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Foreword

Acute Effects of Air Pollution on Human Health in China: Evidence and Prospects

The adverse impacts of air pollution on human health have already been a major environmental issue globally, and the challenges are even more severe in China. The World Health Organization (WHO) estimates that 4.2 million deaths annually can be attributed to outdoor air pollution in 2016 (1). For example, ambient fine particulate matter (PM_{2.5}) has been ranked as the fourth leading risk factor for disease in China (2). Atmospheric ozone (O₃) pollution has demonstrated an increasing trend year by year, and the problem of regional compound pollution has become prominent. Therefore, the acute health hazard of air pollution is a major environmental, medical, and public health burden in China. Clarifying the exposure-response relationships between complex air pollution and population-based acute health effects are great strategic demands. With funding from the National Key Research and Development Program of the Ministry of Science and Technology, the “China Short-Term Health Effects of Air Pollution Study” (China SHEAP Study) project was carried out in 2016 and hosted by the National Institute of Environmental Health (NIEH) of China CDC. This project gathered domestic research and development institutions specialized in national public health and clinical medicine to jointly undertake the task. During the four-year implementation period, the project has achieved a series of innovative findings: 1) it clarified the acute impact of short-term exposure of air pollutants on death of residents and their spatiotemporal distribution characteristics in 106 regions nationwide; 2) it systematically evaluated the acute exposure-response relationships between particulate matter (PM) as well as gaseous pollutants and death, morbidities and symptoms of respiratory and cardiovascular diseases in typically polluted cities from three regions and ten urban agglomerations that conducted national air pollution prevention and control; 3) identified acute health effects of differential particle size and chemical component exposures on children, healthy adults, and patients with cardiopulmonary diseases and determined the particles and their components with major toxicity potency; and 4) conducted intervention research to assess the impact of different intervening measures on acute health hazards of air pollution. Through multilevel and multidimension data as well as the integration of key technologies, this project illustrated the distribution characteristics of population-based acute health risks of complex air pollution and established a dataset for complex air pollution and health as well as a data integration platform.

In this special issue, we invited colleagues and collaborators involving in the China SHEAP study project to report their latest findings. For example, Niu et al. examined the associations between air pollutants with daily hospitalizations and outpatient visits of chronic obstructive pulmonary disease (COPD) and asthma within 5 Chinese cities. The results showed that air pollutants were significantly related to the increasing outpatient and hospitalization rates of chronic respiratory diseases (3). Liu et al. assessed the associations of short-term PM_{2.5} mass exposure with several ambulatory blood pressure (BP) monitoring indicators from a panel study conducted in Beijing, Shanghai, Wuhan, and Xi'an. The results indicated that short-term PM_{2.5} exposure was significantly associated with BP elevations (4). Xia and Niu et al. evaluated the associations between personal O₃ exposure and biomarkers of inflammation, oxidative stress, and mitochondria oxidative damage among 43 college students in Shanghai. They found that short-term exposure to low concentrations of O₃ was significantly associated with vascular inflammation, lipid peroxidation, and mitochondrial oxidative damage (5). By conducting a randomized crossover study in Beijing, Zhang et al. found that short-term co-exposure to multiple ambient pollutants could disturb the cardiac autonomic function, and that black carbon (BC) and noise were the two pollutants with the greatest contribution (6). Finally, Chen et al. applied two time-series approaches with a two-stage statistical analysis to estimate whether and how temperature-modified acute effects of O₃ affected mortality in Beijing Municipality, Tianjin Municipality, Hebei Province, and surrounding areas. The results suggested that short-term exposure to O₃ was significantly associated with the increased risk of mortality and that the association was positively modified by relative higher (>75th 24 h-average temperature) or extreme cold temperature (<10th 24 h-average temperature) (7).

In summary, the above studies employed different epidemiological designs to assess the impact of short-term air pollution exposure on multidimensionally adverse health outcomes. These provocative findings warrant a

multiomics approach to comprehensively explore the etiological evidence, the underlying mechanisms, and the causal linkages between air pollution and health effects in China, relying on the available list of biomarkers associated with key toxic components of air pollutants. In view of the compound characteristics of air pollution complex in China, establishing innovative technologies and methods for health risk assessments of multiple exposures simultaneously as well as illustrating their joint effects and mechanisms are highly needed. In addition, the development of early warning techniques for health risks may promote residents to efficiently take actions and protections against air pollution exposures and their health hazards.

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Preplanned Studies

Exposure Response Relationship of Acute Effects of Air Pollution on Respiratory Diseases — China, 2013–2018

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Summary

What is already known about this topic?

Short-term exposure to air pollutants has been associated with chronic obstructive pulmonary disease (COPD) and asthma, which needs continuous observation.

What is added by this report?

This study uses the longest time series data so far from 2013 to 2018 and adds additional data analysis for ozone (O₃) to existing studies.

What are the implications for public health practice?

This study suggests that air pollutants have certain acute effects on outpatient and hospital admission of patients with COPD and asthma, which can be combined with the disease diagnosis and treatment guidelines to guide clinical practice.

Chronic obstructive pulmonary disease (COPD) and asthma are two major chronic airway diseases. Recent studies have focused on the relationship between air pollution and the development of acute exacerbations of COPD and asthma. In 2021, Liu et al. found that fine particulate matter (particles with aerodynamic diameter ≤ 2.5 μm ; PM_{2.5}) and nitrogen dioxide (NO₂) increased the risk of COPD and asthma (1). Doiron et al. found that PM_{2.5}, particles with aerodynamic diameter ≤ 10 μm (PM₁₀) and NO₂ significantly enhanced the morbidity of COPD (2). However, in 2014, a study found that neither NO₂ nor PM levels were associated with COPD morbidity (3). It can be concluded that there is no clear conclusion whether short-term exposure to air pollution increases the health risk of COPD and asthma patients. Meanwhile, in China, the available studies about air pollution are based on a three-year time series of data from 2013–2015 (4), which may not reflect the health effects of recent air quality improvement initiatives. Therefore, we analyzed daily outpatient and hospitalization data from the China CDC Disease Surveillance Point System (DSPs) from

January 1, 2013 to December 31, 2018 to explore the impact of short-term exposure to air pollution on the acute effects of patients with COPD and asthma.

This study collected inpatient and outpatient data for respiratory diseases, concentration of each air pollutant, as well as temperature and relative humidity data from January 1, 2013 to December 31, 2018 in 16 hospitals in China in 5 cities (6 districts and counties). We used the International Classification of Diseases Revision 10 (ICD-10) codes J40–J44 for COPD visits and codes J45–J46 for asthma. Relevant air pollution data was obtained from the National Urban Air Quality Real-Time Release Platform, and temperature and relative humidity was obtained from the National Meteorological Information Center.

Pollutant concentrations were aggregated to daily means [carbon monoxide (CO), sulfur dioxides (SO₂), NO₂, PM_{2.5}, and PM₁₀] and daily maximum 8-hour means (O₃).

We used a time-stratified case-crossover design to analyze the associations between air pollution and hospital admissions for respiratory diseases. A time stratum was defined as a combination of year, month, and day-of-week levels. This design allows for the adjustment of long-term and seasonal trends. We then fit a generalized linear model (GLM) with a Poisson distribution. Daily mean temperature and relative humidity were also controlled by the natural spline function in the model. The “stats” package in R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria) was used for analysis. Results were presented as the percentage changes and 95% confidence intervals (CIs) in daily inpatient and outpatient rates associated with a per 10 $\mu\text{g}/\text{m}^3$ increase in air pollutants (CO is mg/m^3). We also assessed the single-day lag effect (from 0 to 3) and the cumulative lag effect (0–1, 0–2, and 0–3) of air pollutants on daily outpatient and hospitalization rates.

In total, 85,961 outpatient visits and 62,381 hospital admissions were observed for COPD and asthma in 16 hospitals from 2013 to 2018.

Table 1 shows the mean pollutant concentrations,

TABLE 1. Daily counts of hospitalizations and outpatient visit for respiratory diseases and air pollution levels in China, 2013–2018.

Variables	Mean (SD)
Outpatient visit (daily counts per county)	
COPD	38 (18)
Asthma	8 (5)
Hospitalizations (daily counts per county)	
COPD	6 (4)
Asthma	3 (2)
Pollutants	
PM _{2.5} (µg/m ³)	59.1 (43.4)
PM ₁₀ (µg/m ³)	95.9 (61.9)
O ₃ (µg/m ³)	112.8 (59.3)
SO ₂ (µg/m ³)	19.8.2 (17.2)
NO ₂ (µg/m ³)	47.9 (21.3)
CO (mg/m ³)	1.1 (0.7)

Abbreviations: SD=standard deviation; COPD=chronic obstructive pulmonary disease; PM_{2.5}=particulate matter ≤2.5 m in diameter; PM₁₀=particulate matter ≤10 m in diameter; SO₂=sulfur dioxides; NO₂=nitrogen dioxide; CO=carbon monoxide; O₃=ozone.

and the average daily respiratory disease hospitalizations and outpatient visits in the study areas (expressed as mean and standard deviation). The average daily respiratory disease outpatient visits were approximately 38 for COPD and 8 for asthma, 6 for COPD, and 3 for asthma in daily hospital admissions.

Atmospheric pollutants had an acute effect on the risk of hospitalization for COPD (Figure 1A), and the acute effects of PM_{2.5}, O₃, and CO on the risk of hospitalization for COPD were most pronounced at lag02, with each 10 µg/m³ increase in PM_{2.5}, O₃, and CO increasing the risk of hospitalization for COPD by 1.1% (95% CI: 0.6%–1.7%), 1.7% (95% CI: 1.3%–2.1%), and 88.2% (95% CI: 6.7%–232%). However, no acute effect of air pollutants on the risk of hospitalization for asthma was seen (Figure 1B).

In patients with COPD, O₃ was negatively associated with an increased risk of outpatient visits for COPD (Figure 2A), and NO₂ was positively associated with increased risk of outpatient visits for COPD, most strongly at lag02, with each 10 µg/m³ increase in NO₂ associated with a 2.4% (95% CI: 0.4%, 4.4%) increase in risk of outpatient visits for patients with COPD.

Among asthma patients, PM_{2.5} and PM₁₀ were negatively associated with the risk of outpatient visits (Figure 2B), with the strongest at lag1, where each 10 µg/m³ increase in PM_{2.5} and PM₁₀ was associated

with a 0.6% (95% CI: –0.9%, –0.2%) and 0.4% (95% CI: –0.7%, –0.2%) decrease in the risk of outpatient visits for asthma patients, respectively. O₃, SO₂, and NO₂ were positively associated with increased risk of outpatient asthma visits and were strongest at lag02, with each 10 µg/m³ increase in O₃ and NO₂ increasing the risk of outpatient asthma visits by 0.9% (95% CI: 0.5%, 1.3%) and 2.9% (95% CI: 2%, 3.8%), respectively. The acute effect of SO₂ on outpatient asthma visits was strongest at lag2, with each 10 µg/m³ increase in SO₂ increasing the risk of outpatient visits for asthma patients by 1.1% (95% CI: 0.1%, 2.1%).

DISCUSSION

This study showed that air pollutants were related to increasing outpatient and hospitalization rates of chronic respiratory diseases. PM_{2.5}, O₃, and CO had an acute effect on the risk of hospitalization, and NO₂ was positively associated with an increased risk of outpatient visits for COPD. In asthma patients, O₃, SO₂, and NO₂ were positively associated with an increased risk of outpatient asthma visits. These results were basically consistent with the results of previous studies. Each 10 µg/m³ increase in PM_{2.5} was associated with a 1.61% increase in the risk of hospitalization for patients with COPD in the United States and 0.82% in Beijing (5–6).

