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Intraday effects of ambient PM$_1$ on emergency department visits in Guangzhou, China: a case-crossover study

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Abstract

Background

Short-term exposure to $PM_{2.5}$ has been widely associated with human morbidity and mortality. However, most up-to-date research was conducted at a daily timescale, neglecting the intra-day variations in both exposure and outcome. As an important fraction in $PM_{2.5}$, PM_1 has not been investigated about the very acute effects within a few hours.

Methods

Hourly data for size-specific PMs (i.e., PM_1, $PM_{2.5}$, and PM_{10}), all-cause emergency department (ED) visits and meteorological factors were collected from Guangzhou, China, 2015–2016. A time-stratified case-crossover design with conditional logistic regression analysis was performed to evaluate the hourly association between size-specific PMs and ED visits, adjusting for hourly mean temperature and relative humidity. Subgroup analyses stratified by age, sex and season were conducted to identify potential effect modifiers.

Results

A total of 292743 cases of ED visits were included. The effects of size-specific PMs exhibited highly similar lag patterns, wherein estimated odds ratio (OR) experienced a slight rise from lag 0–3 to 4–6 h and subsequently attenuated to null along with the extension of lag periods. In comparison with $PM_{2.5}$ and PM_{10}, PM_1 induced slightly larger effects on ED visits. At lag 0–3 h, for instance, ED visits increased by 1.49% (95% confidence interval: 1.18–1.79%), 1.39% (1.12–1.66%) and 1.18% (0.97–1.40%) associated with a 10-$\mu g/m^3$ rise, respectively, in PM_1, $PM_{2.5}$ and PM_{10}. We have detected a significant effect modification by season, with larger

PM_1-associated OR during the cold months (1.017, 1.013 to 1.021) compared with the warm months (1.010, 1.005 to 1.015).

Conclusions

Our study provided brand-new evidence regarding the adverse impact of PM_1 exposure on human health within several hours. PM-associated effects were significantly more potent during the cold months. These findings may aid health policy-makers in establishing hourly air quality standards and optimizing the allocation of emergency medical resources.

Keywords

PM_1; Hourly effects; Emergency department visits; Case-crossover design; China

Introduction

Ambient particulate matter has been linked to adverse health outcomes, including morbidity and mortality (Liu et al., 2019; Tian et al., 2019b). Reported by *State of Global Air 2019*, ambient particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) contributed to nearly three million deaths in 2017, and more than half of this disease burden fell on densely populated countries, such as China and India (Institute, 2019). China has been experiencing severe particulate pollution, particularly in metropolises such as Beijing and Guangzhou (Guo et al., 2016; Guo et al., 2018; Zhou et al., 2019). In China, $PM_{2.5}$ pollution ranked fourth in 2017 as a risk factor for both the magnitude of deaths and disability adjusted life years (DALYs) (Zhou et al., 2019). A large-scale modeling study in China estimated that 0.14 and 0.06 years of gain in life expectancy could be achieved by reducing concentrations of ambient $PM_{2.5}$ to 25 and 75 μg/m^3, respectively (Qi et al., 2020).

Numerous epidemiological studies found that long- and short-term exposures to ambient particulate matter with an aerodynamic diameter less than 10 μm (PM_{10}) or $PM_{2.5}$ are closely associated with increased morbidity and mortality, including but not limited to cardiovascular and respiratory diseases (Bhaskaran et al., 2011; Huang et al., 2019; Hvidtfeldt et al., 2019; Yin et al., 2020). For the short-term effects of PM, emergency department (ED) visits have been frequently used as a surrogate of acute disease events (Yorifuji et al., 2014a; Zhang et al., 2019b). Other proxies include hospital admissions (Liu et al., 2018), emergency ambulance calls (Ai et al., 2019) and so forth. However, most existing studies were conducted at a daily timescale, without considering the intra-day variations in both exposure and outcome (Lin et al., 2017b). In recent years, hourly associations between exposure to ambient fine and inhalable PMs and human morbidity have been received increasing attention, being focused on outcomes of hospital admission for cardiovascular and respiratory diseases (Bhaskaran et al., 2012; Chen et al., 2020a; Kim et al., 2015), as well as ambulance calls and ED visits (Ai et al., 2019; Chen et al., 2019a; Phung et al., 2020). Nevertheless, particulate matter with an aerodynamic diameter less than 1 µm (PM_1) has not been investigated in the aforementioned studies. Additionally, few studies investigated the associations between PM_1 and health outcomes at other longer timescales (e.g., daily), probably due to the lack of routine surveillance and very sparse data from ground measurements of PM_1 (Chen et al., 2018; Zhang et al., 2019b).

Compared with larger PM, PM_1 has higher surface-to-volume ratios and greater vascular penetration, and contains more toxins (Chen et al., 2017; Chen et al., 2019b; Yang et al., 2019). It is noteworthy that, consistently high $PM_1/PM_{2.5}$ ratios (i.e., range from 0.75 to 0.88) were reported across China (Chen et al., 2018; Guo et al., 2009; Zang et al., 2019), suggesting that PM_1 is a crucial driver of PM pollution and accounts for a large proportion of $PM_{2.5}$ (Wang et al., 2019; Zang et al., 2018). Another study in China also supported the notion that smaller size fractions of PM have more detrimental mortality impacts (Hu et al., 2018). Nevertheless, the influential mechanisms have yet to be well understood, especially for the associations of PM_1 with human health, which merits further analyses.

To fill the research gap, this study aimed to investigate the hourly associations between emergency department (ED) visits and exposures to ambient size-specific PMs, particularly PM_1, by adopting a time-stratified case-crossover design. Subgroup analyses stratified by age group and sex were conducted to identify potentially vulnerable subpopulations. We also assessed seasonal patterns of PM-related effects by dividing the whole study period into warm (April to September) and cold (October to March of next year) months.

Materials and methods

Study setting and population

Guangzhou, the capital of Guangdong province, China, has a typical subtropical humid monsoon climate. Because of the rapid development of economy and the increment of energy consumption during the past several decades, Guangzhou has been affected by severe air pollution. Huadu District People' Hospital is a large-scale tertiary general hospital, situated in an urban area of Huadu District in Guangzhou. In 2018, over one million permanent residents lived in this district (http://tjj.gz.gov.cn/). Our study included patients who presented to the emergency department (ED) of this hospital during 2015–2016.

