

Decline in Peak Expiratory Flow According to Hourly Short-Term Concentration of Particulate Matter in Asthmatic Children

Hiroshi Odajima

Fukuoka National Hospital, Fukuoka, Japan

Shin Yamazaki

Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan

Hiroshi Nitta

Environmental Health Science Division, National Institute for Environmental Studies, Tsukuba, Japan

The aim was to investigate the effects of the 3-h mean concentration of suspended particulate matter (SPM) on peak expiratory flow (PEF) in asthmatic children. Subjects were 4- to 11-year-old boys and girls with asthma in Fukuoka, Japan. Daily measurements of PEF were made between April 2002 and March 2003. PEF was measured morning and evening. To assess the association between 3-h mean concentrations of SPM and morning PEF and evening PEF separately, we used generalized estimating equations. All models took into consideration seasonal effects: modified effects were examined using a two-level indicator variable for the warmer months (April through September) and the colder months (October through March). Among the 70 asthmatic children, 44 were boys. In warmer months, declines in morning PEF for 10 $\mu\text{g}/\text{m}^3$ differences in 3-h concentration of SPM measured at 2 a.m. to 5 a.m. of the same day and 11 p.m. to 2 a.m. and 8 p.m. to 11 p.m. of the previous day were -0.78 L/min (95% CI: -1.40 , -0.16), -0.61 L/min (-1.18 , -0.05) and -0.73 L/min (-1.32 , -0.15), respectively. Results were robust even after adjustment for other air pollutants. We also found that declines in evening PEF were weakly associated with increases in 3-h concentrations of SPM in warmer months, but the associations were not statistically significant. In colder months we did not find any robust association between SPM and morning/evening PEF. In conclusion, an increased 3-h concentration of SPM is associated with declines in PEF in warmer months.

INTRODUCTION

Many epidemiological studies across varied environmental conditions have indicated an acute impact of ambient air pollution on lung function (USEPA, 2004; Ward and Ayres, 2004). Children are considered to be more sensitive to air pollution than adults (Pope and Dockery, 1992). Environmental causes of asthma are usually related to climatic conditions that promote the

appreciable concentration of atmospheric pollutants and antigens. Under these circumstances, although those in the general population can develop respiratory symptoms, persons with asthma and other respiratory diseases tend to be more severely affected. For example, the sensitivity to ambient particulate matter (PM) differs between asthmatic and non-asthmatic children. Results of examination of the association between daily concentrations of PM and peak expiratory flow (PEF) in asthmatic children tended to show decrements with increasing concentrations of PM (USEPA, 2004). On the other hand, results of studies that examined the association between daily concentrations of PM and PEF in non-asthmatic children were inconsistent, with fewer studies reporting results similar to those for asthmatic children (USEPA, 2004). Given the conclusion that asthmatic children were more sensitive to PM than non-asthmatic children, the effects of transiently high concentrations of PM on lung function remain unclear. Nemmar et al. (2002) found that

Received 27 February 2008; accepted 30 June 2008.

This study was funded by the Japanese Ministry of the Environment. The work has not been published before, is not being considered for publication elsewhere, and has been read and approved by all of the authors.

Address correspondence to Shin Yamazaki, Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Yoshida-konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. E-mail address: syam@pbh.med.kyoto-u.ac.jp

inhaled nanoparticles could be detected in blood as early as 1 min after inhalation and could remain at their maximum level in blood for up to 60 min, concluding that inhaled particles pass rapidly into the systemic circulation. On the other hand, Mills et al. (2006) found that the majority of inhaled nanoparticles remained within the lung for up to 6 h after inhalation. Whether inhaled nanoparticles can readily access the circulation in humans is controversial and is the subject of intense research debate (Mills et al., 2007). However, evidence of acute health effects of air pollutants has been shown (Salvi et al., 1999; Scapellato et al., 2007). Transiently high concentrations of PM have been observed from hourly data, but have not been observed from daily data (Shoji and Tsukatani, 1973). To look for links between hourly short-term air pollution and pulmonary function, we collected and analyzed hourly air-pollution data and records of lung function testing noted in a health diary among asthmatic children.

MATERIALS AND METHODS

Subjects and PEF Measurements

The study was conducted in Fukuoka, which is designated as a major city by the government of Japan. Subjects were 4 to 11 year olds who were diagnosed as having asthma by a pediatrician and who received treatment at Fukuoka National Hospital. They participated in swimming exercise sessions which were conducted by the hospital to improve the health of asthmatic children. Sessions were held in an indoor swimming pool attached to the hospital. Table 1 summarizes the characteristics of the 70 asthmatic children (44 boys, 36 girls; mean age 7 y, range 4 to 11 y), with a mean height in April 2002 of 118 cm (range: 100 to 139 cm). With respect to medication, 34 children (49%) used medication of any kind for >90% of the days for which the diary was completed and 19 (27%) used medication of any kind for ≤10% of the days for which the diary was completed. With respect to the severity of asthma, 7 (10%) experienced attacks >10% of the days for which the diary was completed. Daily measurements of PEF were made between April 1, 2002 and March 31, 2003. PEF was measured with a MiniWrite peak flow meter (Clement Clark International Limited, Essex, UK) at the child's home twice a day, once before breakfast (hereafter, morning measurement) and once before evening bedtime (hereafter, evening measurement). Both PEF measurements were done before any medication was taken. Participants and their parents were instructed on how to perform the PEF measurements. Each test consisted of three maneuvers, and participants were instructed to enter the largest PEF readings in a diary noting whether the measurement was a morning or evening measurement. The exact time of the measurements was not recorded.

