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

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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

This paper examines 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 ($PM_{2.5}$), and nitrogen dioxide (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 between $PM_{2.5}$ (both near-source and regional) and NO_2 in multi-pollutant models.

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

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: This paper examines the association 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 which 237,201 deaths were observed through 2004. We obtained estimates of O_3 concentrations at the participant residence from a Hierarchical Bayesian Space Time Model. Estimates of fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (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 with all-cause and cause-specific mortality. In two-pollutant models adjusting for $PM_{2.5}$, significant positive associations remained between O_3 and all-cause (HR per 10 ppb = 1.02, 95% 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. There were also positive mortality associations observed with both $PM_{2.5}$ (both near-source and regional) and NO_2 in multi-pollutant models.

Conclusions: Findings 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 through further measures aimed at controlling O_3 concentrations.

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INTRODUCTION

Epidemiological studies investigating short-term exposures (of 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.[2,3,4] 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 adjusting for fine particulate matter with an aerodynamic diameter of $\leq$ 2.5 microns ($PM_{2.5}$), 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 from respiratory (HR per IQR (11.02 ppb) = 1.07, 95% CI 0.97-1.19) and ischemic heart disease (IHD) (HR = 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. ecologic study.[9] Positive associations were observed with cardiometabolic, but not respiratory mortality, in multi-pollutant models adjusting for $PM_{2.5}$ and nitrogen dioxide (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.

Worldwide, mean 3-month hourly maximum O_3 concentrations in 2005 were 54 ppb,[11] and are increasing in densely populated areas of South and East Asia due largely to growing O_3 precursor emissions.[9] O_3 contributes to increased radiative forcing and climate change.[12,13]

Based on findings from the CPS-II, more than 270,000 deaths from 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 U.S. affords a unique opportunity to further examine O_3 effects in larger national-level studies.

We assessed the association between long-term ambient O_3 exposure and all-cause and cause-specific mortality in an extended analysis of the CPS-II 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 to disentangle the independent effects of such ambient air pollutants is a key research priority.[5] Some results were previously reported in 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, ≥ 30 years of age, and had a family member aged ≥ 45 years. A four-page self-administered enrollment questionnaire captured data on demographic, lifestyle, medical, and other factors.[16] Ethics approval 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 missing to follow-up or had follow-up terminated in September 1988 due to insufficient record linkage information. Deaths were classified by underlying cause using International Classification of Disease (ICD) 9 and 10.[18,19] More than 99% of known deaths were assigned a cause.

A total of 669,046 participants were analyzed (Figure E1). The majority of exclusions were due to missing/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 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 Stations (NAMS/SLAMS) 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 x 36 km grids for the entire U.S. 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 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 based on NAMS/SLAMS and CMAQ model data in 12 x 12 km grids for the years 2001-2008. Downscaler 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 only available for the Eastern U.S. for 2002-2004. Model performance using the predictive mean absolute error (PMAE) showed Downscaler O_3 outperformed ordinary kriging or CMAQ models alone, with a PMAE of 5 based on the square root of daily O_3 values.[23] Correlations with hold-out locations for daily predictions ranged from 0.61-0.86 at three sites in the Eastern U.S.

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 ~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 (~4 million measurements, aggregated into annual-average values at 81,743 locations [~ 10 x 10 km grid]) 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, black, 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: 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 < 18 years of age; passive smoking (hours); vegetable, fruit, and fiber and fat intake; beer, wine, and liquor consumption; occupational exposures; and an occupational dirtiness index; as well as six socio-demographic ecological covariates at both the ZIP code and ZIP code minus county level mean from the 1990 U.S. Census (median household income; and percentage of African American residents, Hispanic residents, adults with post-secondary education, unemployment, and poverty; Table E5) as in previous work.[6,20,25,28,29,30]

We examined potential confounding by elevation, metropolitan statistical area (MSA) 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 zero 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 (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.

Analyses used SAS version 9.2 and specialized software developed for the random effects survival model.[30,35] Ethics approval for analysis was obtained from the Ottawa Hospital Research Ethics Board.

