Preplanned Studies

Temperature-Modified Acute Effects of Ozone on Human Mortality — Beijing Municipality, Tianjin Municipality, Hebei Province, and Surrounding Areas, China, 2013–2018

Chen Chen[1]; Jing Liu[1]; Wanying Shi[1]; Tiantian Li[1]; Xiaoming Shi[1,#]

Summary

What is already known about this topic?

Ozone (O_3) is a weather-driven photochemical ambient pollutant, and its harm to human health may be affected by meteorological factors such as temperature. However, there is conflicting evidence regarding whether temperature can modify the effects of ozone on health.

What is added by this report?

Short-term exposure to O_3 in the Beijing Municipality, Tianjin Municipality, Hebei Province, and surrounding areas was associated with an increased risk of human mortality and that association was positive modified by relatively higher (>75th 24 h-average temperature) or extreme cold temperature (<10th 24 h-average temperature). Under extreme temperatures (>90th 24 h-average temperature) modification, the associations were further increased. Cardiopulmonary diseases, as vulnerable diseases of air pollution, their mortality risks associated with O_3 were markedly strengthened by uncomfortable temperatures.

What are the implications for public health practice?

This study suggests that policymakers should pay attention to the synergistic effect between ozone and heat or extreme cold on human health, as well as provide evidence for establishing an integrated early-warning system to protect the public against both uncomfortable temperature and air pollution.

Short-term exposure to ambient ozone (O_3), a weather-driven photochemical pollutant, has been found to be associated with increased risk of mortality in previous epidemiological studies (1–2). Most of these studies analyzed O_3-mortality associations by controlling for meteorological factors in a model fitting process. Regarding the high correlation between O_3 and temperature, a recent area of interest is whether the observed O_3-mortality associations can be modified by temperature. Jhun et al. found both high and low

temperature could strengthen acute effects of O_3 on mortality (3), while Chen et al. and Shi et al. reported that O_3-mortality associations were strengthened in high temperature but not in low temperature settings (4–5), and Liu et al. and Chen et al. only found modifications by low temperature (6–7). In summary, evidence on temperature-modification was inconsistent and needed to be supplemented by regional epidemiological studies involving various meteorological characteristics. Note that in the new air quality guidelines issued by the World Health Organization (WHO), O_3 limits have been distinguished between warm and cold seasons. Beijing Municipality and Tianjin Municipality, along with 26 cities distributed in Hebei, Shandong, Shanxi and Henan Provinces, have formed the regional air pollution transmission channel, and experienced a challenge of regional O_3 pollution increasing steadily. Therefore, additional efforts are needed to better quantify the local health risks of O_3 by considering the influence of temperature in the Beijing, Tianjin, Hebei and surrounding areas.

This study used daily counts of deaths from the Disease Surveillance Point System of China CDC and included 39 counties in the Beijing, Tianjin, Hebei and surrounding areas from January 1, 2013 to December 31, 2018. Three major causes of deaths were classified according to the 10th Revision of the International Statistical Classification of Diseases (ICD-10): non-accidental disease (A00–R99), cardio-cerebrovascular disease (I00–I99), and respiratory disease (J00–J99). Daily ambient O_3 concentrations were collected from the National Urban Air Quality Real-Time Release Platform and calculated to a daily 8-hour moving average maximum (O_3 8 h-average), 1-hour maximum (O_3 1 h-max), and 24 hour-average of O_3 (O_3 24 h-average). Daily average temperature and relative humidity were obtained from the China Meteorological Data Network.

The study applied two time-series approaches with a two-stage statistical analysis to estimate whether and how temperature modified acute effects of O_3 on

mortality in the Beijing, Tianjin, Hebei and surrounding areas. The first approach, a temperature-adjusted approach, aimed to control the cumulative temperature impacts with a cross-basis function using a generalized linear model (GLM) and analyze associations between O_3 and death without considering interactions.

