Long-Term Exposure to Traffic Emissions and Fine Particulate Matter and Lung Function Decline in the Framingham Heart Study

Mary B. Rice[1], Petter L. Ljungman[1,2], Elissa H. Wilker[1], Kirsten S. Dorans[1,3], Diane R. Gold[4], Joel Schwartz[4], Petros Koutrakis[4], George R. Washko[5,6], George T. O'Connor[6,7], and Murray A. Mittleman[1,3]

[1]Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Epidemiology and [4]Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts; [5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [6]NHLBI's Framingham Heart Study, Framingham, Massachusetts; and [7]Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts

Abstract

Rationale: Few studies have examined associations between long-term exposure to fine particulate matter ($PM_{2.5}$) and lung function decline in adults.

Objectives: To determine if exposure to traffic and $PM_{2.5}$ is associated with longitudinal changes in lung function in a population-based cohort in the Northeastern United States, where pollution levels are relatively low.

Methods: FEV_1 and FVC were measured up to two times between 1995 and 2011 among 6,339 participants of the Framingham Offspring or Third Generation studies. We tested associations between residential proximity to a major roadway and $PM_{2.5}$ exposure in 2001 (estimated by a land-use model using satellite measurements of aerosol optical thickness) and lung function. We examined differences in average lung function using mixed-effects models and differences in lung function decline using linear regression models. Current smokers were excluded. Models were adjusted for age, sex, height, weight, pack-years, socioeconomic status indicators, cohort, time, season, and weather.

Measurements and Main Results: Living less than 100 m from a major roadway was associated with a 23.2 ml (95% confidence interval [CI], −44.4 to −1.9) lower FEV_1 and a 5.0 ml/yr (95% CI, −9.0 to −0.9) faster decline in FEV_1 compared with more than 400 m. Each 2 $\mu g/m^3$ increase in average of $PM_{2.5}$ was associated with a 13.5 ml (95% CI, −26.6 to −0.3) lower FEV_1 and a 2.1 ml/yr (95% CI, −4.1 to −0.2) faster decline in FEV_1. There were similar associations with FVC. Associations with FEV_1/FVC ratio were weak or absent.

Conclusions: Long-term exposure to traffic and $PM_{2.5}$, at relatively low levels, was associated with lower FEV_1 and FVC and an accelerated rate of lung function decline.

Keywords: air pollution; respiratory function tests; particulate matter; chronic obstructive pulmonary disease; asthma

Short-term (up to a few days) increases in outdoor air pollution exposure have been found to increase risk of adverse pulmonary outcomes, including chronic obstructive pulmonary disease (COPD) exacerbations and respiratory mortality (1, 2). Multiple studies have also associated short-term exposure to traffic-related air pollutants with reduced lung function (3–5). In the

(Received in original form October 20, 2014; accepted in final form January 3, 2015)

Supported by the U.S. Environmental Protection Agency (R832416, RD834798), the National Institute for Environmental Health Sciences (1F32ES023352), and the NHLBI (the Framingham Heart Study Contract No. N01-HC-25195 and T32HL007575).

Author Contributions: M.B.R. conducted the data analysis, which was supervised by M.A.M., and wrote the first version of the manuscript. P.L.L. and E.H.W. created the air pollution exposure variables. P.L.L., E.H.W., and K.S.D. advised on the data analysis. J.S. developed the $PM_{2.5}$ model. M.A.M., D.R.G., J.S., and P.K. planned the overall study design as part of the Harvard Clean Air Research Center. G.T.O'C. supervised the collection and quality control of spirometry data at the Framingham Heart Study. G.T.O'C. and G.R.W. provided expertise in pulmonary outcomes and the Framingham Heart Study and informed the statistical analysis. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final manuscript.

Correspondence and requests for reprints should be addressed to Mary B. Rice, M.D., Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. E-mail: mrice1@bidmc.harvard.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 191, Iss 6, pp 656–664, Mar 15, 2015

Originally Published in Press as DOI: 10.1164/rccm.201410-1875OC on January 15, 2015
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: There is some evidence that long-term exposure to ambient particulate air pollution, especially at levels seen in the 1990s before strict air-quality regulations were implemented in the United States and Europe, may reduce lung function in adults. It remains unclear whether long-term exposure to traffic emissions and fine particulate matter ($PM_{2.5}$) at relatively low levels in the United States affects lung function in healthy adults.

What This Study Adds to the Field: We found that exposure to traffic emissions and $PM_{2.5}$, estimated by a land-use model using satellite measurements of aerosol optical thickness, were associated with lower FEV_1 and FVC and an accelerated rate of lung function decline of a magnitude comparable with the effect of former smoking in this cohort. These findings suggest that long-term exposure to local traffic and ambient $PM_{2.5}$, at relatively low levels experienced in the Northeastern United States, may contribute to clinically significant declines in lung function over time in healthy adults.

Framingham Heart Study, we recently found that short-term increases in exposure to fine particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), ozone, and nitrogen dioxide (NO_2) at concentrations below the Environmental Protection Agency National Air Quality Standards were associated with a lower FEV_1 and FVC in nonsmoking adults (6). It remains unclear whether long-term exposure to traffic emissions and fine particulate matter ($PM_{2.5}$) at relatively low levels in the United States affects lung function in healthy adults.

