



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

Suebsai Varopichetsan

A Thesis Submitted in Partial Fulfillment of the Requirements for the
Degree of Master of Health Sciences and Clinical Research

Prince of Songkla University

2025

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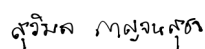
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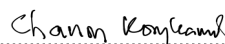
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ชื่อวิทยานิพนธ์	การสัมผัสระยะสั้นต่อฝุ่นละอองอนุภาคละเอียดและโรคหืดกำเริบ: การศึกษาแบบเคส-ครอสโอเวอร์ในจังหวัดสงขลาของประเทศไทย
ผู้เขียน	นายสืบสาย วโรพิเชฐสรรค์
สาขาวิชา	วิทยาศาสตร์สุขภาพและการวิจัยทางคลินิก
ปีการศึกษา	2567

บทคัดย่อ

การกำเริบของโรคหืดยังคงเป็นปัญหาสุขภาพที่สำคัญทั่วโลกถึงแม้จะมีความก้าวหน้าในการรักษาโรคอย่างต่อเนื่อง ทั้งนี้ ฝุ่นละอองอนุภาคละเอียดขนาดไม่เกิน 2.5 ไมครอน ($PM_{2.5}$) ถูกพบว่าเป็นปัจจัยกระตุ้นต่อโรคหืดกำเริบ อย่างไรก็ตาม การศึกษาเรื่องผลกระทบเฉียบพลันของ $PM_{2.5}$ โดยเฉพาะในพื้นที่ซึ่งมีระดับมลพิษค่อนข้างต่ำยังคงมีจำนวนจำกัด การศึกษานี้มีวัตถุประสงค์เพื่อพิจารณาความสัมพันธ์ระหว่างการสัมผัสรายวันต่อ $PM_{2.5}$ และโรคหืดกำเริบในจังหวัดสงขลา ภาคใต้ของประเทศไทย ซึ่งมักจะมีความเข้มข้นของ $PM_{2.5}$ ที่ใกล้เคียงกับแนวทางคุณภาพอากาศโลกขององค์การอนามัยโลก (WHO) และยังได้รับผลกระทบเป็นช่วงเวลาจากหมอกควันข้ามพรมแดนที่เกิดจากไฟป่า การศึกษานี้ใช้วิธีการศึกษาแบบเคสครอสโอเวอร์ โดยอาศัยข้อมูลค่ารายวันของ $PM_{2.5}$ และปัจจัยทางอุตุนิยมวิทยาตั้งแต่เดือนมกราคม พ.ศ. 2553 ถึงเดือนธันวาคม พ.ศ. 2566 ร่วมกับข้อมูลสุขภาพของผู้ป่วยโรคหืดของโรงพยาบาลสงขลานครินทร์ ทั้งนี้ การประมาณค่าความเข้มข้นรายวันของ $PM_{2.5}$ ในระดับอำเภออาศัยวิธีการ inverse distance weighted interpolation (IDW) นอกจากนี้ การวิเคราะห์ทางสถิติใช้แบบจำลองการถดถอยโลจิสติกแบบมีเงื่อนไข (Conditional logistic regression) ร่วมกับแบบจำลองความล่าช้าเชิงเวลาและแบบจำลองความสัมพันธ์ที่ไม่เป็นเชิงเส้นตรงในรูปแบบ cubic splines

การศึกษานี้วิเคราะห์วันซึ่งมีเหตุการณ์โรคหืดกำเริบ (case days) จำนวน 11,848 วัน และวันควบคุม (control days) จำนวน 39,810 วัน โดยมีค่าเฉลี่ยของระดับความเข้มข้นรายวันของ $PM_{2.5}$ ที่ $18.2 \mu g/m^3$ ทั้งนี้ เมื่อเปรียบเทียบกับความเข้มข้นของ $PM_{2.5}$ ที่ $0-15 \mu g/m^3$ พบว่าความเข้มข้นของ $PM_{2.5}$ ที่สูงกว่า $50 \mu g/m^3$ มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการเกิดโรคหืดกำเริบที่ time lag ต่างๆ ซึ่งคือ lag0 lag2 lag01 lag02 และ lag03 โดยมีค่า odds ratios (ORs) ในช่วงค่า 1.41 ถึง 1.64 สำหรับปัจจัยทางอุตุนิยมวิทยา ไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างค่ารายวันของอุณหภูมิและโรคหืดกำเริบ ในขณะที่ค่ารายวันของความชื้นสัมพัทธ์มีความสัมพันธ์อย่างมี

นัยสำคัญกับโรคหืดกำเริบที่ time lag3 lag06 และ lag07 ทั้งนี้ การวิเคราะห์กลุ่มย่อยพบความสัมพันธ์อย่างมีนัยสำคัญระหว่างการสัมผัส $PM_{2.5}$ และโรคหืดกำเริบที่ time lag ช่วงต้นในกลุ่มเพศชายและเพศหญิง นอกจากนี้ พบว่าเด็กอายุ 6-17 ปีมีความไวรับต่อโรคหืดกำเริบโดยเฉพาะการสัมผัสความเข้มข้นของ $PM_{2.5}$ ที่ 15–25 $\mu g/m^3$ กล่าวโดยสรุป การศึกษานี้แสดงถึงผลกระทบระยะสั้นของ $PM_{2.5}$ ต่อโรคหืดกำเริบโดยเฉพาะในช่วงเวลาที่มีมลพิษสูงจากหมอกควันข้ามพรมแดนในพื้นที่ซึ่งโดยรวมมีความเข้มข้นของ $PM_{2.5}$ ในระดับต่ำ ทั้งนี้ ช่วยเน้นย้ำถึงความสำคัญของการจัดการมลพิษเพื่อให้ไปถึงเป้าหมายทางคุณภาพอากาศขององค์การอนามัยโลก ซึ่งจะช่วยบรรเทาผลกระทบทางสุขภาพที่เกิดจาก $PM_{2.5}$ ต่อไป

Thesis Title	Short-term exposure to fine particulate matter and asthma exacerbation: A large population-based case-crossover study in Songkhla, Thailand
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Abstract

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 and are further influenced by seasonal transboundary haze from forest fires. 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.

The study included 11,848 case days and 39,810 control days, with a mean daily PM_{2.5} concentration of 18.2 $\mu\text{g}/\text{m}^3$. PM_{2.5} concentrations >50 $\mu\text{g}/\text{m}^3$ 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 $\mu\text{g}/\text{m}^3$). 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 6–17 years) exhibited greater susceptibility to asthma exacerbations, particularly at $PM_{2.5}$ concentrations of 15–25 $\mu\text{g}/\text{m}^3$. In summary, this study underscores the short-term effects of $PM_{2.5}$ on asthma exacerbations, even in areas with generally low pollution levels, emphasizing the importance of achieving the WHO air quality targets to mitigate health impacts from $PM_{2.5}$.

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I would like to extend my heartfelt thanks to the staff at the Division of Digital Innovation and Data Analytics and the Department of Family Medicine and Preventive Medicine, Faculty of Medicine, Prince of Songkla University, for their support and collaboration throughout the research process. Their invaluable assistance with data requests and navigating the ethical procedures was crucial to the successful completion of this study. I am also grateful to the many individuals who contributed to this research, though they are not named here.

Lastly, I dedicate this thesis to all the patients in Songklanagarind Hospital, with the hope that, in some small way, this work will contribute to a better understanding of the health impacts of air pollution and encourage policymakers to act in the best interests of public health.

Suebsai Varopichetsan

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List of Abbreviations

AIC	Akaike's Information Criterion
AQG	Air Quality Guidelines
AQI	Air Quality Index
CI	Confidence interval
ICD-10	International Classification of Diseases, Tenth Revision
IDW	Inverse Distance Weighted interpolation
MICE	Multivariate Imputation by Chained Equations
MAR	Missing at Random (MAR)
MCAR	Missing Completely at Random (MCAR)
MNAR	Missing Not at Random (MNAR)
OR	Odds Ratio
PM _{0.1}	Particulate matter with an aerodynamic diameter of $\leq 0.1 \mu\text{m}$.
PM _{2.5}	Particulate matter with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$.
PM ₁₀	Particulate matter with an aerodynamic diameter of $\leq 10 \mu\text{m}$
RSV	Respiratory syncytial virus
WHO	World Health Organization

1 Introduction

1.1 Background and Rationale

Asthma is a chronic non-communicable disease that places a significant burden on healthcare systems, affecting approximately 262 million people worldwide, including both children and adults.¹ It results from intricate interactions between genetic and environmental factors, leading to greatly diverse clinical symptoms and 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. Despite advancements in medication that enable effective asthma management, the occurrence of exacerbations remains a major challenge in asthma care. Exacerbations are episodes characterized by worsening symptoms and deteriorating lung function, which represent a significant deviation from the patients' baseline condition and often require treatment adjustments.² Exacerbations can be triggered by various factors, such as air pollutants, particularly fine particulate matter (PM_{2.5}, particles with a diameter ≤ 2.5 μm), viral infections, allergens, and even changes in weather conditions.

Air pollution, particularly from PM_{2.5}, poses a significant environmental health risk and contributes substantially to the global burden of respiratory diseases, including asthma. Approximately 99% of the world's population resides in areas with harmful concentrations of PM_{2.5}, especially in low- and middle-income countries in Asia and Africa.³ Recent studies have shown that even low concentrations of PM_{2.5} can lead to adverse health effects.⁴ Due to its ability to penetrate deep into the lungs and reach the alveoli, PM_{2.5} exposure is linked to the development of cardiopulmonary diseases and lung cancer.⁵ Earlier studies have highlighted the acute effects of PM_{2.5} on asthma exacerbations and lung function deterioration, especially in cities or regions with high PM_{2.5} concentrations.^{6–11} However, research on the acute effects of PM_{2.5} in areas with lower pollution levels, particularly those affected by seasonal transboundary haze in Southeast Asia, remains limited.

In Southeast Asia, air pollution is a pressing concern, with seasonal haze from agricultural and forest fires often elevating $PM_{2.5}$ concentrations and significantly deteriorating air quality, particularly in countries like Thailand. 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 is divided into 16 districts and lies within the Malay Peninsula, experiencing a tropical climate with warm temperatures and high 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 reported as $19.26 \mu\text{g}/\text{m}^3$. Although the province is considered a hypothetically less-polluted area according to the World Health Organization's (WHO) Global Air Quality Guidelines, its air quality can still fluctuate due to seasonal transboundary haze from forest fires, particularly during the June to September period each year.^{13–15}

To fill this research gap, this study aimed to examine the time-lagged association between daily $PM_{2.5}$ exposure and outpatient visits for asthma exacerbation at Songklanagarind Hospital in Songkhla province over a 14-year period, from January 2010 to December 2023. The findings will enhance knowledge of the acute effects of $PM_{2.5}$ on asthma exacerbations. Furthermore, these results can serve as a foundation for health surveillance systems and public health policies focused on preventing and mitigating the impacts of $PM_{2.5}$, especially for vulnerable populations such as children and the elderly.

1.2 Research Question

Is an increase in daily $PM_{2.5}$ concentrations associated with an increased odds of outpatient visits for asthma exacerbation within a short-term period?

1.3 Research Objectives

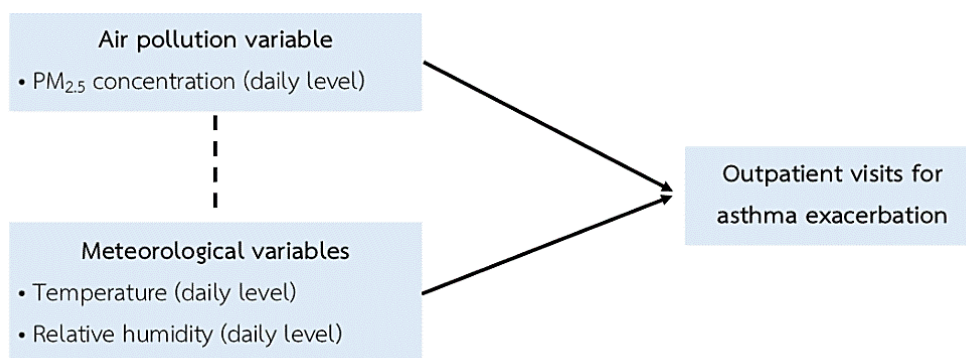
To examine the association between daily $PM_{2.5}$ concentrations and the odds of outpatient visits for asthma exacerbation at a hospital in Songkhla province, southern Thailand, over a specified short-term period.

