

A multifactorial evaluation for the effects of air pollution and meteorologic factors on asthma exacerbation

Hong-Ren Yu

Chang Jung Christian University Graduate Institute of Medical Sciences <https://orcid.org/0000-0003-1242-8760>

Chun-Hung Richard Lin (✉ lin@cse.nsysu.edu.tw)

Sun Yat-Sen University

Jui-Hsiu Tsai

Dalin Tzu Chi Hospital

Yun-Ting Hsieh

Sun Yat-Sen University

Ti-An Tsai

Chang Gung Memorial Hospital

Chang-Ku Tsai

Chang Gung Memorial Hospital

Yi-Chen Lee

Chang Gung University

Ta-Yu Liu

Chang Gung Memorial Hospital

Chih-Min Tsai

Chang Gung Memorial Hospital

Chih-Cheng Chen

Chang Gung Memorial Hospital

Chih-Hao Chang

Chang Gung Memorial Hospital

Te-Yao Hsu

Chang Gung Memorial Hospital

Chen-Kuang Niu

Chang Gung Memorial Hospital

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Abstract

Background: Study identify individual effect of single pollutants on asthma acute exacerbation (AE) may overlook the health effect of the mixture overall. In real world, dynamic changes of air pollutants and meteorologic factors coexist simultaneously. A comprehensive study was carried out to examine the influence of air pollution and meteorologic factors on asthma AE.

Materials and methods: The asthma AE data from emergency room visits were collected from the Taiwan National Health Insurance Research Database from 2005 to 2013. Complete monitoring data for the air pollutants (sulfur dioxide, SO₂; nitrogen dioxide, NO₂; ozone, O₃; carbon monoxide, CO; PM_{2.5}; and PM₁₀) and meteorologic factors (relative humidity, rainfall, and daily average temperature) were collected from Environmental Protection Agency monitoring stations. A bi-directional case-crossover analysis was used to investigate the effects of air pollution and meteorological factors on asthma exacerbation.

Result: Along age group divisions, a 1 °C temperature increase was a protective factor for asthma ER visits, with OR = 0.981 (95% CI 0.971–0.991) and 0.985 (95% CI, 0.975–0.994) for pediatric and young adult patients, respectively. Each 1 mg/m³ increase in the 48-h averages of PM_{2.5} was associated with asthma ER visit for patients older than 65 years of age (OR = 1.008 (95% CI, 1.003–1.014)).

Conclusion: In Taiwan, asthma AE is closely related to low temperature and certain air pollution. Patients can take appropriate protective strategies to minimize risk of asthma AE related to air pollution/meteorological factors according to relevant gender and age.

1. Introduction

According to the 2010 Global Disease Burden Assessment, outdoor air pollution caused more than three percent of annual disability life lost, a pronounced increase from the previous report [1]. Urbanization is an important cause for asthma increase, and some may be attributed to increased outdoor air pollution [2, 3]. In a study of ten European cities, 14% of pediatric asthma occurrences and 15% of pediatric asthma acute exacerbations (AE) were related to traffic-related contaminants [4]. Air pollution promotes the occurrence and progression of asthma through several mechanisms, including tissue damage by oxidative stress, inflammation and immune response, increased airway responsiveness, and airway remodeling [5, 6]. Particulate matter (PM) often contain many immunogenic substances, such as fungal spores and pollen, which are linked to worsening of asthma symptoms [7, 8]. Ozone (O₃) exposure has been proven to induce airway inflammation and airway hyperresponsiveness, lead to lung function impairment, and cause asthma attack [9–11]. Sulfur dioxide (SO₂) can induce bronchospasm and asthma AE for asthmatic patients [12]. High exposure to NO₂ is associated with reduced bronchodilator effect, worsened lung function, and asthma symptom exacerbation [13–15].

In Taiwan, Wang IJ, et al. showed that exposure to PM₁₀, PM_{2.5}, and CO was associated with the risk of asthma in kindergarten children [16]. PM_{2.5} even had a synergistic effect with mite sensation for the development of asthma. While, the asthma prevalence rate of children and adult was about 7.5% and

11.5% in 2011 with increasing trends [17, 18], and there were downward trends for PM_{2.5} and other certain air-pollutants in this period [19]. Thus, single air pollutant effect cannot well explain this observation.

In addition to the effects of pollutants on asthma [10–15], another area among numerous factors affecting asthma occurrence is meteorologic factor. Previous studies have provided the effect of several meteorologic factors on asthma acute attacks, such temperature change, high atmospheric pressure, low relative humidity, and substantial changes in humidity [20–24]. However, in real world, dynamic change of air pollutants and meteorologic factors is always coexist simultaneously. Focusing on the individual effect of a single pollutant or meteorologic factor may overlook the health effect of the mixture overall. Effective methods to address this bias are needed [6].

The influence of air pollution and meteorologic factors leading to asthma exacerbation is also dependent on age. Previous studies showed that asthmatic children were vulnerable to the adverse effects of air pollution because their lungs are still developing, their metabolic capacity immature, and greater outdoor activity [25, 26]. Older people with asthma also seemed susceptible to adverse effects associated with air pollution [25]. Asthma exacerbations are more often and more severe in young boys than in girls, while active asthma is more prevalent among adult women than men [6, 27]. Thus, environment factors do interplay by individual characteristics and lead to the phenotype.

One strategy to reduce outdoor pollution-related asthma exacerbation is early alert when indicated environmental factor is predicted to be harmful. Here we attempt to provide a comprehensive report about the influence of air pollution and meteorologic factors on asthma acute exacerbation for patients with different gender and age.

2. Materials And Methods

2.1. Data source

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201700710B0C501). The Ethics Committee and Institutional Review Board of Chang Gung Memorial Hospital waived the need for informed consent. The information in each computerized claim form included age, sex, medical care institutions, and diagnosis of the patient. Both personal and medical care institutions' identities in the database were omitted in compliance with the Personal Electronic Data Protection Law in Taiwan. The National Health Insurance Research Database was used as the data source for this study. The Taiwan's National Health Insurance program provided healthcare for 99% of the population [28]. A detailed description of the Taiwan's National Health Insurance Research Database (NHIRD) sample and procedures has been reported [29]. Briefly, this study used the claims data of 1 million subjects randomly selected from 23 million insurants registered from 2005 and traced to 2013 (approximately 5% of the total Taiwanese population). All methods were carried out in accordance with relevant guidelines and regulations.

