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**Manuscript title:** The short-term effect of air pollution on cardiovascular mortality in Tianjin, China: comparison of time series and case–crossover analyses

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## Abstract:

**Background:** Many studies have illustrated that ambient air pollution negatively impacts on health. However, little evidence is available for the effects of air pollution on cardiovascular mortality (CVM) in Tianjin, China. Also, no study has examined which strata length for the time-stratified case–crossover analysis gives estimates that most closely match the estimates from time series analysis.

**Objectives:** The purpose of this study was to estimate the effects of air pollutants on CVM in Tianjin, China, and compare time-stratified case–crossover and time series analyses

**Method:** A time-stratified case–crossover and generalized additive model (time series) were applied to examine the impact of air pollution on CVM from 2005 to 2007. Four time-stratified case–crossover analyses were used by varying the stratum length (Calendar month, 28, 21 or 14 days). Jackknifing was used to compare the methods. Residual analysis was used to check whether the models fitted well.

**Results:** Both case–crossover and time series analyses show that air pollutants ($PM_{10}$, $SO_2$ and $NO_2$) were positively associated with CVM. The estimates from the time-stratified case–crossover varied greatly with changing strata length. The estimates from the time series analyses varied slightly with changing degrees of freedom per year for time. The residuals from the time series analyses had less autocorrelation than those from the case–crossover analyses indicating a better fit.

**Conclusion:** Air pollution was associated with an increased risk of CVM in Tianjin, China. Time series analyses performed better than the time-stratified case–crossover analyses in terms of residual checking.

**Key words:** air pollution; cardiovascular mortality; case–crossover; time series;

## 1. Introduction

Many epidemiological studies have shown that short-term increases in ambient air pollutants are associated with an acute rise in mortality (Touloumi et al., 2005), hospital admissions (Dominici et al., 2006), and emergency hospital visits (Guo et al., 2009). However, most studies were conducted in western countries (where people have different demographic characteristics compared with Asian countries) and used time series and case–crossover analysis separately. Also, studies of the health effects of air pollution on mortality and morbidity in China, have mostly been conducted in Beijing (Guo et al., 2009; Guo et al., 2010), Shanghai (Kan et al., 2008), Shenyang (Xu et al., 2000), Wuhan (Qian et al., 2007), and Taiyuan (Zhang et al., 2007). To our knowledge, few studies have assessed the relationship between air pollution and cardiovascular mortality (CVM) in Tianjin, a large industrial city in northern China.

Time series and case–crossover analyses are the most common methods used to estimate the short-term effects of air pollution on health (Fung et al., 2003; Schwartz, 2004). Time series analysis allows for over dispersion associated with the Poisson distribution and controls for long-term trend and seasonality using nonparametric or parametric splines. The generalized additive model (GAM) is often used to examine associations between air pollution and health (Dominici et al., 2002; Samet et al., 2000).

The case–crossover compares exposure during a case day when events occurred (e.g., deaths) with exposures in nearby control days to examine whether the events are associated with a particular exposure. Because the control days are selected close to the case days, seasonality is controlled for by design. Confounding for day of the week can be controlled by choosing control days with the same day of the week as the case days. Confounders related to individual characteristics (e.g., age, sex and smoking) are also controlled by design. There are many different designs for choosing control days relative to a case day. We considered three:

unidirectional, bidirectional and time-stratified.

A unidirectional design selects fixed control day(s) per case day only before or after the case day. For example, the air pollution exposure was selected seven days before or after the case day. This design does not control for trends over time in air pollution or health outcomes, and so is subject to bias (Greenland, 1996).

Bidirectional designs include the full-stratum bidirectional (Navidi, 1998), symmetric bidirectional (Bateson and Schwartz, 1999), and semi-symmetric case–crossover (Navidi and Weinhandl, 2002). The full-stratum bidirectional case–crossover was designed to include all exposures in the time series before and after the case days as control days. This design controls for time trends in exposure, but does not control for seasonal patterns in exposure or health outcomes (Bateson and Schwartz, 1999).

The symmetric bidirectional design uses control days both before and after the case day. This method can successfully control for seasonality in exposures and outcomes. However, there is the potential for selection bias, because the cases at the beginning or end of the data series have fewer control days for matching. Navidi and Weinhandl (2002) noted that the symmetric case–crossover design might still be biased by time trends from exposure.

The semi-symmetric design randomly selects a control day before or after the case day. This design can also control for long-term trends and seasonality. However, because only one control day is selected at a fixed interval, the estimates may still be biased (Levy et al., 2001). Lumley and Levy (2000) illustrated how selection biases do not appear when cases may occur at any time in the strata from which the controls are selected. This design is the initial principle of the time-stratified case–crossover. They demonstrated that most of the above designs are biased because the controls are not chosen independently of the case day. This bias is called the “overlap bias” and occurs in case–crossover designs with non-disjointed strata (Lumley and Levy, 2000). Janes et al. (2005) demonstrated that the overlap bias is not an issue for the time-stratified design.

As the time-stratified case–crossover uses fixed and disjointed time strata (e.g., calendar month), the overlap bias is avoided. Studies have shown that case–crossover analyses are equivalent to time series analyses (Basu et al., 2005; Fung et al., 2003). However, no study has examined which strata length gives results most similar to a time series analysis, and no study has used residual analyses to check the adequacy of time-stratified case–crossover models.

The aims of this study were to explore whether there was any short-term effect of air pollution on CVM in Tianjin, China, and to compare the time series and time-stratified case–crossover analyses.

## 2. Materials and methods

### 2.1. Data collection

Tianjin is a city in northeastern China, and is a directly-controlled municipality by the central government of China. Tianjin is adjacent to the Beijing city and Hebei Province, along the coast of the Bohai Gulf (39° 07' North, 117° 12' East). Tianjin has four clear seasons, with cold, windy, dry winters influenced by the vast Siberian anticyclone, and hot, humid summers due to the monsoon. It is the fifth largest Chinese city in terms of urban land area. The population in the urban area was 4.24 million in 2005.

