

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 (O₃) might be associated with cardiovascular disease risk and premature death. Results from long-term epidemiological studies on O₃ are scarce and inconclusive.

What This Study Adds to the Field

This paper examines the association between chronic ambient O₃ 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 O₃, fine particulate matter (PM_{2.5}), and nitrogen dioxide (NO₂) concentrations. Results from this large-scale prospective study suggest that long-term ambient O₃ 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 NO₂ 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 (O₃) is potentially associated with cardiovascular disease risk and premature death. Results from long-term epidemiological studies on O₃ are scarce and inconclusive.

Objectives: This paper examines the association between chronic ambient O₃ 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 O₃ concentrations at the participant residence from a Hierarchical Bayesian Space Time Model. Estimates of fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) 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 O₃, PM_{2.5}, and NO₂ with all-cause and cause-specific mortality. In two-pollutant models adjusting for PM_{2.5}, significant positive associations remained between O₃ 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 NO₂. There were also positive mortality associations observed with both PM_{2.5} (both near-source and regional) and NO₂ in multi-pollutant models.

Conclusions: Findings from this large-scale prospective study suggest that long-term ambient O₃ contributes to risk of respiratory and circulatory mortality. Substantial health and environmental benefits may be achieved through further measures aimed at controlling O₃ concentrations.

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INTRODUCTION

Epidemiological studies investigating short-term exposures (of hours to a few days) to ambient ozone (O₃) showed positive associations with mortality, exacerbation of respiratory illness, and increased hospital admissions.¹ There is suggestive evidence that short-term O₃ is associated with adverse cardiovascular effects.^{2,3,4} Epidemiological studies of long-term O₃ 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) O₃ 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 ≤ 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 O₃ 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 O₃ 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 (NO₂) 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 O₃ concentrations in 2005 were 54 ppb,¹¹ and are increasing in densely populated areas of South and East Asia due largely to growing O₃ precursor emissions.⁹ O₃ 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 O₃ exposure in 2013.^{6,14} Further evidence for long-term O₃ effects would markedly increase the attributable disease burden. Recent advancements in O₃ 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 O₃ effects in larger national-level studies.

We assessed the association between long-term ambient O₃ exposure and all-cause and cause-specific mortality in an extended analysis of the CPS-II using new national-level estimates of ambient O₃, PM_{2.5}, and NO₂ 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 O₃ 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 O₃ 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 O₃ (2002-2004) values were assigned to the geocoded participant residence at enrollment and used as an indicator of long-term O₃ exposure.

We also examined O₃ concentrations from a Bayesian space-time downscaling fusion model (henceforth termed "Downscaler O₃").²² Daily 8-hour maximum O₃ 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 O₃ outperformed ordinary kriging or CMAQ models alone, with a PMAE of 5 based on the square root of daily O₃ 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 m³. Residual spatiotemporal variation in PM_{2.5} concentrations was interpolated with a BME interpolation model. The two estimates were then combined. The cross-validation R² was ~0.79. Mean PM_{2.5} (1999-2004) concentrations were used here. To address potential confounding of O₃-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 O₃ (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

NO₂ 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 O₃ and follow-up time was used to assess the proportional hazards assumption.

Threshold models, defined by setting the O₃ 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 O₃ 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 O₃ concentrations by participant characteristics.

Year-round O₃ 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 NO₂, average concentrations ranged from 1.4 to 27.9 µg/m³ (mean (SD): 12.6 (2.9)) and 1.0 to 37.6 ppb (mean (SD): 11.6 (5.1)) respectively. Correlations between year-round O₃ 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 O₃ 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 µg/m³ = 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 NO₂ 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 O₃ 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 NO₂ (Table 2). The strongest O₃ 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 NO₂, 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 O₃ 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 O₃ concentrations, except for mortality from dysrhythmias, heart failure, and cardiac arrest; diabetes; and respiratory causes, which were attenuated (Table E9). Results were similar for O₃ 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 O₃ 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 O₃ 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 O₃ (HR using threshold O₃

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 ($p = 0.07$).

O₃ 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/m³ = 1.04, 95% CI 1.03-1.05) and circulatory mortality (HR = 1.06, 95% CI 1.04-1.07) and with O₃ 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 O₃ 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 O₃-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 O₃ 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 NO₂.

We used new national-level O₃ 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 O₃ metrics used in the current vs. the previous study, their correlation was moderately strong ($r = 0.70$).⁶ Analysis linking the current HBM O₃ 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 O₃ data in previous work, indicating larger associations with more refined O₃ 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, O₃ was negatively correlated with PM_{2.5} ($r = -0.39$) and regional patterns in O₃ 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 NO₂. 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 NO₂.²⁹ 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 O₃ in the development and exacerbation of disease. A previous Medicare-based study reported positive associations between long-term O₃ 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 O₃ 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 O₃ mortality coefficients across 18 U.S. cities were related with differences in total O₃ (outdoor + indoor) exposure.⁴² Mitigation of short-term O₃-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 O₃ 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 O₃ 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 O₃ 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 O₃ were similar using Downscaler O₃ concentrations, estimated with a finer spatial resolution (12 x 12 km) (Table E11), compared to HBM O₃. The correlation between HBM and Downscaler O₃ was strong ($r = 0.89$) (Table E3).

We adjusted findings for decomposed LURBME PM_{2.5} and NO₂, to address potential confounding in areas with low O₃ but high near-source pollution.⁴⁴ Negative correlations between Downscaler O₃ and both near-source PM_{2.5} and NO₂ (r 's = -0.41 and -0.42 respectively) were stronger than those for HBM O₃ (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 O₃ (Tables E3, E6, and E11).

Positive associations between NO₂ and circulatory mortality attenuated with adjustment for PM_{2.5} and O₃. The association with all-cause mortality was no longer apparent. Currently, there is suggestive evidence for NO₂ 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 O₃ in two North American studies.^{10,29} Williams et al.⁴⁴ note close linkages between NO₂ and O₃. Correlations between NO₂ and HBM O₃ ($r = -0.08$) 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 O₃ or PM_{2.5} mortality associations in CanCHEC, but strengthened those for more spatially-resolved NO₂.¹⁰ 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 O₃ data, there was little difference in respiratory mortality HRs in previous

work when examining specific exposure time windows or O₃ exposures matched more closely in time.⁵ Recent O₃ 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 O₃ contributes to risk of respiratory and circulatory mortality. Results were robust to adjustment for PM_{2.5} and NO₂. There were also positive mortality associations observed between PM_{2.5} (both near-source and regional) and NO₂ in multi-pollutant models. Substantial health and environmental benefits may be achieved through further measures aimed at controlling O₃ concentrations.

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REFERENCES

1. Berman J, Fann N, Hollingsworth J, Pinkerton KE, Rom WN, Szema AM, Breysse PN, White RH, Curriero FC. Health benefits from large-scale ozone reduction in the United States. *Environ Health Perspect* 2012;120:1404-1410.
2. Ensor K, Raun L, Persse D. A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. *Circulation* 2013;127:1192-1199.
3. Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer MC, Marijon E, Vernerey D, Empana JP, Jouven X. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA* 2012;307:713-721.
4. U.S. Environmental Protection Agency. Integrated Science Assessment of Ozone and Related Photochemical Oxidants (Final Report). Washington, DC.: U.S. Environmental Protection Agency; 2013.
5. World Health Organization. Review of Evidence on Health Aspects of Air Pollution - REVIHAPP Project. Copenhagen: World Health Organization; 2013.
6. Jerrett M, Burnett RT, Pope CA 3rd, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085-1095.

7. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. Long-term exposure to air pollution and cardiorespiratory disease in the California Teachers Study Cohort. *Am J Respir Crit Care Med* 2011;184:828-835.
8. Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med* 2013;187:1226-1233.
9. Hao Y, Balluz L, Strosnider H, Wen XJ, Li C, Qualters JR. Ozone, fine particulate matter, and chronic lower respiratory disease mortality in the United States. *Am J Respir Crit Care Med* 2015;192:337-41.
10. Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, Villeneuve PJ, Jerrett M, Goldberg MS, Pope CA III, Brauer M, Brook RD, Robichaud A, Menard R, Burnett RT. Ambient PM_{2.5}, O₃, and NO₂ exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). *Environ Health Perspect* 2015;123:1180-1186.
11. Brauer M, Amann M, Burnett RT, Cohen A, Dentener F, Ezzati M, Henderson SB, Krzyzanowski M, Martin RV, Van Dingenen R, van Donkelaar A, Thurston GD. Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. *Environ Sci Technol* 2012;46:652-660.

12. Parrish DD, Law KS, Staehelin J, Derwent R, Cooper OR, Tanimoto H, Volz-Thomas A, Gilje S, Scheel HE, Steinbacher M, Chan E. Long-term changes in lower tropospheric baseline ozone concentrations at northern mid-latitudes. *Atmos Chem Phys* 2012;12:11485-11504.

13. IPCC. Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Field CB, Barros VR, Dokken DJ, Mach KJ, Mastrandrea MD, Bilir TE, et al. (eds.)]. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press, 2014.

14. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; Sep 10. pii: S0140-6736(15)00128-2. doi: 10.1016/S0140-6736(15)00128-2. [Epub ahead of print]

15. Turner MC, Jerrett M, Krewski D, Gapstur SM, Diver WR, Beckerman BS, Pope CA 3rd. Long-term ozone and mortality in a large-scale prospective study [abstract]. In: Abstracts of the 2014 Conference of the International Society of Environmental Epidemiology (ISEE). Abstract [1679]. Research Triangle Park, NC: Environmental Health Perspectives; 2014.

16. American Cancer Society. Cancer Prevention Study II (CPS II). Available from: <http://www.cancer.org/research/researchtopreventcancer/currentcancerpreventionstudies/cancer-prevention-study>. Date Accessed: January 22, 2015.
17. Calle E, Terrell D. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. *Am J Epidemiol* 1993;137:235-241.
18. World Health Organization. International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Geneva, Switzerland: World Health Organization; 1977.
19. World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. Geneva, Switzerland: World Health Organization; 1992.
20. Pope CA 3rd, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, Krewski D, Brook RD. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. *Circ Res* 2015;116:108-115.
21. U.S. Environmental Protection Agency. Air quality data for the CDC National Environmental Public Health Tracking Network. Available from: <http://www.epa.gov/heads/research/cdc.html>. Date Accessed: October 13, 2011.

22. U.S. Environmental Protection Agency. Fused air quality surfaces using downscaling. Available from: http://www.epa.gov/esd/land-sci/lcb/lcb_faqs.html. Date Accessed: April 2, 2014.
23. Berrocal VJ, Gelfand AE, Holland DM. Space-time fusion under error in computer model output: an application to modeling air quality. *Biometrics* 2012;68:837-848.
24. Beckerman BS, Jerrett M, Serre M, Martin RV, Lee SJ, van Donkelaar A, Ross Z, Su J, Burnett RT. A hybrid approach to estimating national scale spatiotemporal variability of PM_{2.5} in the contiguous United States. *Environ Sci Technol* 2013;47:7233-7241.
25. Jerrett M, Turner MC, Beckerman B, Pope CA 3rd, van Donkelaar A, Martin RV, Serre M, Crouse D, Gapstur SM, Krewski D, W Ryan Diver, Coogan PF, Thurston GD, Burnett RT. 2015. Comparing remote sensing, atmospheric chemistry, and ground-based estimates of ambient particulate matter on survival. Submitted.
26. McMillan NJ, Holland DM, Morara M, Feng J. Combining numerical model output and particulate data using Bayesian space-time modeling. *Environmetrics* 2010;21:48-65.
27. Novotny EV, Bechle MJ, Millet DB, Marshall JD. National satellite-based land-use regression: NO₂ in the United States. *Environ Sci Technol* 2011;45:4407-4414.

28. U.S. Department of Commerce Bureau of the Census. Census of population and housing, 1990 (United States): summary tape file 3B. ICPSR version. Washington, DC: 1993.
29. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, Gapstur SM, Thun MJ, Pope CA 3rd. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med* 2013;188:593-599.
30. Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA 3rd, Thurston G, Calle EE, Thun MJ, Beckerman B, DeLuca P, Finkelstein N, Ito K, Moore DK, Newbold KB, Ramsay T, Ross Z, Shin H, Tempalski B. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst* 2009;140:5-114; discussion 115-136.
31. US Geologic Survey, EROS Data Center. 1999. National Elevation Dataset. Available from: <http://ned.usgs.gov/>. Date Accessed: October 13, 2011.
32. Centers for Disease Control. North America Land Data Assimilation System (NLDAS) Daily Air Temperatures and Heat Index, years 1979-2011 on CDC WONDER Online Database, released 2013. Available from: <http://wonder.cdc.gov/NASA-NLDAS.html>. Date Accessed July 9, 2014.
33. U.S. Department of Commerce Bureau of the Census. Census of population and housing, 1980 (United States): summary tape file 3B. ICPSR version. Washington, DC; 2008.

34. Turner MC, Krewski D, Chen Y, Pope CA 3rd, Gapstur SM, Thun MJ. Radon and lung cancer in the American Cancer Society cohort. *Cancer Epidemiol Biomarkers Prev* 2011;20:438-448.
35. SAS, version 9.2. Cary, NC: SAS Institute, Inc.; 2008.
36. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109;71-77.
37. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology* 2013;24:44-53.
38. Zanobetti A, Schwartz J. Ozone and survival in four cohorts with potentially predisposing diseases. *Am J Respir Crit Care Med* 2011;184:836-41.
39. Bell ML, Zanobetti A, Dominici F. Who is more affected by ozone pollution? A systematic review and meta-analysis. *Am J Epidemiol* 2014;180;15-28.

40. Brown KW, Sarnat JA, Suh HH, Coull BA, Koutrakis P. Factors influencing relationships between personal and ambient concentrations of gaseous and particulate pollutants. *Sci Total Environ* 2009;407:3754-3765.
41. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359:386-391.
42. Chen C, Zhao B, Weschler CJ. Assessing the influence of indoor exposure to "outdoor ozone" on the relationship between ozone and short-term mortality in U.S. communities. *Environ Health Perspect* 2011;120:235-240.
43. Jhun I, Fann N, Zanobetti A, Hubbell B. Effect modification of ozone-related mortality risks by temperature in 97 US cities. *Environ Int* 2014;73:128-134.
44. Williams ML, Atkinson RW, Anderson HR, Kelly FJ. Associations between daily mortality in London and combined oxidant capacity, ozone and nitrogen dioxide. *Air Qual Atmos Health* 2014;7:407-414.
45. U.S. Environmental Protection Agency. Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (Second External Review Draft). Washington, DC.: U.S. Environmental Protection Agency; 2015.

46. Faustini A, Rapp R, Forastiere F. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. *Eur Respir J* 2014;44:744-753.
47. Fischer PH, Marra M, Ameling CB, Hoek G, Beelen R, de Hoogh K, Breugelmans O, Kruize H, Janssen NA, Houthuijs D. Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). *Environ Health Perspect* 2015;123:697-704.
48. Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, Forastiere F. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect* 2013;121:324-331.

