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Part I

A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China

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with a Commentary by the HEI Health Review Committee

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INVESTIGATORS' REPORT

Part 1. A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China

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ABSTRACT

Although the relation between outdoor air pollution and daily mortality has been examined in several Chinese cities, there are still a number of key scientific issues to be addressed concerning the health effects of air pollution in China. Given the changes over the past decade in concentrations and sources of air pollution (e.g., the change from one predominant source [coal combustion], which was typical of the twentieth century, to a mix of sources [coal combustion and motor-vehicle emissions]) and transition in China, it is worthwhile to investigate the acute effects of outdoor air pollution on mortality outcomes in the country. We conducted a time-series study to investigate the relation between outdoor air pollution and daily mortality in Shanghai using four years of daily data (2001–2004). This study is a part of the Public Health and Air Pollution in Asia (PAPA*) program supported by the Health Effects Institute (HEI).

We collected data on daily mortality, air pollution, and weather from the Shanghai Municipal Center of Disease Control and Prevention (SMCDCP), Shanghai Environmental Monitoring Center, and Shanghai Meteorologic Bureau. An independent auditing team assigned by HEI validated all the data. Our statistical analysis followed the Common Protocol of the PAPA program (found at the end of this volume). Briefly, a natural-spline model was used to analyze the mortality, air pollution, and covariate data. We first constructed the basic models for various mortality outcomes excluding variables for air pollution, and used the partial autocorrelation function of the residuals to guide the selection of degrees of freedom for time trend and lag days for the autoregression terms. Thereafter, we introduced the pollutant variables and analyzed their effects on mortality outcomes, including both mortality due to all natural (nonaccidental) causes and cause-specific mortality. We fitted single- and multipollutant models to assess the stability of the effects of the pollutants. For mortality due to all natural causes, we also examined the associations stratified by sex and age. Stratified analyses by education level, used as a measure of socioeconomic status, were conducted as well. In addition to an analysis of the entire study period, the effects of air pollution in just the warm season (from April to September) and cool season (from October to March) were analyzed. We also examined the effects of alternative model specifications — such as lag effects of pollutants and temperature, degrees of freedom for time trend and weather conditions, statistical approaches, and averaging methods for pollutant concentrations — on the estimated effects of air pollution.

We found significant associations between the air pollutants — particulate matter 10 μm or less in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) — and daily mortality from all natural causes and from cardiopulmonary diseases. The increased mortality risks found in the data from Shanghai

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*A list of abbreviations and other terms appears at the end of the Investigators' Report.

were generally similar in magnitude, per concentration of pollutant, to the risks found in research from other parts of the world. An increase of 10 μg/m^3 in 2-day moving average concentrations of PM_{10}, SO_2, NO_2, and O_3 corresponded to 0.26% (95% confidence interval [CI], 0.14–0.37), 0.95% (95% CI, 0.62–1.28), 0.97% (95% CI, 0.66–1.27), and 0.31% (95% CI, 0.04–0.58) increases, respectively, in mortality due to all natural causes. Sensitivity analyses suggested that our findings were generally insensitive to alternative model specifications. We found significant effects of the gaseous pollutants SO_2 and NO_2 on daily mortality after adjustment for PM_{10}. Our analysis also provided preliminary, but not conclusive, evidence that women, older people, and people with a low level of education might be more vulnerable to air pollution than men, younger people, and people with a high level of education. In addition, the associations between air pollution and daily mortality appeared to be more pronounced in the cool season than in the warm. We concluded that short-term exposure to outdoor air pollution (PM_{10}, SO_2, NO_2, and O_3) was associated with daily mortality in Shanghai and that gaseous pollutants might have independent health effects in the city. Overall, the results of the study appeared largely consistent with those reported in other locations worldwide. Further research will be needed to disentangle the effects of the various pollutants and to gain more conclusive insights into the influence of various sociodemographic characteristics (e.g., sex, age, and socioeconomic status) and of season on the associations between air pollution and daily mortality.

INTRODUCTION

Short-term exposure to outdoor air pollution has been linked to adverse health effects, including increased mortality, increased rates of hospital admissions and emergency-department visits, exacerbation of chronic respiratory conditions (e.g., asthma), and decreased lung function (Samet and Krewski 2007). Recent multicity analyses conducted in the United States, Canada, and Europe have provided further evidence supporting the coherence and plausibility of the acute effects of ambient pollutants on the cardiopulmonary system (Katsouyanni et al. 1997, 2001; Burnett et al. 2000; Samet et al. 2000a; Dominici et al. 2006). Most of these studies were conducted in developed countries; only a small number have been conducted in Asia (HEI 2004). In general, there remains a need for studies in the cities of developing countries, where the characteristics of outdoor air pollution (e.g., concentrations, mixtures, and transport of pollutants) and the sociodemographic characteristics of the local population (e.g., disease patterns, age structure, and socioeconomic variables) might be different from those encountered in studies conducted in North America and Europe.

The concentrations of outdoor air pollutants in China are among the highest in the world. Coal supplies about 75% of the energy used in China; consequently, air pollution in China derives predominantly from coal smoke. The principal pollutants in coal smoke are particulate matter (PM) and SO_2. However, the rapid increase in the number of motor vehicles in recent years has changed the character of outdoor air pollution in China's large cities from a type derived from one principal source, the combustion of coal, to a mixed type derived from two principal sources, emissions from motor vehicles as well as the combustion of coal (Chen et al. 2004).

The relation between outdoor air pollution and daily mortality and morbidity has been examined in studies of several large Chinese cities, including Beijing (Xu et al. 1994, 1995; Dong et al. 1996; Chang et al. 2003), Chongqing (Venners et al. 2003), Shanghai (Kan and Chen 2003a,b), and Shenyang (Xu et al. 2000). These studies basically followed the widely used time-series and case–crossover approaches, and their results were in accordance with those reported from developed countries. However, there are still some key scientific issues to be addressed about the health effects of outdoor air pollution in China. For example, in half of the studies mentioned above (Xu et al. 1994, 1995, 2000; Venners et al. 2003), the air pollution and health data were measured in the early 1990s, when concentrations of total suspended particulate (TSP) and SO_2 were much higher than those of recent years and before the last decade's rapid increase in the number of motor vehicles in China's cities with concomitant increases in concentrations of fine particulate (particulate matter 2.5 μm or less in aerodynamic diameter, $PM_{2.5}$), nitrogen oxides (NO_x), O_3, and carbon monoxide (CO). As a result of increased traffic, the photochemically produced components NO_x and O_3 in the air pollution profile of China's cities have gradually increased. However, in several recent studies (Chang et al. 2003; Kan and Chen 2003a,b) the air pollutants considered were still limited to SO_2, NO_2, and PM_{10}. Even though O_3 has been recognized in several recent multicity studies and meta-analyses (Bell et al. 2004, 2005; Ito et al. 2005; Levy et al. 2005) as an air pollutant that could increase the risk of acute effects on mortality, no studies have been conducted in Mainland China to assess the acute effects of O_3. Also, little attention has been paid in the Chinese studies to assessing possible modifiers of air pollution's health effects. These modifiers include preexisting health status (Goldberg et al. 2001; Katsouyanni et al. 2001; Bateson and Schwartz 2004), population demographic characteristics (e.g., sex and age) (Atkinson et al.

2001; Katsouyanni et al. 2001; Bateson and Schwartz 2004; Cakmak et al. 2006), socioeconomic status (O'Neill et al. 2003), and season (Peng et al. 2005; Touloumi et al. 2006; Zeka et al. 2006). More information about these modifiers will aid in determinations of public policy, assessments of pollution risks, and the setting of air-quality standards.

Considering the recent changes in China's air pollution concentrations and characteristics and the knowledge gaps mentioned above, it is worthwhile to initiate more in-depth epidemiologic studies to explore the associations between outdoor air pollutants and mortality based on more recent data. In the present study, we conducted a time-series analysis to evaluate the associations between daily mortality (both all natural and cause-specific) and the major air pollutants PM_{10}, SO_2, NO_2, and O_3 in Metropolitan Shanghai, using daily data from 2001 through 2004.

The study is one of the four first-wave projects (conducted in Bangkok, Hong Kong, Shanghai, and Wuhan) of the PAPA program, supported by the HEI. A Common Protocol (found at the end of this volume) was devised to facilitate a coordinated analysis of the studies in all four cities. This protocol was approved by the Institutional Review Board of the School of Public Health at Fudan University in Shanghai, China.

SPECIFIC AIMS

The study had four specific aims:

- To investigate the short-term effects of the major ambient air pollutants PM_{10}, SO_2, NO_2, and O_3 on all natural and cause-specific mortality in Shanghai;
- To investigate the exposure–response relations between air pollution concentrations and risk of mortality;
- To investigate the possible independent roles of PM_{10} and the gaseous copollutants in producing short-term effects on mortality; and
- To investigate possible modifications of the association between air pollution and mortality by various sociodemographic characteristics (such as sex, age, and socioeconomic status) and by season.

METHODS

STUDY AREA

Shanghai, the most populous city in China, is situated at the tip of the Yangtze River Delta in eastern China. The city has a moderate subtropical climate, with four distinct seasons and abundant rainfall. It comprises urban and suburban districts and counties, with a total area of 6341 km^2, and, at the end of 2000, had a population of 13.2 million, representing 1% of China's total population. Over the past decade, Shanghai has undergone the most rapid development and urbanization in its history. The city's average per capita gross domestic product (GDP), for example, increased from U.S. $720 in 1990 to more than U.S. $7500 in 2007. Pollution associated with coal combustion, e.g., TSP and SO_2, in Shanghai has decreased substantially, whereas pollution from motor vehicles is increasing and becoming a serious public health concern (Chen et al. 2004). Overall, air pollution concentrations in Shanghai are higher than those of Western countries.

Our study area included Huangpu, Jing'an, Luwan, Xuhui, Yangpu, Changning, Hongkou, Putuo, and Zhabei, the nine urban districts of Shanghai. These urban districts cover 289 km^2 (Figure 1). The target population included all permanent residents living in the study area, about 6.3 million people in 2000. In this population, there were 0.9% more men than women, and the elderly (over 65 years of age) accounted for 11.9% of the total. The city's suburban districts and counties were excluded from our analysis because of inadequate air pollution monitoring stations in those areas.

Figure 1. Map of Shanghai, China. The districts included in the study are in the inner-ring of Shanghai (dark gray area) and in the outer ring of Shanghai (light gray hatched area). Shading on far left represents water.

DATA

Mortality Data

Daily mortality data for people living in the nine urban districts from January 1, 2001, to December 31, 2004, were collected from the SMCDCP database. The SMCDCP is the government agency in charge of the collection of health data in Shanghai. A death-report system in Shanghai was put into use in 1951 and has been computerized since 1990.

In Shanghai, all deaths must be reported to the appropriate authorities before cremation. The process for reporting deaths, most of which take place in a hospital or at home, is shown in Figure 2. Either a hospital or a community doctor fills in a death-certificate card (Figure 3). Information routinely provided on death-certificate cards includes name, sex, ethnicity, occupation, identification number, marital status, education level, the name of the company where last employed, date of birth, date of death, age, location of death, address, causes of death, name of hospital making the diagnosis, name of hospital where death occurred, and finally the basis of the diagnosis. The information on the death-certificate card is then sent from the District Center for Disease Control (District CDC) to the SMCDCP.

To follow the relevant rules of the Chinese government, causes of death in 2001 and 2002–2004 were coded according to *International Classification of Diseases*, *Revision 9* (ICD-9) and *Revision 10* (ICD-10), respectively. Mortality data were classified as deaths from all natural (nonaccidental) causes (< 800 [ICD-9] and A00–R99 [ICD-10]), diseases of the circulatory system (390–459 [ICD-9] and I00–I99 [ICD-10], including subcategories such as stroke and heart diseases), and diseases of the respiratory system (460–519 [ICD-9] and J00–J98 [ICD-10], including subcategories such as chronic obstructive pulmonary disease [COPD] and acute respiratory infection). The data for all natural deaths were also classified as to sex (male or female) and age (0–4, 5–44, 45–64, and more than 65 years of age). Level of education has often been used in time-series studies as a surrogate for socioeconomic status (Zanobetti and Schwartz 2000; Jerrett et al. 2004; Cakmak et al. 2006; Zeka et al. 2006). Education level is typically classified as illiterate, primary school, middle school, college, or graduate school and above; but for this study we classified all natural, cardiovascular, and respiratory deaths using a simpler two-category scheme: "low" for illiterate or primary school and "high" for middle school or above.

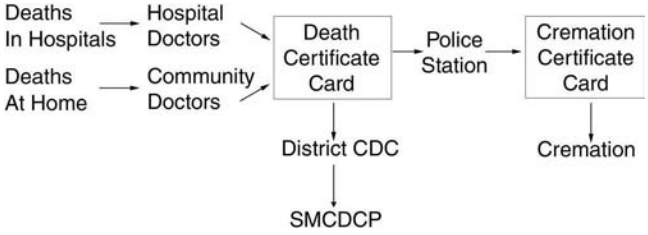


Figure 2. Flow chart for the system of reporting deaths in Shanghai. Abbreviations: CDC, Center for Disease Control; SMCDCP, Shanghai Municipal Center of Disease Control and Prevention.

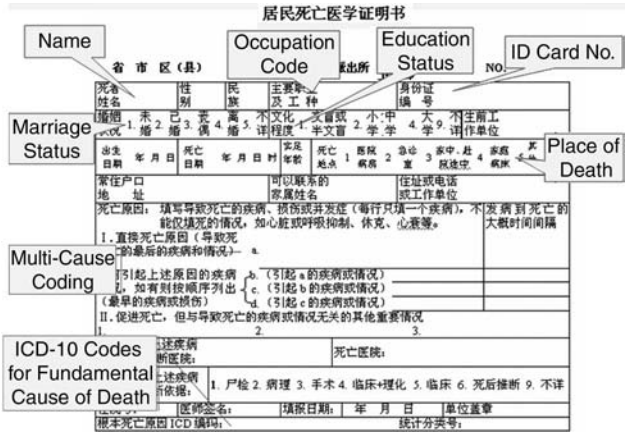


Figure 3. Death Certificate Card used to record information about the death of a Shanghai resident.

Air Pollution Data

Daily air pollution data for PM_{10}, SO_2, NO_2, and O_3 in Metropolitan Shanghai from January 1, 2001, to December 31, 2004, were obtained from the Shanghai Environmental Monitoring Center, the government agency in charge of collecting the city's air pollution data. The values of the daily concentrations for each pollutant were the average of the available data from six fixed-site monitoring stations in urban areas of Shanghai (in Hongkou, Jing'an, Luwan, Putuo, Xuhui, and Yangpu) that were in the China National Quality Control for Air Monitoring network (Figure 4). The China State Environmental Protection Agency (CSEPA) certified the monitoring system in Shanghai (CSEPA 2000). As per the rules of the Chinese government, these stations were not located in the direct vicinity of traffic; industry; boilers burning coal, waste, or oil; furnaces; incinerators; or other local pollution sources. The careful location of the monitoring stations helped to ensure that our pollution data accurately reflected the background urban air pollution of Shanghai rather than pollution from local sources, such as traffic or industrial combustion.

An automatic continuous monitoring system was set up at each station to measure air pollutant concentrations. The monitoring methods were in accordance with the rules of CSEPA (CSEPA 2000). Specifically, methods based on the tapered element oscillating microbalance (TEOM), ultraviolet fluorescence, chemiluminescence, and ultraviolet

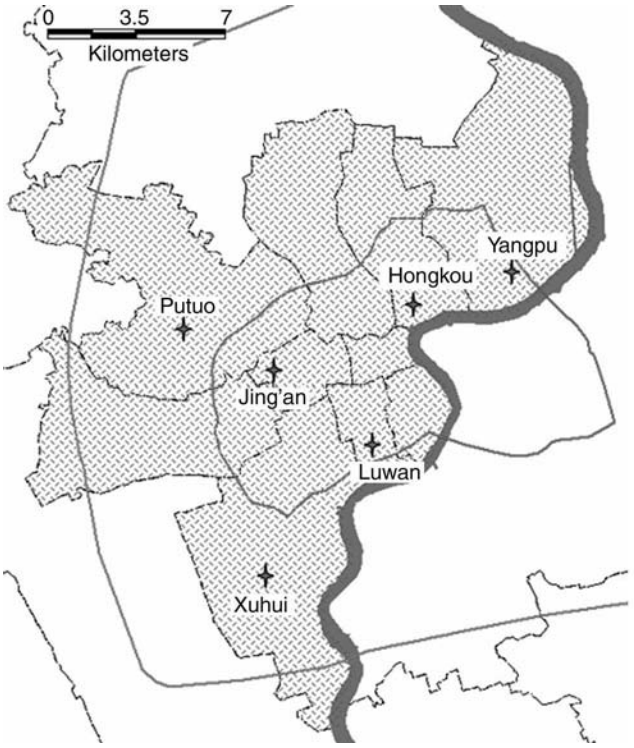


Figure 4. Locations of the six monitoring stations in Metropolitan Shanghai. Solid and dashed lines indicate the inner ring and outer ring, respectively, of Shanghai. The textured gray area indicates our study area. Huangpu River (indicated by heavy black line) runs through the study area. The dagger-like symbols indicate the six monitoring stations. Data on PM_{10}, SO_2, and NO_2 were collected from all six stations. Data on O_3 were collected from Hongkou and Putuo stations only.

absorption were used to measure PM_{10}, SO_2, NO_2, and O_3, respectively.

We collected data for 24-hour average concentrations of PM_{10}, SO_2, and NO_2 and maximum 8-hour mean concentrations of O_3. The maximum 8-hour mean was used because the World Health Organization (WHO) recommends this as the most health-relevant exposure to O_3 (WHO 2000). To calculate 24-hour mean concentrations of PM_{10}, SO_2, and NO_2, and maximum 8-hour mean concentrations of O_3 for a given day, at least 75% of the 1-hour values must have been available for that day. If a station was missing more than 25% of the values for the period of analysis, the entire station was excluded from the analysis.

Measurement results for O_3 were obtained from two monitoring stations — Hongkou and Putuo — for the entire study (2001–2004) and from three other stations for the final year (2004). The final analysis of averaged O_3 measures was based only on data from the stations in Hongkou and Putuo, as the other three stations did not have data that were sufficiently complete (Figure 4).

Weather Data

To allow adjustment for the effects of weather on daily mortality, data on daily mean temperature and relative humidity were obtained from the Shanghai Meteorologic Bureau. These weather data were measured at a fixed-site station located in the Xuhui district.

Quality Assurance, Quality Control, and Data Auditing

The Chinese government has mandated detailed quality assurance and quality control programs at the institutions providing mortality, air pollution, and weather data for this study. An independent auditing team assigned by HEI also validated these data. The team checked a sample of the original death certificates and monitoring records and validated the process by which the mortality, air pollution, and weather data were obtained for use in our time-series analysis.

In addition, staff members from Fudan University reviewed the raw databases to validate the daily values. For the air pollution data, they focused on the implementation of the 75% criterion, in other words, that calculations were based on data from days for which at least 75% of the 1-hour values were available, and the exclusion of potentially abnormal values in the raw hourly data from each station. For the mortality data, they reviewed the raw Death Registry database to validate samples of randomly selected daily death numbers; all the selected daily numbers were successfully reproduced from the raw database.

DATA ANALYSIS

Daily deaths, air pollution measures, and weather conditions can be linked by date and can therefore be analyzed using a time-series study design (Zeger et al. 2006). Because daily deaths approximately follow a Poisson distribution and the relations between daily deaths and explanatory variables (independent variables used as predictors of the dependent or response variable) are mostly nonlinear (Dominici 2004), overdispersed generalized linear Poisson quasi-likelihood models with natural-spline smoothing functions were used to analyze the data for daily mortality, air pollution, and covariables. Our statistical analyses followed the Common Protocol of the PAPA program.

Establishment of Basic Models

First, the basic models for each mortality outcome were constructed excluding the air pollution variables. We incorporated the natural-spline smoothing functions of time trend and weather conditions, which can accommodate nonlinear and non-monotonic relations between mortality and time as well as weather conditions. In accordance with the Common Protocol used in the PAPA studies, the partial

autocorrelation function was used to guide the selection of model parameters. Specifically, we used 4 to 6 degrees of freedom (df) per year for time trend for all mortality outcomes. When the absolute magnitude of the partial autocorrelation function plot was less than 0.1 for the first 2 lag days, the basic model was regarded as adequate; if this criterion was not met, autoregression terms for lags of up to 7 days were introduced to improve the model (Goldberg et al. 2000). For weather conditions, 3 df (for the whole study period) were used for both temperature and relative humidity because this value has been shown to control well for their effects on changes in daily mortality rates (Samet et al. 2000a; Dominici et al. 2006). The day of the week (DOW) was included as a dummy variable (a variable that takes on the values 1 and 0; also called an indicator variable). Residuals of the basic models were examined to check whether there were discernible patterns and autocorrelation was examined by means of residual plots and partial autocorrelation function plots.

Main Analysis

After the basic models were constructed, we introduced the pollutant variables and analyzed their effects on total and cause-specific mortality outcomes. Briefly, the following log-linear models were fitted to obtain the estimated pollution log-relative rate β in Shanghai:

$$\log E(Y_t) = \beta Z_t + DOW + ns(time, df) + ns(temperature/humidity, 3). \quad (1)$$

Here $E(Y_t)$ represented the expected number of deaths at day t; β represented the log-relative rate of mortality associated with a unit increase in air pollutants; Z_t was the pollutant concentrations at day t; DOW was a dummy variable for the day of the week; ns(time, df) was the natural-spline function of time; and ns(temperature/humidity, 3) was the natural-spline function for temperature and relative humidity with 3 df.

Both all natural and cause-specific mortality were assessed. For all natural mortality, the association stratified by sex and age was also examined. Both single-pollutant models and models with various combinations of pollutants (up to two pollutants per model) were fitted to assess the stability of the pollutants' effects. Analyses by education level were conducted for all natural, cardiovascular, and respiratory mortality. The effects of air pollution were analyzed separately for the warm season (from April to September) and cool season (from October to March) as well as for the entire year. The 95% CI was calculated to test the statistical significance of differences between effect estimates for the strata of a potential effect modifier (e.g., the difference between the female and male categories):

$$(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{S\hat{E}_1 + S\hat{E}_2} \quad (2)$$

where $\hat{Q}_1$ and $\hat{Q}_2$ were the estimates for the two categories, and $S\hat{E}_1$ and $S\hat{E}_2$ were their respective standard errors (Zeka et al. 2006). Modifications of effects by a factor of two or more were considered to be important and worthy of attention regardless of significance (Zeka et al. 2006).

Because the assumption of linearity between the log of mortality and the air pollution concentration might not have been justified, smoothing splines, with 3 df for pollutant concentrations, were used to describe their relations graphically. Concentration–response curves for the effect of each pollutant on each mortality outcome were plotted. By computing the difference between the deviances of the two fitted models, the linear and spline models could be compared (Samoli et al. 2005). This difference followed a chi-square distribution with degrees of freedom being the difference in the degrees of freedom of the fitted models.

Sensitivity Analysis

Single-day lag models have been reported to underestimate the cumulative effect of air pollution on mortality (Braga et al. 2001; Bell et al. 2004). The 2-day moving averages of current- and previous-day concentrations of air pollutants (lag 0–1 day [average]) were used for our main analyses. The effects of air pollutants with other lag structures were also examined as a sensitivity analysis, including single-day lag (from lag 0 to 4 days) and multi-day lag (from lag 0–1 day [average] to lag 0–4 days [average]). In single-day lag models, a lag of 0 days ("lag 0 day") refers to the current-day pollutant concentration, and a lag of 1 day ("lag 1 day") refers to the previous-day concentration. In multi-day lag models, "lag 0–4 days (average)" refers to the 5-day moving average of pollutant concentration on the current and previous 4 days.

Current-day (lag 0 day) temperatures were used for our main analysis. As temperature with longer lags might have a greater effect than air pollution on daily mortality (Basu et al. 2005), sensitivity analyses were also conducted to explore the effect of temperature with longer lags (including 0 and 1–2 days; 0 and 3–7 days; and 0, 1–2, and 3–7 days) on the estimated air pollution effects.

Given that it is not easy to determine the optimal values of degrees of freedom for time trend or weather conditions, sensitivity analyses were conducted to test the effect of alternative values of degrees of freedom on the estimated air pollution effects.

In addition to the natural-spline model for the main analysis, a penalized-spline model was used to estimate the air pollution effects.

As stated above, measurements from the various monitoring stations were simply averaged to serve as the proxy for the general population's degree of exposure to air pollution. We also used the centering method, which was first introduced in the APHEA-2 project (Air Pollution on Health: A European Approach – Phase 2) and then used in a Hong Kong study (Wong et al. 2001) to estimate daily exposures to air pollution. Briefly, the following equation was used to calculate the centered daily mean concentrations:

$$X'_j = \overline{X'_{ij}} = (\overline{X_{ij} - X_i + X}). \quad (3)$$

Here X'_j were centered daily mean concentrations for day j, X'_{ij} were centered daily mean concentrations for station i and day j, X_{ij} were daily mean concentrations for station i and day j; X_i were annual mean concentration for station i; and X were annual mean concentrations for all stations.

We compared the effects of air pollutants on daily mortality using pollutant concentrations from the simple averaging and centering methods.

All analyses were conducted in R 2.5.1 statistical software using the multiple generalized cross-validation software package (R Development Core Team 2007). Technical details of the basic model and main analysis are included in Appendix A. Results are presented as the percent change in daily deaths per 10-μg/m^3 increase in 2-day moving average (lag 0–1 day [average]) pollutant concentrations, unless specified otherwise.

RESULTS

DATA DESCRIPTION

Mortality Data

From 2001 to 2004 (1461 days), a total of 173,911 deaths (91,314 males and 82,597 females) were recorded in the study population. From the summary statistics shown in Table 1, the percentages of all natural deaths by age group

Table 1. Summary Statistics of Daily Deaths, Air Pollutant Concentrations, and Meteorologic Conditions in Shanghai, 2001–2004

	Mean ± SD	Minimum	First Quartile	Median	Third Quartile	Maximum
Daily Death Counts (*n*)						
All natural	119.0 ± 22.5	51.0	103.0	115.0	133.0	198.0
Male	62.5 ± 12.7	26.0	54.0	61.0	71.0	114.0
Female	56.5 ± 12.2	22.0	48.0	55.0	63.0	105.0
Ages 0–4	0.3 ± 0.6	0.0	0.0	0.0	1.0	3.0
Ages 5–44	3.7 ± 2.0	0.0	2.0	3.0	5.0	13.0
Ages 45–64	15.5 ± 4.2	3.0	12.0	15.0	18.0	33.0
Ages ≥ 65	99.6 ± 20.6	46.0	84.0	96.0	112.0	175.0
Cardiovascular	44.2 ± 11.0	11.0	36.0	43.0	51.0	85.0
Heart disease	16.8 ± 5.4	3.0	13.0	16.0	20.0	42.0
Stroke	25.5 ± 7.2	7.0	20.0	25.0	30.0	56.0
Respiratory	14.3 ± 6.4	3.0	10.0	13.0	17.0	45.0
Chronic obstructive pulmonary disease	12.2 ± 5.8	1.0	8.0	11.0	15.0	40.0
Acute respiratory infection	1.0 ± 1.0	0.0	0.0	1.0	1.0	6.0
Air Pollutant Concentrations (μg/m^3)[a]						
PM_{10}	102.0 ± 64.8	14.0	56.3	84.0	128.3	566.8
SO_2	44.7 ± 24.2	8.4	27.5	40.0	56.2	183.3
NO_2	66.6 ± 24.9	13.6	50.2	62.5	79.2	253.7
O_3	63.3 ± 36.7	5.3	37.6	56.1	82.7	251.3
Meterologic Conditions						
Mean temperature (°C)	17.7 ± 8.5	−2.4	10.3	18.3	24.7	34.0
Relative humidity (%)	72.9 ± 11.4	33.3	65.5	73.5	81.0	97.0

[a] Using 24-hour averages for PM_{10}, SO_2, and NO_2 and maximum 8-hour means for O_3.

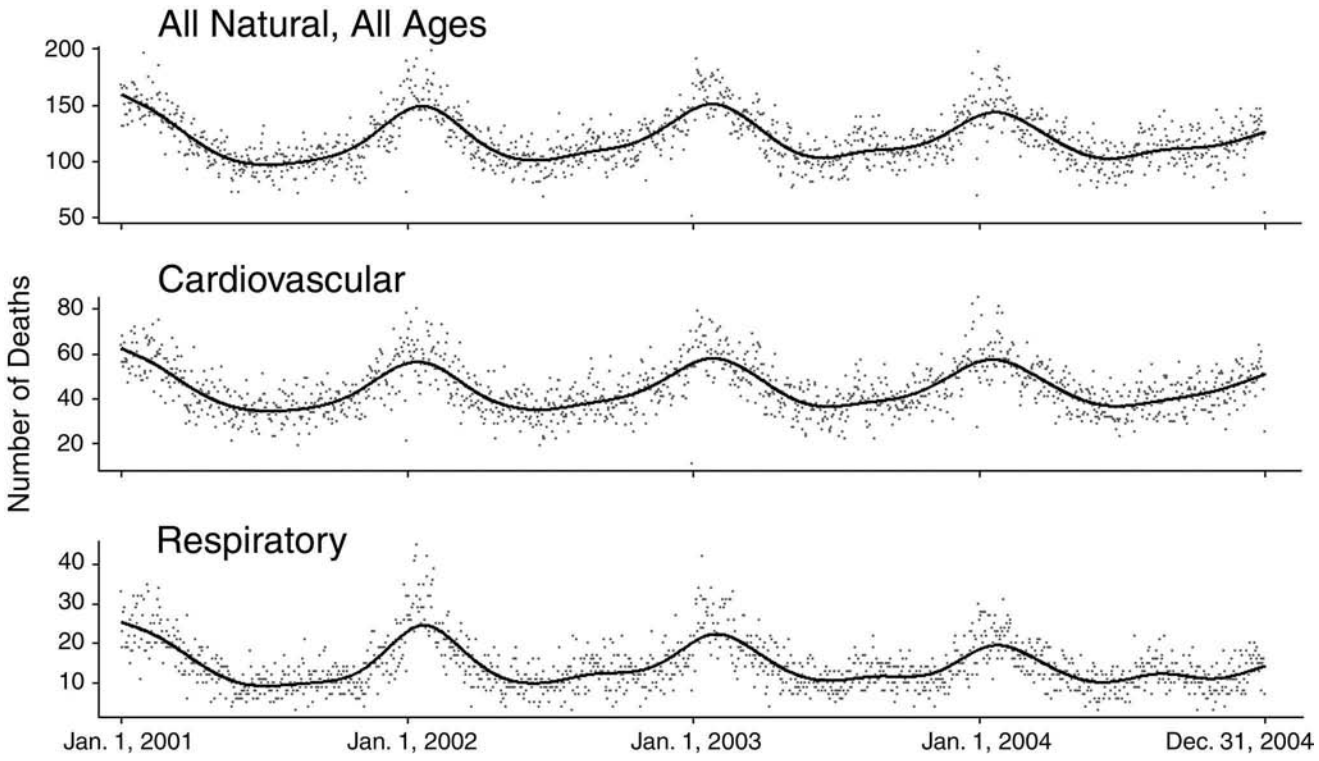


Figure 5. Time-series data of all natural, cardiovascular, and respiratory deaths in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year. Note differences in the scales of the *y*-axes.

were calculated to be 0.3% for ages 0–4, 3.2% for ages 5–44, 13.0% for ages 45–64, and 83.5% for ages 65 or older, respectively. On average, there were approximately 119 nonaccidental deaths per day, of which 44 were from cardiovascular diseases and 14 were from respiratory diseases (Figure 5). Cardiopulmonary diseases accounted for 49.1% of all natural deaths.

Air Pollution and Weather Data

During the study period, the mean daily average concentrations of PM_{10}, SO_2, NO_2, and O_3 were 102.0, 44.7, 66.6, and 63.3 $\mu g/m^3$, respectively (derived from values in Figure 6). The means of daily average temperature and of daily relative humidity were 17.7°C and 72.9%, respectively, reflecting the subtropical climate of Shanghai (derived from values in Figure 7).

Generally, PM_{10}, SO_2, and NO_2 had relatively high correlation coefficients with each other and were negatively correlated with temperature and relative humidity (Table 2). Maximum 8-hour mean concentrations of O_3 were weakly correlated with PM_{10}, SO_2, and NO_2 and moderately correlated with temperature.

More detailed monitor-specific air pollution data are presented in Appendix B (Figures B.1–B.4 and Tables B.1–B.5). Briefly, PM_{10} showed less spatial variability than did gaseous pollutants (Table B.2): the mean correlation coefficients across monitors were 0.93 for PM_{10} (range, 0.88–0.97), 0.70 for SO_2 (range, 0.44–0.83), 0.85 for NO_2 (range, 0.74–0.93), and 0.85 for O_3. Station-specific pollutant concentrations showed correlation patterns (Table B.3) similar to those of station-averaged pollutant concentrations (Table 2). Seasonal and weather corrections did not substantially affect the correlation coefficients between pollutants (Table B.4 and Table B.5).

Table 2. Pearson Correlation Coefficients Between Station-Averaged Daily Air Pollutant Concentrations and Meteorologic Conditions in Shanghai, 2000–2004

	SO_2	NO_2	O_3	Temperature	Relative Humidity
PM_{10}	0.64	0.71	0.19	−0.21	−0.37
SO_2		0.73	0.14	−0.21	−0.52
NO_2			0.01	−0.38	−0.27
O_3				0.48	−0.35
Temperature					0.21

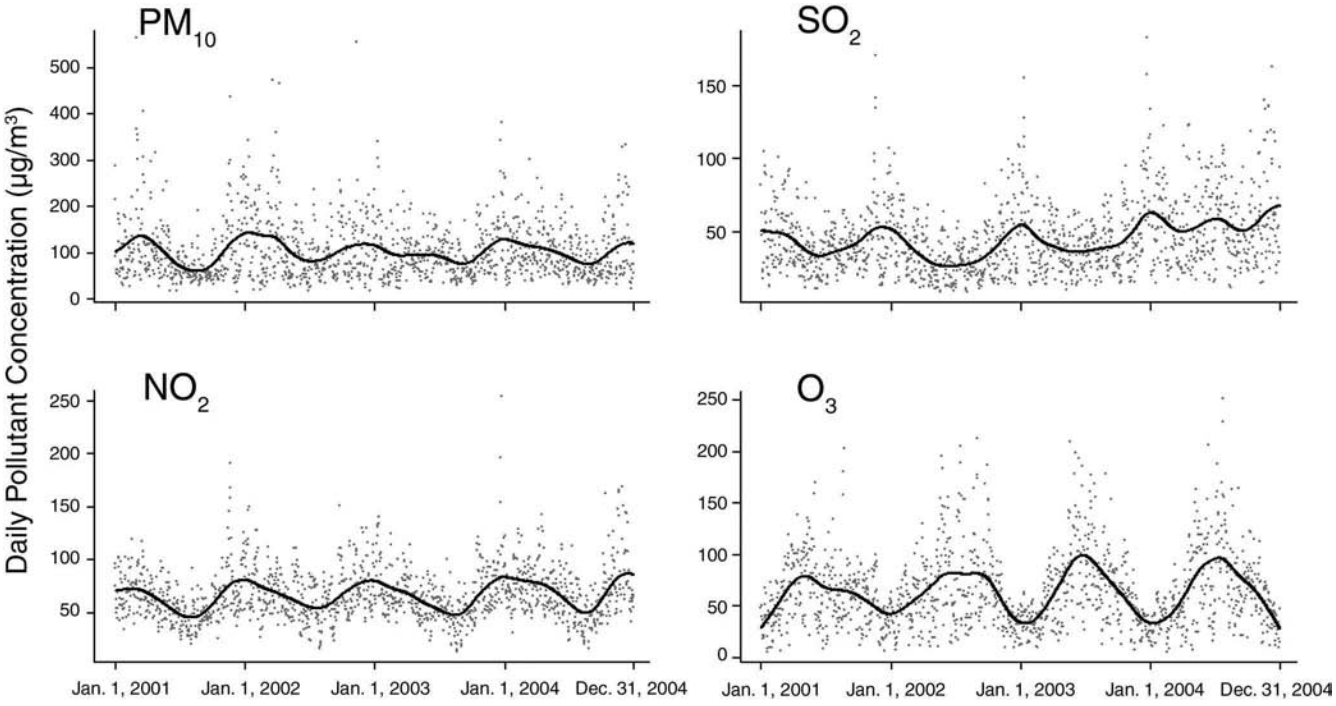


Figure 6. Time-series of pollutant concentrations in Shanghai, 2001–2004. Concentrations are the averages from each monitoring station, using 24-hour averages for PM_{10}, SO_2, and NO_2, and a maximum 8-hour mean for O_3. Solid lines indicate smoothing splines with 5 df per year. Note differences in the scales of the *y*-axes.

