Long-Term Ambient Multipollutant Exposures and Mortality

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Rationale: **Population-based studies have demonstrated associations between ambient air pollution exposures and mortality, but few have been able to adjust for occupational exposures. Additionally, two studies have observed higher risks in individuals with occupational dust, gas, or fume exposure.**

Objectives: **We examined the association of ambient residential exposure to particulate matter less than 10 μm in diameter (PM_{10}), particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), NO_2, SO_2, and mortality in 53,814 men in the U.S. trucking industry.**

Methods: **Exposures for PM_{10}, NO_2, and SO_2 at each residential address were assigned using models combining spatial smoothing and geographic covariates. $PM_{2.5}$ exposures in 2000 were assigned from the nearest available monitor. Single and multipollutant Cox proportional hazard models were used to examine the association of an interquartile range (IQR) change (6 μg/m³ for PM_{10}, 4 μg/m³ for $PM_{2.5}$, 4ppb for SO_2, and 8ppb for NO_2) and the risk of all-cause and cause-specific mortality.**

Measurements and Main Results: **An IQR change in ambient residential exposures to PM_{10} was associated with a 4.3% (95% confidence interval [CI], 1.1–7.7%) increased risk of all-cause mortality. The increase for an IQR change in SO_2 was 6.9% (95% CI, 2.3–11.6%), for NO_2 was 8.2% (95% CI, 4.5–12.1%), and for $PM_{2.5}$ was 3.9% (95% CI, 1.0–6.9%). Elevated associations with cause-specific mortality (lung cancer, cardiovascular and respiratory disease) were observed for $PM_{2.5}$, SO_2, and NO_2, but not PM_{10}. None of the pollutants were confounded by occupational exposures. In multipollutant models, overall, the associations were attenuated, most strongly for PM_{10}. In sensitivity analyses excluding long-haul drivers, who spend days away from home, larger hazard ratios were observed.**

Conclusions: **In this population of men, residential ambient air pollution exposures were associated with mortality.**

Keywords: air pollutants/adverse effects; cardiovascular diseases/mortality; nitrogen dioxide; sulfur dioxide; particulate matter

Increased mortality has been associated with ambient air pollution exposures in several long-term population-based cohort studies (1–20). The majority of these studies have estimated air pollution exposures based on nearby ambient monitors. Control for occupational exposures has been minimal; however, a few of these studies have observed higher risks for individuals with occupational exposures to gas, dust, and fumes (1, 15). We have the unique opportunity to assess the effects of residential ambient air pollution exposures in a population of trucking industry employees with occupational exposures to vehicle exhaust (the Trucking Industry Particle Study [TrIPS]) (21).

We have previously described occupational associations with lung cancer (22) and cardiovascular mortality (21) in this cohort. In this analysis we examine the association of ambient exposures and mortality. We have predicted annual (1985–2000) particulate matter less than 10 μm in diameter (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) at the last known residential address from a statistical model combining spatial smoothing and land use regression (23), and particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) from the 2000 annual value of the nearest monitoring location. We examine the association of ambient residential exposure with all-cause, cardiovascular disease, respiratory disease, and lung cancer mortality, adjusting for occupational exposures using information from job history records. Some of the results of this study have been previously reported in the form of an abstract (24).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Population-based studies have demonstrated associations between chronic ambient air pollution exposures and mortality, but few studies have adjusted for concurrent occupational exposures or multiple pollutants.

What This Study Adds to the Field

Long-term exposures to particulate matter less than 10 μm in diameter, particulate matter less than 2.5 μm in diameter, SO_2, and NO_2 are independently associated with mortality, even after control for occupational traffic exposures. In multipollutant models, the effects were attenuated for particulates and strongest for NO_2.