1.4 Research Hypothesis

An increase in daily $PM_{2.5}$ concentrations is associated with an increased odds of outpatient visits for asthma exacerbation within a short-term period.

1.5 Conceptual Framework

Figure 1 Conceptual Framework



1.6 Practical Application of the Research

The findings of this study will enhance knowledge of the acute effects of PM_{2.5} on asthma exacerbations and guide the development of targeted health surveillance systems, particularly for vulnerable populations such as children and the elderly. Additionally, the results can support public health policies and interventions designed to mitigate the harmful effects of PM_{2.5} exposure, such as early warning systems or initiatives for pollution reduction in areas with high PM_{2.5} concentrations. These efforts could help prevent asthma exacerbations, reduce healthcare costs, and improve the quality of life for individuals at risk. Furthermore, public health authorities could use the results to advocate for stricter air quality standards and regulations, as well as encourage preventive measures, such as wearing masks or staying indoors during high pollution periods.

1.7 Scope of the Research

- Study population Patients aged 6 years and older with a diagnosis of asthma (International Classification of Diseases, Tenth Revision [ICD-10]: J45-J46) who reside in Songkhla province and receive outpatient treatment for asthma exacerbation at Songklanagarind Hospital
- Study area Songklanagarind Hospital
- Study period 1. Data collection period: Jan 1, 2010 – December 31, 2023
2. Analysis period: Jan 1, 2024 – December 31, 2024
- Variables Data from secondary databases are used as follows:

Dependent variable

- 1) Outpatient visits for asthma exacerbation, obtained from the Songklanagarind Hospital database

Independent variables

- 1) Daily PM_{2.5} concentrations in districts of Songkhla province, sourced from the Pollution Control Department database
- 2) Daily temperature levels in districts of Songkhla province, sourced from the Pollution Control Department database
- 3) Daily relative humidity levels in districts of Songkhla province, sourced from the Pollution Control Department database

Control variables for subgroup analysis

- 1) Sex
- 2) Age
- 3) Respiratory viral infection

These variables will be derived from the Songklanagarind Hospital database.

1.8 Operational Definitions

Asthma A heterogeneous respiratory disease, typically characterized by chronic airway inflammation, bronchial remodeling, and airway hyperresponsiveness.² Asthma is often marked by variable respiratory symptoms and expiratory airflow limitation. Common symptoms include cough, wheezing, shortness of breath, and chest tightness. The severity and frequency of symptoms can vary over time, often in response to specific triggers. For the purposes of this study, asthma is defined according to the International Classification of Diseases, Tenth Revision (ICD-10), as follows:¹⁶

- J45 Asthma
 - J45.0 Predominantly allergic asthma
 - J45.1 Nonallergic asthma
 - J45.2 Bronchial hyperresponsiveness
 - J45.8 Mixed asthma
 - J45.9 Asthma, unspecified

	• J46 Status asthmaticus
Asthma exacerbation	An episode characterized by worsening symptoms and deteriorating lung function, which represent a significant deviation from the patients' baseline condition and often require treatment adjustments. ² Exacerbations can be triggered by environmental factors such as air pollutants, particularly PM _{2.5} , respiratory viral infections, and allergens.
Respiratory viral infections	Infections caused by viruses that affect the respiratory system, such as respiratory syncytial virus (RSV), influenza A, and influenza B. Respiratory viral infection status is defined as having at least one positive test result for RSV, influenza A, or influenza B virus. These infections are known to exacerbate asthma symptoms and contribute to asthma attacks, especially in children or individuals with poorly controlled asthma.
Particulate Matter	A mixture of solid and liquid particles suspended in the air. These particles are classified based on their aerodynamic diameter:¹⁷ 1) Coarse particles (PM₁₀): Particulate matter with an aerodynamic diameter of ≤ 10 μm. These particles are typically inhaled into the upper airways. 2) Fine particles (PM_{2.5}): Particulate matter with an aerodynamic diameter of ≤ 2.5 μm. These smaller particles can penetrate deeper into the lungs and are of particular concern due to their potential to reach the alveolar region. 3) Ultrafine particles (PM_{0.1}): Particulate matter with an aerodynamic diameter of ≤ 0.1 μm. These particles are the smallest and can enter the bloodstream via the respiratory tract, posing significant health risks.
WHO's Air Quality Guidelines (AQG)	The World Health Organization's Air Quality Guidelines (AQG) provide global benchmarks for air quality, aiming to safeguard human health by encouraging national, regional, and city governments to reduce air pollution levels. The guidelines set recommended air quality

levels for common pollutants, including particulate matter, ozone, nitrogen dioxide, and sulfur dioxide, to help prevent the adverse health effects of air pollution.

Specifically for PM_{2.5}, the WHO recommends the following AQG levels:³

- Annual target: 5 µg/m³
- 24-hour target: 15 µg/m³

In addition, the WHO provides interim targets for PM_{2.5}, categorized into four levels, with Level 4 being the most stringent (i.e., closest to the AQG level):

- Annual targets: 35, 25, 15, 10 µg/m³ (Levels 1 to 4)
- 24-hour targets: 75, 50, 37.5, 25 µg/m³ (Levels 1 to 4)

The AQG level represents the optimum target for air quality, with the interim targets serving as progressive steps toward achieving this ideal level.

2 Literature Review

2.1 Air Pollution and Fine Particulate Matter (PM_{2.5})

Amid rapid urbanization, the World Health Organization (WHO) estimated in 2019 that approximately 99% of the global population lived in areas with air quality below international standards. Air pollution was linked to 6.7 million premature deaths annually, with the Southeast Asia and Western Pacific regions experiencing the highest mortality rates.³ These air pollutants were associated with essential causes of the deaths, including ischemic heart disease, stroke, lower respiratory tract infections, chronic obstructive pulmonary disease, and respiratory tract cancers.³ Major air pollutants include particulate matter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide.¹⁸ In response to this critical situation, the WHO updated the global Air Quality Guidelines (AQG) in 2021 to set stricter standards for key pollutants, comprising fine particles (PM_{2.5}), coarse particles (PM₁₀), carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. The annual average concentration of PM_{2.5} was reduced from 10 to 5 µg/m³, and the daily average concentration of PM_{2.5} was reduced from 25 to 15 µg/m³.³ In 2022, the WHO reported that the Southeast Asia region had an annual average PM_{2.5} concentration of 59 µg/m³ from 2010 to 2019, far exceeding the new standard, with concentrations ranging from 7 to 191.9 µg/m³.¹⁹

In Thailand, PM_{2.5} concentrations vary across different regions of the country.²⁰ A study conducted between 2014 and 2019 found that the daily average PM_{2.5} concentration was 37.53 µg/m³. Between 2020 and 2023, data from the Pollution Control Department's monitoring indicated that the daily PM_{2.5} concentration consistently exceeded the national standard of 50 µg/m³.²¹ As a result, in 2023, Thailand revised the national standard for air quality, lowering the annual average PM_{2.5} concentration from 25 to 15 µg/m³ and the daily average PM_{2.5} concentration from 50 to 37.5 µg/m³.²² In terms of regional differences in air pollution, southern Thailand exhibited a significantly better Air Quality Index (AQI) compared to the northern, central, and northeastern regions.¹³ Additionally, a 2019 study reported that the daily average PM_{2.5} concentration in Songkhla province, southern Thailand was 19.26 µg/m³.

However, the province is seasonally affected by transboundary haze from forest fires, particularly during the June to September period each year.¹⁵

2.2 Health Effects of PM_{2.5} on Asthma Exacerbation

Fine particulate matter (PM_{2.5}) is a crucial indicator for assessing the health impacts of air pollution.¹⁷ Due to its small diameter and large surface area, PM_{2.5} can easily absorb metals and other pollutants, remaining suspended in the air longer than larger particles. The respiratory system is the primary route of exposure. Once inhaled, PM_{2.5} can penetrate deep into the lungs, accumulating in the alveoli, where it induces oxidative stress, inflammatory responses, and apoptosis. These effects contribute to the development of cardiopulmonary diseases and lung cancer.^{5,23} Recent studies have shown that even low concentrations of PM_{2.5} can lead to significant health effects.⁴ Furthermore, a 2017 meta-analysis found that short-term exposure to PM_{2.5} was associated with increased mortality from all causes, as well as from cardiovascular and respiratory diseases.²⁴

Asthma is a chronic non-communicable disease that imposes a significant burden on healthcare systems, affecting approximately 262 million people worldwide in 2019, including both children and adults.¹ The global prevalence of asthma was estimated at 3,416 cases per 100,000 population.²⁵ In Thailand, asthma affects about 7% of the population.²⁶ Asthma arises from complex interactions between genetic predisposition and environmental factors, leading to diverse clinical symptoms and 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 are often exacerbated at night. Diagnosis is based on medical history, physical examination, and pulmonary function tests, which show reversible airway obstruction with bronchodilators. Asthma treatment primarily focuses on bronchodilators and anti-inflammatory medications to reduce symptoms, prevent exacerbations, and improve quality of life.

Asthma exacerbation refers to an episode marked by worsening symptoms and deteriorating lung function, which represent a significant deviation from the patients'

baseline condition and often require treatment adjustments.² Key triggers include air pollutants, especially PM_{2.5}; viral respiratory infections, such as respiratory syncytial virus (RSV), influenza, and rhinovirus; allergens, including dust mites, pet dander, and pollen; changes in weather; smoking; and exercise.^{27–29} Exacerbations can range from mild to severe, with some requiring emergency treatment or leading to fatal outcomes. Episodes of exacerbation may subside spontaneously or improve with treatment. They can remain absent for extended periods, ranging from weeks to months. Various clinical phenotypes have been proposed to classify asthma patients based on their characteristics, including allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity. However, these phenotypes show weak correlations with pathological findings or treatment responses, limiting their clinical utility.

Several studies, particularly in regions with high PM_{2.5} concentrations, demonstrated acute effects of PM_{2.5} exposure on asthma exacerbations, including increased emergency department visits and hospital admissions.^{6–10} In China, a study reported lung function deterioration in asthma patients after short-term exposure to PM_{2.5}.¹¹ However, research on the acute effects of PM_{2.5} exposure in areas with lower pollution levels, particularly those affected by seasonal transboundary haze in Southeast Asia, remains limited. Further investigation is needed to assess how these episodic increases in PM_{2.5} concentrations contribute to asthma exacerbations in areas with fluctuating pollution levels.

