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Acute effect of multiple ozone metrics on mortality by season in 34 Chinese counties in 2013–2015

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Abstract. Sun Q, Wang W, Chen C, Ban J, Xu D, Zhu P, He MZ, Li T (National Institute of Environmental Health Sciences, Beijing, China; Columbia University Mailman School of Public Health, New York, NY, USA). Acute effect of multiple ozone metrics on mortality by season in 34 Chinese counties in 2013–2015. *J Intern Med* 2018; **283**: 481–488.

Background. Although numerous multicentre studies have estimated the association between ozone exposure and mortality, there are currently no nationally representative multicentre studies of the ozone–mortality relationship in China.

Objective. To investigate the effect on total (nonaccidental) and cause-specific mortality of short-term exposure to ambient ozone, and examine different exposure metrics.

Methods. The effects of short-term exposure to ozone were analysed using various metrics (daily 1-h maximum, daily 8-h maximum and daily average) on total (nonaccidental) and cause-specific (circulatory and respiratory) mortality from 2013 to 2015 in 34 counties in 10 cities across China. We used distributed lag nonlinear models for estimating county-specific relative risk of mortality and combined the county-specific relative rates by conducting a random-effects meta-analysis.

Results. In all-year analyses, a 10 μg m^{-3} increase in daily average, daily 1-h maximum and daily 8-h maximum ozone at lag02 corresponded to an increase of 0.6% (95% CI: 0.33, 0.88), 0.26% (95% CI: 0.12, 0.39) and 0.37% (95% CI: 0.2, 0.55) in total (nonaccidental) mortality, 0.66% (95% CI: 0.28, 1.04), 0.31% (95% CI: 0.11, 0.51) and 0.39% (95% CI: 0.16, 0.62) in circulatory mortality, and 0.57% (95% CI: –0.09, 1.23), 0.11% (95% CI: –0.22, 0.44) and 0.22% (95% CI: –0.28, 0.72) in respiratory mortality, respectively. These estimates had a different seasonal pattern by cause of death. In general, the seasonal patterns were consistent with the times of year when ozone concentrations are highest.

Conclusions. Our findings suggest that in China, the acute effects of ozone are more closely related to daily average exposure than any other metric.

Keywords: cardiovascular risk factors, death risk, environmental medicine, mortality, respiratory medicine.

Introduction

Ozone exposure adversely affects respiratory symptoms, lung and cardiovascular function, and inflammation of the airways [1–3]. A relationship between short-term ozone exposure and nonaccidental, circulatory and respiratory mortality has been demonstrated in several studies [4–10], and some previous multicentre studies showed consistent positive associations [11–16]. To date, the majority of studies have been conducted in the USA, Europe and Canada [17] with limited information on the relationship between short-term ozone exposure and mortality in Asia, and especially in China.

China is currently facing a serious situation regarding air pollution, and ozone pollution in particular remains an important priority given its high concentrations within the country. Due to a lack of available air monitoring data, no nationwide multicentre study has been conducted to date to investigate the ozone–mortality relationship in China. Numerous single-city or small-scale, multicentre, time-series studies have shown increased risk of mortality following exposure to elevated ozone levels in Shanghai [6, 18], Jiangsu [19], Zhengzhou [20], Wuhan [6, 21, 22], Guangzhou [23] and Hong Kong [24, 25].

In previously reported analyses, short-term ozone exposure was associated with nonaccidental, circulatory and respiratory mortality [4, 26], and in general, most studies showed significant results in spring and summer, when ozone concentrations are often highest [11, 27]. Furthermore, different metrics (daily 1-h maximum, daily 8-h maximum and daily average) for the time frame of exposure were used to characterize concentrations of ozone. Some studies investigated the human health impact of different ozone metrics and found that the magnitude of the association varied [12, 28].

The aim of this multicentre study was to assess the health effect of ozone exposure in the Chinese population. We conducted time-series analyses with a uniform protocol in 34 counties in 10 cities across China and examined the effects of short-term exposure of 1-h maximum, 8-h maximum and daily average ozone on total (nonaccidental) as well as cause-specific mortality. Sensitivity analyses were performed to assess the evidence for differential associations by season.

Materials and methods

Study design

The study was conducted in 34 counties in 10 cities across China with a population of 30.6 million (2010 census data). The counties are located in mid-eastern and south-western China (Fig. 1), and details are shown in Table S1. The study period was from 2013 to 2015. Seasons were defined as: spring from March to May; summer from June to August; fall from September to November; and winter from December to February.

