Regulatory Toxicology and Pharmacology 88 (2017) 173–184

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Air quality and acute deaths in California, 2000–2012

S. Stanley Young [a, *], Richard L. Smith [b], Keneth K. Lopiano [c]

[a] CGStat, 3401 Caldwell Drive, Raleigh, NC 27607, United States
[b] University of North Carolina, Department of Statistics and Operations Research, University of North Carolina, Chapel Hill, NC 27599-3260, United States
[c] Consultant, Winterville, NC 28590, United States

ARTICLE INFO

Article history:
Received 14 January 2016
Received in revised form
22 May 2017
Accepted 6 June 2017
Available online 13 June 2017

Keywords:
Air quality
Air pollution
$PM_{2.5}$
Ozone
Acute deaths
Time series regression
Mortality

ABSTRACT

Many studies have shown an association between air quality and acute deaths, and such associations are widely interpreted as causal. Several factors call causation and even association into question, for example multiple testing and multiple modeling, publication bias and confirmation bias. Many published studies are difficult or impossible to reproduce because of lack of access to confidential data sources. Here we make publically available a dataset containing daily air quality levels, $PM_{2.5}$ and ozone, daily temperature levels, minimum and maximum and daily maximum relative humidity levels for the eight most populous California air basins, thirteen years, >2M deaths, over 37,000 exposure days. The data are analyzed using standard time series analysis, and a sensitivity analysis is computed varying model parameters, locations and years. Our analysis finds little evidence for association between air quality and acute deaths. These results are consistent with those for the widely cited NMMAPS dataset when the latter are restricted to California. The daily death variability was mostly explained by time of year or weather variables; Neither $PM_{2.5}$ nor ozone added appreciably to the prediction of daily deaths. These results call into question the widespread belief that association between air quality and acute deaths is causal/near-universal.

1. Introduction

The purposes of this paper are threefold: First, we describe a data set that we make publically available that is useful for time-series analyses for air quality and acute deaths for California. Second, we provide a primary and sensitivity analyses of the data set. Third, we discuss the implications of our analysis results. We note that we are looking for association and that association, if it is present, does not prove causation.

Our first objective for the present study is to assemble a new, large dataset available for analysis by other researchers. We obtained daily counts of deaths, air quality levels for ozone and $PM_{2.5}$, daily minimum and maximum temperature and daily maximum relative humidity, in the eight most populous air basins in California for the years 2000–2012. A map showing the air basins is given in Fig. 1. We give the yearly PM2.5 and ozone levels for each air basin in Table 1. We obtained over two million electronic death certificates. We linked daily air quality data, ozone and $PM_{2.5}$. The US Clean Air Act has sections requiring the regulation of "criteria Pollutants." Recent regulatory attention, e.g. Clean Power Plan, is focused on PM2.5 and ozone and those air quality constituents are the focus of this paper. Air quality has improved dramatically over the last 40 years (Schwartz and Hayward (2007)), so release of an up to date data set is timely and important. We note that with the release of our data set, in particular the daily mortality, other constituents can be linked and analyzed. We examined over 37 thousand exposure days. The data are described in more detail in Section 2.

It is important to get air quality/health effects data sets public as data used in most environmental epidemiology papers is not available. Many scientific bodies, Board on Life Sciences (2003), Royal Society (2012), Office of Science and Technology Policy (2013), support open access to data used in scientific papers. In practice, there can be many obstacles both administrative and political. Cecil and Griffin (1985) note that "As an abstract principle, the sharing of research data is a noble goal and meets with little opposition. However, when data sharing is attempted in a particular circumstance, the conflicting interests of the parties can thwart the exchange." Our experience has been that it is difficult to get public access to air quality/health effect data sets. Cecil and Griffin

* Corresponding author.
E-mail addresses: genetree@bellsouth.net (S.S. Young), rls@email.unc.edu (R.L. Smith), klopiano@gmail.com (K.K. Lopiano).

http://dx.doi.org/10.1016/j.yrtph.2017.06.003
0273-2300/

Fig. 1. Map of California air basins (Source: Webpage of the California Air Resources Board).

Table 1
Yearly PM2.5 and ozone levels for each air basin.

PM2.5	mountain-counties	sacramento-valley	salton-sea	san-diego	san-francisco	san-joaquin	south-central	south-coast
2000	10.89	15.21	17.45	19.98	17.76	26.93	16.88	31.48
2001	14.05	21.06	16.27	19.99	15.57	26.63	17.56	36.73
2002	14.60	22.61	25.86	18.05	17.81	36.12	13.95	33.04
2003	18.00	19.40	32.64	17.67	15.65	28.83	14.31	28.76
2004	19.48	20.37	20.42	15.93	16.84	26.34	17.19	27.36
2005	18.18	21.68	18.80	14.13	15.77	25.65	15.69	24.64
2006	18.20	22.49	20.78	14.50	16.14	25.72	15.50	24.00
2007	20.64	19.97	25.53	19.37	17.22	31.32	17.60	23.19
2008	22.66	25.80	20.47	18.70	19.47	29.46	17.03	25.23
2009	19.19	18.42	20.24	17.56	15.07	26.73	14.41	24.93
2010	15.02	15.87	15.97	16.45	13.48	23.70	14.00	23.74
2011	21.46	20.15	17.58	17.94	15.07	25.42	16.70	26.22
2012	26.69	19.81	22.36	16.58	12.54	21.99	14.89	24.27
Ozone								
2000	62.1	57.8	57.2	56.3	40.6	67.4	58.0	65.5
2001	63.1	57.4	60.8	56.1	42.7	71.4	59.0	68.2
2002	65.2	59.5	62.6	55.5	43.6	71.2	58.7	68.9
2003	64.3	57.8	59.8	54.7	43.4	70.2	59.9	70.1
2004	61.3	56.1	59.8	54.2	41.1	67.1	58.6	68.1
2005	58.2	54.9	59.6	55.2	41.1	61.8	57.4	65.7
2006	61.0	57.9	60.3	57.1	43.7	64.2	58.2	65.2
2007	58.3	55.4	58.8	56.1	41.4	62.3	58.1	64.5
2008	59.5	58.1	57.8	57.5	44.7	65.0	59.4	66.1
2009	56.0	55.1	58.7	55.2	42.0	60.6	55.5	64.3
2010	55.4	53.2	58.4	53.3	41.3	59.4	54.8	62.1
2011	55.4	54.7	56.6	52.5	41.3	61.4	55.1	63.2
2012	56.8	55.1	57.9	52.5	43.1	61.9	55.6	63.2

go on to say, “This case suggests that an agency can insulate its actions from public scrutiny by funding a grant for controversial research and then basing its action on those findings. As long as the agency does not take possession or control of the records, the FOIA will not assist those who wish to challenge the findings that underlie the agency action.” Researchers in environmental

epidemiology are making major public health claims, yet very few of the key data sets are available.

Our primary analysis method uses time series regression analysis (Bell et al. (2004), Bhaskaran et al. (2013), Clyde (2000), Dominici et al. (2003), Samet et al. (2000a, 2000b), Smith et al. (2009)). Time series regression analysis is a standard method of analysis for air quality/health effects time series. The basic idea if a time series regression analysis is to predict the mortality on any given day using a variety of covariates, including meteorology, seasonal and long-term trends, and the air pollution variable of interest (in this analysis, either ozone or PM2.5). Typically, lagged values of the meteorological and air pollution variables are included, to take account of effect that may persist over several days. Some analyses use other pollution variables as co-pollutants, to take account of possible interactions among the health effects of different pollutants. The analyses are conducted on more than 4700 days for each air basin for both ozone and $PM_{2.5}$. Initially we treat each air basin separately as we want to be able to judge how any observed effect replicates. Then, results from the individual air basins are combined to obtain an overall estimate of the coefficient between mortality and the air pollutant of interest. The methods are sketched in Section 2 and the results are given in Section 3. More details are provided in the Supplemental Material.

To examine our primary analysis, we conduct an extensive sensitivity analysis. We build models of varying complexity. We hold out data and predict the held out data. In total we compute 78,624 models to examine the reliability of our modeling. We find that adding ozone or PM2.5 to models does not improve our estimate of acute mortality. The air quality variables are essentially without predictive power.

Causal inference methods are being increasingly applied in the analysis of air pollution data (Zigler et al. (2016); Gilliland et al. (2017). However, it is difficult if not impossible to infer a causal relationship in cases when there is not even evidence of association. Our paper presents data and analysis saying there is no association of acute mortality with ozone or $PM_{2.5}$ in California and that calls into question that ozone or $PM_{2.5}$ CAUSE acute mortality.