2.3 A Case-crossover Study Design

The case-crossover design is an epidemiological approach for investigating a transient effect of exposure on an acute event, which is widely used in studies examining air pollution and immediate health outcomes.³⁰ This design employs a self-controlled approach, where each participant serves as their own control, and includes only individuals experiencing the event of interest (referred to as “cases”). For each participant, the analysis compares their exposure right before the event (the “index” time) to exposure at comparable control times (the “referent” times). This within-

subject comparison allows for controlling time-invariant confounders by design, including sex, genetics, and socio-economic status. The case-crossover design assumes that exposure does not follow a time trend across the referent periods.³² Referent selection is critical to the case-crossover design for controlling time-dependent confounders, such as seasonality and the day-of-the-week effect.³²

In air pollution context, several referent selection methods have been used in case-crossover studies, with the time-stratified method being shown to avoid what is known as overlap bias. Overlap bias in case-crossover studies is similar to friend control bias in matched case-control studies.^{32,33} In both situations, potential controls are not randomly selected but are instead drawn from a group (an "overlapping roster") that could include individuals who might have been cases in a different study or context. This overlap can introduce bias, as the controls may not be entirely representative of the general population, thus potentially distorting the study results. The time-stratified referent selection method divides the study period into segments (strata), typically defined by individual months, and adjusts for seasonal and day-of-the-week effects by matching referent times to the same day of the week, month, and year as the index time. This method also avoids bias from time trends because referents are selected without a specific pattern relative to the index time.³² Other referent selection methods include the restricted unidirectional design, which selects referents only from before the index time; the full-stratum bidirectional design, which chooses all potential referents from both before and after the index time; the symmetric bidirectional design, which selects referents from both before and after the index time with specified time gaps (lags) between the referents and the index time; and the semisymmetric bidirectional design, which randomly selects one referent from before and after the index time, with fixed time gaps.³²

In early case-crossover studies with binary exposures, the Mantel-Haenszel estimator was commonly used for statistical analysis.³⁰ However, conditional logistic regression is generally preferred, as it can handle non-binary exposures and provides better control of additional confounders included in the regression model.³²

2.4 Statistical Methods for Case-crossover Studies

2.4.1 Conditional Logistic Regression for Case-crossover Analysis

Conditional logistic regression is an extension of regular logistic regression that is specifically designed for data with matched pairs or groups (strata), often used in case-control studies. In these studies, controls are matched to cases based on certain characteristics, such as age, gender, and marital status, to account for confounding factors. The core difference between conditional logistic regression and regular logistic regression lies in how the dependency between observations is handled. Regular logistic regression assumes that all observations are independent of each other, whereas conditional logistic regression explicitly accounts for the dependency between observations within each matched set or stratum. This dependency arises from the fact that cases and controls within the same stratum share certain characteristics, which are controlled for by the conditioning process in the model. The assumptions for conditional logistic regression are largely similar to those of regular logistic regression, with some additional considerations due to the stratified nature of the data. These assumptions include:³⁴

1. Independence between strata: Each stratum (or matched group) is assumed to be independent of others. There should be no correlation between different strata.
2. Linearity of the logit: There should be a linear relationship between the log-odds of the event and any continuous predictor variables, just as in regular logistic regression.
3. Absence of multicollinearity: The independent variables should not be highly correlated with each other, to avoid inflating the variance of the estimated coefficients.
4. Lack of strongly influential outliers: Outliers or influential points that have a disproportionate impact on the model should be minimized, as they can distort the results.

The conditional logistic regression model for matched pairs with multiple predictors is expressed as:³⁵

$$\text{logit}[P(Y_{ij} = 1)] = \alpha_i + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \dots + \beta_k X_{kij}$$

Where:

- $P(Y_{ij} = 1)$ represents the probability that the dependent variable Y takes the value 1 (i.e., occurrence of the event) for subject i within matched pair j
- α_i denotes the subject-specific intercept for subject i
- X_{kij} denotes the value of predictor X_k , where k is indexed from 1 to k , for subject i within matched pair j
- β_k denotes the coefficient for the predictor X_k , where k is indexed from 1 to k

2.4.2 Spatial Interpolation in Environmental Studies

Spatial interpolation refers to the method used to estimate the values of a variable at locations where measurements are not available, using information from known data points within a specified geographic area. The underlying assumption is that the estimated value for any given location is more strongly influenced by nearby points than by those farther away.³⁶ This method is particularly important in fields such as environmental science, geography, and air pollution monitoring, where data is often sparse or unevenly distributed. Spatial interpolation can be classified into multiple categories based on different criteria, including global and local methods, deterministic and stochastic methods, and exact and inexact methods.³⁶

2.4.2.1 Classification of Spatial Interpolation Methods

1. Global and local methods

Global methods involve interpolation over the entire dataset, assuming that the entire spatial domain influences the value at any point. This approach is generally used when the data exhibit smooth, continuous variation across the area. In contrast, local methods estimate values based on a smaller subset of neighboring data points and are often preferred in cases where spatial variability is localized. Local methods are particularly popular in environmental studies, such as air pollution mapping, because they offer better flexibility in capturing localized patterns. Local methods include techniques like Inverse Distance Weighted (IDW), Kriging, Thiessen polygons, and Density Estimation.

2. Deterministic and stochastic methods

Deterministic methods rely solely on spatial relationships between data points to predict values, producing consistent predictions for a given set of input data. Examples of deterministic methods include IDW and Thiessen polygons. Stochastic methods, on the other hand, incorporate randomness and statistical models to account for uncertainty in the data, producing results that reflect the inherent variability in spatial patterns. Kriging is a prime example of a stochastic method, as it provides not only estimates but also measures of uncertainty.

3. Exact and inexact methods

Exact methods generate interpolated values that perfectly match the known data points, ensuring that the interpolation curve or surface passes through all observed values. For example, Thiessen polygons are considered an exact method. Inexact methods, such as IDW and Kriging, do not necessarily pass through every data point but instead provide an approximation that minimizes overall prediction error.

2.4.2.2 Techniques Under the Local Interpolation Method

1. Inverse Distance Weighted (IDW) interpolation

IDW technique is a widely used local and deterministic method that estimates values at unsampled locations by assigning weights to nearby data points, with closer points having greater influence. The method is simple to implement and effective in situations where the spatial variability of the data decreases with distance. However, IDW method assumes that spatial correlation between points is solely based on distance, which can limit its accuracy when data exhibit more complex spatial patterns. Additionally, IDW method is considered an inexact method, as the interpolated values do not necessarily pass through all observed data points.

2. Kriging

Kriging is a sophisticated local and stochastic method that provides optimal estimates by considering both the distance and spatial correlation between data points. Unlike IDW method, Kriging does not rely solely on distance but models the spatial structure of the data through a variogram, allowing for more accurate predictions in areas with complex spatial relationships. One of the key advantages of Kriging is its ability to provide not only predictions but also quantifiable uncertainty, making it a powerful tool in environmental monitoring and air pollution studies. However, it is computationally intensive and requires a thorough understanding of spatial statistics, which may limit its applicability in some cases. Additionally, Kriging is an inexact method as the interpolated values do not necessarily match the observed data points.

3. Thiessen polygons

Thiessen polygons is a method of spatial interpolation where the space is divided into regions based on the proximity to each data point. Each polygon contains all locations that are closer to its defining data point than to any other. Thiessen polygons are an exact method and a local method, as they depend on the nearest data point, and the resulting interpolation is guaranteed to pass through each observed value. The primary advantage of this method is its simplicity and its suitability for

unevenly distributed data. However, it can result in sharp boundaries between regions, which may not always represent the natural variability of the phenomenon being studied.

4. Density Estimation

Density Estimation involves estimating the spatial distribution of data points within a defined area, often utilizing methods such as kernel smoothing. As a local interpolation method, it provides a smooth estimate of the data distribution, which is particularly useful for representing spatial patterns of phenomena such as air pollution. While this method can effectively capture broad spatial trends, it may also smooth over finer-scale variations and is not well-suited for data with sharp discontinuities.

2.4.2.3 Application of Local Interpolation Methods in Air Pollution Study

In the context of spatial interpolation for the distribution of particulate matter ($PM_{2.5}$ and PM_{10}), a previous study demonstrated that the Inverse Distance Weighted (IDW) method yielded superior results compared to other models, such as Radial Basis Functions, Ordinary Kriging, and Universal Kriging. Specifically, IDW exhibited the lowest mean absolute percentage error.³⁷

2.4.3 Handling Missing Data in Statistical Analysis

2.4.3.1 Missing Data and Missingness Mechanism

Missing data is a prevalent issue across various research fields, including environmental studies, and it requires careful handling to avoid bias and inaccuracies in results. Rubin's classification of missing data mechanisms serves as a crucial framework for understanding how missingness occurs in datasets:³⁸

1. Missing Completely at Random (MCAR)

Missing data are said to be MCAR when the missingness of data is completely independent of both observed and unobserved data. In other words, the probability of a value being missing is unrelated to any other values in the dataset. If the data are MCAR, any analysis performed on the observed data will be unbiased, though it may still reduce statistical power due to reduced sample size.

2. Missing at Random (MAR)

MAR occurs when the missingness of data is related to other observed variables, but not to the value of the missing data itself. For example, if certain measurements are more likely to be missing for individuals with lower income, but once income is accounted for, the missingness is unrelated to other factors. In cases of MAR, missing data can be handled effectively through statistical methods that model the relationship between missingness and observed data.

3. Missing Not at Random (MNAR)

MNAR arises when the missingness of data is related to the unobserved data itself. For instance, in a study of air pollution levels, higher pollution readings may be more likely to be missing in areas with extreme pollution. This type of missing data is the most challenging to handle, as it introduces systematic bias, and methods to address it require strong assumptions about the nature of the missingness mechanism.

Importantly, it is essential to recognize that the mechanism of missingness is often variable-specific. In other words, different variables in the same study may exhibit different types of missingness mechanisms (MCAR, MAR, or MNAR). Distinguishing between MAR and MNAR can be particularly challenging, as both can appear similar, especially when the relationship between missingness and the data is complex.³⁹

2.4.3.2 Methods for Handling Missing Data

Several approaches are available for handling missing data, depending on the underlying mechanism of missingness and the specific research objectives:³⁹

1. Complete case analysis (Listwise deletion)

This method involves removing all cases (i.e., observations) from the analysis that contain missing data for any variable. While this approach is straightforward, it is only valid when the data are MCAR. If the data are MAR or MNAR, this method can introduce substantial bias and inefficiency, as it disregards valuable information from partially missing observations.

2. Imputation of missing data

Imputation techniques replace missing values with estimates based on other available information. Two main types of imputation methods are commonly used:

2.1 Single imputation

Single imputation techniques involve replacing missing values with a single estimate. Examples include mean imputation (substituting the mean of the observed values) and last observation carried forward, which is commonly used in time series data. However, single imputation methods generally underestimate the standard errors, especially when the data are MAR or MNAR.

2.2 Multiple imputation

Multiple Imputation is a more robust and widely recommended technique for handling missing data, particularly when the missingness is MAR. Multiple imputation generates multiple plausible datasets by imputing the missing values using the distribution of observed data. The results from each imputed dataset are then combined to provide estimates that account for both missing data uncertainty and inherent variability. One of the most popular methods for multiple imputation is multivariate imputation by chained equations (MICE).

2.4.3.3 Multivariate Imputation by Chained Equations (MICE)

Multivariate imputation by chained equations (MICE) is an advanced and versatile method for handling missing data, particularly in complex datasets. It works by creating multiple imputations for each missing value through an iterative process. In each iteration, missing values are imputed using a regression model based on other observed variables, and this process continues until convergence is achieved. This creates several imputed datasets separately, which are then combined to account for

the uncertainty in the imputed values. MICE operates under the assumption that the data are missing at random (MAR), meaning the missingness can be explained by the observed data.⁴⁰ The process is termed "chained" because each variable with missing data is imputed one by one, using the imputed values of other variables in the model.

MICE offers several advantages in air pollution studies. It is highly flexible in handling various types of variables, such as continuous and categorical data, and can model complex relationships between them. Unlike single imputation methods, MICE generates multiple imputed datasets, enabling researchers to quantify the uncertainty of the imputed values and draw more robust conclusions. Additionally, by retaining all available data and properly accounting for missingness, MICE improves statistical power compared to methods like listwise deletion. This is particularly beneficial in environmental studies, where missing data may arise from sensor malfunctions or inaccessible regions. However, MICE has certain limitations. It assumes that the data are missing at random (MAR), and if the missingness is not random (e.g., missing not at random, MNAR), the results may be biased. Furthermore, MICE is computationally intensive, particularly for large datasets or when a high number of imputations is required. The process of selecting appropriate imputation models and determining the number of imputations can also be complex, often requiring advanced statistical expertise. The MICE process can be broken down into six key steps, each designed to iteratively improve the accuracy of imputing missing data.⁴⁰

- Step 1: Initial imputation

The first step involves filling in the missing data with basic placeholder values, such as the mean of the observed values. These initial imputations are temporary and serve as starting points for the subsequent steps in the process.

- Step 2: Setting placeholders back to missing

After the initial imputations, the placeholder values for one variable (referred to as "var") are reset to missing. This step allows for refinement of the imputation for this specific variable in the next stage.

- Step 3: Regression for variable "var"

At this stage, a regression model is applied to predict the missing values for the variable “var.” The model uses other variables in the dataset that are related to “var” to make these predictions. The regression model employed may resemble standard approaches such as linear or logistic regression.

- Step 4: Imputing missing values for "var"

Once the regression model has been applied, the missing values for “var” are replaced with the predicted values generated from the model. Both the observed and imputed values for “var” will then be used in the following steps.