Data collection

Individual records of all-cause emergency department visit through January 1, 2015 to December 31, 2016 were collected from Huadu District People's Hospital of Guangzhou, China. The primary characteristics of each case were extracted, including the specific time of admission, sex and age. We aggregated hourly counts of all-cause ED visits as the health outcome at each calendar day during our study period.

Ground-based measurements of hourly mean concentrations of ambient size-specific PMs (i.e., PM_1, $PM_{2.5}$, and PM_{10}) during 2015–2016 were obtained from Atmosphere Watch Network (CAWNET), run by the China Meteorological Administration (Chen et al., 2018). Due to the lack of routine surveillance and the sparse monitoring stations of PM_1 in China, our

PM$_1$ data were collected from two fixed stations which can monitor PM$_1$ in Guangzhou (Wei et al., 2019a). In order to facilitate comparability of risk assessments between size-specific PMs, we also used the same stations' data of PM$_{2.5}$ and PM$_{10}$ for exposure assessments. Owing to data unavailability of residential addresses for ED patients, we averaged these PM measurements from two fixed stations as the substitute of population-level particulate exposure in our analysis. At the same period, we also collected hourly average concentrations of gaseous pollutants (i.e., SO$_2$, NO$_2$, O$_3$ and CO) from the China National Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20035/), and hourly meteorological data (i.e., mean temperature and relative humidity) from the global hourly datasets of United States' National Centers for Environmental Information (NCEI, https://www.ncei.noaa.gov/).

In addition, we collected hourly precipitation data for Guangzhou, 2015-2016, from the ERA-5 reanalysis dataset on the Copernicus climate data store (ECMWF, ERA5 hourly data on single levels from 1979 to present, https://cds.climate.copernicus.eu). Then we transformed hourly precipitation data into a binary variable of rains (whether it rains or not in a specific hour).

Final dataset for analysis was comprised of these hourly ambient data and ED visits matched through the corresponding time windows (i.e., the same hour or hours). Due to monitor network system issues, 748 (4.3%) and 733 (4.2%) hours' data were not registered for size-specific PMs and gaseous pollutants. In our analysis, we thus excluded cases of ED visits during these exposure windows.

Statistical analyses

We adopted a time-stratified case-crossover (TSCC) design to separately investigate the hourly association between size-specific PMs (i.e., PM_1, $PM_{2.5}$, and PM_{10}) exposure and ED visits. Case-crossover design can be deemed to be an extension of the traditional case of matched case-control design, which incorporates the advantages of both case-control and cross-sectional study (Maclure, 1991). Time-stratified case-crossover (TSCC) design was proposed by Lumley and Levy in 2000 based on general case-crossover design, which used the day or days within the same time tier as the control group to control exposures (Lumley and Levy, 2000). TSCC design was widely employed to investigate the short-term effects of environmental factors (e.g., air pollution and extreme weather conditions) on adverse health outcomes, including morbidity and mortality (Bhaskaran et al., 2011; Di et al., 2017; Yorifuji et al., 2014a). In this study design, all cases act as their own controls meanwhile we used calendar month and year as fixed time strata, which can effectively control long-term trends and seasonality and effects of time-invariant individual-level confounders such as age, sex, behavior and metabolic factors (Lumley and Levy, 2000; Wei et al., 2019b). Moreover, to avoid impacts from days of the week and intra-day variation, we selected control periods from the same hour of the same day of the week in the calendar month of ED visits (Chen et al., 2020a; Phung et al., 2020). For each case, we assigned three or four matched controls that have not occurred of ED visits at the timescale.

A conditional logistic regression (CLR) was used to fit TSCC model and separately assess the associations between transient exposures to size-specific particulate matters and ED visits (Di et al., 2017; Wei et al., 2019b). In our analytical models, we used natural cubic spline (NS) function with three degrees of freedom (df) to fit the effects of hourly current temperature ($Temp_0$) and relative humidity (Rh_0). Then we introduced them as covariate terms to eliminate nonlinear confounding effects (Jiao et al., 2020; Zhang et al., 2019b). In this study, the conditional logistic regression model was implemented through Cox proportional hazard regression method (Le and Lindgren, 1988) and presented as below: $\ln[h(t,X)] = \ln[h_0(t)] + \beta(PMs) + NS(Temp_0, df = 3) + NS(Rh_0, df = 3)$, where t refers to the specific hour of interest; X refers to the record of ED visit; $h_0(t)$ and $h(t,X)$ represents the baseline and estimated hazard function at hour t, respectively; β refers to estimated coefficient for PMs and PMs refers to hourly mean concentrations of PM_1,$PM_{2.5}$ and PM_{10}; $NS(Temp_0)$ and $NS(Rh_0)$ are NS functions for $Temp_0$ and Rh_0, respectively.

Meanwhile, we examined the linearity hypothesis between size-specific PMs and ED visits by smoothing exposure-response curves using NS terms with three df for PM_1, $PM_{2.5}$ and PM_{10}. To better capture the very short-term effects on health from size-specific PMs, we divided exposure time windows into a set of lag periods (e.g., 0–3 h, 4–6 h and 7–12 h) up to 72 h before the event of ED visits (Kim et al., 2015). For instance, lag 0–3 h means the moving average concentration of 4 hours before the event of interest. Moreover, these lag periods were selected as a compromise between model parsimony and flexibility. In this study, the risk of ED visits was estimated and reported as odds ratio (OR) and corresponding 95% confidence interval (CI) associated with a 10-μg/m^3 increase in PM_1, $PM_{2.5}$ and PM_{10} concentrations at various lag periods, respectively.

Besides, we performed a string of subgroup analyses stratified by sex (i.e., male and female) and age (i.e., 0–14, 15–34, 35–64 and over 65 years) to identify potential susceptible subpopulations. These age strata comply with the age distribution of the study population and some previous literature (Jiao et al., 2020; Zhang et al., 2019b). Also, seasonal analyses of PM-associated effects were conducted by dividing the whole study period into warm (April to September) and cold (October to March of next year) months. In these subgroup analyses, a two-sample Z test (Zhang et al., 2020) and meta-regression methods (Guo, 2017; Tian et al., 2019b) were applied to assess whether age, sex, and season were sources of potential modification effects.

