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AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201806-1161OC

Long-term Exposure to Ozone and Cause-Specific Mortality Risk in the U.S.

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Abstract

Rationale: Many studies have linked short-term exposure to ozone (O_3) with morbidity and mortality, but epidemiological evidence of associations between long-term ozone exposure and mortality is more limited.

Objectives: We investigated associations of long-term (annual or warm season average) O_3 exposure with all-cause and cause-specific mortality in the NIH-AARP Diet and Health Study, a large prospective cohort of U.S. adults with 17 years of follow-up from 1995 to 2011.

Methods: The cohort (N=548,780) was linked to census tract-level estimates for O_3. Associations between long-term O_3 exposure (averaged values from 2002-2010) and multiple causes of death were evaluated using multivariate Cox proportional hazards models, adjusted for both individual- and census tract-level covariates, as well as potentially confounding co-pollutants and temperature.

Measurements and Main Results: Long-term annual average exposure to O_3 was significantly associated with deaths due to cardiovascular disease (per 10 ppb, HR=1.03; 95% CI: 1.01-1.06), ischemic heart disease (HR=1.06; 95% CI: 1.02-1.09), respiratory disease (HR=1.04; 95% CI: 1.00-1.09), and chronic obstructive pulmonary disease (HR=1.09; 95% CI: 1.03-1.15) in single-pollutant models. The results were robust to alternative models and adjustment for co-pollutants (fine particulate matter and nitrogen dioxide), although some evidence of confounding by temperature was observed. Significantly elevated respiratory disease mortality risk associated with long-term O_3 exposure was found among those living in locations with high temperature (*p-interaction*<0.05).

Conclusions: This study found that long-term exposure to O_3 is associated with increased risk for multiple causes of mortality, suggesting that establishment of annual and/or seasonal federal O_3 standard(s) are needed to more adequately protect public health from ambient O_3 exposures.

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At a Glance Summary

Scientific Knowledge on the Subject: Effects of long-term exposure to O_3 on mortality risk remain unclear. Past epidemiological studies have reported mixed findings or have used exposure estimates for O_3 with relatively coarse spatial resolutions.

What This Study Adds to the Field: This large U.S prospective cohort study examined the association between long-term ambient O_3 exposure and cause-specific mortality using spatiotemporally detailed exposure data from recent prediction models for O_3, $PM_{2.5}$, and NO_2. The findings suggest that long-term exposures to ambient O_3 may be associated with an increased risk of cardiovascular and respiratory disease mortality.

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Introduction

Ozone (O_3) is a known respiratory irritant that causes bronchial inflammation and hyper-responsiveness (1). The dosimetry of O_3 in the lung and its potential to cause oxidative injury and inflammation has been well established in mechanistic and human exposure studies (2). Among epidemiologic investigations, short-term exposures (a day or a few days) to O_3 have been linked with increases in cardiopulmonary mortality and morbidity in many different regions of the world, and among both adults and children (3-6). For example, short-term increases in O_3 increased risk of acute care visits and hospitalization for asthma (7) and chronic obstructive pulmonary disease (COPD) (8), as well as deterioration in asthma control, resulting in increased medication use (9).

In contrast to the robust body evidence from short-term exposure studies, effects of long-term exposure to O_3 on health are less well documented (2), with a recent meta-analysis finding no evidence of an association between long-term annual O_3 concentration and mortality (10). Estimates of the global burden of mortality attributable to O_3 (11-14) have relied on a single study population, analyses of effects of long-term O_3 in the American Cancer Society CPS-II cohort by Jerrett et al. (2009) (15) and the updated CPS-II cohort estimates of mortality risks with longer follow-up and improved exposure estimates by (16) Turner et al. (2016). Thus, additional large cohort studies are required to independently confirm this association between long-term exposure to O_3 on mortality risk and to develop improved concentration-response functions.

In this study, we evaluated the associations between long-term (annual or warm season averages) exposures to O_3 and cause-specific mortality risk in the NIH-AARP Diet and Cancer Study, a prospective cohort of more than a half million participants across multiple U.S. states with 17 years of follow-up from 1995 to 2011, with a detailed consideration of effect modification by individual risk factors and potential confounding by co-pollutants and temperature. We employed recent spatiotemporally resolved national-level estimates for O_3 from the U.S. Environmental Protection Agency (EPA) to assign exposure at the census-tract level.

Methods

Study Population

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Briefly, the NIH-AARP Diet and Health Study was initiated when members of the AARP, 50–71 years of age from six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia; Detroit, Michigan), responded to a mailed questionnaire in 1995-1996. Study participants completed a baseline questionnaire including demographic and lifestyle information. All participants provided written informed consent. The study was approved by the Institutional Review Boards of the National Cancer Institute and the New York University School of Medicine.

Cohort Follow-up and Mortality Ascertainment

Each participant was followed from enrollment to the end of follow-up (31 December 2011), the date of death, or the date a participant moved out of the study state or city where s/he lived at enrollment (movers included 42,786 participants), whichever occurred first. Vital status was ascertained through a periodic linkage of the cohort to the Social Security Administration Death Master File and follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master, cancer registry linkage, questionnaire responses, and responses to other mailings. The International Classification of Diseases, 9th Revision (ICD-9) and the International Statistical Classification of Diseases, 10th Revision (ICD-10) were used to define underlying cause of mortality due to cardiovascular diseases (ICD-9: 390-459; ICD-10: I00-I99); ischemic heart disease (ICD-9: 410-414; ICD-10: I20-I25); cerebrovascular disease (ICD-9: 430-438; ICD-10: I60-I69); cardiac arrests (ICD-9: 420-429; ICD-10: I30-I51); respiratory diseases (ICD-9: 460-519; ICD 10: J00-J98); chronic obstructive pulmonary disease (ICD-9: 491-492, 494, 496; ICD-10: J40-J44); pneumonia and influenza (ICD-9: 480-48; ICD-10: J00-J98); and lung cancer (ICD-9: 162; ICD-10: C33-C34).

Out of 566,398 participants enrolled in the NIH-AARP cohort and available for analysis, after excluding those who responded via a proxy (N=15,760), exited the study on the study entry date (N=49), and those with missing $PM_{2.5}$ (N=740), NO_2 (N=1,796), or temperature (N=858) exposure data, the analytic cohort for this work includes 548,780 participants (96.9% of total cohort).

Exposure Assessment

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Annual O_3 concentrations were assigned to each participant's residence census tract using the EPA Fused Air Quality Surface Using Downscaling (FAQSD) data (17), which is available for the years after 2002. A Bayesian space-time downscaler model is used to "fuse" daily 8-hour maximum O_3 concentrations at the census tract centroid. The downscaler model develops a relationship between observed and modeled concentrations, and uses that relationship to spatially predict measurements at new locations in the spatial domain based on input data. Estimates are based on National Air Monitoring Stations/State and Local Air Monitoring Stations and Model-3/Community Multiscale Air Quality (CMAQ) model data in 12x12-km grids.

