



Air Pollution Levels Related to Peak Expiratory Flow Rates among Adult Asthmatics in Lampang, Thailand

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ABSTRACT

Asthmatics may suffer harmful health effects from air pollution. This year-long study, which was conducted from November 2015 till October 2016 and resulted in 12,045 data points from 33 participants, assessed the relationships (with a 95% confidence interval [CI]) between measured air pollutant (CO, NO₂, O₃, SO₂, PM_{2.5} and PM₁₀) concentrations and peak expiratory flow rates (PEFRs) among adults with asthma in the district of Mae Moh in Lampang, Thailand. A positive correlation was found between the mean daily concentration of NO₂ from 4 days prior (“lag 4”) and the PEFR upon waking (“morning PEFR”), with an increase of 1 ppb in the former being associated with an increase of 1.34 L min⁻¹ (95% CI: 0.25, 2.44) in the latter. Also, the interaction between NO₂ (lag 4) and PM₁₀ (lag 6) was multiplicatively associated with a decrease of -0.015 L min⁻¹ in the morning PEFR, which was also negatively associated with the maximum daily concentration (“max”) of NO₂ (lag 2) and that of PM₁₀ (lag 6), with coefficients of -0.07 and -0.013, respectively. Furthermore, when including PM_{2.5} max in the generalized estimating equation model, only NO₂ max (lag 2) and CO max (lag 6) were negatively associated with the morning PEFR, displaying coefficients of -0.08 and -1.71, respectively. O₃ max (lag 3) and PM_{2.5} max exhibited positive relationships with the PEFR before sleeping (“evening PEFR”), with coefficients of 0.078 and 0.029, respectively. Additionally, the average daily PEFR was positively associated with the average daily concentration of NO₂ (lag 4), with a coefficient of 0.15, but negatively associated with that of SO₂, with a coefficient of -0.47. We also observed a negative relationship between the average daily PEFR and NO₂ max (lag 2), with a coefficient of -0.05, but a positive one between the former and O₃ max (lag 3), with a coefficient of 0.06. Our results indicate that the delayed—and, in some cases, negative—effects of these pollutants on PEFRs must be considered in health forecasting and that preventative measures should be implemented to control certain emissions at the source.

Keywords: Air pollution; Peak expiratory flow rates; Asthmatic patients; Mae Moh.

INTRODUCTION

Air pollution causes millions of premature deaths worldwide (Silva *et al.*, 2013), and is linked to respiratory infections,

heart disease, chronic obstructive pulmonary disease (COPD), stroke and lung cancer. It is associated with dyspnea, wheezing, coughing and asthma (WHO, 2014; Kallawicha *et al.*, 2018; Li *et al.*, 2018) because of its identified impact on lung function (Lee *et al.*, 2011; Arblex *et al.*, 2012; Zhou *et al.*, 2016; Wang *et al.*, 2018).

The World Health Organization (WHO) estimated that in 2015, 383,000 deaths worldwide were due to asthma (WHO, 2020). Many studies have found that ambient air pollution causes adverse effects in asthmatic patients, for example, increased respiratory symptoms (Mann *et al.*, 2010; Kelly and Fussell, 2011), worsened lung function (Aekpalakorn *et al.*, 2003), and decreased peak expiratory

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flow rate (PEFR) (Wiwatanadate and Trakultivakorn, 2010; Zhou *et al.*, 2016). PEFR, a spirometry parameter, is the maximum airflow rate accomplished during forced expiration following maximal inspiration (Ray *et al.*, 1993; Quenier *et al.*, 1997; Skladanowski *et al.*, 2016). It is an especially useful measure for detecting airway obstruction early, when screening asthmatic patients and observing the effects of environmental and occupational exposure (Ray *et al.*, 1993). Reduction in PEFR has been related to exposure to high concentrations of air pollutants, particularly among asthmatic patients (Quanjer *et al.*, 1997; Hong *et al.*, 2010; Wiwatanadate and Trakultivakorn, 2010; Wiwatanadate and Liwsrisakun, 2011; Yamazaki *et al.*, 2011).

The Health Effects Institute (HEI) reported that particulate matter (PM) and ozone (O₃) are the worst threat toward good air quality in the Asian region (HEI, 2010). PM, a complex mixture of extremely small particles and liquid droplets consisting of organic chemicals, acids, and soil and dust particles (U.S. EPA, 2018), is designated as inhalable PM of aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) or PM of aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5} or fine PM). Most PM occurs naturally in the environment, but increasing anthropogenic interferences in the environment have significantly increased the PM burden (Cha *et al.*, 2019). Anthropogenic sources of PM include vehicular emissions and activities such as biomass burning, industrial processing, agricultural operations, and construction activities (Fang *et al.*, 2017; Widiiana *et al.*, 2017; Deshmukh *et al.*, 2019; Hao *et al.*, 2019; Hien *et al.*, 2019; Hu *et al.*, 2019; Liu *et al.*, 2019; Shahid *et al.*, 2019). PM emitted from natural sources and human activities includes carbon monoxide (CO), nitrogen dioxide (NO₂) and sulfur dioxide (SO₂).

