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Authors
Turner, Michelle C
Jerrett, Michael
Pope, C Arden
et al.

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ORIGINAL ARTICLE

Long-Term Ozone Exposure and Mortality in a Large Prospective Study

Michelle C. Turner[1,2,3,4], Michael Jerrett[5], C. Arden Pope III[6], Daniel Krewski[1,7], Susan M. Gapstur[8], W. Ryan Diver[8], Bernardo S. Beckerman[5], Julian D. Marshall[9], Jason Su[5], Daniel L. Crouse[10], and Richard T. Burnett[11]

[1]McLaughlin Centre for Population Health Risk Assessment and [7]School of Epidemiology, Public Health and Disease Prevention, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [2]Centre for Research in Environmental Epidemiology, Barcelona, Spain; [3]Universitat Pompeu Fabra, Barcelona, Spain; [4]CIBER Epidemiología y Salud Pública, Madrid, Spain; [5]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California; [6]Department of Economics, Brigham Young University, Provo, Utah; [8]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia; [9]Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington; [10]Department of Sociology, University of New Brunswick, Fredericton, New Brunswick, Canada; and [11]Population Studies Division, Health Canada, Ottawa, Ontario, Canada

Abstract

Rationale: Tropospheric ozone (O_3) is potentially associated with cardiovascular disease risk and premature death. Results from long-term epidemiological studies on O_3 are scarce and inconclusive.

Objectives: In this study, we examined associations between chronic ambient O_3 exposure and all-cause and cause-specific mortality in a large cohort of U.S. adults.

Methods: Cancer Prevention Study II participants were enrolled in 1982. A total of 669,046 participants were analyzed, among whom 237,201 deaths occurred through 2004. We obtained estimates of O_3 concentrations at the participant's residence from a hierarchical Bayesian space–time model. Estimates of fine particulate matter (particulate matter with an aerodynamic diameter of up to 2.5 μm [$PM_{2.5}$]) and NO_2 concentrations were obtained from land use regression. Cox proportional hazards regression models were used to examine mortality associations adjusted for individual- and ecological-level covariates.

Measurements and Main Results: In single-pollutant models, we observed significant positive associations between O_3, $PM_{2.5}$, and NO_2 concentrations and all-cause and cause-specific mortality. In two-pollutant models adjusted for $PM_{2.5}$, significant positive associations remained between O_3 and all-cause (hazard ratio [HR] per 10 ppb, 1.02; 95% confidence interval [CI], 1.01–1.04), circulatory (HR, 1.03; 95% CI, 1.01–1.05), and respiratory mortality (HR, 1.12; 95% CI, 1.08–1.16) that were unchanged with further adjustment for NO_2. We also observed positive mortality associations with both $PM_{2.5}$ (both near source and regional) and NO_2 in multipollutant models.

Conclusions: Findings derived from this large-scale prospective study suggest that long-term ambient O_3 contributes to risk of respiratory and circulatory mortality. Substantial health and environmental benefits may be achieved by implementing further measures aimed at controlling O_3 concentrations.

Keywords: air pollution; mortality; ozone; prospective study

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Correspondence and requests for reprints should be addressed to Michelle C. Turner, Ph.D., McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, 850 Peter Morand Crescent, Room 118, Ottawa, ON, K1G 3Z7 Canada. E-mail: mturner@uottawa.ca

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At a Glance Commentary

Scientific Knowledge on the Subject: Tropospheric ozone (O_3) might be associated with cardiovascular disease risk and premature death. Results from long-term epidemiological studies on O_3 are scarce and inconclusive.

What This Study Adds to the Field: In this study, we examined the association between chronic ambient O_3 exposure and all-cause and cause-specific mortality in an extended analysis of the Cancer Prevention Study II, using new national-level estimates of ambient O_3, fine particulate matter (particulate matter with an aerodynamic diameter of up to 2.5 μm [$PM_{2.5}$]), and NO_2 concentrations. Results from this large-scale prospective study suggest that long-term ambient O_3 contributes to risk of respiratory and circulatory mortality. There were also positive mortality associations observed with $PM_{2.5}$ (both near source and regional) and NO_2 in multipollutant models.

Epidemiological studies investigating short-term exposures (ranging from hours to a few days) to ambient ozone (O_3) showed positive associations with mortality, exacerbation of respiratory illness, and increased hospital admissions (1). There is suggestive evidence that short-term O_3 is associated with adverse cardiovascular effects (2–4). Epidemiological studies of long-term O_3 exposure are scarce, and the causal nature of associations uncertain (4, 5).

A prior study based on 18 years of follow-up of 448,850 participants, including 118,777 deaths, in the American Cancer Society Cancer Prevention Study-II (CPS-II) showed significant positive associations between long-term (1977–2000) O_3 from available urban government monitors and both respiratory and cardiovascular mortality in single-pollutant models (6). In models adjusted for fine particulate matter (particulate matter with an aerodynamic diameter of up to 2.5 μm [$PM_{2.5}$]), only the association with respiratory mortality remained (hazard ratio [HR] per 10 ppb, 1.04; 95% confidence interval [CI], 1.01–1.07). There was a moderately high correlation between the two pollutants ($r = 0.64$).