Air Pollutants

Suspended particulate matter (SPM) is defined under the Japanese Air Quality Standard as any particle collected with an upper 100% cut-off point of an aerodynamic diameter of

TABLE 1
Demographic characteristics of subjects

	Subject (N = 70)	
Sex		
Boy	44	63%
Girl	26	37%
Age (y)		
4 to 5	26	37%
6 to 7	23	33%
8 to 9	14	20%
10 to 11	7	10%
Height (cm) ^a		
< 110	17	24%
110 to 119	22	31%
120 to 129	18	26%
130 to 140	13	19%
Frequency of medication (%) ^b		
≤ 10	19	27%
11 to 50	9	13%
51 to 90	8	11%
91 to 100	34	49%
Frequency of asthma attack (%) ^c		
0	24	34%
0 < to 1	15	22%
1 < to 10	24	34%
10 < to 100	7	10%
Ethnicity		
Japanese	70	100%

^a Range: 99.5 cm to 139.2 cm.

^b Percentage of any days subjects took medication among measured days.

^c Percentage of asthma attack days among measured days.

10 μ m. The 50% cut-off diameter for SPM is assumed to be approximately 7 μ m; therefore, we referred to this variable as PM₇ (USEPA, 2004). In Japan, hourly and 24 h (0 a.m. to 0 a.m.) mean concentrations of SPM are measured and recorded at government managed monitoring stations. We used data from the monitoring station nearest to the hospital in Minami-Ward, Fukuoka, Japan. The monitoring station was located on a residential street. Hourly concentrations of SPM, nitrogen dioxide (NO₂), and ozone (O₃) from April 2002 through March 2003 were used. For this study, the 3-h mean concentrations of air pollutants were calculated. Hourly temperature data for the area were obtained from the Japan Meteorological Agency.

Statistical Methods

To examine the association between 3-h mean concentrations of air pollutants and PEF, we used generalized estimating equations (GEE) (Liang and Zenger, 1986). We examined 3-h mean concentrations because we could not obtain data on the exact

time when PEF was measured, and we thought that children would awaken between 5 a.m. and 8 a.m. and go to bed between 7 p.m. and 10 p.m. These models correct for repeated measurements in response data. Standard error of the regression estimate is therefore adjusted for the fact that responses from any one subject are likely to be correlated. This method generates robust estimators regardless of the specifications of the covariance matrix. As autocorrelation is included in the covariance, coefficients can be interpreted as usual. We estimated the difference in PEF according to each $10 \mu\text{g}/\text{m}^3$ increment or decrement in SPM adjusted for sex, age at baseline survey, height at baseline survey, growth index and temperature (single-pollutant model). With respect to the growth index, it was defined not only as the growth of children from April 2002 to the month when PEF was measured, but also as a seasonal index, because it was a categorical variable that denoted the number of months passed from April 2002 to the month when PEF was measured. We also estimated the difference in PEF according to each $10 \mu\text{g}/\text{m}^3$ difference in SPM adjusted for 10 ppb differences in NO_2 and 10 ppb differences in O_3 and adjustment for the variables described above (multi-pollutant model). Morning and evening PEF values were used as dependent variables separately because of adjustments for the circadian rhythm. With respect to the temperature as an adjustment variable, it was measured at 8 a.m. of the same day as the morning PEF examination. For the evening PEF test, the temperature at 10 p.m. of the same day was used as an adjustment variable. For the morning PEF examination, the assessed time periods for the 3-h mean concentration of air pollutants were 5 a.m. to 8 a.m. on the same day as the examination and 2 a.m. to 5 a.m., 11 p.m. to 2 a.m., and 8 p.m. to 11 p.m. on the previous day. With respect to the evening PEF examination, the assessed time periods for 3-h mean concentration of air pollutants were 7 p.m. to 10 p.m., 4 p.m. to 7 p.m., 1 p.m. to 4 p.m., and 10 a.m. to 1 p.m. on the same day as the measurement.