Annual census-tract level $PM_{2.5}$ exposure estimates were obtained from a published spatio-temporal prediction model (18) for the continental U.S., available for 1980-2010. In brief, geographic predictors and annual average $PM_{2.5}$ data from 1999 through 2010 were derived from the EPA Federal Reference Method (FRM) network and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network. Temporal trends before 1999 were estimated using a) extrapolation based on $PM_{2.5}$ data in FRM/IMPROVE, b) $PM_{2.5}$ sulfate data in the Clean Air Status and Trends Network, and c) visibility data across the Weather-Bureau-Army-Navy network. The modeling approach was validated using $PM_{2.5}$ data collected before 1999 from other data sources.

Annual NO_2 data were derived at the census-tract level from a recent model (19) available for years 1990-2012, which applied kriging models combining land use regression methods with satellite data to improve model performance. The satellite data consist of total tropospheric NO_2 measured via satellite images from the Ozone Monitoring Instrument on the Aurora satellite, while the estimation regression covariates were dimension-reduced components of 418 geographic variables.

To assess temperature exposure at the census-tract level, climate datasets were obtained from the PRISM Climate Group (20). The dataset utilizes the PRISM (Parameter-elevation Relationships on Independent Slopes Model) interpolation method to develop gridded data sets with 4 km resolution that reflect spatial climate patterns in the United States; surface stations used in the analysis numbered nearly 13,000 for precipitation and 10,000 for temperature. Annual averages calculated from daily maximum (T_{max}) temperature data were linked to study participants from temperature grid value nearest to the census tract centroid.

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Statistical Methods

Person-years were calculated from enrollment date to the date of death, the end of follow-up (31 December 2011), or the date the participant moved out of the study state or city where s/he lived at enrollment, whichever occurred first. Cox proportional hazards models were employed to examine the associations of mean O_3, $PM_{2.5}$, and NO_2 concentration levels (average of annual levels for the years 2002-2010, in order to match more limited O_3 data availability) with all-cause and cause-specific mortality. Warm season O_3 exposure was also assigned by calculating averages for April-September. Hazard ratios (HR) were presented in relation to increments of 10 ppb for O_3 and NO_2 and 10 µg/m^3 for $PM_{2.5}$.

Fully-adjusted multivariable models included the following individual-level variables: age (grouped into 3-year categories), sex, region (6 U.S. states and two cities) as strata; race or ethnic group (Non-Hispanic White; Non-Hispanic Black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; unknown); level of education (less than high school, some high school, high school completed, post-high school or some college, college and post graduate, unknown); marital status (married, never-married, other, unknown); body-mass index (BMI) (<18.5 kg/m^2, 18.5-<25.0, 25.0-<30.0, 30-<35, 35+, unknown); alcohol (none, <1, 1-<2, 2-<3, 3-<5 and 5+ drinks per day); smoking status (never smoker, former smoker of <= 1 pack/d, former smoker of >1 pack/d, current smoker of <= 1 pack/d, current smoker of >1 pack/d, unknown), and diet (by the alternative Mediterranean (aMED) index that measures adherence to a Mediterranean diet pattern (21)), in addition to two contextual characteristics (median census tract household income and percent of census tract population with less than a high school education, based on the 2000 decennial census for the residence at study entry). The proportional hazards assumption was checked by examining the Schoenfeld residuals.

Potential effect modification by risk factors was assessed by including multiplicative interaction terms between the exposure term and covariates of interest in the models, while likelihood ratio tests comparing model fit with and without interaction terms were conducted to test their statistical significance. We similarly assessed potential effect modification as well as confounding by annual mean T_{max}. For additional sensitivity analyses other models were tested, including: adjusting for other comorbid conditions (heart disease, diabetes, stroke history) or limiting analysis to participants without these

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comorbid conditions; adding metropolitan statistical area (MSA)-level random effects; adjusting for other pollutants ($PM_{2.5}$ and NO_2) in multi-pollutant models; and further adjusting for annual mean T_{max} in multi-exposure models. We also evaluated potential differences in ozone-mortality associations by location, grouping the study locations into three regions according to geography: California, North (New Jersey, Pennsylvania, Detroit), and South (Florida, Louisiana, North Carolina, Atlanta); and also tested whether timing of the exposures influenced the effect estimates by restricting the follow-up period to 2003-2011 (to match limited availability of ozone data) and conducting both time-dependent (with 1-year lagged exposures) and time-independent (for comparison purposes) analyses.

Packages "survival", "coxme", and "pspline" in the statistical package R (version 3.4.0) were employed for analysis.

Results

During the follow-up period considered, 126,806 of all study participants (23.1%) died of non-accidental causes, of which 39,529 were due to all cardiovascular diseases, 22,327 were due to ischemic heart disease, 5,592 were due to cerebrovascular disease, 6,811 were due to cardiac arrests, 12,459 were due to respiratory diseases, 7,748 were due to COPD, 1,889 were due to pneumonia, and 13,529 were due to lung cancer.

The overall average annual O_3 concentration during the study period was 39.0 with a standard deviation (SD) of 4.6 (ranging from 26.8 to 56.3) ppb; average warm season O_3 concentration was 46.2 with a SD of 7.6 (ranging from 29.5 to 70.4) ppb; average $PM_{2.5}$ was 11.0 $\mu g/m^3$, with a SD of 2.7 (ranging from 2.8 to 21.2) $\mu g/m^3$; and for NO_2 the average was 11.1 ppb with SD of 5.6 (ranging from 1.5 to 31.7) ppb. The annual O_3 concentration did not exhibit temporal trends over the study period, while $PM_{2.5}$ and NO_2 levels decreased over that time (Figure E1). The mean correlation between annual and warm season O_3 during the study was r=0.71. The correlations between annual O_3 with $PM_{2.5}$ and NO_2 were r=0.12 and r=-0.17, respectively, while correlations between warm season O_3 with $PM_{2.5}$ and NO_2 were r=0.47 and r=0.16, respectively; these values are lower (for annual) or similar (for warm season) than reported for the Turner et al. (2016) study (16). The correlation between annual O_3 and annual T_{max} was 0.35, and during warm season correlation between O_3 and T_{max} was 0.19. There were only small differences in pollutant

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concentrations across the range of cohort characteristics, suggesting that potential confounding by these factors is likely minimal (Table 1).