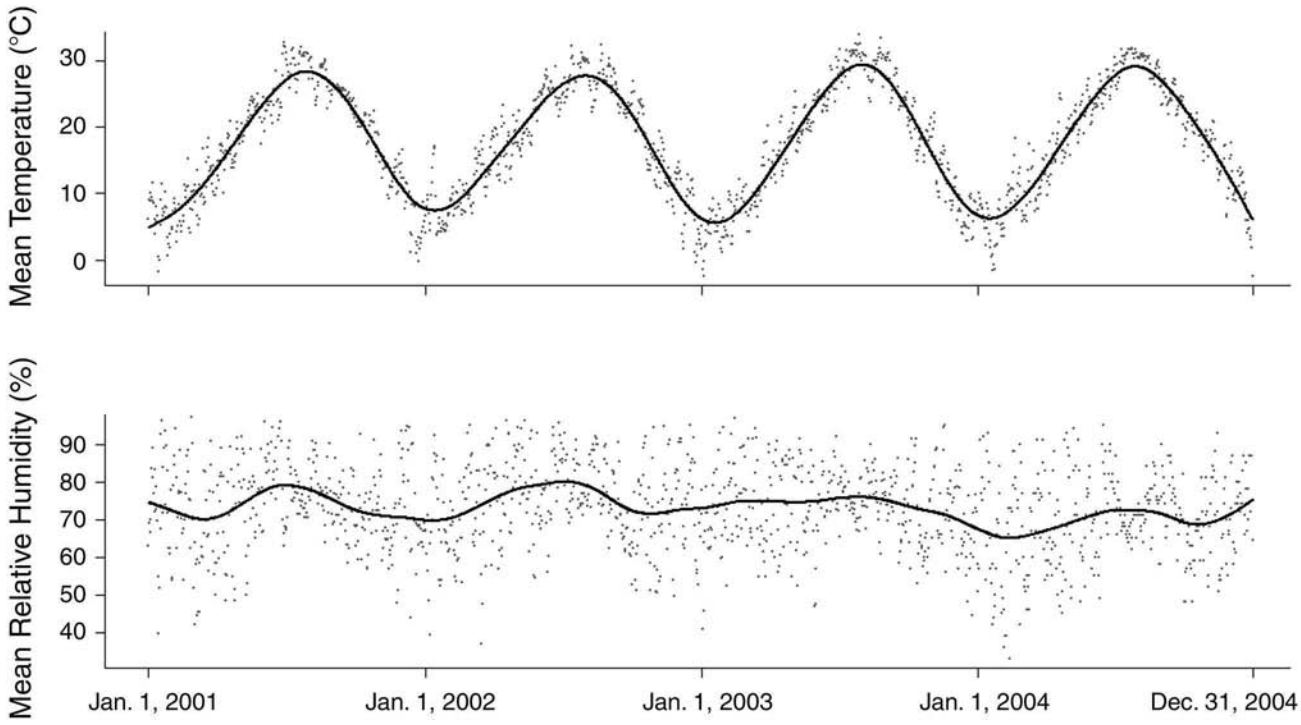


Figure 7. Time-series data of temperature and relative humidity in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year.

MAIN RESULTS

Establishment of Basic Models

Table 3 summarizes the values of degrees of freedom per year for time trend and lag days for autoregression terms in the basic models for each outcome. For example, 4, 4, and 5 df per year for time trend and 3, 2, and 4 lag days for autoregression terms were used in the basic models for all natural, cardiovascular, and respiratory mortality, respectively. As shown in Figure 8, no discernible seasonal or long-term trends were observed for the residuals of the basic models; the partial-autocorrelation-function performance of the residuals also met the criteria required in the Common Protocol used in the PAPA studies.

Effects by Cause of Death

Generally, positive and statistically significant associations were found between concentrations of the air pollutants PM_{10}, SO_2, NO_2, and O_3 and daily mortality from all natural causes and from cardiopulmonary diseases (Table 4). For example, an increase of 10 μg/m^3 in 2-day moving average concentrations of PM_{10}, SO_2, NO_2, and O_3 corresponded to 0.26% (95% CI, 0.14–0.37), 0.95% (95% CI, 0.62–1.28), 0.97% (95% CI, 0.66–1.27), and 0.31% (95% CI, 0.04–0.58) increases, respectively, in all natural mortality.

Table 3. Degrees of Freedom for Time Trend and Lag Days for Autoregression Terms in the Basic Models

Mortality Category	Degrees of Freedom per Year for Time Trend	Lag Days for Autoregression Terms
All natural	4	3
Male	4	2
Female	4	2
Ages 5–44	4	0
Ages 45–64	4	0
Ages ≥ 65	4	3
Cardiopulmonary disease	4	4
Cardiovascular disease	4	2
Stroke	4	0
Heart disease	4	0
Respiratory disease	5	4
Chronic obstructive pulmonary disease	5	4
Acute respiratory infection	4	0
Other causes		
Injury	4	0

Daily deaths caused by cardiovascular diseases were found to be significantly associated with PM_{10}, SO_2, and NO_2 ($P < 0.05$) and marginally significantly associated with O_3 ($P < 0.10$). Daily stroke mortality, a subcategory of cardiovascular diseases, was significantly associated with NO_2 and O_3 and marginally significantly associated with PM_{10} and SO_2. PM_{10}, SO_2, and NO_2 but not O_3 were significantly associated with daily deaths from heart diseases.

Respiratory deaths were found to be significantly associated with SO_2 and NO_2 and marginally significantly associated with PM_{10} but not with O_3. Similar associations were found for daily deaths from COPD. Daily deaths from acute respiratory infection were marginally significantly associated with PM_{10} and SO_2 but not with NO_2 or O_3.

The number of deaths caused by injury each day was used as a "control" mortality category because it was not believed to be associated with pollution. In fact, daily injury deaths were not significantly associated with any of the pollutants.

Exposure–Response Curves

Figure 9 shows the exposure–response relations between each pollutant and three mortality categories (all natural, cardiovascular, and respiratory).

For PM_{10}, *J*-shaped exposure–response relations were observed between PM_{10} and all three mortality categories. At concentrations greater than 70 μg/m^3, positive nonlinear relations were observed between PM_{10} and daily mortality due to all natural causes.

For SO_2, an almost linear relation was observed between SO_2 and all natural and cardiovascular mortality. For respiratory mortality, the curve tended to be flat and nonlinear. We did not observe any obvious threshold concentration below which SO_2 had no effect on mortality outcomes.

For NO_2, *J*-shaped nonlinear relations were observed between NO_2 and the mortality outcomes. At concentrations greater than 60 μg/m^3, almost linear relations were observed between NO_2 and daily mortality.

For O_3, the exposure–response relations with all natural and cardiovascular mortality were essentially linear at concentrations below 50 μg/m^3. The curves tended to flatten at higher concentrations. We did not observe any obvious threshold concentration below which O_3 had no effect on all natural and cardiovascular mortality. For respiratory mortality, no clear relation was observed.

The differences in the deviance between the linear and spline models were statistically significant only for the associations between respiratory mortality and SO_2 ($P < 0.01$) and NO_2 ($P = 0.02$) and marginally significant for the association between all natural mortality and PM_{10} ($P = 0.05$) (Table C.4 in Appendix C).

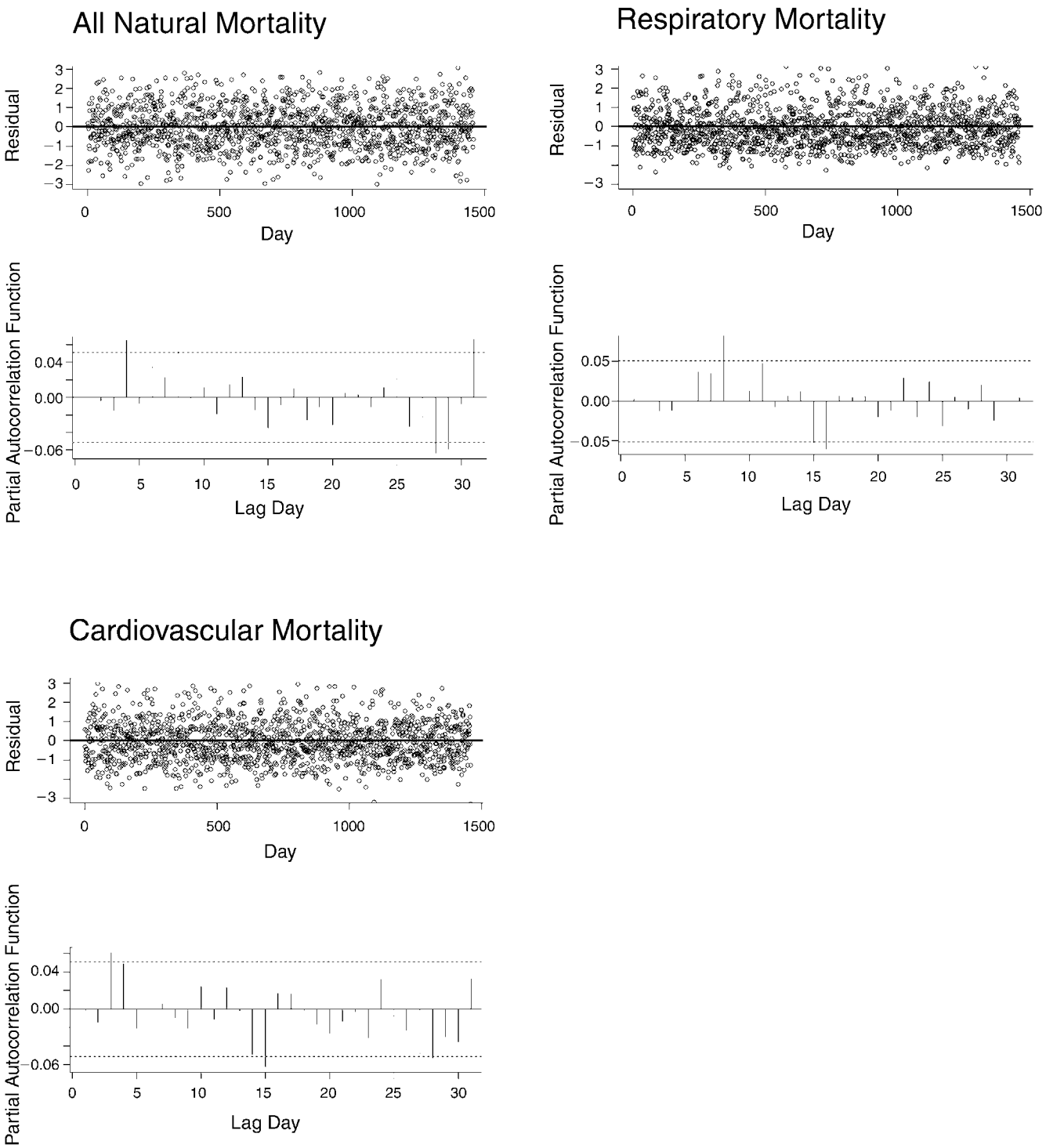


Figure 8. Residual plot and the plot of partial autocorrelation function of the residuals of the basic models for all natural, cardiovascular, and respiratory mortality. See Table 3 for degrees of freedom used for time trend and lag days for autoregression terms; 3 df were used for current-day temperature and for relative humidity.

Table 4. Percentage Changes in Daily Mortality Associated with Increases in Average Pollutant Concentrations in Shanghai, 2001–2004[a]

Mortality Category	Mean Daily Deaths	Percentage Change in Mortality[b]			
		PM_{10} Mean (95% CI)	SO_2 Mean (95% CI)	NO_2 Mean (95% CI)	O_3 Mean (95% CI)
All natural					
Total	119.0	0.26 (0.14 to 0.37)	0.95 (0.62 to 1.28)	0.97 (0.66 to 1.27)	0.31 (0.04 to 0.58)
Male	62.5	0.17 (0.03 to 0.32)	0.85 (0.43 to 1.28)	0.88 (0.49 to 1.28)	0.19 (−0.16 to 0.55)
Female	56.5	0.33 (0.18 to 0.48)	1.06 (0.62 to 1.51)	1.10 (0.69 to 1.51)	0.40 (0.03 to 0.76)
Ages 5–44	3.7	0.04 (−0.52 to 0.59)	1.21 (−0.47 to 2.91)	0.52 (−1.01 to 2.08)	−0.08 (−1.38 to 1.25)
Ages 45–64	15.5	0.17 (−0.11 to 0.45)	0.22 (−0.60 to 1.04)	0.64 (−0.11 to 1.40)	0.47 (−0.19 to 1.12)
Ages ≥ 65	99.6	0.26 (0.15 to 0.38)	1.01 (0.65 to 1.36)	1.01 (0.69 to 1.34)	0.32 (0.03 to 0.61)
Cardiopulmonary disease	58.5	0.29 (0.14 to 0.44)	1.11 (0.67 to 1.55)	1.08 (0.67 to 1.49)	0.28 (−0.10 to 0.65)
Cardiovascular disease	44.2	0.27 (0.10 to 0.44)	0.91 (0.42 to 1.41)	1.01 (0.55 to 1.47)	0.38 (−0.03 to 0.80)
Stroke	16.8	0.15 (−0.07 to 0.37)	0.57 (−0.08 to 1.23)	0.69 (0.08 to 1.29)	0.66 (0.12 to 1.21)
Heart disease	25.5	0.40 (0.13 to 0.66)	1.31 (0.53 to 2.10)	1.54 (0.82 to 2.27)	0.00 (−0.65 to 0.66)
Respiratory disease	14.3	0.27 (−0.01 to 0.56)	1.37 (0.51 to 2.23)	1.22 (0.42 to 2.01)	0.29 (−0.44 to 1.03)
Chronic obstructive pulmonary disease	12.2	0.21 (−0.09 to 0.51)	1.24 (0.33 to 2.16)	1.18 (0.34 to 2.02)	0.01 (−0.77 to 0.80)
Acute respiratory infection	1.0	0.95 (−0.07 to 1.98)	2.99 (−0.19 to 6.27)	1.73 (−1.14 to 4.69)	1.47 (−1.01 to 4.01)
Other causes of death					
Accidental deaths	6.4	0.15 (−0.32 to 0.62)	−0.12 (−1.50 to 1.29)	0.38 (−0.89 to 1.67)	0.62 (−0.50 to 1.75)
Noncardiopulmonary, nonaccidental deaths	60.5	0.23 (0.08 to 0.38)	0.81 (0.38 to 1.24)	0.89 (0.49 to 1.29)	0.35 (0.01 to 0.69)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages.

Single-Pollutant and Multiple-Pollutant Models

Table 5 compares the results from models that include one or two pollutants.

The estimated effects of PM_{10} on all natural, cardiovascular, and respiratory mortality in the one-pollutant model decreased and became insignificant in the two-pollutant models that included SO_2 or NO_2. When the two-pollutant model included O_3, the estimated effects were almost the same as those for PM_{10} alone.

The effects of SO_2 on all natural, cardiovascular, and respiratory mortality remained significant after adding PM_{10} and O_3 to the models; however, the effects decreased and became insignificant for all three mortality outcomes when NO_2 was added.

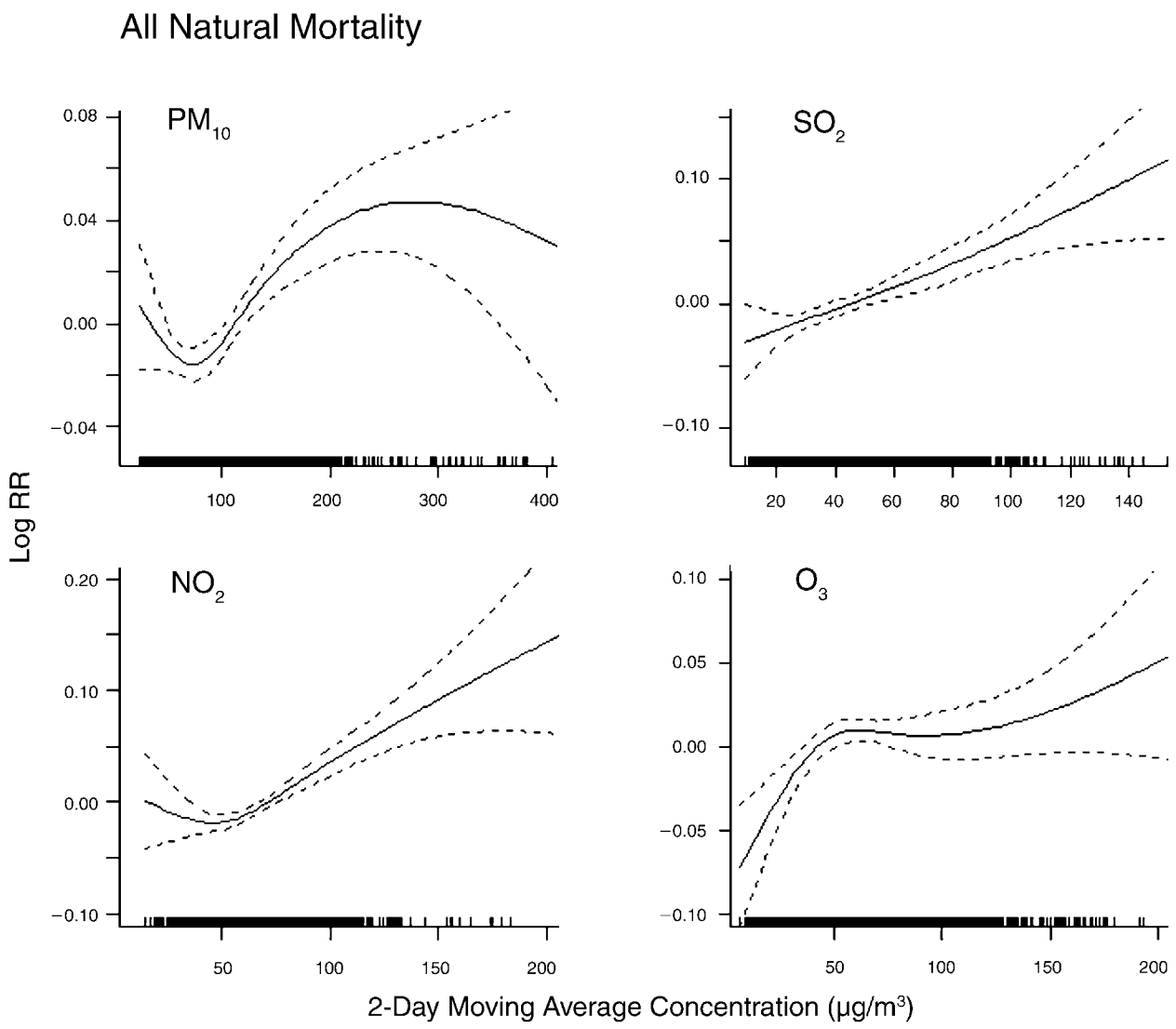
The effects of NO_2 on all natural and cardiovascular mortality did not change much when the other pollutants were added. The effects on respiratory mortality decreased and became insignificant after adding SO_2 but were not affected after adding PM_{10} or O_3.

The effects of O_3 on all natural and cardiovascular mortality did not change much after adding PM_{10} or SO_2; however the effects on all natural and cardiovascular mortality decreased substantially when NO_2 was added to O_3. We did not observe significant effects of O_3 on respiratory mortality in either the single-pollutant or multiple-pollutant models.

Effects by Sex, Age, and Education Level

The percentage increase in all natural mortality associated with higher concentrations of air pollutants varied by sex and age group (Table 4). The estimated effects of PM_{10} and O_3 on females were approximately twice those on males, but these sex differences were not significant. The effects of SO_2 and NO_2 on all natural mortality in females were slightly higher than in males.

Deaths in children under age 5 were few and were therefore excluded from the analysis. No significant effects of air pollution were observed in people aged 5–44 or 45–64 years. Among the elderly (≥ 65 years), effects of all four pollutants were significant and were approximately two to five times higher than among people aged 5–44 or 45–64 years, but the effects' between-age differences were insignificant (Table 4).



(*Figure continues next page*)

Figure 9. Smoothing plots for exposure–response relations between air pollutants and mortality risk (df = 3). The solid lines represent the estimated mean percentage of change in daily mortality associated with 10-µg/m^3 increases in 2-day moving average pollutant concentrations; dotted lines represent twice the standard error. The *x*-axes represent the 2-day average ("lag01") of pollutant concentrations (µg/m^3). Bars along the *x*-axes represent the number of observations used in the study. The *y*-axes represent log relative risk (RR). See Table 3 for degrees of freedom used for time trends and lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. Note differences in the scales of the *y*-axes.

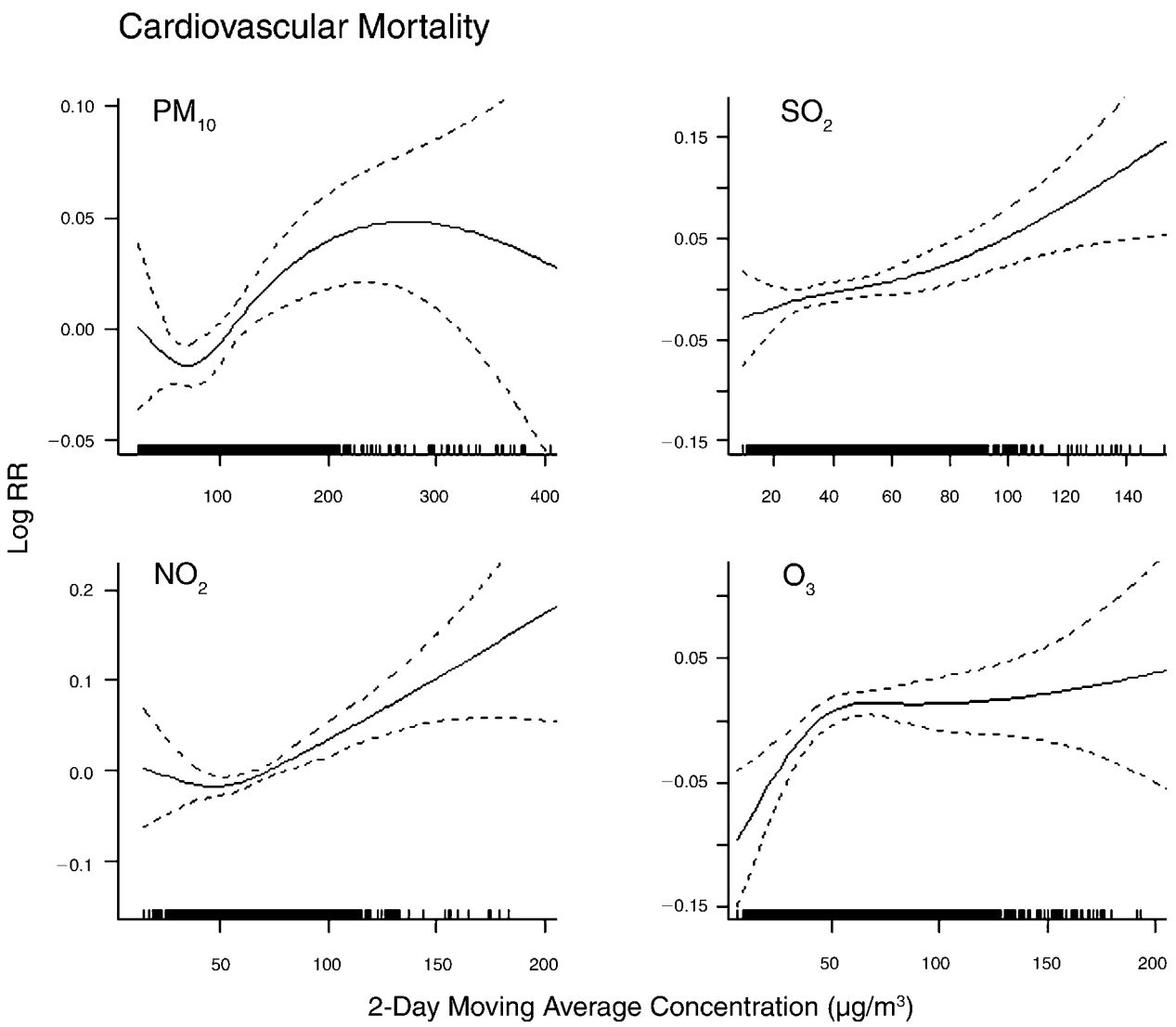


Figure 9 (*Continued*).

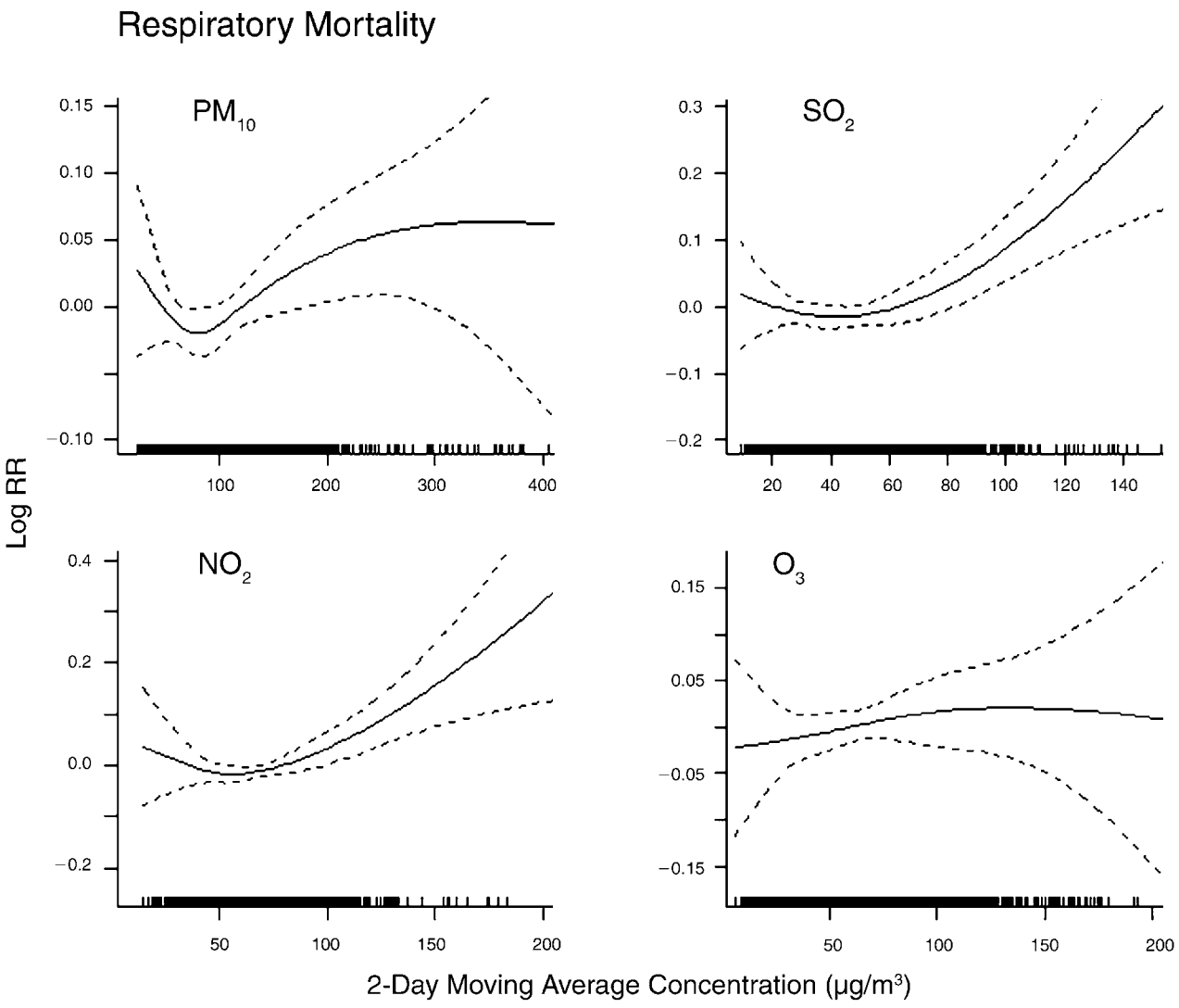


Figure 9 (*Continued*).

Table 5. Comparison of Percentage Increases in Mortality Outcomes Associated with Pollutant Concentrations When Using Models with One or Two Pollutants[a]

Model	Percentage Change in Mortality Outcomes[b]		
	All Natural Mean (95% CI)	Cardiovascular Mean (95% CI)	Respiratory Mean (95% CI)
PM_{10}			
Single-pollutant model	0.26 (0.14 to 0.37)	0.27 (0.10 to 0.44)	0.27 (−0.01 to 0.56)
Two-pollutant model			
PM_{10} + SO_2	0.08 (−0.07 to 0.22)	0.12 (−0.10 to 0.34)	−0.04 (−0.41 to 0.33)
PM_{10} + NO_2	0.01 (−0.14 to 0.17)	0.01 (−0.22 to 0.25)	−0.05 (−0.45 to 0.34)
PM_{10} + O_3	0.24 (0.13 to 0.35)	0.25 (0.08 to 0.42)	0.26 (−0.02 to 0.55)
SO_2			
Single-pollutant model	0.95 (0.62 to 1.28)	0.91 (0.42 to 1.41)	1.37 (0.51 to 2.23)
Two-pollutant model			
SO_2 + PM_{10}	0.80 (0.37 to 1.24)	0.69 (0.04 to 1.34)	1.45 (0.32 to 2.59)
SO_2 + NO_2	0.31 (−0.27 to 0.89)	0.05 (−0.83 to 0.93)	0.95 (−0.59 to 2.50)
SO_2 + O_3	0.92 (0.59 to 1.26)	0.88 (0.38 to 1.38)	1.35 (0.49 to 2.22)
NO_2			
Single-pollutant model	0.97 (0.66 to 1.27)	1.01 (0.55 to 1.47)	1.22 (0.42 to 2.01)
Two-pollutant model			
NO_2 + PM_{10}	0.94 (0.50 to 1.38)	0.98 (0.33 to 1.64)	1.32 (0.21 to 2.45)
NO_2 + SO_2	0.73 (0.19 to 1.27)	0.97 (0.16 to 1.80)	0.47 (−0.94 to 1.91)
NO_2 + O_3	0.94 (0.63 to 1.25)	0.97 (0.50 to 1.43)	1.20 (0.39 to 2.01)
O_3			
Single-pollutant model	0.31 (0.04 to 0.58)	0.38 (−0.03 to 0.80)	0.29 (−0.44 to 1.03)
Two-pollutant model			
O_3 + PM_{10}	0.19 (−0.08 to 0.47)	0.27 (−0.15 to 0.69)	0.17 (−0.57 to 0.92)
O_3 + SO_2	0.21 (−0.06 to 0.49)	0.30 (−0.12 to 0.71)	0.16 (−0.57 to 0.90)
O_3 + NO_2	0.13 (−0.15 to 0.41)	0.20 (−0.22 to 0.62)	0.08 (−0.66 to 0.83)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages.

Generally, people with a low level of education (illiterate or primary school) in Shanghai experienced greater air-pollution–related effects than those with a high level (middle school or above) (Table 6).

For all natural mortality, the effects of PM_{10}, SO_2, and NO_2 were significant in both educational groups. The effects of these three pollutants were 1.8 to 2 times greater among those with a low level of education; however, the differences in all natural mortality were significant only for NO_2. The effects of O_3 on all natural mortality were similar in both groups (Table 6).

For cardiovascular mortality, the effects of PM_{10} and NO_2 were significant or marginally significant ($P < 0.10$) in both groups; the effect of SO_2 was significant only in the group with low education; no significant effect of O_3 was seen in either group. The effects of all four pollutants were 1.3 to 1.9 times greater among those with low education. The between-group differences in cardiovascular mortality were not significant for any pollutant (Table 6).

For respiratory mortality, the effects of PM_{10}, SO_2, and NO_2 were significant only among those with low education and were several times greater in this group. The effect of O_3 on respiratory mortality was not significant in either group. The between-group differences in respiratory mortality were not significant for any pollutant (Table 6).

Effects by Season

In Shanghai, there were more deaths, higher concentrations of pollutants (except for O_3), and drier weather conditions in the cool season than in the warm season (Table C.3 in Appendix C).

Table 6. Percentage Changes in Daily Mortality Associated with Pollutant Concentrations When Stratified by Educational Attainment[a]

Mortality Category / Educational Attainment[b]	Mean Daily Deaths	Percentage Change in Daily Mortality[c]			
		PM_{10} Mean (95% CI)	SO_2 Mean (95% CI)	NO_2 Mean (95% CI)	O_3 Mean (95% CI)
All natural					
Low	67.3	0.33 (0.19 to 0.47)	1.19 (0.77 to 1.61)	1.27 (0.89 to 1.66)[d]	0.26 (−0.09 to 0.60)
High	42.1	0.18 (0.01 to 0.36)	0.66 (0.16 to 1.17)	0.62 (0.15 to 1.09)	0.30 (−0.11 to 0.71)
Cardiovascular					
Low	27.8	0.30 (0.10 to 0.51)	1.08 (0.47 to 1.69)	1.15 (0.58 to 1.72)	0.39 (−0.13 to 0.90)
High	16.4	0.23 (−0.03 to 0.50)	0.57 (−0.20 to 1.35)	0.73 (0.01 to 1.45)	0.26 (−0.38 to 0.91)
Respiratory					
Low	8.9	0.36 (0.000 to 72)	1.54 (0.43 to 2.66)	1.59 (0.57 to 2.62)	0.20 (−0.74 to 1.16)
High	5.4	0.02 (−0.43 to 0.47)	0.73 (−0.61 to 2.09)	0.34 (−0.89 to 1.60)	0.27 (−0.86 to 1.41)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Educational attainment expressed as Low, indicating low educational level (illiterate or primary school), or High, indicating high educational level (middle school or higher).
[c] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages.
[d] The difference between low and high educational attainment was significant ($P < 0.05$).