Mortality data were obtained from the China Information System for Death Register and Report of Chinese Centre for Disease Control and Prevention (China CDC) from January 1, 2005 to December 31, 2007. The mortality data were from six urban districts of Tianjin (Heping, Hedong, Hexi, Nankai, Hebei and Hongqiao). Data on cardiovascular deaths were classified according to the International Classification of Disease, 10th revision (ICD10: I00-I99).

Daily air pollution data on particulate matter less than 10 μm in aerodynamic diameter

($PM_{10}$), sulfur dioxide ($SO_2$) and nitrogen dioxide ($NO_2$) were obtained from the Tianjin Environmental Monitoring Centre. Daily mean temperature and relative humidity were obtained from the China Meteorological Data Sharing Service System.

### 2.2. Data analysis

Applying time series analyses using generalized additive models (GAMs), we controlled for trend and season using a natural spline. In order to investigate the best possible control, the degrees of freedom per year for time were varied. We plotted the relative risks of current day's air pollution against the degrees of freedom per year (Peng and Dominici, 2008). The best degrees of freedom were chosen by finding the value beyond which the relative risks did not change (Peng and Dominici, 2008).

A polynomial distributed lag model was used to examine which day's exposure to air pollution had the strongest association with CVM. We examined the lagged effect for up to ten days, and used a polynomial smooth with four degrees of freedom (Santos et al., 2008).

As a comparison to the time series analysis we used a time-stratified case–crossover analysis. Four types of time-stratified design were used. The data were stratified by calendar month (Method A) and strata of 28 days (Method B), 21 days (Method C) and 14 days (Method D). Control days were also matched to case days by day of the week. This is why all strata used were multiples of seven days except method A.

Jackknifing is used in statistics to estimate standard errors and biases (Rothpearl, 1989). The basic principle is sub-setting the available data into many subsamples, and systematically computing estimates in the new subsamples. The bias and variance for estimates of any statistic can be calculated from these new subsamples. In this study we used jackknifing to sequentially remove strata from the data, and then the time series and case–crossover analyses were repeated. The removed strata for the time series analysis and method A were calendar month. The removed strata for method B were 28 days, for method C 21 days, and for method D 14 days. Using this method we obtained multiple estimates for the effects of air pollution on CVM. The differences between the effect estimates from the time series and case–crossover analyses were assessed using box plots and ANOVA with post hoc testing.

The conditional logistic regression used in case–crossover analysis is a special case of time series log-linear model (Lu et al., 2008; Lu and Zeger, 2007). The log-linear models were used to fit case–crossover analyses in this study. This means we can obtain the model residuals for case-crossover analyses from the log-linear models. Model residuals were examined to evaluate the adequacy of the time series and case–crossover models.

Daily mean temperature, relative humidity, public holidays, and influenza outbreaks were controlled for in all models (Braga et al., 2001). We controlled for day of the week as a categorical covariate in the time series models. Relative risks (RRs) for time series analysis, odds ratios (ORs) for time-stratified case–crossover analysis, and 95% confidence intervals (CIs) were calculated for each pollutant. All statistical tests were two-sided, and values of $P<0.05$ were considered statistically significant. R software (version 2.10.1) was used to do data analysis, the “dlnm” package was used to construct the polynomial distributed lag basis (Armstrong, 2006; Gasparrini et al., 2010), and the “mgcv” package was applied to fit the time series GAM.

## 3. Results

Table 1 gives descriptive statistics for the daily weather conditions, air pollutants, and mortality. The mean concentrations for $PM_{10}$, $SO_2$, and $NO_2$ were 105 $\mu g/m^3$, 68 $\mu g/m^3$, and 47 $\mu g/m^3$, respectively, which were similar to the national secondary ambient air quality standard in China ((GB 3095-1996), $PM_{10} = 100\ \mu g/m^3$, $SO_2 = 60\ \mu g/m^3$, $NO_2 = 40\ \mu g/m^3$). From 2005 to 2007 the mean concentrations for $PM_{10}$, $SO_2$ and $NO_2$ decreased by 10.5%, 16.9% and 8.0%, respectively. There were 30 daily deaths on average and a total of 32,387 cardiovascular deaths during the study period. There were seasonal patterns in air pollutants, as the concentrations of all pollutants were higher in winter (Figure 1).

Figure 2 shows the relative risks of the air pollutants on CVM estimated for a range of degrees of freedom per year using time series GAMs. The largest estimates for all pollutants were for 1 degree of freedom per year. When the degrees of freedom per year were more than 6, the estimates for all pollutants tended to be stable. Therefore, 6 to 9 degrees of freedom per year were used in the following analyses.

Figure 3 shows the distributed lag effects of air pollutants on CVM using 6 degrees of freedom per year for time. The current day's exposure to all three pollutants had the highest hazardous effects on CVM. Therefore, we used the current day's exposure to pollution in the following analyses.

Table 2 shows the associations between a 10 $\mu g/m^3$ increase in the current day's air pollution and CVM, using time series and case–crossover analyses. The results show that both $PM_{10}$ and $NO_2$ were significantly associated with CVM, but no statistically significant associations were found for $SO_2$.

Figure 4 compares the time series and time-stratified case–crossover analyses using jackknifing. The effect estimates from time series analyses were reasonably consistent for the different degrees of freedom per year. The estimates using a time-stratified case–crossover with different strata length varied significantly. The case–crossover with strata length for a calendar month or 28 days had the most similar estimates compared with the time series analyses for exposure to $SO_2$. The estimates using a strata length of 21 days were higher than the time series estimates, while a strata length of 14 days gave lower estimates. The variance in the jackknifed estimates using the smallest strata length of 14 days was greater than for the other methods.

ANOVA with post hoc testing found that the mean effect estimates of all time-stratified case–crossover analyses were significantly different to the time series analyses ($P<0.001$, table S1, S2, and S3), except for the strata length of a calendar month and 28 days for exposure to $SO_2$ ($P>0.1$, table S2), and the strata length of 14 days for exposure to $NO_2$ ($P>0.1$, table S3).

The over-dispersion parameters for the time series and time-stratified case–crossover models showed that there was moderate over-dispersion in all the models (Table S4). The time series analyses had much less autocorrelation in the residuals compared with the case–crossover analyses, which indicates a better fit for the time series (Fig S1 and S2).

