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ORIGINAL ARTICLE

Hourly peak $PM_{2.5}$ concentration associated with increased cardiovascular mortality in Guangzhou, China

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Hourly peak concentration may capture health effects of ambient fine particulate matter pollution ($PM_{2.5}$) better than daily averages. We examined the associations of hourly peak concentration of $PM_{2.5}$ with cardiovascular mortality in Guangzhou, China. We obtained daily data on cardiovascular mortality and hourly $PM_{2.5}$ concentrations in Guangzhou from 19 January 2013 through 30 June 2015. Generalized additive models were applied to evaluate the associations with adjustment for potential confounding factors. Significant associations were found between hourly peak concentrations of $PM_{2.5}$ and cardiovascular mortality, particularly from ischemic heart diseases (IHD) and cerebrovascular diseases (CBD). Every 10 $\mu g/m^3$ increment of hourly peak $PM_{2.5}$ at lag 03 day was associated with a 1.15% (95% CI: 0.67%, 1.63%); 1.02% (95% CI: 0.30%, 1.74%) and 1.09% (95% CI: 0.27%, 1.91%) increase in mortalities from total cardiovascular diseases, IHD and CBD, respectively. The effects remained after adjustment for daily mean $PM_{2.5}$ and gaseous air pollutants, though there was a high correlation between $PM_{2.5}$ peak and $PM_{2.5}$ mean (correlation coefficient = 0.95). No significant association was observed for acute myocardial infarction (AMI). In addition to daily mean concentration of $PM_{2.5}$, hourly peak concentration of $PM_{2.5}$ might be one important risk factor of cardiovascular mortality and should be considered as an important air pollution indicator when assessing the possible cardiovascular effects of $PM_{2.5}$.

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Keywords: Air pollution; exposure; hourly peak; mortality; $PM_{2.5}$

INTRODUCTION

Extensive epidemiological studies have reported significant associations between ambient air pollution and premature mortality, particularly from cardiovascular and respiratory diseases.[1–6] These findings have prompted the World Health Organization (WHO) and a number of countries to formulate and revise their air quality guidelines and standards.[7]

Previous studies have demonstrated that levels of exposure whether in several hours, several days of ambient particulate air pollutants could lead to adverse cardiovascular effects.[8–10] Majority of those studies have relied on daily mean concentration to examine short-term cardiovascular effects. One shortcoming of this approach is that such averages ignore the tremendous variations between different time points, as it is widely known that hourly air pollution concentrations usually vary greatly during a given day.[11] It is possible that peak concentrations may have a more important role in overwhelming the body's defense mechanisms.[12] However, there is limited research on the health effects stemming from exposures to hourly peak concentration of air pollution, mainly due to lack of detailed measuring data.[8,13] It is biologically plausible to hypothesize that hourly peak exposures to ambient air pollution might be more closely associated with acute cardiovascular health than daily average exposures.

Meanwhile, there is evidence that adverse health effects of air pollution are being detected below the air pollution standards/guidelines set by various countries and WHO.[11,14] The underlying reasons might be that hourly peak concentrations might have had a role at days with really low daily mean concentrations. There is also evidence that exposure to peak concentrations of air pollution is related to health effects, including asthma symptoms[12] and myocardial ischemia.[15]

Ambient air pollution has become an important environmental health concern in recent years in Guangzhou, and availability of hourly measured $PM_{2.5}$ concentration data provide a unique opportunity to test the aforementioned hypothesis. This study was therefore conducted to examine the cardiovascular effects of hourly peak concentration of ambient particulate matter $< 2.5\ \mu m$ in aerodynamic diameter ($PM_{2.5}$) with the purpose of evaluating the utility of hourly peak versus daily mean concentrations of $PM_{2.5}$. Findings from the present investigation may offer new evidence in ambient air pollution exposure assessment and its acute effects on cardiovascular mortality.

MATERIALS AND METHODS

Air Pollution Data

The hourly air pollution data from 19 January 2013 to 30 June 2015 were obtained from the Guangzhou Environmental Monitoring Center. There are a total of 11 ambient air-monitoring stations in Guangzhou. Hourly concentrations of $PM_{2.5}$, as well as other air pollutants (SO_2, NO_2, and O_3), were regularly monitored in these stations since 19 January 2013. These stations are not adjacent to traffic, industrial sources, buildings or residential sources of emissions from the burning of coal, waste, or oil,

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and they are believed to be representative of the overall air pollution situation in Guangzhou.

