Vital Surveillances

Interactive Effects Between Temperature and $PM_{2.5}$ on Mortality: A Study of Varying Coefficient Distributed Lag Model — Guangzhou, Guangdong Province, China, 2013–2020

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ABSTRACT

Introduction: There is a large body of epidemiological evidence showing significantly increased mortality risks from air pollution and temperature. However, findings on the modification of the association between air pollution and mortality by temperature are mixed.

Methods: We used a varying coefficient distributed lag model to assess the complex interplay between air temperature and $PM_{2.5}$ on daily mortality in Guangzhou City from 2013 to 2020, with the aim of establishing the $PM_{2.5}$-mortality association at different temperatures and exploring synergetic mortality risks from $PM_{2.5}$ and temperature on vulnerable populations.

Results: We observed near-linear concentration-response associations between $PM_{2.5}$ and mortality across different temperature levels. Each 10 μg/m³ increase of $PM_{2.5}$ in low, medium, and high temperature strata was associated with increments of 0.73% [95% confidence interval (CI): 0.38%, 1.09%], 0.12% (95% CI: −0.27%, 0.52%), and 0.46% (95% CI: 0.11%, 0.81%) in non-accidental mortality, with a statistically significant difference between low and medium temperatures (P=0.02). There were significant modification effects of $PM_{2.5}$ by low temperature for cardiovascular mortality and among individuals 75 years or older.

Conclusions: Low temperatures may exacerbate physiological responses to short-term $PM_{2.5}$ exposure in Guangzhou, China.

INTRODUCTION

Ambient air pollution and temperature are leading environmental challenges to global public health. In 2019, $PM_{2.5}$ was responsible for an estimated 4.14 million deaths and 118 million disability-adjusted life years (DALYs) (*1*). Temperature is an important predictor of many diseases and has been perceived as a key environmental factor in climate change scenarios (*2*). Air pollution was identified as the fourth leading risk factor for death worldwide (*3*). Short-term exposure to $PM_{2.5}$ can increase the risk of death from chronic diseases (*4*).

In the context of climate change, health risk assessment of the joint effect of air pollution and temperature has attracted growing public concern (*5*). In Chengdu, China for example, stronger associations between air pollution and hospital admission for chronic obstructive pulmonary disease (COPD) were found at low-temperatures than at moderate temperatures (*6*). However, other studies have failed to identify synergetic health effects of air pollution and temperature. For example, Jhun and co-authors found that the interaction between ozone and temperature was not statistically significant in 97 US cities (*7*). In addition, potential variations of exposure-response patterns under various temperature levels have been less well documented. As an extension of distributed lag models, the varying-coefficient distributed lag model has been flexibly applied to explore interactive and time-lagged effects between different exposure hazards (*8*).

We aimed to establish the exposure-response association between $PM_{2.5}$ and mortality at different temperature strata using the varying coefficient distributed lag model in Guangzhou, China, and to explore synergetic mortality risks from $PM_{2.5}$ and temperature on vulnerable populations.

METHODS

The study period was 2013–2020. We obtained daily mortality data in Guangzhou from Guangzhou Center for Disease Control and Prevention. Causes of death were classified according to International

Classification of Diseases, Tenth Revision: non-accidental causes (A00–R99), cardiovascular disease (I00–I99), ischemic heart disease (IHD, I20–I25), stroke (I60–I69), respiratory disease (J00–J98), and COPD (J40–J47). Daily counts of non-accidental deaths were stratified by age (<75 and ≥75 years), gender, and educational level (≤9 and >9 years). We obtained daily concentrations of air pollutants (O_3, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO) from Guangzhou monitoring stations and daily meteorological data from basic weather stations in Guangzhou from the China Meteorological Data Service Center (http://data.cma.cn/).

The varying coefficient distributed lag model, based on generalized linear models with a quasi-Poisson family (*9*), was used to estimate the modifying effect of temperature on the association between $PM_{2.5}$ and mortality. We incorporated several covariates in the model: a natural cubic spline with 7 degrees of freedom (df) per year for a time variable; a natural cubic spline with 3 df for relative humidity, air pressure, and moving average temperature (with time lags of 0–10 days); and holidays and day of the week as indicator variables. The cross-product of categorical temperature levels [low (<25th percentile), medium (25th–75th), and high (>75th percentile)] and $PM_{2.5}$ was used to examine the interaction between air pollution and temperature. In addition, stratified analyses were conducted by gender, age group, and education. Relative differences of RRs across strata [relative risk ratios (*RRR*)] were calculated to detect potential effect modifications by temperature. To verify the robustness of our results, we performed a series of sensitivity analyses. Details of the model are provided in the Supplementary Material (available in https://weekly.chinacdc.cn/). All statistical analyses were conducted in the R language environment (R Core Team 2021, Vienna, Austria) using the "dlnm", "mgcv", and "splines" packages.

