

## Preplanned Studies

## Short-Term Exposure to Ambient Ozone and Outpatient Visits for Respiratory Diseases — 5 Cities, China, 2013–2015

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### Summary

#### What is already known about this topic?

Few studies have elucidated the relationships between ambient ozone and respiratory morbidity, especially in developing countries.

#### What is added by this report?

This study involved 5 cities in China with a wide variation in ozone concentrations and therefore could add credible evidence for the associations between short-term ozone exposure and increased respiratory morbidity.

#### What are the implications for public health practice?

The results could be used to better assess disease burden of short-term exposure to ozone and further guide policymaking for reducing ozone air pollution and improving public health.

Few studies have elucidated the associations between short-term exposure to ozone and respiratory morbidity, especially in developing countries. We designed this time series study (from 2013 to 2015) in 5 cities in China to investigate the relationships between ambient ozone concentrations and respiratory outpatient visits. Health data were obtained from 9 hospitals and exposure data were collected from fixed-site monitoring stations. Generalized additive models were used to analyze hospital-specific associations and then a random-effect meta-analysis was used to pool them. The average concentrations of ambient ozone for each city ranged from 40.89  $\mu\text{g}/\text{m}^3$  to 75.56  $\mu\text{g}/\text{m}^3$ , and the daily mean counts of respiratory outpatient visits varied by hospital from 37 to 2,191. In the present study, we observed positive associations between ozone exposure and respiratory outpatient visits, and the associations remained robust in sensitivity analyses. For a 10  $\mu\text{g}/\text{m}^3$  increase in ozone concentration (lag 03 days), there was a 0.91% (95% CI: 0.34%, 1.47%) increase in the count of outpatient visits for respiratory diseases. Furthermore, the significant associations occurred earlier and became

slightly stronger during warm periods. This study suggested a significant and lagged association between short-term exposure to ozone and increased respiratory morbidity.

We conducted this time series study in the cities and municipalities of Shanghai, Zhoushan, Guangzhou, Wuhan, and Xi'an, which are located in different geographic regions with a wide diversity in ozone concentrations. The study period was from January 1, 2013 to December 31, 2015. Data on outpatient visits were obtained from 9 hospitals with 1 to 2 hospitals from each city, including tertiary and secondary hospitals to capture a more representative sample of patients. The hospitals were selected according to data accessibility. Outpatient visits for respiratory diseases were diagnosed and classified according the 10th International Classification of Diseases (ICD-10: J00–J99), and the daily counts were subsequently extracted by experienced physicians. The study was restricted to resident populations. Exposure data on the 5 criterion air pollutants and weather conditions were obtained from the National Urban Air Quality Real-time Publishing Platform and the China Meteorological Data Service Center, respectively. Daily concentrations of each air pollutant were averaged from all available measurements from fixed-site monitoring stations by city.

We applied a two-stage analytic strategy. In the first stage, we estimated hospital-specific associations using generalized additive models with quasi-Poisson regression. Several covariates were *a priori* added into the model (1) and details are provided in the supplementary material (available <http://weekly.chinacdc.cn/>). According to the results from a previous study (2), a moving average of the current and previous 3 days (lag 03 d) exposure was used for the main model. In the second stage, we pooled hospital-specific estimates using a random-effect meta-analysis. To illustrate the pooled association between ozone and respiratory outpatient visits, we plotted an exposure–response (E-R) curve via the same approach as done in a previous study (3). We further conducted

a stratified analysis by season (warm season, from May through October; cool season, from November through April). To examine the robustness of the main models, we performed 2 sensitivity analyses and details are provided in the supplementary material (available in <http://weekly.chinacdc.cn/>). All statistical analyses were conducted in R software (version 3.6.1, R Foundation for Statistical Computing, Austria) using the “*mgcv*” and “*rmeta*” packages. Effect estimates were presented as percentage changes and their 95% confidence intervals (CIs) in the count of respiratory outpatient visits that were associated with a 10  $\mu\text{g}/\text{m}^3$  increase in ozone concentration. A two-sided  $p < 0.05$  was considered statistically significant.

Table 1 summarizes the descriptive statistics on ozone concentrations and counts of respiratory outpatient visits. The mean concentrations of ambient ozone ranged from  $40.89 \pm 23.95 \mu\text{g}/\text{m}^3$  in Xi'an to  $75.56 \pm 24.61 \mu\text{g}/\text{m}^3$  in Zhoushan. The average daily counts of outpatient visits varied substantially by hospital from  $37 \pm 13$  in Hanyang Hospital of Wuhan to  $2,191 \pm 523$  in Xinhua Hospital of Shanghai.