The results of this research are present in two parallel presentations. In this paper we present our work in a largely non-technical manner. The analysis of large observational data sets in necessarily complex so we provide that technical detail in our Supplemental Material. The rest of the non-technical paper is organized as follows. Analysis of large, complex observational time series data sets requires many analysis choices. Methods are described in Section 3 including Time Series Regression and an extensive sensitivity analysis. Results are given in Section 4. In Section 5 we discuss literature and our interpretation of our results.

2. Data

2.1. Mortality

The state of California provides access to the death public use files for the purpose of research. The cause of death is indicated by an ICD 10 code and provided by the Department of Health Services Center for Health Statistics. The mortality data we used can be obtained from the California Department of Public Health, www.cdph.ca.gov. The total number of deaths of individuals over 65–74 and 75 + years of age with group cause of death categorized as AllCauses or HeartLung where HeartLung deaths were attributed to “Diseases of the Circulatory System” or “Diseases of the Respiratory System”. We created four outcome death categories: 65–74 AllCause, 65–74 HeartLung, 75 + AllCause, 75 + HeartLung. *Accidental deaths were excluded.* All deaths were aggregated to a day, year and air basin.

2.2. Air quality

The California Environmental Protection Agency's Air Resources Board provides an Air Quality Data (PST) Query tool at the following website http://www.arb.ca.gov/aqmis2/aqdselect.php. Daily data can be retrieved for each combination of basin, day, and year. The following statistics were retrieved on July 19, 2014:

1. Daily Average $PM_{2.5}$ in $\mu g\ m^{-3}$
2. Daily Average Ozone in parts per billion (ppb)
3. Daily Max 8 Hour Overlapping Average Ozone - State Data in ppb
4. Daily Max 8 Hour Overlapping Average Ozone - National Data in ppb

2.3. Temperature

The Carbon Dioxide Information Analysis Center (CDIAC) maintains data from the United States Historical Climatology Network. Daily temperature data was retrieved from the following website http://cdiac.ornl.gov/ftp/ushcn_daily/ for each combination of basin, day, and year the minimum and maximum temperature was obtained.

2.4. Humidity

The US Environmental Protection Agency maintains daily humidity data. Daily humidity data was downloaded from http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm for each combination of basin, day, and year.

2.5. Data displays

Fig. 2 shows that mortality and ozone levels are out of phase. As ozone goes up, mortality goes down. We follow the usual convention and look at deviations from the time trends. Fig. 3a shows daily mortality data for South Air basin and Fig. 3b shows the daily mortality after the seasonal trend is removed.

3. Statistical methods

3.1. Introduction to time series regression strategy

Time series regression is a highly develop area of statistical regression analysis for examination of a possible linear relationship between a health effect and an air quality variable where data is available at time points, most often daily. It is useful to review multiple linear regression in general and then how it is applied to time series analysis. First consider some necessary notation:

$$f(E(Y_t)) = \beta_0 + \beta_1 X_{1t} + \beta_2 X_{2t} + \beta_3 X_{3t} + \beta_4 X_{4t} + \ldots + \beta_p X_{pt} + \beta_u X_{ut} \quad (1)$$

In words, some function of expected mortality, Y at time t, can be approximated as a linear sum of an intercept, β_0, and p observed quantities. X_u represents one or more unmeasured items, discussed shortly. The β's are theoretical and are estimated from data. The estimated quantities are called regression coefficients, the β's. The linear relationship is not exact so an error term is added to make the relationship an equation. Let X_{1t} be an air quality variable, e.g. ozone or $PM_{2.5}$. The remaining variables are things that might affect mortality; they are called covariates. The interest is in the magnitude and sign of b_1, the estimate of β_1. We can rewrite 3.1 as follows:

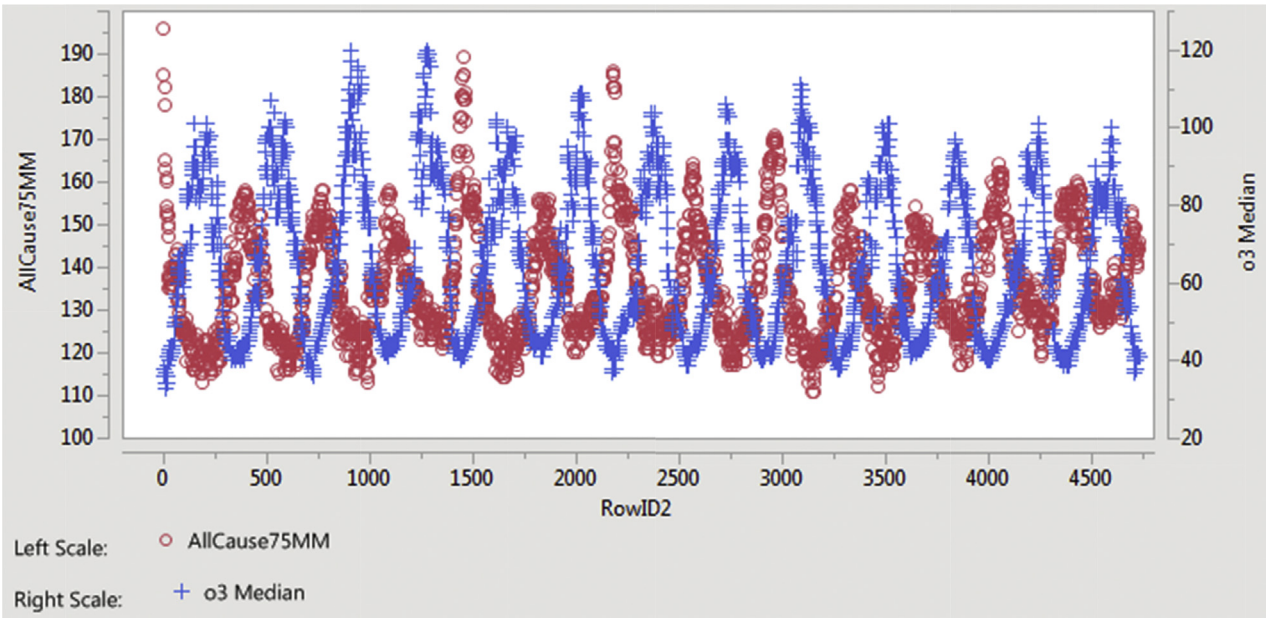

Fig. 2. Plot of the moving medians for All Cause deaths and ozone, o3, versus time in days.

$$Y_t \sim g\Big(.;\ \beta_0 + \beta_1 X_{1t} + \beta_2 X_{2t} + \beta_3 X_{3t} + \beta_4 X_{4t} + \ldots + \beta_p X_{pt} + \beta_u X_{ut},\ \theta\Big) \tag{2}$$

where g is a probability density function and θ is a possible additional parameter representing the scale or shape of the distribution. The basic idea is that some function of mortality, linearly corrected for known confounders, is equal to an air quality effect plus any effect of one or more unknown confounders. We depend that the relationship is linear. We also depend that there are no unmeasured confounders, or that their effect is much smaller than and any air quality effect.

The interpretation of the model is that if one of the variables, say X_{1t}, is the air pollution variable of interest, then the corresponding parameter, β_1, is the coefficient of mortality based on that air pollution variable.

The sophistication comes into the analysis by the selection of the covariates and the care to not have important covariates/confounders left out of the model. It is well-known that mortality varies with the season, higher in winter and lower in summer, so that today's mortality has to be corrected for this seasonal effect. It is thought that air quality today might exert its effect on mortality some days later so that potential lag effects need to be considered. It is thought that the day of the week might have an effect on mortality. It is generally agreed that if there is an effect of air quality on mortality, the effect is stronger on older individuals.

The model is usually assumed to be log-linear; we take the log of expected mortality. The analysis decisions include: What time series smoother is chosen? Do we summarize the time variable to day, week, etc? Which outcome variables are used? Which air quality variables are used as predictors? Weather variables are typical covariates, e.g. min Temp, max Temp, maximum daily relative humidity, and wind speed. Any of the predictor or covariates might be lagged one or more days. Table 2 gives some of the modeling choices. There are many thousands of possible models. Nevertheless, certain choices have become standard in the literature on time series modeling of air quality and daily mortality data. The next section shows how some of these standard choices may be applied to the present datasets.

