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Association of ambient air-pollution levels with acute asthma exacerbation among children in Singapore

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Key words: ambient air pollution; childhood acute asthma exacerbation; time trends; the tropics.

Background: Air-pollution levels have been shown to be associated with increased morbidity of respiratory diseases.

Methods: Data for ambient air-pollutant levels, meteorologic factors, and hospitalization or emergency room (ER) visits for acute asthma in Singapore children over a 5-year period (1990–4) were obtained and analyzed for associations by time-series methods.

Results: Throughout this period, the annual mean and 24-h mean levels for sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and total suspended particles (TSP) and maximum 1-h daily average for ozone were generally within the air-quality guidelines established by the World Health Organization (WHO). However, positive correlation between levels of each of these pollutants and daily ER visits for asthma was observed in children aged 3–12 years, but not among adolescents and young adults (13–21 years old). The association with SO₂ and TSP persisted after standardization for meteorologic and temporal variables. An adjusted increase in 2.9 ER visits for every 20 µg/m³ increase in atmospheric SO₂ levels, lagged by 1 day, was observed on days when levels were above 68 µg/m³. With TSP, an adjusted increase of 5.80 ER visits for every 20 µg/m³ increase in its daily atmospheric levels, lagged by 1 day, was observed on days with levels above 73 µg/m³. Similar results were also obtained after controlling for autocorrelation by time-series analysis.

Conclusions: These associations were observed even though the overall levels of all pollutants were generally within the air-quality guidelines established by the WHO. These findings suggest that asthmatic children are susceptible to increased levels of air pollutants, particularly SO₂ and TSP, although the ambient levels are generally within "acceptable" ranges.

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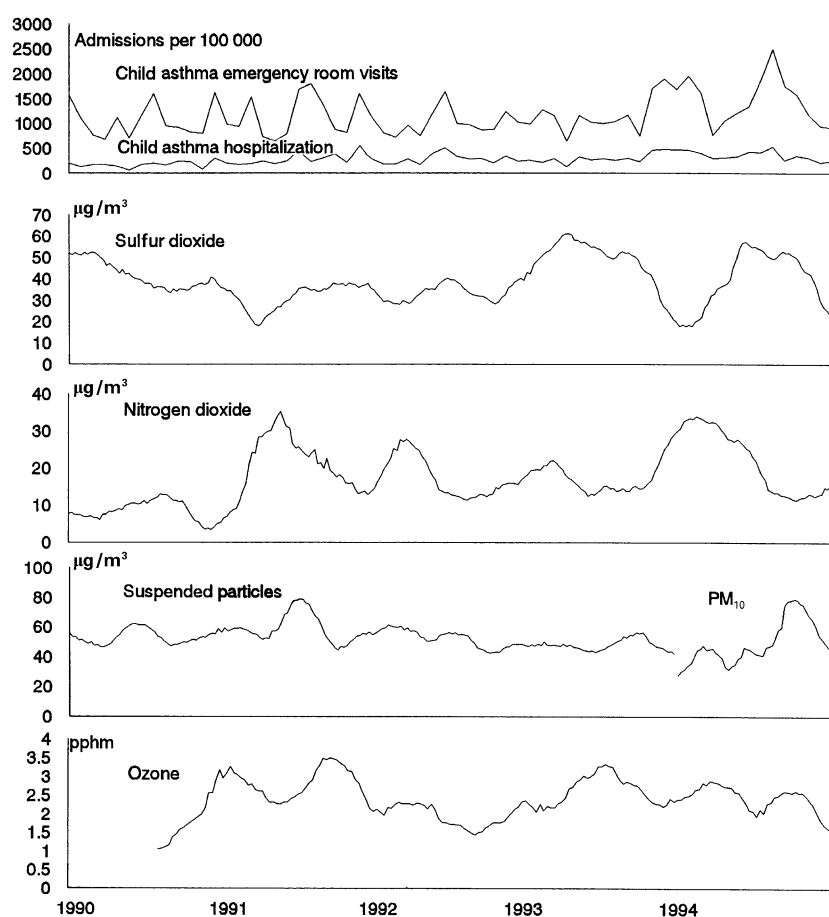


Figure 1. Time trends in asthma admissions and air-pollutant levels in Singapore, 1990–4. Trends for (a) emergency room visits for child (3–12-year-olds) asthma (ICD 493), (b) hospitalization for child asthma, (c) sulfur dioxide, (d) nitrogen dioxide, (e) total suspended particles (and PM_{10} for 1994), and (f) atmospheric ozone. Trends shown are 12-point centered moving averages of weekly means over 5 years.