There is some evidence that long-term exposure to ambient particulate air pollution, especially at levels seen in the 1990s before strict air quality regulations were implemented in the United States and Europe, may reduce lung function in adults. Most of these studies (7–11) examined particles with an aerodynamic diameter less than 10 μm (PM_{10}), which was historically monitored by most regulatory agencies, rather than $PM_{2.5}$. The SAPALDIA study in Switzerland associated estimates of PM_{10} at home address from a dispersion model and two repeated measures of spirometry 11 years apart and found that the declining PM_{10} exposure over the study period was associated with slower longitudinal decline in FEV_1 (9). The multicohort European metaanalysis (ESCAPE study) found that long-term exposure to NO_2 and PM_{10} estimated by land-use regression models was associated with reduced FEV_1 and FVC, but not with longitudinal change in lung function (12). This study also examined $PM_{2.5}$ exposure in a subset of the population but did not find associations with lung function or lung function change.

The Normative Aging Study recently found that long-term exposure to black carbon (a constituent of $PM_{2.5}$ that is emitted by traffic) was associated with lung function decline in a population of elderly men (13). Most particles less than 2.5 μm in diameter deposit in the lower respiratory tract, whereas the larger particles included in PM_{10}, including most particles greater than 4 μm in diameter, deposit in the upper airways (14). It is possible that the fine particle fraction of PM_{10}, which includes submicron particles emitted by traffic and industrial processes, are more toxic to the lung, although there are very few studies on long-term traffic and $PM_{2.5}$ exposure to support this assumption.

Given the paucity of data on long-term $PM_{2.5}$ exposure from all sources (including traffic) and adult pulmonary function, we examined associations between two measures of long-term exposure to ambient air pollution and lung function (FEV_1, FVC, and FEV_1/FVC ratio): the distance from home address to the nearest major roadway as a direct measurement of traffic exposure, and the $PM_{2.5}$ annual average at home address estimated by a land-use model using satellite measurements, in a cohort of nonsmoking adults.

Some of the results of this study have been previously presented at the International Society for Environmental Epidemiology conference in Seattle, Washington, August 24–28, 2014. The abstract can be viewed at: http://www.jrb-pro.com/isee/.

Methods

Further methodologic details are available in the online supplement.

Study Population

The study population consists of the participants in the Framingham Offspring and Third Generation cohorts. The design of these studies has been previously described (15, 16). Subjects included in this analysis are offspring participants with at least one spirometry measurement at examination 6 (n = 2,396; 1995–1998) and 7 (n = 2,252; 1998–2001), and third-generation participants with at least one measurement at examination 1 (n = 3,194; 2002–2005) or 2 (n = 2,844; 2008–2011). Current smokers (n = 915 participants; 1,711 observations) were excluded from the primary analysis because of known acute effects of smoking on lung function. 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.

Exposure Assessment

Distance to roadway. Distance to major roadway was evaluated by determining the distance from home address at the time of the examination to the nearest A1, A2, or A3 road (U.S. Census Features Class). Based on previous work showing that particle levels diminish to neighborhood background levels 100–300 m from major roads (17, 18), we examined associations using categories of distance: less than 100, 100 to less than 200, 200 to less than 400, and 400 to less than 1,000 m. These categories were selected to reflect the decay function of traffic pollution as distance to roadway increases. We have also previously observed that the natural log of residential proximity to a major roadway and mortality are linearly associated (19). We therefore also tested the natural log of distance to roadway as an exposure of interest. Participants living 1,000 m or further from a major road were excluded from the roadway analyses (1,158 observations; 10.8%) because at these locations, distance to roadway is unlikely to be a measure of traffic-related pollution exposure and may be an indicator of semirural or rural exposures.

$PM_{2.5}$ model. Daily estimates of $PM_{2.5}$ at home address were derived from a model using moderate resolution imaging spectroradiometer satellite-derived aerosol

optical thickness measurements at a 10×10-km spatial resolution across the Northeast and then resolved to a specific location within a 50×50-m grid using land-use terms. Aerosol optical thickness is a quantitative measure of particle abundance in the atmospheric column. Details of the $PM_{2.5}$ model have been described in detail elsewhere (20). Briefly, estimates of $PM_{2.5}$ using aerosol optical thickness measurements from the satellite were calibrated daily using measurements from 78 ground monitoring stations. The calibrations resulted in high out-of-sample 10-fold cross-validated R^2 (mean out-of-sample $R^2 = 0.85$). Local land-use terms (distance to primary highways, distance to point source emissions, population density, percent open spaces, elevation, and traffic density) and meteorologic variables (temperature, wind speed, visibility, and elevation) were then used to model the difference between the 10×10-km grid cell predictions and monitored values. The sum of the grid cell predictions and residuals from the land-use model represents a measure of total $PM_{2.5}$.

We estimated the annual $PM_{2.5}$ in the index year 2001, the earliest year for which data were available for the full calendar year, a similar approach to long-term exposure assessment as the Women's Health Initiative study of $PM_{2.5}$ and mortality (21). By using the same index year for all participants, any differences in exposure between participants are attributable to different locations of residence (and their nearby $PM_{2.5}$ sources) and not attributable to differences in the year when the participant performed the examination, because $PM_{2.5}$ levels have declined over the past decade. Observations from Offspring cohort examinations 6 and 7 that occurred before 2001 (all of examination 6 and all but 60 observations from examination 7) were excluded from the $PM_{2.5}$ analysis because our exposure interval of interest occurred after those examinations took place.

Statistical Analyses

We first conducted analyses associating distance to roadway and the 2001 $PM_{2.5}$ average with repeated measures of FEV_1, FVC, and FEV_1/FVC using linear mixed-effects models with a subject-specific random intercept, to estimate associations with average levels of lung function. We then evaluated associations between each exposure and the annual rate of change in FEV_1, FVC, and FEV_1/FVC between examinations using linear regression. Finally, we performed logistic regressions examining associations between each exposure and the odds of FEV_1/FVC less than 0.7 (which we call "obstruction" based on Global Initiative for Chronic Obstructive Lung Disease criteria [22]), asthma, wheeze in the past 12 months, and chronic cough at the participant's last examination. All models were adjusted for sex, age, height, weight, pack-years, education (less than high school, high school diploma, some college, college graduate), median household income from 2000 census tract, time as a continuous linear variable using the date of the examination, and cohort (to account for a difference in spirometry equipment between cohorts). Models with spirometry outcomes were also adjusted for weekday, season (using sine and cosine functions of the examination date to estimate the amplitude and phase of the seasonal cycle), and prior day relative humidity and temperature. The covariates in the model were selected *a priori* based on known associations with lung function or air pollution.