In single-pollutant models, long-term annual average exposure to O_3 was significantly associated with cardiovascular disease mortality (HR=1.03; 95% CI: 1.01-1.06), ischemic heart disease (HR=1.06; 95% CI: 1.02-1.09), respiratory disease mortality (HR=1.04; 95% CI: 1.00-1.09), and chronic obstructive pulmonary disease (HR=1.09; 95% CI: 1.03-1.15) after adjustment for covariates (Table 2). We did not observe a significant association between O_3 and all-cause mortality (HR=0.99; 95% CI: 0.98-1.00), cerebrovascular disease mortality (HR=1.01; 95% CI: 0.95-1.08), cardiac arrests mortality (HR=0.99; 95% CI: 0.93-1.06), pneumonia (HR=1.00; 95% CI: 0.90-1.11), or lung cancer (HR=0.96; 95% CI: 0.92-1.00). Using warm season averages for O_3 changed the effect estimates marginally, but the associations remained statistically significant. Adjusting for $PM_{2.5}$ and NO_2 as co-pollutants in two-pollutant (Table E1) and multi-pollutant models (Table 2) also did not significantly change the results. Additional adjustment for annual T_{max} average in multi-exposure models significantly reduced cerebrovascular disease mortality risk, and cardiovascular and respiratory disease mortality risks were also attenuated. Effect estimates were robust to (i.e., not significantly changed by) consideration of alternative model specifications, including metropolitan-level random effects-level random effects, adjusting for other preexisting comorbidities, and restricting analysis to those without preexisting comorbidities only (results not shown). Restricting the follow-up period to 2003-2011 and assigning O_3 as time-varying exposures also did not significantly change the results (Table E2). Differences in cause-specific mortality risk associated with long-term O_3 exposure were observed across the study regions (Table E3). Examination of the Schoenfeld residuals revealed that the proportional hazards assumption was satisfied.

The overall exposure-response relationship using splines was plotted, with the best degree of freedom (df = 2) selected via Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values. We observed the significant associations between O_3 with cardiovascular disease and respiratory disease mortality to be monotonic, and positively linear across the range of concentration levels in the cohort (Figure 1).

As seen in Table 3, we did not observe effect modification by covariates. We did observe significant effect modification by temperature (Figure 2), with increased respiratory disease mortality risk and higher

annual mean maximum temperature in a U-shaped dose-response relationship (p interaction=0.04); we did not find such modification for cardiovascular disease.

Discussion

In this extensive analysis of a large, well-characterized U.S. prospective cohort, long-term exposure to O_3 was significantly associated with multiple causes of mortality, including cardiovascular disease, ischemic heart disease, respiratory disease, and COPD. The associations here were generally robust to alternative model specifications and additional adjustment for $PM_{2.5}$, NO_2, and temperature. This study leverages a recent national-level O_3 exposure model that estimates both annual and warm season O_3 concentration levels at the census tract level, providing improved spatial resolution for the pollutant compared to similar past studies.

To date, studies examining the effects of long-term exposure to ambient O_3 on mortality have reported mixed results. A recent analysis of the association between long-term O_3 exposure and total mortality in the U.S. Medicare population of more than 60 million reported positive findings; the daily O_3 was estimated using a neural network approach that incorporated monitoring data, satellite-based measurements, a chemical transport model, land use terms, and other data at a 1-km resolution (22). The Turner et al. study (16) linked EPA gridded estimates for daily 8-hour maximum O_3 concentrations in 36-km resolutions in the analysis of multiple mortality causes in the American Cancer Society (ACS) CPS-II Cohort and found that chronic O_3 exposure was significantly associated with multiple causes of death, including all-cause, cardiovascular, and respiratory disease mortality, but not ischemic heart disease mortality. The Turner et al. study also similarly evaluated the 12-km resolution downscaler data utilized in the present study and found similar results between the two exposure estimates, although analysis was limited to a subset of the cohort as an earlier version of the downscaler dataset limited geographically to the Eastern U.S was applied. Analysis of the Canadian Census Health and Environment Cohort (CanCHEC) linked 2.5 million adults to estimates of average daily 8-hr maximum concentrations in the warm seasons with 21-km resolution, and reported significant associations of long-term exposure to O_3 with cardiovascular disease and ischemic heart disease mortality, but not with cerebrovascular disease, respiratory disease or COPD mortality (23). A study linked a national English cohort of 835,607 with 1-km

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gridded estimates from air dispersion models and reported negative associations between long-term O_3 and mortality (24), while another study of a French cohort of 20,327 observed non-significant associations in relation to O_3 estimated from a 2-km resolution chemical transport model (25).

Evidence for a causal association between long-term O_3 exposure and cardiovascular disease is more limited, with the U.S EPA (2) concluding that the evidence is only "suggestive of a causal relationship between long-term exposure to O_3 and cardiovascular effects." Recent estimates of the global burden of disease of ozone did not include cardiovascular diseases in their analyses (13, 14). In this study, we report significant associations between long-term O_3 exposure and both cardiovascular disease and ischemic heart disease mortality but not cerebrovascular mortality in single-pollutant models, providing additional evidence that is consistent with recent results from the aforementioned CPS-II and CanCHEC cohorts. We also report a positive and significant association with COPD mortality, which adds to the limited evidence from previous studies, including an ecologic analysis of the relationship between exposure to O_3 and chronic lower respiratory disease mortality across continental U.S counties (26). We observed smaller respiratory disease mortality and pneumonia mortality risks associated with long-term O_3 exposure than the CPS-II cohort.

Possible biological mechanisms by which O_3 contributes to development of respiratory diseases include airway hyperreactivity and lung inflammation with release of inflammatory mediators and neutrophil recruitment (27). Long-term O_3 exposure resulted in narrowing of the respiratory bronchiole among monkeys, primarily by peribronchiolar inflammation (28). Chronic O_3 exposure in mice resulted in epithelial injury and significant increase in airspace density and airspace diameter along with decrease of the number of airspaces, thereby inducing small airway remodeling and emphysema (29). In a longitudinal panel study of 43 young adults that measured personal-level exposure in Shanghai, China, short-term O_3 resulted in acute respiratory inflammation, with increase in fractional exhaled nitric oxide and inducible nitric oxide synthase (iNOS), and decreased average methylation of *NOS2A*, which encodes iNOS (30). Low levels of O_3 also adversely affects respiratory health; in a randomized, controlled exposure study of 87 healthy adults (MOSES study), exposure to near ambient levels of ozone induced statistically significant lung function decrease, airway injury, and airway inflammation (31).

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The evidence for the relationship between O_3 exposure and cardiovascular outcomes is more mixed, although several studies have observed appreciable changes in circulating biomarkers of inflammation, oxidative stress, coagulation, vasoreactivity, and glucose metabolism (32). Increases in systemic pro-inflammatory markers and adverse changes in cardiac autonomic effects were observed in young, healthy human participants in controlled exposure studies (33, 34). A panel study of air pollution in a population with extant coronary heart disease (N=13) observed alternations in several pathways associated with cardiovascular morbidity and mortality, including fibrinolysis, systemic inflammation, and vascular reactivity at levels below the EPA standards (35). A study of 89 healthy adults in China found that short-term ozone exposure was associated with platelet activation and increased blood pressure (36). On the other hand, in the aforementioned MOSES study no significant effects of ozone exposure on any of the primary or secondary measures of autonomic function, repolarization, ST segment change, arrhythmia, or vascular function were observed (37).

