



## Original Contribution

# Modification of the Association Between Ambient Air Pollution and Lung Function by Frailty Status Among Older Adults in the Cardiovascular Health Study

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The susceptibility of older adults to the health effects of air pollution is well-recognized. Advanced age may act as a partial surrogate for conditions associated with aging. The authors investigated whether gerontologic frailty (a clinical health status metric) modified the association between ambient level of ozone or particulate matter with an aerodynamic diameter less than 10  $\mu\text{m}$  and lung function in 3,382 older adults using 7 years of follow-up data (1990–1997) from the Cardiovascular Health Study and its Environmental Factors Ancillary Study. Monthly average pollution and annual frailty assessments were related to up to 3 repeated measurements of lung function using cumulative summaries of pollution and frailty histories that accounted for duration as well as concentration. Frailty history was found to modify long-term associations of pollutants with forced vital capacity. For example, the decrease in forced vital capacity associated with a 70-ppb/month greater cumulative sum of monthly average ozone exposure was 12.3 mL (95% confidence interval: 10.4, 14.2) for a woman who had spent the prior 7 years prefrail or frail as compared with 4.7 mL (95% confidence interval: 3.8, 5.6) for a similar woman who was robust during all 7 years (interaction  $P < 0.001$ ).

aging; effect modifier, epidemiologic; environmental exposure; frail elderly; respiratory function tests

Abbreviations: CHS, Cardiovascular Health Study; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter less than 2.5  $\mu\text{m}$ ; PM<sub>10</sub>, particulate matter with an aerodynamic diameter less than 10  $\mu\text{m}$ .

A growing body of literature suggests adverse effects of long-term exposure to ambient air pollution on lung function (1). Longitudinal studies with multiple cities or individualized exposures have been primarily conducted in children (2–8), with some conducted in adults (9, 10). In older adults, short- and long-term exposures have been negatively associated with lung function (11–14) and positively associated with respiratory symptoms (15, 16). Older adults are well-recognized as a susceptible subpopulation, and research on these groups is a priority (17–20).

Advanced age alone may not determine susceptibility. Recent evidence suggests that healthy aging may be possible, with morbidity increasingly compressed to the later years of life (21, 22). Susceptibility associated with advanced age may result not from a direct age effect but rather from age acting as an imperfect surrogate for health status. Health status in

older adults is complex and multidimensional. One metric, frailty, is generally conceptualized as a syndrome characterized by multisystem decline (23, 24) and has been shown to increase the risk of adverse health outcomes (25, 26).

We hypothesized that frailty status modifies the associations of ambient ozone and particulate matter with an aerodynamic diameter less than 10  $\mu\text{m}$  (PM<sub>10</sub>) with lung function, as measured by forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC).

## MATERIALS AND METHODS

### Study population

The Cardiovascular Health Study (CHS) (27, 28) is a longitudinal, population-based prospective study of adults

aged 65 years or older that was originally designed to study cardiovascular disease. Between 1989 and 1990, a total of 5,201 study participants (cohort 1) were recruited from 4 US counties through age- and sex-stratified random sampling from Medicare eligibility lists. To be eligible, potential participants could not be institutionalized, unable to give informed consent, in need of a proxy respondent, wheelchair-bound, receiving treatment for cancer, or likely to move away in the next 3 years (27). Between 1992 and 1993, 687 additional African Americans were recruited into the CHS (cohort 2).

### Lung function

During 3 clinical examination periods (1989–1990, 1993–1994, and 1996–1997), trained operators administered spirometry pulmonary function tests (PFTs), which have been described in detail elsewhere (29–31). We used maximal reported FVC and FEV<sub>1</sub>, regardless of assigned quality control grades (A, B, C, D, and F), because many frail participants had maneuvers with low grades.

### Frailty

Participants were considered frail if they satisfied at least 3 of 5 criteria: slow walking speed, poor grip strength, exhaustion, unintended weight loss, and low physical activity (25). Information used to construct these criteria was assessed during most clinical examination periods. For periods when the necessary information was not assessed, we singly imputed the missing data (see section 1 of the Web Appendix, which appears on the *Journal's* website (<http://aje.oxfordjournals.org/>)). We summarized frailty status using a categorical variable (robust = meeting 0 criteria; prefrail = meeting 1–2 criteria; frail = meeting  $\geq 3$  criteria).

### Covariates

At the baseline clinical examination (cohort 1: 1989–1990; cohort 2: 1992–1993), extensive information was gathered, including anthropometric, sociodemographic, and behavioral data, cardiovascular (32) and respiratory disease history and status, and other clinical measures. Some repeated and additional information was collected at follow-up clinical examinations.