We evaluated the linearity of the relationships of distance to roadway and $PM_{2.5}$ exposure estimates with the rate of change in FEV_1 using restricted cubic splines with knots at the five percentiles: 5, 27.5, 50, 72.5, and 95th of the distribution (23) using Stata v.13 (StataCorp, College Station, TX) (24) and compared the fit of these models with the linear models using likelihood ratio tests.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and Stata v.13 software.

Results

Participant characteristics including demographics and pulmonary outcomes are summarized in Table 1. This is a middle- to older-aged cohort with a slight majority of women. Slightly more than half (55.6%) of observations included in the analysis were from never smokers and former smokers had smoked 17 pack-years on average. The cohort was well educated overall, with nearly half achieving a college degree and 78% completing at least some college. Participants lived in neighborhoods with an average census tract median household income in 2000 of $65,118, which is above the U.S. median household income of $42,148 for that year (25).

Table 1. Characteristics of Study Participants

	Mean (SD) or %
Demographics	
Age, yr	50.4 (12.4)
Male sex, %	46.2
Body mass index, kg/m^2	27.7 (5.5)
Smoking status, %	
Never	55.6
Former	44.4
Pack-years	
Never smokers	0 (0)
Former smokers	17.4 (18.0)
Education, %	
<High school	1.8
High school	18.6
Some college	28.5
College graduate school	49.8
Missing education	1.3
Median census tract household income, $	65,118 (21,927)
Pulmonary outcomes	
FEV_1, L	3.18 (0.85)
FVC, L	4.19 (1.06)
FEV_1/FVC, %	75.7 (7.06)
Obstruction, $FEV_1/FVC < 0.7$	16.4
Asthma diagnosis, ever	15.4
Wheeze in past 12 mo	16.1
Cough ⩾3 mo in past year	5.1

Data calculated from 10,686 observations (among 6,339 participants).

Average FEV_1 and FVC were within the normal range. The mean FEV_1 was 97.3% predicted (SD, 14.4%), and mean FVC was 100.9% predicted (SD, 13.0%) using the Hankinson National Health and Nutrition Examination Survey prediction equations (26). Airflow obstruction, asthma, and wheeze in the past 12 months each affected 15–17% of the study population, whereas only 5.1% suffered from chronic cough in the past year.

The distributions of distance to roadway and $PM_{2.5}$ levels are provided in Table 2. The median distance to roadway was 207 m, after excluding observations with a home address greater than or equal to 1,000 m from a major roadway. When divided into categories of distance, nearly one-third (31.5%) of participants lived less than 100 m from a major road. Median $PM_{2.5}$ at home address was 10.8 $\mu g/m^3$ for the year 2001 in this cohort, which is below the current Environmental Protection Agency National Air Quality Standards annual standard of 12 $\mu g/m^3$. The interquartile range of $PM_{2.5}$ was fairly narrow at 2 $\mu g/m^3$ and it ranged from 7.3 to 21.7 $\mu g/m^3$ overall.

Associations between Distance to Roadway and Lung Function

Of 5,513 participants included in the distance-to-roadway analysis, 3,905 (71%) had repeated lung function measures. Living in close proximity to a major roadway was negatively associated with average FEV_1 and FVC and with the annual change in FEV_1 and FVC, as shown in Figures 1 and 2. There was a log-linear association between distance to roadway and both FEV_1 and FVC (Table 3). As distance to roadway increased, lung function also increased: there was a 9.0 ml (95% confidence interval [CI], −0.6 to 18.5) higher FEV_1 and a 2.0 ml/yr (95% CI, 0.1–3.9) slower decline in FEV_1 per interquartile range (from the 25th to the 75th percentile) increase in the log-transformed distance to major roadway. The ratio of FEV_1 to FVC was not associated with distance to roadway. In our analysis examining nonlinear relationships of distance to roadway with the rate of change in FEV_1, we constructed cubic splines but did not observe any statistically significant evidence of departures from linearity ($P = 0.58$ for likelihood ratio test).

Proximity to roadway was associated with higher odds of an asthma diagnosis (Table 4). Participants living 100 to less than 200 m from a major road had 1.35 (95% CI, 1.06–1.72) times the odds of asthma than those greater than or equal to 400 m from a major road. Participants in the less than 100 m and 200 to less than 400 m categories also had elevated risk of asthma, but the CIs spanned the null for the less than 100 m category. Associations between distance to roadway and the other clinical outcomes of obstruction, wheeze, and chronic cough were weak or null.

Associations between $PM_{2.5}$ and Lung Function

Of 2,885 participants included in the $PM_{2.5}$ analysis, 2,222 (77%) had repeated lung function measures. The 2001 average of $PM_{2.5}$ exposure at home address was associated with lower average FEV_1 and FVC and an accelerated decline in FEV_1 and FVC (Table 3). A 2 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 13.5 ml (95% CI, −26.6 to −0.3) lower FEV_1 and a 2.1 ml/yr (−4.1 to −0.2) additional decline in FEV_1 per year. Results were similar for FVC. In our analysis examining nonlinear relationships of $PM_{2.5}$ with change in FEV_1, we did not observe any statistically significant evidence of departures from linearity ($P = 0.14$ for likelihood ratio test). $PM_{2.5}$ exposure was not associated with a difference in the FEV_1/FVC ratio, or with odds of airflow obstruction, asthma, wheeze, or chronic cough (Table 4).

