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MODIFICATION BY FRAILTY STATUS OF AMBIENT AIR POLLUTION EFFECTS ON LUNG FUNCTION IN OLDER ADULTS IN THE CARDIOVASCULAR HEALTH STUDY

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Modification by frailty status of ambient air pollution effects on lung function in older adults in the Cardiovascular Health Study

Sandrah P. Eckel, Thomas A. Louis, Paulo H.M. Chaves, Linda P. Fried, and Helene G. Margolis

Abbreviations: CHS–Cardiovascular Health Study, FEV₁–forced expiratory volume in 1 second, FVC–forced vital capacity, PM–particulate matter, PFT–pulmonary function test.

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Abstract

Older adult susceptibility to air pollution health effects 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 effects of ambient ozone or particulate matter (PM$_{10}$) air pollution on lung function in 3382 older adults using 7 years of followup data from the Cardiovascular Health Study (CHS) and the CHS Environmental Factors Ancillary Study. Monthly average pollution and annual frailty assessments were related to up to 3 repeated measurements of lung function using novel cumulative summaries of pollution and frailty histories that account for duration as well as concentration. Frailty history was found to modify long-term pollution effects on Forced Vital Capacity (FVC). For example, the decrease in FVC associated with a 70 ppb-month increase in the cumulative sum of monthly average O$_3$ exposure was 8.8 mL (95% confidence interval (CI): 7.4, 10.1) for a woman who had spent the prior 7 years prefrail or frail compared to 3.3 mL (95% CI: 2.7, 4.0) for a similar not frail woman (interaction P<0.001).

Key words. Aging; effect modifiers; environmental exposure; frail elderly; respiratory function tests

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Exposure to tropospheric ozone (O\textsubscript{3}) and particulate matter (PM) air pollution has been associated with reduced lung function. Most research on the respiratory effects of long-term ambient exposures has focused on children (1–3). However, short- and long-term O\textsubscript{3} and PM exposures have been associated with reduced lung function and increased incidence of respiratory symptoms in older adults (4–7). Research on susceptible subpopulations is a priority (8–11), and older adults are often cited as susceptible.

However, 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 (12, 13). 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 multi-system decline (14, 15) and has been shown to increase the risk of adverse health outcomes (16, 17).

We hypothesize that frailty status modifies the associations of ambient O\textsubscript{3} and PM\textsubscript{10} with lung function as measured by forced expiratory volume in 1 second (FEV\textsubscript{1}) and forced vital capacity (FVC).

**MATERIALS AND METHODS**

*Study population.* The Cardiovascular Health Study (CHS) (18, 19) is a longitudinal population-based prospective study of adults ages 65 and older originally designed to study cardiovascular disease. Between 1989–1990, 5,201 study participants (Cohort 1) were recruited from 4 U.S. counties by age- and gender-stratified random sampling from Medicare eligibility lists. 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 (18). Between 1992–1993, an additional cohort of 687 African Americans (Cohort 2) was recruited.

tors administered spirometry pulmonary function tests (PFT) which have been described in detail elsewhere (20–22). We used maximal reported FVC and FEV₁, regardless of assigned quality control grades (A, B, C, D and F), because many frail participants had maneuvers with low grades.

**Frailty.** Individuals 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 (16). Information used to construct these criteria was assessed at most clinical exam years. For years when the necessary information was not assessed, we singly imputed the missing data (see Supplementary Data). We summarized frailty status using a categorical variable (robust: 0 criteria; prefrail: 1 to 2; frail: 3 or more).

**Covariates.** At the baseline clinical examination (Cohort 1: 1989–1990, Cohort 2: 1992–1993) extensive information was gathered including anthropometric, socio-demographic and behavioral data, cardiovascular (23) and respiratory disease history and status and other clinical measures. Some repeated and additional information was collected at followup clinical exams.

**Air pollution.** The Environmental Factors Ancillary Study to the CHS assigned participants in 3 of the 4 CHS counties (Forsyth County, NC; Sacramento County, CA and Pittsburgh, PA; but not Washington County, MD) subject-specific monthly average daily ambient PM₁₀, NO₂, O₃, SO₂ and CO exposure estimates from 1989 to 2000. Historical data was obtained from the U.S. Environmental Protection Agency Aerometric Information Retrieval System database and the California Air Resources Board Ambient Air Quality Data Compact Disc. Participant residence address histories were geocoded and monthly average ambient air pollution levels were interpolated to each location using the inverse distance weighted average of the up to 3 nearest air quality monitors within 50 km. Here, we used subject-specific monthly average ambient exposure estimates for 24-hour average PM₁₀ (µg/m³) and 8-hour average daily maximum O₃ (ppb). Sacramento County had O₃ data year-round. During the non-O₃ season (November-March), Pittsburgh had limited O₃ data and Forsyth County had none.