The effects of PM_{10} on all natural mortality were similar in both seasons (Table 7). The effects of SO_2 and NO_2 on all natural mortality were approximately two to three times greater in the cool season than in the warm season. The effect of O_3 was significant in both cool and warm seasons, and the magnitude of the O_3-associated increase in all natural mortality was approximately five times greater in the cool season than in the warm season. Between-season differences in all natural mortality were significant for NO_2 and O_3 but not for PM_{10} or SO_2.

For cardiovascular mortality, the effect of PM_{10} was similar in both seasons. For SO_2, NO_2, and O_3, the effects in the cool season were approximately three to four times greater than in the warm season. Between-season differences in cardiovascular mortality were insignificant for all four pollutants.

For the smaller category of respiratory mortality, the effects of PM_{10}, SO_2, and NO_2 were significant only in the cool season, and their between-season differences were significant. The effect of O_3 on respiratory mortality was insignificant in both seasons.

Table 7. Comparison of Percentage Increases in Daily Mortality Associated with Pollutant Concentrations by Season[a]

Mortality Category / Pollutant[b]	Percentage Increase per Season	
	Cool Season[c] Mean (95% CI)	Warm Season[d] Mean (95% CI)
All natural		
PM_{10}	0.26 (0.12 to 0.39)	0.20 (−0.02 to 0.42)
SO_2	1.10 (0.66 to 1.53)	0.57 (−0.03 to 1.18)
NO_2	1.24 (0.84 to 1.64)	0.46 (−0.07 to 0.98)[e]
O_3	1.19 (0.56 to 1.83)	0.22 (0.03 to 0.41)[e]
Cardiovascular		
PM_{10}	0.25 (0.05 to 0.45)	0.22 (−0.14 to 0.58)
SO_2	1.02 (0.40 to 1.65)	0.31 (−0.65 to 1.29)
NO_2	1.26 (0.68 to 1.84)	0.30 (−0.54 to 1.14)
O_3	1.42 (0.51 to 2.33)	0.32 (−0.05 to 0.69)
Respiratory		
PM_{10}	0.58 (0.25 to 0.92)	−0.28 (−0.93 to 0.38)[e]
SO_2	2.47 (1.41 to 3.54)	−1.13 (−2.86 to 0.62)[e]
NO_2	2.66 (1.67 to 3.65)	−1.37 (−2.86 to 0.15)[e]
O_3	0.94 (−0.60 to 2.50)	0.12 (−0.72 to 0.98)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages.
[c] November to April.
[d] May to October.
[e] The difference between warm season and cool season was significant ($P < 0.05$).

SENSITIVITY ANALYSES

Lag Structure of Pollutants and Temperature

In our analysis of the data, the patterns of lag effects of PM_{10}, SO_2, NO_2, and O_3 on all natural, cardiovascular, and respiratory mortality were similar (Figure 10). For single-day exposures, the risks were increased at lag 0 day, were maximal at lag 1 day to lag 2 days, and then declined; multi-day

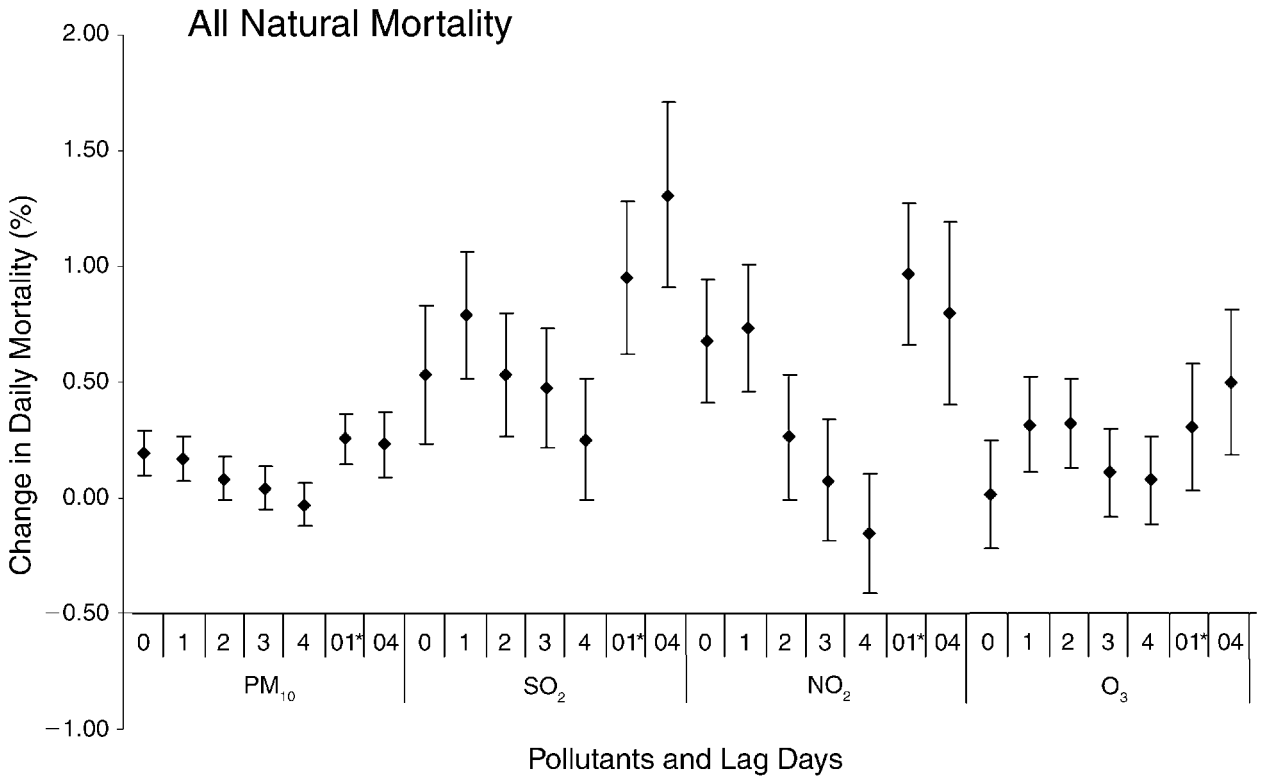


Figure 10. Percentage changes in daily mortality associated with 10-μg/m^3 increases in pollutant concentrations, using various lag-day structures for the pollutants. Asterisks indicate the lag-day values used in the main analysis. The term "01" indicates the 2-day moving average of pollutant concentrations on the current and previous day (lag 0–1 day [average]); the term "04" indicates the 5-day moving average of pollutant concentrations on the current and previous 4 days (lag 0–4 days [average]). See Table 3 for degrees of freedom used for time trend and lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. Note differences in the scales of the *y*-axes.

exposures (lag 0–1 day [average] and lag 0–5 days [average]) usually had greater effects than single-day exposures (lag 0 to 4 days). The effects of the four air pollutants on all natural, cardiovascular, and respiratory mortality were statistically significant for most of the lag days we examined.

The air pollution effects remained significant after controlling for extended temperatures (Figure 11). Compared with the effects when controlling for current-day (lag 0 day) temperature only, additional controlling for extended temperatures attenuated our effect estimates for PM_{10}, SO_2, and NO_2 but not for O_3.

Degrees of Freedom for Time Trend and Weather Conditions

Within a range of 4 to 12 df, a change in the number of degrees of freedom per year for time trend did not substantially affect the estimated effects of the pollutants (Figure 12), suggesting that our findings were relatively robust in this respect.

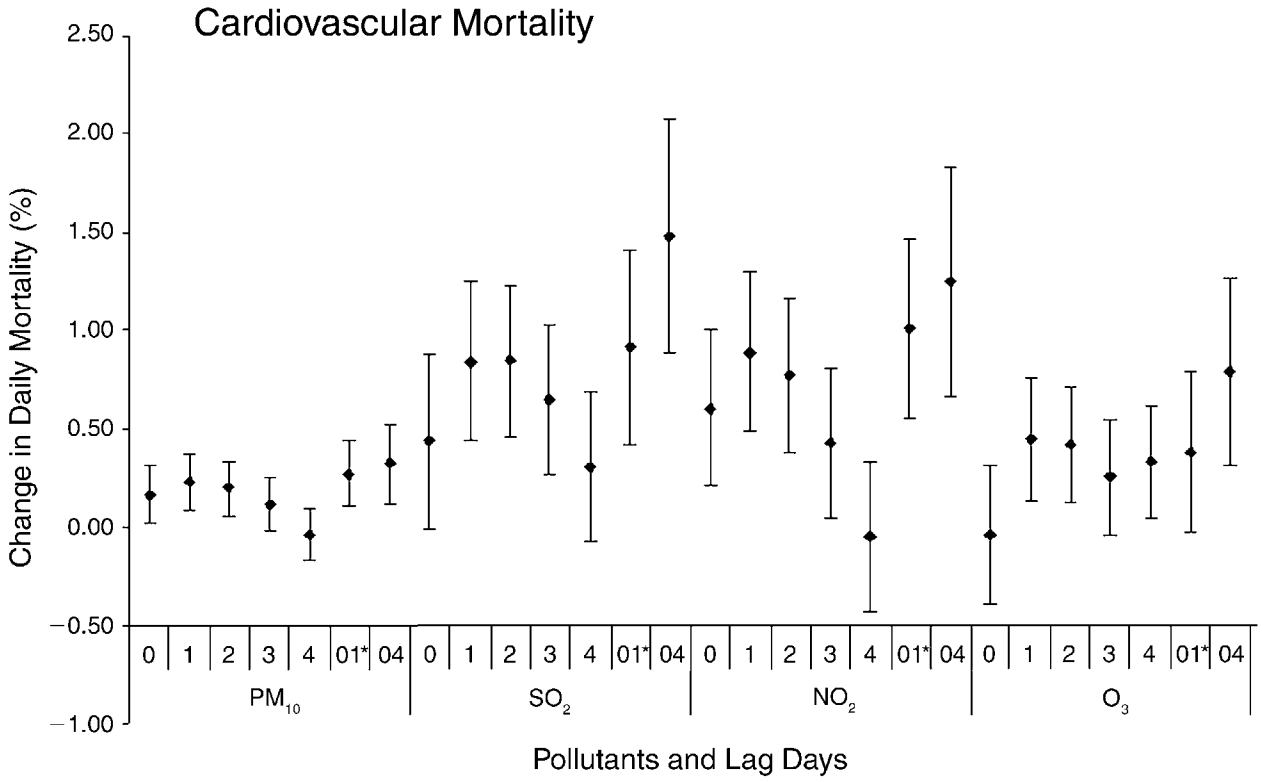
We also compared air pollution effects with alternative values for degrees of freedom for weather conditions. Within a range of 3 to 12 df, a change in the number of degrees of freedom for temperature and relative humidity resulted in almost identical estimated effects of air pollution on both all natural and cause-specific mortality (data not shown).

Statistical Approaches

Our effect estimates for the air pollutants were examined using several statistical models. Generally, natural-spline and penalized-spline models yielded similar regression results (Table 8).

Simple Averaging and Centering Methods for Air Pollution Data

Table 9 compares the effects of air pollution when pollutant-concentration data are derived from the simple averaging method and the centering method. We obtained almost identical results with both methods.



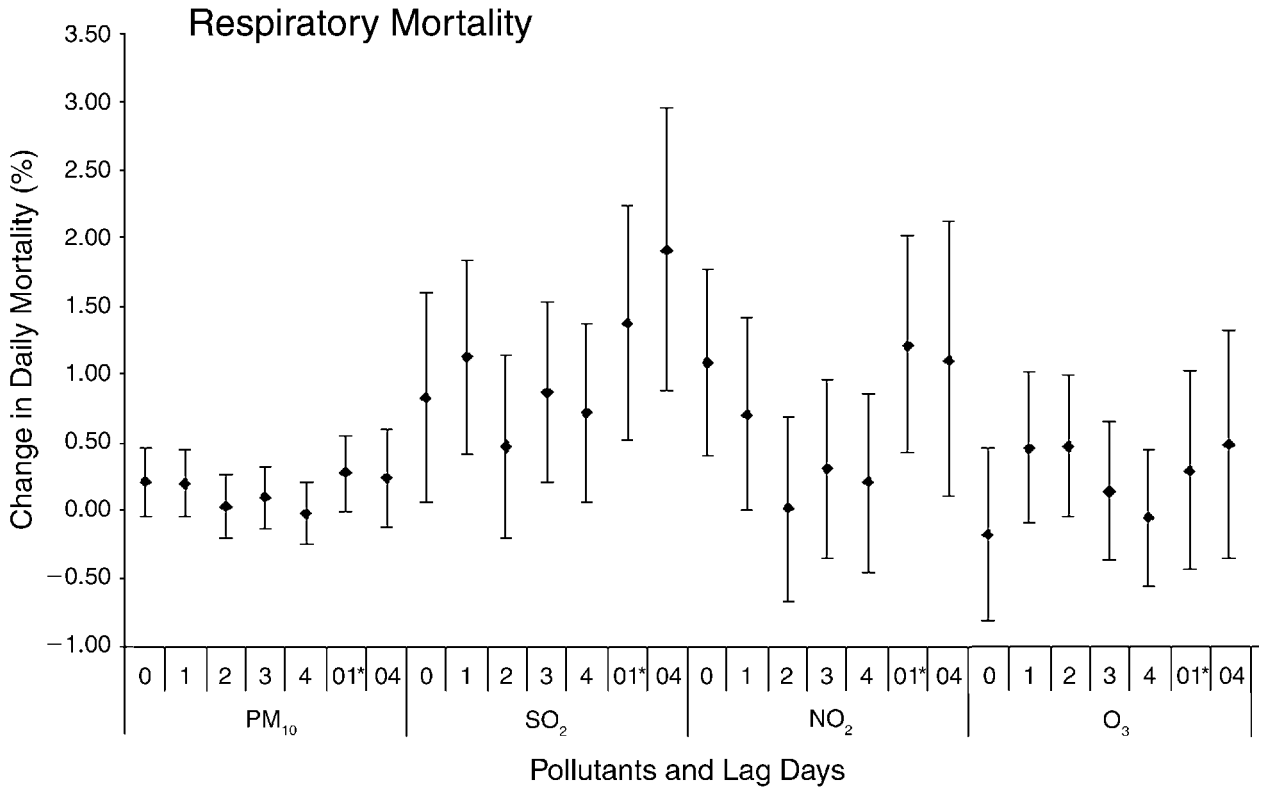


Figure 10 (*Continued*).

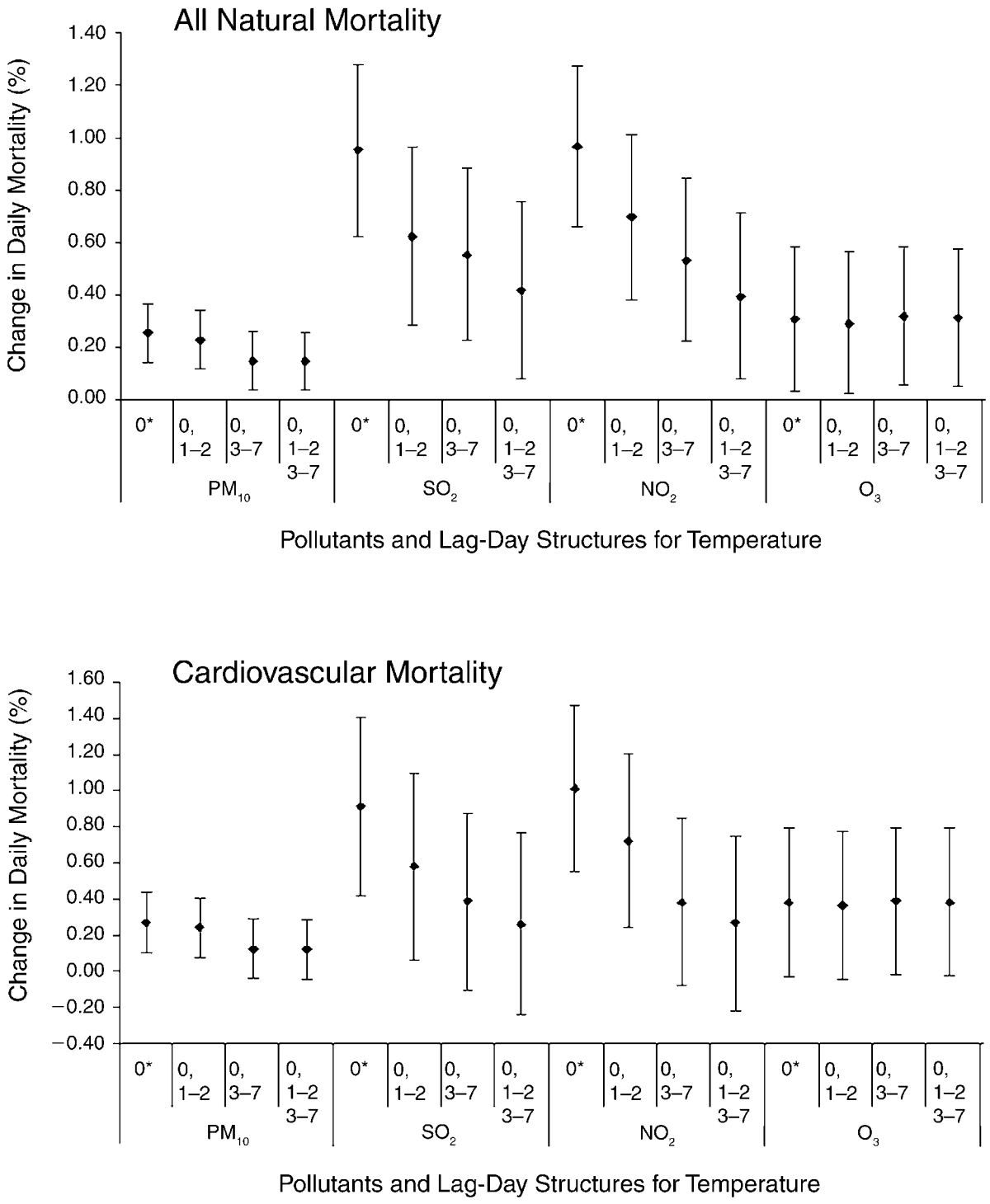


Figure 11. Percentage changes in daily mortality associated with 10-μg/m^3 increases in 2-day moving average pollutant concentrations, using various lag-day structures for temperature. Asterisks indicate the lag-day values used in the main analysis, i.e., lag 0 day. See text for detailed description of lag-day structures. See Table 3 for degrees of freedom used for time trend and lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. Current-day relative humidity (lag 0 day) was used. Note differences in the scales of the *y*-axes.

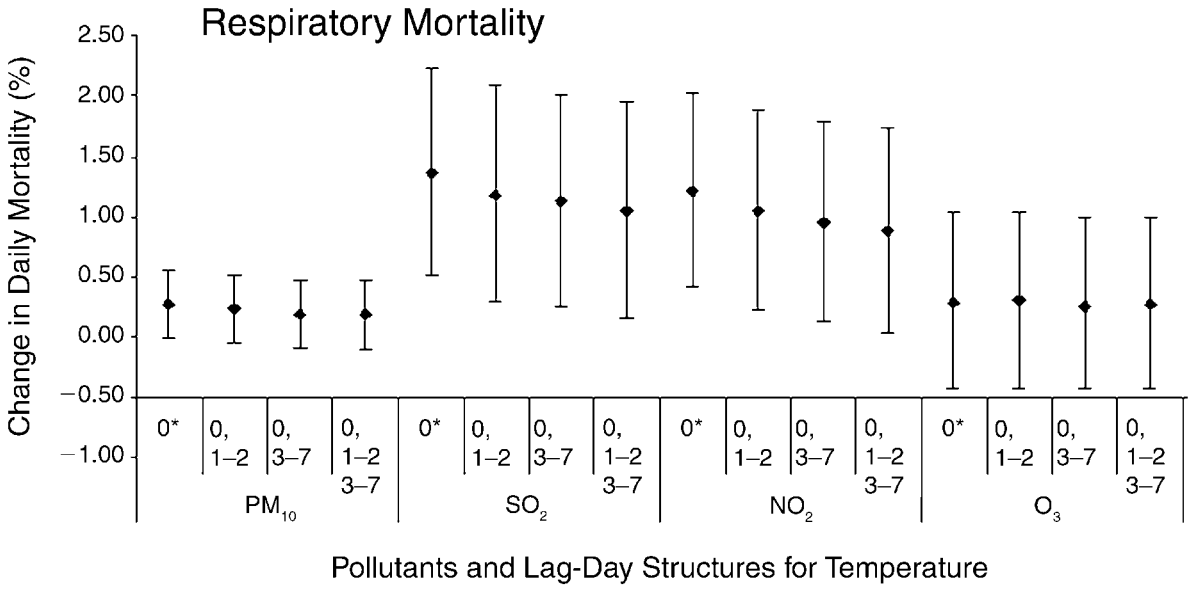


Figure 11 (*Continued*).

Table 8. Comparison of Effect Estimates of Daily Mortality Derived from Natural-Spline and Penalized-Spline Models[a]

Mortality Category / Pollutant	Percentage Increase per Statistical Model	
	Natural Spline Mean (95% CI)	Penalized Spline Mean (95% CI)
All natural		
PM_{10}	0.26 (0.14 to 0.37)	0.26 (0.15 to 0.37)
SO_2	0.95 (0.62 to 1.28)	0.96 (0.63 to 1.28)
NO_2	0.97 (0.66 to 1.27)	0.97 (0.67 to 1.27)
O_3	0.31 (0.04 to 0.58)	0.33 (0.06 to 0.59)
Cardiovascular		
PM_{10}	0.27 (0.10 to 0.44)	0.28 (0.12 to 0.45)
SO_2	0.91 (0.42 to 1.41)	0.96 (0.48 to 1.45)
NO_2	1.01 (0.55 to 1.47)	1.03 (0.59 to 1.48)
O_3	0.38 (−0.03 to 0.80)	0.43 (0.02 to 0.83)
Respiratory		
PM_{10}	0.27 (−0.01 to 0.56)	0.27 (−0.01 to 0.56)
SO_2	1.37 (0.51 to 2.23)	1.35 (0.51 to 2.20)
NO_2	1.22 (0.42 to 2.01)	1.19 (0.41 to 1.97)
O_3	0.29 (−0.44 to 1.03)	0.29 (−0.42 to 1.02)

[a] Effect estimates are percentage increases of daily mortality associated with 10-μg/m^3 increases in 2-day moving averages of pollutant concentrations. See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.

Table 9. Comparison of Percentage Increases in Daily Mortality Associated with Pollutant Concentrations Derived Using Simple Averaging and Centering[a]

Mortality Category / Pollutant	Percentage Increase	
	Simple Averaging Mean (95% CI)	Centering Mean (95% CI)
All natural		
PM_{10}	0.26 (0.14 to 0.37)	0.26 (0.14 to 0.37)
SO_2	0.95 (0.62 to 1.28)	0.95 (0.62 to 1.28)
NO_2	0.97 (0.66 to 1.27)	0.97 (0.66 to 1.27)
O_3	0.31 (0.04 to 0.58)	0.30 (0.03 to 0.57)
Cardiovascular		
PM_{10}	0.27 (0.10 to 0.44)	0.27 (0.11 to 0.44)
SO_2	0.91 (0.42 to 1.41)	0.91 (0.42 to 1.41)
NO_2	1.01 (0.55 to 1.47)	1.01 (0.56 to 1.47)
O_3	0.38 (−0.03 to 0.80)	0.37 (−0.04 to 0.78)
Respiratory		
PM_{10}	0.27 (−0.01 to 0.56)	0.27 (−0.01 to 0.56)
SO_2	1.37 (0.51 to 2.23)	1.37 (0.51 to 2.23)
NO_2	1.22 (0.42 to 2.01)	1.20 (0.41 to 2.00)
O_3	0.29 (−0.44 to 1.03)	0.29 (−0.44 to 1.02)

[a] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages. See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.

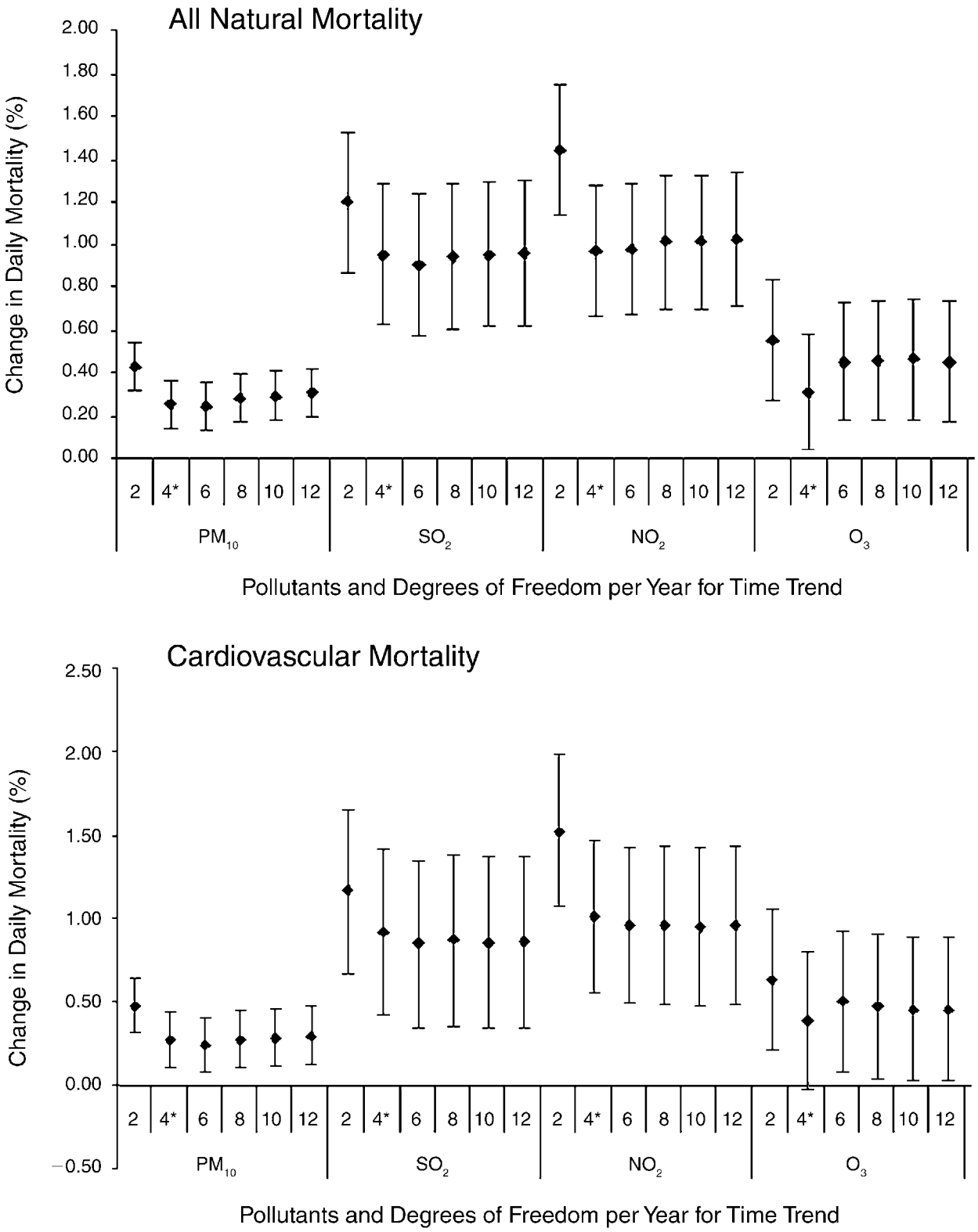


Figure 12. Percentage changes in daily mortality associated with 10-μg/m^3 increases in 2-day moving average pollutant concentrations, using various degrees of freedom per year for time trend. Asterisks indicate the degrees of freedom used in the main analysis (i.e., lag 4 days). See Table 3 for lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. Note differences in the scales of the *y*-axes.

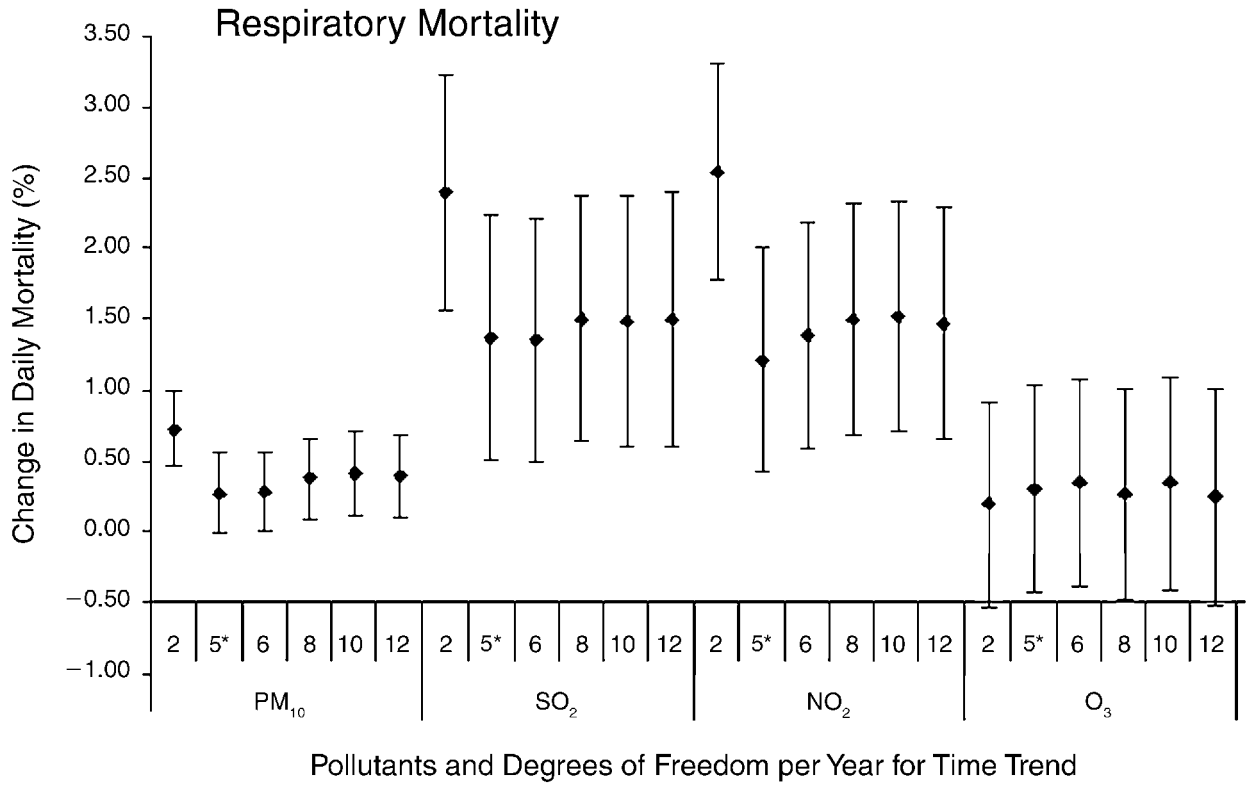


Figure 12 (*Continued*).

DISCUSSION AND CONCLUSIONS

SUMMARY OF RESULTS

The results of this time-series study showed that the outdoor air pollutants PM_{10}, SO_2, NO_2, and O_3 were associated with daily mortality from all natural causes and from cardiopulmonary diseases in Shanghai in 2001–2004. An increase of 10 μg/m^3 in 2-day moving average concentrations of PM_{10}, SO_2, NO_2, and O_3 corresponded to 0.26% (95% CI, 0.14–0.37), 0.95% (95% CI, 0.62–1.28), 0.97% (95% CI, 0.66–1.27), and 0.31% (95% CI, 0.04–0.58) increases, respectively, in all natural daily mortality. Our risk estimates were similar in magnitude to those found in studies from other parts of the world. After adjustment for PM_{10}, significant effects of the gaseous pollutants SO_2 and NO_2 on daily mortality were also found. These findings were generally insensitive to varying the model specifications, such as lag structures for pollutants, degrees of freedom for time trend and weather conditions, statistical approaches, and averaging methods for pollutant concentrations. Significant effects of air pollution were found at concentrations below those mandated by China's air-quality standards (150, 150, and 80 μg/m^3 for daily average concentration of PM_{10}, SO_2, and NO_2, respectively). Our analysis also provided preliminary, but not conclusive, evidence that females, older people, and people with a low level of education might be more vulnerable to air pollution than males, younger people, and people with a high level of education. The associations between air pollution and daily mortality appeared to be more pronounced in the cool season than in the warm season.

These findings might have implications for Shanghai's environmental and social policies as well as for the steps its government might take to protect the city's population in general and sensitive subpopulations in particular. These findings should also shed more light on the differences between air pollution health effects found in Western countries and in China, such as the possibility suggested by our study that in Shanghai the SO_2 and NO_2 can cause adverse health effects independent of PM_{10}.

COMPARISON WITH EARLIER STUDIES

Our study used 24-hour mean concentrations of PM_{10}, SO_2, and NO_2 and maximum 8-hour mean concentrations of O_3. We therefore discuss the first three pollutants and then O_3 separately.

As stated above, an increase of 10 μg/m^3 in 2-day moving average concentrations of PM_{10}, SO_2, and NO_2 was found to correspond to increases in all natural daily mortality. In a previous meta-analysis of 109 time-series studies of air pollution and daily mortality, most of which were conducted in North America and Europe, Stieb and colleagues (2002) estimated that a 10-μg/m^3 change in concentrations of PM_{10}, SO_2, and NO_2 was associated with 0.64% (95% CI, 0.48–0.77), 0.36% (95% CI, 0.28–0.44), and 0.61% (95% CI, 0.46–0.76) increases, respectively, in all natural daily mortality (in single-pollutant models). A meta-analysis of Asian literature by HEI (2004) estimated that a 10-μg/m^3 increase in PM_{10} and SO_2 was associated with 0.49% (95% CI, 0.23–0.76) and 0.52% (95% CI, 0.30–0.74) increases, respectively, in all natural mortality. Another meta-analysis of PM_{10} literature based on Chinese studies estimated that a 10-μg/m^3 increase in PM_{10} corresponded to a 0.44% (95% CI, 0.13–0.76) increase in all natural mortality (Kan et al. 2005). In addition, recent large-scale multicity time-series studies, which could avoid the potential publication bias of meta-analyses, estimated that a 10-μg/m^3 increase in PM_{10} (lag 1 day) corresponded to an increase in all natural mortality of 0.41% (95% CI, 0.23–0.59) in Europe (HEI 2003), 0.21% (95% CI, 0.09–0.33%) in the United States (Dominici et al. 2005), and 0.70% (95% CI, 0.26–1.14) in Canada (HEI 2003).

