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Short-term exposure to fine particulate matter and asthma exacerbation: a large population-based case-crossover study in Southern Thailand

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Abstract

Background Asthma exacerbations remain a significant global health issue despite advances in management. Fine particulate matter ($PM_{2.5}$, particles ≤ 2.5 µm in diameter) is a known trigger for asthma exacerbations. However, studies on the acute effects of $PM_{2.5}$, particularly in regions with relatively low pollution levels, are limited. This study examined the time-lagged association between daily $PM_{2.5}$ exposure and asthma exacerbations in Songkhla province, southern Thailand, where $PM_{2.5}$ concentrations frequently approach the World Health Organization's (WHO) Global Air Quality Guidelines. Approximately 41% of days during the study period had $PM_{2.5}$ concentrations below the 2021 Guideline level of 15 µg/m^3. Additionally, the province is periodically affected by seasonal transboundary haze from forest fires.

Methods A case-crossover study was conducted using daily $PM_{2.5}$ and meteorological data from January 2010 to December 2023, alongside health records of asthma patients from Songklanagarind Hospital. District-level daily $PM_{2.5}$ concentrations were estimated through inverse distance weighted interpolation. Conditional logistic regression, incorporating time-lagged models and cubic splines, was applied.

Results The study included 11,848 case days and 39,810 control days, with a mean daily $PM_{2.5}$ concentration of 18.2 µg/m^3. $PM_{2.5}$ concentrations > 50 µg/m^3 were significantly associated with asthma exacerbations at multiple time lags (lag0, lag2, and lag01 to lag03), with odds ratios ranging from 1.41 to 1.64, compared to the lowest concentration group ($PM_{2.5}$ 0–15 µg/m^3). Temperature showed no significant effect, while relative humidity was positively associated with asthma exacerbations at lag3, lag06, and lag07. Subgroup analyses revealed associations between $PM_{2.5}$ exposure and asthma exacerbations at early lags for both males and females. Additionally, children aged 6–11 years and 12–17 years exhibited greater susceptibility to asthma exacerbations, particularly at $PM_{2.5}$ concentrations of 15–25 µg/m^3.

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Conclusion This study underscores the short-term effects of $PM_{2.5}$ on asthma exacerbations, particularly during high-pollution episodes of transboundary haze in regions that generally experience low levels of air pollution. These findings emphasize the importance of achieving the WHO air quality targets to mitigate the health impacts from $PM_{2.5}$.

Keywords Fine particles, Particulate matter, Asthma exacerbation, Case-crossover study

Background

Asthma, a noncommunicable disease, imposes a significant healthcare burden, affecting approximately 262 million people worldwide, across both children and adults [1]. It arises from complex interactions between genetic and environmental factors, leading to diverse clinical manifestations and varying degrees of airflow limitation. Chronic airway inflammation and bronchial remodeling are central to its pathogenesis [2]. Common symptoms include cough, wheezing, shortness of breath, and chest tightness, which often occur at night and are triggered by factors such as air pollutants, particularly fine particulate matter ($PM_{2.5}$, particles ≤ 2.5 μm in diameter), viral infections, and allergens. Asthma patients may experience exacerbations, episodes characterized by worsening symptoms and lung function, which represent a significant deviation from the patients' baseline condition and often require treatment adjustments [2].

$PM_{2.5}$ is a major environmental health risk, contributing substantially to the global burden of respiratory diseases, including asthma. Approximately 99% of the global population resides in areas with harmful $PM_{2.5}$ concentrations, especially in low- and middle-income countries across Asia and Africa [3]. Recent studies suggested that even low concentrations of $PM_{2.5}$ can adversely affect health [4]. Due to its ability to penetrate deep into the lungs, $PM_{2.5}$ exposure is associated with the development of cardiopulmonary diseases and lung cancer [5]. Although previous studies demonstrated the acute effects of $PM_{2.5}$ on asthma exacerbations and impaired lung function in high-pollution areas, research in regions with relatively low pollution, such as those affected by seasonal transboundary haze in Southeast Asia, remains limited [6, 7, 8, 9, 10, 11].

Songkhla province, located on the eastern coast of southern Thailand, covers an area of 7,394 square kilometers and has a population of approximately 1.4 million people. The province, which lies within the Malay Peninsula, is divided into 16 districts and experiences a tropical climate with high temperatures and humidity [12]. A previous study indicated that air quality in southern Thailand is generally better than in other regions of the country [13]. In 2019, the mean daily $PM_{2.5}$ concentration in Songkhla was 19.26 μg/m³. However, the province is periodically affected by transboundary haze, particularly from forest fires during the June to September period each year [14].

This study aimed to assess the time-lagged association between daily $PM_{2.5}$ exposure and outpatient visits for asthma exacerbation at Songklanagarind Hospital in Songkhla province, southern Thailand. The province generally has low $PM_{2.5}$ concentrations, often close to the 2021 World Health Organization's (WHO) Global Air Quality Guideline level, but periodically experiences high pollution episodes due to transboundary haze [13, 14, 15].

Methods

Study design

A case-crossover design, commonly used in studies of air pollution and acute health effects, is a self-matched case-control approach in which each participant serves as their own control. This design effectively controls for individual-level factors and potential confounders that remain constant over time, such as sex, genetics, and socioeconomic status [16]. In this study, a 'case day' was defined as the first day of a 7-day period during which an individual sought outpatient treatment for asthma exacerbations. This criterion was based on a previous study suggesting that the effects of $PM_{2.5}$ on the respiratory system may persist for up to 7 days following exposure [17]. Using a time-stratified referent selection approach, control days were chosen from days without exacerbations, matched by the same day of the week, month, and year as the case day. This matching controls for seasonality, time trends, and day-of-week effects [18]. Each case day was paired with three to four control days, all occurring on the same weekday within the same month.

Health data and identification of asthma exacerbation

Health data were obtained from the Songklanagarind Hospital database, under the oversight of the Division of Digital Innovation and Data Analytics, Faculty of Medicine, Prince of Songkla University. Medical records with a diagnosis of asthma (International Classification of Diseases, Tenth Revision [ICD-10]: J45-J46) and corresponding drug prescription data for each visit were used to identify episodes of asthma exacerbation. The medications included short-acting bronchodilators (beta-2 agonists and anticholinergics), systemic corticosteroids, and magnesium sulfate. Demographic information, including sex, age, outpatient visit date, respiratory viral infection status, and postal code, was also collected. Respiratory viral infection status was defined as having at least one

positive test result for respiratory syncytial virus (RSV), influenza A, or influenza B. Viral testing was performed only when deemed clinically necessary by the attending physicians, rather than as part of routine testing for all asthma patients visiting the hospital. The study included residents of Songkhla province, aged 6 years and older, who sought treatment for asthma exacerbations at the hospital's outpatient clinics between January 1, 2010, and December 31, 2023. Children under 6 years of age were not included due to difficulties in distinguishing asthma from other respiratory conditions [19]. Individuals with incomplete address information were excluded from the study.