We also observed significant effect modification by long-term temperature, with elevated respiratory disease mortality risks associated with long-term O_3 exposure at high annual mean maximum temperature. Higher temperatures directly influence ozone levels and occurrences of episodes (38), but evidence also points to a potentially interactive effect between ozone and temperature to influence health. A controlled exposure study found that ozone-induced systemic effects varied according to temperature, with ozone impairing the fibrinolytic pathway at elevated (32.5°C) temperature while ozone activated the pathway at moderate (22°C) temperature (39). Examination of the long-term effect of O_3 exposure on cardiovascular mortality in the CanCHEC cohort found that the association was modified by spatial synoptic classification zone, which is a daily weather classification scheme (40). Our findings are consistent with findings from the CPS-II studies (15, 16) that observed effect modification by annual average temperature with higher ozone-related mortality risks observed with both high and low annual temperatures, and also with multiple short-term O_3 exposure studies to date that similarly have observed effect modification by temperature extremes for total and cardiovascular mortality risks (41). Temperature strongly predicts ozone levels and is also a potential confounder (42) of the ozone-mortality association. Unlike the CPS-II cohort, the associations between long-term ozone exposure and several causes of death were confounded by temperature, especially for cerebrovascular disease, suggesting that

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temperature is an important risk factor for this cause of death. The observed disparity between the two cohorts may be due to differences in cohort characteristics as well as the spatial resolution and correlation structure of O_3 and temperature, especially as daily exposure estimates were averaged and applied in this current study.

This study offers many strengths, including: the large size of the cohort, long follow-up period of 17 years, and the availability of detailed individual-level information, especially for behavioral risk factors such as smoking and diet. However, limitations are also present in this study; residence census tract and personal covariates were recorded at baseline and prospective changes in these factors could not be accounted for. Another limitation is that the NIH-AARP cohort has a smaller number of participants in races other than white and black non-Hispanic, limiting power to study other races/ethnicities. We were also unable to control for smoking duration, although it is unlikely that this would be a major source of residual confounding as ozone-related mortality estimates did not vary significantly across major smoking groups, and observed ozone-related mortality effects were generally larger among the never smokers.

Given the ubiquitous nature of outdoor air pollution exposures, the global burden of disease from O_3 is substantial, with estimates that 1.04 to 1.23 million respiratory deaths in adults are attributable to O_3 exposure annually (14). The results from this study suggest that long-term exposure to ambient ozone increases both cardiovascular disease and respiratory disease mortality risk; taken together in consideration with recent evidence consistent with our results (15, 22), these findings suggest that an annual and/or seasonal standard for ambient ozone concentrations, in addition to the present daily standard, is needed in order to adequately protect public health. The correlations between daily O_3 values with annual and warm season averages are 0.41 and 0.68, respectively, suggesting that these metrics (and potential standards) are moderately distinct, especially for annual exposure.

In summary, this analysis of a large U.S. cohort found that long-term exposure to ambient O_3 is associated with elevated risk of death from cardiovascular disease, ischemic heart disease, respiratory disease, and COPD. The results were robust to alternative models and adjustment for co-pollutants, although some evidence of confounding by temperature was observed. We also observed significantly elevated respiratory disease mortality risk associated with long-term O_3 exposure in areas with higher annual average daily maximum temperatures. This study provides additional evidence linking excess

mortality to long-term O_3 exposure, suggesting that policies aimed at lowering the long-term O_3 concentration level are important in alleviating the public health burden associated with ambient O_3 exposures.

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Figure Legends

Figure 1. Concentration-response curves (solid lines) and 95% CIs (dashed lines) relative to the effect at mean concentration, based on natural spline models with 2 degrees of freedom, for standard Cox models adjusted for individual-level and contextual covariates; respiratory disease mortality (A) and cardiovascular disease mortality (B). The tick marks on the x-axis identify the distribution of observations according to annual average ozone concentrations.

Figure 2. Hazard ratios (and 95% CI) for the association between annual average O_3 (per 10 ppb) and respiratory disease (A) and cardiovascular disease mortality (B) as a function of annual average daily maximum temperature

Table 1. Descriptive statistics for the NIH-AARP Cohort, by quintile of annual O_3 concentration exposure

		Q1 (N=109756)	Q2 (N=109756)	Q3 (N=109756)	Q4 (N=109756)	Q5 (N=109756)
O_3	Range (ppb)	26.8-35.1	35.1-38.4	38.4-39.8	39.8-42.0	42.0-56.3
Age	>=65	69724 (63.5%)	68821 (62.7%)	69459 (63.3%)	69687 (63.5%)	69291 (63.1%)
	<65	40032 (36.5%)	40935 (37.3%)	40297 (36.7%)	40069 (36.5%)	40465 (36.9%)
Sex	Male	62301 (56.8%)	66240 (60.4%)	65904 (60.0.%)	65050 (59.3%)	64589 (58.8%)
	Female	47455 (43.2%)	43516 (39.6%)	43852 (40.0%)	44706 (40.7%)	45167 (41.2%)
Race	White	94798 (86.4%)	99944 (91.1%)	102819 (93.7%)	101350 (92.3%)	101597 (92.6%)
	Black	6595 (6.0%)	5062 (4.6%)	3016 (2.7%)	4086 (3.7%)	2822 (2.6%)
	Hispanic	3522 (3.2%)	1559 (1.4%)	1461 (1.3%)	1492 (1.4%)	2163 (2.0%)
	Asian, Pacific	3009 (2.7%)	1665 (1.5%)	1134 (1.0%)	1384 (1.3%)	1687 (1.5%)
Education	Less than high school	6243 (5.7%)	6627 (6.0%)	7834 (7.1%)	6582 (6.0%)	5969 (5.4%)
	Some high school	19252 (17.5%)	24321 (22.2%)	25660 (23.4%)	20331 (18.5%)	17808 (16.2%)
	12 years or high school completed	9519 (8.7%)	10928 (10.0%)	12182 (11.1%)	11145 (10.2%)	9971 (9.1%)
	Post-high school or some college	26260 (23.9%)	22978 (20.9%)	22844 (20.8%)	25982 (23.7%)	29081 (26.5%)
	College and post graduate	45104 (41.1%)	41669 (38.0%)	37863 (34.5%)	42412 (38.6%)	43655 (39.8%)
BMI	<18.5	897 (0.8%)	796 (0.7%)	885 (0.8%)	1003 (0.9%)	1070 (1.0%)
	18.5-25	37826 (34.5%)	35616 (32.5%)	34869 (31.8%)	37303 (34%)	38755 (35.3%)
	25-30	44140 (40.2%)	46314 (42.2%)	45838 (41.8%)	45415 (41.4%)	45119 (41.1%)
	30-35	16473 (15.0%)	17237 (15.7%)	17907 (16.3%)	16705 (15.2%)	15962 (14.5%)
	>35	7195 (6.6%)	6877 (6.3%)	7306 (6.7%)	6444 (5.9%)	6035 (5.5%)
Marriage	Married	68687 (62.6%)	75377 (68.7%)	76575 (69.8%)	75722 (69.0%)	77176 (70.3%)
	Never Married	32382 (29.5%)	27964 (25.5%)	27528 (25.1%)	28464 (25.9%)	27706 (25.2%)
	Other	7582 (6.9%)	5532 (5%)	4778 (4.4%)	4688 (4.3%)	3986 (3.6%)
Smoking	Never	37781 (34.4%)	38550 (35.1%)	38768 (35.3%)	37498 (34.2%)	38419 (35.0%)
	Less than a pack, 1+ year quit	29847 (27.2%)	29126 (26.5%)	28598 (26.1%)	28834 (26.3%)	29475 (26.9%)
	More than a pack, 1+ year quit	4882 (4.4%)	5015 (4.6%)	5706 (5.2%)	5769 (5.3%)	5395 (4.9%)
	Less than a pack, stopped less than a year/current	10181 (9.3%)	9963 (9.1%)	9601 (8.7%)	9684 (8.8%)	9410 (8.6%)
	More than a pack, stopped less than a year or current	4882 (4.4%)	5015 (4.6%)	5706 (5.2%)	5769 (5.3%)	5395 (4.9%)
Alcohol (drinks/day)	0	23684 (21.6%)	23422 (21.3%)	28616 (26.1%)	29259 (26.7%)	30950 (28.2%)
	<1	59235 (54.0%)	60524 (55.1%)	57627 (52.5%)	55398 (50.5%)	53958 (49.2%)
	1-2	13346 (12.2%)	12644 (11.5%)	11354 (10.3%)	12372 (11.3%)	12260 (11.2%)
	2-3	4771 (4.3%)	4141 (3.8%)	3617 (3.3%)	4004 (3.6%)	4164 (3.8%)
	3-5	3938 (3.6%)	4134 (3.8%)	3950 (3.6%)	4036 (3.7%)	3946 (3.6%)
	5+	4782 (4.4%)	4891 (4.5%)	4592 (4.2%)	4687 (4.3%)	4478 (4.1%)