The second approach, a temperature-stratified approach by a Pick-A-Point technique centering on changes of the conditional effect of O_3 across the designated levels of the modifier (8), aimed to construct interaction terms between O_3 and a stratification variable of temperature in the GLM and analyze differences of associations under three different temperature levels: low, moderate, and high temperature. In this model, we used three cutoffs to categorize daily average temperature, including the 10th and 90th (P_{10}/P_{90}), 20th and 80th (P_{20}/P_{80}), and 25th and 75th (P_{25}/P_{75}) percentiles. The model of the temperature-stratified approach was set up as follows:

$$Log[E(Y_t)] = intercept + \beta O_3 + \beta_1 Tem + \beta_2(O_3 : Temstrata) + ns(RH, df) + dow + ns(time, df)$$

Where was the expected value of death on day t; *Tem* represented the daily value of temperature; ($O_3 : Temstrata$) was the interaction term between O_3 and temperature, in which temperature was divided into low, moderate, and high levels of the categorical variable by cutoffs. Both approaches estimated effects of the 2-day average of current and previous-day concentrations (lag 01) of O_3 8 h-average and controlled for seasonal and time trends [*time*, natural smoothing function of 8 degrees of freedom (*df*)], day of the week (*dow*), and relative humidity (*RH*, natural smoothing function of 5 *df*). The effect estimate was expressed as a percent increase (PI) in mortality risk per 10 μg/m³ increase in O_3 exposure.

This study examined the sensitivity of key findings for non-accidental mortality with respect to using the following: 1) the specification of *df* in the smoothing functions of time trend (*df*=6 or 7/year) and relative humidity (*df*=3) in the temperature-adjusted approach to observe model stability; 2) the other two metrics (O_3 1 h-max and O_3 24 h-average) with different lagged exposure [the same day as deaths (lag 0), the previous day (lag 1), and lag 01] in the temperature-adjusted approach to observe impacts from different exposure assessments for the study population; and 3) O_3 1 h-max and O_3 24 h-average with lag 01 exposure in the temperature-stratified approach to observe whether the modification effect of temperature on different ozone metrics was robust. Statistical analyses were conducted in the R Statistical Software (version 4.0.2, the Free Software Foundation's GNU Public License, Vienna, Austria). Statistical significance was considered at a *P*-value <0.05.

From 2013 to 2018, residents in the Beijing, Tianjin, Hebei and surrounding areas were exposed to a concentration of O_3 8 h-average of (95.2±61.4) μg/m³. Approximately 11 deaths for non-accidental disease, 6 for cardiocerebrovascular disease, and 1 for respiratory disease per day per county were recorded (Table 1).

Based on the temperature-adjusted approach without considering interactions, a per 10 μg/m³ increase in exposure to O_3 8 h-average would increase daily mortality risks of non-accidental [PI=0.15%, 95% Confidence Interval (CI): 0.06%, 0.24%], cardio-cerebrovascular (PI=0.20%, 95% CI: 0.07%, 0.33%), and respiratory diseases (PI=−0.08%, 95% CI: −0.42%, 0.25%) in the Beijing, Tianjin, Hebei and surrounding areas. Based on temperature-stratified approach, relatively higher temperature (>75th 24 h-average temperature) significantly strengthened O_3-mortality associations, with a 0.57% risk increase of

TABLE 1. Summary for ambient O_3, meteorological factors, and causes of death in the Beijing, Tianjin, Hebei and surrounding areas, 2013 to 2018.

Variable	Mean±SD	P_{25}	P_{50}	P_{75}
O_3 24 h-average (μg/m³)	56.3±38.7	25.3	49.5	80.2
O_3 8 h-average (μg/m³)	95.2±61.4	48.2	83.8	135.4
O_3 1 h-max (μg/m³)	111.0±71.5	59.7	95.0	155.0
Temperature (°C)	13.3±11.1	2.8	14.6	23.4
Humidity (%)	0.6±0.2	0.4	0.6	0.7
Non-accidental diseases	11±8	6	9	14
Cardio-cerebrovascular diseases	6±4	3	5	7
Respiratory diseases	1±1	0	1	2