FIGURE LEGENDS

Figure 1. Distribution of mean annual daily 8-hour maximum O₃ 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} ($\mu\text{g}/\text{m}^3$) 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)
\geq 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 O₃, near-source and regional PM_{2.5}, and LUR NO₂ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Multipollutant			
			HBM O ₃	Regional PM _{2.5}	Near-source PM _{2.5}	LUR NO ₂
			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; 100-199, 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)

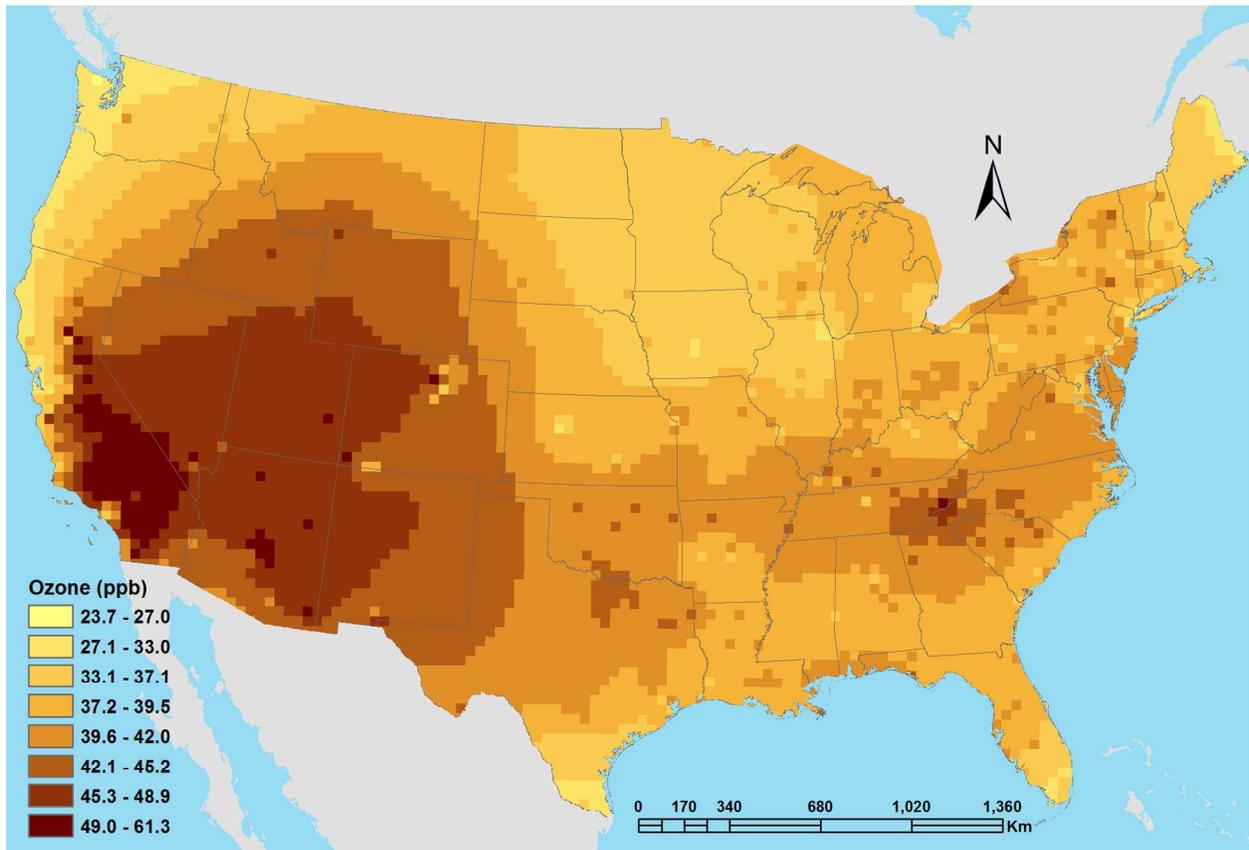
* HRs from multipollutant models including all air pollutants simultaneously; age, race, and sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking < 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 O₃, near-source and regional PM_{2.5}, and LUR NO₂ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	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)
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; 100-199, 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 O₃ concentrations based on a Hierarchical Bayesian Space Time Modeling System (HBM), US, 2002-2004.



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

Michelle C. Turner, Michael Jerrett, C. Arden Pope III, Daniel Krewski, Susan M. Gapstur, W. Ryan Diver, Bernardo S. Beckerman, Julian D. Marshall, Jason Su, Daniel L. Crouse, Richard T. Burnett

Online Data Supplement

Figure E1. Counties with included CPS-II participants in the analytic cohort here compared to the 96 MSAs from Jerrett et al.¹

Figure E2. Distribution of mean monthly LURBME PM_{2.5} concentrations, US, 1999-2004.

Figure E3. Exposure–Response Curve for O₃ associated with Circulatory Mortality (Natural spline, 3 degrees of freedom).

Figure E4. Exposure–Response Curve for O₃ associated with Respiratory Mortality (Natural spline, 3 degrees of freedom).

Table E1. Exclusion of CPS-II participants from the final analytic cohort, follow-up 1982-2004, CPS-II cohort, US.

Table E2. Distribution of air pollution concentrations among CPS-II participants, US (n = 669,046).

Table E3. Correlations between air pollutants.

Table E4. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in PM_{2.5} LURBME concentrations, follow-up 1982-2004, CPS-II cohort, United States (n = 669,046).

Table E5. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, single-pollutant models, impact of 1990 ecological covariates, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E6. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃, near-source and regional PM_{2.5} concentrations, and LUR NO₂ concentrations, single-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E7. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ and near-source and regional PM_{2.5} concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E8. Sensitivity analysis, adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E9. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in summer (April-September) HBM O₃ and near-source and regional PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E10. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ and HBM PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Table E11. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in Downscaler O₃ and near-source and regional PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 545,302).

Table E12. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046), according to different follow-up time periods.

Table E13. Adjusted HRs (95% CIs)* for cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, effect modification, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Figure E1. Counties with included CPS-II participants in the analytic cohort here compared to the 96 MSAs from Jerrett et al.¹.