We also examined the association between the 24-h mean concentration of air pollutants and PEF. With regard to the morning PEF, the hourly data were summarized over a 24-h period (8 a.m. to 8 a.m.) while those for the evening PEF test were from 10 p.m. to 10 p.m. All models took into consideration the effects of the season: modified effects were examined using a two-level indicator variable for the warmer months (April through September) and the colder months (October through March). In addition, we examined details of the seasonally modified effects using a 6-level indicator variable for April through May, June through July, August through September, October through November, December through January, and February through March. The GENMOD procedures of SAS release 9.1 (SAS Institute, Inc., Cary, NC) were used to perform the GEE. All tests were 2-tailed, and alpha was set at 0.05.

RESULTS

Among the 70 asthmatic children there were 16,158 PEF measurements in the morning and 15,240 in the evening, with

an average of 230 per child morning measurements and 218 per child evening measurements. Figure 1 shows the mean PEF and the minimum and the maximum PEF for each child, ordered by age. The 3-h mean concentrations of air pollutants are shown in Table 2. Table 3 shows the correlation coefficient of hourly measured concentrations at 8 a.m. and 10 p.m. and the correlation coefficient of 24-h measured concentrations for the warmer months and colder months from April 2002 through March 2003.

Association Between 3-h Concentration of SPM and PEF

Table 4 shows the association between air pollutants and morning and evening PEF measurements separately for warmer and colder months. In the single-pollutant model, a decline in morning PEF was associated with the 3-h mean concentration of SPM during the period from 5 a.m. to 8 a.m. We also found that a decline in morning PEF was associated with the 3-h mean concentration of SPM measured in the periods of 2 a.m. to 5 a.m., 11 p.m. to 2 a.m., and 8 p.m. to 11 p.m. Some of the significant associations remained even after adjustment for other air pollutants using the multi-pollutant model (2 a.m. to 5 a.m., 11 p.m. to 2 a.m., and 8 p.m. to 11 p.m.). A decline in evening PEF was weakly associated with the 3-h mean concentration of SPM in warmer months, but the associations were not statistically significant with both the single- and multi-pollutant model.

Table 5 shows the association during the colder months between air pollutants and morning and evening PEF measurements separately, but no significant associations were shown with both the single- and multi-pollutant model. The effect estimates were even in the opposite direction.

Figure 2 shows the association between air pollutants and morning and evening PEF measurements separately for specific seasons using a multi-pollutant model. A significant association was found between morning PEF and SPM measured in June through July.

Other than for SPM, we did not find any associations between 3-h O_3 or NO_2 and morning/evening PEF in warmer/colder months. Temperature was associated with an increase in PEF in warmer months in the morning (0.73 L/min (95% confidence interval (CI): 0.18–1.29) increment for 1°C increment) and in the evening (0.67 L/min (95% CI: 0.13–1.21) increment for 1°C increment), but not in colder months.

Association Between 24-h Concentration of SPM and PEF

For warmer months we observed an association between the 24-h concentration of SPM and morning PEF with the single-pollutant model. The difference in morning PEF according to $10 \mu\text{g}/\text{m}^3$ increments in SPM was -0.818 L/min (95% CI: -1.474 , -0.162). However, the statistical significance disappeared when we examined the association using the multi-pollutant model. We did not find any association between air pollutants and evening PEF in warmer months. In colder months we also did not find any association between the 24-h concentration of SPM and morning/evening PEF with the single-/multi-pollutant model.