2.2. Patients and outcome

The study outcome was emergency room (ER) visit for asthma AE. Data were collected on all diagnoses for all patients from January 1, 2005 to December 31, 2013 in Taiwan. Individuals who were included had a diagnosis of asthma (International Classification of Diseases, Ninth Revision, Clinical Modification code 493.xx) as a principal or secondary condition made at an ED visit, as previous reported [30]. The study population was further divided into subgroup according to gender or age.

2.3. Outdoor air pollution and climate factors monitoring

Complete monitoring data for the air pollutants included SO₂, nitrogen dioxide (NO₂), O₃, carbon monoxide (CO), and particles with an aerodynamic diameter less than 2.5 μ m (PM_{2.5}) and less than 10 μ m (PM₁₀). Meteorologic factors, including relative humidity, rainfall, and daily average temperature, were also collected. The air pollutant concentrations were averaged from the results monitored by 74 Environmental Protection Agency monitoring stations of the Taiwanese government. The 24-h average of air pollutants and meteorological factors were used to investigate their association. The 48-h moving averages (including the concurrent day in which ER visit occurred) of air pollution levels resulted in the highest relationship to daily ER visit for asthma, and air pollution generally had a 48-h lag effect [31]. Therefore, we used the 48-h moving average of air pollutant concentrations and temperature for the regression model. For other meteorological factors (humidity and rainfall), the 24-h average was used for analysis. The odds ratios were expressed for each 1 unit increase in the air pollutants concentration and meteorological factors, except for CO. Since CO unit does not change more than 1 ppm, we use 0.1 ppm as one unit for CO when analyzing the relationship between CO level and ER visit for asthma AE. For geographic areas comparison, Taiwan were grouped into six geographic areas according to the Taiwan National Statistics of Regional Standard Classification (area 1: Taipei-New Taipei City-Keelung-Yilan); area 2: Taoyuan-Hsinchu-Miaoli; area 3: Taichung-Changhua-Nan-Tou county; area 4: Yunlin-Jiayi-Tainan; area 5: Kaohsiung- Pingdong; area 6: Hualia-Taidong) (Fig. 1) [29].

2.4. Case-crossover analysis

Case-crossover design has the advantage of controlling for potential confounding caused by fixing individual characteristics, such as sex, age and underlying condition. In this study, bidirectional case-crossover design was used to control for time trends through the use of information about subjects both before and after the event [32]. For case-crossover studies, data were analyzed by standard case-control methods. Exposures close in time to the event (case day) were contrasted with exposure at an indicated time when an event did not occur (control day). In the present study, each ER visit for asthma AE was defined as case day. In bi-directional control samplings, the same weekdays 1, 2 or 3 weeks before and after ER visit for asthma were defined as the control days. For the same person, we compared outdoor pollution/meteorologic factor exposure on the case day with air pollution exposure on the control days. Outdoor pollution/meteorologic data were obtained from nearby geographic Environmental Protection Agency monitoring station based on residence area of the individual. The same weekdays as the control

periods were chosen to avoid the day-of-the-week effect and possible five-day lag effects [33]. Since individual-level covariates remained constant when comparing case days versus control days, they could be ignored and not considered to be confounders. The association between asthma ER visit and outdoor pollution/meteorologic factor was measured with the odds ratio using conditional logistic regression by STATA (StataCorp, College Station, Texas).

2.5. Statistical analysis

Data analysis was performed with the SPSS 22.0 for Windows software package (SPSS, Chicago, Ill). Pearson's analysis was used to establish correlations (r) between each air pollutant and weather factors. Multiple correlation coefficients (R) (multiple regression analysis) were used to explain how much of the variance in the ED visits could be explained by a given set of air pollutants. P values were calculated to determine the significance of regression relationships. ANOVA test with the Bonferroni post hoc was used for multiple comparisons of different areas. $P < 0.05$ was considered significant.

3. Results

3.1. Descriptive statistics of the number of ER visits, air pollution levels, and meteorological measures

Table 1 shows the total number of ED visits due to acute asthma in each month from 2005-2013. There were a total 3287 days during this period. The baseline daily ER visits for asthma attack rate was 7.7 ± 4.0 per 1 million persons for the whole observation period. The 24-hr PM_{2.5} average levels ranged from 8.1 to 97.1 $\mu\text{g}/\text{m}^3$ (mean $29.8 \pm 12.6 \mu\text{g}/\text{m}^3$). The lowest and highest value for 24-hr PM₁₀ average level was 17.9 $\mu\text{g}/\text{m}^3$ and 370.7 $\mu\text{g}/\text{m}^3$, respectively (mean $53.1 \pm 22.2 \mu\text{g}/\text{m}^3$). The timeframes for 24-h average of pollutants and meteorological factors were shown in Figure 2. There were obvious downward trends for SO₂, CO and PM_{2.5} except for O₃ during this period.

Of the 998625 persons enrolled from January 1, 2005, there were 72649 asthmatic patients with a prevalence rate 7.27% (7.63% for male and 6.92% for female) (Supplementary Table 1). The prevalence rate of asthma for pediatric group, younger adult group and older age group was 13.51%, 3.94%, and 15.56%, respectively. The study population was randomly selected from 2005 and traced to 2013 without join of new case. As these children grew up, the young adult group showed the most accumulative number of asthmatic patients since 2010 (Supplementary Table 1). For ER visit for asthma acute exacerbation, the pediatric group had the highest ER visit rate (40.1%) in 2005 among different age groups (Supplementary Table 2). As these children grew up, the young adult group showed the most accumulative number of ER visits for asthma attack since 2010.

3.2. Highly correlation between the level of each outdoor air pollutant and meteorological factors

Table 2. demonstrates the correlation for daily values over the entire period among the air pollutants and weather variables. PM_{2.5}, PM₁₀, SO₂, CO and NO₂ had a strong positive correlation with each other and

were negatively correlated with temperature, rainfall and relative humidity. It is reasonable for the high degree of correlation of PM10 and PM2.5 (Figure 3A). However, outdoor air NO₂ and CO were also highly correlated ($r = 0.9$) (Figure 3B). Our results showed a decrease in outdoor air pollution with rainfall (Figure 3C) and more severe air pollution during the cold season (Figure 3D).