RESULTS

Participants were largely between the ages of 40-69 years, female, and had a greater than 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) (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)) and 1.0 to 37.6 ppb (mean (SD): 11.6 (5.1)) respectively. Correlations between year-round O_3 and both near-source and regional $PM_{2.5}$ were weak (Pearson *r*'s = -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 = 1.03, 95% CI 1.02-1.05), and respiratory mortality (HR = 1.14, 95% CI 1.10-1.18) (Table E6). Significant positive associations were observed for both regional $PM_{2.5}$, ranging up to HR per 10 $\mu g/m^3$ = 1.16 (95% CI 1.10-1.23) for respiratory mortality, and near-source $PM_{2.5}$, ranging up to HR = 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 = 1.08, 95% CI 1.06-1.09), but not respiratory mortality.

In two-pollutant models adjusting for $PM_{2.5}$, significant positive associations between O_3 and all-cause (HR 10 ppb = 1.02, 95% 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) 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 from 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

multi-pollutant 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 percent air conditioning (Table E8). Results were slightly attenuated for both for circulatory and respiratory mortality with inclusion of a county level random effect (HRs = 1.03, 95% CI 1.00-1.05 and 1.11, 95% CI 1.06-1.16 respectively).

Similar results were observed using summer O_3 concentrations, except for mortality from dysrhythmias, heart failure, and cardiac arrest; diabetes; and respiratory causes, which were attenuated (Table E9). Results were similar for O_3 when adjusting for HBM $PM_{2.5}$ as compared to decomposed LURBME $PM_{2.5}$ concentrations (Table E10). Results were slightly stronger using estimated Downscaler O_3 concentrations (HRs = 1.05, 95% CI 1.03-1.07 for all-cause; 1.06, 95% CI 1.03-1.09 for circulatory; and 1.14, 95% CI 1.07-1.21 for respiratory mortality per 10 ppb), 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 were 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 using threshold O_3

indicator at 35 ppb for respiratory = 1.17, 95% CI 1.11-1.22 per 10 ppb, Figure E3 and E4). Results were somewhat 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 < 65 years at enrollment.

For comparability across pollutants, results according to each 5th 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 μg/m^3 = 1.04, 95% CI 1.03-1.05) and circulatory mortality (HR = 1.06, 95% CI 1.04-1.07) 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. A smaller prior study 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 from longer follow-up, robust associations between O_3 and both respiratory and circulatory death would be observed with other co-pollutant adjustment. Results supporting our hypothesis were robust to 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 are also differences in the time period (2002-2004 vs. 1977-2000) and season (year-round vs. summertime) of O_3 metrics used in the current vs. 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 observed 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 5th percentile-mean in two-pollutant models adjusting 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 5th percentile-mean were observed using measured O_3 data in previous work, indicating larger associations with more refined O_3 estimates.[6]

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 findings observed. There was no positive association with respiratory mortality in CanCHEC.[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 prior U.K. study reported no positive association with incident myocardial infarction, stroke, arrhythmia, or heart failure.[37] Analysis of California CPS-II participants revealed a positive association with IHD mortality (HR per IQR (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 findings may relate to participant characteristics, death rates, death certificate coding, or air pollution composition. Positive associations with cardiometabolic disease mortality were observed in multi-pollutant models in CanCHEC, with the strongest findings for diabetes (11% increase per 9.5 ppb) and IHD (6% increase) using a 21 x 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. A previous Medicare-based study reported positive associations between long-term O_3 and mortality in those previously hospitalized for COPD, as well as diabetes, congestive heart failure, or myocardial infarction.[38] Findings were also stronger in younger participants. Little age difference was observed in short-term studies.[39]

Stronger associations were observed in areas of both lower temperature, as well as in the highest temperature category. The relation between ambient and personal O_3 exposure is complex, weaker than with particles, and varies with time spent outdoors, indoor infiltration, and season.[40] Time spent outdoors, engaged in sports, may modify associations for asthma formation.[41] Differences in short-term O_3 mortality coefficients across 18 U.S. cities were related with differences in total O_3 (outdoor + indoor) exposure.[42] Mitigation of short-term O_3-related mortality by air conditioning prevalence was observed at high temperatures in 97 U.S. cities.[43] Though results suggest a threshold for respiratory and, to a lesser extent, circulatory mortality at

