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Air Pollution, Allergic Co-morbidity, and Emergency Department Visit for Pediatric Asthma in Taiwan

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ABSTRACT

Background: Alterations in allergic susceptibility are a central feature of several chronic respiratory diseases. This study was conducted to determine whether variation in individual allergic susceptibility alters the air pollution effects on attacks of pediatric asthma.

Methods: Daily records of personal asthma emergency department visits among children in school-age and ambient air pollutant concentration were obtained from 2000 to 2008 in Taipei basin, Taiwan. Subjects who had ever had a clinical visit in the departments of otolaryngology and pediatrics or a visit to the emergency department due to allergic rhinitis before their first asthma-related emergency department visit were defined as having allergic rhinitis co-morbidities. A time-stratified approach for the case-crossover technique and a conditional logistic regression were used to examine whether allergic co-morbidity modified air pollution-induced asthma attacks.

Results: Particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) was found to be associated with asthma-related emergency department visits on the day of exposure among children with allergic rhinitis co-morbidity (2^{nd} quartile OR = 1.19; 3^{rd} quartile OR = 1.37; 4^{th} quartile OR = 1.38). High ozone levels were associated with emergency room visits for asthma on a 1-day lag assumption among children with allergic rhinitis co-morbidity (4^{th} quartile OR = 1.38).

Conclusion: The negative effects of air pollution were observed for subjects who had an allergic co-morbidity. The variation in allergic co-morbidity was associated with differences in susceptibility to the adverse effects of air pollutants on respiratory disease.

Keywords: Air pollution; Asthma; Allergic rhinitis; Co-morbidity.

INTRODUCTION

Asthma is a disease with high prevalence that affects 1.6% to 36.8% of children worldwide (Beasley *et al.*, 1998). In Taiwan, the asthma prevalence in children is approximately 5.2% (Guo *et al.*, 1999). Several population-based epidemiological studies demonstrate that the prevalence of childhood asthma has been increasing over time (Pearce *et al.*, 2000; Isolauri *et al.*, 2004; Asher *et al.*, 2006). Asthma is not limited to physical symptoms of the target organ. It also provokes disturbances in the general well-being of the affected subjects. It has been suggested that asthma can alter perceived health status, pose limitations in daily activities, and affect school performance in affected children (Weiss and Sullivan 2001; Rodrigues-Silva *et al.*, 2012). Climate factors, air pollutants, fungal spores, indoor environment, and inherent characteristics of children may contribute to the occurrence of asthma (Palmer *et al.*, 1999; Eleftheriadis and Emmanouil, 2011; Lee, 2011).

There is increasing interest in the use of hospital-based data to determine the adverse respiratory health consequences of short-term exposure to air pollutants. Epidemiologic studies on school-age children have shown that exposure to ambient air pollutants were associated with increases in emergency department visits (Norris *et al.*, 1999; Babin *et al.*, 2007; Jalaludin *et al.*, 2008; Strickland *et al.*, 2010; Li *et al.*, 2011) and hospital admissions for asthma (Lin *et al.*, 2002, 2003; Tsai *et al.*, 2006; Yang *et al.*, 2007; Bell *et al.*, 2008).

In addition, some studies have indicated that there is a close relationship between the lower and upper airways in asthma and allergic rhinitis (Bousquet *et al.*, 2004; Bousquet *et al.*, 2008). The presence of allergic rhinitis might exacerbate asthma, increasing the risk of asthma attacks,

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emergency department visits, and hospitalizations for asthma. Given the known role of allergic rhinitis in asthma, we hypothesize that allergic rhinitis influences the association between ambient air pollutant exposure and asthma attacks. Using the Taiwan National Health Insurance (NHI) database, this study was undertaken to examine whether co-morbidity with allergic rhinitis modifies the relationship between childhood emergency department visits due to asthma and the daily air pollution level for the 9-yr period from 2000 to 2008.