After additionally adjusting for previous-day $PM_{2.5}$ levels, associations increased somewhat and CIs narrowed for associations between $PM_{2.5}$ and lung function. Each 2 $\mu g/m^3$ of $PM_{2.5}$ exposure was associated with a 17.6 ml (95% CI, −31.0 to −4.1) lower FEV_1, a 2.9 ml/yr (95% CI, −4.9 to −0.9) more rapid decline in FEV_1, a 22.1 ml (95% CI, −37.3 to −6.9) lower FVC, and a 2.9 ml/yr (95% CI, −5.1 to −0.7) more rapid decline in FVC.

Tests for Susceptible Subgroups and Sensitivity Analyses

We performed several tests of effect modification and sensitivity analyses on our data as described in the online supplement. Adjustment for asthma and inhaler use and for a history of secondhand smoke exposure in the home did not substantially change the associations observed. We did not observe differences by smoking status in relation to distance to roadway. Adding current smokers to the analysis did not affect associations between distance to roadway and FEV_1. We found borderline statistical evidence that former smokers had a lower FEV_1 ($P_{interaction} = 0.07$) and a more rapid decline in FEV_1 ($P_{interaction} = 0.09$) in association with $PM_{2.5}$ exposure compared with never smokers, whereas current smokers did not have reduced lung function in association with $PM_{2.5}$ exposure. When current smokers were added to the $PM_{2.5}$ analyses, the magnitude of associations between $PM_{2.5}$ and lung function diminished somewhat and CIs were wider. When participants living greater than or equal to 1,000 m from a major roadway were added to the distance-to-roadway analyses, results were unchanged and CIs were slightly narrower.

Table 2. Distributions of Distance to Roadway and the Annual Average of $PM_{2.5}$ in 2001

Exposure	Median (IQR) or %	Range
Distance to major roadway, m*	207 (349)	0.01–999.7
Distance to roadway in categories*		
<100 m	31.5	
100 to <200 m	17.4	
200 to <400 m	24.6	
400 to <1,000 m	26.6	
$PM_{2.5}$, $\mu g/m^3$†	10.8 (2.0)	7.3–21.7

Definition of abbreviations: IQR = interquartile range; $PM_{2.5}$ = fine particulate matter less than 2.5 μm in aerodynamic diameter.
*A total of 1,158 observations (10.8%) among 596 participants (9.4%) living ⩾1,000 m from a major roadway were excluded from the distance-to-roadway analyses.
†A total of 4,588 observations (2,396 observations from Offspring cohort examination 6 and 2,192 observations from Offspring cohort examination 7) that occurred before 2001 were excluded from the analysis of $PM_{2.5}$ exposure.

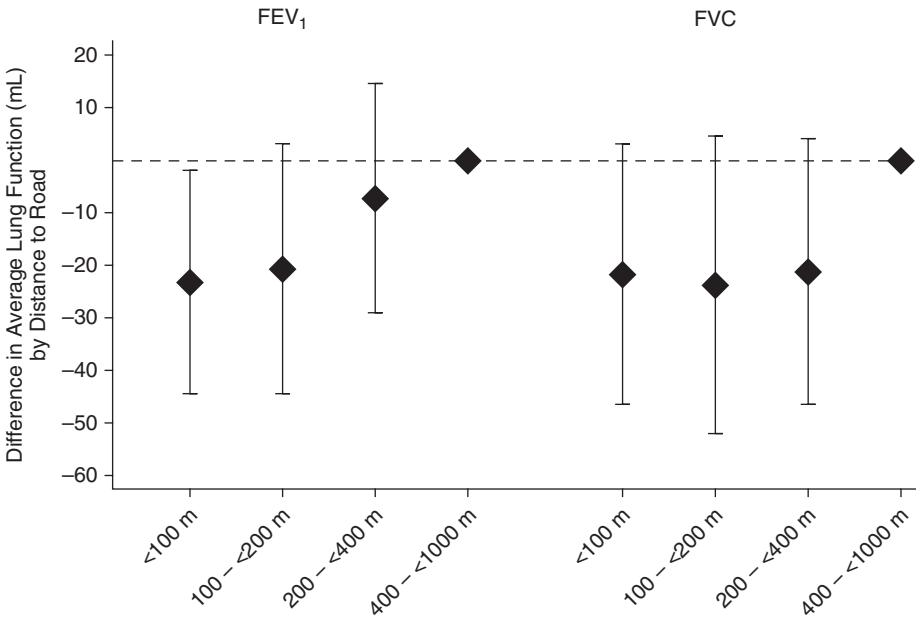

Figure 1. Differences in average lung function (and 95% confidence intervals) by distance-to-roadway category compared with the 400- to 1,000-m reference group. Adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, cohort, date of examination, weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.

We did not find statistical evidence of effect modification of the associations between distance to roadway or exposure to $PM_{2.5}$ with FEV_1 by asthma or COPD, cohort, age, sex, obesity, or measures of socioeconomic status (educational attainment and census tract median household income).