In Thailand, high PM₁₀ concentrations contribute greatly to air pollution, which causes the country significant public health problems. In 2012, Saraburi Province, near Bangkok, recorded the highest PM₁₀ concentration in the country, owing to the stone milling and crushing activity carried out in the area, while areas in the north of the country had the second-highest concentration, due to its annual smog crisis linked to power plant emissions, post-harvest burning, forest fires, and vehicle exhaust fumes (Thepnuan *et al.*, 2019). The problem has been worsening over time as concentrations of PM₁₀ have been increasing continually in every province of Thailand (PCD, 2013). In addition to forest fires, agricultural waste burning, vehicle exhaust emissions, construction work sites and industrial pollution, certain weather conditions are implicated: Temperature inversions and little or no wind helps smog to settle and remain in one place. The northern provinces of Thailand, for example, Chiang Mai, Chiang Rai, Mae Hong Son and Tak, bordering Laos and/or Myanmar, also often suffer pollution that originates from those countries (PCD, 2013; Thepnuan *et al.*, 2019). These diverse causes of smog in the northern provinces produce long- and short-term ill effects among the population. Experimental exposure to PM results in oxidative stress, airway hyper-responsiveness, and airway remodeling, either alone or in combination with allergic sensitization (Stanek *et al.*, 2011), while short-term exposure to ambient PM_{2.5} and PM₁₀ in asthmatic children and adults has been associated with asthma symptoms,

especially in children with allergic sensitization (Weinmayr *et al.*, 2009; Mann *et al.*, 2010; Meng *et al.*, 2010). Long-term exposure to PM is associated with poorly controlled asthma and decrements in lung function in children and adults (Weiss and Ware, 1996; Liu *et al.*, 2009; Jacque *et al.*, 2012). A study in northern Thailand during 2001 and 2002 found that 3.01% of 22–24-year-olds had asthma (Dejsomritrutai *et al.*, 2006). The adverse environmental effects have not only damaged human physical and mental health, but also crops and livestock (Boonlong, 2011).

The northern province of Lampang ranks fourth in the most air-polluted provinces in Thailand, with an average maximum daily PM₁₀ of 237 $\mu\text{g m}^{-3}$, and an average that exceeds the standard level for 23 days a year (PCD, 2013). Within Lampang is Mae Moh district, located in a flat valley that is highly prone to temperature inversions, and also home to a coal-fired steam power plant. The Mae Moh Power Plant uses lignite mined from an open pit (EGAT, 2020). In 1992 and 1998, the plant was involved in major environmental disputes, due to local villagers being exposed to sulfur dioxide released from the power plant, with further disputes since then. Thus, the main sources of air pollution in this area include power plant emissions, post-harvest burning, forest fires, and vehicle exhaust fumes. This study aimed to investigate the effects of air pollutants on daily PEFR in people suffering from asthma living in Mae Moh district in Thailand. A longitudinal design of 1-year duration was used, with 33 participants, producing a sample size of 12,045 person-days, making this among the largest pollution-asthma panel studies ever carried out. Also, the use of time series analysis exposed the strongest lagged effect of each pollutant and on PEFR.

MATERIALS AND METHODS

Study Design, Setting, and Participants

This study used a panel study design for obtaining a time series of repeated outcome measurements and exposures in a closed cohort of 33 adult sufferers of asthma. All 33 (1) had asthma as diagnosed by a physician, (2) experienced asthma symptoms during the past year, (3) were more than 15 years old, and (4) had lived in Mae Moh district for more than 1 year. In addition, all of the participants lived no farther than 25 km from the Mae Moh air quality monitoring station, from which most air quality data was collected. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (CMU-REC No. 270/2015). All of the participants signed an informed consent form before the study began. Data on participants was collected through structured interviews with the principal researcher and questionnaires requesting demographic characteristics, history of illnesses and allergies, and medication used. The participants additionally had a chest X-ray (CXR) and lung function test. The CXR showed no trace of cancer, empyema, emphysema or COPD for any of the 33 participants. All participants were non-smokers or had quit smoking more than 1 year earlier. Each participant was categorized for the severity of their asthma in accordance with the criteria of the U.S. National Heart, Lung, and Blood

Institute (NHLBI, 1997; GINA, 2008).

In orientation, participants were taught individually how to measure their own PEFR and asked to repeat the procedure to confirm that they could do it successfully. Each participant measured their PEFR 3 times and the highest and best value was recorded. The study commenced on 2 November 2015 and completed on 31 October 2016. Every day during the study, each participant recorded their PEFR twice when they woke in the morning and before bed in the evening. The PEFR was measured using a Mini Wright Peak Flow Meter (Clement Clarke International, Ltd., UK). Records of the participants were returned to the researcher at the end of each month, and the researcher also accessed data from participants' hospital visits during the study period.

Measurements of Air Pollutants and Meteorological Data

Data for NO₂, O₃, SO₂, PM_{2.5} and PM₁₀ were collected from Mae Moh subdistrict air monitoring station, and CO data were collected from Sob-pad air quality monitoring station, both stations belonging to the Pollution Control Department, Thailand (PCD, 2013). At these automated air sampling monitoring stations, the concentrations of each pollutant are monitored continuously and reported hourly. CO is analyzed technically using the non-dispersive infrared detection method, SO₂ by pararosaniline, NO₂ and O₃ by chemiluminescence, and PM₁₀ and PM_{2.5} by the gravimetric method (Air Quality and Noise Management Bureau, PCD, Thailand, 2020). Daily average concentrations (00:00–24:00) were computed, and the highest hourly concentration taken as the daily maximum. Meteorological data, including wind speed, temperature, global radiation, and rainfall quantity, were also collected from the PCD stations. Readings of pressure and relative humidity were taken from measurements at Lampang Airport, which is approximately 30 km southwest of the study area (Lampang Meteorological Station). The meteorological and pollutant parameters were computed in the same way, except for pressure and relative humidity, which were based on the daily average and daily maximum data from the Lampang Meteorological Station.

Statistical Analysis

Data on demographic background, and daily meteorological and air pollutant measurements were used to investigate the relationship between concentrations of air pollutants and PEFR by using the generalized estimating equation (GEE) model, which allowed this study to account for the within-subject correlation of repeated measurements. All pollutant variables were recorded as a time series, and it was assumed that their effects were lagged (delayed). *Lag* is the delayed effect. The number means the number of days that the effect is delayed. For example, “NO₂ (lag 4)” means that the NO₂ data is the NO₂ level reported 4 days prior to the data it is being related to. The statistical software used in the analysis was SPSS version 22 (IBM, Singapore).