Air pollution has been associated with increased morbidity and mortality rate from respiratory diseases (1–3). Dramatic episodes of severe air pollution, such as the London fog of December 1952 (4); the Meuse valley, Belgium, in 1931 (5); and Donora, Pennsylvania, in 1948 (6), have clearly indicated that high pollutant levels have definite health implications. With controls and legislation to decrease air pollution in many large cities and urban areas in recent years, such episodes of high level pollution have occurred less frequently.

In Singapore, monitoring of the levels and trends of air pollution has been handled by the Anti-Pollution Unit (APU) since its formation in 1970 (7) and, more recently, by the Environmental Monitoring and Assessment Section of the Ministry of the Environment. In 1994, an episode of increased air pollution due to forest fires and agricultural burning in southern Sumatra and Kalimantan, popularly known by Singaporeans as the “haze”, again highlighted the adverse effects of air pollution on health (8). However, one major concern about air pollution today relates to the

effects of continuous daily exposure to low or ambient levels of air pollutants (9, 10). Various methods, including experiments on laboratory animals (11–13), clinical evaluations of the effects on human volunteers (14–16), and epidemiologic studies (17–19), have shown and quantified the risk of exposure to ambient levels of air pollutants. This study aimed to examine the relationship between the levels of ambient air pollutants and acute asthma in our population.

Material and methods

The population and area studied

The tropical island city-state of Singapore lies 80 km from the equator. The main island is 42 km long by 23 km wide, with a total area of approximately 570 km^2 . Most of the island is less than 15 m above sea level, and the highest point is only 165 m above sea level. Singapore is character-

Table 1. Descriptive statistics for daily hospitalization and emergency room (ER) visits for asthma, mean air-pollutant levels, and meteorologic variables, in Singapore, 1990–4

Variable	Mean	SD	Range	No. of days
<i>Asthma hospitalization and ER visits</i>				
Child ER visits (per day)	12.8	6.3	2–54	1826
Child hospital admissions (per day)	3.8	3.6	0–23	1826
Adolescent ER visits (per day)	12.2	5.8	1–38	1826
Adolescent hospital admissions (per day)	3.0	2.8	0–15	1826
<i>Air pollutants</i>				
Sulfur dioxide (24-h average, $\mu\text{g}/\text{m}^3$)	38.1	21.8	3.0–141.0	1530
Nitrogen dioxide (24-h average, $\mu\text{g}/\text{m}^3$)	18.9	15.0	3.0–89.0	678
Suspended particles (24-h average, $\mu\text{g}/\text{m}^3$)	51.2	20.3	13.0–184.0	562
Ozone (1-h daily maximum, ppm)	2.3	1.5	1.0–12.1	1500
<i>Meteorologic parameters</i>				
Rainfall (mm per day)	7.3	15.3	0.0–123.0	1419
Daily maximum temperature ($^{\circ}\text{C}$)	31.3	1.8	23.2–35.0	1419
Daily minimum temperature ($^{\circ}\text{C}$)	24.6	1.3	19.0–29.6	1419
Daily average temperature ($^{\circ}\text{C}$)	27.1	1.5	21.7–30.6	1419
Daily total wind speed (m/s)	101.7	48.3	18–354	1419
Daily total solar radiation (MJ.m)	13.2	4.6	0.9–33.4	1419
Relative humidity at 0900 (%)	87.4	7.7	67–99	1419
Relative humidity at 1500 (%)	79.2	11.9	50–99	1419
<i>Control disease diagnosis (hospitalization)</i>				
Appendicitis (per day)	0.4	0.7	0–5	1826
Urinary tract infections (per day)	3.1	2.4	0–14	1826

ized by a generally high temperature, humidity, and rainfall throughout the year, with slight variations in rainfall, cloudiness, and wind speed and direction due to the monsoons (20). According to the census of population in 1990 (21), the population is approximately 2.7 million, with 80% housed in high-rise apartments, mostly in the south central regions of the main island.