In our study, we estimated that a 10-μg/m^3 increase in 2-day moving average concentrations of O_3 corresponded to a 0.31% (95% CI, 0.04–0.58) increase in all natural mortality. To compare this estimate with those of other studies, all the estimates have to be based on the same exposure measure of O_3 concentrations (such as the maximum 8-hour mean used here) and the same lag structure. Most previous meta-analyses and time-series analyses used 1-hour maximum, 8-hour maximum, or daily (24-hour) mean concentrations as O_3 measures (Stieb et al. 2002, 2003; Bell et al. 2004, 2005; Ito et al. 2005; Levy et al. 2005). However, a recent multicity study of 23 European cities found a 0.34% (95% CI, 0.27–0.50) increase in all natural mortality associated with a 10-μg/m^3 increase in the average of the daily maximum 8-hour average on the same day (lag 0 day) and previous day (lag 1 day) (Gryparis et al. 2004), which is roughly comparable to our estimate. The magnitude of our estimate is also comparable to that of a study conducted in Hong Kong using maximum 8-hour mean O_3 concentrations (Wong et al. 2001).

Generally, the magnitudes of our estimates of all natural daily mortality for PM_{10}, SO_2, NO_2, and O_3 in Shanghai are comparable with those of previous single-city and multicity studies and meta-analyses worldwide. Some small differences in estimates from different studies might reflect differences in the analytic techniques used even apart from differences in the study sites. Some earlier estimates of associations between air pollution and acute health effects might be incorrect because of previously unrecognized problems with generalized additive models in S-Plus statistical software (Dominici et al. 2002; Ramsay et al. 2003). Recent studies have shown that the choice of statistical models and of parameter settings in the models (e.g., the selection of degrees of freedom and convergence criteria) can substantially influence effect estimates in time-series studies (Peng et al. 2006). In addition, characteristics of the study sites and their subjects — such as indoor air pollution, the indicators of potential sensitivity of the local population to air pollution (e.g., socioeconomic status, age, and smoking rates), outdoor air pollution concentrations, weather patterns, and especially the composition of the pollution mixture — might affect the magnitudes of exposure–response relations. Compared with air pollution concentrations in developed countries, concentrations in China are much higher. At high concentrations, increases in the risk of death per unit increase in pollutant concentration tend to be smaller, possibly because vulnerable subjects might already have died before the concentrations reached a maximum (Wong et al. 2001). A study in Hong Kong, discussed in the section below, reported that the exposure–response curve of the association between PM_{10} and cardiopulmonary admissions tended to flatten at concentrations greater than 80 μg/m^3 (Wong et al. 2002). In addition, the composition of the motor-vehicle fleet in Europe and North America might be different from that in China. This, together with other differences, such as the widespread use of coal in China, implies that the air pollution mixture might not be the same in China as in the other areas where most time-series studies have been conducted.

SHAPE OF EXPOSURE–RESPONSE RELATIONS

The shape of exposure–response relations is crucial for public-health assessment, and there has been a growing demand for reliable curves. Previous multicity studies in the United States and Europe have explored the exposure–response relation between particulate air pollution and mortality, and generally supported a linear association without threshold (Daniels et al. 2000; Samoli et al. 2005). However, these relations might vary by location, depending on such factors as the air pollution mixture, climate, and health of the study population (Samoli et al. 2005).

In Shanghai, nonlinear exposure–response relations were observed for some pollutant–mortality associations (Figure 9). These nonlinear relations remained after adjustment for extended temperatures, varied values of degrees

of freedom, or changes in the lag structure of pollutant concentrations (data not shown). Similar nonlinear exposure–response relations have been observed in Hong Kong (Wong et al. 2002), London (Samoli et al. 2005), and some southern European cities (Samoli et al. 2005). Residual confounding cannot be excluded as an explanation for the observed nonlinearity; given the high correlation between PM_{10}, SO_2, and NO_2, exposure–response relations for single pollutants might be attributable to the effects of the correlated pollutants.

Our analysis of exposure–response relations was limited by the use of data from a single location. Future multicity studies in China should address this limitation and further explore the role of effect modifiers in explaining the heterogeneity across cities in the shapes of exposure–response relations between air pollution and mortality.

COMPARISON OF ASSOCIATIONS WITH GASEOUS AND PARTICULATE POLLUTANTS

In our study, associations were found not only for PM_{10}, but also for gaseous pollutants. Although this might have been caused by the high correlation between PM_{10}, SO_2, and NO_2 (Table 2), the estimates for SO_2 and NO_2 remained significant after adjustment for PM_{10} (Table 5 and Tables C.1 and C.2 in Appendix C), suggesting that these gaseous pollutants might play a role in the health effects of the city's air pollution mixture. Although it is well known that SO_2 and NO_2 contribute to PM formation, our analysis suggested that they are also independently related to daily mortality.

Although the strongest evidence for an association between outdoor air pollutants and adverse health effects is for particulate pollutants (e.g., PM_{10}), many researchers have reported associations for gaseous pollutants as well. Several multicity analyses, for example, demonstrated independent effects of SO_2, NO_2, and O_3 on daily mortality in Europe (Katsouyanni et al. 1997; Samoli et al. 2006), the United States (Bell et al. 2004), and Canada (Burnett et al. 2004).

Independent health effects have previously been reported for SO_2. In China, Xu and colleagues (1994) found that it was SO_2, not TSP, that was associated with daily mortality in Beijing. Venners and colleagues (2003) found that SO_2 had significant effects on daily mortality in Chongqing even after adjustment for $PM_{2.5}$, while the effects of $PM_{2.5}$ decreased after adjustment for SO_2. Zhang and colleagues (2000) found that the concentration of SO_4^{2-} in the air was closely associated with mortality from chronic diseases in Beijing. Similar independent effects of SO_2 were found in a multicity study in Europe (Katsouyanni et al. 1997). The most convincing evidence of the independent health effects of SO_2 thus far is from an intervention study in Hong Kong, which showed that the SO_2 resulting from the combustion of sulfur-rich fuels had a direct effect on cardiopulmonary deaths (Hedley et al. 2002).

Of the pollutants examined in Shanghai, only NO_2 remained significantly associated with all natural and cardiovascular mortality after adjustment for copollutants. This result is consistent with that of a recent multicity study in Europe (APHEA-2) (Samoli et al. 2006). However, in an analysis of 20 cities in the United States in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), no consistent pattern of association between all natural mortality and NO_2 was found (Samet et al. 2000c). The difference between the APHEA-2 and NMMAPS findings might be attributable to the variety of air pollution sources and mixtures in Europe and the United States (Samoli et al. 2006).

Another gaseous pollutant that merits attention is O_3, because even though it has become a widespread pollutant in many Chinese cities, it has seldom been studied. Increases in O_3 concentrations primarily reflect the increased numbers of motor vehicles in these cities. (Motor-vehicle emissions are a major source of precursor hydrocarbons and NO_2.) Our finding, interpreted in the context of the already extensive epidemiologic and toxicologic evidence on O_3 (Bell et al. 2004, 2005; Ito et al. 2005; Levy et al. 2005), indicated that this widespread pollutant adversely affects mortality.

The biologic mechanism by which exposure to gaseous pollutants might increase mortality is not well understood but has received considerable attention. SO_2, for example, is a known respiratory irritant and bronchoconstrictor, but its effects seem limited to patients with asthma and bronchitis, although sensitivity to exposure varies widely (Katsouyanni et al. 1997; Nowak et al. 1997). It has been suggested that the principal mechanisms underlying the toxicity of NO_2 involve lipid peroxidation in cell membranes and various actions of free radicals (Kelly et al. 1996). NO_2 can also induce airway inflammation, although probably restricted to smaller airways and the terminal bronchioles (Blomberg et al. 1997).

Most epidemiologic studies of air pollution use ambient pollutant concentrations as surrogates for personal exposure. It is therefore possible that the observed health effects attributed to SO_2 and NO_2 are actually caused by exposures to fine particles or traffic-related emissions (Sarnat et al. 2001, 2005). Seaton and Dennekamp (2003), for example, suggested that NO_2 is a surrogate for ultrafine-particle (UFP) number, and so there is a possibility that the effect we observed for NO_2 might be due to some other unmeasured pollutant such as UFP. The observed effects of O_3 might also reflect the risk from the photochemical pollution mixture

more generally. Based on our findings, we cannot conclude that these gaseous pollutants are surrogates for particulate pollution or that they have direct effects on mortality. The role of exposure to outdoor gaseous pollutants should be investigated further.

POTENTIAL MODIFIERS OF THE HEALTH EFFECTS OF AIR POLLUTION

Although the associations between outdoor air pollution and adverse health effects are now well established, it is still unknown which groups of people are more sensitive than others. The U.S. National Academy of Sciences pointed out that it is important to understand the characteristics of individuals who are at increased risk of adverse health effects caused by outdoor air pollution (National Research Council 1998).

We found greater effects of air pollution on all natural mortality in females than in males, but the differences were statistically insignificant. Results of earlier studies on sex-specific acute effects of outdoor pollution were discordant. Ito and Thurston (1996), for example, found the highest risk of mortality related with air pollution exposure among black women in Cook County, Illinois. Hong and colleagues (2002) found that elderly women were most susceptible to the adverse effects of PM_{10} on the risk of acute mortality from stroke in Seoul, South Korea. However, Cakmak and colleagues (2006) found that sex did not modify the hospitalization risk of cardiac diseases caused by air pollution exposure in 10 large Canadian cities. The reasons for our sex-specific observations are unclear and deserve further investigation. In Shanghai, females have a much lower smoking rate than males (0.6% in females versus 50.6% in males) (Xu 2005). One study suggested that the effects of air pollution might be greater in nonsmokers compared with smokers (Künzli et al. 2005). Similarly, the oxidative and inflammatory effects of smoking in males may so dominate the pathways leading to adverse effects that exposure to air pollution in males may not enhance effects that utilize the same pathophysiologic pathways. In addition, compared with males, females in Shanghai had less education — the percentage of people with a low level of education (illiterate or primary school) was 73.9% in females and 41.0% in males — meaning that lower socioeconomic status might have contributed to the greater effects of air pollution observed in females. Moreover, females also have slightly greater airway reactivity and smaller airways than males (Yunginger et al. 1992), meaning that dose–response relations might be detected more easily in females than in males.

As in a few other studies (Gouveia and Fletcher 2000; Katsouyanni et al. 2001), we found significant health effects of air pollution only in the elderly (older than 65 years age group). Two age groups, the elderly and the very young, are presumed to be at greater risk for air-pollution–related effects (Gouveia and Fletcher 2000; Schwartz 2004). The small numbers of deaths in the very young (0–4 years age group) in our study limited our power to detect effects of air pollution even if they existed. For the elderly, preexisting respiratory or cardiovascular conditions are more prevalent than in younger age groups; there is thus some overlap between potentially susceptible groups of older adults and people with heart or lung diseases. Considering the aging population and the changes in disease patterns in Shanghai (from traditional infectious diseases to chronic noncommunicable diseases such as cardiopulmonary diseases), the effects of air pollution on public health could be substantial in the city. For example, according to a recent census, people over 65 years of age accounted for 11.9% of the population of Shanghai, which means that a large proportion of the city's residents are in the group likely to be at increased risk for air-pollution–related health effects.

It has long been known that socioeconomic status can affect health indicators and mortality rates (Mackenbach et al. 1997). Recently, studies have begun to examine the role of socioeconomic status in the vulnerability of subpopulations to outdoor air pollution, especially for PM and O_3, although the results remain inconsistent (O'Neill et al. 2003). In a recent review article, Laurent and colleagues (2007) found that studies using socioeconomic characteristics measured at somewhat coarse geographic resolutions (i.e., city- or county-wide) often found no effect modification among subpopulations but that most studies using characteristics measured at the finer level of the individual subject found that pollution affected disadvantaged subjects more. Our study, which used the level of education of individuals as a measure of socioeconomic status, found that people with a low level of education appeared to be more sensitive to outdoor air pollution than those with a high level of education. The difference was statistically significant only for the effect of NO_2 on all natural mortality, and thus the possibility of having positive findings only by chance could not be ruled out.

Socioeconomic factors such as education level might modify the health effects of outdoor air pollution in several ways. People with lower socioeconomic status might be more sensitive to health hazards related to air pollution because they are more likely to have a greater prevalence of preexisting diseases that confer a greater risk of death in association with exposure to pollution. They might also be receiving inferior medical treatment for preexisting diseases. Disadvantaged living conditions might also contribute to the effect modification. People with lower socioeconomic status might have poor nutritional status, for

example, more limited access to fish, fresh fruits, and vegetables, resulting in reduced intake of antioxidant polyunsaturated fatty acids and vitamins that might protect against adverse consequences of exposure to air pollution (Romieu et al. 2005). In addition, exposure patterns might contribute to the effect modification by socioeconomic status. People with lower socioeconomic status are more likely to live close to busy roadways and to have co-exposures caused by poor housing or occupation. Finally, as Jerrett and colleagues (2004) pointed out, people with less education are less mobile and therefore experience less exposure-measurement error, thereby reducing bias toward the null.

It should be emphasized that our findings provided preliminary, but not conclusive, evidence that sex, age, and socioeconomic status might modify air pollution effects in Shanghai. The confidence limits around the risk estimates for these subpopulations were wide and overlapping. Most statistical tests showed that the differences between strata of potential effect modifiers were insignificant. The potential multiple testing requires caution in interpreting our analysis of the subpopulations. Residual confounding cannot be excluded as an alternative explanation for the observed effects. For these reasons, it is difficult to draw conclusions about the effects based on the current analysis. Further research will be needed to gain insights into the modification of air pollution health effects by individual sociodemographic characteristics (such as sex, age, and socioeconomic status) in China.

EFFECTS BY SEASON

The effects of outdoor air pollution on mortality outcomes appeared to be more evident in the cool season than in the warm season in Shanghai. This finding is consistent with those of several prior studies in Hong Kong and Athens (Touloumi et al. 1996; Wong et al. 1999, 2001) but is in conflict with others reporting greater effects in the warm season (Anderson et al. 1996; Bell et al. 2005; Nawrot et al. 2007).

In Shanghai, concentrations of PM_{10}, SO_2, and NO_2 were higher and more variable in the cool season than in the warm season (Table C.3 of Appendix C). Because these three pollutants were highly correlated (Table 2), the greater effects observed for any one of them during the cool season might have been caused by the fact that concentrations of the other two were higher, too, at the time. Concentrations of O_3 were higher in the warm season than in the cool season, and the O_3 exposure–response relation had a flatter slope at higher concentrations than at lower concentrations; the effect of O_3 on daily mortality in the warm season may thus be higher than in the cool season (Figure 9).

Exposure patterns might contribute to our season-specific observations. During the warm season, Shanghai residents use air conditioning more frequently because of the season's relatively higher temperatures and humidity, thus reducing their exposure indoors. In a recent survey of 1106 families in Shanghai, for example, 32.7% never turn on their air conditioner in winter versus 3.7% in summer (Long et al. 2007). In addition, frequent rains in the warm season might reduce time outdoors and thus personal exposure. In contrast, the cool season in Shanghai is drier and less variable, so people are more likely to open their windows and go outdoors. Nevertheless, the fact that a consistently significant health effect of air pollution was observed only in the cool season in two subtropical Asian cities (Shanghai and Hong Kong) (Wong et al. 1999, 2001) suggests that the interaction between air pollution exposure and season might vary by location.

LIMITATIONS

Our monitoring results, like those of most time-series studies, were simply averaged across the various stations as a surrogate for the general population's exposure to air pollution. This averaging method might raise a number of issues, given that pollutant measurements can differ from monitoring location to location (Appendix B) and that ambient measurements differ from personal-exposure measurements (Sarnat et al. 2005). Numerous factors, such as air-conditioning use and ventilation-exchange rates between indoor and outdoor air, can affect the results from monitoring stations as surrogates for personal exposure (Janssen et al. 2002).

Although we believe it is reasonable to consider these measurements as good surrogates for the population's true exposure, the differences between surrogate values and personal-exposure values are an inherent and unavoidable type of measurement error. The resulting error might have substantial implications for interpreting time-series studies of air pollution (Zeger et al. 2000), although Samet and colleagues (2000b) suggested that errors of this type would tend to bias estimates downward. Because we were unable to measure the population's true exposures in Shanghai, we were not able to determine the magnitude or direction of such a bias or its effect on our conclusions.

Our assessment of weather conditions was derived entirely from a single monitoring station; however, the variability of weather across our study area is small, and there was little reason to expect that temperature or relative humidity varies substantially within the city limits.

Compared with data from studies in Europe and North America, the data we collected were limited in sample size, in duration, and in pertaining only to a single city. In

addition, the high correlation between particulate matter (PM_{10}) and gaseous pollutants (SO_2 and NO_2) (Table 2) limited our ability to distinguish independent effects for each pollutant.

Although our results indicated a substantial health effect from outdoor air pollution, we probably underestimated the total mortality burden because we accounted only for pollution's short-term effects (Künzli et al. 2001). Future research should focus on the long-term effects as well. Further, our analysis was limited to the urban area of Shanghai. Although the suburban and rural communities surrounding Shanghai have lower concentrations of PM_{10}, SO_2, and NO_2, they might experience elevated exposures to O_3 because of large biogenic emissions of volatile organic compounds and the transport of O_3 and its precursors from urban areas.

CONCLUSIONS

Short-term exposure to the outdoor air pollutants PM_{10}, SO_2, NO_2, and O_3 was associated with an increased mortality risk in Shanghai. The increased risk was similar in magnitude, per amount of pollution, to the risks found in other parts of the world. The gaseous pollutants SO_2 and NO_2 might have independent health effects in Shanghai. Further research will be needed to disentangle the effects of the various pollutants and to gain conclusive insights into the potential modifications of air pollution's health effects caused by sociodemographic characteristics and season.

IMPLICATIONS OF FINDINGS

Our study might have several implications for environmental and social policies in Shanghai government as it takes steps to protect the population in general and sensitive subpopulations in particular. It should also shed additional light on the difference between air pollution health effects found in Western and in developing countries (discussed below).

The increased mortality risk found in Shanghai was, again, similar in magnitude, per unit of pollution, to the risks found in other parts of the world. However, the importance of this increased risk is greater than in North America or Europe because air-pollutant concentrations in Shanghai are much higher, suggesting that outdoor air pollution represents a major and growing public-health problem in the city.

Unlike some prior studies, our study found significant effects of SO_2 and NO_2 on mortality outcomes even after adjustment for PM_{10}. This finding, combined with those of other studies showing a consistently significant effect of gaseous pollutants on mortality, suggests that the role of outdoor exposure to SO_2 and NO_2 should be investigated further. In addition, our analyses found an adverse health effect of O_3, strengthening the rationale for further limiting O_3 concentrations in outdoor air in the city. The observed effects of NO_2 and O_3 might actually represent the health hazard caused by air pollution from traffic in Shanghai, which is also worthy of more attention in the future. These results might give local policy-makers useful information in deciding which future air-pollution-control programs could yield the largest health benefits.

We found significant effects of outdoor air pollution even below the concentrations set by China's air-quality standards. This suggests that the current standards might not be sufficiently stringent to protect the public health in Shanghai. Further control of air pollution is likely to result in health benefits. A reduction in morbidity and mortality after the implementation of an intervention program will add evidence to the hypothesis of a causal link between air pollution and ill health.

Our results provide preliminary, but not conclusive, evidence that sociodemographic characteristics (e.g., sex, age, and socioeconomic status) and seasonal changes might modify the health effects of air pollution in Shanghai. These findings might provide useful information for local government as it takes steps to protect vulnerable subpopulations. Further investigation of these effect modifications is warranted.

When setting policy to control air pollution from the viewpoint of public health, it is important to use local data in identifying the health effects of air pollutants. When local data are not available, foreign data can be helpful, but they might not be applicable because of differences in climate or other conditions. For example, unlike some studies in Western countries, our study suggests that SO_2 and NO_2 can cause adverse health effects independent of PM_{10} and that threshold concentrations may exist for the health hazards caused by PM_{10} and NO_2 in Shanghai. Our study should contribute to the understanding of the health effects of air pollutants in China and might help clarify the differences between effects found in Western and in developing countries.

Shanghai will host the World Expo in 2010 and plans to invest billions of dollars in environmental protection to prepare for this momentous event. The results of the current study might supplement key scientific information on air-pollution–related health effects in the city, thereby giving local decision-makers useful information needed to set priorities in deciding which air-pollution-control measures could yield the largest health benefits.

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REFERENCES

Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP. 1996. Air pollution and daily mortality in London: 1987–1992. BMJ 312:665–669.

Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. 2001. Acute effects of particulate air pollution on respiratory admissions: Results from APHEA 2 project. Air Pollution and Health: A European Approach. Am J Respir Crit Care Med 164:1860–1866.

Basu R, Dominici F, Samet JM. 2005. Temperature and mortality among the elderly in the United States: A comparison of epidemiologic methods. Epidemiology 16:58–66.

Bateson TF, Schwartz J. 2004. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. Epidemiology 15:143–149.

Bell ML, Dominici F, Samet JM. 2005. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology 16:436–445.

Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2004. Ozone and short-term mortality in 95 US urban communities, 1987-2000. JAMA 292:2372–2378.

Blomberg A, Krishna MT, Bocchino V, Biscione GL, Shute JK, Kelly FJ, Frew AJ, Holgate ST, Sandstrom T. 1997. The inflammatory effects of 2 ppm NO_2 on the airways of healthy subjects. Am J Respir Crit Care Med 156:418–424.

Braga AL, Zanobetti A, Schwartz J. 2001. The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities. J Occup Environ Med 43: 927–933.

Burnett RT, Brook J, Dann T, Delocla C, Philips O, Cakmak S, Vincent R, Goldberg MA, Krewski D. 2000. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol 12 Suppl 4:15–39.

Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, Vincent R, Dann T. 2004. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Health 59:228–236.

Cakmak S, Dales RE, Judek S. 2006. Do gender, education, and income modify the effect of air pollution gases on cardiac disease? J Occup Environ Med 48:89–94.

Chang G, Pan X, Xie X, Gao Y. 2003. [Time-series analysis on the relationship between air pollution and daily mortality in Beijing]. Wei Sheng Yan Jiu 32:565–568.

Chen B, Hong C, Kan H. 2004. Exposures and health outcomes from outdoor air pollutants in China. Toxicology 198: 291–300.

China State Environmental Protection Agency. 2000. Monitoring methods for air pollutants. China Environmental Science Press, Beijing, China.

Daniels MJ, Dominici F, Samet JM, Zeger SL. 2000. Estimating particulate matter-mortality dose-response curves and threshold levels: An analysis of daily time-series for the 20 largest US cities. Am J Epidemiol 152:397–406.

Dominici F. 2004. Time-Series Analysis of Air Pollution and Mortality: A Statistical Review. Research Report 123. Health Effects Institute, Boston, MA.

Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. 2005. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: Mortality among residents of 90 cities. J Toxicol Environ Health A 68:1071–1092.

Dominici F, McDermott A, Zeger SL, Samet JM. 2002. On the use of generalized additive models in time-series studies of air pollution and health. Am J Epidemiol 156:193–203.

Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 295:1127–1134.

Dong JW, Xu XP, Dockery DW. 1996. [Association of air pollution with unscheduled outpatient visits in Beijing Longfu Hospital, 1991]. Zhonghua Liu Xing Bing Xue Za Zhi 17:13–16.

Goldberg MS, Bailar JC III, Burnett RT, Brook JR, Tamblyn R, Bonvalot Y, Ernst P, Flegel KM, Singh RK, Valois M-F. 2000. Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: A time-series study in Montreal, Quebec. Research Report 97. Health Effects Institute, Cambridge, MA.

Goldberg MS, Burnett RT, Bailar JC III, Tamblyn R, Ernst P, Flegel K, Brook J, Bonvalot Y, Singh R, Valois MF, Vincent R. 2001. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ Health Perspect 109 Suppl 4:487–494.

Gouveia N, Fletcher T. 2000. Time series analysis of air pollution and mortality: Effects by cause, age and socioeconomic status. J Epidemiol Community Health 54:750–755.

Gryparis A, Forsberg B, Katsouyanni K, Analitis A, Touloumi G, Schwartz J, Samoli E, Medina S, Anderson HR, Niciu EM, Wichmann HE, Kriz B, Kosnik M, Skorkovsky J, Vonk JM, Dortbudak Z. 2004. Acute effects of ozone on mortality from the "air pollution and health: A European approach" project. Am J Respir Crit Care Med 170:1080–1087.

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

Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR. 2002. Cardiorespiratory and all-cause mortality after restrictions on sulfur content of fuel in Hong Kong: An intervention study. Lancet 360:1646–1652.

HEI International Scientific Oversight Committee. 2004. Executive Summary. Health Effects of Outdoor Air Pollution in Developing Countries of Asia: A Literature Review. Special Report 15. Health Effects Institute, Boston, MA.

Hong YC, Lee JT, Kim H, Ha EH, Schwartz J, Christiani DC. 2002. Effects of air pollutants on acute stroke mortality. Environ Health Perspect 110:187–191.

Ito K, De Leon SF, Lippmann M. 2005. Associations between ozone and daily mortality: Analysis and meta-analysis. Epidemiology 16:446–457.

Ito K, Thurston GD. 1996. Daily PM10/mortality associations: An investigation of at-risk subpopulations. J Expo Anal Environ Epidemiol 6:79–95.

Janssen NA, Schwartz J, Zanobetti A, Suh HH. 2002. Air conditioning and source-specific particles as modifiers of the effect of PM(10) on hospital admissions for heart and lung disease. Environ Health Perspect 110:43–49.

Jerrett M, Burnett RT, Brook J, Kanaroglou P, Giovis C, Finkelstein N, Hutchison B. 2004. Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. J Epidemiol Community Health 58:31–40.

Kan H, Chen B. 2003a. A case-crossover analysis of air pollution and daily mortality in Shanghai. J Occup Health 45:119–124.

Kan H, Chen B. 2003b. Air pollution and daily mortality in Shanghai: A time-series study. Arch Environ Health 58: 360–367.

Kan H, Chen B, Chen C, Wang B, Fu Q. 2005. Establishment of exposure-response functions of air particulate matter and adverse health outcomes in China and worldwide. Biomed Environ Sci 18:159–163.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Amirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Padly A, Braunstein R, Pekkanen J, Schindler C, Schwartz J. 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: Results from 29 European cities within the APHEA2 project. Epidemiology 12:521–531.

Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak B, Sunyer J, Bacharova L, Schouten JP, Ponka A, Anderson HR. 1997. Short-term effects of ambient sulfur dioxide and particulate matter on mortality in 12 European cities: Results from time series data from the APHEA project. Air pollution and health: A European approach. BMJ 314:1658–1663.

Kelly FJ, Blomberg A, Frew A, Holgate ST, Sandstrom T. 1996. Antioxidant kinetics in lung lavage fluid following exposure of humans to nitrogen dioxide. Am J Respir Crit Care Med 154:1700–1705.

Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, Hodis HN. 2005. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113:201–206.

Künzli N, Medina S, Kaiser R, Quenel P, Horak F Jr, Studnicka M. 2001. Assessment of deaths attributable to air pollution: Should we use risk estimates based on time series or on cohort studies? Am J Epidemiol 153:1050–1055.

Laurent O, Bard D, Filleul L, Segala C. 2007. Effect of socioeconomic status on the relationship between atmospheric pollution and mortality. J Epidemiol Community Health 61:665–675.

Levy JI, Chemerynski SM, Sarnat JA. 2005. Ozone exposure and mortality: An empiric Bayes metaregression analysis. Epidemiology 16:458–468.

Long W, Zhong T, Zhang B. 2007. China: The Issue of Residential Air Conditioning. Available from *www.iifiir.org/en/doc/1056.pdf*. Accessed 1/27/10.

Mackenbach JP, Kunst AE, Cavelaars AE, Groenhof F, Geurts JJ. 1997. Socioeconomic inequalities in morbidity and mortality in western Europe. The EU Working Group on Socioeconomic Inequalities in Health. Lancet 349: 1655–1659.

National Research Council. 1998. Research Priorities for Airborne Particulate Matter. National Academy Press, Washington DC.

Nawrot TS, Torfs R, Fierens F, De Henauw S, Hoet PH, Van Kersschaever G, De Backer G, Nemery B. 2007. Stronger associations between daily mortality and fine particulate air pollution in summer than in winter: Evidence from a heavily polluted region in western Europe. J Epidemiol Community Health 61:146–149.

Nowak D, Jorres R, Berger J, Claussen M, Magnussen H. 1997. Airway responsiveness to sulfur dioxide in an adult population sample. Am J Respir Crit Care Med 156:1151–1156.

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, Wilkinson P, Fletcher T, Cifuentes L, Schwartz J. Workshop on Air Pollution and Socioeconomic Conditions. 2003. Health, wealth, and air pollution: Advancing theory and methods. Environ Health Perspect 111:1861–1870.

Peng RD, Dominici F, Louis TA. 2006. Model choice in time series studies of air pollution and mortality. J R Stat Soc Ser A Stat Soc 169:179–203.

Peng RD, Dominici F, Pastor-Barriuso R, Zeger SL, Samet JM. 2005. Seasonal analyses of air pollution and mortality in 100 US cities. Am J Epidemiol 161:585–594.

R Development Core Team. 2007. R: A Language and Environment for Statistical Computing, version 2.5.1. R Foundation for Statistical Computing. Vienna.

Ramsay TO, Burnett RT, Krewski D. 2003. The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. Epidemiology 14:18–23.

Romieu I, Tellez-Rojo MM, Lazo M, Manzano-Patino A, Cortez-Lugo M, Julien P, Belanger MC, Hernandez-Avila M, Holguin F. 2005. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. Am J Respir Crit Care Med 172:1534–1540.

Samet J, Krewski D. 2007. Health effects associated with exposure to ambient air pollution. J Toxicol Environ Health A 70:227–242.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000a. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 343:1742–1749.

Samet JM, Dominici F, Zeger SL, Schwartz J, Dockery DW. 2000b. Part I. Methods and methodologic issues. In: The National Morbidity, Mortality, and Air Pollution Study. Research Report 94. Health Effects Institute, Cambridge, MA.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwartz J, Zanobetti A. 2000c. Part II. Morbidity and mortality from air pollution in the United States. In: The National Morbidity, Mortality, and Air Pollution Study. Research Report 94. Health Effects Institute, Cambridge, MA.

Samoli E, Aga E, Touloumi G, Nisiotis K, Forsberg B, Lefranc A, Pekkanen J, Wojtyniak B, Schindler C, Niciu E, Brunstein R, Dodic Fikfak M, Schwartz J, Katsouyanni K. 2006. Short-term effects of nitrogen dioxide on mortality: An analysis within the APHEA project. Eur Respir J 27: 1129–1138.

Samoli E, Analitis A, Touloumi G, Schwartz J, Anderson HR, Sunyer J, Bisanti L, Zimrou D, Vonk JM, Pekkanen J, Goodman P, Padly A, Schindler C, Katsouyanni K. 2005. Estimating the exposure-response relationships between particulate matter and mortality within the APHEA multicity project. Environ Health Perspect 113:88–95.

Sarnat JA, Brown KW, Schwartz J, Coull BA, Koutrakis P. 2005. Ambient gas concentrations and personal particulate matter exposures: Implications for studying the health effects of particles. Epidemiology 16:385–395.

Sarnat JA, Schwartz J, Catalano PJ, Suh HH. 2001. Gaseous pollutants in particulate matter epidemiology: Confounders or surrogates? Environ Health Perspect 109:1053–1061.

Schwartz J. 2004. Air pollution and children's health. Pediatrics 113:1037–1043.

Seaton A, Dennekamp M. 2003. Hypothesis: Ill health associated with low concentrations of nitrogen dioxide — An effect of ultrafine particles? Thorax 58:1012–1015.

Stieb DM, Judek S, Burnett RT. 2002. Meta-analysis of time-series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season. J Air Waste Manag Assoc 52:470–484.

Stieb DM, Judek S, Burnett RT. 2003. Meta-analysis of time-series studies of air pollution and mortality: Update in relation to the use of generalized additive models. J Air Waste Manag Assoc 53:258–261.

Touloumi G, Samoli E, Katsouyanni K. 1996. Daily mortality and "winter type" air pollution in Athens, Greece — A time series analysis within the APHEA project. J Epidemiol Community Health 50 Suppl 1:s47–s51.

Touloumi G, Samoli E, Pipikou M, Le Tertre A, Atkinson R, Katsouyanni K. 2006. Seasonal confounding in air pollution and health time-series studies: Effect on air pollution effect estimates. Stat Med 25:4164–4178.

Venners SA, Wang B, Xu Z, Schlatter Y, Wang L, Xu X. 2003. Particulate matter, sulfur dioxide, and daily mortality in Chongqing, China. Environ Health Perspect 111: 562–567.

Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PY, Lam TH. 2002. A tale of two cities: Effects of air pollution on hospital admissions in Hong Kong and London compared. Environ Health Perspect 110:67–77.

Wong CM, Ma S, Hedley AJ, Lam TH. 2001. Effect of air pollution on daily mortality in Hong Kong. Environ Health Perspect 109:335–340.

Wong CM, Ma S, Hedley AJ, Lam TH. 1999. Does ozone have any effect on daily hospital admissions for circulatory disease? J Epidemiol Community Health 53:580–581.

World Health Organization. 2000. Air Quality Guideline for Europe. World Health Organization Regional Publications, European Series. No. 91. Copenhagen.

Xu X, Gao J, Dockery DW, Chen Y. 1994. Air pollution and daily mortality in residential areas of Beijing, China. Arch Environ Health 49:216–222.

Xu X, Li B, Huang H. 1995. Air pollution and unscheduled hospital outpatient and emergency room visits. Environ Health Perspect 103:286–289.

Xu Z. 2005. Effect evaluation on smoking control plan for one year in Shanghai-China/WHO smoking control capability construction cooperation items [in Chinese]. Chin J Health Educ 21:412–416.

Xu Z, Yu D, Jing L, Xu X. 2000. Air pollution and daily mortality in Shenyang, China. Arch Environ Health 55: 115–120.

Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. 1992. A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. Am Rev Respir Dis 146:888–894.

Zanobetti A, Schwartz J. 2000. Race, gender, and social status as modifiers of the effects of PM10 on mortality. J Occup Environ Med 42:469–474.

Zeger SL, Irizarry R, Peng RD. 2006. On time series analysis of public health and biomedical data. Annu Rev Public Health 27:57–79.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, Cohen A. 2000. Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108:419–426.

Zeka A, Zanobetti A, Schwartz J. 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 163:849–859.

Zhang J, Song H, Tong S, Li L, Liu B, Wan L. 2000. Ambient sulfate concentration and chronic disease mortality in Beijing. Sci Total Environ 262:63–71.

APPENDIX A. Technical Summary

SOFTWARE

We used R 2.5.1 (*www.r-project.org*) software, with mgcv, foreign and splines packages.