$PM_{2.5}$ and meteorological data

Hourly data on $PM_{2.5}$ concentrations, temperature, and relative humidity were collected from seven monitoring stations across southern Thailand (Fig. 1), which were part of the air quality monitoring network established by the Thai Pollution Control Department. The network was designed to monitor air quality in key regions of Thailand, including central, northern, and southern regions. $PM_{2.5}$ concentrations were measured using the Beta Attenuation Monitor 1020, in accordance with standards set by the United States Environmental Protection Agency (US EPA) [20]. Missing data were handled using multivariate imputation by chained equations (MICE) before calculating daily averages for each parameter. The MICE process involved iterative imputation of missing data, utilizing the predictive mean matching (PMM) method, which was specifically applied in this study. Initially, missing values were imputed with placeholder values, such as the means of observed data. In the next step, placeholder values for one variable were reset to missing, allowing for further refinement. The PMM method was then applied, where a regression model predicted the missing values based on other related variables in the dataset. Instead of directly using the predicted values, the missing values were replaced with observed values from the dataset that were closest to the predicted values. This process was repeated for all variables with missing data, completing one cycle of imputation. In this study, imputation was performed with five iterations in R, following the methodology outlined by Azur et al. [21]. Variables included in the MICE imputation were PM_{10} (particles ≤ 10 μm in diameter), $PM_{2.5}$, temperature, relative humidity, wind speed, atmospheric pressure, rainfall, and the coordinates of monitoring stations. Convergence diagnostics were conducted to assess the stability and quality of the imputation, using the method described by Azur et al. [21]. Specifically, density plots were employed to evaluate the convergence of the imputation process. All chains converged after five iterations, as indicated by the overlapping distributions of the imputed values. The density of imputed $PM_{2.5}$ concentrations had a lower peak compared to the observed values, suggesting that the imputed values were less concentrated around a central value. However, the width of the density curve for the imputed values closely matched that of the observed values, indicating that the range and spread of the imputed data were consistent with the observed data (Supplementary Figure S1). These results suggest that the imputation process was stable and appropriately reflected the distribution of the observed data.

Daily measurements of $PM_{2.5}$ concentrations, temperature, and relative humidity at the district level were estimated using the bounding box method to define district centroids, as described by Duncan [22]. This method involves identifying the smallest rectangle that fully encloses the polygon of each district, referred to as the bounding box. The centroid is then computed by determining the horizontal and vertical midpoints of the bounding box, which are the averages of the corresponding coordinates. Following centroid calculation, inverse distance weighted (IDW) interpolation was applied to estimate district-level values for $PM_{2.5}$ and meteorological variables. IDW interpolation relies on data from nearby monitoring stations, giving more weight to stations closer to the district centroid to generate spatially continuous estimates of $PM_{2.5}$ concentrations and meteorological data.

Statistical analyses

Descriptive statistics were used to summarize the distribution of case and control data for asthma exacerbations, $PM_{2.5}$ concentrations, and meteorological variables. To assess the robustness of the missing data imputation, we performed a sensitivity analysis by substituting the PMM method with Random Forest (RF) imputation. The coefficients from conditional logistic regression were visually compared between the two methods. Spearman's rank correlation coefficients were computed to assess the relationships between $PM_{2.5}$ and meteorological variables. Additionally, correlations among $PM_{2.5}$ and other pollutants, including PM_{10}, ozone, nitrogen dioxide, carbon monoxide, and sulfur dioxide, were evaluated using Spearman's rank correlation coefficient. The conditional logistic regressions were implemented to account for the dependency of observations inherent in the case-crossover design. The time lags ranged from the same day (lag0) to 7 days prior to the outpatient visit (lag7). Moving averages of $PM_{2.5}$ concentrations were calculated for lags ranging from lag01 (average of lag0 and lag1) to lag07 (average of lag0 through lag7). The regression model was adjusted for temperature, relative humidity, haze-affected days, and public holidays. To account for the non-linear effects of temperature and relative humidity, we applied natural cubic spline models. The optimal degrees of

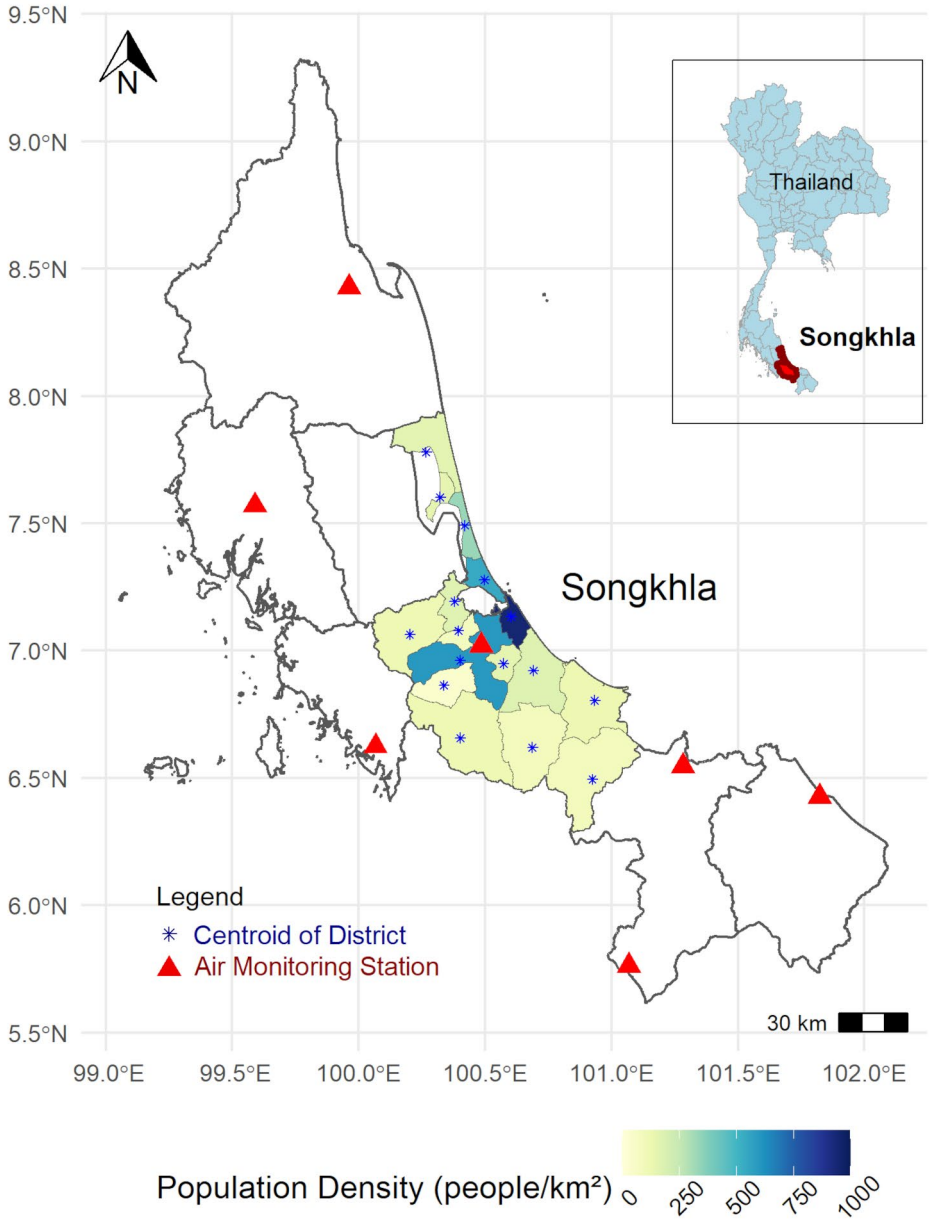

Fig. 1 Geographical location of Songkhla districts and environmental monitoring stations across southern Thailand
Asterisks indicate district centroids, and triangles mark the locations of monitoring stations for $PM_{2.5}$, temperature, and relative humidity in Songkhla and neighboring provinces. The inset map highlights the location of Songkhla province within Thailand. Population density across districts is depicted using a shaded color gradient