Figure 1 shows the lag pattern of the associations between ozone and outpatient visits for respiratory diseases. For the single-day lags, the significant association occurred at a lag of 1 day, became the strongest at a lag of 2 days, and then was attenuated over longer lag periods. When exposure was lagged

over multiple days, the association became the strongest during the 0–3 days lag period. For this lag period, a 10  $\mu\text{g}/\text{m}^3$  increase in ozone concentration was associated with a 0.91% (95% CI: 0.34%, 1.47%) increase in the count of outpatient visits for respiratory diseases. The estimates of hospital-specific associations between ozone and outpatient visits are available in the supplementary material (Supplementary Figure S1, available in <http://weekly.chinacdc.cn/>). Figure 1 also depicts the associations by season. In warm seasons, the association was significant in the present day of exposure and could last for 3 days, whereas the association in cool seasons became significant at a lag of 2 days. For multiple-day lags, the associations in warm seasons were slightly stronger than that in cool seasons. The pooled relationship between ozone and respiratory outpatient visits had no obvious changes after adjusting other air pollutants or altering the degrees of freedom of the smooth functions for time trend and weather conditions (Supplementary Table S1, available in <http://weekly.chinacdc.cn/>).

Figure 2 illustrates the E-R curve for the association of ozone exposure (lag 03 days) with respiratory outpatient visits. Specifically, the curve increases slowly at low concentrations ( $< 50 \mu\text{g}/\text{m}^3$ ) and moderately at  $50 \mu\text{g}/\text{m}^3$  to  $100 \mu\text{g}/\text{m}^3$ , levels off at  $100 \mu\text{g}/\text{m}^3$  to  $120 \mu\text{g}/\text{m}^3$ , and raises rapidly when concentrations were  $> 120 \mu\text{g}/\text{m}^3$ .

TABLE 1. Summary statistics on ambient ozone concentrations in 5 cities and the count of outpatient visits for respiratory diseases in 9 hospitals from 2013 to 2015.

City/Hospital	Mean	SD	Min	P25	Median	P75	Max
Ozone							
Shanghai *	70.22	28.69	9.97	48.68	71.37	89.95	176.23
Zhoushan *	75.56	24.61	4.83	58.18	75.47	92.00	156.88
Guangzhou	46.99	24.32	4.81	27.98	43.27	61.77	147.44
Wuhan	59.38	29.85	7.27	35.27	57.34	79.69	166.25
Xi'an	40.89	23.95	6.70	20.82	35.73	57.25	128.19
Outpatient visit							
Hospital 1 (Shanghai) *	2,191	523	696	1,878	2,186	2,503	3,872
Hospital 2 (Zhoushan) *	412	81	110	360	411	464	678
Hospital 3 (Zhoushan) *	296	82	90	238	296	350	573
Hospital 4 (Guangzhou)	945	330	35	721	991	1,165	2,006
Hospital 5 (Guangzhou)	198	105	1	108	209	275	522
Hospital 6 (Wuhan)	43	17	0	33	43	52	147
Hospital 7 (Wuhan)	37	13	4	28	35	44	96
Hospital 8 (Xi'an)	488	188	44	382	529	621	894
Hospital 9 (Xi'an)	419	127	31	332	424	509	742

Abbreviations: SD=standard deviation; Min=minimum; Max=maximum; P25=25th percentile; P75=75th percentile.

\* Data were from January 1, 2014 to December 31, 2015.

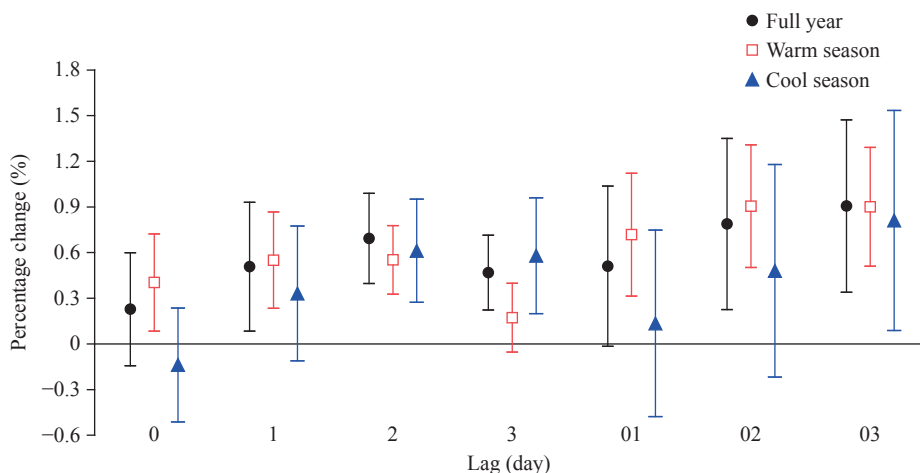


FIGURE 1. Percentage changes in the daily count of outpatient visits for respiratory diseases per 10-  $\mu\text{g}/\text{m}^3$  increase in ambient ozone concentration over different single-day and multiple-day lag periods. Warm season refers to the period from May through October and cool season refers to the period from November through April.