The present study showed that CO was positively associated with the risk of hospitalization in patients with COPD, which was inconsistent with the results of previous relevant studies. A few epidemiological studies have found that low levels of CO may have a protective effect in some cases. A time-series study in Hong Kong, China showed that short-term exposure to CO was associated with a reduced risk of hospitalization for COPD (7). However, in Spain, a retrospective study found that elevated CO levels were associated with increased hospital admissions in patients with COPD (8), which was the same as our results. Therefore, further studies are needed to confirm the direct health effects of CO exposure on patients with COPD. At the same time, our study shows that PM_{2.5} and PM₁₀ were negatively associated with the risk of asthma outpatient visits, which was inconsistent with previous research results. A possible reason is that the concentrations of ozone and PM_{2.5} are seasonal and that asthma is affected by many factors. The overall confounders that could affect the association between pollutants and asthma exacerbations also need to be taken into

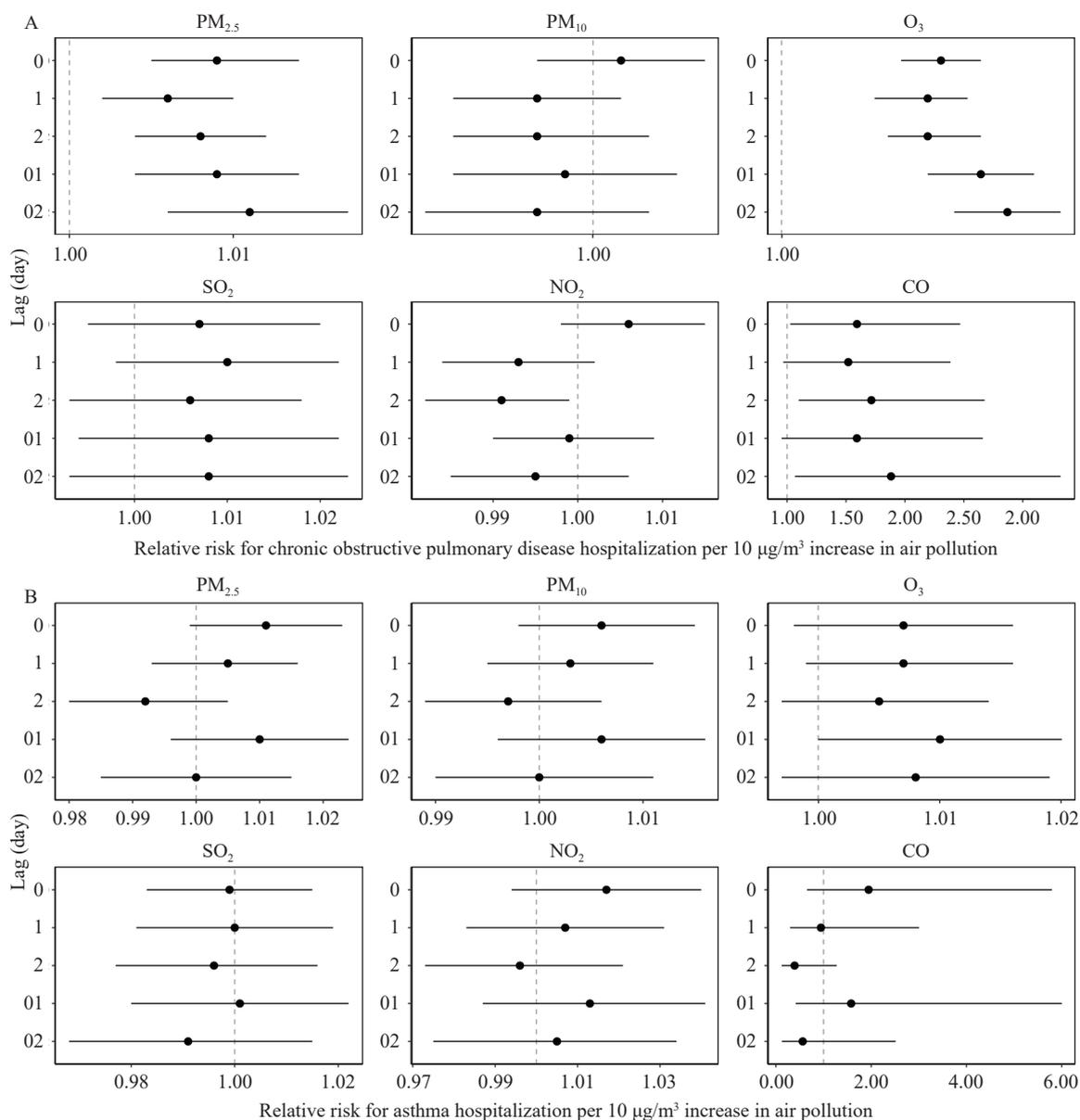


FIGURE 1. Relative risk for chronic obstructive pulmonary disease (A) and asthma (B) daily hospitalization per $10 \mu\text{g}/\text{m}^3$ increase in concentrations of air pollutants with different lag days in 16 hospitals, 2013–2018.

account and include meteorological factors and data for pollen.

The observed acute effects of particulate matters on respiratory diseases could be explained by inducing an imbalance of systemic inflammation, oxidative stress, autophagy, and apoptosis, and by affecting epigenetic modification. Studies showed that elevated level of blood biomarkers of systemic inflammation (e.g., IL-6, IL-8 and TNF- α), coagulation (e.g., fibrinogen), soluble cluster of differentiation 40 ligands (sCD40L), soluble intercellular adhesion molecule-1 (sICAM-1), and fibrinogen, as well as DNA methylation levels were influenced by exposure to air pollutants (9–10).

This study was subject to some limitations. First, the acquisition of air pollution exposure data was from air monitoring stations, which might have some measurement errors. At the same time, the data of the monitoring station cannot fully represent the real exposure of patients, and there will be some exposure errors. Second, we did not obtain data on influenza, seasons and pollen, socioeconomic status, and daily activities, which may be some confounding factors related to outpatient visits and hospitalization. Third, we only analyzed the effects of one air pollutant on disease, but not the effects of exposure to multiple air pollutants. These deficiencies may make our results

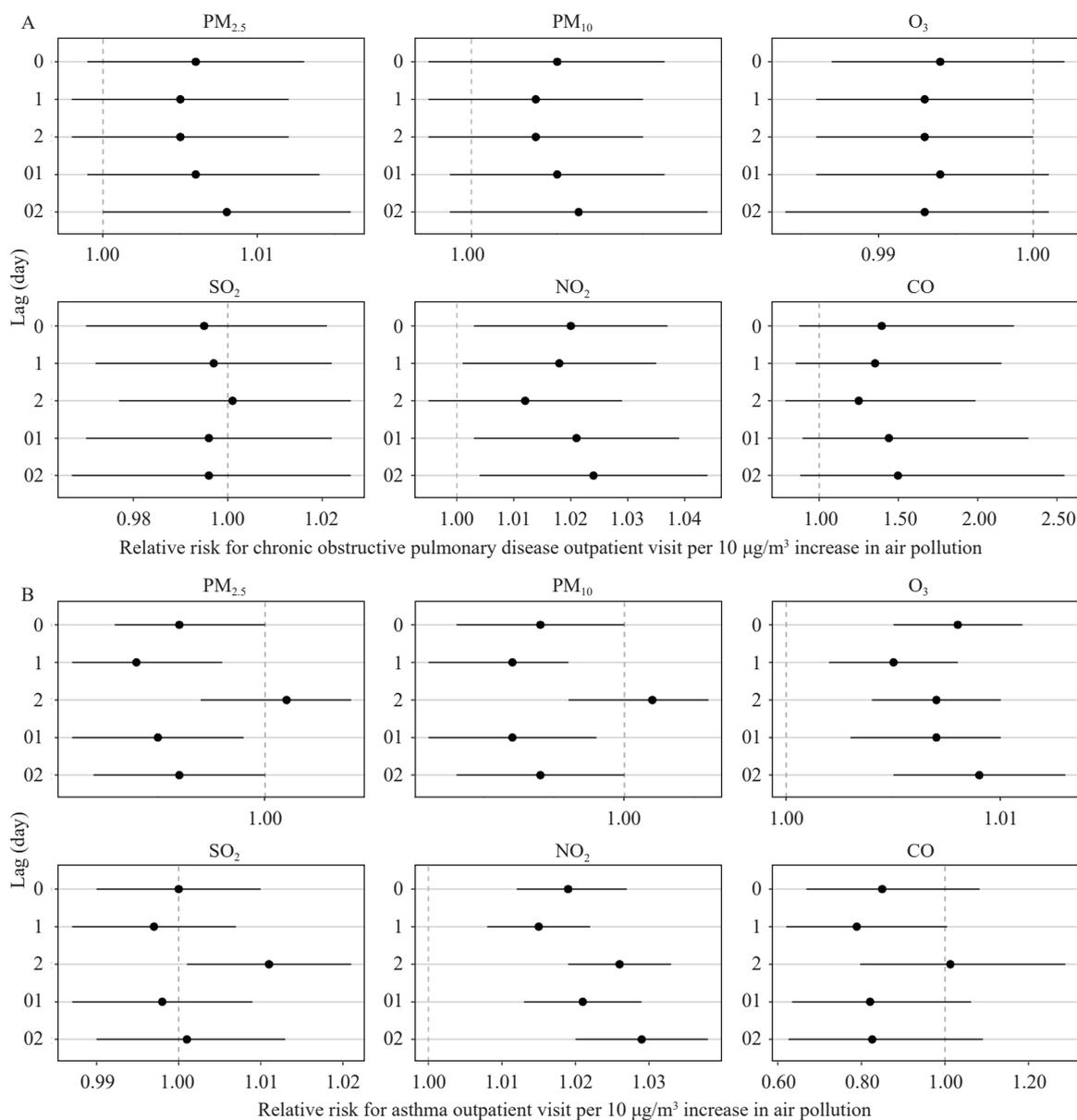


FIGURE 2. Relative risk for chronic obstructive pulmonary disease (A) and asthma (B) outpatient visits per 10 $\mu\text{g}/\text{m}^3$ increase in concentrations of air pollutants with different lag days in 16 hospitals, 2013–2018.

deviate to a certain extent, which needs further exploration.

In conclusion, exposure to PM_{2.5}, O₃, SO₂, NO₂, and CO has certain acute effects on outpatient and hospital admission of patients with COPD and asthma. Relevant susceptible people should try to reduce going out under the condition of air pollution to avoid aggravation of the disease. Meanwhile, these findings should be combined with disease diagnosis and treatment guidelines to guide clinical practice. This study not only paid attention to PM, but also emphasized that ozone cannot be ignored, which provides a reference for future research on the impact

of PM and ozone coordinated prevention and control and on the effects of carbon neutralization on health.

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Preplanned Studies

Impacts of PM_{2.5} on Ambulatory Blood Pressure Monitoring Indicators Attenuated by Blood Pressure Control Status and Treatment — Two Cities and Two Municipalities, China, 2017–2019

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Summary

What is already known about this topic?

Short-term PM_{2.5} exposure has been associated with hourly, 24-hour, daytime, and nighttime blood pressure (BP) levels, and further studies focusing whether and how the associations with other ambulatory BP monitoring indicators are warranted.

What is added by this report?

This study observed that short-term PM_{2.5} exposure was associated with BP elevations and was the first to report the associations of short-term PM_{2.5} exposure with BP variability. Circadian rhythm of BP and BP load among hypertensive patients were found to be modified by controlled BP status or taking angiotensin receptor blockers (ARBs).

What are the implications for public health practice?

This study suggested that antihypertensive therapy, especially with well-controlled BP status may be potential measurements to attenuate adverse impacts of PM_{2.5} for hypertensive patients with intermediate-to-high risk of cardiovascular disease (CVD).

High blood pressure (BP) is the leading risk factor for cardiovascular disease (CVD) in China. Previous studies from either lowly or highly polluted regions have revealed that increased fine particulate matter (particles with aerodynamic diameter ≤ 2.5 μm ; PM_{2.5}) exposure was associated with elevated BP levels and higher risk of hypertension (1). In recent years, using personal portable devices to record individual PM_{2.5} exposure and ambulatory BP monitoring (ABPM) to measure BP levels periodically, panel studies also identified the relationship of short-term PM_{2.5} exposure with hourly, 24-hour, daytime, and nighttime average BP levels (2–3). However, few studies assessed

the adverse impacts of PM_{2.5} with other ABPM indicators, such as BP variability, circadian rhythm of BP, and BP load, and the modifying effects of BP control status and antihypertensive therapy were also unclear. To clarify these issues, these associations were assessed using a multicity and municipality panel study conducted from 2017 to 2019 in China. BP levels and BP load elevation were associated with short-term PM_{2.5} exposure. Further stratified analyses demonstrated that the adverse impacts of PM_{2.5} on BP variability, circadian rhythm of BP, and BP load were attenuated among patients with well-controlled BP or taking angiotensin receptor blockers (ARBs), which provided hints about the prevention of PM_{2.5}-related adverse outcomes.