freedom were determined based on Akaike's Information Criterion (AIC) which assesses model fit. A natural cubic spline with 5 degrees of freedom was selected for both temperature and relative humidity, since this configuration resulted in the lowest AIC value, indicating the best fit. Haze-affected days were initially defined as those with daily $PM_{2.5}$ concentrations exceeding the 95th percentile (31.21 μg/m³) of the observed values. Following this, further refinement was performed by selecting only those days that coincided with hotspots in Indonesia or Malaysia, as identified by the National Aeronautics and Space Administration (NASA) Fire Information for Resource Management System (MODIS satellite). To ensure that the observed air pollution was transported

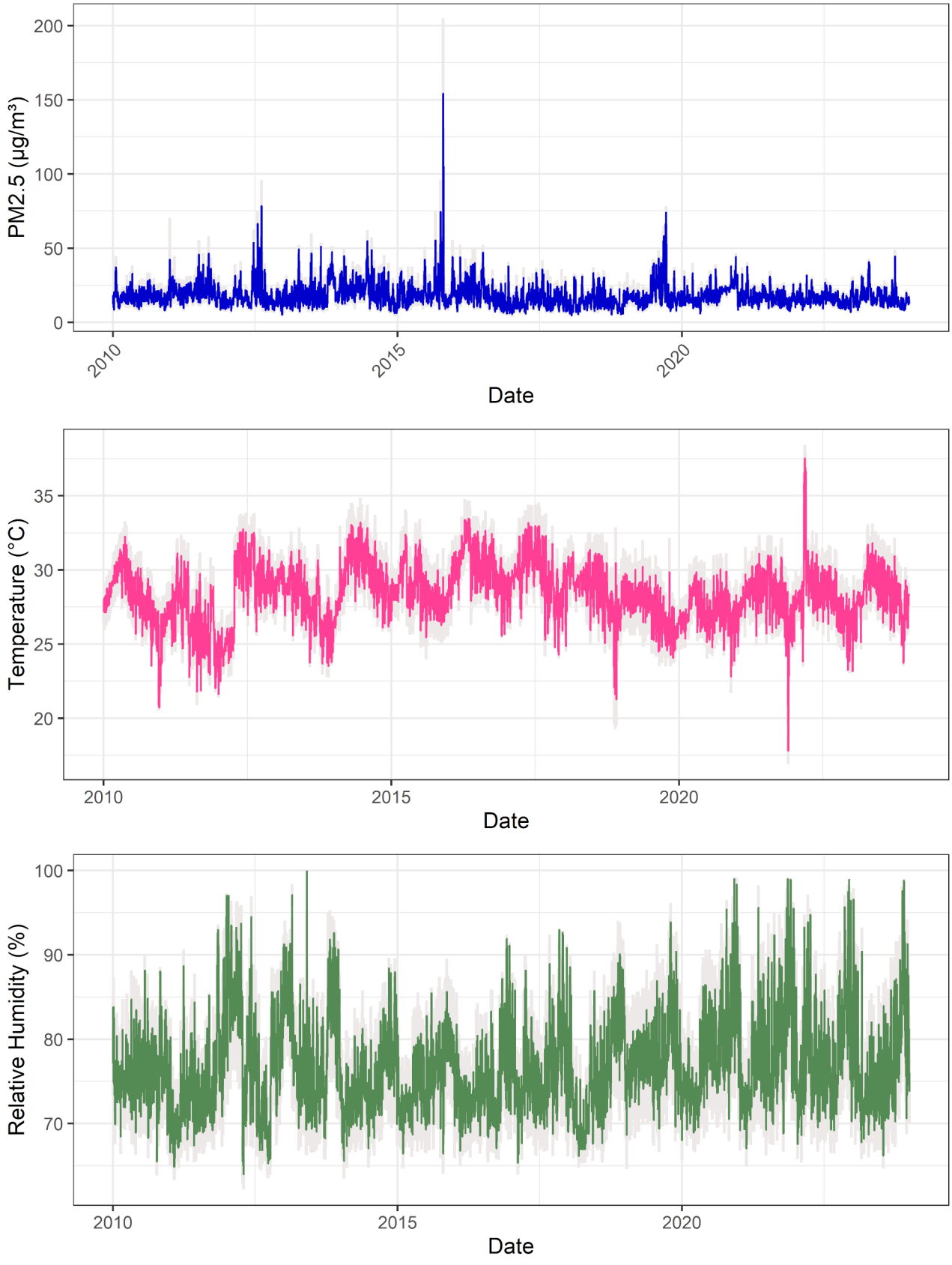

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Time series of daily $PM_{2.5}$ concentrations, temperature, and relative humidity in Songkhla, Thailand (2010–2023)
The light gray-shaded area illustrates the 95% confidence interval of hourly measurements for each variable

from these hotspot regions, we conducted 72-hour backward trajectory analyses using the National Oceanic and Atmospheric Administration (NOAA)'s HYSPLIT model, confirming the presence of relevant air masses. This multi-step approach was consistent with methods employed in prior studies on transboundary haze in Southeast Asia, where the combination of elevated pollutant levels and evidence of specific air mass transport were essential criteria for identifying haze-affected days [14, 23].

To evaluate the associations between asthma exacerbations and $PM_{2.5}$ exposure, two approaches were employed. First, a categorical approach was used, where $PM_{2.5}$ concentrations were categorized into four groups according to the 2021 WHO Air Quality Guidelines (AQG) targets: Very Low (0–15 μg/m³), Low (>15–25 μg/m³), Moderate (>25–50 μg/m³), and High (>50 μg/m³) [3]. Conditional logistic regression was then applied to assess the associations between asthma exacerbations and the categorized $PM_{2.5}$ concentrations, temperature, and relative humidity, considering time lags (lag0 to lag7) and moving-average distributed time lags from 0 to 7 days (lag01 to lag07). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with the lowest $PM_{2.5}$ concentration group (0–15 μg/m³) as the reference. A p-value of <0.05 was considered statistically significant.

Second, a continuous approach was applied, where $PM_{2.5}$ concentrations were treated as a continuous variable to assess the changes in odds of asthma exacerbations per 10 μg/m³ increase in $PM_{2.5}$. A similar conditional logistic regression model with time lags was implemented. Subgroup analyses were conducted by sex, age, and respiratory viral infection status. The age categories for children (6–11 and 12–17 years) were based on a previous study by Trivedi et al., which highlighted distinct clinical characteristics of pediatric asthma within these age ranges [24]. For adults, the age categories were aligned with those used in a prior study, serving as benchmarks for comparison [8]. All statistical analyses were performed using R software version 4.2.2 (R Foundation). The mice package in R was specifically used for the MICE process to handle missing data.