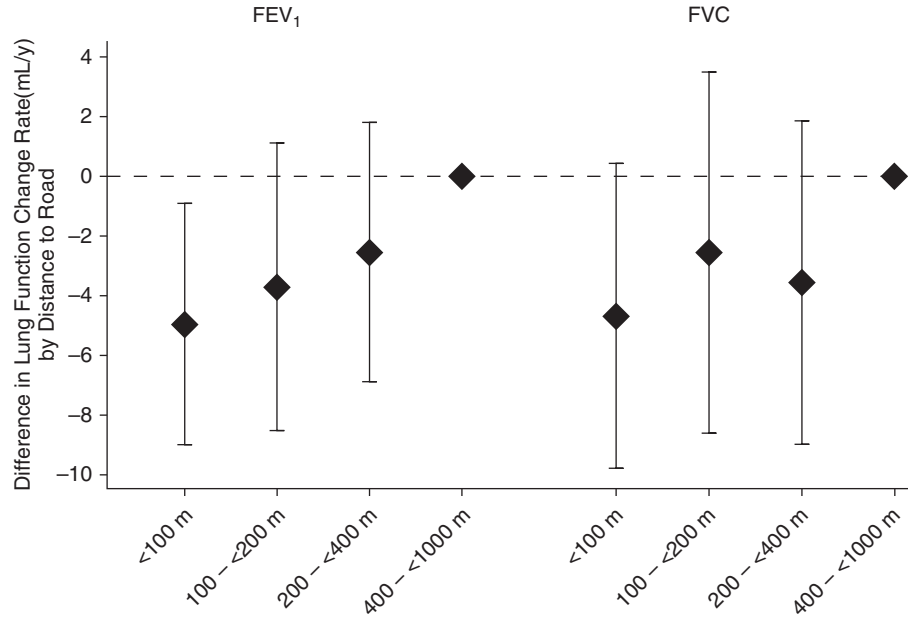

Figure 2. Differences in the rate of change in lung function (and 95% confidence intervals) by distance-to-roadway category compared with the 400- to 1,000-m reference group. Adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, cohort, date of examination, weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.

Discussion

Overall, we observed a consistent pattern that living close to a major roadway and long-term exposure to $PM_{2.5}$ were both associated with lower FEV_1 and FVC and a more rapid rate of lung function decline between examinations in this cohort of adults residing primarily in the Northeastern United States. There was no evidence that long-term air pollution exposure was associated with airflow obstruction, because there was no association with the FEV_1/FVC ratio or with odds of a ratio less than 0.7. We did find that living close to a major roadway in adulthood was associated with an increased risk of an asthma diagnosis during the participant's lifetime, but not with wheeze in the past 12 months.

Both near-roadway exposures and long-term exposure to $PM_{2.5}$ (at relatively low concentrations) were associated with an accelerated annual decline in lung function of a magnitude that may be clinically relevant over time. To place the longitudinal effect sizes in context, in our study population of former and never smokers, former smoking status was associated with an additional annual decline in FEV_1 of 4.9 ml/yr (95% CI, −8.0 to −1.9). The magnitude of the additional decline in FEV_1 each year in association with living less than 100 m from a major roadway was equivalent to the effect of formerly smoking in our study population. The additional annual decline in FEV_1 for each 2 $\mu g/m^3$ increase in the 2001 average of $PM_{2.5}$ exposure was equivalent to 43% of the effect of formerly smoking. It should be noted that these associations with $PM_{2.5}$ exposure were scaled according to the relatively narrow interquartile range of exposure of 2 $\mu g/m^3$ of our study. Recent studies on long-term $PM_{2.5}$ exposure and mortality have scaled results per 10 $\mu g/m^3$ (27, 28). If reported in this way, we found a 68-ml lower FEV_1 and a 10.5 ml/yr additional decline in FEV_1 per 10 $\mu g/m^3$ of $PM_{2.5}$ exposure.

In other parts of the world, particularly highly populated cities in Asia, average $PM_{2.5}$ levels and the range of exposure are much higher than in our study region. In those regions, large lung function

Table 3. Long-Term Exposures to Ambient Air Pollution and Spirometry Measures

Outcome Exposure	Association with Average Lung Function		Association with Change in Lung Function	
	N Examinations	Difference in Outcome (95% CI)	N Examinations	Difference in Outcome Rate of Change (95% CI)
FEV_1, ml and ml/yr				
Log of distance to road*	9,101	9.0 (−0.6 to 18.5)	7,810	2.0 (0.1 to 3.9)
$PM_{2.5}$*	4,872	−13.5 (−26.6 to −0.3)	4,444	−2.1 (−4.1 to −0.2)
FVC, ml and ml/yr				
Log of distance to road*	9,101	8.0 (−3.1 to 19.3)	7,810	1.8 (−0.6 to 4.2)
$PM_{2.5}$*	4,872	−18.7 (−33.6 to −3.8)	4,444	−2.0 (−4.1 to 0.1)
FEV_1/FVC, % points and % points/yr				
Log of distance to road*	9,101	0.06 (−0.09 to 0.2)	7,810	0.01 (−0.03 to 0.04)
$PM_{2.5}$*	4,872	0.0 (−0.2 to 0.2)	4,444	−0.01 (−0.04 to 0.02)

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = fine particulate matter less than 2.5 μm in aerodynamic diameter. All models adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, cohort, date of examination, weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.
*Scaled per IQR in the logarithmic scale for distance to roadway and per IQR of 2 $\mu g/m^3$ for $PM_{2.5}$.

decrements as a result of ambient particulate pollution are likely. Decreases in FEV_1 have been associated with all-cause mortality increases in a monotonic fashion in population studies (29, 30), suggesting that even small decreases in FEV_1 may result in small increases in all-cause mortality.