This study used data from a three-phase (winter, summer, spring/autumn) panel study conducted in Beijing, Shanghai, Wuhan, and Xi'an from 2017 to 2019. This panel study recruited participants at intermediate-to-high risk of CVD who were defined as having prehypertension or hypertension combined with at least 1 of the 3 conditions (i.e., central obesity, diabetes mellitus, and dyslipidemia) from the community (2). Questionnaires were administered to collect demographic characteristics, lifestyle and risk factors, medication uses, etc. Each participant carried a portable monitor to measure real-time individual PM_{2.5} from the first day to the third day during each phase, and a 24-hour ABPM was scheduled on the third day. This study was approved by the Institutional Review Board of Fuwai Hospital in Beijing, and written informed consent was obtained from all participants before data collection.

This study assessed the association of short-term PM_{2.5} exposure with several ABPM indicators, including 24-hour, daytime, and nighttime average systolic BP (SBP) and diastolic BP (DBP), SBP and

DBP variability (i.e., the standard deviation of BP), SBP and DBP load [i.e. the percentage of the counts for BP readings beyond certain threshold (130/80 mmHg, 135/85 mmHg, and 120/70 mmHg for 24-hour, daytime and nighttime, respectively)], and the percentage of nocturnal BP decline [i.e., (daytime BP-nighttime BP)/daytime BP \times 100%]. In addition, three methods were used to calculate morning BP surge, including morning BP (i.e., the average BP during the first 2 hours after waking), pre-waking BP surge (i.e., the mean BP during the 2 hours after waking minus the mean BP during the 2 hours before waking), and sleep-trough BP surge (the mean BP during the 2 hours after waking minus the mean BP of the lowest BP and the BP before and after the lowest one during sleeping). The exposure windows of PM_{2.5} included the concurrent day with ABPM (lag0d), lag 1 day (lag1d), lag 2 days (lag2d), and moving average of previous 2 days (MA2d). Estimated changes and 95% confidence intervals (CIs) with per interquartile range (IQR) increment of PM_{2.5} exposure (41.96 $\mu\text{g}/\text{m}^3$) were calculated using a mixed linear model adjusted for age, gender, current alcohol drinking status, ideal level of physical activity, body mass index (BMI), antihypertensive medication uses, diabetes mellitus, dyslipidemia, and natural splines with 3 degrees of freedom for the daily average of personal environmental temperature and relative humidity at the same exposure windows as PM_{2.5}. City-specific and subject-specific random intercepts were used to account for the variations in different cities and within-subjects correlations. Stratified analysis of BP control status (hypertensive patients with SBP/DBP of less than 140/90 mmHg were defined as individuals with controlled BP, otherwise as uncontrolled BP), and for those with uncontrolled BP, a further stratified analysis of ARB uses was conducted. Z tests were conducted to explore the group difference. All analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA). A 2-side *P* of <0.05 was demonstrated statistical significance.

After excluding participants attending only one visit, those missing ABPM data or not fulfilling the valid criteria of ABPM data and prehypertensive patients, a total of 277 hypertensive patients with 802 visits were included for analysis. At baseline, the average age was 59.1 \pm 8.5 years and 113 (40.8%) participants were men. The mean office SBP and DBP were 134.5 mmHg and 80.4 mmHg, respectively. Overall, 91.7% patients were taking antihypertensive medications,

with 33.2% being taking ARBs (Table 1). Across the three phases, a total of 557 (69.5%) visits reached well-controlled BP status. Among those without controlled BP, 65 (26.5%) visits had been taking ARBs. Generally, short-term PM_{2.5} exposure was associated with BP levels and BP load; for example, the 24-hour, daytime, and nighttime average SBP increased by 0.68 mmHg (95% CI: 0.07–1.29), 0.82 mmHg (95% CI: 0.19–1.45) and 0.93 mmHg (95% CI: 0.17–1.70) per IQR increment of the lag2d PM_{2.5} concentration (Figure 1A). The 24-hour SBP load and DBP load increased by 1.28% (95% CI: 0.01%–2.56%) and 1.38% (95% CI: 0.22%–2.54%), respectively, with per IQR increment of the lag1d PM_{2.5} concentration (Figure 1C). However, short-term PM_{2.5} exposure may not be associated with BP variability, morning BP surge, or the percentage of nocturnal BP decline (Figure 1B, 1D, 1E). When stratified by BP control status, the increment of 24-hour or daytime BP levels associated with PM_{2.5} exposure tended to be higher among those with uncontrolled BP, but the difference was not statistically significant (Figure 2A). Those with uncontrolled BP were more prone to have higher morning BP surges than those with controlled BP. For example, per IQR increment of the lag2d PM_{2.5} concentration was associated with 2.19 mmHg (95% CI: 0.47–3.91), 1.72 mmHg (95% CI: 0.20–3.24) and 1.47 mmHg (95% CI: -0.14–3.07) elevation for morning SBP, pre-waking SBP surge, and sleep-trough SBP surge, respectively, among patients without controlled BP, while no significant changes were noted in patients with controlled BP (all *P*<0.05) (Figure 2D). Among patients with uncontrolled BP, the association of PM_{2.5} exposure with 24-hour, daytime SBP variability was modified by treatment with ARB. For example, 24-hour SBP variability increased by 0.49 mmHg (95% CI: -0.22–1.20) per IQR increment of lag0d PM_{2.5} exposure among patients taking ARB, which was significantly higher than those not taking ARB (Figure 2G). In addition, patients taking ARB were more likely to have better circadian rhythms for DBP (Figure 2J).

DISCUSSION

This study observed that short-term PM_{2.5} exposure was associated with BP elevations and BP load and was the first to report the associations of short-term PM_{2.5} exposure with BP variability, as well as the circadian rhythm of BP among hypertensive patients being

TABLE 1. Baseline characteristics of study participants in two cities and two municipalities, China, 2017–2019.

Characteristics	Overall (n=277)	Beijing (n=64)	Shanghai (n=68)	Wuhan (n=75)	Xi'an (n=70)
Age, years	59.1±8.5	53.5±8.1	60.3±8.6	62.6±6.0	59.3±8.8
Male, n (%)	113 (40.8)	35 (54.7)	23 (33.8)	23 (30.7)	32 (45.7)
BMI, kg/m ²	26.2±3.2	27.2±2.6	25.0±3.0	26.1±3.5	26.6±3.2
Current alcohol drinking status, n (%)	67 (24.2)	29 (45.3)	11 (16.2)	12 (16.0)	15 (21.4)
Ideal level of physical activity, n (%)	101 (36.5)	23 (35.9)	14 (20.6)	35 (46.7)	29 (41.4)
Central obesity, n (%)	184 (66.4)	53 (82.8)	28 (41.2)	57 (76.0)	46 (65.7)
Office SBP, mmHg	134.5±13.6	134.1±11.4	134.4±12.0	132.6±15.4	137.2±14.7
Office DBP, mmHg	80.4±10.8	83.3±9.4	79.9±13.0	76.7±8.6	82.1±10.7
Diabetes mellitus, n (%)	78 (28.2)	13 (20.3)	29 (42.6)	16 (21.3)	20 (28.6)
Dyslipidemia, n (%)	224 (80.9)	54 (84.4)	55 (80.9)	63 (84.0)	52 (74.3)
Antihypertensive drug use, n (%)	254 (91.7)	54 (84.4)	64 (94.1)	70 (93.3)	66 (94.3)
ACE inhibitor	18 (6.5)	4 (6.3)	2 (2.9)	5 (6.7)	7 (10.0)
ARB	92 (33.2)	15 (23.4)	36 (52.9)	27 (36.0)	14 (20.0)
β-receptor blocker	36 (13.0)	14 (21.9)	6 (8.8)	5 (6.7)	11 (15.7)
CCB	161 (58.1)	42 (65.6)	30 (44.1)	49 (65.3)	40 (57.1)
Diuretics	16 (5.8)	2 (3.1)	6 (8.8)	4 (5.3)	4 (5.7)
Others	13 (4.7)	5 (7.8)	1 (1.5)	2 (2.7)	5 (7.1)
One type of medications	178 (64.3)	32 (50.0)	48 (70.6)	49 (65.3)	49 (70.0)
Two types of medications	61 (22.0)	16 (25.0)	12 (17.6)	18 (24.0)	15 (21.4)
Three or more types of medications	15 (5.4)	6 (9.4)	4 (5.9)	3 (4.0)	2 (2.9)
PM _{2.5} , µg/m ³					
Lag0d	50.1±43.9	49.8±45.3	33.6±32.3	57.4±37.8	57.5±52.3
Lag1d	48.5±46.0	48.4±47.9	31.3±26.0	52.4±36.6	60.1±60.4
Lag2d	54.2±50.9	64.6±66.8	34.0±34.6	66.6±45.6	51.8±47.0
MA2d	51.2±44.6	56.5±51.0	32.9±29.0	59.4±38.2	55.8±51.7
PET, °C					
Lag0d	22.3±5.5	23.8±3.8	20.9±6.1	21.8±7.1	22.5±4.3
Lag1d	22.1±5.7	23.7±4.2	21.1±5.9	21.3±7.3	22.5±4.5
Lag2d	22.2±5.6	23.6±3.8	21.2±5.8	21.2±7.3	22.9±4.2
MA2d	22.1±5.6	23.6±3.9	21.1±5.8	21.2±7.3	22.7±4.3
Relative humidity, %					
Lag0d	53.5±16.2	40.8±17.3	66.1±11.1	59.6±10.8	49.3±12.6
Lag1d	54.7±16.0	41.8±17.3	67.5±10.6	61.1±10.0	49.4±12.0
Lag2d	54.1±15.6	41.6±17.9	64.7±7.9	62.7±8.7	47.2±12.2
MA2d	54.5±15.4	41.7±17.3	65.7±8.6	61.9±9.0	48.3±11.8

Note: Results are presented as mean±SD for continuous variables, and frequency (proportion) for categorical variables.

Abbreviations: SD=standard deviation; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blockers; CCB=calcium channel blocker; PM_{2.5}=particles with aerodynamic diameter ≤2.5 µm; PET=personal environmental temperature; lag0d=current day with BP measurement; lag1d=lager of 1 day; lag2d=lager of 2 days; MA2d=the 2-day moving average of PM_{2.5}.

modified by a controlled BP status or by taking ARBs.

