



# Spatial Analysis of Air Pollution and Mortality in California

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**Rationale:** Although substantial scientific evidence suggests that chronic exposure to ambient air pollution contributes to premature mortality, uncertainties exist in the size and consistency of this association. Uncertainty may arise from inaccurate exposure assessment. **Objectives:** To assess the associations of three types of air pollutants (fine particulate matter, ozone [O<sub>3</sub>], and nitrogen dioxide [NO<sub>2</sub>]) with the risk of mortality in a large cohort of California adults using individualized exposure assessments.

**Methods:** For fine particulate matter and NO<sub>2</sub>, we used land use regression models to derive predicted individualized exposure at the home address. For O<sub>3</sub>, we estimated exposure with an inverse distance weighting interpolation. Standard and multilevel Cox survival models were used to assess the association between air pollution and mortality.

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**Author Contributions:** M.J. conceived the study, led all analyses, contributed to the development of the exposure models, drafted much of the text, and responded to comments from co-author reviewers. B.S.B. ran many of the statistical models that led to the exposure assessments, conducted geographic analyses, contributed text, and assisted with interpreting the results. R.T.B. supplied expert statistical advice on the analyses, drafted sections of the paper, and assisted with the interpretation of the results. E.H. developed the statistical programs used to interpret the random effects models, helped to interpret the results, and supplied key statistical advice on the interpretation. D.K. contributed to the original grant proposal, assisted with interpretation of the results, and wrote sections of the paper. C.A.P. contributed to the statistical analyses, wrote sections of the text, and assisted with interpreting the results. S.M.G. is the Principal Investigator of the ACS CPS-II cohort and commented on the final draft of the paper. She also oversaw the geocoding process for exposure assignment. M.J.T. assisted with interpretation of the statistical models and supplied expert medical epidemiological advice on the results. G.T. assisted with the conception of the study, supplied key information on interpreting the pollution models, and commented on several drafts of the paper, which changed the interpretation of the results. M.C.T. contributed text and tables, helped to assemble supporting data, assisted with the statistical modeling, interpreted the results, and served as a liaison with the American Cancer Society for code review and data access. R.V.M. and A.V.D. contributed the remote sensing models used to derive estimates of PM<sub>2.5</sub>, supplied text, edited versions of the paper, and gave advice on atmospheric chemistry issues. Y.S. ran the statistical models, managed the data, prepared code for review by the American Cancer Society, prepared all of the tables and associated text, and assisted with the interpretation of the results.

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Several cohort studies have examined whether long-term exposure to air pollution is associated with premature death. The results of these studies have been mixed, possibly due to errors introduced in the exposure assessment process.

### What This Study Adds to the Field

To address this potential problem, this study assigned members of the American Cancer Society Cancer Prevention Study II Cohort residing in California more precise exposure assignments at their home address using advanced exposure models. The study provides the first evidence that ozone is significantly associated with cardiovascular mortality, particularly from ischemic heart disease; shows a strong association between nitrogen dioxide (NO<sub>2</sub>) and lung cancer; and demonstrates that that fine particulate matter with aerodynamic diameter of 2.5 μm or less (PM<sub>2.5</sub>) and NO<sub>2</sub> associate independently with premature death from all causes and cardiovascular disease. The findings from this study confirm earlier evidence on PM<sub>2.5</sub> associations with mortality and expand the evidence base markedly on associations between ozone or NO<sub>2</sub> and premature death.

**Measurements and Main Results:** Data for 73,711 subjects who resided in California were abstracted from the American Cancer Society Cancer Prevention II Study cohort, with baseline ascertainment of individual characteristics in 1982 and follow-up of vital status through to 2000. Exposure data were derived from government monitors. Exposure to fine particulate matter, O<sub>3</sub>, and NO<sub>2</sub> was positively associated with ischemic heart disease mortality. NO<sub>2</sub> (a marker for traffic pollution) and fine particulate matter were also associated with mortality from all causes combined. Only NO<sub>2</sub> had significant positive association with lung cancer mortality.

**Conclusions:** Using the first individualized exposure assignments in this important cohort, we found positive associations of fine particulate matter, O<sub>3</sub>, and NO<sub>2</sub> with mortality. The positive associations of NO<sub>2</sub> suggest that traffic pollution relates to premature death.

**Keywords:** air pollution; mortality; survival analyses; GIS; spatial analyses

A substantial body of evidence suggests that long-term exposure to combustion-related air pollution contributes to the development of chronic disease and can lead to premature death (1–6). Exposure to air pollution affects huge populations globally. As a result, the public health impact can be large (7, 8).

Using data from the American Cancer Society's (ACS) Cancer Prevention Study II (CPS-II), a nationwide cohort study of nearly 1.2 million adults who have been followed for mortality since 1982, several studies have been published examining associations of metropolitan-level air pollution and mortality (3, 9–11). In those studies, exposure data were derived at the metropolitan scale, relying on between-city exposure contrasts using central monitor data.

In addition, two studies using CPS-II data evaluated within-city (i.e., Los Angeles and New York) exposure contrasts in fine particulate matter with aerodynamic diameter of 2.5  $\mu\text{m}$  or less ( $\text{PM}_{2.5}$ ) (2, 3). Both studies assigned exposure to the ZIP code postal area of residence, but in the study from Los Angeles (2), the  $\text{PM}_{2.5}$ –mortality dose–response relationship was stronger than that for the full nationwide cohort, and in the study from New York City, the relationship was weaker (3). Although the ZIP code areas were more specific than the metropolitan area, they may have introduced error in the exposure assignment that led to the inconsistent results. Another recent study based on individualized exposures found little association between  $\text{PM}_{2.5}$  exposure and mortality in a cohort of male health professionals (12); however, in that study if home address records were missing, then workplace addresses were used for exposure assignment, possibly leading to measurement error. Conversely, an earlier study based on a large cohort of nurses reported strong and significant associations of  $\text{PM}_{2.5}$  with mortality, using essentially the same exposure model but with complete home address information for exposure assignment (13). Viewed together, these findings suggest that uncertainties in the characterization of the dose–response relationship may be due partly to the errors in exposure estimates arising from the lack of specificity of the coordinates used to link addresses to the exposure estimates. A need therefore exists to investigate how individualized estimates of exposure at the home address influence the observed dose–response function.

In the present analysis, individualized exposure estimates were developed and assigned to the home address for more than 73,000 California residents enrolled in CPS-II. These estimates were used to assess the association of three types of air pollutants ( $\text{PM}_{2.5}$ , ozone [ $\text{O}_3$ ], and nitrogen dioxide [ $\text{NO}_2$ ]) with risk of mortality. We also sought to understand the joint effects of the pollutants in co- and multipollutant models. Although CPS-II is a nationwide cohort, we limited this analysis to California because the state has a wide range of pollution exposures and a good monitoring network.

## METHODS

The ACS CPS-II cohort was enrolled in 1982 (details are presented in References 3 and 14). For the purposes of this paper, vital status was ascertained through to 2000. Subjects with valid postal addresses had their residential locations geocoded. After limiting to residence in the State of California and making exclusions for missing data on key covariates, there were 73,711 subjects available for analysis.

We assigned exposure for  $\text{PM}_{2.5}$ ,  $\text{NO}_2$ , and  $\text{O}_3$ . Monthly average monitoring data for  $\text{PM}_{2.5}$  were available at 112 sites between 1998 and 2002.  $\text{NO}_2$  and  $\text{O}_3$  data were available over the period 1988 to 2002 at 138 and 262 sites, respectively.  $\text{PM}_{2.5}$  and  $\text{NO}_2$  exposures were assessed using land use regression (LUR) models that were selected from more than 70 possible land use covariates (15). The  $\text{PM}_{2.5}$  model included an advanced remote sensing model coupled with atmospheric modeling (16). LUR models were selected with the deletion/substitution/addition algorithm (17). The deletion/substitution/addition algorithm, which aggressively tests nearly all polynomial covariate combinations, uses  $v$ -fold cross-validation to evaluate potential models. In this instance of  $v$ -fold cross-validation, data are first partitioned into 10 roughly equal parts (i.e., folds). The model is then trained on nine folds and cross-validated on the left out fold. This is repeated 10 times so every fold is used as a cross-validation data set. The model selection method avoids the potential