The California Teachers Study showed positive associations between year-round O_3 concentrations and mortality due to respiratory causes (HR per interquartile range [11.02 ppb], 1.07; 95% CI, 0.97–1.19) and ischemic heart disease (IHD) (HR per 11.02 ppb, 1.06; 95% CI, 0.99–1.14) (7). In two-pollutant models, the association with IHD was confounded by $PM_{2.5}$. No positive mortality associations were observed in a U.K. patient cohort (8).

There was a positive association between long-term (2001–2008) county-level O_3 concentrations and chronic lower respiratory disease mortality in a U.S. ecological study (9). Positive associations were observed with cardiometabolic but not respiratory mortality in multipollutant models adjusted for $PM_{2.5}$ and NO_2 in the Canadian CanCHEC study (10). There were no data on potential individual-level behavioral confounding factors, including cigarette smoking, in either study.

The worldwide mean 3-month hourly maximum O_3 concentration in 2005 was 54 ppb (11), and it is increasing in densely populated areas of South Asia and East Asia due largely to growing O_3 precursor emissions (9). O_3 contributes to increased radiative forcing and climate change (12, 13).

On the basis of findings from the previous CPS-II study, more than 217,000 deaths caused by chronic obstructive pulmonary disease (COPD) worldwide were attributed to long-term O_3 exposure in 2013 (6, 14). Further evidence for long-term O_3 effects would markedly increase the attributable disease burden. Recent advancements in O_3 exposure assessment integrating air quality data from government monitors with estimates from photochemical models across the United States afford a unique opportunity to further examine O_3 effects in larger national-level studies.

We assessed associations between long-term ambient O_3 exposure and all-cause and cause-specific mortality in an extended analysis of the CPS-II study using new national-level estimates of ambient O_3, $PM_{2.5}$, and NO_2 concentrations. The increased number of included participants and extended follow-up period (from 1982 to 2004) resulted in nearly double the number of deaths investigated previously (6). Research designed to disentangle the independent effects of such ambient air pollutants is a key research priority (5). Some results were previously reported in the form of an abstract (15).

Methods

Study Population

CPS-II is a prospective study of nearly 1.2 million participants enrolled in all 50 U.S. states, the District of Columbia, and Puerto Rico by 77,000 volunteers in 1982. Participants were largely friends and family members of volunteers, at least 30 years of age, and had a family member aged 45 years or older. A four-page, self-administered enrollment questionnaire was used to capture data on demographic, lifestyle, medical, and other factors (16). Ethical approval for CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee.

In 1984, 1986, and 1988, vital status was ascertained by study volunteers and confirmed by corresponding death certificates. After 1989, computerized linkage to the National Death Index was used (17). Through 2004, 743,543 (62.8%) participants were alive, 438,123 (37.0%) had died, and 2,921 (0.2%) were lost to follow-up or had follow-up terminated in September 1988 due to insufficient record linkage information. Deaths were classified by underlying cause using the *International Classification of Diseases*, 9th and 10th revisions (18, 19). More than 99% of known deaths were assigned a cause.

A total of 669,046 participants were analyzed (see Figure E1 in the online supplement). The majority of exclusions were due to missing or invalid residence (n = 385,422) (20) or covariate (n = 130,119) data (Table E1). The study cohort included 237,201 deaths in 12,662,562 person-years of follow-up.

Estimates of Ambient Air Pollution Concentrations

Estimated O_3 concentrations were obtained from the hierarchical Bayesian space–time model (HBM) of the U.S. Environmental Protection Agency and Centers for Disease Control and Prevention Environmental Public Health Tracking Network (Figure 1) (21). The HBM combines ambient measurement data from the National Air Monitoring Stations/State and Local Air Monitoring

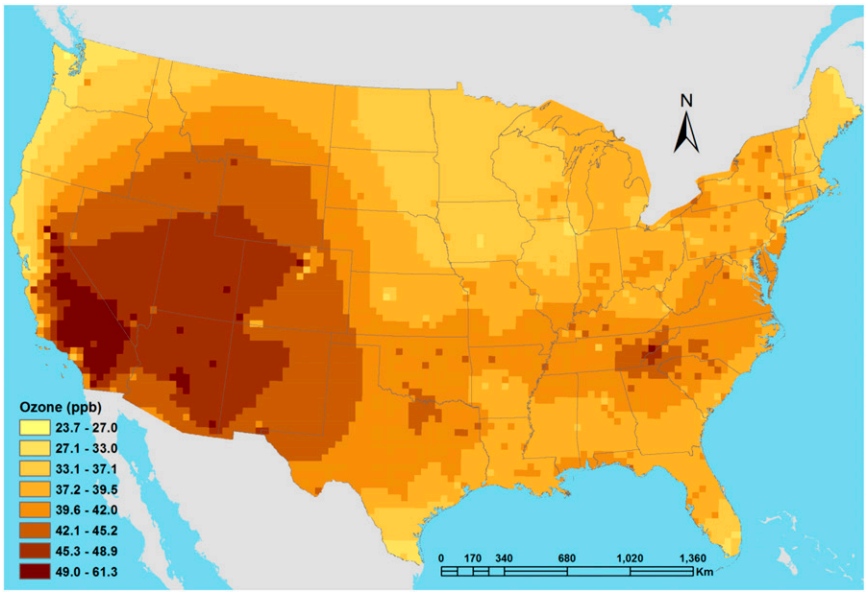

Figure 1. Distribution of mean annual daily 8-hour maximum tropospheric ozone concentrations based on a hierarchical Bayesian space–time modeling system, United States, 2002–2004.

