Long-Term Residence in Areas of High Ozone: Associations with Respiratory Health in a Nationwide Sample of Nonsmoking Young Adults

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Few studies have examined the respiratory effects of multyear ozone exposures in human populations. We examined associations between current respiratory health status and long-term ozone exposure histories in 520 Yale College (New Haven, CT) students who never smoked. Questionnaires addressed current respiratory symptoms, respiratory disease history, residential history, and other factors. The symptoms of cough, phlegm, wheeze apart from colds, and a composite respiratory symptom index (RSI) were selected as outcome measures. Forced vital capacity (FVC), forced expired volume in 1 sec (FEV1), forced expired flow rate between 25 and 75% of FVC (FEF25-75), and forced expiratory flow rate at 75% of FVC (FEF75) were obtained by forced expiration into spirometers. Ozone exposure was treated as a dichotomous variable, where subjects were assigned to the high-exposure group if they lived for 4 or more years in a U.S. county with 10-year average summer-season daily 1-hr maximum ozone levels ≥ 80 ppb. Lung function and respiratory symptoms were analyzed by multiple linear and logistic regression on ozone exposure, controlling for covariates. Lung function was lower in the group with high ozone exposures: differences were statistically significant for FEV1 (-3.1%; 95% confidence interval [CI], -0.2 to -5.9%) and FEF25-75 (-8.1%; CI, -2.3 to -13.9%), and nearly so for FEF75 (-6.7%; CI, 1.4 to -14.8%). Gender-specific analyses revealed stronger associations for males than for females. The symptoms of chronic phlegm, wheeze apart from colds, and RSI were increased in the ozone-exposed group, with odds ratios of 1.79 (CI, 0.83–3.82), 1.97 (CI, 1.06–3.66), and 2.00 (CI, 1.15–3.46), respectively. We conclude that living for 4 or more years in regions of the country with high levels of ozone and related copollutants is associated with diminished lung function and more frequent reports of respiratory symptoms. Key words: chronic effects, epidemiology, human, lung function, ozone. Environ Health Perspect 107:675–679 (1999).

The acute respiratory health effects of ozone are well documented and include diminished lung function and increased airway reactivity, symptoms of cough, and pulmonary inflammation (1–3). However, the public health significance of these short-term reversible effects remains uncertain. Of greater concern would be persistent changes in pulmonary structure or function that develop over many years of ozone exposure. Long-term animal studies have observed morphological changes consistent with early stages of fibrosis at the bronchiolar/alveolar junction in the deep lung—changes that mimic those observed in autopsies of young cigarette smokers (4–6). Whether similar changes occur in humans exposed repeatedly over long periods to ambient ozone concentrations is a major remaining uncertainty regarding ozone health effects (7).

Several epidemiologic studies have attempted to assess the respiratory effects of long-term ozone exposures, with variable results. Two early studies conducted in California found little evidence for differences in lung function or respiratory symptoms in adults living in two areas with contrasting ozone levels (8,9). A subsequent and substantially larger California study detected reduced lung function and elevated respiratory symptoms among adults aged 25–39 years living in Glendora (high ozone and other pollutants) as compared to Lancaster (low ozone) (10). Evidence for cross-sectional differences in lung function associated with local ozone concentrations was also observed in a study of 1,005 persons 6–24 years of age from 60 U.S. communities from the second National Health and Nutrition Examination Survey (NHANES II) (11). Two recent college-based pilot studies found associations between diminished current lung function and retrospectively estimated long-term ozone exposures in young adults (12,13).

College-based cohorts offer several advantages for studies addressing the respiratory health impacts of long-term ozone exposures. Many colleges draw large and geographically diverse student populations, which bring with them broad air pollution exposure histories. Ozone concentration profiles can be estimated in most parts of the United States back to the late 1970s using available computerized monitoring data—a period spanning the entire lifetimes of students entering college from the mid 1990s onward. Residential histories, activity patterns, and occupational histories are less complicated in young adults than in older subjects, thus simplifying the task of exposure assessment. Finally, the fact that students congregate in one location to attend college simplifies the logistics of collecting questionnaire and health data in a population with diverse residential histories.