**TABLE 1. PARTICIPANT CHARACTERISTICS IN THE NATIONWIDE STUDY COMPARED WITH THE CALIFORNIA COHORT**

Variable	Nationwide	California
Participants, n	485,426	73,711
Participants died from, %		
All causes	26.4	26.8
CPD	13.1	13.6
CVD	10.9	10.9
IHD	6.1	6.2
Respiratory	2.2	2.7
Lung cancer	2.0	2.0
All other causes	11.3	11.2
Demographics		
Mean (SD) age, yr	56.6 (10.5)	57.4 (10.6)
Female, %	56.6	56.2
White, %	94.2	91.6
Education, %		
<High school	12.1	8.7
High school	31.3	22.9
>High school	56.6	68.4
Alcohol consumption, %		
Beer	22.9	24.1
No beer	9.5	10.9
Missing beer	67.6	65.0
Liquor	27.6	35.1
No liquor	8.7	8.9
Missing liquor	63.7	56.0
Wine	23.1	37.3
No Wine	8.9	7.7
Missing wine	68.0	55.0
Smoking status		
Current smoker, %	21.6	19.4
Cigarettes per day	22.1 (12.4)	21.5 (12.6)
Years of smoking	33.5 (11.0)	34.1 (11.4)
Former smoker, %	25.9	28.9
Cigarettes per day	21.4 (14.7)	20.8 (14.7)
Years of smoking	22.2 (12.6)	22.1 (12.7)
Age when started smoking, %		
<18 yr (current smoker)	8.9	7.7
<18 yr (former smoker)	10.0	10.3
Hours per day exposed to smoking	3.2 (4.4)	2.7 (4.1)

*Definition of abbreviations:* CPD = cardiopulmonary disease; CVD = cardiovascular disease; IHD = ischemic heart disease.

problems of over-fitting on all the data or on a large training set and then using a cross-validation subset (details presented References 15 and 18). For  $\text{O}_3$ , we extracted monthly averaged values from 1988 to 2002 and calculated the inverse distance weighting (IDW) models with the decay parameter set to the inverse of the square of the distance from all sites within a 50-km radius of operational monitors during any particular month. Estimates for all pollutants were then assigned to geocoded baseline residential addresses of the CPS-II subjects, and the monthly values were averaged for the entire time period available.

We used a comprehensive set of individual risk factor variables operationalized through 42 covariates similar to those used in previous studies of the CPS-II cohort (3, 18). Individual-level variables controlled for lifestyle, dietary, demographic, occupational, and educational factors, and ecological variables extracted from the 1990 US Census in the ZIP code of residence were used to control for potential “contextual” neighborhood confounding (including unemployment, poverty, income inequality, and racial composition).

We assessed the association between air pollution and mortality using standard and multilevel Cox proportional hazards regression models. Control for place of residence was also applied in the five largest conurbations—defined by the four consolidated metropolitan statistical areas of California and the metropolitan statistical area of San Diego—that potentially have lower mortality rates than nonmetropolitan areas. This pattern is consistent with what has been termed the “nonmetropolitan mortality penalty,” where nonmetropolitan areas tend to have higher death rates compared with metropolitan areas (19). Because metropolitan areas generally have higher pollution, failure to control for residence in large urban areas has the potential to confound associations between mortality and air pollution.

**TABLE 2. DISTRIBUTION OF AIR POLLUTANTS AT THE INDIVIDUAL LEVEL\***

Air Pollution	Subjects (n)	Mean	Variance	Percentiles								
				0	5	10	25	50	75	90	95	100
PM <sub>2.5</sub> LUR, µg/m <sup>3</sup>	73,711	14.09	12.42	4.25	8.29	9.45	11.60	14.03	16.90	18.42	19.36	25.09
NO <sub>2</sub> LUR, ppb	73,711	12.27	8.54	3.04	7.93	8.81	10.21	12.12	14.33	16.22	17.09	21.94
Ozone IDW, ppb	73,711	50.35	212.18	17.11	28.81	31.13	36.83	50.80	61.00	68.56	74.18	89.33

*Definition of abbreviations:* IDW = inverse distance weighting model; LUR = land use regression.

\*Years represented by air pollution exposure estimates: PM<sub>2.5</sub> LUR, 1998–2002; NO<sub>2</sub> LUR and ozone IDW, 1988–2002.

We evaluated the association between air pollution and several causes of death, including cardiovascular disease (CVD), ischemic heart disease (IHD), stroke, respiratory disease, and lung cancer. We also evaluated “all other” causes of death, excluding the preceding causes, to serve as a negative control. Finally, we evaluated mortality from all causes combined.

**RESULTS**

Table 1 compares characteristics of the nationwide CPS-II cohort used in previous analyses to the subset selected for this analysis (a detailed description of exclusions and sample selection is provided in Reference 18). Minor differences in alcohol consumption and education are apparent, but overall the California cohort appears to have characteristics similar to the nationwide cohort. Subjects included in this analysis were widely distributed across California, giving comprehensive coverage for much of the State’s population (54/58 California counties were represented).

Table 2 shows the mean, variance, and percentiles of each pollutant as estimated by the different models used in this study. All models display considerable variation in the exposures assigned to the home address. Most pollutants show moderate to high positive correlations (Table 3). The exception is between interpolated ozone and NO<sub>2</sub> estimates, which displays a weak negative correlation.

Estimates of adjusted relative risk (RR) and 95% confidence intervals (CIs) are reported in Table 4. All RR estimates are given over the interquartile range of each pollutant. We assessed residual spatial autocorrelation in the health effect estimates with a multilevel Cox model (3). Because the multilevel clustering and autocorrelation analysis had minimal impact on the risk estimates, only results for the standard Cox models are reported.

For PM<sub>2.5</sub> we observed significantly elevated RR for mortality from all causes (RR, 1.032; 95% CI, 1.002–1.068), CVD (RR, 1.064; 95% CI, 1.016–1.114), and IHD (RR, 1.111; 95% CI, 1.045–1.181). Deaths from stroke, respiratory causes, and lung cancer had positive RRs with less precision and CIs that included unity. No association is present with other causes.

NO<sub>2</sub> is significantly and positively associated with all-cause (RR, 1.031; 95% CI, 1.008–1.056), CVD (RR, 1.048; 95% CI, 1.010–1.087), IHD (RR, 1.066; 95% CI, 1.015–1.119), stroke (RR, 1.078; 95% CI, 1.016–1.145), and lung cancer (RR, 1.111; 95% CI, 1.020–1.210) mortality. Respiratory deaths and those from all other causes were not associated with NO<sub>2</sub>.

Although there was no association between O<sub>3</sub> and all-cause mortality, there was a positive association with CVD mortality (RR, 1.045; 95% CI, 0.986–1.108) and a significantly elevated risk for IHD death (RR, 1.104; 95% CI, 1.021–1.194). O<sub>3</sub> had a positive association with stroke and respiratory deaths that lacked precision and a marginally significant negative association with deaths from lung cancer. There was no association with other causes.

We compared the risk estimates obtained from single-pollutant models with risk estimates from two-pollutant and multipollutant models (Table 5). In models that included PM<sub>2.5</sub> and NO<sub>2</sub>, the PM<sub>2.5</sub> associations with mortality from all causes were reduced to about half the size of those in the single pollutant models, and the estimates became insignificant. When O<sub>3</sub> and PM<sub>2.5</sub> were

included in the same all-cause mortality model, the effects from PM<sub>2.5</sub> remained significantly elevated and became slightly larger. A similar pattern was observed with CVD and IHD, where the effects of PM<sub>2.5</sub> were attenuated with NO<sub>2</sub> but remained unchanged in the presence of the O<sub>3</sub> estimates (Figure 1).

The NO<sub>2</sub> associations with CVD and IHD were attenuated when PM<sub>2.5</sub> was included in the model, but they became slightly larger when O<sub>3</sub> was included. O<sub>3</sub> continued to show elevated risks for CVD and IHD in the two-pollutant models with either NO<sub>2</sub> or PM<sub>2.5</sub> included. For respiratory deaths, PM<sub>2.5</sub> continued to have elevated but insignificant risk estimates, whereas neither of the other pollutants was associated with respiratory mortality. For lung cancer, NO<sub>2</sub> consistently displayed significantly elevated risks in two-pollutant models. When combined with O<sub>3</sub>, PM<sub>2.5</sub> associations with lung cancer increased but remained insignificant.

In multipollutant models containing all three pollutants, NO<sub>2</sub> had the strongest associations with all-cause mortality and CVD and with lung cancer, whereas PM<sub>2.5</sub> tended to have stronger effects on deaths from IHD. Intercorrelations among the various pollutants, however, likely contribute to bias in individual pollutant risk estimates in such simultaneous pollutant models, so these results must be interpreted with caution. In multipollutant models, PM<sub>2.5</sub> continued to produce elevated risks for all-cause, CVD, IHD, and respiratory mortality, but none of these estimates were statistically significant. O<sub>3</sub> had elevated risks on CVD and remained a significant predictor of IHD deaths even with the other pollutants in the model.

There was little evidence of associations with the other causes of death in the two-pollutant or multipollutant models.

Figure 1 presents results from cumulative risk index (CRI) models for CVD and IHD mortality that show the extent to which one pollutant confounds the others (details of the CRI methods are provided in the online supplement). Comparisons of CRI based on combinations of pollutants estimated jointly and independently can also provide a means of understanding the joint impacts of the atmospheric mixture on survival. For example, with CVD mortality, the combined hazard ratio (HR) of NO<sub>2</sub> and O<sub>3</sub> assuming independence is 1.048 × 1.045 = 1.095. However, the combined HR based on the two-pollutant survival model is 1.121, suggesting a synergy of effect among the pollutants. A similar pattern of synergy is also observed for IHD mortality.