Results

Daily measurements of $PM_{2.5}$ concentrations, temperature, and relative humidity by monitoring station during the study period are presented in Supplementary Table S1. The mean daily $PM_{2.5}$ concentrations ranged from 10.20 μg/m³ to 18.15 μg/m³, with the mean daily temperature ranging from 25.82 °C to 28.44 °C and the mean daily relative humidity ranging from 76.70% to 83.29%. Time series data of daily $PM_{2.5}$ concentrations and meteorological variables from a monitoring station in Songkhla are displayed in Fig. 2.

At the district level, the mean daily $PM_{2.5}$ concentrations ranged from 17.03 μg/m³ to 18.06 μg/m³, with minimum and maximum values of 4.99 μg/m³ and 154.11 μg/m³, respectively. The mean daily temperature ranged from 27.82 °C to 28.42 °C, and the mean daily relative humidity ranged from 76.79% to 78.03% (Supplementary Table S2).

A total of 5,796 asthma patients visited the outpatient clinics during the 14-year study period. Of these, 2,282 patients were excluded because their home addresses were not in Songkhla province, and 10 patients were excluded due to incomplete address information. Ultimately, 3,504 patients who experienced asthma exacerbation episodes were included in the analysis (Fig. 3). Among these, 2,177 were females (62.1%) and 1,327 were males (37.9%). The mean age of the patients at the time of their outpatient or emergency visits was 55.6 years. A total of 835 (1.6%) visits underwent respiratory viral testing (Table 1). The analysis included 11,848 case days and 39,810 control days. The daily averages of $PM_{2.5}$ concentration, temperature, and relative humidity on the case and control days were as follows: 18.2 μg/m³ (case days) and 18.1 μg/m³ (control days); 28.3 °C (case days) and 28.3 °C (control days); and 76.9% (case days) and 76.9% (control days), respectively (Table 2). Spearman's rank correlation revealed a weak positive correlation between $PM_{2.5}$ and temperature ($r=0.09$, $p<0.01$), a moderate negative correlation between temperature and relative humidity (r = -0.50, $p<0.01$), and a weak negative correlation between $PM_{2.5}$ and relative humidity (r = -0.23, $p<0.01$), as shown in Supplementary Table S3. Additionally, a strong positive correlation was found between $PM_{2.5}$ and PM_{10} ($r=0.69$, $p<0.01$). Furthermore, a moderate positive correlation was found between $PM_{2.5}$ and nitrogen dioxide ($r=0.36$, $p<0.01$). A weak negative correlation was observed between $PM_{2.5}$ and ozone (r = -0.08, $p<0.01$). These results are illustrated in Supplementary Table S4.

For the categorical approach, the number of case and control days in each $PM_{2.5}$ concentration group was as follows: for the 'Very Low' group, 4,400 case days and 15,036 control days; for the 'Low' group, 5,871 case days and 19,622 control days; for the 'Moderate' group, 1,480 case days and 4,899 control days; and for the 'High' group, 97 case days and 253 control days (Supplementary Table S5). Table 3 presents the time-lagged association between categorized daily $PM_{2.5}$ exposure and asthma

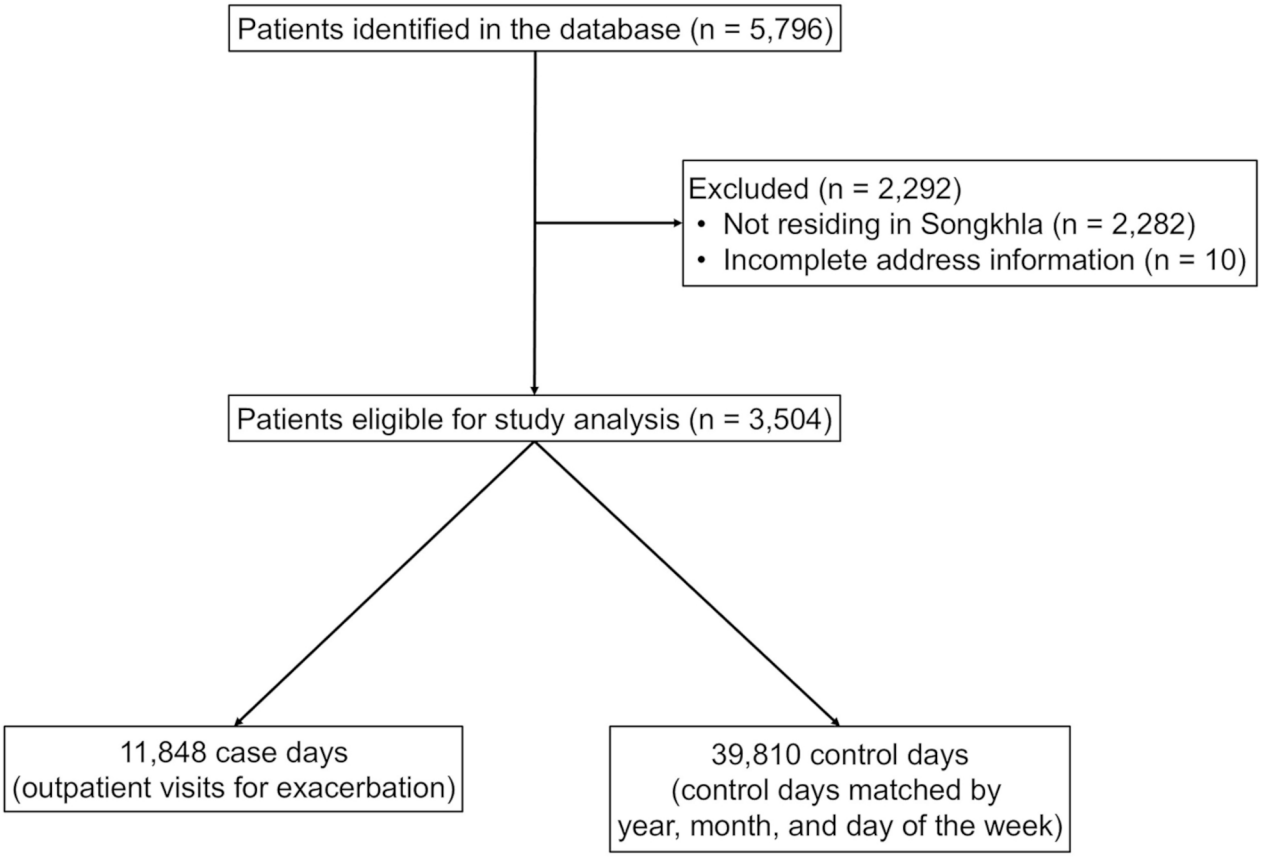

Fig. 3 Flowchart of study participants

Table 1 Characteristics of asthma patients

Variable	*N* (%)
Sex	
Male	1,327 (37.9%)
Female	2,177 (62.1%)
Age group at outpatient visits (years)*	
6–11	2,740 (5.3%)
12–17	1,309 (2.5%)
18–44	9,399 (18.2%)
45–64	18,290 (35.4%)
≥ 65	19,920 (38.6%)
Viral infection status at outpatient visits*	
Detected	67 (0.1%)
Not detected	768 (1.5%)