The steps of analysis were as follows:

1) Separate univariate analysis of mean and maximum levels of the meteorological variables was performed (at lags of 0–6) with three separate measurements of PEFR,

morning PEFR, evening PEFR, and daily average PEFR ((morning PEFR + evening PEFR)/2), resulting in a total of three reported outcomes. 2) Each of the mean and maximum (“max”) pollutants (lags 0–6) were (univariately) analyzed separately with each outcome. The best lagged effect (i.e., the smallest *p*-value) was entered into the proceeding steps. 3) Demographic factors (gender, age, asthma severity, weight, and height) and day of the week were included in the model, together with the best lagged meteorological covariates for each outcome from the previous step. Those with a *p*-value < 0.25 were kept for further analysis (Wiwatanadate and Trakultivakorn, 2010). Selection of the 0.25 level was made by following the work of Bendel and Afifi (1977), which showed that use of a more conventional level (e.g., 0.05) often fails to identify variables that are considered important. Due to the autocorrelation nature of repeated measurements over time, this study produced plots of the autocorrelation functions (ACF) (Fig. 1) and partial autocorrelation functions (PACF) (Fig. 2) of all three PEFR outcomes, in order to visualize the characteristics of the correlation: There was an exponential decay pattern for all of the outcome variables, starting at lag 1, in both ACF and PACF plots, indicating that the appropriate structure was first-order autoregressive (StatSoft, Inc., 2007). An autocorrelation plot shows the value of the autocorrelation function on the vertical axis. It can range from –1 to 1. The horizontal axis of the plot shows the size of the lag between the elements of the time series. 4) All demographic data were applied to all meteorological variables for analysis of each outcome, with *p*-value < 0.25 from Step 3 and the best lag of each pollutant from Step 2. 5) If more than one pollutant was found to be statistically significant, the pollutants were chosen and adjusted with a demographic and meteorological variable. 6) The correlation structure with the smallest quasi-likelihood under the independence model criterion (QIC) was selected. 7) The parsimonious model was chosen by the lesser value of quasi-likelihood under the independence model criterion (QICC) (Pan, 2001; Cui and Qian, 2007).

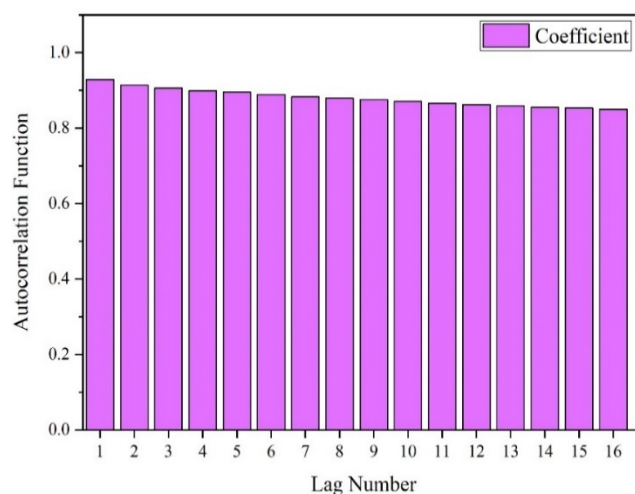


Fig. 1. Autocorrelation function plot of daily morning PEFR of 33 asthmatic patients in Mae Moh district, Lampang, Thailand.

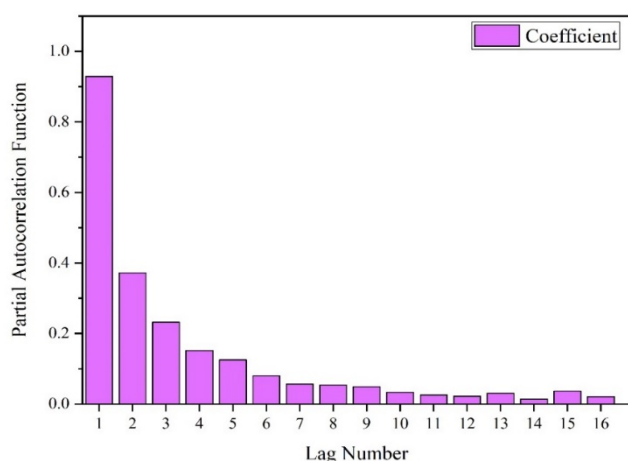


Fig. 2. Partial autocorrelation function plot of daily morning PEFR of 33 asthmatic patients in Mae Moh district, Lampang, Thailand.

RESULTS

Demographic and Asthma Characteristics of the Cohort

The asthma severity classification according to the Global Initiative for Asthma (GINA, 2008) were categorized into 4 levels: *intermittent*, *mild persistent*, *moderate persistent* and *severe persistent* (Bateman et al., 2008). Table 1 presents descriptive statistics of the demographic and asthma characteristics of the cohort. After 4 participants withdrew from this study, 33 remained (11 males and 22 females). Their mean age was 49.4 ± 10.0 years, mean body weight, 63.2 ± 13.1 kg and mean height, 157.1 ± 6.2 cm, and their asthma severity was categorized as *intermittent* (13; 39.4%), *mild persistent* (11; 33.3%) and *moderate persistent* (9; 27.3%).

Description of Ambient Pollutants

Concentrations of NO_2 , O_3 , CO, SO_2 , PM_{10} , and $\text{PM}_{2.5}$ were collected daily for the 365 days of the study. Due to monitoring equipment malfunction, records for NO_2 , O_3 and CO were missing for 17 days (4.66%), 3 days (0.82%) and

Table 1. Descriptive statistics of 33 asthmatic patients in Mae Moh district, Lampang, Thailand, 2 November 2015–31 October 2016.