3.2. Specific time series regression model

The time series model is adapted from models previously used for the National Morbidity, Mortality and Air Pollution Study (NMMAPS) data series; see in particular Dominici et al. (2003), Bell et al. (2004), and Smith et al. (2009). These methods are reviewed in Bhaskaran et al. (2013). The code used for the results in the present paper is at www.unc.edu/~rls/EpiTimeSeriesCodeRLS.txt, S02 Supplement Code for Time Series. A data dictionary is given in S03a. The data used in this analysis is given in S03b. The specific models use for time series regression and the sensitivity analysis are given in our arXiv technical report, arXiv.org > stat > arXiv:1502.03062. Smith (2015) give R code for time series regression modeling.

3.3. Sensitivity analysis

The purpose of this analysis is to understand the sensitivity of the models to different modeling selections. The two goals of the sensitivity analysis were to determine if is there a consistent model that best predicts mortality across years and air basins and the sensitivity of the predictions to the modeling assumptions. We assessed sensitivity using a leave-one-year-out, cross-validation strategy where, for each model, each year (2001–2012) was left out, the remaining 11 years was used to fit the model, and predictions were obtained for each day in the year omitted from the model fitting. Year 2000 was omitted from the sensitivity analysis due to the complications of missing data. This sensitivity analysis was accomplished by designing a factorial experiment to define the model specifications. We consider the following variables with the corresponding number of levels: air basins (8); health endpoints (4); air quality (7); maximum relative humidity (3); maximum temperature (3); minimum temperature (3); and time (1). An additional 13-level factor was considered by holding out each year from the model fitting process. Crossing the levels and omitting duplicate situations yielded 78,624 models that were considered. Predictions from the corresponding hold out years of each model

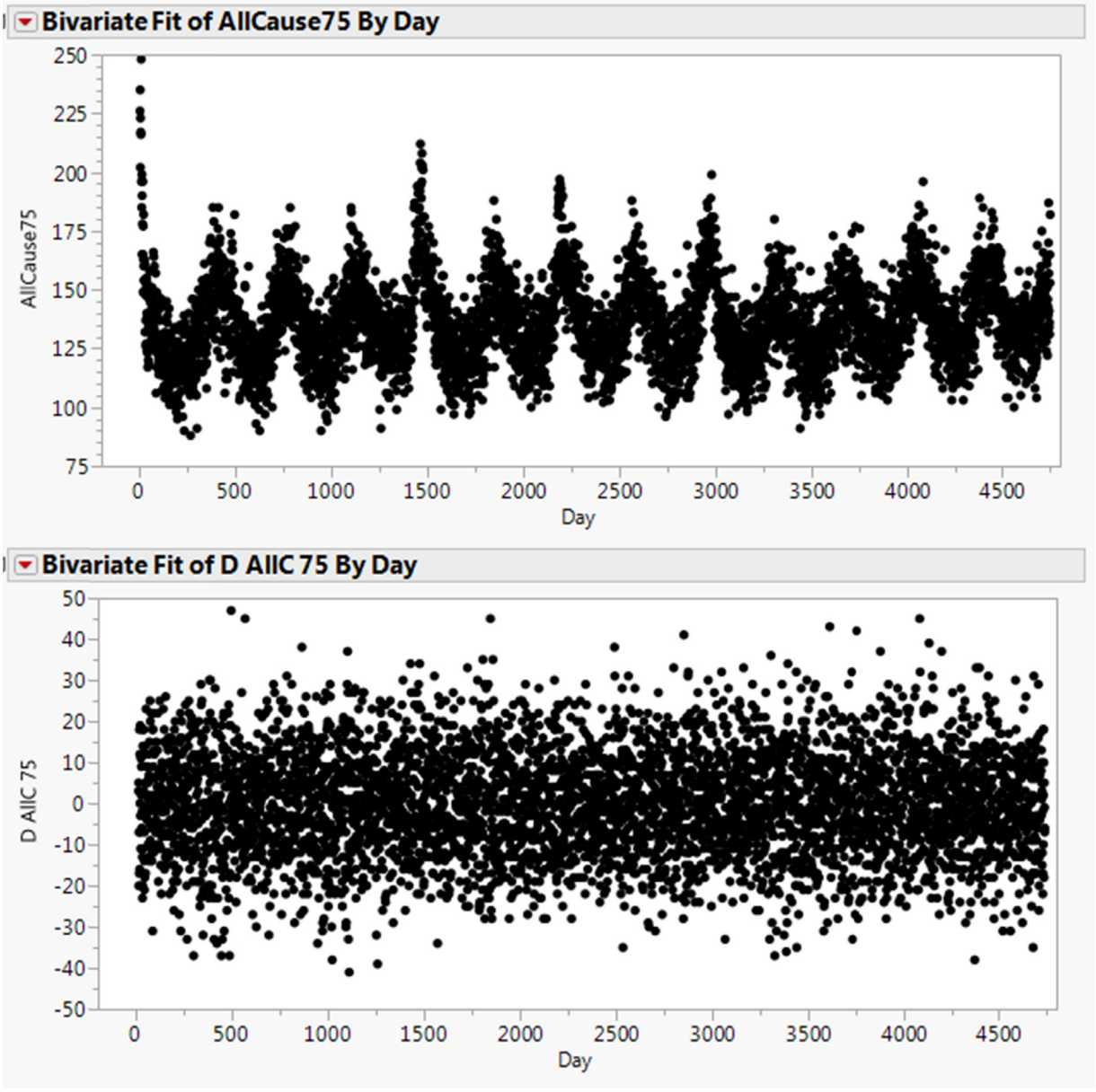

Fig. 3. a. Daily All Cause deaths versus day and b. daily AllCause deaths versus day after removing time trend.

Table 2
Analysis decisions for Time Series Regression.

RowID	Model Item	Values
1	Time Series Smoother	Spline, moving average, …
2	Unit of Time	Day, week, month, etc.
3	Predictor	PM2.5, ozone, NO2, SO2, CO, …
4	Lag	No lag, lags of 1 day, etc. Sums of lags of two or more days, …
5	Weather Covariates	MinTemp, maxTemp, avTemp, RH, wind speed, …
6	Events	Forest fires, windblown air pollution, changed regulations, …

were calculated.

In summary, for each of $13 \times 8 \times 4 = 416$ unique combinations of "hold out year", basin and health endpoint, 7x3x3x3x1 = 189 models are fit using the remaining 12 years of data. Predictions for "hold out year" are obtained for each of the 189 models and the predictive capabilities are compared.

4. Results

4.1. Selected results for time series regression

4.1.1. South Coast air basin

The approach outlined in Section 3.2 is applied to data from each of eight California air basins, Fig. 1. We concentrate initially on the two most populated air basins, South Coast and San Francisco Bay. The response variable is total non-accidental mortality among people aged 65 and over. For South Coast, running the analysis initially without air quality variables, Table S1 in S04 shows that five of the six meteorological variables (the exception is current-day maximum relative humidity) are very highly significant; since there is no obvious advantage to dropping the one non-

significant variable, we retain all six for subsequent analysis.

Table 3 shows the estimates, standard errors (SE), t-values and p-values of percent rise in mortality per 10 ppb rise in ozone, at various combinations of lags. The strongest positive estimate is based on lags 0, 1, 2 and 3, for which the model predicts a 0.1% rise in mortality per 10 ppb rise in ozone, but neither this nor any of the other values in the table is statistically significant; we detect no increase in mortality as ozone increases.

Corresponding results using $PM_{2.5}$ are shown in Table 4. Several estimates appear statistically significant at $p < 0.05$ (smallest $p = 0.017$), but all slopes are negative, which is not biologically plausible as it indicates a decrease in mortality. We conclude that either the small p-values are an artifact of chance, selection bias, or there is some other biological mechanism leading to a confounded result.

In these analyses, the over-dispersion parameter was of the order of 1.07 – in other words, the variance of the mortality variables is inflated by a factor of 1.07 compared with the Poisson distribution. This is typical for this kind of analysis and does not indicate a problem. A much larger over-dispersion parameter could indicate some important missing covariates.

4.1.2. San Francisco Bay air basin

The meteorological analysis shows that daily maximum and daily minimum temperature are significant, but neither current-day nor lagged maximum relative humidity. See Table 5. The ozone models show a statistically significant result for lag 0 or distributed lags 0 and 1 *only* when maximum relative humidity is omitted from the model; for example, the distributed lags (0,1) coefficient is 0.59 with a standard error of 0.26 and p-value 0.02. Results for $PM_{2.5}$ are similar: mildly significant results ($p = 0.02$ or 0.04) are obtained in distributed lag models without maximum relative humidity and including multiple lags (0 through 5 or 6); other models do not yield a statistically significant results. Given the large number of models tried and the relatively moderate p-values, we doubt that these results are evidence of a causal effect. More details are given in the **S04**.