BP follows a circadian rhythm with an increase in the morning after waking and a dip during sleep. The existing studies have demonstrated that a disturbed

circadian rhythm, including increases of pre-waking BP surges or blunted nocturnal BP declines were associated with increased CVD risk (4). In addition, BP variability and BP load were also associated with

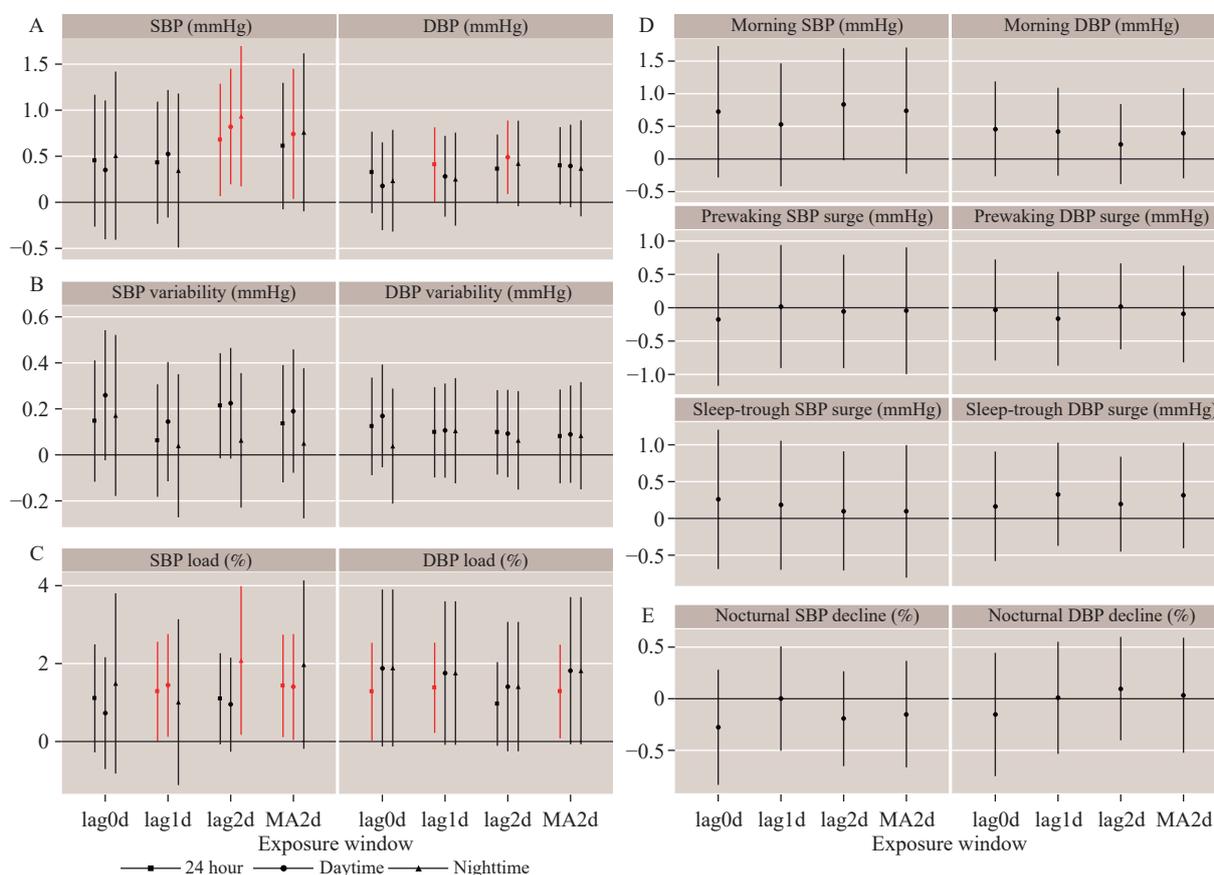


FIGURE 1. Estimated changes and 95% CIs of BP levels (A), BP variability (B), BP load (C), morning BP surge (D) and the percentage of nocturnal BP decline (E) with per IQR ($41.96 \mu\text{g}/\text{m}^3$) of $\text{PM}_{2.5}$ exposure among participants in two cities and two municipalities, China, 2017–2019

Note: Statistically significant changes were shown in red.

Abbreviations: CI=confidence interval; BP=blood pressure; IQR=interquartile range; $\text{PM}_{2.5}$ =particles with aerodynamic diameter $\leq 2.5 \mu\text{m}$; SBP=systolic blood pressure; DBP=diastolic blood pressure; lag0d=current day with BP measurement; lag1d=lag of 1 day; lag2d=lag of 2 days; MA2d=the 2-day moving average of $\text{PM}_{2.5}$.

CVD or all-cause mortality (5–6). Up to now, only one study has found that increased short-term PM_{10} exposure was associated with blunted SBP dipping, and evidence for $\text{PM}_{2.5}$ is still very lacking (7). Therefore, findings from the current study may provide evidence on the mechanism linking air pollution to increased CVD risk, and potential preventive measurements, such as a well-controlled BP and taking ARBs, to attenuate the adverse impacts of $\text{PM}_{2.5}$.

Sympathetic nerve activation may play a role in the morning BP surge (8), and nocturnal BP non-dipping may be associated with endothelial dysfunction (9). In accordance with the findings of this study, people reaching well-controlled BP had more stable ANS, hence the adverse impacts of $\text{PM}_{2.5}$ on morning BP surges were attenuated. On the other hand, exposure to $\text{PM}_{2.5}$ may increase angiotensin II (10), which could induce oxidative stress and inflammation and further

promote endothelial dysfunction. ARBs could inhibit the effects of angiotensin II. The potential endothelial dysfunction among patients without taking ARBs interfered the dipping of nocturnal BP. Additionally, the different lag effect trends of $\text{PM}_{2.5}$ on different BP traits may be due to the various mechanisms of $\text{PM}_{2.5}$ -mediated BP elevation, which is an issue worth to exploring in future.

This study firstly reported the association of short-term $\text{PM}_{2.5}$ exposure with various ABPM indicators, which may provide hints for preventing people from the influences of $\text{PM}_{2.5}$. Additionally, this study was a stringent panel study with a multiphase and multicity design, with individual $\text{PM}_{2.5}$ monitoring and ABPM, which allowed time-dependent covariates to be adjusted, and was less likely to cause misclassification, making the findings more accurate. However, this study was still subject to some limitations. First, owing

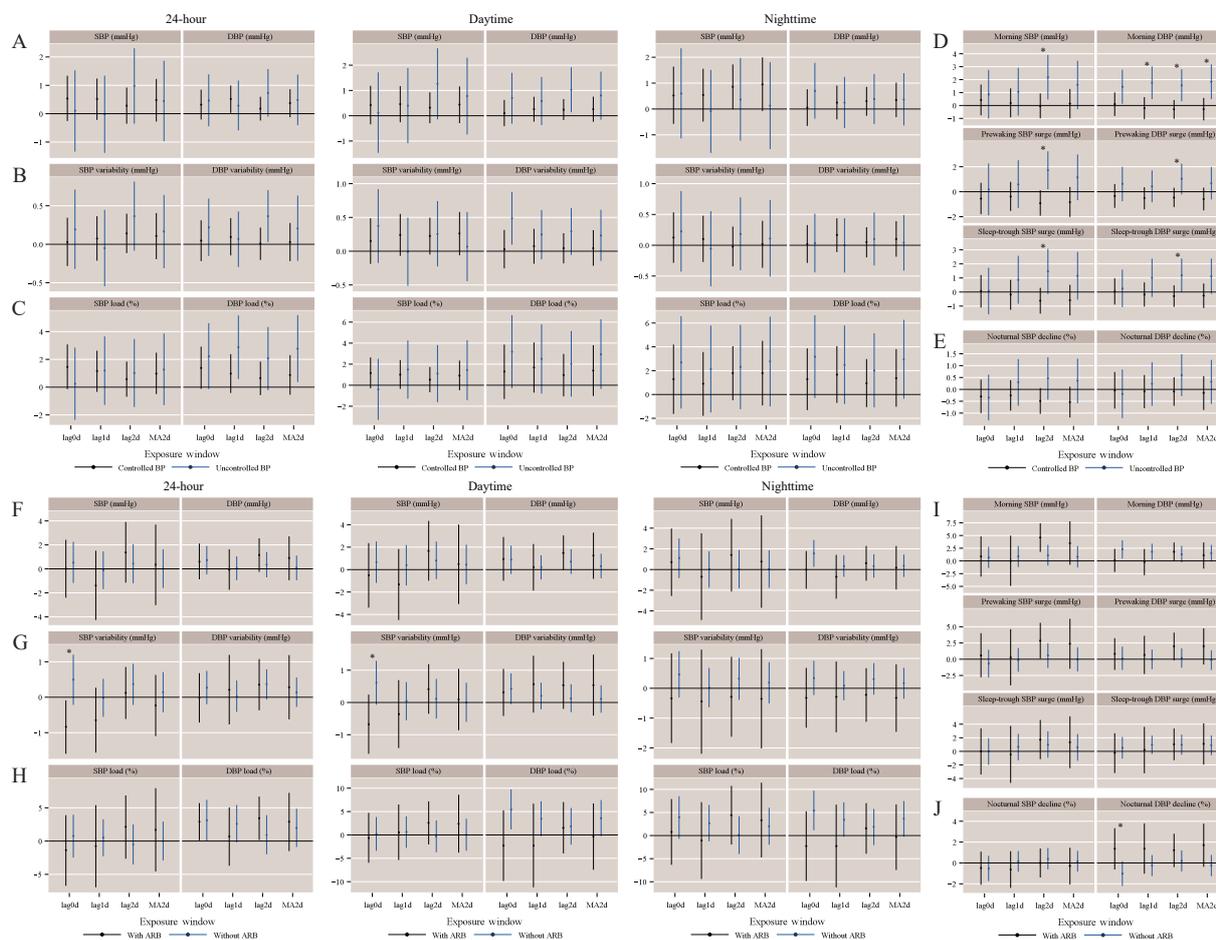


FIGURE 2. Estimated changes and 95% CIs of BP levels (A, F), BP variability (B, G), BP load (C, H), morning BP surge (D, I) and the percentage of nocturnal BP decline (E, J) with per IQR ($41.96 \mu\text{g}/\text{m}^3$) of the $\text{PM}_{2.5}$ exposure, stratified by BP control status in overall population and by ARB use in patients without controlled BP in two cities and two municipalities, China, 2017–2019.

* $P < 0.05$ for differences between two groups.

Abbreviations: CI=confidence interval; BP=blood pressure; IQR=interquartile range; $\text{PM}_{2.5}$ =particles with aerodynamic diameter $\leq 2.5 \mu\text{m}$; SBP=systolic blood pressure; DBP=diastolic blood pressure; ARB=angiotensin receptor blockers; lag0d=current day with BP measurement; lag1d=lag of 1 day; lag2d=lag of 2 days; MA2d=the 2-day moving average of $\text{PM}_{2.5}$.

to the absence of individual gaseous pollutants, the independent effects of $\text{PM}_{2.5}$ have not been assessed. Second, this study used BP measurements from 06:00 to 08:00 instead of BP levels 2 hours after waking to calculate morning surge due to missing information on waking time in this study.

In conclusion, this study added evidence of the associations between short-term $\text{PM}_{2.5}$ exposure and ABPM indicators, and further highlighted antihypertensive therapy, especially with well-controlled BP status, which may be a potential measurement to attenuate adverse impacts of $\text{PM}_{2.5}$ for patients with intermediate-to-high risk of CVD.

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Preplanned Studies

Acute Effects of Personal Ozone Exposure on Biomarkers of Inflammation, Oxidative Stress, and Mitochondrial Oxidative Damage — Shanghai Municipality, China, May–October 2016

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Summary

What is already known on this topic?

It remains inconclusive whether short-term ozone exposure can cause an inflammatory response and oxidative damage in the circulatory system, particularly at low concentrations.

What is added by this report?

This study made an accurate exposure assessment by conducting personal ozone monitoring, thus minimizing the exposure misclassification commonly found in previous environmental epidemiological studies. Our study found that even short-term exposure to low concentrations of ozone was associated with inflammation, lipid peroxidation, and mitochondrial oxidative damage.

What are the implications for public health practice?

Short-term exposure to low concentrations of ozone can still lead to subclinical cardiovascular effects, suggesting the current air quality standards for ozone need to be further tightened in China.

It remains inconclusive whether short-term ozone exposure can cause an inflammatory response and oxidative damage in the circulatory system. We conducted a longitudinal panel study of 43 non-smoking college students with four rounds of visits in Shanghai Municipality, China, from May to October 2016. Personal real-time ozone exposure was monitored for 3 days per visit, followed by blood sample collection. We measured 10 inflammatory biomarkers, 2 oxidative stress biomarkers, and 2 indicators of mitochondrial oxidative damage in the blood. Linear mixed-effect (LME) models were used to analyze their associations with ozone in R software (V 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) and a *P*-value <0.05 was considered statistically significant. During the study period, mean ozone exposure levels ranged from 18.0 ppb to 22.7 ppb at different lag periods. Each 10-ppb increase in

ozone exposure was greatly associated with a 4.86% increase in tumor necrosis factor alpha (TNF- α), 3.14% in soluble intercellular adhesion molecule-1 (sICAM-1), and 0.89% in malondialdehyde (MDA), as well as a decrease of 0.23 in the average methylation (%5mC) of the mitochondria displacement loop (D-loop) region. Our results suggest that even short-term exposure to low-level ozone may lead to inflammation, lipid peroxidation, and mitochondrial oxidative damage.