RESULTS

Table 1 depicts summary statistics on daily air pollution, weather conditions, and mortality. The average $PM_{2.5}$ value was 35.1 μg/m^3 during 2013–2020. During the study period, there were 403,492 deaths registered in Guangzhou, among which cardiovascular diseases, IHD, stroke, respiratory disease, and COPD accounted for 39.5%, 16.7%, 10.3%, 14.4%, and 6.1%, respectively.

Supplementary Figure S1 (available in https://weekly.chinacdc.cn/) shows Spearman's correlations between air pollution and weather conditions. There were negative correlations between temperature and relative humidity and air pollutants (except for O_3) and positive correlations among air pollutants.

Figure 1 shows lag patterns of $PM_{2.5}$ on cause-specific mortality at different temperature levels. Effect

TABLE 1. Summary statistics for daily weather conditions, air pollution, and mortality in Guangzhou, 2013–2018.

Variable	Mean	Minimum	Percentiles			Maximum
			25th	50th	75th	
Temperature (℃)	22.2	3.4	17.4	23.3	27.3	32.0
Low (<25th)	13.6	4.6	11.8	14.0	15.8	17.7
Medium (25th–75th)	23.1	17.8	20.7	23.3	25.7	27.3
High (>75th)	28.9	27.4	27.9	28.8	29 .6	31.9
Mean humidity (%)	80.4	31.0	75.0	81.5	88.0	100.0
Mean pressure (hPa)	1,007.1	985.7	1,000.3	1,005.4	1,010.8	3,276.6
$PM_{2.5}$ (μg/m³)	35.1	3.5	20.0	30.0	45.0	150.0
Cause (Number of deaths per day)						
Non-accidental	131	79	115	128	143	238
Cardiovascular disease	55	21	45	53	62	115
Ischemic heart disease	23	6	18	22	27	51
Stroke	14	0	11	14	17	34
Respiratory disease	20	6	15	19	24	48
COPD	8	0	6	8	11	30

Abbreviation: COPD=chronic obstructive pulmonary disease.