* Since asthma exacerbations may recur, individuals can be counted multiple times during outpatient visits

Table 2 Distribution of daily $PM_{2.5}$, temperature, and relative humidity across case and control days

Variable	Mean	SD	Min	Median	Max
Case days (*n* = 11,848)					
$PM_{2.5}$ (μg/m^3)	18.2	7.9	5.0	16.7	154.1
Temperature (°C)	28.3	1.9	18.3	28.4	36.8
Relative humidity (%)	76.9	5.4	64.0	76.0	99.9
Control days (*n* = 39,810)					
$PM_{2.5}$ (μg/m^3)	18.1	8.2	5.0	16.7	154.1
Temperature (°C)	28.3	2.0	18.3	28.4	36.8
Relative humidity (%)	76.9	5.4	64.0	76.0	99.9
Overall (*n* = 51,658)					
$PM_{2.5}$ (μg/m^3)	18.2	8.1	5.0	16.7	154.1
Temperature (°C)	28.3	2.0	18.3	28.4	36.8
Relative humidity (%)	76.9	5.4	64.0	76.0	99.9

SD, standard deviation; Min, minimum; Max, maximum

exacerbation, with the 'Very Low' group (0–15 μg/m^3) as the reference. For lag0 and lag2, $PM_{2.5}$ concentrations in the 'High' group were associated with increased odds ratios (ORs) of 1.54 (95% CI: 1.17, 2.03) and 1.41 (95% CI: 1.07, 1.85), respectively. Regarding cumulative effects, exposure in the 'High' group at lag01 to lag03 showed similar associations, with ORs of 1.59 (95% CI: 1.17, 2.17), 1.64 (95% CI: 1.16, 2.30), and 1.51 (95% CI: 1.07, 2.13), respectively. In contrast, exposure in the 'High' group at lag7 demonstrated a decreased OR of 0.59. Similarly, for the 'Moderate' group, exposure at lag3, lag6, lag7, and lag07 showed decreased ORs of 0.92, 0.92, 0.91, and 0.90, respectively (Table 3).

Regarding meteorological factors, no significant associations were found between daily temperature and asthma exacerbations (Supplementary Table S6). In

Table 3 Time-lagged associations between $PM_{2.5}$ exposure groups and asthma exacerbation, with the 0–15 μg/m³ group as the reference

Lag days	$PM_{2.5}$ >15–25 μg/m³		$PM_{2.5}$ >25–50 μg/m³		$PM_{2.5}$ >50 μg/m³	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Lag0	1.01 (0.96, 1.06)	0.600	1.06 (0.98, 1.14)	0.176	1.54 (1.17, 2.03)	0.002*
Lag1	1.03 (0.98, 1.08)	0.308	0.96 (0.89, 1.04)	0.313	1.14 (0.86, 1.50)	0.370
Lag2	1.01 (0.96, 1.06)	0.675	0.99 (0.91, 1.07)	0.735	1.41 (1.07, 1.85)	0.014*
Lag3	0.97 (0.92, 1.02)	0.218	0.92 (0.85, 0.99)	0.036*	1.12 (0.84, 1.50)	0.447
Lag4	0.99 (0.94, 1.04)	0.696	0.94 (0.87, 1.02)	0.158	0.98 (0.73, 1.33)	0.916
Lag5	0.96 (0.92, 1.01)	0.149	0.94 (0.87, 1.02)	0.137	0.88 (0.66, 1.17)	0.365
Lag6	0.97 (0.93, 1.02)	0.280	0.92 (0.85, 0.99)	0.037*	0.93 (0.70, 1.23)	0.608
Lag7	0.99 (0.95, 1.04)	0.835	0.91 (0.84, 0.99)	0.022*	0.59 (0.43, 0.81)	0.001*
Lag01	1.03 (0.98, 1.09)	0.206	1.04 (0.95, 1.13)	0.410	1.59 (1.17, 2.17)	0.003*
Lag02	1.01 (0.96, 1.07)	0.612	1.03 (0.94, 1.12)	0.521	1.64 (1.16, 2.30)	0.005*
Lag03	1.02 (0.97, 1.07)	0.506	1.01 (0.92, 1.10)	0.819	1.51 (1.07, 2.13)	0.019*
Lag04	0.99 (0.94, 1.04)	0.654	0.98 (0.89, 1.07)	0.603	1.28 (0.92, 1.78)	0.142
Lag05	0.97 (0.92, 1.02)	0.287	0.96 (0.87, 1.05)	0.359	0.97 (0.67, 1.41)	0.872
Lag06	0.96 (0.91, 1.02)	0.186	0.92 (0.83, 1.01)	0.081	0.72 (0.48, 1.08)	0.112
Lag07	0.96 (0.91, 1.01)	0.142	0.90 (0.82, 1.00)	0.043*	0.82 (0.53, 1.25)	0.349

OR, odds ratio; CI, confidence interval; * P-value < 0.05

contrast, relative humidity was significantly associated with asthma exacerbations at lag3, lag06, and lag07, with ORs of 1.35, 1.35, and 1.37, respectively (Supplementary Table S6).

For the continuous approach, a plot of predicted probabilities revealed a non-linear relationship between $PM_{2.5}$ exposure and the likelihood of asthma exacerbations. The curve initially rises gradually between 6 and 30 μg/m³, then slopes downward to 40 μg/m³. As the concentration increases from 40 to 60 μg/m³, the curve steepens sharply, reaching a distinct peak at approximately 60 μg/m³. This is followed by a steep downslope from 60 to 80 μg/m³. Beyond this point, the curve continues to descend more gradually, tapering off towards the highest concentrations (up to 154 μg/m³) (Fig. 4). No significant associations were found between $PM_{2.5}$ exposure and asthma exacerbations (Table 4).

From the sensitivity analysis comparing the results of PMM and RF imputation for the categorical approach, both methods showed positive associations between $PM_{2.5}$ exposure and asthma exacerbations in the initial days of exposure. For the PMM imputation, positive effects were observed for $PM_{2.5}$ concentrations > 50 μg/m³ at lag0, lag2, and lag01 to lag03, whereas the RF imputation showed positive effects for $PM_{2.5}$ concentrations > 25–50 μg/m³ at lag0 and $PM_{2.5}$ concentrations > 50 μg/m³ at lag2. Both methods also revealed negative associations. The PMM imputation showed negative effects for $PM_{2.5}$ concentrations > 25–50 μg/m³ at lag3, lag6, lag7, and lag07, as well as for $PM_{2.5}$ concentrations > 50 μg/m³ at lag7. In contrast, the RF imputation showed negative effects for $PM_{2.5}$ concentrations > 25–50 μg/m³ at lag2 and lag5 (Supplementary Table S7). In the continuous approach, however, neither imputation method showed significant associations with asthma exacerbations (Supplementary Table S8).