Abbreviations: SD=standard deviation; P_{25}=25th percentile; P_{50}=50th percentile; P_{75}=75th percentile.
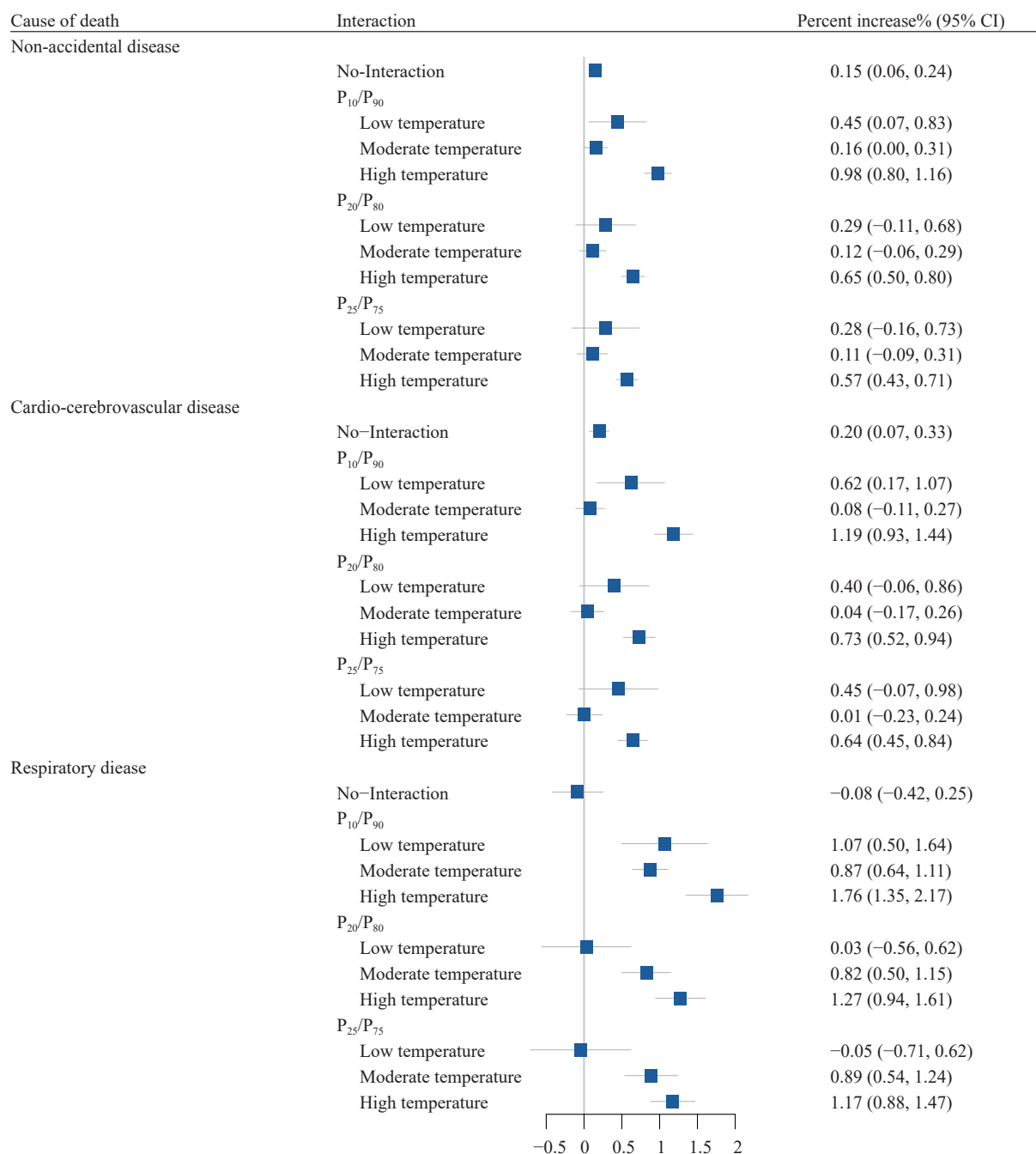
FIGURE 1. Mortality risk estimates associated with Lag 01 exposure of O_3 by using the temperature-adjusted and temperature-stratified approach in the Beijing, Tianjin, Hebei and surrounding areas, 2013–2018.
Abbreviations: P_{10}=10th percentile; P_{90}=90th percentile; P_{20}=20th percentile; P_{80}=80th percentile; P_{25}=25th percentile; P_{75}=75th percentile.