For each visit, personal ozone exposure was monitored in real time for 3 days during daytime (from 8:00 to 18:00) using Personal Ozone Monitors (POMs, 2B Technologies, US). In addition, we used HOBO data loggers (Onset Computer Corporation, Pocasset, MA, US) to monitor temperature and relative humidity at the individual level. For each individual, we collected blood samples immediately after ozone monitoring. Serum levels of 10 inflammatory biomarkers were measured using the MILLIPLEX MAP Human Cytokine/Chemokine Kit (Millipore Corp., Billerica, MA, US), including interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-17 alpha (IL-17 α), TNF- α , monocyte chemoattractant protein-1 (MCP-1), granulocyte macrophage colony stimulating factor (GM-CSF), sICAM-1, soluble vascular cell adhesion molecule-1 (sVCAM-1), and vascular endothelial growth factor (VEGF). Overall, 2 markers of oxidative stress, including 8-isoprostaglandin F2 alpha (8-iso-PGF2 α) and MDA, were measured in serum using enzyme linked immunosorbent assay (Oxford Medical, UK). We also measured the relative mitochondrial DNA copy number (RMtDNA_{cn}) and the methylation of the mitochondria D-loop region in blood to indicate mitochondrial oxidative damage, according to previous methods (1). The study was approved by the Institutional Review Board of the School of Public Health, Fudan University (No. 2014-07-0523). All participants signed informed consent at enrollment.

We applied LME models to analyze the associations between personal ozone exposure and these

biomarkers, with each participant's identification number incorporated as random intercepts. Data on 10 inflammatory biomarkers, 2 oxidative stress biomarkers, and RmtDNAcn were naturally log-transformed before statistical analyses. To capture the lagged effects of ozone, we considered exposure windows of 0–2 hours, 3–5 hours, 6–8 hours, 0–8 hours, 1 day, and 2 days preceding the blood sample collection. We also included: 1) individual characteristics, including age, sex, body mass index (BMI); 2) two natural cubic smooth functions of temperature and relative humidity with 3 degrees of freedom (dfs) for both; and 3) a natural cubic smooth function of the day within the study period with 3 dfs. We further performed a sensitivity analysis by adjusting for fine particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide, separately.

Three asthmatic patients were excluded, leaving 40 participants (30 females and 10 males) for the current analysis. Their mean age was 24 years, and their mean BMI was 21 kg/m². As shown in Supplementary Table S1 (available in <http://weekly.chinacdc.cn/>), the average personal ozone exposure at different lags

ranged from 17.8±20.5 ppb to 22.7±17.4 ppb, which was far below the current ambient air quality standard in China (i.e., 8-hour maximum: 160 µg/m³, equivalent to 75 ppb). The mean levels of 14 biomarkers varied appreciably, and detailed descriptive data can be found in Table 1.

Among the 10 inflammatory biomarkers, we observed significant increases in TNF-α, sICAM-1, sVCAM-1, and VEGF with ozone exposure (Figure 1). However, we did not find any significant associations of ozone with IL-6, IL-8, IL-10, IL-17α, MCP-1, GM-CSF (Supplementary Figure S1, available in <http://weekly.chinacdc.cn/>). We also found that ozone exposure showed a positive and statistically significant association with MDA, while the association with 8-iso-PGF2α was insignificant (Figure 2). In addition, we observed a significant increase in RmtDNAcn but a significant decrease in the D-loop methylation with ozone exposure (Figure 2).

The lag patterns of these significant associations were similar, except for the association with MDA. These effects mostly occurred within 2 hours of exposure, then were gradually attenuated over longer

TABLE 1. Summary statistics on biomarkers of inflammation, oxidative stress, and mitochondrial oxidative damage in 40 college students in Shanghai Municipality, China, May–October 2016.

Biomarker	Mean	SD	Min	Median	Max	IQR
Inflammation						
IL-6 (pg/mL)	1.40	1.35	0.41	0.91	10.01	0.90
IL-8 (pg/mL)	9.51	7.18	2.74	6.93	33.22	8.67
IL-10 (pg/mL)	2.05	4.00	0.21	0.70	24.53	0.90
IL-17α (pg/mL)	9.33	16.50	0.82	2.96	122.67	6.86
TNF-α (pg/mL)	7.27	4.21	1.70	6.65	24.57	4.33
MCP-1 (pg/mL)	392.32	156.15	160.24	361.94	1,005.00	181.06
GM-CSF (pg/mL)	6.76	10.36	0.72	1.87	50.88	5.32
sICAM-1 (ng/mL)	133.18	69.43	25.79	112.08	440.74	45.44
sVCAM-1 (ng/mL)	519.97	131.90	34.15	504.76	907.56	178..27
VEGF (pg/mL)	205.32	333.76	7.35	88.17	1,737.00	154.40
Oxidative stress						
8-iso-PGF2α (ng/mL)	0.56	2.46	0.01	0.16	19.80	0.20
MDA (µmol/L)	29.26	2.45	16.81	29.35	35.83	2.76
Mitochondrial oxidative damage						
RmtDNAcn	1.00	2.05	0.00	0.62	20.71	0.42
Methylation (%5mC)*	2.55	2.15	0.00	2.47	8.62	3.99

Abbreviations: SD=standard deviation; Min=minimum; Max=maximum; IQR=interquartile range; pg=picogram; ng=nanogram; IL-6=interleukin-6; IL-8=interleukin-8; IL-10=interleukin-10; IL-17α=interleukin-17 alpha; TNF-α=tumor necrosis factor alpha; MCP-1=monocyte chemoattractant protein-1; GM-CSF=granulocyte macrophage colony stimulating factor; sICAM-1=soluble intercellular adhesionmolecule-1; sVCAM-1=soluble vascular cell adhesion molecule-1; VEGF=vascular endothelial growth factor; 8-iso-PGF2α=8-isoprostaglandin F2 alpha; MDA=malonaldehyde; RmtDNAcn=relative mitochondrial DNA copy number.

* Methylation levels of the D-loop region in mitochondrial DNA.

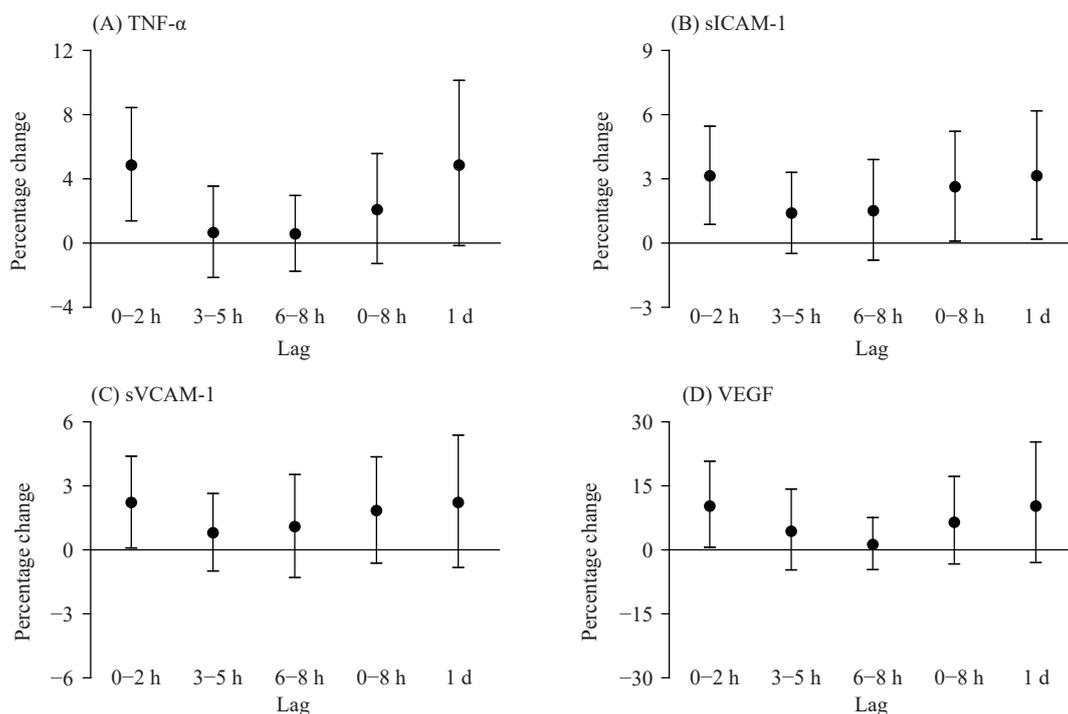


FIGURE 1. Percentage changes in TNF- α (A), sICAM-1 (B), sVCAM-1 (C), and VEGF (D) associated with a 10-ppb increase in personal ozone exposure at different lag periods in 40 college students in Shanghai Municipality, China, May–October 2016.

Note: X-axis denotes to the different lag periods; Y-axis denotes the corresponding percentage change in biomarkers.

Abbreviations: TNF- α =tumor necrosis factor alpha; sICAM-1=soluble intercellular adhesionmolecule-1; sVCAM-1=soluble vascular cell adhesion molecule-1; VEGF=vascular endothelial growth factor.

lags, and lost statistical significance at a lag of 2 days. At lag 0–2 hours, a 10-ppb increase in ozone concentrations was associated with the following increases: 4.86% [95% confidence interval (CI): 1.39%–8.45%] in TNF- α ; 3.14% (95% CI: 0.87%–5.46%) in sICAM-1; 2.23% (95% CI: 0.09%–4.40%) in sVCAM-1; 10.26% (95% CI: 0.65%–20.79%) in VEGF; and 30.51% (95% CI: 0.31%–69.81%) in RMtDNAcn. A decrease of 0.23 (95% CI: 0.01%–0.45%) was found in the D-loop methylation (%5mC). The significant association with MDA was observed at lag 3–5 hours only, with a 0.89% (95% CI: 0.14%–1.65%) increase in MDA per 10-ppb increase in ozone exposure at this lag. After adjusting for other air pollutants, the associations of ozone with TNF- α , sICAM-1, MDA, and the D-loop methylation were almost unchanged, while the associations with sVCAM-1, VEGF, and RMtDNAcn were unstable (Supplementary Table S2, available in <http://weekly.chinacdc.cn/>).

DISCUSSION

In this longitudinal panel study, we found that

short-term exposure to low concentrations of ozone may lead to increased biomarkers of inflammation and oxidative stress, including TNF- α , sICAM-1, and MDA. We also observed reduced methylation of the mitochondria D-loop region with ozone exposure.

It remains inconclusive whether ozone exposure could induce an inflammatory response in the circulatory system, although extensive evidence suggested that short-term ozone exposure was associated with respiratory inflammation. Consistent with previous studies (2–3), we found ozone exposure was associated with increased sICAM-1 in this study. An increased circulating level of sICAM-1 was relevant to endothelial injury due to inflammation and may be an independent risk factor for atherosclerosis and cardiovascular disease (4–5). In addition, we found ozone exposure was associated with elevated TNF- α , a marker of systemic inflammation. However, we did not find any significant associations with other common markers of systemic inflammation (i.e., interleukins, MCP-1, and GM-CSF). Previous studies have also showed mixed results on the inflammatory effects of ozone (6–7), and further studies are needed to confirm our findings.