3.3. Great differences of outdoor air pollutants among different geographic areas

In further study, we tried to compare the air pollution in different geographic areas. Taiwan was grouped into six geographic areas. ANOVA analysis revealed great differences for each air pollutant among different geographic areas in Taiwan (Supplementary Table 3). After plotted the outdoor air pollutant and meteorological factors by geographic area into heatmaps (Supplementary Figure 1), CO and NO₂ levels were higher in area 1, 2, and 3 than other areas (Supplementary Figure 1A, 1B), while PM2.5 and PM10 levels were higher in area 4 and 5 than others (Supplementary Figure 1C, 1D). Area 5 had the highest level of O₃ and SO₂ (Supplementary Figure 1E, 1F). Since there was great variations in outdoor air pollutants among different geographic areas, data from a nation-wide study cannot provide information for how outdoor air pollutants/meteorological factors will necessarily influence every asthma ER visit.

When we combined the monthly mean values of PM2.5, monthly mean temperature, and ER visit for asthma attack, we found the number of ER visits for asthma AE to be positively correlated with the PM2.5 value (Figure 4). However, there were more ED visits due to asthma in the winter and spring and fewer during summer and early autumn. Thus, there will be oversight if only a single air pollutant is considered during asthma ER visits. As shown in Table 2, there was close interplay among each air pollutant and meteorological factor. Therefore, the contribution of each air pollutant and meteorological factor for asthma ER visit is needed to be further clarified.

3.4. The relationship of air pollution/ meteorologic factor to ED visits for asthma by case cross-over study

In further study, the case-crossover design was applied to evaluate the relationship between air pollution/ meteorological factors and daily ER visits for asthma acute attack. Individuals with a verified date of ER visit for asthma attack between January 1, 2005, and December 31, 2013, were included. During the study period, there were 25 167 case days and 149 442 control days. For case-crossover analysis, a total of 25 167 ER visits (7.7 ± 4.0 per day in 3287 days) for asthma AE and 149 442 control days were included. The gender ratio for male to female was 56.7 to 43.3 with dominant in age 18 to 64-year-old (37.6%). Here meteorological factor was considered to be a variable rather than adjusted factor, because meteorologic factor was also an important risk factor for asthma AE in the real world. Using six reference periods (7, 14 and 21 d before and after the case period), a 1 mg/m³ increase in the 48-h averages of PM2.5 and 1 °C decrease in temperature were associated with asthma ER visit [odds ratio (OR) = 1.004 (95% CI 1.001–1.007) and 0.986 (95% CI 0.980–0.991) respectively] (Table 3-1). As the study cases were divided by male

and female, a 1 mg/m³ increase in the 48-h averages of PM_{2.5} and 1 °C increase in temperature were associated with asthma ER visit [OR = 1.004 (95% CI, 1.000–1.008) and 0.986 (95% CI, 0.979–0.994) respectively] for male patients. A 1 ppb increase in the 48-h averages of O₃ and a 1 °C increase in temperature were associated with asthma ER visit [OR = 1.003 (95% CI, 1.000–1.007) and 0.985 (95% CI, 0.976–0.993) respectively] for female patients. As the study cases were divided according to age, temperature increase was a protective factor for asthma ER visit, with a 1 °C increase in temperature associated with OR = 0.981 (95% CI 0.971–0.991) and 0.985 (95% CI, 0.975–0.994) for the pediatric age group and young adult group, respectively (Table 3-2). Each 1 mg/m³ increase in the 48-h averages of PM_{2.5} was associated with asthma ER visit for patients older than 65 years of age (OR = 1.008 (95% CI, 1.003–1.014)). We also analyzed the effect of air pollutants on asthma AE without meteorologic factor considered (Supplementary Table 4). If temperature, humidity, and rainfall were not considered, more air pollutants showed significant impacts on asthma AE. For example, O₃ and NO₂ will show harmful effects for asthma AE in the group of 0-17 years old boy and girl, respectively. Thus, meteorologic factor is important and should be considered simultaneously with air pollution.

Since younger children may suffer higher rates of respiratory illness. We further stratified the pediatric group and determined the effect of air pollution and meteorologic factor on asthma AE (Table 3-3). The major impact of outdoor air pollution and meteorologic factor on pediatric asthma AE was for age 6 to 11-year-old. A 1 mm/day increase in the 24-h averages of rainfall and 1°C increase in temperature were associated with asthma ER visit [odds ratio (OR) = 0.897 (95% CI 0.816–0.986) and 0.972 (95% CI 0.949–0.995) respectively] for age 6 to 11-year-old boy. A 1 ppb increase in the 48-h averages of NO₂ were associated with asthma ER visit [odds ratio (OR) = 1.054 (95% CI 1.007–1.102)] for age 6 to 11-year-old girl.

4. Discussion

The adverse impact of single air pollution on asthma has been confirmed [10–14, 25, 34]. Besides air pollution, meteorologic factors such as temperatures, atmospheric pressure and humidity also contributed to asthma acute attacks [20, 22–24]. However, in real world, dynamic changes of air pollutants and meteorologic factors always coexist simultaneously. The precise collaborative influences of several combined air pollutants and meteorological factors are important and significant. Thus, we designed a more comprehensive study to analyze the impact of indicated environmental factors on asthma AE. A highly correlation between each outdoor air pollutant level and meteorological factor was found in our study (Table 2). In Taiwan, the air pollution problem was worse in winter than other seasons. However, asthma AE is also closely related to low temperature (Fig. 4). Therefore, the important meteorologic factor will be neglected during studies on the effects of environment on asthma if only single air pollutant considered. In addition to temperature, most air pollutant concentrations were negatively correlated with rainfall and humidity (Fig. 3C and Table 2), suggesting partial air pollution is removed from rain.

Taiwan's air quality problems are determined largely by topography, polluting industries concentration, and motorcycle traffic compounds [35, 36]. There was great variation in outdoor air pollutants among urban and suburban areas in Taiwan, data from a nation-wide study cannot really reflect the effects of outdoor air pollutants/meteorological factors on asthma ER visit. In the present study, we investigated the relationship between air pollution/meteorological factors and asthma ER visit by using case-crossover study. The advantage of case-crossover study is the case serves as oneself referent to control potential confounding factors as measuring the transient effects of intermittent exposure [37]. Compared with a previous report in Taiwan [38], the influence of air pollutants seems to be overestimated when using a population-based study.

