

A Longitudinal Study of Ambient Air Pollutants and the Lung Peak Expiratory Flow Rates among Asthmatic Children in Hungary

MARY M AGÓCS,* MARY C WHITE,* GABRIELLA URSICZ,** DAVID R OLSON* AND ADRIEN VÁMOS†

Agócs M M (Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC), CDC-Washington DC Office, 200 Independence Ave SW, HHH Building, Room 714 B, Washington DC 20201, USA), White M C, Ursicz G, Olson D R and Vámos A. A longitudinal study of ambient air pollutants and the lung peak expiratory flow rates among asthmatic children in Hungary. *International Journal of Epidemiology* 1997; **26**: 1272–1280.

Background. We conducted this study in Budapest, Hungary, to better characterize the effects of exposure to ambient air pollutants on the lung function of asthmatic children.

Methods. The 60 study participants were 9–14 years old, had physician-diagnosed asthma, and were symptomatic during the previous year. Their ambient air pollutant exposures to total suspended particulates (TSP) and sulphur dioxide (SO₂) were estimated from measurements made at the air monitor nearest their residence. We used analysis of variance and a fixed-effects model to assess the impact of the pollutants upon their morning and evening peak expiratory flow rates (PEFR) from 13 September to 5 December 1993.

Results. Total suspended particulates and SO₂ concentrations exceeded World Health Organization guideline limits on several days. Pollutant concentrations and PEFR increased during the study period. After adjusting for temperature, humidity, weekend/weekday, and the time trend, we found no consistent association between air pollutant concentrations and PEFR.

Conclusions. Fall to winter seasonal changes had a large influence on PEFR and may have overshadowed the effects of the air pollutants during the study period. Seasonal influences should be carefully considered when planning future studies.

Keywords: asthma, children, peak expiratory flow rate, air pollutants, sulphur dioxide, particulate matter

Asthma is a chronic lung disease that affects people in all age groups but disproportionately affects the health of children. In several countries, the prevalence and hospitalization rates for asthma are higher among children than adults.^{1–8} Furthermore, asthma is one of the most common chronic diseases of childhood in the US and many other countries.⁹ The onset of asthma also usually occurs in the very young; in the US, most children with asthma have their asthma diagnosed before they are 3 years old.¹⁰

Children with asthma are regarded as being particularly sensitive to the effects of air pollutants.¹¹

People with asthma may experience decreased pulmonary function, increased respiratory symptoms, and increased frequency of respiratory illnesses after exposure to particulate matter and sulphur dioxide (SO₂) pollution.^{11–15} Particulate matter can consist of carbon, hydrocarbons, and dust, which are generated during fuel combustion by industry, vehicular traffic, and heating systems or by natural sources such as dust storms.^{11,16} Sulphur dioxide is produced by burning or processing sulphur-containing fossil fuels and ores such as coal. Particulate matter and SO₂ are often produced by the same sources in urban, industrialized areas and can combine together to form acid aerosols that may also irritate the respiratory system.

Air pollution is an important environmental health problem in the Republic of Hungary.¹⁷ Serious levels of SO₂, nitrogen oxides, and particulate matter reportedly cover 11% of the country's territory, where 44% of the population resides.¹⁷ Particulate matter concentrations

* Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC), CDC-Washington DC Office, 200 Independence Ave SW, HHH Building, Room 714 B, Washington DC 20201, USA.

** Department of Child and Adolescent Health, † Department of Community and Environmental Hygiene, Budapest Institute of Public Health and Medical Officer Service.

in Budapest have frequently exceeded recommended health limits.¹⁸ Industrial activity occurs throughout the city. Each year on 15 October, centrally operated heating systems begin to provide heat to large portions of the city. Many residents also use indoor heating systems fuelled by gas and electricity, and a few use coal or wood.

Asthma is considered an important health problem in Hungary, which has ranked highly among industrialized nations in the incidence of deaths due to asthma or bronchitis.¹⁹ The problem seems to be getting worse: the reported prevalence of childhood asthma in Hungary has increased during the past several years (personal communication: Peter Rudnai, MD, Head, Department of Community Hygiene, Hungarian National Institute of Hygiene).

We conducted this study to determine whether increased ambient air concentrations of total suspended particulates (TSP) and SO₂ during the heating season were associated with decreased lung peak expiratory flow rates (PEFR) among a group of children with asthma in Budapest, Hungary. The 12-week study period included time periods before and after the 15 October onset of the heating season. We hypothesized that exposure to increased concentrations of either TSP or SO₂ during each of the previous 4 days or during the past week would be associated with a significant decrease in the children's daily PEFR. We also hypothesized that these pollutants had a combined effect over the past 4 days in decreasing the children's daily PEFR.

