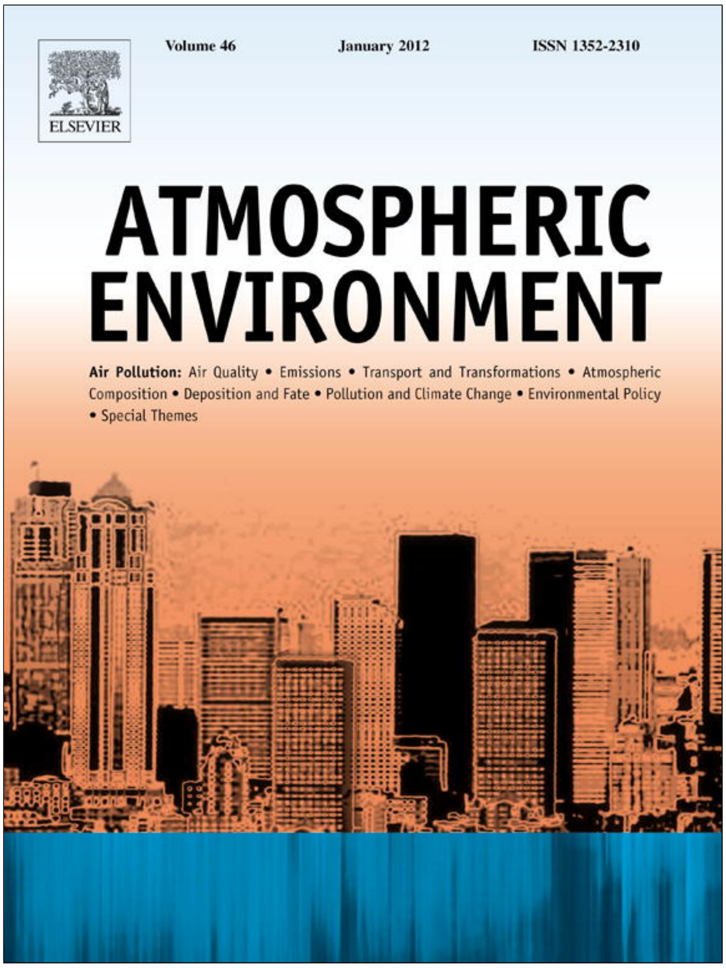
Volume 46
January 2012
ISSN 1352-2310
ELSEVIER
ATMOSPHERIC ENVIRONMENT
Air Pollution: Air Quality • Emissions • Transport and Transformations • Atmospheric Composition • Deposition and Fate • Pollution and Climate Change • Environmental Policy • Special Themes

Atmospheric Environment 75 (2013) 206–216

Contents lists available at SciVerse ScienceDirect

Atmospheric Environment

journal homepage: www.elsevier.com/locate/atmosenv

Fluctuations in air pollution give risk warning signals of asthma hospitalization

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HIGHLIGHTS

- Fluctuations in air pollution may imply risks of asthma hospitalization.
- Statistical indicators of air pollution and asthma hospital admissions are associated.
- Statistical indicators based regression model can forecast asthma hospitalizations.
- Variation and skewness of are leading indicators to detect asthma admission.

ARTICLE INFO

Article history:
Received 29 January 2013
Received in revised form
7 April 2013
Accepted 15 April 2013

Keywords:
Asthma hospitalization
Air pollution
Statistical indicators
Fluctuation
Warning signal
Risk

ABSTRACT

Recent studies have implicated that air pollution has been associated with asthma exacerbations. However, the key link between specific air pollutant and the consequent impact on asthma has not been shown. The purpose of this study was to quantify the fluctuations in air pollution time-series dynamics to correlate the relationships between statistical indicators and age-specific asthma hospital admissions. An indicators-based regression model was developed to predict the time-trend of asthma hospital admissions in Taiwan in the period 1998–2010. Five major pollutants such as particulate matters with aerodynamic diameter less than 10 μm (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) were included. We used Spearman's rank correlation to detect the relationships between time-series based statistical indicators of standard deviation, coefficient of variation, skewness, and kurtosis and monthly asthma hospitalization. We further used the indicators-guided Poisson regression model to test and predict the impact of target air pollutants on asthma incidence. Here we showed that standard deviation of PM_{10} data was the most correlated indicators for asthma hospitalization for all age groups, particularly for elderly. The skewness of O_3 data gives the highest correlation to adult asthmatics. The proposed regression model shows a better predictability in annual asthma hospitalization trends for pediatrics. Our results suggest that a set of statistical indicators inferred from time-series information of major air pollutants can provide advance risk warning signals in complex air pollution-asthma systems and aid in asthma management that depends heavily on monitoring the dynamics of asthma incidence and environmental stimuli.

1. Introduction

It is generally recognized that air pollution is the major environmental stimuli which may induce respiratory diseases exacerbations (Chen et al., 2012). Asthma is an allergic respiratory disease affecting millions of population worldwide. Since the growing epidemic of asthma, recent studies had taken more efforts to predict the disease progression and control (Frey et al., 2005; Thamrin et al., 2011). Several statistical methods have been applied to assess the severity and control of asthma (Que et al., 2001; Frey et al., 2011). It is known that much more clinical and basic researches are needed to understand the asthma due to the complexity of disease progression. Plausibly, effective assessment approaches are capable of predicting asthma and its various co-morbidities in the future.

Air pollutants such as particulates and oxidative chemicals are most likely associated with asthma hospital admission and emergency room visits among different age groups (Lee et al., 2003; Hwang et al., 2005; Tsai et al., 2006; Chen et al., 2012; Makra et al., 2012). It is evident that exposed to traffic-related air pollution included particulate matter with an aerodynamic diameter less than

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http://dx.doi.org/10.1016/j.atmosenv.2013.04.043

10 μm (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) are much likely to increase the exacerbation risk of asthma and asthma-like respiratory symptoms. Chen et al. (2006) found that air pollutant levels of O_3, SO_2, and CO were significantly associated with adult asthma admission in Taiwan. In addition, PM_{10} and O_3 contributed significantly to pediatric asthma admission (Xirasagar et al., 2006). Liao et al. (2011) found a strong association between long-term fluctuations in SO_2 time-trend and asthma admission rate. NO_2 is chemically reactive pollutant in the atmospheric environment. The nitric vapor can produce the amount of photo oxidation from automobile emissions which can induce lung damage (Yang and Omaye, 2009).

Frey et al. (2011) indicted that respiratory system has memory characteristics like many other physiological systems with complex structure. Therefore, the susceptible system can have cumulative memory effects under environmental triggers, and further cause respiratory symptoms or lung function variation associated-asthma exacerbations. The cumulative effect can occur due to the existence of lag effects which were confirmed in many epidemiological studies (Lewis et al., 2005; Bell et al., 2008; Chang et al., 2012). Thus, previous environmental stimuli are important because each specific stimulus in the past has potential to add to the cumulative effect (Frey and Suki, 2008). Therefore, the fluctuation properties in environmental stimuli may result in the short- and long-term effects in the respiratory system (Frey, 2007; Frey and Suki, 2008; Thamrin et al., 2010). Yuval and Broday (2010) indicated that meteorological and air quality variables have the statistical predictability that can implicate to exposure assessment. In light of this concept, the fluctuations in environmental triggers may imply different levels of lung failure and disease incidence (Frey et al., 2011).