Sensitivity analyses

To verify the robustness of our findings, we changed the parameter specifications in our modeling strategies by (1) performing a two-pollutant analysis through separately including gaseous pollutants (i.e., SO_2, NO_2, O_3 and CO), (2) treating whether it rains or not in a specific hour as a binary covariate and including it in our main model, and (3) varying dfs from 3 to 6 for NCS function terms and exposure periods of meteorological factor (i.e., from lag 0 to lags 0–3 and 0–6 h). Moreover, we used the aforementioned meta-regression method to test the statistical significance of difference before and after adjustment.

All data analyses were run on R software (version 3.6.2). We used the “survival” package for conditional logistic regression modeling and the “mvmeta” package for meta-regression analysis. Two-sided tests with a p-value of less than 0.05 were considered to be statistically significant.

Results

Table 1 describes the basic characteristics of all-cause ED patients. A total of 292743 cases were involved, with hourly mean visits of 16.7 (standard deviation [SD], 12.1). Approximately 53.3% of patients were male and over two-thirds were young people aged less than 35 years old. Relatively more ED visits occurred in the warm months and accounted for 53.4% of total cases. Characteristics in seasonal patterns of ED visits were summarized in Table S1, stratified by sex and age group.

Table 2 outlines the distribution characteristics of ambient air pollution and meteorological factors during 2015–2016 in Guangzhou. Hourly mean (SD) concentrations were 26.7 (16.4) μg/m^3 for PM_1, 31.0 (18.3) μg/m^3 for $PM_{2.5}$ and 40.2 (23.4) μg/m^3 for PM_{10}, respectively. Annual average temperature and relative humidity was 23.4°C (Range: 2.5–37.5°C) and 74.9% (Range: 16.5–100%), respectively. Ambient levels of all pollutants were higher during the cold months, except for ozone (Table S2). Fig. 1 shows high correlations between size-fractional PMs, with Spearman correlation coefficients ranging from 0.93 to 0.98. Conversely, PMs were low-to-moderate correlated with gaseous pollutants and climate variables.

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Table 1 Basic characteristics of emergency department visits in Guangzhou, China, 2015–2016.

Group	Total		Hourly	
	Count (n)	Percentage (%)	Mean	SD
All	292793	100.0	16.7	12.1
Sex				
Male	161953	55.3	9.2	6.8
Female	130840	44.7	7.5	6.0
Age, years				
< 15	97508	33.3	5.6	5.5
15–34	90847	31.0	5.1	4.4
35–64	79796	27.3	4.5	3.4
≥ 65	24642	8.4	1.4	1.5
Season				
Warm	156247	53.4	17.8	12.5
Cold	136546	46.6	15.9	11.5

Abbreviations: SD, standard deviation; Warm season, April to September; Cold season, October to March of the next year.

Table 2 Hourly distributions in ambient air pollution and meteorological factors during 2015–2016 in Guangzhou.

Variable	Mean	SD	Min	Percentiles			Max
				25th	50th	75th	
Particulate pollutants							
PM_1, µg/m^3	26.7	16.4	0.6	14.1	23.5	35.4	121.5
$PM_{2.5}$, µg/m^3	31.0	18.3	1.0	17.1	27.3	40.7	164.1
PM_{10}, µg/m^3	40.2	23.4	1.1	22.7	35.3	53.1	223.7
Gaseous pollutants							
NO_2, µg/m^3	43.9	23.1	4.0	28.0	39.0	53.0	225.0
SO_2, µg/m^3	11.7	6.7	2.0	7.0	10.0	15.0	106.0
O_3, µg/m^3	43.3	44.8	1.0	12.0	27.0	58.0	334.0
CO, mg/m^3	1.0	0.3	0.4	0.8	0.9	1.1	3.0
Weather conditions							
Temperature, °C	23.4	6.7	2.5	18.5	25.0	28.0	37.5
Relative humidity, %	74.9	16.5	16.5	64.0	77.1	88.5	100.0

Abbreviations: SD, standard deviation; PM_1, particulate matter with aerodynamic diameter ≤1 µm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤10 µm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; CO, carbon monoxide.

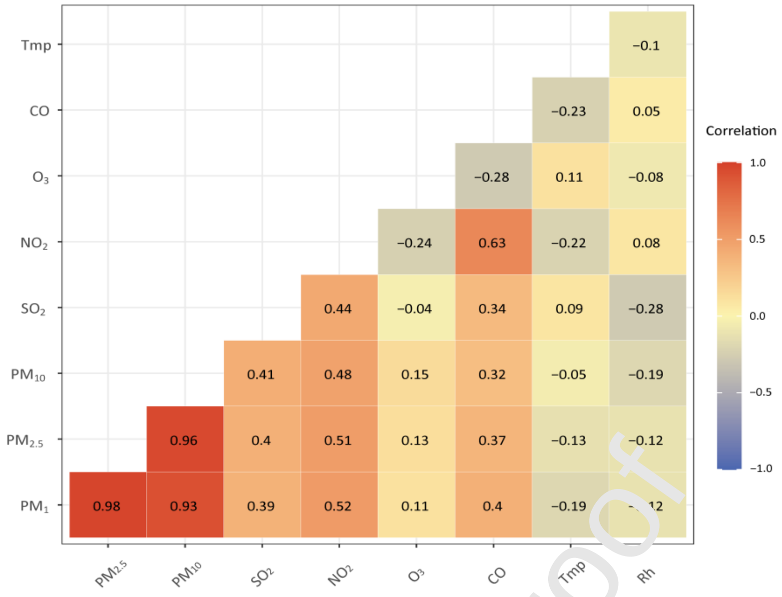


Fig. 1. Spearman correlation matrix between ambient air pollutants and meteorological factors in Guangzhou, China, 2015–2016. Abbreviations: PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; Tmp., temperature; Rh, relative humidity.