MATERIALS AND METHODS

Subjects

Daily records of emergency department visits during 2000–2008 were extracted from the Taiwan NHI database. The Taiwan NHI program was implemented in 1995 and covered most of the population (the coverage rate was 99.6% in 2010) (Bureau of National Health Insurance, Taiwan, 2010). Computerized records of identification number, gender, date, birthday, and the diagnostic code of each medical visit were available for each contracted medical institution. The study area focused on Taipei Basin. Taipei Basin, including Taipei City and flat terrain area of New Taipei City, is the largest metropolitan area (664.95 km^2) in Taiwan with a population of approximately 5.69 million. Using the International Classification of Diseases, 9th revision (ICD-9), we defined an emergency department visit for pediatric asthma as visits with a code for asthma (ICD-9-CM: 493) among children aged 5 to 15 years.

Exposure Assessment

Concentration for particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}), particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) were obtained from the 11 Environmental Protection Administration (EPA) monitoring stations established in Taipei basin. PM_{10} and $PM_{2.5}$ was measured by beta-ray absorption. $PM_{2.5-10}$ was derived by subtracting $PM_{2.5}$ from PM_{10}. O_3 was measured by ultraviolet absorption, CO by nondispersive infrared absorption, NO_2 by hemiluminescence, and SO_2 by ultraviolet fluorescence. The concentrations of air pollutants were measured continuously and reported hourly. The 24-hour mean was calculated. For each day, air pollution data were extracted from 11 monitoring stations and averaged. When data were missing for a particular monitoring station on a given day, the values from the remaining monitors were used to compute the average.

Potential Covariates

Subjects (children with an emergency department visit due to asthma) who had ever had a clinical visit in the departments of otolaryngology and pediatrics or a visit to the emergency department due to allergic rhinitis (ICD-9-CM: 477) before their first asthma-related emergency department visit were defined as having allergic rhinitis co-morbidities.

Daily information for ambient temperature and relative humidity were obtained from the 11 EPA monitoring stations established in Taipei basin.

Statistical Analysis

To evaluate the associations between childhood asthma-related emergency department visits and the levels of each air pollutants, the time-stratified approach for the case-crossover technique were used (Levy *et al.*, 2001). A stratification of time into separate months was made to select referent days as the days falling on the same day of the week within the same month as the date of asthma-related emergency department visits. A lag of up to 3 previous days (i.e., 1-, 2-, and 3-day-lag assumptions) of exposure assessment was also used. Exposure levels to air pollutants were entered into the models as quartile-specific dummy variables, adjusted for ambient temperature and relative humidity. Conditional logistic regression analysis was fitted to the data to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs). Interaction terms of air pollutant and allergic rhinitis co-morbidity was added to the model to examine whether interaction existed. The allergic rhinitis co-morbidity-stratified analysis would be used if the interaction existed. In addition, two-pollutant models were used to adjust for the potential confounding effects of co-pollutants. Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The descriptive statistics for asthma-related emergency department visits and the corresponding environmental data are shown in Table 1. There were 0.58 daily asthma-related emergency department visits in Taipei Basin during the study period. The annual average levels of ambient air pollutants during the years 2000–2008 were 48.2 $\mu g/m^3$ for PM_{10} (annual standard: 65 $\mu g/m^3$), 27.6 $\mu g/m^3$ for $PM_{2.5}$ (annual standard not under regulation in Taiwan by the end of 2011; annual standard in the United States: 15 $\mu g/m^3$ (US Environmental Protection Agency, 2012)), 24.4 ppb for O_3 (8-hour standard in Taiwan: 60 ppb (Taiwan Environmental Protection Administration, 2012)), 0.73 ppm for CO (8-hour standard: 9 ppm), 24.8 ppb for NO_2 (annual standard: 50 ppb), and 4.1 for SO_2 (annual standard: 30 ppb), respectively.

The Pearson correlation coefficients of the air pollutants show that the air pollutants were correlated with each other (Table 2).

