

ORIGINAL ARTICLE

## Long-Term Ozone Exposure and Mortality

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### ABSTRACT

#### BACKGROUND

Although many studies have linked elevations in tropospheric ozone to adverse health outcomes, the effect of long-term exposure to ozone on air pollution-related mortality remains uncertain. We examined the potential contribution of exposure to ozone to the risk of death from cardiopulmonary causes and specifically to death from respiratory causes.

#### METHODS

Data from the study cohort of the American Cancer Society Cancer Prevention Study II were correlated with air-pollution data from 96 metropolitan statistical areas in the United States. Data were analyzed from 448,850 subjects, with 118,777 deaths in an 18-year follow-up period. Data on daily maximum ozone concentrations were obtained from April 1 to September 30 for the years 1977 through 2000. Data on concentrations of fine particulate matter (particles that are  $\leq 2.5 \mu\text{m}$  in aerodynamic diameter [ $\text{PM}_{2.5}$ ]) were obtained for the years 1999 and 2000. Associations between ozone concentrations and the risk of death were evaluated with the use of standard and multilevel Cox regression models.

#### RESULTS

In single-pollutant models, increased concentrations of either  $\text{PM}_{2.5}$  or ozone were significantly associated with an increased risk of death from cardiopulmonary causes. In two-pollutant models,  $\text{PM}_{2.5}$  was associated with the risk of death from cardiovascular causes, whereas ozone was associated with the risk of death from respiratory causes. The estimated relative risk of death from respiratory causes that was associated with an increment in ozone concentration of 10 ppb was 1.040 (95% confidence interval, 1.010 to 1.067). The association of ozone with the risk of death from respiratory causes was insensitive to adjustment for confounders and to the type of statistical model used.

#### CONCLUSIONS

In this large study, we were not able to detect an effect of ozone on the risk of death from cardiovascular causes when the concentration of  $\text{PM}_{2.5}$  was taken into account. We did, however, demonstrate a significant increase in the risk of death from respiratory causes in association with an increase in ozone concentration.

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**S**TUDIES CONDUCTED OVER THE PAST 15 years have provided substantial evidence that long-term exposure to air pollution is a risk factor for cardiopulmonary disease and death.<sup>1-5</sup> Recent reviews of this literature suggest that fine particulate matter (particles that are  $\leq 2.5 \mu\text{m}$  in aerodynamic diameter [ $\text{PM}_{2.5}$ ]) has a primary role in these adverse health effects.<sup>6,7</sup> The particulate-matter component of air pollution includes complex mixtures of metals, black carbon, sulfates, nitrates, and other direct and indirect byproducts of incomplete combustion and high-temperature industrial processes.

Ozone is a single, well-defined pollutant, yet the effect of exposure to ozone on air pollution-related mortality remains inconclusive. Several studies have evaluated this issue, but they have been short-term studies,<sup>8-10</sup> have failed to show a statistically significant effect,<sup>4,3</sup> or have been based on limited mortality data.<sup>11</sup> Recent reviews by the Environmental Protection Agency (EPA)<sup>12</sup> and the National Research Council<sup>13</sup> have questioned the overall consistency of the available data correlating exposure to ozone and mortality. Similar conclusions about the evidence base for the long-term effects of ozone on mortality were drawn by a panel of experts in the United Kingdom.<sup>14</sup>

Nonetheless, previous studies have suggested that a measurable effect of ozone may exist, particularly with respect to the risk of death from cardiopulmonary causes. In one of the larger studies, ozone was significantly associated with death from cardiopulmonary causes<sup>15</sup> but not with death from ischemic heart disease. However, the estimated effect of ozone on the risk of death from cardiopulmonary causes in this study was attenuated when  $\text{PM}_{2.5}$  was added to the analysis in copollutant models. On the basis of suggested effects of ozone on the risk of death from cardiopulmonary causes (which includes death from respiratory causes) but an absence of evidence for effects of ozone on the risk of death from ischemic heart disease, we hypothesized that ozone might have a primary effect on the risk of death from respiratory causes.

## METHODS

### HEALTH, MORTALITY, AND CONFOUNDING DATA

Our study used data from the American Cancer Society Cancer Prevention Study II (CPS II) cohort.<sup>16</sup> The CPS II cohort consists of more than

1.2 million participants who were enrolled by American Cancer Society volunteers between September 1982 and February 1983 in all 50 states, the District of Columbia, and Puerto Rico. Enrollment was restricted to persons who were at least 30 years of age living in households with at least one person 45 years of age or older. After providing written informed consent, the participants completed a confidential questionnaire that included questions on demographic characteristics, smoking history, alcohol use, diet, and education.<sup>17</sup> Deaths were ascertained until August 1988 by personal inquiries of family members by the volunteers and thereafter by linkage with the National Death Index. Through 1995, death certificates were obtained and coded for cause of death. Beginning in 1996, codes for cause of death were provided by the National Death Index.<sup>18</sup>

The study population for our analysis included only those participants in CPS II who resided in U.S. metropolitan statistical areas within the 48 contiguous states or the District of Columbia (according to their address at the time of enrollment) and for whom data were available from at least one pollution monitor within their metropolitan area. The study was approved by the Ottawa Hospital Research Ethics Board, Canada.