We report results from the first year of a 3-year study designed to examine associations between respiratory health status (lung function and chronic respiratory symptoms) in college freshmen and individual long-term estimates of prior ozone exposures, controlling for age, sex, race, exposure to environmental tobacco smoke, and other factors.

Methods

Recruitment and measurement protocol. In the first year of a 3-year study at Yale College (New Haven, CT), 623 freshmen students were recruited and measured during the 1995 spring semester. Prior to initiation of the measurements, letters were sent to all of the approximately 1,330 Yale freshmen announcing the study and listing the times during which interested students could walk in, provide informed consent, and be evaluated. Additional recruitment tools included an article in the college newspaper and posters placed around campus. Recruitment materials referred to the study as the Columbia/Yale Lung Health Study without mentioning the study hypothesis regarding air pollution effects. Subjects were recruited on a first-come, first-served basis, with a recruitment goal of 600 subjects. Upon entering the study area at a central campus location, each student’s name was checked against a roster of first-year students. After verification of freshman status, potential subjects were asked if they had a chest cold

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in the last 7 days; if so, they were asked to return at a later time. Eligible subjects were recruited after informed consent was obtained by the project coordinator. Enrolled subjects completed a 15-min self-administered questionnaire, had their height measured without shoes, then performed spirometric lung function tests. Subjects were offered $10 in appreciation for their participation. The study protocol was approved by the Columbia Presbyterian Medical Center's Institutional Review Board and by the Yale University Human Subjects Committee.

Of a total of 623 subjects recruited, complete data were obtained on 618. Five subjects who reported a current cold on the day of initial recruitment (and questionnaire completion) did not return as scheduled for subsequent spirometry measurements. The present analysis of ozone effects is restricted to a subset of 520 subjects who reported never having smoked cigarettes, cigars, pipes, or other smoking products. Those who never smoked ranged from 17 to 21 years of age (mean 18.9 ± 0.5) and included 262 females and 258 males.

Questionnaire. Each subject completed a questionnaire addressing respiratory symptoms, respiratory disease history, residential history, home characteristics, personal and passive smoking history, physical activity history, and parental education. The respiratory symptom and disease history questions were adapted from the American Thoracic Society adult questionnaire (14). Symptoms included cough ("Do you usually bring up phlegm from your chest?") and wheeze ("Does your chest ever sound wheezy or whistling occasionally apart from colds?"). In addition to these individual symptoms, we constructed a composite respiratory symptom index (RSI) variable that was assigned a value of 1 if any of the three individual symptoms were reported. Residential history consisted of the time course of all residential locations since birth, with changes in residence resolved to the nearest month and locations resolved to the level of state and town. The town or city name was used to locate the county of residence for the evaluation of ozone exposures. Data on indoor home characteristics were ascertained for the three most recent residences. Questions addressed the heating system, air conditioner and fan use, the use of a gas stove, and numbers and types of pets. These variables were treated as potential covariates in the analyses described below. Questions elicited information on personal smoking and exposure to smoke in the home while growing up. Subjects (n = 103) who reported either current or former regular cigarette, cigar, pipe, or other smoking were eliminated from the present analysis. Regular cigarette smoking was defined as at least five packs of cigarettes ever or at least one cigarette per day for at least 6 months. Exposure to other people's smoke at home was evaluated by a series of questions that evaluated whether regular smokers were present, whether the regular smoker was the father, mother, or other person, and the level of smoking. As a measure of socioeconomic status, the education level achieved by the father and mother was ascertained.

