

© Copyright 2016

Xiao Zhang

Ambient ozone pollution and daily mortality in three megacities in China

Xiao Zhang

A thesis

submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2016

Committee:

Joel D. Kaufman

Sverre Vedal

Adam A. Szpiro

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Ambient ozone pollution and daily mortality in three megacities in China

Xiao Zhang

Chair of the Supervisory Committee:
Professor Joel D. Kaufman
Department of Environmental & Occupational Health Sciences

Background: In mainland China, limited studies have been published on the association of ambient ozone pollution with daily mortality. Given that the air pollution has changed from conventional coal combustion to the mixed coal combustion/motor vehicle emissions(primary source of ambient ozone pollution) in the metropolis in China, it is the time to investigate the effect of ozone on adverse outcomes in the big cities. This study was designed to examine the acute mortality effects of ambient ozone pollution in Beijing, Tianjin, and Chongqing during October 1, 2013 to June 30, 2015.

Methods: The relationship between daily mortality and 24-hour average ambient ozone concentrations was analyzed using generalized additive models(GAM) with Quasi-Poisson

standard errors. All pollution mortality associations were adjusted for time trend, mean temperature, relative humidity, and day of the week. Sensitivity analyses were also conducted to examine the stability of the model. Effect estimates were determined for each city and then for the cities combined using a random effect method.

Results: In the city-specific analysis, the percent change in daily total, respiratory, chronic lower respiratory disease (CLRD), and chronic obstructive pulmonary disease (COPD) mortality associated with an increase of 10 $\mu\text{g}/\text{m}^3$ ozone concentration ranged from 0.06% (95%CI: -0.79%, 0.91%) to 0.47% (95%CI: 0.02%, 0.93%), -0.37% (95%CI: -1.80%, 1.06%) to 0.60% (95%CI: -0.66%, 1.85%), -0.04% (95%CI: -2.13%, 2.06%) to 0.48% (95%CI: -0.83%, 1.79%), and -0.22% (95%CI: -2.41%, 1.96%) to 0.68% (95%CI: -1.49%, 2.86%), respectively. The pooled estimates across the cities were 0.31% (95%CI: 0.01%, 0.62%), 0.17% (95%CI: -0.63%, 0.96%), 0.33% (95%CI: -0.65%, 1.31%), and 0.32% (95%CI: -0.68%, 1.33%) for total, respiratory, CLRD, and COPD mortality, respectively. The estimates were fairly robust to the change in degree of freedoms (df) for time trend (3-10/year). However, the direction of the association and the effect size were sensitive to the different lag structures. In the two-pollutant model analysis, the effect estimates indicating the association of O_3 and mortality outcomes became larger after adjusting for NO_2 .

Conclusions: A positive yet statistically insignificant association between ambient ozone pollution and daily total mortality was observed in the three cities. Future cohort study aiming to assess the long-term health effects of ozone pollution in China should be considered.

TABLE OF CONTENTS

List of Figures	ii
List of Tables	iii
1. Introduction	1
2. Materials and Methods	2
2.1 Air pollution monitoring station	2
2.2 Mortality data	3
2.3 Air pollutant and meteorological data	4
2.4 Statistical methods	4
3. Results	6
3.1 Descriptive results	6
3.2 Correlation analysis results	8
3.3 Regression analysis results	8
3.4 Sensitivity analysis results	9
4. Discussion	10
5. Conclusions	15
6. References	15

LIST OF FIGURES

Figure 1. Daily death counts and 24-hour average O ₃ concentrations(10/1/2013-6/30/2015)....	19
Figure 2. Relative excess risk(RER) for mortality associated with 10 µg/m ³ increase of 24-hour average O ₃ concentrations, classified by degrees of freedom for time trend per year.....	20
Figure 3. RER for mortality associated with 10 µg/m ³ increase of 24-hour average O ₃ concentrations in different lag days	21

LIST OF TABLES

Table 1. Summary statistics of daily deaths, air pollutant concentrations, and weather conditions.....	22
Table 2. Correlation coefficients between daily air pollutant concentrations and weather conditions.....	24
Table 3. RER for daily mortality associated with 10 $\mu\text{g}/\text{m}^3$ increase in 24-hour average O_3 concentrations, based on single- and two-pollutant models*[percent(95%CI)].....	25

ACKNOWLEDGEMENTS

After an intensive period of three months, writing this note of thanks is the finishing touch on my thesis. I would like to reflect on the people who have supported and helped me so much throughout the process.

I would first like to express my thanks to my committee for their continued support and encouragement: Dr. Joel D. Kaufman, my committee chair; Dr. Sverre Vedal; and Dr. Adam A. Szpiro. I offer my sincere appreciation for the learning opportunities provided by them.

My completion of this thesis project could not have been accomplished without the help of my site supervisor, Dr. Peng Yin. Thanks for providing me with this great opportunity of working at the China CDC and making connections with professionals in this field.

Finally, to my parents and my caring, loving, and supportive husband, Luyang: my deepest gratitude. Your encouragement when the times got rough are much appreciated and duly noted. Thank you so much for always being there for me!

1. INTRODUCTION

Asia has been experiencing fast urbanization and transportation development in the past decades. As a result, air pollution levels in many Asian cities rival the levels that existed in Europe and North America in the first decades of the 20th century(HEI 2010). As the largest developing country in Asia, China may have the worst air quality in the world(Kan 2012), and air pollution-related health impacts have become a growing concern(Lin 2011).

With the rapid increase in the number of motor vehicles, the main air pollution source in China has gradually changed from conventional coal combustion to mixed coal combustion/motor vehicle emissions, which is the main source of ambient ozone pollution(Kan 2009). In the past few decades, a lot of studies that aimed to evaluate the association between ambient ozone pollution and human health outcomes have been conducted in the United States and Western Europe(Anderson 1996; Hoek 2000; Jerrett 2009), whereas in mainland China, quite few similar studies were conducted due to a lack of monitoring data(Kan 2012). While several previous studies identified a significantly positive association between outdoor ozone concentrations and daily all-cause and respiratory mortalities(Zhang 2006; Yang 2012), others produced null results or inconclusive evidence(Wang 2008; Tao 2012). These seemingly conflicting findings might result from many factors such as different study areas(surrogate for population geographic characteristics and health status, time spending outdoors, etc.), statistical power discrepancy due to various sample sizes, issues related to the data quality and measurement errors, and different model specifications. Therefore, research studies conducted in different geographic areas with a reliable data source and an appropriate model selection are needed to obtain a comprehensive

understanding of the underlying relationship between ozone concentration and mortality. Besides, previous animal experiments indicated that ozone exposure exaggerates airway hyper-responsiveness (AHR) and pulmonary inflammation, and promotes the production of epithelial mucus(Bao 2015). This may be modest for a healthy individual, but it presumably increases hazards for the individual with chronic lung diseases(Bergofsky 1991), such as Chronic Obstructive Pulmonary Disease(COPD), the third leading cause of death globally and fourth leading cause of death in China(World Health Organization(WHO) 2014; Center for Disease Control and Prevention(CDC) 2014). However, to our knowledge, no research concerning the short-term effect of ozone pollution on daily COPD mortality was conducted in Beijing, Tianjin, and Chongqing, three of the most air-polluted megacities in China. Thus, in this article, we conducted a multicity time-series study using most recent daily mortality and air pollutant surveillance data from Oct 1, 2013 to Jun 30, 2015 to examine the city-specific and overall pooled estimates of the association between ozone concentrations and daily total/respiratory/chronic lower respiratory disease(CLRD)/COPD mortality in Beijing, Tianjin, and Chongqing. This study also aimed to provide the latest research evidence for emissions restriction policies in China.