### Air pollution

The CHS Environmental Factors Ancillary Study assigned participants in 3 of the 4 CHS counties (Forsyth County, North Carolina; Sacramento County, California; and Pittsburgh, Pennsylvania) subject-specific monthly average daily ambient PM<sub>10</sub>, nitrogen dioxide, ozone, sulfur dioxide, and carbon monoxide exposure estimates from 1989 to 2000. Ambient air pollution data were obtained from the Environmental Protection Agency's Aerometric Information Retrieval System and the California Air Resources Board's Ambient Air Quality Data compact disk. Participants' residential address histories were geocoded, and monthly average pollution levels were interpolated to each location

using the inverse-distance-weighted average of up to 3 of the nearest air quality monitors within 50 km (see section 2 of the Web Appendix). Here, we used subject-specific monthly averages for 24-hour average PM<sub>10</sub> ( $\mu\text{g}/\text{m}^3$ ) and 8-hour average daily maximum ozone (ppb). Sacramento County had ozone data year-round. During the nonozone season (November–March), Pittsburgh had limited ozone data and Forsyth County had none.

### Exclusion criteria

We excluded participants who, at baseline, had a history of Parkinson's disease ( $n = 47$ ), adjudicated stroke ( $n = 249$ ), or Mini-Mental State Examination score  $< 18$  ( $n = 74$ ) or who were taking Sinemet (carbidopa-levodopa; Merck & Company, Inc., Whitehouse Station, New Jersey), Aricept (donepezil hydrochloride; Eisai Company Ltd., Kawashima, Japan), or antidepressants ( $n = 235$ ), since these participants might have displayed frailty characteristics as a consequence of a single disease (25). We excluded participants with a self-reported race/ethnicity other than white or African-American ( $n = 31$ ). Missing or unreasonable PFT values (1 observation with FEV<sub>1</sub>  $> 9$  L and 4 observations with FEV<sub>1</sub> = 0 L) were also excluded. We included the subset of observations with complete information on FEV<sub>1</sub>, FVC, pollution exposure, frailty status, and adjustment covariates.

### Statistical methods

All models were fitted separately by sex because of sex differences in frailty prevalence (27) and pulmonary function (33). The same covariates were included in models for FEV<sub>1</sub> and FVC. Data from baseline (cohort 1: 1989–1990; cohort 2: 1992–1993) or the initial PFT (cohort 1: 1989–1990; cohort 2: 1993–1994), if available, were used to develop cross-sectional “base” models (34) for which Akaike's Information Criterion guided inclusion of a set of relevant candidate covariates and interactions from prior analyses in the CHS (31, 35). Exploratory generalized additive models (36) informed the creation of piecewise linear splines with a single sex-specific knot for continuous covariates. The final set of anthropometric, demographic, and behavioral adjustment covariates were: height (knot at 174 cm for women, 189 cm for men), weight (knot at 158 pounds (72 kg) for women, 245 pounds (111 kg) for men), waist circumference (knot at 81 cm for women, 87 cm for men), an indicator for African-American race/ethnicity, pack-years of smoking (knot at 80 years for men and women), years since quitting smoking, smoking status, education, an indicator for CHS community, age, and the interactions of race with age and smoking status. Additional adjustment covariates for cardiovascular and respiratory disease were: use of any beta blockers, a self-report of ever having physician-diagnosed pneumonia, symptoms of dyspnea upon exertion, current asthma diagnosis by a physician, and systolic blood pressure.

Longitudinal models with random intercepts were subsequently developed that included 1) fixed effects for time-constant adjustment covariates and time-varying age and 2) season and its interaction with community, to account

for potential confounding. For  $Y_{ij}$  (FEV<sub>1</sub> or FVC) from participant  $i$  at observation  $j$ , the model was

$$Y_{ij} = \beta_0 + \alpha X_{ij} + \beta_1 w_{ij} + \beta_2 a_{ij} + \beta_3 w_{ij} a_{ij} + U_i + \varepsilon_{ij},$$

where  $X_{ij}$  represents adjustment covariates,  $w_{ij}$  summarizes frailty history, and  $a_{ij}$  summarizes individual-level PM<sub>10</sub> or ozone history. We accounted for dependence in unequally spaced repeated measures by including an individual-level random intercept  $U_i \sim N(0, \tau^2)$  and multivariate normal errors  $\varepsilon_{ij}$  with mean 0 and a continuous-time first-order autoregressive correlation structure (37, 38). Longitudinal models were estimated by means of restricted maximum likelihood using lme in the nlme R package (39).  $P$  values for interactions were obtained from likelihood ratio tests comparing models—estimated by maximum likelihood—with and without the interaction term(s).

We quantified midterm (subchronic) and long-term (chronic) associations of air pollution with lung function and investigated evidence for modification by frailty history. Midterm exposure was summarized as the average of the current month, the prior month, or the 5 months prior to and including the current month. In these models, we considered modification by current frailty status and included indicators for calendar year to control for potential confounding by long-term trends. For long-term exposure, we used cumulative summaries of pollution (typical pollution months) and frailty (number of years spent frail) motivated by models for change in lung function (see section 3 of the Web Appendix). Similar cumulative summaries have been suggested previously (40) and applied elsewhere (9). Calendar year was a rough surrogate for cumulative exposure, so we excluded it to avoid unstable coefficient estimates. Because of seasonal availability, analyses of midterm ozone associations were performed for an abbreviated ozone season (May–October) to allow for investigation of prior-month associations. Long-term ozone exposure was quantified by typical ozone-season months accumulated only during the ozone season (April–October).