The statistical techniques have been used to characterize the internal fluctuating phenomena in response to external triggers on disease exacerbations risk for describing the properties of such complexity phenomenon (Frey et al., 2005). There has been a growing interest in using statistical indicators as early warning signals of abnormal change in dynamic processes for various fields such as physiology and climate systems (Que et al., 2001; Frey et al., 2005; Dakos et al., 2008; Gorban et al., 2010; Lenton, 2011). These indicators include variance, coefficient of variation (COV), skewness, and kurtosis.

For asthma attack, statistical signatures of COV and skewness in lung ventilation were found to be correlated with the levels of disease exacerbations (Frey et al., 2005; Venegas et al., 2005). The statistical indicators in lung function measurements have been used to assess the risk of future asthma episodes, and thereby improve the assessment and management of asthma severity. Que et al. (2001) found that the spontaneous variation in airway caliber in normal subjects and asthmatic patients can be assessed over a period of minutes by measured and analyzed the variability and kurtosis of respiratory impendence. Recent studies revealed that the quantified indicators can improve the predictability and detectability in a variety of dynamical systems (Ditlevsen and Johnsen, 2010; Lenton et al., 2012; Scheffer et al., 2012).

Although recent studies have implicated an association between air pollutant and asthma exacerbations, the key link between specific air pollution and consequence impacts has not been shown. Because exacerbations of asthma are strongly related to environmental conditions, we thought that fluctuating properties in air pollution may imply advance warning signals of risk of the asthma incidence.

The purpose of this study was threefold: (1) to quantify the fluctuations in air pollutants for higher asthma epidemic areas in Taiwan, (2) to correlate the relationship between statistical indicators of air pollution and age-specific asthma hospital admissions, and (3) to predict asthma hospitalization trends by statistical indicators-based regression model. This study investigated the air pollution-associated asthma hospitalization in Taiwan in the period 1998–2010.

2. Materials and methods

2.1. Study data

Air pollution data were adopted from Taiwan Air Quality Monitoring Network (http://taqm.epa.gov.tw/taqm/en/default.aspx). There were more than seventy monitoring stations established by Taiwan Environmental Protection Administration. The hourly monitoring data were described clearly the distributions of pollutant dynamics. We selected major air monitoring stations in the highest epidemic City/County in four divided regions. Daily reading of major air pollutant levels such as PM_{10}, NO_2, SO_2, CO, and O_3 were included. We used daily average concentrations for PM_{10}, NO_2, SO_2, CO and average of daily maximum 8-h O_3 concentrations based on the air quality guideline suggested by World Health Organization (WHO) and U.S. Environmental Protection Agency (USEPA) (WHO, 2006; Weinhold, 2008).

The asthma admission records were collected from National Health Insurance database. We selected all hospitalization patients on the basis of the International Classification of Disease, Clinical Modification (ICD-9-CM) code for asthma (493). The data were recorded as number of asthma per year in terms of age, gender, and region. The annual numbers of case were divided by the year-end population to obtain the asthma hospitalization rate as the admission rate per 100,000 population based on annual population data released by Population Affairs Administration, Ministry of Interior, Taiwan.

We extracted the site-specific asthma hospitalization rate to determine the levels of epidemic in northern, eastern, central, and western Taiwan divided based on Taiwan Council for Economic Planning and Development. We estimated the annual age-specific asthma hospital admission data in the period 1998–2010. In addition, this study adopted the population–based study from Chen et al. (2006) in that the monthly age-specific asthma hospitalization rates were shown in the period 1998–2001. The asthma hospitalization were categorized into five age groups of 0–4, 5–14, 15–44, 45–64, and ≥65 yrs (Chen et al., 2006). We simplified the age group to 0–14, 15–64, and ≥65 yrs to reasonably represent the pediatric, adult and elderly asthmatics, respectively.

2.2. Statistical indicators

To investigate the relationships between statistical indicators of air pollution and age-specific asthma hospital admissions, we calculated four statistical indicators of standard deviation (SD), COV, skewness, and kurtosis (Table 1). The monthly statistical

Table 1
Equations of statistical indicator used in time-series analysis.[a]

Indicator	Equation	
Standard deviation	$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i-\bar{x})^2}$	(T1)
Coefficient of variation	$\frac{\sqrt{\sum_{i=1}^{n}(x_i-\bar{x})^2/(n-1)}}{\bar{x}}$	(T2)
Skewness	$\frac{\frac{1}{n}\sum_{i=1}^{n}(x_i-\bar{x})^3}{\left(\frac{1}{n}\sum_{i=1}^{n}(x_i-\bar{x})^2\right)^{3/2}}$	(T3)
Kurtosis	$\frac{\frac{1}{n}\sum_{i=1}^{n}(x_i-\bar{x})^4}{\left(\frac{1}{n}\sum_{i=1}^{n}(x_i-\bar{x})^2\right)^{2}}-3$	(T4)

[a] n is sample size and $\bar{x}$ is sample mean.

indicators were calculated based on time-series air pollution datasets. Each time-dependent indicator was correlated to asthma hospitalization for determining the most related air pollutant and age-specific asthma hospital admissions in Taiwan during the study periods. We used Spearman correlation to investigate the overall correlation between asthma hospitalization rates and statistical indicators of air pollutants.

2.3. Asthma incidence prediction

This study used the Poisson probability distribution-based generalized linear regression model, considering long-term trends and well-correlated statistical indicators for each pollutant, to determine the best-fitted model in relation to age-specific asthma hospitalization. The proposed model can estimate the fluctuations of air pollution-associated asthma as

$$\ln(Y_t) = \beta_0 + \beta_1 t + \beta_2 S_{PM_{10},t} + \beta_3 S_{O_3,t} + \beta_4 S_{NO_2,t} + \beta_5 S_{SO_2,t} + \beta_6 S_{CO,t}, \quad (1)$$

where Y_t is the hospitalization rate of age-specific asthma at time t, S is the specific statistical indicator, β_0 is the intercept, and β_1 through β_6 represent the coefficients for significant statistical indicators corresponding to PM_{10}, O_3, NO_2, SO_2, and CO, respectively.

The predicted asthma hospitalization rates can be further used to estimate the excess morbidity with observed hospitalization rates by baseline predicted asthma incidence. The excess morbidity was the observed asthma hospitalization that exceeds the model predicted baseline. The baseline hospitalization rates can be defined by setting the lower bound of 95% confidence interval (CI) (i.e., 1.96-fold of SD with sample size during the study period) from predicted model. Thus, the estimates of monthly excess morbidity can be calculated as the differences between observed and the baseline hospitalization rates. The calculated excess morbidities were then used to characterize the probability distribution by Monte Carlo (MC) simulation technique with 10,000 iterations in each year and overall time-period 1998–2001.