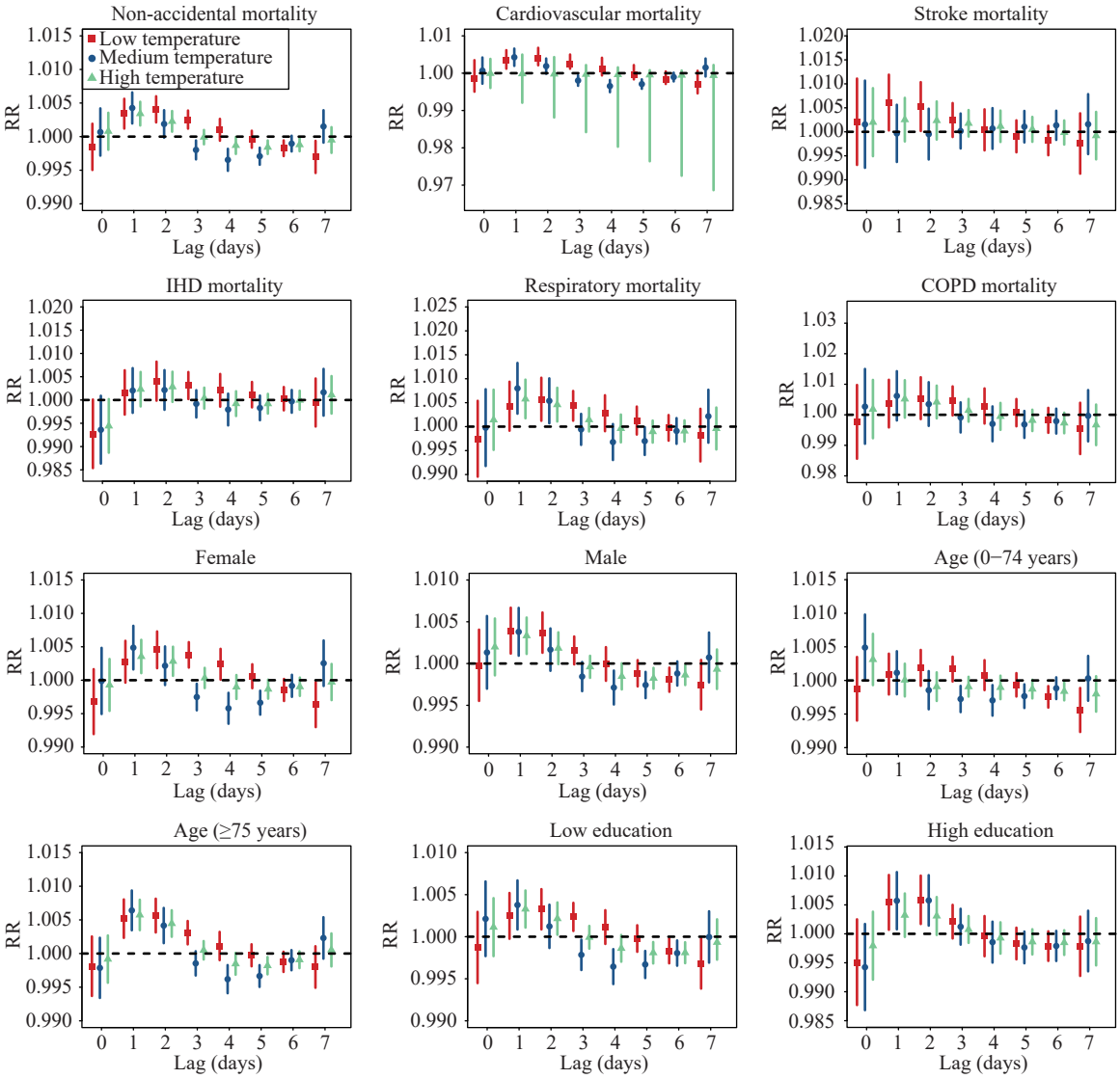

FIGURE 1. RR (95% CI) of mortality associated with 10 μg/m³ increase of $PM_{2.5}$ by a time lag of 0–7 days.
Note: dots and vertical lines represent point estimates and 95% confidence intervals of $PM_{2.5}$ at individual lag days.
Abbreviations: RR=relative risk; IHD=ischemic heart disease; COPD=chronic obstructive pulmonary disease; CI=confidence interval.

of $PM_{2.5}$ on the daily death toll of different diseases had consistent and evident trends in which mortality risks reached maximum within 1–2 lag days of exposure, then leveled off, and disappeared within 4–5 days.

Figure 2 shows the estimates of exposure-response relationships between $PM_{2.5}$ and mortality at different temperature levels. We found approximately linear associations between $PM_{2.5}$ and mortality. The highest effect estimates of $PM_{2.5}$ on mortality were consistently observed at the lower temperatures, while lower effect estimates were seen at the higher temperatures. Each 10 μg/m³ increase of $PM_{2.5}$ in low, medium, and high temperature strata was associated with respective increments of 0.73% [95% confidence interval (CI): 0.38%, 1.09%], 0.12% (95% CI: −0.27%, 0.52%), and 0.46% (95% CI: 0.11%, 0.81%) in non-accidental mortality (Table 2). There was an *RRR* of 1.01 (95% CI: 1.00, 1.01) between low and medium temperatures (*P*=0.02) (Supplementary Table S1, available in https://weekly.chinacdc.cn/). For cause-specific mortality, statistically significant differences between the risk of $PM_{2.5}$ across temperature levels were only observed for cardiovascular mortality, with effect estimates of 0.88% (95% CI: 0.37%, 1.39%), 0.04% (95% CI: −0.52%, 0.60%) and 0.50% (95% CI: 0.00%, 0.99%) at low, medium and high temperature levels (Table 2),