The hourly peak concentration of $PM_{2.5}$ was defined as the maximum concentration of 24-h $PM_{2.5}$ within a given day.[13] We calculated hourly peak concentration from non-missing data if at least 16 of 24 hourly concentrations of $PM_{2.5}$ were available. During the study period, there were 39–91 days with missing information among the 11 stations, which accounted for 4.4–10.2% of the observation days. However, there were only 6 days for the whole study city where monitoring stations were unable to collect $PM_{2.5}$.

We also calculated daily mean concentrations of $PM_{2.5}$, NO_2, SO_2, and O_3 using data from these stations. Daily meteorological data for the same period, including mean daily mean temperature (°C) and relative humidity (%), were also obtained from the Guangzhou Observatory.

Mortality Data

Guangdong Provincial Center for Disease Control and Prevention (GDCDC) provided the daily mortality data for the same time period. Obtained records included information from death certificates, such as sex, date of death, age at death, residential address, and the underlying cause of death. In Guangzhou, regardless of where a death occurred (e.g., in a hospital or at home), all deaths must be reported to the death registry system before remains can be cremated. In addition, all physicians are required to report the cause of death on the death certificate. The Chinese government has mandated detailed quality assurance (QA) and quality control (QC) programs for the national death registry.[16] The cause of death as reported on the death certificates was coded using the Tenth Revision of the International Classification of Diseases (ICD-10).[17] The mortality data used in this analysis were classified into: cardiovascular diseases (CVD, ICD10: I00–I99), ischemic heart diseases (IHD, ICD10: I20–I25), acute myocardial infarction (AMI, ICD10: I21), and cerebrovascular diseases (CBD, ICD10: I60–I69).

Approval to conduct this study was granted by the Medical Ethics Committee of Saint Louis University.

Statistical Methods

We examined the short-term association between hourly peak concentrations of $PM_{2.5}$ and cardiovascular mortalities using generalized additive models (GAM); a quasi-Poisson function was applied to account for overdispersion in daily cardiovascular mortality.[18] A penalized smoothing spline was used to filter out seasonality and long-term trend in daily mortality, as well as temperature and relative humidity.[19] We included day of the week (DOW) and public holidays (Holiday) in the model as dummy variables.[20]

To reduce the potential concerns caused by multiple statistical testing and model specifications, we followed guidelines established by previous studies and selected model specifications and the degrees of freedom (d.f.) *a priori* for the smoothing function of temporal trend and meteorological factors.[21–23] We used a d.f. of 6 per year for time trend. A d.f. of 6 for mean temperature for current day temperature ($Temp_0$) and previous 3 days' moving average ($Temp_{1-3}$) was selected. A d.f. of 3 was selected for current day's relative humidity ($Humidity_0$). For the smoothing function of calendar time, 6 d.f. per year was chosen to filter out the information at time scales of 2 months. For temperatures, 6 d.f. was chosen to account for the potential non-linear relationship between temperature and mortality.[24] Briefly, we set up a core model to remove the long-term trends, seasonal variations and adjust for time varying confounders as follows:

$$\log[E(Y_t)] = \alpha + s(t, \text{d.f.} = 6/\text{year}) + +s(\text{Temp}_0, \text{d.f.} = 6) + s(\text{Temp}_{1-3}, \text{d.f.} = 6) + s(\text{Humidity}_0, \text{d.f.} = 3) + \beta_1 * \text{DOW} + \beta_2 * \text{PH}$$

where $E(Y_t)$ is the expected cardiovascular mortality count on day t, α is the model intercept, $s()$ indicates a smoother based on penalized splines, d.f. is the degree of freedom, t represents time to adjust for long-term trend and seasonality, $Temp_0$ is the mean temperature on the current day, $Temp_{1-3}$ is the moving average for the previous 3 days' temperature, $Humidity_0$ presents the humidity on the current day, PH represents a binary variable for the public holiday, DOW is an indicator for day of the week, and β is the regression coefficient.

After the core model was established, we included the $PM_{2.5}$ peak in the model to analyze the association between hourly peak $PM_{2.5}$ and mortalities from each of the cardiovascular diseases.