Stations with gridded estimates from the Models-3/Community Multiscale Air Quality (CMAQ) photochemical model to obtain daily 8-hour maximum O_3 concentrations in 36 × 36-km grids for the entire United States for the years 2001–2006. To coincide with our cohort follow-up, we examined both mean annual and summertime (April–September) estimates for the years 2002–2004; year 2001 estimates were omitted due to differences in model input meteorological parameters. Mean O_3 (2002–2004) values were assigned to the geocoded participant residence at enrollment and used as an indicator of long-term O_3 exposure.

We also examined O_3 concentrations derived from a Bayesian space–time downscaling fusion model (henceforth termed "Downscaler O_3") (22). Daily 8-hour maximum O_3 concentrations at the census tract centroid were estimated on the basis of National Air Monitoring Stations/State and Local Air Monitoring Stations and CMAQ model data in 12 × 12-km grids for the years 2001–2008. Downscaler O_3 estimates consider all monitors, as opposed to the most prevalent monitor, where there are multiple monitors per site. We assigned mean monthly daily estimates to 545,302 CPS-II participants, as data were available only for the eastern United States for 2002–2004. Model performance using the predictive mean absolute error showed that Downscaler O_3 outperformed ordinary kriging or CMAQ models alone, with a predictive mean absolute error of 5 based on the square root of daily O_3 values (23). Correlations with holdout locations for daily predictions ranged from 0.61 to 0.86 at three sites in the eastern United States.

Estimated $PM_{2.5}$ concentrations were obtained using a national-level hybrid land use regression (LUR) and Bayesian maximum entropy (BME) interpolation model (Figure E2) (24). Monthly $PM_{2.5}$ monitoring data were collected from 1,464 sites from 1999 through 2008, with 10% reserved for cross-validation. The base LUR model that predicted $PM_{2.5}$ concentrations included traffic within 1 km and green space within 100 m^3. Residual spatiotemporal variation in $PM_{2.5}$ concentrations was interpolated with a BME interpolation model. The two estimates were then combined. The cross-validation R^2 was approximately 0.79. Mean $PM_{2.5}$ (1999–2004) concentrations were used here. To address potential confounding of O_3–mortality associations by $PM_{2.5}$, estimates of $PM_{2.5}$ were decomposed *a priori* into near-source (LUR) and regional (LURBME-LUR) components to more accurately account for differences in correlation structure with O_3 (Tables E2 and E3). Results for the overall LURBME $PM_{2.5}$ are presented in Table E4 and elsewhere for selected mortality endpoints (20, 25). HBM $PM_{2.5}$ data were also examined (above) (26).

NO_2 concentrations were based on a national LUR model using regulatory monitoring (hourly data from 423 monitors) and satellite-based measurements (approximately 4 million measurements, aggregated into annual average values at 81,743 locations [approximately 10 × 10-km grids]) at the census block group level for the year 2006 (27). Additional independent variables included population; satellite-based classification of land uses, impervious surfaces, tree coverage, and distance to roadways (model $R^2 = 0.78$).

Statistical Analysis

We used Cox proportional hazards regression models to examine associations between mean O_3 (2002–2004), $PM_{2.5}$ (1999–2004), and NO_2 (2006) concentrations and all-cause and cause-specific mortality. Models were stratified by 1-year age categories, sex, and race (white, African American, or other). Follow-up time in days since enrollment was used as the time axis. The survival times of those alive at the end of follow-up were censored.

Models were adjusted *a priori* for the following covariates assessed at enrollment as in previous work (6, 20, 25, 28–30): education; marital status; body mass index (BMI) and BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; started smoking at younger than 18 years of age; passive smoking (hours); vegetable, fruit, fiber, and fat intake; beer, wine, and liquor consumption; occupational exposures; an occupational dirtiness index; and six sociodemographic ecological covariates at both the postal code and postal code minus county-level mean derived from the 1990 U.S. Census (median household income and percentage of African American residents, Hispanic residents, adults with postsecondary education, unemployment, and poverty) (Table E5).

We examined potential confounding by elevation, metropolitan statistical area size, annual average daily maximum air temperature, and 1980 percentage of air conditioning (and mean county-level residential radon concentrations for respiratory and lung cancer mortality only)

(6, 29, 31–34). We also used a proportional hazards model with a random effect for county of residence at enrollment. An interaction term between O_3 and follow-up time was used to assess the proportional hazards assumption.