**Exclusion criteria.** We excluded participants at baseline who had a history of Parkinson’s disease (N=47), adjudicated stroke (N=249), Mini-Mental status score < 18 (N=74) or who were
taking Sinemet, Aricept, or antidepressants (N=235) since these participants might have displayed frailty characteristics as a consequence of a single disease (16). We excluded participants with self-reported race 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 fit separately by sex. 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, was used to develop cross-sectional “base” models (3) for which Akaike’s Information Criteria (AIC) guided inclusion of a set of relevant candidate covariates and interactions from prior analyses in the CHS (22, 24). Exploratory generalized additive models (25) informed the creation of piecewise linear splines with a single gender-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 lbs for women, 245 lbs for men), waist circumference (knot at 81 cm for women, 87 cm for men), indicator of African American race, pack years smoked (knot at 80 years for men and women), years since quit smoking, smoking status, education, indicator of CHS community, age, and the interactions of race with age and race with smoking status. Additional adjustment covariates for cardiovascular and respiratory disease were: taking any beta blockers, self report of doctor diagnosed pneumonia, symptoms of dyspnea on exertion, current asthma diagnosis by a doctor, and systolic blood pressure.

Longitudinal models with random intercepts were subsequently developed that included: (a) fixed effects for time-constant base model adjustment covariates and time-varying age, and (b) season and its interaction with community, to account for potential confounding. For Y<sub>ij</sub> (FEV<sub>1</sub> or
FVC) from participant $i$ at observation $j$, the model was:

$$Y_{ij} = \beta_0 + \alpha X_{ij} + \beta_1 w_{ij} + \beta_2 a_{ij} + \beta_3 w_{ij} a_{ij} + U_i + \epsilon_{ij} \quad (1)$$

where $X_{ij}$ represents adjustment covariates, $w_{ij}$ summarizes frailty history and $a_{ij}$ summarises individual-level ambient air pollution (PM$_{10}$ or O$_3$) history. Dependence in unequally spaced repeated measures was accounted for by including an individual-level random intercept $U_i \sim N(0, \tau^2)$ and multivariate normal errors $\epsilon_{ij}$ with mean 0 and a continuous time first-order autoregressive (AR(1)) correlation structure (26, 27). Longitudinal models were estimated by restricted maximum likelihood using lme in the nlme (28) R package. P-values for interactions were from likelihood ratio tests comparing models – estimated by maximum likelihood – with and without the interaction term(s).

We summarized evidence for mid-term (subchronic) and long-term (chronic) associations of air pollution with lung function and investigated evidence for modification by frailty history. Mid-term exposure was summarized by the average of the: current month, prior month, or 5 months prior to and including the current month. In these models, modification by current frailty status was considered and indicators for calendar year were included to control for confounding by long-term trends. For long-term exposure, we applied novel cumulative summaries of pollution (typical pollution months) and frailty (number of years spent frail) motivated by models for change in lung function (see Supplementary Data). Calendar year was a rough surrogate for cumulative exposure, so we excluded it in these models to avoid unstable effect estimates. Due to seasonal availability, analyses of mid-term O$_3$ effects were performed for an abbreviated O$_3$ season (May–October) to allow for investigation of prior month effects. Long-term O$_3$ exposure was quantified by typical O$_3$ season months accumulated only during the O$_3$ season (April–October).

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

\[ \sum_{m \in \text{months exposed}} \frac{\text{average daily pollution in month } m}{\text{typical unit}} \]  

(2)

where the normalizing “typical units” were selected based on the data: 30 µg/m³ for 24-hour average PM₁₀ and 70 ppb for 8-hour average daily maximum O₃ during O₃ season. To translate a typical pollution months effect estimate to a 10 µg/m³-months (or 10 ppb-months) scale, divide by the corresponding typical unit and then multiply by 10. In models of long-term pollutant effects, we considered modification by the following cumulative summary of frailty.