Fig. 2 manifests dose-response associations of all-cause ED visits with PM_1, $PM_{2.5}$ and PM_{10}, respectively. Size-fractional PMs' curves share approximate linearity and similar pattern with a steeper slope in the low concentrations. As illustrated in Fig. 3, transient exposures to PM_1, $PM_{2.5}$ and PM_{10} were significantly associated with increased risks of ED visits in the ensuing 48 hours. Also, the effects of size-specific PMs exhibited highly similar lag patterns, wherein estimated ORs experienced a slight rise from lag 0–3 to 4–6 h and subsequently attenuated to null along with the extension of lag periods. In comparison with $PM_{2.5}$ and PM_{10}, PM_1 induced slightly larger effects on ED visits. With a 10-μg/m^3 rise in PM exposure, for instance, risks at lag 0–3 h increased by 1.49% (95% CI: 1.18–1.79%) for PM_1, 1.39% (1.12–1.66%) for $PM_{2.5}$, and 1.18% (0.97–1.40%) for PM_{10}, respectively. Estimates for PM-associated ORs across various lag periods were detailed in Table S3.

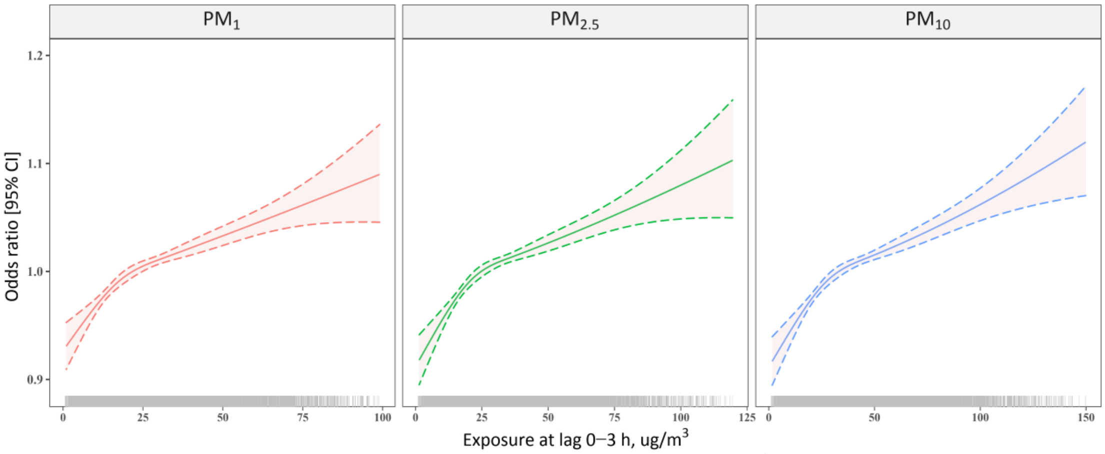


Fig. 2. Exposure-response curves for PM$_1$, PM$_{2.5}$ and PM$_{10}$ associated with all-cause ED visits at lag 0–3 h, respectively. Abbreviations: ED, emergency department; PM$_1$, particulate matter with aerodynamic diameter ≤1 µm; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm; PM$_{10}$, particulate matter with aerodynamic diameter ≤10 µm.

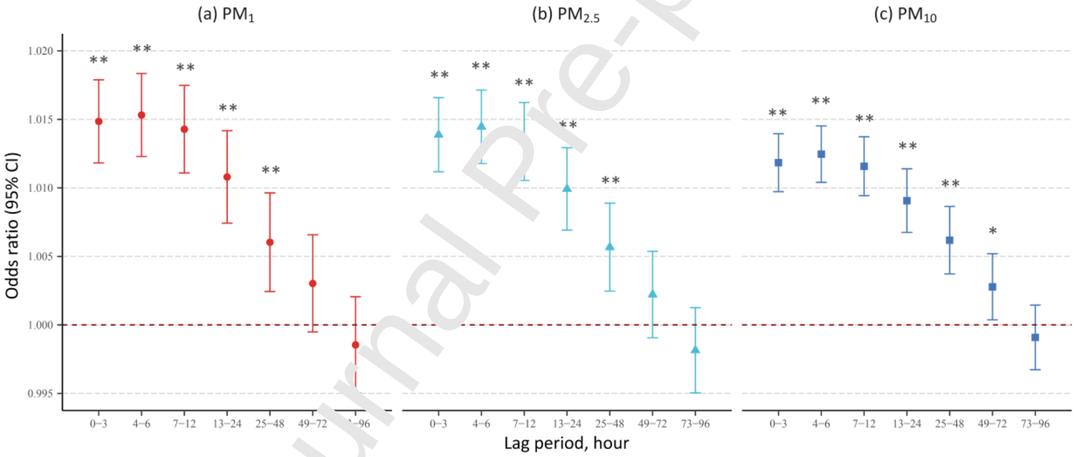
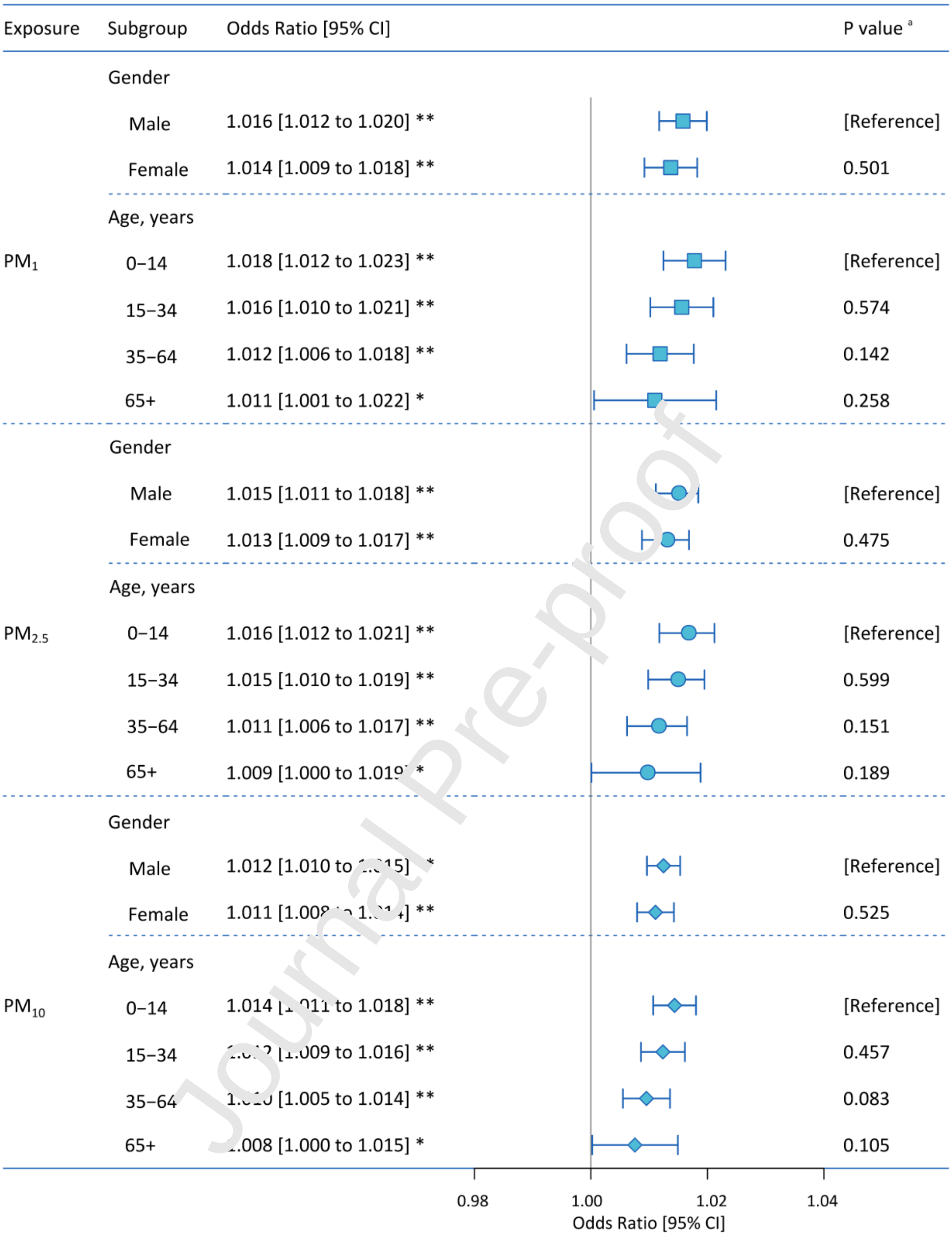


