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Acute effects of air pollution on peak expiratory flow rates and symptoms among asthmatic patients in Chiang Mai, Thailand

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ABSTRACT

The open burnings and forest fires have been recognized as the major sources of severe air pollution in the upper north of Thailand; however, there have been no clear evidences to show the associations between the air pollution and health effects in the area. We assessed the effects of air pollutants on the peak expiratory flow rates (PEFR) and symptoms in asthmatics. A cohort of 121 asthmatics was followed daily, for 306 days, for their PEFR and asthma symptoms. The daily air pollutants, including particulate matter with aerodynamic diameter $<2.5 \mu\text{m}$, particulate matter with aerodynamic diameter $<10 \mu\text{m}$ (PM_{10}), carbon monoxide, ozone, nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), and the meteorological parameters, including pressure, temperature, relative humidity, rain quantity, and sunshine duration, were monitored. The PEFRs were fitted with general linear mixed models. The asthma symptoms were analyzed with the generalized estimating equations. There were positive associations of NO_2 with morning PEFR, with a coefficient of 0.06 [95% confidence interval (CI), 0.00–0.12]; of SO_2 with evening PEFR [with a range of coefficients of 0.88–1.00 (95% CI, 0.31–1.54)] and daily average PEFR [with a coefficient of 0.47 (95% CI, 0.00–0.94)]; of PM_{10} with evening PEFR, with a coefficient of 0.02 (95% CI, 0.00–0.04). There was also negative association of PM_{10} with ΔPEFR , with a coefficient of -0.01 (95% CI, -0.01 to -0.00). No pollutants were related to asthma symptoms. More studies are needed, particularly at low dose in adult asthmatics, to validate our findings.

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Introduction

The air pollution in northern Thailand has been recognized as smog crisis during January to April every year since 2007. The severe air pollution from hazes of northern Thailand had been empirical from the air quality data of the Pollution Control Department's monitoring stations in the northern areas showing that, in 2010, the number of days that the levels of particulate matter less than $10 \mu\text{m}$ in aerodynamic diameter (PM_{10}) exceeded the 24-h average standard level of $120 \mu\text{g}/\text{m}^3$ was 60 days out of 365 days (16.4%); particularly in March 2010, the exceeding days occurred every day.

The highest level was on 18 March, 2010 at $518.5 \mu\text{g}/\text{m}^3$, which is the all-time record (Pollution Control Department, Thailand, 2010). The major sources of hazes during crisis were forest fires; open burnings in the agricultural settings; and garbage burnings.

Asthma is among chronic diseases that has affected people worldwide. The prevalence of asthma in adults aged 20–44 years of northern Thailand in 2001–2002 was 3.01% (Dejsomritrutai et al., 2006). Several researches have been well documented showing the adverse effects of air pollution on the sensitive groups: asthma, chronic obstructive pulmonary disease (COPD), ischemic heart diseases, congestive heart failure, heart rhythm disorders, and diabetes (Brunekreef and Holgate, 2002; Forastiere et al., 2002; Pope and Dockery, 2006; Wiwatanadate and Trakultivakorn, 2010). However, most studies conducted on asthmatic children, whereas very few studies related to peak expiratory flow rate (PEFR) (Higgins et al., 2000; Qian et al., 2009), or to asthma symptom (Lindgren et al., 2009; Mar et al., 2004; Rage et al., 2009) among adult asthmatics or COPD patients. Moreover, there have been controversial results on respiratory effects of pollutants on asthmatic patients. For example, few studies showed that PM_{10} , particulate matter less than $2.5 \mu\text{m}$ in aerodynamic diameter ($\text{PM}_{2.5}$), and other gaseous pollutants are significantly associated with lower PEFR (Lewis et al., 2005; Mortimer et al., 2002).

Abbreviations: ΔPEFR , daily percent deviation of PEFR (ΔPEFR is defined as each patient's mean PEFR during the study period used as a reference from which to calculate that patient's daily percent deviations from their mean PEFR value); ACF, autocorrelation function; CI, confidence interval; CO, carbon monoxide; GEE, generalized estimating equation; GLMM, general linear mixed models; NAAQS, national Ambient Air Quality Standard; NO_2 , nitrogen dioxide; O_3 , ozone; OR, odds ratio; PACF, partial autocorrelation function; PEFR, peak expiratory flow rate; PM_{10} , particulate matter with aerodynamic diameter $<10 \mu\text{m}$; $\text{PM}_{2.5}$, particulate matter with aerodynamic diameter $<2.5 \mu\text{m}$; SO_2 , sulfur dioxide.