Several studies have suggested that long-term outdoor air pollution exposure may accelerate lung function decline in adults. The most convincing evidence for this is the SAPALDIA study, which found that each 10 $\mu g/m^3$ meter decline in PM_{10} over the study period was associated with a 9% decrease in the FEV_1 decline rate (9). The UCLA Population Studies of Chronic Obstructive Respiratory Disease measured lung function twice in subjects in three regions of Southern California with different mixtures of ambient pollutants and found a 23.6 ml/yr decline in FEV_1 associated with living in the most polluted region. This represents 71% of the decline rate in FEV_1 attributable to smoking more than one pack of cigarettes per day in this study (31). The effects on FEV_1 were mostly attributed to particulate matter, sulfates, and nitrogen oxides exposures. Similarly, a study in Japan examining lung function in women from three different regions of Tokyo found that women in the highest pollution exposure group had more than twice the rate of decline in FEV_1 (20 vs. 9 ml/yr) from 1987 to 1994 compared with the lowest exposure group (32). Air pollution gradients were primarily attributable to differences in traffic density. Interestingly, the ESCAPE metaanalysis in Europe found only cross-sectional associations between long-term particle exposures and lung function, but no association with lung function decline (12).

We did not find an association between long-term air pollution exposure and airflow obstruction (in terms of a reduction in the ratio of FEV_1 to FVC or increased odds of $FEV_1/FVC < 0.7$), but rather we found similar effect sizes for FEV_1 and FVC. Our findings may indicate a restrictive effect of long-term air pollution exposure on lung function or perhaps a slight obstructive effect, because associations with the ratio of FEV_1 to FVC, although not statistically significant, were small in magnitude and negative in direction. The findings from the limited investigations on long-term air

Table 4. Long-Term Exposures to Ambient Air Pollution and Odds of Pulmonary Clinical Outcomes

Exposure	Obstruction (FEV_1:FVC < 0.7)	Asthma Diagnosis (Ever)	Wheeze in Past 12 mo	Chronic Cough (>3 mo/yr)
Distance to roadway in categories				
<100 m	1.06 (0.87–1.29)	1.18 (0.95–1.46)	1.02 (0.84–1.25)	1.22 (0.89–1.66)
100 to <200 m	1.10 (0.88–1.38)	1.35 (1.06–1.72)	0.89 (0.70–1.13)	0.89 (0.61–1.30)
200 to <400 m	0.97 (0.79–1.20)	1.26 (1.01–1.58)	0.94 (0.76–1.16)	1.17 (0.84–1.63)
400 to <1,000 m	—	—	—	—
Log of distance to road*	0.96 (0.88–1.05)	0.93 (0.84–1.02)	0.96 (0.87–1.05)	0.95 (0.83–1.10)
$PM_{2.5}$*	1.00 (0.86–1.16)	0.97 (0.85–1.10)	0.98 (0.86–1.11)	1.08 (0.84–1.38)

Definition of abbreviations: IQR = interquartile range; $PM_{2.5}$ = fine particulate matter less than 2.5 μm in aerodynamic diameter.
These analyses included 5,494 observations for the distance-to-roadway analyses and 2,783 observations for the $PM_{2.5}$ analyses. All models adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, date of examination, and cohort. Model for obstruction additionally adjusted for weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.
*Scaled per IQR in the logarithmic scale for distance to roadway and per IQR of 2 $\mu g/m^3$ for $PM_{2.5}$.

pollution and lung function in adults have been mixed, with some studies observing restrictive patterns and others finding obstructive patterns of lung function decline.

Using a land use regression model for the greater Boston area, the Normative Aging Study of elderly men recently found that long-term estimates of exposure to black carbon, a traffic-related constituent of particulate matter weighted toward diesel, were associated with accelerated decline in both FEV_1 and FVC (13). This study found that the cross-sectional effect of black carbon exposure on baseline lung function was slightly stronger for FEV_1 than FVC, suggesting an obstructive effect, but the longitudinal effect of black carbon on lung function decline was stronger on FVC compared with FEV_1, a restrictive pattern. The Normative Aging Study also examined medium-term (28-d) exposure to $PM_{2.5}$, NO_2, and black carbon and found stronger negative associations with FVC than FEV_1 (33). The longitudinal SAPALDIA study found that reductions in PM_{10} over an 11-year period were associated with a slower decline in FEV_1 and FEV_1 as a percentage of FVC, but not FVC (9), suggesting an obstructive pattern of the effect of particulate pollution on lung function decline. But the initial cross-sectional analysis of the SAPALDIA study found a restrictive pattern, with the most consistent associations between PM_{10} and FVC (8).

The ESCAPE metaanalysis involving four European cohorts found nonsignificant, but positive, associations between long-term estimates of NO_2, nitrogen oxides, and PM_{10} and odds of COPD (defined as $FEV_1/FVC < 0.7$), suggesting a possible obstructive effect (34). But a second metaanalysis by the ESCAPE group including repeated measures from five cohorts found significant and similar-magnitude cross-sectional associations of NO_2 and PM_{10} with both FEV_1 and FVC, in a restrictive pattern (12). All of these studies examined slightly different long-term air pollution exposures (black carbon and PM_{10} compared with distance to roadway and modeled $PM_{2.5}$ using satellite data in the present study). Because the literature on long-term effects of traffic and particulate air pollution on adult lung function is still emerging, additional research is needed to examine whether these chronic effects are more obstructive or restrictive and whether the pollutant-specific effects are different.

We observed an association between distance to roadway and odds of an asthma diagnosis. However, we did not observe a similar association between $PM_{2.5}$ exposure and asthma, nor did we observe any associations with odds of wheeze in the past 12 months. This suggests that proximity to roadway was associated with receiving an asthma diagnosis at some point in time, but perhaps not with current, symptomatic asthma. Because we were unable to ascertain the timing of asthma diagnosis, there is a possibility of selection bias—that those who were previously diagnosed with asthma were more likely to live closer to major roads in adulthood. Alternatively, the association could be causal and indicative of an association of near-roadway exposures, but not $PM_{2.5}$, with nonwheezy asthma phenotypes. It is also possible that many of the participants reporting wheeze had COPD and not asthma, potentially explaining the lack of an association with wheeze.