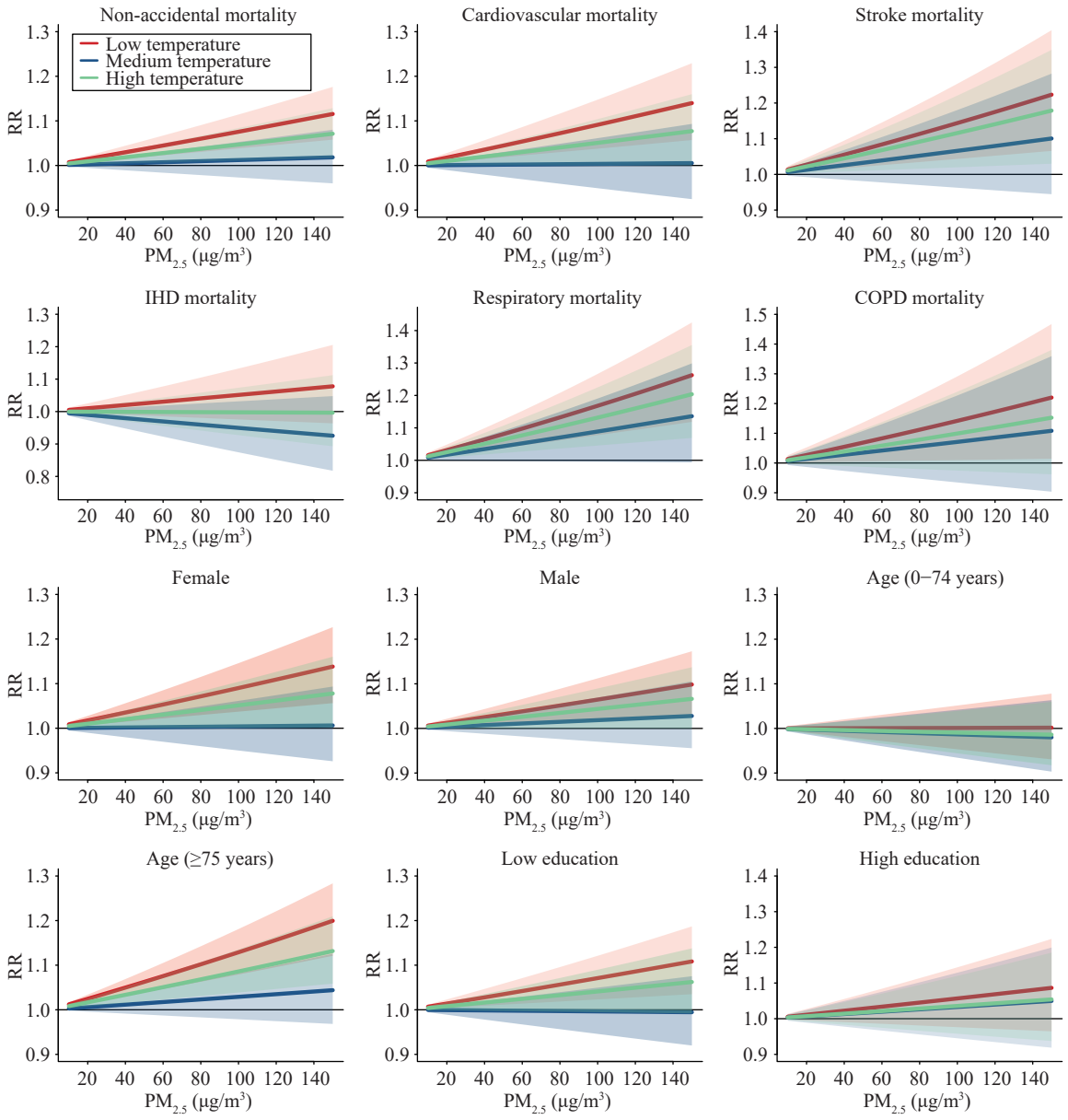

FIGURE 2. Concentration-response associations between $PM_{2.5}$ and mortality under different temperature conditions. Abbreviations: RR=relative risk; IHD=ischemic heart disease; COPD=chronic obstructive pulmonary disease.

and an *RRR* of 1.01 (95% CI: 1.00, 1.02) between low temperature and medium temperature (P=0.03). The highest effect of $PM_{2.5}$ was found in respiratory mortality at low temperatures, with an effect estimate of 1.57% (95% CI: 0.75%, 2.39%); however, difference by temperature was not statistically significant.

In analyses stratified by personal characteristics, we found consistently higher effects of $PM_{2.5}$ at low temperatures compared with medium temperatures, but the only statistically significant difference was among individuals of 75 years or older. Each 10 μg/m³ increase of $PM_{2.5}$ in the low, medium, and high temperature strata was associated with increments of 1.22% (95% CI: 0.76%, 1.68%), 0.29% (95% CI: −0.22%, 0.79%), and 0.83% (95% CI: 0.38%, 1.28%) in mortality of the elderly, respectively, with *RRR* of 1.01 (95% CI: 1.00, 1.02) between low and medium temperature strata (P=0.01). The elderly were more susceptible to $PM_{2.5}$ compared with younger age groups under both low and high temperature conditions.

Using different degrees of freedom for time trend analyses adjusting for co-pollutants changed the effect estimates only slightly (Supplementary Tables S2–S3, available in https://weekly.chinacdc.cn/), indicating

TABLE 2. Cumulative (lag 0–4 days) mortality risk of each 10 μg/m³ increase in $PM_{2.5}$ at different temperature strata (ER, 95% CI).