We estimated the linear effect of hourly peak $PM_{2.5}$ with different lag structures including both single-day lag (from the current day (lag_0)) up to 5 lag days (lag_5), because previous studies in China showed little evidence of association with a lag beyond three days.[10,25] We also examined the cardiovascular mortality effects of multi-day lags (moving averages for the current day and the previous 1, 2, and 3 days: lag_{01}, lag_{02}, and lag_{03}, respectively).

In order to justify the assumption of linearity between the logarithm of cardiovascular mortality and hourly peak concentration of $PM_{2.5}$, we used a smoothing function to graphically examine the exposure–response relationship between hourly peak concentration of $PM_{2.5}$ and cardiovascular mortality.[26]

In addition, we calculated hourly peak concentrations using the measures during two daily rush-hour periods (0700–0900 and 1700–1900 hours). These were used to represent the periods with the highest pollution concentrations in the study area during the day.

Sensitivity Analysis

The sensitivity of the key results was assessed in terms of the degrees of freedom in the smoothing function of time trends and meteorological variables. We also included other air pollutants in two-pollutant models to check whether the observed effects could be confounded by these air pollutants.

All analyses were conducted using the "mgcv" package in R (version 2.14.1; R Development Core Team, Vienna, Austria). We reported the results as excess risk (ER, with 95% CI) in daily cardiovascular mortality for an interquartile range (IQR) increase in hourly peak concentration of $PM_{2.5}$. Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 46,850 deaths from total cardiovascular diseases were recorded in Guangzhou between 19 January 2013 and 30 June 2015. Among them, 19,371 (41.35%) were from ischemic heart diseases, 9 242 (19.73%) from acute myocardial infarction, and 13,992 (29.87%) from cerebrovascular diseases. On average, there were 52, 22, 10, and 16 deaths per day from total cardiovascular diseases, ischemic heart diseases, acute myocardial infarction and cerebrovascular diseases, respectively.

Table 1 shows the descriptive summary of the daily mortality, air pollutants, and weather conditions in Guangzhou. During the study period, the daily mean and peak concentrations of $PM_{2.5}$ were 46.4 and 66.9 $\mu g/m^3$, respectively. The daily mean concentrations of NO_2, SO_2 and O_3 were 47.4, 19.5, and 56.3 $\mu g/m^3$, respectively. And during the study period, the daily mean temperature and relative humidity were 21.7 °C and 79.6%, respectively.

Table 2 shows the correlation between air pollutants and weather factors in Guangzhou. Generally, $PM_{2.5}$ peak was moderately to highly correlated with other variables. For example, the correlation coefficients were 0.95 between peak concentration of $PM_{2.5}$ and mean concentration of $PM_{2.5}$, 0.75 between peak $PM_{2.5}$ and NO_2 concentration, and − 0.28 between $PM_{2.5}$ peak and relative humidity. The daily mean concentration of $PM_{2.5}$ was also moderately or highly correlated with other variables, for example, there was a high correlation between $PM_{2.5}$ mean and NO_2 ($r = 0.78$), and a moderate correlation with O_3 ($r = 0.41$) and mean temperature ($r = -0.40$). There were also significant correlations between other air pollutants and weather variables, except between NO_2 and relative humidity, for example, there was a low, but statistically significant correlation between NO_2 and O_3 ($r = 0.14$), and a moderate correlation between SO_2 and O_3 ($r = 0.34$).

Figure 1 shows the effects of daily mean and peak concentrations of $PM_{2.5}$ on mortality from total cardiovascular diseases, IHD, AMI and CBD along different lag days in single pollutant models. We found that both mean and peak concentrations of $PM_{2.5}$ were significantly associated with mortality from total cardiovascular diseases, IHD and CBD at most of the lag days examined. And among the lag days, the effects of moving average of previous

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Table 1. Summary statistics of daily cardiovascular mortality, air pollutants, and weather conditions in Guangzhou, 2013-2015.