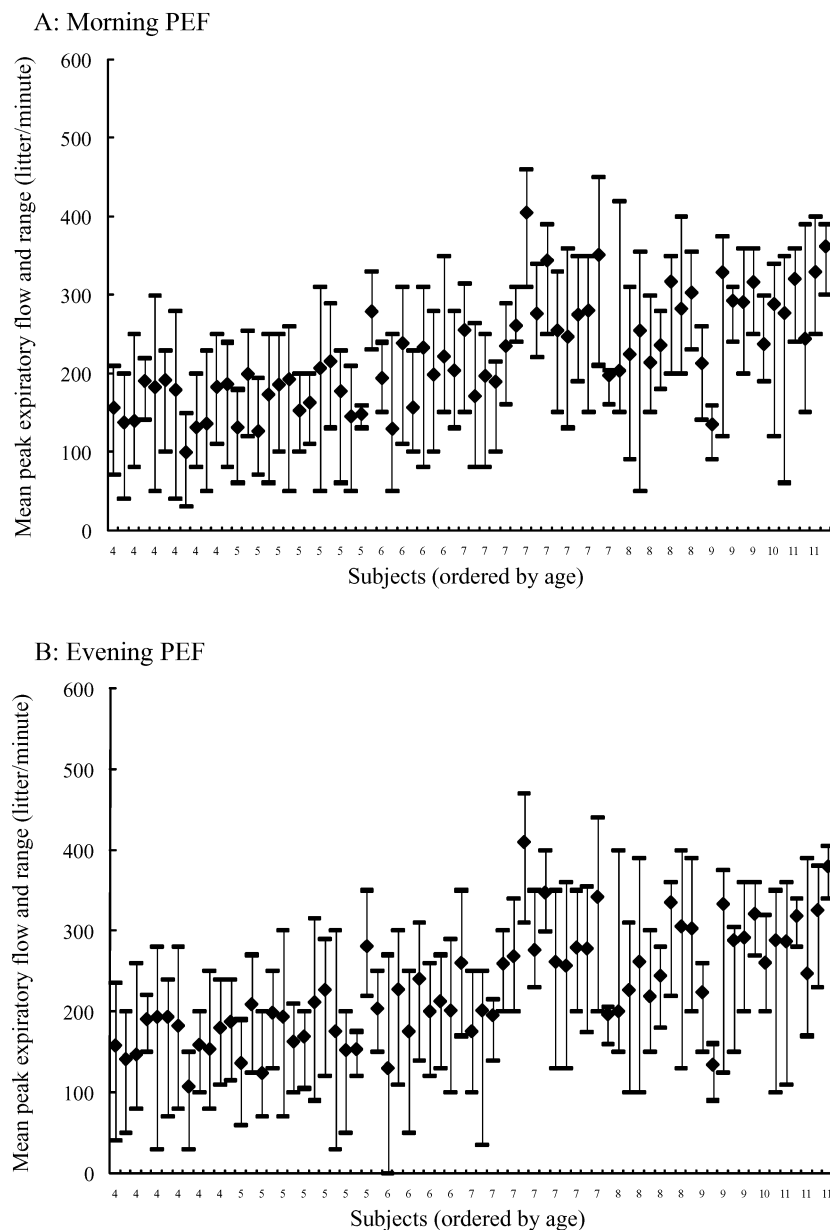


FIG. 1. Mean peak expiratory flow (PEF) and minimum and maximum PEF in each child in order of age. (A) morning PEF, (B) evening PEF.

Other than SPM, we did not find any association between 24-h O_3 or NO_2 and morning/evening PEF in warmer/colder months.

DISCUSSION

In this study, declines in morning PEF were associated with increasing 3-h concentrations of SPM in warmer months, a result that persisted even after adjustment for other air pollutants. We also found that declines in evening PEF were weakly associated with increasing 3-h concentrations of SPM in warmer months, but the associations were not statistically significant. We did not find any robust associations between SPM and both

morning and evening PEF in colder months, and the effect estimates were even in the opposite direction. With respect to the 24-h mean concentration of SPM, we found a significant association between SPM and morning PEF in warmer months with the single-pollutant model. However, when we analyzed the association using the multi-pollutant model, the significant association disappeared.

There is a question as to why the association between SPM and PEF was found only in warmer months. Previous studies have not resolved this question. For example, Roemer et al. (1993) found an association between the daily concentration of

TABLE 2
Summary statistics of 3-h mean concentration of air pollutants

	Days for measurement	Mean	Standard deviation	Minimum	Maximum
Warmer months ^a					
5 a.m. to 8 a.m.					
SPM ($\mu\text{g}/\text{m}^3$)	130	40.7	23.3	11.0	126.0
NO ₂ (ppb)	130	15.2	7.2	1.3	44.7
O ₃ (ppb)	130	17.7	12.4	0.3	52.3
7 p.m. to 10 p.m.					
SPM ($\mu\text{g}/\text{m}^3$)	131	41.5	28.2	8.3	191.3
NO ₂ (ppb)	131	20.0	9.4	3.0	51.3
O ₃ (ppb)	131	28.1	15.5	1.3	71.3
Colder months ^a					
5 a.m. to 8 a.m.					
SPM ($\mu\text{g}/\text{m}^3$)	170	32.6	19.9	9.0	160.3
NO ₂ (ppb)	170	20.5	8.8	1.3	44.0
O ₃ (ppb)	170	17.5	14.3	0.6	48.7
7 p.m. to 10 p.m.					
SPM ($\mu\text{g}/\text{m}^3$)	170	34.7	18.8	10.3	131.0
NO ₂ (ppb)	170	28.0	11.0	3.6	49.0
O ₃ (ppb)	170	19.4	14.6	1.0	60.0

SPM: suspended particulate matter (considered as PM₇); NO₂: nitrogen dioxide; O₃: ozone.

^a Warmer months: April to September; colder months: October to March.

PM₁₀ and PEF in children with chronic respiratory symptoms in winter in the Netherlands. Neas et al. (1996) found a weak association in the summer in the USA between the 12-h day-time concentration of PM_{2.5} and evening PEF of children who

were not being medicated for asthma. Tiittanen et al. (1999) found an association between the daily concentration of PM and PEF in children with chronic respiratory symptoms in March through April in Finland. On the other hand, Just et al. (2002) found no association between daily concentrations of PM and PEF in asthmatic children in April through July in Paris. There are some differences between these previous studies and the present study, such as ethnicity, concentration of air pollutants, correlation coefficients for air pollutants, and perhaps even composition of particulate matter. Moreover, the difference between indoor and outdoor pollution in winter might be larger than in summer because of indoor heating. That is, potential explanations could include better exposure characterization by central site monitoring because children spend more time outdoors in warmer months than in colder months, and the indoor/outdoor relationship may be stronger in warmer months than in colder months (Koenig et al., 2005; Katsouyanni et al., 2001). These factors may have obscured a possible association of PEF with SPM in colder months in this study.

