Short-Term Exposure to Air Pollution and Lung Function in the Framingham Heart Study

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Rationale: Short-term exposure to ambient air pollution has been associated with lower lung function. Few studies have examined whether these associations are detectable at relatively low levels of pollution within current U.S. Environmental Protection Agency (EPA) standards. **Objectives:** To examine exposure to ambient air pollutants within EPA standards and lung function in a large cohort study.

Methods: We included 3,262 participants of the Framingham Offspring and Third Generation cohorts living within 40 km of the Harvard Supersite monitor in Boston, Massachusetts (5,358 examinations, 1995–2011) who were not current smokers, with previous-day pollutant levels in compliance with EPA standards. We compared lung function (FEV₁ and FVC) after previous-day exposure to particulate matter less than 2.5 μm in diameter (PM_{2.5}), nitrogen dioxide (NO₂), and ozone (O₃) in the “moderate” range of the EPA Air Quality Index to exposure in the “good” range. We also examined linear relationships between moving averages of pollutant concentrations 1, 2, 3, 5, and 7 days before spirometry and lung function.

Measurements and Main Results: Exposure to pollutant concentrations in the “moderate” range of the EPA Air Quality Index was associated with a 20.1-ml lower FEV₁ for PM_{2.5} (95% confidence interval [CI], –33.4, –6.9), a 30.6-ml lower FEV₁ for NO₂ (95% CI, –60.9, –0.2), and a 55.7-ml lower FEV₁ for O₃ (95% CI, –100.7, –10.8) compared with the “good” range. The 1- and 2-day moving averages of PM_{2.5}, NO₂, and O₃ before testing were negatively associated with FEV₁ and FVC.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Short-term exposure to ambient air pollution has been associated with reduced lung function. However, as air quality has improved, few adult cohort studies have examined whether adverse effects are detectable at relatively low levels of ambient pollution within current U.S. Environmental Protection Agency (EPA) standards.

What This Study Adds to the Field

In this large cohort study of adult men and women in the Boston, MA, area, we found that short-term exposure to ambient criteria air pollutants within current EPA standards was associated with poorer lung function. We found that lung function after exposure to pollutant concentrations in the “moderate” EPA Air Quality Index range was lower compared with the “good” range. Our study suggests that the general population, not just “unusually sensitive” people, may experience respiratory effects from ambient pollution at levels that are considered to be safe.

Conclusions: Short-term exposure to PM_{2.5}, NO₂, and O₃ within current EPA standards was associated with lower lung function in this cohort of adults.

Keywords: chronic obstructive pulmonary disease; asthma; air pollutants; U.S. Environmental Protection Agency

A substantial body of evidence has shown that modest short-term increases in ambient air pollution, especially PM_{2.5} (particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$) and ground level ozone (O₃), but also nitrogen dioxide (NO₂), increase risk of hospitalization for chronic obstructive pulmonary disease (COPD) and respiratory mortality (1–4). Several studies have found that short-term (1–3 d) increases in PM_{2.5}, NO₂, and O₃ are associated with decreases in FEV₁, FVC, and/or peak expiratory flow rate in healthy subjects (5–11) and in those with preexisting COPD or asthma (12–15).

Air quality has improved substantially since the 1980s and 1990s, when many epidemiologic investigations of lung function and air pollution were completed (16). To protect public health and in accordance with its mandate, the EPA has continued to review the latest evidence and reevaluate air quality standards. Recently, the EPA lowered the annual standard for PM_{2.5} from 15 to 12 $\mu\text{g}/\text{m}^3$ and reduced the daily Air Quality Index (AQI) cut-off for “moderate” PM_{2.5} from 15.4 to 12 $\mu\text{g}/\text{m}^3$. It remains unclear whether acute effects of criteria air pollutants (including

PM_{2.5}, NO₂, and O₃) at contemporary ambient levels that are in compliance with today's more stringent EPA standards affect lung function in the general population. Few studies have examined repeated measures of lung function in a large, well-documented cohort with detailed covariate data to answer this question.

We hypothesized that short-term exposure to ambient criteria air pollutants (PM_{2.5}, NO₂, and O₃) in the Boston metropolitan area, where pollutant levels are relatively low and adherent to current EPA air quality standards, are associated with lower levels of lung function in the Framingham Heart Study Offspring and Third Generation cohorts of adult men and women. Some of the results of these studies have been previously reported in the form of an abstract (17).