CODES FOR THE MAIN ANALYSIS

Code for Autoregression (AR) Model in R

```
gamar.fun <-
function(initialfit , ar.ord=0) {
if (ar.ord==0)
return(initialfit)
#Initial model controlling for over-dispersion.
ar.order <- ar.ord
niter <- 0
if (is.null(dim(initialfit$data))) {
mydata<-numeric()
data.names<-names(attr(initialfit$term,"dataClasses"))[-1]
data.names.tmp<-attr(initialfit$term,"term.labels")
for (i in 1:length(data.names.tmp)){
mydata<-cbind(mydata,get(data.names[i]))
}
dimnames(mydata)<- list(1:dim(mydata)[1],data.names)
mydata<- data.frame(mydata)
} else {
mydata<-initialfit$data
}
mod.init <- initialfit
usedata <- as.numeric(names(initialfit$hat))
b0 <- summary(mod.init)$p.coef
b1 <- b0 + 0.011
b0 <- c(b0, rep(0, ar.order))
#b1 is defined in this way due to the division in the
   iteration criterion
b1 <- c(b1, rep(0.011, ar.order))
fit0 <- fitted(mod.init)
pred0 <- predict(mod.init)#Define criteria for the iterations
crit0 <- ((b1 - b0)/b1)
acrit <- abs(crit0)
macrit <- max(acrit)# create object to store AR terms
auto <- matrix(0, nrow=length(mod.init$y), ncol=ar.order)
```

```
auto <- as.data.frame(auto)
#Different value in the criterion does not change
   the outcome
while(macrit > 0.01) {
#Defining the autoregressive terms
b0 <- b1
res <- (mod.init$y - fit0)/fit0
sigma <- (1/sqrt(fit0))
for(i in 1:ar.order) {
auto[,i] <- ((sigma * c(rep(mean(res), i), res[1:(length(mod.
   init$y) - i)]))/
c(rep(mean(res),i), sigma[1:(length(mod.init$y) - i)]))
auto[is.na(auto[,i]),i]<-mean(auto[,i],na.rm=T)
auto.names <- paste("auto", 1:ar.order, sep = '')
assign(auto.names[i], auto[, i],env = .GlobalEnv)
}
ez0 <- exp(pred0 + res)
assign("ez0" , ez0 ,env = .GlobalEnv)
#Fitting the model controlling for over-dispersion
   and autoregression
auto.part <- paste(auto.names, sep = " ", collapse = "+")
new.form <- eval(parse(text = paste("ez0 ~ . +", auto.part)))
modpol <- update(mod.init, new.form,sp=mod.init$sp,
   data=mydata[usedata,])
b1 <- summary(modpol)$p.coef
niter <- niter + 1
predinit <- predict(modpol, type = "terms")
# calculate predicted values without the contribution
   from AR terms
pred0 <- rowSums(predinit[,-c((length(attr(mod.init$p
   terms,"term.labels"))+1):
(length(attr(mod.init$pterms,"term.labels"))+ar.order))],
   dims=1)+b1[1]
fit0 <- exp(pred0)
crit0 <- ((b1 - b0)/b1)
macrit <- max(abs(crit0))
# As it can be long, give you an indication on convergence.
   #print(paste("convergence criteria: ", macrit, collapse = " "))
   }
   modpol <- modpol
   return(modpol)
   }
```

Code for the Basic Models

```
gamar.fun (gam (outcome ~ s(trend, k=a*n+1, fx=T,
   bs= "cr") + s(temperature, k=3+1, fx=T, bs="cr") +
   s(humidity, k=3+1, fx=T,bs="cr") + as.factor(weekday),
   data=Shanghai, family=quasipoisson),b))
```

Here a and b are df/year for time trend and lag days for the autoregression term, respectively (Table 3); n is the number of years (n = 4 in Shanghai).

Code for the Main Analysis

```
gamar.fun (gam (outcome ~ s(trend, k=a*n+1, fx=T,
   bs= "cr") + s(temperature, k=3+1, fx=T, bs="cr")
   + s(humidity, k=3+1, fx=T,bs="cr") +
   as.factor(weekday) + air_pollutant, data=Shanghai,
   family=quasipoisson),b))
```

Here air_pollutant is the air pollutant concentrations.

OVERDISPERSION PARAMETER UNDER THE BASIC MODEL IN SHANGHAI

Table A.1. Overdispersion Parameter Under the Basic Model in Shanghai, 2001–2004

Mortality Class	Overdispersion Parameter
All natural mortality	1.39
All natural mortality, ages ≥ 65	1.16
Cardiovascular mortality	1.34
Respiratory mortality	1.25

APPENDIX B. Supplemental Description of Air Pollution Data

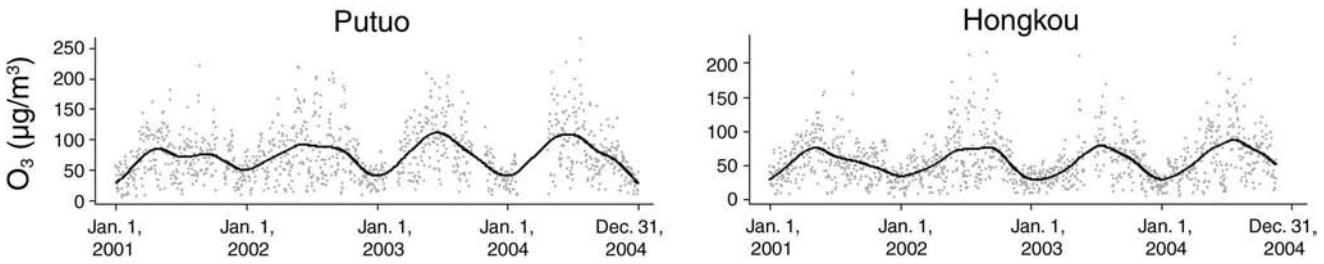


Figure B.1. Daily time series of maximum 8-hour mean O_3 concentrations (in µg/m^3) at two of the monitoring stations in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year. No measurements were available from stations in Luwan, Jing'an, Yangpu, and Xuhui. Note differences in the scales of the *y*-axes.

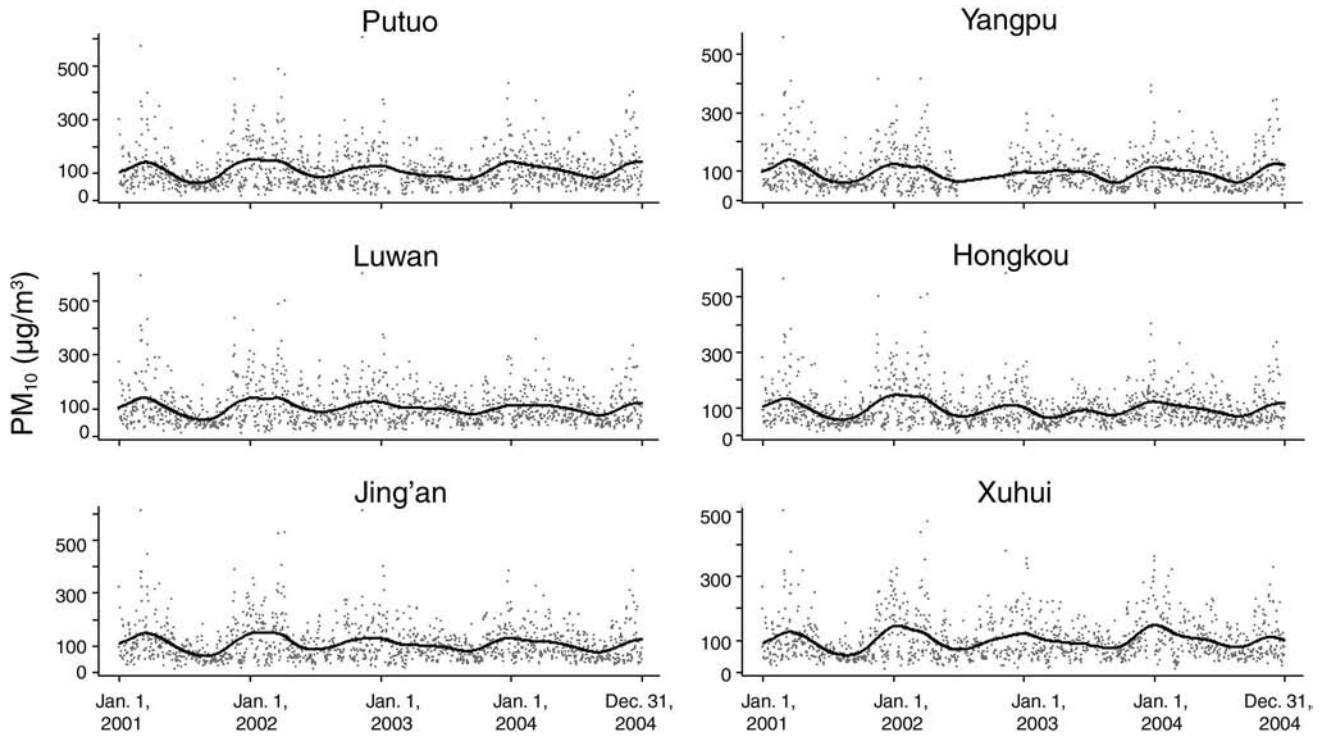


Figure B.2. Time series of 24-hour average PM_{10} concentrations (in µg/m^3) at the six monitoring stations in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year. Note differences in the scales of the *y*-axes.

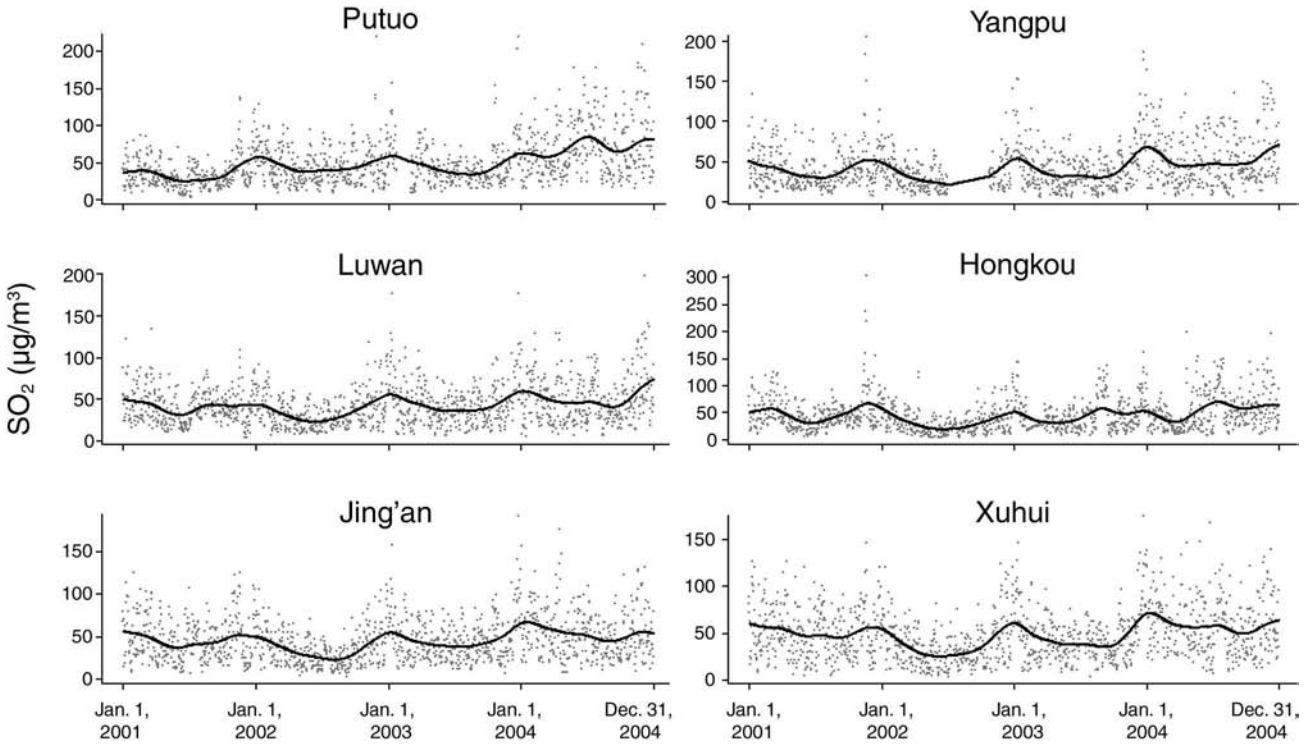


Figure B.3. Time series of 24-hour average SO_2 concentrations (in μg/m^3) at the six monitoring stations in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year. Note differences in the scales of the *y*-axes.

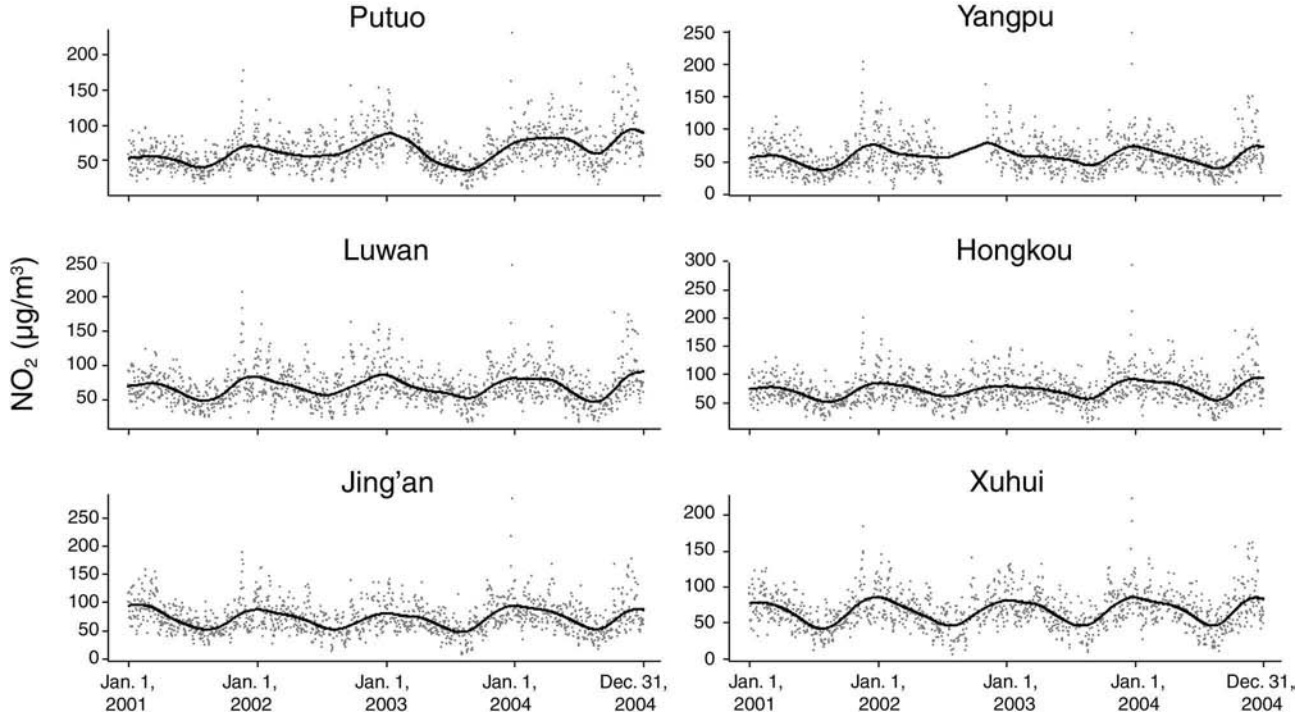


Figure B.4. Time series of 24-hour average NO_2 concentrations (in μg/m^3) at the six monitoring stations in Shanghai, 2001–2004. The solid lines indicate smoothing splines with 5 df per year. Note differences in the scales of the *y*-axes.

Table B.1. Summary Statistics of Station-Specific Daily Concentrations of Pollutants in Shanghai, 2001–2004

Pollutant	Station	Days (*n*)	Daily Concentration (μg/m^3)					
			Minimum	First Quartile	Median	Mean	Third Quartile	Maximum
PM_{10}	Putuo	1372	15.0	62.0	91.0	110.9	141.0	603.0
	Yangpu	1243	14.0	51.0	78.0	95.0	122.0	555.0
	Luwan	1416	11.0	56.0	86.0	104.6	134.3	599.0
	Hongkou	1432	9.0	51.0	77.0	95.4	120.0	582.0
	Jing'an	1421	10.0	58.0	89.0	107.0	134.0	614.0
	Xuhui	1341	10.0	55.0	82.0	100.3	128.0	504.0
SO_2	Putuo	1354	3.0	27.0	41.0	49.0	63.0	220.0
	Yangpu	1279	5.0	22.0	35.0	42.0	53.0	205.0
	Luwan	1434	4.0	24.0	37.0	42.0	54.0	197.0
	Hongkou	1439	4.0	22.0	37.0	44.4	57.0	302.0
	Jing'an	1430	2.0	25.0	39.5	44.6	58.8	192.0
	Xuhui	1381	3.0	28.0	43.0	47.9	63.0	175.0
NO_2	Putuo	1376	9.0	44.0	59.0	63.0	76.0	230.0
	Yangpu	1268	7.0	39.0	52.5	57.1	71.0	248.0
	Luwan	1421	17.0	51.0	64.0	68.0	81.0	245.0
	Hongkou	1433	15.0	54.0	68.0	72.2	86.0	292.0
	Jing'an	1421	7.0	52.0	67.0	71.9	87.0	284.0
	Xuhui	1388	5.0	50.0	64.0	66.3	80.0	223.0
O_3	Putuo	1251	4.0	43.0	65.0	73.5	97.0	266.0
	Hongkou	1352	3.0	31.8	48.0	55.6	73.0	237.0

Table B.2. Pearson Correlation Coefficients of Daily Pollutant Concentrations Between Stations in Shanghai, 2001–2004

Pollutant	Station	Yangpu	Luwan	Hongkou	Jing'an	Xuhui
PM_{10}	Putuo	0.94	0.95	0.95	0.97	0.91
	Yangpu	—	0.94	0.93	0.94	0.88
	Luwan	—	—	0.94	0.97	0.89
	Hongkou	—	—	—	0.95	0.88
	Jing'an	—	—	—	—	0.91
SO_2	Putuo	0.61	0.68	0.66	0.75	0.73
	Yangpu	—	0.78	0.68	0.68	0.44
	Luwan	—	—	0.74	0.77	0.74
	Hongkou	—	—	—	0.69	0.68
	Jing'an	—	—	—	—	0.83
NO_2	Putuo	0.74	0.81	0.85	0.83	0.83
	Yangpu	—	0.89	0.86	0.83	0.78
	Luwan	—	—	0.92	0.90	0.89
	Hongkou	—	—	—	0.93	0.89
	Jing'an	—	—	—	—	0.91
O_3	Putuo	—	—	0.85	—	—

Table B.3. Pearson Correlation Coefficients Between Station-Specific Pollutant Concentrations in Shanghai, 2001–2004

Station / Pollutant	SO_2	NO_2	O_3
Putuo			
PM_{10}	0.56	0.62	0.18
SO_2	—	0.75	0.15
NO_2	—	—	0.02
Yangpu			
PM_{10}	0.60	0.72	—
SO_2	—	0.69	—
Luwan			
PM_{10}	0.57	0.69	—
SO_2	—	0.66	—
Hongkou			
PM_{10}	0.50	0.63	0.18
SO_2	—	0.51	0.19
NO_2	—	—	0.05
Jing'an			
PM_{10}	0.56	0.66	—
SO_2	—	0.71	—
Xuhui			
SO_2	0.55	0.63	—
NO_2	—	0.60	—

Table B.4. Pearson Correlation Coefficients Between Station-Averaged Pollutant Concentrations with Seasonal and Meteorologic Corrections in Shanghai, 2001–2004[a]

Pollutant	SO_2	NO_2	O_3
PM_{10}	0.62	0.68	0.16
SO_2	1.00	0.80	0.04
NO_2	—	1.00	0.15
O_3	—	—	1.00

[a] Seasonal and meteorologic corrections used the natural spline model, with 4 df/year for time trend and 3 df for temperature and relative humidity.

Table B.5. Regression Results of Pollutant Concentrations After Adjustment for Temperature and Relative Humidity[a]

Independent Variable	Dependant Variable	Intercept		Regression Coefficient	
		Mean	SE	Mean	SE
PM_{10}	SO_2	16.89	4.80	1.63	0.06
	NO_2	−13.16	4.53	1.82	0.05
	O_3	67.15	5.49	0.42	0.06
SO_2	PM_{10}	27.24	1.50	0.19	0.01
	NO_2	3.82	1.33	0.72	0.02
	O_3	45.05	1.93	−0.01	0.02
NO_2	PM_{10}	33.82	1.44	0.25	0.01
	SO_2	18.85	1.35	0.84	0.02
	O_3	51.33	2.07	0.10	0.02
O_3	PM_{10}	45.12	2.38	0.09	0.01
	SO_2	53.84	2.68	−0.01	0.04
	NO_2	44.82	2.82	0.15	0.03

[a] Temperature and relative humidity were adjusted with nature spline smoother (df = 3). Pollutant concentrations are $\mu g/m^3$. SE indicates standard error.

APPENDIX C. Supplemental Results

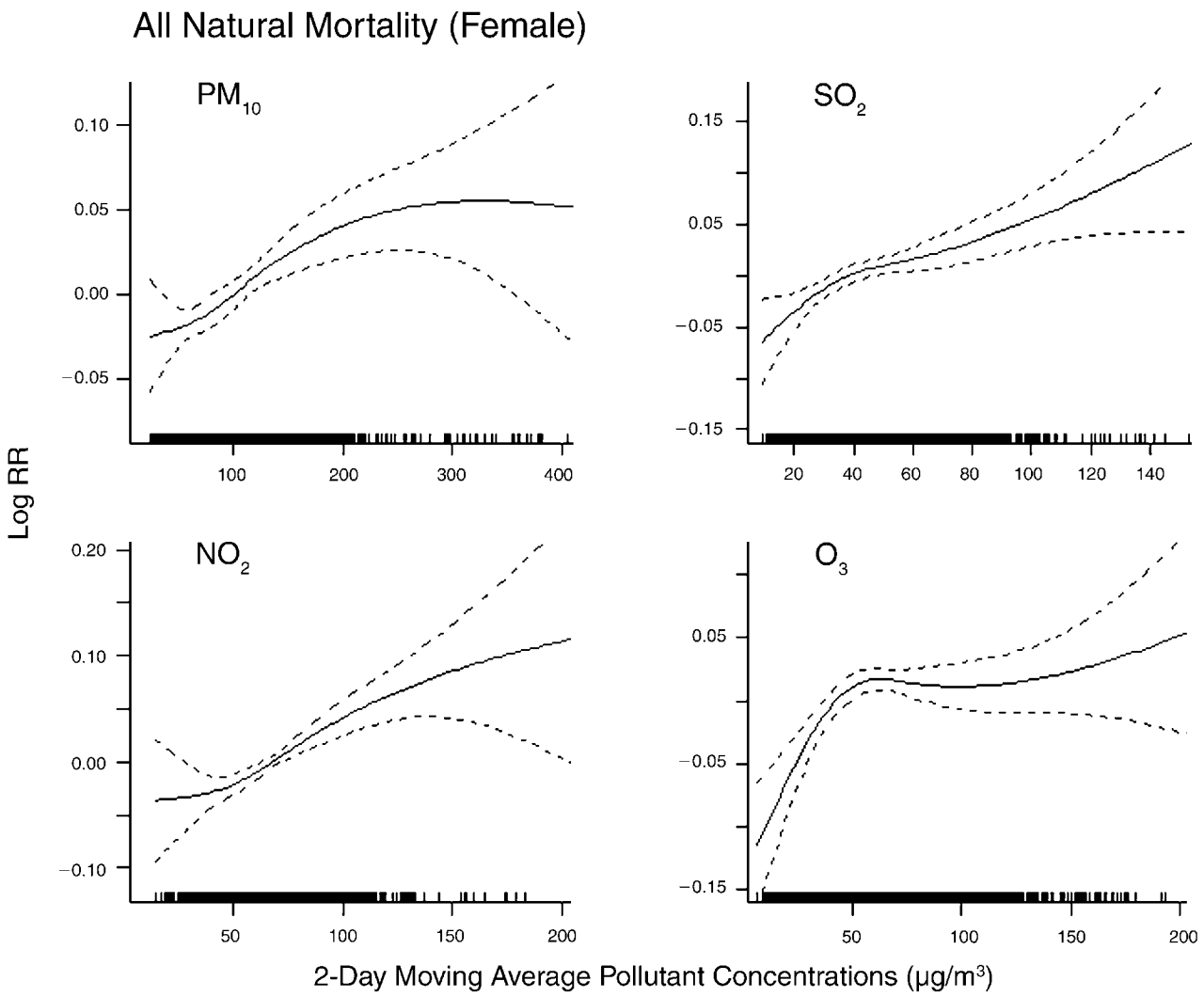
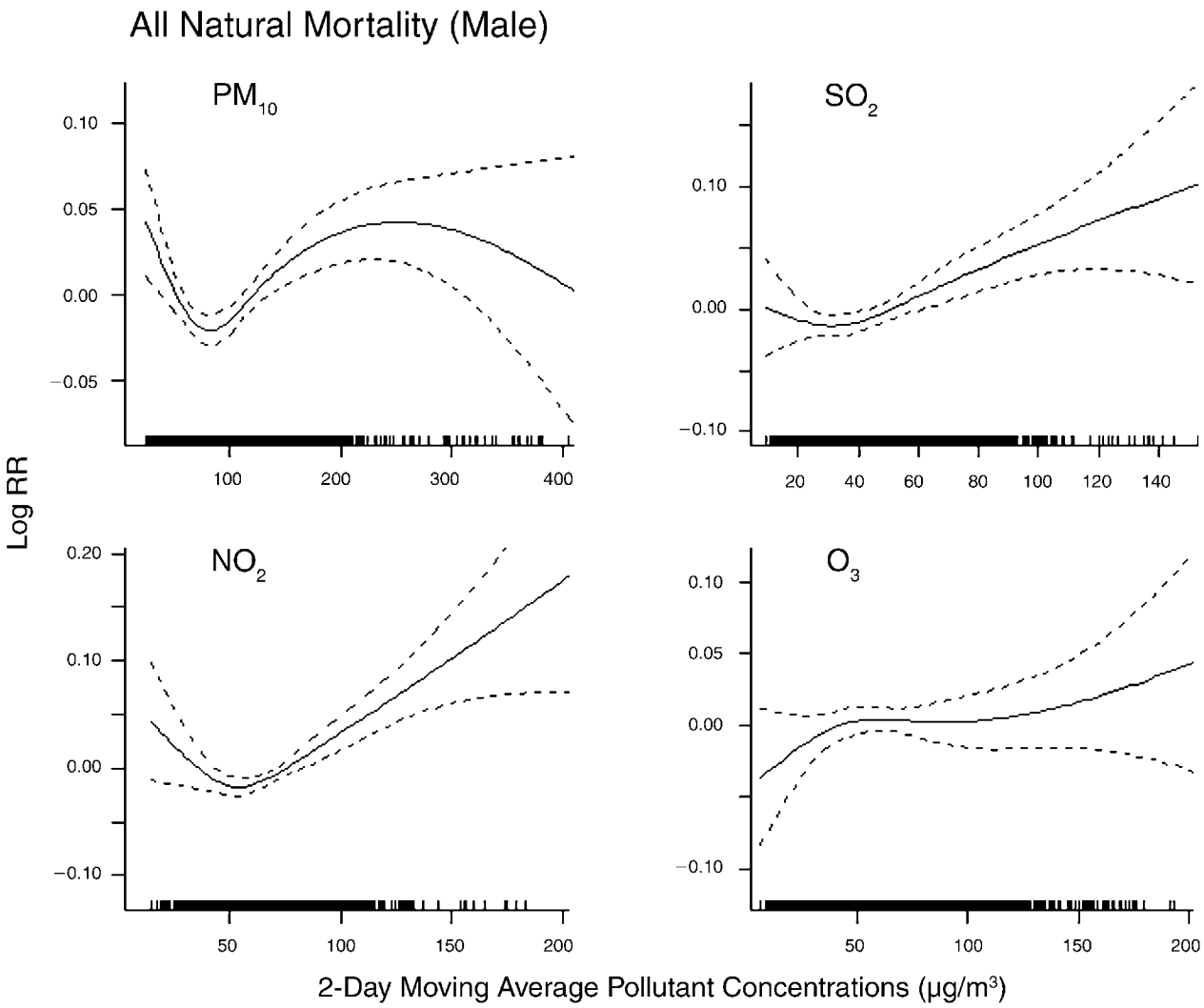


Figure C.1. Smoothing plots for exposure–response relations between air pollutants and various mortality risks. Bars along the *x*-axes represent the number of observations associated with 10-μg/m^3 increases in 2-day moving average pollutant concentrations used in the study. Mortality risks have 3 df and are expressed as log RR. The solid lines indicate the estimated mean percentage of change in daily mortality, and the dotted lines represent twice the standard error. See Table 3 for the degrees of freedom used for time trend and lag days for autoregression terms; 3 df were used for current-day temperature and humidity. Note differences in the scales of some of the *y*-axes.



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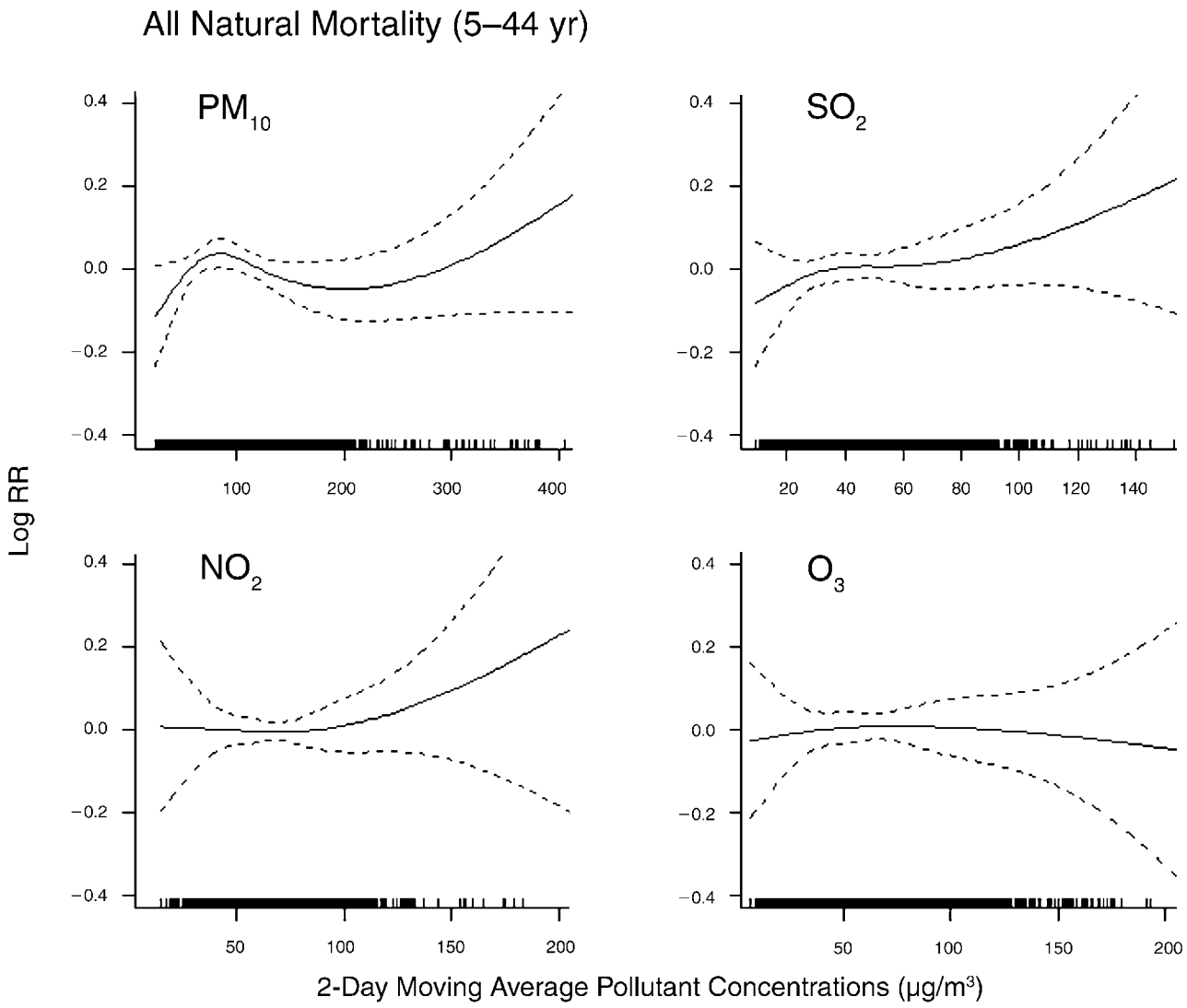

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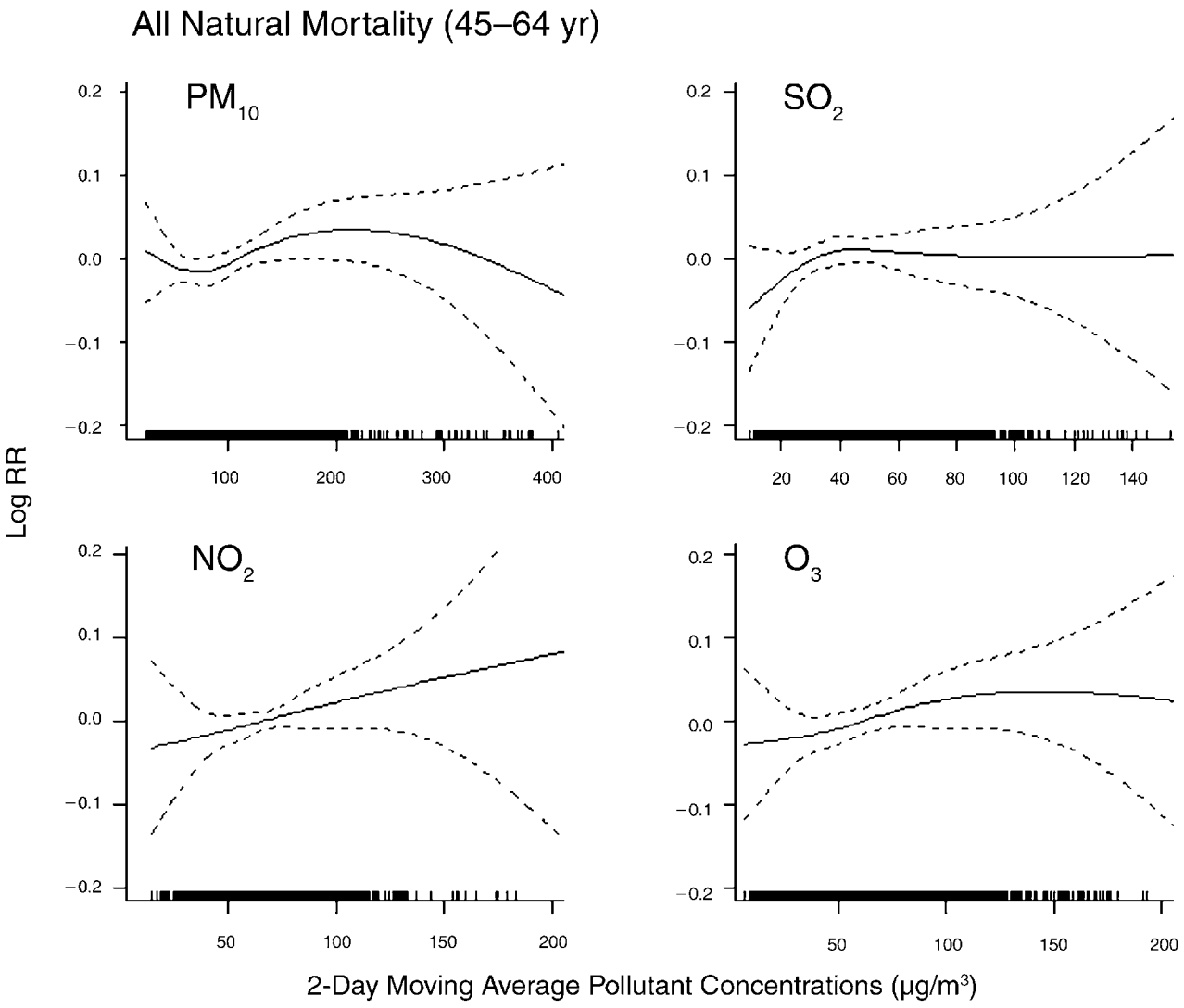