Table 3 presents the changes in the risk of asthma-related emergency department visits in relation to each quartile increase of exposure in a single-pollutant model. The interaction term of $PM_{2.5}$ and allergic rhinitis co-morbidity were significant ($p = 0.01$). Therefore, subjects with/without allergic rhinitis co-morbidity were analyzed separately. The levels of $PM_{2.5}$ was found to be associated with asthma-related emergency department visits on the day of exposure among subjects with allergic rhinitis co-morbidity (2^{nd} quartile OR = 1.19; 3^{rd} quartile OR = 1.37; 4^{th} quartile OR = 1.38). The interaction term of O_3 and allergic rhinitis co-morbidity were also significant ($p = 0.03$). Therefore, allergic

Table 1. Characteristics of subjects and corresponding environmental factors during the study period (From January 1, 2000 to December 31, 2008).

Characteristics	Subjects (n = 1,912)	
	%	Mean (SD)
No. of daily emergency visit duo to asthma		0.58 (0.85)
Subjects' age, years		8.52 (2.63)
Subjects' gender ratio (boys/girl)	1.93	
Air pollutants		
PM_{10}, μg/m^3		48.17 (23.52)
$PM_{2.5}$, μg/m^3		27.61 (14.90)
$PM_{2.5–10}$, μg/m^3		20.56 (12.61)
O_3, ppb		24.40 (9.09)
CO, ppm		0.73 (0.26)
NO_2, ppb		24.81 (8.06)
SO_2, ppb		4.13 (2.02)
Meteorology		
Temperature, °C		23.54 (5.32)
Relative Humidity, %		72.30 (8.56)

Table 2. Pearson correlation coefficient of air pollutants in Taipei basin, Taiwan. (From January 1, 2000 to December 31, 2008).

Variable	$PM_{2.5–10}$	O_3	CO	NO_2	SO_2
$PM_{2.5}$	0.52	0.34	0.48	0.53	0.62
$PM_{2.5–10}$		0.22	0.29	0.33	0.42
O_3			–0.24	–0.08	0.05
CO				0.88	0.47
NO_2					0.54

Table 3. Association of ambient air pollutants concentration with childhood emergency visit due to asthma, single-pollutant models.

	Subjects with co-morbidity of allergic rhinitis	Subjects without co-morbidity of allergic rhinitis
	OR (95%CI)	OR (95%CI)
0-day lag $PM_{2.5}$, μg/m^3		
< 17.0	1.00	1.00
17.0–25.0	1.19 (0.92, 1.53)	0.68 (0.43, 1.07)
25.0–36.0	**1.37 (1.07, 1.76)**	0.97 (0.61, 1.54)
≥ 36.0	**1.38 (1.08, 1.75)**	0.66 (0.42, 1.05)
1-day lag O_3, ppb		
< 18.7	1.00	1.00
18.7–24.4	1.23 (0.98, 1.56)	1.01 (0.65, 1.58)
24.4–30.3	1.28 (0.98, 1.66)	0.81 (0.51, 1.28)
≥ 30.3	**1.38 (1.09, 1.75)**	0.67 (0.41, 1.12)

Results were adjusted for ambient temperature and relative humidity.

rhinitis co-morbidity-stratified analysis was also used. The levels of O_3 were associated with asthma-related emergency department visits on a 1-day lag assumption among subjects with co-morbidity of allergic rhinitis. Exposure to $PM_{2.5–10}$, CO, NO_2, and SO_2 was not found to affect childhood asthma-related emergency department visits (data not shown).

Two-pollutant models were used to adjust for the potential confounding effects of co-pollutants (Table 4). For $PM_{2.5}$ and O_3, the coefficients and statistical significance were essentially unchanged in the two-pollutant model compared to the single-pollutant model.