4.1.3. Combining results across air basins

In the NMMAPS papers on ozone, Smith et al. (2009) and Bell et al. (2004), single-city analyses were repeated for up to 98 US cities and then combined using a hierarchical model, based on an algorithm originally due to Everson and Morris (2000) and coded by Roger Peng into the R function "tlnise" (R Core Team, 2015). The same method is used to produce estimates that are combined across all eight air basins in our study.

The results of this analysis are shown in Table 6. None of the analyses shows a statistically significant effect when combined across all eight air basins.

In S04, we report sensitivity analyses associated with different choices of response variable or degrees of freedom for the nonlinear spline components, and also, comparisons with results for the NMMAPS dataset.

4.1.4. Nonlinear distributed lag models

Additional analyses, S04, replaces the linear exposure-response relations with nonlinear relationships (modeled by splines). Selected model results are shown here in Figs. 4 and 5. These two figures show no effect of ozone or $PM_{2.5}$ on mortality after other covariates are taken into account across the entire range of the air quality variables.

4.2. Sensitivity analysis results

We considered the total deaths in four categories:

1. All cause deaths with accidents removed of individuals age [65,74]
2. All cause deaths with accidents removed for individuals age ≥ 75
3. Death by diseases of the respiratory or circulatory systems for individuals age [65,74]

Table 3
Statistical significance of ozone component with various combinations of lags: based on model (1) $df_0 = 7$, $df_1 = df_2 = 6$. Estimate is percent rise in mortality for 10 ppb rise in ozone. South Coast air basin; response variable is non-accidental mortality aged 65 and over.

Lags Included	Estimate	SE	t-value	p-value
0	0.0869	0.1136	0.76	0.44
1	−0.0540	0.1134	−0.48	0.63
2	0.0443	0.1142	0.39	0.70
0,1	0.0222	0.1315	0.17	0.87
1,2	−0.0062	0.1329	−0.05	0.96
0,1,2	0.0788	0.1508	0.52	0.60
0,1,2,3	0.1143	0.1673	0.68	0.49
0,1,2,3,4	0.0857	0.1803	0.48	0.63
0,1,2,3,4,5	0.0047	0.1906	0.03	0.98
0,1,2,3,4,5,6	−0.0537	0.1993	−0.27	0.79

Table 4
Statistical significance of $PM_{2.5}$ components with various combinations of lags: based on model (1) $df_0 = 7$, $df_1 = df_2 = 6$. Estimate is percent rise in mortality for 10 $\mu g/m^3$ rise in $PM_{2.5}$. South Coast air basin; response variable is non-accidental mortality aged 65 and over.

Lags Included	Estimate	SE	t-value	p-value
0	0.1212	0.0999	1.21	0.220
1	−0.1981	0.0992	−2.00	0.046
2	−0.2131	0.0996	−2.14	0.032
0,1	−0.0469	0.1146	−0.41	0.680
1,2	−0.2744	0.1153	−2.38	0.017
0,1,2	−0.1179	0.1297	−0.91	0.360
0,1,2,3	−0.1657	0.1508	0.52	0.600
0,1,2,3,4	−0.1624	0.1503	−1.08	0.280
0,1,2,3,4,5	−0.2621	0.1586	−1.65	0.098
0,1,2,3,4,5,6	−0.2437	0.1663	−1.46	0.140

Table 5
Statistical significance of meteorological components: based on model (1) without air pollution component and with $df_0 = 7$, $df_1 = df_2 = 6$, fitted to nonaccidental mortality for ages 65 and up, San Francisco Bay air basin.

Variable	Lags	p-value
Daily Max Temperature	Current day 0	6.40E-10
Daily Max Temperature	Mean of 1,2,3	0.0075
Daily Min Temperature	Current day 0	0.001
Daily Min Temperature	Mean of 1,2,3	0.048
Mean Daily Relative Humidity	Current day 0	0.56
Mean Daily Relative Humidity	Mean of 1,2,3	0.34

Table 6
Combined results across all eight air basins.

Variable	Lags	Estimate	SE	t-value	p-value
Ozone	0,1	0.3376	0.2434	1.39	0.17
Ozone	0,1,2	0.3165	0.2466	1.28	0.20
Ozone	0,1,2,3	0.4149	0.3260	1.28	0.20
PM2.5	0,1	0.0126	0.2034	0.06	0.95
PM2.5	0,1,2,3	−0.0006	0.2464	0.00	1.00
PM2.5	0,1,2,3,4,5	0.0689	0.2799	0.25	0.81

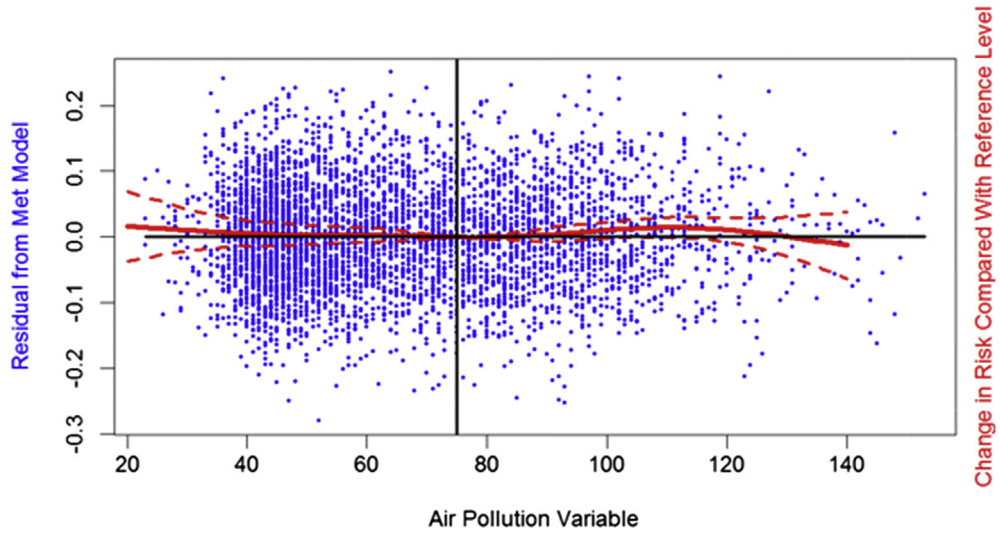

Fig. 4. Nonlinear dependence of mortality on ozone for South Coast air basin. Blue dots: residuals from the model that includes long-term trends, day of week and meteorology, plotted against the air pollution variable (ozone). Red solid and dashed curves: implied change of relative risk with respect to ozone level 0.075 ppm (the current ozone standard), with pointwise 95% confidence bands. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Death by diseases of the respiratory or circulatory for individuals age $\geq$ 75

All methods were carried out for each health endpoint. For the sake of notation, let Y_{ijk} generically indicate the response variable for the corresponding basin, day and year. For the sensitivity analysis only, due to missing data in 2000, results for that year as the hold-out year are omitted due to large numbers of missing predictions. The following levels of covariates were considered in the subsequently defined generalized linear model, GLM.

By partitioning the air quality variable into two groups, Ozone (design levels 1, 2, 3, and 4) and $PM_{2.5}$ (design levels 1, 5, 6, and 7), 108 models were isolated for each combination of air quality group, basin, year, and response. Note 27 models appear in both groups because of the null level (level 1) of the air quality variable. A total of 78,624 models were computed. A data set of modeling results is available, S07.

The observed values for each combination of basin, year, and response were plotted (open circles) and the predictions from the 108 models were added to the same plot (solid red lines). Consider the results for the number of deaths caused by diseases of the respiratory or circulatory systems individuals age greater than or equal to 75 for the South Coast air basin for the Ozone group, Fig. 6.