METHODS

Study Population

The study population consists of the participants in the Offspring and Third Generation cohorts living within 40 km of the Harvard Supersite monitor in Boston, Massachusetts. The design of these studies has been previously described (18, 19). Subjects included in this analysis are Offspring participants with at least one spirometry measurement at examination 6 (1995–1998) or 7 (1998–2001) and Third Generation participants with at least one measurement at examination 1 (2002–2005) or 2 (2008–2011). At each examination, data were collected on demographics, medication use, smoking history, and respiratory symptoms and diagnoses. Current smokers ($n = 636$ participants, 890 observations) were excluded from the primary analysis, as tobacco exposure has known acute effects on lung function. There were 3,262 participants with a total of 5,358 spirometry measurements in our primary analysis. Of these, 1,697 were Offspring and 1,565 were Third Generation Cohort participants. All participants provided written informed consent for the study examinations, and the institutional review boards of Beth Israel Deaconess Medical Center and Boston University Medical Center approved this work.

Spirometry

FEV₁ and FVC were measured at each examination visit by spirometry. For the sixth and seventh Offspring examinations, spirometric data were obtained using a Collins Survey II spirometer, interfaced to pulmonary function data acquisition and quality control software (S&M Instruments, Doylestown, PA), calibrated daily. For the first and second Third Generation examinations, spirometric data were obtained using a Collins CPL system (nSpire Health, Inc., Longmont, CO), calibrated daily. Spirometric maneuvers were performed according to American Thoracic Society standards (20). The largest FEV₁ and FVC of acceptable maneuvers were used in this analysis.

Exposure Assessment

We used hourly PM_{2.5} concentration data from the Harvard Boston Supersite in Boston, Massachusetts five stories above ground level and 50 m from the nearest street. PM_{2.5} concentrations were measured using a tapered element oscillating microbalance (TEOM, model 1400A; Rupprecht and Pataschnick Co, Albany, NY). The gaseous pollutants O₃ and NO₂ were measured from state monitors in the Boston area and exposures were estimated by averaging data from available sites. O₃ exposure was only examined during the EPA monitoring season for Massachusetts (April–September). Hourly temperature and relative humidity data were obtained from the Boston Airport weather station (12 km from the central monitoring site).

We categorized exposure to each pollutant for the 24-h period ending at 9 A.M. the day of spirometry according to the current cut-offs for the EPA AQI (21). Observations exceeding the “moderate” AQI range for the pollutant were excluded from the analysis. The current pollutant-specific AQI ranges are: 24-hour PM_{2.5} less than or equal to 12 $\mu\text{g}/\text{m}^3$ is “good,” and greater than 12 $\mu\text{g}/\text{m}^3$ and less than or equal to 35.4 $\mu\text{g}/\text{m}^3$ is “moderate”; 1-hour maximum NO₂ less than or equal to 53 ppb is “good,” and greater than 53 ppb and less than or equal to 100 ppb is “moderate”; and 8-hour maximum O₃ less than or equal to

59 ppb is “good,” and greater than 59 ppb and less than or equal to 75 ppb is “moderate.”

To examine linear relationships between exposure to each pollutant and lung function, we defined short-term exposures as 1, 2, 3, 5, and 7-day moving averages of pollutant concentrations preceding spirometry testing based on our *a priori* hypothesis that shorter-term (1–3 d) exposures would have the strongest associations with lung function. We used the same datasets in the continuous pollutant concentration analyses as in the categorical AQI analysis, excluding observations exceeding EPA standards.

Statistical Analysis

We fit linear mixed effects models with a subject-specific random intercept adjusted for sex, age, height, weight, smoking history, asthma/COPD, education, median household income from 2000 census tract, time trends, weekday, season, relative humidity, temperature, and cohort to estimate associations between air pollutant exposures before testing and FEV₁ and FVC. The covariates in the model were selected *a priori* based on known associations with lung function or air pollution. A quadratic term was added for age because of the known nonlinear relationship between age and lung function after age 35 years. We used sine and cosine functions of the examination date to estimate the amplitude and phase of the seasonal cycle. We adjusted for time as a continuous linear variable. We defined asthma/COPD as meeting one of the following criteria: (1) currently on bronchodilator therapy, (2) report of wheeze in the past 12 months, (3) chronic cough 3 or more months per year, or (4) report of a doctor diagnosis of asthma or COPD. We then evaluated the linearity of previous-day air pollutant exposure and FEV₁ relationships using restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the distribution (22) and compared the fit of these models to the linear models using likelihood ratio tests.