DISCUSSION

In this study, we analyzed emergency department visits for pediatric asthma in relation to ambient air pollutant concentrations. We observed positive and statistically significant associations between childhood asthma-related emergency department visits and exposure to $PM_{2.5}$ at levels greater than 25.0 μg/m^3 and O_3 at levels greater than 30.3 ppb. Particulate matter can directly generate reactive oxygen species through the presence of free radicals and oxidants on the particle surface (Risom *et al.*, 2005). The

Table 4. Association of ambient air pollutants concentration with childhood emergency visit due to asthma, two-pollutants models.

	Subjects with co-morbidity of allergic rhinitis			
	0-day lag $PM_{2.5}$ effect		1-day lag O_3 effect	
	Exposure level, μg/m^3	OR (95%CI)	Exposure level, ppb	OR (95%CI)
With co-pollutant of $PM_{2.5}$	< 17.0	--	< 1 8.7	1.00
	17.0–25.0	--	18.7–24.4	1.25 (0.99, 1.59)
	25.0–36.0	--	24.4–30.3	1.27 (0.98, 1.66)
	≥ 36.0	--	≥ 30.3	**1.39 (1.09, 1.77)**
With co-pollutant of $PM_{2.5–10}$	< 17.0	1.00	< 18.7	
	17.0–25.0	1.27 (0.95, 1.69)	18.7–24.4	1.23 (0.97, 1.56)
	25.0–36.0	**1.42 (1.10, 1.83)**	24.4–30.3	1.28 (0.98, 1.67)
	≥ 36.0	**1.44 (1.13, 1.83)**	≥ 30.3	**1.38 (1.09, 1.76)**
With co-pollutant of O_3	< 17.0		< 18.7	--
	17.0–25.0	1.15 (0.89, 1.49)	18.7–24.4	--
	25.0–36.0	**1.37 (1.08, 1.74)**	24.4–30.3	--
	≥ 36.0	**1.37 (1.07, 1.75)**	≥ 30.3	--
With co-pollutant of CO	< 17.0		< 18.7	
	17.0–25.0	1.38 (1.00, 1.89)	18.7–24.4	1.26 (0.99, 1.59)
	25.0–36.0	**1.44 (1.13, 1.85)**	24.4–30.3	1.32 (1.01, 1.73)
	≥ 36.0	**1.50 (1.14, 1.96)**	≥ 30.3	**1.42 (1.11, 1.81)**
With co-pollutant of NO_2	< 17.0		< 18.7	
	17.0–25.0	1.23 (0.91, 1.67)	18.7–24.4	1.24 (0.98, 1.57)
	25.0–36.0	**1.39 (1.09, 1.78)**	24.4–30.3	1.31 (1.01, 1.71)
	≥ 36.0	**1.41 (1.08, 1.83)**	≥ 30.3	**1.41 (1.10, 1.79)**
With co-pollutant of SO_2	< 17.0		< 18.7	
	17.0–25.0	1.32 (0.97, 1.79)	18.7–24.4	1.23 (0.98, 1.56)
	25.0–36.0	**1.40 (1.10, 1.78)**	24.4–30.3	1.28 (0.99, 1.66)
	≥ 36.0	**1.45 (1.12, 1.89)**	≥ 30.3	**1.38 (1.09, 1.75)**

Results were adjusted for ambient temperature and relative humidity.

production of reactive oxygen species has been suggested to play an important role in subsequent oxidative stress and the inflammatory response (Dye *et al.*, 1997). Epidemiologic studies have indicated that $PM_{2.5}$ at levels ranging from 7.0 μg/m^3 to 27.5 μg/m^3 might be associated with childhood asthma exacerbations (Norris *et al.*, 1999; Jalaludin *et al.*, 2008; Li *et al.*, 2011). Ozone reacts slowly with water to yield reactive hydroxyl radicals, which oxidize a wide range of biomolecules. Ozone can diffuse freely into cells and lead to sulfhydryl oxidation and inflammation (Frischer *et al.*, 2001). An increased risk of asthma exacerbation associated with O_3 at levels ranging from 24.3 ppb to 60.0 ppb has been reported in previous studies (Jalaludin *et al.*, 2008; Strickland *et al.*, 2010).