Despite various forms of the 108 models, variability of the predicted values is relatively small as illustrated by overlapping red lines. Because the predictions are point estimates, prediction

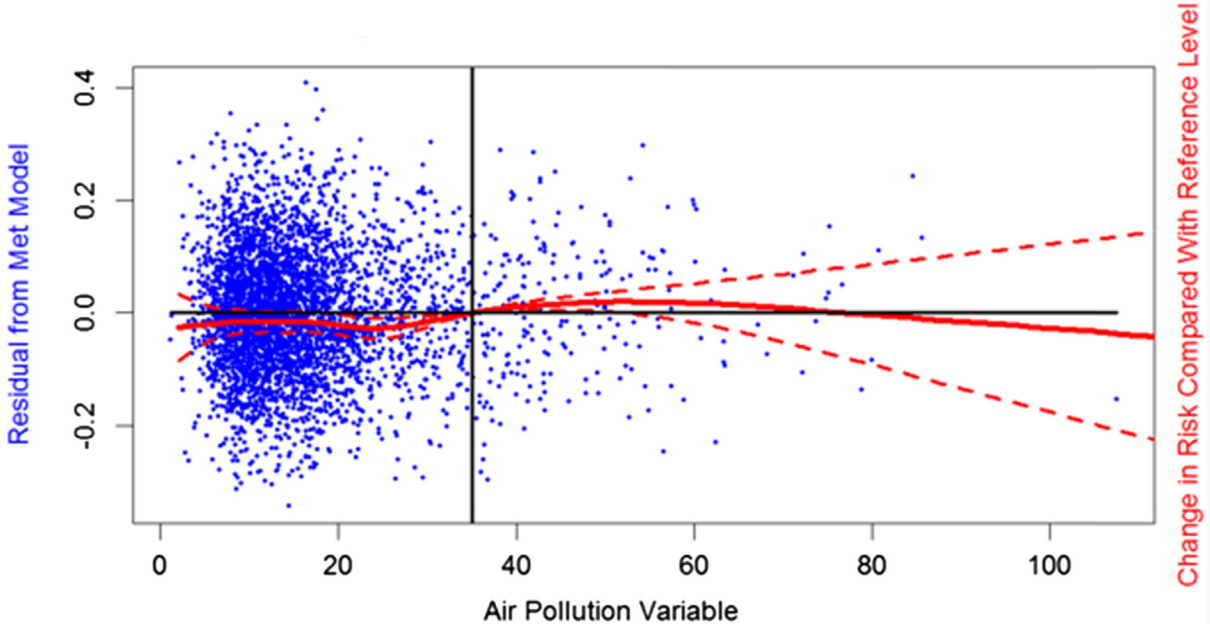

Fig. 5. Nonlinear dependence of mortality on $PM_{2.5}$ for San Francisco Bay air basin. Analogous to Fig. S4, using the full meteorological model (including relative humidity), and a nonlinear model for the relationship between $PM_{2.5}$ and mortality. The relative risk was computed with respect to a reference level of 35 $\mu g/m^3$, the current standard for daily max of $PM_{2.5}$.

intervals accounting for uncertainty overlap and thus make predictions virtually indistinguishable, Gasparrini and Armstrong (2013), Gasparrini, (2011). In terms of predictive performance, the models perform equally well. Note a similar result for the other air basins in both ozone groups and the $PM_{2.5}$ groups regardless of outcome (S05 Figs. A1-A32 and S06 Figs. B1-B32).

Mean squared prediction error (MSPE) was obtained for each model using data from the year that was held out. For each combination of air quality group, basin, year, and response, the MSPE of the *model that only includes time as a covariate*, $MSPE_t$, was used to calculate the ratio

$$R_{m/t} = \frac{MSPE_m}{MSPE_t},$$

for each value $m = 1, \ldots, 108$ indexing the 108 models considered for that combination of air quality group, basin, year and response. For a given model, if the ratio is greater than 1, then the model that only included time had a smaller MSPE and if the ratio is less than 1, then the corresponding model had an MSPE smaller than the model that only included time. A boxplot of the 108 MSPE ratios, $R_{m/t}$, for each combination of air quality group, basin, year, and response are presented in Fig. 7. S08 (ozone) and S09 ($PM_{2.5}$) give Box plots for different combinations of air basin, age class, and year. With few exceptions, the MSPE ratios all overlap 1.00. We interpreted this result that the extra variables did not improve the fit of the model, i.e. the terms were not necessary.

Consider the ratios of the MSPE of each of the 108 models for the same subset of data, number of deaths caused by diseases of the respiratory or circulatory systems individuals age greater than or equal to 75 for the South Coast air basin for Ozone group, Fig. 7. Recall a $R_{m/t}$ value greater than 1 indicates the model had an MSPE larger than the model that include time effects only, and if the value of $R_{m/t}$ is less than 1 then the model had an MSPE smaller than the model that included time only. Note that in general the ratio fell between 0.98 and 1.02. The variability of the ratio changes depending on which year is held out. The form of the model with the best MSPE (i.e. the smallest ratio) was not the consistent across year (S07 Supplementary data file, Prediction analysis results). In summary, the boxplots indicate that the differences in point-estimate predictions for hold-out years are small and there is not a consistent best form of the model. This result is consistent across health endpoint, air quality group, and basin, S08 and S09.

None of the model variables, including ozone or $PM_{2.5}$, consistently improve on the model using just day of year; histograms of the ratios of predictive performance, any model relative to a model with just day of year. Fig. 8, show ratios consistently near one indicating that no model for mortality improves on a model with just day of year as a predictor.

5. Discussion

There is considerable literature in support of the current paradigm that air quality is associated with acute mortality. See, for

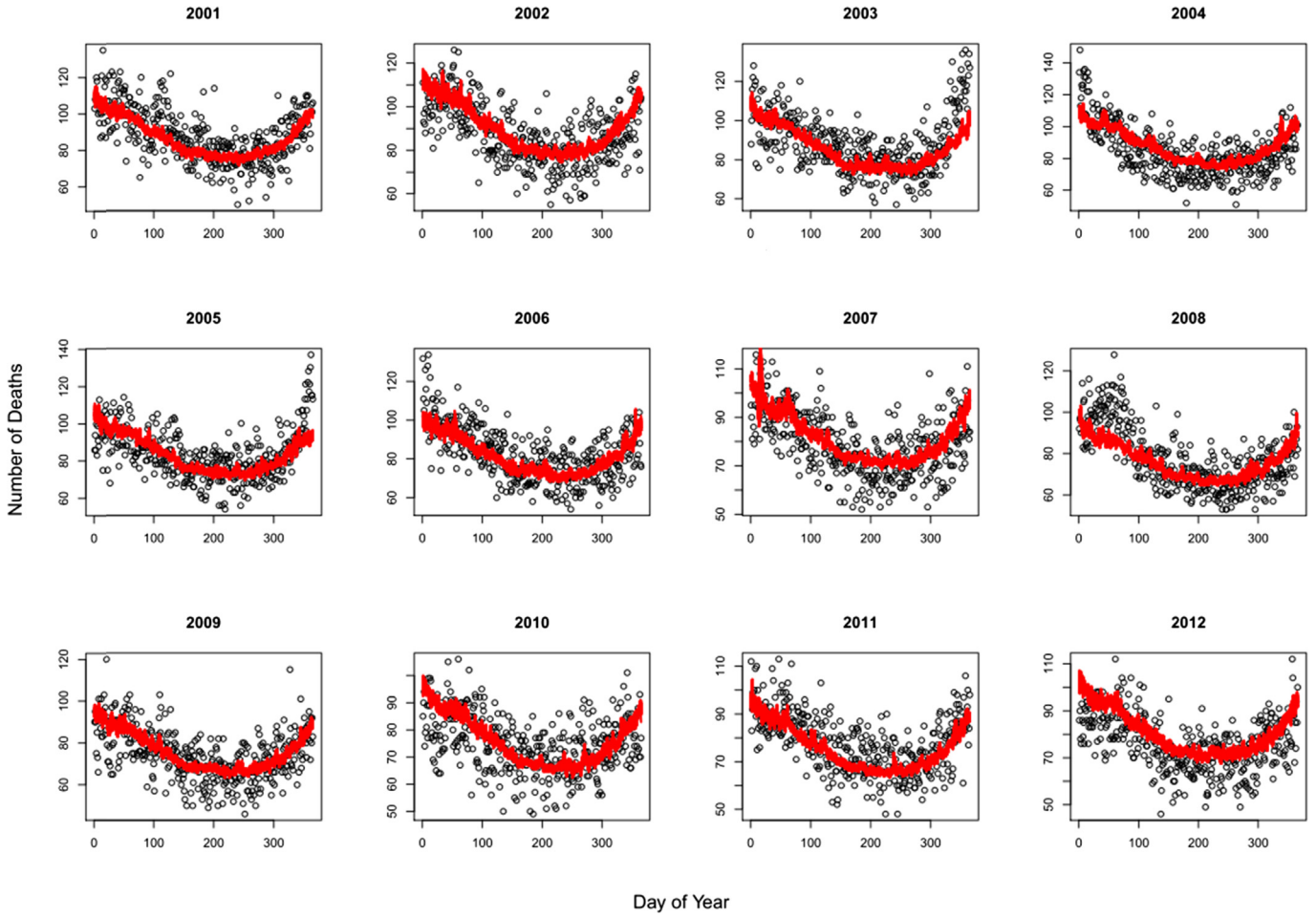

Fig. 6. South Coast (LA). Model hold out predictions for each year except 2000. "o" are observed deaths and the red overlay are model predictions. Note variability in predictions across the models is negligible as illustrated by overlapping red lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

example, the review paper by Atkinson et al. (2014). Here we make the case that there is literature support for our findings of no association, and we offer some explanation for claims made in the current literature.