Such a comparative assessment is illustrated in Figure 1 for three pollutants (NO<sub>2</sub>, O<sub>3</sub>, and PM<sub>2.5</sub>) and two causes of death (CVD and IHD). The HRs evaluated at their respective interquartile

**TABLE 3. PEARSON CORRELATIONS (×100) BETWEEN AIR POLLUTANTS (CALIFORNIA OVERALL)**

	PM <sub>2.5</sub> LUR	NO <sub>2</sub> LUR
PM <sub>2.5</sub> LUR	—	—
NO <sub>2</sub> LUR	55.10	—
Ozone IDW	55.81	-0.71

*Definition of abbreviations:* IDW = inverse distance weighting model; LUR = land use regression; PM<sub>2.5</sub> = particulate matter with aerodynamic diameter of 2.5 µm or less.

**TABLE 4. AMERICAN CANCER SOCIETY COHORT WITH FOLLOW-UP FROM 1982 TO 2000, ADJUSTING FOR 42 INDIVIDUAL-LEVEL COVARIATES, FIVE CONSOLIDATED METROPOLITAN STATISTICAL AREA CITY INDICATORS, SEVEN 1990 ECOLOGIC COVARIATES STRATIFYING THE BASELINE HAZARD FUNCTION BY AGE (1-YR GROUPINGS), GENDER, AND RACE USING THE STANDARD COX SURVIVAL MODEL**

Air Pollutant	Cause of Death						
	All Causes (n = 19,733)	Cardiovascular (n = 8,046)	Ischemic Heart (n = 4,540)	Stroke (n = 3,068)	Respiratory (n = 1,973)	Lung Cancer (n = 1,481)	All Others (n = 8,233)
PM <sub>2.5</sub> LUR	1.032 (1.002–1.062)*	1.064 (1.016–1.114)	1.111 (1.045–1.181)	1.065 (0.988–1.148)	1.046 (0.953–1.148)	1.062 (0.954–1.183)	0.994 (0.950–1.040)
NO <sub>2</sub> LUR	1.031 (1.008–1.056)	1.048 (1.010–1.087)	1.066 (1.015–1.119)	1.078 (1.016–1.145)	0.999 (0.927–1.077)	1.111 (1.020–1.210)	1.009 (0.973–1.046)
Ozone IDW	0.998 (0.960–1.036)	1.045 (0.986–1.109)	1.104 (1.021–1.194)	1.011 (0.919–1.112)	1.017 (0.902–1.147)	0.861 (0.747–0.992)	0.967 (0.911–1.027)

Definition of abbreviations: IDW = inverse distance weighting model; LUR = land use regression; PM<sub>2.5</sub> = particulate matter with aerodynamic diameter of 2.5 μm or less.

\*Relative risks are shown for the interquartile range of exposure in each pollutant (i.e., 5.3037 μg/m<sup>3</sup> for PM<sub>2.5</sub>, 4.1167 ppb NO<sub>2</sub>, and 24.1782 ppb for O<sub>3</sub>). Values in parentheses are 95% confidence intervals.

ranges for the three pollutants are presented singly, based on the three possible two-pollutant models, and based on the single three-pollutant model. There is some modest increase in the CRI for models containing PM<sub>2.5</sub> and either NO<sub>2</sub> or O<sub>3</sub> compared with each of the single-pollutant models. The model with NO<sub>2</sub> and O<sub>3</sub>, however, is larger than either of the other two-pollutant models and has a similar CRI to the three-pollutant model, suggesting that a combination of NO<sub>2</sub> and O<sub>3</sub> is sufficient to characterize the toxicity of the pollutant mixture in this study, at least with respect to the three pollutants considered.

The CRI implies that there is little marginal contribution to CVD and IHD mortality from the addition of PM<sub>2.5</sub> in the presence of the mixture represented by NO<sub>2</sub> and O<sub>3</sub>. We also caution that in this interpretation the CIs clearly overlap each of the CRIs we have calculated. This limits our ability to infer the set of minimally sufficient pollutants required to fully capture the toxicity of the atmosphere in California.

## DISCUSSION

We sought to estimate the effects of three criteria air pollutants on premature death in California. This study was motivated by earlier research from Los Angeles that showed PM<sub>2.5</sub> exerted a large significant effect on all-cause mortality and mortality from CVD. Other studies, including those based on data from the ACS CPS-II, showed heterogeneous health effect estimates that potentially resulted from a lack of precision in the exposure assessment. To address this problem, we developed detailed exposure assessment models that included auxiliary information and

assigned resulting estimates of exposure to the baseline residential address of more than 73,000 subjects with valid data from the ACS CPS-II cohort.

Several important results deserve mention. First, findings of associations of PM<sub>2.5</sub> with all-cause and cardiovascular mortality are consistent with those reported from our previous analyses of the full, nationwide CPS-II cohort (3). Table 6 shows that results for all-cause, CVD, and IHD mortality from the current study are similar, although they are slightly weaker than from the study of the nationwide cohort. The difference in exposure metrics had little impact on the risk estimates for PM<sub>2.5</sub>. We also fit models specifically for Los Angeles to compare with earlier results (2). Although the sample size is different here due to limitations in the geocoding, the results show that the effects in Los Angeles continue to be higher than those in the national study or in the rest of the state. We also examined the dose–response function for nonlinearity because levels in Los Angeles are generally higher than in many other parts of the state, but we found no evidence of nonlinearity in the dose–response function based on visual inspection of spline plots and formal measures of model fit (Akaike information criteria and Bayesian information criteria results not shown). This suggests that the population of Los Angeles is more susceptible to air pollution, that the air pollution there is more toxic, or both.

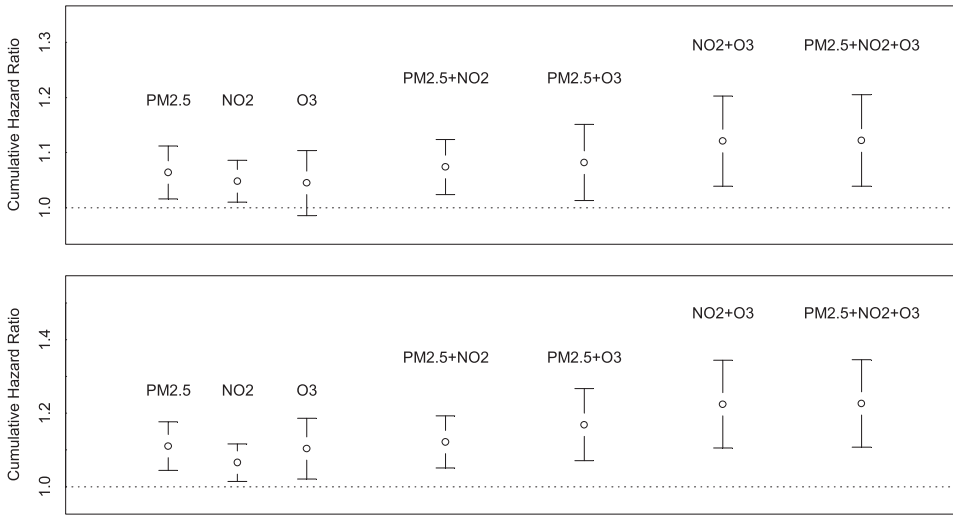
The strongest associations with mortality appear to be for exposures that are markers for traffic-related air pollution. The largest predictors of NO<sub>2</sub> in the LUR model were measures of roadway length near the monitors, although we cannot rule out other contributions to the modeled concentrations, such as heating and industrial sources, particularly given the generally higher

**TABLE 5. TWO-POLLUTANT AND MULTIPOLLUTANT MODEL RESULTS FROM THE AMERICAN CANCER SOCIETY COHORT WITH FOLLOW-UP FROM 1982 TO 2000, ADJUSTING FOR 42 INDIVIDUAL-LEVEL COVARIATES, FIVE CONSOLIDATED METROPOLITAN STATISTICAL AREA CITY INDICATORS, SEVEN 1990 ECOLOGIC COVARIATES STRATIFYING THE BASELINE HAZARD FUNCTION BY AGE (1-YR GROUPINGS), GENDER, AND RACE USING THE STANDARD COX SURVIVAL MODEL**