## 4. Discussion

### 4.1. The health effects of air pollution

We examined the relationship between air pollution and CVM in Tianjin, China. The three air pollutants studied were positively associated with CVM, using both time series and time-stratified case–crossover analysis.

Ambient air quality is a serious issue closely related to cardiovascular mortality and morbidity. Many studies have shown that air pollution has adverse effects on CVM (Brook et al., 2010; Lopez-Villarrubia et al., 2010). For example, Touloumi et al. (2005) illustrated that a 10 $ug/m^3$ increase in PM10 (lag 0–1 days) was associated with a 0.86% (95% CI: 0.53–1.19%) increase in CVM. Jerrett et al. (2009) found that an increase of 4 ppb in $NO_2$ was associated with a 40% increase in CVM. Also, studies have found air pollution has impacts on heart rate variability (Zanobetti et al., 2010) and T-wave alternans (a marker of cardiac electrical instability) (Zanobetti et al., 2009).

Previous studies on biologic mechanisms show that air pollution is associated with aconitine-induced cardiac arrhythmia in hypertensive rats (Hazari et al., 2009), blood pressure (Bartoli et al., 2009), acute arterial vasoconstriction (Brook et al., 2002), and C-reactive protein (Pope et al., 2004). All those factors are directly or indirectly related to the function of the cardiovascular system.

The impacts of air pollution on human health have been drawing increasing concern from the environmental health research community, government, society, industries, and the general population. It is estimated that over 600 million people living in urban areas throughout the world are exposed to hazardous levels of air pollution (Cacciola et al., 2002). Ambient air pollution is also one of the most serious environmental problems in the urban area of Tianjin, where air pollution is mainly from industrial sources. Currently, $PM_{10}$, $SO_2$ and $NO_2$ are criteria pollutants that are regularly monitored in Tianjin (Wang, 2009). Coal burning constitutes the biggest part of all energy sources, especially in winter. However, because the number of motor vehicles has rapidly increased in recent years, the composition of air pollution has changed from conventional coal combustion to mixed coal combustion and motor vehicle emissions.

### 4.2. Comparison of time series and time-stratified case–crossover analyses

We compared the time series and time-stratified case–crossover analyses using jackknifing and residual checking. One aim was to assess which strata length for the case–crossover was most consistent with the time series analyses. Figure 4 shows that it is difficult to define which strata length consistently produces similar results to a time series analysis. This is probably because of differences between pollutants in the strength of their seasonal pattern. Based on residual checking, the time series analyses gave better estimates than the time-stratified case–crossover analyses, as there was far less autocorrelation in the residuals. This could be caused by the case–crossover assuming a step-like seasonal change (Barnett and Dobson, 2010), whereas the time series models used here assumed a smoothly changing seasonal pattern. Therefore, the case–crossover control for season is too crude, and some residual seasonal pattern remains.

Previous studies comparing time series and case–crossover analysis only used the overall results (i.e., single estimates), and so had no variance from which to compare the estimates. In this paper we used jackknifing in order to more broadly compare the time series and case–crossover analyses. Therefore, we obtained many estimates for each design, and used box plots and ANOVA to compare the differences in estimates. The time-stratified case–crossover with different strata length produced significantly different estimates compared with the time series analyses, except for a strata length of 28 days or calendar month for exposure to $SO_2$.

The residual checks indicate that the time series controlled better for autocorrelation compared with the time-stratified case–crossover analyses, especially for the strata length of 14 and 21 days (Figure S1 and figure S2). Figueiras et al. (2005) pointed out that if the impact of autocorrelation on estimates has been successfully controlled for, the case–crossover analysis can be a good alternative to time series analysis using Poisson regression. However, the time-stratified case–crossover analysis has the advantage that the effects of unmeasured confounding variables that do not vary over time are controlled for by design.

Sensitivity analyses were performed by changing the smoothing degrees of freedom from 12 to 24 per year for time in time series, which roughly corresponds with the degrees of freedom used by our time-stratified designs. The estimated effects did not change greatly. However, these models gave a poorer fit to the data as judged by the residual checking, as there were relatively large negative correlations at short lags for 18 degrees of freedom or more.

### 4.3. Strengths and limitations

This study has two key strengths. Firstly, it supplies new evidence that exposure to ambient air pollution is a hazard to cardiovascular health in Tianjin China, which may have implications for local environmental and social policies. Secondly, jackknifing and residual analyses were used to compare time series and time-stratified case–crossover analyses. The results show that time series were more suitable for this particularly study. This study also gives additional information on choosing the strata length when using the time-stratified case–crossover.

This study also has two major limitations. We only used data from one city, and caution is required in the generalisability of our findings. Also, as with other similar studies in this field, we obtained the available data on ambient air pollution and weather conditions from fixed monitoring stations and assumed that they adequately represent the exposure for the population. There will inevitably be some measurement error for exposure. However, such bias is likely to lead to an underestimate of the health effects of pollution.

## Conclusion

In this study, the air pollution levels in Tianjin were slightly higher than the national secondary ambient air quality standard in China, and the elevated concentration of air pollution was positively associated with CVM.

We found that the time series analyses was superior to time-stratified case–crossover analyses due to two reasons: time series analyses gave more consistent estimates with changing degrees of freedom, the residuals from the time series showed less autocorrelation.

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## References

Armstrong B. Models for the relationship between ambient temperature and daily mortality. Epidemiology 2006; 17: 624-31.

Barnett AG, Dobson AJ. Analysing Seasonal Health Data. Berlin, Heidelberg: Springer, 2010.

Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, et al. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. Environ Health Perspect 2009; 117: 361-6.

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

Bateson TF, Schwartz J. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. Epidemiology 1999; 10: 539-44.

Braga AL, Zanobetti A, Schwartz J. The time course of weather-related deaths. Epidemiology 2001; 12: 662-7.

Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation 2002; 105: 1534-6.

Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 2010; 121: 2331-78.

Cacciola RR, Sarva M, Polosa R. Adverse respiratory effects and allergic susceptibility in relation to particulate air pollution: flirting with disaster. Allergy 2002; 57: 281-6.