In this paper we analyze daily death data for the eight most populous air basins in California for associations with air quality. We found no associations using regression-based time series analysis. Extensive sensitivity analyses found air quality variables do not add to the predictive ability of the models examined. Even when the predictive ability is improved, the improvement is negligible relative to a model that only uses time of year. The form of the air quality variable that comes into models is inconsistent across basin/year combinations. In short, we were unable to find a consistent and meaningful relationship between air quality and acute death in any of the eight California air basins considered.

This result appears to contradict results from the well-known NMMAPS study that studied ozone and PM10, and subsequent studies involving PM2.5, e.g. HEI reports, Samet et al. (2000a, 2000b), Health Effects Institute (2003), Bell et al. (2004), Dominici et al. (2007), Zanobetti and Schwartz (2009), Smith et al. (2009). However, all of these were national studies. The present study is restricted to California, because we have been unable so far to compile a full-US dataset for post-2001. The ozone results that we have derived are consistent with those of the NMMAPS dataset when restricted to California, as shown in the S04. Note that in the context of ozone, Bell and Dominici (2008) and Smith et al. (2009) both drew attention to geographical heterogeneity in the pollution-mortality relationship; the present results show that this is an issue in post-2001 data as well. In addition, we find no effect for $PM_{2.5}$ for California.

The question of chronic air quality mortality effects are addressed by Enstrom (2005) who found no chronic effects in California. His summary for all cause deaths for California is given in Table 7. The average risk ratio was 0.9979, with a standard error of 0.0126.

The standard method for showing cause and effect is through an experiment. A factor is changed and the result is examined. If the result changes with a change in the factor, then there is evidence for causality; See the Craig et al. (2012) discussion of natural experiments. Chay et al. (2003) examined a natural experiment: the EPA mandated reductions in air pollution for 270 of 501 counties studied. They found that air pollution levels were reduced, but *there was no reduction in deaths after adjustments for covariates*. Recently, an increase in PM2.5 due to forest fires, a natural experiment, did not lead to an increase in mortality, Zu et al. (2016). Their result that improved air quality did not improve mortality was confirmed in an observational study by Cox et al. (2013).

How can the disparate claims be rectified? Multiple testing, multiple modeling, Clyde (2000), and publication bias might contribute. Covariate adjustments offers an additional explanation. Greven et al. (2011) state in their abstract, " … Results based on the global coefficient indicate a large increase in the national life expectancy for reductions in … the average of $PM_{2.5}$. However, … trends in $PM_{2.5}$ and mortality is likely to be confounded by other variables trending on the national level …. *Based on the local coefficient alone, we are not able to demonstrate any change in life expectancy for a reduction in* $PM_{2.5}$." (Italics added.) In short, the claims made depend on how well covariates are taken into account. When they are taken into account, Styer et al. (1995), Chay et al. (2003), Janes et al. (2007), Greven et al. (2011), Cox et al. (2013), and Young and Fogel (2014) and the analysis provided here, there is no association of air quality with deaths.

Many authors have noted "geographic heterogeneity", the measured effect of air quality is not the same in different locations, Smith et al. (2009), Young and Xia (2013), Greven et al. (2011), Young and Fogel (2014). Multiple authors, Smith et al. (2009),

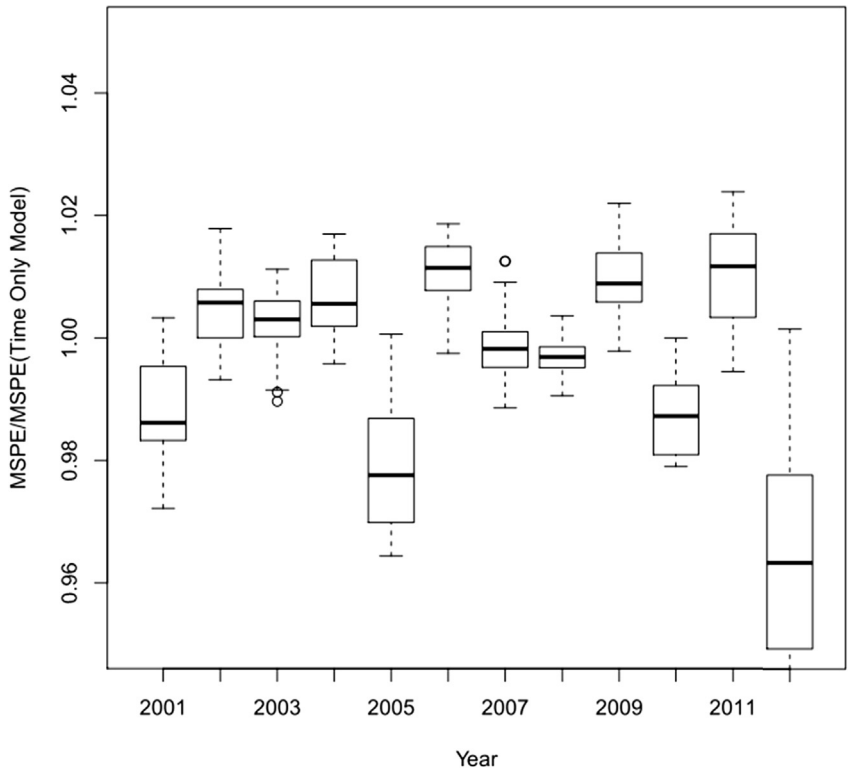

Fig. 7. South Coast, ozone, respiratory or circulatory systems deaths, 75 and older. Box plots of hold one year out of mean square prediction errors, MSPE. The predictions are made by varying the modeling variables.