Lung function. Spirometry was preceded by measurement of height (without shoes). Two 10-L dry rolling-seal spirometers (Model VRS 2000, S&M Instrument Company, Doylestown, PA), connected to laptop personal computers for data retrieval, were used to measure lung function. Spirometers were calibrated and leak-checked each day before measurements began. Subjects performed the lung function maneuver seated and wearing a nose clip. A maximum of eight forced expiratory maneuvers were performed by each subject to obtain a minimum of three acceptable flow/volume tracings, two of which were reproducible. Volumes were corrected to standard temperature and pressure. For analytical purposes, we extracted four lung function parameters: forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), forced expiratory flow rate between 25 and 75% of FVC (FEF25-75), and forced expiratory flow rate at 75% of FVC (FEF75). Following usual practice, FVC and FEV1 were selected from the blow with the maximum value, whereas FEF25-75 and FEF75 were taken from the blow that had the maximum sum of FVC and FEV1.

Ozone exposure assessment. The Aerometric Information and Retrieval System (AIRS) database (15) serves as the central repository of all routine air monitoring data collected by governmental agencies in the United States. As part of a previous study addressing methods to characterize long-term ozone exposures, hourly concentrations of ozone for all monitoring sites (n = 1,112) in operation from 1981 to 1990 were downloaded from the AIRS database. From the hourly records, we computed monthly averages of the daily 1-hr maximum values for each monitoring site. These were then averaged over the months of June, July, and August over all 10 years to yield a single measure of long-term ozone levels at each monitoring site. If only one monitoring site was located in a county, the 10-year average summer month value for that monitoring site was used to describe the county. If more than one site was located in a county, the average of all the monitoring sites was used to represent the county. Our ozone exposure data set was limited to the years 1981–1990 because those data were readily available from a previous study and were considered adequate to estimate long-term average concentrations over the 18-year life spans of study subjects.

Ozone exposure was assessed for the purposes of this report as a dichotomous variable by identifying individuals (based on residential histories) who had lived at any time for at least 4 years in U.S. counties with average summer concentrations ≥ 80 ppb. Subjects satisfying this criterion were assigned to the high-exposure class. Those not satisfying this criterion were assigned to the low-exposure class. The 80-ppb level was the 95th percentile of the distribution of long-term average concentrations across all sites. The residential counties with summer average concentrations > 80 ppb were Maricopa County, Arizona; Los Angeles County, California; Fairfield County, Connecticut; Anne Arundel County, Maryland; Gloucester County, New Jersey; New York County, New York; and Davis County, Utah.

Statistical methods. Lung function was analyzed by multiple linear regression on ozone exposure, controlling for covariates. Covariates included in all models were age, height, height squared, sex, race, parental education, and maternal smoking. Race was treated as a five-level discrete variable (White, Asian, black, Hispanic, other). Other covariates, including paternal smoking, other persons smoking, air conditioner use, fan use, gas stove use, and the presence of pets, were retained only if their p-values were < 0.20 in the multiple regression models. Only one of the latter variables (other persons smoking) remained in the reduced model—for FVC only. Regression models were fit separately for each of the four lung function parameters FVC, FEV1, FEF25-75, and FEF75. From the slope estimates for ozone and the mean levels of lung function, we computed the percent effect of high versus low ozone exposure. The one-stage approach used here to control for the effects of height and age on lung function assumes that the relationships between lung function and height, and between lung function and age, do not differ by gender or by race. Our adoption of this one-stage modeling approach was based on the small sample size, which precluded meaningful estimation of gender- and race-specific prediction equations, as well as the absence of directly relevant prediction equations from the literature. The one-stage approach might lead to an increase in error variance, diminishing analytical power. Confounding of the lung function/ozone relationship might occur if ozone exposure status was associated with age, gender, race, or height. However, no association was observed between ozone exposure status
and age, gender, race, or height, alleviating concerns about potential confounding.