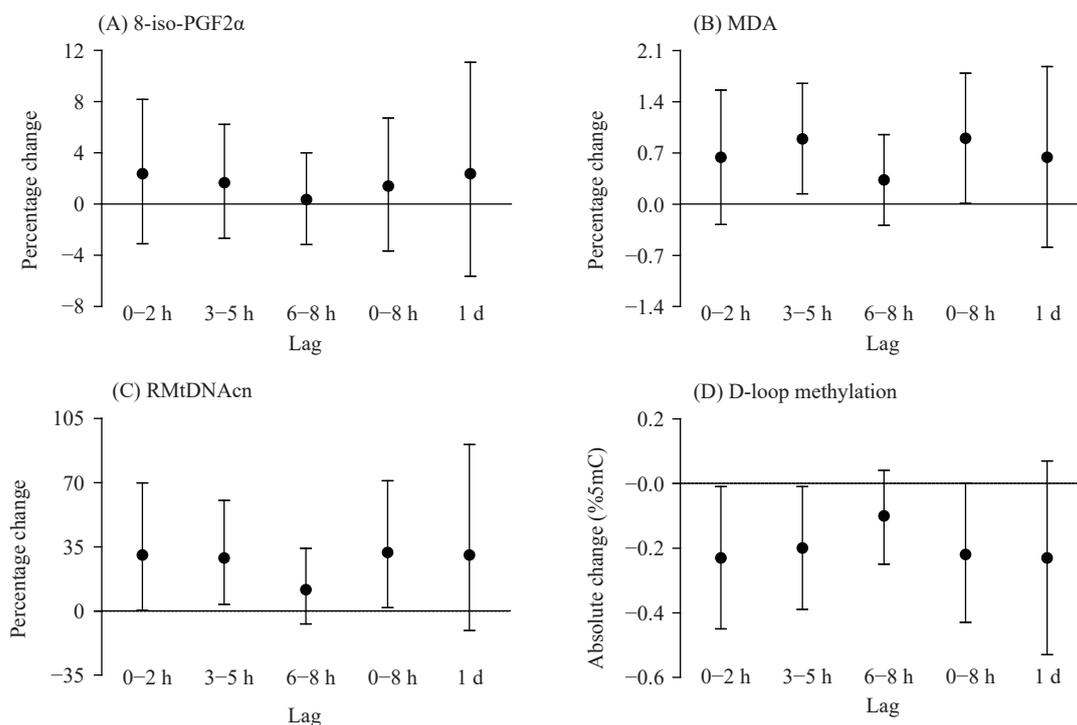


FIGURE 2. Percentage changes in 8-iso-PGF2 α (A), MDA (B), and RMtDNAcn (C), and absolute change in mitochondria D-loop methylation levels (D) associated with a 10-ppb increase in personal ozone exposure at different lag periods in 40 college students in Shanghai Municipality, China, May–October 2016.

Note: X-axis denotes to the different lag periods; Y-axis denotes the corresponding percentage/absolute change in biomarkers.

Abbreviations: 8-iso-PGF2 α =8-isoprostaglandin F2 alpha; MDA=malonaldehyde; RMtDNAcn=relative mitochondrial DNA copy number.

Mitochondrial DNA is sensitive to reactive oxygen species as it lacks protective histones and DNA repair mechanisms. Mitochondrial DNA methylation is an indicator of mitochondrial oxidative damage (1). To the best of our knowledge, this is the first study to find an association between ozone exposure and hypomethylation of the mitochondria D-loop region. This finding suggests that ozone exposure may trigger mitochondrial damage and dysfunction, thereby disrupting cellular homeostasis and leading to metabolic alterations (8). We also observed an increase in RMtDNAcn, another indicator of mitochondrial oxidative damage, with ozone exposure. However, the observed increase became statistically insignificant when adjusting for other air pollutants. Notably, these pollutants were measured by fixed-site monitoring rather than personal monitoring, and therefore one should be cautious in interpreting the results of the two-pollutant models. In addition, we found that ozone exposure was associated with increased MDA, which is one of the final products of polyunsaturated fatty acids peroxidation and plays a role in the development of cardiovascular disease (9). A previous

study found increased 8-iso-PGF after exposure to high levels of ozone (10), but the results of this study did not report such an association at low concentrations.

Our study was subject to at least three limitations. First, the statistical power may be restricted due to the small sample size. As a result, the confidence intervals for the effect estimates in this study were wide. Second, the participants were only college students, which may limit the generalizability of our findings to other populations and settings. Third, all health outcomes were measured at the same time, restricting the ability to evaluate the causality between ozone exposure and blood biomarkers.

In conclusion, our study found that even short-term exposure to low concentrations of ozone was associated with inflammation, lipid peroxidation, and mitochondrial oxidative damage. Our results suggest that the current air quality standards for ozone need to be further tightened in China.

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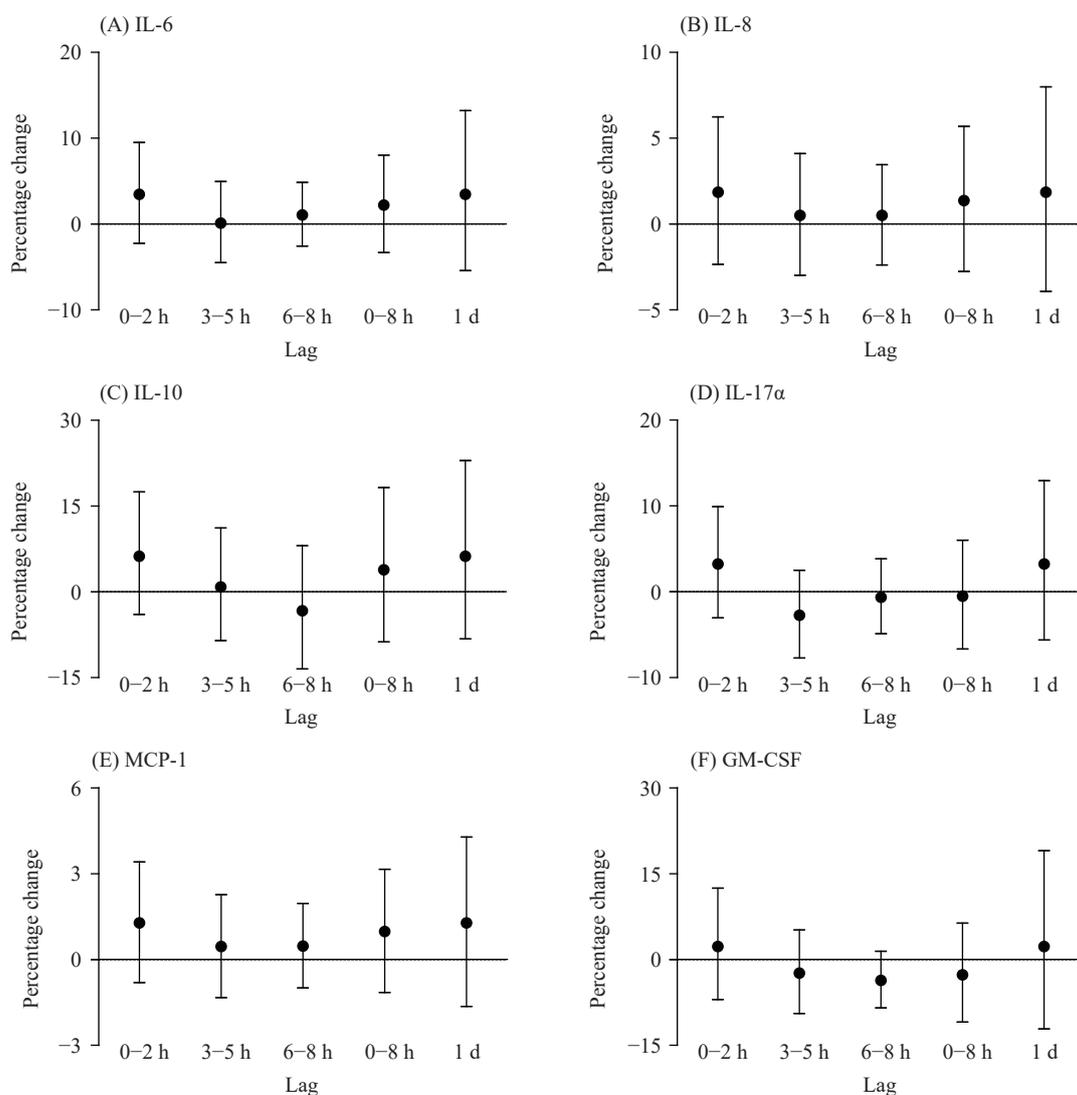
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SUPPLEMENTARY TABLE S1. Descriptive statistics on personal ozone exposure during different periods preceding the blood sample collection in Shanghai Municipality, China, May–October 2016.

Lag	Mean	SD	P ₅	P ₂₅	Median	P ₇₅	P ₉₅
0–2 h	22.2	14.2	4.5	12.3	19.8	28.1	53.1
3–5 h	22.7	17.4	4.5	11.2	18.2	30.3	65.6
6–8 h	18.0	20.5	4.5	7.6	13.3	21.3	53.6
0–8 h	21.0	14.7	4.5	11.5	17.4	26.1	54.1
1 d	19.4	11.2	5.2	10.9	18.4	25.9	40.7
2 d	19.6	11.5	6.0	10.7	17.3	25.7	40.8

Abbreviations: SD=standard deviation; P₅=5th percentile; P₂₅=25th percentile; P₇₅=75th percentile; P₉₅=95th percentile.



SUPPLEMENTARY FIGURE S1. Percentage changes in IL-6 (A), IL-8 (B), IL-10 (C), IL-17 α (D), MCP-1 (E), and GM-CSF (F) associated with a 10-ppb increase in personal ozone exposure at different lag periods in 40 college students in Shanghai Municipality, China, May–October 2016.

Note: X-axis denotes the different lag periods; Y-axis denotes the corresponding percentage change in biomarkers.

Abbreviations=IL-6=interleukin-6; IL-8=interleukin-8; IL-10=interleukin-10; IL-17 α =interleukin-17 alpha; MCP-1=monocyte chemoattractant protein-1; GM-CSF=granulocyte macrophage colony stimulating factor.

SUPPLEMENTARY TABLE S2. Percentage changes in biomarkers with a 10-ppb increase in personal ozone exposure* in 40 college students in Shanghai Municipality, China, May–October 2016, with adjustments of other air pollutants on the day of the blood sample collection.

Item	Ozone + PM _{2.5}	Ozone + SO ₂	Ozone + NO ₂	Ozone + CO
TNF- α	4.62 (0.82, 8.56)	4.07 (0.24, 8.05)	4.29 (0.32, 8.42)	4.75 (0.76, 8.90)
sICAM-1	3.21 (0.30, 6.20)	3.32 (0.35, 6.38)	3.06 (0.05, 6.16)	2.60 (-0.41, 5.69)
sVCAM-1	2.05 (-0.72, 4.91)	2.25 (-0.05, 4.59)	2.11 (-0.23, 4.50)	1.94 (-0.46, 4.40)
VEGF	10.57 (-0.10, 22.38)	10.89 (0.24, 22.63)	9.87 (-0.74, 21.60)	10.12 (-0.53, 21.90)
MDA	0.90 (0.09, 1.72)	0.88 (0.10, 1.66)	0.88 (0.09, 1.67)	0.87 (0.08, 1.65)
RMtDNAcn	30.51 (-3.77, 76.99)	31.45 (0.07, 72.66)	27.82 (-2.70, 67.92)	30.86 (-0.41, 71.94)
Methylation [†]	-0.24 (-0.48, 0.01)	-0.22 (-0.43, -0.01)	-0.24 (-0.45, -0.02)	-0.25 (-0.47, -0.04)

Abbreviations: TNF- α =tumor necrosis factor alpha; sICAM-1=soluble intercellular adhesionmolecule-1; sVCAM-1=soluble vascular cell adhesion molecule-1; VEGF=vascular endothelial growth factor; MDA=malonaldehyde; RMtDNAcn=relative mitochondrial DNA copy number; PM_{2.5}=ambient particulate matter with aerodynamic diameter less than 2.5 μ m; SO₂=sulfur dioxide; NO₂=nitrogen dioxide; CO=carbon monoxide.

* Lag 3–5 hours for MDA and lag 0–2 hours for other biomarkers.

[†] Methylation levels of the D-loop region in mitochondrial DNA.