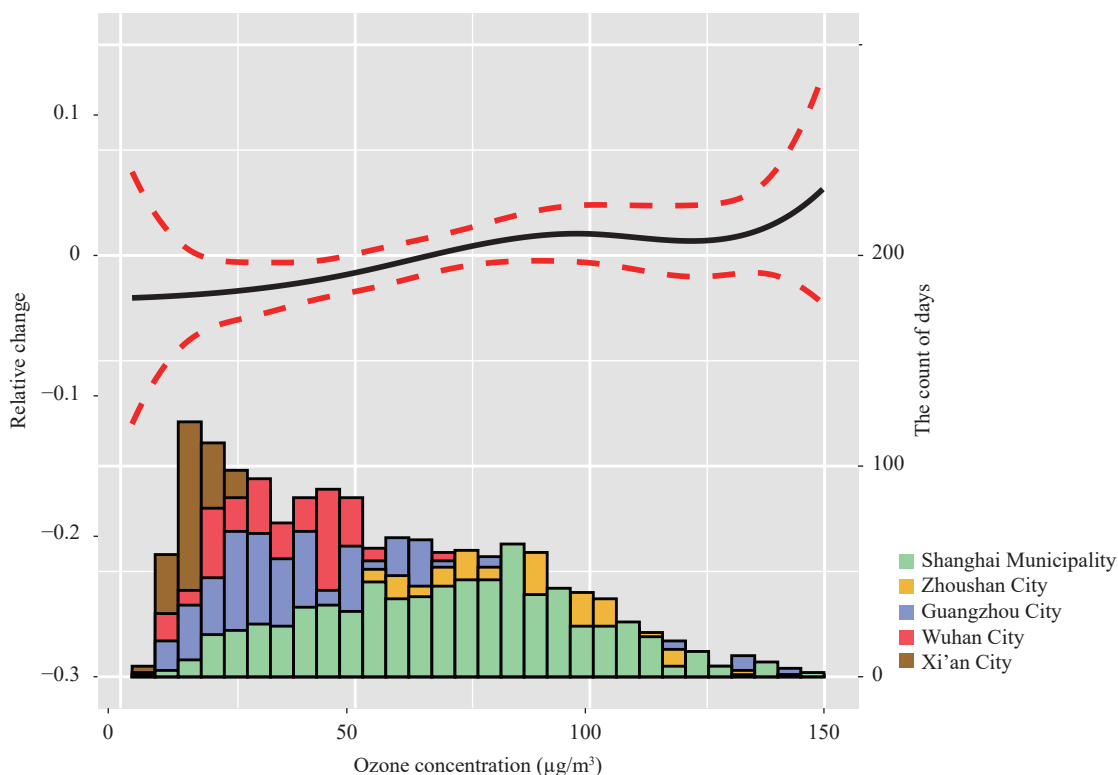


FIGURE 2. Exposure-response curve for the association of ozone concentrations (lag 03 days) with outpatient visits for respiratory diseases and distributions of daily mean ozone concentrations by cities. The left Y-axis can be interpreted as the log-relative change from the mean effect of ozone on outpatient visits. The solid line represents the mean estimate, and the dashed lines represent 95% confidence intervals. The height of each bar in the histogram represents the number of days in each bin of ozone concentration.

## DISCUSSION

We conducted a time series study in 5 cities in China to investigate the relationships between ozone exposure and respiratory morbidity. In this study, we

found a significantly positive association between ambient ozone concentrations and outpatient visits for respiratory diseases. The pooled effect occurred earlier and were slightly stronger during warm periods. The E-R curve showed the strongest effects of ozone

on respiratory outpatient visits at concentrations  $>120 \mu\text{g}/\text{m}^3$ .