35 ppb of O_3 compared to that of 56 ppb (p = 0.06) in previous work,[6] it remains unclear if results represent a biological threshold *per se*, or other such temperature, 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 adjusting for HBM $PM_{2.5}$, 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 x 12 km) (Table E11), compared to 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.[44] Negative correlations between Downscaler O_3 and both near-source $PM_{2.5}$ and NO_2 (r's = -0.41 and -0.42 respectively) were stronger than those for HBM O_3 (r's = -0.13 and -0.08 respectively). Downscaler HRs for

all-cause and circulatory mortality also increased to a greater extent in multipollutant models compared to those for HBM O_3 (Tables E3, E6, and E11).

Positive associations between NO_2 and circulatory mortality 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.[5,45,46] Results in two European studies revealed small positive associations with non-accidental mortality that remained in two-pollutant models with $PM_{2.5}$.[47,48] There were also small positive mortality associations in multi-pollutant models with both $PM_{2.5}$ and O_3 in two North American studies.[10,29] Williams et al.[44] note 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 include a lack of updated data on residential history, leading to potential misclassification of both air pollution concentrations and socio-demographic ecologic covariates over time, as well as individual covariate data. There were no data on residential history prior to enrollment. Accounting for residential mobility, however, had little impact on long-term O_3 or $PM_{2.5}$ mortality associations in CanCHEC, 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/invalid residence data, excluded participants were similar in terms of baseline sociodemographic factors (~61% between 50-69 years of age, ~57% female, ~47% with a greater than high school level of educational attainment, and ~21% current cigarette smokers). Though we lacked historical O_3 data, there was little difference in respiratory mortality HRs in previous

work when examining 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 year 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 sum, findings from this large-scale prospective study suggest that long-term ambient O_3 contributes to risk of respiratory and circulatory mortality. Results were robust to 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 multi-pollutant models. Substantial health and environmental benefits may be achieved through further measures aimed at controlling O_3 concentrations.

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FIGURE LEGENDS

Figure 1. Distribution of mean annual daily 8-hour maximum O_3 concentrations based on a Hierarchical Bayesian Space Time Modeling System (HBM), US, 2002-2004.

Table 1. Distribution (n, %) of selected participant characteristics at enrollment (1982), CPS-II cohort, US (n = 669,046).

Characteristic	n (%)	HBM O_3 (ppb) Mean (SD)	LURBME $PM_{2.5}$ ($\mu g/m^3$) Mean (SD)	LUR NO_2 (ppb) Mean (SD)
Age (years)				
<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)
Black	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				
<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	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/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)	-	-	-
Post-secondary education (%)	38.6 (13.3)	-	-	-
Unemployment (%)	5.6 (2.9)	-	-	-
Poverty (%)	10.5 (7.8)	-	-	-

Table 2. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O_3, near-source and regional $PM_{2.5}$, and LUR NO_2 concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

			Multipollutant			
			HBM O_3	Regional $PM_{2.5}$	Near-source $PM_{2.5}$	LUR NO_2
Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*
All-cause	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)[36]	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)

* HRs from multipollutant models including all air pollutants simultaneously; age, race, and sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking < 18 years; passive smoking; vegetable, fruit, fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index, 1990 ecological covariates: median household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty.

Table 3. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 5th percentile-mean increment in HBM O_3, near-source and regional $PM_{2.5}$, and LUR NO_2 concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

			Multi-pollutant			
			HBM O_3 (per 7.1 ppb)	Regional $PM_{2.5}$ (per 4.5 µg/m^3)	Near-source $PM_{2.5}$ (per 1.6 µg/m^3)	LUR NO_2 (per 6.5 ppb)
Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*
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)[36]	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)

* HRs from multipollutant models including all air pollutants simultaneously; age, race, sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking < 18 years; passive smoking; vegetable, fruit, fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index, 1990 ecological covariates: median household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty.

Figure 1. Distribution of mean annual daily 8-hour maximum O_3 concentrations based on a Hierarchical Bayesian Space Time Modeling System (HBM), US, 2002-2004.