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PM <sub>2.5</sub> LUR	1.015 (0.980–1.050) <sup>†</sup>	1.043 (0.989–1.101)	1.090 (1.015–1.170)	1.019 (0.934–1.112)	1.064 (0.954–1.185)	0.985 (0.867–1.119)	0.984 (0.933–1.038)
NO <sub>2</sub> LUR	1.025 (0.997–1.054)	1.030 (0.987–1.075)	1.029 (0.972–1.090)	1.070 (0.998–1.147)	0.973 (0.891–1.063)	1.118 (1.010–1.236)	1.016 (0.973–1.060)
PM <sub>2.5</sub> LUR	1.035 (1.004–1.067)	1.057 (1.008–1.109)	1.093 (1.027–1.165)	1.067 (0.987–1.153)	1.045 (0.949–1.151)	1.103 (0.985–1.234)	1.002 (0.955–1.050)
Ozone IDW	0.985 (0.947–1.025)	1.025 (0.964–1.089)	1.070 (0.987–1.161)	0.988 (0.894–1.091)	1.001 (0.883–1.134)	0.832 (0.719–0.964)	0.966 (0.908–1.029)
NO <sub>2</sub> LUR	1.032 (1.008–1.057)	1.055 (1.016–1.095)	1.082 (1.029–1.137)	1.082 (1.019–1.150)	1.001 (0.928–1.080)	1.097 (1.006–1.196)	1.006 (0.970–1.043)
Ozone IDW	1.006 (0.968–1.046)	1.062 (1.000–1.127)	1.132 (1.045–1.227)	1.034 (0.938–1.140)	1.017 (0.901–1.149)	0.882 (0.764–1.019)	0.968 (0.912–1.029)
PM <sub>2.5</sub> LUR	1.015 (0.977–1.055)	1.024 (0.965–1.086)	1.048 (0.969–1.133)	1.008 (0.915–1.110)	1.070 (0.949–1.207)	1.040 (0.902–1.198)	0.995 (0.938–1.056)
NO <sub>2</sub> LUR	1.025 (0.995–1.056)	1.044 (0.996–1.093)	1.059 (0.995–1.126)	1.079 (1.000–1.163)	0.969 (0.881–1.066)	1.078 (0.967–1.201)	1.008 (0.963–1.056)
Ozone IDW	0.999 (0.957–1.042)	1.050 (0.982–1.122)	1.106 (1.012–1.209)	1.031 (0.925–1.149)	0.984 (0.860–1.126)	0.866 (0.739–1.015)	0.971 (0.908–1.038)

Definition of abbreviations: IDW = inverse distance weighting model; LUR = land use regression model; PM<sub>2.5</sub> = particulate matter with aerodynamic diameter of 2.5 μm or less.

<sup>†</sup>Relative risks are shown for the interquartile range of exposure in each pollutant (i.e., 5.3037 μg/m<sup>3</sup> for PM<sub>2.5</sub>; 4.1167 ppb NO<sub>2</sub>; and 24.1782 ppb for O<sub>3</sub>). Values in parentheses are 95% confidence intervals.



**Figure 1.** Summary plot of individual and multipollutant cumulative hazard ratios. *Top:* Cardiovascular mortality. *Bottom:* Ischemic heart disease mortality.

concentrations of NO<sub>2</sub> during the winter when home heating contributes to emissions of NO<sub>2</sub> precursors (20). This exposure measure demonstrated significant associations with all-cause, CVD, IHD, and lung cancer mortality. In multipollutant models, these associations remained elevated but became insignificant in some models, possibly due to multicollinearity among the pollutants. We also examined direct measures of proximity to roadways in earlier studies (18) and found these markers of traffic had positive coefficients, but the findings were null, suggesting that the improved exposure estimates with the LUR model may have reduced exposure measurement error.

Our results are broadly consistent with several studies from Europe in which NO<sub>2</sub> exposure was positively associated with mortality (21, 22). In an American study of male truck drivers, NO<sub>2</sub> was found to be independently associated with all-cause and cause-specific mortality even after controlling for occupational exposures (23). In a comprehensive review by the Health Effects Institute, effects of traffic-related pollution on mortality were identified as suggestive but insufficient to establish a causal association (24). When viewed in the context of the emerging literature, our results strengthen the evidence base on the effects of traffic-related air pollution on mortality.

Although acute exposure to O<sub>3</sub> has been related to mortality (25), here we observed a significant positive association between long-term O<sub>3</sub> exposure and CVD mortality, notably for IHD. The strength of association for O<sub>3</sub> was similar to that of PM<sub>2.5</sub> and NO<sub>2</sub>. The association of O<sub>3</sub> with IHD was mildly confounded by PM<sub>2.5</sub>; however, the two exposures had moderately high correlation, and, given the extensive auxiliary information in the PM<sub>2.5</sub> model, the PM<sub>2.5</sub> estimates may have dominated by virtue of lower exposure measurement error (26). Nevertheless, O<sub>3</sub> continued to exhibit a significant association with IHD, even with PM<sub>2.5</sub> in the model.

Positive RR estimates for O<sub>3</sub> became larger when NO<sub>2</sub> was included in the model (see Figure 1). We hypothesize that this results from the negative correlation between the two pollutants due to the atmospheric chemistry, such that in areas where O<sub>3</sub> is high, NO<sub>2</sub> tends to be low, and *vice versa* (27, 28). If both pollutants represent harmful constituents of the complex mixture of ambient air pollutions, each would contaminate the comparison for calculating “clean” atmospheres when assessing the risk of the other pollutant. In such instances, the comparison groups with lower pollution levels may also have higher mortality, resulting in part from higher levels of the other pollutant that occupies the opposite spatial pattern. We found a negative, significant association between O<sub>3</sub> and lung cancer, which became insignificant

when NO<sub>2</sub> was included in the model. These findings together suggest the importance of having both O<sub>3</sub> and NO<sub>2</sub> in models that attempt to predict health effects from either pollutant. We did observe a weak negative correlation between the two pollutants; however, subsequent analyses showed that in four of the five major urban regions of California, NO<sub>2</sub> had moderately high negative correlations with O<sub>3</sub> (details are provided in the online supplement), which supports the possibility of the positive confounding we have observed here and of the hypothesis that both pollutants need to be in the model for correct inference on either.

Unlike previous analyses (14), we did not see a significant association between respiratory disease and O<sub>3</sub>. In the present analysis, however, the number of respiratory deaths was much smaller than in the earlier national study. The point estimate here was elevated and of similar size to that reported in an earlier analysis of the nationwide cohort (3); consequently, the lack of significant association may have resulted from the lower event numbers. In contrast to earlier results, PM<sub>2.5</sub> did have a positive association with respiratory mortality, which tended to get stronger with the inclusion of copollutants, particularly O<sub>3</sub>. In the correlational analyses done by major urban regions (see APPENDIX), we observed significant negative correlations between O<sub>3</sub> and PM<sub>2.5</sub> suggesting again the potential for positive confounding.

**TABLE 6. COMPARISON OF RELATIVE RISK ESTIMATES FROM THE CALIFORNIA AND NATIONAL AMERICAN CANCER SOCIETY COHORTS FOR PM<sub>2.5</sub> USING A 10 μg/m<sup>3</sup> EXPOSURE INCREMENT\***

	California <sup>†</sup>	National Level <sup>‡</sup>	Los Angeles Only <sup>†</sup>
All-cause	1.060 (1.003–1.120) <sup>§</sup>	1.065 (1.035–1.096)	1.104 (0.968–1.260)
CVD	1.122 (1.030–1.223)	1.141 (1.086–1.198)	1.124 (0.918–1.375)
IHD	1.217 (1.085–1.365)	1.248 (1.160–1.342)	1.385 (1.058–1.814)

*Definition of abbreviations:* CVD = cardiovascular disease; IHD = ischemic heart disease; PM<sub>2.5</sub> = particulate matter with aerodynamic diameter of 2.5 μm or less.

\*Models for both risk estimates control for an identical set of individual risk factors (e.g., smoking) and contextual risk factors (e.g., unemployment in area of residence) and are stratified by age, race, and sex. Results for the California cohort are additionally adjusted for place of residence in five major urban conurbations. The follow-up period for all studies was from 1982 to 2000.

<sup>†</sup> California and Los Angeles use residential address with a land use regression estimate of exposure results using standard Cox model.

<sup>‡</sup> The national-level study uses metropolitan area of residence with the average of all fine particulate matter (PM<sub>2.5</sub>) monitors within the metropolitan area as the exposure estimate; results were determined using two-level random effects assuming no spatial autocorrelation.

<sup>§</sup> Values are relative risk with 95% confidence interval in parentheses.

Several strengths and limitations merit mention. For NO<sub>2</sub> and PM<sub>2.5</sub>, we used advanced exposure assessment models informed by auxiliary information that had good predictive capacity. These models, however, were based on government monitoring data, and the placement of the government monitoring sites might be less representative of all exposure domains because they are chosen to represent background conditions. For the most part, near-road environments are not well represented in this network, limiting the ability to predict small-area variations near roadways. Our estimates of O<sub>3</sub> exposure likely do not capture the small area variation that can occur in open space areas and other areas away from roadways (27). Nonetheless, by assigning exposures that vary among individuals within cities, this study extends the applicability of the risk estimates to support studies that have an interest in assessing the health impacts of air pollutants within cities, which is being increasingly done to justify the health benefits of urban planning and climate mitigation interventions (29, 30).

Regarding limitations, there were no follow-up surveys conducted in the full CPS-II, and key lifestyle characteristics may have changed during the follow-up (e.g., smoking rates declined precipitously across California between 1982 and 2000) (31). If the declines in smoking rates were spatially associated with the air pollution levels, these would have the potential to confound our air pollution risk estimates. We also lacked information on mobility during the follow-up and on key microenvironments such as in-transit exposures, which contribute substantially to interindividual variability in air pollution exposures (32).