Our results suggested a significant association between short-term ozone exposure and increased respiratory morbidity. This finding was consistent with a number of previous epidemiological studies. For instance, a meta-analysis demonstrated that a 10-ppb increase in ozone concentration was associated with a 0.80% (95% CI: 0.19%–1.41%) increase in emergency department visits for respiratory diseases (4). A multi-site study in the US observed a 0.8% (95% CI: 0.6%–1.0%) increase in respiratory emergency department visits in relation to a 10-ppb increase in ozone concentration (5). Such positive associations were also found in Japan (6). For cause-specific respiratory morbidity, the associations between ozone exposure and increased hospital admission for pneumonia and chronic obstructive pulmonary disease have been reported previously (1,7). However, inconsistently, some studies did not find that ozone exposure could cause elevated risks for respiratory morbidity (8), which may result from differences in study population and ozone levels. The results of our study also suggested that there were relatively weaker relationships between ozone exposure and respiratory morbidity in cities with lower levels of ozone air pollution.

Furthermore, we found that the lag pattern of the associations was somewhat different between warm and cool seasons, and the magnitude of associations was slightly greater in warm seasons, suggesting a potential modification effect of ambient temperature on ozone-related respiratory morbidity. This finding was similar with many previous studies that found a significant interaction effect between temperature and ozone on health outcomes (9). Higher ozone concentrations and more outdoor activities on warm days may lead to higher ozone exposure and reduce exposure misclassification. This would consequently add more credibility to the results. The modification effect of temperature may be indicated by the E-R curve that slope is relatively small at low concentrations and becomes the largest when concentrations are  $>120 \mu\text{g}/\text{m}^3$ .

This study was subject to at least three limitations. First, exposure misclassification was inevitable because we used fixed-site monitoring measurements as population exposure, and diagnosis misclassification was possible because cases were extracted according to ICD-10 codes from the database. Second, study areas and hospitals included in the study were selected according to data accessibility, which may lead to selection bias. Therefore, further studies conducted on

a larger scale are warranted to confirm our results. Third, we cannot recognize susceptible populations to ozone exposure in this study because demographic data (such as age, sex, and education levels) were unavailable.

In summary, our findings provided relatively creditable evidence for the associations between ozone exposure and increased respiratory morbidity. The results could be used to better assess disease burden of short-term exposure to ozone and further guide policymaking to reduce ozone air pollution and improve public health.

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## Supplementary Material

### Statistical model

We used generalized additive models with quasi-Poisson regression to analyze the associations between ozone concentrations and respiratory outpatient visits. Several covariates were added into the models, including: (1) natural cubic spline regression to control time trend with 7 degrees of freedom (dfs) per year; (2) an indicator variable for day of the week; (3) a binary dummy variable for holidays; and (4) natural cubic spline regression to control ambient temperature and relative humidity with 3 dfs for both.