Demographic Data	Value
No. males/females	11/22
Mean age (years)	49.4 (10.0) ^a
Mean weight (kg)	63.2 (13.1) ^a
Mean height (cm)	157.1 (6.2) ^a
Asthma severity (%)	
Intermittent	13 (39.4) ^b
Mild persistent	11 (33.3) ^b
Moderate persistent	9 (27.3) ^b
Severe persistent	0

^a The number in parentheses is standard deviation.

^b The number in parentheses is the frequency of each category.

2 days (0.55%), respectively. The daily average concentrations were 4.87 ppb, 1.28 ppb, 33.92 ppb, $49.09 \mu\text{g m}^{-3}$, $28.91 \mu\text{g m}^{-3}$ and 0.76 ppm for NO_2 , SO_2 , O_3 , PM_{10} , $\text{PM}_{2.5}$, and CO, respectively. The meteorological daily averages were 0.98 m s^{-1} for wind speed, 26.03°C for temperature, 72.4% for relative humidity, 163.14 w m^{-2} for global radiation, 1009.96 mbar for pressure and 0.14 mm for rain quantity.

Daily mean and max pollutants and meteorological parameters are shown in Table 2. The daily average PM_{10} and $\text{PM}_{2.5}$ concentration exceeded the Thai standard concentrations of $120 \mu\text{g m}^{-3}$ and $50 \mu\text{g m}^{-3}$ for 18 days and 76 days, respectively.

Table 3(a) shows the correlation matrix of mean ambient air pollutants and mean meteorological parameters. The highest correlation of ambient air pollutants was that between PM_{10} and $\text{PM}_{2.5}$, $r = 0.981$.

Table 3(b) shows the correlation matrix of max ambient air pollutants and max meteorological parameters. The highest correlation of max ambient air pollutants was that between PM_{10} max and $\text{PM}_{2.5}$ max, $r = 0.918$.

Association between Daily Average Pollutant Levels and PEFR

Morning PEFR

A separate single-pollutant model was performed, and adjustments to each best-lagged pollutant made for gender, asthma severity, day of the week, age, weight, wind speed (lag 5), temperature (lag 1), global radiation (lag 4), pressure (lag 1) and rain quantity (lag 6). It was found that NO_2 (lag 4) associated positively with morning PEFR, with a coefficient of 0.23 (95% confidence interval [CI]: 0.03, 0.43). PM_{10} (lag 6) and CO (lag 6) associated negatively with morning PEFR, with coefficients of -0.05 (95% CI: $-0.07, -0.02$) and -3.93 (95% CI: $-7.43, -0.43$), respectively. The multi-pollutant models were analyzed further with all possible combinations of pollutants from the single-pollutant model [excluding SO_2 (lag 4), O_3 (lag 3) and $\text{PM}_{2.5}$ (lag 6)]. It was found that the ambient daily mean concentration of NO_2 (lag 4) associated positively with morning PEFR, with a coefficient of 1.34 (95% CI: 0.25, 2.44). This meant that an increase of 1 ppb in the daily mean ambient concentration of NO_2 (lag 4) was associated with an increase in morning PEFR of 1.34 L min^{-1} . Meanwhile, NO_2 (lag 4) and PM_{10} (lag 6) [NO_2 (lag 4) \times PM_{10} (lag 6)] associated negatively with a coefficient of -0.015 (95% CI: $-0.030, -0.001$). This meant that the interaction between the daily mean concentration of NO_2 (lag 4) and PM_{10} (lag 6) associated multiplicatively with a decreased morning PEFR by -0.015 (95% CI: $-0.030, -0.001$) (Table 4).

Evening PEFR

Evening PEFR was analyzed using the single-pollutant model in the same manner as the method mentioned above. The results showed that there was no statistical significance.

Daily Average PEFR

The single-pollutant model showed that NO_2 (lag 4) was statistically positively related to the daily average PEFR with a coefficient of 0.15 (95% CI: 0.02, 0.29), while SO_2

Table 2. Daily meteorological and pollutant measurements; daily max meteorological and max pollutant measurements in Mae Moh district, Lampang, Thailand, 2 November 2015–30 November 2016.

Exposure (24-h average)	No. observations	Min/Max	Mean ± S.D.	90 th percentile	Exposure (24-h max)	No. observations	Min/Max	Mean ± S.D.	90 th percentile
WS	365	0.38/2.22	0.98 (0.39)	1.49	WS	365	0.80/4.20	2.08/11.50	3.1
Temp	365	9.11/34.94	26.03 (3.63)	30.73	Temp	365	10.10/41.80	31.83/4.34	38.5
RH	365	43.25/95.13	72.40 (11.67)	85.88	RH	365	63.00/99.00	91.95/23.92	98
GR	365	2.63/292.47	163.14 (46.55)	223.29	GR	365	21.00/940.00	690.18/63.04	860
Press	365	1000.56/1024.26	1009.96 (4.24)	1015.95	Pressure	365	1002.60/1027.10	1012.71/44.51	1018.37
RQ	365	0.00/2.82	0.14 (0.39)	0.5	RQ	365	0.00/67.60	3.38/0.65	12
NO ₂	348	0.74/29.55	4.87 (3.31)	9.26	NO ₂	348	3.00/91.00	13.16/0.72	27
SO ₂	365	0.00/6.14	1.28 (1.05)	2.52	SO ₂	365	0.00/34.00	3.56/4.20	7
O ₃	362	12.04/77.41	33.92 (16.53)	61.96	O ₃	362	18.00/131.00	52.64/7.76	88
PM ₁₀	365	9.46/188.71	49.09 (35.34)	101.54	PM ₁₀	365	17.00/443.00	84.91/63.04	174.4
PM _{2.5}	365	5.00/155.96	28.91 (26.12)	67.92	PM _{2.5}	365	9.00/407.00	49.92/44.51	105.8
CO	363	0.30/2.08	0.76 (0.38)	1.4	CO	363	0.35/3.53	1.12/0.65	2.15