In conclusion, our results suggest that several components of the combustion-related air pollution mixture are significantly associated with increased all-cause and cause-specific mortality. Associations with CVD deaths in general and with IHD in particular stand out as most consistent in our analyses. The strong associations of NO<sub>2</sub> with all-cause, CVD, and lung cancer mortality are suggestive of traffic-related pollution as a cause of premature death. The potential for positive confounding between O<sub>3</sub> and NO<sub>2</sub> requires increased attention in future research. Given the indications that O<sub>3</sub> may relate significantly to CVD mortality, future research may lead to refined O<sub>3</sub> exposure assessment with lower measurement error. In sum, the associations observed here reduce key uncertainties regarding the relationship between air pollution and mortality and confirm that air pollution is a significant risk factor for mortality.

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

## References

1. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, et al; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010;121:2331–2378.
2. Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein N, Calle EE, et al. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology* 2005;16:727–736.
3. Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA III, Thurston G, Calle EE, et al. 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.
4. Pope CA III, 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.
5. Pope CA III, Burnett RT, Turner MC, Cohen A, Krewski D, Jerrett M, Gapstur SM, Thun MJ. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. *Environ Health Perspect* 2011;119:1616–1621.
6. Chen H, Goldberg MS, Villeneuve PJ. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. *Rev Environ Health* 2008;23:243–297.
7. Pope CA III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006;56:709–742.
8. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–2260.
9. Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Abrahamowicz M, White WH. Part I: Replication and validation. In: Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality: a special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute; 2000. pp. 1–295.
10. Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132–1141.
11. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 1995;151:669–674.
12. Puett RC, Hart JE, Schwartz J, Hu FB, Liese AD, Laden F. Are particulate matter exposures associated with risk of type 2 diabetes? *Environ Health Perspect* 2011;119:384–389.
13. Puett RC, Hart JE, Yanosky JD, Paciorek C, Schwartz J, Suh H, Speizer FE, Laden F. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. *Environ Health Perspect* 2009;117:1697–1701.
14. Jerrett M, Burnett RT, Pope CA III, 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.
15. Beckerman BS, Jerrett M, Martin RV, van Donkelaar A, Ross Z, Burnett RT. Application of the deletion/substitution/addition algorithm to selecting land use regression models for interpolating air pollution measurements. *Atmos Environ* 2013;77:172–177.
16. van Donkelaar A, Martin RV, Brauer M, Kahn R, Levy R, Verduzco C, Villeneuve PJ. Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. *Environ Health Perspect* 2010;118:847–855.
17. Sinisi SE, van der Laan MJ. Deletion/substitution/addition algorithm in learning with applications in genomics. *Stat Appl Genet Mol Biol* 2004;3:Article18.
18. Jerrett M, Burnett RT, Pope A III, Krewski D, Thurston G, Christakos G, Hughes E, Ross Z, Shi Y, Thun M, et al. Spatiotemporal analysis of air pollution and mortality in California based on the American Cancer Society Cohort: final report. Sacramento, CA: California Air Resources Board; 2011.
19. Cosby AG, Neaves TT, Cossman RE, Cossman JS, James WL, Feierabend N, Mirvis DM, Jones CA, Farrigan T. Preliminary evidence for an emerging nonmetropolitan mortality penalty in the United States. *Am J Public Health* 2008;98:1470–1472.
20. Spengler J, Schwab M, Ryan PB, Colome S, Wilson AL, Billick I, Becker E. Personal exposure to nitrogen dioxide in the Los Angeles Basin. *Air Waste* 1994;44:39–47.
21. Brunekreef B. Health effects of air pollution observed in cohort studies in Europe. *J Expo Sci Environ Epidemiol* 2007;17:S61–S65.
22. 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.
23. Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med* 2011;183:73–78.

24. Health Effects Institute Panel on the Health Effects of Traffic-Related Air Pollution. Traffic-related air pollution: a critical review of the literature on emissions, exposure and health effects. Special report 17. Boston, MA: HEI; 2009.
25. Henrotin JB, Zeller M, Lorgis L, Cottin Y, Giroud M, Béjot Y. Evidence of the role of short-term exposure to ozone on ischaemic cerebral and cardiac events: the Dijon Vascular Project (DIVA). *Heart* 2010;96:1990–1996.
26. Zidek JV, Wong H, Le ND, Burnett R. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics* 1996;7:441–451.
27. Beckerman B, Jerrett M, Brook JR, Verma DK, Arain MA, Finkelstein MM. Correlation of nitrogen dioxide with other traffic pollutants near a major expressway. *Atmos Environ* 2008;42:275–290.
28. McConnell R, Berhane K, Yao L, Lurmann FW, Avol E, Peters JM. Predicting residential ozone deficits from nearby traffic. *Sci Total Environ* 2006;363:166–174.
29. Woodcock J, Edwards P, Tonne C, Armstrong BG, Ashiru O, Banister D, Beevers S, Chalabi Z, Chowdhury Z, Cohen A, *et al.* Public health benefits of strategies to reduce greenhouse-gas emissions: urban land transport. *Lancet* 2009;374:1930–1943.
30. Rojas-Rueda D, de Nazelle A, Tainio M, Nieuwenhuijsen MJ. The health risks and benefits of cycling in urban environments compared with car use: health impact assessment study. *BMJ* 2011;343:d4521.
31. California Department of Public Health California Tobacco Control Program. Smoking prevalence among California adults, 1984–2010 [prepared 2011 Apr; accessed 2012 Sep 11]. Available from: <http://www.cdph.ca.gov/Pages/NR11-031SmokingChart.aspx>
32. de Nazelle A, Nieuwenhuijsen MJ, Antó JM, Brauer M, Briggs D, Braun-Fahrlander C, Cavill N, Cooper AR, Desqueyroux H, Fruin S, *et al.* Improving health through policies that promote active travel: a review of evidence to support integrated health impact assessment. *Environ Int* 2011;37:766–777.

*Spatiotemporal Analysis of Air Pollution  
and Mortality in California Based on the  
American Cancer Society Cohort: Final Report*

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## ABSTRACT

**Problem:** Studies using the American Cancer Society (ACS) Cancer Prevention II (CPS II) cohort to assess the relation between particulate air pollution and mortality rank among the most influential and widely cited. The original study, a reanalysis that introduced new random effects methods and spatial analytic techniques, and recent studies with longer follow-up and improved exposure assignment, have all demonstrated statistically significant and substantively large air pollution effects on all-cause and cause-specific mortality. Due to this robust association and a lack of other large cohort studies on the long-term effects, the ACS studies have proven important to government regulatory interventions and health burden assessments.

At present there are no ACS CPS II statewide studies in California that investigate whether the risks are similar to or different from those reported in the above-mentioned analyses. Existing estimates come from either national-level ACS studies, in which the California subjects comprise less than 15% of the total national sample, or from select metropolitan or county areas of California, where questions remain about their generalizability to the rest of the state. A need therefore exists to investigate whether the results hold across California. In addition, none of the existing ACS studies have used high-resolution exposure assignment or investigated the temporal dimensions of the dose-response relationship. In this study we used advanced exposure modeling to reduce problems of measurement error, and we investigated time windows of exposure.

**Previous Work:** Our previous work includes the original ACS study of particulate air pollution and mortality, the reanalysis of the ACS study, as well as studies involving analytic extensions to both these studies using new spatial models, and a study providing the first assessment of particulate air pollution at the within-city or “intraurban” scale using Los Angeles as the test site. Our Los Angeles results suggest the chronic health effects associated with intraurban gradients in exposure to fine particulate matter (PM<sub>2.5</sub>) are even larger than those previously reported for the metropolitan areas used in both the original study by Pope et al. [1] and the reanalysis by Krewski et al. [2]. For the within-city models, we observed effects nearly three times greater than those using models relying on between-community exposure contrasts. These findings were confirmed using more refined exposure models in a subsequent Health Effects Institute report [3]. In that report, we also found risks for the national study that were greater than those in earlier studies for deaths due to cardiovascular causes.

**Objectives:** In this context, we pursued the following research objectives: (1) to derive detailed assessments of the health effects from particulate and gaseous air pollution on all-cause and cause-specific mortality in California based on the ACS CPS II cohort, (2) to investigate whether specific particle characteristics associate with larger health effects through examination of intraurban gradients in exposure to different particle constituents and sources, and (3) to determine whether critical exposure time windows exist in the relationship between air pollution and mortality in California.

**Description:** We identified more than 76,000 California subjects in the ACS cohort to serve as the study population (20,432 deaths with an 18 year follow-up ending in 2000). These subjects were widely distributed across California, giving comprehensive coverage for much of the

population of the state (i.e., 54 of 58 California counties have ACS subjects). For the first time in using the ACS CPS-II data, we have geocoded subjects to their home address to refine our exposure assignment.