METHODS

Population

Details of the cohort are provided elsewhere (21). In brief, we obtained work records for 54,319 men employed in 1985 from four trucking companies. Cause and date of death were obtained from the National Death Index from January 1, 1985 to December 31, 2000. We identified all-cause mortality and mortality from lung cancer (ICD-9: 162, ICD-10: C33–34), cardiovascular disease (ICD-9: 401–440, ICD-10: I10–70), ischemic heart disease (ICD-9: 410–414, ICD-10: I20–25), respiratory system disease (ICD-9: 480–519, ICD-10: J10–18, J40–98), and chronic obstructive pulmonary disease and allied conditions (ICD-9: 490–494, 496, ICD-10: J40–47). Lung cancer was identified if listed anywhere on the death certificate, and all other causes of death were based on underlying cause of death (22, 25–29).

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Occupational Exposure Assessment

Occupational exposure was based on job titles extracted from work records. These were classified into eight groups (21, 22): long-haul drivers, pick-up and delivery drivers, dockworkers, combination workers (who are pick-up and delivery drivers or dockworkers as needed), mechanics, hostlers, office workers, and other jobs (trainees, managers, etc.). Exposures in these groups were verified using a nationwide exposure assessment (30–32) and information on historical vehicle use (33). Cumulative years of work was calculated in a time-varying manner each year by adding the number of days spent in each job from the hire date until December 31. Occupational exposure was categorized by a set of eight variables for cumulative years of work in each group.

Ambient Exposure Assessment

Work records also included the last known address. Annual average exposures to PM_{10}, SO_2, and NO_2 were determined for 1985 through 2000 from a model using spatial smoothing and Geographic Information System–based covariates (23). Using the exposure model, each worker was assigned a unique annual exposure based on his address. Exposure was modeled as (*1*) pollution in the current calendar year, and (*2*) long-term average pollution, 1985 through 2000. No equivalent exposure model was available for $PM_{2.5}$; therefore, we assigned $PM_{2.5}$ exposure to each address based on the annual average level in 2000 at the nearest U.S. Environmental Protection Agency monitoring location.

Statistical Methods

The cohort was restricted to the continental United States (n = 53,814). Cox proportional hazard regression was used to examine relationships between cause-specific mortality and exposure to air pollution. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each mortality cause associated with increasing pollution exposure. The HRs were calculated in units of the interquartile range (IQR; difference between the 25th and 75th percentile) of the long-term average. We present results as percent change ($[HR - 1] \times 100$). To closely adjust for age and secular trends, risk sets were generated using attained age in 1-year increments, with separate baseline hazards by decade of age at entry, calendar year, and decade of hire. Race was included as a potential confounder in all models. All eight variables for years of work were included to adjust for potential confounding by occupational exposures. Time-varying variables for years employed and years off work were used to adjust for a healthy worker survivor effect (34). We also considered models including multiple pollutants (including either PM_{10} or $PM_{2.5}$ with SO_2 and NO_2). We conducted sensitivity analyses to determine if there was a stronger effect in those who return nightly to their homes (n = 39,948). Long-haul drivers in these companies spend one to three nights per week away from their homes, whereas all other workers return home each evening. All analyses were performed in SAS 9.2.

RESULTS

The 53,814 members of the cohort were on average 42.1 years of age at the start of follow-up (SD = 9.9; range, 15.3–84.9) and had been hired on average in 1975 (range, 1918–1985) (Table 1). The most frequent job categories in 1985 were long-haul drivers (25.9%), dockworkers (24.8%), pick-up and delivery drivers (17.3%), and combination workers (15.0%). Most of the cohort lived in the South (35.6%) and Midwest (32.1%) regions, as defined by the U.S. Census (35), and were white (83.1%). Most members of the cohort (81.0%) were geocoded to the street level and the remainder were geocoded to at least the 5-digit ZIP code level. The IQR for long-term average pollution (used as the unit of reference for all HRs) was 6 $\mu g/m^3$ for PM_{10}, 4 ppb for SO_2, and 8 ppb for NO_2. The IQR for $PM_{2.5}$ in 2000 was 4 $\mu g/m^3$.