The constructed Poisson generalized linear regression model was validated by collected annually asthma hospitalization in the period 2002–2010. The mean absolute percentage error (MAPE) was used to judge the model performance. The correlation analyses were performed by using Statisitca® (Version 6.0, Statsoft Inc., Tulsa, OK, USA). The MC simulation was performed by using Crystal Ball® software (Version, 2000.2, Decisionerring, Inc., Denver, CO, USA).

3. Results

3.1. Fluctuation properties of air pollution

Fig. 1 demonstrates the time-series of daily air pollution data for PM_{10}, O_3, NO_2, SO_2, and CO in Taiwan in the period 1998–2010. During the study period, the temporal variations for daily PM_{10}, NO_2, CO showed the seasonal pattern that peaked during the winter months. The distributions of daily levels for PM_{10}, O_3, NO_2, SO_2, and CO are 46.23 $\mu g\ m^{-3}$ (95% CI: 22.5–95.1 $\mu g\ m^{-3}$), 38.44 ppb (18.2–63.9 ppb), 14.8 ppb (7.9–25.2 ppb), 2.7 ppb (0.9–5.3 ppb), and 600 ppb (408–929 ppb), respectively. The probability distributions for each air pollutant were approximately to be a lognormal distribution. Our result showed that upper bound of 95% CI for 8-hr maximum O_3 was exceeding the EPA standard in our study periods.

Fig. 2 shows the monthly calculated statistical indicators for each pollutant. The PM_{10} had highest SD ranging from 3.8 to 28.3 $\mu g\ m^{-3}$, indicating seasonal variation that was occurred much higher in spring season (Fig. 2A). The SD of PM_{10}, SO_2, and CO experienced decreasing trends in study period, whereas the increasing trend of SD was observed in NO_2 (Fig. 2A, C, D, E). However, there was no significant changed in monthly trend of SD in O_3 (Fig. 2B). The COVs of SO_2 data ranged from 0.27 to 0.97, indicating that SO_2 had the highest dispersion (Fig. 2I). PM_{10} also had higher dispersion with an average COV of 0.31 (ranging from 0.14 to 0.92) (Fig. 2F). The lower COVs were found in NO_2 (0.15–0.56) and CO (0.08–0.35) time series data (Fig. 2H, J). The estimated skewness were 0.66 (−0.74 to 2.25), −0.04 (−1.33 to 1.19), 0.26 (−2.00 to 1.95), 0.52 (−0.51 to 2.12), and 0.48 (−0.72 to 2.08) for PM_{10}, O_3, NO_2, SO_2, and CO time-series data, respectively (Fig. 2K–O). The results showed that PM_{10} also had the highest positive skewness, indicating that extremely events were occurred frequently. Furthermore, the estimated kurtosis were 0.93 (−1.23 to 5.37), −0.13 (−1.33 to 4.21), 0.42 (−1.14 to 5.84), 0.54 (−1.07 to 8.71), and 0.40 (−1.28 to 6.31) in PM_{10}, O_3, NO_2, SO_2, and CO time-series data, respectively (Fig. 2P–T). The result showed that the highest kurtosis was also observed in PM_{10} data.

3.2. Descriptive statistics of asthma incidence

Results indicated that monthly age-specific asthma hospitalization rates were lowest for adult age group and highest among elderly ranging from 45 to 117 per 100,000 population (Fig. 3A). Generally, the hospitalization peak was observed during January to March, followed by a substantially decreased in April through August, then had an increasing trend starting from September. The estimated annual hospitalization rates of pediatrics, adult, and elderly were 239 ± 23 (mean ± SD), 43 ± 10, and 603 ± 168 per 100,000 population, respectively (Fig. 3B).

Asthma hospitalization rate for elderly was nearly 14 times higher than adult group. The general hospitalization rate decreased from 357 in 1998 to 241 per 100,000 population in following 12 years. As expected, different asthma admission trends were observed among different age groups. The annual hospitalization rates were increased by 2.9% each year in pediatric group. However, there were 1.7 and 5.2% decreases of hospitalization rate in adult and elderly groups, respectively.

There were the highest asthma hospital admission in east Taiwan (380 per 100,000 population), whereas the lowest ones were observed in south Taiwan (301 per 100,000 population) (Fig. 4A–E). This study thus chose Ilan (412 per 100,000 population), Hualien (412 per 100,000 population), Miaoli (338 per 100,000 population), and Pingtung (329 per 100,000 population) Counties as our representative sites where the highest epidemic of asthma hospitalization rates were occurred. The result indicated that north regions of Taiwan contributed nearly 42.2% of asthma hospitalization in the period 1998–2001 (Fig. 4F). The south and central regions were also contributed 24.8% and 26.5% of asthma hospitalization, respectively (Fig. 4F).

3.3. Correlation of pollution variables

Table 2 indicates that SD of PM_{10} data correlated significantly with asthma hospitalization among all age groups ($p < 0.001$) with the highest correlation coefficient in elderly ($\rho = 0.61$). Moreover, PM_{10} also gave a relative good correlation with pediatric and adult asthmatics base on indicator SD (Table 2). Collectively, our results indicated that (*i*) SD of PM_{10}, SO_2, and CO data correlated significantly with elderly asthmatics, (*ii*) skewness of O_3 and NO_2 showed a negative correlation with asthma hospitalization, (*iii*) kurtosis