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In this study, our aim was to assess the effects of air pollutants on daily PEFR and asthma symptoms of asthmatics residing in Muang district of Chiang Mai, Thailand, where – unlike most studies – the major sources of pollutants are coming from open burnings and forest fires.

Materials and methods

Design and study participants

We chose a panel study as our design, which involves a time series of repeated measurements of outcomes and exposures in a closed cohort of asthmatics. The study was conducted in Chiang Mai, located 696 km north of Bangkok, which is one of the largest cities in Thailand. Its population is around 1.7 million people distributing in 24 administrative districts, including Muang district – our study area. Since Chiang Mai has been annually affected by the smog crisis and has an air quality monitoring station located at the center of the city, we recruited asthmatic patients with the following eligibility criteria: (1) had asthma diagnosed by an allergist; (2) experienced asthma symptoms during the past year; (3) aged greater than 12 years old; and (4) had lived in Chiang Mai for more than 1 year. All participants lived within a 10 km radius of the air quality monitoring station, the majority within 5 km.

The study protocol was approved by the research ethics committee of the Faculty of Medicine, Chiang Mai University. Informed written consent was obtained from all subjects prior to the study. Compliance of both recruiting and retaining subjects was enhanced by monetary incentives. All subjects were asthmatic patients who had regularly attended the allergy clinic organized by the Pulmonary Critical Care and Allergy Division of the Department of Internal Medicine, Faculty of Medicine, Chiang Mai University.

At the beginning of the study there were 152 eligible participants. Thirty one subjects were excluded from the project as diary records was less than 70% of the total number of days.

Prior to the study, each asthmatic patient was carefully evaluated, by the same allergist, as having either mild intermittent, mild persistent, moderate persistent, or severe persistent disease, according to the U.S. National Heart, Lung and Blood Institute's criteria (National Institute of Heart, Lung, and Blood Institute, 1997).

Completion of questionnaires and diaries

Prior to the study we arranged the orientation meeting to each participant to complete a signed informed consent form. The subjects were trained on the PEFR measurement and the recording of symptoms at the allergy clinic.

Starting from 15 August 2005 to 30 June 2006, the participants were required to record the maximum results of three PEFR measurements each in the morning upon rising and in the evening before bedtime every day. The PEFR was measured with a Mini-Wright peak flow meter (Clement Clarke International, Ltd., Harlow, U.K.) in standing position and prior to taking any medication. They were also instructed to record their asthma symptoms twice daily. The respiratory symptoms were classified into four categories: 0=No asthma symptoms present; 1=Asthma symptoms present but did not interfere with daily activities or sleep; 2=Asthma symptoms interfered somewhat with daily activities or sleep; and 3=Asthma symptoms interfered with most activities (may have stayed home in bed, returned home early from work, or called a doctor or nurse for advice). At the end of each month, the participants' diaries were returned to the research assistant while they followed up their illness at the allergy clinic, and was thoroughly scrutinized by the authors for any missing or error records. Participants were queried by phone or paid a visit

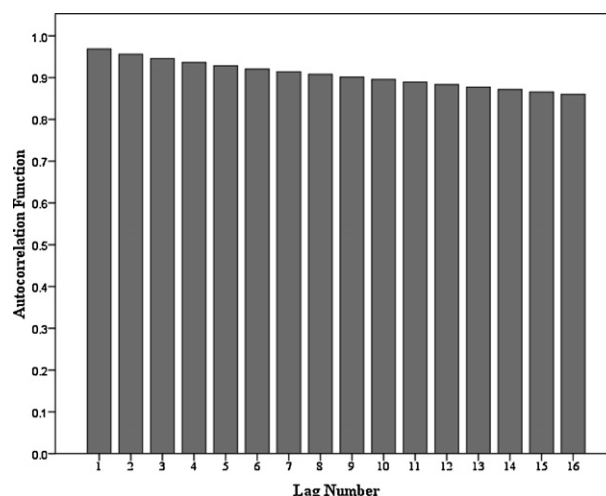


Fig. 1. Autocorrelation function plot of daily morning PEFR of 121 asthmatic patients in Muang district, Chiang Mai, Thailand. ■: Coefficient.