Hospital admissions

Hospital admissions data were obtained from the Singapore General Hospital (SGH) and the National University Hospital (NUH) Information Services Departments' computerized database. These are major public general hospitals, and are responsible for approximately 50% of total admissions in Singapore. Data on daily asthma (ICD 493) admission and emergency room (ER) visits and daily admission for appendicitis (ICD 541) and urinary tract

infections (ICD 599), which served as control data, were obtained. These two disease groups were chosen as controls because they are not known to be associated or confused with respiratory diseases, or to occur seasonally. Data for the period of January 1990 to December 1994 were analyzed. The data were divided into those for children (12 years and below) and for adolescents and young adults (from above the age of 12 to the age of 21 years). This age group of ≤ 12 years was used, as it was the cutoff for the pediatric age group for these hospitals. Data for children of < 3 years were not used, as wheezing in young children with bronchitis and bronchiolitis may be misdiagnosed as asthma (22).

Data used for time-trend analysis were further transformed and expressed as admission rates per 100 000 of the resident population of Singapore of the same age. This was adjusted for the estimated proportion of the population covered by these hospitals. These adjustments were based

Table 2. Daily air-pollutant levels compared with daily number of emergency room (ER) visits for childhood asthma by quartiles

Child ER visits for asthma per day by quartile	Average daily air-pollutant levels		
	Same day†	Lagged by 1 day†	Lagged by 2 days†
<i>Sulfur dioxide, 24-h average, µg/m³</i>			
≤9	27.0 ^a	26.6 ^b	24.3 ^b
10–12	28.8 ^a	27.2 ^b	27.2 ^a
13–16	26.9 ^a	27.2 ^b	28.5 ^a
>16	28.1 ^a	30.4 ^a	29.4 ^a
<i>P</i> value (ANOVA):‡	0.40	0.02	<0.001
<i>r</i> value (correlation):§	0.05	0.12**	0.10**
<i>Nitrogen dioxide, 24-h average, µg/m³</i>			
≤9	13.5 ^c	12.8 ^b	12.3 ^b
10–12	15.2 ^{bc}	16.3 ^a	16.7 ^a
13–16	17.5 ^{ab}	18.4 ^a	18.1 ^a
>16	19.0 ^a	19.4 ^a	19.1 ^a
<i>P</i> value (ANOVA):‡	0.0019	<0.001	<0.001
<i>r</i> value (correlation):§	0.10	0.12*	0.14**
<i>Suspended particles, 24-h average, µg/m³</i>			
≤9	46.8 ^b	45.8 ^b	46.2 ^b
10–12	47.9 ^{ab}	48.6 ^{ab}	46.5 ^b
13–16	50.9 ^{ab}	50.6 ^{ab}	46.5 ^a
>16	52.8 ^a	52.7 ^a	52.9 ^a
<i>P</i> value (ANOVA):‡	0.04	0.05	0.0019
<i>r</i> value (correlation):§	0.12*	0.11*	0.14**
<i>Ozone, 1-h daily maximum, pphm</i>			
≤9	2.7 ^c	2.8 ^b	2.8 ^b
10–12	3.2 ^b	3.1 ^a	3.1 ^b
13–16	3.4 ^a	3.3 ^a	3.3 ^a
>16	3.3 ^{ab}	3.3 ^a	3.3 ^a
<i>P</i> value (ANOVA):‡	<0.001	<0.001	<0.001
<i>r</i> value (correlation):§	0.06	0.07*	0.06

P*<0.05, *P*<0.01, ****P*<0.001. †Means (geometric means) with same letter are not significantly different at α=0.05, analyzed by Duncan's new multiple range test (DNMRT). ‡*P* value: probability (*P*) value calculated by categorical analysis via ANOVA. §*r* value: Pearson correlation coefficient (*r*) using continuous data.

on the national annual hospitalization figures obtained from the Research and Epidemiology Department, Ministry of Health, Singapore. Mid-year estimates of the total resident population used as the denominator were obtained from the Monthly Digest of Statistics (23) published by the Department of Statistics, Singapore.