We tested whether associations between previous-day exposures to air pollutants and FEV₁ vary according to smoking status, asthma/COPD, obesity, sex, age, and cohort. We tested whether associations differed by smoking status in the primary dataset (excluding current smokers) and in an expanded dataset including current smokers. Smoking status was defined as never, former (<20 or ≥ 20 pack-years) and current (<20 or ≥ 20 pack-years), based on evidence that risk of airflow obstruction and COPD increase substantially with a 20 pack-year or greater smoking history (23–25). We hypothesized that associations between air pollution and FEV₁ would be greater among participants with asthma or COPD and tested for effect modification by presence of asthma/COPD. We expected to find stronger associations between exposure to ozone and lung function in obese participants (defined as body mass index $> 30 \text{ kg}/\text{m}^2$) compared with the nonobese, based on experimental and observational studies suggesting that obesity modifies acute pulmonary effects of ozone (9, 26, 27). Finally, we tested for effect modification by sex, age, and cohort. We used the Wald test for cross-product terms to determine statistical significance of potential effect modifiers.

All statistical analyses were performed using SAS 9.3 and Stata v.12 software.

RESULTS

Participant characteristics for the 5,358 observations are summarized in Table 1. This is a middle- to older-aged cohort with a slight majority of women. Approximately one-half of observations included in the analysis were from never smokers, and one-half were from former smokers. The cohort was well educated overall, with 74% completing at least some college. Participants lived in neighborhoods with an average census tract median household income of \$70,299. One-fifth of the observations were from participants with asthma or COPD.

Of the 5,358 observations included in our primary analysis, only 35 observations exceeded the 24-hour PM_{2.5} standard, 64 observations exceeded the 8-hour maximum O₃ standard, and none exceeded the 1-hour maximum NO₂ standard. Mean pollutant and meteorology levels the day preceding spirometry testing and their Spearman correlation coefficients are provided in Table 2.

TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS

	Mean (SD) or %
Age, yr	51.8 (12.7)
Male sex, %	46.9
BMI, kg/m ²	27.8 (5.4)
Smoking status, %	
Never	52.9
Former (<20 pack-years)	31.0
Former (≥20 pack-years)	16.0
Education, %	
<High school	2.4
High school	22.9
Some college	29.5
College graduate	44.5
Missing education	0.7
Median census HH income, \$	70,299 (21,473)
Asthma/COPD (%)	20.7

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; HH = household.

Data calculated from 5,358 observations (among 3,262 participants).

PM_{2.5} was most strongly correlated with NO₂. O₃, temperature, and relative humidity were weakly correlated with other pollutants.

There was a decline in PM_{2.5} and NO₂ over the time span of this study. For example, the mean 24-hour PM_{2.5} level was 12.5 µg/m³ (SD, 6.6) between 1995 and 1998 (Offspring examination 6) and was down to 8.0 µg/m³ (SD, 4.8) for the time period 2008 to 2011 (Third Generation examination 2), a 36% decline. Mean NO₂ levels also declined by 36% between these intervals. Ozone levels remained stable.

Associations between Air Pollutants and Spirometry

Average FEV₁ and FVC were normal. The mean FEV₁ was 3.11 L (SD, 0.86 L) or 96.9% predicted (SD, 14.9%), and mean FVC was 4.11 L (SD, 1.06 L) or 100.5% predicted (SD, 13.3%) using the Hankinson National Health and Nutrition Examination Survey prediction equations (28). Airflow obstruction, defined as an FEV₁/FVC ratio of less than 0.70, was present in 17.3% of observations.

Exposure to each pollutant (PM_{2.5}, NO₂, and O₃) in the “moderate” range of the EPA AQI was associated with a lower FEV₁ and FVC compared with exposure in the “good” range (Table 3). Exposure in the “moderate” range was more common for PM_{2.5} than the other two pollutants (29% of observations for PM_{2.5} compared with 3% for NO₂ and 8% for O₃).

