

Effect of Ambient Air Pollution on Pulmonary Exacerbations and Lung Function in Cystic Fibrosis

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Information concerning the impact of environmental factors on cystic fibrosis (CF) is limited. We conducted a cohort study to assess the impact of air pollutants in CF. The study included patients over the age of 6 years enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Exposure was assessed by linking air pollution values from the Aerometric Information Retrieval System with the patients' home zip code. After adjusting for confounders, a 10 $\mu\text{g}/\text{m}^3$ rise in particulate matter (both with a median aerodynamic diameter of 10 μm (PM_{10}) or less and with an aerodynamic diameter of 2.5 μm or less ($\text{PM}_{2.5}$) was associated with an 8% (95% confidence interval [CI], 2–15%) and 21% (95% CI, 7–33%) increase in the odds of two or more exacerbations, respectively; a 10-ppb rise in ozone was associated with a 10% (95% CI, 3–17%) increase in odds of two or more exacerbations. For every increase in $\text{PM}_{2.5}$ of 10 $\mu\text{g}/\text{m}^3$, there was an associated fall in FEV_1 of 24 ml (7–40) (95% CI) after adjusting for confounders. $\text{PM}_{2.5}$'s association with mortality did not achieve statistical significance (adjusted RR = 1.32 per 10 $\mu\text{g}/\text{m}^3$ 0.91–1.93; 95% CI). Annual average exposures to particulate air pollution was associated with an increased risk of pulmonary exacerbations and a decline in lung function, suggesting a role of environmental exposures on prognosis in CF.

Keywords: cystic fibrosis; air pollutants; survival; outcome; pulmonary exacerbation

There is increasing evidence that there are adverse cardiopulmonary effects associated with levels of air pollution that fall within the current standards, especially for populations with chronic diseases (1–3). More recently, the potential role of particulate pollutants (particulate matter with an aerodynamic diameter of 10 μm or less [PM_{10}] and 2.5 μm or less [$\text{PM}_{2.5}$]) has been increasingly noted (4–10). Children and adults with cystic fibrosis (CF) comprise a potentially at-risk population for which the effects of ambient air pollution have not previously been investigated.

CF is one of the most common inherited fatal diseases in the white population, with a reported incidence from 1 in 2,000 to 1 in 3,200 live births. (11) Known risk factors for accelerated decline in lung function and overall poor prognosis include fe-

male sex, poor nutrition, poor physical fitness, pancreatic insufficiency, respiratory tract colonization with *Pseudomonas aeruginosa* and *Burkholderia cepacia*, and a low socioeconomic status (12–14). The clinical course of CF pulmonary disease continues to be dominated by chronic and recurrent pulmonary infections, inflammation, and a loss of lung function over time, resulting in up to 92% of deaths being caused by cardiopulmonary failure (15, 16).

Current understanding of the risk factors for poor pulmonary prognosis does not fully explain the heterogeneity in the pulmonary course that is observed in this population; environmental influences may be important. Investigating the influence of ambient air pollutant on CF pulmonary disease—a sensitive population—may help elucidate the role of exposure in other populations. For these reasons, we linked data from the Cystic Fibrosis Foundation National Patient Registry (CFFNPR) and the U.S. Environmental Protection Agency's Aerometric Information Retrieval System.

METHODS

Participants

The first data source was the CFFNPR, containing demographic and clinical data collected annually at accredited CF centers in the United States (see the online supplement for more details) (17). Individuals were eligible for inclusion in the study if they were present in the 1999 and 2000 CFFNPR, were at least 6 years old in 1999, listed a residential zip code in 2000, and had complete data for age, sex, lung function, weight, insurance status, and number of exacerbations. This study was approved by the Human Subjects Division of the University of Washington.