Subgroup analysis by age and sex

Supplementary Table S9 presents positive associations between $PM_{2.5}$ exposure and asthma exacerbations at early lags in several subgroups for the categorical approach. Both males and females exhibited positive associations, with males showing associations at lag0 and lag01, and females showing associations at lag2 and lag01 to lag02, with ORs ranging from 1.10 to 2.06. Positive associations were also observed across various age groups. For example, among children aged 6–11 years exposed to $PM_{2.5}$ concentrations in the 'Low' group (> 15–25 μg/m³), significant associations were found at lag6 and lag7. Among children aged 12–17 years exposed to the same $PM_{2.5}$ concentrations, a significant association was found at lag3. In adults aged 18–44 years, exposure to $PM_{2.5}$ concentrations in the 'High' group at lag0 and lag01 was associated with increased odds of asthma exacerbation. For adults aged 45–64 years exposed to both 'Low' and 'High' $PM_{2.5}$ concentrations, significant associations were observed at lag1 and lag2, respectively. Among adults aged 65 years or older, exposure to 'High' $PM_{2.5}$ concentrations at lag0 was also associated with increased odds of asthma exacerbation. In contrast, decreased ORs were predominantly observed at later lags (lag6, lag7, lag06, and lag07) across males, females, and adults aged 18 years and older. Due to the small number of individuals with viral testing results, a subgroup analysis based on viral testing could not be performed. For the continuous approach, no significant positive associations were observed among the subgroups (Supplementary Table S10).

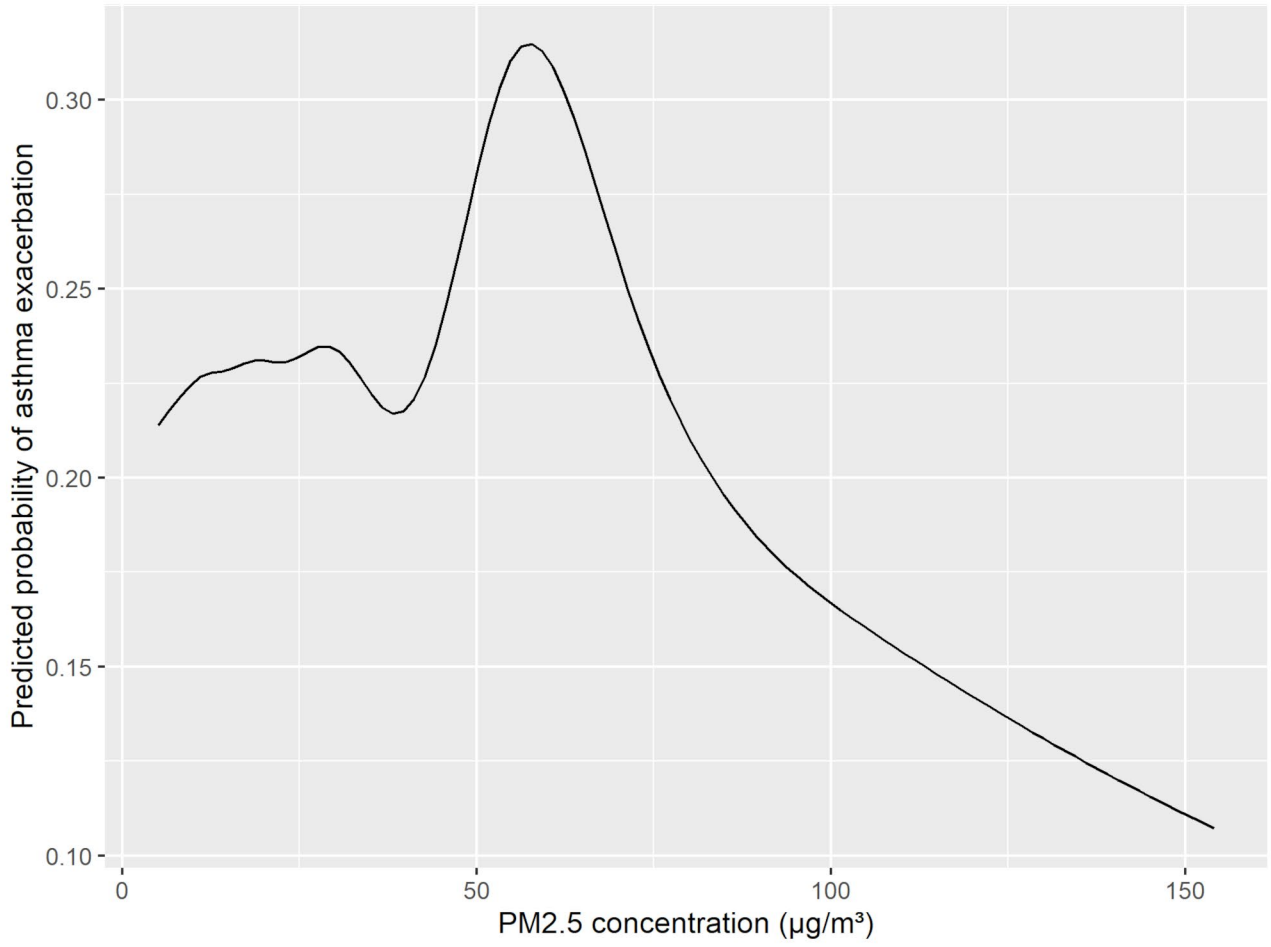

Fig. 4 Predicted probability of asthma exacerbation by $PM_{2.5}$ concentration (μg/m³)

Table 4 Time-lagged associations between $PM_{2.5}$ exposure (per 10 μg/m³ increase) and asthma exacerbation

Lag days	OR (95% CI) (per 10 μg/m³ increase in $PM_{2.5}$)	*P*-value
Lag0	1.18 (0.93, 1.50)	0.184
Lag1	1.23 (0.97, 1.56)	0.093
Lag2	1.25 (0.98, 1.60)	0.077
Lag3	0.97 (0.77, 1.23)	0.807
Lag4	1.08 (0.85, 1.37)	0.518
Lag5	1.01 (0.81, 1.26)	0.932
Lag6	0.86 (0.69, 1.08)	0.202
Lag7	0.94 (0.75, 1.19)	0.613
Lag01	1.19 (0.93, 1.53)	0.163
Lag02	1.23 (0.96, 1.59)	0.107
Lag03	1.10 (0.85, 1.43)	0.453
Lag04	1.18 (0.91, 1.52)	0.204
Lag05	1.18 (0.91, 1.54)	0.205
Lag06	1.13 (0.87, 1.45)	0.364
Lag07	1.09 (0.84, 1.41)	0.532

