

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jerrett M, Burnett RT, Pope CA III, et al. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085-95.

Long-Term Ozone Exposure to Mortality

Online Supplement

Michael Jerrett, PhD, University of California, Berkeley, California, U.S.A.;
Richard T. Burnett, PhD, Health Canada, Ottawa, Canada; C. Arden Pope III,
PhD, Brigham Young University, Provo, Utah, U.S.A.; Kazuhiko Ito, PhD and
George Thurston, ScD, New York University School of Medicine, New York, U.S.A.;
Daniel Krewski, PhD and Yuanli Shi, MD, University of Ottawa, Ottawa, Canada;
Eugenia Calle, PhD and Michael Thun, MD, American Cancer Society, Atlanta,
U.S.A.

ONLINE SUPPLEMENT

This supplement contains information on methods and results related to ecologic covariates, spatial random effects modeling, the time window models, and the threshold analyses.

Ecologic Covariates

Previous American Cancer Society (ACS) studies suggested that conditions in the neighborhood of residence could confound the association between air pollution and mortality.¹⁻³ Information was obtained on neighborhood social confounders for 11,334 ZIP code areas (ZCA) from the 1980 U.S. Census. Several variables are examined in this analysis, including: median household income; proportion living at or below 125% of poverty line; percentage of unemployed persons over the age of 16 years; percentage of adults with less than grade 12 education; percentage of homes with air conditioning; the Gini coefficient of income inequality; and percentage of population that is not white. We used boundary averaging methods to overlay census information at the sub-division level and the ZCA level for which we have location information from the ACS subjects. We

only included those ZCAs that had ACS subjects to represent the contextual environment of the study subjects. In each model, two different terms were entered: the values of the Metropolitan Statistical Area (MSA) averaged from the ZCAs in which the ACS subjects resided and the ZCAs value within with the individual subject resided minus the citywide MSA average (i.e., the ZCA difference from the citywide mean). This method standardized the effects for both within and across city differences.

Because access to medical care may also affect survival, particularly for emergency treatments, we also assembled information on the availability of physicians and hospital beds in each MSA². Annual average temperature and average maximum temperature were also collected for the MSAs as described elsewhere². We obtained this information for only 87 MSAs. We did not include the variables that were available for only 87 MSAs in the main analyses, because this would have reduced the number of MSAs, the sample size, and the variation in ozone concentrations. Thus these variables were included only in single-variable sensitivity analyses, as were the other seven ecological covariates used in the main analysis. Because an ozone association persisted after

adjustment for these variables without complete coverage across all 96 MSAs individually, we concluded that they were not strong confounders to the ozone-mortality association. The same reasoning was applied to ambient temperature in which we could obtain temperature data from airports in only 90 MSAs. Again, temperature was not a confounder to the ozone-mortality association. The results of the ecologic covariate analyses are shown in Table 1S.

Table 1S. Respiratory death relative risk for a 10 ppb change in ambient ozone concentrations, adjusted for individual risk factors.[‡]

Risk Factor Adjustment	Correlation with Ozone	Relative Risk	95% Confidence Interval
None	Na	1.029	1.011 – 1.047
Education*	-0.13	1.031	1.013 - 1.049
Air Conditioning*	0.32	1.034	1.016 - 1.052
Percent Non-White*	0.07	1.030	1.011 - 1.048
Unemployment*	-0.15	1.027	1.009 - 1.045
Household Income*	0.03	1.030	1.012 - 1.048
Income Disparity*	0.05	1.032	1.014 - 1.051
Poverty*	0.03	1.029	1.011 - 1.047
Physicians Per Capita⁺	-0.12	1.026	1.008 - 1.044
Hospital Beds Per Capita⁺	-0.04	1.024	1.006 - 1.041
Temperature[#]	0.42	1.030	1.011 – 1.049

[‡] Ambient ozone concentrations measured from April to September, 1977-2000 in the ACS cohort with follow-up from 1982 to 2000. Baseline hazard function stratified by age (single year groupings), gender, and race, adjusting for selected risk factors. These analyses are based on the single-pollutant model for ozone shown in Table 3 of the main manuscript.

* Information available for 96 MSAs.

⁺ Information available for 87 MSAs.

[#] Information available for 90 MSAs.

Adjustment for Community-level Random Effects

Our analysis allowed for an assessment of residual variation in mortality among communities. The baseline hazard function was modulated by a community-specific random variable representing the residual risk of death for subjects in that community after controlling for individual and ecological risk factors. These random effects have unit expectation and common variance among communities. Statistical procedures for estimation of the unknown regression parameters and random effect variances under the alternative assumptions of no spatial autocorrelation and spatial autocorrelation on the random effects covariates are described elsewhere^{3,4}. The correlation structure of the random effects at the MSA level is specified by the form ρ^d , where $0 \leq \rho < 1$ is the correlation parameter for MSAs and d is a measure of spatial association between two MSAs. As described elsewhere,^{1,3} a nearest neighbor structure based on Thiessen polygon connectivity was used.* Sensitivity analyses using the state of residence as the

* All points within the Thiessen polygon are closer to the centroid of that polygon than to any other centroid in the spatial domain (see¹ for details).

cluster level were also conducted. Results from the random effects spatial autocorrelation analysis are shown in Table 2S.