MATERIALS AND METHODS

Study Participants

Budapest has about 2.1 million residents and 22 administrative districts. Each administrative district within the city has maintained a respiratory disease registry. Asthmatic children were identified from the registry of District V, which was selected on the basis of convenience, and from the records of the three largest paediatric pulmonary treatment facilities in the city. In 1993, the Institute of Public Health and Medical Officer Service of Budapest mailed letters to the parents of all 296 children, then 9–14 years of age, who were identified as having asthma. The letters invited parents and children to attend an introductory meeting if the children met the following enrolment criteria: (1) had asthma diagnosed by a physician; (2) experienced asthma symptoms during the past year; (3) were born between 1979 and 1983; and (4) lived in Budapest.

Of the 296 sets of parents, 101 (34.1%) responded that their children met the eligibility criteria and were willing to participate in the study. Of those, 81 (80.2%)

attended one of three introductory meetings, and 66 (65.3%) of those truly met the enrolment criteria. Subsequently, three (4.5%) of the families withdrew, and three other children were excluded from the study. One child was excluded because he did not have asthma symptoms during the previous year. The second was excluded because his family heated with coal and wood, which possibly caused large indoor TSP and SO₂ exposures. The third child was excluded because he completed less than 75% of the daily PEFR diary. All of the remaining 60 children completed over 75% of their diaries; the majority completed over 90%.

The children's physicians classified each child as having either mild, moderate, or severe disease, according to criteria from the US National Heart, Lung and Blood Institute.²⁰ Children were categorized as exposed to environmental tobacco smoke if either parent smoked.

Completion of Questionnaires and Diaries

During the introductory meeting, parents or adult guardians completed a signed informed consent form and a questionnaire that described the child's demographic characteristics, medical history, activity patterns, and home environment. At this meeting, children also were individually taught to measure their PEFR and were observed doing so. Each child also received a package of diaries with verbal and written instructions on its completion.

Each day from 13 September to 5 December 1993, the children recorded their respiratory symptoms, the number of hours they spent away from Budapest, and the results of three PEFR measurements each in the morning upon rising and in the evening before bedtime. They measured their PEFR with a Mini-Wright peak flow meter while standing and prior to taking any medication. They were instructed to leave blank any diary entries that were missed or forgotten.

At the end of each week, that week's diary was mailed to the city health department and reviewed by study personnel. Participants were contacted by phone at least twice during the study and more often if any irregularities were noted.

Measurements of Air Pollutants

Ambient air concentrations of TSP and SO₂ were measured by eight continuous air sampling monitors, model number MLU FH261N manufactured by Rupprecht & Patashnick Co., Inc. The TSP concentrations were analysed by beta reactive absorption methods with a FAG FH 62 IN Dust Monitor. The SO₂ concentrations were measured by ultra-violet radiation excitation and fluorescence. The monitors were located in the more polluted areas of the city, and each monitor

also recorded temperature and humidity on a continuous basis.

Budapest has a varied topography, with hills to the west of the Danube River and mostly flat land to the east. To estimate daily ambient air TSP and SO₂ exposure, we used 24-hour average measurements from the air monitor nearest the home of each child. On days during which individual monitors did not work, we considered pollutant concentrations to be unknown for children matched to those monitors.

Statistical Analyses

We used SAS for all statistical analyses.²¹ Because of the diurnal pattern of PEFR,^{22–24} morning and evening measurements were analysed separately. For both the morning and evening measurements, we used the largest of the three recorded measurements. To eliminate a learning effect, we excluded the first 2 days of PEFR data. We also excluded PEFR data on days a child spent ≥ 4 hours away from Budapest because air monitoring data was available only from monitors in Budapest; the 4-hour cut-off was arbitrarily chosen.

We conducted the analysis on both a group level and an individual level. The group analysis was primarily descriptive. For the individual analysis, we used each child's mean PEFR during the study as a reference from which to calculate that child's daily per cent deviations from their mean PEFR value. For each day, we averaged these individual daily per cent deviations for all study participants to obtain a group daily mean per cent deviation in PEFR. We then used t-tests to compare differences between the average daily per cent deviations in PEFR for the fall versus winter seasons. We used analysis of variance to compare differences between the average daily per cent deviations in PEFR based on pollutant quintals.