Threshold models, defined by setting the O_3 concentration to 0 below the threshold and the concentration minus the threshold value otherwise, were examined at 1-ppb increments across the entire exposure range. Potential modification of O_3 associations by age at enrollment, sex, education, BMI, cigarette-smoking status, passive smoking, prior cardiovascular disease (high blood pressure, heart disease, stroke, or diabetes) or respiratory disease (asthma, emphysema, or chronic bronchitis) at enrollment, and temperature was assessed using multiplicative interaction terms. Two-sided *P* values based on the likelihood ratio statistic were calculated to assess their significance.

For analyses, we used SAS version 9.2 software (SAS Institute, Cary, NC) and specialized software developed for the random effects survival model (30, 35). Ethical approval for our present analysis was obtained from the Ottawa Hospital Research Ethics Board.

Results

Participants were largely between the ages of 40 and 69 years, female, and had more than a high school education (Table 1). There was little variation in O_3 concentrations by participant characteristics.

Year-round O_3 concentrations ranged from 26.7 to 59.3 ppb, with a mean (SD) of 38.2 (4.0) ppb (Table E2). For $PM_{2.5}$ and NO_2, average concentrations ranged from 1.4 to 27.9 $\mu g/m^3$ (mean [SD], 12.6 [2.9] $\mu g/m^3$) and 1.0 to 37.6 ppb (mean [SD], 11.6 [5.1] ppb), respectively. Correlations between year-round O_3 and both

Table 1. Distribution of Selected Participant Characteristics at Enrollment (1982), American Cancer Society Cancer Prevention Study II Cohort, United States (n = 669,046)

Characteristic	n (%)*	HBM O_3 (*ppb*)	LURBME $PM_{2.5}$ ($\mu g/m^3$)	LUR NO_2 (*ppb*)
Age, yr				
<40	29,615 (4.4)	38.0 (3.9)	12.8 (2.9)	12.4 (5.7)
40–49	137,618 (20.6)	38.0 (3.9)	12.5 (2.8)	11.4 (5.1)
50–59	245,195 (36.7)	38.1 (3.9)	12.6 (2.8)	11.6 (5.0)
60–69	178,062 (26.6)	38.3 (4.1)	12.5 (2.9)	11.6 (5.1)
70–79	66,527 (9.9)	38.4 (4.2)	12.6 (2.9)	11.8 (5.0)
⩾80	12,029 (1.8)	38.3 (4.2)	12.7 (2.9)	12.2 (5.2)
Race				
White	632,919 (94.6)	38.2 (3.9)	12.5 (2.8)	11.5 (5.0)
African American	25,508 (3.8)	38.1 (3.3)	13.7 (2.5)	13.3 (5.2)
Other	10,619 (1.6)	38.3 (5.9)	12.9 (4.3)	15.6 (6.4)
Sex				
Male	292,772 (43.8)	38.2 (4.0)	12.5 (2.8)	11.5 (5.1)
Female	376,274 (56.2)	38.2 (4.0)	12.6 (2.9)	11.7 (5.1)
Education				
Less than high school	78,391 (11.7)	38.1 (3.8)	12.8 (2.8)	11.6 (5.3)
High school	207,710 (31.1)	38.1 (3.7)	12.6 (2.8)	11.4 (5.1)
High school or above	382,945 (57.2)	38.2 (4.1)	12.5 (2.9)	11.7 (5.0)
BMI, kg/m^2				
<18.5	11,904 (1.8)	38.4 (4.0)	12.6 (2.9)	11.7 (5.0)
18.5–24.9	338,528 (50.6)	38.2 (4.0)	12.5 (2.9)	11.6 (5.1)
25–29.9	242,144 (36.2)	38.1 (3.9)	12.6 (2.8)	11.6 (5.1)
⩾30	76,470 (11.4)	38.1 (3.8)	12.8 (2.8)	11.7 (5.2)
Marital status				
Single	21,966 (3.3)	37.5 (3.8)	13.0 (2.8)	13.1 (5.5)
Married	564,186 (84.3)	38.2 (4.0)	12.5 (2.8)	11.5 (5.0)
Other	82,894 (12.4)	38.1 (4.0)	12.9 (2.9)	12.3 (5.3)
Cigarette-smoking status				
Never	299,530 (44.8)	38.4 (4.0)	12.6 (2.9)	11.5 (5.1)
Current	129,876 (19.4)	38.0 (3.8)	12.7 (2.8)	11.8 (5.1)
Former	172,689 (25.8)	38.0 (4.0)	12.5 (2.9)	11.7 (5.1)
Ever pipe and/or cigar	66,951 (10.0)	38.0 (3.8)	12.5 (2.8)	11.5 (5.0)
1990 ecological covariates, mean (SD)				
Median household income, $10,000s	3.5 (1.3)	—	—	—
African American, %	8.9 (15.8)	—	—	—
Hispanic, %	5.9 (10.9)	—	—	—
Postsecondary education, %	38.6 (13.3)	—	—	—
Unemployment, %	5.6 (2.9)	—	—	—
Poverty, %	10.5 (7.8)	—	—	—

Definition of abbreviations: BMI = body mass index; HBM = hierarchical Bayesian space–time model; LUR = land use regression; LURBME = land use regression Bayesian maximum entropy; O_3 = tropospheric ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter of up to 2.5 μm.
*Except where otherwise indicated.

near-source and regional $PM_{2.5}$ were weak (Pearson's $r = -0.13$ and $+0.23$, respectively) (Table E3).