2. MATERIALS AND METHODS

2.1 AIR POLLUTION MONITORING STATION

The 7 fixed-field air pollution monitoring stations in Beijing were located in Dongcheng District, Fengtai District, Mentougou District, Tongzhou District, Changping District, Miyun County,

Yanqing County. The 7 monitoring stations in Tianjin were located in Hexi District, Nankai District, Hongqiao District, Jinnan District, Wuqing District, Baodi District, Ji County.

The 11 monitoring stations in Chongqing were located in Wanzhou District, Yuzhong District, Shapingba District, Beibei District, Qijiang District, Dazu District, Changshou District, Jiangjin District, Fengdu District, Fengjie District, Xiushan Tujia and Miao Autonomous County.

These monitoring stations were not constructed in the direct vicinity of traffic, nor anywhere close to industry, boilers burning coal, or other local pollution sources. Thus, our monitoring data reflect the general air pollution level in the city rather than the air pollution level near local sources such as traffic or industrial combustion. The air pollution monitoring system in the three cities has been certified by the China Ministry of Environmental Protection.

2.2 MORTALITY DATA

Daily mortality data between Oct 1, 2013 and Jun 30, 2015 were collected from the database of the China National Mortality Surveillance System. Mortality data covered all deaths reported from the districts where the monitoring stations were located. The underlying causes of death were coded according to *International Classification of Diseases, Tenth Revision* [ICD-10 (WHO 1994)]. The mortality data were classified into deaths from all natural causes (ICD-10 codes A00–R99), respiratory diseases (ICD-10 codes J00–J98), CLRD (ICD-10 codes J40–J47), and COPD (ICD-10 codes J40–J44).

2.3 AIR POLLUTANT AND METEOROLOGICAL DATA

Daily 24-hour average air pollutant concentrations data between Oct 1, 2013 to Jun 30, 2015, including ozone(O₃), particulate matter ≤ 2.5 μm in diameter(PM_{2.5}), particulate matter ≤ 10 μm in diameter(PM₁₀), sulfur dioxide(SO₂), and nitrogen dioxide(NO₂) were obtained from the National Center for Chronic and Noncommunicable Disease Control and Prevention(NCNCD), Chinese Center for Disease Control and Prevention(China CDC).

To allow adjustment for potential meteorological effects on mortality, daily mean temperature and relative humidity data between Oct 1, 2013 to Jun 30, 2015 were obtained from the China Meteorological Administration. The weather data were measured at a fixed-site monitoring station located in the urban area in each of the three cities.

2.4 STATISTICAL METHODS

As overdispersion may be present in the daily death counts and the relationship between daily mortality and covariates were mostly nonlinear, the semi-parametric generalized additive model(GAM) with log link and Quasi-Poisson standard errors was employed to assess the association between the ambient ozone concentration and daily mortality. 24-hour average O₃ concentration was included as a linear term. Time trend, daily mean temperature and relative humidity were included in the model as natural spline functions, which can accommodate the nonlinear and non-monotonic patterns between mortality and the covariates. A predetermined degree of freedom(df)=7 was used for time trend, df=3 was used for both temperature and

relative humidity. Based on the previous literature, $df=6-8$ for time trend and $df=3$ or 4 for weather conditions(Peng 2006; Qiu 2012) could adequately control for their associations with mortality. Day of the week(DOW) was included in the model as dummy variables.

To obtain the pooled estimates, we applied DerSimonian and Laird random-effect methods to summarize the association of all-cause and cause-specific mortalities with ambient O_3 pollution on average across the cities.

In the sensitivity analysis, we first tested the impact of the selection of df for time trend on the results. We compared the coefficient values when applying $df=3, 4, 5, 6, 7, 8, 9, 10$ for time trend. We also examined the association with different lag structures including the single-day lag(lag0-lag6) and multi-day lag(lag01). In the single-day lag models, a lag of 0 day (lag0) corresponds to the current-day concentration, and a lag of 1 day (lag1) refers to the previous day concentration. In the multi-day lag models, lag 01 corresponds to the 2-day moving average of O_3 concentrations of the current and previous day. Lastly, we fitted both single-pollutant and two-pollutant models to evaluate the stability of the associations: in the single-pollutant models, O_3 was included as the only pollutant in the model; in the two-pollutant models, linear $PM_{2.5}$, PM_{10} , SO_2 , or NO_2 were included jointly. For each city, we also assessed the acute mortality effect of O_3 in the warm season(April to September) and the cold season(October to March), respectively, by adding the binary season variable and the interaction between season and linear O_3 concentration.

Besides, in order to make our results roughly comparable to the studies conducted in the US and other European Countries where 1-hour maximum and 8-hour maximum O₃ concentrations were used as standard measurement metrics, we applied a relationship of 20:15:8 for the 1-hour maximum: 8-hour maximum: 24-hour average O₃ concentrations(United States Environmental Protection Agency(EPA) 2006). For example, a 10 µg/m³ increase in the daily 24-hour average O₃ concentrations corresponds to approximately a $10 \times \frac{15}{8}$ µg/m³ increase in the daily 8-hour maximum O₃ concentration and a $10 \times \frac{20}{8}$ µg/m³ increase in the daily 1-hour maximum O₃ concentration. In addition, we assumed that 1.96 µg/m³ equals 1 ppb to convert the metric in our study comparable to other studies.

Spearman's correlation coefficients were used to evaluate the inter-relations between air pollutants and weather conditions.

The main analyses were conducted using R 3.2.1(R Development Core Team 2014). The results were presented as relative excess risk(RER) for mortality associated with a 10 µg/m³ increase of 24-hour average O₃ concentrations. Statistical significance is defined as $p < 0.05$.