Design and Procedures

CF pulmonary exacerbation was defined as a CF-related pulmonary condition requiring admission to the hospital or use of home intravenous antibiotics. Lung function variables included the average of the highest quarterly measurements of FEV_1 and the percent predicted value (18). Weight percentiles were based on current age-specific values from the U.S. population (<http://www.cdc.gov/nccdphp/dnpa/growthcharts/>). Pancreatic insufficiency was assessed by use of pancreatic enzymes. The pancreatic function status of 26 patients was unknown or missing; these patients were assumed to be pancreatic sufficient. Airway colonization was positive if a culture was documented with *P. aeruginosa* or *B. cepacia* and considered negative in the 714 patients with respiratory cultures coded as unknown or missing. Genotype was categorized based on the presence of the ΔF508 mutation (coded as a homozygote for ΔF508 , a heterozygote for ΔF508 , genotyped without ΔF508 , and not genotyped). Government-financed insurance status was used in the models as a surrogate for low socioeconomic status, categorized as privately financed insurance, government financed insurance, uninsured, and unknown insurance status (13, 19). Additionally, the median household income based on census tracts was also used as a surrogate for socioeconomic status.

Exposure Assignment

Yearly summaries of air pollution monitoring information were extracted from the Aerometric Information Retrieval System database. Each subject was assigned exposure data from the closest population-oriented monitors to the centroid of their residential zip code, if less than 30 miles in distance. The annual mean air pollution values used in this study were calculated from 1-hour averages for ozone (O_3), nitrogen

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dioxide (NO₂), sulfur dioxide (SO₂), and carbon monoxide (CO), and 24-hour averages collected every 1 to 12 days for particulate matter (PM₁₀ and PM_{2.5}). The 2000 annual averages were recorded from all population-oriented monitors that collected more than 50% of their intended observations.

Statistical Analysis

Comparisons between groups were analyzed using Student's two-sample *t* test, Mann Whitney rank-sum tests, and chi-square tests as appropriate. A two-sided *p* value of less than 0.05 was considered statistically significant. Logistic regression models were used to estimate the odds of two or more exacerbations compared with one or zero exacerbations and to assess the risk of mortality (20). Clinically relevant interactions were decided a priori to their statistical assessment in the model (interactions tested included lung function and pollutants, age and pollutants, and insurance status and pollutants). Additionally, polytomous regression models were used to estimate the odds of none, one, and two or more exacerbations. For lung function, multiple linear regression techniques were used (21) (see the online supplement for complete details of statistical modeling).

To assess the impact of using exposure monitoring results within 30 miles of the residence, we also modeled outcomes when a 10- or 50-mile criterion was applied to exposures. In an effort to adjust for regional differences in healthcare practices and air pollution, the United States was divided into six areas, and this term was considered in models (details of the six regions are provided in the online supplement). Because the ozone-monitoring season is not uniform, a variable based on the length and timing of the monitoring season was created and explored in models. Statistical analysis was performed with SAS 8.2 for Windows (SAS Institute Inc., Cary, NC) and Stata 7.0 (StataCorp, College Station, TX). Some of the results of this study have been previously reported in the form of an abstract (22).

RESULTS

Of 22,303 CF patients in the registry, 18,491 were linked to exposure data from appropriate air monitors within the 30-mile radius. Of these, 6,881 were excluded because of insufficient medical information (absence of data regarding any of the following variables: age, sex, lung function, weight, insurance status, and number of exacerbations), 118 patients because of solid organ transplantation in 2000, and 8 because of nonphysiologic weight. These patients were excluded from all subsequent analyses. Characteristics of the final study population of 11,484 patients are described in Table 1 along with the characteristics of the two exacerbation categories; 3,322 (29%) had two or more pulmonary exacerbations. Not all subjects had data available for each specific air pollutant (Table 2). Subjects resembled those previously noted in the CFFNPR (17). The study population had the following characteristics: a mean age of 18.4 years, 92% pancreatic insufficiency, mean weight percentile of 30.5%, and mean FEV₁ of 75% of predicted; 62% and 4% of study patients had positive cultures for *P. aeruginosa* or *B. cepacia*, respectively. The genotype was available in 74% of the population, and of those genotyped, 66% carried one or more ΔF508 deletions.