Data on "ecologic" risk factors at the level of the metropolitan area representing social variables (educational level, percentage of homes with air conditioning, percentage of the population who were nonwhite), economic variables (household income, unemployment, income disparity), access to medical care (number of physicians and hospital beds per capita), and meteorologic variables were obtained from the 1980 U.S. Census and other secondary sources (see the Supplementary Appendix, available with the full text of this article at NEJM.org). These ecologic risk factors, as well as the individual risk factors collected in the CPS II questionnaire, were assessed as potential confounders of the effects of ozone.<sup>3,5,19,20</sup>

### ESTIMATES OF EXPOSURE TO AIR POLLUTION

Ozone data were obtained from 1977 (5 years before the identification of the CPS II cohort) through 2000 for all air-pollution monitors in the study metropolitan areas from the EPA's Aerometric Information Retrieval System. Ozone data at each monitoring site were collected on an hourly basis, and the daily maximum value for the site was determined. All available daily maximum values for the monitoring site were averaged over

each quarter year. The quarterly average values were reported for each monitor only when at least 75% of daily observations for that quarter were available.

The averages of the second (April through June) and third (July through September) quarters were calculated for each monitor if both quarterly averages were available. The period from April through September was selected because ozone concentrations tend to be elevated during the warmer seasons and because fewer data were available for the cooler seasons.

The average of the second and third quarterly averages for each year was then computed for all the monitors within each metropolitan area to form a single annual time series of air-pollution measurements for each metropolitan area for the period from 1977 to 2000. In addition, a summary measure of long-term exposure to ambient warm-season ozone was defined as the average of annual time-series measurements during the entire period from 1977 to 2000. Individual measures of exposure to ozone were then defined by assigning the average for the metropolitan area to each cohort member residing in that area.

Data on exposure to  $PM_{2.5}$  were also obtained from the Aerometric Information Retrieval System database for the 2-year period from 1999 to 2000 (data on  $PM_{2.5}$  were not available before 1999 for most metropolitan areas).<sup>5</sup> The average concentrations of  $PM_{2.5}$  were included in our analyses to distinguish the effect of particulates from that of ozone on outcomes.

#### STATISTICAL ANALYSIS

Standard and multilevel random-effects Cox proportional-hazard models were used to assess the risk of death in relation to exposures to pollution. The subjects were matched according to age (in years), sex, and race. A total of 20 variables with 44 terms were used to control for individual characteristics that might confound or modify the association between air pollution and death. These variables, which were considered to be of potential importance on the basis of previous studies, included individual risk factors for which data had been collected in the CPS II questionnaire. Seven ecologic covariates obtained from the 1980 U.S. Census (median household income, the proportion of persons living in households with an income below 125% of the poverty line, the percentage of persons over the age of 16 years who were unemployed, the percentage of adults

with less than a high-school [12th-grade] education, the percentage of homes with air conditioning, the Gini coefficient of income inequality [ranging from 0 to 1, with 0 indicating an equal distribution of income and 1 indicating that one person has all the income and everyone else has no income<sup>20</sup>], and the percentage of persons who were white) were also included. These variables were included at two levels: as the average for the metropolitan statistical area and as the difference between the average for the ZIP Code of residence and the average for the metropolitan statistical area. Additional sensitivity analyses were undertaken for ecologic variables that were available for only a subgroup of the 96 metropolitan statistical areas (see the Supplementary Appendix). Models were estimated for either ozone or  $PM_{2.5}$ . In addition, models with both  $PM_{2.5}$  and ozone were estimated.

In additional analyses, our basic Cox models were modified by incorporating an adjustment for community-level random effects, which allowed us to take into account residual variation in mortality among communities.<sup>21</sup> The baseline hazard function was modulated by a community-specific random variable representing the residual risk of death for subjects in that community after individual and ecologic risk factors had been controlled for (see the Supplementary Appendix).

A formal analysis was conducted to assess whether a threshold existed for the association between exposure to ozone and the risk of death (see the Supplementary Appendix). A standard threshold model was postulated in which there was no association between exposure to ozone and the risk of death below a specified threshold concentration and a linear association (on the logarithmic scale of the proportional-hazards model) above the threshold.