### Typical pollution months

Ambient air pollution exposure history for observation  $j$  was summarized as the cumulative sum of monthly average exposure from the month after the initial PFT to (and including) the month at observation  $j$ . This is similar to the cumulative exposure metric for smoking: pack-years = (cigarettes per day × years smoked)/20, where 20 is the number of cigarettes in a pack. We defined typical air pollution months as

$$\frac{\sum_{m \in \text{months exposed}} \text{average daily pollution in month } m}{\text{typical unit}}, \quad (2)$$

where the normalizing “typical units” were selected on the basis of the data: 30  $\mu\text{g}/\text{m}^3$  for 24-hour average PM<sub>10</sub> and 70 ppb for 8-hour average daily maximum ozone during ozone season. To translate a typical pollution month’s regression coefficient to a 10- $\mu\text{g}/\text{m}^3/\text{month}$  (or 10-ppb/month) scale, multiply by 10/30 (or 10/70).

### Number of years spent frail

Frailty history at study year  $t_j$  was summarized as the number of years the participant had spent frail (or prefrail/frail) since the initial PFT year ( $t_1 = 0$ ):

$$w_{ij}^* \equiv \left( \frac{1}{2} (w_i(0) + w_i(t_j)) + \sum_{s=1}^{t_j-1} w_i(s) \right), \quad (3)$$

where  $w_i(t_j)$  is binary frailty status (prefrail/frail vs. robust or frail vs. not frail). This assumes that transitions in frailty status occur halfway between equally spaced annual clinical examinations.

## RESULTS

At baseline, the 301 participants excluded because of missing covariates were heavier (165.2 pounds (75.0 kg) vs. 159.6 pounds (72.5 kg)) and more likely to be African-American (29.6% vs. 15.3%) than those included, but they were similar in terms of age, sex, and frailty. After exclusions, there were 7,281 observations on 3,382 participants (1,445, 1,009, and 928 participants had 3, 2, and 1 PFT, respectively). Of the 2,993 cohort 1 participants (336 cohort 2 participants) with PFT at the initial assessment, 70.4% (61.6%) also had a PFT at the following assessment. Participants were approximately evenly divided among the 3 communities. More participants were prefrail than frail (prevalences of 50.3% and 8.2% at the initial PFT, respectively). Transitions in frailty status were common. Although 44.9% of cohort 1 participants had the same categorical frailty status at the initial PFT as they had 4 years later at the second PFT, 70.1% of cohort 1 participants underwent a change in frailty status at least once during this interim (44.1% had 2 or more transitions). The number of years spent frail had a right-skewed distribution, while the number of years spent prefrail or frail was more uniformly distributed. Frail participants were older and more likely to be female, to be African-American, to have less education, and to have emphysema, dyspnea upon exertion, asthma, lower FEV<sub>1</sub>, lower FVC, or a low-quality PFT (grade of D or F) (Table 1).

Pollutant summary distributions and within-county correlations are presented in Tables 2 and 3, respectively. PM<sub>10</sub> levels declined over the course of the study period, while ozone levels remained relatively stable (Figure 1). The correlation between monthly average ozone and PM<sub>10</sub> varied by community ( $r=0.53$  in Forsyth County,  $r=0.36$  in Pittsburgh, and  $r=0.06$  in Sacramento County), so we did not attempt to fit multipollutant models. Typical ozone and PM<sub>10</sub> months were strongly correlated ( $r=-0.86$ ). For cohort 1 participants at the final PFT (when approximately 84 (7 × 12) months or 49 (7 × 7) ozone-season months had passed since the initial PFT), the number of typical pollution months ranged from 66.3 to 107.5 for PM<sub>10</sub> and from 37.8 to 69.0 for ozone.

**Table 1.** Characteristics of Participants According to Categorical Frailty Status at the Time of the Initial Pulmonary Function Test, Cardiovascular Health Study, 1989–1997

	Frailty Status					
	Robust ( <i>n</i> = 1,382)		Prefrail ( <i>n</i> = 1,673)		Frail ( <i>n</i> = 274)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age, years		71.2 (4.4)		73.0 (5.5)		76.6 (6.3)
Height, cm		166.4 (9.3)		164.7 (9.5)		162.4 (9.7)
Weight, pounds <sup>a</sup>		158.9 (29.4)		160.1 (32.0)		160.5 (37.7)
Waist circumference, cm		92.2 (11.8)		95.3 (12.7)		98.0 (15.8)
African-American race/ethnicity	11.1		16.6		29.2	
Male sex	46.6		40.8		32.8	
Education						
<8th grade	5.9		11.7		20.4	
Grades 8–11	11.0		13.7		17.2	
Grade 12 or GED	28.4		29.7		26.6	
≥1 year of vocational school to 4-year college degree	40.6		34.2		28.8	
Graduate/professional school	14.0		10.7		6.9	
Smoking status						
Never smoker	44.9		46.1		52.9	
Former smoker	45.7		41.6		33.6	
Current smoker	9.3		12.3		13.5	
Years since quitting smoking (former smokers)		20.7 (13.2)		19.9 (13.1)		19.9 (14.0)
Pack-years of smoking (ever smokers)		34.7 (29.2)		34.3 (28.5)		36.9 (30.0)
Use of any beta blockers	12.7		13.3		10.9	
Systolic blood pressure, mm Hg		135.7 (21.3)		137.5 (21.3)		140.5 (23.6)
Pneumonia <sup>b</sup>	24.5		29.0		32.8	
Dyspnea symptoms upon exertion	3.8		14.1		30.7	
Current asthma <sup>c</sup>	2.5		3.6		6.2	
FEV <sub>1</sub> , L		2.2 (0.6)		2.0 (0.6)		1.6 (0.6)
Low-quality FEV <sub>1</sub> <sup>d</sup>	7.4		10.3		21.0	
FVC, L		3.1 (0.8)		2.9 (0.9)		2.4 (0.8)
Low-quality FVC <sup>d</sup>	4.7		7.9		15.2	