3. RESULTS

3.1 DESCRIPTIVE RESULTS

During Oct 1, 2013 to Jun 30, 2015(638 days), a total of 54985 deaths(56.1% males) , 64111 deaths(55.4% males) , and 119170 deaths(60.2% males) were observed in the monitoring areas

of Beijing(monitored population: 7.5 million), Tianjin(monitored population: 6.4 million), and Chongqing(monitored population: 9.7 million), respectively. Age of 0~4, 5~44, 45~64, and ≥ 65 years accounted for 0.78%, 3.63%, 20.38%, and 75.21% of the total number of deaths in Beijing, 0.60%, 4.07%, 20.28%, and 75.05% of the total number of deaths in Tianjin, and 0.82%, 6.49%, 22.33%, and 70.36% of the total number of deaths in Chongqing.

Table 1 summarized the daily death counts, air pollutant concentrations and meteorological data in the three cities. On average, the highest number of death counts per day was observed in the 11 monitoring districts in Chongqing, where there were approximately 186.79 non-accidental deaths per day, among which 35.47 were caused by respiratory diseases, 31.21 were caused by CLRD, and 30.52 were caused by COPD. Over the study period, the average death counts per day were similar in the monitoring districts in Beijing and Tianjin. As showed in Table 1, Beijing had the highest mean 24-hour average concentrations of O_3 (56.54 $\mu\text{g}/\text{m}^3$) among the three cities. The mean $PM_{2.5}$, PM_{10} , SO_2 and NO_2 concentrations ranged from 65.33 $\mu\text{g}/\text{m}^3$ to 84.96 $\mu\text{g}/\text{m}^3$, 99.03 $\mu\text{g}/\text{m}^3$ to 141.53 $\mu\text{g}/\text{m}^3$, 20.52 $\mu\text{g}/\text{m}^3$ to 49.45 $\mu\text{g}/\text{m}^3$, and 39.57 $\mu\text{g}/\text{m}^3$ to 53.40 $\mu\text{g}/\text{m}^3$, respectively. The highest mean temperature(17.87°C) and relative humidity(78.30%) were observed in Chongqing. In the warm season, the mean/maximum 24-hour average O_3 concentrations were 89.17/254.45 $\mu\text{g}/\text{m}^3$ in Beijing, 77.74/242.64 $\mu\text{g}/\text{m}^3$ in Tianjin, and 52.07/215.82 $\mu\text{g}/\text{m}^3$ in Chongqing. In the cold season, the mean/maximum 24-hour average O_3 concentrations were 30.47/81.81 $\mu\text{g}/\text{m}^3$ in Beijing, 25.05/87.93 $\mu\text{g}/\text{m}^3$ in Tianjin, and 22.01/80.09 $\mu\text{g}/\text{m}^3$ in Chongqing.

Figure 1 presented a seasonal trend for daily average O₃ concentrations and total death counts per day. The O₃ concentrations reached the highest level in summer and lowest in winter, while daily non-accidental death counts peaked in winter. For daily respiratory disease, CLRD, and COPD death counts, this seasonal trend was apparent in Chongqing, but less pronounced in Beijing and Tianjin.

3.2 CORRELATION ANALYSIS RESULTS

Table 2 indicated that the 24-hour average O₃ concentration was highly positively correlated with daily mean temperature level in all the three cities, moderately and negatively correlated with SO₂ and NO₂ in Beijing and Tianjin, and weakly correlated with SO₂ and NO₂ in Chongqing. PM_{2.5}, PM₁₀, SO₂, and NO₂ had moderate to strong positive correlation with each other in all the three cities((Pearson correlation coefficients ranged from 0.37 to 0.98).

3.3 REGRESSION ANALYSIS RESULTS

City-specific effect estimates and the pooled effect estimates for percent change in daily mortality associated with a 10 µg/m³ increase in 24-hour average O₃ concentrations were presented in Table 3. Without adjusting for other air pollutants, for total mortality, RER ranged from 0.06%(95%CI: -0.79%, 0.91%) in Chongqing to 0.47%(95%CI: 0.02, 0.93) in Beijing. For respiratory mortality, RER ranged from -0.37%(95%CI: -1.80%, 1.06%) in Beijing to 0.60%(95%CI: -0.66%, 1.85%) in Chongqing. For CLRD mortality, RER ranged from

-0.04%(95%CI: -2.13%, 2.06%) in Tianjin to 0.48%(-0.83%, 1.79%) in Chongqing. For COPD mortality, RER ranged from -0.22%(95%CI: -2.41%, 1.96%) in Tianjin to 0.68%(95%CI: -1.49%, 2.86%) in Beijing.

In the single-pollutant models(Table 3), when the city-specific results were combined, the 24-hour average O₃ concentration was positively associated with all mortality outcomes, but the association was tested statistically significant for the total mortality only. An increase of 10 µg/m³ 24-hour average O₃ concentration corresponded to 0.31%(0.01%, 0.62%), 0.17%(-0.63%, 0.96%), 0.33%(-0.65%, 1.31%), and 0.32%(-0.68%, 1.33%) increase in daily total mortality, respiratory mortality, CLRD mortality, and COPD mortality, respectively.

3.4 SENSITIVITY ANALYSIS RESULTS

As indicated in Figure 2, the effect estimates were fairly robust and did not change much in terms of the magnitude of the effect and statistical significance when we altered the dfs for time trend(3-10/year), except for the effect estimates for the total and respiratory mortalities in Tianjin. However, the direction of the association and the effect size were sensitive to the different lag structures(Figure 3). Besides, the lag structure with the largest estimated effect varied across cities. The percent change in daily total, respiratory, CLRD, and COPD mortality associated with an increase of 10 µg/m³ 2-day running average(lag01) O₃ concentration ranged from 0.00%(95%CI: -0.06%, 0.05%) to 0.04%(95%CI:

-0.02%, 0.09%), 0.01%(95%CI: -0.15%, 0.18%) to 0.05%(95%CI: -0.12%, 0.22%), 0.02%(95%CI: -0.12%, 0.17%) to 0.06%(-0.19%, 0.30%), and -0.01%(95%CI: -0.27%, 0.25%) to 0.02%(95%CI: -0.23%, 0.26%), respectively.

The results of fitting the two-pollutant models were showed in Table 3. For each city, the effect estimates indicating the association of O₃ and mortality outcomes became larger(towards positive infinity) after adjusting for NO₂. However, the significance of the association between O₃ and mortality remained the same after adjusting for other air pollutants.

We did not observe a significant association of O₃ with mortality outcomes in neither cold nor warm season. The formal test for the coefficient of the interaction term being zero gave a p-value >0.05(data not shown) .

4. DISCUSSION

In the city-specific analysis, we found ozone was positively associated with daily total non-accidental mortality, but the associations were not always significant over the three cities. When studies from all cities were considered, the pooled estimates describing the percent change in daily all natural causes and cause-specific mortalities associated with an increase of 10 µg/m³ 24-hour average O₃ concentrations were all positive, but statistically significant for the total mortality only.