OR, odds ratio; CI, confidence interval

Discussion

In this study, we aimed to assess the relationship between short-term exposure to $PM_{2.5}$ and asthma exacerbation in a population living in areas with generally low daily $PM_{2.5}$ concentrations, as well as the influence of seasonal transboundary haze originating from neighboring countries. The WHO's interim targets for $PM_{2.5}$ provide milestone levels to guide air quality improvement efforts in countries with limited resources, ultimately aiming for the recommended Air Quality Guideline (AQG) levels. To emphasize the health impacts at different exposure levels, we categorized $PM_{2.5}$ concentrations based on these interim targets, aiming to raise awareness among stakeholders about the importance of achieving these goals. Using $PM_{2.5}$ concentrations of 0–15 μg/m³ as the reference, our results show that higher $PM_{2.5}$ concentrations (>50 μg/m³) were significantly associated with asthma exacerbations during early lags (lag0, lag2, and lag01 to lag03). These findings suggest short-term effects of $PM_{2.5}$ exposure within the first three days, which are consistent with time-series studies conducted in Taiwan, the USA,

and China, where baseline $PM_{2.5}$ concentrations were similarly low to those observed in our study [6, 8, 9]. Our study also highlights the immediate effects of $PM_{2.5}$ exposure from an individual-level perspective, aligning with case-crossover studies in Taiwan and Denmark [7, 10]. Regarding transboundary haze in Southeast Asia, our findings are consistent with a time-series study in Thailand, which reported that $PM_{2.5}$ exposure during periods of transboundary haze increased the number of hospital visits for asthma exacerbations [14]. Similarly, our results align with a study in Singapore, which found that increased air pollution was associated with higher rates of emergency department visits and hospital admissions for respiratory diseases [25]. Regarding the biological mechanisms, $PM_{2.5}$ promotes the generation of reactive oxygen species in the airways, leading to allergic inflammation and airway hyperresponsiveness [26]. However, the exact inflammatory pathways remain unclear. One alternative explanation for the observed early effects of $PM_{2.5}$ on acute asthma exacerbations could be the accessibility to medical services in Thailand, which may reduce the time gap between the onset of exacerbations and hospital visits, unlike in many Western countries.

Regarding meteorological factors, relative humidity was positively associated with asthma exacerbation at lag3, lag06, and lag07. These findings align with a study in China, reporting that both low (20%) and high (90%) relative humidity were associated with increased asthma outpatient visits at different lags (lag0-2 and lag2-4, respectively) [27]. Low humidity can lead to dehydration of airway membranes, triggering inflammation and bronchospasm as the body attempts to preserve moisture. In contrast, high humidity impairs mucus clearance in the airways and promotes the growth of bacteria and pathogens, exacerbating asthma symptoms. Previous studies also reported mixed associations between asthma exacerbation and both low and high temperature extremes [28, 29]. Asthma exacerbations during cold weather may be triggered by the effects of cold, dry air, which can lead to bronchospasm and increased mucus production, resulting in airflow limitation. Additionally, respiratory viral infections, which are more common in cold weather, may worsen asthma symptoms [30]. In contrast, exacerbations during warmer weather may be influenced by factors such as increased outdoor activities, heightened air pollution, and higher concentrations of allergens [31]. In contrast, this study found no significant associations between daily temperature and asthma exacerbation. The lack of statistical significance for temperature in our study may be due to the relatively stable meteorological conditions in Songkhla province, which has a consistently hot and humid climate, limiting the ability to detect associations between temperature and asthma exacerbation.

For analyses using continuous $PM_{2.5}$ concentrations and asthma exacerbations, no significant associations were observed. The lack of significant findings may be due to the nature of the data, where $PM_{2.5}$ concentrations remained relatively low even at the 95^{th} percentile. Notably, a plot of the predicted probability of asthma exacerbations based on $PM_{2.5}$ concentrations revealed a peak at approximately 60 $\mu g/m^3$, suggesting that this concentration may serve as a threshold. Accordingly, the associations could be more pronounced when $PM_{2.5}$ is categorized into meaningful levels that align with health risk thresholds.

In subgroup analyses, positive associations at early lags were observed for both males and females. A study in China reported positive associations for males, while another study in Taiwan found positive associations for females [6, 8]. One hypothesis for male predominance is that males may spend more time outdoors, leading to greater exposure to outdoor air pollutants [8]. Conversely, a meta-analysis suggested that females may be more susceptible to asthma exacerbations and emergency department visits than males [32]. One possible explanation is that females may have a heightened perception of dyspnea during asthma exacerbations and may differ in their attitudes toward chronic illness, influencing their willingness to seek medical assistance during acute exacerbations [33]. Additionally, an alternative explanation for the findings in this study is that the sample size for females is considerably larger than that for males, which could influence the observed results. Notably, our results show that adults exhibited significantly positive relationships with $PM_{2.5}$ exposure at early lags, consistent with studies conducted in China and Taiwan [6, 8]. Interestingly, children exhibited positive associations at lower $PM_{2.5}$ concentrations (>15–25 $\mu g/m^3$) compared to adults, with those aged 6–11 years showing significant effects at lag6 and lag7. This finding aligns with a study in China, reporting that the lagged effects of $PM_{2.5}$ exposure on pediatric outpatient visits for respiratory diseases could last up to 7 days [17]. The observed responses at lower $PM_{2.5}$ concentrations and longer lag periods suggest that children may be more susceptible to the pollutant, potentially due to different underlying biological mechanisms. One plausible explanation is that children have higher ventilation rates and larger lung surface area per unit of body weight compared to adults, leading to greater pollutant exposure [34]. However, it is important to note that these subgroup analyses involved multiple comparisons, which increases the risk of false-positive findings. Therefore, the results from these analyses should be interpreted with caution.

Interestingly, decreased ORs were predominantly observed at later lags for $PM_{2.5}$ concentrations greater than 25 $\mu g/m^3$. This trend was also seen across subgroups

of males, females, and adults at corresponding lags. This phenomenon may reflect the harvesting effect, where the most susceptible individuals are more likely to seek outpatient treatment shortly after exposure to pollution. As a result, the reduced pool of vulnerable individuals could contribute to the diminishing observed effects over time [35]. This pattern can be further understood through the definition of a 'case day', which marks the first day of a 7-day period during which an individual seeks treatment for asthma exacerbations. This captures the initial response to the acute effects of pollution. An alternative explanation for the observed pattern could involve avoidance and prevention behaviors by individuals with asthma. During transboundary haze events, which are often widely broadcast in real time, individuals with respiratory conditions may take proactive measures to minimize exposure to harmful $PM_{2.5}$ concentrations. These actions might include staying indoors or using air purifiers to reduce the impact of air pollution. As a result, individuals might not experience the same severity of health effects as those who do not adopt such behaviors, leading to a reduction in observed effects over time.

In our study, significant positive effects on asthma exacerbations were observed at $PM_{2.5}$ concentrations greater than 50 μg/m³, highlighting the importance of reducing $PM_{2.5}$ pollution to meet WHO air quality targets. These findings further underscore the need to consider the susceptibility of specific populations, particularly children, in public health policies and preventive measures aimed at mitigating the effects of $PM_{2.5}$ pollution. Children of school age, in particular, may be at greater risk of experiencing exacerbated asthma symptoms within a week of exposure, highlighting the importance of targeted interventions. Such interventions could include limiting school activities or offering flexible learning options, such as studying from home, for children with asthma during periods of transboundary haze. While our study identifies statistically significant associations between $PM_{2.5}$ exposure and asthma exacerbations, some of the observed odds ratios were close to 1 at the individual level. However, these associations may still have substantial public health implications. For example, using $PM_{2.5}$ concentrations of 0–15 μg/m³ as the reference, a 41% increase in the likelihood of asthma exacerbations associated with $PM_{2.5}$ concentrations > 50 μg/m³ at lag2 (OR = 1.41) would result in approximately 10,304 additional asthma exacerbations among the 25,132 asthma patients in 2019 across seven southern provinces in Thailand [14]. With an average cost of 1,289 Thai Baht per outpatient visit for asthma exacerbations, this would lead to a total outpatient cost of approximately 13.3 million Baht (around 415,000 USD) [36]. This could place a significant burden on healthcare systems, requiring increased stocks of medications, such as short-acting bronchodilators, systemic corticosteroids, and magnesium sulfate, as well as additional manpower to manage these exacerbations. These findings highlight the importance of considering the broader population-level effects and the potential strain on healthcare resources when interpreting the results.