In single-pollutant models, significant positive associations were present between year-round O_3 and all-cause (HR per 10 ppb, 1.02; 95% CI, 1.01–1.04), circulatory (HR per 10 ppb, 1.03; 95% CI, 1.02–1.05), and respiratory (HR per 10 ppb, 1.14; 95% CI, 1.10–1.18) mortality (Table E6). Significant positive associations were observed for both regional $PM_{2.5}$, ranging up to HR per 10 $\mu g/m^3$ of 1.16 (95% CI, 1.10–1.23) for respiratory mortality, and near-source $PM_{2.5}$, ranging up to HR per 10 $\mu g/m^3$ of 1.45 (95% CI, 1.35–1.57) for circulatory mortality. There were significant positive associations between NO_2 and all-cause (HR per 10 ppb, 1.04; 95% CI, 1.03–1.06) and circulatory (HR per 10 ppb, 1.08; 95% CI, 1.06–1.09) mortality but not respiratory mortality.

In two-pollutant models adjusted for $PM_{2.5}$, significant positive associations between O_3 and all-cause (HR per 10 ppb, 1.02; 95% CI, 1.01–1.04), circulatory (HR per 10 ppb, 1.03; 95% CI, 1.01–1.05), and respiratory (HR per 10 ppb, 1.12; 95% CI, 1.08–1.16) mortality were observed (Table E7). Results were unchanged with further adjustment for NO_2 (Table 2). The strongest O_3 association was noted for diabetes mortality specifically (HR, 1.16; 95% CI, 1.07–1.26), followed by mortality due to dysrhythmias, heart failure, and cardiac arrest; COPD; and pneumonia and influenza. Significant positive mortality associations also remained for both regional and near-source $PM_{2.5}$ in the multipollutant model. For NO_2, the association with circulatory mortality attenuated (HR per 10 ppb, 1.03; 95% CI, 1.01–1.05) and that with all-cause mortality was not apparent.

Results for O_3 strengthened slightly for respiratory mortality with adjustment for percentage with air conditioning (Table E8). Results were slightly attenuated for both for circulatory (HR, 1.03; 95% CI, 1.00–1.05) and respiratory (HR, 1.11; 95% CI, 1.06–1.16) mortality with inclusion of a county-level random effect.

Similar results were observed using summer O_3 concentrations, except for mortality due to dysrhythmias, heart failure, and cardiac arrest; diabetes; and respiratory causes. The latter results were attenuated (Table E9). Results were similar for O_3 when adjusted for HBM $PM_{2.5}$ compared with decomposed LURBME $PM_{2.5}$ concentrations (Table E10). Results were slightly stronger using estimated Downscaler O_3 concentrations (HR per 10 ppb, 1.05; 95% CI, 1.03–1.07 [all-cause mortality]; HR per 10 ppb, 1.06; 95% CI, 1.03–1.09 [circulatory mortality]; HR per 10 ppb, 1.14; 95% CI, 1.07–1.21 [respiratory mortality]), due largely to the subsample of included participants (Tables E2, E3, and E11).

The proportional hazards assumption was violated ($P < 0.05$) for associations between O_3 and all-cause, circulatory, cardiovascular, and IHD mortality, with positive associations (except null results for IHD) observed in the middle 1990–1999 and later 2000–2004 time periods only, although the magnitude of the differences was small (Table E12). There was some evidence that a threshold model improved model fit for respiratory mortality at 35 ppb ($P = 0.002$) compared with a linear model using year-round but not summertime O_3 (HR per 10 ppb using threshold O_3 indicator at 35 ppb for respiratory mortality, 1.17; 95% CI, 1.11–1.22) (Figures E3 and E4). Results were somewhat

Table 2. All-Cause and Cause-Specific Mortality Hazard Ratios in Relation to Each 10-Unit Increase in Air Pollutant Concentrations, 1982–2004 Follow-up in American Cancer Society Cancer Prevention Study II Cohort, United States (n = 669,046)