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

Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA

2006; 295: 1127-34.

Figueiras A, Carracedo-Martinez E, Saez M, Taracido M. Analysis of case-crossover designs using longitudinal approaches: a simulation study. Epidemiology 2005; 16: 239-46.

Fung KY, Krewski D, Chen Y, Burnett R, Cakmak S. Comparison of time series and case-crossover analyses of air pollution and hospital admission data. Int J Epidemiol 2003; 32: 1064-70.

Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. Stat Med 2010; 29: 2224-34.

Greenland S. Confounding and exposure trends in case-crossover and case-time-control designs. Epidemiology 1996; 7: 231-9.

Guo Y, Jia Y, Pan X, Liu L, Wichmann HE. The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing, China. Sci Total Environ 2009; 407: 4826-30.

Guo Y, Tong S, Zhang Y, Barnett AG, Jia Y, Pan X. The relationship between particulate air pollution and emergency hospital visits for hypertension in Beijing, China. Sci Total Environ 2010.

Hazari MS, Haykal-Coates N, Winsett DW, Costa DL, Farraj AK. A single exposure to particulate or gaseous air pollution increases the risk of aconitine-induced cardiac arrhythmia in hypertensive rats. Toxicol Sci 2009; 112: 532-42.

Janes H, Sheppard L, Lumley T. Overlap bias in the case-crossover design, with application to air pollution exposures. Stat Med 2005; 24: 285-300.

Jerrett M, Finkelstein MM, Brook JR, Arain MA, Kanaroglou P, Stieb DM, et al. A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. Environ Health Perspect 2009; 117: 772-7.

Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N, et al. 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 2008; 116: 1183-8.

Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, et al. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 2001; 12: 193-9.

Lopez-Villarrubia E, Ballester F, Iniguez C, Peral N. Air pollution and mortality in the Canary Islands: a time-series analysis. Environ Health 2010; 9: 8.

Lu Y, Symons JM, Geyh AS, Zeger SL. An approach to checking case-crossover analyses based on equivalence with time-series methods. Epidemiology 2008; 19: 169-75.

Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. Biostatistics 2007; 8: 337-44.

Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. Environmetrics 2000; 11: 689-704.

Navidi W. Bidirectional case-crossover designs for exposures with time trends. Biometrics 1998; 54: 596-605.

Navidi W, Weinhandl E. Risk set sampling for case-crossover designs. Epidemiology 2002; 13: 100-5.

Peng RD, Dominici F. Statistical Methods for Environmental Epidemiology in R: A Case Study in Air Pollution and Health: New York, NY: Springer Publishing Company, 2008.

Pope CA, 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 2004; 112: 339-45.

Qian Z, He Q, Lin HM, Kong L, Liao D, Dan J, et al. Association of daily cause-specific mortality with ambient particle air pollution in Wuhan, China. Environ Res 2007; 105: 380-9.

Rothpearl A. The jackknife technique in statistical analysis. Chest 1989; 95: 940.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000; 343: 1742-9.

Santos UP, Terra-Filho M, Lin CA, Pereira LA, Vieira TC, Saldiva PH, et al. Cardiac arrhythmia emergency room visits and environmental air pollution in Sao Paulo, Brazil. J Epidemiol Community Health 2008; 62: 267-72.

Schwartz J. The effects of particulate air pollution on daily deaths: a multi-city case crossover analysis. Occup Environ Med 2004; 61: 956-61.

Touloumi G, Samoli E, Quenel P, Paldy A, Anderson RH, Zmirou D, et al. Short-term effects of air pollution on total and cardiovascular mortality: the confounding effect of influenza epidemics. Epidemiology 2005; 16: 49-57.

Wang Z. Current Status' Analysis of Energy Consumption Structure and Atmosphere's Quality in Tianjin. ENERGY OF CHINA 2009; 31: 35-38.

Xu Z, Yu D, Jing L, Xu X. Air pollution and daily mortality in Shenyang, China. Arch Environ Health 2000; 55: 115-20.

Zanobetti A, Gold DR, Stone PH, Suh HH, Schwartz J, Coull BA, et al. Reduction in heart rate variability with traffic and air pollution in patients with coronary artery disease. Environ Health Perspect 2010; 118: 324-30.

Zanobetti A, Stone PH, Speizer FE, Schwartz JD, Coull BA, Suh HH, et al. T-wave alternans, air pollution and traffic in high-risk subjects. Am J Cardiol 2009; 104: 665-70.

Zhang YP, Zhang ZQ, Liu XH, Zhang XP, Feng BQ, Li HP. [Concentration-response relationship between particulate air pollution and daily mortality in Taiyuan]. Beijing Da Xue Xue Bao 2007; 39: 153-7.

Table 1: Summary statistics of daily air pollutants, weather conditions and cardiovascular mortality Tianjin, China, 2005–2007

| | Minimum | 25% | Median | 75% | Maximum | Mean | SD |
|---|---|---|---|---|---|---|---|
| $PM_{10}$(μg/m$^3$) | 11 | 68 | 92 | 128 | 452 | 105 | 57 |
| $SO_2$ (μg/m$^3$) | 5 | 33 | 49 | 88 | 339 | 68 | 54 |
| $NO_2$ (μg/m$^3$) | 18 | 35 | 43 | 56 | 136 | 47 | 18 |
| Temperature (°C) | –11 | 3 | 14 | 24 | 31 | 13 | 11 |
| Humidity (%) | 13 | 46 | 61 | 74 | 97 | 60 | 19 |
| Cardiovascular deaths | 9 | 24 | 29 | 35 | 67 | 30 | 8 |

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; SD: Standard deviation;