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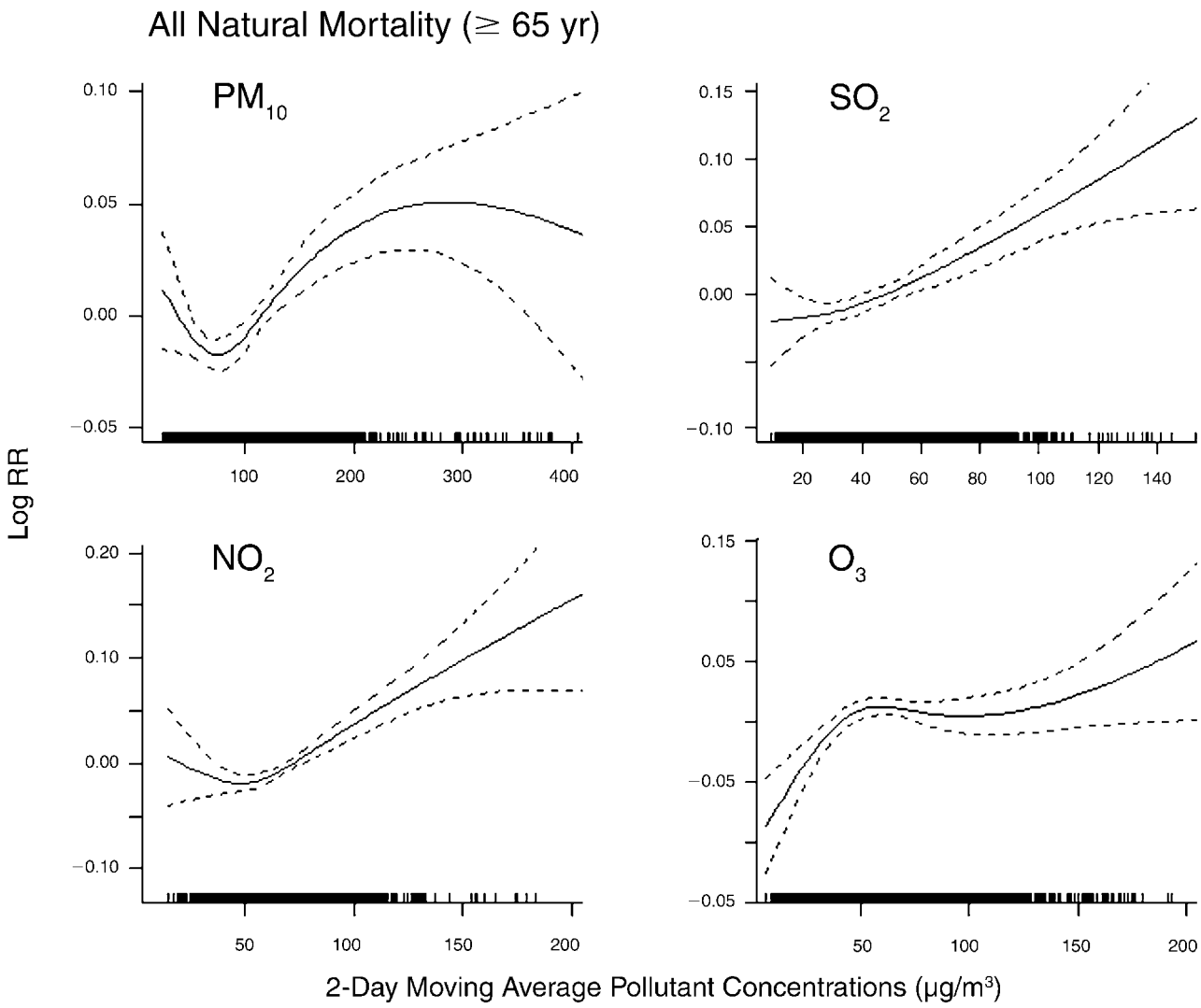

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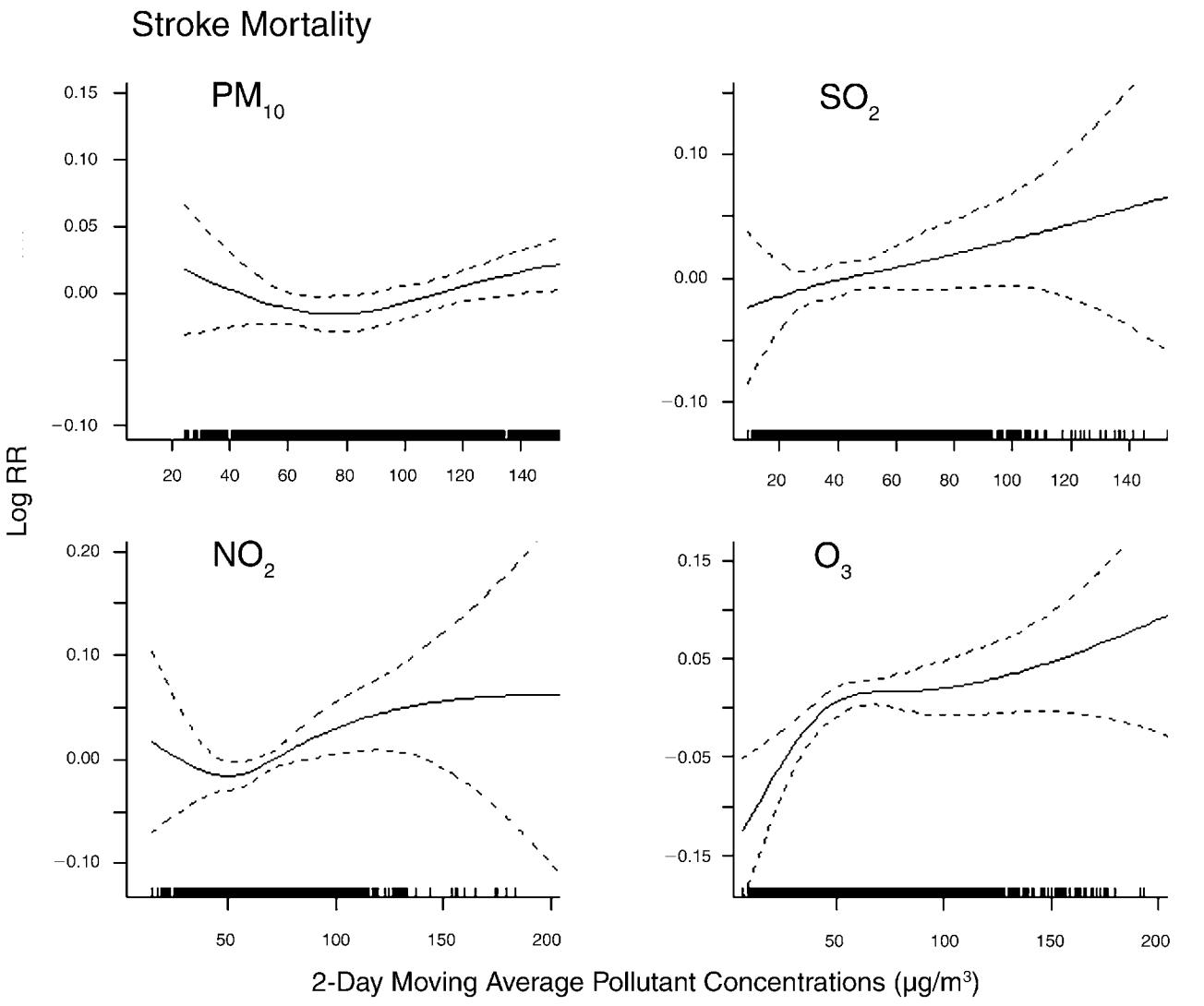

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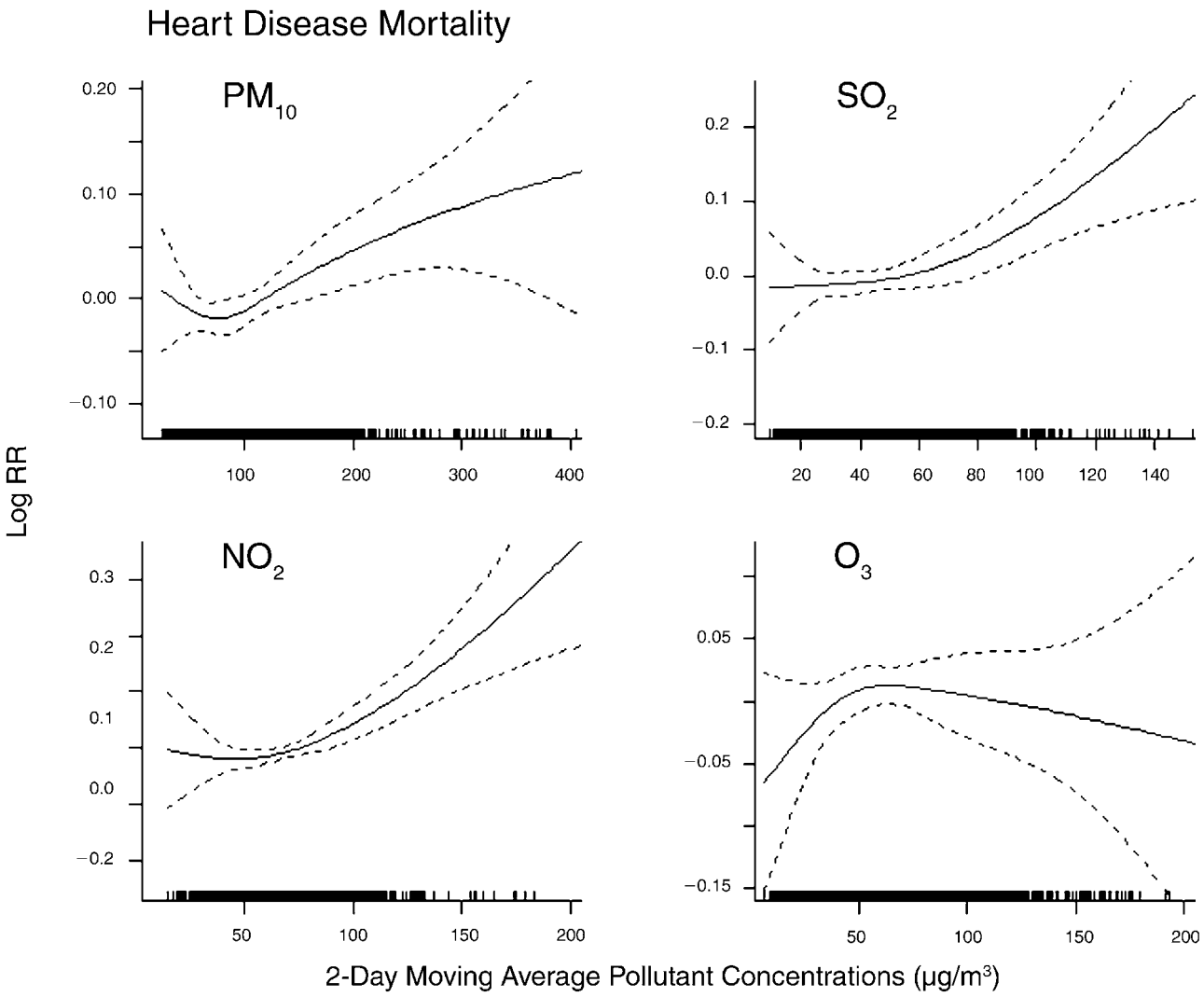

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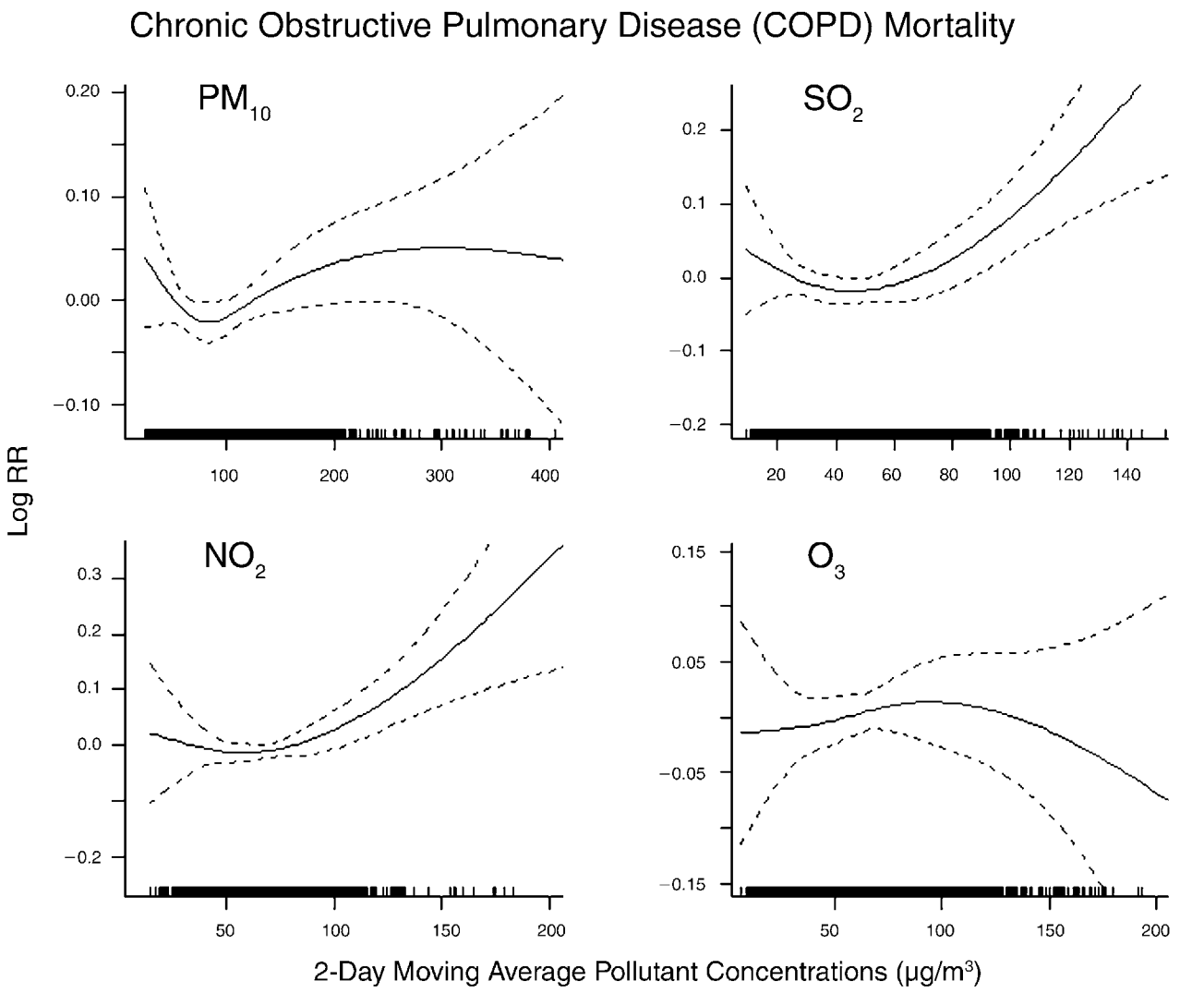

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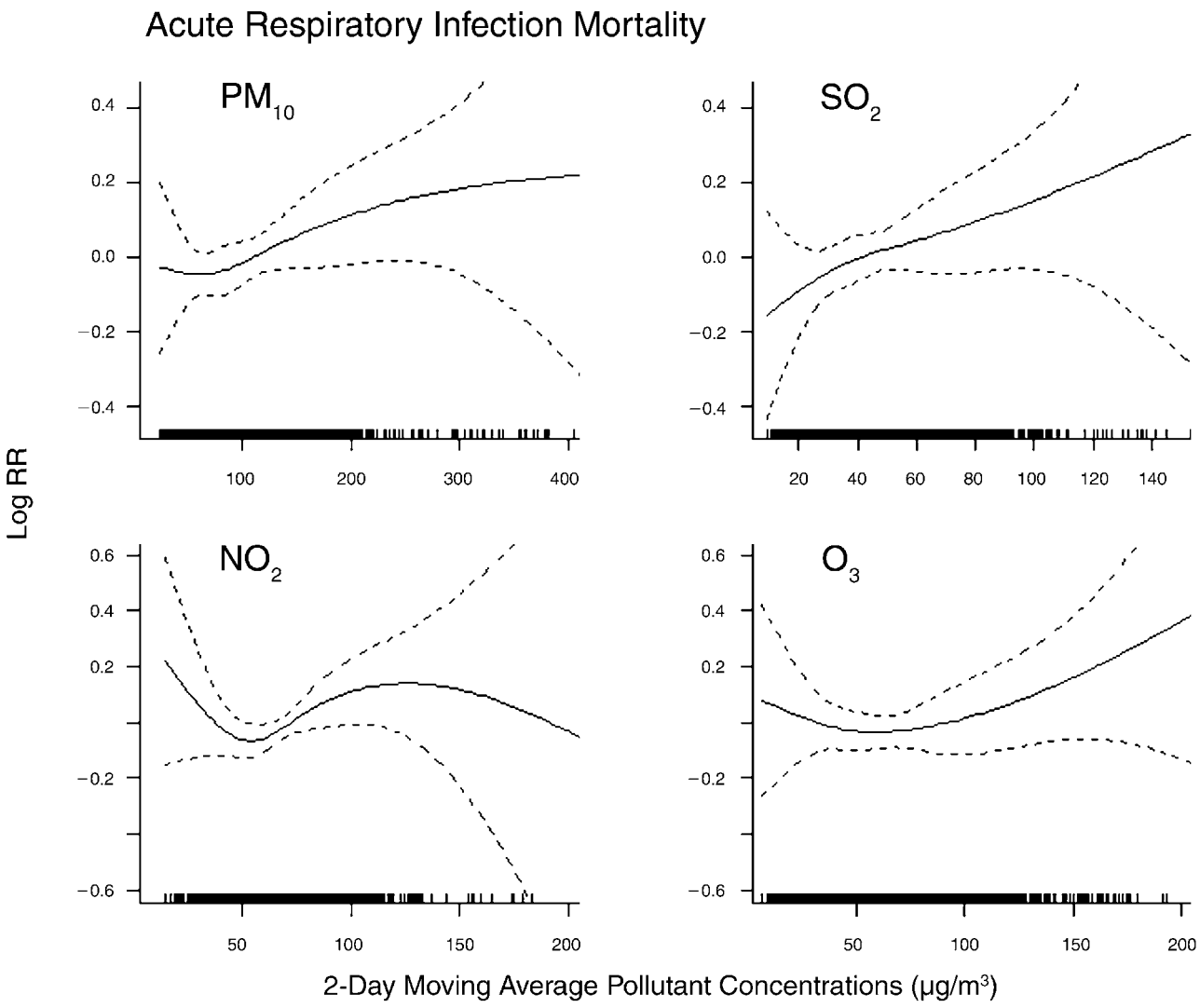

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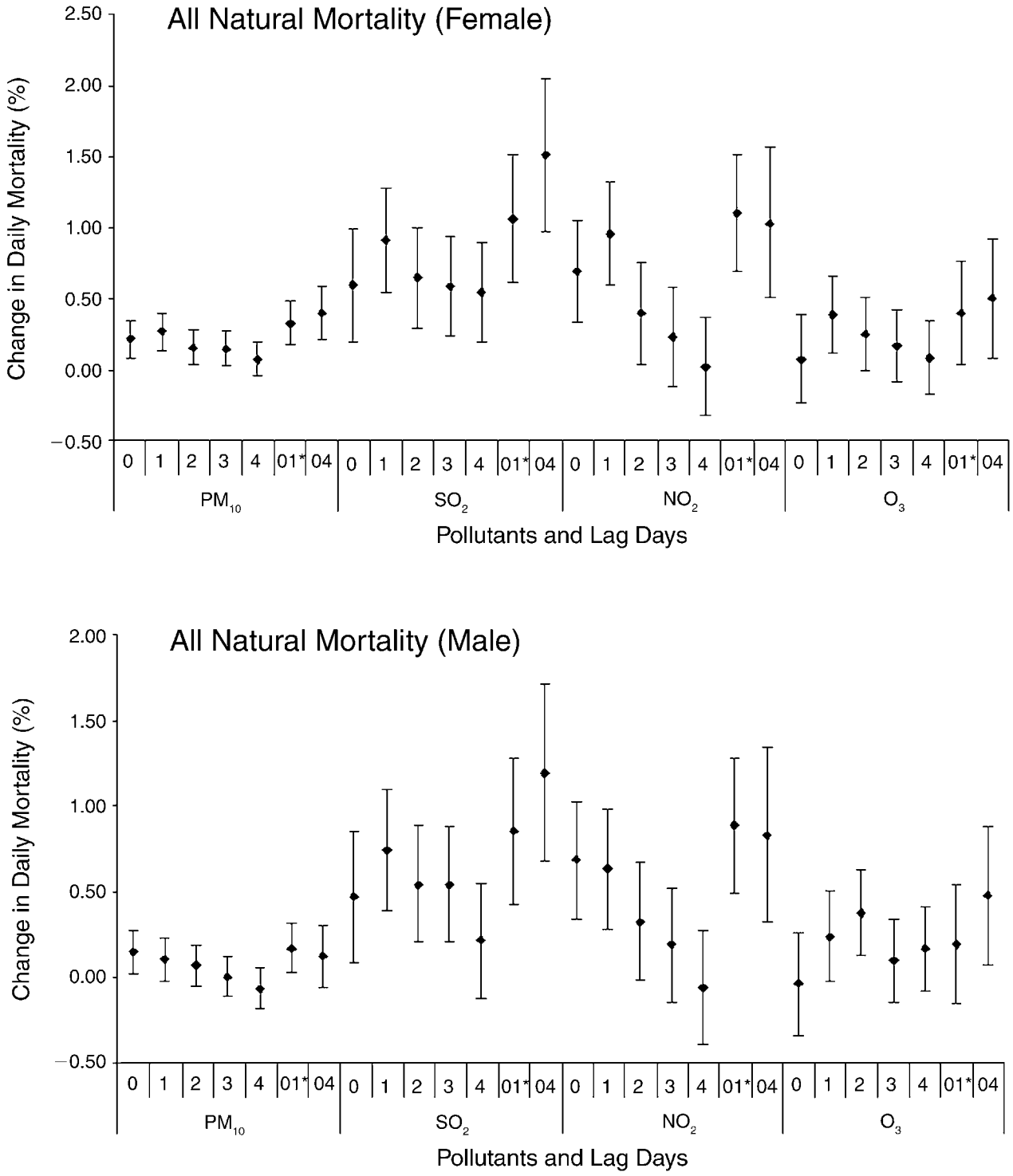

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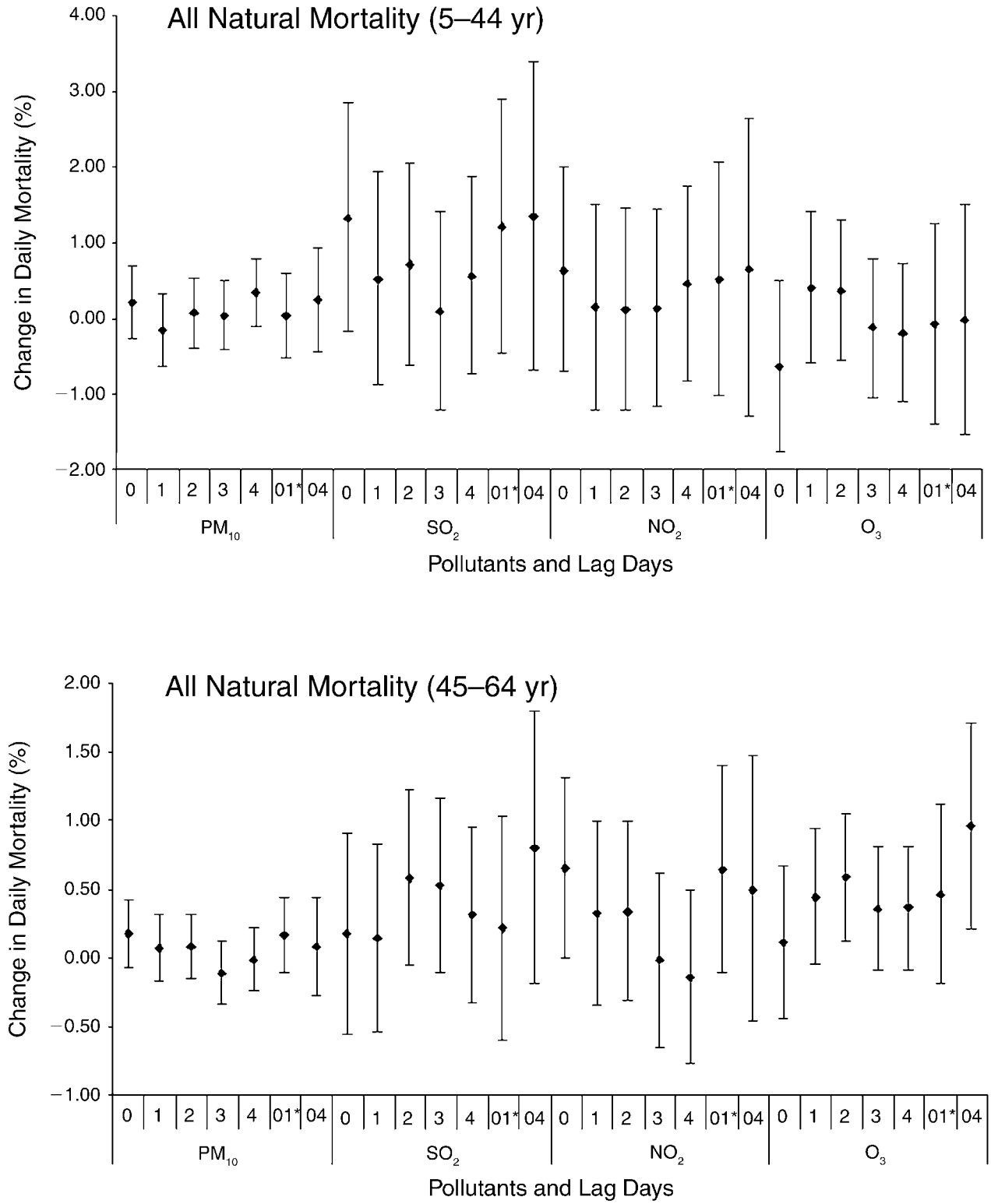
Figure C.2. Percentage changes in daily mortality associated with 10-μg/m^3 increases of pollutant concentrations, using various lag-day structures for pollutants. Asterisks indicate lag-day values used in the main analysis. See Table 3 for degrees of freedom used for time trend and lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. "01" indicates the 2-day moving average of pollutant concentrations on the current and previous day (lag 0–1 day [average]); "04" indicates the 5-day moving average of pollutant concentrations on the current and previous 4 days (lag 0–4 day [average]). Note differences in the scales of the *y*-axes.



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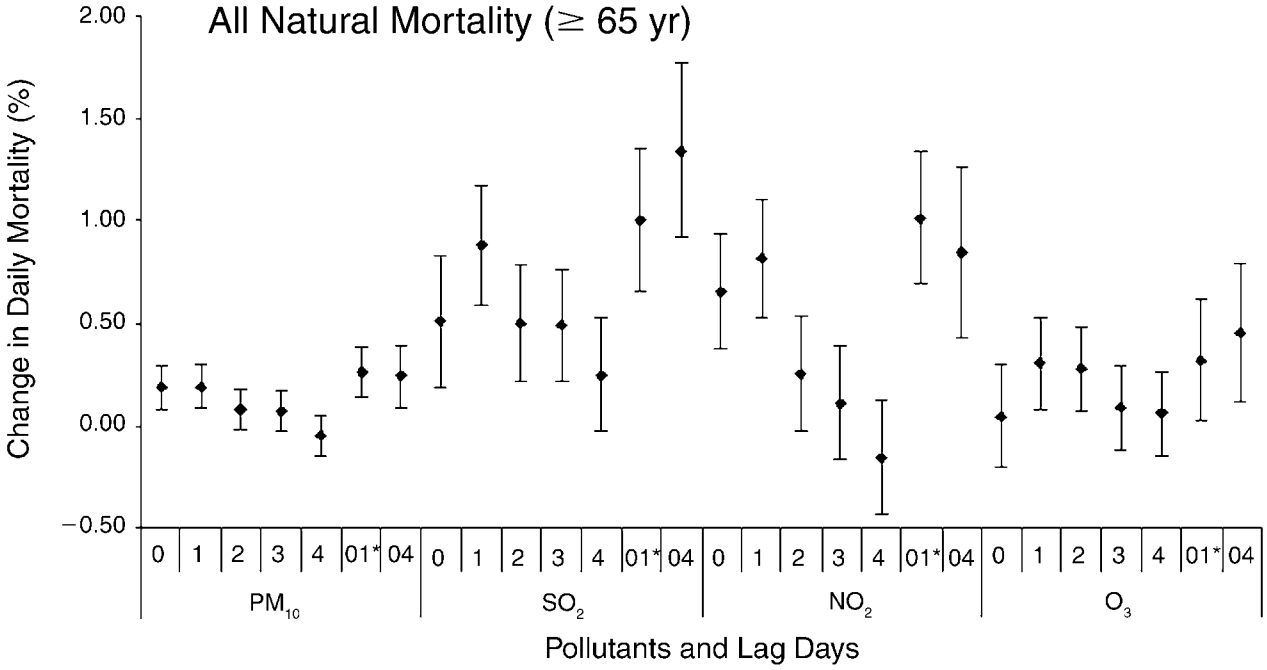

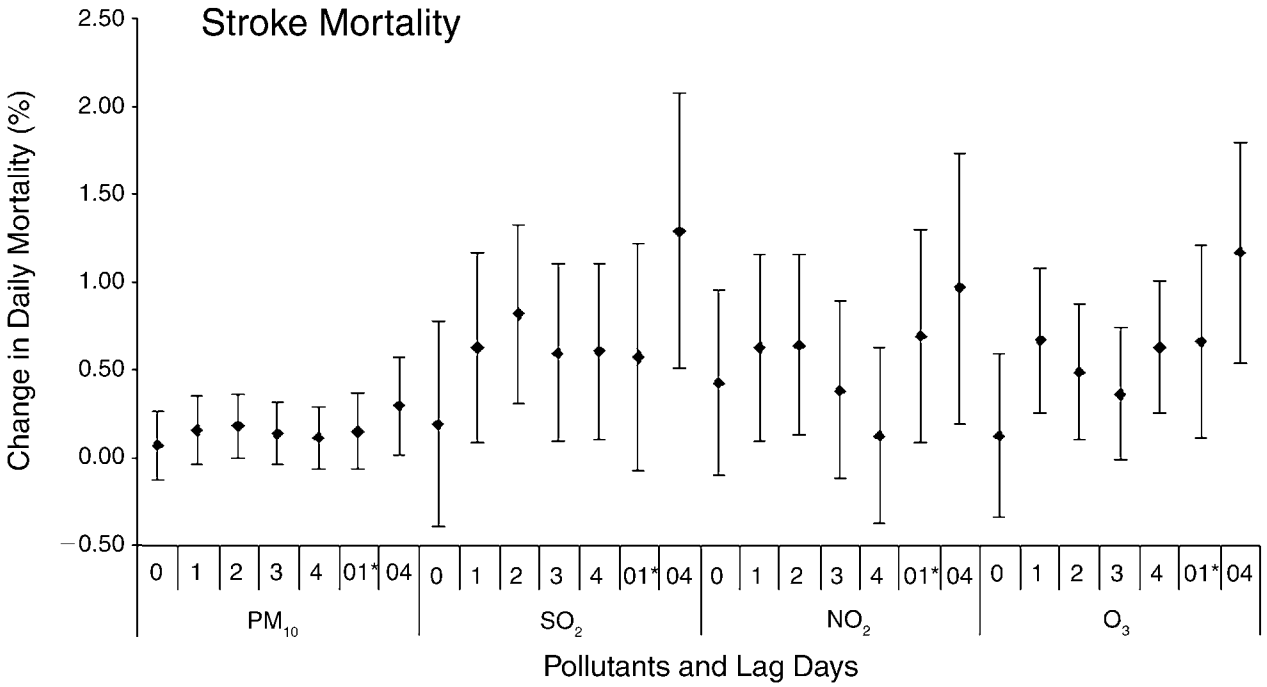

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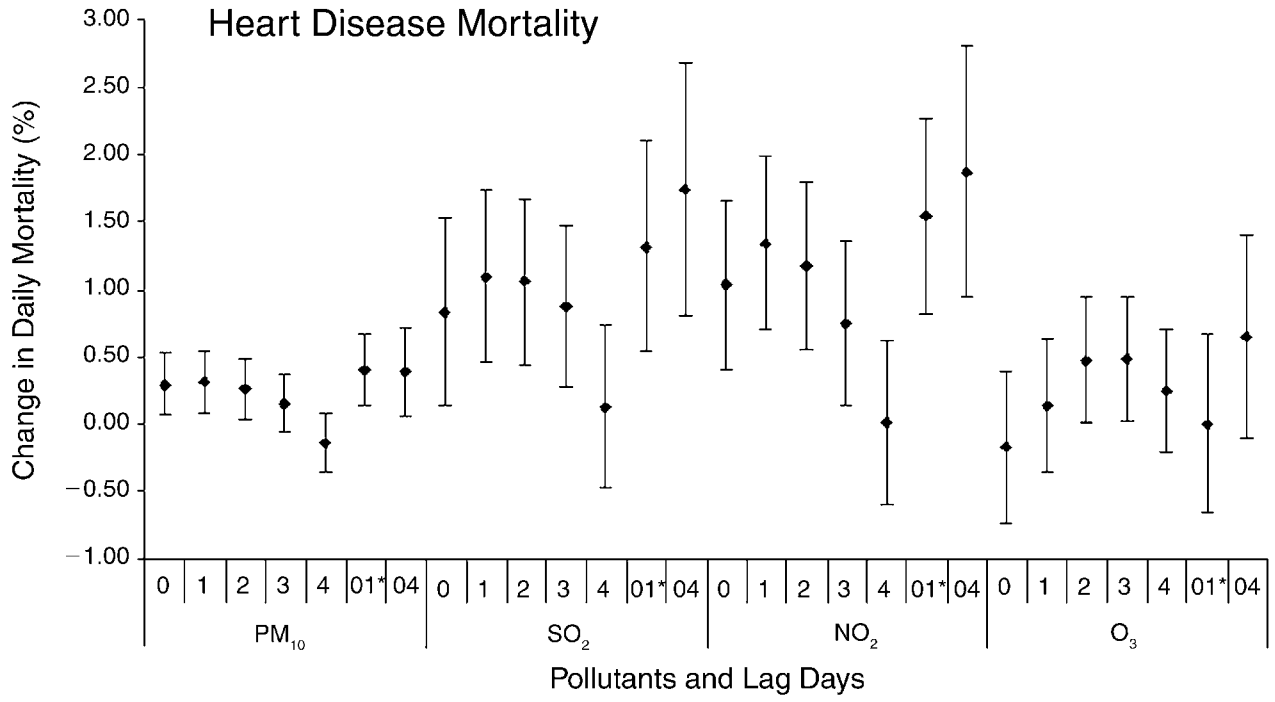