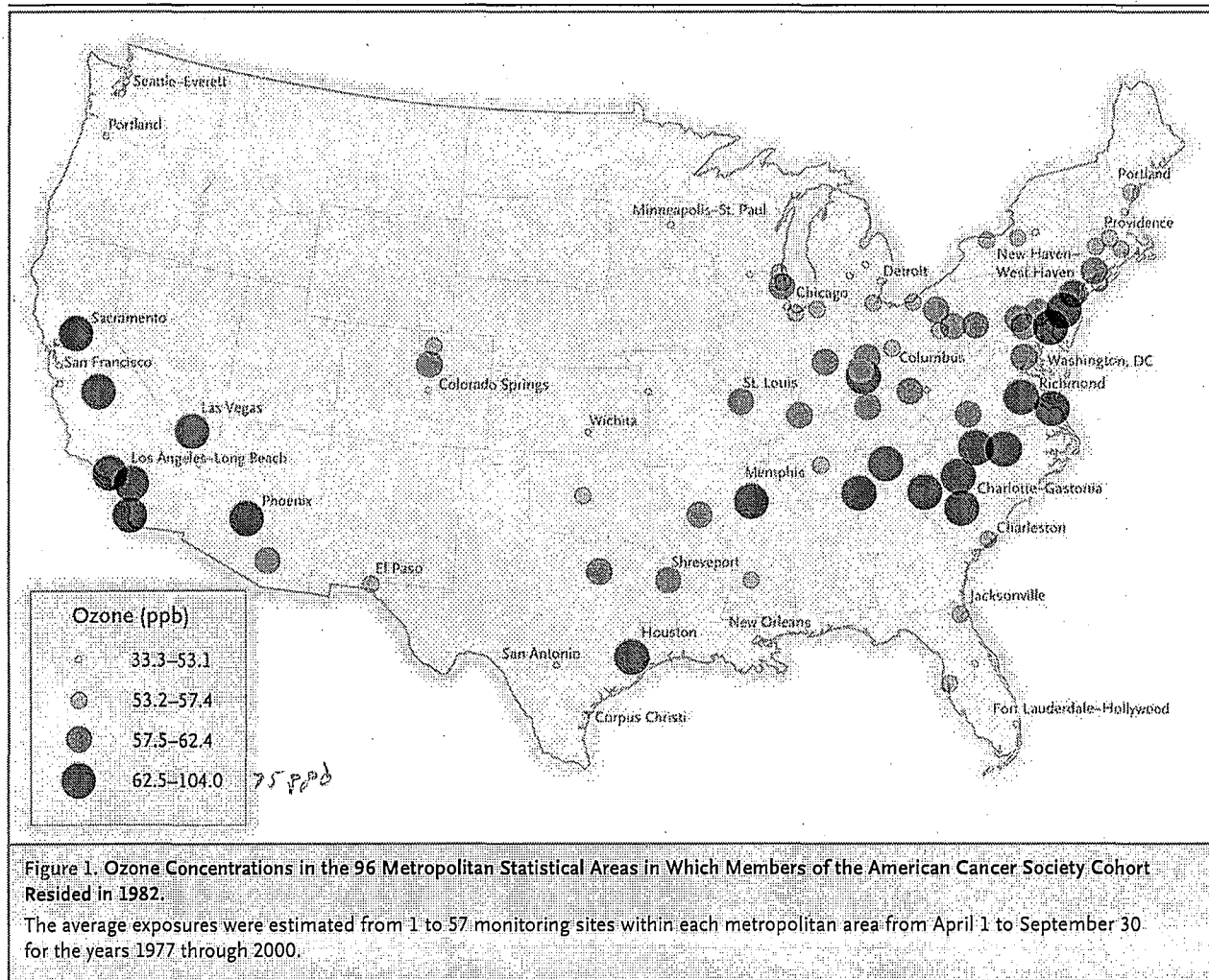
The question of whether specific time windows were associated with the health effects was investigated by subdividing the follow-up interval into four periods (1982 to 1988, 1989 to 1992, 1993 to 1996, and 1997 to 2000). Exposures were matched for each of these periods and also tested for a 10-year average on the basis of the 5-year follow-up period and the 5 years before the follow-up period (see the Supplementary Appendix).

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#### RESULTS

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The analytic cohort included 448,850 subjects residing in 96 metropolitan statistical areas (Fig. 1).



In 1980, the populations of these 96 areas ranged from 94,436 to 8,295,900. Data were available on the concentration of ambient ozone from all 96 areas and on the concentration of  $PM_{2.5}$  from 86 areas. The average number of air-pollution monitors per metropolitan area was 11 (range, 1 to 57), and more than 80% of the areas had 6 or more monitors.

The average ozone concentration for each metropolitan area during the interval from 1977 to 2000 ranged from 33.3 ppb to 104.0 ppb (Fig. 1). The highest regional concentrations were in Southern California and the lowest in the Pacific Northwest and parts of the Great Plains. Moderately elevated concentrations were present in many areas of the East, Midwest, South, and Southwest.

The baseline characteristics of the study population, overall and as a function of exposure to ozone, are presented in Table 1. The mean age

of the cohort was 56.6 years, 43.4% were men, 93.7% were white, 22.4% were current smokers, and 30.5% were former smokers. On the basis of estimates from 1980 Census data, 62.3% of homes had air conditioning at the time of initial data collection.