To our knowledge, this is the first study to investigate the modification effect of allergic susceptibility on the relationship between air pollution and asthma attacks. The concepts regarding nose-lung integration are the anatomical similarities and the functional complementarity that assigns the role of the protector of the lung to the nose (Togias 2003). Subjects with allergic rhinitis have an increased risk of developing asthma and may form a suitable population for secondary intervention to interrupt the atopic march (Bousquet *et al.*, 2003). Categorizing subjects' co-morbidity with allergic rhinitis according to personal longitudinal medical recording allows further in-depth investigation into the variation of etiological factors. In this study, we found that the negative effects of $PM_{2.5}$ and O_3 were observed among subjects with allergic rhinitis co-morbidity. Variation in allergic co-morbidity was truly associated with differences in susceptibility to the adverse effects of air pollutants on respiratory disease. In this study, asthma with allergic rhinitis co-morbidity could be classified as atopic and were activated through IgE and its high-affinity receptor FcεRI (von Bubnoff *et al.*, 2003; Gould and Sutton 2008). The subsequent release of inflammatory mediators is key to the onset of immediate immunological event. In contrast, asthma without allergic rhinitis co-morbidity might be defined as non-atopic and lacked increased serum IgE levels after exposure to ambient air pollutants. Future studies are necessary to further investigate the possible mechanism for this type of chronic inflammatory disorders.

We relied on codes from hospital administrative databases to identify emergency department visits for pediatric asthma. Although the recorded diagnosis was the diagnosis made at the time of discharge from the emergency department, there is the possibility that the asthma diagnosis may have been inaccurate. By excluding children younger than 5 years, children who frequently experience transient wheezing, and asthma diagnoses that may be suspect from our analysis, we reduced diagnosis errors. Further, a previous study (Stieb *et al.*, 1998) reported an absence of an emergency department visit diagnostic bias for asthma between low- and high-pollution days. Therefore, any measurement error is expected

to be non-differential. Seasonal interactions as a confounding factor for exposure to ambient air pollutant and childhood asthma emergency department visits have often been reported. However, in Taipei, Taiwan, the subtropical climate with no apparent four-season cycle. Therefore, the possible confounding influence of seasonality on the effects of air pollutants should be minimal in this study, and temperature was adjusted in the analytical model instead.

Some study limitations need to be considered. First, the racial homogeneity of the study population in this study (95.1% to 98.9% were Taiwanese among children aged 5 to 15 years in Taiwan during the study period (Ministry of Education, Taiwan, 2012)) may increase the difficulty in generalizing these results to other regions. Second, exposure assessment error is inherent in all large epidemiologic studies of district-scale air pollution health effects. Although studies of personal exposure to air pollutants help to advance the understanding of biological responses (Furuuchi *et al.*, 2010), from a regulatory standpoint, the ambient concentrations are of greatest relevance. One prominent component of error in our studies, therefore, is how well the population-weighted spatial average of assessments from monitoring stations approximates the ambient concentration across the entire metropolitan northern Taiwan area. An additional contribution to the assessment error issue is the number of air pollutant monitoring stations. The interpretation of two-pollutant models is complicated by these measurement error issues; the pollutant with the stronger estimated effect may not be the more harmful pollutant but may instead be the pollutant with fewer measurement errors (Tolbert *et al.*, 2007). Third, rhinovirus infections typically peak in the late winter and early spring, which are the cool months of our analysis period. Therefore, although the case-crossover design may have, to some extent, controlled for the winter respiratory virus exacerbation of asthma, some residual confounding effects may be present.

CONCLUSION

In our study, we observed evidence that ambient concentrations of fine particulate matter and ozone from traffic sources independently contributed to the burden of emergency department visits for pediatric asthma in Taiwan. Further, children with allergic co-morbidities were found to increase susceptibility to the adverse respiratory effects of air pollutants.

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