- Step 5: Repeating the process for all variables

Steps 2 to 4 are repeated for every variable in the dataset that contains missing data. This constitutes one complete cycle, where all missing values are replaced with predictions derived from the relationships between variables.

- Step 6: Repeating the cycles for refinement

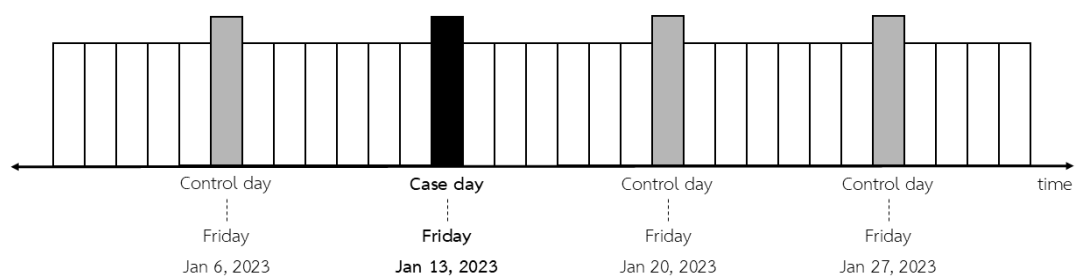
The process outlined in Steps 2 to 5 is repeated over several cycles. With each iteration, the imputed values are refined, gradually improving the accuracy of the imputations as the process progresses.

3 Research Methodology

3.1 The Case-Crossover Study Design and Its Application to Asthma Exacerbation

This retrospective case-crossover study investigated the daily effects of $PM_{2.5}$ concentration, temperature, and relative humidity on asthma exacerbation. Referent selection employed a time-stratified method, which could control for potential confounders such as seasonality, time trends, and day-of-week effects, while avoiding overlap bias.^{32,41} The study period was divided into monthly strata, with a "case day" defined as the first day of a 7-day period during which an individual sought outpatient treatment for asthma exacerbations. Control days, which were free of exacerbations, were selected to match the case day on the same day of the week, month, and year. Each case day was paired with three to four control days, all occurring on the same weekday within the same month. Figure 2 illustrates the process of time-stratified control day selection. For a case day specified as January 13, 2023 (represented by a black bar), control days (shown as gray bars) were selected from other Fridays in January 2023, ensuring the matching of temporal factors such as the day of the week.

Figure 2 Time-stratified control day selection



3.2 Health Data on Asthma Exacerbation

Secondary health data were retrieved from 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 Asthma, J46 Status Asthmaticus) 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, such as outpatient visit date, sex, age, 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 virus. The study population consisted of 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 old were not included due to difficulties in distinguishing asthma from other respiratory conditions.⁴² Individuals with incomplete address information were excluded. This study was approved by the Human Research Ethics Unit, Faculty of Medicine, Prince of Songkla University (REC.67-214-9-4), and was granted a waiver for informed consent due to the deidentified nature of the data.

3.3 Air Pollution and Meteorological Data

Hourly data on PM_{2.5} concentrations, temperature, and relative humidity were collected from seven monitoring stations, established by the Thai Pollution Control Department, across the southern provinces of Thailand (Figure 3). Prior to calculating daily values for these parameters, several preprocessing steps were undertaken to handle missing data, ensuring the integrity and completeness of the dataset. The PM_{2.5} concentration data were categorized into two groups based on the extent of missingness: data with more than 6 hours of missing values in a given day, and data with 6 hours or fewer of missing values. For the first group, missing values were imputed using the Inverse Distance Weighted (IDW) interpolation method, utilizing data from nearby monitoring stations. IDW interpolation is a spatial interpolation method that estimates the value at an unsampled location based on the weighted average of known values from surrounding locations. The weight assigned to each data point is

inversely proportional to its distance from the point being estimated. Specifically, the equation for IDW interpolation is:^{36,43}

$$Y(s) = \sum_{i=1}^N w_i x_i$$

Where:

- $Y(s)$ represents the estimate of PM_{2.5} concentration at point s
- x_i denotes PM_{2.5} concentration observed at a monitoring station at point i , where i is indexed from 1 to N .
- w_i denotes weighting of a monitoring station at point i , where i is indexed from 1 to N . The weighting is specified by $w_i = \frac{d_i^{-k}}{\sum_{i=1}^N d_i^{-k}}$, where d_i is the distance between point i and point s , and k is the specified power controlling the degree of local influence.
- N denotes the number of known points for monitoring stations

This method was applied only if at least two nearby stations had available data for the specified missing hours. In cases where fewer than two nearby stations had data for the missing hours, the missing values were left unfilled and subsequently handled with the second group of data. The monitoring stations included in this study were:

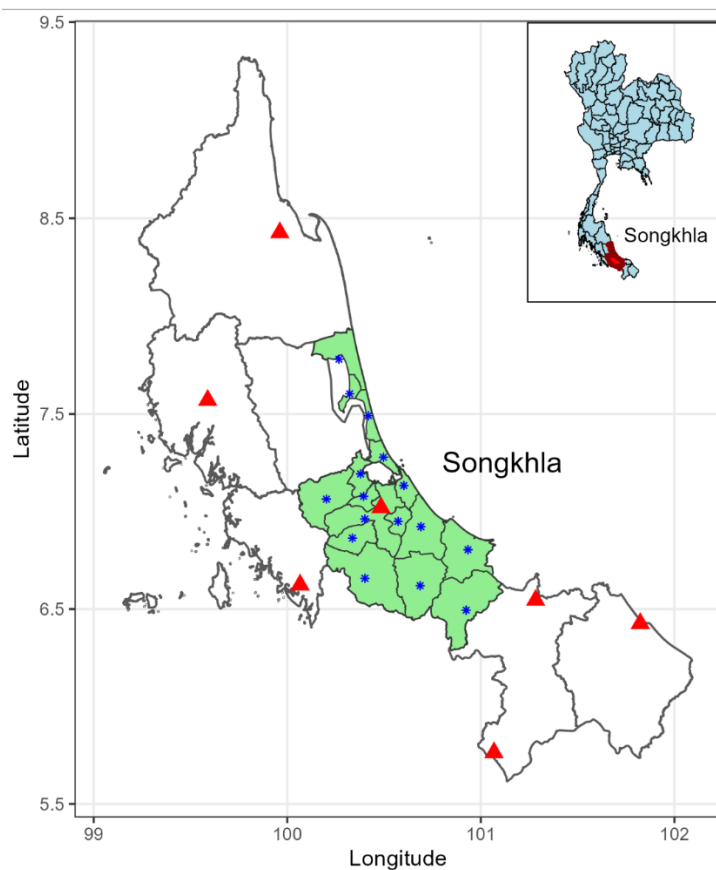
- Station 44t, Hat Yai district, Songkhla province
- Station 93t, Muang district, Trang province
- Station 89t, Muang district, Nakhon Si Thammarat province
- Station 62t, Muang district, Narathiwat province
- Station 63t, Muang district, Yala province
- Station 78t, Betong district, Yala province
- Station 80t, Muang district, Satun province

For the second group, missing values were imputed using the Multivariate Imputation by Chained Equations (MICE) method. This approach accounts for the relationships between PM_{2.5} and other variables, such as temperature and relative humidity. During MICE imputation, missing values for temperature and relative humidity were also imputed simultaneously, enabling the method to consider the

interdependencies among all three variables ($PM_{2.5}$, temperature, and relative humidity). This approach resulted in more consistent and coherent imputations across the dataset. Subsequently, daily values for each parameter were calculated as the averages of the corresponding hourly data.

To estimate daily measurements of $PM_{2.5}$ concentrations, temperature, and relative humidity at the district level, districts in Songkhla province were represented by spatial centroids, defined using the bounding box method as described by Duncan.⁴⁴ IDW interpolation was then applied to estimate district-level measurements based on data from nearby monitoring stations.

Figure 3 Geographical location of districts within Songkhla province (light green areas) and environmental monitoring stations across southern Thailand. Asterisks indicate district centroids, while 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.



3.4 Sample Size Calculation

The sample size was calculated using Dupont's formula for a matched case-control study, as outlined below:⁴⁵

$$N = \left(Z_{\beta} V_{\psi}^{\frac{1}{2}} + Z_{\frac{\alpha}{2}} V_1^{\frac{1}{2}} \right)^2 / (e_1 - e_{\psi})^2$$

Where:

- N represents the total sample size needed
- Z_{β} denotes the Z-value corresponding to the type II error rate (β).
- $Z_{\frac{\alpha}{2}}$ denotes the Z-value corresponding to the type I error rate (α).
- V_{ψ} denotes the variance of odds ratio between the case and control groups.
- V_1 denotes the variance of the exposure level in the case group.
- e_1 denotes the proportion of exposure in the case group.
- e_{ψ} denotes the proportion of exposure in the control group.

The R program (epiR package) was used to assist with the calculations, using the following parameters:

- p_0 : Prevalence of exposure in the control group, assumed to be 0.25.
- ϕ .coef: Correlation coefficient of exposure between the case and control groups, assumed to be 0.3.
- OR: Estimated odds ratio of exposure between the case and control groups, set to 1.17 based on a previous study indicating that an increase of 10 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ increased the likelihood of an emergency visit for asthma by 16.67%.⁶
- r : Ratio of the control group to the case group, set at 4:1, as the control day in each month (on the same weekday as the case day in a case-crossover study) may include 3 or 4 days.
- power: Study power, set to 0.8, corresponding to a β of 0.2.

- `conf.level`: Confidence level of the calculated results, set to 0.95, corresponding to an α of 0.05.

Using these parameters for a case-crossover study examining case and control days of the event of interest, the results of the calculation are as follows:

- Total sample size: 12,605 days (combined case and control days)
- Case days: 2,521 days
- Control days: 10,084 days

3.5 Statistical Analysis Methods

Descriptive statistics were used to summarize the distribution of case and control data for asthma exacerbations, PM_{2.5} concentrations, and meteorological factors. Spearman's rank correlation coefficients were calculated to assess the relationships between PM_{2.5} concentrations, temperature, and relative humidity. Conditional logistic regression was applied to evaluate the associations between asthma exacerbations and these environmental factors, accounting for the dependency of observations inherent in the case-crossover design. To investigate the relationship between exposure at various time points (i.e., PM_{2.5} concentration, temperature, and relative humidity) and the onset of asthma exacerbations, a time lag model (lag0 to lag7, and lag01 to lag07) was utilized in conjunction with conditional logistic regression. The time lags ranged from the same day (lag0) to 7 days prior to the outpatient visit (lag7). Additionally, 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). This time lag model 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.⁴⁶ The equation for the conditional logistic regression is:

$$\text{logit}[P(Y_{ij}^t = 1)] = \alpha_i + \beta_1 X_{1ij}^{t,z} + \beta_2 X_{2ij}^{t,z} + \dots + \beta_k X_{kij}^{t,z} + D + H$$

Where:

- $P(Y_{ij}^t = 1)$ represents the probability that the dependent variable Y takes the value 1 (i.e., occurrence of the event) at time t for subject i within matched pair j
- α_i denotes the subject-specific intercept for subject i
- $X_{kij}^{t,z}$ denotes the value of predictor X_k , where k is indexed from 1 to k , at lag z days prior to time t for subject i within matched pair j . The predictors are as follows:
 - X_1 : PM_{2.5} concentration ($\mu\text{g}/\text{m}^3$)
 - X_2 : Temperature ($^{\circ}\text{C}$)
 - X_3 : Relative humidity (%)
- β_k denotes the coefficient for the predictor X_k , where k is indexed from 1 to k
- D denotes an indicator variable for haze-affected days
- H denotes an indicator variable for public holidays

PM_{2.5} concentrations were categorized based on the WHO's 2021 air quality targets.³ The model was adjusted for temperature, relative humidity, haze-affected days, and public holidays, with daily temperature categorized based on established literature.^{47,48} Non-linear effects of temperature and relative humidity were evaluated using Akaike's information criterion (AIC). A natural cubic spline with 5 degrees of freedom was fitted for both temperature and relative humidity, based on the lowest AIC value. Haze-affected days were identified as days with PM_{2.5} concentrations exceeding the 95th percentile (31.21 $\mu\text{g}/\text{m}^3$), consistent with hotspot locations in Indonesia and Malaysia, based on data from the National Aeronautics and Space Administration (NASA)'s Fire Information for Resource Management System (MODIS satellite). The haze-affected days were further validated using 72-hour backward trajectories of air masses, modeled by the National Oceanic and Atmospheric Administration (NOAA)'s HYSPLIT model.¹⁵ Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, with P-values of less than 0.05 considered statistically significant. Subgroup analyses were conducted by sex, age, and respiratory viral infection status. All statistical analyses were performed using R software version 4.2.2 (R Foundation).

