Impact of Low PM$_{2.5}$ Exposure on Asthma Admission: Age-Specific Differences and Evidence from a Low-Pollution Environment in China

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Abstract

Many epidemiological studies focus on health research in areas with high concentration of PM$_{2.5}$. To fill the research gap, our study investigated the acute effects of low PM$_{2.5}$ level (annual average concentration below 35 μg m$^{-3}$) on asthma admissions in Xiamen, China. Using a time-stratified case-crossover study design, we examined the association between PM$_{2.5}$ concentration and asthma admissions from January 2019 to November 2021. The results showed a positive correlation between PM$_{2.5}$ concentration and the cumulative incidence of asthma, with a lag of 0-7 days. Each 10 μg m$^{-3}$ increased in PM$_{2.5}$ concentration was associated with a 0.49% increase in asthma incidence. Stratified analysis revealed significant effects in children aged 0-4 years (OR = 2.029, 95% CI = 1.359-3.031) and the elderly population aged over 75 years (OR = 1.399, 95% CI = 1.092-1.793). Distributed lag models demonstrated a hysteresis effect, with significant lagged effects observed in children (lag0-5) and the elderly (lag3-lag5). The multi-pollutant model, considering NO$_2$ and O$_3$, showed consistent results. These findings highlight the age-specific susceptibility to PM$_{2.5}$ exposure and its impact on asthma admissions, even at lower levels of pollution. Further research is needed to inform environmental protection policies and public health interventions in low-pollution environments.
1. Introduction

According to recent epidemiological research (D'Oliveira et al., 2023; Jiang et al., 2023; Zhu and Lu, 2023), there are strong evidences supporting a correlation between air pollutants and physiological changes that pose health risks. Asthma, a common chronic inflammatory airway disease affecting over 300 million individuals globally (Florence et al., 2023), often leads to persistent and exacerbated symptoms, compromising individuals' quality of life and increasing the risk of premature death. As of 2019, the worldwide prevalence of asthma was reported to be 3,415.5 cases per 100,000 people, with a mortality rate of 5.8 cases per 100,000 people (Safiri et al., 2022). Previous studies have indicated that environmental factors significantly contribute to short-term increases in asthma prevalence (Fan et al., 2016; Paterson et al., 2021; Liu et al., 2022a). In China, the rapid process of industrialization and urbanization has resulted in deteriorating air quality, exacerbating the severity of asthma prevalence.

However, it is worth noting that the majority of research efforts have concentrated on regions with high PM$_{2.5}$ concentrations, such as Shanghai (Wang et al., 2018; Wang et al., 2019), Beijing (Fan et al., 2021), while cities with low PM$_{2.5}$ levels have received less attention. Nevertheless, studies have indicated that even at lower levels of pollution, PM$_{2.5}$ can still have a significant impact on the health of asthma patients (Christidis et al., 2019). Xiamen, situated in southeastern China, is a coastal urbanized city with a population exceeding 3.6 million, neighboring the Yangtze and Pearl River Deltas. From 2016 to 2018, the average concentration of PM$_{2.5}$ in Xiamen was 2.16% lower than the secondary standard of the Chinese National Ambient Air Quality Standard (CNAAQS), which sets an annual average limit of 35 μg m$^{-3}$ (Wu et al., 2019). Thus, to investigate the health effects at such low-pollution area will help policymakers take proper preventive measure to control the risk caused by PM$_{2.5}$ based on epidemiological evidence.

Building upon this background, our study specifically focuses on Xiamen, a city characterized by low PM$_{2.5}$ concentration, to investigate the acute effects of such levels
on asthma admissions. Employing a time-stratified case-crossover study design, we aim to explore the association between PM$_{2.5}$ concentration and asthma admissions in Xiamen from January 2019 to November 2021. Examining the relationship between PM$_{2.5}$ and asthma in Xiamen will provide a comprehensive understanding of the health implications associated with low PM$_{2.5}$ exposures, contributing valuable insights for governments in formulating environmental protection policies to safeguard public health in low-pollution regions.

2. Methods

2.1 Asthma admission data

Xiamen as an urban city with low PM$_{2.5}$ concentration, which has been selected for this investigation. The asthma admission research data was obtained from the First Affiliated Hospital of Xiamen University, which is internationally recognized by the Joint Commission International and holds a high reputation and authority. In Figure 1, hospital is about 17 km away from the sampling site. It is worth mentioning that the hospital's outpatient and emergency visit volume, as well as the number of discharged patients, exceeds 30% of the total in Xiamen, ensuring that our sample has good representativeness.