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GED, General Education Diploma; SD, standard deviation.

<sup>a</sup> 1 pound = 0.45 kg.

<sup>b</sup> Self-report of ever having physician-diagnosed pneumonia.

<sup>c</sup> Current asthma diagnosis by a physician.

<sup>d</sup> Assigned quality control grade of D or F (possible grades: A, B, C, D, and F).

### Midterm pollution associations

Higher 5-month mean PM<sub>10</sub> level was associated with decreased FEV<sub>1</sub> and FVC after adjustment for anthropometric, demographic, and behavioral covariates (Table 4), and the magnitude of estimated decreases was larger for the prefrail than for the robust (Figure 2). For example, pooling prefrail and frail men, a 10-μg/m<sup>3</sup> increase in 5-month mean PM<sub>10</sub> was associated with a difference in FVC of -34.3 mL (95% confidence interval (CI): -66.0, -2.5) as compared with -26.2 mL (95% CI: -58.7, 6.3) in robust men. For other midterm pollutant summaries, patterns in the associations by current frailty status were less consistent.

None of the interactions between a midterm pollutant summary and frailty were statistically significant ( $P > 0.09$ ).

### Long-term pollution associations

Increased typical PM<sub>10</sub> and ozone months were associated with decreased lung function after adjustment for anthropometric, demographic, and behavioral covariates (Table 4). Participants who spent more years frail or prefrail/frail had significantly larger declines in FVC (frail:  $P < 0.030$ ; prefrail/frail:  $P < 0.001$ ) but not FEV<sub>1</sub> (frail and prefrail/frail:  $P > 0.17$ ) (see Figure 3 and Web Figure 1, where plotted values

**Table 2.** Summary Distributions of Pollutant Levels, Obtained Using Data From All Available Pulmonary Function Test Measurements, Cardiovascular Health Study, 1989–1997

Pollutant and Summary	Mean (SD)	Minimum	Percentile					Maximum
			5th	25th	50th	75th	95th	
PM <sub>10</sub>								
Current-month mean	30.8 (11.2)	12.2	18.8	23.0	27.6	36.3	52.8	92.0
Prior-month mean	31.8 (11.4)	14.0	19.0	24.0	28.9	36.8	54.8	92.0
5-month mean	31.5 (8.6)	14.0	20.9	25.8	29.7	35.6	46.2	74.3
Typical months <sup>a</sup>	86.0 (7.7)	66.3	73.2	79.7	87.1	92.5	96.4	107.5
Ozone								
Current-month mean	39.7 (15.1)	8.3	15.3	27.3	39.7	51.3	64.1	79.6
Prior-month mean	23.9 (9.5)	4.2	9.3	16.6	23.8	30.8	40.4	54.8
Typical months <sup>a</sup>	49.8 (9.0)	37.8	39.5	40.4	48.7	60.9	63.3	69.0

Abbreviations: PM<sub>10</sub>, particulate matter with an aerodynamic diameter less than 10 μm; SD, standard deviation.

<sup>a</sup> Typical-month data are restricted to values obtained from cohort 1 participants at the time of the final pulmonary function test (when approximately 84 (7 × 12) months or 49 (7 × 7) ozone-season months had passed since the initial pulmonary function test), since these cumulative metrics are a function of time.

are  $\hat{\beta}_2 + \hat{\beta}_3 w_{ij}$  from equation 1). For example, the estimated decrease in FVC associated with exposure to an additional typical month (30 μg/m<sup>3</sup> monthly mean) of ambient PM<sub>10</sub> was 2.2 mL (95% CI: 1.7, 2.8) for a female participant who was robust over a 7-year interval as compared with a decrease of 4.4 mL (95% CI: 3.6, 5.2) if the same participant had instead spent 3 of those 7 years prefrail/frail.