Cause of Death	ICD-9 Codes; ICD-10 Codes	Deaths (*n*)	Multipollutant Model Data, Fully Adjusted HR* (95% CI)			
			HBM O_3	Regional $PM_{2.5}$	Near-Source $PM_{2.5}$	LUR NO_2
All-cause mortality	All	237,201	1.02 (1.01–1.04)	1.04 (1.02–1.06)	1.26 (1.19–1.34)	1.01 (1.00–1.03)
Diseases of the circulatory system (plus diabetes) (48)	390–459, 250; I00–I99, E10–E14	105,039	1.03 (1.01–1.05)	1.07 (1.04–1.10)	1.41 (1.29–1.54)	1.03 (1.01–1.05)
Cardiovascular	410–440; I20–I25, I30–I51, I60–I69, I70	84,132	1.03 (1.01–1.05)	1.07 (1.04–1.10)	1.35 (1.23–1.49)	1.03 (1.01–1.06)
Ischemic heart disease	410–414; I20–I25	45,644	0.98 (0.95–1.00)	1.06 (1.02–1.11)	1.40 (1.23–1.60)	1.09 (1.06–1.12)
Dysrhythmias, heart failure, cardiac arrest	420–429; I30–I51	18,314	1.15 (1.10–1.20)	1.06 (1.00–1.13)	1.15 (0.93–1.42)	0.99 (0.95–1.04)
Cerebrovascular disease	430–438; I60–I69	17,085	1.03 (0.98–1.07)	1.13 (1.06–1.21)	1.50 (1.21–1.87)	0.92 (0.88–0.97)
Diabetes	250; E10–E14	4,890	1.16 (1.07–1.26)	1.01 (0.90–1.15)	2.02 (1.33–3.07)	1.01 (0.92–1.10)
Diseases of the respiratory system	460–519; J00–J98	20,484	1.12 (1.08–1.16)	1.11 (1.05–1.18)	1.17 (0.96–1.42)	0.99 (0.95–1.04)
Pneumonia and influenza	480–487; J10–J18	6,599	1.10 (1.03–1.18)	1.24 (1.12–1.37)	1.01 (0.71–1.42)	1.07 (0.99–1.15)
COPD and allied conditions	490–496; J19–J46	9,967	1.14 (1.08–1.21)	1.06 (0.97–1.15)	1.24 (0.94–1.64)	0.97 (0.91–1.04)
Lung cancer	162; C33–34	16,432	0.96 (0.91–1.00)	1.13 (1.06–1.21)	1.31 (1.05–1.63)	0.94 (0.90–0.99)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; HBM = hierarchical Bayesian space–time model; HR = hazard ratio; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, 10th Revision*; LUR = land use regression; O_3 = tropospheric ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter of up to 2.5 μm.
*HRs are derived from multipollutant models including all air pollutants simultaneously. HRs are age, race, and sex stratified and adjusted for education; marital status; body mass index; body mass index squared; cigarette smoking status; cigarettes smoked per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking younger than 18 years; passive smoking; vegetable, fruit, and fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index; and 1990 ecological covariates: median household income and percentage of African Americans, Hispanics, postsecondary education, unemployment, and poverty.

suggestive of a threshold for circulatory mortality at 35 ppb ($P = 0.07$).

O_3 circulatory and respiratory mortality associations varied according to temperature and prior cardiovascular or respiratory disease at enrollment, respectively (Table E13). Positive respiratory associations were also stronger in those younger than 65 years of age at enrollment.

For comparability across pollutants, results according to each fifth percentile–mean increment are presented in Table 3. Results were somewhat stronger with near-source $PM_{2.5}$ for both all-cause (HR per 1.6 $\mu g/m^3$, 1.04; 95% CI, 1.03–1.05) and circulatory (HR per 1.6 $\mu g/m^3$, 1.06; 95% CI, 1.04–1.07) mortality and with O_3 for respiratory mortality (HR per 7.1 ppb, 1.08; 95% CI, 1.05–1.11).

Discussion

We observed significant positive associations between long-term O_3 and all-cause, circulatory, and respiratory mortality with 2%, 3%, and 12% increases in risk per 10 ppb, respectively, in this large-scale study with 22 years of follow-up. In a smaller prior study, researchers first reported long-term O_3–mortality associations, but only that for respiratory mortality remained with adjustment for $PM_{2.5}$ (6). We hypothesized that with improved exposure models and increased statistical power derived from longer follow-up, robust associations between O_3 and both respiratory and circulatory mortality would be observed with adjustment for other copollutants. Results supporting our hypothesis were robust after adjustment for $PM_{2.5}$ and NO_2.

We used new national-level O_3 exposure estimates extending our earlier work based on measured regional levels of air pollutants. Although there were also differences in the time period (2002–2004 vs. 1977–2000) and season (year-round vs. summertime) of O_3 metrics used in the present study versus the previous study, their correlation was moderately strong ($r = 0.70$) (6). Analysis linking the current HBM O_3 estimate to the previous analytic cohort showed stronger respiratory mortality HRs of 1.16 (95% CI, 1.09–1.24) per 10 ppb and 1.11 (95% CI, 1.06–1.17) per each fifth percentile–mean increment in two-pollutant models adjusted for $PM_{2.5}$ (6). In comparison, HRs of 1.04 (95% CI, 1.01–1.07) per 10 ppb and 1.07 (95% CI, 1.02–1.12) per each fifth percentile–mean increment were observed using measured O_3 data in previous work, indicating larger associations with more refined O_3 estimates (6).