Variable	Low temperature		Medium temperature		High temperature	
	ER%	95% CI	ER%	95% CI	ER%	95% CI
Non-accidental mortality	0.73*	(0.38, 1.09)*	0.12	(−0.27, 0.52)	0.46*	(0.11, 0.81)*
Cardiovascular mortality	0.88*	(0.37, 1.39)*	0.04	(−0.52, 0.60)	0.50*	(0.00, 0.99)*
Stroke mortality	1.35*	(0.43, 2.29)*	0.64	(−0.38, 1.67)	1.10*	(0.20, 2.02)*
Ischemic heart mortality	0.50	(−0.25, 1.25)	−0.52	(−1.33, 0.31)	−0.02	(−0.64, 0.77)
Respiratory mortality	1.57*	(0.75, 2.39)*	0.85	(−0.04, 1.76)	1.24*	(0.45, 2.05)*
COPD mortality	1.34*	(0.10, 2.59)*	0.69	(−0.67, 2.07)	0.95	(−0.26, 2.17)
Gender						
Female	0.87*	(0.37, 1.37)*	0.04	(−0.51, 0.60)	0.50*	(0.01, 1.00)*
Male	0.63*	(0.19, 1.07)*	0.18	(−0.30, 0.67)	0.43*	(0.00, 0.86)*
Age (years)						
0–74	0.01	(−0.48, 0.50)	−0.13	(−0.68, 0.41)	−0.09	(−0.57, 0.39)
≥75	1.22*	(0.76, 1.68)*	0.29	(−0.22, 0.79)	0.83*	(0.38, 1.28)*
Education						
Low education	0.69*	(0.23, 1.15)*	−0.04	(−0.56, 0.48)	0.40	(−0.05, 0.86)
High education	0.55	(−0.24, 1.35)	0.32	(−0.56, 1.22)	0.32	(−0.43, 1.14)

Abbreviations: ER=excess risk; CI=confidence interval; COPD=chronic obstructive pulmonary disease.
* indicates statistically significant results.

robustness of our main results. Using different temperature cutoffs (Supplementary Table S4, available in https://weekly.chinacdc.cn/) and different $PM_{2.5}$ time-lags (Supplementary Table S5, available in https://weekly.chinacdc.cn/) did not remarkably change the estimates of temperature-stratified air pollution effects on mortality.

CONCLUSIONS

To the best of our knowledge, this is one of the few studies exploring exposure-response associations between air pollution and mortality under different temperature conditions. Our study consistently observed greater mortality risks from $PM_{2.5}$ in lower temperatures than in moderate temperatures across different causes of death. Interaction effects between $PM_{2.5}$ and low temperatures were more pronounced in the elderly than in younger people.

We observed the highest effect of $PM_{2.5}$ on mortality in low temperature strata compared with high and medium temperature strata. Low temperatures have consistently been found to enhance the effect of $PM_{2.5}$ on cardiovascular mortality in Beijing (*10*), natural and respiratory mortality in Hong Kong (*11*), and COPD mortality in Chengdu (*6*). For instance, Li and coauthors found that each 10 μg/m³ increment of $PM_{2.5}$ during the lowest temperature range was associated with a 1.27% (95% CI: 0.38%, 2.17%) increase in cardiovascular mortality, compared with 0.59% (95% CI: 0.22%, 1.16%) across the whole temperature range (*10*). Likewise, the association between $PM_{2.5}$ and mortality in Hong Kong was stronger at low temperatures than at higher temperatures, with corresponding effect estimates of 0.94% (0.95% CI: 0.65%, 1.24%) and 0.47% (95% CI: 0.65%, 1.24%) for each 10 μg/m³ increment in $PM_{2.5}$ (*11*). The reduced beat frequency of nose and trachea cilia on cold days, which affects the clearance rate of particulate matter and makes people more susceptible to $PM_{2.5}$, is suspected as an underlying mechanism for the greater effect of $PM_{2.5}$ on mortality at low temperatures in Guangzhou (*12*). Some studies found that people living in warm regions probably experience a higher mortality risk during cold weather than do people living in cold regions (*13*). In addition, low temperatures may exacerbate airway inflammation and increase the burden on respiratory functions (*14*).

We also found relatively higher effect estimates of $PM_{2.5}$ on mortality in high temperatures compared to moderate temperatures, although the difference was not statistically significant, consistent with previous studies (*6*,*10*). However, another study reported a statistically significant higher health effect of $PM_{2.5}$ in

high temperature strata (*15*). The discrepant results may be explained by differences in population structure and air pollution exposure patterns.

In this study, we observed a significant modification of the effect of $PM_{2.5}$ on cardiovascular mortality by low temperatures. As ambient temperature decreases, cold receptors in the skin are stimulated, the sympathetic nervous system increases catecholamine levels, blood vessels near the skin constrict to reduce heat loss, and blood pressure suddenly increases (*10*). High blood pressure can lead to oxygen deficiency, myocardial ischemia, or arrhythmia, and become a risk factor for vascular spasms and ruptures of atherosclerotic plaque that cause thromboses (*12*). Such marked changes make people more susceptible to adverse cardiovascular outcomes caused by $PM_{2.5}$. The findings are important from a public health perspective, as 39.5% of all non-accidental deaths in Guangzhou were cardiovascular deaths.