Other study investigated the relationship between ED visit and PM_{2.5}, showing increase of PM_{2.5} lead to more asthma ER visits in the warm season than cold season [34]. However, in our study, we found worsening air pollution lead to more asthma ER visits in the cold season than warm season in Taiwan. This observation was also supported by other study from Taiwan [39]. Other studies even found the climate factors are not important for the prevalence in children asthma [40]. These inconsistent results varied by ethnicity and region. In Taiwan, the factors that contribute to worse air pollution problems in winter than other seasons include topography, fugitive dust at riverbanks during the low-flow season of winter, northeastern winds, and cross-border pollution from China [41, 42]. Therefore, air pollution is closely related to meteorological condition of individual local areas. When studying the influence of air pollution on indicated disease, the local meteorological condition should be considered to achieve comprehensive understanding.

PM is a mixture of many substances that contribute to the inconsistent associations between asthma prevalence and exposure to outdoor PM reported in different areas [43]. However, household indoor PM is highly correlated with outdoor PM (even worse than outdoor PM in certain conditions) [44]. As people may spend more time indoor, indoor air pollutants may have a greater impact on their respiratory health. In cold winter, people may tend to stay indoor with closed window and door. Huang, C, et al showed that, in winter, indoor CO₂ concentration was significantly associated with the increased odds of childhood asthma in Shanghai [44]. The effect of indoor pollutant on asthma AE is an interesting and important issue that worth of well investigation. Other factor that have influence on asthma AE but not considered in this work including allergen exposure and infection. Seasonal pollen allergen may be a component of PM that will contribute to asthma AE [45]. However, in Taiwan, more than 80% atopic individuals sensitize to house dust mite, an annual aeroallergen, in contrast to only 3% to grass pollen [46]. Thus, seasonal allergen is not considered in this study. We also did not investigate the influence of infection on asthma AE because this issue is beyond this work. We have just focused air pollution and meteorologic factors that contribute to asthma exacerbation.

From age stratification data, to our surprise, younger children (less than 5-year-old) are not more susceptible to the effect of outdoor air pollution and meteorologic factor for asthma AE than older children. This may due to younger children tend to stay indoors. Whether younger children with asthma are more vulnerable to indoor air pollution than outdoor pollution need further investigation.

Our study has other several limitations. First, this case-crossover design does not provide estimation of asthma ER visit increase associated with long-term exposure to air pollution. Second, because this study used residential location to ascertain exposure level rather than exact home and school address or place of work, some measurement error is expected. Third, this study demonstrated general behavior for medical visits but not all special conditions. For example, people may delay ER visits during heavy rain. People may also stay indoors or wear a mask when they receive air pollution warnings. All these additional behaviors can change the impact of air pollution and meteorologic factors. Besides we cannot analyze the heterogenous characteristics from population-based data because of limitations posed by personal data availability.

To develop adequate strategies for environment related asthma exacerbation, an improved understanding of the impact of air pollution and meteorologic factors and forecast is needed. Here we demonstrated a comprehensive result about the influence of air pollution and meteorologic factors on asthma AE for patients who were assessed by gender and age. Through this result, asthma patients can take appropriate protective action to avoid asthma AE related to air pollution and meteorological factors according to relevant gender and age. In high risk day for asthma exacerbation, patients should decrease outdoor activity, dress warmly, and maintain inhaled corticosteroid therapy.

Declarations

Ethical Approval and Consent to participate: The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201700710B0C501).

Consent for publication: Not applicable

Availability of supporting data: Upon request after publication

Competing interests: No competing interests

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Authors' contributions: H-RY, J-HT, T-YH and C-HRL contributed to design of the work. H-RY, C-HRL, Y-TH, and T-AT contributed to data acquisition. H-RY, C-KT, Y-CL, C-KN, and T-YL performed data analysis and interpretation. H-RY, C-MT, C-HC, T-YH, and J-HT drafted the manuscript. H-RY, J-HT, C-HRL, C-KN, T-YH, and Y-TH finalized the article. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Tables

Table 1. Descriptive statistics of air pollution and meteorological measures in Taiwan (total 3287 days)

	Mean (\pm SD)	Min	1st Qu.	Median	3rd Qu.	Max
Number of ER visit (per day)	7.7 \pm 4.0	0	5	7	10	33
Number of Hospitalization	3.4 \pm 2.1	0	2	3	5	14
Air pollutants concentrations						
SO ₂ (ppb)	3.7 \pm 1.0	1.5	3.1	3.6	4.1	9.8
CO (ppm)	0.5 \pm 0.1	0.2	0.4	0.4	0.5	1.2
O ₃ (ppb)	28.9 \pm 8.5	9.6	22.6	27.6	33.9	67.6
PM ₁₀ (μ g/m ³)	53.1 \pm 22.2	17.9	36.8	49.2	65.0	370.7
PM _{2.5} (μ g/m ³)	29.8 \pm 12.6	8.1	20.0	27.5	37.3	97.1
NO ₂ (ppb)	14.4 \pm 4.1	3.3	11.0	14.0	16.9	33.9
Meteorological measures						
Temperature (°C)	23.8 \pm 4.7	10.1	20.0	24.6	28.0	31.3
Rainfall (mm/day)	0.3 \pm 0.6	0	0.0	0.1	0.2	8.5
Relative humidity (%)	75.5 \pm 6.1	51.5	72.0	75.8	79.6	91.9

Air pollutants concentrations and meteorological measures are 24-h average.

Abbreviation: Qu.: quarter

Table 2. Pearson correlation coefficients among nation-wide daily weather and air pollution variable in Taiwan from Jan 2005 to Dec 2013

	SO ₂	CO	O ₃	PM ₁₀	PM _{2.5}	NO ₂	Temperature	Rainfall	Relative Humidity
SO ₂	1								
CO	0.6 ***	1							
O ₃	0.1 ***	0.1 ***	1						
PM ₁₀	0.6 ***	0.6 ***	0.5 ***	1					
PM _{2.5}	0.7 ***	0.7 ***	0.5 ***	0.9 ***	1				
NO ₂	0.7 ***	0.9 ***	0.2 ***	0.6 ***	0.7 ***	1			
Temperature	-0.3 ***	-0.6 ***	-0.1 ***	-0.4 ***	-0.4 ***	-0.7 ***	1		
Rainfall	-0.3 ***	-0.2 ***	-0.2 ***	-0.3 ***	-0.3 ***	-0.3 ***	0.2 ***	1	
Relative Humidity	-0.5 ***	-0.0	-0.4 ***	-0.4 ***	-0.4 ***	-0.1 ***	0.1 ***	0.5 ***	1

24-h average of air pollutants and meteorological factors were used to investigate their association.