3.6 Ethical Considerations

This study adheres to ethical principles in human research as follows:

1) Respect for Human Dignity and Confidentiality

The researcher has handled health data, which is secondary data and cannot be traced back to individual identities, according to the procedures established by the Division of Digital Innovation and Data Analytics, Faculty of Medicine, Prince of Songkla University. The data is disclosed to the researcher only as necessary for the research objectives while ensuring confidentiality. Additionally, the results of the study cannot be traced back to identify any individual.

2) Beneficence and Non-maleficence

The researcher has handled health data confidentially, ensuring that it cannot be traced back to any individual, so it does not cause harm either physically or mentally to the participants. If this study is successful, its findings could enhance the air pollution database for Songkhla province. Furthermore, it will serve as a foundation for health surveillance systems and public health policies to prevent and mitigate the impacts of fine particulate matter, ultimately promoting better health and quality of life for the population.

4 Results

4.1 Data Preprocessing and Missing Data Management

Before managing missing values, a thorough data cleaning process was conducted to ensure the accuracy and reliability of the dataset. Initially, the distributions and ranges of the key variables ($PM_{2.5}$ concentration, temperature, and relative humidity) were examined. Descriptive statistics, including mean, median, and standard deviation, were computed for each variable. This allowed for the identification of values that fell outside the expected ranges. Outliers, or extreme values, were flagged based on their deviation from the general distribution. To assess the plausibility of these outliers, a comprehensive review of the literature was performed, along with an evaluation of known environmental or local factors that could explain extreme measurements. Temperature and relative humidity outliers were further assessed against typical seasonal patterns and regional climate data. In cases where extreme values were deemed implausible or likely due to data recording errors, they were removed from the dataset and subsequently addressed during the missing data management process.

Upon cleaning the dataset, the initial percentages of missingness for $PM_{2.5}$ concentration, temperature, and relative humidity were 15.7%, 7%, and 20.9%, respectively. Comparable proportions of missingness were also observed for dates with more than 6 hours of missing values for each variable, relative to the total number of dates in the study. When applying the Inverse Distance Weighted (IDW) interpolation method to replace missing values on such dates, the substituted values showed little variation and were not comparable to the variation observed in the actual data. This could be attributed to the limited number of stations with available data for the specified missing hours. Therefore, the missing values were left unfilled and subsequently imputed using the Multivariate Imputation by Chained Equations (MICE) method, along with the second group of data containing 6 hours or fewer of missing values in a given day. To evaluate the accuracy of the MICE method for $PM_{2.5}$

concentrations, a single validation set approach was applied. The Mean Absolute Error (MAE) for the imputed values was 5.63. The performance of the IDW interpolation model, used to estimate daily district-level values for PM_{2.5} concentrations, temperature, and relative humidity, was evaluated using Leave-One-Out Cross-Validation (LOOCV) for each variable. The Root Mean Square Error (RMSE) values for PM_{2.5} concentrations, temperature, and relative humidity were 2.27, 1.74, and 5.08, respectively.

4.2 Findings

4.2.1 Exposure Data on PM_{2.5}, Temperature, and Relative Humidity

During the study period, daily measurements of PM_{2.5}, temperature, and relative humidity by monitoring station are presented in Table 1. The mean daily PM_{2.5} concentrations ranged from 10.20 µg/m³ to 18.15 µg/m³, with median values between 9.88 µg/m³ and 16.75 µg/m³. The mean daily temperature ranged from 25.82°C to 28.44°C, with median temperatures between 25.69°C and 28.47°C. The mean daily relative humidity ranged from 76.70% to 83.29%, with medians ranging from 75.71% to 83.12%. Trends and variations in PM_{2.5} concentrations, temperature, and relative humidity across monitoring stations are illustrated in Figures 4, 5, and 6, respectively.

Table 1 Descriptive statistics for PM_{2.5}, temperature, and relative humidity by monitoring station in southern Thailand

Station	PM _{2.5} (µg/m ³)			Temperature (°C)			Relative humidity (%)		
	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med
Songkhla	18.15 (7.65)	4.67, 154.1 1	16.75	28.44 (1.97)	17.80, 37.52	28.47	76.70 (5.51)	64.00, 99.92	75.71
Narathiwat	14.87 (6.01)	2.17, 84.08	14.21	27.18 (1.15)	22.37, 30.66	27.22	79.61 (5.11)	67.00, 99.00	78.83
Satun	12.44 (6.15)	2.75, 66.46	11.08	28.31 (2.39)	21.18, 39.71	28.12	80.70 (6.63)	65.54, 98.92	80.96
Yala (Mueang)	17.25 (6.04)	6.79, 68.29	16.25	26.58 (1.62)	20.23, 30.87	26.60	80.60 (5.57)	70.42, 99.00	79.58
Yala (Betong)	10.20 (4.09)	2.04, 34.88	9.88	25.82 (1.38)	21.40, 30.75	25.69	82.32 (4.89)	64.96, 96.42	82.46
Nakhon Si Thammarat	14.38 (5.53)	4.17, 43.33	13.25	27.56 (1.53)	22.77, 32.05	27.52	79.60 (5.54)	67.08, 98.00	78.71
Trang	11.41 (4.55)	4.04, 40.54	10.51	27.24 (1.27)	23.00, 30.73	27.30	83.29 (5.54)	68.62, 97.67	83.12

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

Figure 4 Time series of daily PM_{2.5} concentrations by monitoring station in southern Thailand over a 14-year period (2010–2023)

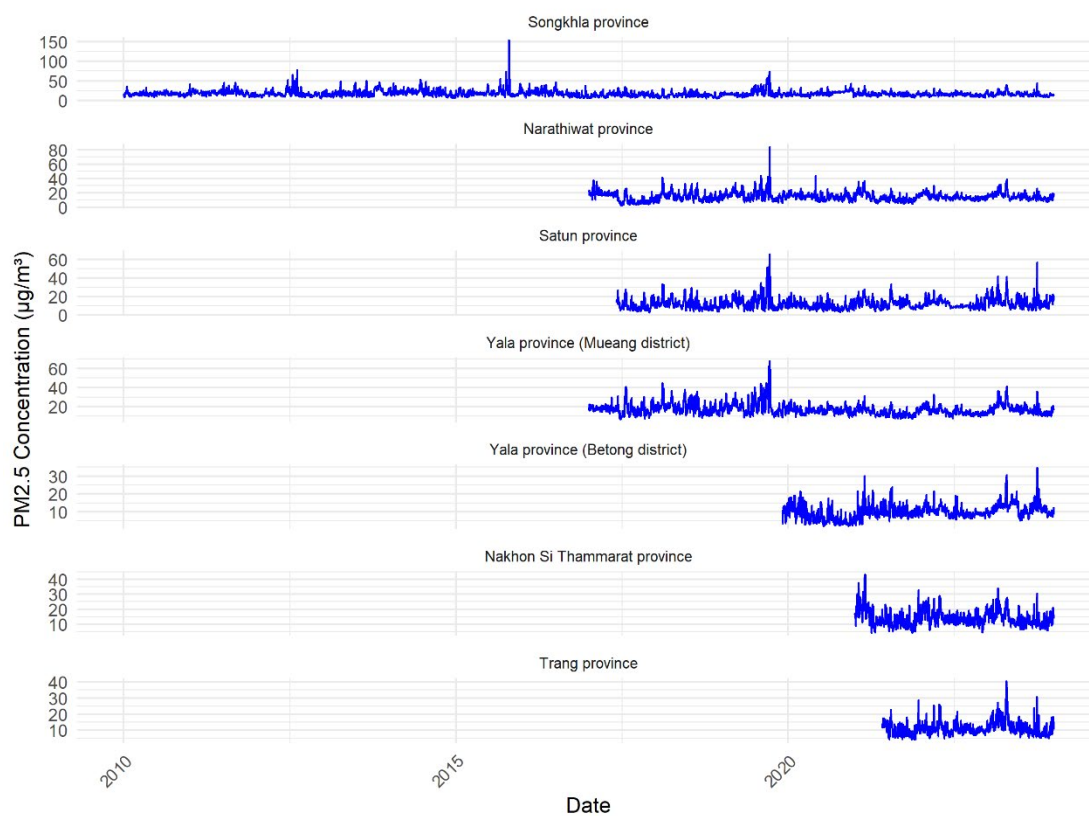


Figure 5 Time series of daily temperature by monitoring station in southern Thailand over a 14-year period (2010–2023)

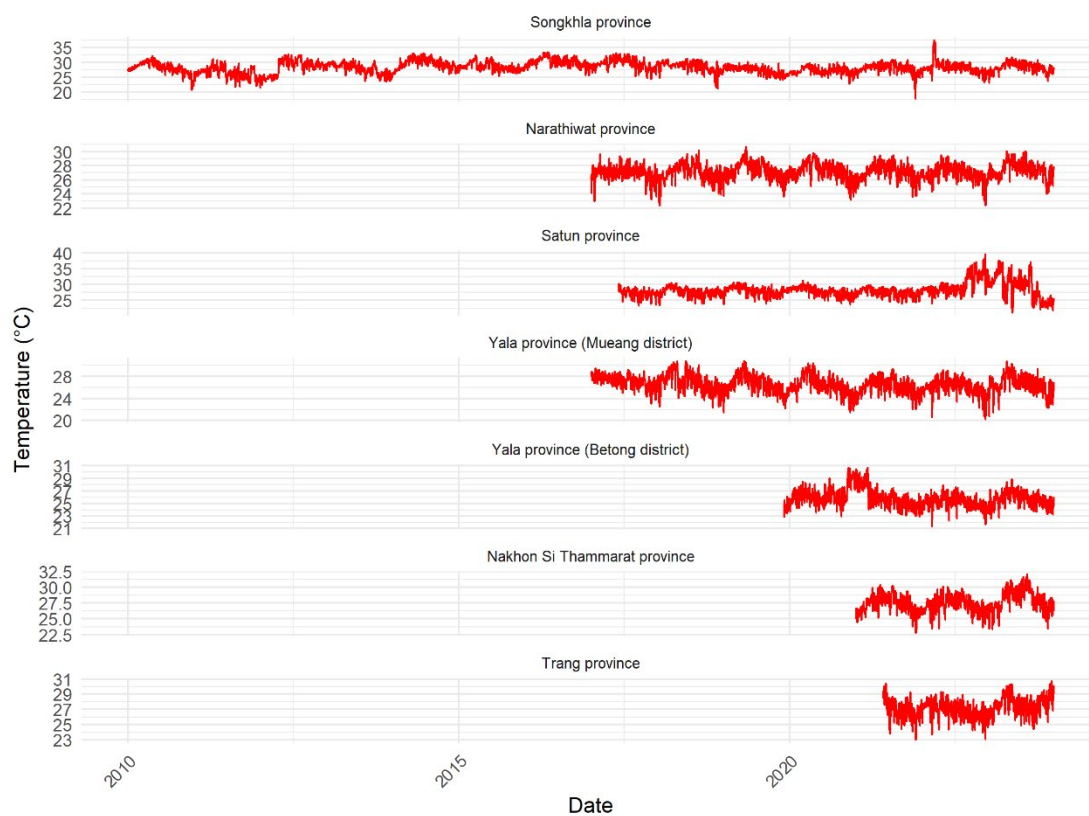
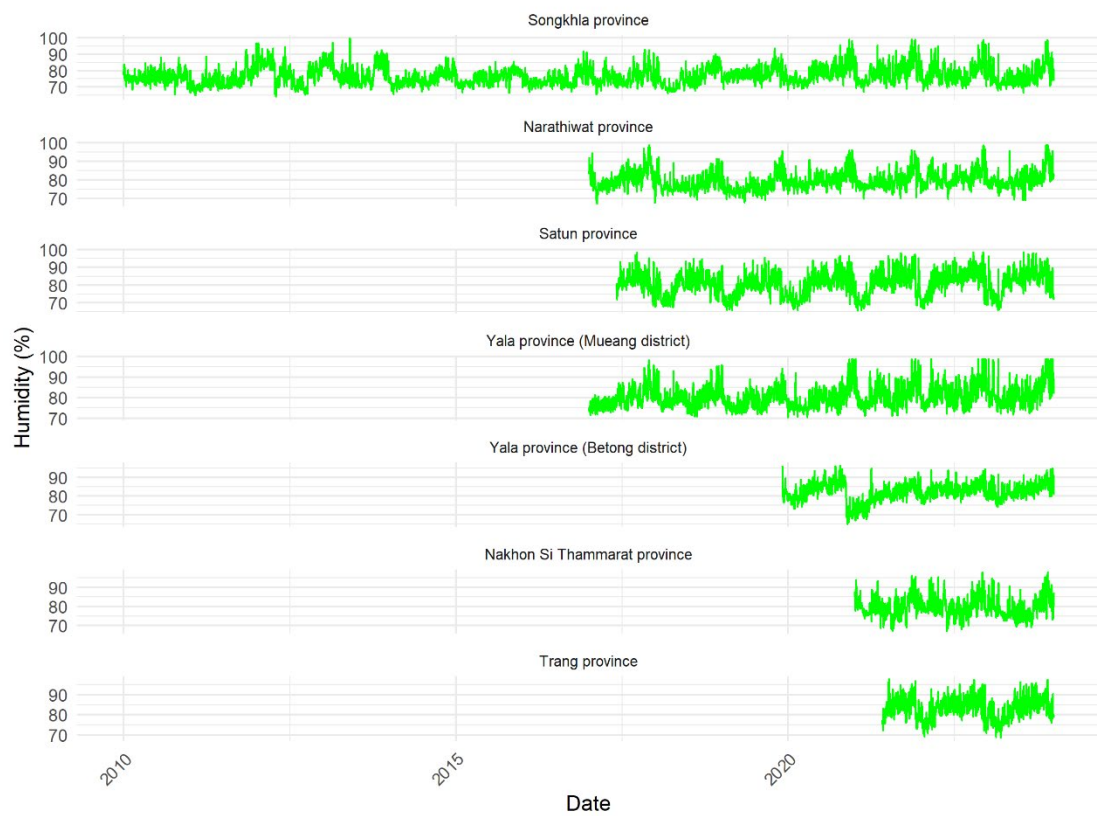