Fig. 3. Odds ratios (with 95% CIs) for all-cause ED visits in Guangzhou at various exposure hours, associated with per 10 µg/m^3 increase in PM$_1$ (a), PM$_{2.5}$ (b), and PM$_{10}$ (c). Notes: $*p < 0.05$; $**p < 0.001$. Abbreviations: CI, confidence interval; ED, emergency department; PM$_1$, particulate matter with aerodynamic diameter ≤1 µm; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm; PM$_{10}$, particulate matter with aerodynamic diameter ≤10 µm.

Fig. 4 shows OR estimates of subgroups stratified by sex and age. We identified remarkable associations between PM and ED visits in all subgroups, while no significant differences existed between genders as well as age groups. Specifically, ORs associated with a 10-µg/m^3 rise in PM$_1$ were comparable between males (1.016, 1.012 to 1.020) and females (1.014, 1.009 to 1.018), but were generally larger among children (1.018, 1.012 to 1.023) than older groups. Similar findings were also observed in associations of ED visits with $PM_{2.5}$ and PM_{10}.

Table 3 gives season-specific OR estimates at two specific lag periods of lag 0–3 and 0–6 h, associated with per 10-μg/m^3 increase in PM exposure. In total population, significant effects from exposure to PM_1, $PM_{2.5}$ and PM_{10} were found in both warm and cold months. However, warm-cold differences in PM effects were solely evident in PM_1 at lag 0–3 h (p-value = 0.033), with a stronger association in the cold months (OR=1.017, 95% CI: 1.013 to 1.021) than in the warm months (1.010, 1.005 to 1.015). Furthermore, in age groups except for children, the effects of hourly PMs on ED visits mostly exist in the cold months (Table S4). Compared with the all-age population, seasonal differences were more conspicuous in the age group of 15–34 years, with insignificance (p=0.061) only occurring in PM_{10} at lag 0–6 h. More details for seasonal analyses stratified by sex and age can be found in Table S4.

Sensitivity analysis demonstrates the robustness of our main findings. The OR estimates changed little (e.g., ranging from 1.015 to 1.014 for PM_1) when varying dfs and lag periods for temperature and humidity (Table S5). In our two-pollutant modeling analyses, the estimated associations did not change dramatically except for adjusting NO_2. For instance, PM_1-associated ORs significantly decreased from 1.015 (1.012 to 1.018) to 1.006 (1.002 to 1.010) after including NO_2 in the two-pollutant model.



Exposure	Subgroup	Odds Ratio [95% CI]	P value [a]
	Gender		
	Male	1.016 [1.012 to 1.020] **	[Reference]
	Female	1.014 [1.009 to 1.018] **	0.501
	Age, years		
PM_1	0–14	1.018 [1.012 to 1.023] **	[Reference]
	15–34	1.016 [1.010 to 1.021] **	0.574
	35–64	1.012 [1.006 to 1.018] **	0.142
	65+	1.011 [1.001 to 1.022] *	0.258
	Gender		
	Male	1.015 [1.011 to 1.018] **	[Reference]
	Female	1.013 [1.009 to 1.017] **	0.475
	Age, years		
$PM_{2.5}$	0–14	1.016 [1.012 to 1.021] **	[Reference]
	15–34	1.015 [1.010 to 1.019] **	0.599
	35–64	1.011 [1.006 to 1.017] **	0.151
	65+	1.009 [1.000 to 1.019] *	0.189
	Gender		
	Male	1.012 [1.010 to 1.015] **	[Reference]
	Female	1.011 [1.008 to 1.014] **	0.525
	Age, years		
PM_{10}	0–14	1.014 [1.011 to 1.018] **	[Reference]
	15–34	1.012 [1.009 to 1.016] **	0.457
	35–64	1.010 [1.005 to 1.014] **	0.083
	65+	1.008 [1.000 to 1.015] *	0.105

Fig. 4. Odds ratios (with 95% CIs) for ED visits in Guangzhou among subgroups stratified by sex and age, associated with per 10 μg/m^3 increase in exposure to PM_1, $PM_{2.5}$, and PM_{10} at lag 0–3 h. Notes: *p<0.05; **p<0.001; ^{a} p-value for difference between subgroups. Abbreviations: CI, confidence interval; ED, emergency department; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

Table 3 Season-specific ORs [95% CIs] of ED visits at lag 0–3 and 0–6 h, associated with per 10-µg/m^3 increase in PM exposures.