For the multivariate analysis, we used the SAS procedure PROC MIXED on the individual-level data to account for the variability in the data both within and between the children. To take advantage of the longitudinal nature of the study design, we considered each child to be his or her own referent. For the morning PEFR, we excluded the current day's pollutant concentrations since most of that day's exposure had not occurred when the PEFR measurement was performed. We used a fixed-effects model to obtain summary estimates by a weighted average of the individual coefficients. Weights were the inverses of the standard errors of each individual's estimate. Intercepts for each child were allowed to differ. We explored a random effects model, but the random effect was not statistically significant.

All models included the variable 'date' to control for a linear change in the seasons from fall to winter, lung

TABLE 1 *Characteristics of study participants at baseline, Budapest, Hungary*

Characteristic	% (n = 60)
Male	71.7
Median age in years (range)	11 (9–14)
Asthma's severity	
mild	63.3
moderate/severe	36.7
Took asthma medication	83.3
Exposed to environmental tobacco smoke	41.7
Asthma symptoms seasonal	91.7
Worst season for asthma ^a	
fall	56.4
spring	54.5
summer	41.8
winter	23.6

^a Limited to 55 children with seasonal symptoms, multiple replies permitted.

growth of the children, and the increase in PEFR during the study period. Models also controlled for the confounding effects of weekday versus weekend, temperature, and humidity. We hypothesized that humidity and temperature had a non-linear effect and categorized these variables into quartiles. Each quartile represented an approximate 25-unit increase in either per cent humidity or °Centigrade. Because the Durbin-Watson test revealed serial autocorrelation in the PEFR, we used a first-order autoregressive model for the residuals.²⁵ We also assessed the influence of a 'cold' on PEFR, but found it to be insignificant and excluded it from our model.

RESULTS

Among the 60 children, about one-third were classified as having moderate to severe asthma, and most of this third took medication for asthma (Table 1). Exposure to environmental tobacco smoke at home was fairly common, but reportedly none of the children smoked tobacco. Nearly all of the parents or their children stated that the children's symptoms varied with the season of the year, and most of these stated that fall was one of the seasons during which symptoms were worst. More than half stated that exacerbations were caused by air pollution. Among the 17 girls aged 9–14, 12 (70.6%) reported that menstruation exacerbated their asthma.

The children's mean PEFR ranged widely from 125 to 627 l/min. Both the morning and evening PEFR daily

TABLE 2 Medians and ranges of the daily average total suspended particulate and sulphur dioxide concentrations measured at the eight ambient air monitoring stations, 15 September–5 December 1993, Budapest, Hungary

Monitor	Total suspended particulates			Sulphur dioxide		
	N	Median (range)	# days $\geq 120\mu\text{g}/\text{m}^3$ ^a	N	Median (range)	# days $\geq 125\mu\text{g}/\text{m}^3$ ^a
1	71	62 (23–117)	9	89	46 (26–185)	1
2	91	80 (36–148)	13	91	32 (21–90)	0
3	85	57 (17–222)	10	91	72 (11–127)	1
4	89	70 (31–165)	3	88	82 (13–183)	2
5	91	61 (26–158)	4	91	41 (16–153)	2
6	89	60 (16–204)	4	91	29 (18–88)	0
7	83	45 (20–116)	0	87	30 (13–154)	3
8	87	48 (19–112)	0	89	57 (11–153)	1
Monitors 1–8 averaged	91	64 (30–162)	4	91	42 (29–145)	1

^a World Health Organization (WHO) health effects limit.

mean deviations for the group increased during the study period. The study group's mean PEFR deviation before 15 October was lower (–1.66% for the morning PEFR, –1.73% for the evening PEFR) than their mean deviation after October 15 (+0.97% for the morning, +1.01% for the evening); these differences were statistically significant ($P < 0.05$).

During the study period, daily average TSP concentrations exceeded the World Health Organization (WHO) health effects limit of $120\mu\text{g}/\text{m}^3$ at least once at six of the eight air monitors (Table 2). The number of days exceeding the limit at each monitor ranged from 3 to 13. The WHO tentative health effects limit for SO_2 of $125\mu\text{g}/\text{m}^3$ was also exceeded at least once at six monitors (range 1–3 days). The SO_2 concentration increased at each monitor following 15 October, the start of the heating season. Figure 1 shows this trend for the monitor in District XI. Of the 60 children, 39 (65.0%) resided near this air monitor.