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	0-2	18865 (17.2%)	22532 (20.5%)	22483 (20.5%)	20198 (18.4%)	18011 (16.4%)
	3	18445 (16.8%)	19980 (18.2%)	20696 (18.9%)	19806 (18.0%)	18629 (17.0%)
	4	22240 (20.3%)	22350 (20.4%)	22818 (20.8%)	22814 (20.8%)	22344 (20.4%)
	5	21397 (19.5%)	20566 (18.7%)	20340 (18.5%)	21371 (19.5%)	22076 (20.1%)
	6-9	28809 (26.2%)	24328 (22.2%)	23419 (21.3%)	25567 (23.3%)	28696 (26.1%)

Table 2. All-cause and cause-specific air pollutant mortality HRs (per 10 µg/m³ for PM$_{2.5}$; per 10 ppb for NO$_2$ and O$_3$) by model specifications

| | | Single-Pollutant Model | | | | | | | | Multi-pollutant Model | | | | Multi-exposure Model | | | |
| | | Annual O$_3$ | | Warm Season O$_3$ | | PM$_{2.5}$ | | NO$_2$ | | Annual O$_3$ adjusting for PM$_{2.5}$ + NO$_2$ | | Warm Season O$_3$ adjusting for PM$_{2.5}$ + NO$_2$ | | Annual O$_3$ adjusting for PM$_{2.5}$ + NO$_2$ + T$_{max}$ | | Warm Season O$_3$ adjusting for PM$_{2.5}$ + NO$_2$ + T$_{max}$ | |
Cause	N	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*
All-cause	126806	0.99	0.98-1.00	1.00	0.99-1.01	1.03	1.01-1.06	1.04	1.02-1.05	1.00	0.96-1.01	1.00	0.99-1.01	0.99	0.97-1.00	1.00	0.99-1.01
Cardiovascular Disease	39529	1.03	1.01-1.06	1.02	1.01-1.04	1.11	1.06-1.16	1.07	1.04-1.09	1.05	1.02-1.08	1.04	1.02-1.06	1.02	0.99-1.05	1.02	0.99-1.03
Ischemic Heart Disease	22327	1.06	1.02-1.09	1.03	1.02-1.05	1.15	1.08-1.22	1.09	1.05-1.12	1.08	1.04-1.12	1.05	1.03-1.08	1.05	1.01-1.10	1.03	1.00-1.06
Cerebrovascular	5592	1.01	0.95-1.08	1.02	0.99-1.06	1.11	0.98-1.25	1.02	0.97-1.09	1.00	0.93-1.07	1.01	0.97-1.06	0.89	0.82-0.97	0.92	0.86-0.98
Cardiac Arrest, Heart Failure	6811	0.99	0.93-1.06	0.99	0.96-1.03	0.97	0.86-1.09	1.02	0.97-1.08	1.01	0.95-1.08	1.01	0.96-1.06	1.01	0.94-1.09	1.01	0.97-1.05
Respiratory Disease	12459	1.04	1.00-1.09	1.04	1.02-1.06	1.09	1.00-1.18	1.04	0.99-1.08	1.05	1.00-1.10	1.05	1.01-1.08	1.04	0.99-1.10	1.04	1.00-1.08
COPD	7748	1.09	1.03-1.15	1.05	1.02-1.08	1.07	0.97-1.18	1.03	0.98-1.08	1.09	1.03-1.16	1.07	1.03-1.11	1.08	1.01-1.15	1.06	1.01-1.12
Pneumonia and Influenza	1889	1.00	0.90-1.11	1.05	0.99-1.10	1.53	1.26-1.86	1.22	1.11-1.35	0.99	0.89-1.11	1.02	0.95-1.10	0.99	0.86-1.13	1.06	0.99-1.14
Lung Cancer	13529	0.96	0.92-1.00	0.98	0.96-1.00	0.96	0.88-1.04	1.00	0.97-1.04	0.97	0.93-1.02	0.98	0.96-1.01	0.96	0.91-1.01	0.98	0.95-1.00

*Adjusted for age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual-level; and for median income and % with high school education, at census-tract level.