Mortality, air pollution and meteorological data

We obtained county-specific mortality data from the Disease Surveillance Point System of the Chinese Center for Disease Control and Prevention. Data were collected for nonaccidental [International Classification of Diseases, 10th revision (ICD-10) codes A00–R99], circulatory (ICD-10 codes I00–I99) and respiratory mortality (ICD-10 codes J00–J99).

Hourly concentrations of ozone and particulate matter with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) were obtained from the National Air Pollution Monitoring System in all counties except in Beijing. The hourly concentrations of ozone and $PM_{2.5}$ from the counties of Beijing were obtained from the Beijing Air Pollution Monitoring System. Measurements from all monitoring stations located in a district were averaged to provide air pollution variables representing the district. In total, monitoring stations are located in 19 of 33 counties. If there were no monitoring stations in a district, we chose the nearest station of the National Air Pollution Monitoring System located in the same city to represent the district. More than 75% of hourly concentrations were available during the study period. For each district, we calculated the daily average concentration of $PM_{2.5}$ based on hourly values. For ozone, the maximum 1-h, 8-h and daily average concentrations were calculated for each day. If ozone concentration data were available for less than 6 h, the 8-h average was presented as ‘not available’ [29].

Daily average temperature and relative humidity for all cities were obtained from the meteorological data network of the China Meteorological Bureau; these data were assigned to each district that comprised the city.

Statistical approach

A two-stage analysis was used to investigate the effects of short-term ambient ozone (daily 8-h maximum, daily 1-h maximum and daily average) levels on mortality throughout the year and in different seasons (spring, summer, fall and winter), accounting for temperature, relative humidity and long-term trends. In the first stage, generalized additive models assuming a Poisson distribution were used to generate county-specific estimates. The 3-day moving average of current and previous 2-day ozone concentrations (lag02) was used in the main model. We selected this lag *a priori* based on our earlier studies (Table S2). We controlled for potential confounders by including daily average temperature and relative humidity, day of the week and calendar date. The covariates were adjusted according to the following: a natural cubic spline with six degrees of freedom (*df*) per year for time was controlled for the long-term trends, a natural cubic spline with three *df* for daily mean temperature and day of the week and a natural cubic spline with three *df* for daily mean relative humidity.

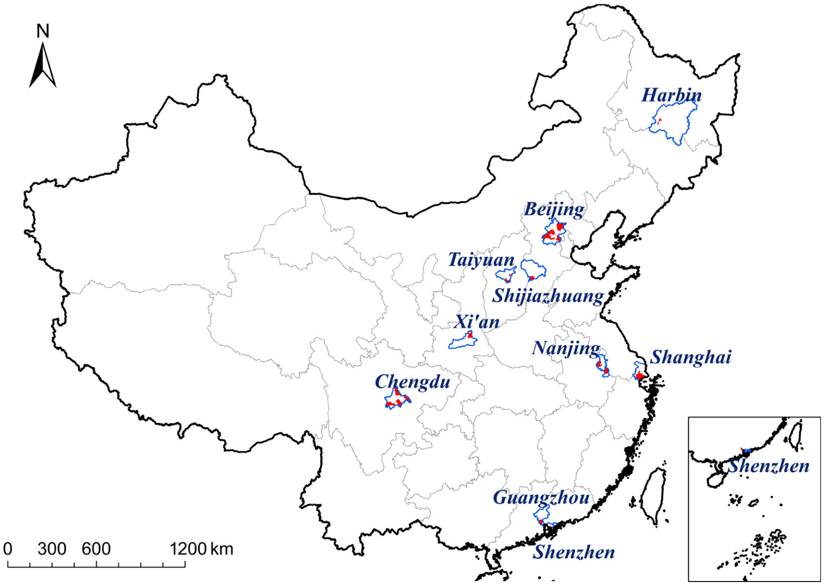

Fig. 1 *Map of the study locations. The red areas show the study counties; the blue regions show the cities in which the counties are located.*

In the second stage, we combined the county-specific risk estimates to generate an overall estimate of the association between ozone and mortality by conducting a random-effects meta-analysis. The meta-analysis was performed separately for each exposure metric, outcome variable and season.