In Xiamen, the departments of Respiratory Medicine, Laboratory Medicine, and Preventive Healthcare demonstrate the strongest clinical and research capabilities. The expertise and experience within these departments could provide robust support for our study. We strictly adhere to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code J45 for the classification of asthma cases, ensuring accurate categorization.

To obtain more detailed data, the following information has been extracted: patient IDs, hospital admission dates, gender and age. Additionally, the discharge diagnosis codes revealed the specific conditions diagnosed upon patients' discharge. These detailed pieces of information will assist us in conducting in-depth analysis and understanding the relationship between asthma and environmental factors.
2.2 Air quality data

PM$_{2.5}$ and related gaseous pollutant concentration were measured at Atmospheric Environment Observation Supersite (Sampling site in Figure 1), located in the Institute of Urban Environment, Chinese Academy of Sciences (IUE, CAS). The other pollutant data from January 1, 2019, to November 30, 2021, was obtained from the website (http://113.108.142.147:20035/emcpublish/) published by the National Environmental Monitoring Center of China (NEMCC). Prior to utilizing this data, quality control measures had been conducted, including averaging the hourly concentrations to obtain daily concentrations. The measurement of PM$_{2.5}$ concentration was carried out at various monitoring sites according to the technical specifications described in the Chinese Environmental Protection Standard document HJ 655-2013. These techniques include the application of gravimetric oscillation balance method and $\beta$ absorption method (refer to the link: http://www.cnemc.cn/jcgf/dqhj). According to Figure 2 and Figure S1 in supplementary, the air quality data in sampling site is comparable with the surrounding observation site. Thus, PM$_{2.5}$ and related gaseous pollutant concentrations in sampling site could well represent the polluted level in Xiamen.

Figure 1. Location of Xiamen (red dot) in China, sampling sites in black triangle and black dot represents hospital in Xiamen.
2.3 Meteorological data

Considering the influence of meteorological conditions, meteorological data were obtained from the National Climate Data Center (NCDC) (ftp://ftp.ncdc.noaa.gov/pub/data/noaa/), including daily mean temperature (T) and relative humidity (RH).

2.4 Statistical analysis

For this study, individuals who were admitted to the hospital with asthma symptoms and received a diagnosis were identified as cases. To establish a comparison, these cases were matched with patients from the same day one week prior or one to two weeks later, serving as their own controls. Cases were assigned a value of 1, while controls were assigned a value of 0. This self-matching design was employed to mitigate the influence of short-term individual differences, such as gender, age, smoking, socioeconomic status, and more. This approach was adopted based on the principles outlined in the study on exposure-response relationships (Han et al., 2016; Chen et al., 2022; He et al., 2022; Liu et al., 2022d).

To examine the relationship between asthma events and elemental exposure, the asthma event data has been paired with corresponding elemental exposure data on the case and control days. Conditional logistic regression models were used to construct exposure-response relationships. To ensure smoothness in the associations with wind speed, relative humidity, and temperature, a natural spline smoothing function with three degrees of freedom was applied (Sheffield et al., 2015).

To account for the impact of public holidays, a dichotomous variable was included in the analysis. Adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to estimate exposure-response relationships for asthma admissions associated with incremental changes represented by interquartile ranges (IQRs) of different trace element concentrations.

To account for potential non-linear cumulative effects, a distributed hysteresis model was employed for each trace element. This involved the use of a cross-basis matrix and natural splines to capture hysteresis responses, considering effects from 0 to
7 days sequentially. All statistical analyses were performed using the "mgcv" package in R Statistical Software version 3.2.4.

3. Results

Asthma admission data were investigated and out of the total 2,207 asthma patients included, 55% (1214) were male, while 45% (993) were female. The distribution of patients based on age groups was as follows: 21.5% (475) aged 0-14, 71.2% (1571) aged 15-75, and 7.3% (161) aged over 75.

Table 1 summarizes the descriptive statistics of air pollutants and meteorological parameters in Huangpu District, Xiamen. During the study period, the daily levels of PM$_{2.5}$ ranged from 1.2-77.0 $\mu$g m$^{-3}$ with an annual mean of 18.5 $\mu$g m$^{-3}$. The annual mean PM$_{2.5}$ concentration is 47% lower than the Grade II Annual PM$_{2.5}$ Standard of CNAAQS (35.0 $\mu$g m$^{-3}$) and 1.9 times of the WHO guideline of annual mean PM$_{2.5}$ (10.0 $\mu$g m$^{-3}$). The daily level of gaseous pollutants ranged from 1.0-94.0 $\mu$g m$^{-3}$ (annual mean, 24.5 $\mu$g m$^{-3}$) for NO$_2$, and 1.6-156.5 $\mu$g m$^{-3}$ (annual mean 58.5 $\mu$g m$^{-3}$) for O$_3$. The average daily temperature during the study period ranged from 7.3 to 34.3°C (annual mean, 23.2°C). Meanwhile, the average daily humidity ranged from 30.8 to 93.6% (annual mean, 70.9%).