Table 2: The associations between a 10 μg/m$^3$ increase in the current day's air pollutants and cardiovascular mortality using time series and case–crossover analyses

| Analysis | | RR or OR (95% CI) [a] | | |
|---|---|---|---|---|
| Time series | | PM$_{10}$ | SO$_2$ | NO$_2$ |
| DF = | 6 | 1.0048 (1.0023, 1.0073)** | 1.0027 (0.9987, 1.0068) | 1.0108 (1.0013, 1.0204)* |
| | 7 | 1.0047 (1.0021, 1.0072)** | 1.0026 (0.9985, 1.0067) | 1.0103 (1.0006, 1.0200)* |
| | 8 | 1.0047 (1.0022, 1.0072)** | 1.0024 (0.9983, 1.0065) | 1.0095 (0.9999, 1.0192) |
| | 9 | 1.0047 (1.0022, 1.0072)** | 1.0023 (0.9981, 1.0065) | 1.0096 (1.0000, 1.0194) |
| Case–crossover | | | | |
| Strata length = | Month | 1.0055 (1.0028, 1.0083)** | 1.0016 (0.9974, 1.0059) | 1.0156 (1.0051, 1.0263)** |
| | 28 | 1.0040 (1.0012, 1.0067)** | 1.0015 (0.9970, 1.0061) | 1.0133 (1.0028, 1.0240)** |
| | 21 | 1.0055 (1.0022, 1.0089)** | 1.0043 (0.9989, 1.0097) | 1.0129 (1.0001, 1.0258)* |
| | 14 | 1.0048 (1.0008, 1.0087)* | 1.0000 (0.9935, 1.0065) | 1.0153 (1.0015, 1.0294)** |

Abbreviations: PM$_{10}$: particulate matter less than 10 μm in aerodynamic diameter; SO$_2$: sulfur dioxide; NO$_2$: nitrogen dioxide; RR: relative risk; CI: confidence interval; OR: odds ratio; DF: degrees of freedom;

*P<0.05; **P<0.01

[a] RR for time series analyses, OR for case–crossover analyses

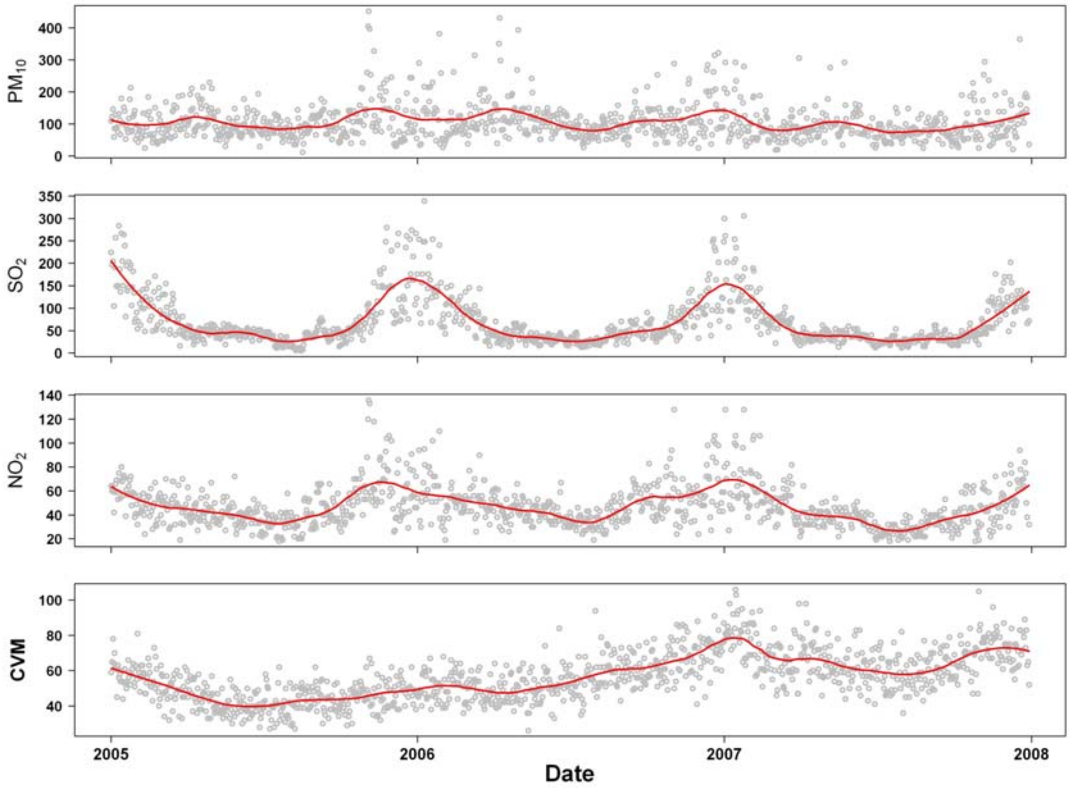

Figure 1: Time series distribution of air pollutants (μg/$m^3$) and cardiovascular mortality (number of daily cases) in Tianjin, China during study period.

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; CVM: cardiovascular mortality