Overall, the children reported being outside and thus exposed to ambient air pollutants a median of 3 hours (range 1–9 hours) during weekdays and 5 hours (range 2–9 hours) during weekends. All but one of the children attended school in the same district in which they resided. Among the 39 children who resided near the monitor in District XI, morning and evening PEFR

daily mean deviations somewhat mirrored the pollutant concentrations (Figure 1). Their daily mean deviations during the 16 days in the lowest quintile of TSP concentrations were similar to deviations measured during the 14 days in the highest quintile of TSP concentrations. However, daily mean PEFR deviations were significantly larger during days in the highest quintile of SO_2 concentrations than during days in the lowest quintile ($P < 0.05$).

Because the increase in PEFR during the study period was likely influenced by temperature, humidity, and the time trend, we used a multivariate analysis to control for such effects. Twenty-two models assessed the effect that individual pollutants had on PEFR, and about one-half of these models demonstrated a negative relationship (Table 3). Only the model for the evening PEFR and the current day's SO_2 concentration reached statistical significance, and it showed an improvement in PEFR with increased SO_2 concentrations. The combined effect of the pollutants was also assessed in 18 models (Table 4). No significant associations were demonstrated between pollutants and morning PEFR. However, increased concentrations of SO_2 the previous day were significantly associated with a decreased evening PEFR: for each $10\mu\text{g}/\text{m}^3$ increase in the previous day's SO_2 concentration, the evening PEFR decreased

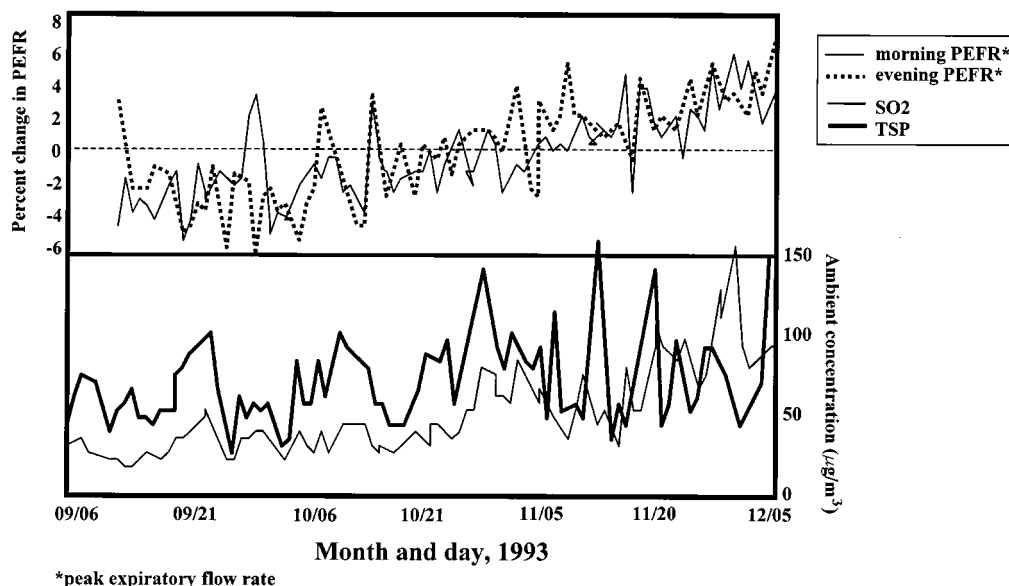


FIGURE 1 The daily mean deviation in morning and evening peak expiratory flow rates (PEFR) and air pollutants among the 39 children who resided near the pollutant monitor in District XI, Budapest, Hungary, 6 September–5 December 1993

TABLE 3 The individual associations between the measured concentrations of total suspended particulates (TSP) and sulphur dioxide (SO_2) during the current day; the past 4 days; and the past week upon the daily peak expiratory flow rates of the 60 asthmatic children, Budapest, Hungary, 15 September–5 December 1993

