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Particulate matter pollution and asthma mortality in China: A nationwide time-stratified case-crossover study from 2015 to 2020

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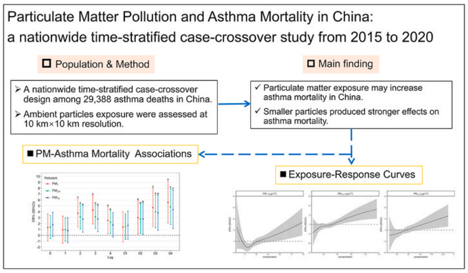
HIGHLIGHTS

- Submicron particulate matter exposure may increase asthma mortality in China.
- Smaller particles produced stronger effects on asthma mortality.
- Risk of asthma mortality related to PM exists even at low concentration levels.

GRAPHICAL ABSTRACT



Particulate Matter Pollution and Asthma Mortality in China:
a nationwide time-stratified case-crossover study from 2015 to 2020

☐ Population & Method

➢ A nationwide time-stratified case-crossover design among 29,388 asthma deaths in China.

➢ Ambient particles exposure were assessed at 10 km×10 km resolution.

☐ Main finding

✓ Particulate matter exposure may increase asthma mortality in China.

✓ Smaller particles produced stronger effects on asthma mortality.

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ABSTRACT

Background: A national and comprehensive evaluation is lacking on the relationship between short-term exposure to submicron particulate matter (PM_1) pollution and asthma mortality.
Methods: Data was obtained from 29,553 asthma deaths from the China National Mortality Surveillance System from 2015 to 2020. We used a bilinear interpolation approach to estimate each participant's daily ambient particulate matter pollution and meteorological variables exposure based on their geocoded residential address and a 10 km × 10 km grid from China High Air Pollutants and the fifth generation of European ReAnalysis-Land

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Abbreviations: CHAP, China High Air Pollutants; ERA5, The fifth generation of European ReAnalysis; ICD-10, The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems; ER, Excess risk; CI, Confidence interval; IQR, interquartile range; PM_1: particulate matter with aerodynamic diameter less than or equal to 1 μm, $PM_{2.5}$: particulate matter with aerodynamic diameter less than or equal to 2.5 μm; PM_{10}: particulate matter with aerodynamic diameter less than or equal to 10 μm, O_3: Ozone; NO_2: Nitrogen dioxide, SO_2: Sulfur dioxide; CO, Carbon monoxide.

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Asthma
Mortality
Particle size

reanalysis data set. The associations were estimated using a time-stratified case-crossover design and conditional logistic regressions.

Results: Our results revealed significant associations between short-term exposure to various particulate matter and asthma mortality. The 5-day moving average of particulate matter exposure produced the most pronounced effect. Compared to fine particulate matter ($PM_{2.5}$) and inhalable particulate matter (PM_{10}), significantly stronger effects on asthma mortality related to PM_1 pollution were noted. The ERs% for asthma mortality associated with each interquartile range (IQR) increase of exposures to PM_1 (IQR: 19.2 μg/m^3) was 5.59% (95% CI: 2.11–9.19), which is 14% and 22% higher than that for $PM_{2.5}$ (IQR: 32.0 μg/m^3, 4.82% (95% CI: 1.84–7.90)) and PM_{10} (IQR: 52.2 μg/m^3, 4.37% (95% CI: 1.16–7.69)), respectively. The estimates remained consistent in various sensitivity analyses.

Conclusions: Our study provided national evidence that acute exposures to various ambient particulate matter pollution can increase mortality due to asthma in China, highlighting stronger associations with ambient PM_1 than $PM_{2.5}$ and PM_{10}. China needs to adjust the current ambient air quality standards urgently and pay greater attention to the adverse health effects of PM_1.

1. Introduction

Asthma remains one of the most important non-communicable diseases (NCDs), characterized by variable airflow obstruction, bronchial hyperresponsiveness, and airway inflammation(Caffrey et al., 2020; Global Asthma Network, 2018). It is estimated that more than 260 million people globally were affected by asthma in 2019, and compared to 2015, its age-standardized prevalence has risen 6.6%(GBD Diseases and Injuries Collaborators, 2020).

Ambient particulate matter pollution has been a severe public health issue worldwide.(World Health Organization, 2018) In 2019, ambient particulate matter pollution led about 1.4 million deaths in China(GBD Diseases and Injuries Collaborators, 2020). Previous epidemiological studies have focused on the adverse effects of fine particulate matter ($PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 μm) and inhalable particulate matter (PM_{10}, particulate matter with an aerodynamic diameter $\leq$10 μm)(Doiron et al., 2019; Hu et al., 2022). Acute exposure to particulate matter was associated with increased morbidity (Liu et al., 2021; Lu et al., 2020) and exacerbation of asthma symptoms (Guaita et al., 2011; Samoli et al., 2011). The relationship between the exposure and mortality due to asthma has rarely been studied due to the small number of asthma deaths(Saez et al., 1999). One recent study from China reported that short-term $PM_{2.5}$ exposures were significantly associated with asthma mortality using data from the Chinese province of Hubei(Liu et al., 2019). Unfortunately, the study was hampered by small sample sizes and restricted study areas, which limited their generalizability. In addition, the study did not analyze the relationship between submicronic particulate matter (PM_1, particulate matter with an aerodynamic diameter$\leq$ 1 μm) and asthma mortality due to its limited data. The most recent research indicated that PM_1 contributed 77–86% of the $PM_{2.5}$ concentration in China(Chen et al., 2018) and particulate matter of smaller size fractions might pose a larger health risk(Chen et al., 2017; Lin et al., 2016a; Meng et al., 2013; Zhang et al., 2021). Some epidemiological studies showed that stronger associations of ambient PM_1 than of larger particles with asthma development(Hu et al., 2022; Yang et al., 2018; Zhang et al., 2021). However, the relationship between asthma mortality and PM_1 remained largely unknown worldwide due to a lack of ground measurement(Hu et al., 2018; Yin et al., 2020). National data is needed to explore and clarify particulate matter's overall effect on asthma mortality.