*** $p < 0.001$

Table 3-1. The relationship of air pollution/ meteorologic factor to ED visits for asthma by case cross-over study

	OR	95% CI	p-value		OR	95% CI	p-value
All				0-17 year-old			
SO2	0.954	0.934 - 0.974	<0.001 *	SO2	0.941	0.909 - 0.975	0.001 *
CO	1.002	0.976 - 1.028	0.898	CO	0.972	0.930 - 1.016	0.207
O3	1.002	1.000 - 1.004	0.126	O3	1.005	1.001 - 1.009	0.011 *
PM10	0.999	0.998 - 1.001	0.235	PM10	1.001	0.999 - 1.003	0.362
PM2.5	1.004	1.001 - 1.007	0.017 *	PM2.5	1.001	0.996 - 1.006	0.731
NO2	0.999	0.992 - 1.007	0.788	NO2	1.010	0.997 - 1.023	0.136
Temperature	0.986	0.980 - 0.991	<0.001 *	Temperature	0.981	0.971 - 0.991	<0.001 *
Rainfall	0.991	0.972 - 1.011	0.390	Rainfall	0.966	0.933 - 1.001	0.058
humidity	0.998	0.996 - 1.001	0.197	humidity	1.001	0.997 - 1.006	0.604
Male				18-64 year-old			
SO2	0.950	0.924 - 0.977	<0.001 *	SO2	0.965	0.932 - 1.000	0.048 *
CO	0.996	0.962 - 1.031	0.814	CO	1.031	0.989 - 1.076	0.152
O3	1.000	0.998 - 1.003	0.758	O3	1.001	0.998 - 1.005	0.570
PM10	0.999	0.998 - 1.001	0.546	PM10	0.998	0.996 - 1.001	0.180
PM2.5	1.004	1.000 - 1.008	0.043 *	PM2.5	1.004	0.999 - 1.009	0.164
NO2	1.000	0.991 - 1.010	0.934	NO2	0.989	0.977 - 1.001	0.069
Temperature	0.986	0.979 - 0.994	0.001 *	Temperature	0.985	0.975 - 0.994	0.002 *
Rainfall	0.991	0.966 - 1.017	0.506	Rainfall	1.023	0.993 - 1.055	0.131
humidity	0.999	0.995 - 1.002	0.467	humidity	0.997	0.993 - 1.002	0.207
Female				>65 year-old			
SO2	0.959	0.928 - 0.991	0.012 *	SO2	0.960	0.920 - 1.001	0.055
CO	1.010	0.970 - 1.050	0.641	CO	1.002	0.955 - 1.052	0.931
O3	1.003	1.000 - 1.007	0.047 *	O3	0.999	0.995 - 1.003	0.608
PM10	0.999	0.997 - 1.001	0.250	PM10	0.997	0.994 - 1.000	0.048 *
PM2.5	1.003	0.999 - 1.008	0.173	PM2.5	1.008	1.003 - 1.014	0.005 *
NO2	0.997	0.986 - 1.009	0.614	NO2	0.998	0.984 - 1.013	0.838
Temperature	0.985	0.976 - 0.993	0.001 *	Temperature	0.993	0.982 - 1.004	0.208
Rainfall	0.991	0.961 - 1.023	0.588	Rainfall	0.971	0.932 - 1.011	0.154
humidity	0.998	0.994 - 1.002	0.257	humidity	0.996	0.991 - 1.001	0.126

Table 3-2. The relationship of air pollution/ meteorologic factor to ED visits for asthma by case cross-over study

	Male			Female		
	OR	95% CI	p-value	OR	95% CI	p-value
0-17 year-old						
SO2	0.946	0.905 - 0.989	0.013 *	0.934	0.879 - 0.991	0.024 *
CO	0.987	0.934 - 1.042	0.628	0.944	0.875 - 1.019	0.138
O3	1.004	0.999 - 1.009	0.097	1.007	1.000 - 1.013	0.041 *
PM10	1.001	0.999 - 1.003	0.362	1.001	0.997 - 1.004	0.753
PM2.5	0.999	0.994 - 1.005	0.780	1.004	0.996 - 1.012	0.343
NO2	1.005	0.989 - 1.021	0.549	1.019	0.997 - 1.041	0.085
Temperature	0.982	0.970 - 0.994	0.003 *	0.979	0.963 - 0.995	0.012 *
Rainfall	0.963	0.922 - 1.006	0.089	0.972	0.914 - 1.034	0.375
Relative humidity	1.002	0.997 - 1.008	0.437	0.999	0.992 - 1.007	0.860
18-64 year-old						
SO2	0.963	0.915 - 1.012	0.139	0.968	0.923 - 1.016	0.191
CO	1.027	0.967 - 1.092	0.384	1.035	0.976 - 1.098	0.252
O3	1.001	0.996 - 1.006	0.656	1.001	0.996 - 1.006	0.713
PM10	0.999	0.995 - 1.002	0.418	0.998	0.994 - 1.002	0.281
PM2.5	1.004	0.997 - 1.011	0.254	1.003	0.996 - 1.010	0.401
NO2	0.987	0.969 - 1.004	0.140	0.99	0.974 - 1.007	0.267
Temperature	0.984	0.970 - 0.998	0.021 *	0.986	0.973 - 0.999	0.032 *
Rainfall	1.019	0.978 - 1.062	0.372	1.028	0.984 - 1.073	0.221
Relative humidity	0.999	0.993 - 1.005	0.757	0.996	0.990 - 1.002	0.149
>65 year-old						
SO2	0.949	0.899 - 1.002	0.060	0.976	0.913 - 1.042	0.467
CO	0.976	0.916 - 1.041	0.465	1.039	0.964 - 1.120	0.320
O3	0.995	0.990 - 1.000	0.072	1.004	0.998 - 1.011	0.170
PM10	0.997	0.994 - 1.001	0.135	0.997	0.992 - 1.002	0.197
PM2.5	1.012	1.004 - 1.019	0.002 *	1.003	0.994 - 1.012	0.479
NO2	1.008	0.989 - 1.027	0.424	0.985	0.963 - 1.008	0.199
Temperature	0.995	0.980 - 1.010	0.509	0.989	0.973 - 1.006	0.223
Rainfall	0.988	0.937 - 1.042	0.654	0.945	0.885 - 1.009	0.092
Relative humidity	0.994	0.988 - 1.000	0.060	0.999	0.992 - 1.007	0.888