Time pollutant concentrations were measured	Morning peak expiratory flow rate ^a			Evening peak expiratory flow rate ^a		
	Coefficient	\pm SE ^b	P	Coefficient	\pm SE ^b	P
TSP – today	–	–	–	0.0122	0.0194	0.53
TSP – 1 day ago	–0.0107	0.0201	0.59	0.0302	0.0201	0.13
TSP – 2 days ago	0.0021	0.0196	0.92	–0.0135	0.0194	0.49
TSP – 3 days ago	0.0049	0.0203	0.81	–0.0280	0.0202	0.17
TSP – 4 days ago	–0.0340	0.0216	0.12	–0.0192	0.0219	0.38
TSP – past week	–0.0029	0.0544	0.95	0.0379	0.0570	0.51
SO_2 – today	–	–	–	0.0798	0.0332	0.02
SO_2 – 1 day ago	0.0001	0.0339	1.00	–0.0312	0.0345	0.36
SO_2 – 2 days ago	–0.0021	0.0330	0.55	–0.0457	0.0334	0.17
SO_2 – 3 days ago	0.0206	0.0306	0.50	0.0271	0.0314	0.39
SO_2 – 4 days ago	–0.0049	0.0379	0.90	–0.0033	0.0387	0.93
SO_2 – past week	–0.0053	0.0636	0.93	0.0582	0.0668	0.38

^a Adjusted for date; quartiles of temperature and humidity; weekend versus weekday; and autocorrelation.

^b Standard error.

an average of 0.78 l/min. However, increased concentrations of SO_2 the current day were associated with a significant increase in the evening PEFR (Table 4).

Air pollutants had a variable influence upon the PEFR of individual children. Figure 2 shows the distribution of the regression coefficients for the individual

children for four models. In each case, the individual coefficients varied and ranged from a positive to a negative association.

We repeated the analysis separately for children with severe as well as mild/moderate asthma; the 39 children who lived near the District XI monitor; and the time

TABLE 4 The combined association between the measured concentrations of total suspended particulates (TSP) and sulphur dioxide (SO₂) during the past 4 days upon daily peak expiratory flow rates of the 60 asthmatic children, Budapest, Hungary, 15 September–5 December 1993

Time pollutant concentrations were measured	Morning peak expiratory flow rate ^a			Evening peak expiratory flow rate ^a		
	Coefficient	± SE ^b	P	Coefficient	± SE ^b	P
TSP – today	–	–	–	–0.0010	0.0214	0.96
TSP – 1 day ago	–0.0035	0.0218	0.87	0.0420	0.0219	0.06
TSP – 2 days ago	0.0010	0.0216	0.96	–0.0016	0.0216	0.94
TSP – 3 days ago	0.0118	0.0218	0.59	–0.0376	0.0217	0.08
TSP – 4 days ago	–0.0380	0.0251	0.13	–0.0420	0.0254	0.10
SO ₂ – today	–	–	–	0.0850	0.0380	0.03
SO ₂ – 1 day ago	–0.0347	0.0392	0.38	–0.0780	0.0400	0.05
SO ₂ – 2 days ago	–0.0040	0.0398	0.92	–0.0693	0.0403	0.09
SO ₂ – 3 days ago	0.0145	0.0357	0.69	0.0647	0.0370	0.08
SO ₂ – 4 days ago	0.0060	0.0499	0.90	0.0653	0.0503	0.19

^a Adjusted for date; quartiles of temperature and humidity; weekend versus weekday; and autocorrelation.

^b Standard error.