**Number of years spent frail.** Frailty history at study year \( t_j \) was summarized by the number of years spent frail (or prefrail/frail) since the baseline PFT year (\( t_1 = 0 \)):

\[ w_{ij}^* \equiv \left( \frac{1}{2}(w_i(0) + w_i(t_j)) + \sum_{s=1}^{t_j-1} w_i(s) \right) \]  

(3)

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

We use subscripts to display the lower bounds (LB) and upper bounds (UB) of 95% confidence intervals: \( \text{LB Estimate UB} \) (29).

**RESULTS**

[Table 1 about here.]

[Figure 1 about here.]

After exclusions, there were 7281 observations on 3382 participants. At baseline, the 301 participants excluded due to missing covariates were heavier (165.2 lbs vs. 159.6 lbs) and more likely to be African American (29.6% vs. 15.3%) than those included, but similar in terms of age, frailty, and gender.

The number of participants with 3, 2, and 1 PFT was 1445, 1009, and 928, respectively. Of the 2993 Cohort 1 participants with a PFT at the initial exam, only 48% had both followup tests.
Relatively few participants were frail at the initial PFT (Table 1). Frail participants were older, more likely to be African American, female, to have less education, and to have emphysema, dyspnea on exertion, asthma, lower FEV$_1$, lower FVC and low quality PFT (D or F grades). The number of years spent frail had a right skewed distribution, while the number of years spent prefrail or frail was more uniformly distributed.

PM$_{10}$ declined over the study period while O$_3$ levels remained relatively stable (Figure 1). The correlation of monthly average O$_3$ and PM$_{10}$ varied by community (0.53 in Forsyth County, 0.36 in Pittsburgh, and 0.06 in Sacramento County), so we did not attempt to fit multipollutant models. Participants were approximately evenly divided amongst the three communities. Typical O$_3$ and PM$_{10}$ months were strongly correlated (-0.86). For Cohort 1 participants at the final PFT (when approximately 84 (7×12) months or 49 (7×7) O$_3$ season months had passed since the initial PFT), the number of typical pollution months ranged from 66.3 to 107.5 for PM$_{10}$ and 37.8 to 69.0 for O$_3$.

[Table 2 about here.]

[Figure 2 about here.]

Mid-term pollution effects. Higher 5 month mean PM$_{10}$ was associated with decreased FEV$_1$ and FVC, after adjusting for anthropometric, demographic and behavioral covariates (Table 2) and the magnitude of estimated decreases was larger for prefrail than for the robust (Figure 2). For example, pooling prefrail and frail men, a 10 $\mu$g/m$^3$ increase in 5 month mean PM$_{10}$ was associated with a difference in FVC of $-68.8 - 36.8 - 4.8$ mL compared to $-59.0 - 26.3 - 6.3$ mL in robust men. For other mid-term pollutant summaries, patterns in the associations by current frailty status were less consistent. None of the interactions between a mid-term pollutant summary and frailty were statistically significant (P>0.09).

[Figure 3 about here.]
Long-term pollution effects. Increased typical PM\textsubscript{10} and O\textsubscript{3} months were associated with decreased lung function, adjusting for anthropometric, demographic and behavioral covariates (Table 2). Participants spending a greater number of years frail or prefrail/frail had significantly larger declines in FVC (frail: P<0.030; prefrail/frail: P<0.001) – but not FEV\textsubscript{1} (frail and prefrail/frail: P>0.17) – (Figure 3, where effect estimates 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 $\mu$g/m\textsuperscript{3} monthly mean) of ambient PM\textsubscript{10} was $1.72.2_{-2.8}^{+2.2}$ mL for a female participant who was robust over a 7 year interval compared to a decrease of $3.6_{-4.4}^{+5.2}$ mL if the same participant had instead spent 3 years prefrail/frail.

Sensitivity analyses. Additional adjustment for cardiovascular and respiratory disease covariates produced similar mid-term (not shown) and long-term pollution effects (Figure 3). Results for the modification of cumulative pollutant exposure by frailty were insensitive to excluding the residual AR(1) correlation structure and to including an additional quadratic term for age. In cumulative pollutant analyses stratified by community, Sacramento County had the largest (negative) magnitude interaction effect estimates for both pollutants. When low quality PFT were excluded, results were quantitatively similar, but less statistically significant. One could alternatively down-weight low quality PFT, but this did not seem appropriate here because the variability in PFT was similar across quality grades. Multiple imputation of missing adjustment covariates produced similar results.