Air pollution and meteorologic data

Air-pollution data were obtained from 15 monitoring stations of the Ministry of the Environment. The data were obtained for the entire 5-year period, and approximately 20–30% of the values were missing (depending on the station) mainly due to instrumentation failure or lagged periods where data were not obtained. This, however, did not affect the analysis, as no significant difference was detected in number of asthma cases between days when air-pollution data were not obtained and days when they were available (data not shown). The 24-h average levels of sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and total suspended particles (TSP) and the maximum 1-h levels of atmospheric ozone (O₃) were obtained. The data for TSP were analyzed until the end of 1993, as the monitoring of TSP was discontinued and replaced with PM₁₀ (particulate matter less than 10 µm) in 1994. The measurements obtained from different samplers for the same air pollutant across the island were highly correlated (*P*<0.001) and thus were averaged. The averaged data were used in the analysis instead of using only the data from the stations closest to the hospitals, as these hospitals served a far wider population than those in the west and central regions where they are located. Additionally, as the island-wide air pollution data were correlated, far fewer missing values would be found by using the averaged data set.

Daily meteorologic data were collected simultaneously during this period at two stations at Clementi and Kent Ridge with the Easidata meteorologic data logger and sensors (Envirodata Co.). Additional meteorologic data were also obtained from the Singapore Meteorologic Services from stations in different parts of Singapore. These data from different sites also correlated with each other (*P*<0.001). The high correlations between readings of the same variables at different sites showed that the general trend of air pollutants and meteorology could be taken as the trend in Singapore.

Statistical analysis

Statistical analysis was carried out with the SAS/STAT and SAS/ETS, version 6.08 (24, 25). The method described by Sunyer et al. (26) was adopted in this study. The relationship between independent daily air-pollution levels and hospital admissions was initially studied singly by Pearson correlation coefficients, followed by categorical analysis by generalized linear models. Multivariate linear-regression models were then built to adjust the putative effects of air pollution

Table 3. Categorical analysis (via ANOVA) probability (*P*) value and Pearson correlation coefficient (*r*) using continuous data comparing daily air-pollutant levels and daily number of hospitalization and emergency room (ER) visits for asthma in Singapore, 1990–4

		Children		Adolescents	
		ER visits†	Admissions†	ER visits†	Admissions†
<i>Sulfur dioxide (24-h average, µg/m³)</i>					
Same day	<i>P</i> value:‡	0.40	<0.001	0.19	0.086
	<i>r</i> value:§	0.05	0.04	0.04	0.05
Lagged by 1 day	<i>P</i> value:‡	0.02	<0.001	0.93	0.016
	<i>r</i> value:§	0.12**	0.10**	0.05	0.06
Lagged by 2 days	<i>P</i> value:‡	<0.001	<0.001	0.91	0.019
	<i>r</i> value:§	0.10**	0.08*	0.03	0.07
<i>Nitrogen dioxide (24-h average, µg/m³)</i>					
Same day	<i>P</i> value:‡	0.0019	0.013	<0.001	0.18
	<i>r</i> value:§	0.10	0.13**	0.09	0.05
Lagged by 1 day	<i>P</i> value:‡	<0.001	0.02	0.0014	0.75
	<i>r</i> value:§	0.12*	0.13**	0.04	0.02
Lagged by 2 days	<i>P</i> value:‡	<0.001	0.012	0.0066	0.35
	<i>r</i> value:§	0.14**	0.13**	0.03	0.07
<i>Suspended particles (24-h average, µg/m³)</i>					
Same day	<i>P</i> value:‡	0.04	0.04	0.0076	0.30
	<i>r</i> value:§	0.12*	0.12*	0.06	0.05
Lagged by 1 day	<i>P</i> value:‡	0.05	0.05	0.053	0.83
	<i>r</i> value:§	0.11*	0.08	0.06	0.03
Lagged by 2 days	<i>P</i> value:‡	0.0019	<0.001	0.081	0.31
	<i>r</i> value:§	0.14**	0.14**	0.02	0.06
<i>Ozone (1-h daily maximum, pphm)</i>					
Same day	<i>P</i> value:‡	<0.001	0.0035	<0.001	<0.001
	<i>r</i> value:§	0.06	0.05	0.07*	0.11***
Lagged by 1 day	<i>P</i> value:‡	<0.001	<0.001	<0.001	<0.001
	<i>r</i> value:§	0.07*	0.09**	0.05	0.09**
Lagged by 2 days	<i>P</i> value:‡	<0.001	0.0016	<0.001	<0.001
	<i>r</i> value:§	0.06	0.05	0.05	0.08**