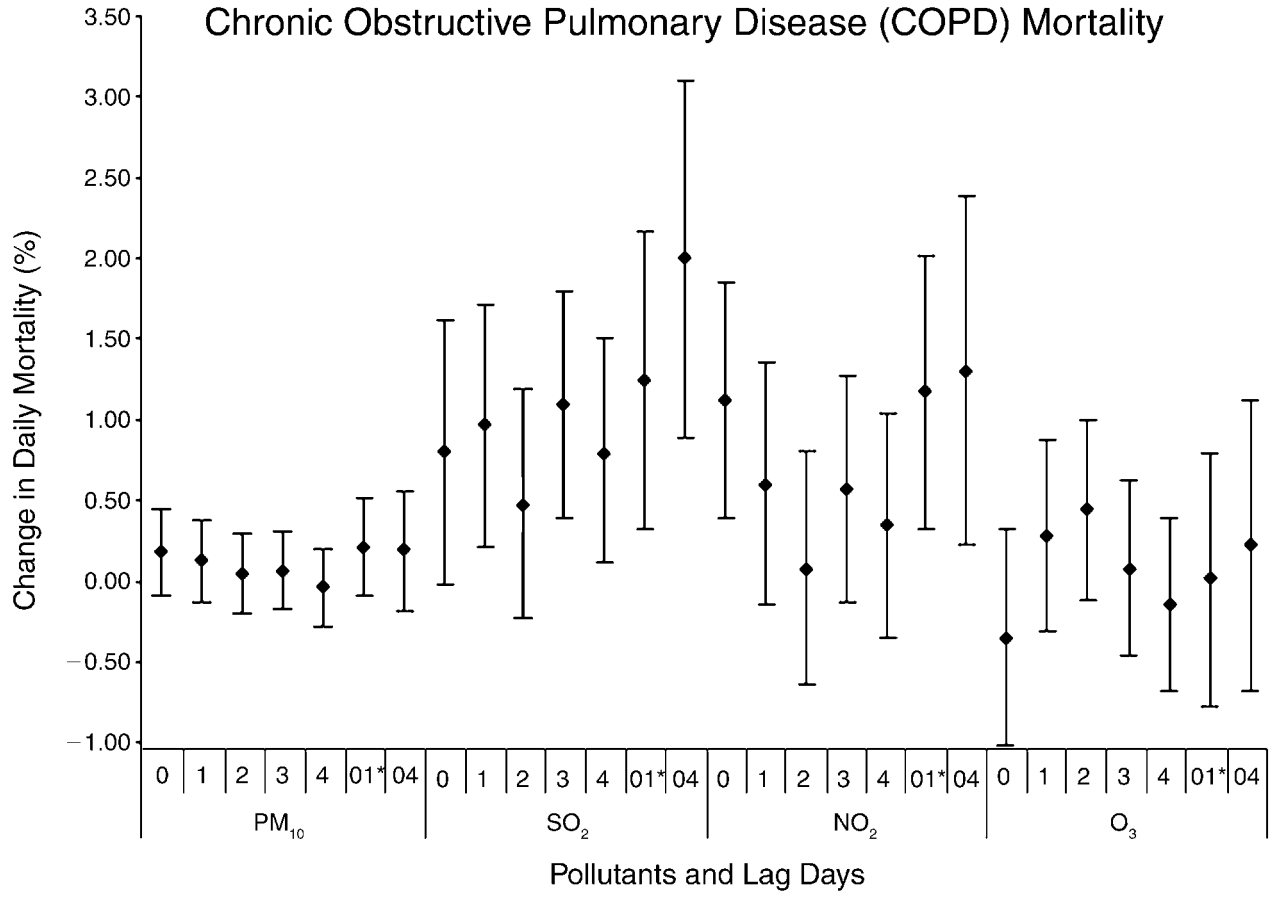

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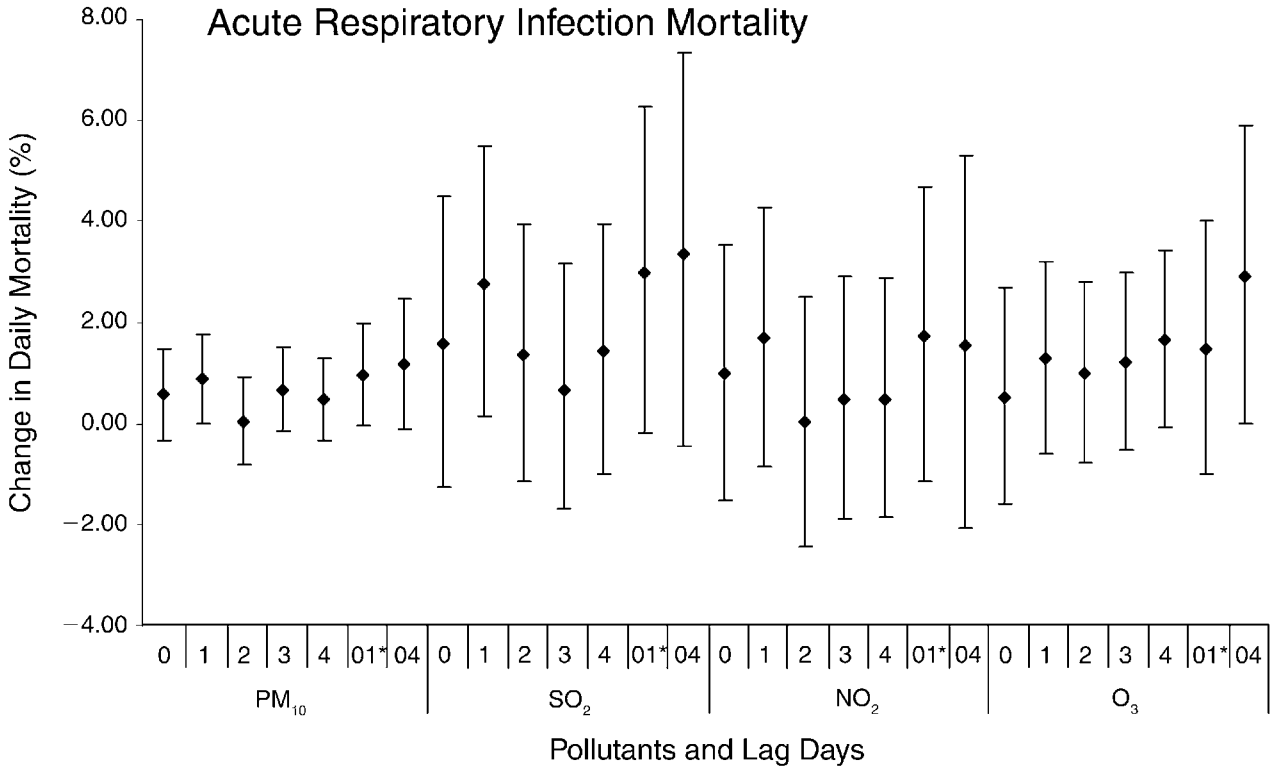

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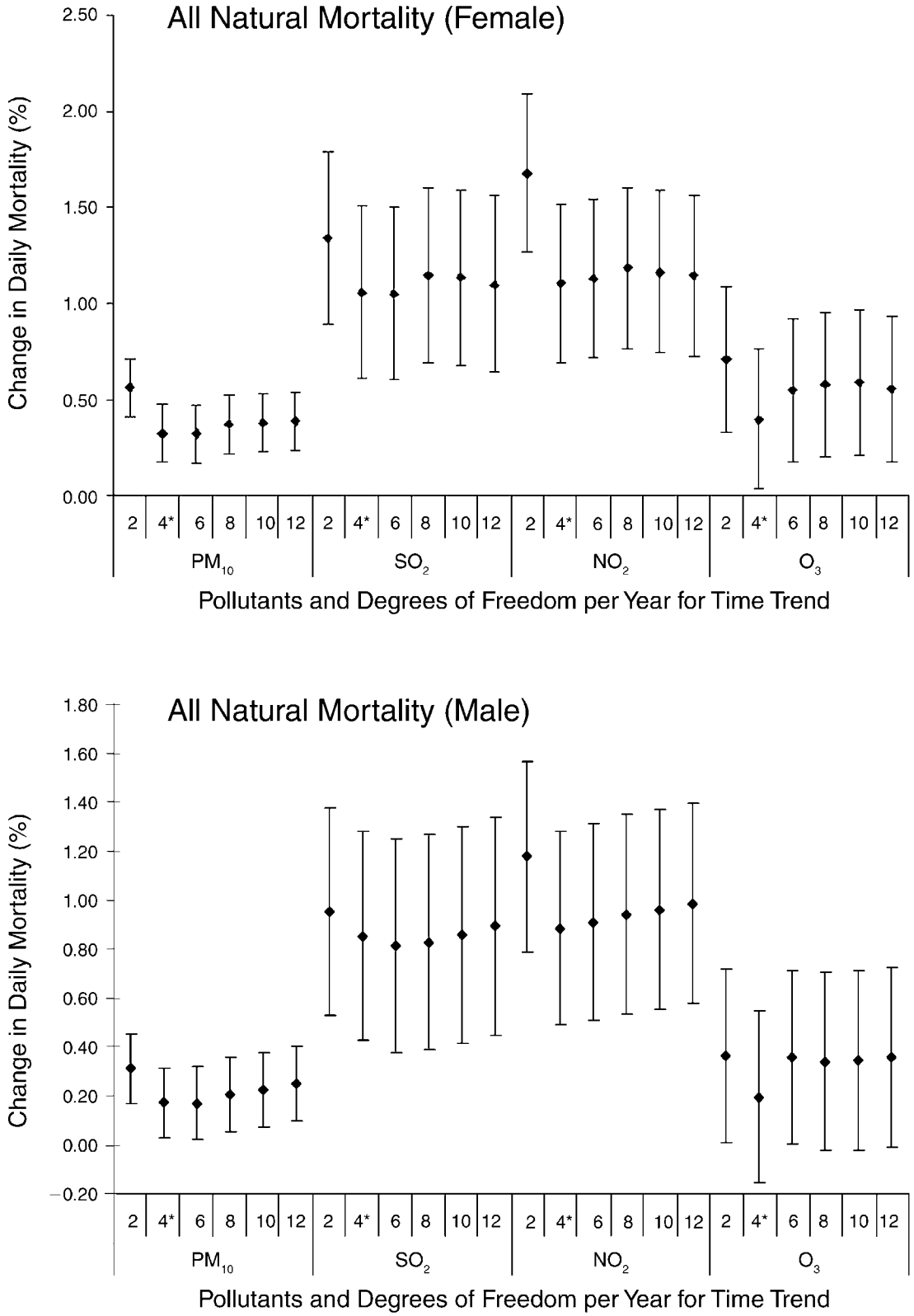
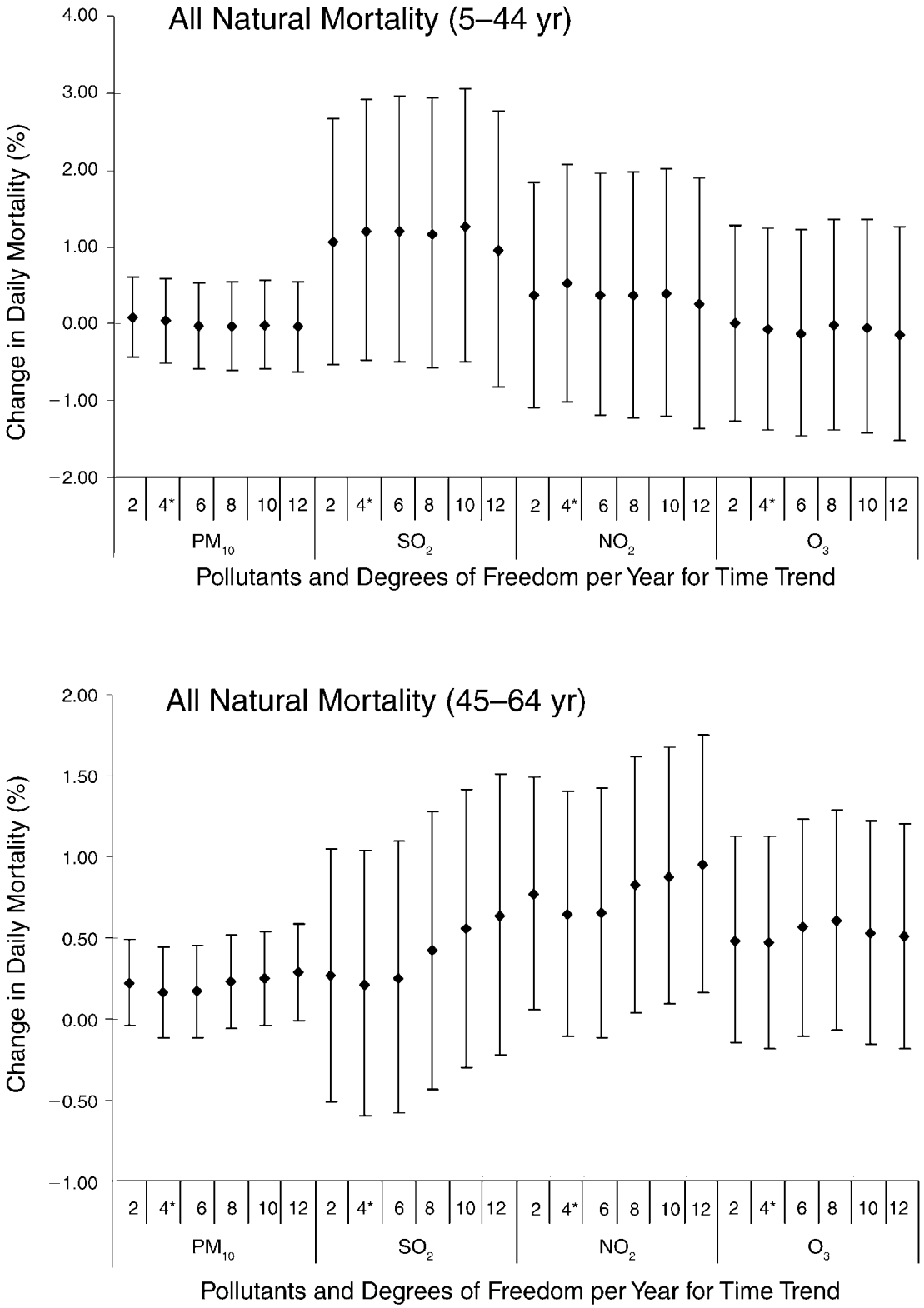


Figure C.3. Percentage changes in daily mortality associated with 10-μg/m^3 increases in 2-day moving average pollutant concentrations, using various degrees of freedom per year for time trend. Asterisks indicate the degrees of freedom used in the main analysis. See Table 3 for lag days for autoregression terms; 3 df were used for current-day temperature and relative humidity. Note differences in the scales of the *y*-axes.



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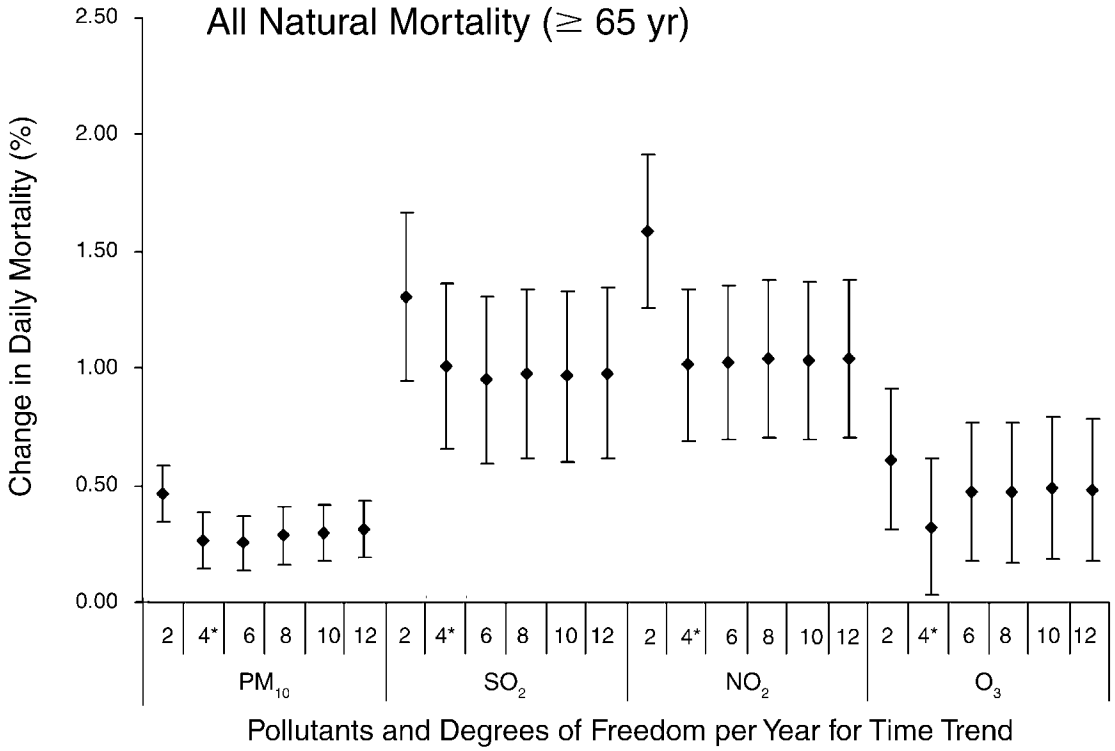

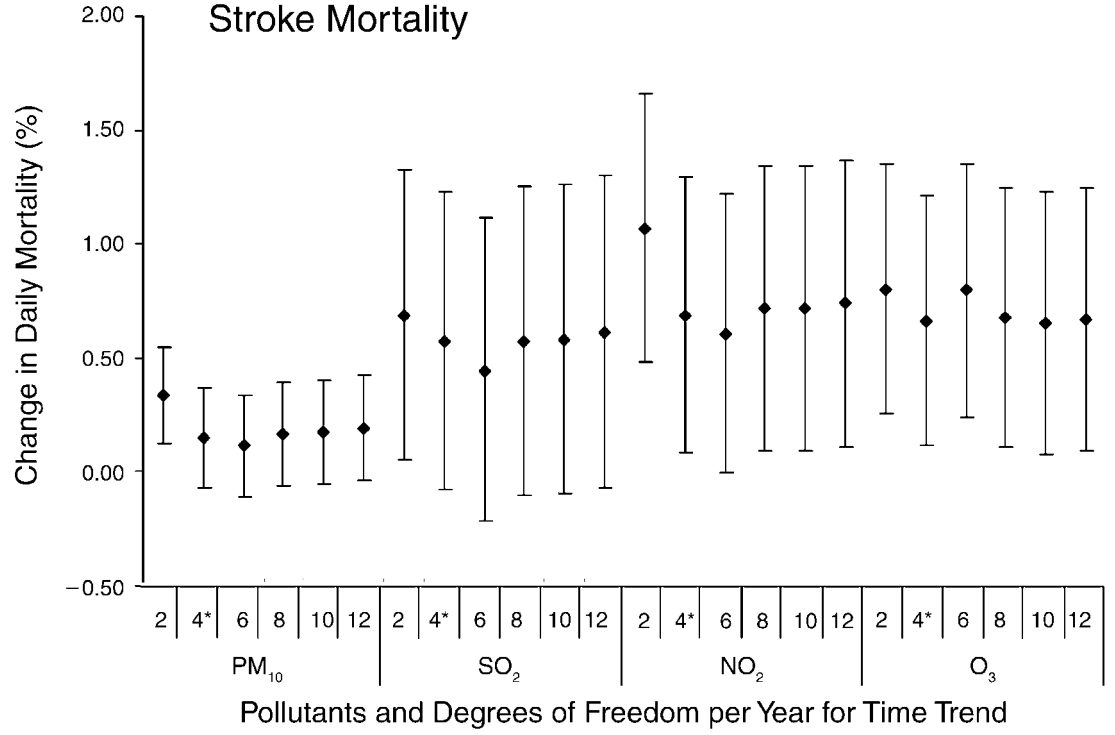

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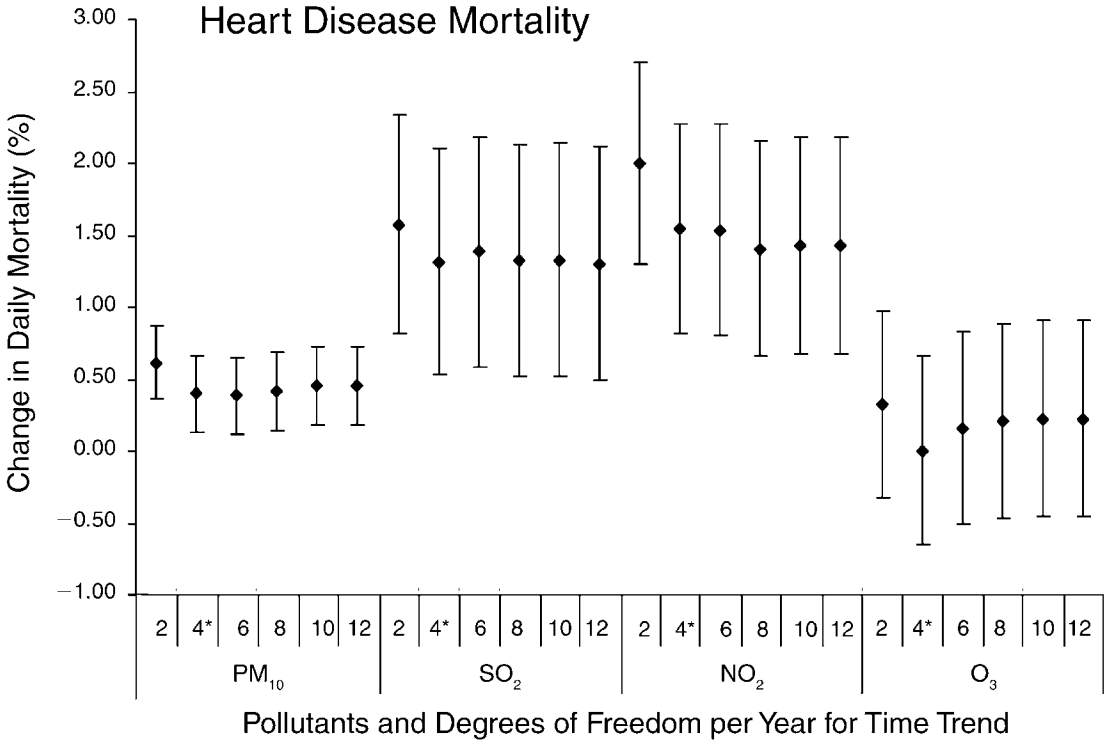

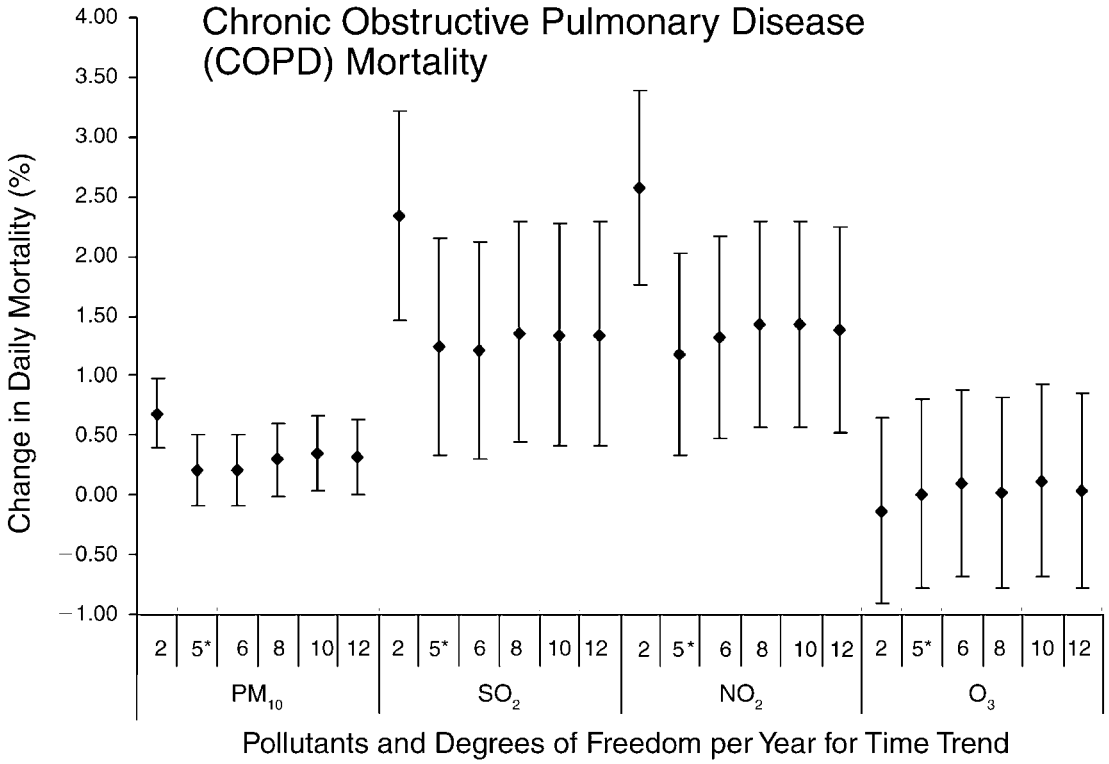

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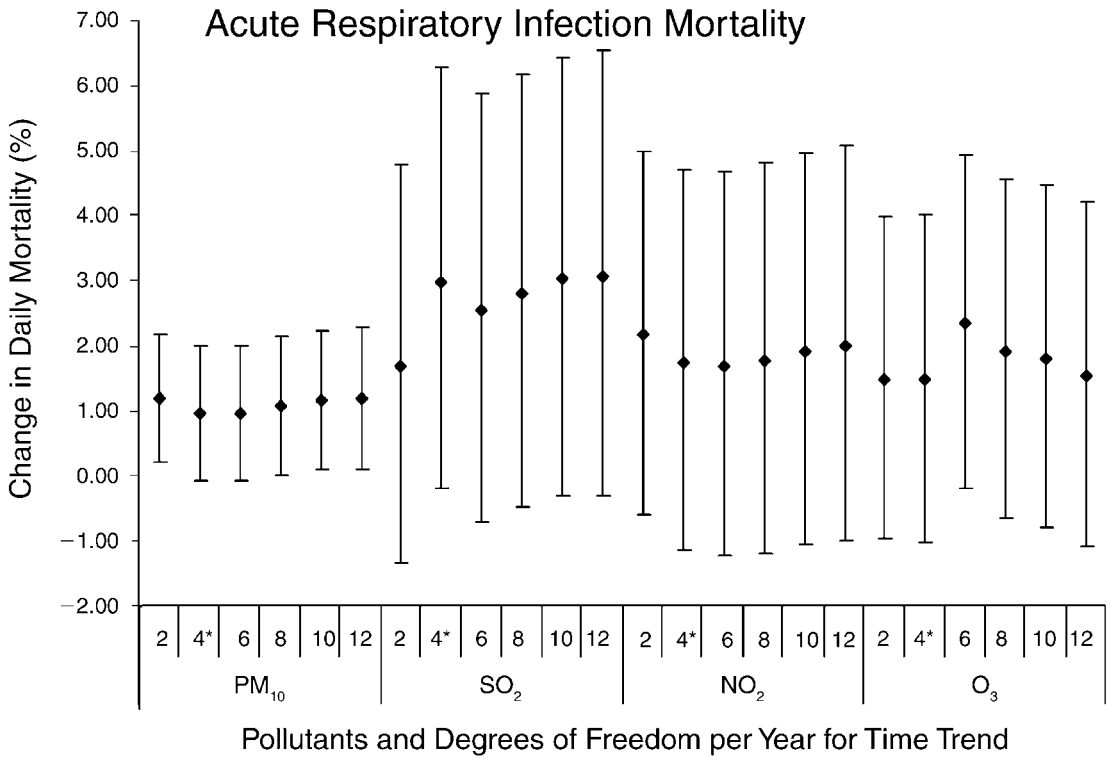

Figure C.3 (*Continued*).

Table C.1. Comparison of Sex- and Age-Specific Percentage Increases of All Natural Deaths Associated with Pollutant Concentrations When Using Models with One or Two Pollutants[a]

	Percentage Change in All Natural Mortality[b]				
	Sex		Age Group		
Models	Male Mean (95% CI)	Female Mean (95% CI)	5–44 Mean (95% CI)	45–64 Mean (95% CI)	≥ 65 Mean (95% CI)
PM_{10}					
Single-pollutant model	0.17 (0.03 to 0.32)	0.33 (0.18 to 0.48)	0.04 (−0.52 to 0.59)	0.17 (−0.11 to 0.45)	0.26 (0.15 to 0.38)
Two-pollutant model					
PM_{10} + SO_2	−0.03 (−0.22 to 0.16)	0.16 (−0.04 to 0.36)	−0.36 (−1.09 to 0.36)	0.20 (−0.16 to 0.57)	0.07 (−0.08 to 0.23)
PM_{10} + NO_2	−0.12 (−0.33 to 0.09)	0.09 (−0.13 to 0.30)	−0.19 (−0.96 to 0.60)	−0.01 (−0.41 to 0.39)	0.01 (−0.16 to 0.18)
PM_{10} + O_3	0.16 (0.02 to 0.31)	0.31 (0.16 to 0.46)	0.04 (−0.52 to 0.61)	0.13 (−0.15 to 0.42)	0.25 (0.13 to 0.37)
SO_2					
Single-pollutant model	0.85 (0.43 to 1.28)	1.06 (0.62 to 1.51)	1.21 (−0.47 to 2.91)	0.22 (−0.60 to 1.04)	1.01 (0.65 to 1.36)
Two-pollutant model					
SO_2 + PM_{10}	0.91 (0.35 to 1.48)	0.75 (0.17 to 1.34)	1.92 (−0.27 to 4.17)	−0.17 (−1.24 to 0.91)	0.87 (0.40 to 1.34)
SO_2 + NO_2	0.20 (−0.55 to 0.96)	0.26 (−0.51 to 1.05)	2.27 (−0.68 to 5.30)	−1.09 (−2.49 to 0.34)	0.35 (−0.27 to 0.98)
SO_2 + O_3	0.84 (0.41 to 1.27)	1.02 (0.58 to 1.47)	1.24 (−0.45 to 2.96)	0.15 (−0.67 to 0.98)	0.98 (0.62 to 1.34)
NO_2					
Single-pollutant model	0.88 (0.49 to 1.28)	1.10 (0.69 to 1.51)	0.52 (−1.01 to 2.08)	0.64 (−0.11 to 1.40)	1.01 (0.69 to 1.34)
Two-pollutant model					
NO_2 + PM_{10}	1.12 (0.55 to 1.69)	0.94 (0.35 to 1.52)	0.88 (−1.27 to 3.09)	0.66 (−0.42 to 1.75)	0.99 (0.53 to 1.46)
NO_2 + SO_2	0.73 (0.03 to 1.43)	0.90 (0.17 to 1.63)	−1.16 (−3.78 to 1.53)	1.48 (0.15 to 2.83)	0.74 (0.16 to 1.32)
NO_2 + O_3	0.88 (0.47 to 1.28)	1.06 (0.64 to 1.48)	0.57 (−1.00 to 2.17)	0.55 (−0.22 to 1.33)	0.98 (0.65 to 1.32)
O_3					
Single-pollutant model	0.19 (−0.16 to 0.55)	0.40 (0.03 to 0.76)	−0.08 (−1.38 to 1.25)	0.47 (−0.19 to 1.12)	0.32 (0.03 to 0.61)
Two-pollutant model					
O_3 + PM_{10}	0.12 (−0.24 to 0.47)	0.26 (−0.11 to 0.63)	−0.10 (−1.42 to 1.25)	0.41 (−0.25 to 1.08)	0.20 (−0.09 to 0.50)
O_3 + SO_2	0.11 (−0.24 to 0.46)	0.30 (−0.07 to 0.66)	−0.20 (−1.51 to 1.13)	0.45 (−0.20 to 1.11)	0.22 (−0.07 to 0.51)
O_3 + NO_2	0.03 (−0.33 to 0.38)	0.20 (−0.17 to 0.57)	−0.18 (−1.52 to 1.17)	0.36 (−0.30 to 1.03)	0.13 (−0.16 to 0.43)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving averages.

Table C.2. Comparison of Percentage Increases in Specific Subcategories of Mortality Outcomes Associated with Pollutant Concentrations When Using Models with One or Two Pollutants[a]

Models	Percentage Change in Mortality[b]			
	Stroke Mean (95% CI)	Heart Diseases Mean (95% CI)	Chronic Obstructive Pulmonary Disease Mean (95% CI)	Acute Respiratory Infection Mean (95% CI)
PM_{10}				
Single-pollutant model	0.15 (−0.07 to 0.37)	0.40 (0.13 to 0.66)	0.21 (−0.09 to 0.51)	0.95 (−0.07 to 1.98)
Two-pollutant model				
PM_{10} + SO_2	0.04 (−0.25 to 0.34)	0.18 (−0.17 to 0.54)	−0.11 (−0.50 to 0.29)	0.58 (−0.75 to 1.92)
PM_{10} + NO_2	−0.05 (−0.37 to 0.26)	−0.01 (−0.39 to 0.37)	−0.16 (−0.58 to 0.27)	1.03 (−0.39 to 2.47)
PM_{10} + O_3	0.11 (−0.11 to 0.33)	0.41 (0.14 to 0.68)	0.22 (−0.09 to 0.52)	0.88 (−0.16 to 1.93)
SO_2				
Single-pollutant model	0.57 (−0.08 to 1.23)	1.31 (0.53 to 2.10)	1.24 (0.33 to 2.16)	2.99 (−0.19 to 6.27)
Two-pollutant model				
SO_2 + PM_{10}	0.49 (−0.37 to 1.36)	0.95 (−0.08 to 1.99)	1.45 (0.25 to 2.66)	1.83 (−2.23 to 6.06)
SO_2 + NO_2	−0.13 (−1.28 to 1.03)	−0.21 (−1.58 to 1.18)	0.66 (−0.97 to 2.32)	4.31 (−1.24 to 10.17)
SO_2 + O_3	0.50 (−0.16 to 1.15)	1.33 (0.54 to 2.12)	1.25 (0.34 to 2.18)	2.84 (−0.36 to 6.14)
NO_2				
Single-pollutant model	0.69 (0.08 to 1.29)	1.54 (0.82 to 2.27)	1.18 (0.34 to 2.02)	1.73 (−1.14 to 4.69)
Two-pollutant model				
NO_2 + PM_{10}	0.79 (−0.07 to 1.66)	1.56 (0.52 to 2.61)	1.49 (0.30 to 2.69)	−0.29 (−4.21 to 3.78)
NO_2 + SO_2	0.79 (−0.29 to 1.88)	1.71 (0.41 to 3.02)	0.65 (−0.86 to 2.19)	−1.41 (−6.20 to 3.64)
NO_2 + O_3	0.56 (−0.05 to 1.18)	1.61 (0.87 to 2.35)	1.22 (0.36 to 2.08)	1.44 (−1.50 to 4.47)
O_3				
Single-pollutant model	0.66 (0.12 to 1.21)	0.00 (−0.65 to 0.66)	0.01 (−0.77 to 0.80)	1.47 (−1.01 to 4.01)
Two-pollutant model				
O_3 + PM_{10}	0.62 (0.06 to 1.17)	−0.17 (−0.83 to 0.49)	−0.09 (−0.88 to 0.71)	1.08 (−1.43 to 3.65)
O_3 + SO_2	0.62 (0.07 to 1.17)	−0.12 (−0.77 to 0.54)	−0.11 (−0.90 to 0.68)	1.26 (−1.23 to 3.80)
O_3 + NO_2	0.56 (0.01 to 1.12)	−0.29 (−0.94 to 0.38)	−0.20 (−1.00 to 0.60)	1.20 (−1.32 to 3.80)

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity were used.
[b] Changes in pollutant concentrations are per 10-μg/m^3 increases of 2-day moving average.