DISCUSSION

In a large community-dwelling cohort of older adults, we found strong evidence that cumulative O\textsubscript{3} or PM\textsubscript{10} exposure was associated with decreased lung function. A history of frailty amplified the adverse effects of cumulative exposure on FVC, but not FEV\textsubscript{1}. Five month average PM\textsubscript{10} was negatively associated with lung function, but there were no significant differences by frailty status in associations between mid-term pollution exposure and lung function.

Previous studies have found associations of short-term PM and O\textsubscript{3} with lung function in older
adults, but few have investigated longer-term associations. For 57 older adults in Seattle, a 10 μg/m³ increase in prior day PM$_{2.5}$ was associated with a $9.6\,40.4\,71.1$ mL decrease in FEV$_1$ (7). For 1100 older men in the Normative Aging Study, a 15 ppb increase in prior 48-hour O$_3$ was associated with decreases in FEV$_1$ and FVC of $0.54\,1.25\,1.96\%$ and $0.63\,1.29\,1.95\%$, respectively (5). One study found evidence of mid-term (6 month) O$_3$ effects on FEV$_1$ and FVC in children (30), though we are not aware of similar studies for older adults. A cohort study of 1391 nonsmokers found that summaries of 20-year PM$_{10}$ exposure (and, to a lesser extent, O$_3$) were associated with lung function (4). Cross-sectional surveys of adults in England related lung function to two-year average ambient pollutant exposures and found decreases in FEV$_1$ associated with increased PM$_{10}$ that were stronger for men and older adults, but no evidence of associations of FEV$_1$ with O$_3$ (31).

A conceptual framework has been developed that describes the most “frail” segment of the population as being at greater risk for air pollution related mortality (32, 33), yet we are not aware of studies that consider gerontologic measures of health status as susceptibility factors. A study of Chinese older adults investigated the effects of air pollution on activities and instrumental activities of daily living, Mini-Mental State Examinations and self-rated health (34), but did not consider these as modifying factors.

The strengths of this study include the large sample size, repeated measurements, long followup, 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 thought to be a dynamic process, with individuals transitioning in both directions along the frailty gradient (35).

In contrast to other cohort studies of long-term exposure effects that use study-period average exposures (2), we related only prior air pollution levels to each lung function measurement by using a cumulative exposure summary. Advantages of the typical pollution months exposure metric 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, some assumptions implied by this metric may be questionable in studies of air pollution health effects, including: no safe level of exposure and no recovery from high past exposures. Alternative cumulative summaries could use thresholds or weighting, but then the pack-years analogy and mathematical motivation would no longer hold. Cumulative exposure summaries have been suggested elsewhere (36) and implemented in an application where they were referred to as “interval exposure” (37), but neither divided by a standardizing unit.

Limitations of the study include the inability to determine whether the strengthening of the midterm association of PM$_{10}$ over a longer timescale (5 versus 1 month means) may have a biological explanation or may be deattenuation from reduced measurement error. We were unable to investigate the effect of different PM size fractions, because PM$_{2.5}$ data were not available. We controlled for community, season and their interaction, but residual confounding may still exist. PM$_{10}$ concentrations are affected by differences in location-specific seasonal patterns and sources of PM$_{2.5}$ and the coarse fraction (PM$_{2.5-10}$). In the east (Forsyth County and to a lesser degree, Pittsburgh), PM$_{2.5}$ concentrations peak in the summer largely due to transport of primary emissions and formulation of secondary aerosols resulting from photochemical processes. In Sacramento County, winter air inversions trap primary fine particles (including PM$_{2.5}$) and, in the fall, higher PM$_{10}$ levels reflect wind-blown coarse fraction particles.

Interpolation of ambient air pollutant levels to participant residences may reduce spatial exposure misclassification which is thought to attenuate associations (38). However, we still lacked indoor/outdoor activity patterns and personal exposure. Personal exposure differs from ambient exposure, but ambient effects are of interest. Previous studies have found associations of ambient exposures with lung function and the National Ambient Air Quality Standards regulate ambient levels. Frail participants might spend more time indoors and have less exposure to ambient pollution, potentially attenuating associations. No data exists for exposures 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 (missing at random, or MAR) (39), a linear mixed effects models 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 (24). 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 likely attenuate the modification by frailty status of pollution effects on lung function.