The current calendar year and 1985 to 2000 average pollution metrics were highly correlated for PM_{10}, NO_2, and SO_2 (Spearman correlations between 0.64 and 0.98) and the results from the mortality analyses were similar. Therefore, we have chosen to present the long-term average for these pollutants. Statistically significant increases in risk of all-cause mortality were seen for an interquartile increase in the average pollution 1985 through 2000 for PM_{10}, NO_2, and SO_2 (Table 2). For cause-specific mortality, elevated HRs were observed for lung cancer, cardiovascular disease, and respiratory disease with both NO_2 and SO_2. Decreased HRs were observed between COPD mortality and both NO_2 and SO_2. Only the association of NO_2 and cardiovascular disease reached statistical significance. Results adjusted and unadjusted for years of work in each job were similar (*see* Table E4 in the online supplement for unadjusted models), indicating that occupational exposures did not confound the association with ambient pollution. The Spearman correlations between pollutants for the long-term average ranged from 0.02 to 0.45. In multipollutant models, including PM_{10}, NO_2, and SO_2 (Table 2), overall, the associations were attenuated, with those for PM_{10} showing the most dramatic attenuation. The only relationship that remained statistically significant was that of NO_2 with all-cause mortality (HR = 7.4%; 95% CI, 2.4–12.5%).

Long-haul drivers spend one to three nights away from home each week. Therefore, we repeated all analyses excluding these workers (Table 3) and observed elevated HRs compared with models including all individuals. When modeled independently, PM_{10}, SO_2, and NO_2 were statistically significant predictors of all-cause mortality. SO_2 and NO_2 were associated with elevated cardiovascular disease and respiratory disease mortality, and the HR for PM_{10} and cardiovascular disease mortality was of

TABLE 1. COHORT DEMOGRAPHICS

N	53,814
Age in 1985, yr, mean (SD)	42.1 (9.9)
Year of hire, mean (SD)	1975 (8.0)
Job in 1985, no. (%)	
Long-haul	13,919 (25.9)
Pick-up and delivery	9,291 (17.3)
Dockworker	13,332 (24.8)
Combination worker	8,055 (15.0)
Mechanic	3,237 (6.0)
Hostler	1,260 (2.3)
Clerk	2,420 (4.5)
Other	2,300 (4.3)
Region of residence, no. (%)	
Northeast	8,730 (16.2)
South	19,142 (35.6)
Midwest	17,289 (32.1)
West	8,653 (16.1)
Race/ethnicity, no. (%)	
Caucasian	44,728 (83.1)
African American	4,901 (9.1)
Hispanic	2,030 (3.8)
Native American	406 (0.8)
Asian	69 (0.1)
Other/unknown	1,680 (3.1)
Geocoding match level, no. (%)	
Street	43,581 (81.0)
ZIP code +4	1,198 (2.2)
ZIP code +2	1,090 (2.0)
ZIP code	7,945 (14.8)
Average pollution, mean (SD)*	
PM_{10}, $\mu g/m_3$	26.8 (6.0)
SO_2, ppb	4.8 (2.9)
NO_2, ppb	14.2 (7.1)
$PM_{2.5}$ in 2000,† $\mu g/m^3$	14.1 (4.0)

Definition of abbreviations: PM_{10} = particulate matter less than 10 μm in diameter; $PM_{2.5}$ = particulate matter less than 2.5 μm in diameter.

* Average annual pollution 1985–2000.

† Annual average from nearest U.S. Environmental Protection Agency monitor.