Table 3-3. The relationship of air pollution/ meteorologic factor to ED visits for pediatric asthma with stratification by case cross-over study

	Male			Female		
	OR	95% CI	p-value	OR	95% CI	p-value
0-5 year-old						
SO2	0.955	0.816 - 1.118	0.568	1.111	0.887 - 1.392	0.358
CO	0.962	0.791 - 1.170	0.700	0.849	0.637 - 1.131	0.264
O3	0.995	0.976 - 1.015	0.641	1.003	0.973 - 1.034	0.832
PM10	1.002	0.986 - 1.019	0.793	0.989	0.965 - 1.014	0.396
PM2.5	0.997	0.971 - 1.025	0.855	1.016	0.976 - 1.059	0.435
NO2	0.996	0.943 - 1.052	0.890	1.041	0.959 - 1.130	0.337
Temperature	0.995	0.949 - 1.044	0.834	0.963	0.898 - 1.033	0.289
Rainfall	0.937	0.798 - 1.101	0.432	0.795	0.530 - 1.194	0.270
RH	1.009	0.984 - 1.035	0.463	1.005	0.965 - 1.046	0.821
6-11 year-old						
SO2	0.929	0.857 - 1.008	0.076	0.952	0.843 - 1.076	0.432
CO	0.989	0.892 - 1.096	0.833	0.873	0.739 - 1.031	0.109
O3	1.007	0.998 - 1.017	0.110	1.014	1.000 - 1.029	0.056
PM10	1.004	1.000 - 1.009	0.077	1.001	0.992 - 1.010	0.823
PM2.5	0.997	0.986 - 1.007	0.541	0.995	0.977 - 1.014	0.591
NO2	1.012	0.983 - 1.042	0.421	1.054	1.007 - 1.102	0.023 *
Temperature	0.972	0.949 - 0.995	0.018 *	0.969	0.934 - 1.005	0.086
Rainfall	0.897	0.816 - 0.986	0.025 *	1.019	0.887 - 1.171	0.790
RH	1.009	0.998 - 1.021	0.106	0.995	0.978 - 1.012	0.559
12-17 year-old						
SO2	0.983	0.854 - 1.131	0.806	0.831	0.691 - 0.999	0.049 *
CO	0.858	0.725 - 1.017	0.077	0.876	0.697 - 1.101	0.256
O3	1.011	0.997 - 1.026	0.123	0.997	0.978 - 1.015	0.719
PM10	0.998	0.990 - 1.005	0.550	1.004	0.997 - 1.012	0.270
PM2.5	1.006	0.988 - 1.024	0.531	1.006	0.982 - 1.030	0.624
NO2	1.030	0.983 - 1.080	0.215	1.049	0.983 - 1.120	0.145
Temperature	0.981	0.945 - 1.019	0.322	0.992	0.943 - 1.044	0.769
Rainfall	0.961	0.836 - 1.104	0.571	1.088	0.940 - 1.258	0.258
RH	1.007	0.990 - 1.024	0.432	1.000	0.979 - 1.022	0.997