A second question is why the association between SPM and PEF was found only in the morning, but not in the evening. Many studies have suggested that the concentration of outdoor particulate air pollution is associated with PEF; however, few have discussed the inconsistency between morning and evening PEF. For example, Roemer et al. (1993) examined daily concentrations of PM₁₀ and PEF in children with chronic respiratory symptoms in winter and found that the difference in morning PEF for 10 $\mu\text{g}/\text{m}^3$ differences in PM₁₀ was -0.41 L/min ($p < 0.05$) and the

TABLE 3

Coefficients of correlation between hourly measured and 24-h concentration of SPM, NO₂, and O₃

	Correlation coefficient	
	Warmer months ^a	Colder months ^a
8 a.m.		
SPM-O ₃	0.092	-0.213
SPM-NO ₂	0.316	0.373
O ₃ -NO ₂	-0.253	-0.692
10 p.m.		
SPM-O ₃	0.203	-0.098
SPM-NO ₂	0.257	0.345
O ₃ -NO ₂	-0.297	-0.782
24-h mean		
SPM-O ₃	0.32	-0.02
SPM-NO ₂	0.30	0.45
O ₃ -NO ₂	0.08	-0.72

SPM: suspended particulate matter (considered as PM₇); NO₂: nitrogen dioxide; O₃: ozone.

^a Warmer months, April to September; Colder months, October to March.

TABLE 4
Change of morning and evening PEF according to unit change in 3-h concentration of air pollutants in April through September (L/min)

Time periods	Multi-pollutant model ^a				Single-pollutant model ^b		
	SPM Change e ^c	(95% CI)	O ₃ Change ^c	95% CI	NO ₂ Change ^c	(95% CI)	SPM Change ^c (95% CI)
For examining morning PEF							
5 a.m.–8 a.m.	–0.600	(–1.228, 0.028)	–0.575	(–1.569, 0.419)	–0.300	(–2.246, 1.645)	–0.670 (–1.236, –0.104)*
2 a.m.–5 a.m.	–0.780	(–1.399, –0.161)*	–0.052	(–0.997, 0.893)	0.265	(–1.354, 1.885)	–0.761 (–1.328, –0.194)*
11 p.m. ^d –2 a.m.	–0.612	(–1.180, –0.045)*	–0.305	(–1.269, 0.658)	–0.187	(–1.447, 1.073)	–0.661 (–1.159, –0.163)*
8 p.m. ^d –11 p.m. ^d	–0.732	(–1.318, –0.145)*	–0.416	(–1.283, 0.451)	0.432	(–0.689, 1.553)	–0.714 (–1.212, –0.215)*
For examining evening PEF							
7 p.m.–10 p.m.	–0.449	(–1.071, 0.174)	–0.220	(–1.171, 0.731)	0.296	(–0.806, 1.397)	–0.449 (–0.956, 0.058)
4 p.m.–7 p.m.	–0.434	(–1.122, 0.254)	–0.118	(–0.809, 0.574)	0.220	(–0.818, 1.258)	–0.449 (–1.029, 0.131)
1 p.m.–4 p.m.	–0.415	(–1.015, 0.184)	–0.186	(–0.888, 0.516)	0.438	(–0.568, 1.444)	–0.414 (–0.943, 0.115)
10 a.m.–1 p.m.	–0.522	(–1.199, 0.155)	–0.315	(–1.123, 0.493)	0.536	(–0.546, 1.617)	–0.486 (–1.051, 0.079)

SPM: suspended particulate matter (considered as PM₁₀); NO₂: nitrogen dioxide; O₃: ozone; PEF: peak expiratory flow.

* P < 0.05.

^a Independent variables in this Model were SPM, O₃, NO₂, age, sex, height, growth index, and temperature.

^b Independent variables in this Model were SPM, age, sex, height, growth index, and temperature.

^c Change of PEF for 10 µg/m³ increase of SPM, and change of PEF for 10 ppb increase of NO₂ / O₃.

^d Day before PEF measurement.