Variable	*Observation days*	*Mean ± SD*	*Percentiles*				
			Min	*P25*	*P50*	*P75*	*Max*
Daily mortality count							
CVD	893	52.5+11.3	27	44	51	60	95
IHD	893	21.7+6.0	7	17	21	25	46
AMI	893	10.4 ± 3.7	1	8	10	13	24
CBD	893	21.6 ± 6.0	6	17	21	25	46
Air pollution (μg/m³)							
$PM_{2.5}$ peak	887	66.9 ± 35.5	10.4	38.8	60.7	86.5	259.2
$PM_{2.5}$ mean	887	46.4 ± 25.5	7.7	26.2	41.2	61.1	153.7
NO_2	888	47.4+20.3	4.4	33.5	42.9	57.9	143.1
SO_2	888	19.5+12.0	4.2	12.8	17.1	22.7	166.4
O_3	885	56.3+33.2	9.1	33.9	50.4	69.7	294.6
Meteorological factors							
Temperature (°C)	893	21.7+6.1	4.8	16.9	22.9	27.0	31.1
Relative humidity (%)	893	79.6+10.8	31.0	74.0	81.0	87.0	100.0

Abbreviations: Max, maximum; Min, minimum; P*x*, *x*th percentile.

Table 2. Pearson correlation coefficients between $PM_{2.5}$ peak, air pollutants, and weather conditions in Guangzhou, 2013-2015.

Pollutants	*$PM_{2.5}$ peak*	*$PM_{2.5}$ mean*	*NO_2*	*SO_2*	*O_3*	*Temperature*
$PM_{2.5}$ mean	0.95*					
NO_2	0.75*	0.78*				
SO_2	0.55*	0.56*	0.49*			
O_3	0.38*	0.41*	0.14*	0.34*		
Temperature	− 0.44*	− 0.40*	− 0.36*	− 0.11*	0.16*	
Humidity	− 0.28*	− 0.30*	0.02	− 0.16*	−0.52*	0.20*

*$P < 0.05$.

4 days were largest. For example, a 10 $\mu g/m^3$ increase in mean $PM_{2.5}$ at lag_{03} corresponded to 1.56% (95% CI: 0.91%, 2.21%); 1.36% (95% CI: 0.40%, 2.33%) and 1.55% (95% CI: 0.45%, 2.65%) increase in mortality from total cardiovascular diseases, IHD and CBD, respectively. Similarly, the largest effects of hourly peak concentration of $PM_{2.5}$ were also observed on lag_{03}; the ERs for a 10 $\mu g/m^3$ increase were 1.15% (95% CI: 0.67%, 1.63%); 1.02% (95% CI: 0.30%, 1.74%) and 1.09% (95% CI: 0.27%, 1.91%) for mortality from total cardiovascular diseases, IHD and CBD, respectively. We did not find any effects of daily mean and peak concentrations of $PM_{2.5}$ on AMI mortality along all the lag days examined.

In the two-pollutant models with adjustment for hourly peak concentrations of $PM_{2.5}$, NO_2, SO_2 or O_3, the effects of daily mean $PM_{2.5}$ on mortality from total cardiovascular, IHD and CBD changed very little and remained statistically significant, except that the effect on CBD became non-significant in the model controlling for NO_2 (Supplementary Table S1). And when we controlled for daily mean concentration of $PM_{2.5}$, NO_2, SO_2 or O_3, the effects of $PM_{2.5}$ peak on mortalities from total cardiovascular, IHD and CBD also changed very little and remained statistically significant, except that the effect on CBD became non-significant in the model controlling for NO_2 (Supplementary Table S2). These consistent results suggested that the effects of daily mean and peak of $PM_{2.5}$ were not confounded by other air pollutants, particularly the effects of hourly peak $PM_{2.5}$ were not confounded by daily mean concentration of $PM_{2.5}$.

Figure 2 shows the smoothing curves of the concentration-response relationship between daily mean and hourly peak concentrations of $PM_{2.5}$ and mortalities from total cardiovascular diseases, IHD and CBD. The curves suggest an approximately linear relationship without obvious evidence of concentration threshold below which there was no effect.

Supplementary Figure S1 depicts the association between various cardiovascular mortalities and hourly peak $PM_{2.5}$ measured at rush hours in the morning (0700–0900 hours) and evening (1700–1900 hours). Consistent effect estimates were observed with those obtained in the main models; we found significant associations with mortalities from total cardiovascular, IHD and CBD, but not with AMI.