To fill these research gaps, we conducted this nationwide study to quantify the exposure-response relationship between acute exposure to particulate matter pollution including PM_1, $PM_{2.5}$, PM_{10} and asthma mortality using sufficient surveillance data in China from 2015 to 2020.

2. Methods

2.1. Asthma mortality data

We obtained asthma mortality data from the National Mortality Surveillance System, which is managed by the Chinese Center for Disease Control and Prevention. A total of 29,553 deaths due to asthma were obtained from January 1, 2015 to December 31, 2020. The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10: J45 and J46) was used to assess the underlying cause of death and confirm mortalities due to asthma. The detailed descriptions of the National Mortality Surveillance System were published elsewhere(Liu et al., 2016). Briefly, this system is comprised of 605 counties or districts from all 31 mainland provinces, municipalities, and autonomous regions based on multi-stage stratified sampling, covering over 300 million residents (24% of the total population). Data from this system, proven to be nationally and provincially representative, have been widely used in policy formulation and disease burden assessment in China(Liu et al., 2016; Zhou et al., 2016). For each asthma mortality, we collected data on sex, age at death, permanent residential address, education level, and date of death.

2.2. Exposure data

We used the China High Air Pollutants (CHAP) 10 km × 10 km daily grid dataset as the data source for assessing short-term exposure to pollutants, including PM_1, $PM_{2.5}$, PM_{10}, ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO)(Wei et al., 2019, 2020; Wei et al., 2021a,b; Wei, 2020). CHAP is a full-coverage, high-resolution, high-accuracy, and ground-level air pollutant data source. Using a combination of advanced satellite remote sensing and space-time models, the cross-validation coefficients for the determination of PM_1, $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO were 0.83, 0.91, 0.86, 0.87, 0.84, 0.84 and 0.80, respectively and the root mean square errors were 9.25 μg/m^3, 12.67 μg/m^3, 24.34 μg/m^3, 17.10 μg/m^3, 7.99 μg/m^3, 10.07 μg/m^3 and 0.29 mg/m^3, respectively(Wei et al., 2019, 2020; Wei et al., 2021a,b; Wei, 2020). The CHAP data set provides concentrations of PM_1, $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO in China on a daily basis from 2015 to 2020. To ensure the stability and accuracy of the exposure data, we excluded air pollutant data for Tibet, Xinjiang and some parts of Heilongjiang province and asthma deaths in these areas were not included in our final analysis. PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO concentrations were measured using daily averages, while O_3 was measured using maximum 8-h averages.

We also obtained daily data on meteorological variables (temperature and relative humidity) measured at 10 km × 10 km grids from the fifth generation of European ReAnalysis (ERA5)-Land reanalysis data set (Muoz-Sabater et al., 2021). These meteorological variables were estimated using state-of-the-art land surface modeling techniques.

2.3. Matching asthma cases with exposure using bilinear interpolation approach

We used a two-stage assessment strategy to evaluate exposure to air pollutants and meteorological variables for asthma death cases. In the first stage, we obtained the latitudes and longitudes of each asthma death case using their residential addresses and then a geocoding programming interface provided by Baidu Maps API (http://lbsyun.baidu.com/), a leading mapping, navigation, and location-based service provider in China. The accuracy of residential addresses and geocoding were enhanced by including the province and cities identified using the postal codes of the death cases. Cases with latitudes and longitudes located outside of the provinces were excluded to eliminate bias caused by outlier locations.

In the second stage, we used bilinear interpolation to estimate the exposure to air pollutants and meteorological variables. This algorithm enhanced the spatial resolution of environmental variables at a specific location by calculating a weighted average of the nearest four grids(Cao et al., 2021; Dong et al., 2020). In locations where fewer than four grids were available (for example, islands or coastal cities), we used the available grids and re-calculated the weights so that the weights summed up to one. These locations accounted for less than 1% of our sample and each had at least one measure similar to a nearby air pollution level and we therefore decided to include them in our final sample.

2.4. *Case-crossover study design*

We used a time-stratified case-crossover study to analyze the relationship between the short-term exposure and asthma mortality(Liu et al., 2019). Estimating referent exposures on the days before or after the date of the event allows each case to serve as his or her own control; this study design accounts for individual-level characteristics and potential confounders that remain temporally constant. The estimates represent the acute triggering effect of air pollution on the outcome.