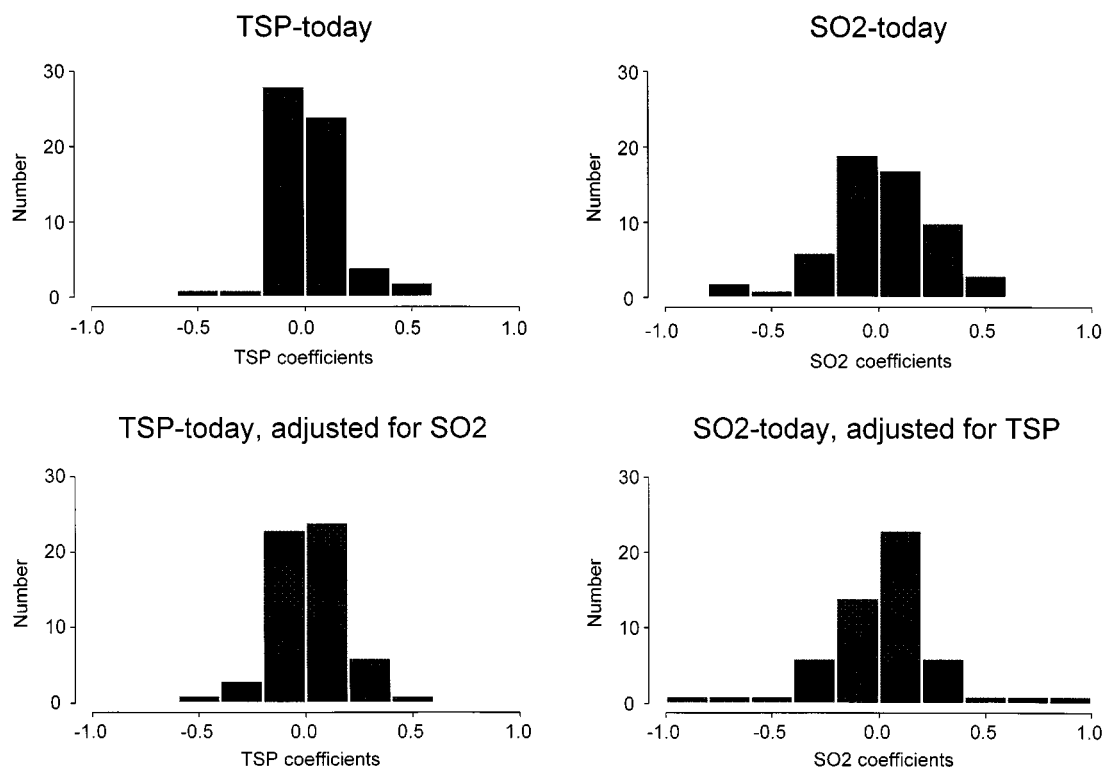


FIGURE 2 Histogram of the distribution of child-specific total suspended particulates (TSP) and sulphur dioxide (SO₂) regression coefficients for four models, Budapest, Hungary

period before and after the heating season (15 October 1993). Results for these analyses were similar to the results that have been presented for the entire group of children for the entire study period.

DISCUSSION

From 13 September to 5 December 1993, TSP and SO₂ concentrations in Budapest exceeded WHO health effects limits on several days, and SO₂ concentrations increased. Most of the days with the largest SO₂ concentrations occurred after the heating season began on 15 October. The children's PEFR were higher after 15 October. On days with the largest SO₂ concentrations, the children's PEFR were significantly higher than on days with the smallest SO₂ concentrations. However, after controlling for the effects of the time trends, temperature, humidity, and weekend versus weekday, we observed no consistent association between PEFR and levels of SO₂ and TSP in the ambient air.

In this study, we first assessed the individual effects of SO₂ and TSP concentrations on PEFR. The only significant finding was an increase in the evening PEFR as that day's SO₂ concentration increased. We then assessed the combined effects of the pollutants and found increased SO₂ concentrations were significantly associated with both an increase and decrease in evening PEFR. One would expect that an increase in pollutant concentrations would be associated with a decrease in PEFR. During the analysis of this data we made 40 comparisons and found three statistically significant results. Our results should thus be interpreted cautiously because at a significance level of $P = 0.05$, one of every 20 comparisons could reach statistical significance purely by chance.

Asthma's seasonal variation has also been documented by other researchers.^{3,6-8,26-28} To control for such seasonal variation, we used a linear time trend variable. However, non-linear changes in seasonal confounders, such as viral respiratory disease outbreaks or sudden decreases in house dust mite concentrations (once a dryness threshold in the home was reached),²⁹ would have been incompletely modelled. Thus, incomplete control of confounding by seasonal factors may have biased the results.

This study had several limitations. We lacked accurate information on children's use of bronchodilators or other medications during the study period. Because most of the children reported taking some asthma medication, the use of these medications may have masked an association between pollutant levels and PEFR, particularly among severe asthmatics. The amount of

medication used could have been a useful outcome indicator. However, this information was not reliably and consistently recorded by the study participants.

In this study, it is possible we overestimated the children's TSP and SO₂ exposures because we used the concentrations measured at the air monitor nearest the children's residences. In Budapest, air monitors were selectively located in the most polluted areas. Furthermore, children spent about 21 hours a day indoors during fall weekdays, and air pollutant levels were possibly lower indoors than outdoors; ill children with decreased PEFR may have spent even more hours indoors. Thus, although WHO health effects levels for TSP and SO₂ were exceeded at the monitors, most children were probably exposed to pollutant concentrations that were considerably lower. Unfortunately, we lacked information to describe the number of hours a day that the children spent outdoors.