P*<0.05, *P*<0.01, ****P*<0.001. †Only *P* value (categorical analysis) and *r* value (correlation) are shown. *P* value‡: probability (*p*) value calculated by categorical analysis via ANOVA. *r* value§: Pearson correlation coefficient (*r*) using continuous data.

to those of other confounders (meteorologic variables). The forms and assumptions of the models were also analyzed to ensure normality in the distribution of the variables, homoscedasticity of variance, and independence. Temporal variation (1- and 2-day lagged data) in the air-pollution and meteorologic variables were also used along with the day-of-the-week effect. The different air pollutants were tested separately to avoid the problem of collinearity. However, direct application of conventional multiple-regression

methods was considered inappropriate in this study, as successive daily counts of admissions were likely to be positively correlated, thus violating the requirement of independence for regression. To overcome this, the response variable (ER visit rates), lagged by 1 day, was included as a regression variable, as recommended by Korn & Whittemore (27). Variables that were significantly associated with hospital admissions or ER visits (*P*<0.05) were retained in the model, and their interaction with other variables was

Table 4. Adjusted change in daily emergency room (ER) visits for asthma per unit change of selected variables according to stepwise multiple regression analysis

Variable	Unit change*	Adjusted change†	Standard error‡	P value§
<i>Inclusion of sulfur dioxide (24-h average, $\mu\text{g}/\text{m}^3$) in model</i>				
Child asthma ER visits lagged 1	Five attendances per day	2.02	0.21	<0.001
Day of week	Weekend (Saturday and Sunday)	0.48	0.06	<0.001
Sulfur dioxide (24-h average) lagged 1 day	20 $\mu\text{g}/\text{m}^3$	2.90	0.81	<0.001
Daily total wind speed lagged 1 day	50 m/s	0.09	0.03	0.0024
<i>Inclusion of nitrogen dioxide (24-h average, $\mu\text{g}/\text{m}^3$) in model</i>				
Child asthma ER visits lagged 1	Five attendances per day	1.54	0.24	<0.001
Day of week	Weekend (Saturday and Sunday)	0.16	0.09	0.05
Daily average temperature lagged 1 day	2°C	0.25	0.09	0.007
Nitrogen dioxide (24-h average) lagged 1 day	15 $\mu\text{g}/\text{m}^3$	0.76	0.43	0.08
<i>Inclusion of suspended particles (24-h average, $\mu\text{g}/\text{m}^3$) in model</i>				
Child asthma ER visits lagged 1	Five attendances per day	1.20	0.34	<0.001
Day of week	Weekend (Saturday and Sunday)	0.32	0.09	<0.001
Suspended particles (24-h average) lagged 1 day	20 $\mu\text{g}/\text{m}^3$	5.80	1.46	<0.001

Durbin-Watson test values for three models ranged between 1.808 and 2.153, with first-order autocorrelation results showing low degree of association between adjacent residuals. *Unit change equivalent to value close to standard deviation of respective variable over study period. †Linear regression coefficient. ‡Standard error of linear regression coefficient. §P value of regression coefficient calculated by stepwise regression analysis.

tested. Separate models were built for the children (3–12 years of age) and adolescents or young adults (>12 years). Overall 5-year models were initially built. Separate models were then built for each year of analysis. In each case, the Durbin-Watson test was used to test the hypothesis of random distribution of the residuals. Since the variables used in this study were time-series observations, autocorrelation was likely to exist. Therefore, to control for autocorrelation, transfer function models were also used for comparison (28).