To check the robustness of the main model, we examined the impact of different *df* values (4, 5, 7 and 8) for the time variable. The potential confounding effects of air pollution, including daily average concentrations of $PM_{2.5}$ and NO_2, were also investigated. A further analysis was carried out, using the average of all air pollution monitors in the city as the exposure of a district, in order to analyse the potential of exposure misclassification.

All statistical analyses were performed using the mgcv and mvmeta packages in R (version 3.2.0, R is freely available under the GNU General Public License).

Results

The daily average numbers of nonaccidental, circulatory and respiratory deaths were 12, five and two, respectively (see Table 1). The population ranged from 244 799 (Zanhuang, Shijiazhuang) to 2 429 372 (Minhang, Shanghai). The number of daily nonaccidental deaths ranged from three (Nanshan, Shenzhen) to 23 (Fengtai, Beijing) (see Table S1).

The means of the daily 1-h maximum, 8-h maximum and the daily average ozone concentrations were 109.7, 88.9 and 56.2 μg m^{-3}, respectively; the means of daily average $PM_{2.5}$ and NO_2 concentrations were 69.0 and 49.5 μg m^{-3}, respectively. Furthermore, the means of daily mean temperature and relative humidity were 15.7 °C and 67.0%, respectively (Table 2). The median daily average ozone concentration ranged from 31 (Shuangliu, Chengdu) to 87 μg m^{-3} (Zanhuang, Shijiazhuang) (Table S1 and Figure S1).

Table 1 *Daily number of deaths during the study period, by cause of death*

Cause of death	*n*	Mean ± SD	Min	P_{25}	P_{50}	P_{75}	Max
Nonaccidental	37 135	12 ± 7	0	7	11	16	44
Circulatory	37 135	5 ± 4	0	2	4	7	27
Respiratory	37 135	2 ± 2	0	0	1	3	19

P_{25}, first quartile; P_{50}, second quartile; P_{75}, third quartile; Min, minimum number of deaths during the study period; Max, maximum number of deaths during the study period.

Table 2 *Air pollution and meteorological data*

	n	Mean ± SD	Min	Max	P_{25}	P_{50}	P_{75}
Ozone (μg m^{-3})							
Daily 1-h maximum	32 355	109.7 ± 65.8	2	494	63	97	147
Daily 8-h maximum	32 352	88.9 ± 55.3	2	473	48	78	121
Daily average	33 557	56.2 ± 35.7	2	363	38	51	79
$PM_{2.5}$ (μg m^{-3})	34 847	69.0 ± 57.2	3.0	802.9	32.3	52.7	86.5
NO_2 (μg m^{-3})	34 779	49.5 ± 24.9	0.8	327.8	32.1	45.6	62.2
T_{mean} (°C)	37 223	15.7 ± 10.2	−28.0	35.5	8.0	17.7	23.9
Relative humidity (%)	37 230	67.0 ± 19.5	2	100	57	71	81

P_{25}, first quartile; P_{50}, second quartile; P_{75}, third quartile; Min, minimum during the study period; Max, maximum during the study period.

For the all-year analyses, daily 1-h maximum, 8-h maximum and average ozone exposures were positively associated with both nonaccidental and circulatory mortality, whilst for respiratory mortality, the strongest association in terms of magnitude and precision was observed for the daily average metric (Fig. 2 and Figure S2). Amongst the three ozone metrics, central estimates were highest for daily average ozone compared with the 1-h and 8-h maximum values. For nonaccidental mortality, a 10 μg m^{-3} increase in daily average, 1-h maximum and 8-h maximum ozone corresponded to an increase in risk of 0.6% (95% CI: 0.33, 0.88), 0.26% (95% CI: 0.12, 0.39) and 0.37% (95% CI: 0.2, 0.55), respectively. The corresponding risk increases were 0.66% (95% CI: 0.28, 1.04), 0.31% (95% CI: 0.11, 0.51) and 0.39% (95% CI: 0.16, 0.62) for circulatory mortality, and 0.57% (95% CI: −0.09, 1.23), 0.11% (95% CI: −0.22, 0.44) and 0.22% (95% CI: −0.28, 0.72) for respiratory mortality.

For the seasonal analysis, the central estimates in spring and summer were larger than for the whole year. For these two seasons, the central estimates were still highest for daily average ozone. No evidence of an association was observed in winter.

The results of copollutant analysis show that when introducing $PM_{2.5}$ or NO_2 into the model as a confounder, association with ozone remained similar in magnitude compared to the main model (see Table 3). The pooled estimate of the model was robust to different *df* values for the time trend (see Table S3). When the average of all air pollution monitors in the city was assigned to each district within the city, the results were comparable with those of the main analysis (see Table S3).