In regions such as southern Thailand, where pollution levels are generally low but occasionally worsened by episodes of transboundary haze, the observed non-linear relationship between $PM_{2.5}$ exposure and asthma exacerbations in this study suggests that public health authorities should proactively implement timely interventions to mitigate the impacts of short-term $PM_{2.5}$ spikes. Establishing specific $PM_{2.5}$ concentration thresholds to trigger alerts and activate protective measures is therefore warranted. To safeguard vulnerable populations, particularly individuals with pre-existing respiratory conditions like asthma, the $PM_{2.5}$ activation threshold for protective measures such as short-duration closures of schools and sports fields should be aligned with or set lower than the World Health Organization's (WHO) guideline of 15 μg/m³, and potentially lower than the current Thailand air quality threshold of 37.5 μg/m³. From a preventive perspective, robust regional cooperation with neighboring Southeast Asian nations, notably Indonesia and Malaysia, is crucial to address the root causes of transboundary haze. This necessitates formal agreements and collaborative efforts to reduce agricultural open burning, a primary source of $PM_{2.5}$ during these events [37]. Additionally, raising public awareness about the health risks associated with transboundary haze and promoting the use of protective measures, such as face masks and air purifiers, could help reduce exposure during peak pollution events.

There are limitations to consider in this study. First, the study sample was restricted to residents of Songkhla province who attended the university-affiliated hospital, which may affect the representativeness of the sample and the generalizability of the findings to other regions. Second, the $PM_{2.5}$ exposure data were obtained from only seven monitoring stations across southern Thailand, which could introduce exposure misclassification. This error is likely non-differential and may lead to an underestimation of the observed associations [38]. Additionally, the use of postal addresses to define residents' districts may impact the accuracy of exposure measurements. Due to the sparse distribution of monitoring stations, the use of inverse distance weighted (IDW) interpolation may introduce exposure misclassification and non-differential estimation errors. These errors arise from the attenuation of pollution estimates at some centroids located far from monitoring stations, where the interpolation assigns lower weights to distant data points. Consequently, the interpolation may fail to capture the

full spatial variability of pollution levels, leading to over-smoothing. This could bias estimates for centroids in areas with limited monitoring, pulling them closer to the null value and potentially reducing the true effect of $PM_{2.5}$ on asthma exacerbations [39]. Despite this potential bias, our findings still showed associations between $PM_{2.5}$ exposure and asthma exacerbations. Third, as compared to the ultimate number of 3,504 patients included for the analysis, 10 individuals with incomplete address information were excluded from this study. This small proportion (0.3%) of excluded individuals is unlikely to introduce significant bias into the study's overall results, although any potential bias due to missing data cannot be completely ruled out [40]. Fourth, the sample in this study was imbalanced in terms of sex, with a considerably larger proportion of females compared to males. This imbalance may influence the study results, potentially leading to an overrepresentation of significant associations for females. Fifth, due to the small number of individuals who underwent respiratory viral testing (1.6% of all visits), and the even smaller proportion of those who tested positive for viral infections (0.1% of all visits), we were unable to perform a subgroup analysis to account for potential confounding by viral infections. These infections are known triggers for asthma exacerbations, which could potentially influence the effects of air pollution on asthma exacerbation [41]. The decision to perform viral testing was based on clinical indications rather than routine screening. Sixth, our study explored the relationships between asthma exacerbation and $PM_{2.5}$, as well as meteorological factors. However, it did not account for potential interactions between $PM_{2.5}$ and other air pollutants. Given the observed correlations between $PM_{2.5}$, ozone, and nitrogen dioxide, these unaccounted interactions may have influenced the associations between $PM_{2.5}$ and asthma exacerbations. Seventh, this study selected case and control days within short strata of a month to minimize the impact of time-varying factors. However, this approach may not fully capture sudden shifts in socioeconomic status during the stratum period, such as job loss or changes in healthcare access. Consequently, residual confounding from these time-varying factors could still influence the observed associations. Despite these limitations, the study has several strengths. The identification of asthma exacerbation episodes was based on both standardized diagnosis codes (ICD-10) and corresponding drug prescription data from the hospital's electronic database, ensuring accurate classification of asthma exacerbations. Moreover, the case-crossover design employed in this study effectively controls for both measured and unmeasured time-invariant confounders within individuals [18]. In addition, to account for missing data, the sensitivity analysis comparing results from PMM and RF imputation methods was conducted. The consistent findings across both imputation methods support the robustness of the results, providing additional confidence in the validity of the association between $PM_{2.5}$ exposure and asthma exacerbations.

Further studies should aim to account for respiratory viral infections and other pollutants, particularly ozone and nitrogen dioxide, given their known effects on asthma exacerbations [30, 42]. Additionally, since air pollution levels vary across different regions of Thailand, future research should investigate the relationship between air pollution and asthma exacerbation in areas with diverse terrain, atmospheric conditions, and pollution profiles.

Conclusion

This study highlights the short-term impact of $PM_{2.5}$ on asthma exacerbations, particularly during high-pollution episodes of transboundary haze, in regions that generally experience low levels of air pollution. Adhering to the WHO air quality targets can help mitigate the health impacts of $PM_{2.5}$, especially for vulnerable populations such as children. Future public health policies should prioritize protective measures for these at-risk groups, particularly in areas with generally low pollution but significant health risks during periods of intense pollution.

Abbreviations

AIC	Akaike's Information Criterion
AQG	Air Quality Guidelines
ICD-10	International Classification of Diseases, Tenth Revision
IDW	Inverse Distance Weighted interpolation
MICE	Multivariate Imputation by Chained Equations
$PM_{2.5}$	Particulate matter with an aerodynamic diameter of ≤ 2.5 μm
PMM	Predictive Mean Matching imputation
RF	Random Forest imputation
RSV	Respiratory syncytial virus
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

SV: Conceptualization, Methodology, Data Collection, Data Analysis, Visualization, Writing– Original Draft, Review & Editing.TI: Conceptualization, Methodology, Data Analysis, Supervision, Writing– Review & Editing.NB: Conceptualization, Data Collection, Data AnalysisRD: Data Analysis, Writing– Review & EditingPT: Data Analysis, Writing– Review & Editing.

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Data availability
Data supporting the results of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Human Research Ethics Unit, Faculty of Medicine, Prince of Songkla University (REC.67-214-9-4). A waiver for informed consent was granted due to the deidentified nature of the data.

Consent for publication
Not applicable.

Consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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