Moving averages of PM_{2.5}, NO₂, and O₃ 1 and 2 days before testing were negatively associated with FEV₁ and FVC, and results are shown in Figure 1. For the 1-day average before testing, a 5-µg/m³ increase in PM_{2.5} concentration was associated with 7.9 ml (95% confidence interval [CI], –13.5, –2.3) lower FEV₁, a 10-ppb increase in NO₂ concentration was associated with a 11.3-ml

lower FEV₁ (95% CI, –20.4, –2.2), and a 10-ppb increase in O₃ was associated with a 17.4-ml lower FEV₁ (95% CI, –30.9, –4.0). The negative associations between exposure to each pollutant and FEV₁ and FVC were weak or absent for longer moving averages (3, 5, or 7 d) of exposures.

In our sensitivity analysis examining nonlinear relationships between each of the pollutants and FEV₁, we constructed restricted cubic splines but did not observe any statistically significant evidence of departures from linearity ($P = 0.11$ for PM_{2.5}, $P = 0.24$ for NO₂, $P = 0.80$ for O₃). We did not find that associations between previous-day air pollution exposure and FEV₁ varied by smoking status, presence of asthma/COPD, cohort, or age. There was also no effect modification by asthma or COPD when these diagnoses were examined separately. Obese participants had a stronger association between previous-day O₃ exposure and FEV₁ ($P_{\text{interaction}} = 0.010$) than nonobese participants. In obese participants, a 10-ppb increase in previous-day O₃ was associated with a 30.4-ml lower FEV₁ (95% CI, –47.0, –13.7) compared with a 12.4-ml lower FEV₁ (95% CI, –26.4, 1.7) in the nonobese. Associations between O₃ and lung function varied by sex ($P_{\text{interaction}} = 0.002$) but not for PM_{2.5} or NO₂. In men, a 10-ppb increase in 1-day exposure to O₃ was associated with a 37.5-ml decrease in FEV₁ (95% CI, –55.9, –19.0) compared with a minimal 3.2-ml decrease in FEV₁ (95% CI, –19.4, 13.0) in women.

DISCUSSION

In this large cohort study of adults residing in the metropolitan area of Boston exposed to ambient air pollution levels within current EPA standards, we found that short-term exposures to criteria pollutants PM_{2.5}, NO₂, and O₃ were associated with lower FEV₁ and FVC. Exposure to each pollutant in the “moderate” range of the EPA’s AQI was associated with a lower FEV₁ and FVC compared with exposure in the “good” range. We also found linear relationships between 1- and 2-day averages of each pollutant and FEV₁ and FVC but not for longer moving averages of exposure, suggesting that adverse effects on lung function occur acutely, within 24 to 48 hours.

According to the EPA’s AQI website, which allows individuals to monitor local air quality, the “moderate” range of pollutant concentration is described as follows: “Air quality is acceptable. However, there may be a moderate health concern for a very small number of people who are unusually sensitive to air pollution” (29). Our study suggests that the general population, not just “unusually sensitive” people, may experience respiratory effects from PM_{2.5}, NO₂, and O₃ exposure in the “moderate” range. The magnitude of the average difference in FEV₁ between “good” and “moderate” exposures is small (20 ml for PM_{2.5}, 31 ml for NO₂, and 56 ml for O₃) and unlikely to be clinically perceptible to the average individual. However, these values represent the average effect estimate for a distribution of effects within the study

TABLE 2. POLLUTANTS AND METEOROLOGY DISTRIBUTIONS

	N Obs	Mean	SD	Range	IQR	Spearman Correlation Coefficients			
						PM _{2.5}	NO ₂	O ₃	Temp
PM _{2.5} , µg/m ³	5,272	10.4	5.5	1.1 to 34.6	6.4 to 12.8	1			
NO ₂ , ppb	5,358	21.3	7.2	6.0 to 57.4	15.9 to 26.0	0.63	1		
O ₃ *, ppb	2,475	28.7	9.9	2.0 to 59.6	21.2 to 35.3	0.33	0.0051	1	
Temp, °C	5,344	10.3	9.1	–18.3 to 30.8	3.6 to 17.7	0.17	–0.17	0.18	1
RH, %	5,344	67.6	16.4	20.7 to 100	55.4 to 81.0	0.20	–0.0048	–0.32	0.16

Definition of abbreviations: IQR = interquartile range; NO₂ = nitrogen dioxide; O₃ = ozone; obs = observations; PM_{2.5} = particulate matter < 2.5 µm in diameter; RH = relative humidity; temp = temperature.

*Ozone data were analyzed during the Environmental Protection Agency ozone monitoring season for Massachusetts (April–September).