The registry population had 13,086 unique zip codes; 12,419 of these zip codes were successfully linked to at least one pollution-monitor combination. The geographic distribution of linked monitor sites is available in the online supplement (Figure E1). The mean distance from the patients' zip code to monitors for PM₁₀ and PM_{2.5} was 11.5 miles (SD 7.9) and 10.8 miles (SD 7.8), respectively, and between 11 and 12.4 miles for the other pollutants. The distribution of air pollution data with the associated number of monitors is shown in Table 2.

Pulmonary Exacerbation and Air Pollutants

Patients with two or more exacerbations were older and had poorer lung function and nutritional status than patients with less than two exacerbations. They were also more likely to be

colonized with *P. aeruginosa* or *B. cepacia* and have pancreatic insufficiency and government-financed insurance. Small significant increases in annual averages for PM₁₀, PM_{2.5}, and ozone were found in patients with two or more pulmonary exacerbations when compared with subjects with less than two pulmonary exacerbations (PM_{2.5} 14.20 vs. 13.91, *p* < 0.001; PM₁₀ 25.41 vs. 25.05, *p* < 0.01; O₃ 50.9 vs. 50.5, *p* < 0.01). There was no difference in the annual mean NO₂, SO₂, or CO between the groups.

Results of single pollutant models are listed in Table 3. Adjusting for sex, age, weight, race, airway colonization with *P. aeruginosa* and *B. cepacia*, pancreatic function, and insurance status, a 10-μg/m³ rise in PM₁₀ and PM_{2.5} was associated with an 8% (95% confidence interval [CI], 2–15%) and 21% (95% CI, 7–33%) increase in the odds of two or more exacerbations, respectively, and a 10-ppb rise in ozone was associated with a 10% (95% CI, 3–17%) increase. An additional model using household median income to adjust for socioeconomic status showed very similar results (see Table E1 in the online supplement). A 10-μg/m³ change in PM₁₀ and PM_{2.5} was used in the analysis because this reflected the effect size commonly reported in the literature. Associations were not noted for NO₂, SO₂, or CO.

Polytomous regression was also used to model the effects of air pollution on pulmonary exacerbation rate adjusted for sex, age, weight, race, airway colonization with *P. aeruginosa* and *B. cepacia*, pancreatic function, and insurance status. Pulmonary exacerbation was coded as 0, 1, or 2 or more, with the comparison group being 0 exacerbations. Because of the smaller number of subjects in each model, the 95% confidence intervals increased. An increase of 10 μg/m³ in PM₁₀ and 10 ppb in O₃ were associated with an increased odds of having one exacerbation compared with no exacerbation, but this did not reach statistical significance; a 10 μg/m³ in PM_{2.5} was associated with a decrease odds of one exacerbation compared with no exacerbations (OR [odds ratio], 0.70; 95% CI, 0.59–0.98). However, an increase of 10 μg/m³ in PM₁₀ and 10 ppb in O₃ was associated with 9% (95% CI, 2 to 17%) and 10% (95% CI, 3 to 17%) increased odds of having two exacerbations compared with no exacerbation, respectively. There was a trend to increased odds of two exacerbations compared with no exacerbation for every 10 μg/m³ in PM_{2.5} (13%; 95% CI, –1% to 29%). The full results of the polytomous regression models are available in online supplement (Table E4).

Inclusion of the baseline percent predicted FEV₁ in the single pollutant models resulted in attenuation of the estimates and a loss of statistical significance for particulate air pollution but not ozone. The estimate for ozone was unaffected by adding FEV₁ to the model. The ozone-monitoring season covariate was forced in the model so that patients from identical monitoring seasons could be compared; no significant effect was detected on the models. Regional effects were also assessed and not found to affect the models significantly. Sensitivity analysis with 10- and 50-mile radius from residence did not substantially change the results (see Tables E2 and E3 in the online supplement). In these analyses, the point estimates for PM_{2.5} and PM₁₀ were very similar; the 95% confidence intervals increased in the analyses using the 10-mile radius data with the fall in sample size. No significant interactions were found.