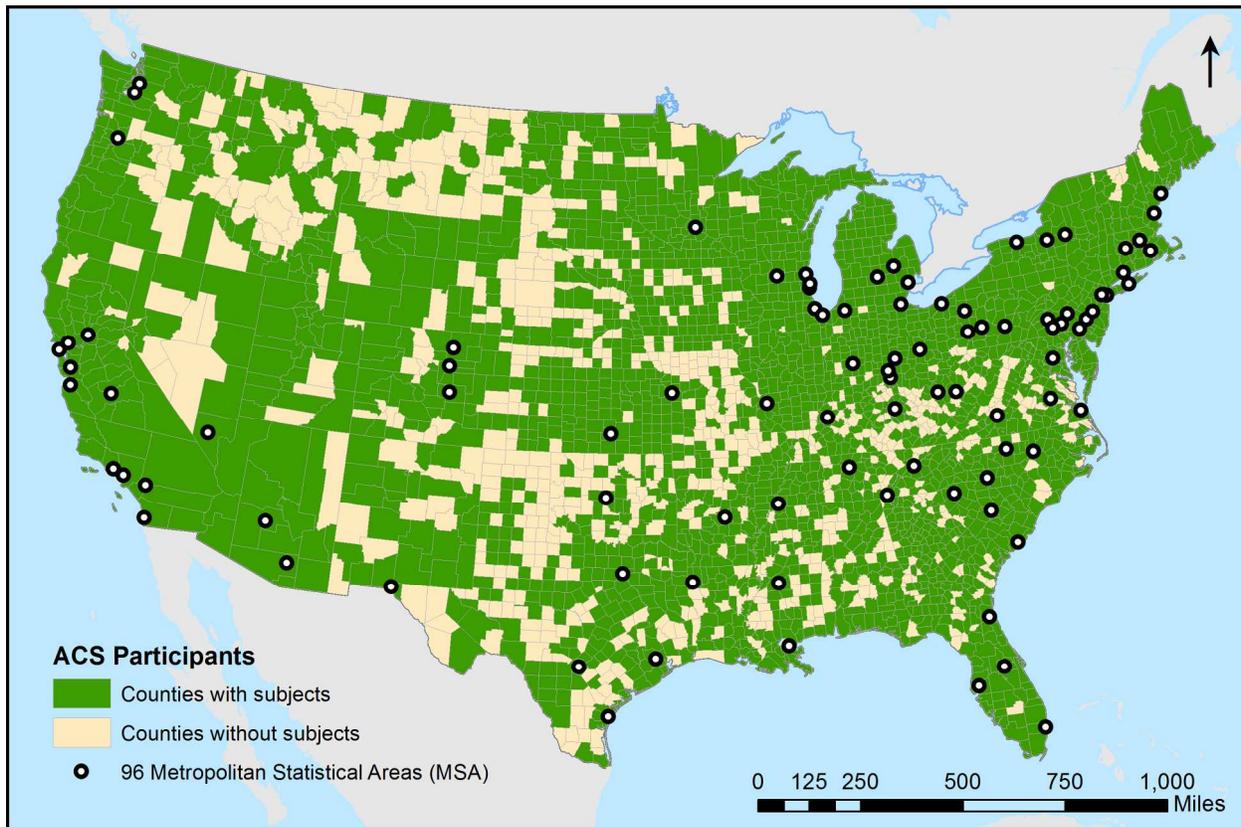


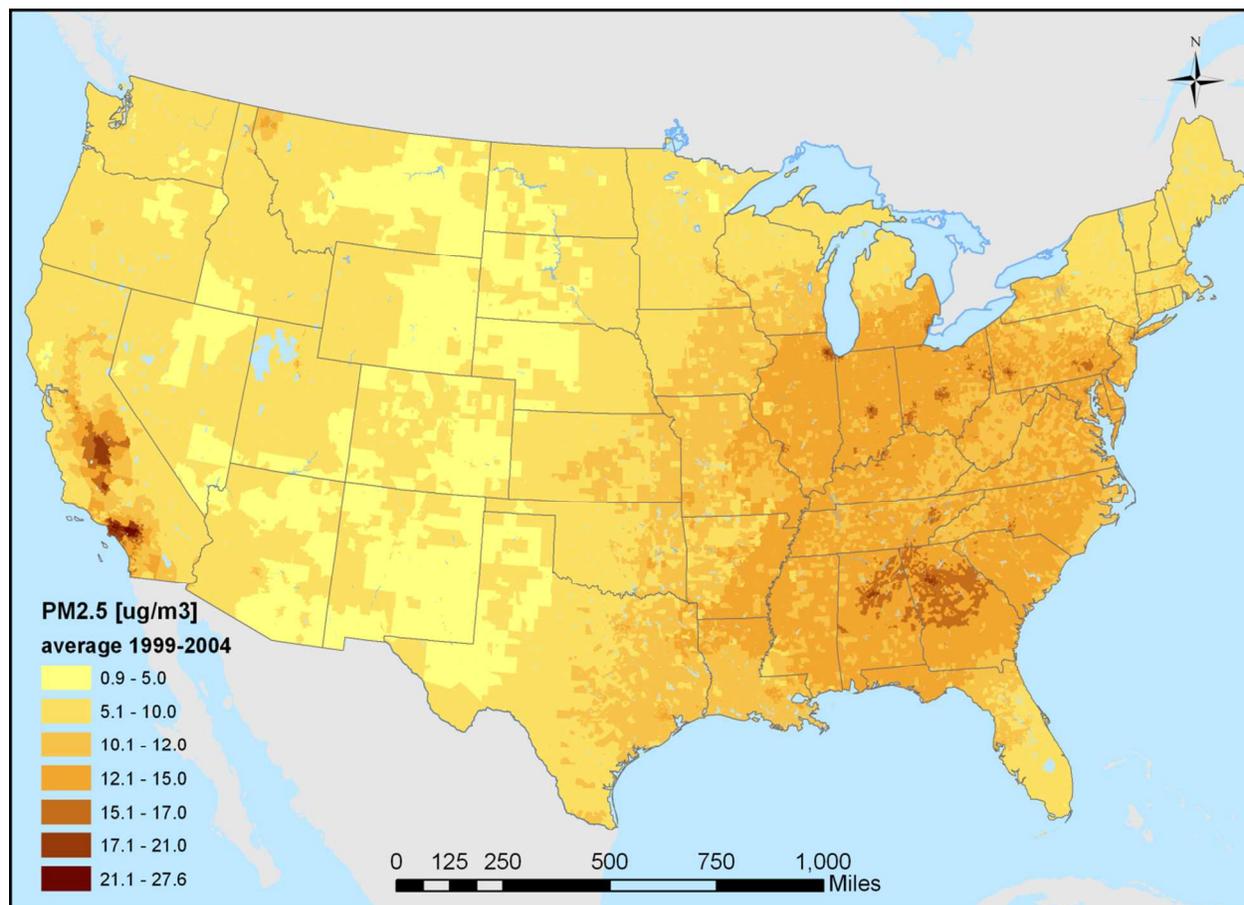
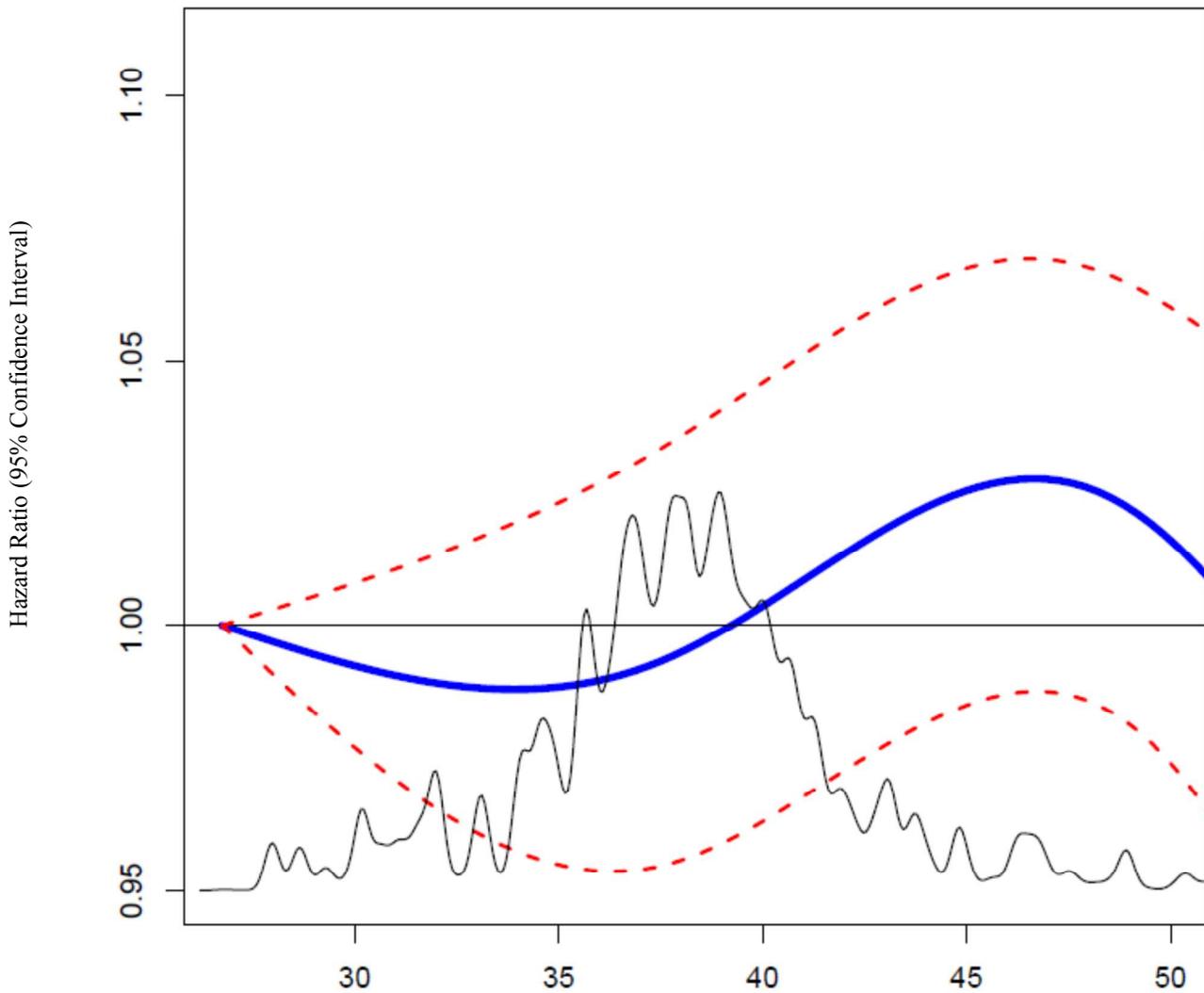
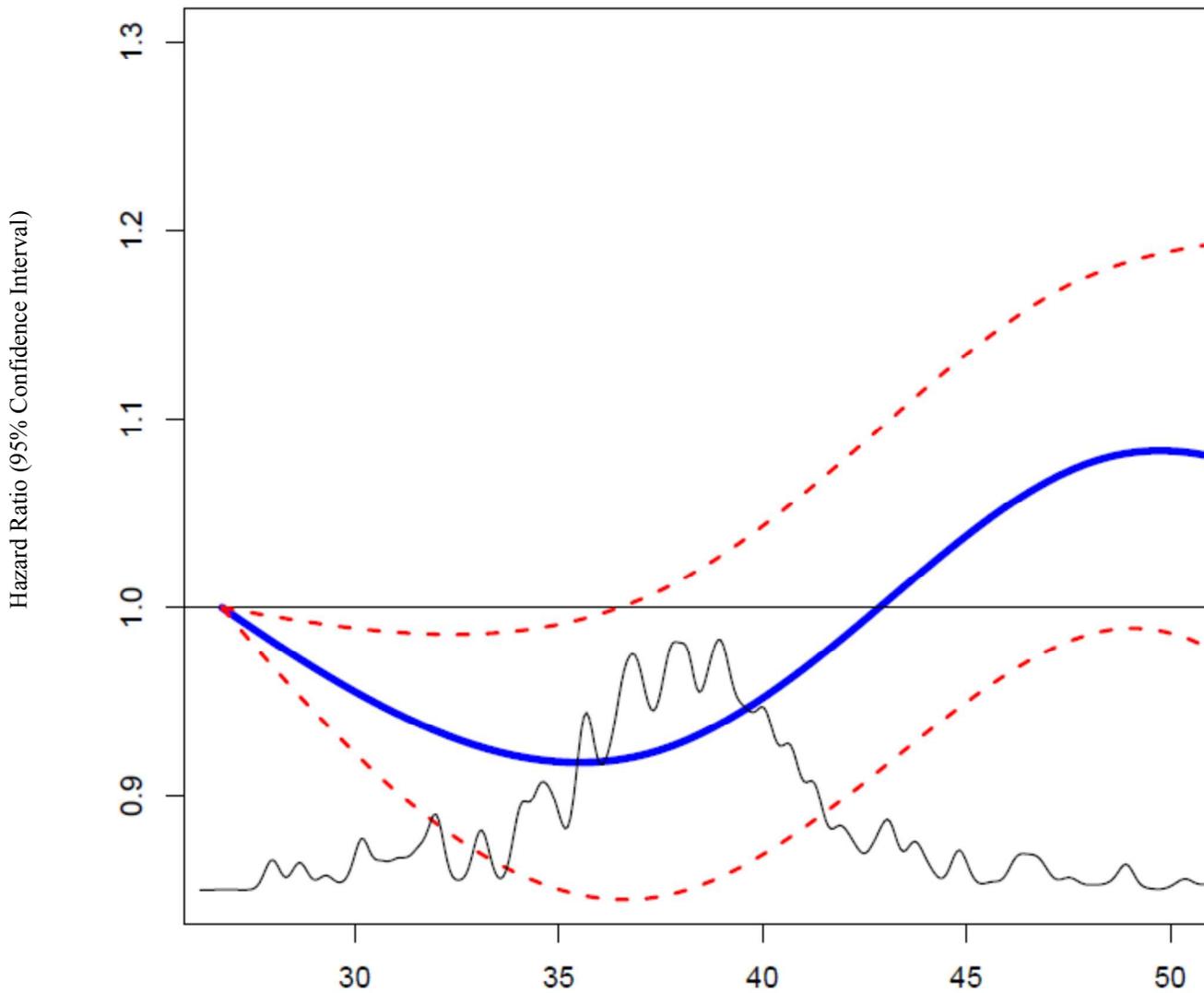
Figure E2. Distribution of mean monthly LURBME PM_{2.5} concentrations, US, 1999-2004.