Respiratory symptom outcomes were analyzed by multiple logistic regression on ozone exposure, controlling for covariates. The outcomes of interest for these analyses included cough, phlegm, wheeze apart from colds, and RSI. Covariates included in all models were sex, race, parental education, and maternal smoking. Other covariates, including paternal smoking, other persons smoking, air conditioner use, fan use, gas stove use, and the presence of pets, were retained only if their p-values were < 0.20 in the multiple regression models. Covariates that remained in reduced models included air conditioner, fan, and gas stove use. We report odds ratios for the association between respiratory symptoms and ozone exposure class.

As noted above, to control for potential confounding of the relationship between ozone and respiratory health measures, other variables were considered as covariates. All available covariates were initially placed in the models and the then-reduced models were identified based on a p-value criterion for inclusion. To examine whether residual confounding may have been present in the reduced models, we compared the final ozone effect estimates with those obtained in the full models. No meaningful differences in the ozone coefficients were found when comparing the full model with the reduced model.

Results

Of the 520 subjects who never smoked analyzed here, 262 were female (50.4%) and 258 were male (49.6%). Sixty-five subjects (12.5%) were assigned to the high ozone exposure category based on having lived for at least 4 years in U.S. counties with 10-year average summer-season daily 1-hr maximum concentrations ≥ 80 ppb. The percentages of subjects assigned to high exposure did not differ by gender (12.6% for females; 12.4% for males). Fifty-six percent of subjects were white (n = 293), 20% were Asian (n = 104), 11% were black (n = 56), 6% were Hispanic (n = 32), and 7% reported other races (n = 35).

Table 1 displays basic demographic data as well as the raw means and standard deviations for FVC, FEV₁, FEF₂₅-₇₅, and FEF₇₅ overall and stratified by gender and ozone exposure. As expected, lung volumes were lower for female subjects. In addition, average levels of all four lung function variables were lower in the high ozone exposure group. Differences in lung function between the high ozone exposure group and other subjects, adjusted for height, gender, race and other covariates, are displayed in Table 2. Differences are expressed as percent of mean lung function in the study population as a whole. Percent differences were negative for all four lung function variables, implying diminished lung function in the group with the highest long-term ozone exposures. Differences were statistically significant for FEV₁ [-3.1%; 95% confidence interval (CI), -0.2 to -5.9%] and FEF₂₅-₇₅ [-8.1%; CI, -2.5 to -13.9%], and nearly so for FEF₇₅ [-6.7%; CI, 1.4 to -14.8%]. Stratification by sex revealed substantially larger effects among male subjects. Among males, the differences due to ozone exposure for FEV₁, FEF₂₅-₇₅, and FEF₇₅ were -4.7% (CI, -0.7 to -8.8%), -13.0% (CI, -4.9 to -21.1%), and -10.0% (CI, 1.3 to -21.3%), respectively. Differences related to ozone exposure in females were smaller and nonsignificant.

Unadjusted respiratory symptom and disease frequencies are shown in Table 3. Overall, cough, phlegm, and wheezing apart from colds were reported in 3.1, 10.4, and 21.5% of subjects, respectively. Thirty percent of the subjects answered yes on at least one of these symptoms (i.e., RSI = 1). Doctor diagnosis of asthma at any time was reported in 16.2% of subjects. Respiratory symptom rates were similar in males and females. However, the prevalence of an asthma diagnosis by a doctor was higher in males (17.4%) than in females (14.7%). Among subjects exposed to high ozone levels, respiratory symptom rates were generally elevated. For example, the RSI rate was 41.5% among ozone-exposed subjects as compared to 28.0% among subjects not exposed.

Odds ratios comparing respiratory symptoms across ozone strata, adjusting for covariates, are displayed in Table 4. Odds ratios were > 1 for phlegm, wheezing, and RSI, indicating increased rates of respiratory symptoms among subjects with elevated long-term ozone exposures, controlling for covariates. These associations were statistically significant for wheezing apart from colds (1.97; CI, 1.06–3.66) and for RSI (2.00; CI, 1.15–3.46), but not for phlegm (1.79; CI, 0.83–3.82). Because of small frequencies of individual symptoms, stratification by sex was only possible for RSI. Male subjects exhibited a statistically significant odds ratio for RSI of 2.30 (CI, 1.04–5.11), whereas the odds ratio for females was
slightly lower (1.79) and not statistically significant.