The strengths of this study included its longitudinal design, which allowed for the prospective assessment of air pollution's effects on the PEFR of individual children with asthma.³⁰ The study design also allowed each child to serve as their own reference. Thus, the results are probably valid even though the children enrolled in the study were self-selected and were probably not representative of all asthmatic children in Budapest. The design also permitted us to evaluate the daily variability in PEFR in conjunction with the daily variability in TSP and SO₂ pollutant concentrations. Children also remained in their normal environments during the study. Furthermore, serial PEFR measurements are considered sensitive markers of airway obstruction, and asthmatic children have been shown to accurately measure their PEFR.^{22-24,26,31}

At least four other researchers have used panel studies to investigate the relationship between PEFR and particulate matter (PM) or SO₂ air pollution.³²⁻³⁵ Three studies were conducted in the US and one in the Netherlands. Enrolment criteria varied among these studies, with one each including adults with asthma; children with and without respiratory diseases; children and adults with respiratory diseases; and children with chronic respiratory symptoms. In these studies, particulate matter and SO₂ concentrations were low and comparable with those in Budapest. Three of the four authors found negative relationships between SO₂ concentration and PEFR and two found negative associations between PEFR and concentrations of particulate matter 10 microns or smaller in diameter. Thus, other researchers have found negative associations between these pollutants and PEFR among people who probably had milder forms of respiratory disease, overall, than the children in Budapest.

We did not find a consistent association between air pollutant exposure in Budapest and PEFR among asthmatic children. Given the large prevalence of asthma in this city, further research is needed to better clarify the impact of air pollution in Budapest on children's health. Researchers conducting future studies of asthmatic children could benefit from our experiences. Studies should give attention to controlling seasonal influences (perhaps by restricting the study period to one season), obtaining good information on medication use, and developing estimates of individual exposure, possibly using personal air sampling devices or stationary sampling devices in participants' bedrooms.

DISCLAIMER

The use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the US Department of Health and Human Services.

ACKNOWLEDGEMENTS

The US-Hungarian Joint Fund financed this study (JF No. 281/92).

Dr Katherin Lun, Director; Dr Barbara Keleman, The Department of Community and Environmental Hygiene; and the staff of the Department of Childhood and Adolescent Hygiene; all at the Budapest City Institute of State Public Health and Health Officer Service provided support for data collection. Dr David Leon, London School of Hygiene and Tropical Medicine, gave many insightful suggestions about the data analysis. Dr Michael Hills, London School of Hygiene and Tropical Medicine, provided valuable statistical assistance. The authors also thank the following people from the Centers for Disease Control and Prevention for their generous assistance in many technical and administrative matters throughout this project: Dr Ruth Etzel, Dr Bud Spierto, Ms Tami Laplante, Mrs Mary Boyd, and Mr James Rifenburg.