During the 18-year follow-up period (from initial CPS II data collection in 1982 through the end of follow-up in 2000), there were 118,777 deaths in the study cohort (Table 2). Of these, 58,775 were from cardiopulmonary causes, including 48,884 from cardiovascular causes (of which 27,642 were due to ischemic heart disease) and 9891 from respiratory causes.

In the single-pollutant models, exposure to ozone was not associated with the overall risk of death (relative risk, 1.001; 95% confidence interval [CI], 0.996 to 1.007) (Table 3). However, it was significantly correlated with an increase in the risk of death from cardiopulmonary causes. A

10-ppb increment in exposure to ozone elevated the relative risk of death from the following causes: cardiopulmonary causes (relative risk, 1.014; 95% CI, 1.007 to 1.022), cardiovascular causes (relative risk, 1.011; 95% CI, 1.003 to 1.023), ischemic heart disease (relative risk, 1.015; 95% CI, 1.003 to 1.026), and respiratory causes (relative risk, 1.029; 95% CI, 1.010 to 1.048).

Inclusion of the concentration of PM<sub>2.5</sub> measured in 1999 and 2000 as a copollutant (Table 3)

attenuated the association with exposure to ozone for all the end points except death from respiratory causes, for which a significant correlation persisted (relative risk, 1.040; 95% CI, 1.013 to 1.067). The concentrations of ozone and PM<sub>2.5</sub> were positively correlated ( $r=0.64$  at the subject level and  $r=0.56$  at the metropolitan-area level), resulting in unstable risk estimates for both pollutants. The concentration of PM<sub>2.5</sub> remained significantly associated with death from cardio-

Table 1. Baseline Characteristics of the Study Population in the Entire Cohort and According to Exposure to Ozone.\*

Variable	Entire Cohort (N=448,850)	Concentration of Ozone			
		33.3–53.1 ppb (N=126,206)	53.2–57.4 ppb (N=95,740)	57.5–62.4 ppb (N=106,545)	62.5–104.0 ppb (N=120,359)
No. of MSAs	96	24	24	24	24
No. of MSAs with data on PM <sub>2.5</sub>	86	21	20	23	22
Concentration of PM <sub>2.5</sub> (μg/m <sup>3</sup> )		11.9±2.5	13.1±2.9	14.7±2.1	15.4±3.2
<b>Individual risk factors</b>					
Age (yr)	56.6±10.5	56.7±10.4	56.4±10.7	56.3±10.4	56.9±10.5
Male sex (%)	43.4	43.5	43.1	43.5	43.2
White race (%)	93.7	94.3	95.1	93.9	91.8
<b>Education (%)</b>					
Less than high school	12.1	11.5	13.6	12.1	11.6
High school	30.6	30.2	33.6	32.1	27.4
Beyond high school	57.3	58.3	52.8	55.8	61.0
<b>Smoking status</b>					
<b>Current smokers</b>					
Percentage of subjects	22.4	22.0	23.5	22.2	21.9
No. of cigarettes/day	22.0±12.4	22.0±12.3	22.0±12.5	22.2±12.5	21.9±12.4
Duration of smoking (yr)	33.5±11.0	33.4±10.8	33.4±11.1	33.4±11.0	33.9±11.2
Started smoking <18 yr of age (%)	9.6	9.3	10.5	9.4	9.3
Started smoking ≥18 yr of age (%)	13.2	13.3	13.4	13.3	13.0
<b>Former smokers</b>					
Percentage of subjects	30.5	31.2	30.8	29.5	30.4
No. of cigarettes/day	21.6±14.7	21.6±14.6	22.2±15.1	21.6±14.6	21.3±14.6
Duration of smoking (yr)	22.2±12.6	22.1±12.5	22.6±12.6	22.0±12.5	22.4±12.7
Started smoking <18 yr of age (%)	11.9	11.8	12.7	11.5	11.8
Started smoking ≥18 yr of age (%)	18.5	19.3	17.9	17.9	18.5
Exposure to smoking (hr/day)	3.3±4.4	3.2±4.4	3.4±4.5	3.4±4.5	3.1±4.4
Pipe or cigar smoker only (%)	4.1	4.0	4.2	4.3	3.8
<b>Marital status (%)</b>					
Married	83.5	84.2	83.0	83.7	83.1
Single	3.6	3.4	4.0	3.8	3.2
Separated, divorced, or widowed	12.9	12.4	13.0	12.5	13.7