The estimates of the individual risk factors for two or more exacerbations were consistently significantly increased in all models for female sex, colonization with *P. aeruginosa* and *B. cepacia*, and government-financed insurance. Pancreatic insufficiency was also associated with increased odds of two or more exacerbations. Odds of two or more exacerbations by the 5-year age group tended to increase until age 35 and then decline. Inverse associations were consistently statistically significant for weight and percent-age-predicted FEV₁.

Additional models were run to assess the impact of assessing

TABLE 1. STUDY POPULATION CHARACTERISTICS AND CHARACTERISTICS BY EXACERBATION CATEGORY

Variable	Total (n = 11,484)	Less than Two Exacerbations (n = 8,162)	Two or More Exacerbations (n = 3,322)
Age, mean $\pm$ SD	18.4 $\pm$ 10	17.4 $\pm$ 10	20.6 $\pm$ 9.7
Percentage FEV ₁ , mean $\pm$ SD	75 $\pm$ 25.9	81 $\pm$ 23.7	59 $\pm$ 24.2
Weight percentile, mean $\pm$ SD	30.5 $\pm$ 26	33.6 $\pm$ 26.6	23 $\pm$ 22.9
Female, n (%)	5,391 (47)	3,606 (44)	1,786 (54)
Race, n (%)			
White	10,977 (96)	7,783 (95)	3,194 (96)
Black	431 (4)	329 (4)	102 (3)
Other	76 (< 1)	50 (< 1)	26 (1)
Airway colonization, n (%)			
<i>Pseudomonas aeruginosa</i>	7,152 (62)	4,518 (55)	2,634 (79)
<i>Burkholderia cepacia</i>	410 (4)	182 (2)	228 (7)
Pancreatic insufficiency, n (%)	10,722 (93)	7,572 (93)	3,150 (95)
Genotype, n (%)			
Homozygous F508	4,433 (39)	3,119 (38)	1,314 (40)
Heterozygous F508	3,083 (27)	2,231 (27)	852 (26)
Other mutation	885 (8)	679 (8)	206 (6)
Not genotyped	3,083 (27)	2,133 (26)	950 (29)
Insurance, n (%)			
Private/HMO	6,738 (59)	5,081 (62)	1,657 (50)
Government	4,584 (40)	2,966 (36)	1,618 (49)
Uninsured	85 (< 1)	60 (< 1)	25 (< 1)
Unknown	77 (< 1)	55 (< 1)	22 (< 1)
Deaths, n (%)	213 (1.8)	58 (0.7)	155 (4.7)

Definition of abbreviation: HMO = health maintenance organization.

the impact of O₃ after adjusting for PM₁₀ and PM_{2.5}. After adjusting for PM₁₀ and additional confounders, a 10- μ g/m³ increase in O₃ was still associated with an increased odds of having two or more pulmonary exacerbations compared with less than two exacerbations (OR, 1.08; 95% CI, 1.01–1.15). After adjusting for PM_{2.5} and additional confounders, a 10- μ g/m³ increase in O₃ was also still associated with an increase odds of having two or more pulmonary exacerbations compared with less than two exacerbations with the same OR (OR, 1.08; 95% CI, 1.01–1.15). Thus, the impact of O₃ on exacerbation rate did not disappear when adjusting for particulate air pollutants, and PM₁₀ and PM_{2.5} continued to have a significant association with increased odds of pulmonary exacerbation.