REFERENCES

- ¹ Evans R, Mullally D I, Wilson R W *et al.* National trends in the morbidity and mortality of asthma in the US, prevalence, hospitalization, and death from asthma over two decades: 1965–1984. *Chest* 1987; **91** (Suppl.): 65S–74S.
- ² Weiss K B, Wagener D K. Changing patterns of asthma mortality. *JAMA* 1990; **264**: 1683–87.
- ³ Friday G A, Fireman P. Morbidity and mortality of asthma. *Pediatr Allergic Dis* 1988; **35**: 1149–62.
- ⁴ Mitchell E A. International trends in hospital admission rates for asthma. *Arch Dis Child* 1985; **60**: 376–78.
- ⁵ Mitchell E A. Increasing prevalence of asthma in children. *NZ Med J* 1983; **96**: 463–64.
- ⁶ Infante-Rivard C, Sukia S E, Roberge D, Baumgarten M. The changing frequency of childhood asthma. *J Asthma* 1987; **24**: 283–88.
- ⁷ Centers for Disease Control. Asthma mortality and hospitalization among children and young adults—United States, 1980–1993. *MMWR* 1996; **45**: 350–53.
- ⁸ Halfon N, Newacheck P W. Trends in the hospitalization for acute childhood asthma, 1970–84. *Am J Public Health* 1986; **76**: 1306–11.
- ⁹ Phelan P D. Asthma in children: epidemiology. *Br Med J* 1994; **308**: 1584–85.
- ¹⁰ Gergen P J, Mullally D I, Evans R III. National survey of prevalence of asthma among children in the United States, 1976–1980. *Pediatrics* 1988; **81**: 1–7.
- ¹¹ World Health Organization. *Air Quality Guidelines for Europe*. Copenhagen: WHO Regional Office for Europe. WHO Regional Publications, European Series No. 23, 1987.
- ¹² Richards W, Azen S P, Weiss J, Stocking S, Church J. Los Angeles air pollution and asthma in children. *Ann Allergy* 1981; **47**: 348–54.
- ¹³ Pope C A. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am J Public Health* 1989; **79**: 197–201.
- ¹⁴ Berciano F A, Dominguez J, Alvarez F V. Influence of air pollution on extrinsic childhood asthma. *Ann Allergy* 1989; **62**: 135–41.
- ¹⁵ Bates D V, Baker-Anderson M, Sizto R. Asthma attack periodicity: a study of hospital emergency visits in Vancouver. *Environ Res* 1990; **51**: 51–70.
- ¹⁶ Cotton P. 'Best data yet' say air pollution kills below levels currently considered safe. *JAMA* 1993; **269**: 3087–88.
- ¹⁷ Levy B. *The Environmental Health Crisis in Eastern Europe*. The OEM Report. Boston: OEM Health Information Inc., 1991, pp. 53–56.
- ¹⁸ Hertzman C, Ayres W, Levy B, Krzyzanowski M. *World Bank, Environment and Health in Central and Eastern Europe*. Report No. 12270-ECA, 21 February 1994, Environment Division, Technical Department, Europe and Central Asia, Middle East, and North Africa Regions.
- ¹⁹ Orszagos Egesszegvedelmi Tanacs Informacios Kozpontja: Tenyek as elemzesek az egesszegmegorzesi program szolgaltatlaban. Budapest, 1988.
- ²⁰ National Institute of Heart, Lung, and Blood Institute, National Institutes of Health (US). Guidelines for the diagnosis and management of asthma. Bethesda, MD: NIH: 1991. NIH Publication No. 91–3042.
- ²¹ SAS Institute Inc. *SAS/STAT User's Guide. Version 6.03 edn*. Cary, NC: SAS Institute, 1988.
- ²² Enright P L, Lebowitz M D, Cockcroft D W. Physiologic measures: pulmonary function tests. *Am J Respir Crit Care Med* 1994; **149**: S9–S18.
- ²³ Lebowitz M D, Krzyzanowski M, Quackenboss J J. Diurnal variation of PEF and its usage in epidemiological studies. *Am Rev Respir Dis* (In Press), 1997.
- ²⁴ Quackenboss J J, Lebowitz M D, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. *Am Rev Respir Dis* 1991; **143**: 323–30.
- ²⁵ Kendall M G. *Time Series*. London: Charles Griffin, 1973, pp. 164–65.
- ²⁶ Clough J B, Holgate S T. Episodes of respiratory morbidity in children with cough and wheeze. *Am J Respir Crit Care Med* 1994; **150**: 48–53.

- ²⁷ Weiss K B. Seasonal trends in US asthma hospitalizations and mortality. *JAMA* 1990; **263**: 2323–28.
- ²⁸ Goldstein I F, Currie B. Seasonal patterns of asthma: a clue to etiology. *Environ Res* 1984; **33**: 201–15.
- ²⁹ Lintner T J, Brame K A. The effects of season, climate, and air-conditioning on the prevalence of *Dermatophagoides* mite allergens in household dust. *J Allergy Clin Immunol* 1993; **91**: 862–67.
- ³⁰ Schwartz J, Wypij D, Dockery D *et al.* Daily diaries of respiratory symptoms and air pollution: methodological issues and results. *Environ Health Perspect* 1991; **90**: 181–87.
- ³¹ Lebowitz M D. The use of peak expiratory flow rate measurements in respiratory disease. *Pediatr Pulmonol* 1991; **11**: 166–74.
- ³² Perry G B, Chai H, Dickey D W *et al.* Effects of particulate air pollution on asthmatics. *Am J Public Health* 1983; **73**: 50–56.
- ³³ Vedal S, Schenker M B, Munoz A, Samet J M, Batterman S, Speizer F E. Daily air pollution effects on children's respiratory symptoms and peak expiratory flow rate. *Am J Public Health* 1987; **77**: 694–98.
- ³⁴ Pope C A, Dockery D W, Spengler J D, Raizenne M E. Respiratory health and PM₁₀ pollution: a daily time series analysis. *Am Rev Respir Dis* 1991; **144**: 668–74.
- ³⁵ Roemer W, Hoek G, Brunekreef B. Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. *Am Rev Respir Dis* 1993; **147**: 118–24.

(Revised version received April 1997)