TABLE 3. ASSOCIATIONS BETWEEN PREVIOUS-DAY POLLUTANT EXPOSURE IN THE “MODERATE” VERSUS “GOOD” ENVIRONMENTAL PROTECTION AGENCY AIR QUALITY INDEX RANGE AND LUNG FUNCTION

	“Good” AQI (n)	“Moderate” AQI (n)	Difference in FEV ₁ , ml (95% CI)	Difference in FVC, ml (95% CI)
PM _{2.5}	3,733	1,539	−20.1 (−33.4 to −6.9)	−20.4 (−36.2 to −4.5)
NO ₂	5,178	180	−30.6 (−60.9 to −0.2)	−34.2 (−70.6 to 2.3)
O ₃	2,282	193	−55.7 (−100.7 to −10.8)	−50.6 (−103.6 to 2.4)

Definition of abbreviations: AQI = air quality index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter < 2.5 μm in diameter.

Adjusted for sex, age, height, weight, smoking history, asthma/COPD, education, median household income from 2000 census tract, time trends, weekday, season, relative humidity, temperature, and cohort.

AQI ranges: 24-h PM_{2.5} “good” 0–12 μg/m³, “moderate” > 12 μg/m³ and ≤ 35.4 μg/m³. Maximum 1-h NO₂ “good” 0–53 ppb, “moderate” > 53 ppb and ≤ 100 ppb. Maximum 8-h O₃ “good” 0–59 ppb, “moderate” > 59 ppb and ≤ 75 ppb (21).

population. Acute inflammatory responses to air pollution resulting in reduced lung function may be part of the triggering mechanism for the reported association between short-term air pollution exposure and respiratory hospitalization and mortality (2–4). Few studies have examined health outcomes in association with exposure levels defined by the AQI. One recent study found that exposure to PM_{2.5} in the “moderate” range of the AQI (previously defined as 15–40 μg/m³) was associated with increased risk of acute ischemic stroke (30).

Over the course of this study, there have been substantial improvements in air quality in the Boston area, primarily as a result of measures to reduce traffic-related emissions, including improved catalytic converters, lower sulfur diesel fuel, and requirements for diesel engine particle filters. For example, between 1995 and 1998, 41% of observations were in the “moderate” range for PM_{2.5}, compared with only 11% between 2008 and 2011. However, the presence of a linear association between each pollutant and lung function, when the vast majority of observations were obtained in

FEV₁ (mL)

FVC (mL)

Figure 1. Associations between moving averages of pollutants exposures before testing and lung function. Adjusted for sex, age, height, weight, smoking history, asthma/chronic obstructive pulmonary disease, education, median household income from 2000 census tract, time trends, weekday, season, relative humidity, temperature, and cohort. Associations with lung function are scaled per 5-μg/m³ increase in particulate matter less than 2.5 μm in diameter (PM_{2.5}) concentration and per 10-ppb increase in nitrogen dioxide (NO₂) and ozone (O₃) concentration for each moving average.

the “good” range of exposure defined by the AQI, suggests that adverse effects on lung function likely exist below the EPA cut-off for the “good” range, where air pollution is believed to present little to no risk. Greater than 90% of observations for NO₂ and O₃ in this study were obtained after exposure to the “good” AQI range.

The magnitude of the associations we found between short-term pollutant exposure and lung function is comparable to those reported by studies that included pollution levels above current EPA standards (5, 6, 10). For example, a recent study on short-term effects of air pollution in adolescents in Taiwan found that each 10 ppb of previous-day NO₂ was associated with a 16-ml decrease in FEV₁ and FVC (10), which is close to the 11- and 14-ml decrease in FEV₁ and FVC, respectively, that we associated with 10 ppb of NO₂ in adults.

Surprisingly, we did not find that previous-day air pollution exposure and FEV₁ varied by smoking status. We had sufficient power to evaluate effect modification by former smoking and found no evidence of heightened susceptibility to short-term air pollution among former smokers. The number of current smokers in our study was small, and our power to detect effect modification by current smoking was limited. As anticipated, obese people had a larger decrease in FEV₁ in association with previous-day O₃ exposure than nonobese participants. The association per 10 ppb of O₃ was more than twice as large for obese participants (30.4 ml lower FEV₁) compared with the nonobese (12.4 ml lower FEV₁). A similar result was found in the Normative Aging Study (9). Several experimental studies in mice have identified augmented responses to ozone in obese animals (26, 27). A recent experimental study in mice found that adiponectin, which is deficient in the obese, protects against the inflammatory effects of ozone exposure (31). Several studies have identified obesity as a risk factor for asthma (32, 33). Obesity may modify airway inflammation, which affects the sensitivity of the lung to ozone.