Table 1. Descriptive statistics of air quality data and meteorological parameters in Jimei District, Xiamen.

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<th>Mean</th>
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<td><strong>Air quality data</strong></td>
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<td>PM$_{2.5}$ ($\mu$g m$^{-3}$)</td>
<td>18.5</td>
<td>11.3</td>
<td>1.2</td>
<td>9.7</td>
<td>16.0</td>
<td>24.9</td>
<td>77.0</td>
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<tr>
<td>NO$_2$ ($\mu$g m$^{-3}$)</td>
<td>24.5</td>
<td>13.7</td>
<td>1.0</td>
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<td>21.7</td>
<td>32.4</td>
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<td>8h-O$_3$ ($\mu$g m$^{-3}$)</td>
<td>58.5</td>
<td>24.2</td>
<td>1.6</td>
<td>42.0</td>
<td>53.8</td>
<td>71.6</td>
<td>156.5</td>
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<td><strong>Meteorological parameters</strong></td>
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<td>T (°C)</td>
<td>23.2</td>
<td>5.7</td>
<td>7.3</td>
<td>18.5</td>
<td>23.3</td>
<td>28.9</td>
<td>34.3</td>
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<td>RH (%)</td>
<td>70.9</td>
<td>10.0</td>
<td>30.8</td>
<td>64.9</td>
<td>72.1</td>
<td>77.5</td>
<td>93.6</td>
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Figure 2 illustrates the variations in air pollutant levels and daily admissions for asthma. Specifically, Figure 2 depicts the temporal pattern of PM$_{2.5}$ concentration in sampling and surrounding observation site (daily mean values). It is observed that PM$_{2.5}$ concentration tended to be higher during colder seasons and lower during warmer seasons. On the other hand, Figure 2 represents the daily count of asthma admissions. It is worth noting that the frequency of admissions for asthma remained in steady level during the entire study period (Figure S2).

![Time series of PM$_{2.5}$ concentration and daily asthma admissions](chart.png)

Figure 2. Time series of PM$_{2.5}$ concentration (daily mean concentration) in sampling and surrounding site, coupled with the daily asthma admission in Xiamen, China.

Figure 3 presents the findings indicating a positive correlation between PM$_{2.5}$ concentration and the cumulative incidence of asthma, with a lag of 0-7 days. Specifically, each 10 $\mu$g m$^{-3}$ increase in PM$_{2.5}$ concentration was associated with a 0.49% increase in the incidence of asthma (odds ratio [OR] = 1.059, 95% confidence interval [CI] = 1.007-1.113). Stratifying the results by age revealed varying impacts of PM$_{2.5}$ on different age groups. The most significant effect was observed in children aged 0-4 years, with a 2.029-fold increase in the odds of developing asthma (95% CI = 1.359-3.031) within 0-7 days after exposure. Similarly, the elderly population aged over 75 years exhibited a heightened risk of asthma (OR = 1.399, 95% CI = 1.092-1.793). However, no significant association was found between PM$_{2.5}$ and the cumulative incidence of asthma in the age groups of 0-14 years (OR = 1.175, 95% CI = 0.996-1.387) and 14-75 years (OR = 1.042, 95% CI = 0.980-1.108). These results highlight the age-specific susceptibility to PM$_{2.5}$ exposure and its impact on asthma development.
Figure 3. Overall cumulative OR of PM$_{2.5}$ exposure in different age groups with a lag of 0-7 days from 2019 to 2021 in Xiamen.