Our analysis also found significant interaction effects of $PM_{2.5}$ and low temperature among the elderly but not among young people, which is consistent with a previous study (*6*). The body's homeostasis and thermoregulatory functions, and the capacity to eliminate chemicals from the body decrease with age (*16*), which may contribute to the combined health hazards of $PM_{2.5}$ and temperature change. The elderly also suffer from higher rates of comorbidities, which may further enhance their vulnerability to environmental exposure.

The study was subject to some limitations. First, we substituted measured air pollution and air temperature at fixed outdoor monitoring stations for personal exposures, which will lead to some exposure measurement errors. Second, only adverse associations of $PM_{2.5}$ were examined in this study, leaving confounding by other factors unexplored. Last, our results may not generalize to areas with different population structures and air pollution compositions.

In summary, we observed an interaction between $PM_{2.5}$ and low temperature on mortality, especially for non-accidental and cardiovascular mortality and among the elderly. Considering the synergetic health risks of air pollution and temperature, cooperation from multiple sectors with the aim of protecting vulnerable populations may mitigate health challenges from climate change and air pollution.

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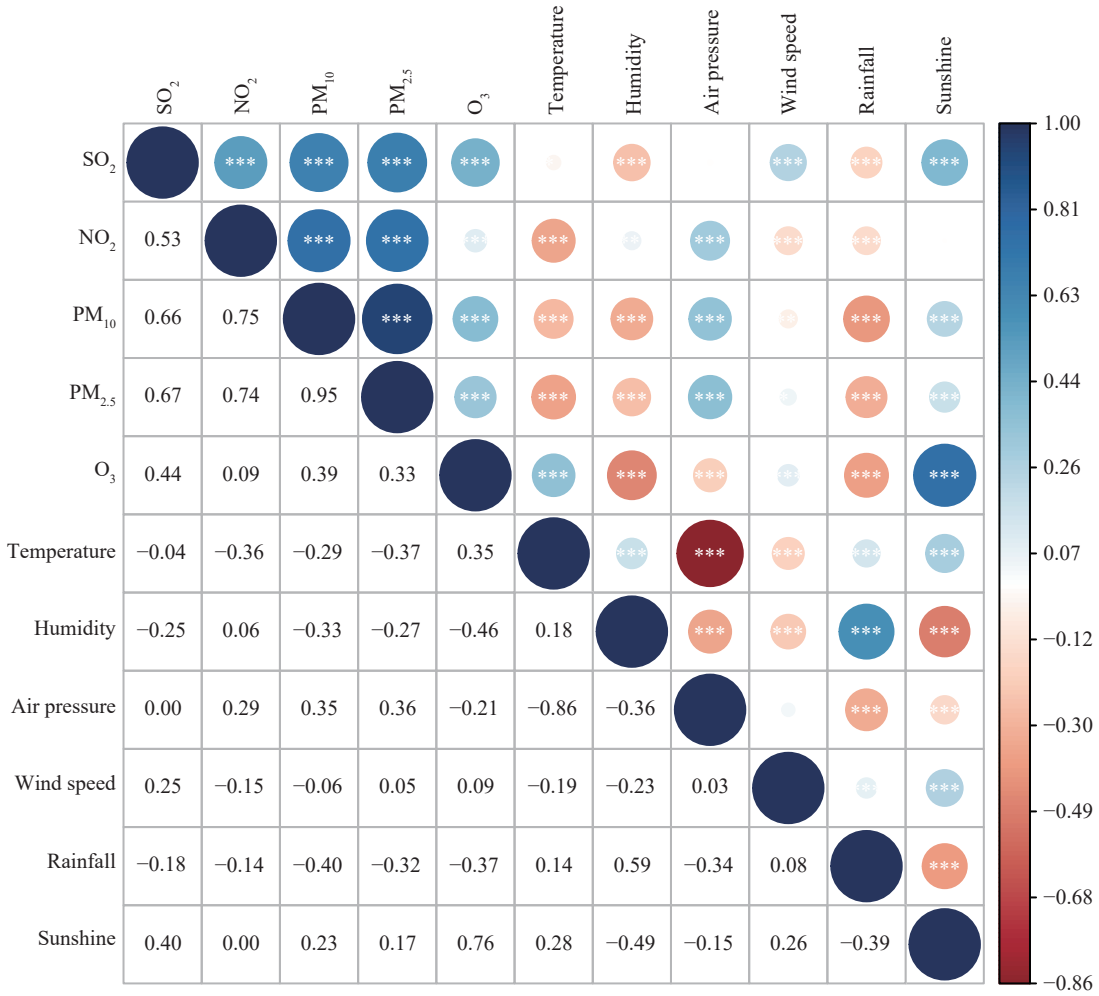
SUPPLEMENTARY MATERIAL