The primary finding of this study is generally consistent with previous similar multicity studies conducted in the US, Asia, and European cities. PAPA(Wang 2008) study conducted in four Asian cities(Hongkong, Shanghai, Wuhan, Bankok) found a positive association between O₃ and daily total mortality. The percent change in all natural causes mortality for a 10 µg/m³ increase in the 8-hour maximum O₃ concentration ranged from 0.29%(95%CI: -0.05%, 0.63%) in Wuhan to 0.63%(95%CI: 0.30%, 0.95%) in Bangkok. After metric conversion to the 24-hour average O₃ concentrations, the range of estimates changed to 0.54%(95%CI: -0.09%, 1.18%) to 1.18%(95%CI: 0.56%, 1.78%). In the NMMAPS(Bell 2005), the effect estimate for total mortality associated with an increase of 10 ppb daily average O₃ concentration was 0.25%(95%CI: 0.12%, 0.39%), which corresponded to 0.13%(95%CI: 0.06%, 0.20%) increase in daily total mortality for a 10 µg/m³ increase in daily average O₃ concentration. APHENA study(Peng 2013) conducted in 125 cities in Europe, the US, and Canada found the pooled estimated RER associated with a 10 µg/m³ increase of 1-hour daily maximum O₃ was 0.26%(95%CI: 0.15%, 0.37%), so the corresponding RER associated with 24-hour average O₃ is 0.65%(95%CI: 0.38%, 0.93%). The higher uncertainty of estimates exhibited in our study as compared to PAPA study, NMMAPS, and APHENA study was possibly due to the relative shorter time series data collected from the three cities. The slightly smaller effect size found in our study and other Asian studies compared to those conducted in the North America and European countries may be explained by the discrepancy in the adaption of the population to O₃ pollution, and the population susceptibility. Also, due to bad air quality(haze or smog) in some Asian cities, people may spend more time indoors where air purifiers or air conditioners are equipped, and they are more likely to wear masks when staying outside as compared to the

people in the US or European cities(Zhou 2013). This may reduce the adverse effect of air pollution on the health outcomes to some extent.

Although several underlying mechanisms have been proposed to explain the possible link between O₃ exposure and respiratory diseases(Ahmad 2005; Kinney 1996; Mudway 2004), we did not observe a significant acute effect of O₃ on the respiratory mortality, CLRD mortality, or COPD mortality. This is consistent with single-city studies conducted in Shanghai, Hongkong, and Suzhou(Zhang 2006; Wong 2002; Yang 2012). In the multi-city studies(Peng 2013; Tao 2012; Wong 2008), the results for respiratory mortality were not consistent across cities and not statically significant in most cases. This is likely attributable to the relatively small number of deaths per day due to respiratory diseases and the inherently small association between O₃ and daily mortality that is being estimated(Kinney 1991).

The results from the sensitivity analysis using different dfs for time trend exhibited a minimal change in terms of the effect size and statistical significance, which is consistent with recent studies(Zhang 2006; Tao 2012). The pooled estimates were robust to the PM adjustment; similar findings were reported in the recent NMMAPS analyses(Bell 2004). Because of the moderate correlation between SO₂/NO₂ and O₃ in Beijing and Tianjin, adjustment for SO₂ or NO₂ slightly changed the magnitude of the effect estimates and made the confidence interval of the estimate wider than it was in the single-pollutant model. Consistent with studies conducted elsewhere, in the distributed lag day analysis, we found the estimates for mortality were sensitive to different lag structures. However, we did not find any common patterns as reported in the other

studies(Peng 2013; Zhou 2013), where lag01 or lag 1 day generated the largest excess risk. Besides, the effect estimates were not significant for most lag days. The small sample size of our study may lead to the unstable estimates of the lag effects, therefore we did not observe the similar pattern reported in other studies with larger sample size. Also, the residual confounding from unmeasured seasonal, meteorological or other factors that were not adequately controlled for in our model may have an influence in estimating the association and therefore contributed to the inconsistency of the largest lag effect estimates across cities.

The mean 24-hour average O₃ concentration measured in this study(ranged from 34.92 to 56.54 µg/m³) were lower than the range reported in the studies conducted in Beijing, Tianjin, Guangzhou, Jinan and Quanzhou during 1983-2005(Kan 2012), roughly comparable to the mean reported in the time-series study using 2006-2008 air pollutants data in Suzhou(Yang 2012), where the same ozone metric was applied. There might have been a decreasing trend of O₃ pollution in China since several environmental protection regulations and laws were implemented(Ministry of Environmental Protection of the People's Republic of China 1996; Standing Committee of the National People's Congress 1998; State Council 2013). But due to the limited availability of data with the same metric, this conclusion remains uncertain. Because the air pollutant data accessible during the time of our study were 24-hour average O₃ concentrations, the mean cannot be easily compared to those reported in the studies conducted in the US, European countries, and other places using 1-maximum O₃ concentration or 8-maximum O₃ concentration as the standard measurement metric.

Limitations should be noted in interpreting the results of our study. Firstly, we used the averaged monitoring results across various stations as the proxy of population-level ozone exposure. This mean ozone concentration, however, may not be well representative of the true population ozone exposure level, if the observed ozone concentration pattern varies a lot from the monitoring station to station. Also, different monitors were active on different days, simply averaging different monitors on different days would induce quite a bit of day-to-day variability in the exposure. In the study proposal, we considered using the following method mentioned in the NMMAPS(Samet, 2000) to address this problem: for each pollutant, we would first calculate the annual mean concentration for each monitor each year. After that, we would subtract these monitor- and year- specific means from the daily measurement for each monitor, and then divide the difference by the monitor specific standard deviation to produce a standardised deviation. The standardised deviations for all monitors in the city would be averaged for each day. In the end, we would multiply the average standardised deviation by the standard deviation of the centered measurements for the year and add it to the annual average of all the monitors to get an average concentration for each day. However, during the time of study, due to some unexpected reasons, we were not able to obtain access to the monitor-specific air pollutant data, and therefore could not account for the changes in the mean exposure estimates from day to day. Besides, we were unlikely to get confirmatory information about potential effect modifiers (e.g., smoking prevalence, time spent outdoors, use of air conditioning, comorbidity in the population) in the three cities during the study period, making it difficult to explain quantitative differences in the effect estimates among the cities. In addition, the relatively small number of deaths due to CLRD/COPD and potential misclassification of COPD/CLRD may have limited our ability to

detect the relatively small associations. Lastly, less than two years' time-series data available might make it difficult to draw a robust inference, but it provides us the latest research evidence for the adverse effects of ozone on the health outcomes in the megacities in China.