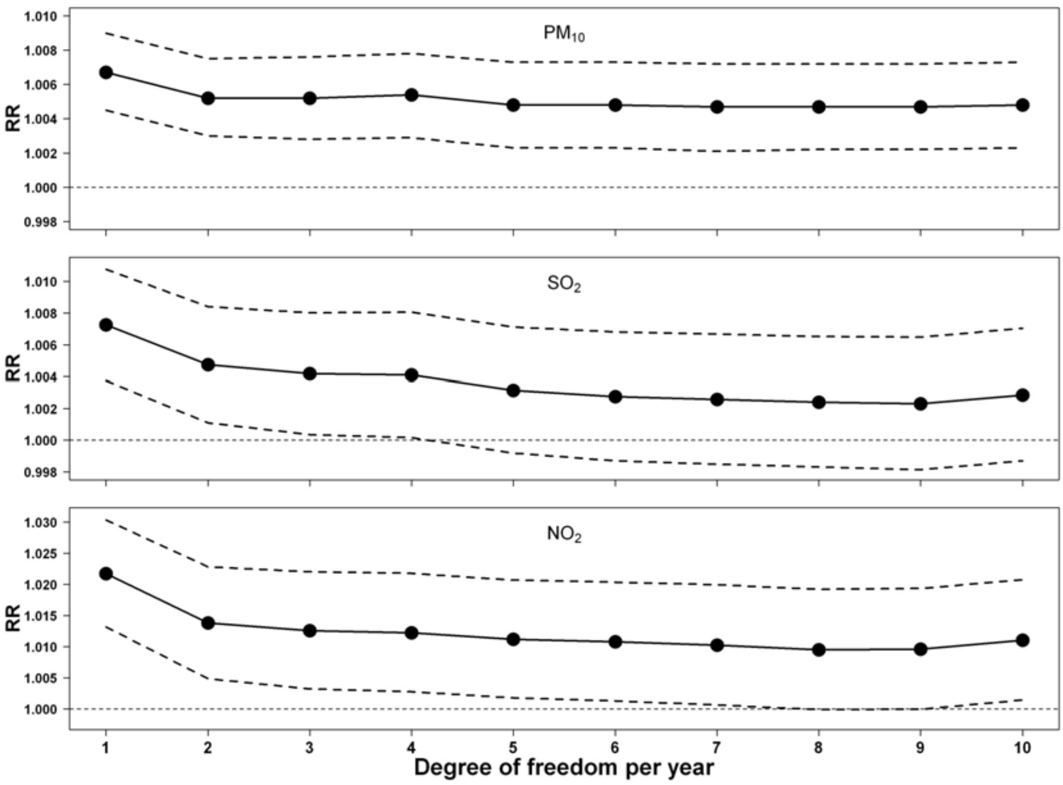

Figure 2: The associations between a 10 μg/m$^3$ increase in the current day's air pollutants and cardiovascular mortality for 1 to 10 degrees of freedom per year for time using GAMs. The dashed lines are 95% confidence intervals and the solid lines are the mean relative risks. A dotted horizontal line is shown at a relative risk of 1.

Abbreviations: PM$_{10}$: particulate matter less than 10 μm in aerodynamic diameter; SO$_2$: sulfur dioxide; NO$_2$: nitrogen dioxide; RR: relative risk; CI: confidence interval

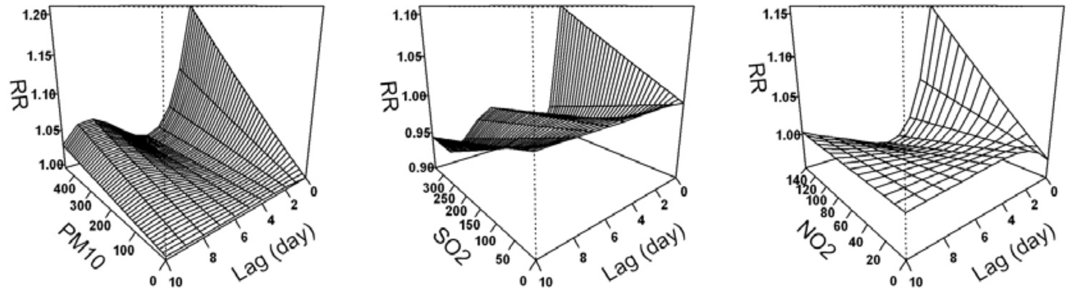

Figure 3: Bivariate response surfaces of the air pollutants and distributed lag days for cardiovascular mortality.

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; RR: relative risk;

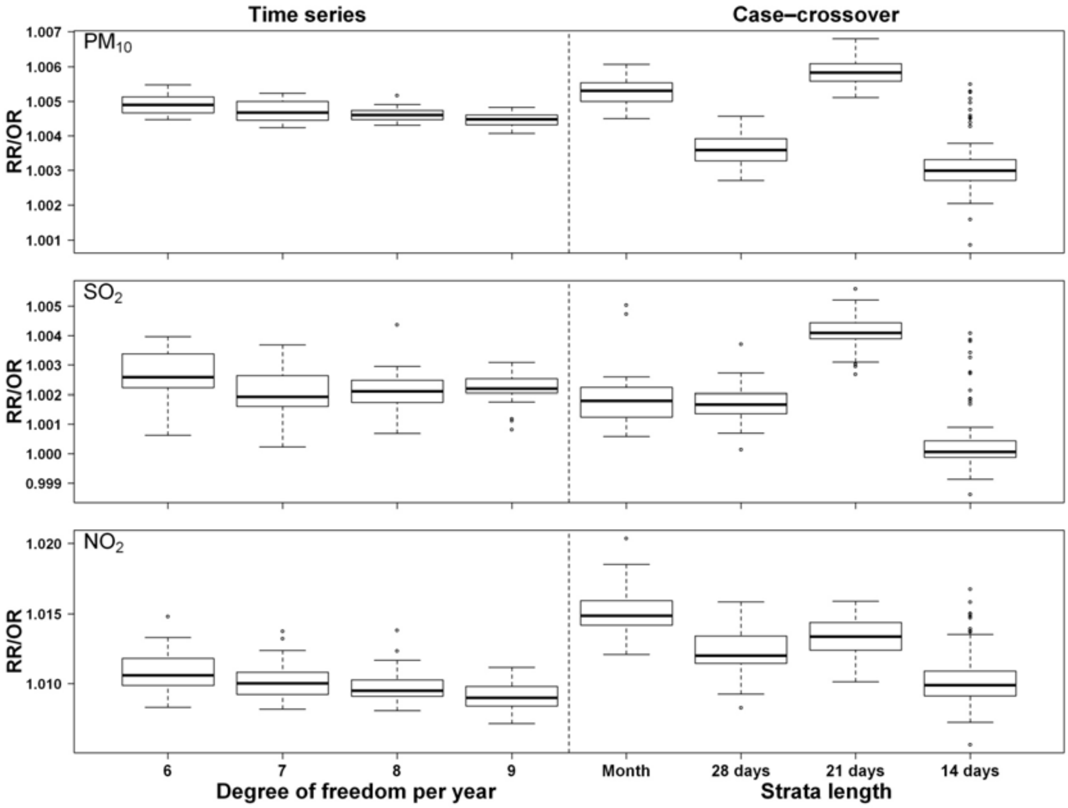

Figure 4: Box plots comparing the time series and time-stratified case–crossover analyses using jackknifing. Relative risks or odds ratios are shown for a 10 μg/m$^3$ increase in air pollutants.