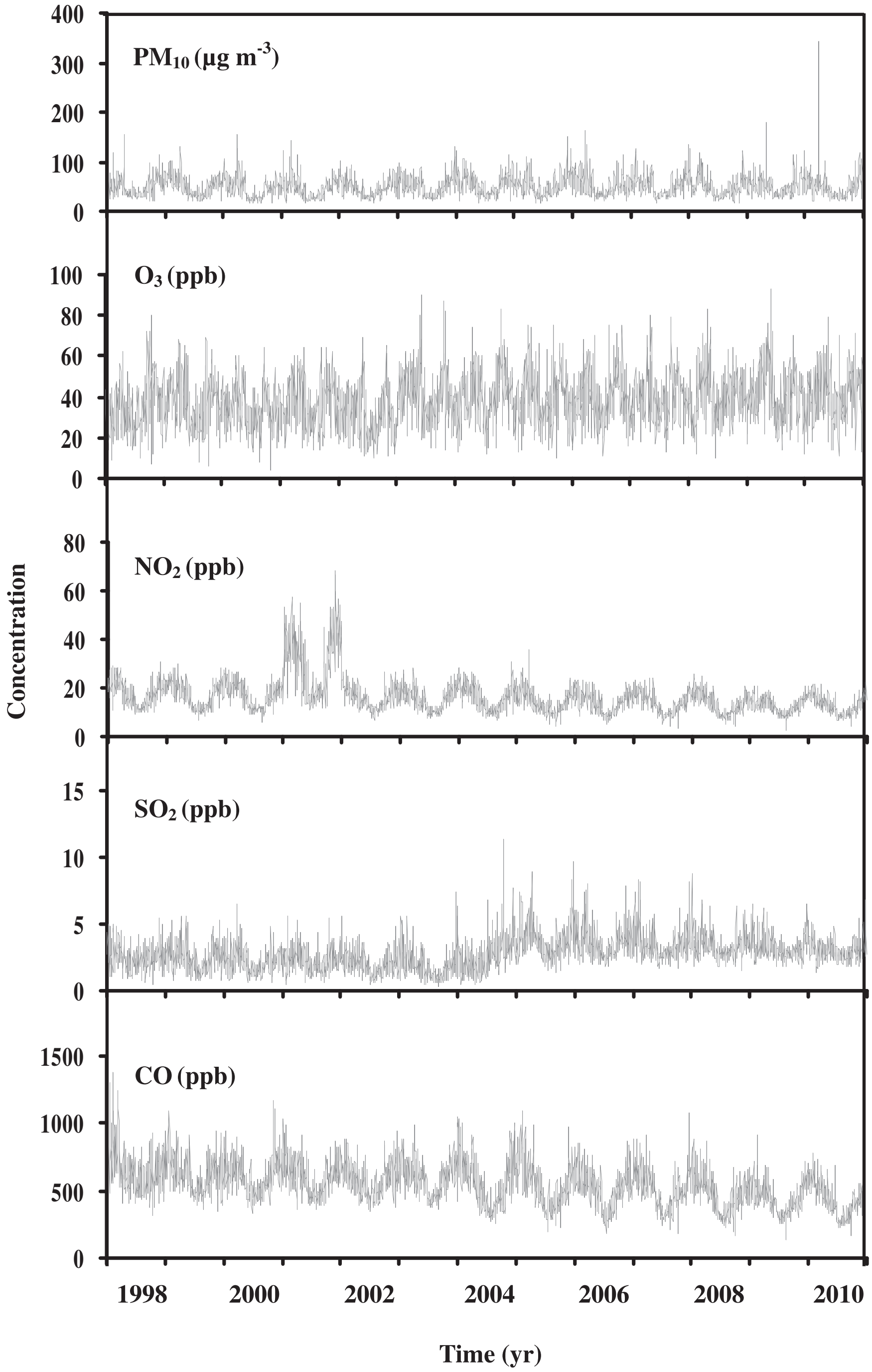

Fig. 1. Time-series of air pollution levels in Taiwan for PM_{10}, O_3, NO_2, SO_2, and CO in the period 1998–2010.

only correlated significantly with elderly asthmatics in NO_2 ($\rho = -0.39$), and (*iv*) COV only had significant correlation with adult asthmatics in O_3 ($\rho = -0.39$) (Table 2).

Statistical indicators-based Poisson regression model were used to estimate the asthma hospitalization rate, allowing us to capture quantitative (magnitude) and qualitative (shape) trends (Table 3). The estimated MAPEs of all age group-specific asthma hospitalization rates were less than 20%, indicating the robust predictability of the proposed regression model. Skewness of O_3 time-series data showed the significant contribution to asthma hospital admission in adult group ($p < 0.001$) and slightly contributes to pediatric asthma ($p < 0.05$). Moreover, SD of CO time-series data was a common significant indicator to asthma hospital admission of pediatric and elderly (Table 3).

Fig. 5 shows the predicted time-series dynamics of asthma hospitalization rates in the period 1998–2001 by the proposed Poisson regression model. The proposed Poisson regression model can estimate the hospitalization rates for all age groups significantly ($p < 0.01$). The estimations were reasonably well in adult and elderly groups in that correlation coefficients were 0.76 and 0.75, respectively, whereas the pediatric population had relative lower correlation ($r = 0.66$). The SD of CO approximately contributed more than 50% morbidity of asthma hospitalization among age group of 0–14 and 15–64 years old (Fig. 5D, E). The SD

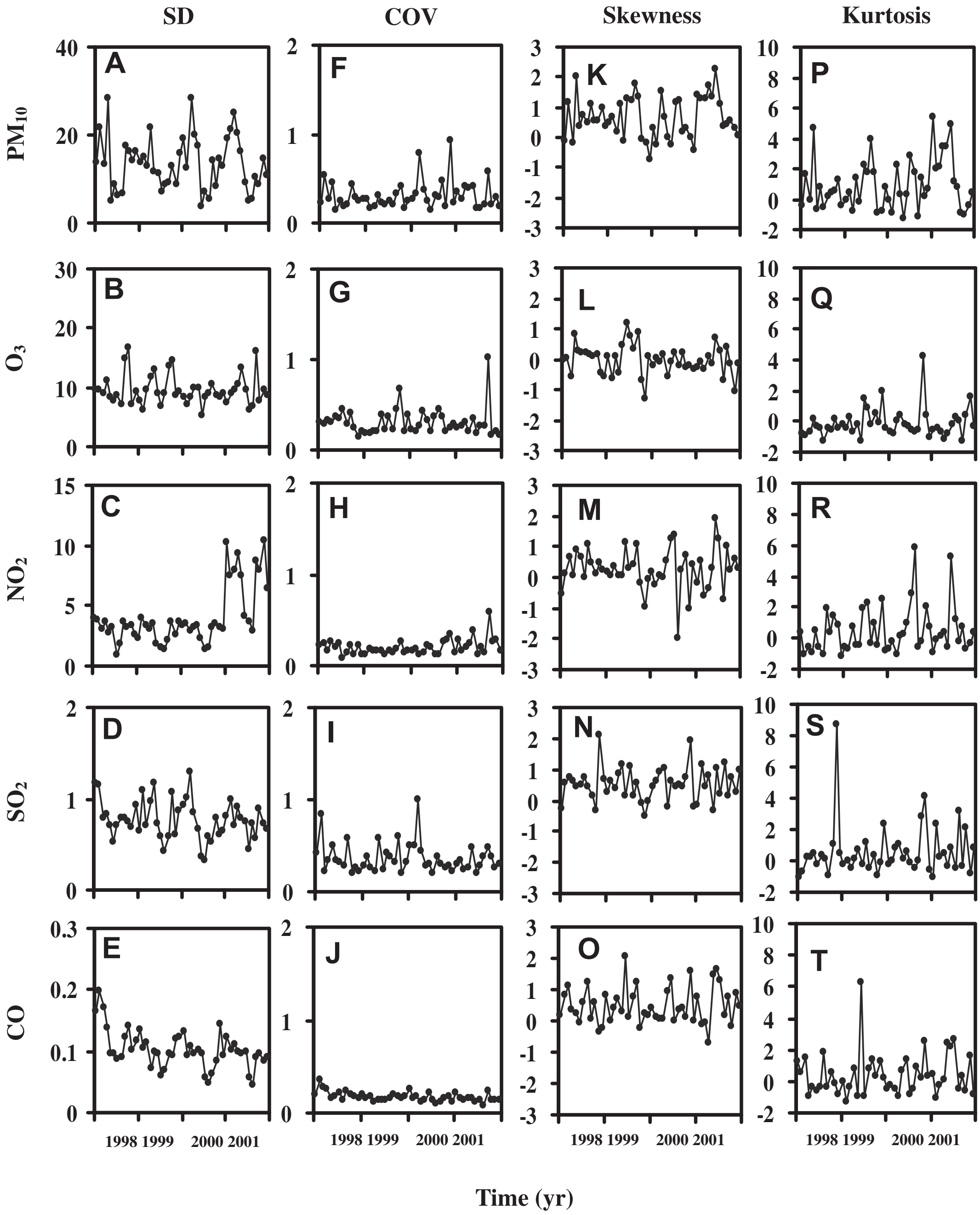

Fig. 2. Time-course of monthly statistical indicators for (A–E) standard deviation, (F–J) coefficient of variation, (K–O) skewness, and (P–T) kurtosis in the period 1998–2001.

of PM_{10} is the minor important factor which contributed 7.4%, 6.7%, and 5.4% for pediatric, adult, and elderly asthma group, respectively (Fig. 5D–E). In addition, the intercept given the higher contribution in asthma hospitalization for all age groups ranged from 34%–60%.