Group	**Season**	**0-3h**		**0-6h**	
		OR [95% CI]	P for interaction	OR [95% CI]	P for interaction
All	PM$_1$		0.033		0.053
	Cold	1.017 [1.013 to 1.021] **		1.017 [1.013 to 1.021] **	
	Warm	1.010 [1.005 to 1.015] **		1.011 [1.006 to 1.016] **	
	PM$_{2.5}$		0.103		0.183
	Cold	1.015 [1.011 to 1.018] **		1.015 [1.012 to 1.019] **	
	Warm	1.010 [1.006 to 1.014] **		1.012 [1.007 to 1.016] **	
	PM$_{10}$		0.109		0.265
	Cold	1.013 [1.010 to 1.015] **		1.013 [1.010 to 1.016] **	
	Warm	1.009 [1.006 to 1.012] **		1.011 [1.007 to 1.014] **	
Age 15–34					
	PM$_1$		0.007		0.016
	Cold	1.021 [1.014 to 1.028] **		1.021 [1.014 to 1.028] **	
	Warm	1.006 [0.998 to 1.015]		1.007 [0.998 to 1.016]	
	PM$_{2.5}$		0.019		0.036
	Cold	1.019 [1.013 to 1.025] **		1.019 [1.012 to 1.025] **	
	Warm	1.007 [0.999 to 1.015]		1.008 [1.000 to 1.016] *	
	PM$_{10}$		0.039		0.061
	Cold	1.015 [1.010 to 1.020] **		1.015 [1.010 to 1.020] **	
	Warm	1.007 [1.001 to 1.013] *		1.008 [1.002 to 1.014] *	

Abbreviations: OR, odds ratio; CI, confidence interval; ED, emergency department; PM$_1$, particulate matter with aerodynamic diameter ≤1 µm; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm; PM$_{10}$, particulate matter with aerodynamic diameter ≤10 µm; Warm season, April to September; Cold season, October to March of the next year. Notes: *$p < 0.05$; **$p < 0.001$.

Discussion

To the best of our knowledge, this is the first study concurrently assessing the associations between exposure to PM_1, $PM_{2.5}$ and PM_{10} and all-cause ED visits at a sub-daily timescale. In this study, we employed a time-stratified case-crossover design to evaluate acute effects from specific-PMs on human health. We found that transient exposures to ambient PM_1, $PM_{2.5}$ and PM_{10} significantly increased risks of ED visits in a few hours. Seasonal modification effects were detected in subgroup analyses, with PM_1-associated OR estimates substantially larger during the cold months.

Over the past years, some researchers reported hourly associations between exposures to ambient fine and inhalable PMs and human morbidity, being focused on outcomes of hospital admission for cardiovascular and respiratory diseases (Bhaskaran et al., 2012; Chen et al., 2020a; Kim et al., 2015), as well as ambulance calls and ED visits (Ai et al., 2019; Chen et al., 2019a; Phung et al., 2020). However, PM_1, a smaller particulate matter, has not been taken into account in the studies mentioned above. In our study, through using hourly mean concentrations of size-specific PMs as independent variables in analytic models, we incorporated the information of variation within a day or even a few hours.

Our results showed that increased all-cause ED visits were significantly associated with exposures to PM_1, $PM_{2.5}$ and PM_{10} within a few hours. Moreover, a mild and transient ascending trend in PM-associated ORs was observed from lag 0–3 to 4–6 h, followed by a descending trend at longer lags, suggesting that the first few hours may be the critical exposure window. These significant associations of interest remained up to 48 hours after exposures. Our findings were echoed with a case-crossover study of eleven cities in Japan (Phung et al., 2020) and another study in Shenzhen city, China (Chen et al., 2019a). The former study (Phung et al., 2020) revealed that transient exposure to ambient $PM_{2.5}$ in a few hours might trigger elevated all-cause emergency ambulance dispatches, and their results manifested that these effects remained significant until to 24 hours later. Furthermore, hourly associations between PMs (i.e., $PM_{2.5}$ and PM_{10}) and ED visits persisted for about 10 hours before the event of interest in the latter study (Chen et al., 2019a). Compared with the two studies above, our findings manifest longer sustained effects from specific-PMs on acute disease events, which might be explained by different demographic characteristics and pollutant levels. Nevertheless, the overall conclusion is still consistent, suggesting that daily air quality guidelines based on mean concentrations of air pollutants may be inadequate to protect human health (Lin et al., 2017a; Yorifuji et al., 2014b). Relevant studies are warranted in the future as references for the appropriate temporal scale of air quality standards.

The exposure-response relationships have a monotonic increasing trend, while we observed the steeper slope in low PM concentrations. This finding suggested that people may be more sensitive to adverse effects from ambient PMs at low levels, which is echoed with previous studies. A large time-series study in 184 major Chinese cities (Tian et al., 2019b) found that the dose-response curve increased sharply at low $PM_{2.5}$ concentrations without a discernible threshold. Another study (Liu et al., 2019) also reported that both curves were steeper at levels lower than 20 μg/m^3 for $PM_{2.5}$ and 40 μg/m^3 for PM_{10}. More investigations on hourly associations between ambient PM and human health are needed, which may provide a valuable reference for establishing hourly air quality limits.