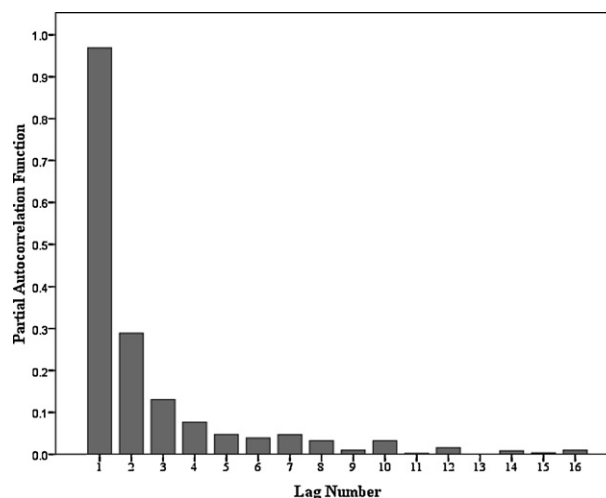


Fig. 2. Partial autocorrelation function plot of daily morning PEFR of 121 asthmatic patients in Muang district, Chiang Mai, Thailand. ■: Coefficient.

immediately if any irregularities were found. All patients in the study were always investigated by the same allergist; however, in order to eliminate the inconsistency of data record due to the learning effects, measurements during the first 14 days were disregarded.

Measurements of air pollutants and meteorological parameters

Ambient air concentrations of pollutants were measured by the Pollution Control Department, Ministry of National Resources and Environment with the continuous automated air sampling monitoring station located at the center of the city. The analysis method for carbon monoxide (CO) concentrations was non-dispersive infrared detection; for sulfur dioxide (SO₂) concentrations was pararosaniline technique; for nitrogen dioxide (NO₂) and ozone (O₃) concentrations was chemiluminescence technique; and for PM₁₀ and PM_{2.5} was gravimetric technique (Air Quality and Noise Management Bureau, 2004). The data reported were daily average concentrations for all parameters, except for PM_{2.5} and PM₁₀ that the hourly average concentrations were obtained and the hourly maximums of each day were selected as daily maximums. We, also, obtained the meteorological data, i.e., pressure, temperature, relative humidity, rain quantity, and sunshine duration, from the

Table 1

Descriptive statistics for 121 asthmatic patients in Muang district, Chiang Mai, Thailand, 29 August 2005, 30 June 2006.

Subject characteristic	Value
No. males/females	48/73
Median age (age range, years)	53 (13–78)
Mean height (SD) (cm)	158.7 (8.6)
Mean weight (SD) (kg)	59.2 (12.6)
No. asthma severity (%)	
Mild intermittent	16 (13.2)
Mild persistent	47 (38.8)
Moderate persistent	51 (42.2)
Severe persistent	7 (5.8)

Northern Meteorology Center, Chiang Mai province on a daily average basis.

Statistical analysis methods

Associations between PEFR and concentrations of air pollutants were analyzed by the general linear mixed models (GLMM) and associations between asthma symptoms (categories 0 and 1 were grouped as symptoms negative, and categories 2 and 3 were grouped as symptoms positive) and concentrations of air pollutants were analyzed by the generalized estimating equations (GEE) with binary response. Both models are suitable because the within-subject correlation of the repeated measures could be accounted for. For the GLMMs, the random effects at subject-specific levels were also assessed and for the GEEs, the relative risks were estimated using odds ratios (OR) with 95% confidence intervals (CI). The statistical software used in the analyses was the R version 2.8.1

(R Development Core Team, 2008). Since all meteorological variables were recorded as a time series and we assumed that they had lagged (or delayed) effects on the PEFRs and asthma symptoms, we began the analyses by performing separate univariate analysis of each meteorological variable at lags 0–6 with each of six outcomes: morning PEFR, evening PEFR, daily average PEFR, daily percent deviation of PEFR (Δ PEFR) (each subject's mean PEFR during the study period was used as a reference from which to calculate that subject's daily percent deviations from their mean PEFR value), daytime symptom, and nighttime symptom. The best lagged effect, i.e., the least *p*-value, was entered in the next step. The separate multivariate regressions (MVR) without air pollutants were subsequently used to screen the key outcome-related personal factors [date (time trend), gender, age, asthma severity, day of week, height, and weight] and all best-lagged meteorological covariates from the previous step for each outcome. Those with a *p*-value <0.25 were kept for further analyses according to the methods of Peters et al. (1999) and Wiwatanadate and Trakultivakorn (2010). The selection of 0.25 level is based on the work by Bendel and Afifi (1977) showing that use of a more traditional level (e.g., 0.05) often fails to identify variables known to be important. Because of the autocorrelation nature of repeated measurements over time, we performed plots of the autocorrelation (ACF) (Fig. 1) and partial autocorrelation (PACF) functions (Fig. 2) of all six outcomes of PEFRs and asthma symptoms to determine the characteristics of correlation. The results showed that all had an exponential decay pattern starting at lag 1 both in ACF and PACF plots. Therefore, for the GLMMs, the appropriate covariance structure for the residuals contains one autoregressive and one moving average parameters so-called a first-order autoregressive moving average structure. Regarding the GEEs, the appropriate

Table 2

Daily meteorological and air pollution measurements in Muang district, Chiang Mai, Thailand, 29 August 2005, 30 June 2006.

