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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.

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 (PM10), ozone (O3), nitrogen dioxide (NO2), sulfur dioxide (SO2), 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 PM10 data was the most correlated indicators for asthma hospitalization for all age groups, particularly for elderly. The skewness of O3 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...
10 μm (PM10), ozone (O3), nitrogen dioxide (NO2), sulfur dioxide (SO2), 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 O3, SO2, and CO were significantly associated with adult asthma admission in Taiwan. In addition, PM2.5 and O3 contributed significantly to pediatric asthma admission (Xirasagar et al., 2006). Liao et al. (2011) found a strong association between long-term fluctuations in SO2 time-trend and asthma admission rate. NO2 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) indicated 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 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 impedance. Recent studies revealed that the quantified indicators can improve the predictability and detectability in a variety of dynamical systems (Ditlevsen and Johansen, 2010; Lenton et al., 2012; Schefler 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 PM10, NO2, SO2, CO, and O3 were included. We used daily average concentrations for PM10, NO2, SO2, CO and average of daily maximum 8-h O3 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

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Indicator & Equation \\
\hline
\text{Standard deviation} & \( \frac{1}{n-1} \sum_{i=1}^{n} (x_i - \overline{x})^2 \) \\
\text{Coefficient of variation} & \( \frac{\overline{x}}{\sum_{i=1}^{n} (x_i - \overline{x})^2 / (n-1)} \) \\
\text{Skewness} & \( n \frac{\sum_{i=1}^{n} (x_i - \overline{x})^3}{\left(\sum_{i=1}^{n} (x_i - \overline{x})^2 / (n-1)\right)^{3/2}} \) \\
\text{Kurtosis} & \( n \frac{\sum_{i=1}^{n} (x_i - \overline{x})^4}{\left(\sum_{i=1}^{n} (x_i - \overline{x})^2 / (n-1)\right)^{2}} - 3 \) \\
\hline
\end{tabular}
\caption{Equations of statistical indicator used in time-series analysis.\textsuperscript{a}}
\end{table}

\textsuperscript{a} n is sample size and \( \overline{x} \) 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

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

where \(Y_t\) is the hospitalization rate of age-specific asthma at time \(t\), \(S\) is the specific statistical indicator, \(\beta_0\) is the intercept, and \(\beta_1\) through \(\beta_6\) 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 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 morbidity rates 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 Statistica® (Version 6.0, Statsoft Inc., Tulsa, OK, USA). The MC simulation was performed by using Crystal Ball® software (Version, 2000.2, Decisionerving, 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 \(PM_{10}, NO_2, SO_2,\) and \(CO\) 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 approximately 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 (−0.7 to 2.25), −0.04 (−1.33 to 1.19), 0.26 (−2.0 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 pediatric, 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 \((p = 0.61)\). 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...
only correlated significantly with elderly asthmatics in NO₂ ($r = -0.39$), and (iv) COV only had significant correlation with adult asthmatics in O₃ ($r = -0.39$) (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 O₃ 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
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).
Moreover, our study found that skewness of O₃ time-series data was also associated with asthma hospitalizations among pediatric and adult groups. Recent studies have assessed the effects of ambient O₃ exposure on asthma prevalence in Taiwan. Hwang and Lee (2010) indicated that O₃ concentration had strong association with schoolchildren asthma than PM₁₀ levels. Furthermore, Hwang and Lee (2010) found that long-term exposure to O₃ can increase bronchitis symptoms among Taiwanese children. Jerrett et al. (2009) indicated a strong association between O₃ concentration and the risk of death from respiratory causes. Recent studies also found that traffic-related air pollution such as O₃ and NO₂ 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 SO₂ data may have potential influence on asthma hospitalization of elderly. Liao et al. (2011) found that long-term SO₂ levels were associated with annual asthma admission rate which included outpatient, hospitalization, and emergency room visits. Ko et al. (2007) reported that SO₂ and O₃ 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 SO₂ levels. However, the densely motor vehicles are also the major source or secondary air pollution which increase the photochemical oxidative species of O₃, NO₂, and SO₂.