The case day was the date of death; days with the same year, month, and day of week as the case day were designated as control days to control for the effects of time trends, seasonality, and day of the week. With our time-stratified case-crossover design, each case day was assigned three to four control days that fell on the same weekday in the given month. We chose 99,690 control days for the 29,388 asthma death cases in the analyses. The ethics committee at the School of Public Health, Sun Yat-sen University, approved the study with a waiver of informed consent.

2.5. *Statistical analysis*

The correlation between air pollutants and meteorologic conditions was measured using the Spearman correlation coefficient. Conditional logistic regressions were used to estimate the exposure-response relationships between acute exposures to various particulate matter of different lag periods and asthma mortality. Natural cubic spline functions with degrees of freedom (df) = 5 of daily mean temperature and relative humidity were included to account for the possible confounding (Cai et al., 2022). We introduced each particulate matter as a continuous variable in its own separate model, and estimated excess risks (ERs) and their 95% confidence intervals (CIs) for asthma mortality with each interquartile range (IQR) increase of exposure to PM_1, $PM_{2.5}$ and PM_{10}. $ER = [\exp(\beta \times IQR) - 1] \times 100\%$, where β is the exposure-response relationship coefficient obtained by conditional logistic regression. A natural cubic spline function (df = 4) of particulate matter exposure was incorporated into the model to test for the nonlinearity of the association between pollutants and asthma mortality and visualize its exposure-response relationship.

We analyzed the effects across different lag structures, including single-day lags from lag0 to lag7 and moving average of multi-day lags of lag01 (the day and previous one day) and lag07 (the day and previous seven days). We performed subgroup analyses stratified by sex, age (<75 years and ≥75 years), season (warm: May to October and cold: November to April), marital status (unmarried, married and divorced/widowed), urbanicity (urban and rural) to identify potentially susceptible populations and examine their possible effect modifications. Modification was tested for by comparing strata-specific estimates of ERs. The effect modification was then tested by comparing the strata-specific ER estimates using the point estimate and standard error(Liu et al., 2019).

We conducted multiple sensitivity analyses to test the robustness of the results. We fitted two-pollutant models and used the likelihood ratio test to compare the results. Additionally, we conducted the analyses in a subsample from 2015 to 2019 to exclude the effect of the COVID-19 pandemic in the year of 2020 on both the level of particulate matter pollution(Chen et al., 2020) and the development and deaths of asthma diseases(Skevaki et al., 2020). We also set natural cubic spline functions with different degrees of freedom for daily mean temperature and relative humidity as sensitivity analysis.

All analyses were performed with SAS (version 9.4) and R (version 4.1.1). A *p*-value was reported as two-sided values and regarded statistically significant if it is less than 0.05.

3. Results

3.1. *Descriptive results*

We initially identified 29,553 asthma deaths during the study period. We excluded three cases due to incomplete information on home address and 162 cases lacking air pollution data; the remaining 29,388 (99.4%) cases were included in the final data analyses (Table 1). Of the 29,388 cases, 56.9% were males, 60.3% were married, 92.8% had a low education level, 57.6% died in the cold season and 59.1% lived in rural areas (Fig. 1). Table S1 depicts the descriptive statistics for seven pollutants during case and control days by sex, age group, marital status, season, and urban/rural. The median concentrations of PM_1, $PM_{2.5}$ and PM_{10} in cold season were 31.5 $\mu g/m^3$, 46.3 $\mu g/m^3$ and 76.3 $\mu g/m^3$, respectively. A total of 99,690 control days were matched to the death cases, resulting in an average of 3.4 control days for each case day. The mean concentrations of particulate matter on case day were 30.0 $\mu g/m^3$ for PM_1, 45.4 $\mu g/m^3$ for $PM_{2.5}$ and 75.1 $\mu g/m^3$ for PM_{10}. The daily mean temperature was 14.3 °C and the relative humidity was 69.0%. Compared with the control days, concentration of air pollutants was slightly higher on case days (Table 2). Table S2 summarizes the spearman correlation coefficients between different particulate matter and meteorologic factors.

Table 1
Characteristics of study population, 2015–2020.

Baseline Characteristic	No. (%)
Overall	129,078 (100)
Case days	29,388 (22.8)
Control days	99,690 (77.2)
Sex	
Male	16,722 (56.9)
Female	12,666 (43.1)
Age group (years)	
<65	5316 (18.1)
65–74	5149 (17.5)
75–84	10,782 (36.7)
>84	8141 (27.7)
Education	
Junior High school and below	27,260 (92.8)
High school	1608 (5.5)
College degree or above	515 (1.7)
Marital status	
Unmarried	1042 (3.6)
Married	17,709 (60.3)
Divorced/Widowed	10,492 (35.7)
Season	
Cold	16,935 (57.6)
Warm	12,453 (42.4)
Urban or Rural	
Urban	12,005 (40.9)
Rural	17,383 (59.1)