TABLE 2. PERCENT INCREASE AND 95% CONFIDENCE INTERVALS OF CAUSE-SPECIFIC MORTALITY ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE OF AVERAGE AMBIENT AIR POLLUTION 1985–2000 (N = 53,814)

		Single-Pollutant Models			Multi-Pollutant Model		
Cause of Death	Cases (no.)	PM_{10} (6 μg/m³)	SO_2 (4 ppb)	NO_2 (8 ppb)	PM_{10} (6 μg/m³)	SO_2 (4 ppb)	NO_2 (8 ppb)
All-cause	4,806	4.3 (1.1, 7.7)	6.9 (2.3, 11.6)	8.2 (4.5, 12.1)	−0.3 (−4.3, 3.9)	4.4 (−0.3, 9.2)	7.4 (2.4, 12.5)
Lung cancer	800	−0.1 (−7.9, 8.2)	9.0 (−1.8, 20.9)	5.5 (−3.4, 15.3)	−4.9 (−14.2, 5.4)	7.7 (−3.4, 20.1)	7.2 (−4.6, 20.5)
Cardiovascular disease	1,682	2.9 (−2.6, 8.7)	6.6 (−1.0, 14.8)	6.9 (0.6, 13.6)	−1.4 (−8.2, 5.8)	4.5 (−3.3, 13.0)	6.8 (−1.4, 15.7)
IHD	1,109	1.2 (−5.5, 8.4)	6.0 (−3.2, 16.1)	0.6 (−6.8, 8.6)	1.4 (−7.0, 10.7)	6.3 (−3.3, 16.9)	−1.8 (−11.1, 8.4)
Respiratory disease	317	2.5 (−9.0, 15.5)	7.7 (−8.9, 27.4)	5.9 (−7.4, 21.1)	−1.3 (−15.7, 15.6)	6.1 (−11.0, 26.4)	5.6 (−12.0, 26.6)
COPD	209	0.7 (−12.8, 16.4)	−5.5 (−23.8, 17.2)	−2.2 (−17.0, 15.3)	3.4 (−14.5, 25.0)	−5.0 (−24.1, 18.9)	−3.5 (−22.7, 20.5)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; PM_{10} = particulate matter less than 10 μm in diameter.

Values are given as percent increase and 95% CI unless otherwise noted. Percent increase and 95% CIs generated in Cox proportional hazard models with risk sets were generated using attained age in 1-year increments as the timeline, with separate baseline hazards based on decade of age at entry, calendar year and decade of hire, and adjusted for race, Census region of residence, the healthy worker survivor effect, and years of work in each of the eight job groups. Twenty-four lung cancer cases had cardiovascular disease as the underlying cause of death (10 from IHD) and 21 had respiratory disease as an underlying cause (12 from COPD).

borderline significance. Unlike in the full cohort, COPD mortality was positively associated with all three pollutants, although not significantly so. In the multipollutant model, only NO_2 and all-cause mortality remained statistically significantly elevated.

Statistically significant elevated risks of all-cause mortality were also observed with an IQR increase in $PM_{2.5}$ in the full cohort and the cohort excluding long-haul drivers (Table 4). For cause-specific mortality, elevated HRs were observed for lung cancer, cardiovascular disease, and respiratory disease. In multipollutant models, similar patterns and attenuations were seen to those models including PM_{10}.

DISCUSSION

Among this population of U.S. trucking industry employees, ambient residential air pollution exposures (PM_{10}, SO_2, NO_2) 1985 through 2000, as well as $PM_{2.5}$ exposures in 2000, were associated with increased all-cause mortality. These associations were attenuated for PM_{10}, $PM_{2.5}$, and SO_2 in multipollutant models. Overall, results were stronger when we restricted the cohort to those individuals whose jobs allowed them to return home each evening. For cause-specific mortality, elevated HRs were observed for lung cancer, cardiovascular disease, and respiratory disease with both NO_2 and SO_2. Importantly, these exposures were not confounded by occupational exposures measured by job title.