Exposure (24 h average)	No. observations	Minimum/maximum	Mean (SD)	90th percentile	#Days exceeded standards (percent)
Pressure (hPa)	306	1002.27/1018.54	1009.50 (3.43)	1014.40	–
Temperature (°C)	306	18.30/32.00	25.47 (2.79)	28.50	–
Relative humidity (%)	306	45.00/97.00	76.61 (11.89)	90.00	–
Rain quantity (mm) ^a	296	0.00/73.90	4.44 (12.05)	12.49	–
Sunshine duration (h)	306	0.00/10.90	6.60 (2.99)	9.40	–
PM _{2.5} (μg/m ³) ^a	276	13.19/223.83	43.75 (31.03)	88.07	124 (44.9) ^b
PM _{2.5} daily max (μg/m ³) ^a	276	21.00/310.00	77.62 (47.16)	140.00	–
PM ₁₀ (μg/m ³) ^a	303	15.68/237.04	58.07 (32.76)	100.01	17 (5.6) ^c
PM ₁₀ daily max (μg/m ³) ^a	303	31.00/335.00	118.64 (53.71)	189.60	– ^c
CO (ppm) ^a	294	0.33/2.38	1.09 (0.30)	1.52	–
O ₃ (ppb) ^a	281	5.55/34.65	17.50 (6.52)	26.82	–
NO ₂ (ppb) ^a	294	7.91/37.35	17.24 (6.13)	26.46	–
SO ₂ (ppb) ^a	217	0.00/3.89	1.73 (0.62)	2.42	0 (0.0) ^d

^a Missing because of equipment malfunction.

^b According, U.S. NAAQS = 35 μg/m³.

^c According, Thailand NAAQS = 120 μg/m³.

^d According, Thailand NAAQS = 120 ppb.

Table 3

Correlation matrix of ambient air pollutants and meteorological parameters, Muang district, Chiang Mai, Thailand, 29 August 2005, 30 June 2006.

	Temp	RH	Rain	SD	PM _{2.5}	PM ₁₀	CO	O ₃	NO ₂	SO ₂
Pressure	–0.72**	0.04	–0.27**	0.10	–0.25**	0.03	0.20**	–0.22**	0.16**	0.40**
Temp		–0.28**	0.06	0.16**	0.38**	0.11	–0.14*	0.37**	–0.13*	–0.23**
RH			0.34**	–0.62**	–0.78**	–0.75**	–0.40**	–0.66**	–0.66**	0.08
Rain				–0.33**	–0.17**	–0.28**	–0.27**	–0.09	–0.31**	–0.14*
SD					0.29**	0.34**	0.19**	0.38**	0.40**	–0.06
PM _{2.5}						0.88**	0.53**	0.67**	0.67**	–0.07
PM ₁₀							0.73**	0.57**	0.83**	0.23**
CO								0.22**	0.82**	0.38**
O ₃									0.46**	–0.04
NO ₂										0.23**

Abbreviations: RH, relative humidity; SD, sunshine duration; temp, temperature.

* Correlation is significant at *p* < 0.05.

** Correlation is significant at *p* < 0.01.

Table 4
The multi-pollutant GLMMs of daily average PM_{2.5} (lag 5), PM₁₀ (lags 5, 6), O₃ (lag 6), NO₂ (lags 5, 6), SO₂ (lags 4, 6) and evening PEFR [regression coefficient (95% CI)].

	PM _{2.5} (lag 5)	PM ₁₀ (lag 5)	PM ₁₀ (lag 6)	O ₃ (lag 6)	NO ₂ (lag 5)	NO ₂ (lag 6)	SO ₂ (lag 4)	SO ₂ (lag 6)
Evening PEFR ^a								
Model 1	0.01 (−0.05, 0.08)			0.02 (−0.05, 0.08)	0.02 (−0.08, 0.11)		0.88* (0.31, 1.46)	0.45 (−0.16, 1.05)
Model 2	0.01 (−0.01, 0.03)			0.03 (−0.03, 0.10)	0.06 (−0.04, 0.15)		0.90* (0.34, 1.47)	0.48 (−0.15, 1.11)
Model 3	0.02 (−0.01, 0.04)			0.02 (−0.05, 0.08)		−0.01 (−0.10, 0.08)		
Model 4	0.01 (−0.01, 0.04)			0.03 (−0.04, 0.10)		−0.01 (−0.10, 0.09)		
Model 5		0.01 (−0.01, 0.03)		0.03 (−0.03, 0.09)	0.01 (−0.09, 0.11)		0.90* (0.34, 1.45)	
Model 6		0.02 (−0.00, 0.04)		0.02 (−0.04, 0.08)	0.00 (−0.10, 0.10)		0.91* (0.36, 1.45)	
Model 7		0.01 (−0.01, 0.03)		0.03 (−0.03, 0.09)		−0.00 (−0.09, 0.08)		
Model 8		0.02* (0.00, 0.04)		0.02 (−0.04, 0.08)		−0.02 (−0.11, 0.08)		
Model 9			0.01 (−0.01, 0.02)	0.03 (−0.03, 0.09)	0.04 (−0.04, 0.11)		0.93* (0.37, 1.49)	
Model 10			−0.00 (−0.02, 0.01)	0.04 (−0.02, 0.10)	0.07 (−0.01, 0.15)			0.54 (−0.10, 1.18)
Model 11			0.01 (−0.01, 0.03)	0.03 (−0.03, 0.09)		0.01 (−0.09, 0.11)	1.00* (0.44, 1.54)	
Model 12			−0.00 (−0.02, 0.02)	0.04 (−0.02, 0.10)		0.05 (−0.05, 0.15)		0.52 (−0.13, 1.16)