non-accidental disease, 0.64% risk increase of cardio-cerebrovascular disease, and 1.17% risk increase of respiratory disease (Figure 1). Under extreme temperature (>90th 24 h-average temperature) modification, the associations between O_3 and human mortality has further increased: a 0.98% risk increase of non-accidental disease, 1.19% risk increase of cardio-cerebrovascular disease, and 1.76% risk increase

of respiratory disease (Figure 1). Moreover, extreme low temperature (<10th 24 h-average temperature) was also found to strengthen the acute effects of O_3 on mortality (Figure 1).

Associations between short-term exposure to O_3 8 h-average and mortality peaked at Lag 01 exposure. Analyses with different metrics of O_3 exposure and more or less stringent time trends and relative

TABLE 2. Percent increase (95% CI) in mortality risks associated with short-term exposure to O_3 for sensitivity analysis by using the temperature-adjusted approach in the Beijing, Tianjin, Hebei and surrounding areas, 2013–2018. (%)

Pollutants	Lag	$df_{tem/rh}$=3, df_{time}=6	$df_{tem/rh}$=5, df_{time}=8	$df_{tem/rh}$=5, df_{time}=7	$df_{tem/rh}$=3	$df_{tem/rh}$=3, df_{time}=7
O_3 8 h-average	Lag 0	0.11 (0.04, 0.19)	0.14 (0.06, 0.22)	0.14 (0.07, 0.22)	0.13 (0.05, 0.21)	0.13 (0.05, 0.20)
	Lag 1	0.03 (−0.05, 0.10)	0.07 (−0.01, 0.14)	0.06 (−0.01, 0.14)	0.05 (−0.02, 0.13)	0.04 (−0.04, 0.11)
	Lag 01	0.09 (−0.00, 0.18)	0.15 (0.06, 0.24)	0.14 (0.04, 0.23)	0.13 (0.04, 0.22)	0.10 (0.01, 0.20)
O_3 1 h-max	Lag 0	0.07 (0.01, 0.13)	0.08 (0.03, 0.14)	0.08 (0.03, 0.14)	0.08 (0.02, 0.14)	0.08 (0.02, 0.13)
	Lag 1	0.06 (−0.00, 0.11)	0.08 (0.02, 0.13)	0.07 (0.01, 0.13)	0.07 (0.01, 0.12)	0.06 (0.00, 0.12)
	Lag 01	0.10 (0.02, 0.17)	0.13 (0.06, 0.21)	0.12 (0.05, 0.20)	0.12 (0.04, 0.19)	0.10 (0.03, 0.18)
O_3 24 h-average	Lag 0	0.13 (0.01, 0.24)	0.14 (0.02, 0.25)	0.17 (0.06, 0.28)	0.13 (0.02, 0.24)	0.15 (0.04, 0.26)
	Lag 1	0.12 (0.01, 0.23)	0.16 (0.05, 0.27)	0.17 (0.06, 0.28)	0.14 (0.03, 0.25)	0.14 (0.03, 0.25)
	Lag 01	0.17 (0.03, 0.30)	0.21 (0.07, 0.35)	0.24 (0.10, 0.38)	0.19 (0.05, 0.32)	0.20 (0.06, 0.34)

Note: $df_{tem/rh}$ is the degree of freedom of natural smoothing function for temperature or relative humidity, df_{time} is the degree of freedom of natural smoothing function for the seasonal and time trends.
Abbreviation: CI=confidence interval.