5. CONCLUSIONS

We identified a positive association between ozone and daily non-accidental mortality across the three megacities in China. Evidence showed a potentially decreasing trend of ozone pollution in our study, possibly due to the emission restrictions and environmental protection regulations that have been implemented to improve the air quality in China in recent years. However, the short-term adverse effect of ozone still exists at current ozone level. The ecological nature of this study might limit the power to detect the relative small associations in some cities. Future cohort studies aiming to exam the long-term health effects of ozone should be considered.

6. REFERENCES

Ahmad S, Ahmad A, McConville G, Schneider BK, Allen CB, Manzer R, et al. Lung epithelial cells release ATP during ozone exposure: signaling for cell survival. *Free Radic Biol Med* 2005;39:213–26.

Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP. Air pollution and daily mortality in London: 1987-92. *BMJ*. 1996;312(7032):665-9.

Bao A et al. Effects of ozone oxidative stress on the airway hyperresponsiveness and mucus production in mice with acute allergic airway inflammation. *Chinese Journal of Tuberculosis and Respiratory Diseases*. 2015;38(3):179-84.

- Bell ML, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology*. 2005;16(4):436-45.
- Bell ML, McDermott A, Zeger SL, et al. Ozone and mortality in 95 US urban communities, 1987– 2000. *JAMA*. 2004; 292:2372–2378. [PubMed: 15547165]
- Bergofsky EH. The lung mucosa: a critical environmental battleground. *Am J Med*. 1991;91(4A):4S-10S.
- Center for Disease Control and Prevention(CDC). Factsheet: CDC in China. <http://www.cdc.gov/globalhealth/countries/china/pdf/china>. Publication Date: April 2014.
- HEI (Health Effects Institute). Outdoor air pollution and health in the developing countries of Asia: a comprehensive review. Special Report, 18; 2010.
- Hoek G, Brunekreef B, Verhoeff A, van Wijnen J, Fischer P. Daily mortality and air pollution in The Netherlands. *J Air Waste Manag Assoc*. 2000;50(8):1380-9.
- Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, et al. Long-term ozone exposure and mortality. *N Engl J Med*. 2009;360(11):1085-95.
- Kan H, Chen B, Hong C. Health impact of outdoor air pollution in China: current knowledge and future research needs. *Environ Health Perspect*. 2009;117(5):A187.
- Kan H, Chen R, Tong S. Ambient air pollution, climate change, and population health in China. *Environ Int*. 2012;42:10-9.
- Kinney PL, Nilsen DM, Lippmann M, Brescia M, Gordon T, McGovern T, El-Fawal H, Devlin RB, Rom WN. Biomarkers of lung inflammation in recreational joggers exposed to ozone. *Am J Respir Crit Care Med* 1996;154:1430–1435.
- Kinney PL, Ozkaynak H. Associations of daily mortality and air pollution in Los Angeles County. *Environ Res*. 1991, 54:99–120.
- Lin W, Huang W, Zhu T, Hu M, Brunefreef B, Zhang Y, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. *Environ Health Perspect* 2011;119(10):1507–12.
- Ministry of Environmental Protection of the People’s Republic of China. Ambient air quality standard 1996. GB3095-1996. Effect as of October 1, 1996.
- Mudway IS, Kelly FJ. An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med* 2004;169:1089–1095.

Peng RD, Dominici F, Louis TA. Model choice in time series studies of air pollution and mortality. *J R Stat Soc A* 2006;169:179–98.

Peng RD, Samoli E, Pham L, Dominici F, Touloumi G, Ramsay T, et al. Acute effects of ambient ozone on mortality in Europe and North America: results from the APHENA study. *Air Qual Atmos Health*. 2013;6(2):445-53.

Qiu, H., IT-s, Yu, Tian, L., Wang, X., Tse, L.A., Tam, W., et al. Effects of coarse particulate matter on emergency hospital admissions for respiratory diseases: a time-series analysis in hong kong. *Environ. Health Perspect*. 2012;120:572-576.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, et al. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. *Res Rep Health Eff Inst*. 2000;94(Pt 2):5-70; discussion 1-9.

Standing Committee of the National People's Congress. Law of the People's Republic of China on the Prevention and Control of Atmospheric Pollution. Effective as of June 1, 1988.

State Council. Air Pollution Prevention and Control Action Plan. Effective as of September 10, 2013.

Tao Y, Huang W, Huang X, Zhong L, Lu SE, Li Y, et al. Estimated acute effects of ambient ozone and nitrogen dioxide on mortality in the Pearl River Delta of southern China. *Environ Health Perspect*. 2012;120(3):393-8.

United States Environmental Protection Agency(EPA). Air Quality Criteria for Ozone and Related Photochemical Oxidants Volume I of III. EPA 600/R-05/004aF February 2006.

Wong CM, Vichit-Vadakan N, Kan H, Qian Z. Public Health and Air Pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environ Health Perspect*. 2008;116(9):1195-202.

Wong T, Tam W, Yu T, Wong A. Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. *Occup Environ Med*. 2002 Jan; 59(1): 30–35.

World Health Organization(WHO). Fact sheet: the top 10 causes of death. <http://www.who.int/mediacentre/factsheets/fs310/en/>. Updated May 2014.

Yang C, Yang H, Guo S, Wang Z, Xu X, Duan X, et al. Alternative ozone metrics and daily mortality in Suzhou: the China Air Pollution and Health Effects Study (CAPES). *Sci Total Environ*. 2012;426:83-9.

Zhang Y, Huang W, London SJ, Song G, Chen G, Jiang L, et al. Ozone and daily mortality in Shanghai, China. *Environ Health Perspect*. 2006;114(8):1227-32.