Table 2S. Sensitivity of ozone association with respiratory mortality (based on 10 ppb change in ozone concentration) to specification of stochastic structure of survival model.*

Cluster Level 1	Cluster Level 2	Ozone Relative Risk (95% CI)	Cluster Level 1 Variance ($\times 10^{-3}$)	Cluster Level 1 Spatial Correlation	Cluster Level 2 Variance ($\times 10^{-3}$)	Cluster Level 2 Spatial Correlation
None	None	1.029 (1.010-1.048)	$\equiv 0$	$\equiv 0$	$\equiv 0$	$\equiv 0$
MSA	None	1.038 (1.008, 1.069)	6.48	$\equiv 0$	$\equiv 0$	$\equiv 0$
MSA	None	1.033 (1.001, 1.067)	6.81	0.27	$\equiv 0$	$\equiv 0$
STATE	MSA	1.031 (1.001-1.062)	0.76	$\equiv 0$	5.42	$\equiv 0$
STATE	MSA	1.033 (1.002-1.066)	2.83	$\equiv 0$	5.89	0.19

* Based on the single-pollutant model for ozone for 96 MSAs shown in Table 3. All individual and ecologic covariates with data for the 96 MSAs are included. See Table 1S for the variables with data from all 96 MSAs. (Metropolitan Statistical Area [MSA]; state of residence [STATE]; and presence of spatial autocorrelation between these areas based on nearest neighbor connectivity).

Threshold Analysis

A threshold model was fit to the survival data, with a threshold estimate of 56 ppb based on minimizing the log-likelihood, with a 95% confidence interval based on the log-likelihood of 0 to 60 ppb. Inclusion of 0 ppb in the confidence interval, a value less than the minimum ozone concentration of 33 ppb, indicates that the threshold model is not clearly a better fit to the data ($p > 0.05$) than a linear representation of the overall ozone-mortality association (see Table 3S below). The estimate of the log-relative risk for the linear component of the threshold model was 0.00390 ppb^{-1} , with a corresponding standard error of 0.00108 ppb^{-1} .

Table 3S. -2*log likelihood values based on the threshold concentration response model.[£]

Threshold Value (ppb)	Without Adjustment for Ecological Covariates	With Adjustment for Ecological Covariates
No Ozone	144,472.51	143,797.72
0	144,420.88	143,758.93
45	144,418.96	143,756.73
50	144,419.60	143,756.72
55	144,418.63 (p=0.134)	143,755.58 (p=0.067)
56*	144,418.39 (p=0.1146) (β=0.00390, se=0.00108)	143,755.39 (p=0.0600) (β=0.00432, se=0.00121)
57	144,418.77 (p=0.1416)	143,755.87(p=0.0802)
60	144,421.82	143,759.48
65	144,425.11	143,763.47

[£]: -2*log likelihood values based on the threshold concentration response model for ozone concentrations measured from April to September, 1977-2000 in the ACS cohort with follow-up from 1982 to 2000, adjusted for 44 individual risk factors, baseline hazard function stratified by age (single year groupings), gender, and race, with or without adjustment for the ecological covariates. -2*log likelihood values for various threshold model specifications summarize how well the model fits the data. Lower values represent models with a better fit to the data than those models with higher values.

*: Smallest -2*log likelihood values, indicating the best fit to the data.

Exposure Time Windows Analysis

We investigated whether specific time windows were associated with larger health effects by subdividing the follow-up interval into four periods (1982-88, 1989-1992, 1993-1996, and 1997-2000). Exposures were matched for each of these periods and also tested for a 10 year average based on the 5 year follow up period and the 5 years prior to the follow-up period.

Table 4S displays results from the time window and exposure lag analysis (also mentioned in the Methods section of the main paper). The point estimates tend to increase through the follow up, with later periods demonstrating the largest effects, but none of the model specifications were significantly different from one another. Pooled estimates are very similar to those reported in Table 3 of the main paper. The largest point estimates are for the years matched to follow-up or those lagged five years prior to death during the last period (1997-2000). Although these estimates for the later period were not significantly different than other periods, the larger effects are consistent with

what would be expected if there was reduced measurement error in the time-matched exposure windows.

Table 4S. Hazard ratios for respiratory deaths and ozone exposure by period of exposure and follow-up.[‡]

Follow up Period	Mean Ozone Concentration (ppb)	Number of Respiratory Deaths	Exposure Period		
			1977-2000	Same As Follow up	Follow up & Five Years Prior
1982-1988	60.7	1,811	1.018 (0.978, 1.060)	1.013 (0.980, 1.047)	1.010 (0.979, 1.042)
1989-1992	56.7	2,001	1.028 (0.989, 1.068)	1.035 (0.995, 1.077)	1.027 (0.991, 1.064)
1993-1996	56.7	2,680	1.019 (0.986, 1.054)	1.028 (0.987, 1.070)	1.023 (0.986, 1.062)
1997-2000	56.8	3,399	1.043 (1.013, 1.075)	1.075 (1.027, 1.125)	1.073 (1.031, 1.117)
Pooled	57.7	9,891	1.029 (1.011, 1.047) (p=0.7032)*	1.033 (1.013, 1.053) (p=0.2253)*	1.029 (1.011, 1.047) (p=0.1284)*

[‡]: Based on the single-pollutant model for ozone shown in Table 3 of the main paper.

*: p-value for testing differences in hazard ratios across follow-up periods.

REFERENCES

1. Jerrett M, Burnett R, Willis A, et al. Spatial analysis of the air pollution-mortality relationship in the context of ecologic confounders. *J Toxicol Env Health A* 2003;66:1735-1777.
2. Willis A, Krewski D, Jerrett M, Goldberg MS, Burnett RT. Selection of ecologic covariates in the American Cancer Society study. *J Toxicol Env Health A* 2003;66:1563-1589.
3. Krewski D, Jerrett M, Burnett RT, et al. Extended follow-up and spatial analysis of The American Cancer Society study linking particulate air pollution and mortality. Boston, MA: Health Effects Institute; 2008 (in press).
4. Ma R, Krewski D, Burnett RT. Random effects Cox models: A Poisson modelling approach. *Biometrika* 2003;90:157-169.