As a basis for exposure assessment, we utilized interpolation estimates derived by Air Resources Board staff for the California Teachers Cohort Study led by Dr. Michael Lipsett, with Dr. Jerrett as co-investigator. We also implemented geostatistical kriging, advanced remote sensing coupled with atmospheric modeling, land use regression, and Bayesian models capable of assessing space-time patterns in exposure to improve exposure assignment.

We employed a comprehensive set of 20 individual risk factor variables similar to those used in previous ACS studies. These variables control for lifestyle, dietary, demographic, occupational, and educational influences that may confound the air pollution-mortality association. We used ecological variables in the neighborhoods of residence to control for “contextual” neighborhood confounding (e.g., unemployment). Although we used similar variables as in previous analyses to promote comparison to earlier results, we also tested other model specifications.

We assessed the association between air pollution and several causes of death, including cardiovascular (CVD), ischemic heart disease (IHD), respiratory, lung cancer, and other causes. We also evaluated all-cause mortality. There is some debate about the efficacy of evaluating associations between all-cause mortality and air pollution because several causes of deaths in this broad categorization likely have little association with air pollution. We have included the all-cause metric for several reasons. First, the all-cause metric has been used in most of the other published studies to date, and therefore we used this outcome for comparability with previous results. Second, the all-cause measure avoids the potential cross-classification bias between respiratory and CVD deaths. Third, the all-cause metric can be useful in burden of mortality assessments, and it has been used extensively for this purpose. Finally, we use the all-cause metric to compare with the cause-specific effects that we hypothesized should be more strongly related to pollution exposures (i.e., CVD deaths). A related point is the use of the combined "all other" causes of death to serve as a negative "control". The overall results are more compelling if one observes associations only for those causes of deaths for which there exists biological plausibility or where previous results have provided an a priori hypothesis (CVD, IHD, lung cancer), and where the risks for all other effects are null.

We assessed the association between air pollution and death using standard and multilevel Cox proportional hazards models. Control was also applied for residence in the five largest urban conurbations, which potentially have different mortality rates than non-metropolitan areas. We also assessed spatial autocorrelation in the health effect estimates.

**Key Results:** Below we summarize the key results from our investigation.

1. Cardiovascular disease (CVD) deaths, especially those from ischemic heart disease (IHD), are consistently and robustly associated with measures of fine particulate and traffic-related air pollution. The effects on CVD and IHD in California are virtually identical to those of the national ACS study (see **Abstract Table 1**).

**Abstract Table 1: Comparison of Relative Risk Estimates from the California and National American Cancer Society Cohorts for PM<sub>2.5</sub> using a 10 µg/m<sup>3</sup> Exposure Increment**

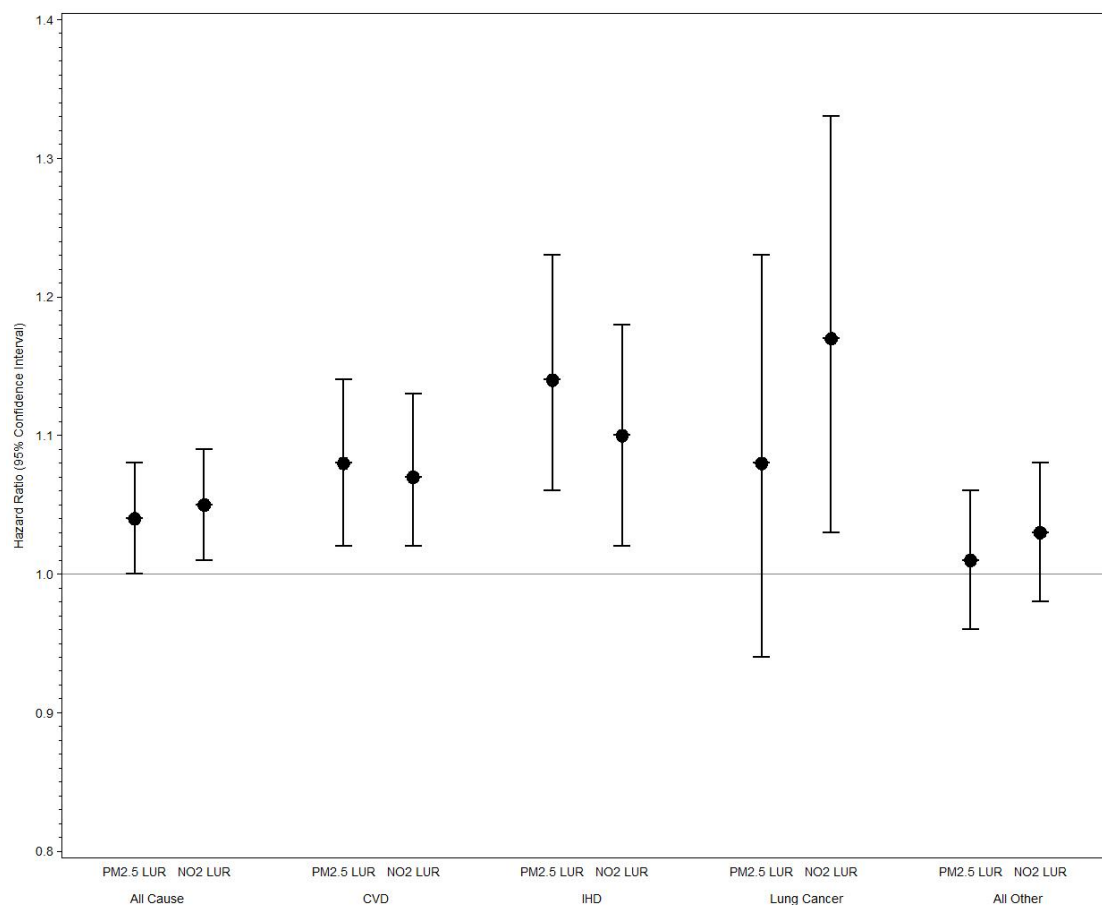
	California*		National Level**	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
<b>All-cause</b>	1.08	(1.00, 1.15)	1.08	(1.04, 1.11)
<b>CVD</b>	1.15	(1.04, 1.28)	1.17	(1.11, 1.24)
<b>IHD</b>	1.28	(1.12, 1.47)	1.29	(1.18, 1.40)

\* California study uses residential address with a Land Use Regression estimate of exposure with statistical control for individual and ecologic covariates and residence in the five largest conurbations in California.

\*\*National level study uses metropolitan area of residence with the average of all PM<sub>2.5</sub> monitors within the metropolitan area as the exposure estimate; source for the National estimate for all-cause and IHD from Krewski et al. 2009 [3] Table 9; CVD estimate produced for this report for comparison with the California using the same model and sample as in the Krewski report (i.e., two level random effects, with no spatial autocorrelation – referred to as MSA and DIFF in Table 9). Note numbers slightly differ from the Krewski report due to rounding.

Models for both risk estimates control for individual risk factors (e.g., smoking), contextual risk factors (e.g., unemployment in area of residence) and are stratified by age, race and sex. Results for the California cohort are also additionally adjusted for place of residence in five major urban conurbations. Follow up period for both studies was from 1982-2000.

2. All-cause mortality is significantly associated with PM<sub>2.5</sub> exposure, but the results are sensitive to statistical model specification and to the exposure model used to generate the estimates. When we applied control for residence in the largest urban conurbations, and we employed the land use regression (LUR) model, we found significantly elevated effects on all-cause mortality. For reasons explained in the main report this model specification with land use regression exposures and control for residence in the large conurbations is most likely to produce scientifically valid results. Many of the other results presented were included to satisfy contractual requirements to investigate methodological issues of interest to the Air Resources Board. When we use the fully specified models, the effect sizes are the same as those in the national study (see **Abstract Table 1** for a comparison). We observed effects that were of similar size, but of borderline significance when using other exposure models.
3. The strongest and most consistent effects are observed when there is finer-scale spatial resolution in the exposure predictions. In models using the LUR estimate that serve as markers of relatively local variation in pollution we see all-cause effects from NO<sub>2</sub> and PM<sub>2.5</sub> (see **Abstract Figure 1** for a comparison of the risks from statewide LUR models of PM<sub>2.5</sub> and NO<sub>2</sub> for various causes of death).