Abbreviations: PM$_{10}$: particulate matter less than 10 μm in aerodynamic diameter; SO$_2$: sulfur dioxide; NO$_2$: nitrogen dioxide; RR: relative risk; OR: odds ratio;

**Supplements:**

Table S1: The P-values from ANOVA with post hoc testing that examines the differences between all time series and time-stratified case–crossover analyses for exposure to particulate matter less than 10 μm in aerodynamic diameter

| Designs | | Time series<br>DF= | | | | Case–crossover<br>Strata length= | | |
|---|---|---|---|---|---|---|---|---|
| | | 6 | 7 | 8 | 9 | Month | 28 | 21 |
| Time series | 7 | 0.732 | | | | | | |
| DF= | 8 | 0.170 | 0.982 | | | | | |
| | 9 | 0.002 | 0.285 | 0.866 | | | | |
| Case–crossover | Month | 0.022 | <0.001 | <0.001 | <0.001 | | | |
| Strata length= | 28 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | | |
| | 21 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | |
| | 14 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Abbreviations: DF: degree of freedom;

Table S2: The P-values from ANOVA with post hoc testing that examines the differences between all time series and time-stratified case–crossover analyses for exposure to sulfur dioxide

| Designs | | Time series DF= | | | | Case–crossover Strata length= | | |
|---|---|---|---|---|---|---|---|---|
| | | 6 | 7 | 8 | 9 | Month | 28 | 21 |
| Time series DF= | 7 | 0.017 | | | | | | |
| | 8 | 0.026 | 1.000 | | | | | |
| | 9 | 0.109 | 0.998 | 1.000 | | | | |
| Case–crossover Strata length= | Month | <0.001 | 0.862 | 0.799 | 0.467 | | | |
| | 28 | <0.001 | 0.442 | 0.358 | 0.122 | 0.998 | | |
| | 21 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | |
| | 14 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Abbreviations: DF: degree of freedom;

Table S3: The P-values from ANOVA with post hoc testing that examines the differences between all time series and time-stratified case–crossover analyses for exposure to nitrogen dioxide

| Designs | | Time series DF= | | | | Case–crossover Strata length= | | |
|---|---|---|---|---|---|---|---|---|
| | | 6 | 7 | 8 | 9 | Month | 28 | 21 |
| Time series DF= | 7 | 0.719 | | | | | | |
| | 8 | 0.122 | 0.964 | | | | | |
| | 9 | <0.001 | 0.075 | 0.592 | | | | |
| Case–crossover Strata length= | Month | <0.001 | <0.001 | <0.001 | <0.001 | | | |
| | 28 | 0.003 | <0.001 | <0.001 | <0.001 | <0.001 | | |
| | 21 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.024 | |
| | 14 | 0.891 | 0.999 | 0.578 | 0.002 | <0.001 | <0.001 | <0.001 |

Abbreviations: DF: degree of freedom;

Table S4: Over-dispersion parameters for time series and time-stratified case–crossover models for estimating the associations between air pollutants and cardiovascular mortality.

| Designs | | Pollutants | | |
|---|---|---|---|---|
| Time series | | $PM_{10}$ | $SO_2$ | $NO_2$ |
| DF= | 6 | 1.21 | 1.23 | 1.23 |
| | 7 | 1.21 | 1.22 | 1.22 |
| | 8 | 1.20 | 1.22 | 1.22 |
| | 9 | 1.20 | 1.22 | 1.22 |
| Case–crossover | Month | 1.18 | 1.20 | 1.18 |
| Strata length= | 28 | 1.17 | 1.19 | 1.18 |
| | 21 | 1.17 | 1.19 | 1.18 |
| | 14 | 1.11 | 1.12 | 1.11 |

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; DF: degrees of freedom;

[a] The over-dispersion parameters for time-stratified case–crossover models were obtained using log-linear models; An over-dispersion parameter of 1 indicates that the mean and variance are equal and there is no over-dispersion.