Figure E3. Exposure–Response Curve for O₃ associated with Circulatory Mortality (Natural spline, 3 degrees of freedom).



Mean annual daily 8-hour maximum O₃ concentrations (ppb), Hierarchical Bayesian Space Time Model (HBM), US, 2002-2004, truncated at 99th percentile. Grey line along abscissa indicates data density.

Figure E4. Exposure–Response Curve for O₃ associated with Respiratory Mortality (Natural spline, 3 degrees of freedom).



Mean annual daily 8-hour maximum O₃ concentrations (ppb), Hierarchical Bayesian Space Time Model (HBM), US, 2002-2004, truncated at 99th percentile. Grey line along abscissa indicates data density.

Table E1. Exclusion of CPS-II participants from the final analytic cohort, follow-up 1982-2004, CPS-II cohort, US.

1. Total CPS-II Population	1,184,587
2. Missing zip code	34,094
3. Missing county	34,271
4. 'PO Box/co' in address	166,471
5. Not geocoded or geocoding score < 80	150,586
6. Missing/erroneous covariate data	
Race	3,661
Education	11,685
Marital Status	3,668
BMI	20,881
Passive Smoking	7,140
Cigarette Smoking	79,625
Radon	3,446
HBM O ₃	13
Total	130,119
7. Total CPS-II population analyzed	669,046

Table E2. Distribution of air pollution concentrations among CPS-II participants, US (n = 669,046).

Air Pollutant (units)	Time Period	Mean (SD)	Minimum	5th	25th	50th	75th	95th	Maximum
HBM O ₃ (ppb)	2002-2004	38.2 (4.0)	26.7	31.1	36.2	38.1	40.1	45.0	59.3
HBM O ₃ (Apr-Sept) (ppb)	2002-2004	47.1 (5.9)	29.1	35.7	44.2	47.4	50.5	56.0	77.2
Downscaler O ₃ (ppb)*	2002-2004	38.5 (3.0)	29.0	32.6	37.0	38.8	40.4	43.0	48.9
LURBME PM _{2.5} (µg/m ³)	1999-2004	12.6 (2.9)	1.4	8.2	10.5	12.5	14.4	17.1	27.9
Near-source PM _{2.5} (µg/m ³)	1999-2004	12.0 (0.9)	8.6	10.4	11.6	12.0	12.5	13.5	19.7
Regional PM _{2.5} (µg/m ³) [†]	1999-2004	0.5 (2.8)	-7.9	-4.0	-1.4	0.5	2.4	4.6	13.0
HBM PM _{2.5} (µg/m ³)	2002-2004	12.1 (2.6)	2.8	7.4	10.4	12.1	14.0	15.9	21.4
LUR NO ₂ (ppb)	2006	11.6 (5.1)	1.0	5.1	8.1	10.8	14.1	21.2	37.6

* n = 545,302 participants

[†] The LURBME PM_{2.5} model was created in three main steps: (1) A base LUR model predicted PM_{2.5} concentrations based on traffic within 1 km and green space within 100 m³; (2) A BME interpolation model was then used to interpolate residual spatiotemporal variation in PM_{2.5} concentrations; (3) The two estimates were then combined. Regional PM_{2.5} concentrations therefore represent a residual with some observations less than zero.

Table E3. Correlations between air pollutants.