WS: wind speed (m s⁻¹); Temp: temperature (°C); RH: relative humidity (%); GR: global radiation (W m⁻²); Press: pressure (mbar); RQ: rain quantity (mm); NO₂: nitrogen dioxide (ppb); SO₂: sulfur dioxide (ppb); O₃: ozone (ppb); PM₁₀: particulate matter with a 50% cut-off of aerodynamic diameter ≤ 10 μm (μg m⁻³); PM_{2.5}: particulate matter with a 50% cut-off of aerodynamic diameter ≤ 2.5 μm (μg m⁻³); CO: carbon monoxide (ppm).

Table 3(a). Correlation matrix of mean ambient air pollutants and mean meteorological parameters in Mae Moh district, Lampang, Thailand, 2 November 2015–31 October 2016.

Mean	NO ₂	SO ₂	O ₃	PM ₁₀	PM _{2.5}	CO	WS	Temp	RH	GR	Pressure
SO ₂	0.509**										
O ₃	0.488**	0.237**									
PM ₁₀	0.588**	0.308**	0.881**								
PM _{2.5}	0.582**	0.308**	0.881**	0.981**							
CO	0.499**	0.282**	0.755**	0.821**	0.829**						
WS	-0.022*	-0.065**	0.529**	0.368**	0.360**	0.313**					
Temp	-0.231**	-0.283**	0.348**	0.275**	0.275**	0.059**	0.491**				
RH	-0.346**	-0.152**	-0.842**	-0.735**	-0.728**	-0.539**	-0.619**	-0.595**			
GR	0.156**	0.127**	0.568**	0.485**	0.475**	0.313**	0.443**	0.608**	-0.725**		
Pressure	0.498**	0.303**	0.170**	0.128**	0.137**	0.328**	-0.189**	-0.677**	0.073**	-0.218**	
RQ	-0.196**	-0.138**	-0.285**	-0.260**	-0.254**	-0.237**	-0.204**	-0.168**	0.388**	-0.333**	-0.078**

WS: wind speed; Temp: temperature; RH: relative humidity; GR: global radiation; RQ: rain quantity.

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 3(b). Correlation matrix of max ambient air pollutants and max meteorological parameters in Mae Moh district, Lampang, Thailand, 2 November 2015–31 October 2016.

Max	NO ₂	SO ₂	O ₃	PM ₁₀	PM _{2.5}	CO	WS	Temp	RH	GR	Pressure
SO ₂	0.630**										
O ₃	0.464**	0.269**									
PM ₁₀	0.467**	0.186**	0.830**								
PM _{2.5}	0.426**	0.183**	0.801**	0.918**							
CO	0.347**	0.141**	0.749**	0.785**	0.755**						
WS	-0.144**	-0.193**	0.260**	0.222**	0.169**	0.230**					
Temp	-0.001	-0.124**	0.559**	0.465**	0.462**	0.336**	0.429**				
Rh	0.031**	0.098**	-0.518**	-0.391**	-0.416**	-0.335**	-0.416**	-0.718**			
GR	0.078**	0.070**	0.405**	0.304**	0.311**	0.215**	0.202**	0.669**	-0.365**		
Pressure	0.518**	0.417**	0.328**	0.229**	0.217**	0.356**	-0.197**	-0.384**	0.230**	-0.124**	
RQ	-0.136**	-0.118**	-0.317**	-0.215**	-0.254**	-0.247**	-0.084**	-0.300**	0.181**	-0.247**	-0.092**

WS: wind speed; Temp: temperature; RH: relative humidity; GR: global radiation; RQ: rain quantity.

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 4. The multi-pollutant model of daily average NO₂ (lag 4), PM₁₀ (lag 6), CO (lag 6), NO₂ (lag 4)×PM₁₀ (lag 6) and morning PEFR.

morning PEFR	NO ₂ (lag 4)		PM ₁₀ (lag 6)		CO (lag 6)		NO ₂ (lag 4)×PM ₁₀ (lag 6)								
	β	p-value	β	p-value	β	p-value	β	p-value							
	1.34	0.25	2.44	0.02	-0.08	0.12	0.66	-0.34	-9.53	8.85	0.94	-0.015	-0.030	-0.001	0.04

Adjusted for gender, severity of asthma, day of the week, age, weight, wind speed (lag 5), temperature (lag 1), global radiation (lag 4) and rain quantity (lag 6).

was statistically negatively related to the daily average PEFR with a coefficient of -0.52 (95% CI: $-1.03, -0.02$).

The multi-pollutant model showed that NO_2 (lag 4) associated positively with PEFR with a coefficient of 0.15 (95% CI: $0.01, 0.29$), while SO_2 associated negatively, with a coefficient of -0.47 (95% CI: $-0.92, -0.01$) (Table 5).

Association between Daily Maximum Pollutant Levels and PEFR

Morning PEFR

The single-pollutant model showed that $\text{PM}_{2.5}$ max (lag 4) related both statistically and positively to morning PEFR with a coefficient of 0.02 (95% CI: $0.001, 0.04$). NO_2 max (lag 2), PM_{10} max (lag 6) and CO max (lag 6) associated negatively with morning PEFR, with coefficients of -0.07 (95% CI: $-0.13, -0.01$), -0.02 (95% CI: $-0.03, -0.01$), and -1.68 (95% CI: $-3.08, -0.27$), respectively. Both PM_{10} and $\text{PM}_{2.5}$ were significant, due to analysis of the single-pollutant model. Analysis of the multi-pollutant model of morning PEFR was made separately for $\text{PM}_{2.5}$ and PM_{10} .