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Table 3. Annual average ozone mortality HRs (per 10 ppb), by category of selected risk factors

		Cardiovascular Disease			Ischemic Heart Disease			Respiratory Disease			COPD		
		HR*	95% CI*	p-int	HR*	95% CI*	p-int	HR*	95% CI*	p-int	HR*	95% CI*	p-int
Sex	Male	1.01	0.97-1.05	0.92	1.03	0.97-1.10	0.64	1.09	1.02-1.17	0.39	1.13	1.05-1.23	0.66
	Female	1.05	1.02-1.08		1.06	1.02-1.10		1.02	0.96-1.13		1.06	0.98-1.13	
Age	>=65	1.04	1.01-1.07	0.60	1.05	1.01-1.09	0.49	1.05	0.99-1.10	0.50	1.09	1.03-1.17	0.48
	<65	1.01	0.97-1.05		1.07	1.02-1.12		1.06	0.99-1.21		1.11	1.02-1.21	
Race	White	1.03	1.00-1.06	0.36	1.05	1.02-1.09	0.29	1.03	0.99-1.07	0.08	1.07	1.02-1.13	0.15
	Black	1.02	0.89-1.17		0.97	0.81-1.16		1.28	0.97-1.68		1.16	0.76-1.55	
	Other	1.08	0.92-1.27		1.08	0.87-1.32		1.11	0.77-1.60		1.29	0.77-2.17	
BMI	<25	1.00	0.96-1.04	0.54	1.02	0.96-1.08	0.24	1.06	0.99-1.13	0.29	1.09	1.01-1.18	0.50
	25-35	1.07	1.03-1.11		1.08	1.03-1.14		1.04	0.97-1.12		1.10	1.00-1.21	
	>35	1.02	0.97-1.07		1.06	1.00-1.13		1.02	0.93-1.11		1.06	0.94-1.20	
Education	<=High School	1.04	1.00-1.09	0.58	1.06	1.00-1.12	0.99	1.02	0.96-1.09	0.21	1.08	0.99-1.17	0.27
	Some College	0.99	0.95-1.04		1.01	0.95-1.08		1.05	0.97-1.14		1.12	1.02-1.24	
	College or Post	1.05	1.01-1.10		1.09	1.04-1.15		1.05	0.97-1.14		1.04	0.94-1.16	
Smoking	Never	1.03	0.99-1.09	0.26	1.03	0.97-1.11	0.08	1.13	1.00-1.27	0.69	1.35	1.07-1.69	0.54
	Former	1.03	0.99-1.06		1.05	1.01-1.10		1.02	0.96-1.07		1.05	0.98-1.13	
	Current	1.05	0.99-1.11		1.06	0.98-1.15		1.08	0.99-1.17		1.13	1.03-1.23	
aMED Index	Quintile 1	1.06	1.01-1.12	0.43	1.11	1.03-1.19	0.18	1.07	0.99-1.17	0.65	1.14	1.03-1.26	0.55
	Quintile 2	1.04	0.98-1.10		1.07	0.99-1.16		1.03	0.93-1.12		1.07	0.95-1.19	
	Quintile 3	1.01	0.96-1.06		1.05	0.98-1.13		1.01	0.92-1.11		1.03	0.92-1.15	
	Quintile 4	1.00	0.95-1.06		1.00	0.93-1.07		1.08	0.97-1.19		1.07	0.94-1.22	
	Quintile 5	1.05	0.99-1.10		1.05	0.99-1.12		1.03	0.93-1.15		1.13	0.99-1.30	

*Adjusted for age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual-level; and for median income and % with high school education, at census-tract level.
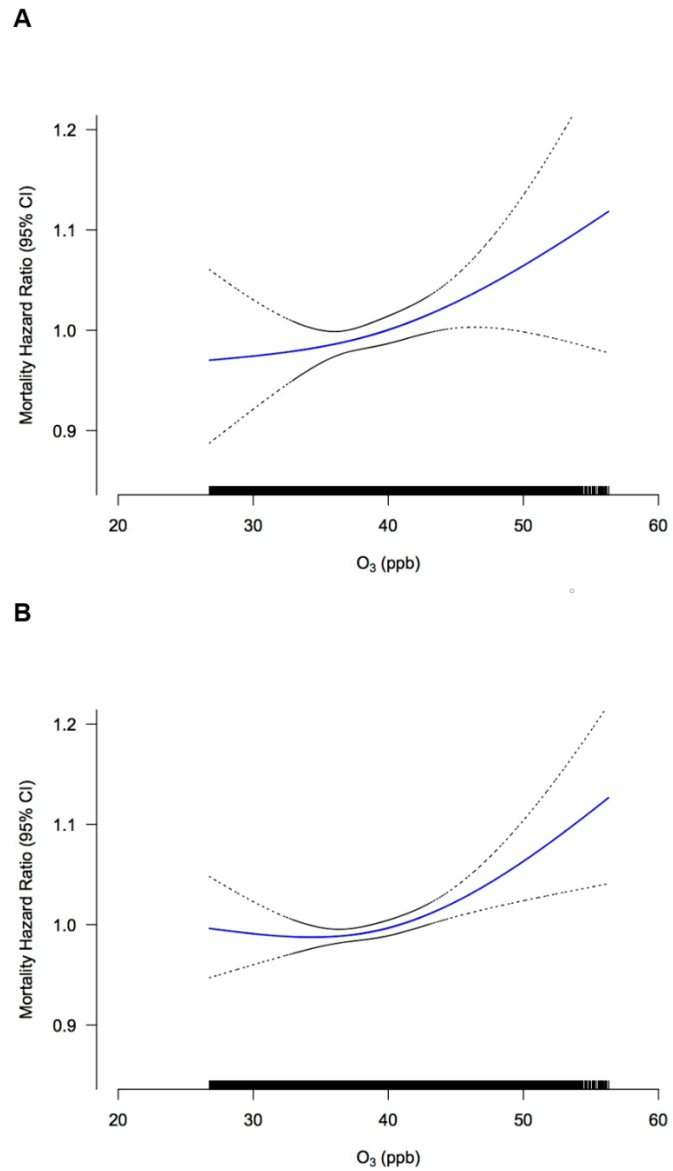
Figure One

229x365mm (96 x 96 DPI)