As shown in Table 3, 16.2% of subjects reported having been diagnosed with asthma by a doctor. These subjects reported substantially more respiratory symptoms than did nonasthmatic subjects. For example, RSI prevalence among asthmatics was 66.7%, whereas among nonasthmatics it was 22.9%.

To examine whether the ozone results reported above were influenced by the inclusion of asthmatic subjects, we repeated the analysis of respiratory symptoms and ozone after excluding asthmatics. The odds ratios for ozone exposure were essentially unchanged (data not shown).

**Discussion**

We detected associations between respiratory health indicators and long-term ozone exposures in data from the first year of a multiyear study of respiratory health among students at Yale College. Mean levels of the lung function parameters FEV₁ and FEF₂₅₋₇₅ were significantly lower in a subgroup of subjects who had previously lived in areas with elevated long-term ozone concentrations, controlling for important covariates. In addition, the high-exposure group had a higher prevalence of respiratory symptoms of wheeze apart from colds and of a composite chronic symptom index, RSI. These results support the hypothesis that long-term exposures to ambient ozone and associated copollutants result in adverse respiratory health outcomes in young adults.

Our results are qualitatively similar to results from previous studies that differed in the design of the present study. Detels and associates (16) found decreases in FVC, FEV₁, and FEF₂₅₋₇₅, and elevations in respiratory symptoms, in 5,561 subjects 25–39 years of age exposed to high levels of oxidants, nitrogen dioxide (NO₂), and sulfates in southern California. Exposure classification was based on residence at the time of data collection in one of two communities that differed in air pollution profiles, rather than on individual long-term exposure estimates as in the present study. Schwartz (17) reported highly significant relationships between FVC, FEV₁, and peak expiratory flow rate and ozone concentrations in a group of 1,005 young people 6–24 years of age from 60 U.S. neighborhoods who had been measured in NHANES II. Exposure was characterized based on average local ozone concentrations in the 12 months preceding the lung function assessment. Significant associations were also observed with NO₂ and total suspended particulate matter concentrations in that study. In a pilot study, Kinney et al. (12) studied associations between lung function and prior residence in high ozone areas among 136 students 17–22 years of age at the U.S. Military Academy at West Point, New York. Mean levels of adjusted FVC and FEV₁ were lower in subjects with histories of long-term exposure to high ozone concentrations. In a more recent pilot study, Kuenzli and associates (13) studied lung function in relation to lifetime ozone exposure estimates in a group of 130 freshman students at the University of California at Berkeley. Subjects had lived their entire lives in either the Los Angeles (high ozone) or San Francisco (low ozone) areas. Individual ozone exposure estimates were derived for each subject residence for each month from birth until the time of the study by interpolating data from extensive ozone monitoring networks. In multivariate linear regression models, decreases in lung function parameters related to small airway caliber (i.e., FEF₂₅₋₇₅ and FEF₁₂₋₂₀) were observed in association with elevated lifetime ozone exposures. Taken together with the results of the present paper, these findings suggest that respiratory effects of long-term ozone may be observable in young adult subjects. As noted, studies in this age group possess several advantages, the most important being the ability to account for long-term exposure using the extensive U.S. ambient ozone monitoring data available starting in the late 1970s.

The relationships of ozone with diminished lung function and elevated respiratory symptoms in the present study were stronger for male than for female subjects. Gender-specific results have not been reported in previous long-term ozone epidemiology studies. We speculate that male children may on average receive higher ozone doses at a given ambient ozone concentration as a result of spending more time outdoors in vigorous physical activity.