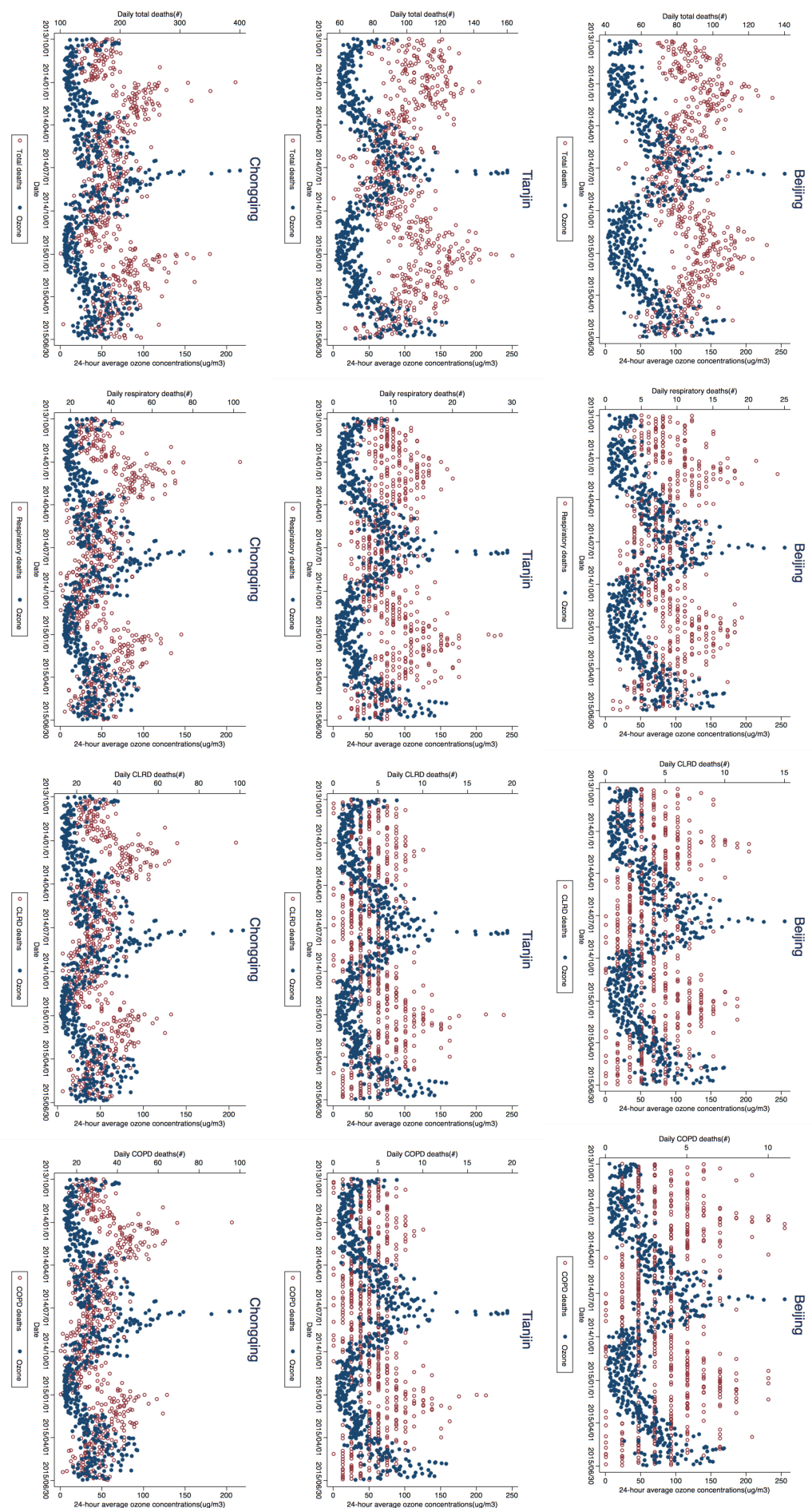


Figure 1. Daily death counts and 24-hour average O₃ concentrations(10/1/2013-6/30/2015)

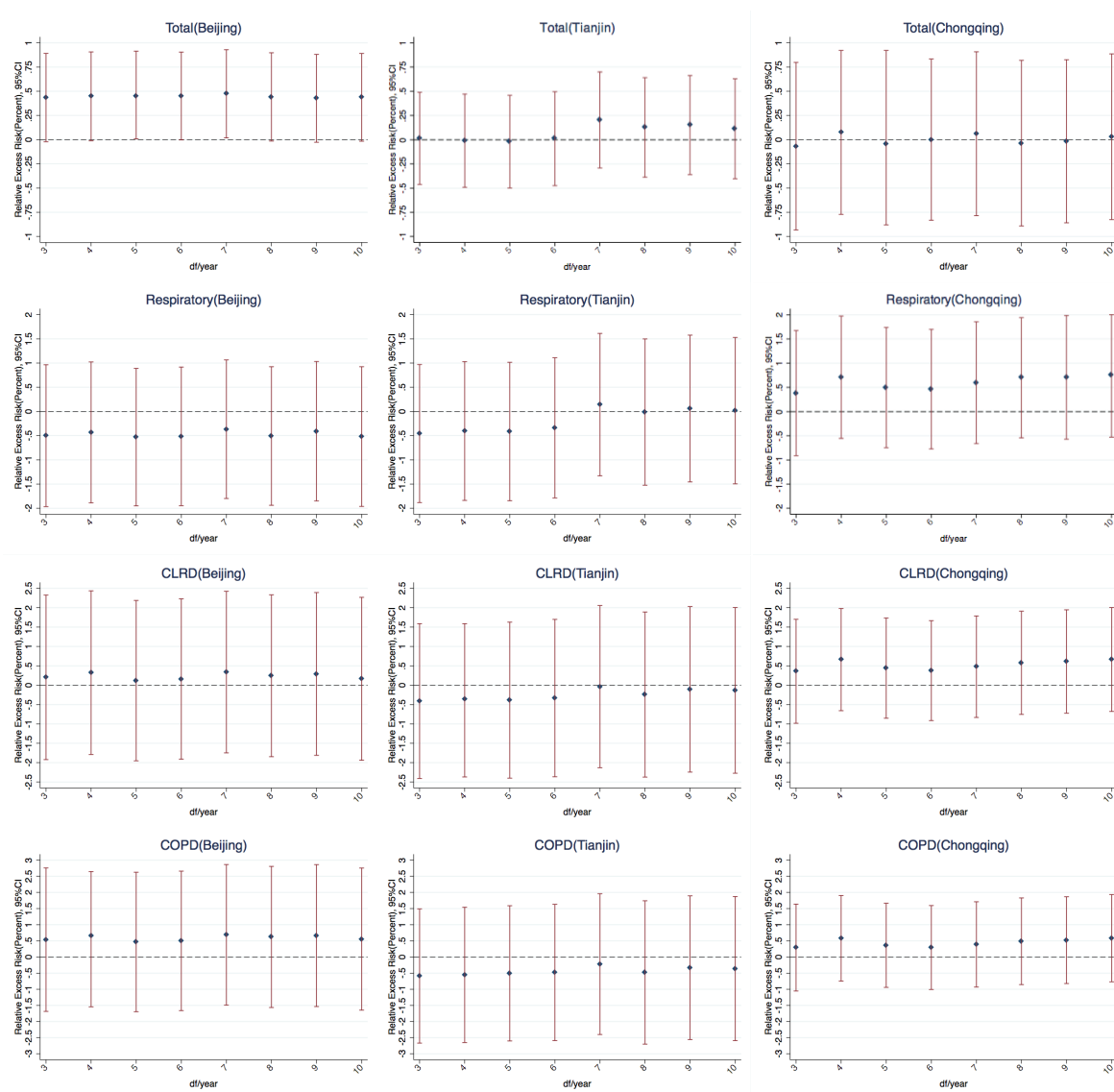


Figure 2. RER for mortality associated with $10 \mu\text{g}/\text{m}^3$ increase of 24-hour average O_3 concentrations, classified by degrees of freedom for time trend per year