The multi-pollutant model with all possible combinations of pollutants [excluding SO_2 max (lag 4), and O_3 max (lag 4)] from the single-pollutant model applied showed that NO_2 max (lag 2) and CO max (lag 6) were negatively related to morning PEFR with coefficients of -0.08 (95% CI: $-0.14,$

-0.02) and -1.71 (95% CI: $-3.11, -0.30$), respectively (Table 6(a)).

NO_2 max (lag 2) and PM_{10} max (lag 6) associated negatively with coefficients of -0.07 (95% CI: $-0.13, -0.01$) and -0.013 (95% CI: $-0.024, -0.002$), respectively (Table 6(b)).

Evening PEFR

The single-pollutant model showed that O_3 max (lag 3) and $\text{PM}_{2.5}$ max associated positively with evening PEFR, with coefficients of 0.09 (95% CI: $0.04, 0.14$) and 0.03 (95% CI: $0.01, 0.05$), respectively. The multi-pollutant model, with all possible combinations of pollutants [excluding NO_2 max (lag 1), SO_2 max (lag 5), PM_{10} max (lag 3), and CO max (lag 1)] from the single-pollutant model showed that both O_3 max (lag 3) and $\text{PM}_{2.5}$ max were positively associated with evening PEFR with coefficients of 0.098 (95% CI: $0.03, 0.127$) and 0.029 (95% CI: $0.007, 0.051$) (Table 7).

Daily Average PEFR

The single-pollutant model showed that NO_2 max (lag 2) associated negatively with daily average PEFR, with a coefficient of -0.05 (95% CI: $-0.10, -0.01$), while O_3 max (lag 3) associated positively with daily average PEFR, with a coefficient of 0.05 (95% CI: $0.02, 0.08$). The multi-pollutant model with all possible combinations of pollutants

Table 5. The multi-pollutant model of daily average NO_2 (lag 4), SO_2 and daily average PEFR.

Daily average	NO_2 (lag 4)				SO_2			
	β	(95% CI)		<i>p</i> -value	β	(95% CI)		<i>p</i> -value
PEFR	0.15	0.01	0.29	0.03	-0.47	-0.92	-0.01	0.04

Adjusted for gender, severity of asthma, day of the week, age, weight, wind speed (lag 5), temperature (lag 1), global radiation (lag 4), pressure (lag 1) and rain quantity (lag 2).

Table 6(a). The multi-pollutant model of daily average NO_2 max (lag 2), $\text{PM}_{2.5}$ max (lag 4), CO max (lag 6) and morning PEFR.

NO_2 max (lag 2)				$\text{PM}_{2.5}$ max (lag 4)			CO max (lag 6)				
β	(95% CI)		<i>p</i> -value	β	(95% CI)	<i>p</i> -value	β	(95% CI)	<i>p</i> -value		
-0.08	-0.14	-0.02	0.01	0.016	-0.003	0.036	0.105	-1.71	-3.11	-0.30	0.02

Adjusted for gender, asthma severity, day of the week, age, weight, wind speed max (lag 6), temperature max (lag 4), relative humidity max (lag 1), global radiation max (lag 4), pressure max (lag 1) and rain quantity max (lag 6).

Table 6(b). The multi-pollutant model of daily average NO_2 max (lag 2), PM_{10} max (lag 6), CO max (lag 6), and morning PEFR.

NO_2 max (lag 2)				PM_{10} max (lag 6)			CO max (lag 6)				
β	(95% CI)		<i>p</i> -value	β	(95% CI)	<i>p</i> -value	β	(95% CI)	<i>p</i> -value		
-0.07	-0.13	-0.01	0.02	-0.013	-0.024	-0.002	0.02	-1.42	-2.90	0.06	0.06

Adjusted for gender, asthma severity, day of the week, age, weight, wind speed max (lag 6), temperature max (lag 4), relative humidity max (lag 1), pressure max (lag 1) and rain quantity max (lag 6).

Table 7. The multi-pollutant model of O_3 max (lag 3), $\text{PM}_{2.5}$ max and evening PEFR.

O_3 max (lag 3)				$\text{PM}_{2.5}$ max			
β	(95% CI)		<i>p</i> -value	β	(95% CI)		<i>p</i> -value
0.078	0.03	0.127	0.002	0.029	0.007	0.051	0.01

Adjusted for gender, asthma severity, age, weight, global radiation max (lag 1), pressure max (lag 1) and rain quantity max (lag 5).

[excluding SO₂ max (lag 4), PM₁₀ max, PM_{2.5} max, and CO max] from the single-pollutant model showed that NO₂ max (lag 2) was negatively related to daily average PEFR with a coefficient of -0.05 (95% CI: -0.10 , -0.01), and O₃ max (lag 3) was positively related to daily average PEFR with a coefficient of 0.06 (95% CI: 0.02 , 0.09) (Table 8).

DISCUSSION

A negative relationship between pollutant level and PEFR allows for the possibility that the pollutant harms PEFR. It follows that a positive relationship between pollutant level and PEFR allows for the possibility that the pollutant improves PEFR. In this study, the following negative relationships were found: NO₂ max (lag 2) was found to be related negatively to both morning and daily average PEFR, and SO₂ was related negatively to daily average PEFR. PM₁₀ max (lag 6) appeared to associate negatively with morning PEFR. Also, CO max (lag 6) was negatively associated with morning PEFR. Conversely, NO₂ (lag 4) had a consistently positive association with morning and daily average PEFR, and O₃ max (lag 3) was found to relate positively to daily average PEFR.