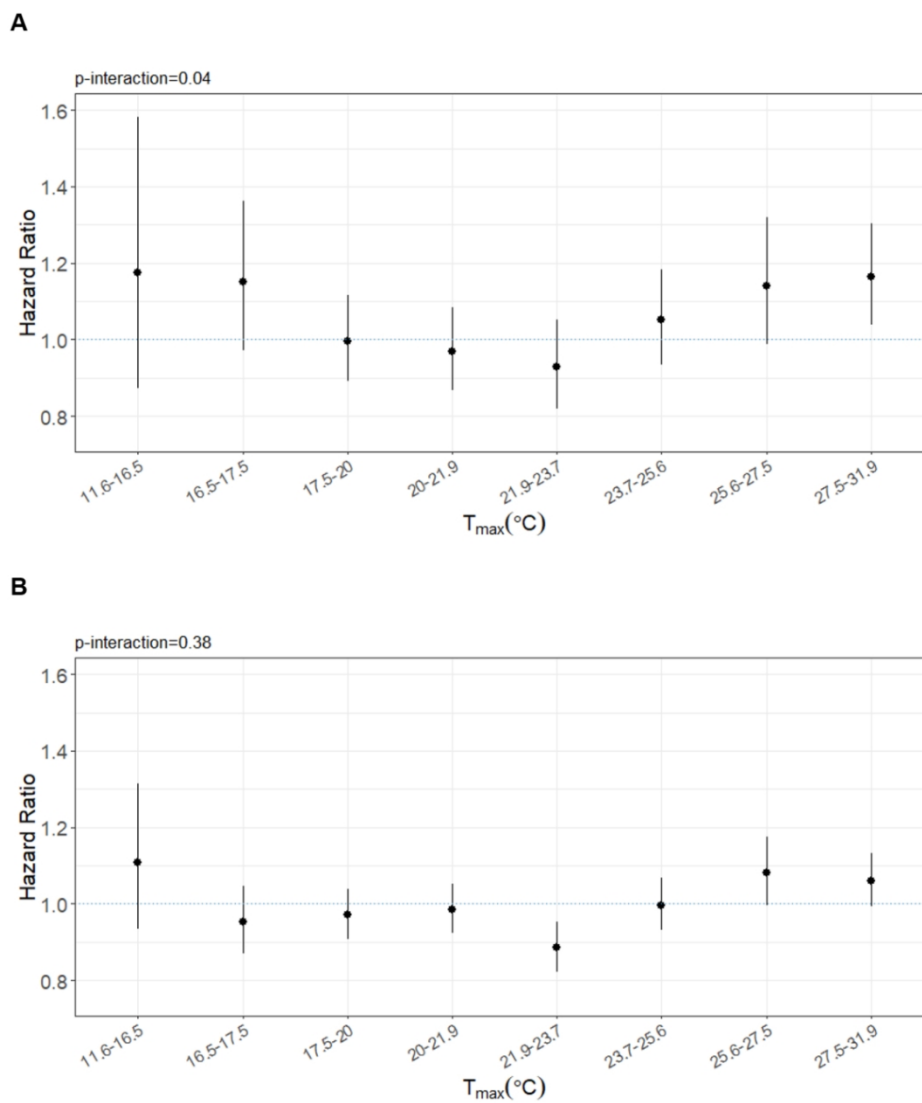AJRCCM Articles in Press. Published on 03-May-2019 as 10.1164/rccm.201806-1161OC

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A

B

Figure Two

319x359mm (96 x 96 DPI)

ONLINE DATA SUPPLEMENT

Long-term Exposure to Ozone and Cause-Specific Mortality Risk in the U.S.

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Figure E1. Annual average concentrations of air pollutants by study states (2002-2010)
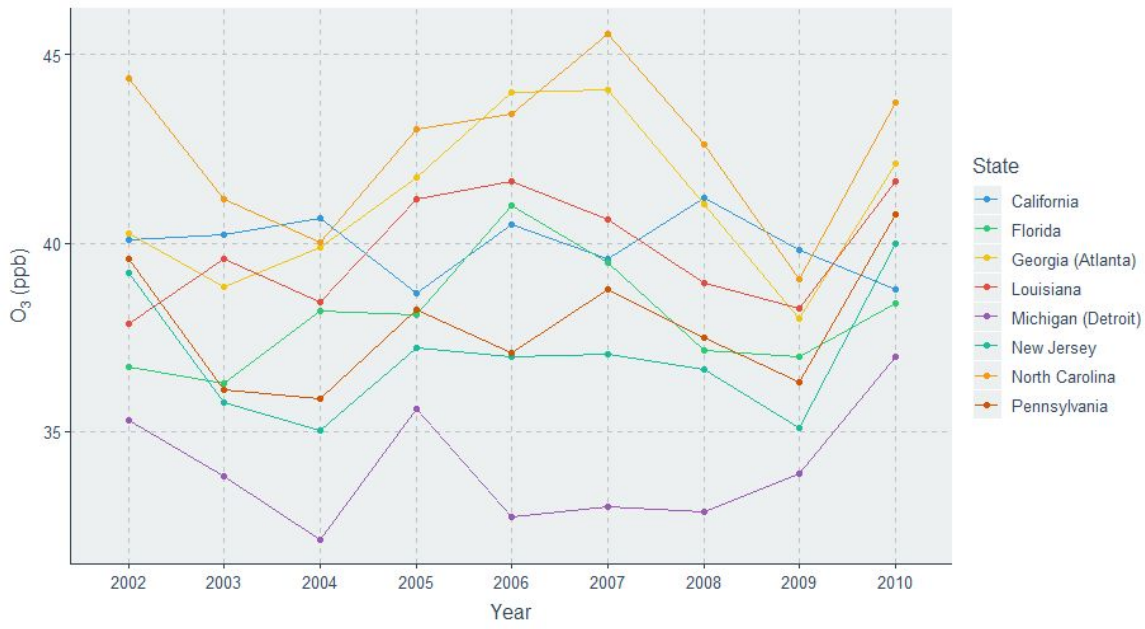
a) Annual average O_3 concentrations by study states (2002-2010)

b) Annual average $PM_{2.5}$ concentrations by study states (2002-2010)

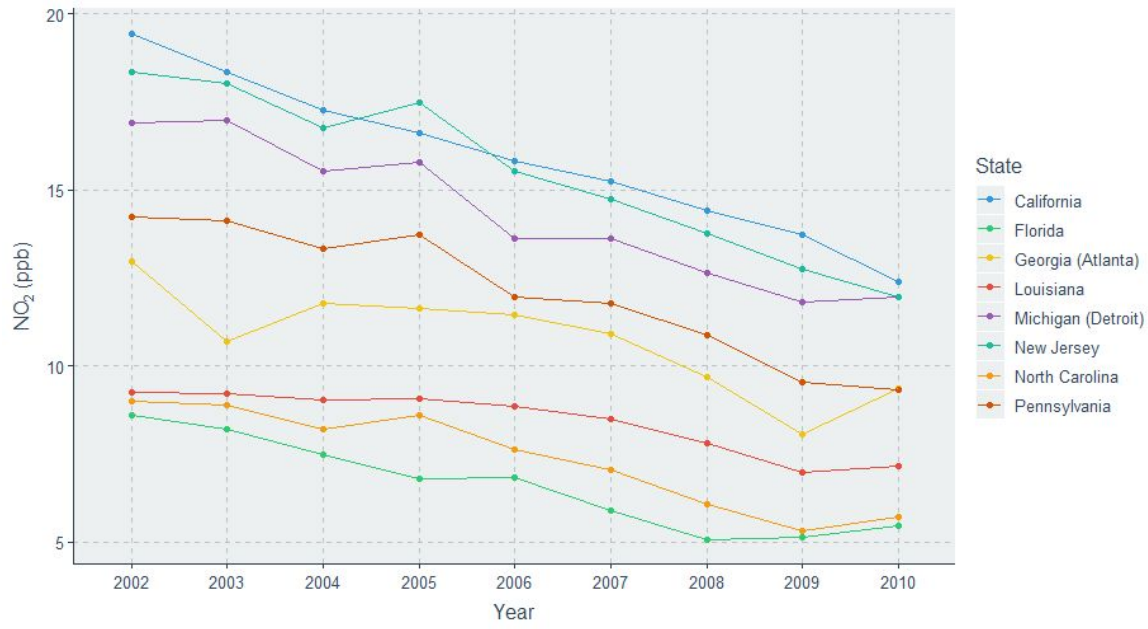c) Annual average NO$_2$ concentrations by study states (2002-2010)