Variable	Entire Cohort (N=448,850)	Concentration of Ozone			
		33.3–53.1 ppb (N=126,206)	53.2–57.4 ppb (N=95,740)	57.5–62.4 ppb (N=106,545)	62.5–104.0 ppb (N=120,359)
Body-mass index†	25.1±4.1	25.1±4.1	25.3±4.2	25.1±4.1	24.8±4.0
Level of occupational exposure to particulate matter (%)‡					
0	50.7	50.9	50.0	50.8	51.0
1	13.3	13.4	13.1	13.3	13.3
2	11.4	11.5	10.8	11.4	11.9
3	4.6	4.7	4.8	4.6	4.5
4	6.1	6.2	6.2	6.1	6.0
5	4.2	4.2	4.3	4.1	4.1
6	1.1	1.0	9.5	1.4	8.4
Not able to ascertain	8.6	8.2	1.2	8.4	0.9
Self-reported exposure to dust or fumes (%)	19.5	19.5	19.8	19.7	19.1
Level of dietary-fat consumption (%)§					
0	14.5	13.7	14.9	14.1	15.3
1	15.9	15.8	16.5	15.6	15.9
2	17.4	17.6	17.7	17.2	17.1
3	21.2	21.8	21.1	21.3	20.8
4	30.9	31.1	29.8	31.9	30.9
Level of dietary-fiber consumption (%)¶					
0	16.6	16.0	17.5	16.7	16.6
1	19.9	19.4	20.5	20.1	19.7
2	18.8	18.6	19.2	19.1	18.5
3	22.8	23.0	22.4	22.8	22.7
4	21.9	23.0	20.4	21.3	22.5
Alcohol consumption (%)					
Beer					
Drinks beer	22.9	24.3	23.2	22.9	21.4
Does not drink beer	9.7	9.5	9.3	9.5	10.2
No data	67.4	66.2	67.5	67.6	68.4
Liquor					
Drinks liquor	28.0	30.4	27.9	25.4	27.9
Does not drink liquor	8.8	8.4	8.5	10.1	9.2
No data	63.2	61.2	63.6	65.5	62.9
Wine					
Drinks wine	23.5	25.4	22.5	21.1	24.3
Does not drink wine	8.9	8.7	8.8	9.3	9.1
No data	67.6	65.9	68.7	69.6	66.6

Variable	Entire Cohort (N=448,850)	Concentration of Ozone			
		33.3–53.1 ppb (N=126,206)	53.2–57.4 ppb (N=95,740)	57.5–62.4 ppb (N=106,545)	62.5–104.0 ppb (N=120,359)
<b>Ecologic risk factors  </b>					
Nonwhite race (%)	11.6±16.8	10.5±16.4	9.3±15.5	10.2±16.0	15.9±18.3
Home with air conditioning (%)	62.3±27.0	55.4±31.2	59.4±24.0	65.3±24.8	69.1±24.3
High-school education or greater (%)	51.7±8.2	53.5±7.9	52.4±7.5	50.8±7.2	50.0±9.5
Unemployment rate (%)	11.7±3.1	12.1±3.4	11.3±2.6	11.3±2.9	11.8±3.4
Gini coefficient of income inequality**	0.37±0.04	0.37±0.05	0.37±0.04	0.37±0.04	0.38±0.04
Proportion of population with income <125% of poverty line	0.12±0.08	0.11±0.08	0.12±0.08	0.11±0.07	0.13±0.09
Annual household income (thousands of dollars)††	20.7±6.6	21.9±7.1	19.8±6.0	21.2±6.7	19.7±6.3

- \* MSA denotes metropolitan statistical area, and PM<sub>2.5</sub> fine particulate matter consisting of particles that are 2.5 μm or less in aerodynamic diameter. Plus-minus values are means ±SD. Because of rounding, percentages may not total 100. All baseline characteristics included in the survival model are listed (age, sex, and race were included as stratification factors). The model also includes squared terms for the number of cigarettes smoked per day and the number of years of smoking for both current and former smokers and a squared term for body-mass index.
- † The body-mass index is the weight in kilograms divided by the square of the height in meters.
- ‡ Occupational exposure to particulate matter increases with increasing index number. The index was calculated by assigning a relative level of exposure to PM<sub>2.5</sub> associated with a cohort member's job and industry. These assignments were performed by industrial hygienists on the basis of their knowledge of typical exposure patterns for each occupation and specific job.<sup>22</sup>
- § Dietary-fat consumption increases with increasing index number. Dietary information from cohort members was used to define the level of fat consumption according to five ordered categories.<sup>20</sup>
- ¶ Dietary-fiber consumption increases with increasing index number. Dietary information from cohort members was used to define the level of fiber consumption according to five ordered categories.<sup>23</sup>
- || For the ecologic variables, the model included terms for influences at the level of the average for the metropolitan statistical area and at the level of the difference between the value for the ZIP Code of residence and the average for the metropolitan statistical area to represent between- and within-metropolitan area confounding influence. Some values for ecologic variables and individual variables differ, although they appear to measure the same risk factor. For example, for the entire cohort, the percentage of whites as listed under individual variables is 93.7, whereas the percentage of nonwhites as listed under ecologic variables is 11.6±16.8. This apparent contradiction is explained by the fact that the former is an exact figure based on the individual reports of the study participants in the CPS II questionnaire, whereas the latter is a mean (±SD) for the population based on Census estimates for each metropolitan statistical area.
- \*\* The Gini coefficient is a statistical dispersion measure used to calculate income inequality. The coefficient ranges from 0 to 1, with 0 indicating an equal distribution of income and 1 indicating that one person has all the income and everyone else has no income.<sup>20</sup> A coefficient of 0.37 indicates that on average there is a measurable inequality in the distribution of income among the different income groups within the MSAs.
- †† Average household incomes for the cohort and for each quartile of ozone concentration were calculated from the median household income for the metropolitan statistical area.

pulmonary causes, cardiovascular causes, and ischemic heart disease when ozone was included in the model. The association of ozone concentrations with death from respiratory causes remained significant after adjustment for PM<sub>2.5</sub>.