Discussion

This is the first large-scale multicentre study focusing on the health effects of ozone in China. We found that: (i) the pooled estimates for daily 1-h maximum, daily 8-h maximum and daily average ozone exposure for the whole year were strongly associated with all mortality outcomes (nonaccidental, circulatory and respiratory); (ii) the seasonal patterns were consistent with the times of year when ozone concentrations are highest; and (iii) in general, central estimates were highest for daily average ozone exposure, and lowest for daily 1-h maximum ozone exposure.

We compared our results with those of previous multicentre studies according to ozone metrics (Table S4) [11, 12, 14, 15, 30–32]. Previous studies also showed an increase in risk of nonaccidental, circulatory and respiratory mortality following exposure to elevated daily average, daily 1-h maximum and daily 8-h maximum ozone concentrations. The differences in estimates from different studies may be due to variations in study location, demographic characteristics and analytical method. We also compared the estimates from our studies with those of previous studies using the three ozone metrics. A study conducted in Guangzhou demonstrated that amongst these three ozone metrics, daily average ozone showed the largest central estimate for total mortality and 1-h maximum ozone the smallest [23]. This finding was consistent with our results, in contrast to those of a study conducted in Suzhou [28]; the difference in the latter study may have been due to issues related to data quality or measurement error [33].

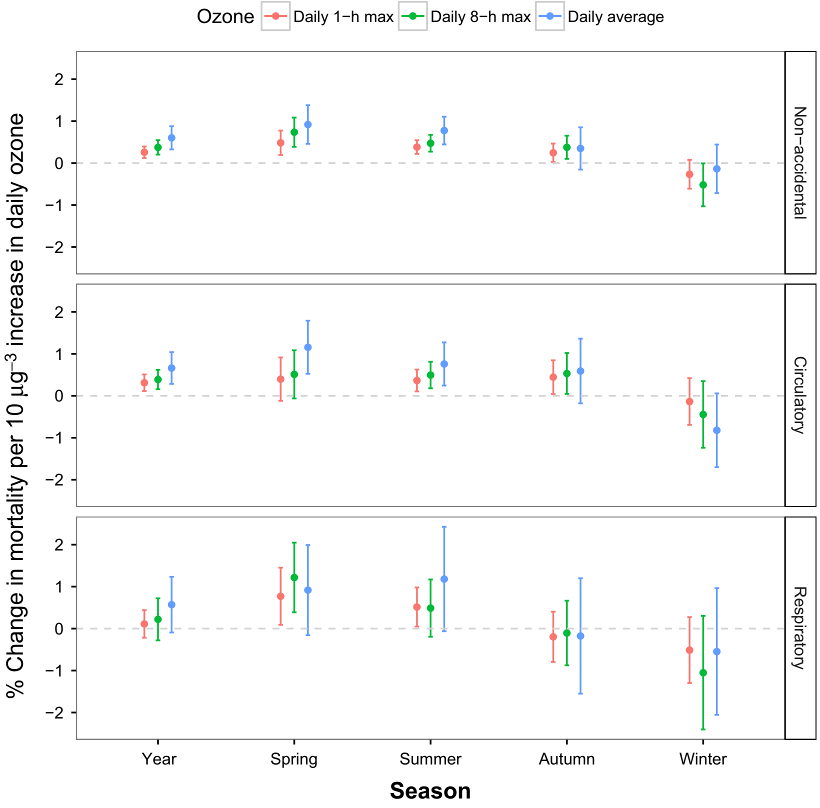

Fig. 2 *Pooled estimates for the percentage increase in nonaccidental, circulatory and respiratory mortality associated with an increase of 10 μg m^{-3} in 1-h, 8-h and daily average ozone level by season.*

Table 3 *Copollutant analysis for the whole year*

		Per cent increase (95% CI) in daily number of deaths associated with increase in ozone concentration of 10 μg m^{-3}		
Mortality	Copollutant	Daily average	1-h maximum	8-h maximum
Nonaccidental	$PM_{2.5}$	0.56 (0.27, 0.84)	0.23 (0.1, 0.36)	0.34 (0.17, 0.51)
	NO_2	0.63 (0.35, 0.9)	0.22 (0.08, 0.36)	0.34 (0.17, 0.52)
Circulatory	$PM_{2.5}$	0.62 (0.25, 0.99)	0.28 (0.08, 0.48)	0.36 (0.12, 0.59)
	NO_2	0.69 (0.31, 1.07)	0.3 (0.09, 0.5)	0.38 (0.14, 0.61)
Respiratory	$PM_{2.5}$	0.56 (−0.1, 1.21)	0.08 (−0.26, 0.41)	0.21 (−0.3, 0.71)
	NO_2	0.6 (−0.04, 1.25)	0.04 (−0.3, 0.38)	0.16 (−0.34, 0.67)

$PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm.