3.4. *Regression analysis-based asthma prediction*

Fig. 6A shows the estimated monthly age-specific excess morbidities of asthma hospitalization in the period 1998–2001. A lognormal distribution (LN(geometric mean, geometric standard deviation)) was optimal fitted to the average excess morbidity estimates per 100,000 population based on the lower bound of 95% CI as baseline, resulting in LN(4.8, 1.7) for 0–14 yrs, LN(1.6, 1.7) for 15–64 yrs, and LN(19.8, 1.9) for ≥65 yrs (Fig. 6B–D). The result also showed that the excess morbidities were higher with 6.4 (95% CI: 2.4–17.6), 2.0 (0.8–4.9), 24.4 (5.8–98.3) per 100,000 population for 0–14, 15–64, and ≥65 yrs, respectively, in 1999 (Table 4).

The fitted Poisson regression models were also tested by forecasting time-series dynamics of asthma hospital admission based on asthma data in the period 1998–2001. Results showed that the estimated age-specific asthma hospitalization rates were in apparent agreement with the observed data for 0–14 (MAPE = 8.1%) and ≥65 yrs (MAPE = 18.3%) in the period 1998–2010 (Fig. 7A, C). However, the model is not capable of predicting the time-trend of asthma hospitalization for 15–64 yrs group accurately (MAPE = 82.3%) (Fig. 7B).

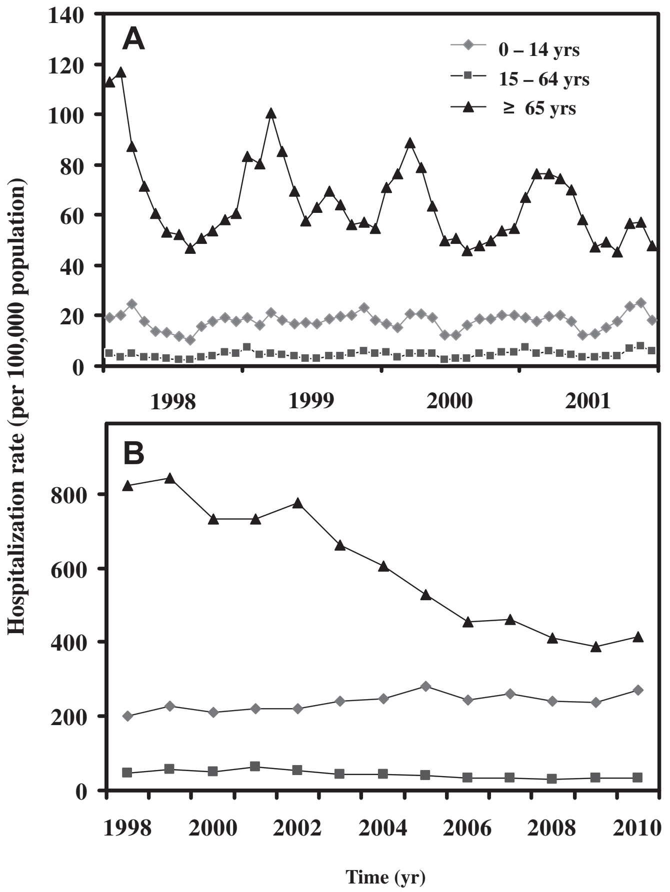

Fig. 3. Time-series dynamics of mean values of (A) monthly and (B) annual age-specific asthma hospitalization rates in the periods of 1998–2001 and 1998–2010, respectively.

4. Discussion

4.1. Association between air pollutions and asthma

Our study found an association of fluctuating properties in air pollution with age-specific asthma admissions based on the data in the period 1998–2010. Result showed that variations of PM_{10} play crucial role in affecting the asthma hospitalization on all age groups. The seasonality in asthma admission is strongly associated with monthly variation of PM_{10} which may increase the asthma severity. Chen et al. (2006) indicated that the asthma-related hospitalization had the seasonality properties, which stayed low in summer and autumn and increased in the period of winter to spring. The impact of PM_{10} on the association of hospitalization in patients with asthma found in our study is consistent with previous epidemiologic studies, showing increasingly susceptible to particulate pollutant exposure in individuals with existing chronic respiratory diseases (Sacks et al., 2011). Particulate pollutants are the respiratory tract irritant that have shown to cause acute respiratory tract effects, including lung function decrement, respiratory symptoms, and significant airway injury (Chen et al., 2007; Gupta et al., 2012; Leung et al., 2012). Canova et al. (2012) indicated that increase in PM_{10} concentration was associated with a 35% increased risk of exacerbations requiring hospital admission in chronic respiratory diseases patients for asthma and chronic obstructive pulmonary disease (COPD), with the effect being greater in the elderly individuals and in smokers.

Moreover, our study found that skewness of O_3 time-series data was also associated with asthma hospitalizations among pediatric and adult groups. Recent studies have assessed the effects of ambient O_3 exposure on asthma prevalence in Taiwan. Hwang and Lee (2010) indicated that O_3 concentration had strong association with schoolchildren asthma than PM_{10} levels. Furthermore, Hwang and Lee (2010) found that long-term exposure to O_3 can increase bronchitis symptoms among Taiwanese children. Jerrett et al. (2009) indicated a strong association between O_3 concentration and the risk of death from respiratory causes. Recent studies also found that traffic-related air pollution such as O_3 and NO_2 may become increasingly susceptible to chronic pulmonary diseases and even induce more severity respiratory illness (Chen et al., 2008; Balmes et al., 2009; Hwang and Lee, 2010).

In our study, the variations in CO data show a positive association with asthma hospitalization among all age groups. Recent epidemiology studies found that the prevalence of asthma symptoms was highly correlated with CO exposure in Taiwan (Hwang and Lee, 2010). Our study found that the elderly had higher correlation with asthma hospitalization than pediatric and adult populations. Recent studies indicated significant association between asthma prevalence and CO exposure among schoolchildren (Ho et al., 2007; Guo et al., 2009). Our study also found that variations in SO_2 data may have potential influence on asthma hospitalization of elderly. Liao et al. (2011) found that long-term SO_2 levels were associated with annual asthma admission rate which included outpatient, hospitalization, and emergency room visits. Ko et al. (2007) reported that SO_2 and O_3 had a greater effect than particulate pollutants on COPD in Hong Kong. Leung et al. (2012) indicated that there were densely populated in many Asia countries burning the biomass of coal, resulting in an increasing of particulate pollutants and SO_2 levels. However, the densely motor vehicles are also the major source or secondary air pollution which increase the photochemical oxidative species of O_3, NO_2, and SO_2.