Risk estimates for ozone-related death from respiratory causes were insensitive to the use of a random-effects survival model allowing for spatial clustering within the metropolitan area and state of residence (Table 1S in the Supplementary Appendix). The association between increased ozone concentrations and increased risk

of death from respiratory causes was also insensitive to adjustment for several ecologic variables considered individually (Table 2S in the Supplementary Appendix).

Subgroup analyses showed that environmental temperature and region of the country, but not sex, age at enrollment, body-mass index, education, or concentration of PM<sub>2.5</sub>, significantly modified the effects of ozone on the risk of death from respiratory causes (Table 4).

Figure 2 illustrates the shape of the relation between exposure to ozone and death from re-

Table 2. Number of Deaths in the Entire Cohort and According to Exposure to Ozone.

Cause of Death	Entire Cohort (N=448,850)	Concentration of Ozone			
		33.3–53.1 ppb (N=126,206)	53.2–57.4 ppb (N=95,740)	57.5–62.4 ppb (N=106,545)	62.5–104.0 ppb (N=120,359)
<i>number of deaths</i>					
Any cause	118,777	32,957	25,642	27,782	32,396
Cardiopulmonary	58,775	16,328	12,621	13,544	16,282
Cardiovascular	48,884	13,605	10,657	11,280	13,342
Ischemic heart disease	27,642	7,714	6,384	6,276	7,268
Respiratory	9,891	2,723	1,964	2,264	2,940

Table 3. Relative Risk of Death Attributable to a 10-ppb Change in the Ambient Ozone Concentration.\*

Cause of Death	Single-Pollutant Model†			Two-Pollutant Model‡	
	Ozone (96 MSAs)	Ozone (86 MSAs)	PM <sub>2.5</sub> (86 MSAs)	Ozone (86 MSAs)	PM <sub>2.5</sub> (86 MSAs)
<i>relative risk (95% CI)</i>					
Any cause	1.001 (0.996–1.007)	1.001 (0.996–1.007)	1.048 (1.024–1.071)	0.989 (0.981–0.996)	1.080 (1.048–1.113)
Cardiopulmonary	1.014 (1.007–1.022)	1.016 (1.008–1.024)	1.129 (1.094–1.071)	0.992 (0.982–1.003)	1.153 (1.104–1.204)
Respiratory	1.029 (1.010–1.048)	1.027 (1.007–1.046)	1.031 (0.955–1.113)	1.040 (1.013–1.067)	0.927 (0.836–1.029)
Cardiovascular	1.011 (1.003–1.023)	1.014 (1.005–1.023)	1.150 (1.111–1.191)	0.983 (0.971–0.994)	1.206 (1.150–1.264)
Ischemic heart disease	1.015 (1.003–1.026)	1.017 (1.006–1.029)	1.211 (1.156–1.268)	0.973 (0.958–0.988)	1.306 (1.226–1.390)

\* MSA denotes metropolitan statistical area, and PM<sub>2.5</sub> fine particulate matter consisting of particles that are 2.5  $\mu\text{m}$  or less in aerodynamic diameter. Ozone concentrations were measured from April to September during the years from 1977 to 2000, with follow-up from 1982 to 2000; changes in the concentration of PM<sub>2.5</sub> of 10  $\mu\text{g}$  per cubic meter were recorded for members of the cohort in 1999 and 2000. These models are adjusted for all the individual and ecologic risk factors listed in Table 1. For the ecologic variables, the model included terms for influences at the level of the average for the metropolitan statistical area and at the level of the difference between the value for the ZIP Code of residence and the average for the metropolitan statistical area to represent between- and within-metropolitan area confounding influence. The risk of death was stratified according to age (in years), sex, and race.

† The single-pollutant models were based on 96 metropolitan statistical areas for which information on ozone was available and 86 metropolitan statistical areas for which information on both ozone and fine particulate matter was available.

‡ The two-pollutant models were based on 86 metropolitan statistical areas for which information on both ozone and fine particulate matter was available.

spiratory causes. There was limited evidence that a threshold model specification improved model fit as compared with a nonthreshold linear model ( $P=0.06$ ) (Table 3S in the Supplementary Appendix).

Because air-pollution data from 1977 to 2000 were averaged, exposure values for persons who died during this period are based partly on data that were obtained after death had occurred. Further investigation by dividing this interval into specific time windows of exposure revealed no significant difference between the effects of earlier and later time windows within the period of follow-up. Allowing for a 10-year period of exposure to ozone (5 years of follow-up and 5 years

before the follow-up period) did not appreciably alter the risk estimates (Table 4S in the Supplementary Appendix). Thus, when exposure values were matched more closely to the follow-up period and when exposure values were based on data obtained before the deaths, there was little change in the results.