Table C.3. Comparison of Mortality Outcomes, Air Pollutant Concentrations, and Meteorologic Conditions in Warm and Cool Seasons in Shanghai, 2001–2004

Data / Season	Days (*n*)	Mean ± SD	Minimum	First Quartile	Median	Third Quartile	Maximum
Mortality Counts							
All natural							
Warm	732	106.1 ± 13.3	69.0	97.0	105.0	114.0	150.0
Cool	729	132.0 ± 22.4	51.0	117.0	131.0	146.0	198.0
Cardiovascular							
Warm	732	37.9 ± 7.0	19.0	33.0	38.0	42.0	63.0
Cool	729	50.5 ± 10.7	11.0	43.0	50.0	58.0	85.0
Respiratory							
Warm	732	11.4 ± 3.7	9.0	9.0	11.0	14.0	22.0
Cool	729	17.2 ± 7.2	3.0	12.0	16.0	22.0	45.0
Air Pollutant Concentrations (μg/m^3)[a]							
PM_{10}							
Warm	732	87.4 ± 48.2	15.6	53.3	75.8	109.0	166.8
Cool	729	116.7 ± 75.2	14.0	61.0	97.2	155.7	566.8
SO_2							
Warm	732	39.4 ± 19.8	8.4	25.0	36.0	49.4	123.0
Cool	729	50.1 ± 26.9	11.7	29.8	45.3	63.2	183.3
NO_2							
Warm	732	57.3 ± 20.3	13.6	44.2	54.2	69.0	151.0
Cool	729	76.0 ± 25.7	26.3	58.5	71.0	89.2	253.7
O_3							
Warm	732	78.4 ± 40.4	7.5	49.1	72.9	100.8	251.3
Cool	729	48.3 ± 24.7	5.3	30.8	44.0	62.4	187.0
Meteorologic Conditions							
Temperature (°C)							
Warm	732	24.3 ± 5.1	9.8	20.9	24.6	28.6	34.0
Cool	729	11.2 ± 5.8	−2.4	7.0	10.3	15.4	26.9
Relative humidity (%)							
Warm	732	75.1 ± 9.9	44.7	69.3	75.3	82.3	96.3
Cool	729	70.6 ± 12.3	33.3	62.5	70.0	79.0	97.0

[a] Using 24-hour averages for PM_{10}, SO_2, and NO_2 and maximum 8-hour means for O_3.

Table C.4. Linearity Test of the Exposure–Response Curve for All Natural, Cardiovascular, and Respiratory Mortality[a]

Pollutant / Mortality Category	χ^2	P
PM_{10}		
All natural	6.00	0.05
Cardiovascular	3.04	0.22
Respiratory	4.82	0.09
SO_2		
All natural	0.19	0.91
Cardiovascular	1.84	0.40
Respiratory	12.53	< 0.01
NO_2		
All natural	3.36	0.19
Cardiovascular	2.88	0.24
Respiratory	7.64	0.02
O_3		
All natural	4.95	0.08
Cardiovascular	2.18	0.34
Respiratory	0.03	0.99

[a] See Table 3 for degrees of freedom for time trend and lag days for autoregression terms; 3 df for current-day temperature and relative humidity and 2-day moving average pollutant concentrations were used.

APPENDIX D. HEI Quality Assurance Statement

The conduct of this study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of auditors with experience in toxicology, epidemiology, and air quality data. The audits included in-process monitoring of study activities for conformance to the study protocols and examination of records and supporting data. The dates of each audit are listed in the table below with the phase of the study examined:

QUALITY ASSURANCE AUDITS

Date	Phase of Study
May 23–24, 2005	This audit encompassed all aspects of the HEI study including visits to Fudan University, School of Public Health, Shanghai Municipal Center for Disease Control and Prevention, the local Xuhui District office of the Center for Disease Control and Prevention, the Shanghai Environmental Monitoring Center, and one air pollution monitoring site (Putuo) where $PM_{2.5}$ measurements are being made. HEI provided the audit team with copies of the 5- and 10-Month Progress Reports prior to the site visit. At Fudan University, the investigators provided copies of their individual research protocol (dated April 30, 2004) and a descriptive analysis of NO_2, O_3, SO_2, and PM_{10} concentration statistics. The descriptive analysis consisted of 16 tables of summary statistics, resolved by site and year, for the distributions of concentrations and their correlations between sites and between species.

Underlying air quality data were available on site at the Shanghai Environmental Monitoring Center, where requested selections were pasted by Mr. Guohai Chen and colleagues into a spreadsheet for inspection and manipulation by the auditor. In deference to expressions of discomfort by Center personnel, individual requests were generally limited in size to one or two site-pollutant-years of daily data or one or two site-pollutant-weeks of hourly data. As the 5- and 10-Month Progress Reports contain site- and year-resolved statistics only for data completeness and not for concentration, the more detailed statistics in the descriptive analysis were selected as the reference for the audit. The audit team learned only at the end of the visit that the data on which the descriptive analysis was based had not undergone the same level of validation as those summarized in the progress reports. All of the selected statistics from the descriptive analysis for SO_2, NO_2, and PM_{10} were successfully reproduced. More specifically, all distributional statistics in Tables 1 and 4 were reproduced exactly from the daily data for the following site-pollutant-years: SO_2 at Yangpu in 2001, PM_{10} at Xuhui in 2001, NO_2 at Putuo in 2004, and PM_{10} at Xuhui in 2004. The daily data were reproduced exactly from the hourly data for SO_2 at Yangpu, 4/7/01–4/13/01, PM_{10} at Xuhui, 7/1/01–7/7/01, NO_2 at Putuo, 10/20/04–10/25/04, and PM_{10} at Xuhui,

1/1/04–1/6/04. The weeks of hourly data were selected to include missing daily values, allowing us to confirm that 18 or more hours were required for a 24-hour average.

During a one-hour meeting at Fudan University, the audit team was allowed to examine binders that contained:

- Contracts and budgets: Fudan University Statement of Work (SOW), IRB approval, individual protocol, support letters, CVs, common protocol, etc.
- Minutes and correspondence: Printouts of all e-mails, presentations, and meeting minutes
- Progress reports: 5- and 10-Month Progress Reports and time table for PAPA projects
- Mortality data: Daily age- and sex-specific data for total mortality, daily cause-specific mortality data, health endpoints and the relevant codes in ICD-9 and ICD-10, blank death certificate, and training materials
- Meteorologic data: Temperature, daily max, min and mean in Celsius and atmospheric pressure and daily mean. Dew point temperature and daily mean and relative humidity (%) daily mean
- SOPs: ICD-10 and other QA/QC documents
- Air pollution monitoring QAPP and SOP
- Weather data guidelines for ground-level meteorologic monitoring with protocol and quality manual in Chinese

These records at Fudan University generally represented ancillary study documentation instead of primary data for audit. Where mortality summaries existed, a sample was photocopied so that it could be checked against other primary source data.

The audit team visited the Shanghai Center for Disease Control and Prevention, but hard-copy death certificates for the decedents in this study were not available at this location. A more recent set of death certificates was available from the Districts because they had been submitted to the Shanghai CDC as part of their routine audit functions. Since these death certificates were for decedents outside the study cohort, the audit team made several queries for mortality data that would verify the photocopies of study data previously obtained from Fudan University. Initially, these requests were formulated in database terms, but personnel had limited familiarity with this software (FoxPro) so queries were reformulated as spreadsheet (Excel) manipulations. This also proved difficult as it was clear that these queries were nonroutine and outside the scope of normal operations so a printed list of deaths occurring in the Xuhui District was requested on specific days. The audit team was then able to visit the Xuhui District office where 111 death certificates were pulled and 11 variables were compared to the previously obtained printout. The "fundamental" or underlying cause of death was audited against the ICD-10 classification in the study file to determine that proper coding had occurred.

April 4, 2008 — A draft of the final study report was examined for internal consistency and conformance with the study proposal. Comments were provided to HEI via e-mail.

A written report of the May 2005 audit was provided to the Director of Science of the Health Effects Institute, who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by experienced professionals in accordance with both study protocols. The final report appears to be an accurate representation of the study.

B. Kristin Hoover
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ABOUT THE AUTHORS

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OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Kan H, London SJ, Chen H, Song G, Chen G, Jiang L, Zhao N, Zhang Y, Chen B. 2007. Diurnal temperature range and daily mortality in Shanghai, China. Environ Res 103:424–431.

Zhang Y, Huang W, London SJ, Song G, Chen G, Jiang L, Zhao N, Chen B, Kan H. 2006. Ozone and daily mortality in Shanghai, China. Environ Health Perspect 114:1227–1232.

ABBREVIATIONS AND OTHER TERMS

APHEA-2	Air Pollution and Health: A European Approach – Phase 2
CI	confidence interval
COPD	chronic obstructive pulmonary disease
df	degrees of freedom
DOW	day of the week
GDP	gross domestic product
ICD-9	*International Classification of Diseases*, 9th revision
ICD-10	*International Classification of Diseases*, 10th revision
NMMAPS	National Morbidity, Mortality and Air Pollution Study
NO_2	nitrogen dioxide
O_3	ozone
PAPA	Public Health and Air Pollution in Asia
PM	particulate matter
$PM_{2.5}$	particulate matter ≤ 2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤ 10 μm in aerodynamic diameter
RR	relative risk
SD	standard deviation
SMCDCP	Shanghai Municipal Center of Disease Control and Prevention
SO_2	sulfur dioxide
TSP	total suspended particulate
UFP	ultrafine particle
VOC	volatile organic compounds

Research Report 154, Part 1. *A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China*, H. Kan et al.

INTRODUCTION

"A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China," by Dr. Haidong Kan and his colleagues from Fudan University in Shanghai, China, was conducted as part of four coordinated time-series studies of the health effects of short-term exposure to air pollution in major Asian cities. The studies are a principal component of HEI's Public Health and Air Pollution in Asia (PAPA*) program. Information on the origins, objectives, and scope of the PAPA program is provided in the Preface to this report. Background information on the demographic, health, and environmental conditions in the Shanghai study area and a brief review of previous epidemiologic research on the health effects of air pollution in Asia, including the Shanghai region, are presented in the Overview in this report.

Increases in concentrations of ambient air pollution have been associated with increases in mortality (Kinney and Ozkaynak 1991, Anderson et al. 1996, Ostro et al. 1996, Saez et al. 1996, Sunyer et al. 1996, Wietlisbach and Pope 1996, Touloumi et al. 1997). Most studies showing these associations have been conducted in cities in the United States or Europe; relatively few studies have been conducted in cities in Asia. The current study was conducted in Shanghai, the most populous city in China, and analyzed information on socioeconomic status in conjunction with daily ambient air pollution concentrations and mortality counts; data on socioeconomic status are important for environmental and social policy development in Asia.

Dr. Haidong Kan's 2-year study, "A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China," began in June 2004. Total expenditures were $148,250. The draft Investigators' Report from Kan and colleagues was received for review in September 2006. The revised report received in October 2007 was accepted for publication in December 2007. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

*A list of abbreviations and other terms appears at the end of the Investigators' Report.

OBJECTIVES AND SPECIFIC AIMS OF THE STUDY

Dr. Kan and his colleagues proposed a time-series study to investigate the short-term effects of several air pollutants on mortality, stratified by age, sex, and cause of death, in Shanghai. The investigators had access to data on ambient air pollutant concentrations of particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) and daily mortality data for the 4 years covering the period from January 1, 2001, to December 31, 2004. They also proposed to study the possible modification by gaseous copollutants of PM-related short-term adverse health effects and to explore the association between air pollution and previously reported age- and cause-specific mortalities, including acute respiratory infection in children. The specific aims addressed in the final report were as follows:

1. To investigate the short-term effects of the air pollutants PM_{10}, SO_2, NO_2, and O_3 on all natural and cause-specific mortality in Shanghai;
2. To examine the exposure–response relationships between air pollution concentrations and risk of mortality;
3. To study the possible independent roles of particulate matter (PM) and gaseous pollutants in producing short-term adverse health effects; and
4. To examine possible modifications of the air pollution–mortality association by individual socio-demographic characteristics and season.

DATA SOURCES

Computerized daily mortality data were obtained from January 1, 2001, to December 31, 2004, from the Shanghai Municipal Center of Disease Control and Prevention. Cause of death was classified using *International Classification of Diseases, Revision 9* (ICD-9) codes for deaths in 2001 and *Revision 10* (ICD-10) codes for deaths in 2002–2004. Deaths were classified as all natural (non-accidental), cardiovascular, respiratory, and accidental mortality. Air pollution data were obtained from the Shanghai Environmental Monitoring Center. The center provides semicontinuous data using quality assurance and control programs mandated by the State Environmental Protection Administration of China, which also certifies the system. Specific pollutant

species' indicators (8-hr mean for O_3 and 24-hr averages for the others) used in this study were derived from these measurements. Data on PM_{10}, NO_2, and SO_2 concentrations were obtained from five ambient monitoring stations, and data on ambient O_3 concentrations were obtained from two stations. Daily data that met the quality control criteria set forth in the Common Protocol (found at the end of this volume) were averaged to obtain values for use in centering analyses of air quality and health associations. Daily meteorologic data for the study period, including daily mean temperature and daily mean relative humidity, were obtained from the Shanghai Meteorologic Bureau.

Data on socioeconomic status consisted primarily of information on level of education obtained from death certificate data on individual decedents. Education levels were classified as "low" (illiterate or primary school only) and "high" (middle school or higher). Age strata and sex were also included in the analyses; these might also reflect some components of socioeconomic status.

DATA ANALYSIS

All statistical analyses were conducted in accordance with the Common Protocol for the PAPA program, using generalized additive models to examine associations between daily mortality (all natural and cause-specific) and air pollution over the study period. Regression models used natural spline smoothers with 4 to 6 degrees of freedom (df) per year to control for time trend and 3 df to control for potential confounding effects of weather. Two-day moving averages of current- and previous-day concentrations of pollutants (lag 0–1 day [average]) were used in the main analyses, with analytic control for the potentially confounding effects of current-day temperature (lag day 0). Unless otherwise specified, all results are presented as percent change in daily mortality per 10-μg/m^3 increase in the 2-day moving average of pollutant concentrations.

In sensitivity analyses, the impact of alternative specifications of pollutant lag structures, extended temperature lags, different degrees of temporal smoothing, and alternative pollutant concentration metrics (e.g., average pollutant concentrations versus centering) was considered. All analyses were conducted using R software and the mgcv package.

RESULTS

DAILY MORTALITY AND POLLUTANT INFORMATION

Commentary Table 1, which summarizes information from Table 1 of the Investigators' Report as well as Table 1 of Kan et al. 2008, shows that during the study period Shanghai had an average of 119 deaths/day from all natural causes, 44.2 deaths/day from cardiovascular causes, and 14.3 deaths/day from respiratory causes.

Commentary Table 2 shows that Shanghai had an average PM_{10} concentration of 102 μg/m^3, though the maximum observed (567 μg/m^3) was quite high when compared with

Commentary Table 1. Mean Daily Deaths[a] in Shanghai, 2001–2004

Mortality Category	Entire Period	Warm Season	Cool Season
All natural (nonaccidental)	119.0 ± 22.5	106.1 ± 13.3	132.0 ± 22.4
Cardiovascular	44.2 ± 11.0	37.9 ± 7.0	50.5 ± 10.7
Respiratory	14.3 ± 6.4	11.4 ± 3.7	17.2 ± 7.2

[a] Values are expressed as mean ± standard deviation.

Commentary Table 2. Average Pollutant Concentrations and Weather Conditions in Shanghai, 2001–2004

	Entire Period Mean ± SD	Maximum	Warm Season Mean ± SD	Cool Season Mean ± SD
Air Pollutant Concentrations (μg/m^3)				
PM_{10}	102.0 ± 64.8	567	87.4 ± 48.2	116.7 ± 75.2
SO_2	44.7 ± 24.2	183	39.4 ± 19.8	50.1 ± 26.9
NO_2	66.6 ± 24.9	254	57.3 ± 20.3	76.0 ± 25.7
O_3	63.3 ± 36.7	251	78.4 ± 40.4	48.3 ± 24.7
Meteorologic Conditions				
Temperature (°C)	17.7 ± 8.5	34	24.3 ± 5.1	11.2 ± 5.8
Relative humidity (%)	72.9 ± 11.4	97	75.1 ± 9.9	70.6 ± 12.3

data in the literature. These PM_{10} concentrations were consistent with those for Hong Kong and Wuhan, the other PAPA study locations in China. SO_2 concentrations were higher on average in Shanghai than in the other PAPA study locations, and O_3 concentrations were roughly consistent for all locations. Day-to-day variability in measurements of pollutants was large, particularly for PM_{10}.

The investigators reported moderate Pearson correlations between NO_2 and PM_{10} ($r = 0.71$), NO_2 and SO_2 ($r = 0.73$), and PM_{10} and SO_2 ($r = 0.64$). O_3 was weakly correlated with the other three pollutants (r values less than 0.2) (adapted from Kan et al. 2008, Table 1).

ASSOCIATIONS BETWEEN DAILY MORTALITY AND INDIVIDUAL POLLUTANTS

Commentary Table 3 summarizes the key associations found between daily deaths by mortality category and individual pollutants in single-pollutant models. These data are also shown in Figure 9 and Table 4 of the Investigators' Report.

The main findings in Shanghai were that short-term increases in the concentrations of all of the air pollutants (PM_{10}, NO_2, SO_2, and O_3), using mean pollutant concentrations at lag 0–1 day (average), were associated with increased daily all natural (non-accidental) mortality.

The estimated excess risks for pollutant effects stratified by age subgroups were generally consistent with the overall estimate for all ages, although the individual subgroup estimates were less stable. Estimates were similar to the overall estimate for those who died of cardiovascular causes (Table 4 in the Investigators' Report). For respiratory deaths, effect estimates for NO_2 and SO_2 were slightly larger than those for the other categories of death, but their confidence intervals overlapped heavily (Table 4). None of the pollutants showed evidence of association with increases in accidental mortality, but for all of the pollutants there was some evidence of an increase in non-accidental, non-cardiopulmonary mortality on days with increased pollutant concentrations.

The dose–response models (Figure 9 in the Investigators' Report) showed a range of shapes; not all were linear. However, once uncertainty in the estimates was taken into account, most effects were consistent with linear dose–response associations. The primary exceptions were PM_{10} for all natural mortality and O_3 for all natural and cardiovascular-related mortality.

TWO-POLLUTANT MODELS

In two-pollutant models, only the associations of NO_2 were relatively insensitive to the inclusion of other pollutant terms (Table 5 in the Investigators' Report). This implies that only the health effects attributed to NO_2 were not likely to have been confounded or modified by the effects of pollutants with correlated measurements, whereas the health effects associated with PM_{10}, SO_2, and O_3 might be partly attributed to or modified by the effects of correlated pollutants.

ANALYSIS OF EFFECT MODIFICATION

The mortality effects of the pollutants (except for O_3) were greater in people with a lower level of education; effect estimates for all natural mortality for all pollutants (except for O_3) were approximately two times higher for these people (Table 6 in the Investigators' Report). Several pollutant effects were different in the warm and cool seasons, and test results for interactions were significant for three pollutants in the respiratory-mortality subgroup (Table 7 in the Investigators' Report). However, this subgroup had the smallest number of deaths, and several of the warm-season estimates for PM_{10}, SO_2, NO_2, and respiratory mortality indicated possible protective effects (although their confidence intervals [CIs] overlap 0), suggesting that these interactions should be interpreted with extreme caution.

Commentary Table 3. Summary Table of Key Associations Between Daily Mortality by Mortality Category and Individual Pollutants in Single-Pollutant Models

Mortality Category	Percentage Increase in Daily Mortality[a]			
	PM_{10}	SO_2	NO_2	O_3
All natural	0.26 (0.14 to 0.37)	0.95 (0.62 to 1.28)	0.97 (0.66 to 1.27)	0.31 (0.04 to 0.58)
Cardiovascular	0.27 (0.10 to 0.44)	0.91 (0.42 to 1.41)	1.01 (0.55 to 1.47)	0.38 (−0.03 to 0.80)
Respiratory	0.27 (−0.01 to 0.56)	1.37 (0.51 to 2.23)	1.22 (0.42 to 2.01)	0.29 (−0.44 to 1.03)

[a] Percentage increase in daily mortality per 10-μg/m^3 increase in respective pollutant at lag days 0–1 (average) for entire sample. Values expressed as excess risk (95% CI).

SENSITIVITY ANALYSES

The positive associations between individual pollutants and daily mortality in single-pollutant models were largely robust to differences in degree of smoothing for time (Table 8 of the Investigators' Report), choice of regression spline (natural or penalized) (Table 8), and centering of pollutant concentrations (Table 9 of Investigators' Report). The effects of PM_{10} were only slightly attenuated by inclusion of longer lags for humidity and temperature, but the effects of NO_2 and SO_2 were more substantially attenuated; the effects of O_3 were unaffected by the longer lags for weather conditions (Figure 11 in the Investigators' Report).

HEI EVALUATION OF THE STUDY

The HEI Review Committee assessed the quality of the data, the analytic design and methods, and the results reported by Dr. Kan and colleagues. The Committee then reviewed the investigators' conclusions about the health effects of short-term exposure to air pollution on mortality and the extent to which these effects were modified by the socioeconomic variables in the data and correlations between measurements of pollutants. General comments on analytic methods in the Common Protocol (found at the end of this volume) that apply to this and the other PAPA studies are included in the Integrated Discussion (in Part 5 of the volume).

ASSESSMENT OF HEALTH OUTCOMES

Health endpoints commonly investigated in time-series studies were also investigated in the current study. In contrast to the findings of most time-series mortality studies, pollutant effect estimates (excess risk) were not in general substantially larger for those who died of cardiovascular causes. Increased effect estimates for this subgroup are generally taken to reflect the fact that those with underlying cardiovascular disease are more susceptible than others to health effects caused by air pollution. For those who died of respiratory causes, excess risk estimates for NO_2 and SO_2 were slightly larger than for those who died of other causes, whereas estimates for PM_{10} and O_3 were of similar magnitude.

As in the finding of the other PAPA studies, all of the pollutants were significantly associated with increases in non-accidental, non-cardiopulmonary mortality, and no pollutant was associated with increases in accidental mortality.

MONITORING AND EXPOSURE ESTIMATION IN SHANGHAI

Like the other PAPA studies, the current study relied on routine monitoring data from a government-operated network that was largely made up of standard data-collection methods. Measurements were made of gases (NO_2, SO_2, and O_3) and PM_{10}. Following the Common Protocol, the investigators used statistical centering to develop averaged concentrations for use in their analyses. It was not apparent why the investigators chose the monitors used or what their reasoning was for excluding other monitors in the Shanghai area. Only a very brief characterization was made of the region's pollution sources and dynamics, and there was no discussion of how specific sources might have affected specific monitoring locations. Such a discussion would have allowed readers to better assess the appropriateness of using the selected monitors.

Only two O_3 monitors met the data-completeness criteria specified in the Common Protocol; O_3 exposure estimation was thus driven by O_3 concentrations measured at the stations of just these two monitors. If one of the stations was missing data, the measurements from the other station drove the entire daily value, though the centering approach used minimized the impact of having different station means. Further, correlations between O_3 concentrations at the two stations were reasonably high. One concern is that the median measured O_3 concentration was lower than global atmospheric background concentrations, and even the 75th percentile was near global background concentrations, indicating that O_3 concentrations were being affected, and usually reduced, by local sources (O_3 concentrations are reduced by fresh emissions of other pollutants). O_3 and PM_{10} data (see Table B.4 of the Investigators' Report) were not highly correlated ($r = 0.16$), suggesting that there would be relatively little confounding between the two pollutants. Likewise, O_3 was not highly correlated with SO_2 ($r = 0.04$) or NO_2 ($r = 0.15$). On the other hand, PM_{10} was moderately correlated with SO_2 and NO_2 ($r = 0.62$ and $r = 0.68$, respectively). The low O_3 correlations with the other pollutants reinforce the likelihood that local sources were affecting O_3 concentrations and that reduced O_3 concentrations might reflect, in part, increases in other pollutants.

Regional concentrations of PM_{10}, SO_2, and NO_2 appeared to vary over time in a similar fashion (site-to-site Pearson correlations ranged from 0.44 to 0.78 for NO_2 and from 0.88 to 0.97 for PM_{10}), suggesting that the averaged concentrations accurately reflected the daily variation in those pollutant concentrations. The site-to-site Pearson correlation for O_3 was 0.85. These results suggest that the average calculated values captured the day-to-day regional variations in pollutant concentrations and that there was relatively low spatial variation in these pollutant species in Shanghai. The results also indicate that the temporal variations in pollutant concentrations were driven by regional weather: however, this might have been caused partially by the investigators' choice of monitoring

stations. If the relatively high site-to-site correlations reflect the region's pollutant concentrations, then the centering approach used should still provide a good estimate of local exposure variability.

Concentrations of NO_2, PM_{10}, and SO_2 were all moderately correlated (*r* values ranged from 0.62 to 0.80), suggesting that the various sources affecting the region were more or less homogeneously distributed and had a regional impact. These pollutant concentrations also suggest that traffic, industry, and power production all contribute to pollution in Shanghai. The investigators noted that, although pollution related to coal combustion is decreasing, pollution related to traffic is increasing. O_3 was weakly correlated with the other pollutants (*r* values ranged from 0.04 to 0.16).

ASSESSMENT OF ANALYTIC AND STATISTICAL METHODS

Analyses of the sensitivity of key results to the degrees of freedom in the time smoother (up to 12 df/year; Figure 12 in the Investigators' Report) were reassuring, with little sensitivity identified for 4 df/year or more, which was the minimum allowed. Sensitivity to inclusion of lags for temperature greater than the default lag 0 day (lag 1–2 days [average], 3–7 [average], and both; Figure 11 in Investigators' Report) was higher, though all associations remained after further adjustment. The changes in estimated risk for daily all natural mortality, associated with SO_2 for example, decreased from about 0.9% (95% CI, 0.6 to 1.3) in the default model (lag 0 day) to about 0.4% (95% CI, 0.1 to 0.7) for the two larger temperature lags taken together. The PM_{10} and O_3 percentage changes were more robust. All effects remained statistically significant, even with the most aggressive control for weather. The robustness to degree of temporal smoothing and the persistence of effects even with more aggressive control for weather are reassuring in that they show the effects were not caused by arbitrary specifications of confounders in the models.

The approach to investigating modification of pollution effects by other factors (age, sex, education, and season) was a little different from that taken in the other PAPA studies. In the current study, separate models were fitted to each category of age, sex, season, and education, and the resulting pollution coefficient estimates were compared on the assumption that they were independent. This approach uses distinct time and temperature smoothing for each category. It gains robustness by allowing factors such as season to have different effects in each category, though the separate models cannot borrow strength across categories. This is a particular concern for season-specific categories where smooth functions of time have disconnected segments. It is thus possible not only that these models might sacrifice some power compared with single models with interaction terms, but also that they are likely to give less stable estimates of the effects of long-term time trend and seasonality. However, it is not clear how a smooth function of time was incorporated into the seasonally stratified models.

EPIDEMIOLOGY AND INTERPRETATION

Features of Shanghai

Like all of the PAPA cities, Shanghai has a relatively large population that experiences a large number of deaths per day (119 deaths per day on average, as reported by Dr. Kan and colleagues). This should translate into better power to detect pollutant effects than existed for studies carried out in cities with smaller populations. The age distribution of Shanghai is more similar to that of Hong Kong and the United States than that of the other PAPA cities (Bangkok and Wuhan). People aged 65 years or older made up more than 10% of the population during the time period of the time series used by the investigators. To the extent that the elderly are more susceptible to air pollution effects, possibly because of increased susceptibility to adverse health events, a study in Shanghai should have had as much opportunity to detect effects as time-series studies in the West do. In addition, concentrations of air pollutants in Shanghai were high compared with those typically measured in Western cities.

Pollutant-Specific Effects and Robustness

Overall, this study did not provide strong evidence favoring any of the four pollutants over the others in producing the estimated short-term effects of pollution on mortality. The investigators found increased mortality due to all natural causes for all four of the pollutants they studied. These excess-risk estimates were highest for NO_2 and SO_2. However, only the effects of NO_2 were largely robust to adjustment for the effects of the other pollutants in two-pollutant models. Effects of both PM_{10} and SO_2 were sensitive to adjustment for NO_2. In contrast, the effect of NO_2 was more sensitive to more aggressive control for the effects of weather than for the effects of O_3 or PM_{10}. The dose–response evaluation suggested some nonlinearity in the dose–response curves, particularly for PM_{10} and O_3. These relationships affected the overall linear dose–response estimates. The authors noted that the relationships remained after additional sensitivity analyses and suggested that alternative explanations could include residual confounding in multiple-pollutant effects. At face value, these findings indicate a dominant role for NO_2 in Shanghai compared with the other three air pollutants. There is little

justification, however, at least based on what is known at this point about NO_2 toxicity, for attributing effects on all natural mortality, and therefore cardiovascular mortality, to direct toxic effects of NO_2. Overall, the current study, like the other three PAPA time-series studies, does not provide convincing evidence that would favor one pollutant over another in having produced the estimated short-term exposure effects on mortality.

Interactions and Stratified Analyses for Sensitive Subgroups

The authors noted that stratified analyses by sex showed a tendency for effect estimates to be higher for women. Results of analyses by age were variable but largely consistent in magnitude with the estimate for the total natural mortality effect. The confidence intervals for these subgroups generally overlapped, and there was no strong evidence of effect modification by sex or age in this study. Similarly, effect modification analyses for level of education and for season detected only a few interactions.

Interpretation of stratified and effect-modification results should take into account the multiplicity of comparisons made. The authors should be commended for having directly tested for interactions between their effect estimates in their assessment of effect modification. Very few statistically significant interactions were found, as one would expect in the absence of effect modifications. For season, for which the largest number of interactions were detected, potential residual confounding should be considered. Futhermore, several of the warm-season estimates indicated possible protective effects, a result that does not seem to be biologically plausible (Weiss 2008). The absence of any analyses of the sensitivity of these results to the extent of control for smooth variation over time (which are problematic in any case for seasonally stratified analyses) or for weather gives us additional reasons to exercise particular caution when interpreting these results.

CONCLUSION

The results from this study suggest that outdoor air pollution in Shanghai was associated with mortality from all natural causes and cardiopulmonary-related mortality. The authors noted that these associations were present even at pollutant concentrations below those of the current Chinese air quality standards (150, 150, and 80 $\mu g/m^3$ for daily average concentration of PM_{10}, SO_2, and NO_2, respectively). The findings were generally unchanged by alternative model specifications, and the methods employed by the investigators were generally sound.

The results from the study and the magnitude and direction of the observed associations were broadly consistent with estimates from meta-analyses of relevant published studies of other parts of China (Kan et al. 2005) and Asia (HEI International Scientific Oversight Committee 2004) and with meta-analyses of time-series studies conducted in North America and Europe (Stieb et al. 2002). Although this study reported suggestive evidence that individuals with lower levels of education might experience greater health effects caused by pollutant exposure, the Committee urges that this evidence be interpreted cautiously, given the multiplicity of tests conducted and the conflicting evidence in the literature (O'Neill et al. 2003). The Committee also feels that the evidence of effect modification by season was even weaker and that, given the analysis approach, residual confounding cannot be ruled out.

The study, although well conducted, had several limitations. In addition to issues discussed in the Integrated Discussion (in Part 5 of this volume), the time series analyzed for this study was relatively short (4 years). Given the high correlation between PM and certain gaseous pollutants (NO_2 and SO_2), it would be difficult, based on this study, to disentangle the individual effects of the pollutants on daily mortality. High intercorrelation between pollutants is a common challenge in time-series studies.

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REFERENCES

Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP. 1996. Air pollution and daily mortality in London: 1987-92. BMJ 312:665–669.

HEI International Scientific Oversight Committee. 2004. Health Effects of Outdoor Air Pollution in Developing Countries of Asia: A Literature Review. Special Report 15. Health Effects Institute, Boston, MA.

Kan HD, Chen BH, Chen CH, Wang BY, Fu QY. 2005. Establishment of exposure–response functions of air particulate

matter and adverse health outcomes in China and worldwide. Biomed Environ Sci 18:159–163.

Kan H, London S, Chen G, Zhang YH, Song GX, Zhao NQ, Jiang L. 2008. Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: The Public Health and Air Pollution in Asia (PAPA) Study. Environ Health Perspect 116: 1183–1188.

Kinney PL, Ozkaynak H. 1991. Associations of daily mortality and air pollution in Los Angeles County. Environ Res 54:99–120.

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, Wilkinson P, Fletcher T, Cifuentes L, Schwartz J; Workshop on Air Pollution and Socioeconomic Conditions. 2003. Health, wealth, and air pollution: Advancing theory and methods. Environ Health Perspect 111: 1861–1870.

Ostro B, Sanchez JM, Aranda C, Eskeland GS. 1996. Air pollution and mortality: Results from a study of Santiago, Chile. J Expo Anal Environ Epidemiol 6:97–114.

Saez M, Tobias A, Munoz P, Campbell MJ. 1999. A GEE moving average analysis of the relationship between air pollution and mortality for asthma in Barcelona, Spain. Stat Med 18:2077–2086.

Stieb DM, Judek S, Burnett RT. 2002. Meta-analysis of time-series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season. J Air Waste Manag Assoc 52:470–484.

Sunyer J, Castellsague J, Saez M, Tobias A, Anto JM. 1996. Air pollution and mortality in Barcelona. J Epidemiol Community Health 50:s76–s80.

Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, Ponce de Leon A, Tobias A, Quennel P, Rabczenko D, Bacharova L, Bisanti L, Vonk JM, Ponka A. 1997. Short-term effects of ambient oxidant exposure on mortality: A combined analysis within the APHEA project. Air Pollution and Health: A European Approach. Am J Epidemiol 146:177–185.

Weiss NS. 2008. Subgroup-specific associations in the face of overall null results: Should we rush in or fear to tread? Cancer Epidemiol Biomarkers Prev 17:1297.

Wietlisbach V, Pope CA III, Ackermann-Liebrich U. 1996. Air pollution and daily mortality in three Swiss urban areas. Soz Praventivmed 41:107–115.

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