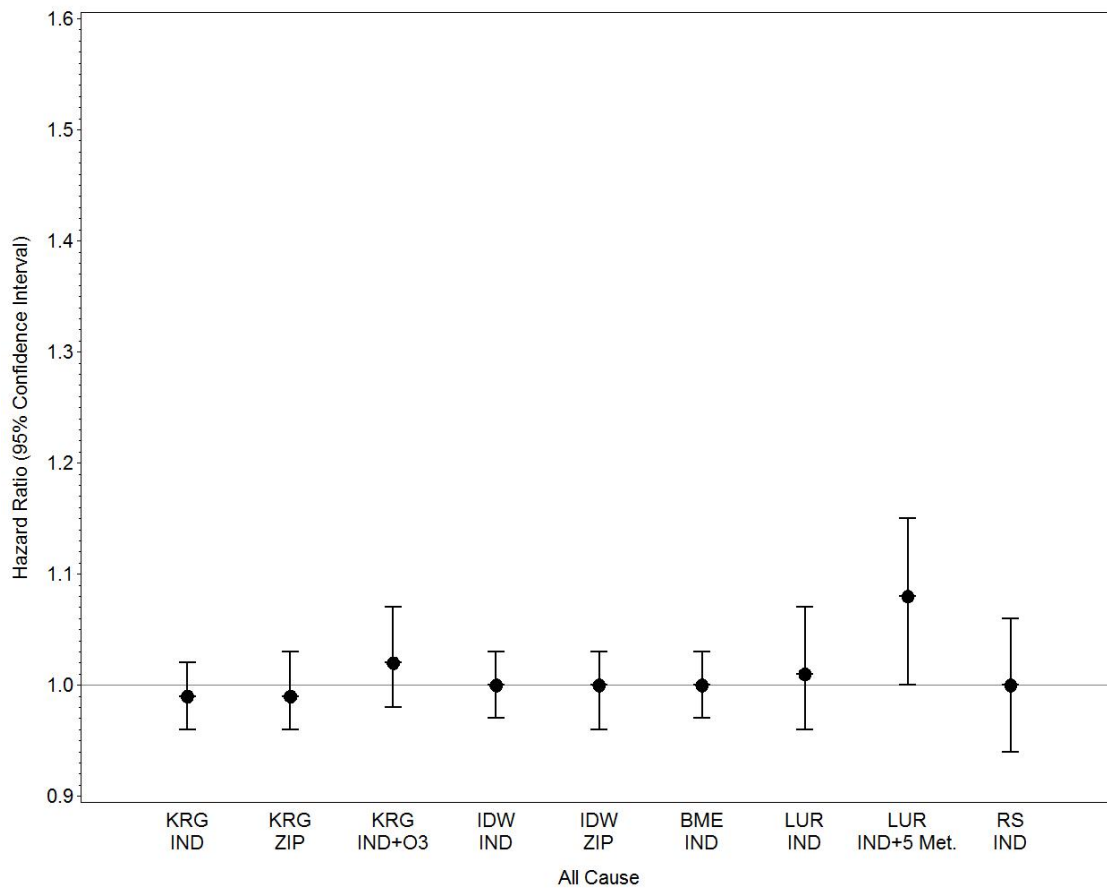
**Abstract Figure 1: Summary of key results for PM<sub>2.5</sub> and NO<sub>2</sub> with all-cause and cause specific death. Estimates derived from single pollutant models and calibrated to the inter-quartile range of exposure for each pollutant where statistical models control for individual and ecologic covariates and residence in the five largest conurbations in California.**

4. The strongest evidence of mortality effects is with exposure models that are markers of traffic-related air pollution. The NO<sub>2</sub> LUR estimate has significant associations with all-cause, CVD, IHD, and lung cancer deaths. Exposure estimates based on roadway proximity had elevated, but insignificant risks, suggesting weaker effects than with the NO<sub>2</sub> model, probably due to increased exposure measurement error.
5. With regard to other causes of death, there was no evidence of an air pollution effect. In fact for some regional PM<sub>2.5</sub> exposure there was some evidence of negative association, but when residence in the five largest urban conurbations was accounted for in the model, the effects became positive, but insignificant.
6. Other pollutants – namely PM<sub>10</sub>, sulfate derived from PM<sub>10</sub> filters, NO<sub>2</sub>, and ozone estimates from interpolation models – all showed consistent associations with CVD that are similar in size to those observed for PM<sub>2.5</sub>. In general, the interpolation estimates of these pollutants were highly correlated with each other and with PM<sub>2.5</sub>. Therefore caution

must be exercised in interpreting effects from any single pollutant when the exposure estimate relies solely on interpolation.

## CONCLUSION

**Taken together, the results from this investigation indicate consistent and robust effects of  $PM_{2.5}$  – and other pollutants commonly found in the combustion-source mixture with  $PM_{2.5}$  – on deaths from CVD and IHD. We also found significant associations between  $PM_{2.5}$  and all causes of death, although these findings were sensitive to model specification.** In Los Angeles, where the monitoring network is capable of detecting intraurban variations in  $PM_{2.5}$ , we observed large effects on death from all causes, CVD, IHD, and respiratory disease. These results were consistent with past ACS analyses and with findings from other national or international studies reviewed in this report. Our strongest results were from a land use regression estimate of  $NO_2$ , which is generally thought to represent traffic sources, where significantly elevated effects were found on deaths from all causes, CVD, IHD, and lung cancer. **We therefore conclude that combustion-source air pollution is significantly associated with premature death in this large cohort of Californians.**



**Figure 22: Hazard ratios and 95% confidence intervals for the association between different PM<sub>2.5</sub> indicators (each 10 ug/m3) at both the individual and ZIP code-level and all cause mortality, follow-up from 1982 to 2000, adjusting for individual level covariates and ecologic level covariates (1990), stratifying the baseline hazard function by age (1-year groupings), gender and race using the Random Effects model, 1 cluster level (ZIP)**

## DISCUSSION

In these analyses we sought to estimate the effects of PM<sub>2.5</sub> and other air pollutants on premature death in California. This study was motivated by earlier research from Los Angeles that showed PM<sub>2.5</sub> exerted a large, significant effect on all cause mortality and mortality from CVD and by a lack of statewide dose-response functions for benefits estimates. In the earlier analyses, effects for all causes, CVD, and IHD outcomes were larger than those observed in our national level studies using the ACS CPS II [5]. But in a more recent follow up [3], the effects tended to increase for CVD and IHD in the national study and were of similar size to those observed in LA. The effects on all cause mortality were still about twice the size in LA compared to the recent national study, although they were more uncertain due to the smaller sample size. Consequently, uncertainty exists as to the effects that would be observed in a statewide model for California.

Below we summarize the key findings from the present investigation. We then offer narrative interpretation.

### **Key Findings**

1. Cardiovascular disease (CVD) deaths, especially those from ischemic heart disease (IHD), are consistently and robustly associated with measures of fine particulate and traffic-related air pollution. The effects on CVD and IHD in California are virtually identical to those of the national ACS study (see **Abstract Table 1**).

**Abstract Table 1: Comparison of Relative Risk Estimates from the California and National American Cancer Society Cohorts for PM<sub>2.5</sub> using a 10 µg/m<sup>3</sup> Exposure Increment**

	California*		National Level**	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
All-cause	1.08	(1.00, 1.15)	1.08	(1.04, 1.11)
CVD	1.15	(1.04, 1.28)	1.17	(1.11, 1.24)
IHD	1.28	(1.12, 1.47)	1.29	(1.18, 1.40)

\* California study uses residential address with a Land Use Regression estimate of exposure with statistical control for individual and ecologic covariates and residence in the five largest conurbations in California.

\*\*National level study uses metropolitan area of residence with the average of all PM<sub>2.5</sub> monitors within the metropolitan area as the exposure estimate; source for the National estimate for all-cause and IHD from Krewski et al. 2009 [3] Table 9; CVD estimate produced for this report for comparison with the California using the same model and sample as in the Krewski report (i.e., two level random effects, with no spatial autocorrelation – referred to as MSA and DIFF in Table 9). Note numbers slightly differ from the Krewski report due to rounding.

Models for both risk estimates control for individual risk factors (e.g., smoking), contextual risk factors (e.g., unemployment in area of residence) and are stratified by age, race and sex. Results for the California cohort are also additionally adjusted for place of residence in five major urban conurbations. Follow up period for both studies was from 1982-2000.

2. All-cause mortality is significantly associated with PM<sub>2.5</sub> exposure, but the results are sensitive to statistical model specification and to the exposure model used to generate the estimates. When we applied control for residence in the largest urban conurbations, and

**Summary Table.** Epidemiologic cohort studies of PM<sub>2.5</sub> and total mortality in California, 2000-2016  
Relative risk of death from all causes (RR and 95% CI) associated with increase of 10 µg/m<sup>3</sup> in PM<sub>2.5</sub>  
<http://scientificintegrityinstitute.org/NoPMDeaths112215.pdf>