^a Adjusted for gender, age, asthma severity, day of week, weight, pressure (lag 0), temperature (lag 0), sunshine duration (lag 0), and rain quantity (lag 1).* $p < 0.05$.

structure is first-order autoregressive (StatSoft, Inc., 2007). Next, we used the GLMMs or GEEs to estimate the pollution effects (lags 0–6) accounted for only personal and meteorological covariates obtained from the previous step on each of six outcomes separately. For the morning PEFR and daytime symptom, we excluded the same day (lag 0)'s pollutant levels because the exposure had not occurred yet when the outcomes were measured and/or recorded. Regarding the GLMMs, the personal and meteorological covariates were treated as fixed factors, whereas the intercept and the slope for date were allowed to be subject-specific random effects. However, after we performed the residual maximum likelihood-based likelihood ratio tests (Self and Liang, 1987), only the intercept random effects had been kept in the models. If more than one pollutant was statistically significant, a multi-pollutant effects model was then conducted to adjust for each other's effect on the outcomes.

Results

Demographic and asthma characteristics of cohort

Table 1 summarizes the characteristics of the participants. The number of the eligible asthmatic patients recruited into the study was 121 with 48 males and 73 females. Their median age was 53 years with a range of 13–78 years. Their mean $\pm$ SD of height was 158.7 ± 8.6 cm and that of weight was 59.2 ± 12.6 kg. The asthmatic severity was categorized as mild intermittent 16 (13.2%), mild persistent 47 (38.8%), moderate persistent 51 (42.2%), and severe persistent 7 (5.8%).

Description of ambient exposure measurement

Table 2 indicates the exposure parameters. Due to air quality monitoring equipment malfunction, there were 30 out of 306 days (9.8%) missing for the PM_{2.5} and PM_{2.5} maximum (max), 3 days (1.0%) for PM₁₀ and PM₁₀ max, 12 days (3.9%) for CO, 25 days (8.2%) for O₃, 12 days (3.9%) for NO₂, and 89 days (29.1%) for SO₂ data. There were 124 out of 276 days (44.9%) that 24-h average of PM_{2.5} exceeded the U.S. National Ambient Air Quality Standard (NAAQS) of $35 \mu\text{g}/\text{m}^3$, but there were 17 out of 303 days (5.6%) that 24-h average of PM₁₀ exceeded the current Thailand's NAAQS limit of 120 ppb. Pearson correlation coefficients among air pollutants and meteorological parameters are shown in Table 3.

Association of exposure and PEFR

As mentioned above in the screening step for morning PEFR-related covariates using MVR without air pollutants, gender, age, asthma severity, day of week, weight, pressure (lag 1), temperature (lag 1), sunshine duration (lag 6), and rain quantity (lag 1) variables were accounted for in the single-pollutant mixed effects models, including intercept random effect. It was found that only NO₂ (lag 5) was positively associated with morning PEFR with a coefficient of 0.06 (95% CI, 0.00–0.12).

Considering evening PEFR; gender, age, asthma severity, day of week, weight, pressure (lag 0), temperature (lag 0), sunshine duration (lag 5), and rain quantity (lag 1) were accounted for. The single-pollutant models showed that PM_{2.5} (lag 5), PM₁₀ (lags 5 and 6), O₃ (lag 6), NO₂ (lags 5 and 6), SO₂ (lags 4 and 6), PM_{2.5} max (lag 6), and PM₁₀ max (lag 1) were all statistically positively related to the evening PEFR with a coefficient of 0.02 (95% CI, 0.00–0.03), 0.02 (95% CI, 0.01–0.03), 0.01 (95% CI, 0.00–0.02), 0.05 (95% CI, 0.00–0.10), 0.09 (95% CI, 0.03–0.15), 0.07 (95% CI, 0.01–0.13), 0.91 (95% CI, 0.38–1.44), 0.64 (95% CI, 0.10–1.18), 0.01

Table 5The multi-pollutant GLMMs of daily average PM_{2.5} (lag 5), PM₁₀ (lag 5), NO₂ (lag 5), SO₂ (lags 4, 6), and daily average PEFR [regression coefficient (95% CI)].