### Sensitivity analyses

Results were qualitatively similar (unless specified, results not shown) when we 1) additionally adjusted for cardiovascular and respiratory disease covariates (long-term associations: Figure 3), 2) excluded low-quality PFT (Web Table 1 and Web Figures 2–4), 3) included an additional quadratic term for age, 4) multiply imputed missing

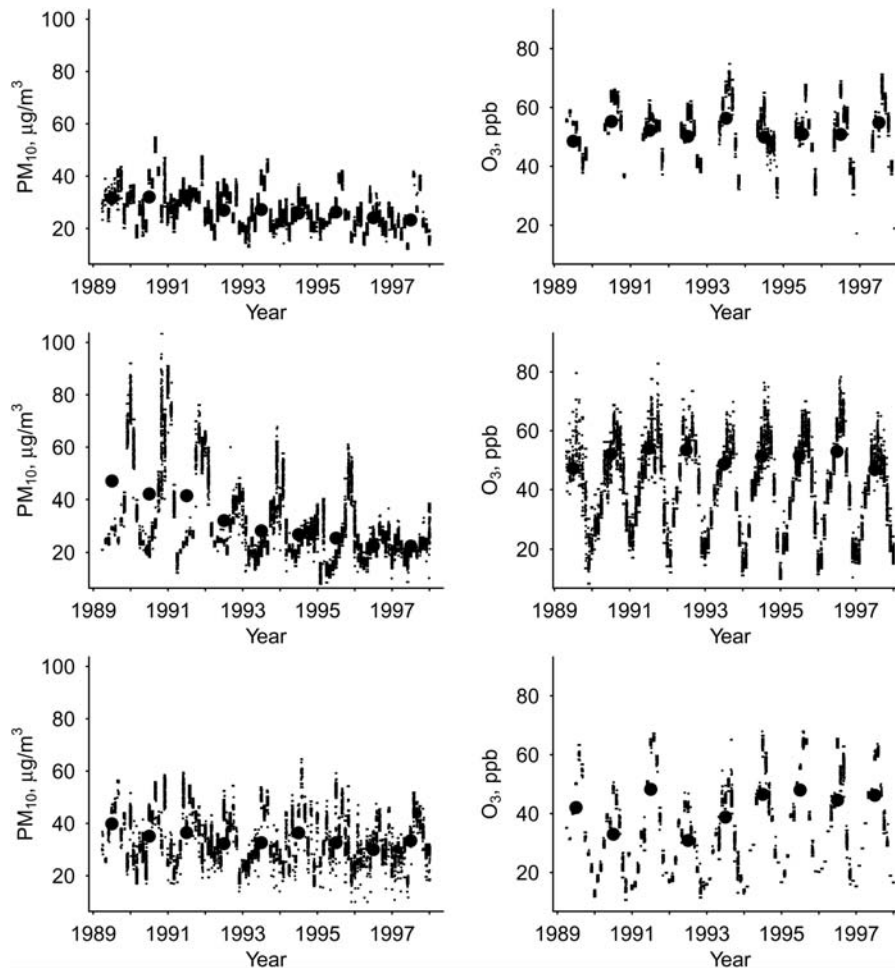
adjustment covariates, 5) adjusted for baseline frailty status instead of current frailty status, and 6) excluded current-year frailty status from the cumulative frailty metric. When we considered modification of recent pollution associations by baseline frailty instead of current frailty, again only 5-month mean PM<sub>10</sub> level showed a trend (not significant). In models including multiple summaries for the same pollutant on different time scales, the estimated associations of current-month and 5-month mean pollution were attenuated, while associations of cumulative pollution were similar. In multipollutant models, associations of 5-month mean PM<sub>10</sub> were attenuated and statistically significant only for FVC in women (Web Table 2). When we stratified results by community, Sacramento County had the largest-magnitude (negative) interaction regression coefficients for both cumulative pollutant exposures.

**Table 3.** Within-County Correlations Between Summary Pollutant Levels, Obtained Using Data From All Available Pulmonary Function Test Measurements, Cardiovascular Health Study, 1989–1997

Pollutant and Summary	PM <sub>10</sub>				Ozone		
	Current-Month Mean	Prior-Month Mean	5-Month Mean	Typical Months	Current-Month Mean	Prior-Month Mean	Typical Months
PM <sub>10</sub>							
Current-month mean	1.00						
Prior-month mean	0.56	1.00					
5-month mean	0.59	0.79	1.00				
Typical months	−0.22	−0.27	−0.41	1.00			
Ozone							
Current-month mean	−0.04	−0.16	−0.32	0.10	1.00		
Prior-month mean	−0.02	−0.08	−0.27	0.12	0.83	1.00	
Typical months	−0.24	−0.27	−0.41	0.96	0.10	0.11	1.00

Abbreviation: PM<sub>10</sub>, particulate matter with an aerodynamic diameter less than 10 μm.





**Figure 1.** Participant-level interpolated monthly mean 24-hour average level of particulate matter with an aerodynamic diameter less than  $10\ \mu\text{m}$  ( $\text{PM}_{10}$ ) (left) and 8-hour average daily maximum level of ozone ( $\text{O}_3$ ) (right) for Forsythe County, North Carolina (top), Sacramento County, California (middle), and Pittsburgh, Pennsylvania (bottom), Cardiovascular Health Study, 1989–1997. Annual mean values are plotted at the midpoint of each year (for ozone, the mean was calculated for April–October).