Compared with $PM_{2.5}$ and PM_{10}, PM_1 has been considered with more detrimental impacts on human health, likely owing to the higher surface-to-volume ratios, greater vascular penetration, and more toxins (Chen et al., 2017; Franck et al., 2011; Wu et al., 2020; Yin et al., 2020) . A recent nationwide study (Yin et al., 2020) found that PM_1-related excess CVD risk (0.29%, 95%CI: 0.12 to 0.47%) was significantly higher than $PM_{2.5}$ (0.24%) and PM_{10} (0.21%). A multi-city study (Chen et al., 2017) also supported this notion and compared the effects of specific-PMs (i.e., PM_1, $PM_{2.5}$ and $PM_{1-2.5}$) on ED visits. Their findings suggested that most of ED visits attributed to $PM_{2.5}$ are accounted for PM_1, in that no associations between $PM_{1-2.5}$ and ED visits. In the present study, our comparative analyses also showed that smaller PM fraction exhibited more adverse effects on risks of ED visits. Specifically, risks for ED visits at lag 0-3 h increased by 1.49% (95% CI: 1.18–1.79%), 1.39% (1.12–1.66%) and 1.18% (0.97–1.40%) associated with a 10-μg/m^3 increment in PM_1, $PM_{2.5}$ and PM_{10} concentrations, respectively. Previously proposed biological mechanisms for the associations between particulate matter and acute disease events involved PM-augmented systematic inflammation and oxidative stress (Chen et al., 2020a; Lin et al., 2016; Yang et al., 2018). More mechanism researches are recommended to elucidate the exact biological pathway about the associations between ambient PM and acute disease events, particularly in smaller matters (e.g., PM_1 and ultrafine particles).

Prior evidence about PM effects modified by age and sex were mixed. In the present study, we observed comparable PM-associated effects between genders, in line with a nationwide time-series study (Tian et al., 2019a) on adult hospital admissions in 200 Chinese cities. However, another multi-city study (Chen et al., 2017) on daily ED visits reported higher relative risks of PM_1 and $PM_{2.5}$ on women. Kan and colleagues (Kan et al., 2008) also found that females were more vulnerable to ambient air pollution. Further research is needed to explore the source of sex differences in PM effects. In terms of age, we found generally more substantial impacts on children than older groups. Meanwhile these adverse effects diminished with age. Nevertheless, no significant differences between age groups were found, although children (Chen et al., 2019a; Chen et al., 2017; Zhang et al., 2019b) and the elderly (Hassanvand et al., 2017; Tian et al., 2019a) have been widely reported as vulnerable subpopulations for ambient particulate matters.

Besides, we observed significantly stronger PM-associated effects during the cold months, coincided with previous studies on ambulance emergency call-outs (Chen et al., 2020b), ED visits (Chen et al., 2019a) and hospital admissions for respiratory diseases (Zhang et al., 2019a). However, a study on ambulance emergency calls (Ai et al., 2019) found remarkably larger effects of $PM_{2.5}$ on all-cause and cardiovascular morbidity in the warm months, and slightly stronger effects on respiratory morbidity in the cold months. Furthermore, no substantially warm-cold differences were detected in another study on hourly pollutants level and the risk of myocardial infarction in England and Wales (Bhaskaran et al., 2011). These inconsistencies across studies might be attributable to discrepancies in regions, exposure patterns, pollution source and chemical compositions, as well as demographic characteristics (Shah et al., 2013; Zhang et al., 2019b). In addition, the exposure-response curves (Fig. 2) with a slower slope in the high concentrations suggested that more severe PM emissions in the cold months could not be possibly responsible for the more harmful PM effects during the cold months. More sophisticated researches are needed to further clarify effects modification by warm-cold season.

Several limitations should be noted in this study. First, our exposure assessments of ambient PMs were averaged from the fixed stations, rather than individual measurements. This substitution may entail exposure misclassification (Zeger et al., 2000) and then underestimate the health effects of particulate matter (Li et al., 2019; Li et al., 2015). Second, our ED data were originated from one large-scale general hospital in Guangzhou city, so the results should be generalized to other regions with caution. Additionally, due to a lack of the corresponding classification of diseases, we were unable to investigate associations between size-specific PMs and cause-specific ED visits. Similarly, we cannot exclude ED visits caused by accident such as road traffic injuries and fires. Hence, we may underestimate the impacts of PMs on hourly ED visits to some extent (Cao et al., 2009).

Conclusions

In summary, we found very short-term impacts of ambient particulate matters on human health. Specifically, exposures to size-specific PMs may elevate risks of acute disease events in a few hours, and PM_1 entailed slightly stronger effects. In the cold months, these adverse effects were remarkably larger.

This study added to the evidence of PM_1 detrimental impact on human health at the hourly timescale, which may provide an informative reference in the establishment of hourly air quality standards and optimization of emergency medical resources. Additionally, this is a first study assessing detrimental effects of PM_1 of sub-daily exposures, thus the generalizability of our findings warrants further verification in the future research. To better alleviate disease burdens caused by ambient particulate matter, health policy makers and healthcare provider should take into consideration sub-micrometric and ultrafine particles, as well as finer temporal scales.

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Author Contributions

Yunquan Zhang conceived and designed the study; Jiaying Fang, Jing Wei, Yimeng Song, Yuanyuan Zhang and Lu Wang collected and cleaned the data; Linjiong Liu and Yunquan Zhang performed the data analysis and drafted the original manuscript; Fujian Song, Hung Chak Ho, Zhiming Yang and Chengyang Hu helped revise the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare they have no competing financial interests.

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Table 1 Basic characteristics of emergency department visits in Guangzhou, China, 2015–2016.

Group	Total		Hourly	
	Count (n)	Percentage (%)	Mean	SD
All	292793	100.0	16.7	12.1
Sex				
Male	161953	55.3	9.2	6.8
Female	130840	44.7	7.5	6.0
Age, years				
< 15	97508	33.3	5.6	5.5
15–34	90847	31.0	5.1	4.4
35–64	79796	27.3	4.5	3.4
≥ 65	24642	8.4	1.4	1.5
Season				
Warm	156247	53.4	17.8	12.5
Cold	136546	46.6	15.9	11.5

Abbreviations: SD, standard deviation; Warm season, April to September; Cold season, October to March of the next year.

Table 2 Hourly distributions in ambient air pollution and meteorological factors during 2015–2016 in Guangzhou.