In a cross-sectional analysis of the SAPALDIA study, measures of long-term exposure to NO_2 (an indicator of traffic-related pollution) and PM_{10} were associated with cough, phlegm production, and dyspnea on exertion, but not with wheeze or current asthma (35). The Sister Study in the United States was the first study of long-term exposure to $PM_{2.5}$ and incident asthma in adults and found that each 3.6 $\mu g/m^3$ in estimated $PM_{2.5}$ was associated with a 1.20 (95% CI, 0.99–1.46) higher odds of incident asthma. The authors also found positive associations of $PM_{2.5}$ and NO_2 with wheeze but not cough (36). The question of whether long-term particulate pollution exposure contributes to asthma risk in adults deserves further study.

We found borderline statistical evidence of greater susceptibility to $PM_{2.5}$ exposure among former smokers compared with never smokers ($P_{interaction} = 0.07$ for average FEV_1 and $P_{interaction} = 0.09$ for decline in FEV_1). Also, we observed negative associations between $PM_{2.5}$ exposure and lung function among never and former smokers, but not current smokers. Although these findings did not meet criteria for statistical significance, they suggest that former smokers may be at higher risk for long-term pulmonary effects of air pollution exposure than never smokers, perhaps because their airways were damaged by the former smoking, whereas current smokers may be less susceptible because the daily injury by active smoking may overwhelm any incremental damage by long-term pollution exposure.

There is some prior literature to suggest that former smokers may be more susceptible to air pollution exposure than never smokers. For example, Tashkin and colleagues (31) found that female former smokers had faster declines in FEV_1 than never or current smokers in association with living in the most polluted areas in Southern California, but there was no interaction between smoking status and area of residence among males. Other studies have found that never smokers may be the most susceptible (13, 35). The Normative Aging Study found that ever smokers (92% of whom were former smokers) had a slower decline in FEV_1 in association with black carbon exposure compared with never smokers (−0.5% vs. −1.5% annual FEV_1 decline per 0.5 $\mu g/m^3$ in 5-yr average of black carbon) (13). These findings may be consistent with our study results if the smaller effect size among ever smokers was a result of the current smokers, but it is more likely that former smokers had a smaller effect than never smokers in that study. The ESCAPE metaanalysis of five European cohort studies found no evidence of different associations between long-term air pollution exposure and lung function among never versus ever smokers (12). Overall, it remains unclear whether former smoking is a risk factor for larger lung function decrements from air pollution exposure and we found only borderline evidence of greater susceptibility.

We examined two different measures of long-term air pollution exposure: distance to roadway, which measures microscale exposure to pollution from nearby traffic on the scale of a few hundred meters; and $PM_{2.5}$, which is a measure of both regional and urban background pollution from traffic and other local sources, such as home heating, airport, and seaport. The fact that we observed associations of both distance to roadway and $PM_{2.5}$ with lung function may suggest that traffic is a primary driver behind the associations between $PM_{2.5}$ exposure and lung function in our study. This would be consistent with the distribution of pollution sources

in our study region, because traffic is the major source of urban background $PM_{2.5}$ in the Northeastern United States. However, the Spearman correlation coefficient between proximity to roadway and $PM_{2.5}$ exposure in the year 2001 was only 0.20 and it is likely that other sources of $PM_{2.5}$ also contributed to the associations with lung function. Additionally, near-roadway exposures other than $PM_{2.5}$, such as gases (ozone, carbon monoxide, and NO_2) and noise, and social factors, such as housing stock and stress, may play a role in the association between distance to roadway and lung function.

The biologic mechanisms of air pollution toxicity on the adult lung are not well-studied in humans, because controlled human exposure studies do not lend themselves well to the study of long-term air pollution exposure. Animal studies suggest that long-term exposures result in pulmonary inflammation, oxidative stress, and pulmonary remodeling (37, 38). A chamber study exposing mice prenatally and postnatally to filtered air versus concentrated ambient $PM_{2.5}$ at a level of 16.8 ± 8.3 $\mu g/m^3$ found that the chronically exposed mice had reduced inspiratory and expiratory volumes at higher levels of transpulmonary pressure compared with unexposed mice (39). If our finding is true that the pulmonary effects of chronic air pollution exposure are restrictive rather than obstructive, the underlying mechanisms are likely different from that of cigarette smoke, which is well known to cause obstructive disease.

In conclusion, we found that proximity of the home to a major roadway and long-term exposure to $PM_{2.5}$ were both associated with reduced lung function and accelerated lung function decline in this cohort of generally healthy adult men and women in the Northeastern United States. We observed these associations at relatively low ambient pollution levels with an effect magnitude comparable with former smoking. ■

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

Acknowledgment: The authors thank Erin Reese of the BIDMC Cardiovascular Epidemiology Research Unit for her assistance with this study and the participants of the Framingham Offspring and Third Generation cohorts.