	PM _{2.5} (lag 5)	PM ₁₀ (lag 5)	NO ₂ (lag 5)	SO ₂ (lag 4)	SO ₂ (lag 6)
Average PEFR ^a					
Model 1	0.01 (−0.01, 0.03)		0.02 (−0.05, 0.10)	0.48 (−0.00, 0.96)	
Model 2	0.01 (−0.01, 0.02)		0.05 (−0.03, 0.13)		0.37 (−0.13, 0.86)
Model 3		0.01 (−0.01, 0.02)	0.04 (−0.04, 0.12)	0.47* (0.00, 0.94)	
Model 4		0.01 (−0.00, 0.03)	0.02 (−0.07, 0.10)		0.37 (−0.14, 0.87)

^a Adjusted for gender, age, asthma severity, day of week, weight, pressure (lag 1), temperature (lag 0), sunshine duration (lag 6), and rain quantity (lag 1).* $p < 0.05$.

(95% CI, 0.00–0.01), and 0.01 (95% CI, 0.00–0.01), respectively. Subsequently, we analyzed using the multi-pollutant mixed effects models, including intercept random effect, with all possible combinations of pollutants from the single-pollutant models [excluding PM_{2.5} max (lag 6) and PM₁₀ max (lag 1)] and found that SO₂ (lag 4) was statistically positively related to the evening PEFR in models 1, 3, 5, 7, 9, and 11 with a coefficient of 0.88 (95% CI, 0.31–1.46), 0.90 (95% CI, 0.34–1.47), 0.90 (95% CI, 0.34–1.45), 0.91 (95% CI, 0.36–1.45), 0.93 (95% CI, 0.37–1.49), and 1.00 (95% CI, 0.44–1.54), respectively, and PM₁₀ (lag 5) was statistically positively related to the evening PEFR in model 8 with a coefficient of 0.02 (95% CI, 0.00–0.04) (see Table 4). We also performed separate mixed effects models including the interaction terms between each of pollutants and meteorological parameters that were found significantly correlated in Table 3, but none were statistically significant.

Regarding daily average PEFR; gender, age, asthma severity, day of week, weight, pressure (lag 1), temperature (lag 0), sunshine duration (lag 6), and rain quantity (lag 1) covariates were accounted for in the models, and PM_{2.5} (lag 5), PM₁₀ (lag 5), NO₂ (lag 5), SO₂ (lags 4 and 6), and PM₁₀ max (lag 1) were all statistically positively related to the daily average PEFR with a coefficient of 0.01 (95% CI, 0.00–0.03), 0.01 (95% CI, 0.01–0.02), 0.08 (95% CI, 0.03–0.14), 0.50 (95% CI, 0.04–0.96), 0.57 (95% CI, 0.10–1.03), and 0.01 (95% CI, 0.00–0.01), respectively. Again, we further analyzed using the multi-pollutant mixed effects model with all possible combinations of positively associated pollutants [excluding PM₁₀ max (lag 1)] and found that only SO₂ (lag 4) was statistically positively related to the daily average PEFR in model 3 with a coefficient of 0.47 (95% CI, 0.00–0.94) (see Table 5). Similarly, the interaction terms had been tested, but none were statistically significant.

Finally, for Δ PEFR, the age, day of week, height, pressure (lag 1), temperature (lag 1), sunshine duration (lag 6), and rain quantity (lag 1) covariates were accounted for, and PM₁₀ (lags 5 and 6), CO (lag 2), NO₂ (lags 2, 5, 6), SO₂ (lag 6), and PM₁₀ max (lag 1) were statistically related to the Δ PEFR with a coefficient of −0.00 (95% CI, −0.01 to −0.00), −0.00 (95% CI, −0.01 to −0.00), 0.02 (95% CI, 0.00–0.04), −0.03 (95% CI, −0.04 to −0.01), −0.02 (95% CI, −0.04 to −0.00), −0.20 (95% CI, −0.35 to −0.04), and −0.00 (95% CI, −0.00 to −0.00), respectively. We further analyzed using the multi-pollutant mixed effects model with all possible combinations of significant pollutants [excluding PM₁₀ max (lag 1)] and found that only PM₁₀ (lag 5) was statistically negatively related to the Δ PEFR in models 1–3 with a coefficient of −0.01 (95% CI, −0.01 to −0.00), −0.01 (95% CI, −0.01 to −0.00), and −0.01 (95% CI, −0.01 to −0.00), respectively (see Table 6). Again, the interaction terms could be ignored after the tests were not significant.