Model Construction

The varying coefficient distributed lag model:

$$Log[E(Y_t)] = \alpha + ns(Hum_t, 3) + ns(Press_t, 3) + ns(Temp_t, 3) + ns(Time_t, 78) + \upsilon Holiday_t + cb(PM_{2.5}) + T_l \times cb(PM_{2.5})$$

Where $E(Y_t)$ denotes the daily expected number of deaths on day t; α is the intercept; ns is a natural cubic spline. 7 degrees of freedom (df) per year for time ($Time_t$) was used to control for long-term trends and seasonal variables of daily mortality (*1*). $Holiday_t$ is an indicator variable of population dynamics due to holidays. T_l is a categorical variable indicating various temperature levels. To explore the possible effect modification by ambient temperature, we divided the ambient temperature into three levels: low (<25th percentile), medium (25th–75th), and high (>75th percentile), which was consistent with previous studies (*2*). ns (natural cubic splines) with three df was adapted for daily relative humidity and air pressure (*3*). And we applied the natural cubic spline (ns) to fit the moving average (lag 0–10 days) of temperature to control the confounding effects of temperature ($Temp_t$). In the basic model, we used a distributed lag model (DLM) to describe the association with $PM_{2.5}$. Lag effects were described by a cross-basis function (cb) in the distributed lag model (*4*). Specifically, we applied a cross-basis



SUPPLEMENTARY FIGURE S1. Correlations (Spearman correlation coefficient) among air pollution and weather conditions.
*: P<0.05;
**: P<0.01;
***: P<0.001.

SUPPLEMENTARY TABLE S1. *RRR*, 95% confidence intervals (CI), and *P*-values of significance test of effects of $PM_{2.5}$ (per 10 μg/m^3) on mortality under different temperature levels.

Variable	Medium temperature	Low temperature			High temperature		
		RRR	95% CI	*P*	*RRR*	95% CI	*P*
Cause							
Non-accidental mortality	Reference	1.006*	(1.001, 1.011)*	0.024*	1.003	(0.998, 1.009)	0.207
Cardiovascular mortality	Reference	1.008*	(1.001, 1.016)*	0.030*	1.005	(0.997, 1.012)	0.228
Stroke mortality	Reference	1.007	(0.993, 1.021)	0.315	1.005	(0.991, 1.018)	0.511
IHD mortality	Reference	1.010	(0.999, 1.022)	0.072	1.005	(0.994, 1.016)	0.365
Respiratory mortality	Reference	1.007	(0.995, 1.019)	0.247	1.004	(0.992, 1.016)	0.526
COPD mortality	Reference	1.006	(0.99, 1.023)	0.434	1.003	(0.987, 1.019)	0.751
Gender							
Female	Reference	1.005	(0.997, 1.012)	0.219	1.001	(0.994, 1.008)	0.793
Male	Reference	1.004	(0.998, 1.011)	0.178	1.002	(0.996, 1.009)	0.450
Age (years)							
0–74	Reference	1.001	(0.994, 1.009)	0.708	1.000	(0.993, 1.008)	0.914
≥75	Reference	1.009*	(1.002, 1.016)*	0.008*	1.005	(0.999, 1.012)	0.118
Education level							
Low education	Reference	1.007	(0.997, 1.017)	0.153	1.004	(0.997, 1.011)	0.212
High education	Reference	1.002	(0.991, 1.014)	0.698	1.000	(0.988, 1.012)	1.000

Abbreviations: *RRR*=relative risk ratios; IHD=ischemic heart disease; COPD=chronic obstructive pulmonary disease.
* indicate statistically significant results.

SUPPLEMENTARY TABLE S2. Sensitivity analysis of the modification by the temperature on the $PM_{2.5}$-mortality association using 5–8 degrees of freedom (df) per year for the time trend.

Degrees of freedom (df)	Low temperature		Medium temperature		High temperature	
	ER	95% CI	ER	95% CI	ER	95% CI
df=6	0.73	(0.38, 1.09)	0.12	(−0.27, 0.52)	0.46	(0.11, 0.81)
df=5	0.81	(0.46, 1.16)	0.17	(−0.21, 0.54)	0.49	(0.15, 0.83)
df=7	0.68	(0.32, 1.04)	0.11	(−0.29, 0.51)	0.39	(0.03, 0.75)
df=8	0.74	(0.38, 1.10)	0.20	(−0.19, 0.60)	0.46	(0.11, 0.82)

Abbreviations: ER=excess risk; CI=confidence interval.