TABLE 5
Change in morning and evening PEF according to unit change in 3-h concentration of air pollutants in October through March (L/min)

Time periods	Multi-pollutant model ^a				Single-pollutant model ^b		
	SPM Change ^c	(95% CI)	O ₃ Change ^c	95% CI	NO ₂ Change ^c	(95% CI)	SPM Change ^c (95% CI)
For examining morning PEF							
5 a.m.–8 a.m.	0.290	(–0.279, 0.859)	–0.415	(–1.568, 0.738)	–0.319	(–2.269, 1.631)	0.308 (–0.189, 0.805)
2 a.m.–5 a.m.	0.431	(–0.173, 1.036)	–0.046	(–1.245, 1.153)	0.262	(–1.777, 2.300)	0.485 (–0.026, 0.996)
11 p.m. ^d –2 a.m.	0.304	(–0.311, 0.919)	0.004	(–1.265, 1.273)	0.609	(–1.132, 2.350)	0.486 (–0.049, 1.022)
8 p.m. ^d –11 p.m. ^d	0.010	(–0.523, 0.543)	–0.470	(–2.017, 1.077)	0.155	(–1.545, 1.856)	0.100 (–0.414, 0.613)
For examining evening PEF							
7 p.m.–10 p.m.	0.059	(–0.397, 0.515)	–0.656	(–2.394, 1.083)	–0.415	(–2.444, 1.613)	0.071 (–0.388, 0.529)
4 p.m.–7 p.m.	0.360	(–0.093, 0.812)	0.046	(–1.140, 1.232)	–0.144	(–1.490, 1.202)	0.318 (–0.123, 0.758)
1 p.m.–4 p.m.	0.357	(–0.157, 0.871)	0.164	(–1.038, 1.365)	–0.181	(–1.821, 1.459)	0.317 (–0.171, 0.804)
10 a.m.–1 p.m.	0.169	(–0.394, 0.731)	0.665	(–0.613, 1.942)	0.194	(–1.503, 1.890)	0.112 (–0.412, 0.636)

SPM: suspended particulate matter (considered as PM₁₀); NO₂: nitrogen dioxide; O₃: ozone; PEF: peak expiratory flow.
*P < 0.05.

^a Independent variables in this Model were SPM, O₃, NO₂, age, sex, height, growth index, and temperature.

^b Independent variables in this Model were SPM, age, sex, height, growth index, and temperature.

^c Change in PEF for 10 µg/m³ increase of SPM, and change of PEF for 10 ppb increase of NO₂ / O₃.

^d Day before PEF measurement.

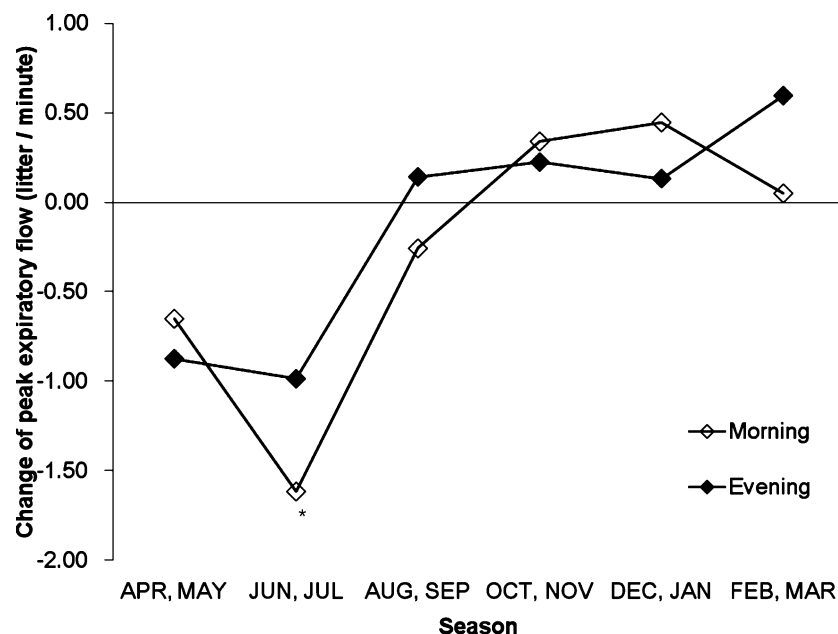


FIG. 2. Change in morning and evening PEF according to increase in 3-h concentration of SPM in units of $10 \mu\text{g}/\text{m}^3$. Independent variables in this Model were SPM, O_3 , NO_2 , age, sex, height, growth index, and temperature. * $P < 0.05$.