The region-specific air pollution observations were pooled to represent the average daily air pollution data in Taiwan due to no region-specific data available for the age-specific hospital admissions of asthma. Although the air pollutant levels were estimated differently in study regions, it did not cause the changing of fluctuation properties in statistical indicators of air pollution among study regions.

4.2. Statistical indicators-based asthma prediction

This study applied a time-series Poison regression model to predict the monthly and annual hospital admissions of asthma in Taiwan in the period 1998–2010. Results showed that the leading statistical indicators derived from air pollution data can well predict the seasonality and time-trend of age-specific asthma hospital admissions effectively. The proposed best-fitted Poisson regression model captures the association of annual trends of statistical prosperities in air pollution time-series dynamics with age-specific asthma hospitalizations.

Our developed statistical indicators-based regression model reveals several important findings: (*i*) the model performed well for the adult and elderly age groups, (*ii*) the fluctuations in air pollution show a strong correlation with asthma epidemics, implicating the risk warning signals of asthma incidence, and (*iii*) the change in skewness of O_3 data for measuring the asymmetry of fluctuations, is also a good warning signal of adult asthma hospitalization. Scheffer et al. (2012) indicated that rising variance can reflect the changing stability in stochastic systems such as climate, ecology, sociology, and physiology systems. Several researches have also used generalized linear regression model to describe asthma hospital admissions and emergency room visits (Schwartz et al.,

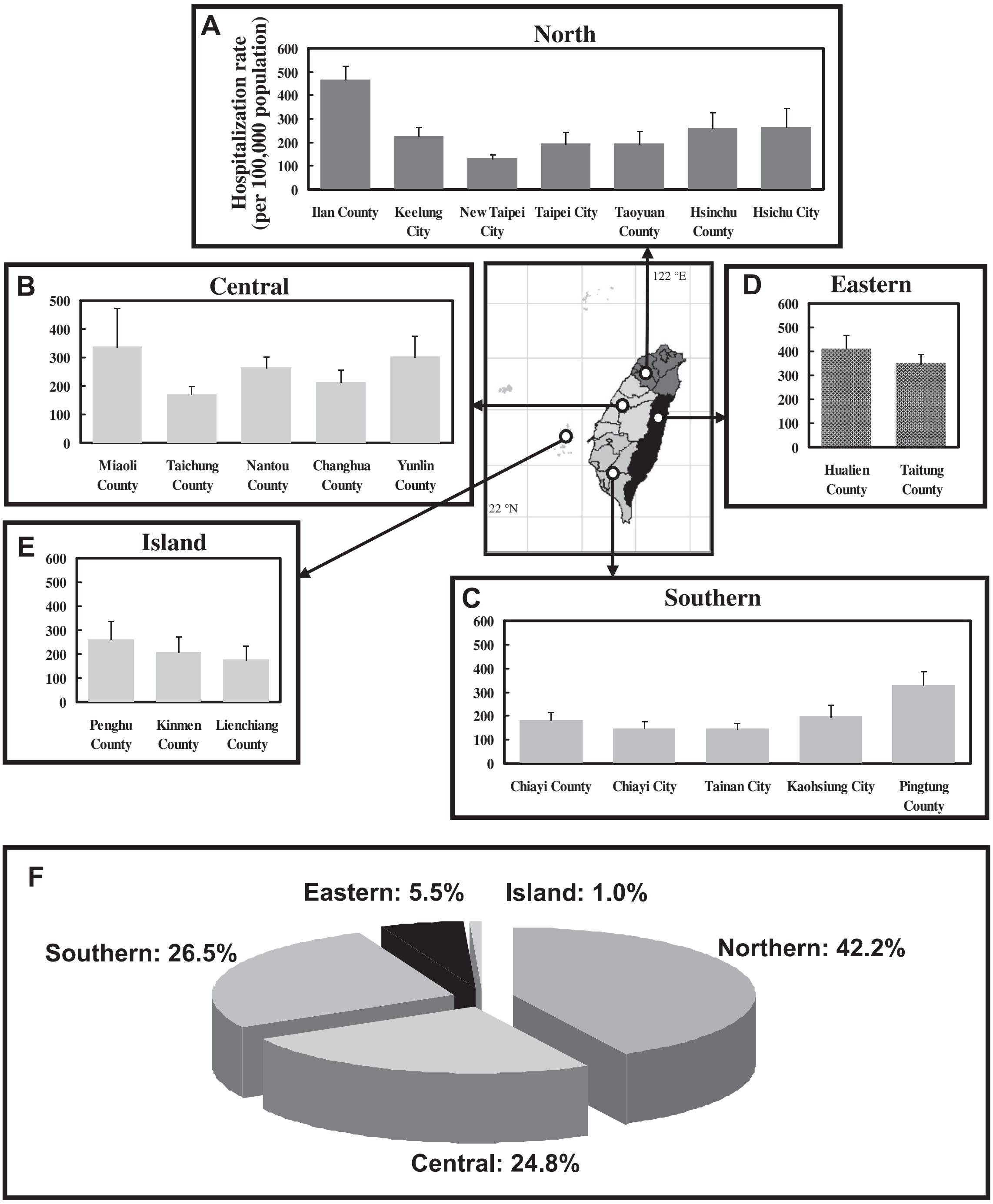

Fig. 4. Distributions of the asthma hospitalization rates in (A) north, (B) central, (C) south, (D) east, and (E) island in Taiwan in the period 1998–2010, respectively. (F) Region-specific contributions of asthma hospitalization in Taiwan.

1993; Genuneit et al., 2006; Ostro et al., 2009). In addition, Zhao et al. (2007) have developed the receptor model which can also be used to understanding the potential mechanisms of asthma exacerbation.

The contributory percentages of the model intercept in our developed regression model were approximately 34% for pediatric and adult asthma groups, whereas a highest in elderly of 59.9% was found. Besides the common air pollutants, the other risk factors were the important triggers that could cause asthma hospitalization especially for elderly, affecting the contribution properties in model parameter of intercept. However, the fluctuating air pollution was the common factor for pediatric and adult asthma, contributing 65.2% and 66% in asthma hospital admission for pediatric and adult groups, respectively.