Air Pollutant	HBM O ₃	HBM O ₃ (Apr-Sept)	Downscaler O ₃	LURBME PM _{2.5}	Near- source PM _{2.5}	Regional PM _{2.5}	HBM PM _{2.5}	LUR NO ₂
HBM O ₃	-	0.83	0.89	0.18	-0.13	0.23	0.04	-0.08
HBM O ₃ (Apr-Sept)		-	0.58	0.43	-0.12	0.49	0.37	0.12
Downscaler O ₃			-	-0.10	-0.41	0.06	-0.10	-0.42
LURBME PM _{2.5}				-	0.27	0.94	0.84	0.40
Near-source PM _{2.5}					-	-0.06	0.07	0.60
Regional PM _{2.5}						-	0.85	0.21
HBM PM _{2.5}							-	0.39
LUR NO ₂								-

Table E4. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in PM_{2.5} LURBME concentrations, follow-up 1982-2004, CPS-II cohort, United States (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)*
All-cause	All	237,201	1.07 (1.06-1.09)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.13 (1.10-1.15)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.12 (1.09-1.15)
Ischemic heart disease	410-414; I20-I25	45,644	1.14 (1.10-1.18)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.11 (1.05-1.18)
Cerebrovascular disease	430-438; I60-I69	17,085	1.11 (1.05-1.17)
Diabetes	250; E10-E14	4,890	1.13 (1.02-1.26)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.16 (1.10-1.22)
Pneumonia and influenza	480-487; J10-J18	6,599	1.31 (1.20-1.44)
COPD and allied conditions	490-496; J19-J46	9,967	1.10 (1.02-1.19)
Lung Cancer	162; C33-34	16,432	1.09 (1.03-1.16)

* 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 black, Hispanic, post-secondary education, unemployment, and poverty.

Table E5. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, single-pollutant models, impact of 1990 ecological covariates, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)* No ecol. covs.	Fully-adjusted HR (95% CI)* + 6 ecol. covs.	Fully-adjusted HR (95% CI)* + median household income alone	Fully-adjusted HR (95% CI)* + % African American alone	Fully-adjusted HR (95% CI)* + % Hispanic alone	Fully-adjusted HR (95% CI)* + % post-secondary education alone	Fully-adjusted HR (95% CI)* + % unemployment alone	Fully-adjusted HR (95% CI)* + % poverty alone
All-cause	All	237,201	1.02 (1.01-1.03)	1.02 (1.01-1.04)	1.02 (1.01-1.03)	1.02 (1.01-1.04)	1.03 (1.02-1.04)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.03)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.04 (1.02-1.05)	1.03 (1.02-1.05)	1.03 (1.01-1.05)	1.04 (1.02-1.05)	1.04 (1.03-1.06)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	1.03 (1.01-1.05)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.03 (1.02-1.05)	1.03 (1.01-1.05)	1.03 (1.01-1.04)	1.03 (1.02-1.05)	1.04 (1.02-1.06)	1.02 (1.00-1.04)	1.02 (1.01-1.04)	1.03 (1.01-1.05)
Ischemic heart disease	410-414; I20-I25	45,644	0.98 (0.96-1.00)	0.98 (0.95-1.00)	0.99 (0.96-1.01)	0.98 (0.96-1.00)	0.97 (0.95-1.00)	0.97 (0.95-0.99)	0.97 (0.95-0.99)	0.98 (0.96-1.00)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.13 (1.09-1.17)	1.16 (1.11-1.20)	1.11 (1.07-1.15)	1.13 (1.09-1.17)	1.17 (1.13-1.22)	1.12 (1.08-1.16)	1.12 (1.08-1.17)	1.12 (1.08-1.16)
Cerebrovascular disease	430-438; I60-I69	17,085	1.06 (1.02-1.10)	1.04 (1.00-1.08)	1.04 (1.00-1.08)	1.06 (1.02-1.10)	1.07 (1.03-1.11)	1.06 (1.02-1.10)	1.06 (1.02-1.10)	1.05 (1.01-1.09)
Diabetes	250; E10-E14	4,890	1.11 (1.04-1.19)	1.14 (1.05-1.23)	1.11 (1.03-1.20)	1.11 (1.04-1.19)	1.12 (1.04-1.20)	1.12 (1.04-1.20)	1.10 (1.03-1.18)	1.12 (1.04-1.20)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.13 (1.09-1.17)	1.14 (1.10-1.18)	1.13 (1.09-1.17)	1.13 (1.09-1.16)	1.13 (1.09-1.17)	1.14 (1.10-1.18)	1.12 (1.08-1.16)	1.13 (1.09-1.17)
Pneumonia and influenza	480-487; J10-J18	6,599	1.12 (1.06-1.09)	1.15 (1.08-1.23)	1.15 (1.08-1.22)	1.12 (1.05-1.19)	1.11 (1.04-1.17)	1.14 (1.07-1.21)	1.11 (1.05-1.18)	1.13 (1.06-1.20)
COPD and allied conditions	490-496; J19-J46	9,967	1.17 (1.11-1.22)	1.14 (1.09-1.21)	1.15 (1.09-1.21)	1.16 (1.11-1.22)	1.16 (1.10-1.22)	1.18 (1.12-1.24)	1.16 (1.10-1.22)	1.16 (1.10-1.22)
Lung Cancer	162; C33-34	16,432	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.97 (0.93-1.01)	0.98 (0.94-1.02)	0.99 (0.95-1.03)	0.98 (0.94-1.02)	0.98 (0.94-1.02)	0.97 (0.93-1.01)

* 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 plus year 1990 ecological covariates: median household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty as indicated above.

Table E6. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃, near-source and regional PM_{2.5} concentrations, and LUR NO₂ concentrations, single-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Single-pollutant			
			HBM O ₃	Regional PM _{2.5}	Near-source PM _{2.5}	LUR NO ₂
			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)	1.05 (1.03-1.07)	1.27 (1.21-1.34)	1.04 (1.03-1.06)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.03 (1.02-1.05)	1.09 (1.07-1.12)	1.45 (1.35-1.57)	1.08 (1.06-1.09)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.03 (1.01-1.05)	1.09 (1.06-1.12)	1.42 (1.31-1.54)	1.08 (1.06-1.10)
Ischemic heart disease	410-414; I20-I25	45,644	0.98 (0.95-1.00)	1.09 (1.05-1.13)	1.74 (1.55-1.94)	1.14 (1.11-1.17)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.16 (1.11-1.20)	1.12 (1.06-1.19)	1.02 (0.86-1.22)	1.02 (0.98-1.06)
Cerebrovascular disease	430-438; I60-I69	17,085	1.04 (1.00-1.08)	1.09 (1.03-1.16)	1.20 (1.00-1.45)	0.99 (0.95-1.02)
Diabetes	250; E10-E14	4,890	1.14 (1.05-1.23)	1.07 (0.96-1.20)	1.88 (1.32-2.66)	1.09 (1.01-1.17)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.14 (1.10-1.18)	1.16 (1.10-1.23)	1.06 (0.89-1.25)	1.03 (0.99-1.07)
Pneumonia and influenza	480-487; J10-J18	6,599	1.15 (1.08-1.23)	1.33 (1.21-1.46)	1.07 (0.80-1.44)	1.11 (1.05-1.18)
COPD and allied conditions	490-496; J19-J46	9,967	1.14 (1.09-1.21)	1.10 (1.02-1.19)	1.06 (0.84-1.34)	1.01 (0.96-1.06)
Lung Cancer	162; C33-34	16,432	0.98 (0.93-1.02)	1.08 (1.01-1.15)	1.16 (0.96-1.39)	0.99 (0.95-1.03)

* 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.