Figures

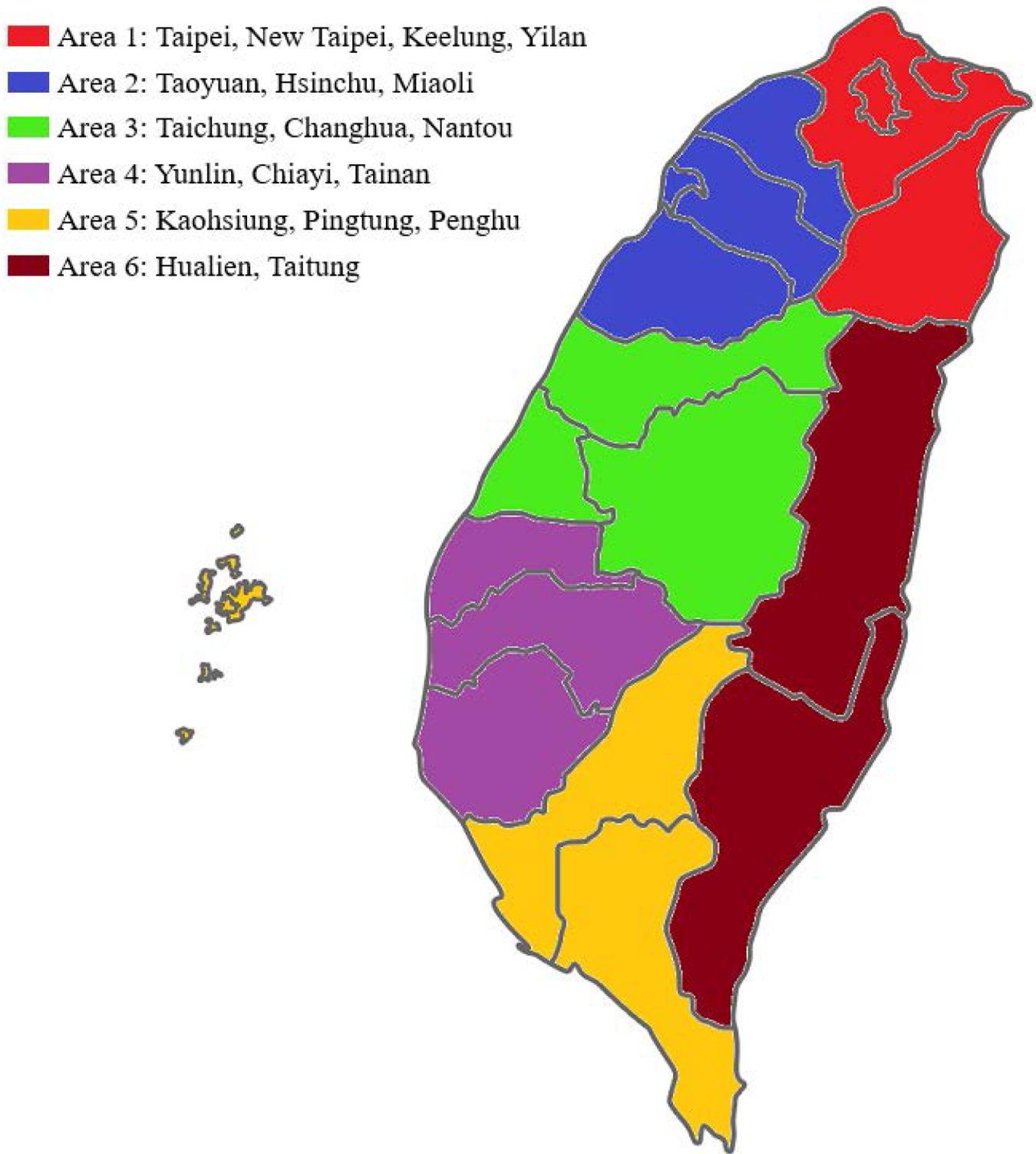


Figure 1

Geographic areas grouped in Taiwan. Six geographic areas are grouped according to the Taiwan National Statistics of Regional Standard Classification (area 1: Taipei-New Taipei City-Keelung-Yilan; area 2: Taoyuan-Hsinchu-Miaoli; area 3: Taichung-Changhua-Nan-Tou county; area 4: Yunlin-Jiayi-Tainan; area 5: Kaohsiung- Pingdong; area 6: Hualia-Taidong). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research

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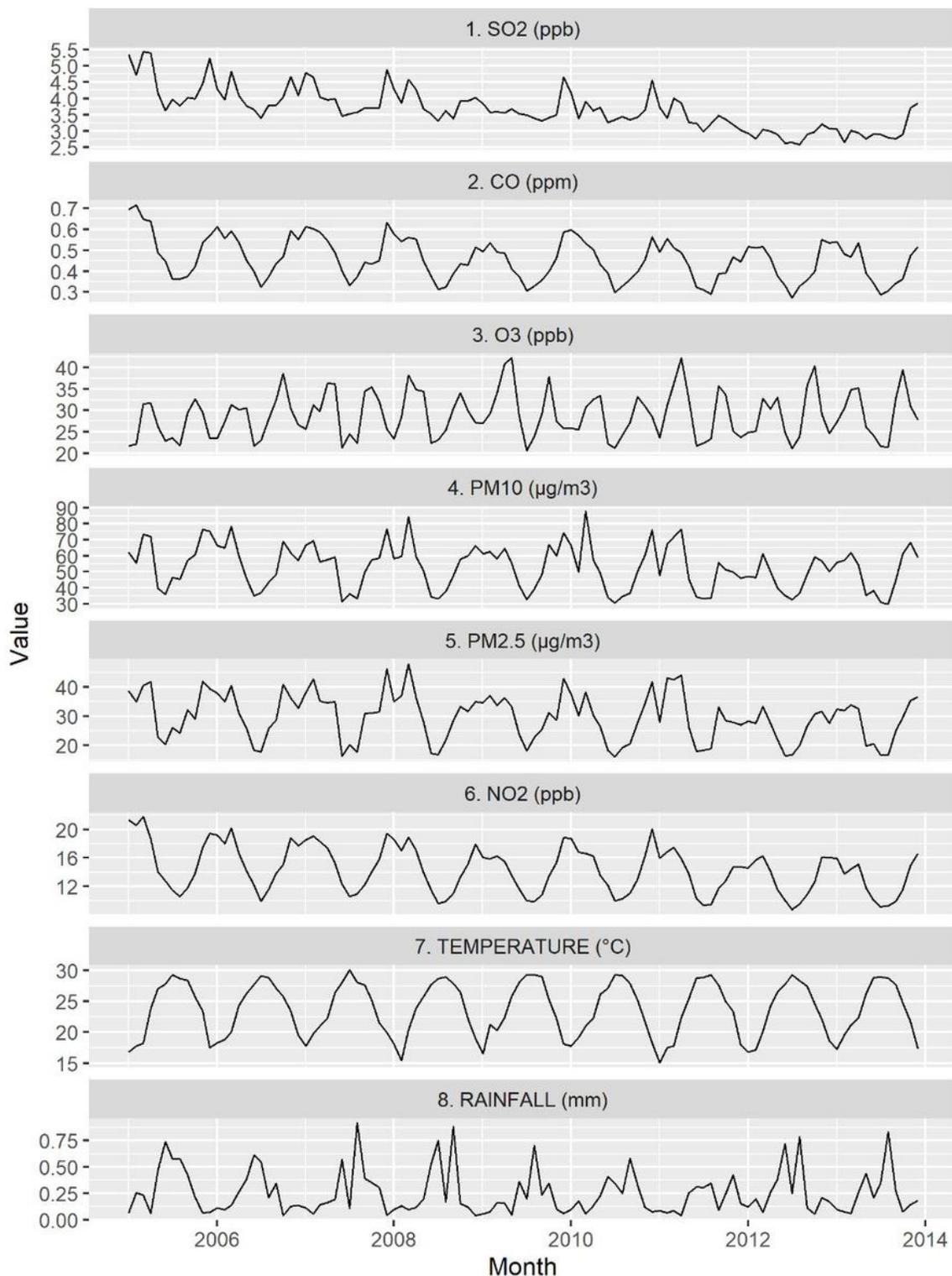


Figure 2

The timeframes for 24-h average of pollutants and meteorological factors from 2005 to 2013 of Taiwan.