We found evidence to suggest that men are more susceptible to the pulmonary effects of ozone than women. This has not been widely reported, and there is some evidence that women may be more susceptible to mortality attributed to ozone pollution (34). Our isolated finding should be interpreted with caution. The topic of differential susceptibility to O₃ exposure deserves further study, especially because O₃ levels are not declining, and recent measurements in Boston have found a slight increase in O₃ concentrations.

Unexpectedly, we did not find that associations between air pollutant exposures and lung function were stronger in participants with asthma or COPD. Several studies have found stronger associations in individuals with asthma or COPD (6, 9, 13, 35, 36), although many have found associations between air pollution and lung function in normal subjects (5–8). Only 20% of our study population met our definition of asthma/COPD, and thus our power to detect susceptibility in this subgroup was limited. Furthermore, our study protocol did not include the measurement of airway reactivity or the reversibility of airflow obstruction after bronchodilator use. We relied on self-reported symptoms and diagnoses to identify participants with asthma, in whom the expectation of increased susceptibility was highest. We can conclude that the associations between air pollution and lung function in our study were not limited to people with known asthma or COPD and were observed in a population with normal lung function on average.

The mechanisms of acute airway responses to short-term air pollutant exposures are well studied, and the overwhelming evidence suggests there is activation of inflammatory pathways in the small airways in response to particulate and gaseous pollutant exposure, resulting in the recruitment of inflammatory cells and the generation of inflammatory mediators, including cytokines, chemokines,

and adhesion molecules (37, 38). Particles, nitrogen dioxide, and ozone are all oxidants that can trigger intracellular oxidative stress through the generation of free radicals (39–41). PM_{2.5} likely shares mechanistic pathways with cigarette smoke exposure, which induces small airways constriction by stimulating endothelin release and via direct oxidant effects (42). O₃ exposure has been found to prime innate immunity and up-regulate expression of injury repair genes in mouse lung (43). There is also a neurological component of the acute pulmonary response to O₃, involving increased excitability of pulmonary afferent C fibers, an effect that may be exerted directly by O₃ or via inflammatory pathways (44, 45).

Despite the large literature demonstrating negative associations between NO₂ and lung function and adverse pulmonary outcomes, including respiratory hospitalization and mortality (4, 10, 11, 46), it remains unclear whether these associations are caused by the NO₂ itself. NO₂ may be a surrogate of ultra-fine particles (particles < 0.1 μm in diameter) or other traffic-related copollutants that induce pulmonary inflammation. A review of more than 50 controlled human exposure studies examining the short-term effects of NO₂ concluded that there is no evidence of harm, including no adverse effects on spirometry, for 1-hour exposures to NO₂ below 200 ppb (an order of magnitude higher than ambient levels) (47). Nonetheless, identifying ambient NO₂ levels beneath which population health effects are no longer observed remains an important scientific and public health priority.

There are a number of limitations to our study. This investigation included a population of predominantly white, middle- and older-aged men and women residing in the Boston area, which limits generalizability to other groups. We had a maximum of two repeated measures of lung function on each participant and cannot infer causality from these associations. We used outdoor air pollution exposure measured within 40 km of each individual's home address to estimate individual exposure levels, which may not reflect actual exposures. These differences in individual exposures may diminish the precision of our estimates (and reduce our power to detect associations) or introduce non-differential exposure misclassification, which would bias our results toward the null, but should not cause overestimation of associations. Recent studies in Boston have shown that PM_{2.5} levels measured at the central site monitor provide good proxies for personal exposure to ambient particulate pollution (48).

This study also had a number of strengths. Its long time span (1995–2011) allowed us to consider a wide range of pollution levels and implications for respiratory health. We analyzed associations between daily pollutant levels and lung function in a well-characterized cohort of men and women with a longitudinal study design that improved statistical efficiency. Our results were adjusted for a robust list of potential confounders and predictors of lung function, including measures of income from census tract data, personal education, detailed smoking history, and history of obstructive lung disease from questionnaires.