Figure 6 Time series of daily relative humidity by monitoring station in southern Thailand over a 14-year period (2010–2023)



At the district level, daily measurements of PM_{2.5}, temperature, and relative humidity are detailed in Table 2. The mean daily PM_{2.5} concentrations ranged from 17.03 µg/m³ to 18.06 µg/m³, with median values between 15.45 µg/m³ and 16.63 µg/m³. The minimum and maximum daily PM_{2.5} concentrations were 4.99 µg/m³ and 154.11 µg/m³, respectively. The mean daily temperature ranged from 27.82°C to 28.42°C, with median temperatures between 27.71°C and 28.45°C. The mean daily relative humidity ranged from 76.79% to 78.03%, with medians ranging from 75.83% to 77.51%. Trends and variations in PM_{2.5} concentrations across districts are illustrated in Figure 7.

Table 2 Descriptive statistics for PM_{2.5}, temperature, and relative humidity by district in Songkhla province, Thailand

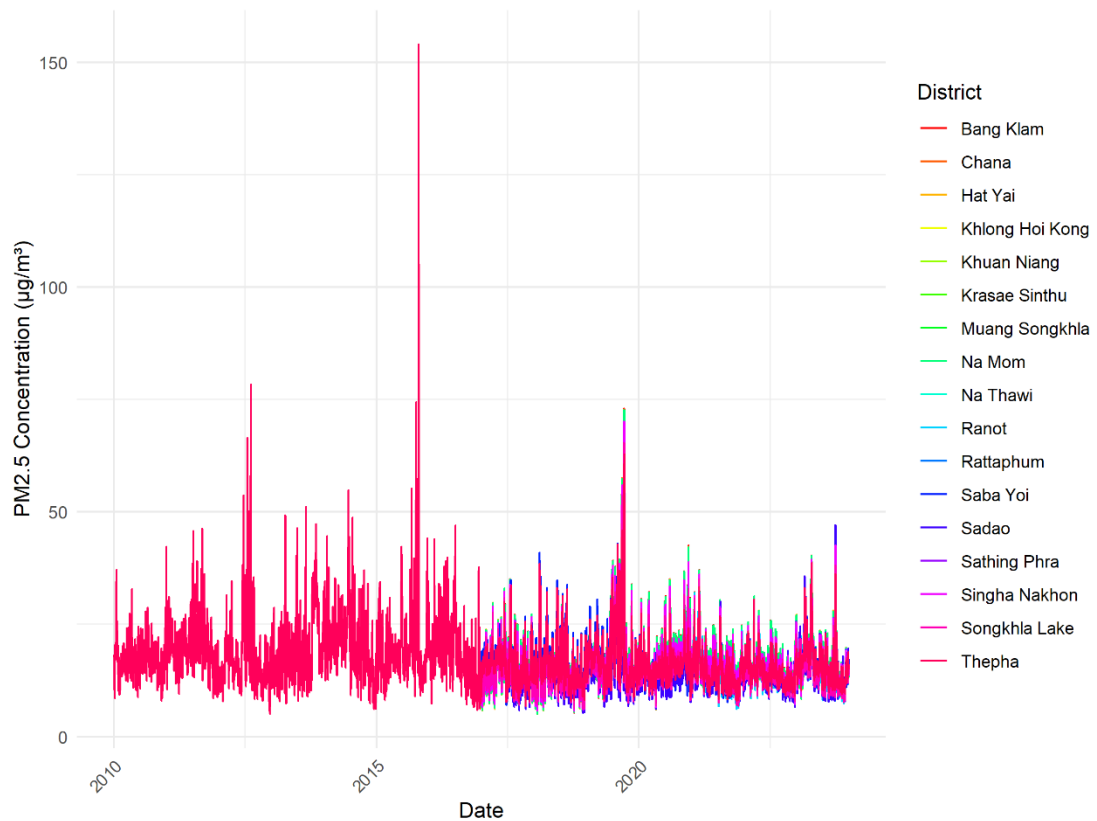
District	PM _{2.5} (µg/m ³)			Temperature (°C)			Relative humidity (%)		
	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med
Bang Klam	18.06 (7.61)	4.99, 154.1	16.62	28.42 (1.94)	18.30, 36.88	28.44	76.79 (5.45)	64.00, 99.92	75.83
		1							
Chana	17.89 (7.49)	5.06, 154.1	16.46	28.33 (1.89)	19.46, 35.12	28.35	77.05 (5.31)	64.00, 99.92	76.21
		1							
Hat Yai	18.04 (7.61)	5.04, 154.1	16.62	28.42 (1.94)	18.35, 36.84	28.45	76.81 (5.44)	64.00, 99.92	75.87
		1							

District	PM _{2.5} (µg/m ³)			Temperature (°C)			Relative humidity (%)		
	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med
Khlong Hoi Kong	17.57 (7.53)	5.06, 154.1	16.17	28.39 (1.86)	20.34, 34.50	28.43	77.18 (5.31)	64.00, 99.92	76.42
		1							
Khuan Niang	17.90 (7.56)	5.06, 154.1	16.47	28.39 (1.90)	19.17, 35.73	28.41	76.95 (5.36)	64.00, 99.92	76.08
		1							
Krasae Sinthu	17.39 (7.49)	5.06, 154.1	15.88	28.23 (1.82)	20.73, 33.47	28.22	77.48 (5.21)	64.00, 99.92	76.91
		1							
Muang Songkhla	18.01 (7.57)	5.06, 154.1	16.60	28.39 (1.93)	18.65, 36.34	28.41	76.87 (5.40)	64.00, 99.92	75.96
		1							
Na Mom	18.06 (7.60)	5.06, 154.1	16.63	28.41 (1.94)	18.33, 36.80	28.43	76.81 (5.44)	64.00, 99.92	75.88
		1							
Na Thawi	17.49 (7.39)	5.06, 154.1	15.87	28.14 (1.83)	20.73, 33.47	28.12	77.61 (5.20)	64.00, 99.92	77.12
		1							
Ranot	17.28 (7.50)	5.06, 154.1	15.75	28.19 (1.81)	20.73, 33.47	28.15	77.58 (5.18)	64.00, 99.92	77.09
		1							

District	PM _{2.5} (µg/m ³)			Temperature (°C)			Relative humidity (%)		
	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med	Mean (SD)	Min, Max	Med
Rattaphum	17.50 (7.52)	5.06, 154.1	16.08	28.37 (1.85)	20.73, 33.89	28.40	77.25 (5.30)	64.00, 99.92	76.58
		1							
Saba Yoi	17.77 (7.38)	5.06, 154.1	16.36	27.82 (1.94)	20.73, 33.47	27.71	78.03 (5.36)	64.00, 99.92	77.51
		1							
Sadao	17.03 (7.58)	5.06, 154.1	15.42	28.34 (1.86)	20.73, 33.47	28.36	77.63 (5.41)	64.00, 99.92	77.17
		1							
Sathing Phra	17.55 (7.48)	5.06, 154.1	16.08	28.27 (1.84)	20.73, 33.47	28.27	77.33 (5.22)	64.00, 99.92	76.67
		1							
Singha Nakhon	17.86 (7.53)	5.06, 154.1	16.45	28.36 (1.89)	19.53, 35.17	28.38	77.02 (5.33)	64.00, 99.92	76.17
		1							
Thepha	17.81 (7.32)	5.06, 154.1	16.30	27.97 (1.88)	20.73, 33.47	27.93	77.75 (5.26)	64.00, 99.92	77.17
		1							

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

Figure 7 Time series of daily PM_{2.5} concentrations by district in Songkhla province, Thailand, over a 14-year period (2010–2023)



4.2.2 Impact of PM_{2.5} Exposure on Asthma Exacerbation

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 (Figure 8). 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 3). 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 4). 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 Table 5.

Figure 8 Flowchart of study participants

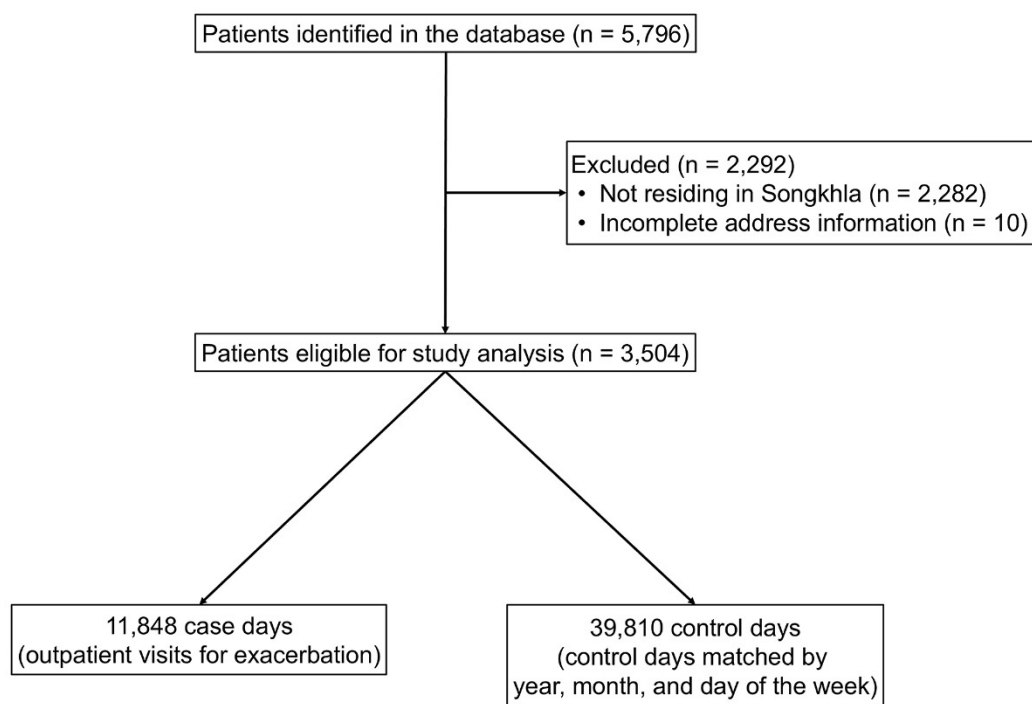


Table 3 Characteristics of asthma patients

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 – 24	1,799 (3.5%)
25 – 34	2,960 (5.7%)
35 – 44	4,640 (9.0%)
45 – 54	7,746 (15.0%)
≥55	30,464 (59.0%)
Viral infection status at outpatient visits*	
Detected	67 (0.1%)
Not detected	768 (1.5%)

* Since asthma exacerbations may recur, individuals may be counted more than once during outpatient visits

Table 4 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}	18.2	7.9	5.0	16.7	154.1
Temperature	28.3	1.9	18.3	28.4	36.8
Humidity	76.9	5.4	64.0	76.0	99.9
Control days (n = 39,810)					
PM _{2.5}	18.1	8.2	5.0	16.7	154.1
Temperature	28.3	2.0	18.3	28.4	36.8
Humidity	76.9	5.4	64.0	76.0	99.9

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

Table 5 Spearman's correlation of PM_{2.5}, temperature, and relative humidity.