## DISCUSSION

In a large community-dwelling cohort of older adults, we found strong evidence that cumulative ozone or  $\text{PM}_{10}$  exposure was associated with decreased lung function. A history of frailty amplified the adverse associations of cumulative exposure with FVC but not  $\text{FEV}_1$ . Five-month average  $\text{PM}_{10}$  level was negatively associated with lung function, but there were no significant differences by frailty status.

Previous studies have found associations of particulate matter and ozone with lung function in older adults. For 57 older adults in Seattle, Washington, a  $10\text{-}\mu\text{g}/\text{m}^3$  increase in prior-day particulate matter with an aerodynamic diameter less than  $2.5\ \mu\text{m}$  ( $\text{PM}_{2.5}$ ) was associated with a 40.4-mL decrease (95% CI: 9.6, 71.1) in  $\text{FEV}_1$  (11). For 1,100 older men in the Normative Aging Study, a 15-ppb increase in prior-48-hour ozone was associated with decreases in  $\text{FEV}_1$  and FVC of 1.25% (95% CI: 0.54, 1.96) and 1.29% (95%

CI: 0.63, 1.95), respectively (13). Midterm (6-month) ozone associations with  $\text{FEV}_1$  and FVC have been found in children (6), though we are not aware of similar studies in older adults. In a study by Abbey et al. (41), summaries of 20-year  $\text{PM}_{10}$  exposure (and, to a lesser extent, ozone) were negatively associated with lung function in 1,391 adult non-smokers. Cross-sectional surveys of adults in England related lung function to 2-year average ambient pollutant exposures and found negative associations of  $\text{PM}_{10}$  with  $\text{FEV}_1$  that were stronger for men and older adults, but no evidence of associations of ozone with  $\text{FEV}_1$  (14).

A previously developed conceptual framework describes the most “frail” segment of the population as being at greater risk for air-pollution-related mortality (42, 43). To our knowledge, no studies have considered gerontologic measures of health status as susceptibility factors. In a study of Chinese older adults, Sun and Gu (44) investigated the associations of air pollution with Activities of Daily Living,

**Table 4.** Adjusted<sup>a</sup> Difference in FEV<sub>1</sub> or FVC Associated With a 10- $\mu\text{g}/\text{m}^3$  Increase in Recent PM<sub>10</sub> Level, a 10-ppb Increase in Recent Ozone Level (During Ozone Season), or a 1-Month Increase in Typical PM<sub>10</sub> Months or Typical Ozone Months (During Ozone Season), by Sex, Cardiovascular Health Study, 1989–1997

Pollutant and Summary	Difference in FEV <sub>1</sub> , mL				Difference in FVC, mL			
	Men		Women		Men		Women	
	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
<b>PM<sub>10</sub></b>								
Current-month mean	-1.7	-13.9, 10.4	-8.4	-16.1, -0.7	-10.3	-26.9, 6.3	-16.9	-28.3, -5.6
Prior-month mean	3.1	-9.0, 15.1	-3.3	-10.8, 4.3	-7.3	-23.8, 9.2	-7.7	-18.7, 3.4
5-month mean	-6.7	-26.9, 13.4	-20.2	-32.6, -7.7	-29.8	-56.9, -2.7	-31.8	-49.9, -13.6
Typical months	-0.9	-1.4, -0.4	-0.5	-0.8, -0.2	-4.3	-5.0, -3.7	-2.6	-3.0, -2.2
<b>Ozone</b>								
Current-month mean	-5.3	-23.2, 12.6	3.6	-7.3, 14.5	-4.9	-28.5, 18.7	-0.3	-16.5, 16.0
Prior-month mean	7.5	-25.7, 40.8	8.0	-12.2, 28.3	-18.5	-63.2, 26.2	-3.3	-34.2, 27.6
Typical months	-2.4	-3.3, -1.5	-1.2	-1.7, -0.7	-8.7	-9.8, -7.6	-5.3	-6.0, -4.6

Abbreviations: CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; PM<sub>10</sub>, particulate matter with an aerodynamic diameter less than 10  $\mu\text{m}$ .