In conclusion, we found that short-term exposure to higher levels of the three EPA criteria air pollutants PM_{2.5}, NO₂, and O₃ within current EPA standards were associated with lower lung function in this population of adult men and women in the Boston area. Further research is needed to clarify differential susceptibility to these pollutants and to determine if there is a threshold concentration beneath which adverse effects on lung function are no longer observed.

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

- Ko FWS, Tam W, Wong TW, Chan DPS, Tung AH, Lai CKW, Hui DSC. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 2007; 62:780–785.
- Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: a review. *Eur Respir J* 2001;17:1024–1033.
- Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002;360: 1233–1242.
- Faustini A, Stafoggia M, Cappai G, Forastiere F. Short-term effects of air pollution in a cohort of patients with chronic obstructive pulmonary disease. *Epidemiology* 2012;23:861–879.
- Cakmak S, Dales R, Leech J, Liu L. The influence of air pollution on cardiovascular and pulmonary function and exercise capacity: Canadian Health Measures Survey (CHMS). *Environ Res* 2011;111: 1309–1312.
- Korrick SA, Neas LM, Dockery DW, Gold DR, Allen GA, Hill LB, Kimball KD, Rosner BA, Speizer FE. Effects of ozone and other pollutants on the pulmonary function of adult hikers. *Environ Health Perspect* 1998;106:93–99.
- Son JY, Bell ML, Lee JT. Individual exposure to air pollution and lung function in Korea: spatial analysis using multiple exposure approaches. *Environ Res* 2010;110:739–749.
- Lee J-T, Son J-Y, Cho Y-S. The adverse effects of fine particle air pollution on respiratory function in the elderly. *Sci Total Environ* 2007;385:28–36.
- Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: effect modified by obesity and airways hyperresponsiveness in the VA normative aging study. *Chest* 2007;132:1890–1897.
- Chang YK, Wu CC, Lee LT, Lin RS, Yu YH, Chen YC. The short-term effects of air pollution on adolescent lung function in Taiwan. *Chemosphere* 2012;87:26–30.
- Schindler C, Künzli N, Bongard JP, Leuenberger P, Karrer W, Rapp R, Monn C, Ackermann-Lieblich U. Short-term variation in air pollution and in average lung function among never-smokers. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA). *Am J Respir Crit Care Med* 2001;163:356–361.
- Ko FW, Hui DS. Air pollution and chronic obstructive pulmonary disease. *Respirology* 2012;17:395–401.
- Lagorio S, Forastiere F, Pistelli R, Iavarone I, Michelozzi P, Fano V, Marconi A, Ziemacki G, Ostro BD. Air pollution and lung function among susceptible adult subjects: a panel study. *Environ Health* 2006; 5:11.
- Trenga CA, Sullivan JH, Schildcrout JS, Shepherd KP, Shapiro GG, Liu LJ, Kaufman JD, Koenig JQ. Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest* 2006;129:1614–1622.
- Pope CA III, Kanner RE. Acute effects of PM10 pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;147:1336–1340.
- Brunekreef B, Dockery DW, Krzyzanowski M. Epidemiologic studies on short-term effects of low levels of major ambient air pollution components. *Environ Health Perspect* 1995;103:3–13.
- Rice M, Ljungman P, Wilker E, Gold D, Schwartz J, Koutrakis P, Washko G, O'Connor G, Mittleman M. Short-term exposure to air pollution and lung function in the Framingham Heart Study [abstract]. Abstracts of the 2013 Conference of the International Society of Environmental Epidemiology (ISEE), the International Society of Exposure Science (ISES), and the International Society of Indoor Air Quality and Climate (ISIAQ), August 19–23, 2013, Basel, Switzerland. *Environ Health Perspect* 2013; <http://dx.doi.org/10.1289/ehp.ehbasel13>
- Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;110:281–290.
- Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB, Fox CS, Larson MG, Murabito JM, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007;165:1328–1335.
- American Thoracic Society. Standardization of spirometry. 1994 Update. *Am J Respir Crit Care Med* 1995;152:1107–1136.
- Rules and regulations, 78 *Federal Register* 2013;10:3286.