Table E7. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ and near-source and regional PM_{2.5} concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Multipollutant		
			HBM O ₃	Regional PM _{2.5}	Near-source PM _{2.5}
			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)	1.05 (1.03-1.06)	1.30 (1.24-1.37)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; I00-I99, E10-E14	105,039	1.03 (1.01-1.05)	1.08 (1.06-1.11)	1.50 (1.39-1.62)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.03 (1.01-1.05)	1.09 (1.06-1.12)	1.46 (1.34-1.59)
Ischemic heart disease	410-414; I20-I25	45,644	0.97 (0.95-1.00)	1.11 (1.07-1.15)	1.73 (1.54-1.94)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.15 (1.10-1.20)	1.06 (1.00-1.13)	1.13 (0.95-1.35)
Cerebrovascular disease	430-438; I60-I69	17,085	1.03 (0.99-1.07)	1.09 (1.02-1.16)	1.24 (1.03-1.50)
Diabetes	250; E10-E14	4,890	1.16 (1.07-1.26)	1.02 (0.91-1.14)	2.07 (1.45-2.95)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.12 (1.08-1.16)	1.11 (1.05-1.17)	1.15 (0.98-1.36)
Pneumonia and influenza	480-487; J10-J18	6,599	1.10 (1.03-1.18)	1.28 (1.16-1.41)	1.17 (0.87-1.57)
COPD and allied conditions	490-496; J19-J46	9,967	1.14 (1.08-1.21)	1.05 (0.96-1.13)	1.16 (0.92-1.48)
Lung Cancer	162; C33-34	16,432	0.96 (0.92-1.01)	1.10 (1.03-1.17)	1.14 (0.95-1.37)

* 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.

Table E8. Sensitivity analysis, adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)* + elevation alone	Fully-adjusted HR (95% CI)* + MSA size alone	Fully-adjusted HR (95% CI)* + temperature alone	Fully-adjusted HR (95% CI)* + % air conditioning alone
All-cause	All	237,201	1.02 (1.01-1.04)	1.02 (1.01-1.04)	1.02 (1.01-1.04)	1.03 (1.02-1.04)	1.03 (1.02-1.05)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.04 (1.02-1.06)
Cardiovascular	410-440; I20-I25, I30-I51, 160-169, I70	84,132	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.02 (1.00-1.04)	1.02 (1.00-1.04)	1.03 (1.01-1.06)
Ischemic heart disease	410-414; I20-I25	45,644	0.97 (0.95-1.00)	0.97 (0.95-1.00)	0.98 (0.95-1.01)	0.97 (0.94-0.99)	0.98 (0.95-1.01)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.15 (1.10-1.20)	1.15 (1.10-1.20)	1.13 (1.08-1.17)	1.17 (1.12-1.22)	1.15 (1.10-1.20)
Cerebrovascular disease	430-438; I60-I69	17,085	1.03 (0.99-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.08)	1.02 (0.97-1.06)	1.05 (1.01-1.10)
Diabetes	250; E10-E14	4,890	1.16 (1.07-1.26)	1.16 (1.07-1.26)	1.16 (1.07-1.26)	1.19 (1.09-1.29)	1.16 (1.07-1.26)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.12 (1.08-1.16)	1.12 (1.08-1.16)	1.12 (1.07-1.16)	1.12 (1.08-1.17)	1.15 (1.10-1.19)
Pneumonia and influenza	480-487; J10-J18	6,599	1.10 (1.03-1.18)	1.10 (1.03-1.18)	1.11 (1.03-1.19)	1.11 (1.03-1.19)	1.15 (1.07-1.23)
COPD and allied conditions	490-496; J19-J46	9,967	1.14 (1.08-1.21)	1.14 (1.08-1.21)	1.14 (1.07-1.21)	1.14 (1.08-1.21)	1.16 (1.10-1.23)
Lung Cancer	162; C33-34	16,432	0.96 (0.92-1.01)	0.96 (0.92-1.01)	0.96 (0.91-1.00)	0.93 (0.89-0.98)	0.95 (0.91-1.00)

* Age, race, sex stratified and adjusted for near-source and regional PM_{2.5}, 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 as well as elevation (\geq 95th percentile vs < 95th percentile), MSA size (categories of no MSA; <100,000; 100,000 to 249,999; 250,000 to 499,999; 500,000 to 999,999; 1,000,000+ population), annual average daily maximum air temperature (2002-2004) (cutpoints at the 10th, 20th, 30th, 40th, 60th, 70th, 80th, and 90th percentiles), and 1980 percent air conditioning as indicated.

Table E9. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in summer (April-September) HBM O₃ and near-source and regional PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

			Single pollutant			Multipollutant		
			HBM O ₃ (Aug-Sept)	Regional PM _{2.5}	Near source PM _{2.5}	HBM O ₃ (Aug-Sept)	Regional PM _{2.5}	Near source PM _{2.5}
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)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*
All-cause	All	237,201	1.02 (1.02-1.03)	1.05 (1.03-1.07)	1.27 (1.21-1.34)	1.02 (1.01-1.03)	1.03 (1.01-1.05)	1.31 (1.24-1.37)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.03 (1.02-1.04)	1.09 (1.07-1.12)	1.45 (1.35-1.57)	1.02 (1.01-1.03)	1.07 (1.04-1.11)	1.50 (1.39-1.61)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.02 (1.01-1.04)	1.09 (1.06-1.12)	1.42 (1.31-1.54)	1.01 (1.00-1.03)	1.08 (1.05-1.12)	1.46 (1.34-1.59)
Ischemic heart disease	410-414; I20-I25	45,644	0.99 (0.98-1.01)	1.09 (1.05-1.13)	1.74 (1.55-1.94)	0.98 (0.96-1.00)	1.13 (1.08-1.18)	1.72 (1.54-1.93)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.09 (1.07-1.12)	1.12 (1.06-1.19)	1.02 (0.86-1.22)	1.09 (1.06-1.13)	1.01 (0.94-1.08)	1.12 (0.94-1.35)
Cerebrovascular disease	430-438; I60-I69	17,085	1.03 (1.01-1.06)	1.09 (1.03-1.16)	1.20 (1.00-1.45)	1.02 (0.99-1.05)	1.07 (1.00-1.15)	1.25 (1.04-1.50)
Diabetes	250; E10-E14	4,890	1.08 (1.03-1.14)	1.07 (0.96-1.20)	1.88 (1.32-2.66)	1.11 (1.05-1.17)	0.96 (0.84-1.09)	2.07 (1.45-2.96)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.10 (1.07-1.12)	1.16 (1.10-1.23)	1.06 (0.89-1.25)	1.08 (1.06-1.11)	1.06 (0.99-1.13)	1.16 (0.98-1.37)
Pneumonia and influenza	480-487; J10-J18	6,599	1.14 (1.10-1.19)	1.33 (1.21-1.46)	1.07 (0.80-1.44)	1.10 (1.05-1.16)	1.19 (1.06-1.32)	1.21 (0.90-1.62)
COPD and allied conditions	490-496; J19-J46	9,967	1.08 (1.05-1.12)	1.10 (1.02-1.19)	1.06 (0.84-1.34)	1.09 (1.05-1.13)	1.00 (0.92-1.10)	1.16 (0.91-1.47)
Lung Cancer	162; C33-34	16,432	0.99 (0.97-1.02)	1.08 (1.01-1.15)	1.16 (0.96-1.39)	0.97 (0.94-1.00)	1.12 (1.05-1.21)	1.14 (0.94-1.37)

* 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. Multipollutant models include all air pollutants simultaneously.

Table E10. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ and HBM PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Cause of Death	ICD 9; 10	No. of Deaths	Single pollutant		Multipollutant	
			HBM O ₃	HBM PM _{2.5}	HBM O ₃	HBM PM _{2.5}
			Fully-adjusted HR (95% CI)*			
All-cause	All	237,201	1.02 (1.01-1.04)	1.06 (1.04-1.08)	1.02 (1.01-1.03)	1.06 (1.04-1.08)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	105,039	1.03 (1.02-1.05)	1.09 (1.07-1.12)	1.03 (1.01-1.04)	1.09 (1.06-1.12)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	84,132	1.03 (1.01-1.05)	1.09 (1.06-1.12)	1.02 (1.00-1.04)	1.08 (1.05-1.11)
Ischemic heart disease	410-414; I20-I25	45,644	0.98 (0.95-1.00)	1.11 (1.07-1.16)	0.97 (0.94-0.99)	1.12 (1.08-1.17)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,314	1.16 (1.11-1.20)	1.04 (0.97-1.11)	1.15 (1.11-1.20)	1.00 (0.94-1.07)
Cerebrovascular disease	430-438; I60-I69	17,085	1.04 (1.00-1.08)	1.11 (1.04-1.19)	1.03 (0.99-1.07)	1.11 (1.03-1.18)
Diabetes	250; E10-E14	4,890	1.14 (1.05-1.23)	1.14 (1.01-1.29)	1.13 (1.04-1.22)	1.11 (0.98-1.26)
Diseases of the respiratory system	460-519; J00-J98	20,484	1.14 (1.10-1.18)	1.12 (1.05-1.18)	1.13 (1.09-1.17)	1.08 (1.02-1.15)
Pneumonia and influenza	480-487; J10-J18	6,599	1.15 (1.08-1.23)	1.33 (1.20-1.47)	1.13 (1.06-1.20)	1.29 (1.16-1.43)
COPD and allied conditions	490-496; J19-J46	9,967	1.14 (1.09-1.21)	1.04 (0.96-1.14)	1.14 (1.08-1.21)	1.01 (0.93-1.10)
Lung Cancer	162; C33-34	16,432	0.98 (0.93-1.02)	1.11 (1.04-1.18)	0.96 (0.92-1.01)	1.12 (1.04-1.20)

* 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. Multipollutant models include both air pollutants simultaneously.