In the sensitivity analyses we used alternative degrees of freedom to adjust for temporal trends and meteorological factors, and the results remained (Supplementary Tables S1 and S2). All these suggested that the associations between daily mean and hourly peak concentrations of $PM_{2.5}$ and cardiovascular mortalities obtained from the main models were robust.

DISCUSSION

Previous studies investigating the health effects of ambient air pollution have predominately employed daily mean air pollution concentration as an exposure indicator. Air pollution concentrations may vary widely within a given day. The hourly peak concentration might be more closely related to its adverse health effects. However, studies on the health effects of hourly peak/maximum concentration of air pollution are limited.[12,13] To our knowledge, this is the first study to investigate the association

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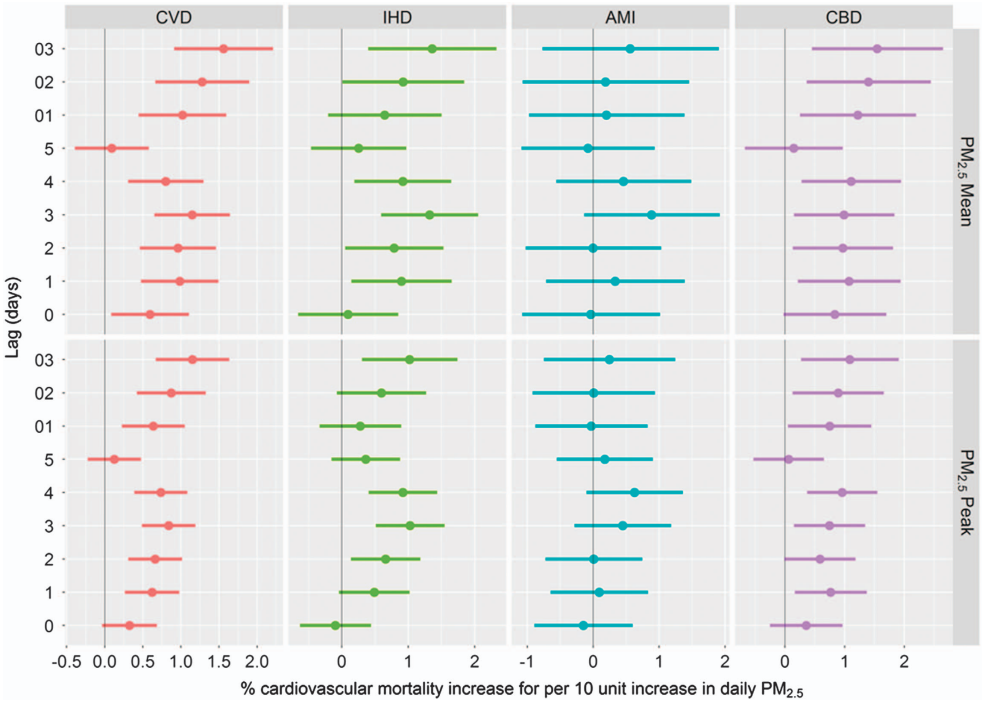

Figure 1. Excess risk (%) in cardiovascular mortality for per 10 $\mu g/m^3$ increase in hourly peak and daily mean concentrations of $PM_{2.5}$ with different lag days (single lags for the current day (lag0) to 5 days before the current day (lag5) and multiday lags for the current day and prior 1 day before (lag01), 2 days (lag02), or 3 days (lag03)).