difference in evening PEF for $10 \mu\text{g}/\text{m}^3$ differences in PM_{10} was -0.28 L/min “(not significant (NS))”. Romieu et al. (1997) examined the daily concentration of PM_{10} and PEF in children with mild asthma in April through July and November through February in Mexico City. The differences in morning and evening PEF for $20 \mu\text{g}/\text{m}^3$ differences in PM_{10} were -1.37 L/min (NS) and -0.53 L/min (NS), respectively. Pekkanen et al. (1997) examined the daily concentration of PM_{10} and PEF in children with asthmatic symptoms from February through April in Finland. The difference in morning PEF for the inter quartile range of PM_{10} on the same day was -0.73 L/min (NS) and that of the evening PEF was -0.09 L/min (NS). In examination of daily concentrations of PM and PEF in children with chronic respiratory symptoms in March through April, Tittanen et al. (1999) found that the difference in morning PEF for the inter quartile range of PM_{10} on the previous day was -1.01 L/min (NS) and was -0.33 L/min for evening PEF (NS). In addition, they also showed that the difference in morning PEF for the inter quartile range of $\text{PM}_{2.5}$ on the previous day was -1.06 L/min ($p < 0.05$) and the difference in evening PEF for the inter quartile range of PM_{10} on the previous day was -0.43 L/min (NS). On the other hand, inconsistent results were shown in other studies. For example, Roemer et al. (1998) examined daily concentrations of PM_{10} and PEF in children with chronic respiratory symptoms in winter in 14 European centers, and showed that the difference in morning PEF for $10 \mu\text{g}/\text{m}^3$ differences in PM_{10} was 0.01 L/min (NS) and that of evening PEF was -0.06 L/min ($p < 0.05$). They speculated that stratifications between air pollution and morning delta-PEF did not have clear patterns, which might be explained by the timing of the morning PEF measurement.

These measurements were made just after the child arose, which meant that a long period of indoor exposure preceded the measurement. This might have obscured a possible association of morning delta-PEF with outdoor air pollution.

In the present Japanese study we considered several factors in explaining the results. First, the time period for morning PEF measurement might have been narrower than that for evening PEF measurement because the time before arising and leaving for school was shorter than the time during which the evening PEF could be measured. Second, evening PEF measurements might have been affected by factors other than air pollution. Exercise-induced bronchoconstriction (EIB) would affect evening PEF, because a child's activity during the day could affect the severity of EIB. Third, although subjects were instructed to measure their PEF before medication, we did not know if they were compliant with their medications after the PEF measurement. Thus, the evening PEF might be affected by whether or not they adhered to the morning treatment regimen. All of these points may have obscured a possible association of evening delta-PEF with SPM.

Clinically Significant Size of Effect

In this study, the size of the change of PEF was about -0.7 L/min for $10 \mu\text{g}/\text{m}^3$ differences in SPM. Ward and Ayres (2004) reviewed particulate air pollution and panel studies in children, and found that a wide range of results was observed (mean estimates from -1.6 to 0.1 L/min) for $10 \mu\text{g}/\text{m}^3$ differences in PM_{10} among the 13 studies that were reviewed. From the clinical point of view, the size of the effect was very small. The small PEF

decrements may have been mitigated by increased bronchodilator use. However, Hoek et al. (1998) showed that these small changes can be accompanied by sizable differences in the percentage of subjects showing clinically meaningful decrements of PEF; moreover, because so many people are exposed to air pollutants, a small difference in PEF is very important evidence in considering issues of public health.

Characteristics of Asthmatic Children

Since the subjects of this study were asthmatic children, they had practice in using a PEF meter and knew how to correctly measure their own pulmonary function. Moreover, these children participated in swimming exercise sessions. Swimming is considered to be effective training for asthmatic children because an asthma attack in relation to physical exercise would be less likely to occur because of higher temperatures and higher relative humidity than with other types of exercise. Because these study subjects trained their lung function and physical function, their lung function might be stronger than in other asthmatic children. Therefore, the association between the concentration of SPM and PEF might have been stronger if the study subjects were asthmatic children who were not undergoing training to improve or maintain pulmonary function.

Limitations

Results of this study should be viewed cautiously for five reasons. First, we did not obtain data on the exact time when PEF was measured. Therefore, we could not determine the actual time lag between the time when air pollutants were assessed and the time when PEF was measured. This may have obscured a possible association of PEF with SPM for the reason of non-differential misclassification. Second, we could not measure the effect of indoor space heaters on the concentration of air pollutants. In Japan, indoor space heaters are usually used in the winter, especially December through February. Therefore, we believe that, at least, the effect of indoor space heaters on the association between the concentration of SPM and PEF in warmer months was small. Third, we did not have detailed data on what medications were used, data on pollen, and data on influenza. We thought that these effects on association would be a non-differential misclassification and that the estimated association in this study would be weakened because these factors might not be associated with the hourly concentration of air pollutants. Fourth, ambient concentrations of air pollution might act as surrogate measures of exposure to other agents or to specific pollution sources that are in fact responsible for the observed association between SPM and PEF. Fifth, in the first analysis in which we used a subgroup analysis to reveal seasonally modified effects using a two-level indicator, results of which are shown in Table 4 and Table 5, we only estimated the common associations between air pollutants and PEF in each of two 6-month periods representing subgroups, which were the warmer or colder months, respectively. Moreover, we adjusted for months as the growth index, which was a categorical variable denoting the

number of months passed from April 2002 to the month when PEF was measured; we could not distinguish between the growth effect and seasonal effect in the regression analysis. The results should be viewed cautiously for these reasons.