Preplanned Studies

Co-Exposure to Multiple Pollutants and Its Cardiovascular Effects in a Subway System — Beijing Municipality, China, 2017

Wenlou Zhang¹; Xuan Yang¹; Xu Jia¹; Wei Dong¹; Hongyu Li¹; Lu Pan^{1,2}; Jiao Shan¹; Shaowei Wu³; Xinbiao Guo¹; Furong Deng^{1,#}

Summary

What is already known on this topic?

With rapid urbanization, traffic-related air pollution has become a global concern. However, its association with cardiovascular health has not been fully elucidated.

What is added by this report?

This study provided novel evidence of the joint cardiovascular effect of multiple pollutants in subway cabins, further identified two pollutants that played dominant roles, and validated the effectiveness of targeted interventions.

What are the implications for public health practice?

The findings were helpful to guide the formulation and development of prevention and control strategies for key traffic-related pollutants that endanger the cardiovascular health of commuters.

With rapid global urbanization, air and noise pollution in subway systems (also called metro systems) and the potential cardiovascular hazards they pose have become a global public health issue. However, the joint effect of multiple pollutants, as well as the key pollutants that play a dominant role in cardiovascular health, remain unclear. A randomized crossover study with respirator and/or headphone interventions was conducted among healthy young adults from March 11 to May 28, 2017 in the Beijing subway. This study found that co-exposure to size-fractionated particulate matter (PM), black carbon (BC), and noise was strongly associated with changes in heart rate variability (HRV) indices. BC and noise may be the two dominant pollutants causing the overall impact. Analysis based on data from intervention phases suggested that the impact of BC or noise might be attenuated or even reversed when reducing the level of another pollutant (noise or BC). The findings were helpful in guiding the formulation and development of prevention and control strategies for key traffic-related

pollutants that endanger the cardiovascular health of commuters.

Overall, 40 healthy young adults were recruited for this randomized crossover study from March 11 to May 28, 2017, in Beijing. Details of the study implementation could be found in previous publications (1–2). In brief, participants commuted for about 4 hours between 9:00–13:00 in the subway during 4 different periods with/without intervention (wearing respirator and/or headphone). The personal real-time levels of PM₁ (aerodynamic diameters < 1 μm), PM_{1–2.5} (aerodynamic diameter ≥1 μm and < 2.5 μm), PM_{2.5–10} (aerodynamic diameter ≥2.5 μm and <10 μm), BC, and noise were measured. Simultaneously, HRV parameters were obtained using a 12-channel ambulatory ECG monitor. Total power (TP), very-low-frequency power (VLF), low-frequency power (LF), high-frequency power (HF), LF/HF and standard deviation of normal-to-normal intervals (SDNN) were included in this study. Bayesian kernel machine regression (BKMR) was used to further examine the joint health effect of multiple pollutants in the subway cabin. This model allows nonlinear relationships and potential interactions and has been used widely to assess the overall effect of mixed pollutants (3). Posterior inclusion probability (PIP) was estimated through variable selection to assess the relative importance of exposure variables. PIP values range from 0 to 1 and a larger PIP value means a higher importance. All exposure and outcome variables were standardized. The covariates included gender, age, body mass index (BMI), temperature, relative humidity and CO₂ level. The number of subjects was used as a random effect term to control the correlation between repeated measurements. The lag effects from 5 min to 2 hours were examined, and the most significant effect was reported at 30 min lag. BKMR analysis was conducted using R software (version 4.0.3; R project for Statistical Computing) with the “bkmr” package. The study protocol was approved by the Institutional Review Board of Peking University Health Science

Center (IRB number: 00001052-16066) and informed consent was obtained from each participant.

In total, 39 participants completed this study, of whom 18 (46.2%) were females. Their mean age and BMI were 21.2 years and 21.6 kg/m², respectively. The mean levels of PM₁, PM_{1-2.5}, PM_{2.5-10}, BC, and noise were 34.1, 51.6, 145.2, 9.5 µg/m³, and 75.9 dBA, respectively. Increased levels of co-exposure to these pollutants were significantly associated with decreased TP, VLF, SDNN, and increased LF/HF (Figure 1). According to the results of PIPs in Table 1, BC had a higher PIP than other pollutants in most HRV indices, ranging from 0.69 to 1.00. Specifically, BC had the highest PIP value in TP (1.00), VLF (1.00), LF (1.00), and SDNN (0.96), indicating the largest contribution to the overall effect. Noise was the

second most important because it had a high PIP in LF (1.00), HF (0.96), and LF/HF (0.72).

To clarify the effectiveness and necessity of BC and noise prevention and control in the subway system, the exposure-response relationships of BC and noise with HRV indices were plotted based on the data from both no-intervention and headphone/respirator intervention phases. As shown in Figure 2, a weaker effect of BC on VLF, LF, HF, and SDNN was observed in the headphone intervention phase (low noise level) than the no-intervention one (high noise level), and the effect on LF/HF was even slightly reversed from a positive to negative association. For the effect of noise on all HRV indices, the relationships significantly differed in the respirator intervention phase (low BC concentration), and positive associations between noise

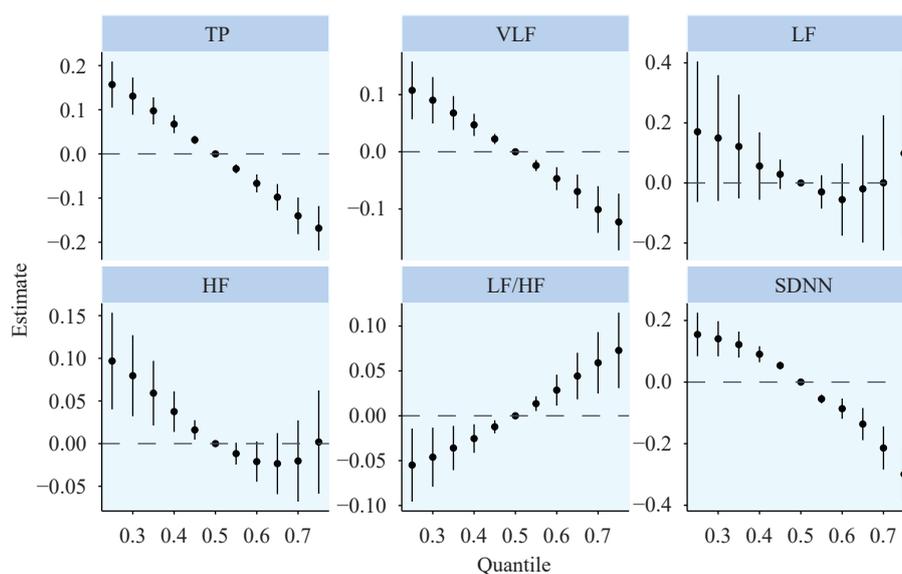


FIGURE 1. The joint effect estimates and 95% confidence interval (CI) of multiple air pollutants (PM₁, PM_{1-2.5}, PM_{2.5-10}, BC, and noise) in subway cabin on HRV parameters of study participants in Beijing, 2017

Note: The plot compared each HRV index when all exposures were at a particular quantile to when all were at the median (reference).

Abbreviations: TP=total power; VLF=very low frequency power; LF=low frequency power; HF=high frequency power; SDNN=standard deviation of normal-to-normal intervals; HRV=heart rate variability.

TABLE 1. Posterior inclusion probabilities (PIPs) from Bayesian kernel machine regression model for heart rate variability parameters of healthy young adults in Beijing, 2017*.

Variable	TP	VLF	LF	HF	LF/HF	SDNN
PM ₁	0.51	0.45	1.00	0.80	0.61	0.26
PM _{1-2.5}	0.48	0.43	0.76	0.70	0.73	0.27
PM _{2.5-10}	0.59	0.63	1.00	0.75	0.76	0.62
Black carbon	1.00	1.00	1.00	0.90	0.69	0.96
Noise	0.60	0.53	1.00	0.96	0.72	0.21

Abbreviations: PM=particulate matter; TP=total power; VLF=very low frequency power; LF=low frequency power; HF=high frequency power; SDNN=standard deviation of normal-to-normal intervals.

* PIP is a measure of the importance of exposure variables, and a larger value means a higher importance.

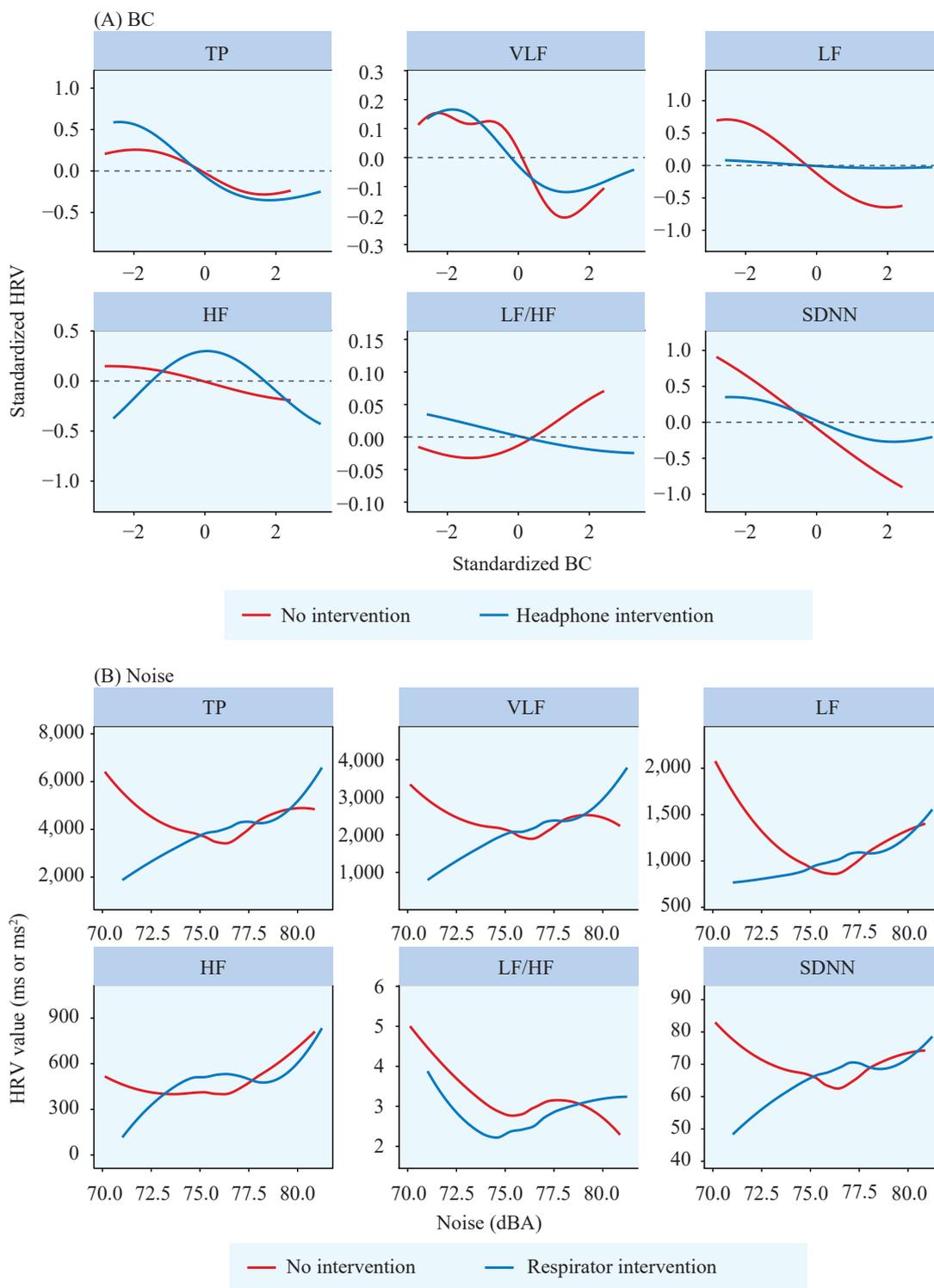


FIGURE 2. The exposure-response relationship of black carbon (BC) and noise in subway cabin with heart rate variability (HRV) indices of participants in Beijing, 2017.