## DISCUSSION

Our principal finding is that ozone and PM<sub>2.5</sub> contributed independently to increased annual mortality rates in this large, U.S. cohort study in analyses that controlled for many individual and ecologic risk factors. In two-pollutant models that



included ozone and PM<sub>2.5</sub>, ozone was significantly associated only with death from respiratory causes.

For every 10-ppb increase in exposure to ozone, we observed an increase in the risk of death from respiratory causes of about 2.9% in single-pollutant models and 4% in two-pollutant models. Although this increase may appear moderate, the risk of dying from a respiratory cause is more than three times as great in the metropolitan areas with the highest ozone concentrations as in those with the lowest ozone concentrations. The effects of ozone on the risk of death from respiratory causes were insensitive to adjustment for individual, neighborhood, and metropolitan-area confounders or to differences in multilevel-model specifications.

There is biologic plausibility for a respiratory effect of ozone. In laboratory studies, ozone can increase airway inflammation<sup>24</sup> and can worsen pulmonary function and gas exchange.<sup>25</sup> In addition, exposure to elevated concentrations of tropospheric ozone has been associated with numerous adverse health effects, including the induction<sup>26</sup> and exacerbation<sup>27,28</sup> of asthma, pulmonary dysfunction,<sup>29,30</sup> and hospitalization for respiratory causes.<sup>31</sup>

Despite these observations, previous studies linking long-term exposure to ozone with death have been inconclusive. One cohort study conducted in the Midwest and eastern United States reported an inverse but nonsignificant association between ozone concentrations and mortality.<sup>1</sup> Subsequent reanalyses of this study replicated these findings but also suggested a positive association with exposure to ozone during warm seasons.<sup>3</sup> A study of approximately 6000 non-smoking Seventh-Day Adventists living in Southern California showed elevated risks among men after long-term exposure to ozone,<sup>11</sup> but this finding was based on limited mortality data.

Previous studies using the CPS II cohort have also produced mixed results for ozone. An earlier examination based on a large sample of more than 500,000 people from 117 metropolitan areas and 8 years of follow-up indicated nonsignificant results for the relation between ozone and death from any cause and a significant inverse association between ozone and death from lung cancer. A positive association between death from cardiopulmonary causes and summertime exposure to ozone was observed in single-pollutant

Table 4. Relative Risk of Death from Respiratory Causes Attributable to a 10-ppb Change in the Ambient Ozone Concentration, Stratified According to Selected Risk Factors.\*

Stratification Variable	% of Subjects in Stratum	Relative Risk (95% CI)	P Value of Effect Modification
Sex			0.11
Male	43	1.01 (0.99–1.04)	
Female	57	1.04 (1.03–1.07)	
Age at enrollment (yr)			0.74
<50	26	1.00 (0.90–1.11)	
50–65	54	1.03 (1.01–1.06)	
>65	20	1.02 (1.00–1.05)	
Education			0.48
High school or less	43	1.02 (1.00–1.05)	
Beyond high school	57	1.03 (1.01–1.06)	
Body-mass index†			0.96
<25.0	53	1.03 (1.01–1.06)	
25.0–29.9	36	1.03 (0.99–1.06)	
≥30.0	11	1.03 (0.96–1.10)	
PM <sub>2.5</sub> (μg/m <sup>3</sup> )‡			0.38
<14.3	44	1.05 (1.01–1.09)	
>14.3	56	1.03 (1.00–1.05)	
Region§			0.05
Northeast	24.8	0.99 (0.92–1.07)	
Industrial Midwest	29.7	1.00 (0.91–1.09)	
Southeast	21.0	1.12 (1.05–1.19)	
Upper Midwest	5.2	1.14 (0.68–1.90)	
Northwest	7.7	1.06 (1.00–1.13)	
Southwest	3.9	1.21 (1.04–1.40)	
Southern California	7.8	1.01 (0.96–1.07)	
External temperature (°C)‡¶			0.01
<23.3	24	0.96 (0.90–1.01)	
>23.3 to <25.4	29	0.97 (0.87–1.08)	
>25.4 to <28.7	22	1.04 (0.92–1.16)	
>28.7	25	1.05 (1.03–1.08)	