Association of exposure and asthma symptoms

In the screening step for daytime symptom-related covariates using MVR without air pollutants, asthma severity, day of week, day (time trend), pressure (lag 4), and humidity (lag 3) variables were included in the single-pollutant models. It was found that PM_{2.5} (lag 3), PM₁₀ (lag 3), O₃ (lag 4), and SO₂ (lag 2) were all statistically negatively associated with daytime symptom with an OR

of 0.995 (95% CI, 0.990–0.999), 0.996 (95% CI, 0.994–0.999), 0.985 (95% CI, 0.972–0.998), and 0.898 (95% CI, 0.811–0.994), respectively. We further analyzed the multi-pollutant models with all possible combinations of significant pollutants and found that none were statistically associated with the daytime symptom. For nighttime symptom, asthma severity, day of week, temperature (lag 3), humidity (lag 4), and rain quantity (lag 0) covariates were accounted for in the models, and NO₂ (lag 5), SO₂ (lag 5), and PM₁₀ max (lag 5) were all statistically positively related to the nighttime symptom with an OR of 1.020 (95% CI, 1.005–1.035), 1.159 (95% CI, 1.041–1.290), and 1.002 (95% CI, 1.000–1.003), respectively. However, when NO₂ (lag 5) and SO₂ (lag 5), excluding PM₁₀ max (lag 5), were tested in the two-pollutant model, neither were significant.

Discussion

Our study reveals that only NO₂ (lag 5) was positively associated with morning PEFR, whereas SO₂ (lag 4) and PM₁₀ (lag 5) had consistently positive association with the evening PEFR. Moreover, SO₂ (lag 4) had consistently effects on the daily average PEFR and PM₁₀ (lag 5) was negatively related to the Δ PEFR. For NO₂ effect on lung function, our study is contradictory to most studies finding inverse association between NO₂ and PEFR (Ng et al., 2001; Qian et al., 2009). Others found no association between NO₂ and PEFR (Kwon et al., 2007; Van Der Zee et al., 2000). To our best knowledge, no studies found positive association like our study. Likewise, the SO₂ effects on evening and daily average PEFR are contradictory to few studies that demonstrated the inverse association with the PEFR (Qian et al., 2009; Schwela, 2000; Wichmann and Heinrich, 1995), whereas other studies found no association between SO₂ and PEFR (Uno et al., 2005) in adult asthmatic patients. Again, not surprisingly, there have been no studies relating positive correlation between SO₂ and PEFR. The explanations for this might be: firstly, there might be the publication bias occurring when the publication of research results depends on their nature and direction (Dickerson, 1990). Secondly, it is possible that NO₂ and SO₂ might enhance the lung function at the very low doses, whereas they reduce the lung function at high doses. The empirical evidences can be seen as most studies tend to show significant inverse association between pollutants and PEFR at high concentrations of pollutants (Wichmann and Heinrich, 1995), whereas there have been no significant associations at low dose of exposure (Kwon et al., 2007). In fact, some toxic agents might be beneficial to health at low dose; for example, bacterial endotoxins might help reduce the risk of asthma in children (Obihara et al., 2007; Sordillo et al., 2010) and lifelong farm exposure may strongly reduce the risk of asthma in adults (Douwes et al., 2007). Thirdly, the NO₂ and SO₂ might be beneficial to adult asthmatics, but not in children as found in most studies (Aekplakorn et al., 2004; Wiwatanadate and Trakultivakorn, 2010). Finally, our findings might be confounded by other factors that were not accounted for in this study: aeroallergens, asthma medications, volatile organic compounds, indoor air pollutants (household dust, cooking fume, incense or candle smoke, etc.).

The associations between PM₁₀ or PM_{2.5} concentrations and the decreases of lung function have been found repeatedly in vari-

Table 6
The multi-pollutant mixed effects models of daily average PM₁₀ (lag 5), PM₁₀ (lag 6), CO (lag 2), NO₂ (lag 2), NO₂ (lag 5), NO₂ (lag 6), SO₂ (lag 6) and ΔPEFR [regression coefficient (95% CI)].