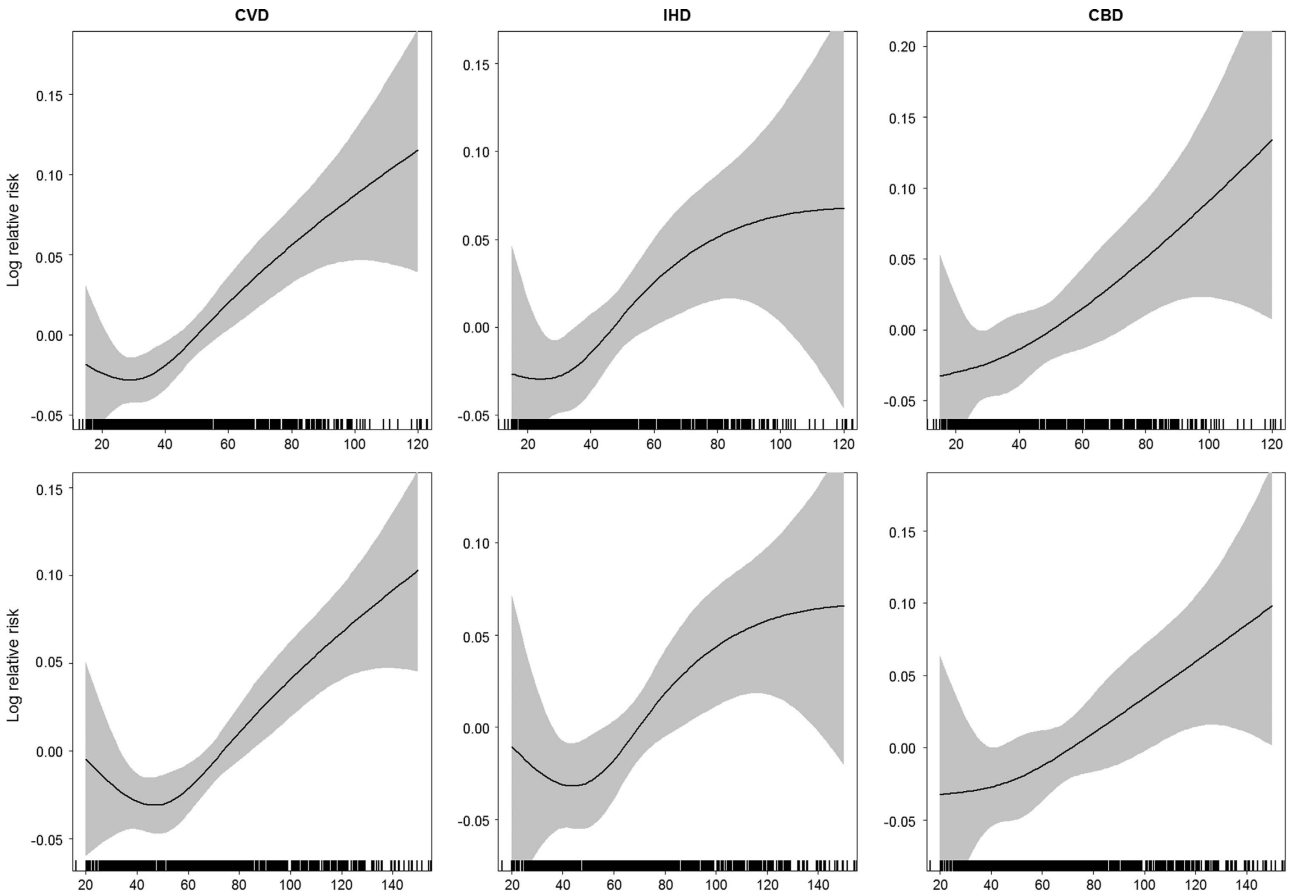

Figure 2. Smoothing plots of hourly peak and daily mean concentrations of $PM_{2.5}$ against cardiovascular mortality. *x* axis is the $PM_{2.5}$ concentration ($\mu g/m^3$). Confounding factors included DOW, public holidays, temporal trend, influenza epidemic, and meteorological factors.

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between hourly peak concentration of $PM_{2.5}$ and cardiovascular mortality in China. Among the 46,850 cardiovascular mortalities in Guangzhou, this study found that the hourly peak concentration of $PM_{2.5}$ might be another important air pollution predictor of cardiovascular mortality in addition to daily mean concentration of $PM_{2.5}$.

The observed acute effects of hourly peak concentration of $PM_{2.5}$ were consistent with previous research, though few in number, in other regions of the world. For example, in a recent study from Norway, Madsen, et al.[13] found a significant health effect of peak $PM_{2.5}$, with an excess risk of 1.7% (95% CI: 0.3%, 3.1%) in cardiovascular mortality for per 10 $\mu g/m^3$ increase in hourly peak $PM_{2.5}$ exposure. Another study from Southern California also suggested that hourly peak PM_{10} exposures were more relevant to acute adverse health effects among children.[12] Huang et al. (2015) found that increase in peak NO_2 concentrations, rather than the mean concentration, was significantly associated with higher hospital admissions for respiratory disease in Scotland, suggesting that peak concentrations might be more correlated with health risk than average concentrations. These findings led to the question of which metric one should use to examine the health effects. This issue, however, has received little attention to date in the literature, as most of the epidemiological studies, if not all, have used the average (mean) concentration.[27,28] Given the consistency across these studies, it is necessary to compare the daily mean and peak concentrations in future research.