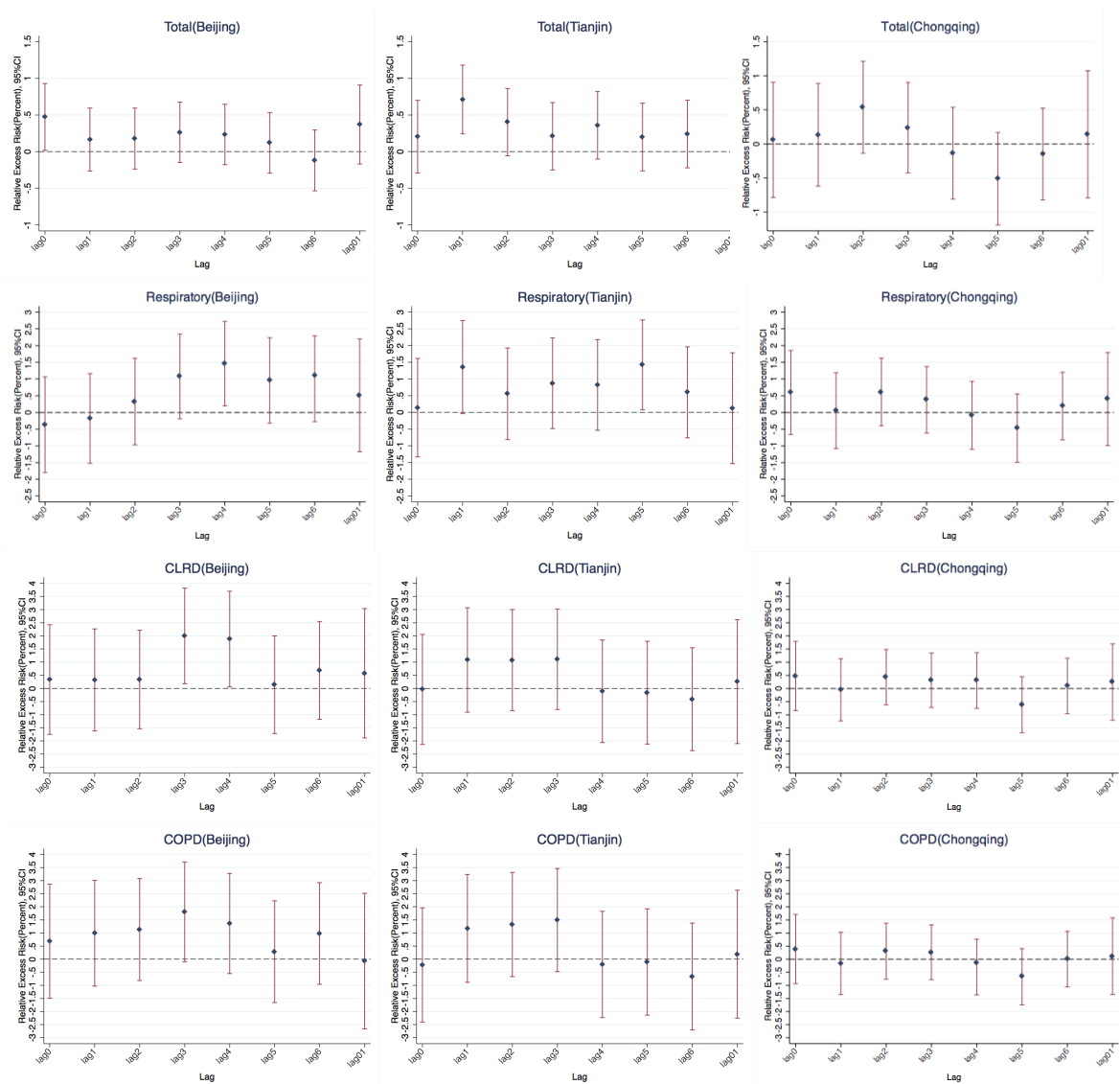


Figure 3. RER for mortality associated with 10 µg/m³ increase of 24-hour average O₃ concentrations in different lag days

Table 1. Summary statistics of daily deaths, air pollutant concentrations, and weather conditions

Variable	Mean±SD	Min	P25	Median	P75	Max
<i>Daily death counts</i>						
Total						
Beijing	86.18±13.49	47.00	77.00	85.00	95.00	133.00
Tianjin	100.49±16.83	56.00	89.00	99.00	112.00	163.00
Chongqing	186.79±38.50	100.00	160.25	180.00	208.75	392.00
Respiratory diseases						
Beijing	8.66±3.67	1.00	6.00	8.00	11.00	24.00
Tianjin	9.50±4.07	1.00	7.00	9.00	12.00	28.00
Chongqing	35.47±11.59	15.00	27.00	33.00	42.00	103.00
Chronic Lower Respiratory Disease(CLRD)						
Beijing	4.07±2.35	0	2.00	4.00	6.00	12.00
Tianjin	4.55±2.59	0	3.00	4.00	6.00	19.00
Chongqing	31.21±10.52	12.00	24.00	29.00	37.00	98.00
Chronic Obstructive Pulmonary Disease(COPD)						
Beijing	3.64±2.17	0	2.00	3.00	5.00	11.00
Tianjin	4.26±2.47	0	3.00	4.00	6.00	17.00
Chongqing	30.52±10.35	12.00	23.00	28.00	36.75	96.00
<i>Air pollutant concentrations*</i>						
O ₃ (μg/m ³)						
Beijing	56.54±40.26	3.13	25.83	48.15	77.85	254.50
Tianjin	47.68±37.71	3.73	20.96	36.17	66.28	242.64
Chongqing	34.92±26.69	3.87	13.92	28.46	47.18	215.82
PM _{2.5} (μg/m ³)						
Beijing	82.94±66.24	5.63	34.25	64.23	115.38	391.16
Tianjin	84.96±55.49	12.82	45.73	72.26	107.53	382.63
Chongqing	65.33±40.15	9.21	35.55	51.43	86.84	213.65
PM ₁₀ (μg/m ³)						
Beijing	119.30±77.04	9.60	63.67	102.16	153.26	495.05
Tianjin	141.53±76.78	25.80	85.97	124.33	180.40	492.20
Chongqing	99.03±52.49	14.71	60.19	85.15	124.58	295.03
SO ₂ (μg/m ³)						
Beijing	20.52±20.59	2.02	6.03	12.81	27.61	126.64
Tianjin	49.45±41.99	4.11	19.14	34.31	66.39	262.18
Chongqing	23.92±13.97	5.27	13.89	20.11	30.13	78.75

NO ₂ (μg/m ³)						
Beijing	52.89±23.63	7.47	36.42	47.53	65.91	136.20
Tianjin	53.40±23.66	10.96	35.60	49.31	66.64	177.39
Chongqing	39.57±11.97	16.10	30.78	37.31	46.22	86.27

Meteorological measures

Mean temperature(°C)

Beijing	12.46±10.44	-5.70	2.60	12.70	22.08	31.80
Tianjin	12.41±10.54	-7.00	2.23	12.70	22.30	31.00
Chongqing	17.87±7.07	4.60	11.80	17.70	23.27	35.30

Relative humidity(%)

Beijing	48.89±18.71	8.00	34.00	49.00	63.00	97.00
Tianjin	54.18±18.20	8.00	39.00	54.00	68.00	99.00
Chongqing	78.30±10.58	47.00	71.00	79.00	87.00	97.00

*24h average concentrations.