(A) Comparison of the effects of BC on HRV indices between no intervention (high-noise level) and headphone intervention (low-noise level) phase based on bayesian kernel machine regression analysis; (B) Comparison of the effects of noise on HRV indices between no intervention (high-BC concentration) and headphone intervention (low-BC concentration) phase based on LOESS.

Abbreviations: BC=black carbon; HRV=heart rate variability; TP=total power; VLF=very low frequency power; LF=low frequency power; HF=high frequency power; SDNN=standard deviation of normal-to-normal intervals; LOESS=locally weighted regression.

and TP, VLF, LF, HF, and SDNN were found during this phase.

DISCUSSION

The metro system has become an indispensable part of megacities, and its environmental quality and potential health hazards are attracting more and more attention. This study found that short-term (30 min) co-exposure to size-fractioned PM, BC, and noise was strongly associated with changes in HRV indices. HRV can reflect the activities of the sympathetic nervous system (SNS) and the parasympathetic nervous systems (PNS), and its reduction has been related to higher cardiovascular risks (4). TP and SDNN are global indicators of HRV, and VLF is thought to be strongly associated with all-cause mortality and other diseases. LF/HF was thought to represent the balance of SNS and PNS and is positively related to SNS activity. In this study, positive association with LF/HF was found, indicating SNS activity increased more than PNS, which was consistent with previous studies (2–3,5–6).

To achieve the maximum input-output ratio of pollution prevention and control based on health benefits, it is imperative to identify the pollutants that contribute most to health hazards. The study found that BC mediated most of the cardiovascular health damage, followed by noise. The effects of BC and noise on cardiac autonomic nerve function have also been demonstrated in other studies (5–7). BC is mainly emitted by traffic transport, where a high level of noise is usually produced simultaneously. They may be two crucial targets for traffic-related air pollution prevention and control, and they seem to deserve more concern in the subway system because of the higher exposure levels compared to other modes of transport, including taxi, bus, cycling, and walking (8–9).

Our previous study demonstrated the cardiovascular benefits of respirator and headphone interventions (2). Considering the potential interaction of BC and noise on cardiovascular health (6–7), this study further explored the exposure-response relationships between BC or noise and HRV indices, controlling each pollutant at different levels. When reducing the exposure level of BC or noise using respirators or headphones, the adverse effects of another pollutant (noise or BC) on cardiac autonomic nerve function were significantly attenuated and even reversed. The results further validated the effectiveness of the target intervention. In addition, the findings also suggested that healthy adults may develop a protective

compensatory response to the adverse effects of single pollutant (BC or noise), though it may be not enough when co-exposed to multiple pollutants. Similarly, a panel study found a weaker association between BC and HRV indices when noise was controlled in the regression model (6). Another randomized crossover study also observed the effect of BC on HRV indices of health adults was stronger in a high noise environment (traffic center) than a low noise one (park) (7).

This is the first study to explore the joint effect of multiple pollutants in the subway on the cardiac autonomic function and to determine which pollutants deserve particular concern in a near-real exposure scenario. This study further clarified the effectiveness and necessity of targeted interventions for air pollution in the subway system.

This study was still subject to some limitations. First, gaseous pollutants were not included. Second, participants in this study were healthy young adults, which might limit the generalizability of the findings. But it could be expected that similar or even stronger effects might be observed in susceptible populations.

In summary, short-term co-exposure to multiple pollutants could disturb the cardiac autonomic function. BC and noise may be the two pollutants with the greatest contribution. In addition to the direct cardiovascular benefits of wearing a respirators or headphones (2), this study further verified that such interventions were also helpful to reduce the susceptibility of the cardiovascular system to other pollutants, possibly because the compensatory response of healthy young people is adequate to cope with short-term high levels of exposure to a single pollutant. Therefore, this study confirmed the potential public health implications of traffic-related air pollution interventions, and highlighted that BC and noise may be key to urban traffic-related air pollution prevention and control to avoid cardiovascular lesions. It is urgent and necessary for individuals and relevant departments to take targeted measures to protect cardiovascular health from air pollution during commuting.

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Preplanned Studies

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

Chen Chen¹; Jing Liu¹; Wanying Shi¹; Tiantian Li¹; Xiaoming Shi^{1, #}

Summary

What is already known about this topic?

Ozone (O₃) 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 O₃ 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 O₃ 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 (O₃), 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 O₃-mortality associations by controlling for meteorological factors in a model fitting process. Regarding the high correlation between O₃ and temperature, a recent area of interest is whether the observed O₃-mortality associations can be modified by temperature. Jhun et al. found both high and low

temperature could strengthen acute effects of O₃ on mortality (3), while Chen et al. and Shi et al. reported that O₃-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), O₃ 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 O₃ pollution increasing steadily. Therefore, additional efforts are needed to better quantify the local health risks of O₃ 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 O₃ concentrations were collected from the National Urban Air Quality Real-Time Release Platform and calculated to a daily 8-hour moving average maximum (O₃ 8 h-average), 1-hour maximum (O₃ 1 h-max), and 24 hour-average of O₃ (O₃ 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 O₃ 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 O₃ 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 O₃ across the designated levels of the modifier (8), aimed to construct interaction terms between O₃ 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 (P₁₀/P₉₀), 20th and 80th (P₂₀/P₈₀), and 25th and 75th (P₂₅/P₇₅) percentiles. The model of the temperature-stratified approach was set up as follows:

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

Where was the expected value of death on day *t*; *Tem* represented the daily value of temperature; (*O₃ : Temstrata*) was the interaction term between O₃ 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 O₃ 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 O₃ 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 (O₃ 1 h-max and O₃ 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) O₃ 1 h-max and O₃ 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 O₃ 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 O₃ 8 h-average would increase daily mortality risks of non-accidental [PI=0.15%, 95% Confidence Interval (CI): 0.06%, 0.24%], cardiocerebrovascular (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 O₃-mortality associations, with a 0.57% risk increase of

TABLE 1. Summary for ambient O₃, 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/m ³)	56.3±38.7	25.3	49.5	80.2
O ₃ 8 h-average (µg/m ³)	95.2±61.4	48.2	83.8	135.4
O ₃ 1 h-max (µg/m ³)	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; P₂₅=25th percentile; P₅₀=50th percentile; P₇₅=75th percentile.

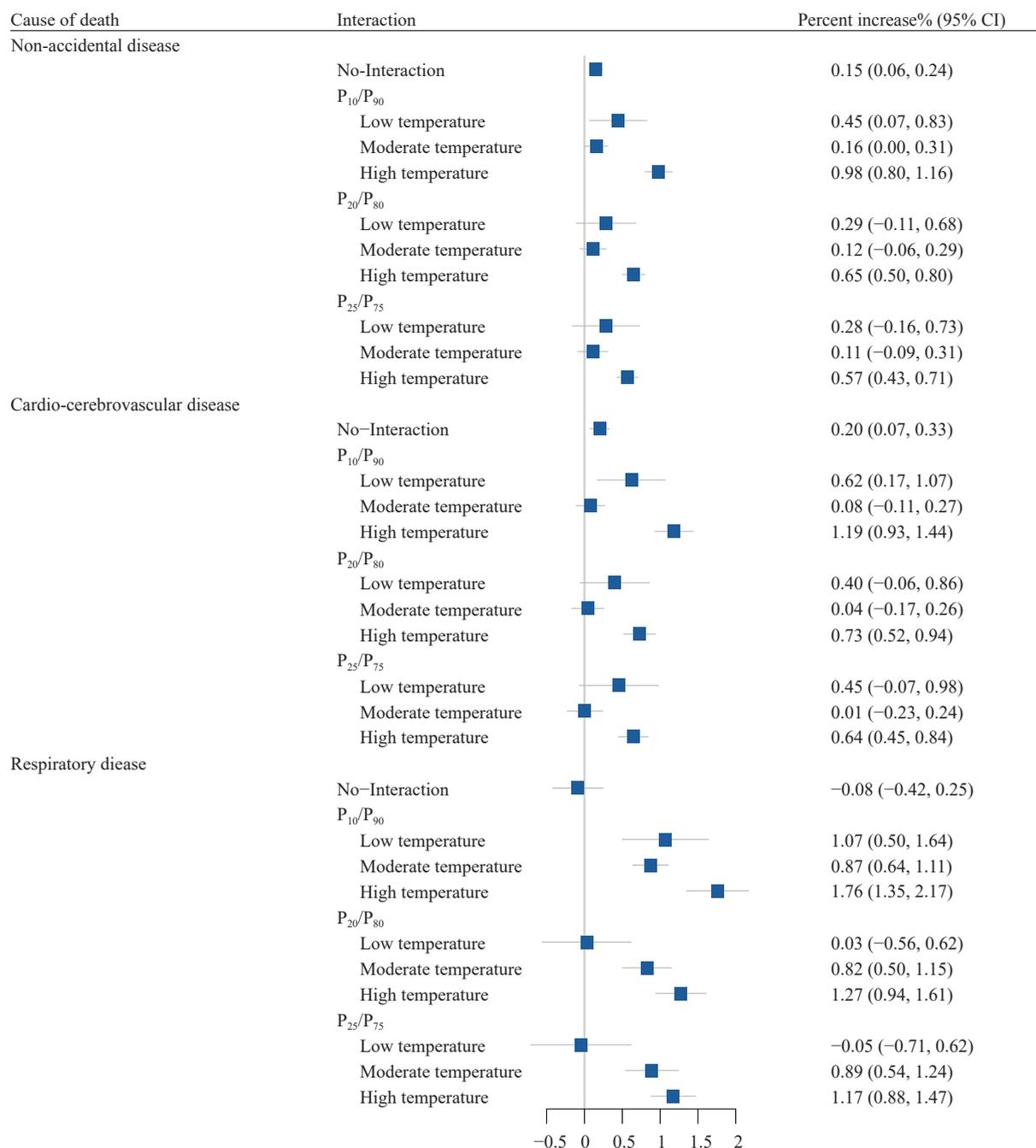


FIGURE 1. Mortality risk estimates associated with Lag 01 exposure of O₃ by using the temperature-adjusted and temperature-stratified approach in the Beijing, Tianjin, Hebei and surrounding areas, 2013–2018.

Abbreviations: P₁₀=10th percentile; P₉₀=90th percentile; P₂₀=20th percentile; P₈₀=80th percentile; P₂₅=25th percentile; P₇₅=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 O₃ 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 O₃ on mortality (Figure 1).

Associations between short-term exposure to O₃ 8 h-average and mortality peaked at Lag 01 exposure. Analyses with different metrics of O₃ 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 O₃ 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 O₃ 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; P₁₀=10th percentile; P₉₀=90th percentile; P₂₀=20th percentile; P₈₀=80th percentile; P₂₅=25th percentile; P₇₅=75th percentile.

humidity controlled by varying dfs did not meaningfully change our findings (Table 2). For the three cutoffs of P₁₀/P₉₀, P₂₀/P₈₀, and P₂₅/P₇₅, the associations between the other two O₃ metrics and mortality were both increased under high temperature levels (Table 3). The extreme low temperature was found to only significantly modify the association between O₃ 24 h-average and mortality.

DISCUSSION

We used two time-series approaches to explore the effects of short-term exposure to O₃ 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 O₃ 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 O₃ is usually formed by photochemical reactions of precursor pollutants under the presence of light; as the temperature increases, the formation of O₃ accelerates, and the emission of precursor pollutants increases, resulting in an increase in effect size of O₃ along with increased pollution.

The study also found that the O₃-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 O₃ 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 O₃-mortality association varied across different regions (3,9). In addition to different climates and characteristics of O₃ pollution, various adaptive measures of local residents to mitigate exposure to O₃ 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 O₃ and temperature due to physical adaptation and higher air conditioning usage rates.

Experimental studies have observed that exposure to O₃ 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). O₃ 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 O₃ 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 O₃ 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 O₃-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 O₃ 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 O₃-related mortality risks.

Our findings suggest that policymakers should pay attention to the synergistic effect between heat or extreme cold and O₃ on human health, as well as provide evidence for establishing an integrated early-

warning system for protecting the public against both unsuitable temperature and air pollution.

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