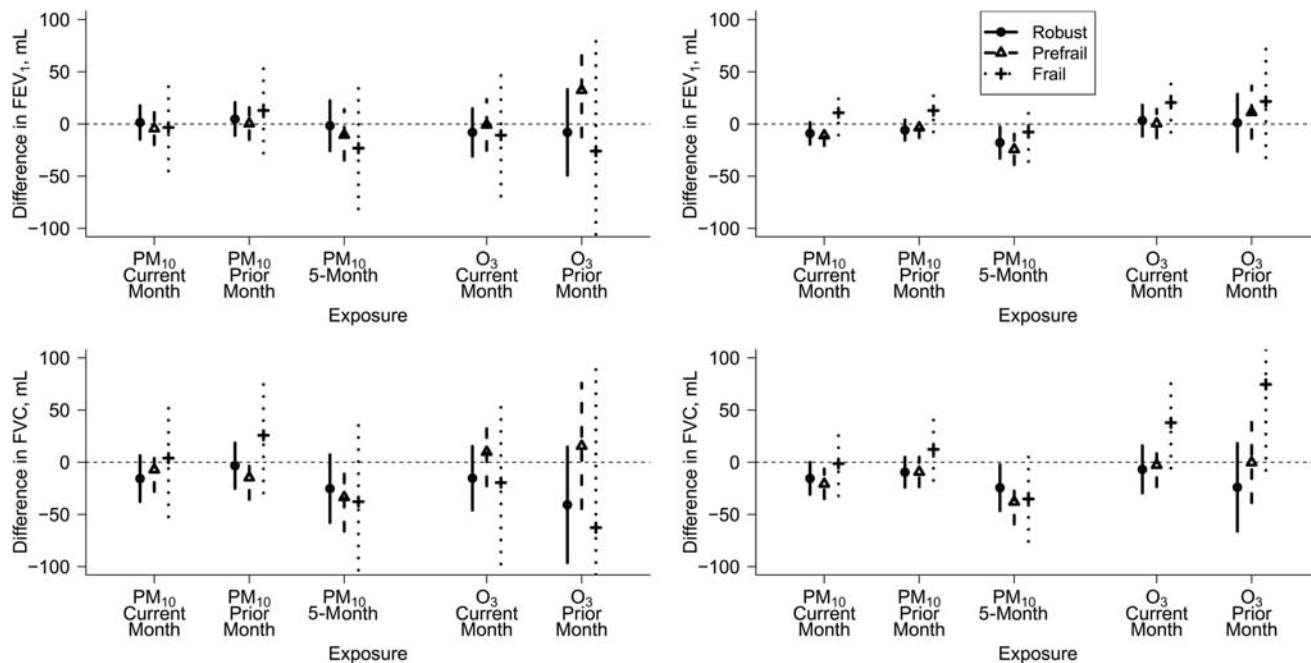
<sup>a</sup> Adjusted for anthropometric, demographic, and behavioral covariates and current frailty status.

Instrumental Activities of Daily Living, Mini-Mental State Examination score, and self-rated health but did not consider these as modifying factors.

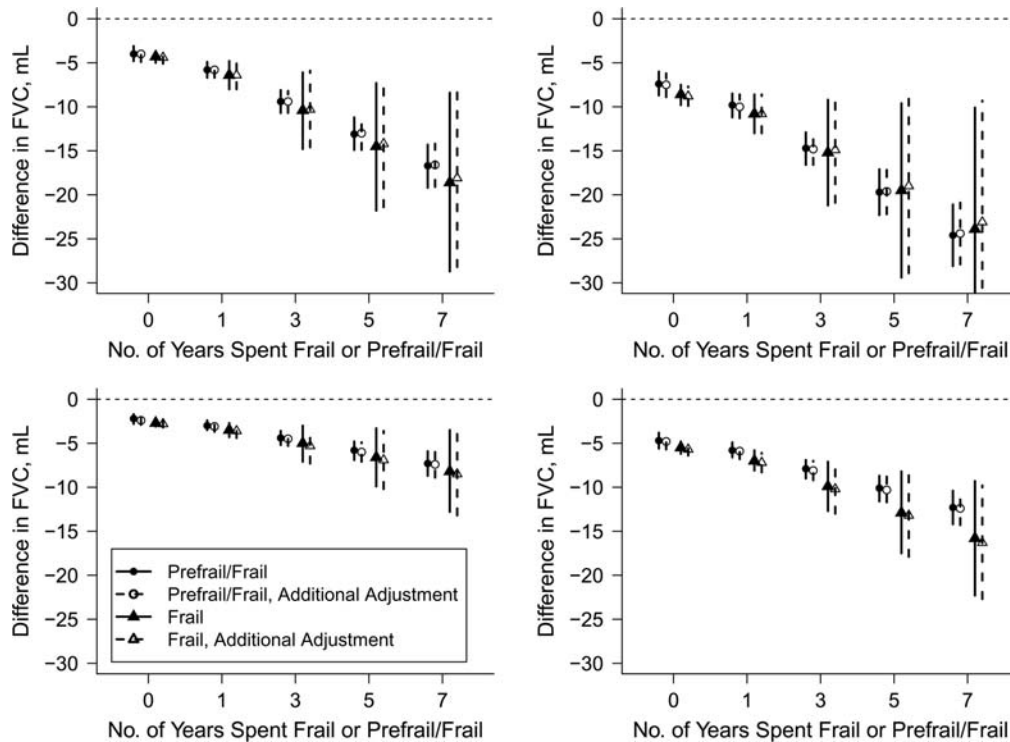
Strengths of this study include the large sample size, repeated measurements, the long follow-up period, individualized ambient pollutant exposures, and annual frailty assessment in a population where frailty has been well-studied. Frequent frailty assessment and summaries of frailty history are

important because frailty is a dynamic process, with individuals transitioning in both directions along the frailty gradient (45).