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Table E1. All-cause and cause-specific mortality HRs associated with O_3 (per 10 ppb), for two-pollutant/exposure models

	Annual O_3 adjusting for $PM_{2.5}$		Warm Season O_3 adjusting for $PM_{2.5}$		Annual O_3 adjusting for NO_2		Warm Season O_3 adjusting for NO_2		Annual O_3 adjusting for T_{max}		Warm Season O_3 adjusting for T_{max}	
Cause	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*
All-cause	0.99	0.97-1.00	0.99	0.98-1.00	0.99	0.98-1.01	1.00	0.99-1.01	0.98	0.96-1.00	0.99	0.97-1.00
Cardiovascular Disease	1.03	1.00-1.05	1.02	1.00-1.04	1.05	1.02-1.07	1.03	1.01-1.05	1.00	0.97-1.02	0.99	0.98-1.02
Ischemic Heart Disease	1.05	1.02-1.08	1.03	1.01-1.06	1.07	1.04-1.11	1.04	1.02-1.07	1.01	0.97-1.05	1.02	1.00-1.05
Cerebrovascular Disease	1.01	0.95-1.07	1.02	0.97-1.06	1.02	0.96-1.08	1.03	0.98-1.07	0.93	0.87-0.99	0.94	0.89-0.99
Cardiac Arrest, Heart Failure	0.99	0.93-1.06	0.99	0.95-1.04	1.00	0.93-1.06	0.99	0.95-1.03	0.99	0.92-1.05	0.97	0.92-1.03
Respiratory Disease	1.04	1.00-1.08	1.04	1.01-1.07	1.05	1.01-1.10	1.05	1.02-1.07	1.03	0.98-1.08	1.04	1.00-1.07
COPD	1.08	1.03-1.14	1.06	1.03-1.10	1.09	1.04-1.15	1.07	1.03-1.10	1.07	1.01-1.13	1.06	1.01-1.11
Pneumonia and Influenza	0.97	0.87-1.08	1.00	0.93-1.08	1.03	0.93-1.14	1.05	0.98-1.12	0.95	0.85-1.07	1.03	0.95-1.14
Lung Cancer	0.96	0.92-1.00	0.98	0.95-1.01	0.96	0.92-1.00	0.97	0.95-1.00	0.95	0.91-0.99	0.96	0.92-0.99

*Adjusted for age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual-level; and for median income and % with high school education, at census-tract level.

Table E2. All-cause and cause-specific mortality HRs associated with O_3 (per 10 ppb) with time-dependent and time-independent exposures, restricting the follow-up period to 2003-2011

		Time-Dependent				Time-Independent			
		Annual O_3		Warm Season O_3		Annual O_3		Warm Season O_3	
Cause	N	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*	HR*	95% CI*
All-cause	86566	0.98	0.96-1.00	0.99	0.98-1.00	0.99	0.97-1.01	0.99	0.99-1.01
Cardiovascular Disease	26764	1.02	0.99-1.05	1.02	1.00-1.04	1.04	1.01-1.07	1.03	1.01-1.05
Ischemic Heart Disease	14629	1.07	1.03-1.11	1.05	1.03-1.08	1.08	1.04-1.13	1.06	1.04-1.09
Cerebrovascular Disease	4085	0.98	0.92-1.06	1.01	0.96-1.06	1.01	0.94-1.09	1.02	0.97-1.07
Cardiac Arrest, Heart Failure	4788	0.97	0.90-1.04	0.98	0.93-1.03	0.97	0.90-1.05	0.98	0.93-1.03
Respiratory Disease	9332	1.01	0.96-1.06	1.03	0.99-1.06	1.04	0.99-1.09	1.04	1.01-1.08
COPD	5712	1.06	1.00-1.12	1.06	1.01-1.10	1.09	1.03-1.16	1.07	1.03-1.12
Pneumonia and Influenza	1460	0.99	0.89-1.12	1.04	0.96-1.13	0.99	0.89-1.12	1.04	0.96-1.13
Lung Cancer	8560	0.97	0.92-1.02	0.98	0.94-1.01	0.98	0.93-1.03	0.98	0.94-1.01

*Adjusted for age (as time-varying for the time-dependent model), sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at

individual-level; and for median income and % with high school education, at census-tract level.

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Table E3. All-cause and cause-specific mortality HRs associated with O$_3$ (per 10 ppb), by study location region

Cause	N	California (n= 170,774) Annual O$_3$ HR*	95% CI*	Warm Season O$_3$ HR*	95% CI*	N	North (n= 179,578) Annual O$_3$ HR*	95% CI*	Warm Season O$_3$ HR*	95% CI*	N	South (n=198,418) Annual O$_3$ HR*	95% CI*	Warm Season O$_3$ HR*	95% CI*
All-cause	37437	0.99	0.97-1.00	1.00	0.99-1.01	41971	0.99	0.94-1.03	1.02	0.97-1.06	47398	0.98	0.94-1.02	0.99	0.97-1.03
Cardiovascular Disease	11616	1.05	1.02-1.08	1.04	1.02-1.06	13247	0.94	0.87-1.02	0.97	0.89-1.05	14666	1.01	0.93-1.09	0.99	0.94-1.03
Ischemic Heart Disease	6621	1.08	1.04-1.12	1.06	1.04-1.09	7492	0.99	0.89-1.10	1.02	0.92-1.14	8214	0.98	0.88-1.09	0.96	0.91-1.02
Cerebrovascular Disease	1769	1.01	0.94-1.08	1.02	0.97-1.06	1716	0.87	0.69-1.09	1.06	0.84-1.34	2107	1.05	0.85-1.29	1.02	0.89-1.15
Cardiac Arrest, Heart Failure	1681	0.99	0.92-1.06	1.00	0.95-1.05	2570	1.06	0.88-1.28	0.94	0.78-1.14	2560	0.90	0.74-1.09	0.92	0.82-1.04
Respiratory Disease	3925	1.02	0.97-1.07	1.02	0.99-1.05	3706	1.07	0.92-1.25	1.16	0.99-1.36	4828	1.17	1.02-1.34	1.18	1.08-1.28
COPD	2515	1.06	1.00-1.13	1.04	0.99-1.08	2169	1.13	0.92-1.38	1.25	1.02-1.53	3064	1.19	1.01-1.42	1.18	1.07-1.31
Pneumonia and Influenza	695	1.02	0.92-1.14	1.06	0.98-1.14	550	0.69	0.46-1.03	0.68	0.45-1.01	644	1.05	0.72-1.54	1.11	0.88-1.40
Lung Cancer	3871	0.97	0.92-1.01	0.97	0.94-1.01	4287	0.97	0.85-1.12	1.02	0.88-1.17	5371	0.91	0.80-1.03	0.95	0.88-1.02

*Adjusted for age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual-level; and for median income and % with high school education, at census-tract level.