TABLE 3. Percent increase (95% CI) in mortality risks associated with short-term exposure to O_3 for sensitivity analysis by using the temperature-stratified approach in the Beijing, Tianjin, Hebei and surrounding areas, 2013–2018. (%)

Pollutants	Temperature	P_{10}/P_{90}	P_{20}/P_{80}	P_{25}/P_{75}
O_3 1 h-max	Low	0.30 (−0.01, 0.61)	0.23 (−0.09, 0.54)	0.24 (−0.12, 0.6)
	Moderate	0.14 (0.02, 0.25)	0.13 (−0.01, 0.27)	0.13 (−0.03, 0.28)
	High	0.81 (0.66, 0.97)	0.55 (0.43, 0.68)	0.49 (0.37, 0.61)
O_3 24 h-average	Low	0.61 (0.11, 1.12)	0.31 (−0.24, 0.86)	0.32 (−0.3, 0.94)
	Moderate	0.14 (−0.11, 0.4)	0.08 (−0.22, 0.39)	0.06 (−0.28, 0.41)
	High	1.47 (1.22, 1.73)	1.02 (0.81, 1.24)	0.90 (0.68, 1.12)

Abbreviations: CI=confidence interval; P_{10}=10th percentile; P_{90}=90th percentile; P_{20}=20th percentile; P_{80}=80th percentile; P_{25}=25th percentile; P_{75}=75th percentile.

humidity controlled by varying *df*'s did not meaningfully change our findings (Table 2). For the three cutoffs of P_{10}/P_{90}, P_{20}/P_{80}, and P_{25}/P_{75}, the associations between the other two O_3 metrics and morality were both increased under high temperature levels (Table 3). The extreme low temperature was found to only significantly modify the association between O_3 24 h-average and mortality.

DISCUSSION

We used two time-series approaches to explore the effects of short-term exposure to O_3 on mortality across temperature levels in the Beijing, Tianjin, Hebei and surrounding areas throughout a six-year period. Both the temperature-adjusted and temperature-stratified approaches indicated that short-term exposure to O_3 was associated with an increased risk of mortality, and that the association was positive modified by high-temperature levels, especially

modified by extreme heat. These findings were consistent with epidemiological evidence from several previous national-level studies *(3,5,9)*. From an exposure standpoint, it may be because ground-level O_3 is usually formed by photochemical reactions of precursor pollutants under the presence of light; as the temperature increases, the formation of O_3 accelerates, and the emission of precursor pollutants increases, resulting in an increase in effect size of O_3 along with increased pollution.

The study also found that the O_3-mortality risks of cardiopulmonary diseases, as vulnerable diseases of air pollution, were further strengthened in the presence of high temperature. However, studies in some southern cities in China *(6–7)* have not observed this modification effect. For example, a study conducted by Chen et al. in Jiangsu showed that O_3 has a higher impact on death from cardiovascular diseases in a low temperature environment. The conflicting results indicated that the modification may vary considerably

across different climatic regions. Represented by previous national studies conducted in the United States, Jhun et al. and Ren et al. consistently emphasized that the modification of temperature on the O_3-mortality association varied across different regions (*3,9*). In addition to different climates and characteristics of O_3 pollution, various adaptive measures of local residents to mitigate exposure to O_3 and temperature may be another reason for the regional differences (*9*). Residents in the regions of southern China may become less sensitive to the variability of O_3 and temperature due to physical adaptation and higher air conditioning usage rates.

Experimental studies have observed that exposure to O_3 can result in injuries (including cellular response, metabolic activity, and physiological changes in respiratory function) to the nasal cavity, trachea and proximal bronchi, central acinar bronchioles, and alveolar ducts (*9*). O_3 inhaled through respiratory airways can also affect the regulation of the autonomic nervous system and then cause damage to human cardiovascular health. Meanwhile, although the mechanism of low temperature modification is not clear yet, marked changes in temperature can cause physiological stress and make individuals' physiological response vulnerable to toxic pollutants (*10*). This would be the possible reason why we found that the acute effects of a low O_3 exposure on mortality for non-accidental and cardiopulmonary diseases were strengthened by extreme low temperature. What has caught our attention is that when a cold wave hits, even if O_3 is at a low pollution level, it will have an adverse effect on health and should not be underestimated or ignored.