Several studies have reported significant associations between ozone exposure and mortality in summer but weak or null relationships during other seasons [11, 27, 31]. This is consistent with our findings: the highest central estimates appeared in spring and summer, and there was no evidence of an association in winter. These results revealed that the ozone-related health risk is mainly seen during warm seasons when ozone concentrations are highest. This may be due to the pathogenic mechanism of ozone or differences in human time–activity patterns in different seasons.

In epidemiological studies, selecting exposure estimates is a major analytical challenge [34]. The use of a given time metric may be justified by biological plausibility, spatial representativeness, human time–activity patterns or data availability. We selected the optimum ozone metric in our study based on: (i) model selection, (ii) the pathogenic mechanism and (iii) the estimate objective. First, with regard to model selection, we compared the associations between various ozone metrics and causes of mortality. The central estimates of daily average ozone were the largest, whilst the central estimates of 1-h maximum ozone were the smallest. In spring and summer, with high ozone concentrations, the same pattern was observed (except for respiratory mortality in spring). The daily average was found to be the optimal metric in China, compared to daily 1-h maximum and 8-h maximum, in association with mortality based on model selection. This trend was consistent with the results from previous studies [11, 28, 35, 36]. Secondly, the pathogenic mechanism of ozone was an important reference in choosing the ozone metric. Temporal metrics (e.g. 1-h maximum) may be the most biologically relevant if the health effect is triggered by a high, short-term dose [37]. Based on a series of studies, Lippmann [1] argued that the acute effects of ozone were more closely related to cumulative daily exposure than to 1-h peak concentrations. Thirdly, peak concentrations are frequently associated with episodic, local emission events. Meanwhile, an 8-h average concentration is an appropriate metric in the USA and elsewhere given the reactions that form ozone (e.g. NO_x scavenging), and a 24-h average concentration metric may often be more representative of average population exposures [37]. In the present study, we sought an optimum ozone metric to estimate the health effect of ozone in China under normal circumstances. Based on the above three issues, we suggest that daily average ozone is the best predictor of mortality in China.

The results of this study have demonstrated more accurate associations that can enable researchers to study the health risks associated with ozone exposure in China. Several limitations of this study should be noted. First, we only utilized data from a 3-year period, which reduces statistical power. Secondly, the sample sizes for determining the 1-h maximum were different from those for the 8-h maximum, which may decrease the comparability of different ozone metrics. Thirdly, because there were no air pollution monitors in some counties, we assigned exposure in these counties from the nearest monitor. Therefore, there is the potential for exposure misclassification. In order to reduce this possibility, we performed a sensitivity analysis assigning exposure from the average of all monitors in the entire city and calculated a comparable association.

Conclusions

In summary, our results show a robust positive association between short-term exposures of ozone and nonaccidental, circulatory and respiratory mortality risk in 34 districts in China, and ozone-related mortality risk is mainly seen during warm seasons when ozone concentrations are highest.

We suggest that the acute effects of ozone are more closely related to daily average exposure than any other metric in China. This may contribute to future revisions of the ambient standard for ozone. The current ambient air quality standard for ozone in China is based on the 1-h maximum and 8-h maximum values. According to our study, adding a daily average requirement for ozone will provide a greater health benefit.

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Conflict of interest statement

The authors declare that they have no actual or potential competing financial interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Ozone concentration of 34 counties in 10 cities.

Figure S2. County-specific and pooled estimates for nonaccidental mortality during different time periods.

Table S1. Description of population, mortality, meteorological, and air pollution data during the study period by districts.

Table S2. Effects of different lag structures.

Table S3. Pooled estimates for the annual effect of different ozone metrics on mortality for different *df* values of time trend and exposure.

Table S4. Comparison of the results of this study and other multicenter studies by causes of death and ozone metrics.

Table S5. Detailed data for Fig. 2. ■