Finally, to obtain information on possible threshold levels of the effect of the pollutants, days with increased levels of the air pollutants were successively excluded from the analysis in a stepwise manner until the percentile where no association was detected with the regression model was reached. This analysis was simultaneously performed with appendicitis and urinary tract infection as a control to ensure unbiased selection and interpretation of results.

Results

During the period of analysis, more than 6000 admissions and an estimated 23 000 ER visits were recorded for asthma (ICD 493) in children 3–12 years old. The descriptive statistics of the variables used in this study are shown in

Table 1. The average number of daily asthma hospital admissions during the period of study were 3.8 and 3.0 for children 3–12 years of age and young adults, respectively. With asthma, the mean number of ER visits per day were 12.8 and 12.2, respectively. The fluctuations in asthma admissions and ER visits over the period of study are shown in Fig. 1.

Air-pollutant levels were low and generally well within the permissible levels for 24-h exposure established by the World Health Organization (WHO) and the US Environmental Protection Agency (EPA). The arithmetic means (SD) and ranges are shown in Table 1. Levels of TSP were only slightly raised on a number of occasions in 1991 (Fig. 1). This increase was attributed to the Mount Pinatubo volcanic eruption in June 1991 and the forest fires in Indonesia from mid-August to early November 1991. In 1994, Singapore experienced another episode of severe haze between the months of August and October, when PM_{10} levels rose sharply (Fig. 1). The effects of PM_{10} on ER admissions for asthma, however, were not included in this study and have been reported elsewhere (8). Atmospheric ozone levels were also found to rise marginally only on one occasion in 1994 above the US EPA standard of 12 pphm (parts per hundred million) ozone (1-h maximum) (1 pphm $\text{O}_3=20 \mu\text{g}/\text{m}^3$).

Correlation existed between the levels of the various air pollutants, with a magnitude of correlation coefficient (r)

ranging from 0.02 (not significant) to 0.23 ($P<0.001$). Therefore, each pollutant was analyzed separately to avoid collinearity in the regression models. In particular, SO₂ levels were inversely correlated with NO₂ ($r=-0.22$, $P<0.001$) and positively correlated with TSP ($r=0.17$, $P<0.01$), while TSP was correlated with atmospheric ozone ($r=0.20$, $P<0.001$). NO₂ levels were also correlated with TSP ($r=0.23$, $P<0.001$) and ozone ($r=0.17$, $P<0.01$). Air-pollutant levels were also observed to correlate with meteorologic factors. SO₂ levels were inversely correlated with temperature parameters ($r=-0.16$, $P<0.001$) and positively correlated with daily rainfall ($r=0.12$, $P<0.001$). TSP levels were positively correlated with temperature ($r=0.16$, $P<0.01$).

Significant positive correlation was found between the levels of SO₂ (lagged by 1 or 2 days) and daily asthma ER visits in children (Table 2). Similarly, significant P values were obtained when categoric data analysis was performed via analysis of variance (ANOVA) in place of continuous data analysis via Pearson's correlation coefficient. Likewise, the daily asthma ER visit rates were found to be associated with NO₂ levels (lagged by 1 or 2 days), and TSP levels (on the same day and lagged up to 2 days). With ozone, however, only a weak correlation was observed.

Table 3 shows the association between the same daily air-pollutant levels and ER asthma visits of children (aged 3–12 years) and adolescents or young adults (>12 years). Only correlation r values and ANOVA P values are shown. Parameters for children were more correlated with daily air-pollutant levels than for adolescents or young adults. A significant association was observed between air pollution levels and asthma ER visits in children. With the adolescents, however, only weak correlation was observed with ozone levels.