Pulmonary Function and Air Pollutants

A negative linear association was found between lung function (FEV₁) and particulate air pollution when assessed cross-sectionally in 2000, specifically PM_{2.5} and PM₁₀ after adjustment for age, sex, and height. Every increase in PM_{2.5} of 10 μ g/m³ was associated with decrease in mean FEV₁ of 155 ml (95% CI, 115–194);

every increase in PM₁₀ of 10 μ g/m³ was associated with decrease in FEV₁ of 38 ml (95% CI, 18–58).

After adjusting for age, sex, height, and mean FEV₁ in 1999, every 10 μ g/m³ increase in PM_{2.5} was associated with a decrease in mean FEV₁ in 2000 of 24 ml (95% CI, 7–40). A change in PM₁₀ of 10 μ g/m³ was not associated with a significant change in lung function in 2000 (1 ml; 95% CI, –7 to 10) after adjusting for age, sex, height, and mean FEV₁ in 1999. No clear associations were found with other pollutants (O₃, NO₂, SO₂, or CO). In these models, age was modeled as a continuous variable; a piece-wise regression using an age cut point of 18 did not change the estimate of the coefficient and standard error for PM_{2.5} or the other pollutants. When lung function was modeled using FEV_{1%} predicted instead of age, sex, and height, every 10- μ g/m³ increase in PM_{2.5} was associated with a decrease in mean FEV_{1%} predicted in 2000 of 0.5% (95% CI, 0.3–0.9%).

Mortality and Air Pollutants

During 2000, there were 419 (1.9%) deaths in the 22,303 CF patients in the initial cohort. A total of 213 (1.8%) deaths oc-

TABLE 2. NUMBER OF MONITORS AND ASSOCIATED AIR POLLUTION WITH MEAN, SD, AND MINIMUM AND MAXIMUM VALUES

Pollutant	n	Number of Monitors	Mean $\pm$ SD	Median (IQR)
PM ₁₀ , mg/m ³	9,502	626	24.8 $\pm$ 7.8	24.0 (20.3–28.9)
PM _{2.5} , μ g/m ³	10,294	713	13.7 $\pm$ 4.2	13.9 (11.8–15.9)
O ₃ , ppb	10,239	616	51.0 $\pm$ 7.3	51.2 (46.1–55.7)
SO ₂ , ppb	8,150	287	4.91 $\pm$ 2.6	4.3 (2.7–5.9)
NO ₂ , ppb	7,351	255	17.1 $\pm$ 7.7	18.0 (15.3–22.0)
CO, ppm	8,573	328	0.692 $\pm$ 0.295	0.59 (0.48–0.83)

Definition of abbreviations: CO = carbon monoxide; IQR = interquartile range (25th and 75th percentile); NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter with a median diameter of 2.5 μ m or less; PM₁₀ = particulate matter with a median diameter of 10 μ m or less; SO₂ = sulfur dioxide.

TABLE 3. RESULTS OF SINGLE POLLUTANT MODELS ASSESSING THE ODDS OF HAVING TWO OR MORE PULMONARY EXACERBATIONS DURING 2000*[†]

Pollutant	Odds Ratio	p Value	95% CI
PM ₁₀ , µg/m ³	1.08	0.014	1.02–1.15
PM _{2.5} , µg/m ³	1.21	0.001	1.07–1.33
O ₃ , ppb	1.10	0.005	1.03–1.17
NO ₂ , ppb	0.98	0.719	0.91–1.07
SO ₂ , ppb	0.83	0.068	0.71–1.01
CO, ppm	1.02	0.867	0.85–1.22

Definition of abbreviations: CI = confidence interval; CO = carbon monoxide; NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter with a median diameter of 2.5 µm or less; PM₁₀ = particulate matter with a median diameter of 10 µm or less; SO₂ = sulfur dioxide.

* Adjusted for sex, age, weight, race, airway colonization, pancreatic function, and insurance status. Ozone includes adjustment of monitoring season.