Table E11. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in Downscaler O₃ and near-source and regional PM_{2.5} concentrations, single- and multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 545,302).

Cause of Death	ICD 9; 10	No. of Deaths	Single pollutant			Multipollutant		
			Downscaler O ₃	Regional PM _{2.5}	Near-source PM _{2.5}	Downscaler O ₃	Regional PM _{2.5}	Near-source PM _{2.5}
			Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*
All-cause	All	191,553	1.02 (1.01-1.04)	1.10 (1.08-1.13)	1.26 (1.19-1.33)	1.05 (1.03-1.07)	1.11 (1.09-1.14)	1.39 (1.31-1.48)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	84,873	1.01 (0.99-1.04)	1.13 (1.09-1.17)	1.46 (1.34-1.58)	1.06 (1.03-1.09)	1.15 (1.11-1.19)	1.64 (1.50-1.80)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	67,877	1.01 (0.98-1.04)	1.10 (1.06-1.15)	1.44 (1.31-1.58)	1.06 (1.03-1.09)	1.12 (1.08-1.17)	1.61 (1.45-1.78)
Ischemic heart disease	410-414; I20-I25	37,024	0.92 (0.89-0.96)	1.00 (0.95-1.05)	1.81 (1.59-2.06)	0.98 (0.94-1.02)	1.03 (0.98-1.09)	1.77 (1.54-2.04)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	15,036	1.21 (1.14-1.29)	1.30 (1.20-1.41)	1.01 (0.83-1.24)	1.24 (1.16-1.32)	1.29 (1.19-1.40)	1.43 (1.15-1.78)
Cerebrovascular disease	430-438; I60-I69	13,312	1.06 (1.00-1.13)	1.22 (1.12-1.33)	1.15 (0.93-1.43)	1.08 (1.01-1.15)	1.23 (1.13-1.34)	1.36 (1.08-1.71)
Diabetes	250; E10-E14	3,960	1.10 (0.98-1.24)	1.37 (1.17-1.60)	1.92 (1.29-2.86)	1.21 (1.06-1.37)	1.41 (1.20-1.65)	2.71 (1.75-4.20)
Diseases of the respiratory system	460-519; J00-J98	16,127	1.14 (1.08-1.21)	1.17 (1.08-1.26)	0.87 (0.72-1.05)	1.14 (1.07-1.21)	1.15 (1.07-1.25)	1.07 (0.87-1.31)
Pneumonia and influenza	480-487; J10-J18	4,990	1.17 (1.06-1.30)	1.32 (1.15-1.52)	0.76 (0.54-1.06)	1.15 (1.03-1.28)	1.30 (1.13-1.49)	0.97 (0.67-1.41)
COPD and allied conditions	490-496; J19-J46	7,932	1.11 (1.03-1.21)	1.07 (0.96-1.19)	0.88 (0.67-1.15)	1.11 (1.02-1.21)	1.05 (0.94-1.17)	1.02 (0.76-1.36)
Lung Cancer	162; C33-34	13,683	0.99 (0.93-1.06)	1.11 (1.02-1.20)	1.22 (0.99-1.50)	1.02 (0.95-1.09)	1.12 (1.03-1.22)	1.29 (1.03-1.61)

* 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. Multipollutant models include all air pollutants simultaneously. Note HRs among the same 545,302 participants here using HBM O₃ in the two-pollutant model for all-cause, circulatory, and respiratory mortality respectively were 1.06, 95% CI 1.04-1.08; 1.06, 95% CI 1.03-1.09; and 1.18, 95% CI 1.10-1.26 respectively.

Table E12. Adjusted HRs (95% CIs)* for all-cause and cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046), according to different follow-up time periods.

Time Period		1982-1989		1990-1999		2000-2004	
Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)*	No. of Deaths	Fully-adjusted HR (95% CI)*	No. of Deaths	Fully-adjusted HR (95% CI)*
All-cause	All	59,588	1.01 (0.98-1.03)	115,614	1.03 (1.01-1.05)	61,999	1.03 (1.01-1.06)
Diseases of the circulatory system (plus diabetes) ²	390-459, 250; 100-199, E10-E14	26,746	1.00 (0.96-1.03)	51,870	1.04 (1.02-1.07)	26,423	1.04 (1.00-1.07)
Cardiovascular	410-440; I20-I25, I30-I51, I60-I69, I70	23,902	0.99 (0.96-1.03)	37,380	1.04 (1.01-1.07)	22,850	1.03 (1.00-1.07)
Ischemic heart disease	410-414; I20-I25	15,252	0.95 (0.91-0.99)	17,490	0.98 (0.94-1.03)	12,902	0.99 (0.95-1.05)

* Age, race, sex stratified and adjusted for near-source and regional PM_{2.5}, 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 E13. Adjusted HRs (95% CIs)* for cause-specific mortality in relation to each 10 unit increase in HBM O₃ concentrations, effect modification, multi-pollutant models, follow-up 1982-2004, CPS-II cohort, US (n = 669,046).

Stratification variable	Subjects in stratum	Diseases of the circulatory system (plus diabetes) ²	Respiratory
	n	Fully-adjusted HR (95% CI)*	Fully-adjusted HR (95% CI)*
Temperature (°C)			
<12.6	66,838	1.20 (1.11-1.30)	1.31 (1.09-1.57)
12.6-<13.8	66,924	1.02 (0.96-1.09)	0.99 (0.85-1.15)
13.8-<14.4	66,586	1.06 (0.98-1.14)	1.26 (1.05-1.50)
14.4-<15.4	67,185	1.08 (1.01-1.16)	1.31 (1.11-1.56)
15.4-<17.9	133,379	1.02 (0.97-1.07)	1.31 (1.18-1.46)
17.9-<20.4	67,108	0.94 (0.88-1.01)	0.97 (0.83-1.12)
20.4-<22.4	60,584	1.00 (0.94-1.06)	0.96 (0.85-1.10)
22.4-<25.2	72,514	1.03 (0.97-1.09)	0.92 (0.81-1.06)
25.2+	67,928	1.08 (1.03-1.15)	1.29 (1.14-1.46)
<i>p</i> value		< 0.001	< 0.001
Respiratory Disease			
None	611,989	-	1.13 (1.08-1.18)
Any	57,057		1.01 (0.94-1.09)
<i>p</i> value			0.009
Cardiovascular Disease			
None	436,759	1.04 (1.01-1.07)	-
Any	232,287	1.01 (0.99-1.04)	
<i>p</i> value		0.01	
Age			
< 65 years	516,426	-	1.22 (1.15-1.30)
>= 65 years	152,620		1.07 (1.01-1.12)
<i>p</i> value			< 0.001

* Age, race, sex stratified and adjusted for near-source and regional PM_{2.5}, 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 where appropriate. Results presented where significant effect modification was observed ($p < 0.05$).

References

1. Jerrett M, Burnett R, Pope CA 3rd, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085-1095.
2. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109;71-77.