For distributed lag model analysis, a hysteresis effect of PM$_{2.5}$ on asthma admissions across different age groups in Xiamen has been shown in Figure 4. Specifically, for the 0-4-year-old population, the lagged effect of PM$_{2.5}$ exhibited significance at lag0-5, with the highest impact observed on the first day (OR = 1.134, 95% CI = 1.037-1.240). However, no significant effect was found in the population aged 0-14 and 15-75. For individuals over 75 years old, the lag effect of PM$_{2.5}$ displayed significance at lag3-lag5, with the odds ratio showing an upward trend. Specifically, at lag5, the odds ratio was 1.049 (95% CI = 1.008-1.092). These findings emphasize the age-specific variations in the lagged effect of PM$_{2.5}$ and its influence on asthma admissions.
In addition to the single-pollutant model for PM$_{2.5}$, the multi-pollutant model has been examined and investigated the effect of other pollutants, including ozone (O$_3$) and nitrogen dioxide (NO$_2$) on the model. Figure 5 illustrates the 7-day cumulative odds ratio risk associated with PM$_{2.5}$ exposure among the 0-4-year-old population. The analysis accounts for the impact of gaseous pollutants, namely NO$_2$ and O$_3$, through adjustment. After adjusting for these pollutants and considering all included factors, the OR were calculated as follows: OR = 2.040 (95% CI = 1.217-3.420), OR = 2.057 (95% CI = 1.215-3.483), and OR = 2.052 (95% CI = 1.204-3.499).

Figure 4. Odds ratio from current (lag0) to lag7 of exposure to PM$_{2.5}$ to asthma admissions in different age groups during study period in Xiamen.

Figure 5. After adjustment for multiple pollutants, cumulative odds ratio from current (lag0) to lag7 of exposure to PM$_{2.5}$ to asthma admissions in 0-4 age groups from 2019 to 2021 in Xiamen, China.
4. Discussions

Our study provides empirical evidence regarding the association between short-term exposure (0-7 days) to PM$_{2.5}$ and the risk of asthma exacerbation in Xiamen, China. Specifically, our findings indicate a substantial risk of asthma in two vulnerable populations: children aged 0-4 years and older adults aged 75 and above. Moreover, the impact of PM$_{2.5}$ on asthma differs significantly between these age groups, with children being more susceptible compared to the elderly. Notably, children face a significant risk of asthma exacerbation following 1-4 days of exposure to PM$_{2.5}$. On the other hand, the elderly population primarily experiences an effect with a delayed onset, typically occurring 3-5 days after exposure to ambient environment.

Several recent studies have examined the short-term exacerbation of asthma in response to PM$_{2.5}$ exposure in different locations, including Adelaide, Korea, and Taipei (Chen et al., 2016; Chang et al., 2017; Kim et al., 2017). According to our research findings, our result further confirms that there is a significant correlation between an increase of 10 $\mu$g m$^{-3}$ in PM$_{2.5}$ concentration and a 0.49% increase in the incidence of asthma (OR = 1.059, 95% CI= 1.007-1.113). Multiple studies have demonstrated that metal ions and organic compounds present in PM$_{2.5}$ particles can induce oxidative stress reactions, leading to cell damage, inflammatory responses, and increased airway hyperresponsiveness, further exacerbating asthma symptoms (Riva et al., 2011; Bates et al., 2015; Piao et al., 2021; Liu et al., 2022b). Recent research has also indicated that chemicals within PM$_{2.5}$ particles can stimulate airway receptors and nerve endings, disrupting the normal functioning of the autonomic nervous system. This may result in increased airway smooth muscle contraction and mucus production, further intensifying asthma symptoms (Liu et al., 2022c). Furthermore, these chemicals can disrupt the normal functioning of the immune system, leading to abnormal activation of immune cells and increased release of inflammatory mediators, thereby exacerbating airway inflammation and asthma symptoms (Hodge et al., 2021; Piao et al., 2021; Xu et al., 2023). Additionally, studies have shown that PM$_{2.5}$ particles can directly damage respiratory epithelial cells, compromising the integrity of the airway epithelial barrier.
This makes the airways more susceptible to infection and inflammation, further exacerbating asthma symptoms (Zhao et al., 2020; Celebi Sozener et al., 2022).

Our study found a significant association between the risk of admission for childhood asthma (0-4 years old) and PM$_{2.5}$ (OR = 2.029, 95% CI = 1.359-3.031). Previous research has indicated that children are more susceptible to PM-related diseases due to higher respiratory rates, narrower airways, immature lung tissue, and longer exposure to outdoor air (Kim, 2004; Bateson and Schwartz, 2007). Similar effects have been observed in studies conducted in other regions (Norris et al., 1999; Chen et al., 2016; Wu et al., 2019). For instance, a study conducted in Seattle, Washington, revealed that for every 11 $\mu$g m$^{-3}$ increased in PM$_{2.5}$ concentration, the odds ratio for childhood asthma was 1.15 (95% CI: 1.08-1.23). Additionally, our results show a higher risk of PM$_{2.5}$-related asthma in Xiamen compared to the United States, particularly in areas with lower PM$_{2.5}$ levels. There is evidence suggesting that the health impact of environmental PM$_{2.5}$ depends not only on its total mass but also on its chemical composition. The carbonaceous components of PM$_{2.5}$, such as black carbon (BC) and organic matter (OM), have been associated with childhood asthma/wheezing (Khreis et al., 2017). Recent studies have shown that PM$_{2.5}$-bound trace elements might increase neutrophil infiltration by increasing tumor necrosis factor alpha and interferon gamma excretion based on the Murine asthma models and high levels of Cu and Fe may induce oxidative stress and chronic inflammation in asthma cases (Huang et al., 2016; Mao et al., 2018). Although PM$_{2.5}$ levels in Xiamen are lower than in other cities, the BC concentration in Xiamen is comparable to moderate polluted Chinese cities such as Beijing, Guangzhou, and Nanjing (Deng et al., 2020).