When inhaled, NO₂ penetrates to the trachea, bronchi, bronchiole, and alveoli and is an irritant to the mucosa of the eyes, nose, throat, and lower respiratory tract. It also increases bronchial reactivity and increases susceptibility to infections and allergens. It is considered a good marker of vehicular pollution (Arbex et al., 2013). The finding in the present study that NO₂ (lag 4) had a consistently positive association with morning and daily average PEFR was at odds with its “pollutant” status and was contradictory to the results of most other studies, which show an inverse association between NO₂ and PEFR (Pekkanen et al., 1997; Timonen and Pekkanen, 1997; Castro et al., 2009; Qian et al., 2009). Meanwhile, in some studies, no link has been found between NO₂ and PEFR (van der Zee et al., 2000; Kwon et al., 2007; Amadeo et al., 2015). As in the present study, Wiwatanadate and Trakultivakorn (2010) found that NO₂ (lag 5) associated positively with morning PEFR. Although NO₂ (lag 4) in the present study was associated statistically, significantly and positively with morning and daily average PEFR, the interaction of NO₂ (lag 4) and PM₁₀ (lag 6) produced a significantly inverse effect on morning PEFR, with a coefficient of -0.015 (95% CI: -0.03 , -0.001) (Table 4). Furthermore, our result showed that NO₂ max (lag 2) had a significantly inverse association with morning and average PEFR. Specifically, a 1 ppb increase in NO₂ max (lag 2) with PM_{2.5} was associated with a morning PEFR decrease of 0.08 L min⁻¹ (Table 6(a)), while a 1 ppb increase in NO₂ max (lag 2) with PM₁₀ was associated with a

morning PEFR decrease of 0.07 L min⁻¹ (Table 6(b)). A 1 ppb increase in NO₂ max (lag 2) was associated with an average PEFR decrease of 0.05 L min⁻¹ (Table 8). These results show that NO₂ max (lag 2) had a significant inverse association with morning and daily average PEFR and indicate a potential harmful effect of this pollutant. It is possible that NO₂ enhances lung function at very low doses, while high doses reduce lung function. Studies have tended to conclude that significant inverse association between air pollutants and PEFR exists at high pollutant concentrations (Wichmann and Heinrich, 1995), while no significant associations exist at low dose exposures (Kwon et al., 2007).

This study found that O₃ max (lag 3) had a consistently positive association with daily average PEFR, and O₃ appeared to be a protective factor in enhancing PEFR. It is known that some toxic agents can be beneficial to health at a low dose, such as bacterial endotoxins, which help to decrease the risk of asthma in children (Obihara et al., 2007; Sordillo et al., 2010), and lifelong exposure to farms may effectively reduce asthma risk in adults (Douwes et al., 2007). Regarding O₃, the results in the present study are in agreement with a study in Brazil showing that a 10 μg m⁻³ increase in O₃ (lag 1) enhanced morning PEFR by 0.2 L min⁻¹ in asthmatic children (Castro et al., 2009). However, other studies have found a negative association between the O₃ concentrations and lung function. O₃ is one of the most well-studied air pollutants, with initial speculation about health effects dating to the mid-nineteenth century (Rohr, 2018). O₃ exposure results in airway inflammation, airway hyper-responsiveness, and decrements in lung function in healthy and asthmatic adults (Seltzer et al., 1986). Schachter et al. (2016) evaluated asthmatic children in New York and found that O₃ was associated with decreased forced expiratory volume in 1 second (FEV₁) in summer. A panel study of Australian children, who had bronchial hyperactivity and asthma, revealed a significant inverse association between mean daytime O₃ and mean daily deviation in the PEFR (coefficient = -2.61 and p -value = 0.001) (Jalaludin et al., 2000). However, a study of children in northern France found that this association was not significant (Declercq et al., 2000). Dales et al. (2009) similarly found no significant associations for ozone concentration and FEV₁, and Samoli et al. (2017) followed 186 children for 5 weeks and found that personal ozone exposure was not associated with PEFR.

SO₂ penetrates into upper airways, trachea, bronchi, and bronchioles, and affects the mucosa of the eyes, nose, throat, and respiratory tract. It causes cough and increases bronchial reactivity, facilitating bronchoconstriction (Arbex et al., 2012). In the present study, a mean daily increase of 1 ppb of SO₂ was associated with a decrease in daily average PEFR of

Table 8. The multi-pollutant model of daily average NO₂ max (lag 2), O₃ max (lag 3) and daily average PEFR.

β	NO ₂ max (lag 2)			β	O ₃ max (lag 3)		
	(95% CI)		p -value		(95% CI)		p -value
-0.05	-0.10	-0.01	0.02	0.06	0.02	0.09	0.01

Adjusted for gender, asthma severity, day of the week, age, weight, wind speed max (lag 6), temperature max (lag 4) and pressure max (lag 1).

0.47 L min⁻¹. Once again, the literature offers other works that also reported a negative association (Qian *et al.*, 2009; Wiwatanadate and Trakultivakorn, 2010), and those that report no association between SO₂ and PEFR (Aekplakorn *et al.*, 2003; Park *et al.*, 2005; Uno *et al.*, 2005; Canova *et al.*, 2010). It is noteworthy that SO₂ appeared to have adverse effects on lung function in adult asthmatic patients in the present study even though the 24-h average levels of SO₂ never exceeded the standard value for Thailand of 120 ppb during the study period.

This study found that CO max (lag 6) associated negatively with morning PEFR, with a coefficient of -1.71 (95% CI: -3.1, -0.30) (Table 6(a)); a 1 ppm increase of daily ambient CO max (lag 6) was associated with a decrease in morning PEFR of 1.71 L min⁻¹. This result supports previous works: Park *et al.* (2005) found that in a panel of 64 asthmatic adults, CO associated negatively with PEFR variability and mean daily average PEFR; Penttinen *et al.* (2001) found that CO associated negatively with daily average, morning and evening PEFR in adult asthmatic patients; Canova *et al.* (2010) revealed that CO negatively associated with morning and evening PEFR in adult asthmatic patients.