Statistically, since FVC and FEV$_1$ were highly correlated (0.90), we might expect to see similar strong interactions between cumulative exposure and frailty history for FVC and FEV$_1$, had the interactions been spuriously induced by uncontrolled confounding. However, we observed interactions only for FVC, which may be evidence that these interactions were not due to uncontrolled confounding. FEV$_1$ measures large airway flow, with declines indicative of obstructive disease. FVC measures total capacity, including large and small airways, and is reduced (along with FEV$_1$) 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: decreased physiologic (especially cardiopulmonary) reserve for offsetting the pathways by which air pollution affects pulmonary function; potentially increased air pollution related inflammation in the frail as compared to the non-frail; and repercussions of frailty-related sarcopenia. Future work might investigate whether a chain reaction exists where 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 air pollution effects on older adult lung function. This potentially offers insight into older adult susceptibility and may have implications for identifying which older adults are at increased risk.
References


Figure 1: Participant level interpolated monthly mean 24-hour average PM$_{10}$ (a) and 8-hour average daily maximum O$_3$ (b). Annual means are plotted at the midpoint of the year (for O$_3$, the mean is calculated from April-October).
Figure 2: Difference in FEV\textsubscript{1} or FVC (mL) associated with a 10 µg/m\textsuperscript{3} increase in recent PM\textsubscript{10} or a 10 ppb increase in recent O\textsubscript{3} during O\textsubscript{3} season according to current frailty status (robust: solid lines, prefrail: dashed lines, frail: dotted lines), after adjusting for anthropometric, demographic and behavioral covariates.
Figure 3: Difference in FVC associated with a 1 month increase in typical pollution months according to the number of years spent frail or prefrail/frail, after adjusting for anthropometric, demographic and behavioral covariates (solid lines) and additionally adjusting for cardiovascular and respiratory disease covariates (dashed lines).
Table 1: Participant characteristics by categorical frailty status at the initial PFT.

<table>
<thead>
<tr>
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<th>Robust (N=1382)</th>
<th>Prefrail (N=1673)</th>
<th>Frail (N=274)</th>
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<td>Mean (or %)</td>
<td>Mean (or %)</td>
<td>Mean (or %)</td>
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<tr>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
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<tr>
<td>Height (cm)</td>
<td>71.2 (4.4)</td>
<td>73.0 (5.5)</td>
<td>76.6 (6.3)</td>
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<td>164.7 (9.5)</td>
<td>162.4 (9.7)</td>
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<td>Waist circumference (cm)</td>
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<td>95.3 (12.7)</td>
<td>98.0 (15.8)</td>
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<td>% African American</td>
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<td>% Male</td>
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<td>Education</td>
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<td>% &lt; 8th grade</td>
<td>5.9</td>
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<td>20.4</td>
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<tr>
<td>% grade 12–GED</td>
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<td>29.7</td>
<td>26.6</td>
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<tr>
<td>% 1 year vocational–college</td>
<td>40.6</td>
<td>34.2</td>
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<tr>
<td>% graduate/professional</td>
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<tr>
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<td>% former</td>
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<tr>
<td>% current</td>
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<tr>
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<tr>
<td>% Low quality FVC</td>
<td>4.7</td>
<td>7.9</td>
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Table 2: Difference in FEV$_1$ or FVC (mL) associated with a 10 $\mu$g/m$^3$ increase in recent PM$_{10}$, a 10 ppb increase in recent O$_3$ during O$_3$ season, or a 1 month increase in typical PM$_{10}$ months or typical O$_3$ months during O$_3$ season after adjusting for anthropometric, demographic, behavioral covariates and current frailty status.