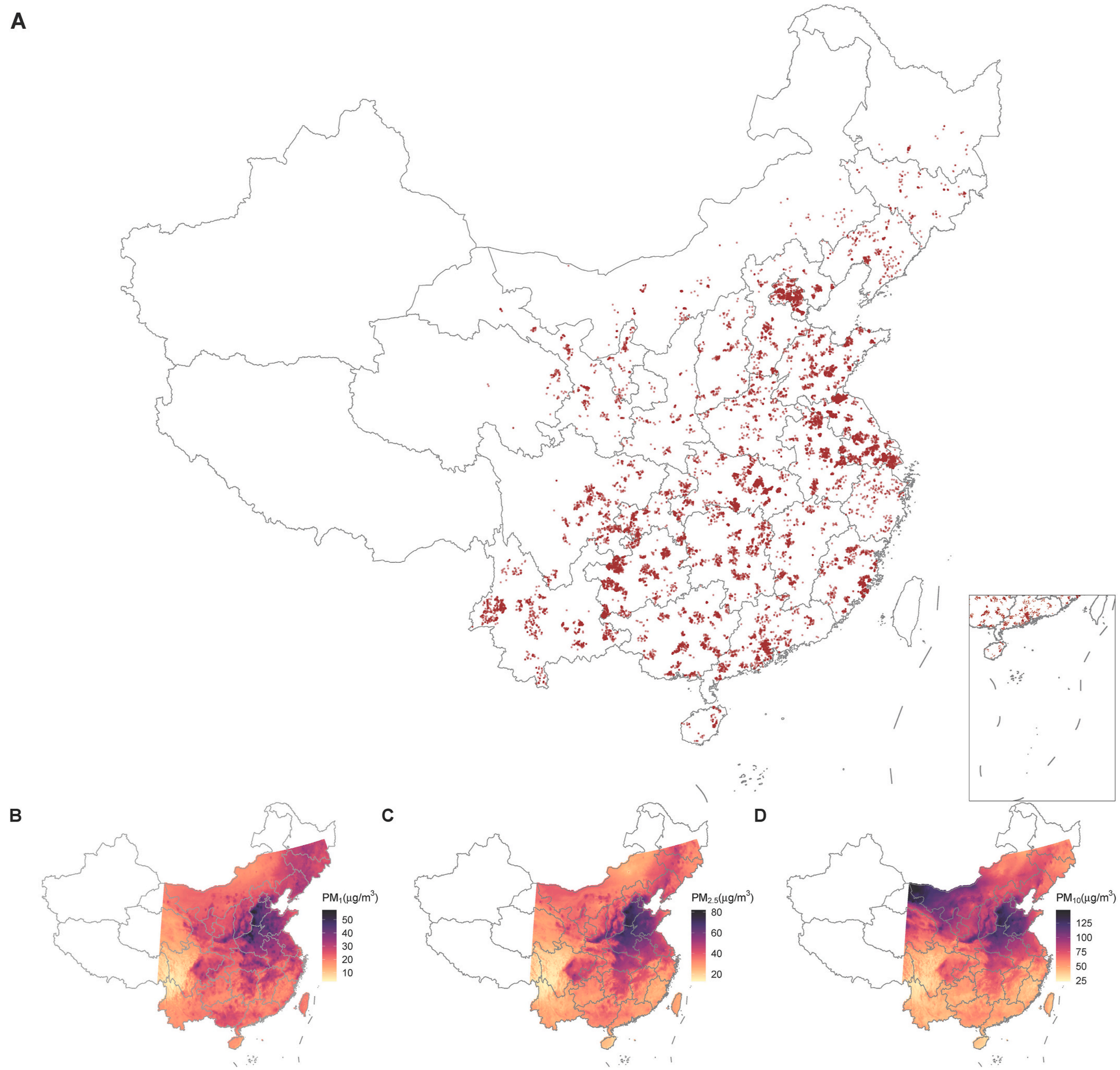

Fig. 1. (A) Spatial distribution of deaths attributable to asthma in China, 2015) to 2020 (N = 29,388). Each point indicates an asthma death case. **(B–D)** Geographical maps of annual mean levels of ambient air pollution (PM_1 for Fig. 1B, $PM_{2.5}$ for Fig. 1C, PM_{10} for Fig. 1D) in China from 2015 to 2020. Abbreviations: PM_1, particulate matter with an aerodynamic diameter $\leq$ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter $\leq$10 μm.

3.2. *Regression results*

Most lag structures of PM_1, $PM_{2.5}$ and PM_{10} produced statistically significant associations (Fig. 2). The risk for a single-day lag pattern was maximal at lag-day 2-3; overall, multi-day exposures (lag01 to lag04) usually produced greater effects than single-day exposures (lag0-4), and the lag 04-day exposure produced the most pronounced effect. Each IQR increase in the 5-day moving average of PM_1, $PM_{2.5}$ and PM_{10} concentrations was significantly associated with increased asthma mortality. Compared to $PM_{2.5}$ and PM_{10}, significantly stronger effects on asthma mortality related to PM_1 pollution were noted. The ERs% for asthma mortality associated with each IQR increase of exposures to PM_1 (IQR: 19.2 μg/m^3) was 5.59% (95% CI: 2.11–9.19), which is 14% and 22% higher than that for $PM_{2.5}$ (IQR: 32.0 μg/m^3, 4.82% (95% CI: 1.84–7.90)) and PM_{10} (IQR: 52.2 μg/m^3, 4.37% (95% CI: 1.16–7.69)), respectively. The ERs (95% CI) for asthma mortality associated each 10 μg/m^3 increase of exposures to particulate matter pollution are summarized in Fig. S1. As shown in different lag structures in Fig. S2, even if we used longer lag day structures, the estimated results were still significant. Fig. 3 shows the concentration–response relationships between various particulate matter and asthma mortality on lag 04 day. The smoothing curves of the relationships between various pollutants and asthma mortality were approximately linear.