Regarding PM_{2.5} and PM₁₀, epidemiological studies suggest that PM_{2.5} may exert greater toxicity than larger particles (Xing *et al.*, 2016). Toxicological studies have demonstrated that PM exposure may impact respiratory health by inducing both lung inflammation and systemic inflammation (Li *et al.*, 2017; Maciejczyk *et al.*, 2018).

Various studies have found an association between PM_{2.5} concentrations and decreased lung function (Li *et al.*, 2017; Wang *et al.*, 2018; Huang *et al.*, 2019; Rahma *et al.*, 2019) but this was not the case in this study, even when ambient PM_{2.5} levels frequently exceeded the U.S. NAAQS during the study period. This was not surprising because the causal components and susceptible subgroups of particulate matter are not clear (Delfino *et al.*, 2003). Also, the major sources of air pollution in this study were located in northern Thailand, where there are forest fires and open field burning, which is different from most other studies that relate air pollution to traffic (Wiwatanadate and Liwsrisaku, 2010). Regarding the positive association between O₃ max (lag 3), PM_{2.5} max and evening PEFR, our study showed that 84% of participants used Budesonide meter dose inhaler (MDI) and Salbutamol MDI. These medications can attenuate the effects of air pollution and PEFR. Peters *et al.* (1997) found that medication use in asthmatics attenuated the associations between particulate air pollution and PEFR. There may also be other uncontrolled factors affecting this association. PM₁₀ max (lag 6) associated negatively with morning PEFR, with a coefficient of -0.01 (95% CI: -0.024, -0.002). Specifically, a 1 µg m⁻³ increase in daily ambient PM₁₀ max (lag 6) was associated with a decrease in morning PEFR of 0.01 L min⁻¹. These results support previous findings (Hoek *et al.*, 1998; Qian *et al.*, 2009; Wiwatanadate and Liwsrisakun, 2011; Missagia *et al.*, 2018). Missagia *et al.* (2018) studied 117 children and adolescents in a Brazilian public school and found that an increase of 14 µg m⁻³ in PM₁₀ associated with decreased morning PEFR by -1.04% (95% CI: -1.32, -0.77). Hoek *et al.* (1998) analyzed

and averaged data from five panel studies and reported an increase of 10 µg m⁻³ in PM₁₀ related to a decrease of 0.07% in mean PEFR. In the present study, no adverse effects were identified for PM₁₀ and evening PEFR. This may be because airway narrowing/symptoms felt on waking up were immediately recorded by participants (i.e., before taking any remedial action), whereas remedial actions (including self-medication) taken during the day may have alleviated or removed symptoms at the time of the evening PEFR (Pride, 1992; Timonen and Pekkanen, 1997). A systematic review by Ward and Ayres (2004) showed air pollution effects on children. It indicated that PM_{2.5} produced more adverse effects than PM₁₀, as an increase in PM_{2.5} and PM₁₀ levels of 10 µg m⁻³ associated with a decrease in PEFR of -0.063 L min⁻¹ (95% CI: -0.091, -0.034) and -0.012 L min⁻¹ (95% CI: -0.017, -0.008), respectively. In contrast, the present study found that PM₁₀ produced more adverse effects than PM_{2.5}.

The main implications of findings reported in this study are, first, that information regarding pollutants' delayed effects will enable the forecasting of health effects and help the concerned health organizations to be prepared for patients in advance of likely increases in demand. Second, knowledge of the negative effects of some pollutants on PEFR will encourage health policy makers to take serious actions to prevent those pollutants at their sources.

Limitation

The use of a steroid inhaler (Budesonide MDI) and bronchodilator (Salbutamol MDI) by 84% of the participants in this study could weaken or confound the effects of the pollutants. This is because the use of anti-inflammatory medication could either intensify the effects of ambient pollutants on lung function (Lewis *et al.*, 2005) or guard against the pro-inflammatory effects of air pollutants (Delfino *et al.*, 2002). Peter *et al.* (1997) found that the use of medication in asthmatic patients diminished the association between particulate air pollution and PEFR. Also, existing resources for this study were inadequate for comprehensively taking into account several likely confounding factors such as aeroallergens and indoor air pollution (household dust, cooking fumes, second-hand smoke, or incense smoke) and indoor allergens from pets and working patterns and places. Furthermore, the concentrations of ambient pollutants might not represent the individual's exposure doses due to different physiology.

CONCLUSIONS

In this study, SO₂, PM₁₀ max (lag 6) and NO₂ max (lag 2) exhibited significant inverse relationships with the PEFR. Also, the interaction between NO₂ (lag 4) and PM₁₀ (lag 6) appeared to produce a significantly negative additive effect on the flow rate. Hence, these pollutants, after the specified delays, potentially reduced the PEFR. Conversely, we observed positive associations between several of the species and the flow rate, suggesting that increased concentrations of the former, including NO₂ (lag 4) and O₃ max (lag 3), enhanced the latter. As discussed, low concentrations of

certain pollutants have been reported to potentially increase the PEFR, and other researchers have observed positive as well as negative relationships between supposed “pollutants” and the flow rate. Nonetheless, expecting a positive association between these two parameters is counterintuitive, and we recommend further investigation. Our results also demonstrate that the various species (and meteorological factors) did not necessarily cause identical delayed effects. The combination of NO₂ max (lag 2) and PM₁₀ max (lag 6), for example, was significantly associated with the decreased morning PEFR, indicating that the effects of both pollutants on lung function require time to manifest.

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