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 Poisson 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 O₃ 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.,...
In addition, Zhao et al. (2007) have developed the receptor model which can also be used to understand 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

<table>
<thead>
<tr>
<th>Pollution-indicators b</th>
<th>Age groups (yrs)</th>
<th>0–14 yrs</th>
<th>15–64 yrs</th>
<th>≥65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM10</td>
<td>SD</td>
<td>0.4610***</td>
<td>0.4700***</td>
<td>0.6108***</td>
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<tr>
<td></td>
<td>COV</td>
<td>0.3135*</td>
<td>0.1614</td>
<td>0.2065</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>-0.1422</td>
<td>-0.2416</td>
<td>0.1893</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>-0.1656</td>
<td>-0.2133</td>
<td>0.1312</td>
</tr>
<tr>
<td>O3</td>
<td>SD</td>
<td>0.2772</td>
<td>0.0754</td>
<td>0.1438</td>
</tr>
<tr>
<td></td>
<td>COV</td>
<td>-0.1599</td>
<td>-0.3905**</td>
<td>-0.2073</td>
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<tr>
<td></td>
<td>Skewness</td>
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<td>-0.5656***</td>
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</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>0.1290</td>
<td>0.0408</td>
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<tr>
<td>NO2</td>
<td>SD</td>
<td>0.2903*</td>
<td>0.4375**</td>
<td>0.1769</td>
</tr>
<tr>
<td></td>
<td>COV</td>
<td>0.2366</td>
<td>0.2293</td>
<td>-0.0502</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>-0.3051*</td>
<td>-0.3534*</td>
<td>-0.2742</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>-0.1948</td>
<td>-0.2623</td>
<td>-0.3878**</td>
</tr>
<tr>
<td>SO2</td>
<td>SD</td>
<td>0.1820</td>
<td>0.1914</td>
<td>0.5553***</td>
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<tr>
<td></td>
<td>COV</td>
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<td>Skewness</td>
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<td>-0.0803</td>
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<tr>
<td></td>
<td>Kurtosis</td>
<td>-0.0432</td>
<td>0.0272</td>
<td>0.0990</td>
</tr>
<tr>
<td>CO</td>
<td>SD</td>
<td>0.3556*</td>
<td>0.3874**</td>
<td>0.5399***</td>
</tr>
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<td></td>
<td>COV</td>
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<tr>
<td></td>
<td>Kurtosis</td>
<td>0.1415</td>
<td>0.0013</td>
<td>-0.1316</td>
</tr>
</tbody>
</table>

|                  |                  |          |            |          |

**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.

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

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>0–14 yrs</th>
<th>15–64 yrs</th>
<th>≥65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM10 (SD)</td>
<td>0.0058</td>
<td>0.66*</td>
<td>12.3</td>
</tr>
<tr>
<td>O3 (Skewness)</td>
<td>-0.1280*</td>
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<tr>
<td>NO2 (Skewness)</td>
<td>-0.0293</td>
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<td></td>
</tr>
<tr>
<td>CO (SD)</td>
<td>2.2281*</td>
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<td></td>
</tr>
<tr>
<td>Trend</td>
<td>0.0037</td>
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<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>2.4825***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM10 (SD)</td>
<td>0.0054</td>
<td>0.76**</td>
<td>15.3</td>
</tr>
<tr>
<td>O3 (Skewness)</td>
<td>-0.2427***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO2 (SD)</td>
<td>0.0287</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (SD)</td>
<td>2.6102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend</td>
<td>0.0060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.1443***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM10 (SD)</td>
<td>0.0075</td>
<td>0.75**</td>
<td>13.0</td>
</tr>
<tr>
<td>NO2 (Kurtosis)</td>
<td>-0.0019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO2 (SD)</td>
<td>0.4206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (SD)</td>
<td>2.5776**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend</td>
<td>-0.0026*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>3.5330***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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 the period 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.

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.
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).

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

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**Table 4**

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Excess morbidity (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–14</td>
</tr>
<tr>
<td>1998</td>
<td>4.5 (1.6–12.4)</td>
</tr>
<tr>
<td>1999</td>
<td>6.4 (2.4–17.6)</td>
</tr>
<tr>
<td>2000</td>
<td>4.6 (1.5–13.9)</td>
</tr>
<tr>
<td>2001</td>
<td>4.1 (1.6–10.4)</td>
</tr>
</tbody>
</table>

* Mean (95% CI).
prediction approach can be extended to the context of other high asthma epidemic regions to understand the major risk triggers for asthma severity.

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References


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