Table 2. Correlation coefficients between daily air pollutant concentrations and weather conditions

	O ₃	SO ₂	NO ₂	PM _{2.5}	PM ₁₀	Temperature	Humidity
<i>Beijing</i>							
O ₃	1.0000						
SO ₂	-0.4742	1.0000					
NO ₂	-0.4812	0.6758	1.0000				
PM _{2.5}	-0.1991	0.5906	0.7500	1.0000			
PM ₁₀	-0.1343	0.5232	0.6981	0.9013	1.0000		
Temperature	0.7569	-0.5666	-0.2827	-0.1169	-0.0476	1.0000	
Humidity	0.0104	0.0522	0.3567	0.5617	0.4263	0.2745	1.0000
<i>Tianjin</i>							
O ₃	1.0000						
SO ₂	-0.4940	1.0000					
NO ₂	-0.4696	0.7953	1.0000				
PM _{2.5}	-0.2713	0.6308	0.7756	1.0000			
PM ₁₀	-0.2920	0.6246	0.7446	0.9166	1.0000		
Temperature	0.7442	-0.6534	-0.4407	-0.2330	-0.2448	1.0000	
Humidity	0.0161	0.0620	0.1648	0.3699	0.1899	0.2124	1.0000
<i>Chongqing</i>							
O ₃	1.0000						
SO ₂	-0.2345	1.0000					
NO ₂	-0.0725	0.3746	1.0000				
PM _{2.5}	-0.3622	0.6280	0.5863	1.0000			
PM ₁₀	-0.2758	0.6586	0.6438	0.9757	1.0000		
Temperature	0.6998	-0.4349	-0.1606	-0.5259	-0.4433	1.0000	
Humidity	-0.5807	-0.1255	-0.2603	0.0675	-0.0464	-0.3349	1.0000

Table 3. RER for daily mortality associated with 10 $\mu\text{g}/\text{m}^3$ increase in 24-hour average ozone concentrations, based on single- and two-pollutant models*[percent(95%CI)]

Mortality	Model	RER[percent(95%CI)]			
		Beijing	Tianjin	Chongqing	Pooled
Total	Single-pollutant model	0.47(0.02, 0.93)	0.20(-0.29, 0.70)	0.06(-0.79, 0.91)	0.31(0.01, 0.62)
	Adjusted for PM _{2.5}	0.48(0.02, 0.94)	0.21(-0.29, 0.70)	0.08(-0.76, 0.93)	0.32(0.01, 0.63)
	Adjusted for PM ₁₀	0.48(0.02, 0.94)	0.21(-0.29, 0.71)	0.09(-0.75, 0.93)	0.32(0.01, 0.63)
	Adjusted for NO ₂	0.55(0.07, 1.04)	0.26(-0.25, 0.77)	0.11(-0.74, 0.96)	0.37(0.04, 0.69)
	Adjusted for SO ₂	0.53(0.06, 0.99)	0.19(-0.31, 0.69)	0.24(-0.62, 1.10)	0.36(0.04, 0.67)
Respiratory	Single-pollutant model	-0.37(-1.80, 1.06)	0.14(-1.32, 1.61)	0.60(-0.66, 1.85)	0.17(-0.63, 0.96)
	Adjusted for PM _{2.5}	-0.30(-1.73, 1.14)	0.13(-1.34, 1.61)	0.62(-0.63, 1.88)	0.20(-0.60, 0.99)
	Adjusted for PM ₁₀	-0.28(-1.71, 1.16)	0.10(-1.39, 1.58)	0.63(-0.62, 1.88)	0.20(-0.60, 1.00)
	Adjusted for NO ₂	0.01(-1.53, 1.54)	0.22(-1.29, 1.73)	0.71(-0.56, 1.97)	0.36(-0.46, 1.18)
	Adjusted for SO ₂	0.03(-1.43, 1.49)	0.13(-1.37, 1.62)	0.96(-0.31, 2.22)	0.36(-0.37, 1.24)
CLRD	Single-pollutant model	0.34(-1.75, 2.42)	-0.04(-2.13, 2.06)	0.48(-0.83, 1.79)	0.33(-0.65, 1.31)
	Adjusted for PM _{2.5}	0.31(-1.78, 2.41)	-0.07(-2.17, 2.03)	0.50(-0.81, 1.81)	0.33(-0.64, 1.32)
	Adjusted for PM ₁₀	0.40(-1.70, 2.50)	-0.17(-2.27, 1.94)	0.50(-0.80, 1.81)	0.34(-0.65, 1.32)
	Adjusted for NO ₂	1.09(-1.06, 3.34)	0.22(-1.93, 2.37)	0.54(-0.78, 1.87)	0.51(-0.50, 1.51)
	Adjusted for SO ₂	0.83(-1.30, 2.97)	-0.19(-2.31, 1.94)	0.83(-0.50, 2.15)	0.61(-0.39, 1.60)
COPD	Single-pollutant model	0.68(-1.49, 2.86)	-0.22(-2.41, 1.96)	0.39(-0.93, 1.71)	0.32(-0.68, 1.33)
	Adjusted for PM _{2.5}	0.67(-2.52, 2.87)	-0.26(-2.45, 1.93)	0.41(-0.91, 1.73)	0.32(-0.68, 1.33)
	Adjusted for PM ₁₀	0.78(-1.42, 2.97)	-0.35(-2.54, 1.84)	0.42(-0.90, 1.73)	0.33(-0.67, 1.33)
	Adjusted for NO ₂	1.10(-1.25, 3.45)	0.01(-0.22, 2.25)	0.46(-0.87, 1.79)	0.76(-0.54, 1.52)
	Adjusted for SO ₂	1.18(-1.04, 3.41)	-0.38(-2.59, 1.84)	0.73(-0.60, 2.07)	0.59(-0.43, 1.61)

*Adjusted for time trend, temperature, relative humidity, and day of the week