Numerous chronic exposure studies have observed increases in all-cause mortality with increases in PM exposures (1–7, 9, 11–13, 15, 18–20, 36). Although direct comparisons to all studies are not appropriate due to the measurement of different particulate size-fractions, our results for PM_{10} are elevated compared with two studies measuring PM_{10} (Electric Power Research Institute [EPRI]–Washington Veteran's Cohort Study and Adventist Health Study of Smog [ASHMOG]) (9, 19) and quite similar to those from a recent analysis in the Nurses' Health Study (16). Expressing our results in units of 10 μg/m³ (the most common unit in studies of PM), the association of PM_{10} and all-cause mortality in our study was 1.07 (95% CI, 1.02–1.13) in the full cohort and 1.17 (95% CI, 1.09–1.25) after excluding long-haul drivers. In general, long-term cohort studies in which $PM_{2.5}$, as opposed to PM_{10}, was examined as the size-fraction have observed higher estimates of all-cause mortality risk. Expressing our results in units of 10 μg/m³, the association of $PM_{2.5}$ in the full cohort was 1.10 (95% CI, 1.02–1.18) and 1.15 (95% CI, 1.05–1.27) after excluding long-haul drivers, which are of a similar magnitude to the other studies of long-term exposures.

Our findings for all-cause mortality and ambient NO_2 exposures are also consistent with those from other studies. For all-cause mortality, we observed HRs of 1.10 (95% CI, 1.06–1.15), expressed in units of 10-ppb increase in NO_2, in the full cohort, and 1.19 (95% CI, 1.13–1.26) in the cohort excluding long-haul drivers. Expressing results from previous studies in the same units, an HR of 1.14 (95% CI, 0.87–1.49) was observed for men in the AHSMOG study (8, 9), 1.04 (95% CI, 0.97–1.13) in the EPRI–Washington Veteran's Study (12), 1.03 (95% CI, 1.00–1.05) in the Dutch Netherlands Cohort Study on Diet and Cancer (NLCS) study (18), 1.16 (95% CI, 1.06–1.26) in a cohort of Norwegian men (37), and 1.23 (95% CI, 1.02–1.47) in a cohort of German women (38).

For cause-specific analyses, our elevations in cardiovascular (HR = 1.09; 95% CI, 1.01–1.17 for the whole cohort; HR =

TABLE 3. PERCENT INCREASE AND 95% CONFIDENCE INTERVALS OF CAUSE-SPECIFIC MORTALITY ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE OF AVERAGE AMBIENT AIR POLLUTION 1985–2000, EXCLUDING LONG-HAUL DRIVERS (N = 39,948)

		Single Pollutant Models			Multi-Pollutant Model		
Cause of Death	Cases	PM_{10} (6 μg/m³)	SO_2 (4 ppb)	NO_2 (8 ppb)	PM_{10} (6 μg/m³)	SO_2 (4 ppb)	NO_2 (8 ppb)
All-cause	2,816	9.7 (5.2, 14.5)	10.6 (4.6, 16.9)	14.9 (9.9, 20.2)	1.3 (−4.3, 7.2)	5.7 (−0.4, 12.2)	12.5 (5.8, 19.5)
Lung cancer	475	4.7 (−5.9, 16.5)	9.1 (−4.6, 24.8)	7.3 (−3.9, 19.9)	0.4 (−12.8, 15.5)	7.0 (−7.2, 23.4)	5.3 (−9.3, 22.2)
Cardiovascular disease	972	7.6 (−0.2, 16.0)	9.6 (−0.4, 20.7)	10.9 (2.7, 19.8)	1.4 (−8.2, 12.0)	6.0 (−4.3, 17.4)	8.3 (−2.5, 20.4)
IHD	602	2.0 (−7.4, 12.3)	7.3 (−5.1, 21.2)	5.7 (−4.2, 16.7)	−2.7 (−14.4, 10.7)	5.5 (−7.3, 20.2)	6.2 (−7.2, 21.6)
Respiratory disease	184	8.2 (−8.6, 28.0)	25.1 (2.0, 53.5)	20.1 (0.9, 42.8)	−6.2 (−25.6, 18.3)	19.5 (−4.0, 48.7)	20.7 (−5.5, 54.0)
COPD	117	7.0 (−13.6, 32.4)	9.2 (−16.9, 43.4)	7.0 (−14.4, 33.6)	4.7 (−21.2, 39.1)	7.3 (−19.5, 43.1)	1.9 (−24.8, 38.0)

For definition of abbreviations, see Table 2.