Table 2

Distribution of air pollutants and meteorologic factors during case and control days in China, 2015–2020.

	Mean	SD	Min	25th	Median	75th	Max
Case days							
Air pollutant							
PM_1, μg/m^3	30.0	18.9	0.8	17.8	25.8	37.0	262.0
$PM_{2.5}$, μg/m^3	45.4	32.9	1.3	24.3	36.3	56.4	462.6
PM_{10}, μg/m^3	75.1	51.7	2.3	42.2	62.4	94.5	2431.8
O_3, μg/m^3	86.9	40.3	3.7	58.5	79.9	109.4	305.6
NO_2, μg/m^3	30.7	16.9	1.0	18.8	26.5	38.6	175.0
SO_2, μg/m^3	16.8	15.6	0.4	8.8	12.6	19.2	373.6
CO, mg/m^3	1.0	0.4	0.03	0.7	0.9	1.1	8.4
Meteorological factors							
Temperature, °C	14.3	9.8	−30.1	6.9	15.0	22.4	35.2
Relative humidity, %	69.0	17.8	0.3	59.0	72.7	82.5	99.9
Control days							
Air pollutant							
PM_1, μg/m^3	29.9	18.8	0.9	17.8	25.7	36.9	263.0
$PM_{2.5}$, μg/m^3	45.2	32.8	1.4	24.1	36.0	56.1	449.4
PM_{10}, μg/m^3	74.7	49.1	2.7	42.0	62.1	94.2	1298.2
O_3, μg/m^3	87.0	40.3	3.3	58.6	80.2	110.0	310.2
NO_2, μg/m^3	30.7	16.9	0.9	18.8	26.5	38.7	175.8
SO_2, μg/m^3	16.6	15.2	0.4	8.8	12.6	19.1	422.6
CO, mg/m^3	1.0	0.5	0.03	0.7	0.9	1.1	9.0
Meteorological factors							
Temperature, °C	14.4	9.7	−32.1	7.1	15.2	22.4	38.4
Relative humidity, %	69.1	17.9	0.3	59.2	72.8	82.6	99.9

Abbreviations: SD, standardized deviation; 25th, the 25th percentile; 75th, the 75th percentile; PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide.

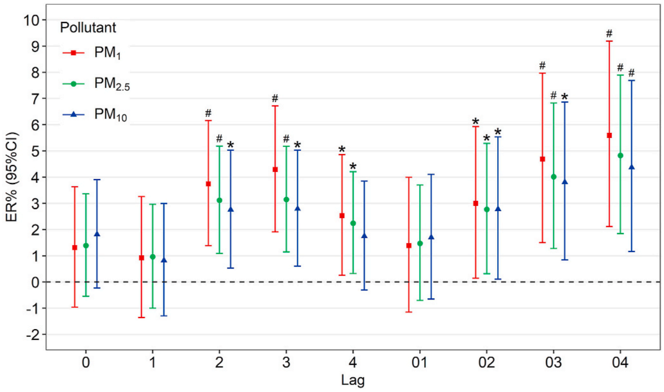

Fig. 2. ERs% (95% CIs) for asthma mortality associated with each IQR increase in exposure to PM_1 (IQR: 19.2 μg/m^3), $PM_{2.5}$ (IQR: 32.0 μg/m^3) and PM_{10} (IQR: 52.2 μg/m^3) with different lag periods. The ERs% were estimated using conditional logistic regression models. Temperature and relative humidity (at lag04) were accounted for in the models. Abbreviations: ER, excess risk; CI, confidence interval; IQR, interquartile range; PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm. Note: $^*P < 0.05$; $^{\#}P < 0.01$.

3.3. *Stratified analysis*

For PM_1, $PM_{2.5}$ and PM_{10}, although the associations among cases who were males, divorced or widowed, above 75 years old and lived in urban areas were significant, while the effect modification of sex, marital status, age and residential location (urban or rural) was not significant (P-value > 0.1). We also found that the effect modification of season was close to being statistically significant (both P for effect modification <0.1). Compared to $PM_{2.5}$ and PM_{10}, significantly stronger effects on asthma mortality related to PM_1 pollution were also noted in these groups (Table 3).