When the data were adjusted for the effects of meteorologic parameters, the significant association between SO₂ levels and childhood asthma ER visits was stronger on days with higher total wind speed (data not shown). Similarly, when stratified by temperature, the association between ER visits for childhood asthma and NO₂ levels was stronger on days with higher daily temperature.

The associations with asthma in children remained significant for SO₂ ($P<0.001$), NO₂ ($P<0.05$), and TSP ($P<0.001$), when analyzed by stepwise multiple regression, taking into account temporal variables, meteorologic parameters, and pollutant levels lagged 1 day (Table 4). The adjusted change in childhood ER visits per unit standard deviation change of significantly associated pollutants was also determined. Adjusted increases of approximately 1.80, 2.90, and 2.64 ER visits for every 20 µg/m³ increase in daily

atmospheric SO₂ levels, on the same day, lagged by 1 day and lagged by 2 days, respectively, were observed. With TSP, adjusted increases of 4.58, 5.80, and 5.12 ER visits for every 20 µg/m³ increase in its daily atmospheric levels, on the same day, lagged by 1 day and lagged by 2 days, respectively, were observed ($P<0.001$ for all three regression models). The adjusted effect for ozone was not statistically significant ($P>0.05$).

When autocorrelation and partial autocorrelation diagrams of the regression models were plotted, they revealed that the distribution of the residuals was not autocorrelated. Durbin-Watson (DW) test values ranged between 1.80 and 2.15, with first-order autocorrelation results showing a low degree of association between adjacent residuals (DW value of 2, indicating no autocorrelation). Nevertheless, for comparisons, transfer-function models were also used to analyze the regression variables. The transfer-function models included the same variables as the regression models, without the day of the week, and the response variable lagged by 1 day. The air-pollutant coefficient estimates obtained in the transfer-function models were found to be similar to those of the multiple-regression models.

When the analysis was stratified annually, SO₂ and TSP levels remained associated with childhood asthma ER visit rates throughout the entire period of analysis. NO₂ levels, however, were found to be significantly associated with childhood asthma ER visit rates only in 1991, 1992, and 1994.

The regression coefficient for SO₂ remained significant even after successive removal of days with levels above 68 µg/m³ (90th percentile). However, the regression coefficient was not significant after the removal of data up to the 75th percentile (50 µg/m³) (data not shown). With TSP, the regression coefficient remained significant up to the level of 73 µg/m³ (90th percentile).

The analysis comparing the control data for appendicitis (ICD 541) and urinary tract infections (ICD 599) with air-pollutant levels showed significant associations only with ozone up to $P<0.05$, via bivariate correlation (data not shown). No significant associations were observed in the multiple-regression models.

Discussion

Studies elsewhere have demonstrated that asthmatics are prone to the effects of ambient air pollutants (29–31). Several mechanisms have been proposed to explain pollution-

induced airways disease such as asthma. These include damage to airway epithelium (32), induced changes in lung function (33), and enhanced release of inflammatory mediators (34, 35). Epidemiologic studies have also shown a striking temporal association between ambient air-pollution levels and asthma attacks in children requiring hospitalization (19, 36–37). We have recently found seasonal variation in ER visits for asthma among children in Singapore's tropical climate (22). One indication that air pollution may affect acute asthma was the increase in admissions above the normal annual trend in 1991 and 1994, an increase which coincided with increased air pollution and heavy haze due to forest fires and volcano eruptions in countries near to Singapore (8). Further analysis made in this study suggests that these air pollutants also influence acute asthma outside the episodes of increased pollution.