The strongest associations for $PM_{2.5}$ mean and peak concentrations were observed at lag 2 or 3 days exposure and a 4-day moving average (lag_{03}). Given that the time course of cardiovascular response, and subsequent mortality, can be on the order of hours to days for late-stage reactions,[8,9] it was within the expectation that cardiovascular mortality was acutely related to airborne particulate pollution within 3 days of exposure. We further observed slightly stronger associations with a 4-day moving average than with individual lag days, suggesting cumulative effects to some extent; which was in agreement with our recent studies on the health effects of characteristics of PM pollution in the study area.[10,23]

The adverse cardiovascular effects of hourly peak concentration of $PM_{2.5}$ identified in our study are biologically plausible. For example, it is possible that people inhale more particles during the days with a higher peak concentration of $PM_{2.5}$. Some vulnerable populations may be more prone to exposure to a higher $PM_{2.5}$ concentration within a short time and thus have more serious health outcomes. The large hourly peak concentration of $PM_{2.5}$ may also trigger the biologic responses of humans when it overwhelms immune defense mechanisms.[12] Another possibility is that people may not adapt to extremely high $PM_{2.5}$ exposure and that the response ability of the cardiovascular system may be stressed in some persons. Such adaptive ability may be reduced among those with existing medical conditions. One recent study from the U.K. suggested that exposure to high levels of particulate matter pollution with a lag of 1–6 h before disease onset was associated with higher risk of acute myocardial infarction.[8] Another experimental study found that inhalation of diesel exhaust could impair the regulation of vascular tone two hours after exposure.[29] The exact pathways by which the inhaled fine particles cause cardiovascular effects is still unknown, but cell damage due to oxidative stress is strongly implicated. Toxicological studies have reported that $PM_{2.5}$ usually contains various strong oxidant components, some of which can initiate an acute inflammatory reaction.[30,31]

We found statistically significant associations between hourly peak $PM_{2.5}$ and mortality from total cardiovascular diseases, ischemic heart diseases and cerebrovascular diseases, while no significant effects were detected for AMI mortality. The underlying reasons remained unknown; it is possible that people with AMI had fewer outdoor activities and thus reduced their exposure to ambient $PM_{2.5}$. Future studies are necessary to investigate the underlying mechanisms.

Our study findings should be interpreted in light of a few limitations. First, this was an ecological study design, which did not allow us to examine the association at the individual level and limited our capacity for causal inference. Nevertheless, the authors suggested similar studies should be conducted in other areas, and if similar findings were obtained, it may indicate that the mentioned concern may be minimal, and hourly peak concentration of $PM_{2.5}$ should be considered in environmental control. Second, ambient air pollution data from fixed air-monitoring stations were used to represent the population exposure levels, which might not accurately reflect the individual exposures and might have caused some degree of exposure misclassification.

We observed that the effect magnitude of $PM_{2.5}$ peak increased when including $PM_{2.5}$ mean in the model (and vice versa, Supplementary Tables S1 and S2), which contradicted our original expectations. We expected that the estimated effects of $PM_{2.5}$ mean would fall when $PM_{2.5}$ peak was added to the model, because these two variables were highly corrected ($r = 0.95$) and they would carry the same information to some extent. Although we do not have any satisfactory explanations for this observation, we argue that $PM_{2.5}$ peak values may contain additional independent exposure information, which makes it possible for the current study to explore whether $PM_{2.5}$ peak can be used as a new exposure variable in mortality time series studies. In addition, the collinearity issue may exist by including both $PM_{2.5}$ mean and $PM_{2.5}$ peak in the same model. The collinearity would cause the effect estimates become either larger or smaller, especially when several other important covariates exist in the same model simultaneously.

In summary, this study suggests that the overall cardiovascular impacts of ambient $PM_{2.5}$ are related not only to average concentrations inhaled over a few days, but also to times when air pollutants rise to a peak level when concentrations may be high enough to overwhelm bodily defenses. We suggest that hourly peak $PM_{2.5}$ should be considered in both environmental control and health impact assessment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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