	PM _{2.5}	Temperature	Relative Humidity
PM _{2.5}	1.00	0.09	-0.23
Temperature	0.09	1.00	-0.50
Relative Humidity	-0.23	-0.50	1.00

According to the WHO's 2021 Air Quality Guidelines (AQG), daily PM_{2.5} concentrations were categorized into four groups: Very Low (0–15 µg/m³), Low (>15–25 µg/m³), Moderate (>25–50 µg/m³), and High (>50 µg/m³). 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 (Table 6). Table 7 presents the time-lagged association between categorized daily PM_{2.5} exposure and asthma exacerbation, with the Very Low group (0-15 µg/m³) as the reference. For lag0, PM_{2.5} concentrations in the ‘Low’, ‘Moderate’, and ‘High’ groups were associated with increased odds ratios (ORs) of 1.01, 1.06, and 1.54, respectively, with a significant association observed for the ‘High’ group. Similar association patterns were observed for lag2. For lag3 to lag7, most associations showed decreased ORs, although some positive associations were noted for the ‘High’ group. Regarding cumulative effects, lag01 to lag03 showed positive associations between PM_{2.5} and asthma exacerbation, consistent with those observed for lag0 and lag2. In contrast, lag04 to lag07 displayed patterns similar to those seen for lag3 to lag7, with decreased ORs in several lags and few statistically significant associations (Table 7).

Table 6 Total number of case and control days by PM_{2.5} exposure group

PM _{2.5} group	Case days	Control days	Total days
0 – 15 µg/m ³	4,400	15,036	19,436
>15 – 25 µg/m ³	5,871	19,622	25,493
>25 – 50 µg/m ³	1,480	4,899	6,379
>50 µg/m ³	97	253	350

Table 7 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/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lag0	1.01 (0.96, 1.06)	1.06 (0.98, 1.14)	1.54 (1.17, 2.03)*
Lag1	1.03 (0.98, 1.08)	0.96 (0.89, 1.04)	1.14 (0.86, 1.50)
Lag2	1.01 (0.96, 1.06)	0.99 (0.91, 1.07)	1.41 (1.07, 1.85)*
Lag3	0.97 (0.92, 1.02)	0.92 (0.85, 0.99)*	1.12 (0.84, 1.50)
Lag4	0.99 (0.94, 1.04)	0.94 (0.87, 1.02)	0.98 (0.73, 1.33)
Lag5	0.96 (0.92, 1.01)	0.94 (0.87, 1.02)	0.88 (0.66, 1.17)
Lag6	0.97 (0.93, 1.02)	0.92 (0.85, 0.99)*	0.93 (0.70, 1.23)
Lag7	0.99 (0.95, 1.04)	0.91 (0.84, 0.99)*	0.59 (0.43, 0.81)*
Lag01	1.03 (0.98, 1.09)	1.04 (0.95, 1.13)	1.59 (1.17, 2.17)*
Lag02	1.01 (0.96, 1.07)	1.03 (0.94, 1.12)	1.64 (1.16, 2.30)*
Lag03	1.02 (0.97, 1.07)	1.01 (0.92, 1.10)	1.51 (1.07, 2.13)*
Lag04	0.99 (0.94, 1.04)	0.98 (0.89, 1.07)	1.28 (0.92, 1.78)
Lag05	0.97 (0.92, 1.02)	0.96 (0.87, 1.05)	0.97 (0.67, 1.41)
Lag06	0.96 (0.91, 1.02)	0.92 (0.83, 1.01)	0.72 (0.48, 1.08)
Lag07	0.96 (0.91, 1.01)	0.90 (0.82, 1.00)*	0.82 (0.53, 1.25)

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

4.2.3 Influence of Temperature and Relative Humidity on Asthma Exacerbation

Although daily temperature was associated with increased odds of asthma exacerbations at several lags (lag0 to lag2, lag5, and lag01 to lag07), none of these associations reached statistical significance (Table 8). In contrast, relative humidity was positively associated with asthma exacerbations across all lags, with significant associations observed at lag3, lag06, and lag07 (Table 8).

Table 8 Time-lagged associations between temperature, relative humidity, and asthma exacerbation

Lag days	Temperature	Relative humidity
	OR (95% CI)	OR (95% CI)
Lag0	1.41 (0.71, 2.79)	1.08 (0.81, 1.43)
Lag1	1.04 (0.54, 1.98)	1.16 (0.87, 1.54)
Lag2	1.03 (0.56, 1.91)	1.12 (0.84, 1.50)
Lag3	0.76 (0.40, 1.43)	1.35 (1.02, 1.78)*
Lag4	0.99 (0.53, 1.84)	1.27 (0.96, 1.68)
Lag5	1.24 (0.67, 2.32)	1.22 (0.92, 1.61)
Lag6	0.94 (0.55, 1.63)	1.13 (0.85, 1.50)
Lag7	0.98 (0.54, 1.78)	1.06 (0.80, 1.40)
Lag01	1.38 (0.82, 2.34)	1.17 (0.87, 1.56)
Lag02	1.39 (0.85, 2.26)	1.19 (0.88, 1.61)

Lag days	Temperature	Relative humidity
	OR (95% CI)	OR (95% CI)
Lag03	1.15 (0.77, 1.70)	1.25 (0.96, 1.63)
Lag04	1.13 (0.77, 1.68)	1.27 (0.97, 1.68)
Lag05	1.08 (0.74, 1.60)	1.32 (0.99, 1.76)
Lag06	1.05 (0.72, 1.52)	1.35 (1.01, 1.81)*
Lag07	1.01 (0.69, 1.48)	1.37 (1.01, 1.85)*

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

4.2.4 Subgroup Analysis by Age and Sex

Table 9 presents positive associations between PM_{2.5} exposure and asthma exacerbations at early lags in several subgroups. 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 an 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. Due to the small

number of individuals with viral testing results, a subgroup analysis based on viral testing could not be performed.

Table 9 Subgroup analysis of time-lagged associations between PM_{2.5} exposure and asthma exacerbation by sex and age group

Subgroup	Lag days	PM _{2.5} >15–25	PM _{2.5} >25–50	PM _{2.5} >50 µg/m ³
		µg/m ³	µg/m ³	
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex				
Male	lag0	1.04 (0.96, 1.13)	1.15 (1.00, 1.31)*	2.06 (1.29, 3.30)*
Male	lag1	1.06 (0.97, 1.15)	0.99 (0.86, 1.13)	1.14 (0.72, 1.82)
Male	lag2	1.03 (0.95, 1.12)	1.02 (0.89, 1.17)	1.14 (0.71, 1.83)
Male	lag3	0.92 (0.85, 1.00)	0.88 (0.77, 1.01)	0.83 (0.50, 1.38)
Male	lag4	0.97 (0.89, 1.05)	0.86 (0.75, 0.98)*	0.68 (0.40, 1.15)
Male	lag5	1.01 (0.93, 1.09)	0.98 (0.86, 1.13)	0.63 (0.36, 1.10)
Male	lag6	0.97 (0.89, 1.05)	0.92 (0.80, 1.06)	0.69 (0.41, 1.15)
Male	lag7	1.05 (0.96, 1.14)	0.86 (0.74, 0.98)*	0.50 (0.29, 0.86)*
Male	lag01	1.10 (1.01, 1.20)*	1.09 (0.94, 1.26)	1.47 (0.86, 2.53)
Male	lag02	1.04 (0.95, 1.13)	1.03 (0.89, 1.20)	1.71 (0.97, 3.00)
Male	lag03	1.06 (0.97, 1.16)	1.02 (0.87, 1.18)	1.51 (0.86, 2.65)
Male	lag04	0.97 (0.88, 1.06)	0.92 (0.79, 1.08)	0.98 (0.56, 1.72)

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Male	lag05	0.97 (0.88, 1.06)	0.92 (0.78, 1.07)	0.71 (0.37, 1.37)
Male	lag06	0.95 (0.87, 1.04)	0.86 (0.73, 1.01)	0.42 (0.19, 0.90)*
Male	lag07	0.93 (0.85, 1.03)	0.84 (0.71, 0.99)*	0.52 (0.23, 1.18)
Female	lag0	1.00 (0.94, 1.06)	1.01 (0.92, 1.12)	1.33 (0.94, 1.87)
Female	lag1	1.01 (0.95, 1.07)	0.95 (0.86, 1.04)	1.14 (0.80, 1.61)
Female	lag2	1.00 (0.94, 1.06)	0.97 (0.88, 1.07)	1.57 (1.12, 2.20)*
Female	lag3	0.99 (0.94, 1.06)	0.94 (0.85, 1.04)	1.31 (0.92, 1.87)
Female	lag4	1.00 (0.94, 1.06)	0.99 (0.90, 1.10)	1.19 (0.82, 1.71)
Female	lag5	0.94 (0.89, 1.00)	0.92 (0.83, 1.01)	1.00 (0.71, 1.40)
Female	lag6	0.97 (0.92, 1.04)	0.91 (0.83, 1.01)	1.07 (0.76, 1.50)
Female	lag7	0.97 (0.91, 1.03)	0.94 (0.85, 1.04)	0.64 (0.44, 0.93)*
Female	lag01	1.00 (0.94, 1.06)	1.01 (0.91, 1.12)	1.65 (1.13, 2.40)*
Female	lag02	1.00 (0.94, 1.07)	1.03 (0.92, 1.14)	1.59 (1.04, 2.44)*
Female	lag03	1.00 (0.94, 1.06)	1.01 (0.90, 1.12)	1.51 (0.98, 2.32)
Female	lag04	1.00 (0.94, 1.07)	1.01 (0.90, 1.12)	1.48 (0.98, 2.24)
Female	lag05	0.98 (0.91, 1.04)	0.98 (0.87, 1.10)	1.14 (0.72, 1.81)
Female	lag06	0.97 (0.91, 1.04)	0.95 (0.84, 1.07)	0.93 (0.57, 1.51)

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Female	lag07	0.97 (0.91, 1.04)	0.94 (0.83, 1.06)	1.00 (0.60, 1.65)
Age group				
6–11 yr	lag0	1.06 (0.86, 1.31)	1.22 (0.87, 1.73)	1.54 (0.37, 6.31)
6–11 yr	lag1	1.11 (0.90, 1.38)	1.10 (0.77, 1.56)	3.61 (0.85, 15.32)
6–11 yr	lag2	1.19 (0.96, 1.48)	1.18 (0.82, 1.69)	3.02 (0.76, 11.94)
6–11 yr	lag3	0.92 (0.75, 1.13)	0.82 (0.57, 1.19)	0.43 (0.08, 2.20)
6–11 yr	lag4	0.99 (0.80, 1.22)	0.89 (0.63, 1.27)	0.75 (0.15, 3.84)
6–11 yr	lag5	1.08 (0.87, 1.33)	1.13 (0.78, 1.62)	—**
6–11 yr	lag6	1.31 (1.06, 1.62)*	1.03 (0.71, 1.49)	0.38 (0.04, 3.43)
6–11 yr	lag7	1.25 (1.01, 1.55)*	0.84 (0.58, 1.23)	0.41 (0.05, 3.42)
6–11 yr	lag01	0.97 (0.79, 1.21)	1.05 (0.73, 1.52)	1.76 (0.31, 9.82)
6–11 yr	lag02	1.02 (0.82, 1.28)	1.01 (0.69, 1.48)	1.76 (0.31, 9.87)
6–11 yr	lag03	1.13 (0.90, 1.41)	1.02 (0.69, 1.50)	1.92 (0.29, 12.67)
6–11 yr	lag04	1.03 (0.82, 1.29)	0.85 (0.57, 1.27)	0.85 (0.09, 7.85)
6–11 yr	lag05	1.02 (0.81, 1.27)	0.81 (0.53, 1.22)	—**
6–11 yr	lag06	1.09 (0.86, 1.37)	0.94 (0.61, 1.43)	—**
6–11 yr	lag07	1.10 (0.87, 1.39)	0.96 (0.63, 1.46)	—**