Due to the ecologic design of the study, several issues would need to be addressed to overcome problems associated with ecologic biases, such as overinterpretation of the data, unstandardized observation units or population in comparison, validity of the dependent variable measures (hospital data), and reliability of the air-pollution measurements. The temporal nature of the present study, as opposed to geographic investigations, has helped reduce the possibility of methodological and statistical bias, such as seen in the standardization of observation units and population in a previous study (26). One way to overcome the problem of "overinterpretation" of statistical data is to use control diagnoses and subject them to the same analysis. Control diagnoses are intended to test possible "false-positive" associations, and in such time-series studies, such diagnoses would include those disorders which are unlikely to respond to variations in ambient air-pollutant levels. In this study, appendicitis and urinary tract infections were used. In contrast to asthma, only a weak association was found with ozone and hospitalization rates for these disorders ($P=0.05$), and this association was not observed in multiple-regression models. With regard to the validity of the dependent-variable measures, asthma hospitalization and ER were selected primarily due to their objectivity and sensitivity as indicators of "adverse" health effects. These "end-points" measurements generally reflect the extreme events of poorly managed asthma. These parameters are effective measure variables with which to elucidate the putative effects of environmental factors, as a visit to the hospital is a voluntary response by the affected individuals, based on their perceived need. Furthermore, misclassification due to other respiratory diseases such as bronchitis was excluded by differentiating the data by age groups. (Children under 2

years of age with acute bronchitis and bronchiolitis may be misclassified as having asthma, and they were thus excluded from the analysis.)

However, the reliability of air-pollutant measurements is a difficult issue to address. This is mainly due to methodological problems associated with precise quantification of air-pollutant levels and whether these measurements truly represent the actual exposure levels of the population in general. Although standardized international methods were used, there is no universal or ideal method which addresses these issues precisely. Nevertheless, the presence of random error in the measurements and the imprecision of the measurements biases the association (if any) only downward, thus underestimating the effects.

In the last two decades, the detrimental effects of air pollutants on asthma, even at concentrations below proposed air-quality standards, have also been observed in controlled laboratory studies, *in vivo* (38) and *in vitro* (39), and in epidemiologic settings (40). In our study, we found that ambient air-pollutant levels, in particular, those of SO_2 , TSP, and NO_2 , were consistently associated with ER visits for asthma in children. Lagged air-pollutant data, particularly those lagged by 1 day, were more strongly associated with childhood asthma ER visits. In fact, the stronger lagged data have been found in various other studies (19, 26) and have been attributed to either delayed onset of symptomatic responses or delay in seeking treatment. Our data were also controlled for meteorologic factors, and suggested that the combinations of higher temperature and NO_2 concentrations, and wind speed and SO_2 , are important predictors of ER visits for asthma in children. Inclusion of the daily total wind speed variable increased the magnitude and statistical significance of the SO_2 coefficient. A similar influence was seen with the inclusion of the average daily temperature variable in the regression model analyzing the effects of NO_2 . As the pollutant levels were generally below those of the WHO air-quality guidelines, these results support the premise that asthmatics are more susceptible to air pollutants than the general population, and that children are more susceptible than adolescents or young adults.

The effects of the air pollutants under study have, however, been well documented. SO_2 , for example, has been shown to increase bronchial constriction in asthmatic individuals (41). On the other hand, particulate matter has been associated with increased morbidity and mortality rate, and reduced pulmonary function (42). The present findings in this study are in agreement with various other studies whether in a controlled laboratory setting (11–13), or via clinical evaluations of asthmatics (15, 16). The epidemiolo-

gic influence of air pollution on asthma ER visits or hospitalization has also been reported by others (19, 36, 37). Schwartz et al. (19) found that daily counts of ER visits were significantly associated with PM₁₀ exposure on the previous day. They reported that although the daily PM₁₀ concentrations never exceeded 70% of the current EPA ambient air-quality standards, the associations consistently persisted. Similarly, the frequency of ER visits for asthma were found to be associated with ambient air quality in Birmingham, UK (36), Toronto (37), and Oulu, Finland (43), in all of which ambient air-pollutant levels below their respective air-quality guidelines were reported. These findings, together with those of this study, suggest that

exposure to increased levels of certain air pollutants, albeit within the “acceptable” range stipulated by current guidelines, may still help to trigger acute asthma.

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