[†] Odds ratios for a 10 µg/m³ in PM₁₀ and PM_{2.5}; a 10-ppb rise in ozone, SO₂, NO₂, and a 1-ppm rise in CO.

current in our study population of 11,484 patients. Of these deaths, 196 and 177 had associated air pollutant data within 30 miles of their resident zip code for PM_{2.5} and PM₁₀, respectively. After adjusting for sex, age, pancreatic insufficiency, genotype, *P. aeruginosa* and *B. cepacia* colonization, and insurance status, an increase of PM_{2.5} by 10 µg/m³ was associated with an increased risk of death that did not achieve statistical significance (OR = 1.32; 95% CI, 0.91–1.93). The effect was attenuated with widening confidence intervals after adjusting for lung function (RR 1.12; p = 0.67; 95% CI, 0.76–1.65). No clear significant association or trend was found with other pollutants (PM₁₀, O₃, NO₂, SO₂, or CO).

Assessment of Bias

In these analyses, only a subset of patients was successfully matched with pollution data, and only a subset of patients with pollution data had complete clinical data. To assess the potential for selection bias, patients with pollution data were compared with those without pollution data. There were 4,209 patients who fulfilled entry criteria but did not have associated pollution monitor data compared with 11,484 who had pollution monitor data within 30 miles of the centroid of their zip code (6,610 patients without associated pollution monitor data did not fulfill the inclusion criteria). When comparing these two populations, patients who had associated pollution data were more likely to be genotyped (73.3% vs. 70.3%), have documented *P. infection* (68% vs. 62%), have more pulmonary exacerbations (mean annual rate of 1.2 vs. 1.0), have slightly lower FEV₁ percentage predicted in 2000 (73% compared with 74%), and were more likely to have private health insurance (40% vs. 45%). The two groups were not significantly different with regard to sex, age, or mortality in 2000 (1.4% vs. 1.3%).

DISCUSSION

In this study of CF patients, increased annual average exposure to ambient air pollutants, specifically PM₁₀, PM_{2.5}, and ozone, was associated with increased odds of two or more pulmonary exacerbations after adjusting for individual risk factors for severity of the underlying disease. The association was most prominent for patients who experienced two or more exacerbations per year. No reports on this association have previously been published. We also found a significant loss of ventilatory function in association with increased PM_{2.5} and a substantial (32%) increased risk of death (that did not reach statistical significance) in association with increased PM_{2.5}. This study was underpowered

to assess the outcome of mortality. Further study is warranted on the impact of individual air pollutants over a longer time period on lung health in CF.

The estimates for the associations between pulmonary exacerbations and death and PM₁₀ and PM_{2.5} were attenuated when the models were adjusted for lung function. It is possible that patients with worse lung function and more frequent exacerbations may migrate to urban areas (with higher air pollution) to be closer to specialized medical care, thus confounding the relationship between pollution exposure and lung health. However, we believe it is more likely that lung function decline may be intimately associated with chronic exposure to air pollutants and may be part of the causal pathway in worsening prognosis in CF (4); in support of this explanation, we found both cross-sectional and longitudinal strong inverse relationships between FEV₁ and PM levels.

CF patients have evidence of airway infection, inflammation, and products from tissue destruction even when they have no symptoms; the process leading to destruction of the integrity of the CF airway is life long (23, 24). The CF lung contains large amounts of free myeloperoxidase and neutrophil-derived proteases and decreased levels of S-nitrosoglutathione (25–27). In this setting of excessive oxidative stress and inflammation, air pollutants could lead to further airway irritation and injury. This in turn may affect the rate and extent of airway infection. In our analyses, PM_{2.5} and PM₁₀ had the most consistent associations with important clinical outcome measures. Recent evidence in CF patients may support this finding. Brown and colleagues studied the deposition and retention of technetium-99m-labeled iron oxide particles (5 micron) in CF patients compared with healthy volunteers. They found that particulate deposition was increased in CF and that the distribution of particle deposition was enhanced in the tracheobronchial regions of poorly ventilated lung regions in CF patients (28). Such focal deposition may partially explain the association of particulate air pollutants and pulmonary exacerbation rate.