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
12–17 yr	lag0	0.97 (0.71, 1.31)	0.75 (0.47, 1.22)	1.11 (0.19, 6.40)
12–17 yr	lag1	1.04 (0.76, 1.42)	0.60 (0.35, 1.01)	0.27 (0.03, 2.74)
12–17 yr	lag2	1.18 (0.87, 1.62)	1.00 (0.61, 1.64)	0.20 (0.02, 1.88)
12–17 yr	lag3	1.41 (1.02, 1.94)*	1.41 (0.87, 2.27)	0.38 (0.04, 3.35)
12–17 yr	lag4	1.05 (0.77, 1.43)	0.79 (0.46, 1.33)	0.10 (0.01, 0.92)*
12–17 yr	lag5	1.10 (0.81, 1.49)	0.79 (0.46, 1.33)	0.25 (0.03, 2.21)
12–17 yr	lag6	0.94 (0.69, 1.29)	0.87 (0.53, 1.44)	0.48 (0.10, 2.23)
12–17 yr	lag7	0.99 (0.72, 1.36)	0.96 (0.59, 1.56)	1.61 (0.42, 6.19)
12–17 yr	lag01	1.00 (0.72, 1.39)	0.68 (0.40, 1.16)	0.54 (0.06, 5.20)
12–17 yr	lag02	1.09 (0.79, 1.52)	0.76 (0.44, 1.30)	0.58 (0.06, 5.63)
12–17 yr	lag03	1.01 (0.72, 1.41)	0.80 (0.46, 1.39)	0.72 (0.07, 7.22)
12–17 yr	lag04	1.02 (0.72, 1.45)	0.92 (0.53, 1.62)	0.43 (0.05, 3.80)
12–17 yr	lag05	0.96 (0.68, 1.37)	0.82 (0.46, 1.46)	—**
12–17 yr	lag06	1.07 (0.74, 1.54)	0.89 (0.49, 1.63)	—**
12–17 yr	lag07	1.17 (0.81, 1.69)	0.75 (0.41, 1.39)	—**
18–44 yr	lag0	1.03 (0.92, 1.16)	1.12 (0.94, 1.34)	2.49 (1.37, 4.52)*
18–44 yr	lag1	1.00 (0.90, 1.13)	0.95 (0.79, 1.14)	1.14 (0.59, 2.22)

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
18–44 yr	lag2	0.96 (0.86, 1.08)	0.91 (0.76, 1.10)	1.15 (0.61, 2.16)
18–44 yr	lag3	0.98 (0.87, 1.10)	0.88 (0.73, 1.06)	1.37 (0.69, 2.70)
18–44 yr	lag4	0.99 (0.88, 1.11)	0.98 (0.81, 1.17)	1.36 (0.69, 2.70)
18–44 yr	lag5	0.96 (0.85, 1.07)	1.11 (0.92, 1.33)	0.78 (0.37, 1.66)
18–44 yr	lag6	0.95 (0.84, 1.07)	1.05 (0.88, 1.26)	0.89 (0.45, 1.78)
18–44 yr	lag7	0.97 (0.86, 1.09)	0.91 (0.75, 1.09)	0.46 (0.22, 0.97)*
18–44 yr	lag01	1.11 (0.99, 1.25)	1.05 (0.87, 1.27)	2.77 (1.33, 5.77)*
18–44 yr	lag02	1.02 (0.90, 1.15)	1.08 (0.89, 1.32)	2.09 (0.91, 4.83)
18–44 yr	lag03	1.00 (0.88, 1.13)	1.13 (0.93, 1.39)	2.05 (0.86, 4.91)
18–44 yr	lag04	0.94 (0.83, 1.07)	1.10 (0.90, 1.35)	2.00 (0.91, 4.41)
18–44 yr	lag05	0.96 (0.84, 1.09)	1.14 (0.92, 1.40)	1.18 (0.49, 2.85)
18–44 yr	lag06	0.92 (0.80, 1.04)	0.96 (0.78, 1.19)	0.69 (0.25, 1.89)
18–44 yr	lag07	0.89 (0.78, 1.02)	0.92 (0.74, 1.14)	0.83 (0.30, 2.28)
45–64 yr	lag0	1.08 (0.99, 1.17)	1.04 (0.91, 1.19)	0.93 (0.56, 1.52)
45–64 yr	lag1	1.09 (1.01, 1.19)*	1.05 (0.92, 1.21)	1.32 (0.82, 2.13)
45–64 yr	lag2	1.03 (0.95, 1.12)	1.08 (0.95, 1.23)	1.91 (1.21, 3.02)*
45–64 yr	lag3	0.97 (0.89, 1.05)	0.96 (0.84, 1.09)	1.14 (0.69, 1.89)

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
45–64 yr	lag4	1.04 (0.96, 1.13)	1.01 (0.88, 1.15)	0.73 (0.42, 1.27)
45–64 yr	lag5	0.99 (0.91, 1.08)	0.91 (0.80, 1.04)	0.93 (0.58, 1.49)
45–64 yr	lag6	0.94 (0.86, 1.02)	0.89 (0.78, 1.02)	0.75 (0.46, 1.20)
45–64 yr	lag7	0.99 (0.91, 1.08)	0.91 (0.79, 1.04)	0.55 (0.33, 0.93)*
45–64 yr	lag01	1.07 (0.98, 1.16)	1.10 (0.96, 1.27)	1.42 (0.82, 2.45)
45–64 yr	lag02	1.06 (0.97, 1.15)	1.10 (0.95, 1.27)	1.65 (0.91, 2.99)
45–64 yr	lag03	1.07 (0.98, 1.17)	1.02 (0.88, 1.19)	1.54 (0.86, 2.76)
45–64 yr	lag04	1.08 (0.98, 1.18)	1.03 (0.88, 1.20)	1.23 (0.69, 2.19)
45–64 yr	lag05	1.03 (0.94, 1.13)	0.97 (0.83, 1.14)	0.90 (0.47, 1.71)
45–64 yr	lag06	1.01 (0.92, 1.11)	0.95 (0.81, 1.12)	0.73 (0.37, 1.46)
45–64 yr	lag07	0.98 (0.89, 1.08)	0.92 (0.78, 1.08)	0.69 (0.33, 1.43)
≥65 yr	lag0	0.95 (0.88, 1.03)	1.04 (0.91, 1.18)	1.88 (1.20, 2.94)*
≥65 yr	lag1	0.97 (0.90, 1.05)	0.90 (0.79, 1.03)	0.96 (0.62, 1.48)
≥65 yr	lag2	0.99 (0.92, 1.07)	0.91 (0.80, 1.04)	1.21 (0.77, 1.90)
≥65 yr	lag3	0.95 (0.88, 1.03)	0.89 (0.78, 1.01)	1.16 (0.74, 1.82)
≥65 yr	lag4	0.95 (0.88, 1.02)	0.88 (0.77, 1.01)	1.27 (0.81, 2.00)
≥65 yr	lag5	0.92 (0.85, 1.00)*	0.87 (0.76, 1.00)	1.03 (0.66, 1.60)

Subgroup	Lag days	PM _{2.5} >15–25 µg/m ³	PM _{2.5} >25–50 µg/m ³	PM _{2.5} >50 µg/m ³
		OR (95% CI)	OR (95% CI)	OR (95% CI)
≥65 yr	lag6	0.97 (0.90, 1.05)	0.86 (0.75, 0.98)*	1.24 (0.80, 1.93)
≥65 yr	lag7	0.98 (0.91, 1.06)	0.92 (0.80, 1.05)	0.64 (0.39, 1.06)
≥65 yr	lag01	0.98 (0.91, 1.06)	1.00 (0.87, 1.14)	1.45 (0.90, 2.33)
≥65 yr	lag02	0.97 (0.89, 1.05)	0.96 (0.83, 1.11)	1.54 (0.92, 2.58)
≥65 yr	lag03	0.96 (0.89, 1.04)	0.95 (0.82, 1.10)	1.33 (0.79, 2.24)
≥65 yr	lag04	0.93 (0.85, 1.01)	0.89 (0.76, 1.03)	1.21 (0.73, 2.01)
≥65 yr	lag05	0.92 (0.85, 1.00)	0.88 (0.75, 1.03)	1.10 (0.63, 1.94)
≥65 yr	lag06	0.92 (0.85, 1.01)	0.86 (0.73, 1.01)	0.81 (0.44, 1.48)
≥65 yr	lag07	0.94 (0.86, 1.02)	0.89 (0.75, 1.04)	1.02 (0.54, 1.91)

OR, odds ratio; CI, confidence interval; * P-value <0.05; ** Odds ratio could not be calculated due to insufficient sample size for the specified lag period.

5 Discussion and Conclusion

5.1 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} establish milestone levels to guide air quality improvement efforts in resource-limited countries, with the ultimate goal of achieving the recommended Air Quality Guideline (AQG) levels. These levels are grounded in scientific evidence that links varying PM_{2.5} exposure concentrations to increased mortality risks, supported by expert consensus. To emphasize the health impacts associated with 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, consistent with time-series studies conducted in Taiwan, China, and the USA.^{6,8,9} Specifically, this study highlights the immediate effects of PM_{2.5} exposure from an individual-level perspective, aligning with findings from previous case-crossover studies conducted in Taiwan and Denmark.^{7,10} Additionally, case-crossover studies during wildfire events in the USA and Australia also reported acute responses to PM_{2.5} exposure.^{49,50} PM_{2.5} promotes the generation of reactive oxygen species in the airways, leading to allergic inflammation and airway hyperresponsiveness.⁵¹ 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.

In our study, significant positive effects were observed only for PM_{2.5} concentrations greater than 50 µg/m³, highlighting the importance of reducing PM_{2.5} pollution to meet WHO air quality targets. On the other hand, the marginally negative associations observed at later lags could be attributed to avoidance and prevention behaviors by individuals with asthma. Transboundary haze events and their associated health effects, particularly for individuals with respiratory and cardiovascular diseases, are often broadcast in real time. Therefore, individuals with asthma may take timely actions to mitigate their exposure to PM_{2.5}, such as staying indoors or using air purifiers. These protective measures may help reduce the likelihood of asthma exacerbations, thus explaining the reverse associations observed at later time lags.

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).⁵² 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. Temperature was also positively associated with asthma exacerbation at several lags, although none of these associations reached statistical significance. Previous studies reported mixed associations between asthma exacerbation and both low and high temperature extremes.^{47,48} 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.⁵³ In contrast, exacerbations during warmer weather may be influenced by factors such as increased outdoor activities, heightened air pollution, and higher concentrations of allergens.⁵⁴ 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.

In subgroup analyses, positive associations at early lags were observed for both males and females. A study in China found 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.⁵⁵ 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.⁵⁶ 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 µg/m³) 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.⁴⁶ 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.⁵⁷

These findings 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.

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.⁵⁸ Additionally, the use of postal addresses to define residents' districts may impact the accuracy of exposure measurements. Third, due to the small number of individuals who underwent respiratory viral testing, we were unable to perform a subgroup analysis to account for potential confounding by viral infections, which had been shown to influence the effects of air pollution on asthma exacerbation.²⁸ 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.³²

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.^{6,53} 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.

5.2 Conclusion

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

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