- Harrell FE. Regression modeling strategies with applications to linear models, logistic regression and survival analysis. New York: Springer-Verlag; 2001.
- Reilly KH, Gu D, Duan X, Wu X, Chen C-S, Huang J, Kelly TN, Chen J, Liu X, Yu L, et al. Risk factors for chronic obstructive pulmonary disease mortality in Chinese adults. *Am J Epidemiol* 2008;167: 998–1004.
- Prescott E, Bjerg A, Andersen P, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997;10:822–827.
- Ohar JA, Sadeghnejad A, Meyers DA, Donohue JF, Bleecker ER. Do symptoms predict COPD in smokers? *Chest* 2010;137:1345–1353.
- Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. *J Appl Physiol* 2003;95:938–945.
- Johnston RA, Theman TA, Shore SA. Augmented responses to ozone in obese carboxypeptidase E-deficient mice. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R126–R133.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;159:179–187.
- Environmental Protection Agency. Air Quality Index. 2013 [2013 Nov 16]. Available from: <http://www.airnow.gov/>
- Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, Schlaug G, Gold DR, Mittleman MA. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med* 2012;172: 229–234.
- Kasahara DI, Kim HY, Williams AS, Verbout NG, Tran J, Si H, Wurmbbrand AP, Jastrab J, Hug C, Umetsu DT, et al. Pulmonary inflammation induced by subacute ozone is augmented in adiponectin-deficient mice: role of IL-17A. *J Immunol* 2012;188: 4558–4567.
- Von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001;56: 835–838.
- Shore SA, Johnston RA. Obesity and asthma. *Pharmacol Ther* 2006;110: 83–102.
- Medina-Ramón M, Schwartz J. Who is more vulnerable to die from ozone air pollution? *Epidemiology* 2008;19:672–679.
- Van der Zee SC, Hoek G, Boezen MH, Schouten JP, Van Wijnen JH, Brunekreef B. Acute effects of air pollution on respiratory health of 50–70 yr old adults. *Eur Respir J* 2000;15:700–709.
- Khatir SB, Holguin FC, Ryan PB, Mannino D, Erzurum SC, Teague WG. Association of ambient ozone exposure with airway inflammation and allergy in adults with asthma. *J Asthma* 2009;46:777–785.
- Kelly FJ, Fussell JC. Air pollution and airway disease. *Clin Exp Allergy* 2011;41:1059–1071.
- Zhang JJ, McCreanor JE, Cullinan P, Chung KF, Ohman-Strickland P, Han I-K, Järup L, Nieuwenhuijsen MJ. Health effects of real-world exposure to diesel exhaust in persons with asthma. *Res Rep Health Eff Inst* 2009;(138):5–109, discussion 111–123.
- Rahman I, MacNee W. Oxidative stress and regulation of glutathione in lung inflammation. *Eur Respir J* 2000;16:534–554.
- Stringer B, Kobzik L. Environmental particulate-mediated cytokine production in lung epithelial cells (A549): role of preexisting inflammation and oxidant stress. *J Toxicol Environ Health A* 1998; 55:31–44.
- Velsor LW, Ballinger CA, Patel J, Postlethwait EM. Influence of epithelial lining fluid lipids on NO(2)-induced membrane oxidation and nitration. *Free Radic Biol Med* 2003;34:720–733.
- Wright JL, Sun JP, Chung A. Cigarette smoke exposure causes constriction of rat lung. *Eur Respir J* 1999;14:1095–1099.
- Oakes JL, O'Connor BP, Warg LA, Burton R, Hock A, Loader J, Laflamme D, Jing J, Hui L, Schwartz DA, et al. Ozone enhances pulmonary innate immune response to a Toll-like receptor-2 agonist. *Am J Respir Cell Mol Biol* 2013;48:27–34.
- Ho CY, Lee LY. Ozone enhances excitabilities of pulmonary C fibers to chemical and mechanical stimuli in anesthetized rats. *J Appl Physiol* 1998;85:1509–1515.

45. Lee LY, Widdicombe JG. Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators. *Environ Health Perspect* 2001; 109:585–589.
46. Strak M, Janssen NAH, Godri KJ, Gosens I, Mudway IS, Cassee FR, Lebret E, Kelly FJ, Harrison RM, Brunekreef B, *et al.* Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential-the RAPTES project. *Environ Health Perspect* 2012;120:1183–1189.
47. Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. Critical review of the human data on short-term nitrogen dioxide (NO₂) exposures: evidence for NO₂ no-effect levels. *Crit Rev Toxicol* 2009;39:743–781.
48. Brown KW, Sarnat JA, Suh HH, Coull BA, Koutrakis P. Factors influencing relationships between personal and ambient concentrations of gaseous and particulate pollutants. *Sci Total Environ* 2009;407: 3754–3765.