Krewski 2000 & 2010	CA CPS II Cohort	N=40,408	RR = 0.872 (0.805-0.944)	1982-1989
(N=[18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM <sub>2.5</sub> ; 44 covariates)				
McDonnell 2000	CA AHSMOG Cohort	N~3,800	RR ~ 1.00 (0.95 – 1.05)	1977-1992
(N~[1,347 M + 2,422 F]; SC&SD&SF AB; M RR=1.09(0.98-1.21) & F RR~0.98(0.92-1.03))				
Jerrett 2005	CPS II Cohort in LA Basin	N=22,905	RR = 1.11 (0.99 - 1.25)	1982-2000
(N=22,905 M & F; 267 zip code areas; 1999-2000 PM <sub>2.5</sub> ; 44 cov + max confounders)				
Enstrom 2005	CA CPS I Cohort	N=35,783	RR = 1.039 (1.010-1.069)	1973-1982
(N=[15,573 M + 20,210 F]; 11 counties; 1979-1983 PM <sub>2.5</sub> )				
Enstrom 2006	CA CPS I Cohort	N=35,783	RR = 1.061 (1.017-1.106)	1973-1982
(11 counties; 1979-1983 & 1999-2001 PM <sub>2.5</sub> )				
Zeger 2008	MCAPS Cohort “West”	N=3,100,000	RR = 0.989 (0.970-1.008)	2000-2005
(N=[1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA (CA=73%); 2000-2005 PM <sub>2.5</sub> )				
Jerrett 2010	CA CPS II Cohort	N=77,767	RR ~ 0.994 (0.965-1.025)	1982-2000
(N=[34,367 M + 43,400 F]; 54 counties; 2000 PM <sub>2.5</sub> ; KRG ZIP; 20 ind cov+7 eco var; Slide 12)				
Krewski 2010 (2009)	CA CPS II Cohort			
(4 MSAs; 1979-1983 PM <sub>2.5</sub> ; 44 cov)		N=40,408	RR = 0.960 (0.920-1.002)	1982-2000
(7 MSAs; 1999-2000 PM <sub>2.5</sub> ; 44 cov)		N=50,930	RR = 0.968 (0.916-1.022)	1982-2000
Jerrett 2011	CA CPS II Cohort	N=73,609	RR = 0.994 (0.965-1.024)	1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM <sub>2.5</sub> ; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)				
Jerrett 2011	CA CPS II Cohort	N=73,609	RR = 1.002 (0.992-1.012)	1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM <sub>2.5</sub> ; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)				
Lipsett 2011	CA Teachers Cohort	N=73,489	RR = 1.01 (0.95 – 1.09)	2000-2005
(N=[73,489 F]; 2000-2005 PM <sub>2.5</sub> )				
Ostro 2011	CA Teachers Cohort	N=43,220	RR = 1.06 (0.96 – 1.16)	2002-2007
(N=[43,220 F]; 2002-2007 PM <sub>2.5</sub> )				
Jerrett 2013	CA CPS II Cohort	N=73,711	RR = 1.060 (1.003–1.120)	1982-2000
(N=[~32,550 M + ~41,161 F]; 54 counties; 2000 PM <sub>2.5</sub> ; LUR Conurb Model; 42 ind cov+7 eco var+5 metro; Table 6)				
Jerrett 2013	CA CPS II Cohort	N=73,711	RR = 1.028 (0.957-1.104)	1982-2000
(same parameters and model as above, except including co-pollutants NO <sub>2</sub> and Ozone; Table 5)				
Ostro 2015	CA Teachers Cohort	N=101,884	RR = 1.01 (0.98 -1.05)	2001-2007
(N=[101,881 F]; 2002-2007 PM <sub>2.5</sub> ) (all natural causes of death)				
Thurston 2016	CA NIH-AARP Cohort	N=160,209	RR = 1.02 (0.99 -1.04)	2000-2009
(N=[~95,965 M + ~64,245 F]; full baseline model: PM <sub>2.5</sub> by zip code; Table 3) (all natural causes of death)				
Enstrom 2016 unpub	CA NIH-AARP Cohort	N=160,368	RR = 1.001 (0.949-1.055)	2000-2009
(N=[~96,059 M + ~64,309 F]; full baseline model: 2000 PM <sub>2.5</sub> by county)				



## References for Appendix Table 2

- Enstrom JE (2005). Fine particulate air pollution and total mortality among elderly Californians, 1973-2002. *Inhal Toxicol* 2005;17:803-816 ([http://www.arb.ca.gov/planning/gmerp/dec1plan/gmerp\\_comments/enstrom.pdf](http://www.arb.ca.gov/planning/gmerp/dec1plan/gmerp_comments/enstrom.pdf)) and (<http://www.scientificintegrityinstitute.org/IT121505.pdf>)
- Enstrom JE (2006). Response to “A Critique of 'Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973-2002’ by Bert Brunekreef, PhD, and Gerard Hoek, PhD’, *Inhal Toxicol* 2006;18:509-514 (<http://www.scientificintegrityinstitute.org/IT060106.pdf>) and (<http://www.scientificintegrityinstitute.org/ITBH060106.pdf>)
- Enstrom JE (2012). Particulate Matter is Not Killing Californians. Proceedings of the American Statistical Association Joint Statistical Meeting, Section on Risk Analysis, San Diego, CA, pages 2324-2336, 2012. (<http://www.scientificintegrityinstitute.org/ASAS092812.pdf>)
- Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein N, Calle EE, Thun MJ (2005). Spatial Analysis of Air Pollution and Mortality in Los Angeles. *Epidemiology* 2005;16:727–736 (<http://www.scientificintegrityinstitute.org/Jerrett110105.pdf>)
- Jerrett M (2010). February 26, 2010 CARB Symposium Presentation by Principal Investigator, Michael Jerrett, UC Berkeley/CARB Proposal No. 2624-254 "Spatiotemporal Analysis of Air Pollution and Mortality in California Based on the American Cancer Society Cohort" (<http://www.scientificintegrityinstitute.org/CARBJerrett022610.pdf>)
- Jerrett M (2011). October 28, 2011 Revised Final Report for Contract No. 06-332 to CARB Research Screening Committee, Principal Investigator Michael Jerrett, “Spatiotemporal Analysis of Air Pollution and Mortality in California Based on the American Cancer Society Cohort” Co-Investigators: Burnett RT, Pope CA III, Krewski D, Thurston G, Christakos G, Hughes E, Ross Z, Shi Y, Thun M (<http://www.arb.ca.gov/research/rsc/10-28-11/item1dfr06-332.pdf>) and (<http://www.scientificintegrityinstitute.org/Jerrett012510.pdf>) and (<http://www.scientificintegrityinstitute.org/JerrettCriticism102811.pdf>)
- 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 Sep 1;188(5):593-9. doi: 10.1164/rccm.201303-0609OC. PMID: 23805824
- Krewski D (2000). "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: HEI Special Report. July 2000" (<http://pubs.healtheffects.org/view.php?id=6>). Figure 5 and Figure 21 of Part II: Sensitivity Analyses (<http://pubs.healtheffects.org/getfile.php?u=275>) and (<http://www.scientificintegrityinstitute.org/HEIFigure5093010.pdf>)
- Krewski D (2009). Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA III, Thurston G, Calle EE, Thun MJ. [Extended Analysis of the American Cancer Society Study of Particulate Air Pollution and Mortality](#). HEI Research Report 140. May 2009 (<http://pubs.healtheffects.org/view.php?id=315>)

Krewski D (2010). August 31, 2010 letter from Krewski to Health Effects Institute and CARB with California-specific PM2.5 mortality results from Table 33 in Krewski 2009 ([http://www.arb.ca.gov/research/health/pm-mort/HEI\\_Correspondence.pdf](http://www.arb.ca.gov/research/health/pm-mort/HEI_Correspondence.pdf))

Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L (2011). 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 (<http://ajrccm.atsjournals.org/content/184/7/828.full.pdf>)

McDonnell WF; Nishino-Ishikawa N; Petersen FF; Chen LH; Abbey DE (2000). Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. *J Expo Anal Environ Epidemiol* 2000;10:427-436 (<http://www.scientificintegrityinstitute.org/JEAEE090100.pdf>)

Ostro B, Lipsett M, Reynolds P, Goldberg D, Hertz A, Garcia C, Henderson KD, Bernstein L (2010). Long-Term Exposure to Constituents of Fine Particulate Air Pollution and Mortality: Results from the California Teachers Study. *Environ Health Perspect* 2010;118:363-369 with June 2011 Erratum (<http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.0901181>)

Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, Kleeman MJ (2015). Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort. *Environ Health Perspect* 2015;123:549–556 (<http://ehp.niehs.nih.gov/1408565/>) or (<http://dx.doi.org/10.1289/ehp.1408565>)

Pope CA III, Dockery DW. (2006). Health Effects of Fine Particulate Air Pollution: Lines that Connect. *JAWMA, Critical Review*. 56(6):709-742 (<http://www.scientificintegrityinstitute.org/PopeDockery2006.pdf>) and (<http://www.scientificintegrityinstitute.org/PopePPT2006.pdf>)

Thurston GD, Ahn J, Cromar KR, Shao Y, Reynolds HR, Jerrett M, Lim CC, Shanley R, Park Y, Hayes RB (2016). Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort. *Environ Health Perspect* 2016;124:484-490 (<http://ehp.niehs.nih.gov/1509676/>)

U.S. EPA (2012). Regulatory Impact Analysis related to the Proposed Revisions to the National Ambient Air Quality Standards for Particulate Matter EPA-452/R-12-003 ([http://www.epa.gov/ttn/ecas/regdata/RIAs/PMRIACombinedFile\\_Bookmarked.pdf](http://www.epa.gov/ttn/ecas/regdata/RIAs/PMRIACombinedFile_Bookmarked.pdf))

Zeger SL, Dominici F, McDermott A, Samet JM (2008). Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005). *Environ Health Perspect* 2008;116:1614-1619 (<http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.11449>)