Variable	Mean	SD	Min	Percentiles			Max
				25th	50th	75th	
Particulate pollutants							
PM_1, µg/m^3	26.7	16.4	0.6	14.1	23.5	35.4	121.5
$PM_{2.5}$, µg/m^3	31.0	18.3	1.0	17.1	27.3	40.7	164.1
PM_{10}, µg/m^3	40.2	23.4	1.1	22.7	35.3	53.1	223.7
Gaseous pollutants							
NO_2, µg/m^3	43.9	23.1	4.0	28.0	39.0	53.0	225.0
SO_2, µg/m^3	11.7	6.7	2.0	7.0	10.0	15.0	106.0
O_3, µg/m^3	43.3	44.8	1.0	12.0	27.0	58.0	334.0
CO, mg/m^3	1.0	0.3	0.4	0.8	0.9	1.1	3.0
Weather conditions							
Temperature, °C	23.4	6.7	2.5	18.5	25.0	28.0	37.5
Relative humidity, %	74.9	16.5	16.5	64.0	77.1	88.5	100.0

Abbreviations: SD, standard deviation; PM_1, particulate matter with aerodynamic diameter ≤1 µm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤10 µm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; CO, carbon monoxide.

Table 3 Season-specific ORs [95% CIs] of ED visits at lag 0–3 and 0–6 h, associated with per 10-μg/m^3 increase in PM exposures.

Group	**Season**	**0-3h**		**0-6h**	
		OR [95% CI]	P for interaction	OR [95% CI]	P for interaction
All	PM$_1$		0.033		0.053
	Cold	1.017 [1.013 to 1.021] **		1.017 [1.013 to 1.021] **	
	Warm	1.010 [1.005 to 1.015] **		1.011 [1.006 to 1.016] **	
	PM$_{2.5}$		0.103		0.183
	Cold	1.015 [1.011 to 1.018] **		1.015 [1.012 to 1.019] **	
	Warm	1.010 [1.006 to 1.014] **		1.012 [1.007 to 1.016] **	
	PM$_{10}$		0.109		0.265
	Cold	1.013 [1.010 to 1.015] **		1.013 [1.010 to 1.016] **	
	Warm	1.009 [1.006 to 1.012] **		1.011 [1.007 to 1.014] **	
Age 15–34					
	PM$_1$		0.007		0.016
	Cold	1.021 [1.014 to 1.028] **		1.021 [1.014 to 1.028] **	
	Warm	1.006 [0.998 to 1.015]		1.007 [0.998 to 1.016]	
	PM$_{2.5}$		0.019		0.036
	Cold	1.019 [1.013 to 1.025] **		1.019 [1.012 to 1.025] **	
	Warm	1.007 [0.999 to 1.015]		1.008 [1.000 to 1.016] *	
	PM$_{10}$		0.039		0.061
	Cold	1.015 [1.010 to 1.020] **		1.015 [1.010 to 1.020] **	
	Warm	1.007 [1.001 to 1.013] *		1.008 [1.002 to 1.014] *	

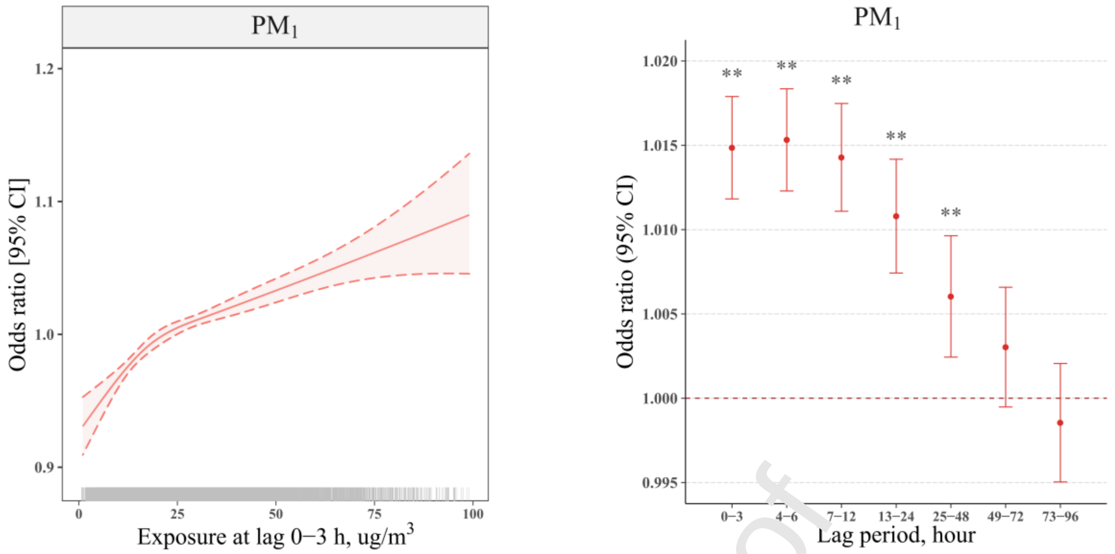
Abbreviations: OR, odds ratio; CI, confidence interval; ED, emergency department; PM$_1$, particulate matter with aerodynamic diameter ≤1 μm; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM$_{10}$, particulate matter with aerodynamic diameter ≤10 μm; Warm season, April to September; Cold season, October to March of the next year. Notes: *$p < 0.05$; **$p < 0.001$.

Credit Author Statement

Yunquan Zhang: Conceptualization, Methodology, Data Curation, Writing - Original Draft, Formal analysis. Linjiong Liu: Formal analysis, Writing - Original Draft, Writing - Review & Editing Visualization; Fujian Song: Writing - Review & Editing. Jiaying Fang: Resources. Jing We: Resources. Hung Chak Ho: Writing - Review & Editing. Yimeng Song: Resources. Yuanyuan Zhang: Data Curation. Lu Wang: Data Curation. Zhiming Yang: Writing - Review & Editing. Chengyang Hu: Writing - Review & Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Graphical abstract

Highlights

- First study to assess detrimental effects of PM_1 at a sub-daily timescale.
- Exposure to ambient PMs will elevate risks of ED visits in a few hours.
- PM_1 can induce slightly stronger effects compared with $PM_{2.5}$ and PM_{10}.
- Significantly more potent PM-associated effects during the cold months.