<table>
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<tr>
<th>Pollutant</th>
<th>Summary</th>
<th>Men</th>
<th></th>
<th>Women</th>
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<td>95% CI</td>
<td>Women</td>
<td>95% CI</td>
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<td>PM$_{10}$</td>
<td>Current month mean</td>
<td>-1.9 (-14.0, 10.3)</td>
<td>-8.2 (-15.9, -0.5)</td>
<td>-10.4 (-27.0, 6.1)</td>
<td>-16.7 (-28.0, -5.3)</td>
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<td></td>
<td>Prior month mean</td>
<td>2.9 (-9.2, 14.9)</td>
<td>-3.4 (-10.9, 4.1)</td>
<td>-7.6 (-24.1, 8.9)</td>
<td>-7.8 (-18.9, 3.2)</td>
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<td></td>
<td>5 month mean</td>
<td>-6.9 (-27.0, 13.3)</td>
<td>-20.0 (-32.4, -7.6)</td>
<td>-29.9 (-57.0, -2.8)</td>
<td>-31.5 (-49.6, -13.4)</td>
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<tr>
<td></td>
<td>Typical months</td>
<td>-1.0 (-1.6, -0.5)</td>
<td>-0.7 (-1.0, -0.3)</td>
<td>-4.4 (-5.1, -3.8)</td>
<td>-2.7 (-3.2, -2.3)</td>
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<tr>
<td>O$_3$</td>
<td>Current month mean</td>
<td>-5.1 (-23.0, 12.7)</td>
<td>4.2 (-6.7, 15.0)</td>
<td>-4.7 (-28.3, 18.9)</td>
<td>0.5 (-15.7, 16.8)</td>
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<tr>
<td></td>
<td>Prior month mean</td>
<td>7.1 (-26.1, 40.3)</td>
<td>8.2 (-12.0, 28.4)</td>
<td>-19.0 (-63.7, 25.7)</td>
<td>-2.9 (-33.7, 27.9)</td>
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<tr>
<td></td>
<td>Typical months</td>
<td>-2.6 (-3.5, -1.7)</td>
<td>-1.4 (-2.0, -0.9)</td>
<td>-8.8 (-9.9, -7.7)</td>
<td>-5.6 (-6.3, -4.9)</td>
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</tbody>
</table>
Supplementary web data:

**Modification by frailty status of ambient air pollution effects on lung function in older adults in the Cardiovascular Health Study**

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**Cumulative summary motivation**

Consider $Y_{ij}$ for participant $i$ at observation $j$, baseline ($x_{i0}$) and time-varying covariates ($z_{ij}$), and a random intercept $U_i \sim N(0, \tau^2)$. To investigate change over time in $Y_{ij}$, a standard longitudinal model can be reformulated as a function of time $t$, replacing age$_{ij}$ with $t$:

$$Y_{ij} = \beta_0 + \beta_1 x_{i0} + \beta_2 \text{age}_{ij} + \beta_3 x_{i0} \times \text{age}_{ij} + \beta_4 z_{ij} + U_i + \epsilon_{ij}$$

(1)

$$Y_{i}(t) = \beta_0 + \beta_1 x_{i0} + \beta_2 t + \beta_3 x_{i0} \times t + \beta_4 z_i(t) + U_i + \epsilon_{i}(t).$$

(2)

Taking the derivative reveals that change in $Y_i(t)$ is a function of the level of $x_{i0}$ and change in $z_i(t)$:

$$Y'_i(t) = \beta_2 + \beta_3 x_{i0} + \beta_4 z'_i(t) + \epsilon'_i(t).$$

(3)

To allow the level of $z_i(t)$ to affect change in $Y_i(t)$, we define the following model for change

$$Y'_i(t) = \beta_2 + \beta_3 x_{i0} + \beta_4 z'_i(t) + \beta_5 z_i(t) + \epsilon'_i(t)$$

(4)

which can be translated back to the cross-sectional scale, with constant $c_i$, using integration:

$$Y_i(t) = c_i + \beta_2 t + \beta_3 x_{i0} t + \beta_4 z_i(t) + \beta_5 \int_0^t z_i(s) + \epsilon_i(t).$$

(5)

When $z_i(t)$ is measured at discrete times $(0, 1, \ldots, t-1, t)$, Equation 5 can be rewritten as:

$$Y_i(t) = c_i + \beta_2 t + \beta_3 x_{i0} t + \beta_4 z_i(t) + \beta_5 \sum_{s=0}^t z_i(s) + \epsilon_i(t).$$

(6)
Single imputation of missing frailty information

Grip strength was not assessed in 1990–1991, so we carried forward the value recorded in 1989–1990. Reason for weight change was not assessed in 1991–1992, so we assigned unintentional weight change to those participants who had lost weight that year and had self-reported unintentional weight change in the 2 years before or after this exam. Physical activity was assessed by questionnaire at only 3 exam years (1989–1990, 1992–1993, and 1996–1997). We filled in low physical activity status at other years using previously developed generalized boosted models (1, 2) that predict low physical activity status using other available measures of physical activity.

Long-term pollution associations with FEV$_1$

Figure 1: Difference in FEV associated with a 1 month increase in typical pollution months according to the number of years spent frail or prefrail/frail, after adjusting for anthropometric, demographic and behavioral covariates (solid lines) and additionally adjusting for cardiovascular and respiratory disease covariates (dashed lines).
References