Values are given as percent increase and 95% CI unless otherwise noted. Percent increase and 95% CIs generated in Cox proportional hazard models with risk sets were generated using attained age in 1-year increments as the timeline, with separate baseline hazards based on decade of age at entry, calendar year and decade of hire, and adjusted for race, Census region of residence, the healthy worker survivor effect, and years of work in each of the eight job groups. Nine lung cancer cases had cardiovascular disease as the underlying cause of death (four from IHD) and nine had respiratory disease as an underlying cause (four from COPD).

TABLE 4. PERCENT INCREASE AND 95% CONFIDENCE INTERVALS OF CAUSE-SPECIFIC MORTALITY ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE (4 μg/m³) OF $PM_{2.5}$ FROM THE NEAREST MONITOR IN 2000

Cause of Death	Whole Cohort	Excluding Long-Haul Drivers
All-cause	3.9 (1.0, 6.9)	5.9 (2.0, 9.9)
Lung cancer	2.1 (−5.0, 9.7)	6.6 (−2.8, 16.8)
Cardiovascular disease	2.1 (−2.9, 7.3)	2.0 (−4.7, 9.1)
IHD	0.7 (−5.4, 7.3)	−1.1 (−9.5, 8.1)
Respiratory disease	7.0 (−3.5, 18.7)	20.6 (7.1, 35.8)
COPD	−1.2 (−13.9, 13.5)	11.6 (−5.7, 32.1)

Values are given as percent increase and 95% CI unless otherwise noted. Percent increase and 95% CIs generated in Cox proportional hazard models with risk sets were generated using attained age in 1-year increments as the timeline, with separate baseline hazards based on decade of age at entry, calendar year and decade of hire, and adjusted for race, Census region of residence, the healthy worker survivor effect, and years of work in each of the eight job groups.

1.14; 95% CI, 1.03–1.25 excluding long-haul drivers) and respiratory mortality (HR = 1.07; 95% CI, 0.91–1.27 for the whole cohort; HR = 1.26; 95% CI, 1.01–1.56 excluding long-haul drivers) expressed for a 10-ppb increase in NO_2 are lower than those observed in most other studies. In a study of men living in Norway, HRs were 1.32 (95% CI, 1.12–1.57) and 1.16 (95% CI, 1.06–1.26) for respiratory and ischemic heart disease mortality, respectively, for each 10-ppb increase in NO_x, which includes NO_2 (37). An HR of 2.84 (95% CI, 1.62–4.99) for cardiopulmonary mortality was observed for each 10-ppb increase in NO_2 in a cohort of women in Germany (38). In the PAARC study, a 10-ppb increase in NO_2 was associated with an HR of 1.57 (95% CI, 1.08–2.29) for cardiopulmonary mortality (15). The HRs in the AHSMOG study for a 10-ppb increase in NO_2 were 1.01 (95% CI, 0.93–1.09) for cardiopulmonary mortality in men (9).

Fewer studies have examined the effects of long-term exposures to SO_2. Most long-term studies haven't reported elevated risks (9, 15, 18, 37) with all-cause mortality. Positive effects have been observed in a study in Great Britain (39), in a recent reanalysis of the American Cancer Society cohort (40), and in many short-term studies with cardiovascular deaths and/or hospital admissions (41).

One of the unique features of this study was our ability to model the mortality effects of exposures to multiple pollutants. In our multipollutant models, adverse effects were mainly seen with NO_2 and SO_2 exposures, but were quite attenuated for PM_{10} and $PM_{2.5}$. As in previous studies (18, 42), these findings suggest that traffic (the primary source of NO_2) is an important source of exposure. Sources of PM_{10} include traffic and other combustion processes that contribute to the fine fraction ($PM_{2.5}$). However, grinding, windblown dust, and agricultural activities are also contributors, especially in the coarse fraction ($PM_{10-2.5}$). SO_2, however, is primarily formed through electricity generation by power plants and fossil fuel combustion from heating oil and some mobile sources. Therefore, our multipollutant analysis suggests that traffic and other sources of fossil fuel combustion are important pollution sources that result in greater overall, lung cancer, cardiovascular, and respiratory disease mortality in this cohort.