3.4. *Sensitivity analysis*

Considering the potential influence of the COVID-19 pandemic in 2020 on both the level of particulate matter pollution and incidence of and deaths due to asthma, we conducted the analyses by using the data from 2015 to 2019. Fig. S3 shows that the ERs in the pre-pandemic period were consistently larger than the overall estimates in our main analyses (Fig. 2). In two-pollutant models, we found that the results remained consistently significant with no substantial change after adjusting for NO_2 and O_3 (Fig. S4). Using natural cubic spline functions with different degrees of freedom for daily mean temperature and relative humidity also showed similar results (Fig. S5).

4. Discussion

By surmounting previous limitations identified in the literature we sought to clarify the role of particulate matter pollution on asthma mortality. We observed significant associations between acute exposures to PM_1, $PM_{2.5}$ and PM_{10} and increased asthma mortality in this nationwide study. Compared to $PM_{2.5}$ and PM_{10}, significantly stronger effects on asthma mortality related to PM_1 pollution were noted. The pattern of results remained generally consistent in sensitivity analyses using different lag periods, two-pollutant models, and excluding the sample generated in the COVID-19 pandemic period.

To our knowledge, investigating the associations between short-term exposure to ambient particulate matter pollution and asthma mortality has been conducted by only one study to date. The study(Liu et al., 2019) carried out in a Chinese province (Hubei) from 2013 to 2018 showed that $PM_{2.5}$ significantly increased asthma mortality, as observed in our study. Hubei study, however, did not report a significant association between PM_{10} and increased asthma mortality, which is different from our findings. The difference may be due to data sources, data scales, air pollution levels and exposure assessment strategies. We used the same design as the Hubei study, but we employed different sources of pollutant data and different methods to evaluate individual exposure. We used CHAP data, which consists of a combination of advanced satellite remote sensing and space-time models and achieved a high cross-validation coefficient of determination and low root mean square

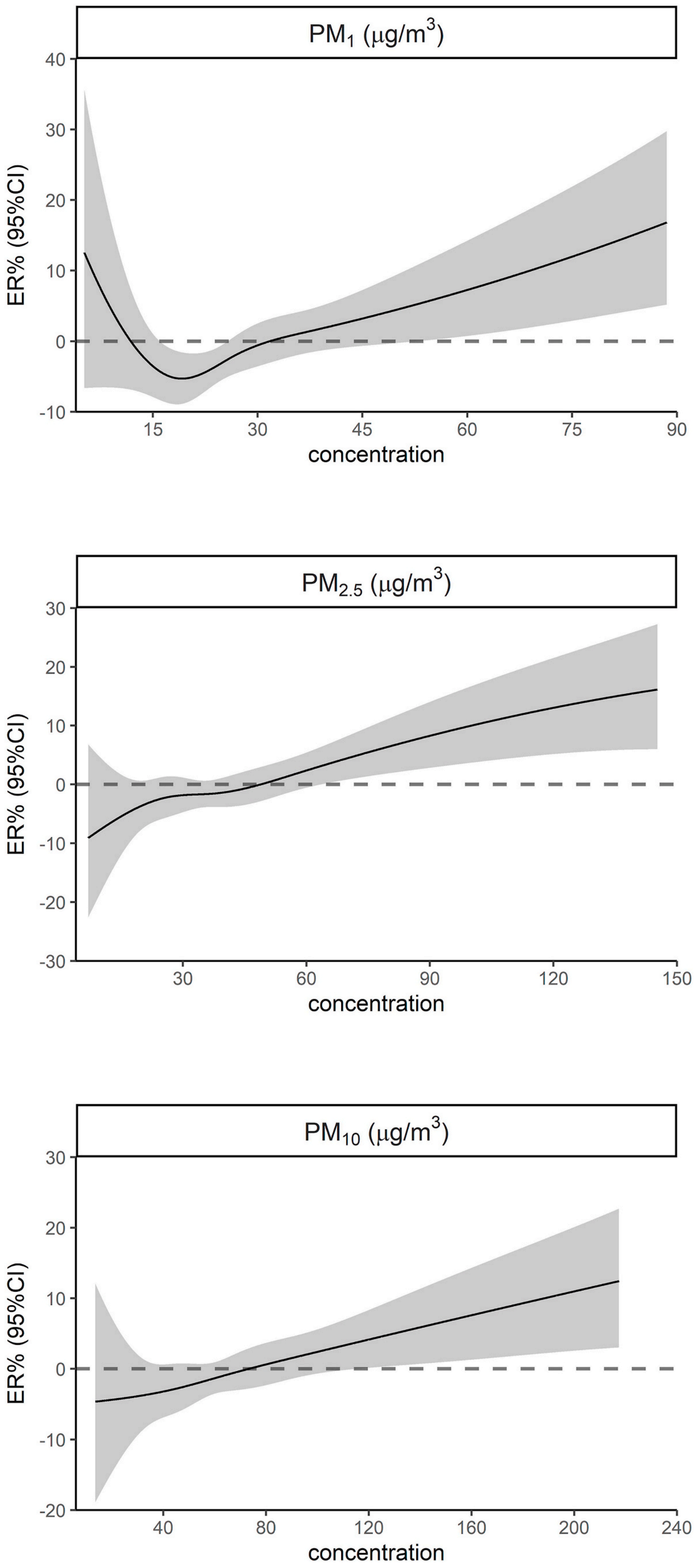

Fig. 3. Exposure-response relationship between short-term exposure to air pollutants (lag04) PM$_1$, PM$_{2.5}$, PM$_{10}$ and ERs% of asthma mortality. Abbreviations: ER, excess risk; CI, confidence interval; PM$_1$, particulate matter with an aerodynamic diameter $\leq$ 1 μm; PM$_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 μm; PM$_{10}$, particulate matter with an aerodynamic diameter $\leq$10 μm.