Long-term ozone exposure was treated as a simple dichotomous variable in the present study. Thus, we made no assumptions nor obtained any results on the shape of the exposure/response functions linking respiratory status and ozone exposure. The effect of our decision to use ozone as a dichotomous variable rather than a continuous variable on the regression is not known. However, given the skewed nature of the distribution of long-term ozone concentrations and the fact that a large fraction (43%) of the subjects we studied had lived in only one residence (and 86% had three or fewer residences), we believe that the simple dichotomization of exposure used here likely provided a valid ordering of long-term ozone exposures for these subjects. A more thorough exposure assessment would assign concentrations by interpolation to each subject’s residence and then cumulate concentrations over residences to derive individual long-term estimates (13). This method would also make it possible to explore the impact of age-specific exposures. We intend to implement and compare this approach in the analysis of the full study data set using interpolation methods developed recently (17).

Subjects were assigned to the high-exposure category if they had lived at least 4 years in a U.S. county with 10-year summer month average ambient concentrations above the 95th percentile of the U.S. distribution. Monitoring sites within counties were averaged. This approach was chosen for ease of implementation in a preliminary analysis. However, the method ignores possible geographic variations in both ozone concentrations and residential locations within counties. To the extent that such variations exist, exposure assignments in the present study may have been misclassified, which would typically bias effect estimates towards the null.

Like most previous epidemiology studies of long-term ozone, the present analysis assessed exposure using outdoor ozone monitoring data and did not account for factors that modify individual ozone dose, such as indoor penetration fraction, hours spent outdoors, and levels of outdoor physical activity. Our approach is justifiable on regulatory grounds because air quality standards are based on ambient concentrations. Further, it is not clear that useful individual data on dose modifiers can be obtained retrospectively by questionnaire. In their study of University of California at Berkeley college students, Kuenzli et al. (13) compared several methods of deriving long-term ozone exposure/dose estimates that differed in the extent to which data on dose modifiers obtained by questionnaire, such as time spent outdoors and levels of physical activity, were taken into account. They found that a simple exposure assessment based on ambient ozone concentrations at the home location performed as well, in
terms of the precision of the effect estimates, as did the dosimetric exposure estimates. These results imply that some modifiers do not vary to a significant extent across individuals or that retrospective questionnaires are unable to accurately capture the variability that exists.

Ozone was the only air pollutant included in the analyses presented in this paper. Some previous large-scale epidemiology studies have implicated particulate matter (PM) in adverse respiratory outcomes, especially for chronic respiratory symptoms (18,19). On the other hand, a recent pilot study found no evidence for independent effects on lung function of airborne particles ≤ 10 μm (PM10) in diameter once ozone exposure was taken into account (13). We are unaware of any previous studies that possessed sufficient statistical power to conclusively separate the roles of ozone and PM in chronic respiratory health effects, due in part to the tendency for ozone and PM to covary on broad geographic scales. At present, it is not possible to determine whether, and to what extent, the present results reflect health effects of ozone alone or ozone in combination with unmeasured copollutants.

In conclusion, we observed evidence for diminished lung function and elevated chronic respiratory symptoms in Yale College students with histories of long-term residence in high-ozone areas of the United States. Analyses controlled for potential confounding variables at the individual level, including sex, race, body size, socioeconomic status, and indoor environmental factors. Stratified analyses indicated stronger relationships among male subjects. By themselves, these results do not implicate ozone per se but rather ozone and associated copollutants. Results were qualitatively consistent with those of recent pilot studies in college cohorts.

The data analyzed here were from subjects recruited in the spring of 1995, the first year of a 3-year data collection effort at Yale College. Data collection on the full cohort is now complete and analyses are underway. Future work will seek to confirm these preliminary results in the full cohort, to expand the exposure assessment to include PM10, and to carry out additional subgroup analyses to examine effect modification by sex, race, and health status.

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