The association of O₃ levels with pulmonary exacerbations was more unexpected. High ozone levels have been associated with an increase in asthma exacerbations in children with asthma and a reduced rate of growth in peak flow rates in children living in Southern California. A longer duration of follow-up in a CF cohort may clarify both the short-term (29) and long-term role of ozone in lung health of CF patients (30).

There are some important limitations to our current analysis. Residual confounding caused by unmeasured risk factors is of concern. Control of individual risk factors in the analysis included adjustment for sex, age, race, nutritional status, airway colonization, pancreatic function, and insurance status (or median household income). An important individual risk factor not available in the CFFNPR is tobacco use or exposure to environmental tobacco smoke. Cigarette smoking has been associated with persons of low socioeconomic status who may also tend to live in areas of higher ambient air pollution. Cigarette smoking, through both mainstream and sidestream exposures, has also been associated with worse prognosis in CF, notably increased risk of hospitalization for pulmonary exacerbations. (31) Adjustments made for socioeconomic status in the study may have adjusted in part for tobacco use. Spatial effects such as climate, weather patterns, regional variation in medical care practices, and rural and urban differences are also potential confounders that we were unable to address fully. The tendency for spatial autocorrelation between nearby sites could create difficulty in meeting the assumption for independence of observations in the logistic regression models and lead to misstatement of the pollution standard error estimates. Because air pollution monitors are more commonly situated in urban areas, our sample may

have had higher air pollutant exposure than the CF population as a whole. However, this should not have affected the associations that we found. Misclassification of exposure status could occur in two additional settings. Patients with more severe disease may limit their exposure to ambient air by staying inside. Also, given our inclusion criteria for pollution data, some sites could have had as few as 30 measurements during the year. Both of these examples of misclassification should be random and thus bias the results to the null.

Previous studies evaluating monitor-to-monitor correlation have demonstrated pollution levels to correlate well for PM₁₀, O₃, and NO₂ between monitors up to a distance of 100 miles (r , 0.8–0.6) (32). However, SO₂ and CO were found to have a lower correlation ($r < 0.5$) that is likely due to the influences of local sources (32). Thus, there is likely to be more measurement error affecting the estimates of the associations for SO₂ and CO. The correlation between ambient monitors and actual subject exposure also depends on factors other than the distance from the monitor. The amount of time the subject spends outdoors, the degree to which various pollutants penetrate into buildings, the distance from point sources, and weather patterns all contribute to variations in individual exposures to ambient air pollutants (32, 33). Therefore, there is certainly potential for exposure misclassification in this study, which would be of concern if the misclassification occurred in a differential manner between those with less than two or two or more exacerbations, as this could lead to bias in the results. It is more likely, however, that the misclassification in this study occurred equally in both exacerbation categories, which would tend to shift the ORs for the pollutants toward one.

The ability to generalize the results of this study to the entire CF population may be limited by the inclusion criteria set for study patients. CF patients who had complete medical information in the CFFNPR and who live in proximity to air pollution monitors did differ compared with those who had complete medical information but did not have associated pollution data. However, the absolute differences were small between these two groups, and no differences were seen in age or death rate. The differences seen may be attributable the effect of air pollution; there is less monitoring in less polluted areas.

In conclusion, exposure to ambient PM₁₀, PM_{2.5}, and ozone may increase the risk for pulmonary exacerbations and increase the rate of change in lung function in the CF population. Ambient air pollution may also impact survival. These findings would be consistent with the overall literature that has examined the effects of ambient air pollution on other sensitive populations. The findings would also continue to support the importance of subchronic and chronic exposure of ambient air pollutants. Future studies should focus on increasing the length of follow-up in CF patients, improved exposure assignment, and analytic methods to assess spatial effects, which may lead to continued improvement in our understanding of the effects of ambient air pollution on CF pulmonary disease.

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