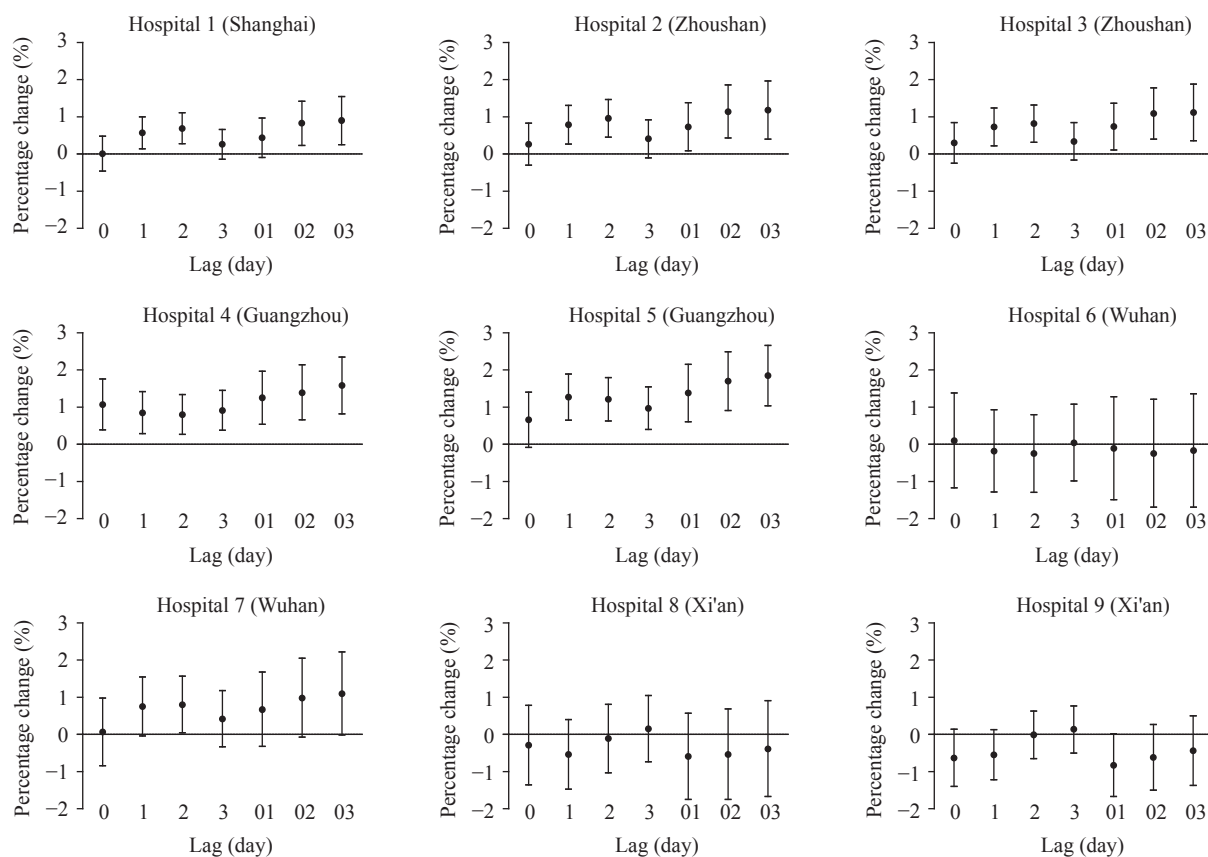
### Sensitivity analyses

To examine the robustness of the main model, we performed 2 sensitivity analyses. First, we adjusted fine particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide individually in the main model. Second, we assessed alternative dfs of the smooth functions for time trend (dfs=6 or 8), ambient temperature (dfs=6), and relative humidity (dfs=6).

We applied a Z-test to examine the difference between the adjusted models and the main model.

$$Z = \frac{(\beta_1 - \beta_2)}{\sqrt{Se_1^2 + Se_2^2}} \quad (1)$$

where  $\beta_1$  and  $\beta_2$  refer to the coefficient of outpatient visits associated with one unit change in ozone concentration in the main model and adjusted model, respectively;  $Se_1$  and  $Se_2$  refer to their standard errors, respectively;  $Z$  refer to Z test score for pairwise comparison. A  $p$ -value  $<0.05$  was considered statistically significant.



SUPPLEMENTARY FIGURE S1. Hospital-specific percentage changes in the count of outpatient visits for respiratory diseases per 10- $\mu\text{g}/\text{m}^3$  increase in ozone concentration over different single-day and multiple-day lag periods.

SUPPLEMENTARY TABLE S1. Summary estimates of sensitivity analyses for the associations between ozone concentrations (lag 03 days) and outpatient visits for respiratory diseases

Item	Percentage Change (95% CI)	p-value*
Main Model		
Single-pollutant, df <sub>time</sub> =7, df <sub>temp</sub> =3, df <sub>rh</sub> =3	0.91% (0.34%–1.47%)	–
Two-pollutant Model		
Main Model + PM <sub>2.5</sub>	0.67% (0.27%–1.07%)	0.502
Main Model + SO <sub>2</sub>	0.80% (0.40%–1.21%)	0.776
Main Model + NO <sub>2</sub>	0.72% (0.38%–1.06%)	0.574
Main Model + CO	0.80% (0.37%–1.22%)	0.763
Alternative Degrees of Freedom		
Single-pollutant, df <sub>time</sub> =6, df <sub>temp</sub> =3, df <sub>rh</sub> =3	0.70% (0.15%–1.26%)	0.615
Single-pollutant, df <sub>time</sub> =8, df <sub>temp</sub> =3, df <sub>rh</sub> =3	0.77% (0.37%–1.18%)	0.706
Single-pollutant, df <sub>time</sub> =7, df <sub>temp</sub> =6, df <sub>rh</sub> =3	0.77% (0.24%–1.29%)	0.723
Single-pollutant, df <sub>time</sub> =7, df <sub>temp</sub> =3, df <sub>rh</sub> =6	0.89% (0.41%–1.37%)	0.967
Single-pollutant, df <sub>time</sub> =7, df <sub>temp</sub> =6, df <sub>rh</sub> =6	0.81% (0.29%–1.33%)	0.805

\* p values for difference between estimates from the adjusted models and the main model.

**Abbreviations:** CI=confidence interval; PM<sub>2.5</sub>=fine particulate matter; SO<sub>2</sub>=sulfur dioxide; NO<sub>2</sub>=nitrogen dioxide; CO=carbon monoxide; df<sub>time</sub>=degree of freedom for time trend; df<sub>temp</sub>=degree of freedom for ambient temperature; df<sub>rh</sub>=degree of freedom for ambient relative humidity.