References

1. Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: a review. *Eur Respir J* 2001;17:1024–1033.
2. 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.
3. 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.
4. 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.
5. 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.
6. Rice MB, Ljungman PL, Wilker EH, Gold DR, Schwartz JD, Koutrakis P, Washko GR, O'Connor GT, Mittleman MA. Short-term exposure to air pollution and lung function in the Framingham Heart Study. *Am J Respir Crit Care Med* 2013;188:1351–1357.
7. Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE, Krämer U. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respir Res* 2005; 6:152.
8. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brändli O, Domenighetti G, Elsasser S, *et al*.; Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Lung function and long term exposure to air pollutants in Switzerland. *Am J Respir Crit Care Med* 1997;155:122–129.
9. Downs SH, Schindler C, Liu L-JS, Keidel D, Bayer-Oglesby L, Brutsche MH, Gerbase MW, Keller R, Künzli N, Leuenberger P, *et al*.; SAPALDIA Team. Reduced exposure to PM10 and attenuated age-related decline in lung function. *N Engl J Med* 2007;357: 2338–2347.
10. Forbes LJL, Kapetanakis V, Rudnicka AR, Cook DG, Bush T, Stedman JR, Whincup PH, Strachan DP, Anderson HR. Chronic exposure to outdoor air pollution and lung function in adults. *Thorax* 2009;64: 657–663.
11. Eckel SP, Louis TA, Chaves PH, Fried LP, Margolis AH. Modification of the association between ambient air pollution and lung function by frailty status among older adults in the Cardiovascular Health Study. *Am J Epidemiol* 2012;176:214–223.
12. Adam M, Schikowski T, Carsin AE, Cai Y, Jacquemin B, Sanchez M, Vierkötter A, Marcon A, Keidel D, Sugiri D, *et al*. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. *Eur Respir J* 2014;45:38–50.
13. Lepeule J, Litonjua AA, Coull B, Koutrakis P, Sparrow D, Vokonas PS, Schwartz J. Long-term effects of traffic particles on lung function decline in the elderly. *Am J Respir Crit Care Med* 2014;190:542–548.
14. Asgharian B, Price OT, Oldham M, Chen L-C, Saunders EL, Gordon T, Mikheev VB, Minard KR, Teeguarden JG. Computational modeling of nanoscale and microscale particle deposition, retention and dosimetry in the mouse respiratory tract. *Inhal Toxicol* 2014;26: 829–842.
15. 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.
16. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, 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.
17. Zhou Y, Levy JI. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. *BMC Public Health* 2007;7:89.
18. Massoli P, Fortner EC, Canagaratna MR, Williams LR, Zhang Q, Sun Y, Schwab JJ, Trimborn A, Onasch TB, Demerjian KL, *et al*. Pollution gradients and chemical characterization of particulate matter from vehicular traffic near major roadways: results from the 2009 Queens College air quality study in NYC. *Aerosol Sci Technol* 2012;46: 1201–1218.
19. Rosenbloom JI, Wilker EH, Mukamal KJ, Schwartz J, Mittleman MA. Residential proximity to major roadway and 10-year all-cause mortality after myocardial infarction. *Circulation* 2012;125: 2197–2203.
20. Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. Using new satellite based exposure methods to study the association between pregnancy $PM_{2.5}$ exposure, premature birth and birth weight in Massachusetts. *Environ Health* 2012;11:40.
21. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; 356:447–458.
22. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2014 [accessed 2015 Feb 6]. Available from: http://www.goldcopd.org

23. Harrell FE. Regression modeling strategies with applications to linear models, logistic regression and survival analysis. New York: Springer-Verlag; 2001.
24. Buis M. POSTRCSPLINE: Stata module containing post-estimation commands for models using a restricted cubic spline. 2009 [accessed 2015 Feb 6]. Available from: http://ideas.repec.org/c/boc/bocode/s456928.html
25. DeNavas-Walt C, Cleveland RW, Roemer MI. Money income in the United States: 2000. Washington, DC: US Census Bureau; 2001. Current Population Reports P60-213.
26. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
27. Pope III CA, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 2009;360:376–386.
28. Pope III CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287: 1132–1141.
29. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000;118:656–664.
30. Miller MR, Pedersen OF, Lange P, Vestbo J. Improved survival prediction from lung function data in a large population sample. *Respir Med* 2009;103:442–448.
31. Tashkin DP, Detels R, Simmons M, Liu H, Coulson AH, Sayre J, Rokaw S. The UCLA population studies of chronic obstructive respiratory disease: XI. Impact of air pollution and smoking on annual change in forced expiratory volume in one second. *Am J Respir Crit Care Med* 1994;149:1209–1217.
32. Sekine K, Shima M, Nitta Y, Adachi M. Long term effects of exposure to automobile exhaust on the pulmonary function of female adults in Tokyo, Japan. *Occup Environ Med* 2004;61:350–357.
33. Lepeule J, Bind M-AC, Baccarelli AA, Koutrakis P, Tarantini L, Litonjua A, Sparrow D, Vokonas P, Schwartz JD. Epigenetic influences on associations between air pollutants and lung function in elderly men: the normative aging study. *Environ Health Perspect* 2014;122:566–572.
34. Schikowski T, Adam M, Marcon A, Cai Y, Vierkötter A, Carsin AE, Jacquemin B, Al Kanani Z, Beelen R, Birk M, *et al*. Association of ambient air pollution with the prevalence and incidence of COPD. *Eur Respir J* 2014;44:614–626.
35. Zemp E, Elsasser S, Schindler C, Künzli N, Perruchoud AP, Domenighetti G, Medici T, Ackermann-Liebrich U, Leuenberger P, Monn C, *et al*.; The SAPALDIA Team. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). *Am J Respir Crit Care Med* 1999;159:1257–1266.
36. Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 2014;190:914–921.
37. Wang JM, Ueng TH, Lin JK. Biochemical and morphological alterations in the lungs and livers of mice following exposure to polluted air in a traffic tunnel. *Proc Natl Sci Counc Repub China B* 1992;16:77–83.
38. Hatzis C, Godleski JJ, González-Flecha B, Wolfson JM, Koutrakis P. Ambient particulate matter exhibits direct inhibitory effects on oxidative stress enzymes. *Environ Sci Technol* 2006;40:2805–2811.
39. Mauad T, Rivero DHRF, de Oliveira RC, Lichtenfels AJ de FC, Guimarães ET, de Andre PA, Kasahara DI, Bueno HM de S, Saldiva PHN. Chronic exposure to ambient levels of urban particles affects mouse lung development. *Am J Respir Crit Care Med* 2008;178: 721–728.