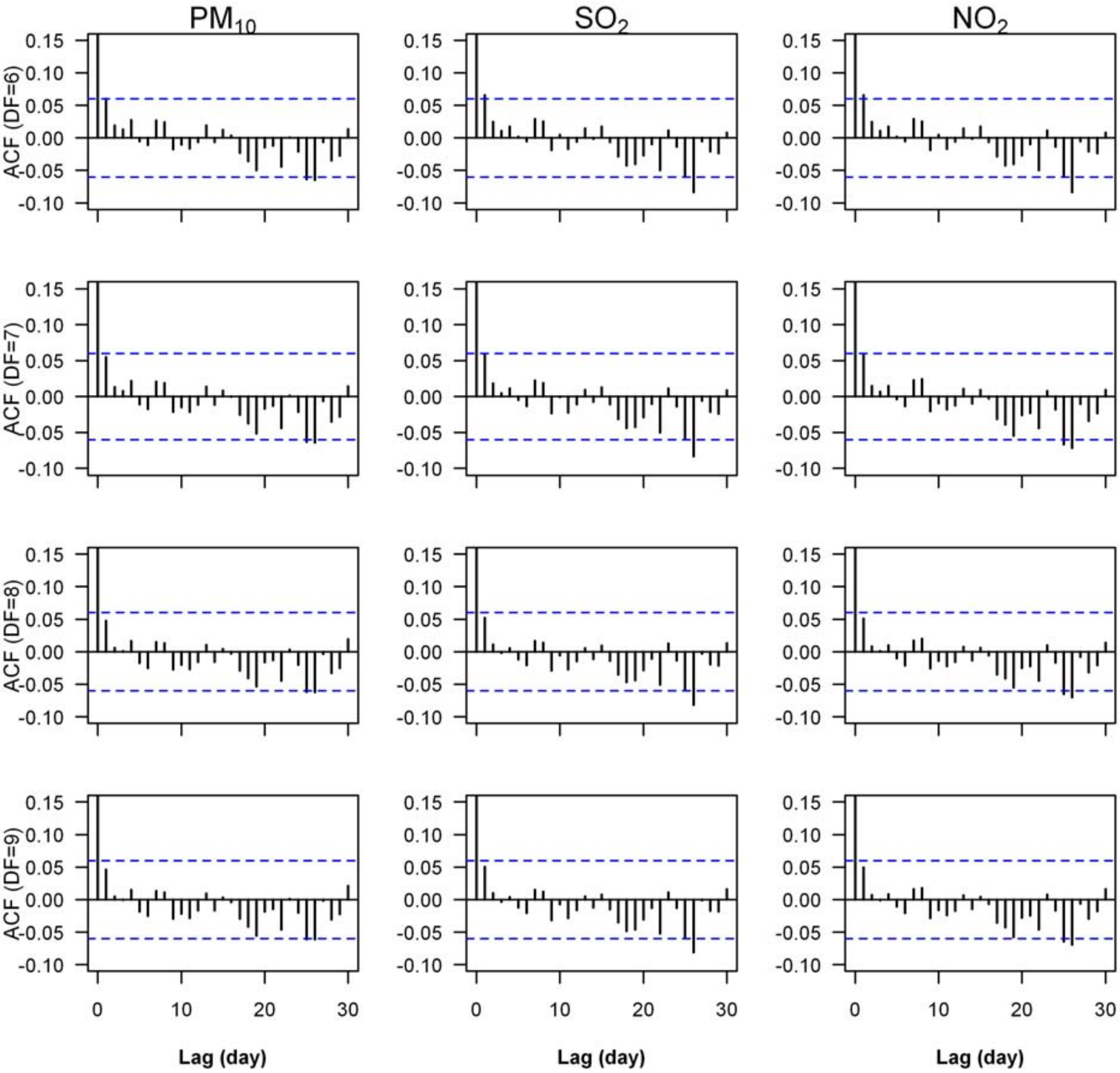

Figure S1: Autocorrelation functions for the residuals from the time series analyses with different degrees of freedom per year. Dashed horizontal lines show the test that the autocorrelation is non-zero.

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; ACF: autocorrelation function; DF: degrees of freedom;

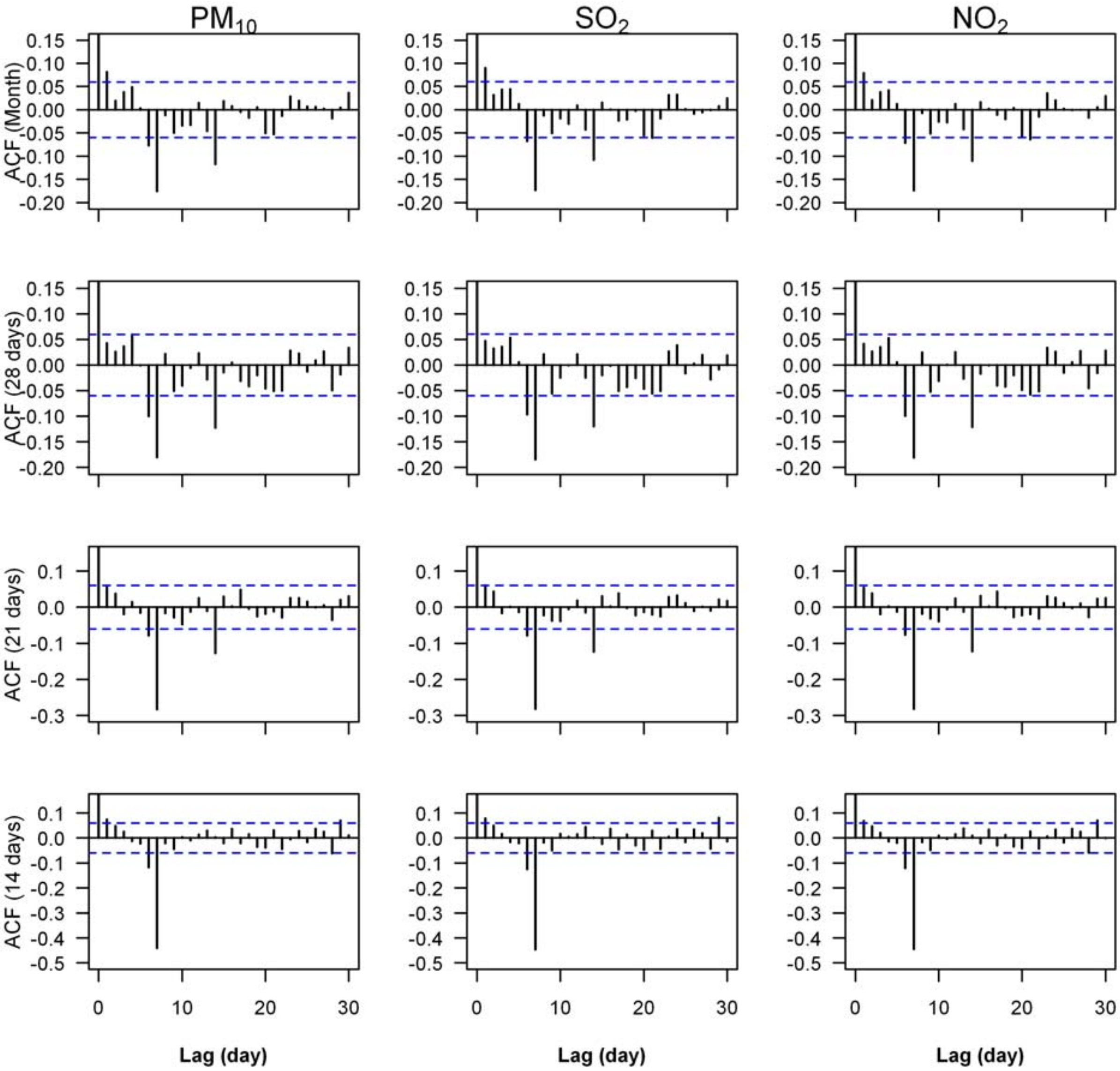

Figure S2: Autocorrelation functions for the residuals from the time-stratified case–crossover analyses with different strata length. Dashed horizontal lines show the test that the autocorrelation is non-zero.

Abbreviations: $PM_{10}$: particulate matter less than 10 μm in aerodynamic diameter; $SO_2$: sulfur dioxide; $NO_2$: nitrogen dioxide; ACF: autocorrelation function;