4.3. Limitations and implications

There are some limitations in our analyses. First, we could not validate the model performance for monthly asthma admission in the period 2002–2010 due to the data limitation. We predicted the annual asthma hospitalization in the period 2002–2010 to judge the model performance. Unfortunately, the data limitation

Table 2
Spearman's coefficient of rank correlation for variability of air pollution.[a]

Pollution-indicators[b]	Age groups (yrs)		
	0–14	15–64	≥65
PM_{10}			
SD[b]	**0.4610*****	**0.4700*****	**0.6108*****
COV[b]	0.3135*	0.1614	0.2065
Skewness	−0.1422	−0.2416	0.1893
Kurtosis	−0.1656	−0.2133	0.1312
O_3			
SD	0.2772	0.0754	0.1438
COV	−0.1599	−0.3905**	−0.2073
Skewness	**−0.4201****	**−0.5656*****	−0.0927
Kurtosis	0.1290	0.0408	−0.1401
NO_2			
SD	0.2903*	**0.4375****	0.1769
COV	0.2366	0.2293	−0.0502
Skewness	**−0.3051***	−0.3534*	−0.2742
Kurtosis	−0.1948	−0.2623	**−0.3878****
SO_2			
SD	0.1820	0.1914	**0.5553*****
COV	−0.1189	−0.1861	0.1384
Skewness	−0.0946	−0.0903	0.0963
Kurtosis	−0.0432	0.0327	−0.0800
CO			
SD	**0.3556***	**0.3874****	**0.5399*****
COV	0.1059	0.0436	0.2321
Skewness	−0.1341	−0.2171	−0.0943
Kurtosis	0.1415	0.0013	−0.1316

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Boldface denotes the largest value of correlation coefficient in each pollution.
[b] SD: Standard deviation, COV: Coefficient of variation.

constrained the model accuracy for adult asthma group in the period 2002–2010. Our proposed model was built on the observations of asthma hospitalization in the period 1998–2001. This would result in the wrong predictions in the following years during 2002–2010. Therefore, the proposed model could not well-predict the adult asthma trends (MAPE = 82.3%). It may need more dataset to adjust the model performance for adult asthmatics. With these limitations, the results and forecasts present here should be interpreted with caution. Moreover, risk warning signals revealed by statistical indicators based on time-series dynamics usually need observations over a long span that are difficult, if not impossible, to obtain in the real situations.

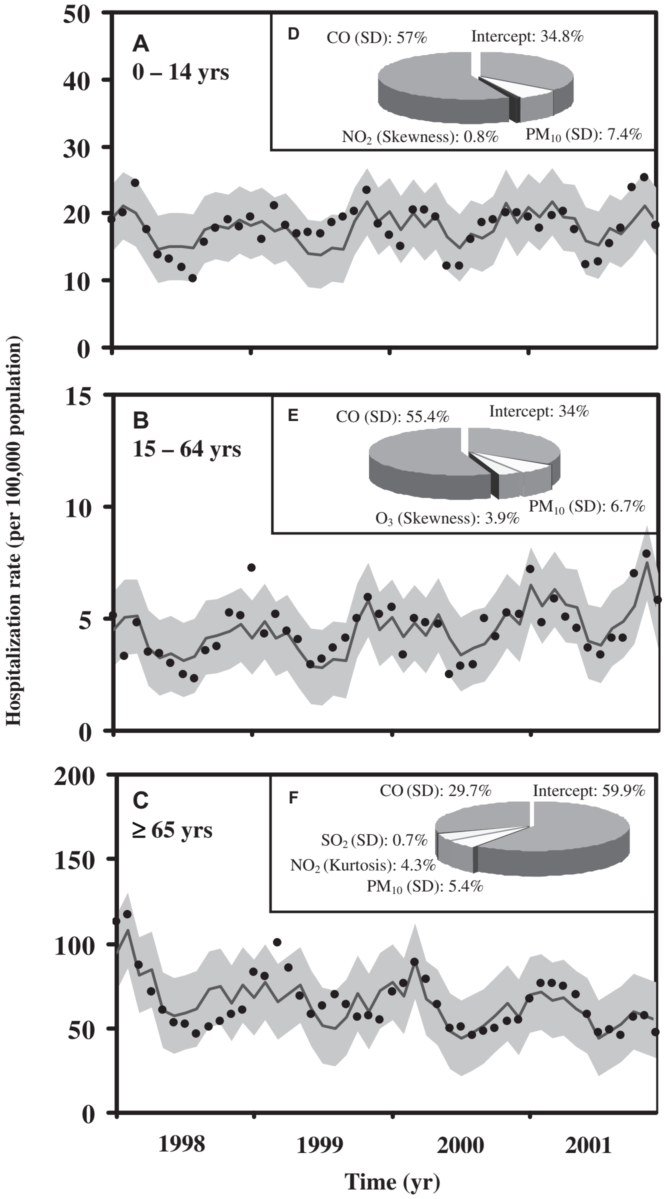

Fig. 5. Fitting of Poisson regression models with statistical indicators of air pollution for asthma hospital admissions for (A) 0–14, (B) 15–64, and (C) ≥65 yrs, respectively. Contribution of indicators and intercept to asthma hospitalization for (D) 0–14, (E) 15–64, and (F) ≥65 yrs, respectively.

Table 3
Model performance of fluctuating air pollution-based Poisson regression analysis.

	Coefficient	r	MAPE (%)
0–14 yrs		0.66*	12.3
PM_{10} (SD)[a]	0.0058		
O_3 (Skewness)	−0.1280*		
NO_2 (Skewness)	−0.0293		
CO (SD)	2.2281*		
Trend	0.0037		
Intercept	2.4825***		
15–64 yrs		0.76**	15.3
PM_{10} (SD)	0.0054		
O_3 (Skewness)	−0.2427***		
NO_2 (SD)	0.0287		
CO (SD)	2.6102		
Trend	0.0060		
Intercept	1.1443***		
≥65 yrs		0.75**	13.0
PM_{10} (SD)	0.0075		
NO_2 (Kurtosis)	−0.0019		
SO_2 (SD)	0.4206		
CO (SD)	2.5776**		
Trend	−0.0026*		
Intercept	3.5330***		

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] SD: Standard deviation.

Second, our study did not consider the other external stimuli such as virus infections and allergen events which are the major risk factors for asthma exacerbation and incidence (Sears, 2008). Ly et al. (2011) indicated that asthma exacerbations have potential link with gut microbiota, probiotics, and Vitamin D in human subjects. These internal factors can regulate the immune system to recover the tissue inflammation. Thus, those factors may be incorporated into the current regression model to improve predictability in the future research. Additionally, the decreasing trend for adult and elderly asthma hospitalizations may be affected by public health factors. Lee et al. (2007) speculated that the decreasing in the severity asthma might due in part to the improvement of asthma care. Yeh et al. (2008) also indicated that the prevalence of the asthma admission was remained stable or declined in recent years.