Similarly, individuals aged 75 and above who are exposed to PM$_{2.5}$ have been found are more susceptible to asthma compared to adults (OR = 1.399, 95% CI = 1.092-1.793). Studies have shown that aging brings about physiological and morphological changes in the lungs, which may impact the development of asthma in the elderly (Estenne et al., 1985). Moreover, significant age-related physiological and immune changes complicate the presentation, diagnosis, and treatment of asthma in the elderly population. Furthermore, the pathological physiology and treatment characteristics of
asthma in elderly patients are not as well-defined as in younger individuals and children (Pate et al., 2021). There is evidence suggesting that elderly asthma patients are more likely to be underdiagnosed and undertreated. For example, inhaled corticosteroids (ICS), which are a cornerstone of chronic asthma treatment, are not fully utilized in elderly patients (Burrows et al., 1991; Tu and Sin, 2001). With the aging population, the number of elderly asthma patients is expected to increase, necessitating further research to better understand the underlying pathophysiology in this population.

Our findings revealed significant effects of PM$_{2.5}$ exposure on children within 0-5 days of exposure, whereas for the elderly, the effects became significant after a lag of 3-5 days. Children typically have higher respiratory rates and narrower airways, rendering them more vulnerable to the direct impact of PM$_{2.5}$ (Were et al., 2020). On the other hand, older adults may undergo age-related alterations in their lung physiology and immune system, resulting in a comparatively long response time to PM$_{2.5}$ (Liu et al., 2021). Further investigation into these disparities would contribute to a more comprehensive comprehension of the health effects of air pollution across different age groups and offer guidance for relevant public health interventions.

Our study has several noteworthy limitations that should be considered. Firstly, the generalizability of our findings may be limited due to the focus on a specific geographic area (Xiamen). The air pollution characteristics and population demographics in other regions may differ, and caution should be exercised when extrapolating the results to different settings. Replication of the study in diverse locations would enhance the external validity and strengthen the broader applicability of the findings. Secondly, although we made efforts to account for potential confounding factors, the presence of residual confounding cannot be completely ruled out. There may be additional unmeasured or unknown factors that influence the relationship between PM$_{2.5}$ and asthma admissions. Future studies could consider the inclusion of more comprehensive data on relevant confounders to further mitigate potential confounding effects. Additionally, our study focused solely on the association between PM$_{2.5}$ and asthma admissions, without exploring other health outcomes or underlying mechanisms. Considering the multifaceted nature of air pollution and its
potential impacts on various health conditions, future research should investigate a broader range of health outcomes and explore the underlying biological pathways to provide a more comprehensive understanding of the topic. Despite these limitations, our study contributes valuable insights into the relationship between PM$_{2.5}$ and asthma admissions, within the specific context of Xiamen. The findings should be interpreted considering these limitations, and further research is warranted to address these gaps and strengthen the evidence base in this field.

5. Conclusions

In conclusion, this study examined the impact of low levels of PM$_{2.5}$ exposure on the risk of asthma admissions. In contrast to previous studies that primarily focused on areas with high PM$_{2.5}$ concentration, this study investigated asthma admissions in a low PM$_{2.5}$ environment. The findings revealed the significant impact of low PM$_{2.5}$ concentration on the risk of asthma admissions, addressing a research gap in this area. The study specifically considered the differences among age groups, with a particular focus on vulnerable populations such as children and older adults who are more susceptible to the effects of air pollution. The results demonstrated distinct age-specific responses to PM$_{2.5}$ exposure, with a notable increase in asthma risk observed in children within 1-4 days of exposure and a delayed response in the elderly population, typically occurring 3-5 days after exposure. This finding contributes to a better understanding of the health effects of air pollution across different age groups. These findings have important implications for addressing the health effects of air pollution in low-pollution regions and informing relevant policy and intervention strategies.

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