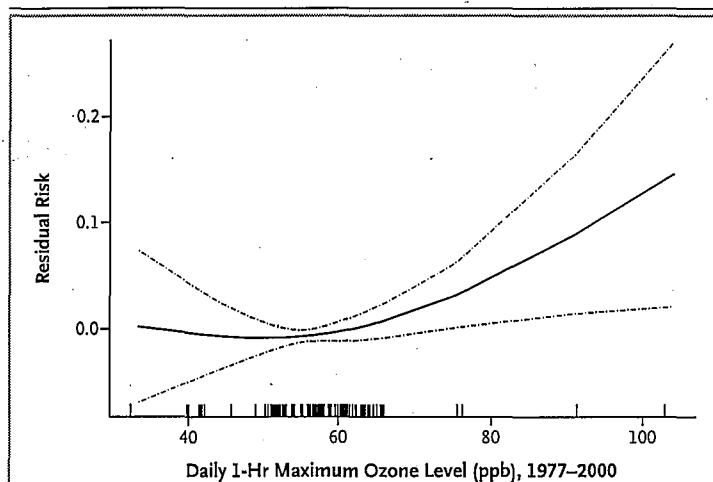
\* PM<sub>2.5</sub> denotes fine particulate matter consisting of particles that are 2.5 μm or less in aerodynamic diameter. Ozone exposures for the cohort were measured from April to September during the years from 1977 to 2000, with follow-up from 1982 to 2000, with adjustment for individual risk factors, and with baseline hazard function stratified according to age (single-year groupings), sex, and race. These analyses are based on the single-pollutant model for ozone shown in Table 3. Because of rounding, percentages may not total 100.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Stratum cutoff is based on the median of the distribution at the metropolitan-area level, not at the subject level.

§ Definitions of regions are those used by the Environmental Protection Agency.<sup>3</sup>

¶ External temperature is calculated as the average daily maximum temperature recorded between April and September from 1977 to 2000.



**Figure 2. Exposure-Response Curve for the Relation between Exposure to Ozone and the Risk of Death from Respiratory Causes.**

The curve is based on a natural spline with 2 df estimated from the residual relative risk of death within a metropolitan statistical area (MSA) according to a random-effects survival model. The dashed lines indicate the 95% confidence interval of fit, and the hash marks indicate the ozone levels of each of the 96 MSAs.

models, but the association with ozone was non-significant in two-pollutant models.<sup>3</sup> Further analyses based on 16 years of follow-up in 134 cities produced similarly elevated but non-significant associations that were suggestive of effects of summertime (July to September) exposure to ozone on death from cardiopulmonary causes.<sup>5</sup>

The increase in deaths from respiratory causes with increasing exposure to ozone may represent a combination of short-term effects of ozone on susceptible subjects who have influenza or pneumonia and long-term effects on the respiratory system caused by airway inflammation,<sup>24</sup> with subsequent loss of lung function in childhood,<sup>32</sup> young adulthood,<sup>33,34</sup> and possibly later life.<sup>35</sup> If exposure to ozone accelerates the natural loss of adult lung function with age, those exposed to higher concentrations of ozone would be at greater risk of dying from a respiratory-related syndrome.

In our two-pollutant models, the adjusted estimates of relative risk for the effect of ozone on the risk of death from cardiovascular causes were significantly less than 1.0, seemingly suggesting a protective effect. Such a beneficial influence of ozone, however, is unlikely from a biologic standpoint. The association of ozone with cardiovascular end points was sensitive to adjustment for exposure to  $PM_{2.5}$ , making it difficult to deter-

mine precisely the independent contributions of these copollutants to the risk of death. There was notable collinearity between the concentrations of ozone and  $PM_{2.5}$ .

Furthermore, measurement at central monitors probably represents population exposure to  $PM_{2.5}$  more accurately than it represents exposure to ozone. Ozone concentration tends to vary spatially within cities more than does  $PM_{2.5}$  concentration, because of scavenging of ozone by nitrogen oxide near roadways.<sup>36</sup> In the presence of a high density of local traffic, the measurement error is probably higher for exposure to ozone than for exposure to  $PM_{2.5}$ . The effects of ozone could therefore be confounded by the presence of  $PM_{2.5}$  because of collinearity between the measurements of the two pollutants and the higher precision of measurements of  $PM_{2.5}$ .<sup>37</sup>

Measurements of  $PM_{2.5}$  were available only for the end of the study follow-up period (1999 and 2000). Widespread collection of these data began only after the EPA adopted regulatory limits on such particulates in 1997. Since particulate air pollution has probably decreased in most metropolitan areas during the follow-up interval of our study, it is likely that we have underestimated the effect of  $PM_{2.5}$  in our analysis.

A limitation of our study is that we were not able to account for the geographic mobility of the population during the follow-up period. We had information on home addresses for the CPS II cohort only at the time of initial enrollment in 1982 and 1983. Census data indicate that during the interval between 1982 and 2000, approximately 2 to 3% of the population moved from one state to another annually (with the highest rates in an age group younger than that of our study population).<sup>38</sup> However, any bias due to a failure to account for geographic mobility is likely to have attenuated, rather than exaggerated, the effects of ozone on mortality.

In summary, we investigated the effect of tropospheric ozone on the risk of death from any cause and cause-specific death in a large cohort, using data from 96 metropolitan statistical areas across the United States and controlling for the effect of particulate air pollutants. We were unable to detect a significant effect of exposure to ozone on the risk of death from cardiovascular causes when particulates were taken into account, but we did demonstrate a significant effect of exposure to ozone on the risk of death from respiratory causes.

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