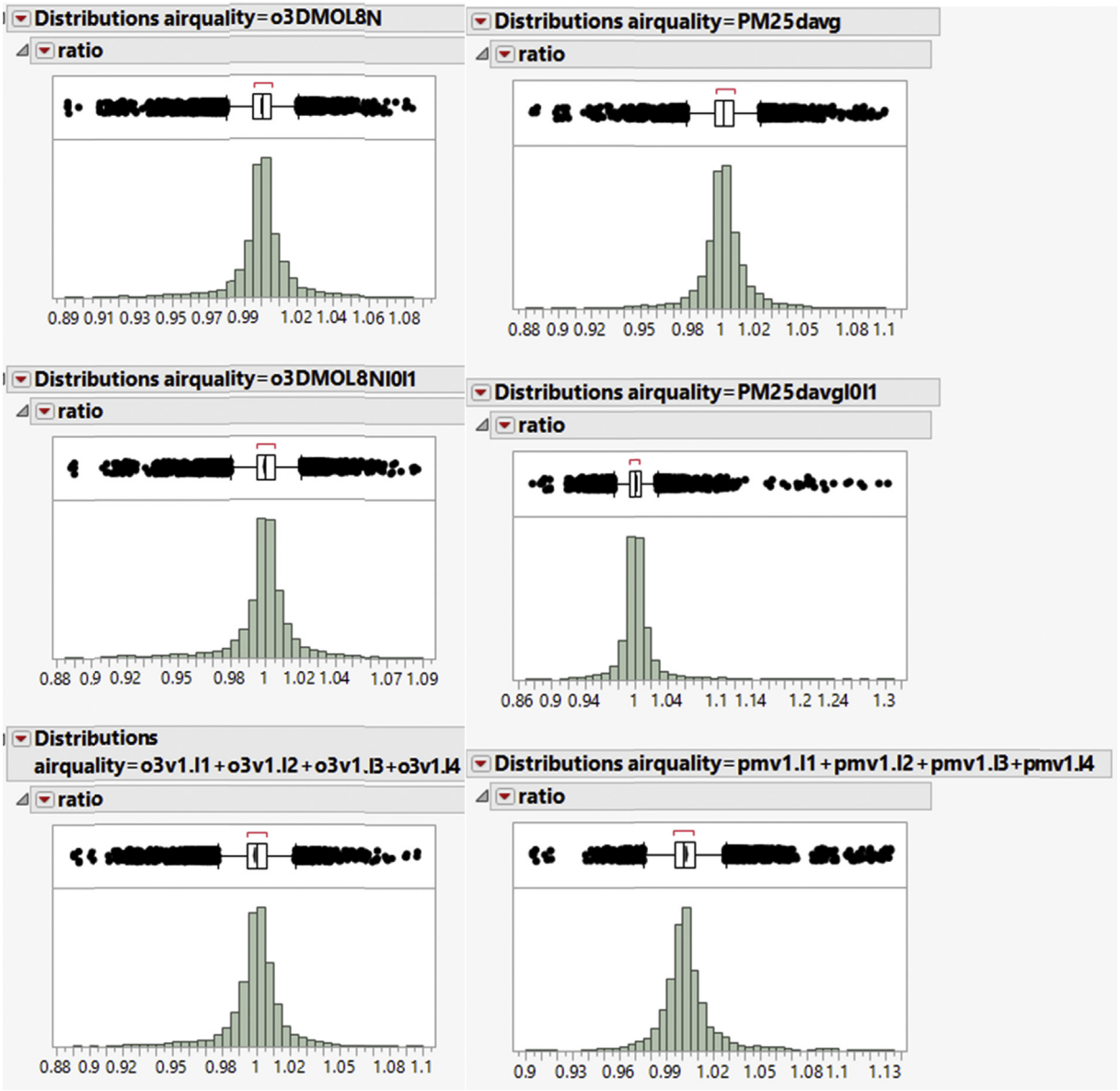

Fig. 8. Distribution of ratios of models fit with only time of year as a predictor and models that included air quality as well as weather variables. For a given model, if the ratio is greater than 1, then the model that only included time had a smaller MSPE; if the ratio is less than 1 then the corresponding model had an MSPE smaller than the model that only included time.

Table 7
All Cause risk ratios for PM2.5 deaths in California (See Enstrom, 2011).

References	Years	Risk Ratio	Confidence Limits
McDonnell et al. (2000)	1976–1992	1.03_	0.95_–1.12_
Krewski (2000)	1982–1989	0.872	0.805–0.944
Enstrom (2005)	1973–1982	1.039	1.010–1.069
Enstrom (2005)	1983–2002	0.997	0.978–1.016
Enstrom (2006)	1973–1982	1.061	1.017–1.106
Enstrom (2006)	1983–2002	0.995	0.968–1.024
Zeger et al. (2008)	2000–2005	0.989	0.970–1.008
Jerrett (2010)	1982–2000	0.994	0.965–1.025
Krewski (2010)	1982–2000	0.960	0.920–1.002
Krewski (2010)	1982–2000	0.968	0.916–1.022
Jerrett (2011)	1982–2000	0.994	0.965–1.024
Jerrett (2011)	1982–2000	1.002	0.992–1.012
Lipsett et al. (2011)	2000–2005	1.01_	0.95_–1.09_
Ostro et al. (2010)	2002–2007	1.06_	0.96_–1.16_

Young and Xia (2013), Krewski et al. (2000), Jerrett (2010), have not found any association of air quality with acute deaths in California. Nor did our reanalysis of the California data from NMMAPS. The existence of this "geographic heterogeneity" shows it is unlikely that air quality is *causing* deaths everywhere. Given that geographic heterogeneity exists, how should it be interpreted? First, statistical practice says that if interaction exists, recommendations should be site-specific. At a minimum, our analysis and literature data indicate that California should be considered separately from the rest of the US.

The question of interactions of air quality with geography deserves deeper consideration. Both Greven and Chay state there is no local or covariate adjusted effect of air quality on mortality. Milojevic et al. (2014) studied heart attacks and stroke in a very large UK data set. They determined the time of the event down to the hour. They studied six air components: CO, NO_2, O_3, PM_{10},

$PM_{2.5}$, and SO_2. They examined possible lag effects and they found no lag effects. They also essentially found no association of air quality, in particular ozone and $PM_{2.5}$, with heart attacks or stroke. There were ten necropsies (among the 60 deaths) with the air pollution disaster in 1930 in the Meuse Valley reported on by Nemery et al. (2001). They report no effect on heart. They go on to state, "However, carbon particles should have been innocuous, unless they had adsorbed irritant acids. … After a process of successive elimination, the commission concluded 'that the sulphur produced by coal burning had a deleterious effect, either as sulphurous anhydride of acid, or as sulphuric acid, the production of which was made possible by unusual weather conditions.'" Together these papers effectively remove heart attacks and stroke as a possible etiology for acute air quality deaths. Given the known poor reliability, Ravakhah (2006), of death certificate cause of death, analysis of all cause deaths make sense as the primary endpoint of analysis.

The EPA states that "An extensive body of scientific evidence indicates that breathing in $PM_{2.5}$ over the course of hours to days (short-term exposure) and months to years (long-term exposure) can cause serious public health effects that include premature death and adverse cardiovascular effects." See *www3.epa.gov/pm/2012/decfshealth.pdf.* The EPA goes on to say, "Most of the economic benefits (about 85 percent) are attributable to reductions in premature mortality associated with reductions in ambient particulate matter." These and similar quotes from EPA seem to imply that *causal* associations are assumed. The present study calls into question whether those associations are genuine at all in the state of California. Given that California is the most populous state of the Union, the national benefits of recent tightening of the ozone and $PM_{2.5}$ standards may have to be re-assessed. We provide our analysis code, data set and sensitivity analysis results so that others can do their own evaluation.

As a note, the current standards (a) for $PM_{2.5}$ – daily limit of 35 $\mu g/m^3$, annual mean 12 $\mu g/m^3$ averaged over three years and (b) Ozone: daily max 8-h average less than 70 ppb; based on the three-year average of fourth highest value per year. Past justifications for these standards rely heavily on positive associations for ozone or PM2.5 with acute mortality, which do not accord with our results in California.

In summary, our empirical evidence, supported by literature and logic, is that current levels of air quality, ozone and $PM_{2.5}$, are not associated with or causally related to acute deaths for California. Our results, well summarized in Figs. 4 and 5, show no effect of ozone or PM2.5 at 12 μg/m3 or across all doses examined. There is no indication of any effect at low doses, for example. These results should be taken into account in any future revisions of the NAAQS for PM2.5 and O3.

Acknowledgements

Funding from National Black Chamber of Commerce and the American Petroleum Institute.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2017.06.003.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2017.06.003.

References

Atkinson, R.W., Kang, S., Anderson, H.R., Mills, I.C., Walton, H.A., 2014. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax 69, 660–665.

Bell, M.L., McDermott, A., Zeger, S.L., Samet, J.M., Dominici, F., 2004. Ozone and short-term mortality in 95 US urban communities, 1987-2000. J. Am. Med. Assoc. 292 (19), 2372–2378.

Bell, M.L., Dominici, F., 2008. Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 U.S. communities. Am. J. Epidemiol. 167, 986–997.

Bhaskaran, K., Gasparrini, A., Hajat, S., Smeeth, L., Armstrong, B., 2013. Time series regression studies in environmental Epidemiology. Int. J. Epidemiol. 42, 1187–1195.

Board on Life Sciences, 2003. Sharing Publication-related Data and Materials: Responsibilities of Authorship in the Life Sciences. National Academies Press, Washington, DC. www.nap.edu/books/0309088593/html/.

Carbon Dioxide Information Analysis Center (CDIAC). United States Historical Climatology Network. Daily temperature data. http://cdiac.ornl.gov/ftp/ushcn_daily/.

California Department of Public Health. www.cdph.ca.gov.

California Environmental Protection Agency, Air Quality Data (PST) Query tool. http://www.arb.ca.gov/aqmis2/aqdselect.php.

Cecil, J.S., Griffin, E., 1985. The role of legal policies in data sharing. In: Fienberg, Stephen E., Martin, Margaret E., Straf, Miron L. (Eds.), Sharing Research Data (1985). National Academies Press.

Clyde, M., 2000. Model uncertainty and health effect studies for particulate matter. Environmetrics 11, 745–763.

Chay, K., Dobkin, C., Greenstone, M., 2003. The Clean Air Act of 1970 and adult mortality. J. Risk Uncertain. 27, 279–300.