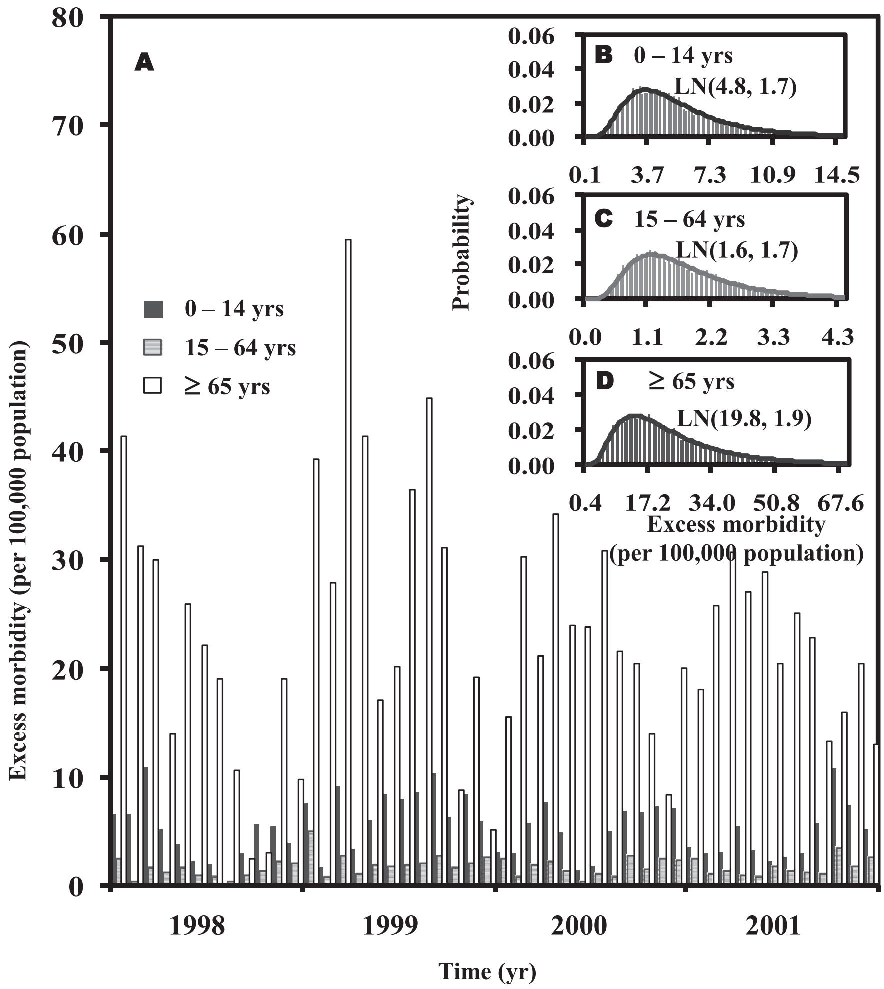

Fig. 6. (A) Estimated time-series of excess morbidity for age-specific asthma hospitalization for 0–14, 15–64, and ≥65 yrs, respectively, in the period 1998–2001. Lognormal (LN) distribution for the excess asthma hospitalizations for (B) 0–14, (C) 15–64, and (D) ≥65 yrs, respectively.

Therefore, the asthma education and self-care should be enhanced for pediatric group.

Third, this study used asthma hospital admission to represent the disease severity in the current model. Velthove et al. (2010) indicated that using hospital admission as a measurement to estimate asthma incidence might lead to an underestimation of disease exacerbations due to a trend toward outpatient care. Therefore, they suggested that more information of disease incidence should be taken into account. Our approach may extend to link with fluctuating physiological signals such as lung function, symptoms, and inflammatory biomarkers for understanding the relationships between environmental triggers and systematic diseases (Frey and Suki, 2008; Frey et al., 2011).

Table 4
Estimated fluctuating air pollution-associated excess morbidity (mean with 95% confidence interval) in Taiwan.

Year	Excess morbidity (per 100,000 population)		
	0–14	15–64	≥65
1998	4.5 (1.6–12.4)[a]	1.2 (0.4–3.6)	14.6 (2.6–82.5)
1999	6.4 (2.4–17.6)	2.0 (0.8–4.9)	24.4 (5.8–98.3)
2000	4.6 (1.5–13.9)	1.5 (0.5–4.9)	20.7 (9.7–43.5)
2001	4.1 (1.6–10.4)	1.5 (0.7–3.6)	21.1 (12.0–37.0)

[a] Mean (95% CI).

In view of the current knowledge of multiple factors of asthma severity and control, we should consider to integrate more indicators to assess and predict asthma events. Therefore, uncertainties in future predictions of statistical indicators of environmental stimuli-associated asthma incidence can be quantified by constraining the present predictive model to reproduce the temporal dynamics of asthma severity and fluctuating environmental stimuli (Frey et al., 2011). We think that there is plenty of room for further improvement, such as the collection of the completely study data and develop the comprehensive regression model to predict the asthma events accurately. Moreover, the experimental investigation may improve the knowledge of disease prevalence (Wong et al., 2009; Murdoch and Jennings, 2009).

In conclusion, we quantified the statistical properties of air pollution time-series dynamics to correlate the relationship between fluctuations in air pollution and age-specific asthma hospital admission. Our study shows that changes in SD and skewness in time-series of major air pollutants can provide advance risk warning signals for asthma hospitalization. The proposed Poisson regression model is capable of forecasting the time-trend of asthma hospitalization for pediatric and elderly based on the available data information. We suggest that a set of statistical indicators may aid in the asthma management which depends heavily on continuously monitoring the dynamics of asthma incidence and environmental stimuli. We anticipate that our statistical indicators-based disease

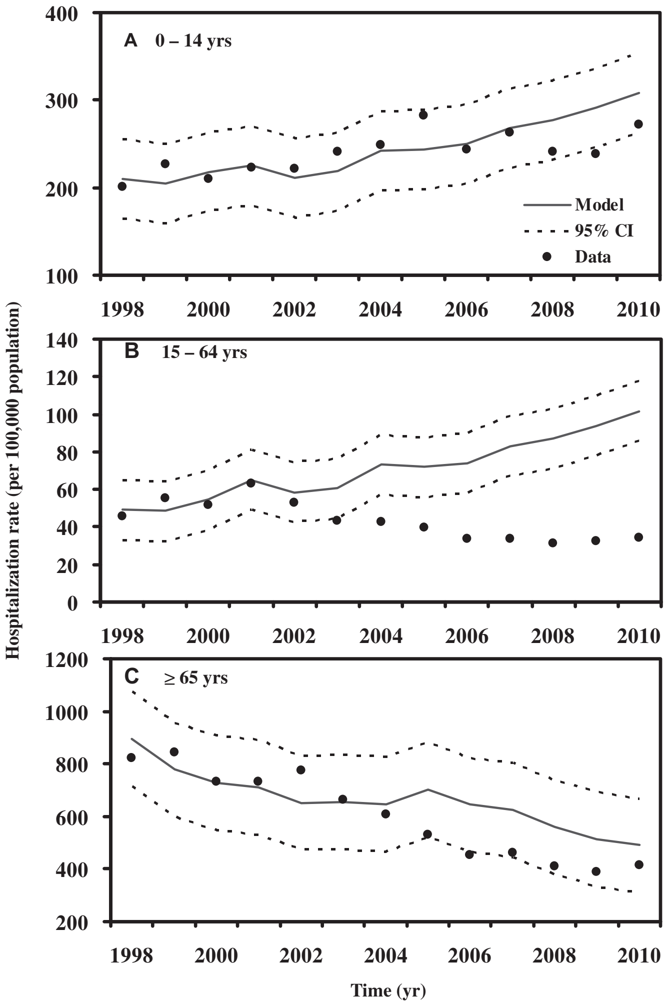

Fig. 7. Forecasted time-series dynamics of annual age-specific asthma hospitalization by Poisson regression model based on the asthma data in the period 1998–2010.

prediction approach can be extended to the context of other high asthma epidemic regions to understand the major risk triggers for asthma severity.

Acknowledgments

The authors acknowledge the financial support by National Science Council of Republic of China under the Grant NSC 100-2313-B-002-012-MY3.

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