In contrast to other studies of long-term exposure associations that use study-period average exposures (5), we used a cumulative exposure summary to relate only prior air pollution levels to each lung function measurement. Advantages of the typical pollution month's exposure metric



**Figure 2.** Difference in forced expiratory volume in 1 second (FEV<sub>1</sub>) (top) or forced vital capacity (FVC) (bottom) associated with a 10- $\mu\text{g}/\text{m}^3$  increase in recent particulate matter with an aerodynamic diameter less than 10  $\mu\text{m}$  (PM<sub>10</sub>) or a 10-ppb increase in recent ozone (O<sub>3</sub>) during ozone season, according to current frailty status, for men (left) and women (right), after adjustment for anthropometric, demographic, and behavioral covariates, Cardiovascular Health Study, 1989–1997.



**Figure 3.** Difference in forced vital capacity (FVC) associated with a 1-month increase in typical pollution months (left, particulate matter with an aerodynamic diameter less than  $10\ \mu\text{m}$ ; right, ozone) for men (top) and women (bottom), according to the number of years spent frail or prefrail/frail, after adjustment for anthropometric, demographic, and behavioral covariates (solid lines) and additional adjustment for cardiovascular and respiratory disease covariates (dashed lines), Cardiovascular Health Study, 1989–1997.

include its 1) temporal ordering of exposure and outcome assessment, 2) accounting for exposure as a function not only of concentration but also of duration, 3) interpretability due to its similarity to the pack-years metric for smoking history, and 4) mathematical motivation stemming from models for change. However, implied assumptions of no safe level of exposure and no recovery from high past exposures may be questionable in studies of air pollution associations with health. Alternative cumulative summaries could use thresholds or weighting, but then the pack-years analogy and mathematical motivation would no longer hold.

Limitations of this study include the inability to determine whether the strengthening of the midterm association of  $\text{PM}_{10}$  over a longer time scale (5-month mean vs. 1-month mean) may have a biologic explanation or may be deattenuation from reduced measurement error. We were unable to investigate the associations with different particulate matter size fractions, because  $\text{PM}_{2.5}$  data were not available. We controlled for community, season, and their interaction, but residual confounding may still have existed.  $\text{PM}_{10}$  concentrations are affected by differences in location-specific seasonal patterns and sources of  $\text{PM}_{2.5}$  and the coarse fraction ( $\text{PM}_{2.5-10}$ ). In the East (Forsyth County and, to a lesser degree, Pittsburgh),  $\text{PM}_{2.5}$  concentrations peak in the summer, largely because of the transport of primary emissions and the formation of secondary aerosols resulting

from photochemical processes. In Sacramento County, winter air inversions trap primary fine particles (including  $\text{PM}_{2.5}$ ), and in the fall, higher  $\text{PM}_{10}$  levels reflect wind-blown coarse fraction particles.

Interpolation of ambient air pollutant levels to participants' residences may reduce spatial exposure misclassification, which can attenuate associations (46). However, we still lacked data on indoor/outdoor activity patterns and personal exposure. Ambient exposures differ from personal exposure but are still of interest. Previous studies have found associations of ambient exposures with lung function, and the National Ambient Air Quality Standards regulate ambient levels of air pollutants. Frail participants might spend more time indoors and have less exposure to ambient pollution, potentially attenuating associations. No data exist for exposures incurred prior to baseline in the CHS, but we may have partially accounted for previous exposure effects by adjusting for respiratory and cardiovascular disease, age, community, and individual-level random intercepts.

Participants dropped out of the study or had intermittent missing spirometry data for many reasons, including morbidity and death. Under the assumption that the missingness mechanism for PFT is related only to observed data (i.e., that data are missing at random) (47), a linear mixed-effects model that is "correct" for the mean and covariance structure is an appropriate analytic method, and there is no need to



multiply impute the missing response values, as has been done previously (35). Dropout due to morbidity or death prior to frailty diagnosis has been hypothesized as an explanation for lower-than-expected frailty incidence rates in many studies. Differential dropout of the frail would probably attenuate the modification by frailty status of pollution associations with lung function.

The high correlation between FVC and FEV<sub>1</sub> ( $r=0.90$ ) suggests that we would have seen similar strong interactions between cumulative exposure and frailty history had the interaction been spuriously induced by uncontrolled confounding, yet we observed the interaction for FVC and not FEV<sub>1</sub>. FEV<sub>1</sub> measures large airway flow, with declines being indicative of obstructive disease. FVC measures total capacity, including large and small airways, and it is reduced (along with FEV<sub>1</sub>) in restrictive disease. Since cumulative exposure was more strongly associated with decreases in FVC, particularly in participants with histories of frailty, chronic pollution exposure in older adults may more adversely affect smaller airways and may contribute to restrictive disease.

Increased susceptibility in older adults with frailty histories may arise from: 1) decreased physiologic (especially cardiopulmonary) reserve for offsetting the pathways by which air pollution affects pulmonary function; 2) potentially increased air-pollution-related inflammation in the frail as compared with the nonfrail; and 3) repercussions of frailty-related sarcopenia. In future work, researchers might investigate whether a chain reaction exists wherein reductions in lung function (potentially from air pollution) causally contribute to frailty, which could further increase susceptibility to air pollution.

In conclusion, this study provides novel evidence that frailty history modifies cumulative associations between air pollution and lung function in older adults. This offers insight into older adult susceptibility to air pollution and may have clinical implications for identifying which older adults are at increased risk.

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