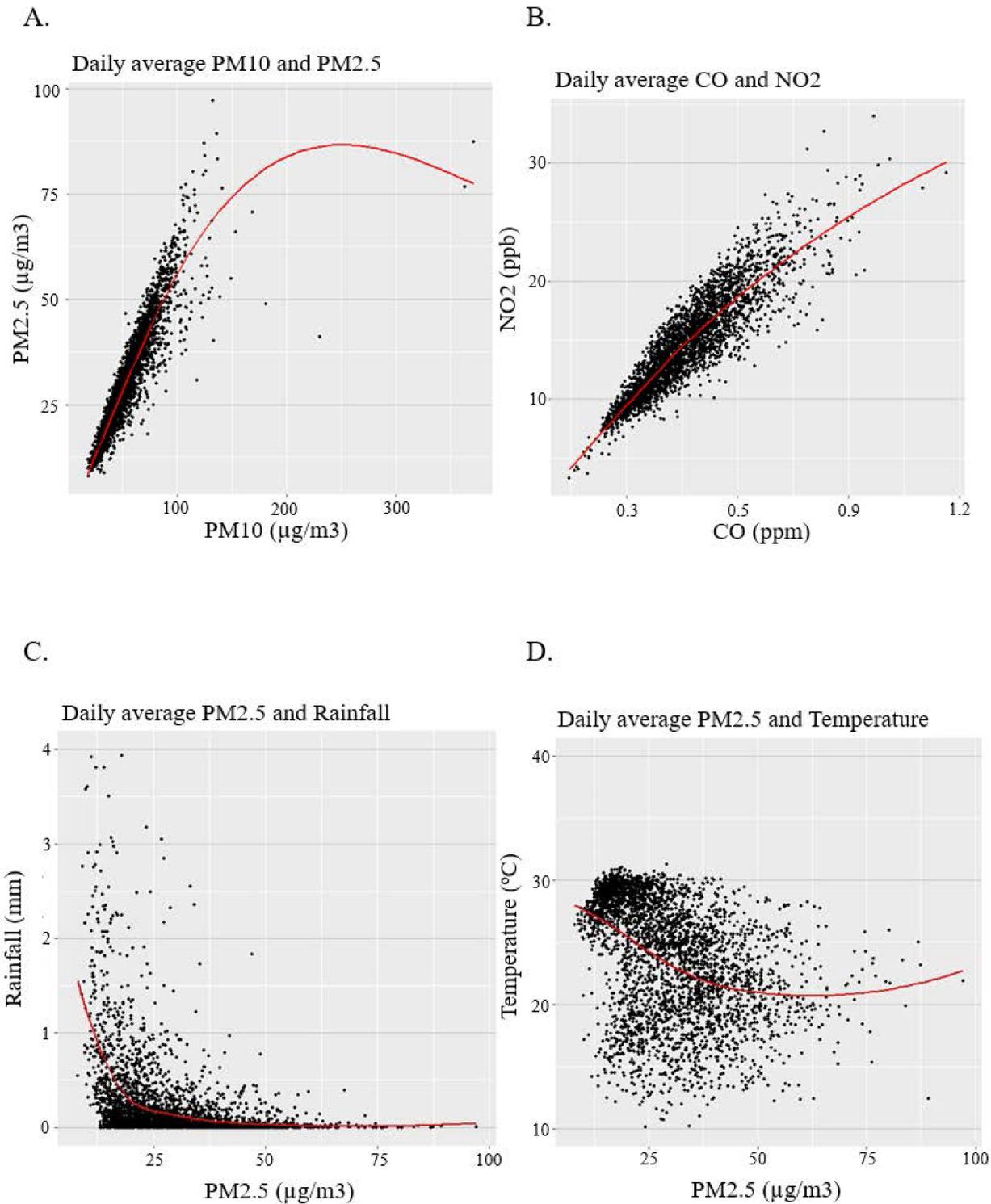


Figure 3

High correlation observed between the daily level of each outdoor air pollutant and meteorological factor. (A) correlation between outdoor particulate matter (PM)10 and PM2.5 (B) correlation between outdoor air nitrogen dioxide (NO2) and carbon monoxide (CO) (C) correlation between outdoor PM 2.5 and rainfall (D) correlation between outdoor PM2.5 and temperature. (24-h average of air pollutants and meteorological factors were used to investigate their association.)

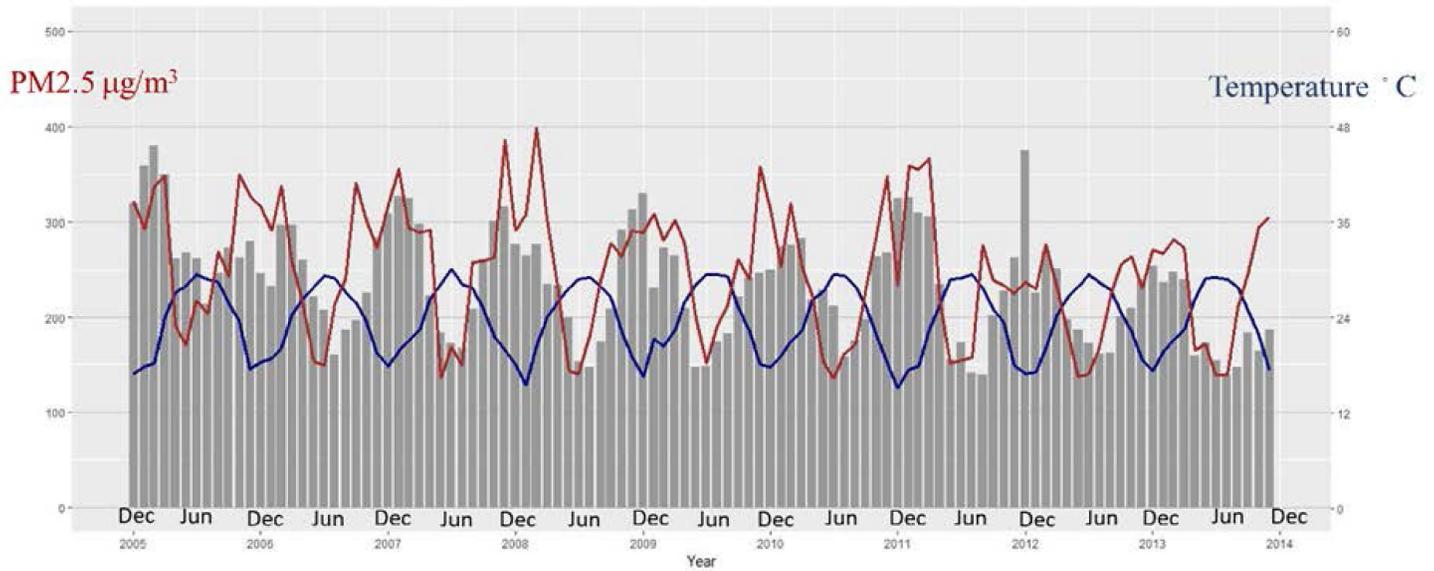


Figure 4

The time-series plot indicates the dynamic change in the national monthly number of visits to the ER for asthma (gray column), mean value of fine particulate matter (PM2.5) (red curve), and mean value of temperature (blue curve) across all locations.

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