Table 3

ERs% (95% CIs) for asthma mortality associated with each IQR increase in exposure to PM_1 (IQR: 19.2 μg/m^3), $PM_{2.5}$ (IQR: 32.0 μg/m^3) and PM_{10} (52.2 μg/m^3) stratified by sex, age, marital status, season and urban-rural locale.

	PM_1	$PM_{2.5}$	PM_{10}
Sex			
Male	6.63(1.91–11.56)*	5.90(1.87–10.08)*	5.00(0.73–9.46)*
Female	4.27(-0.82–9.62)	3.46(-0.93–8.04)	3.49(-1.30–8.52)
P value†	0.52	0.43	0.65
Age group (years)			
<75	4.26 (-1.75–10.63)	3.53(-1.60–8.93)	2.34(-2.95–7.93)
≥75	6.03(1.80–10.44)*	5.33(1.70–9.10)*	5.34(1.34–9.50)*
P value†	0.65	0.58	0.39
Marital status			
Unmarried	1.90 (-15.67–23.13)	−1.15 (-15.46–15.58)	−5.45 (-20.25–12.10)
Married	4.36(-0.18–9.10)	3.60(-0.31–7.67)	3.17(-0.98–7.49)
Divorced/ Widowed	7.62(2.04–13.50)*	7.14(2.37–12.14)*	7.31(2.00–12.89)*
P value†	0.64	0.41	0.25
Season			
Cold	6.95(3.10–10.95)*	5.90(2.60–9.30)*	5.83(2.16–9.63)*
Warm	−2.37 (-10.61–6.63)	−1.73 (-9.01–6.14)	−1.17 (-8.02–6.19)
P value†	0.06	0.08	0.09
Urban or Rural			
Urban	6.14(1.50–11.00)*	5.15(1.10–9.36)*	4.41(0.19–8.81)*
Rural	5.26(0.03–10.76)*	4.56(0.19–9.13)*	4.16(-0.73–9.29)
P value†	0.81	0.85	0.94

Abbreviations: ER, excess risk; CI, confidence interval; IQR, interquartile range; PM_1, particulate matter with an aerodynamic diameter $\leq$ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter $\leq$10 μm.

Note: *$P < 0.05$; †P value < 0.05 indicates significant effect modification.

error, and bilinear interpolation to evaluate individual exposure. Hubei used monitoring data and estimated individual exposure by the inverse distance weighting method. This may be one of the reasons for the different results observed. Another reason may be that the national data we used has a substantially larger sample size and wider geographical coverage. The results from Hubei might be a reflection of what is actually happening in the particular province, while our study is a better reflection of the results in the lager region or the nation overall.

Special techniques are needed to measure and estimate the exposure level of PM_1 over a wide range of areas(Hu et al., 2022), so there is a wide lack of ground PM_1 measurements worldwide(Hu et al., 2018; Lin et al., 2016b). Although several studies indicated that stronger associations of PM_1 than of $PM_{2.5}$ and PM_{10} with asthma development(Hu et al., 2022; Yang et al., 2018; Zhang et al., 2021), the effect on asthma mortality related to PM_1 pollution remain largely unknown in China. Such research gap has largely hampered in-depth understanding of PM-associated impacts on asthma mortality. Our nationwide study found that PM_1 (ER: 5.59%, 95% CI: 2.11–9.19) also significantly increased asthma death. Compared to $PM_{2.5}$ and PM_{10}, PM_1 produced stronger effects on asthma mortality. There may be gaseous pollutants as confounding factors that affect the relationship between particulate matter and asthma death. However, we fitted several two-pollutant models with one particulate matter air pollutant and one gaseous pollutant and the association remained significant. A nationwide estimate in China found a 0.19% (95% CI 0.09–0.28%) increase in total mortality per 10 μg/m^3 increase in PM_1 concentration, which is higher than that for $PM_{2.5}$ and PM_{10}(Yin et al., 2020). As determined in a previous study that PM_1 contributed 77–86% of the $PM_{2.5}$ concentration in China(Chen et al., 2018), which may be related to the huge energy demands associated with rapid industrial development in China, which have resulted in differences in the physicochemical properties in fractioned PM, and has further altered the relatively higher risk associated with smaller size-fractioned PM(Yin et al., 2020). Several studies have shown that inhalation of PM may lead to inflammation and oxidative stress(Valavanidis et al., 2008; Zou et al., 2020). PM_1 is easier to enter and deposit in the deeper respiratory tract. The endocytosis of PM_1 by respiratory epithelial cells can induce oxidative stress and inflammatory response, which may play an important role in the effect of PM_1 on pulmonary function(Hu et al., 2022; Mazzarella et al., 2012; Valavanidis et al., 2008). In addition, PM_1 has a higher surface area-to-volume ratio, which makes it easier to enter the alveoli and systemic circulation and to carry more toxins, including metal and organic compounds, which can cause lung injury, genetic damage and epigenetic changes(Yin et al., 2020). Our study supports the idea that PM_1 may be a higher risk factor for asthma mortality, suggesting that swift action to mitigate finer particulate matter emission is justified. Besides, we found that the association between the concentration of pollutants and asthma mortality was significant in cold season and the effect modification of season was close to being statistically significant. It has been reported that cold is one of the risk factors for asthma attack(Mohr et al., 2008). Another possible reason may be related to the increase of particulate matter pollution levels caused by the increase of winter heating demand in China(Xiao et al., 2015). In addition, our study also observed significant associations for particulate matter pollution among cases who were males, divorced or widowed and died above 75 years old. The mortality rate of asthma in males has always been higher than that in females, both in China and around the world(GBD Diseases and Injuries Collaborators, 2020). The reasons for the significant effect of acute particulate matter exposure on asthma mortality in people over 75 years old may be due to fact that older adults were more susceptible to asthma and had more common diseases(Hsu et al., 2018). We also found that air pollution plays a significant role in the death rate of asthma in divorced or widowed people. We speculate that this group of people have fewer caregivers than other groups. Nevertheless, most of the covariates considered as potential effect modifiers did not turn out to have significant interaction terms.

