might be very different, at least in subgroups of populations, than what monitor readings might suggest.

Our attempt to consider time–activity cannot fully capture truly individual lifetime patterns, but rather relies on a mixed concept using external population data (CARB) with age-specific averages and individual residence-specific activity data. Fortunately, these CARB data were derived from a population sample from the same California regions in which our students were raised. Other elements and assumptions of our concept may be questioned as well. Our restriction to two microenvironments, indoor and outdoor, within one single location (zip code) are justified by the limited mobility patterns of children. Questions on school locations revealed that a high percentage of schools were located within 3 miles from home (73% of elementary schools, 86% of high schools; not shown). For 75% of all high schools, time to go to school was 15 min at most and 90% were in the 30-min range (data not shown), which indicates that home and school were mostly within geographic ranges of likely similar O₃ concentrations (not shown). This increases the likelihood that exposure assignments based on residence were valid for school locations as well.

Another limitation of our approach relates to treating indoor/outdoor concentration ratios on an ecologic rather than individual level. In general, air-conditioned, indoor environments have lower O₃ concentrations than rooms with natural air exchange [see Chap. 4 in (31)], and one could argue for application of individual data on air conditioning use to assign *i/o* ratios, given the very strong impact of *i/o* ratio on absolute values of effective exposure (as shown in Table 4). Technical details of air conditioning systems and use, however, are influential determinants of true *i/o* ratios which may vary— independent of air conditioning—considerably across buildings (31). Such relevant details cannot be assessed retrospectively. Thus, an ecologic assignment of *i/o* ratios is preferable to assumed individual *i/o* ratios. In general, our LA population reported a higher prevalence of air conditioning use. Thus, effective exposure might be overestimated compared to SF students. This bias would cause our estimates of the adverse effects of O₃ to be underestimated. Recent Southern California measurements on residential *i/o* ratio, however, suggest that ratios increase with increasing outdoor O₃ concentrations. If this pattern can be generalized, the above-mentioned underestimation would be reduced.

Our conceptual restriction to an 8-hr time window and the assumption that time outdoors occurred during these O₃ peak hours are supported by survey data on time–activity patterns from a comparable California population (22, 55). This survey showed that time spent outdoors, by and large, occurred during O₃ peak hours, particularly among children. The inherent error due to this assumption is most likely unrelated to levels of ambient O₃ concentrations and, therefore, unlikely to cause spurious effects.

None of our exposure measures can be considered a gold standard, i.e., exposure is measured with error. Our study was conducted as a repeatability study (24) and the entire set of individual variables was measured twice, including residential history. The correlation coefficient between repeated measures of exposure approximates the squared correlation between the proxy measure and the unknown true value (39) which is an estimate of the reliability coefficient, R (9). Ideally, our effect estimates b^* are an attenuated measure of the true b , where $b = b^*/R$ (52). The test–retest correlation of all our measures of exposure was very high, i.e., literally 1 for the ecologic measures and 0.93–0.98 for effective exposure measures (not shown). Thus even after correction for attenuation bias, coefficients increase at most by 5–10% (time–activity approach), and therefore point estimates remain robust to the exposure specification.

In conclusion, this study showed a strong and negative association of lifetime ozone exposure with lung function measures that reflect small-airway physiology. Known acute effects of ozone include induction of an inflammatory response that can be measured in bronchoalveolar lavage (33, 19). Recurrent inflammation in the terminal bronchiole may cause chronic bronchiolitis, and reduction in pulmonary flow measures as observed in this study may be early markers of such a response (11). Given the large populations still experiencing oxidant exposure at levels well above the national standards and a number of limitations of our study, it is important to confirm our findings in a more appropriate sample, including sufficient sample size within relevant gender–ethnicity strata. We propose adoption of similar design features to limit the impact of exposure misclassification. A feasible step would be the use of lifetime residential history and corresponding monitor data, which we showed to be more efficient than data from the last residence only. In the future, as data from dense monitor networks and extended time series become increasingly available, there should be opportunity to implement improved exposure assignment of lifetime ozone exposure and

to address heterogeneity in susceptibility as a function of age.

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