Our findings support previous associations with respiratory mortality in U.S. studies (6, 7). Possible biological mechanisms include oxidative stress and inflammatory pathways as well as adverse neural, epithelial, smooth muscle, and immune system impacts (4). In contrast, no positive association was observed in a large (n = 800,000) U.K. patient cohort (8). There O_3 was negatively correlated with $PM_{2.5}$ ($r = -0.39$), and regional patterns in O_3 and mortality may explain the findings observed. There was no positive association with respiratory mortality in the CanCHEC study (10).

We observed a positive association with circulatory mortality that remained after adjustment for $PM_{2.5}$ and NO_2. Results from some previous studies were confounded by $PM_{2.5}$ (6, 7). The researchers in the prior U.K. study reported no positive association with incident myocardial infarction, stroke, arrhythmia, or heart failure (36). Analysis of

Table 3. All-Cause and Cause-Specific Mortality Hazard Ratios in Relation to Each Fifth Percentile–Mean Increment in Air Pollutant Concentrations, 1982–2004 Follow-up in American Cancer Society Cancer Prevention Study II Cohort, United States (n = 669,046)

Cause of Death	ICD-9 Codes; ICD-10 Codes	Deaths (*n*)	Multipollutant Model Data, Fully Adjusted HR* (95% CI)			
			HBM O_3 (*per 7.1 ppb*)	Regional $PM_{2.5}$ (*per 4.5 $\mu g/m^3$*)	Near-Source $PM_{2.5}$ (*per 1.6 $\mu g/m^3$*)	LUR NO_2 (*per 6.5 ppb*)
All-cause	All	237,201	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.04 (1.03–1.05)	1.01 (1.00–1.02)
Diseases of the circulatory system (plus diabetes) (48)	390–459, 250; I00–I99, E10–E14	105,039	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.06 (1.04–1.07)	1.02 (1.00–1.03)
Cardiovascular	410–440; I20–I25, I30–I51, I60–I69, I70	84,132	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.05 (1.03–1.07)	1.02 (1.01–1.04)
Ischemic heart disease	410–414; I20–I25	45,644	0.98 (0.97–1.00)	1.03 (1.01–1.05)	1.06 (1.03–1.08)	1.06 (1.04–1.08)
Dysrhythmias, heart failure, cardiac arrest	420–429; I30–I51	18,314	1.10 (1.07–1.14)	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.00 (0.97–1.03)
Cerebrovascular disease	430–438; I60–I69	17,085	1.02 (0.99–1.05)	1.06 (1.02–1.09)	1.07 (1.03–1.11)	0.95 (0.92–0.98)
Diabetes	250; E10–E14	4,890	1.11 (1.05–1.18)	1.01 (0.95–1.06)	1.12 (1.05–1.20)	1.01 (0.95–1.07)
Diseases of the respiratory system	460–519; J00–J98	20,484	1.08 (1.05–1.11)	1.05 (1.02–1.08)	1.03 (0.99–1.06)	1.00 (0.97–1.02)
Pneumonia and influenza	480–487; J10–J18	6,599	1.07 (1.02–1.12)	1.10 (1.05–1.15)	1.00 (0.95–1.06)	1.04 (0.99–1.10)
COPD and allied conditions	490–496; J19–J46	9,967	1.10 (1.05–1.14)	1.03 (0.99–1.07)	1.04 (0.99–1.08)	0.98 (0.94–1.02)
Lung cancer	162; C33–34	16,432	0.97 (0.94–1.00)	1.06 (1.03–1.09)	1.04 (1.01–1.08)	0.96 (0.93–0.99)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; HBM = hierarchical Bayesian space–time model; HR = hazard ratio; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, 10th Revision*; LUR = land use regression; O_3 = tropospheric ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter of up to 2.5 μm.

*HRs are derived from multipollutant models including all air pollutants simultaneously. HRs are age, race, and sex stratified and adjusted for education; marital status; body mass index; body mass index squared; cigarette smoking status; cigarettes smoked per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking younger than 18 years; passive smoking; vegetable, fruit, and fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index; and 1990 ecological covariates: median household income and percentage of African Americans, Hispanics, postsecondary education, unemployment, and poverty.

California CPS-II participants revealed a positive association with IHD mortality (HR per interquartile range [24.2 ppb], 1.10; 95% CI, 1.02–1.19), which remained after adjusting for $PM_{2.5}$ and NO_2 (29). Although we observed no association with IHD mortality here, upon restriction to California participants there was a weak positive association (HR per 10 ppb, 1.07; 95% CI, 0.99–1.14). Regional differences in these findings may relate to participant characteristics, death rates, death certificate coding, or air pollution composition. Positive associations with cardiometabolic disease mortality were observed in multipollutant models in the CanCHEC study, with the strongest findings being for diabetes (11% increase per 9.5 ppb) and IHD (6% increase) using a 21 × 21-km grid surface (10).