SUPPLEMENTARY TABLE S3. Sensitivity analysis of the modification by the temperature on the air pollution-mortality association with adjustments for different co-pollutants.

Co-pollutants	Low temperature		Medium temperature		High temperature	
	ER	95% CI	ER	95% CI	ER	95% CI
Main model	0.73	(0.38, 1.09)	0.12	(−0.27, 0.52)	0.46	(0.11, 0.81)
$PM_{2.5}$ + SO_2	0.41	(−0.01, 0.84)	−0.19	(−0.65, 0.27)	0.14	(−0.28, 0.56)
$PM_{2.5}$ + NO_2	0.86	(0.42, 1.31)	0.24	(−0.23, 0.71)	0.53	(0.09, 0.97)
$PM_{2.5}$ + O_3	0.59	(0.21, 0.97)	−0.04	(−0.46, 0.38)	0.33	(−0.05, 0.71)

Abbreviations: ER=excess risk; CI=confidence interval.

composed of a linear function for exposure-response, and a natural cubic B-spline for the lag response with an intercept and two internal knots placed at equally spaced values in the log scale. We chose 4 days to examine the lag effect of $PM_{2.5}$.

In this study, we extended distributed lag model (DLM) to the varying coefficient DLM by including a linear interaction between temperature (T_l) and the cross-basis variables. We directly incorporated the principal and

SUPPLEMENTARY TABLE S4. Sensitivity analysis of the modification by the temperature on the $PM_{2.5}$-mortality association using different temperature cutoffs.

Temperature cutoffs	Low temperature		Medium temperature		High temperature	
	ER	95% CI	ER	95% CI	ER	95% CI
25th/75th	0.73	(0.38, 1.09)	0.12	(−0.27, 0.52)	0.46	(0.11, 0.81)
20th/80th	0.61	(0.26, 0.96)	0.20	(−0.21, 0.60)	0.45	(0.10, 0.80)
15th/85th	0.51	(0.16, 0.86)	0.46	(0.02, 0.89)	0.45	(0.10, 0.80)
10th/90th	0.50	(0.14, 0.85)	0.73	(0.26, 1.21)	0.44	(0.09, 0.79)

Abbreviations: ER=excess risk; CI=confidence interval.

SUPPLEMENTARY TABLE S5. Sensitivity analysis of the modification by the temperature on the $PM_{2.5}$-mortality association using different days of lag.

Days of lag	Low temperature		Medium temperature		High temperature	
	ER	95% CI	ER	95% CI	ER	95% CI
Lag 0–4	0.73	(0.38, 1.09)	0.12	(−0.27, 0.52)	0.46	(0.11, 0.81)
Lag 0–3	0.81	(0.48, 1.15)	0.24	(−0.14, 0.61)	0.57	(0.24, 0.89)
Lag 0–5	0.56	(0.19, 0.94)	−0.05	(−0.46, 0.37)	0.29	(−0.08, 0.66)
Lag 0–6	0.43	(0.03, 0.83)	−0.15	(−0.58, 0.28)	0.17	(−0.22, 0.56)

Abbreviations: ER=excess risk; CI=confidence interval.

interaction terms in the model during a special parameterization to satisfy the DLM software specifications. The interaction term, the cross-product of the categorical temperature variable and $PM_{2.5}$ were used to examine the interaction effects between air pollution and temperature. We can estimate the effects of air pollution at a specific temperature from the three-dimensional curve. For instance, to obtain the effect of temperature at the specific concentration of air pollution, we only need to provide 3 coefficients of unidimensional NS splines that modeled the overall cumulative exposure-response relationship. Further, with the temperature divided into three levels, the model specifications and interpretations were similar. We then used this varying coefficient DLM to predict the exposure-lag-response association for different temperature strata. To examine potentially vulnerable populations, we repeated statistical analyses by gender, age group, and education to examine the changes in effect estimates across subgroups.

In order to detect the potential effect modifications of temperature, we calculated the relative differences of RRs across strata [relative risk ratio (*RRR*)] with the following equation.

$$RRR = exp\left[(E_1 - E_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2}\right]$$

where E_1 and E_2 denote the effect estimates [i.e. ln(RR)] of two subgroups; $SE(E_1)$ and $SE(E_2)$ are corresponding standard errors of E_1 and E_2 (*5*).

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