This study was subject to at least three limitations. First, the analytical methods used in our study can semi-quantitatively assess the difference in O_3-related mortality risks across different temperature stratifications, but a more flexible statistical method is needed to quantify nonlinear modifications. Second, due to differences in climate patterns, the modification of temperature on the acute effect of O_3 found here would not be applicable to other regions. We suggest that a more in-depth study of different climate regions in future studies. Finally, our study did not include information regarding the use of air conditioning or heating devices, which could influence the modification of temperature on O_3-related mortality risks.

Our findings suggest that policymakers should pay attention to the synergistic effect between heat or extreme cold and O_3 on human heath, as well as provide evidence for establishing an integrated early-warning system for protecting the public against both unsuitable temperature and air pollution.

Conflicts of interest: No conflicts of interest.

[#] Corresponding author: Xiaoming Shi, shixm@chinacdc.cn.

[1] China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China.

REFERENCES

1. Vicedo-Cabrera AM, Sera F, Liu C, Armstrong B, Milojevic A, Guo YM, et al. Short term association between ozone and mortality: global two stage time series study in 406 locations in 20 countries. BMJ 2020;368:m108. http://dx.doi.org/10.1136/BMJ.M108.
2. Yin P, Chen RJ, Wang LJ, Meng X, Liu C, Niu Y, et al. Ambient ozone pollution and daily mortality: a nationwide study in 272 Chinese cities. Environ Health Perspect 2017;125(11):117006. http://dx.doi.org/10.1289/EHP1849.
3. Jhun I, Fann N, Zanobetti A, Hubbell B. Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ Int 2014;73:128 – 34. http://dx.doi.org/10.1016/j.envint.2014.07.009.
4. Chen K, Wolf K, Breitner S, Gasparrini A, Stafoggia M, Samoli E, et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. Environ Int 2018;116:186 – 96. http://dx.doi.org/10.1016/j.envint.2018.04.021.
5. Shi WY, Sun QH, Du P, Tang S, Chen C, Sun ZY, et al. Modification effects of temperature on the ozone-mortality relationship: a nationwide multicounty study in China. Environ Sci Technol 2020;54(5):2859 – 68. http://dx.doi.org/10.1021/acs.est.9b05978.
6. Liu T, Li TT, Zhang YH, Xu YJ, Lao XQ, Rutherford S, et al. The short-term effect of ambient ozone on mortality is modified by temperature in Guangzhou, China. Atmos Environ 2013;76:59 – 67. http://dx.doi.org/10.1016/j.atmosenv.2012.07.011.
7. Chen K, Yang HB, Ma ZW, Bi J, Huang L. Influence of temperature to the short-term effects of various ozone metrics on daily mortality in Suzhou, China. Atmos Environ 2013;79:119 – 28. http://dx.doi.org/10.1016/j.atmosenv.2013.06.004.
8. Bauer DJ, Curran PJ. Probing interactions in fixed and multilevel regression: inferential and graphical techniques. Multivariate Behav Res 2005;40(3):373 – 400. http://dx.doi.org/10.1207/s15327906mbr4003_5.
9. Ren CZ, Williams GM, Mengersen K, Morawska L, Tong SL. Temperature enhanced effects of ozone on cardiovascular mortality in 95 large US communities, 1987-2000: assessment using the NMMAPS data. Arch Environ Occup Health 2009;64(3):177 – 84. http://dx.doi.org/10.1080/19338240903240749.
10. Schwartz J. How sensitive is the association between ozone and daily deaths to control for temperature? Am J Respir Crit Care Med 2005;171(6):627-31. http://dx.doi.org/10.1164/rccm.200407-933OC.