	PM ₁₀ (lag 5)	PM ₁₀ (lag 6)	CO (lag 2)	NO ₂ (lag 2)	NO ₂ (lag 5)	NO ₂ (lag 6)	SO ₂ (lag 6)
ΔPEFR ^a							
Model 1	−0.01 [*] (−0.01, −0.00)		0.02 (−0.47, 0.50)	0.00 (−0.03, 0.03)			−0.10 (−0.27, 0.07)
Model 2	−0.01 [*] (−0.01, −0.00)		0.01 (−0.33, 0.35)		−0.00 (−0.03, 0.03)		−0.12 (−0.30, 0.06)
Model 3	−0.01 [*] (−0.01, −0.00)		0.02 (−0.32, 0.36)			0.00 (−0.03, 0.03)	−0.11 (−0.30, 0.07)
Model 4		−0.00 (−0.01, 0.00)	0.05 (−0.44, 0.53)	0.01 (−0.03, 0.04)	−0.02 (−0.04, 0.00)		−0.12 (−0.31, 0.07)
Model 5		−0.00 (−0.01, 0.00)	0.04 (−0.30, 0.38)				−0.15 (−0.34, 0.05)
Model 6		−0.00 (−0.01, 0.00)	0.08 (−0.26, 0.42)			−0.01 (−0.04, 0.02)	−0.12 (−0.32, 0.07)

^a Adjusted for age, day of week, height, pressure (lag 1), temperature (lag 1), sunshine duration (lag 6), and rain quantity (lag 1).

^{*} *p* < 0.05.

ous studies, but it is not the case in our study as we discovered in opposite direction concerning PM₁₀. The reasons might, however, rely on the fact that the causal components and susceptible subgroups of particulate matter have been unclear (Delfino et al., 2003b). Moreover, the major sources of air pollutions in our study location – northern Thailand – come from open burnings and forest fires, unlike most studies that sources of air pollutions are traffic-related. In fact, surrogate measures for organic compounds in PM₁₀ and diesel exhaust particles (Cass and Gray, 1995) showed more robust associations than did PM₁₀ (Delfino et al., 2003b). Nevertheless, our finding must be interpreted cautiously due to the fact that, as discussed above, it might be confounded by uncontrolled factors.

Concerning asthma symptoms, our study shows, in single-pollutant models, that PM_{2.5} (lag 3), PM₁₀ (lag 3), O₃ (lag 4), and SO₂ (lag 2) reduced the risk of daytime symptom. In contrast, NO₂ (lag 5), SO₂ (lag 5), and PM₁₀ max (lag 5) increased the risk of the nighttime symptom. The conflict of results might reflect the influences of uncontrolled confounding factors, as mentioned above and discussed later in the limitations of this study. However, when they were included in the multi-pollutant models, the associations were not significant.

The strengths of this study should be notified. First, although there were 121 subjects recruited in this study, the sample size provided 37,026 person-days of observations, which makes our study one of the largest pollution-asthma panel studies. Second, the study design using time series has been advantageous in finding the most robust lagged effect of each pollutant and meteorological factor on concerned outcomes. In other words, they exert delayed effects.

Some limitations of this study should be denoted. First, as always found in other such studies, the ambient pollution concentrations may not adequately reflect exposures of individuals (Delfino et al., 2002) resulting in the misclassification of actual exposure. However, this limitation might be minimal since the forest fires and open burnings occurred everywhere around the study site and the pollutant levels had been well-mixed and distributed evenly. Second, as stated above, this study failed to account for several potential confounding factors such as aeroallergens that might be enhanced by ozone on PEFR (Higgins et al., 2000), several air pollutants, e.g., volatile organic compounds possibly presenting inverse relationships with evening PEFR (Delfino et al., 2003a), and anti-inflammatory medication uses that could either protect against the proinflammatory effects of air pollutants (Delfino et al., 2002) or enhance the effects of ambient pollutants on lung function (Lewis et al., 2005). In turns, exposure to air pollution increases airway responsiveness to aeroallergens in atopic subjects (D'Amato et al., 2002). Furthermore, the indoor conditions, e.g., having pets in home, having cigarette smokers at home, having exposure to organic pollutants (e.g., mold and food) have been found as the aggravating factors to allergic diseases in Chiang Mai, Thailand (Sriyaraj et al., 2008). As a matter of fact, home microenvironment concentrations of some pollutants were strongly associated with personal exposures than the ambient concentrations indicating that the home is the driving factor determining personal exposures (Delgado-Saborit et al., 2011). Finally, the 89 days with missing SO₂ data might bias the findings of this study.

Conclusions

Our study on a cohort of asthmatics demonstrated that there were consistently positive associations of NO₂, SO₂, and PM₁₀ with PEFR, which are contradictory to most previous studies. We suggest that more studies be conducted, particularly at low dose in adult asthmatics, to validate the findings.

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