Our study has several important limitations. First, we do not have information on other risk factors for mortality, such as cigarette smoking, body mass index (BMI), medication use, high cholesterol or blood pressure diagnoses, or existing comorbidities. In many previous studies of ambient air pollution these have not been shown to be important confounders of the air pollution–mortality association (1, 14); however, there is likely some residual confounding if they are also associated with pollution. The homogeneity of the cohort reduces the likelihood of potential confounding by socioeconomic status. In supplemental analyses (*see* Appendix in the online supplement) we used information on smoking and BMI from a questionnaire (43) sent to a sample of current employees and recent retirees from the same companies as the cohort members to examine the associations between these potential confounders and the 1985 through 2000 average pollution metrics used in this study. There was no association of BMI with the pollution measures. Current smoking, however, was associated with small increases in PM_{10} and NO_2. Given that current smoking is an important predictor of many of the causes of mortality in our study, there is a possibility that positive confounding may be occurring in our analyses. In an analysis of the potential bias in our observed estimates due to unmeasured positive confounding by current cigarette smoking (Table E3), we determined that the potential bias did not fully explain our single-pollutant results for NO_2 or PM_{10} with all-cause mortality.

A second limitation is that exposure is based on exposure model predictions at the last known home address of the cohort members. Using predicted values of pollution may lead to confidence intervals that are too small, because we did not incorporate the model errors into our CIs (44, 45). Additionally, although in surveys of this cohort the average time living in the current residence is 17 years, we cannot be certain that we have the correct home address for all participants in all years. This would add to the nondifferential misclassification of exposures and may help to explain some of the nonsignificant results we observe. Only 81% of the cohort was successfully geocoded to the street level. For those members of the cohort geocoded to a ZIP code centroid, the predicted air pollution levels would be a poorer proxy for the levels actually experienced outside the home. However, in sensitivity analyses conducted in just those individuals geocoded to the street level, the conclusions were not different than those from the whole cohort (Table E5).

Another weakness of this study is the differences in the temporality of our exposure measures. Our exposure metrics for PM_{10}, NO_2, and SO_2 cover the full period of cohort follow-up, 1985 through 2000, whereas our exposure to $PM_{2.5}$ is based solely on annual exposures from 2000. Unfortunately, the U.S. Environmental Protection Agency did not start wide-scale monitoring of $PM_{2.5}$ until the year 1999, providing only 1 year of data during the period of cohort follow-up. However, in this cohort we observed a high level of correlation (Spearman correlation coefficient, 0.63) between the annual values of PM_{10} and the overall long-term average 1985 through 2000, so this may introduce only minor exposure misclassification.

Finally, we used death certificates to determine our outcomes of interest. For many of the outcomes this may lead to some misclassification in the cause-specific analyses, because some outcomes may not always be appropriately coded. For example, death certificates have been shown to underestimate the true number of workers with severe COPD at death. In the Tucson Epidemiologic Study of Obstructive Airways Disease, 25% of deaths with clinically documented moderate to severe obstructive lung disease were identified using underlying cause of death only, whereas 81% had COPD noted as either underlying or contributing cause on the death certificate (46). Again, this would likely lead to nondifferential misclassification. However, although we control for region in our analyses, there is still a potential for differential misclassification if physicians in more heavily polluted areas within a region code causes of death differently than in less polluted areas.

Although other studies have controlled for occupational exposures (1, 15, 47, 48), our study is the first to assess the

effects of multiple air pollutants on mortality with fine control for occupation within workers from a single industry. Overall, our results are consistent with the large body of air pollution literature in general population studies that indicate that there are distinct effects of ambient air pollution exposures on health.

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