We found that mortality increased significantly with increasing concentrations of PM_1, $PM_{2.5}$ and PM_{10} throughout the exposure range, indicating that hazardous health outcomes due to particulate matter pollution exist even at low concentration levels. Thus, we suggest that more stringent air pollution control standards should be considered in China.(Ministry of Ecology and Environment of the People's Republic of China, 2016) World Health Organization's (WHO) recently updated air quality guidelines and called on governments to strive to improve urban air quality and protect people's health.(World Health Organization, 2021) Our results reveal that China urgently needs to reduce the acceptable concentration limit of ambient particulate matter pollutants in residential areas. In addition, attention should be paid to the concentration limit of PM_1 due to its smaller particle size. It has a significant effect on health, and its concentration should be limited early to reduce its associated disease burden.

There are several strengths of our study. First, our study has a large nationwide sample to ascertain if particulate matter pollution increases the risk of asthma mortality. This study represents the asthma death cases of more than 300 million individuals between 2015 and 2020, which provided sufficient statistical power to perform exposure–response analyses and ample data for subgroup analysis. Second, exposure to pollutants was assessed based on home address and this approach would reduce misclassifications. Finally, the time-stratified case-crossover design of this study would account for long-term and seasonal trends, and would control for the influence of individual-level confounders.

This study has some limitations. First, particulate matter pollution was estimated at the 10 km × 10 km grid level based on residential addresses and we were unable to include personalized measurements of air pollution. This may lead to potential exposure misclassification bias, but this is likely a minor issue since the physical activity of patients with asthma prior to their deaths is usually restricted and unlikely to take place far away from their residential address. Second, we excluded air pollutant data for Tibet, Xinjiang and some parts of Heilongjiang province to ensure the stability and accuracy of the exposure data. Although we excluded the data for three provinces, it is unlikely that this exclusion would bias our results because these are sparsely-populated area and there are few asthma deaths in these regions. Third, although the time-stratified case-crossover design eliminates time-invariant factors and we accounted for meteorological variables, our study may be still subject to residual confounding caused by unmeasured time-varying factors. Fourth, this is a national sample of deaths from asthma in China supplemented by several subgroup analyses by different dimensions. However, the results may not be generalizable to other regions of the globe due to population differences and a different spectrum of air pollution.

5. Conclusions

In conclusion, our study provides nationwide evidence that short-term exposures to PM$_1$, PM$_{2.5}$ and PM$_{10}$ may increase asthma mortality in China. Comparative analyses highlighted stronger associations of ambient PM$_1$ than of larger particles with asthma mortality. China needs to adjust the current ambient air quality standards urgently and pay greater attention to the adverse health effects of PM$_1$, so as to further reduce the disease burden caused by asthma associated with particulate air pollution.

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Authorship contributions statement

Wei Liu: Methodology, Formal analysis, Validation, Writing – original draft, Visualization. **Jing Wei:** Data curation, Methodology, Validation. **Miao Cai:** Methodology, Data curation, Formal analysis, Validation, Visualization. **Zhengmin Qian:** Methodology, Validation. **Zheng Long:** Visualization, Validation. **Lijun Wang:** Data curation, Validation. **Michael G. Vaughn:** Visualization, Validation. **Hannah E. Aaron:** Visualization, Validation. **Xunliang Tong:** Visualization, Validation. **Yanming Li:** Visualization, Validation. **Peng Yin:** Conceptualization, Supervision, Methodology, Resources Validation, Writing – review & editing. **Hualiang Lin:** Conceptualization, Supervision, Methodology, Resources Validation, Writing – review & editing. **Maigeng Zhou:** Conceptualization, Supervision, Methodology, Resources Validation.

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.

Data availability

Data will be made available on request.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2022.136316.

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