CONCLUSION

We conclude that increased 3-h concentration of SPM is associated with declines in PEF in warmer months, especially in morning measurements. Further studies are needed to clarify the association in different populations to explain the reason for the seasonal inconsistency.

REFERENCES

- Gold, D.R., Litonjua, A., Schwartz, J., Lovett, E., Larson, A., Nearing, B., Allen, G., Verrier, M., Cherry, R., and Verrier, R., 2000. Ambient pollution and heart rate variability. *Circulation* 101:1267–1273.
- Hoek, G., Dockery, D.W., Pope, A., Neas, L., Roemer, W., and Brunekreef, B., 1998. Association between PM₁₀ and decrements in peak expiratory flow rates in children: reanalysis of data from five panel studies. *Eur. Respir. J.* 11:1307–1311.
- Just, J., Segala, C., Sahraoui, F., Priol, G., Grimfeld, A., and Neukirch, F. 2002. Short-term health effects of particulate and photochemical air pollution in asthmatic children. *Eur. Respir. J.* 20:899–906.
- Katsouyanni, K., Touloumi, G., Samoli, E., Gryparis, A., Le, Tertre A., Monopolis, Y., Rossi, G., Zmirou, D., Ballester, F., Boumghar, A., Anderson, H.R., Wojtyniak, B., Paldy, A., Braunstein, R., Pekkanen, J., Schindler, C., and Schwartz, J., 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* 12:521–531.
- Koenig, J.Q., Mar, T.F., Allen, R.W., Jansen, K., Lumley, T., Sullivan, J.H., Trenga, C.A., Larson, T., and Liu, L.J., 2005. Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. *Environ. Health Perspect.* 113:499–503.
- Liang, K.Y., and Zenger, S.L., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73:13–22.
- Mills, N.L., Amin, N., Robinson, S.D., Anand, A., Davies, J., Patel, D., de la Fuente, J.M., Cassee, F.R., Boon, N.A., Macnee, W., Millar, A.M., Donaldson, K., and Newby, D.E., 2006. Do inhaled carbon nanoparticles translocate directly into the circulation in humans? *Am. J. Respir. Crit. Care Med.* 173:426–431.
- Mills, N.L., Törnqvist, H., Robinson, S.D., Gonzalez, M.C., Söderberg, S., Sandström, T., Blomberg, A., Newby, D.E., and Donaldson, K., 2007. Air pollution and atherothrombosis. *Inhal. Toxicol.* 19:S81–89 Review.
- Neas, L.M., Dockery, D.W., Burge, H., Koutrakis, P., and Speizer, F.E., 1996. Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. *Am. J. Epidemiol.* 143:797–807.
- Nemmar, A., Hoet, P.H.M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbilloen, H., Mortelmans, L., and Nemery, B., 2002. Passage of inhaled particles into blood circulation in humans. *Circulation* 105:411–414.
- Pekkanen, J., Timonen, K.L., Ruuskanen, J., Reponen, A., and Mirmé, A., 1997. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. *Environ. Res.* 74:24–33.

- Pope, C.A., III, and Dockery, D.W., 1992. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 145:1123–1128.
- Roemer, W., Hoek, G., and Brunekreef, B., 1993. Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. *Am. Rev. Respir. Dis.* 147:118–124.
- Roemer, W., Hoek, G., Brunekreef, B., Haluszka, J., Kalandidi, A., and Pekkanen, J., 1998. Daily variations in air pollution and respiratory health in a multicentre study: The PEACE project. Pollution Effects on Asthmatic Children in Europe. *Eur. Respir. J.* 12:1354–1361.
- Romieu, I., Meneses, F., Ruiz, S., Huerta, J., Sienra, J.J., White, M., Etzel, R., and Hernandez, M., 1997. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. *Arch. Environ. Health* 52:368–376.
- Salvi, S., Blomberg, A., Rudell, B., Kelly, F., Sandstrom, T., Holgate, S.T., and Frew, A., 1999. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am. J. Respir. Crit. Care Med.* 159:702–709.
- Sacpellato, M.L., and Lotti, M., 2007. Short-term effects of particulate matter: An inflammatory mechanism? *Crit. Rev. Toxicol.* 37:461–487. Review.
- Shoji, H., and Tsukatani, T., 1973. Statistical model of air pollutant concentration and its application to the air quality standards. *Atmos. Environ.* 7:485–501.
- Tiittanen, P., Timonen, K.L., Ruuskanen, J., Mirme, A., and Pekkanen, J., 1999. Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. *Eur. Respir. J.* 13:266–273.
- USEPA 2004. *Air Quality Criteria for Particulate Matter*. US Environmental Protection Agency. Research Triangle Park, NC. Available from <http://cfpub2.epa.gov/ncea/cfm/recorddisplay.cfm?deid=87903> (accessed 28 January 2008).
- Ward, D.J., and Ayres, J.G., 2004. Particulate air pollution and panel studies in children: a systematic review. *Occup. Environ. Med.* 61:13. Review.