Findings for respiratory mortality were stronger among those with no prior respiratory disease at enrollment, suggesting a role for O_3 in the development and exacerbation of disease. In a previous Medicare-based study, researchers reported positive associations between long-term O_3 and mortality in those previously hospitalized for COPD, as well as in those with diabetes, congestive heart failure, or myocardial infarction (37). Findings were also stronger in younger participants. Little age difference was observed in short-term studies (38).

Stronger associations were observed in areas with lower temperature as well as in the highest temperature category. The relationship between ambient and personal O_3 exposure is complex, weaker than with particles, and varies with time spent outdoors, indoor infiltration, and season (39). Time spent outdoors and engaged in sports may modify associations for asthma formation (40). Differences in short-term O_3 mortality coefficients across 18 U.S. cities were related to differences in total O_3 (outdoor plus indoor) exposure (41). Mitigation of short-term O_3-related mortality by air conditioning prevalence was observed at high temperatures in 97 U.S. cities (42). Though results suggest a threshold for respiratory and, to a lesser extent, circulatory mortality at 35 ppb of O_3 compared with that of 56 ppb ($P = 0.06$) in previous work (6), it remains unclear if the results represent a biological threshold *per se* or other such temperature-related, behavioral, or region-related processes. There were no data on time–activity patterns here.

We observed positive mortality associations with estimated LURBME $PM_{2.5}$ concentrations (30). The LURBME $PM_{2.5}$ model outperformed other remote sensing, geostatistical, and HBM models in CPS-II (25). Results were somewhat stronger with regional $PM_{2.5}$ for respiratory mortality and near-source $PM_{2.5}$ for circulatory mortality.

Correlations between O_3 and $PM_{2.5}$ were weak. Though air pollutants were estimated at different time periods using different methods and geographic units of scale, possibly complicating interpretation of their correlation structure, results for O_3 were robust in two-pollutant models adjusted for HBM $PM_{2.5}$ and estimated for the same time period and unit of scale. Their correlation was also weak ($r = 0.04$) (Tables E3 and E10). Results for O_3 were similar using Downscaler O_3 concentrations, estimated with a finer spatial resolution (12 × 12 km) (Table E11), compared with HBM O_3. The correlation between HBM and Downscaler O_3 was strong ($r = 0.89$) (Table E3).

We adjusted findings for decomposed LURBME $PM_{2.5}$ and NO_2 to address potential confounding in areas with low O_3 but high near-source pollution (43). Negative correlations between Downscaler O_3 and both near-source $PM_{2.5}$ and NO_2 ($r = -0.41$ and -0.42, respectively) were stronger than those for HBM O_3 ($r = -0.13$ and -0.08, respectively). Downscaler HRs for all-cause and circulatory mortality also increased to a greater extent in multipollutant models compared with those for HBM O_3 (Tables E3, E6, and E11).

Positive associations between NO_2 and circulatory mortality were attenuated with adjustment for $PM_{2.5}$ and O_3. The association with all-cause mortality was no longer apparent. Currently, there is suggestive evidence for NO_2-associated cardiovascular effects but uncertainty regarding its independent role (5, 44, 45). Results in two European studies revealed small positive associations with nonaccidental mortality that remained in two-pollutant models with $PM_{2.5}$ (46, 47). There were also small positive mortality associations in multipollutant models with both $PM_{2.5}$ and O_3 in two North American studies (10, 29). Williams and colleagues (43) noted close linkages between NO_2 and O_3. Correlations between NO_2 and HBM O_3 ($r = -0.08$) were weak, possibly due to different units of scale and broad regional patterns of pollutants.

Limitations of this study include a lack of updated data on residential history, leading to potential misclassification of both air pollution concentrations and sociodemographic ecologic covariates over time, as well as of individual covariate data. There were no data on residential history before enrollment. Accounting for residential mobility, however, had little impact on long-term O_3 or $PM_{2.5}$ mortality associations in the CanCHEC study but strengthened those for more spatially resolved NO_2 (10). Though there may be some selection bias due to the exclusion of participants with missing or invalid residence data, excluded participants were similar in terms of baseline sociodemographic factors (approximately 61% between 50 and 69 years of age, approximately 57% female, approximately 47% with more than high school level of education, and approximately 21% current cigarette smokers). Though we lacked historical O_3 data, there was little difference in respiratory mortality HRs in previous work when researchers examined specific exposure time windows or O_3 exposures matched more closely in time (5). Recent O_3 concentrations are correlated with past estimates. Correlations between 1998–2000 concentrations and those from 1988–1990 and 1978–1980 were 0.80 and 0.58, respectively (6). Little is known regarding the most relevant exposure time window. Finally, multiple comparisons were performed, and some results may be due to chance.

In summary, findings derived from this large-scale prospective study suggest that long-term ambient O_3 contributes to risk of respiratory and circulatory mortality. Results were robust after adjustment for $PM_{2.5}$ and NO_2. There were also positive mortality associations observed between $PM_{2.5}$ (both near source and regional) and NO_2 in multipollutant models. Substantial health and environmental benefits may be achieved by implementing further measures aimed at controlling O_3 concentrations. ■

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