Cox Jr., L.A., Popken, D.A., Ricci, P.F., 2013. Warmer is healthier: effects on mortality rates of changes in average fine particulate matter ($PM_{2.5}$) concentrations and temperatures in 100 U.S. cities. Regul. Toxicol. Pharmacol. 66, 336–346.

Craig, P., Cooper, C., Gunnell, D., Haw, S., Lawson, K., Macintyre, S., Ogilvie, D., Petticrew, M., Reeves, B., Sutton, M., Thompson, S., 2012. Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. J. Epidemiol. Community Health 66, 1182–1186.

Dominici, F., McDermott, A., Daniels, M., Zeger, S.L., Samet, J.M., 2003. Mortality among residents of 90 cities. In: Revised Analyses of the National Morbidity Mortality and Air Pollution Study, Part II. Health Effects Institute, Cambridge, MA, pp. 9–24.

Dominici, F., Peng, R.D., Zeger, S.L., White, R.H., Samet, J.M., 2007. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am. J. Epidemiol. 166 (8), 880–888.

Enstrom, J.E., 2005. Fine particulate air pollution and total mortality among elderly Californians. 1973–2002. Inhal. Toxicol. 17, 803–816.

Enstrom, J.E., 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. 18, 509–514. http://www.scientificintegrityinstitute.org/IT060106.pdf. http://www.scientificintegrityinstitute.org/ITBH060106.pdf.

Enstrom, J.E., 2011. Risk Ratios for California. http://scientificintegrityinstitute.org/Enstrom081111.pdf.

Environmental Protection Agency. Daily humidity data. http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm.

Everson, P.J., Morris, C.N., 2000. Inference for multivariate normal hierarchical models. J. R. Stat. Soc. B 62, 399–412.

Gasparrini, A., 2011. Distributed lag linear and non-linear models in R: the package dlnm. J. Stat. Softw. 43 (8), 1–20. http://www.jstatsoft.org/v43/i08/.

Gasparrini, A., Armstrong, B., 2013. Reducing and meta-analysing estimates from distributed lag non-linear models. BMC Med. Res. Methodol. 13.1, 1.

Gilliland, F., Avol, E.L., McConnell, R., Berhane, K.T., Gauderman, W.J., Lurmann, F.W., Urman, R., Chang, R., Rappaport, E.B., Howland, S., 2017. The Effects of Policy-driven Air Quality Improvements on Children's Respiratory Health. Research Report 190. Health Effects Institute, Boston, MA. www.healtheffects.org.

Greven, S., Dominici, F., Zeger, S., 2011. An approach to the estimation of chronic air pollution effects using spatio-temporal information. J. Amer. Stat. Assoc. 106, 396–406.

Health Effects Institute, 2003. Revised Analyses of Time-series Studies of Air Pollution and Health. Special Report.

Janes, H., Dominici, F., Zeger, S., 2007. Trends in air pollution and mortality: an approach to the assessment of unmeasured confounding. Epidemiology 18, 416–423.

Jerrett, M., 2010. California-specific Studies on the $PM_{2.5}$ Mortality Association. See slides 12 and 13, no increase in "All causes" death rate. http://www.arb.ca.gov/research/health/pm-mort/jerrett.pdf.

Jerrett, M. October 28, 2011 Revised Final Report for Contract No. 06-332 to CARB Research Screening Committee, Principal Investigator Michael Jerrett, "Spatio-temporal Analysis of Air Pollution and Mortality in California Based on the American Cancer Society Cohort" Co-Investigators: Burnett R.T., Pope C.A. III, Krewski D., Thurston G., Christakos G., Hughes E., Ross Z., Shi Y., Thun M., 2011, 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.

Krewski, D., July 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: HEI Special Report. Figure 5 and Figure 21 of Part II: Sensitivity Analyses http://www.scientificintegrityinstitute.org/HEIFigure5093010.pdf.

Krewski, D., 2010. August 31, 2010 letter from Krewski to Health Effects Institute and CARB with California-specific PM 2.5 Mortality Results from Table 33 in Krewski 2009. http://www.arb.ca.gov/research/health/pm-mort/HEI_Correspondence.pdf.

Krewski, D., Burnett, R.T., Goldberg, M.S., Hoover, K., Siemiatycki, J., Jerrett, M., Abrahamowicz, M., White, W.H., 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Part II: Sensitivity Analysis. HEI Publications. http://pubs.healtheffects.org/view.php?id=6. See Figure 21, in particular.

Lipsett, M.J., Ostro, B.D., Reynolds, P., et al., 2011. Long-term exposure to air pollution and cardiorespiratory disease in the California Teachers Study Cohort. Am. J. Respir. Crit. Care Med. 184 (7), 828–835. http://ajrccm.atsjournals.org/content/184/7/828.full.pdf.

McDonnell, W.F., Nishino-Ishikawa, N., Petersen, F.F., Chen, L.H., Abbey, D.E., 2000. Relationships of mortality with the fine and coarse fractions of long-term ambient PM 10 concentrations in nonsmokers. J. Expo. Anal. Environ. Epidemiol. 10 (5), 427–436. http://www.scientificintegrityinstitute.org/JEAEE090100.pdf.

Milojevic, A., Wilkinson, P., Armstrong, B., Bhaskaran, K., Smeeth, L., Hajat, S., 2014. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. Heart 100, 1093–1098.

Nemery, B., Hoet, P.H.M., Nemmar, A., 2001. The Meuse Valley fog of 1930: and air pollution disaster. Lancet 357, 704–708.

Office of Science and Technology Policy, 2013. Increasing Access to the Results of Federally Funded Scientific Research. http://www.whitehouse.gov/sites/default/files/microsites/ostp/ostp_public_access_memo_2013.pdf.

Ostro, B., Lipsett, M., Reynolds, P., et al., 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. Environ. Health Perspect. 118 (3), 363–369. http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.0901181.

R Core Team, 2015. R: a Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org.

Ravakhah, K., 2006. Death certificates are not reliable: revivification of the autopsy. South Med. J. 99, 728–733.

Royal Society, 2012. Science as an Open Enterprise. https://royalsociety.org/policy/projects/science-public-enterprise/Report/.

Samet, J.M., Dominici, F., Zeger, S.L., Schwartz, J., Dockery, D.W., 2000a. The National Morbidity, Mortality, and Air Pollution Study. Part I: Methods and Methodologic Issues. Research Report 094-I. Health Effects Institute, Boston, MA.

Samet, J.M., Zeger, S.L., Dominici, F., Curriero, F., Coursac, I., Dockery, D.W., Schwartz, J., Zanobetti, A., 2000b. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and Mortality from Air Pollution in the United States. Research Report 094-II. Health Effects Institute, Boston, MA.

Schwartz, J.M., Hayward, S.F., 2007. Air Quality in America. AEI Press, Washington, DC.

Smith, R.L., 2015. R Code for Analysis. www.unc.edu/~rls/EpiTimeSeriesCodeRLS.txt.

Smith, R.L., Xu, B., Switzer, P.P., 2009. Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. Inhal. Toxicol. 29 (S2), 37–61.

Styer, P., McMillan, N., Gao, F., Davis, J., Sacks, J., 1995. Effect of outdoor airborne particulate matter on daily death counts. Environ. Health Perspect. 103, 490–497.

Young, S.S., Fogel, P., 2014. Air pollution and daily deaths in California. In: Proceedings, 2014 Discovery Summit. https://community.jmp.com/docs/DOC-6691/.

Young, S.S., Xia, J.Q., 2013. Assessing geographic heterogeneity and variable importance in an air pollution data set. Stat. Anal. Data Min. 6, 375–386.

Zanobetti, A., Schwartz, J., 2009. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ. Health Perspect. 117 (6), 898–903.

Zeger, S.L., Dominici, F., McDermott, A., Samet, J.M., 2008. Mortality in the medicare population and chronic exposure to fine particulate air pollution in urban centers (2000–2005). Environ. Health Perspect. 116, 1614–1619. http://dx.doi.org/10.1289/ehp.11449. http://ehp03.niehs.nih.gov/article/info.

Zigler, C.M., Kim, C., Choirat, C., Hansen, J.B., Wang, Y., Hund, L., Samet, J., King, G., Dominici, F., 2016. Causal Inference Methods for Estimating Long-term Health Effects of Air Quality Regulations. Research Report 187. Health Effects Institute, Boston, MA. www.healtheffects.org.

Zu, K., Tao, G., Long, C., Goodman, J., Valberg, P., 2016. Long-range fine particulate matter from the 2002 Quebec forest fires and daily mortality in Greater Boston and New York City. Air Qual. Atmos. Health 9, 213–221.