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Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children

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ABSTRACT: Short-term effects of air pollution (consisting primarily of sulphur dioxide and particulate matter but with low acidity) on respiratory morbidity were studied in asthmatic children from Sokolov, Czech Republic.

Eighty nine children with asthma, who recorded daily peak expiratory flow measurements, symptoms and medication use in a diary, were analysed for 7 months during the winter of 1991–1992. Air pollution measurements included: SO_2, total suspended particulates (TSPs), inhalable particles, *i.e.* particulate matter of aerodynamic diameter ≤10 µm, particle strong acidity (PSA) and fine particle sulphate concentration (SO_4). Linear and logistic regression analyses estimated the impact of air pollutants adjusted for trend, temperature and weekend and autocorrelated errors.

Exposure to elevated levels of air pollution was associated with decreased peak expiratory flow rates, increased respiratory symptoms, increased prevalence of school absence and fever, and increased medication use. Prolonged exposure to particle SO_4 showed the largest effect estimates. At the end of January, an air pollution episode occurred, during which respiratory symptoms, prevalence of fever, school absence and asthma medication increased. The association between respiratory symptoms and particulate SO_4 was highly dependent on this episode, whilst the associations between lung function and SO_4 as well as between fever and SO_4 were still observed when this air pollution episode was excluded. Some evidence was found that exposure to air pollution might have enhanced the respiratory symptoms while children were experiencing respiratory infections.

In this study, a panel of children with mild asthma experienced small decreases in peak expiratory flow and increased dyspnoea in association with fine particles formed during air pollution episodes.

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Particulate air pollution has been implicated as contributing to the incidence and severity of respiratory disease. An elevated prevalence of respiratory symptoms [1], bronchitis [1, 2], or respiratory infection [3] has been found in association with particulate pollution in the general population. In panel studies, acute episodes of particulate air pollution have been associated with increased incidence of respiratory symptoms [4–8], and decreased lung function [4, 5, 7–9]. Asthmatic patients have been reported to increase their bronchodilator use in association with air pollution [5, 7]. Inhalable particles with an aerodynamic diameter of ≤10 µm (PM_{10}) have been suspected as the specific toxic agent [10–12]. Evidence for the role of PM_{10} has been collected in Utah Valley [4, 5], where particles frequently exceeded the standards, but sulphur dioxide (SO_2) and aerosol acidity were low. Increased prevalence of symptoms and decreased peak expiratory flow (PEF) associated with PM_{10} concentrations were observed even when days above the American standard of 150 $\mu g \cdot m^{-3}$ were excluded. Acute effects of PM_{10} have been observed in children with respiratory symptoms [4, 7, 9], nonsymptomatic children [4], and less consistently in asthmatic patients [5, 8].

In most locations in Europe and the United States, particulate and SO_2 pollution are highly correlated [7, 8, 13–15]. For some studies, data on SO_2 but not on particulate matter were available [16, 17]. Concurrent exposures to multiple air pollutants diminish the possibility of distinguishing between the contributions of the individual components in complex air pollution mixtures. Some studies have failed to show consistent associations between air pollution and lung function [14, 17] or respiratory symptoms [8, 14, 17] during air pollution episodes.

At high levels of air pollution, associations between increased air pollution and decreased PEF have been observed for asthmatics in Central and Eastern Europe [8]. A combined analysis showed larger decreases in PEF in the evening in association with SO_2 and particulate air pollution in children than in adults from Erfurt, Weimar and Sokolov. In addition, a symptom score increased both for children and adults in association with

5 day mean concentrations of SO_2. The previous analyses, however, did not allow a direct comparison between the effect estimates calculated for SO_2 and particulate air pollution, as respirable particulates were only measured during the second of two consecutive winters. Therefore, a more detailed analysis of the panel of children from Sokolov, Czech Republic, considering respiratory symptoms individually has been attempted and the findings are reported in this paper.

Materials and methods

Study area

Sokolov is a city with approximately 60,000 inhabitants, located in a hilly region in the northwest of the Czech Republic. A large power plant located west of the city provided central heating for 70% of the buildings in Sokolov. Small scale industry and domestic heating were sources of additional pollution in winter time. Glass and china manufacturing plants are scattered around Sokolov within a radius of 30 km. Brown coal or lignite, with high sulphur and ash content, was widely-used both in domestic heating and power production.

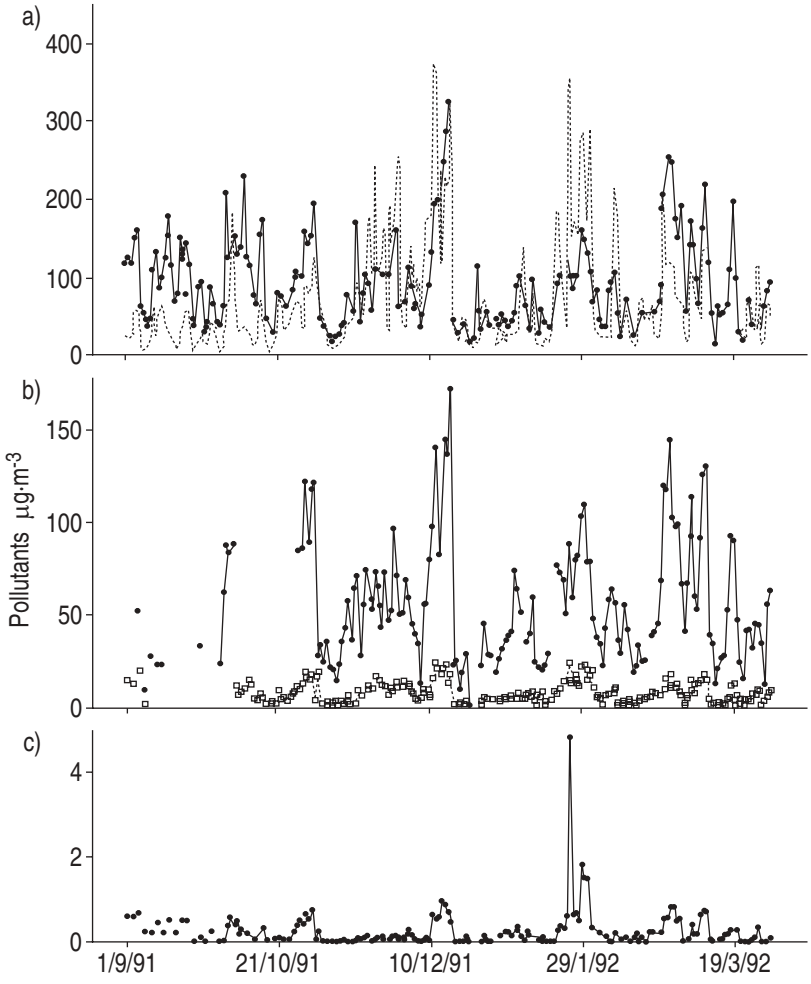

Fig. 1. – Air pollution in Sokolov, Czech Republic, during the winter of 1991–1992. a) total suspended particulates (—●—) and sulphur dioxide (- - -); b) inhalable particulate matter with aerodynamic diameter ≤10 µm (—●—) and fine particle sulphate concentration (-▫-); c) particle strong acidity (—●—). Several episodes of elevated pollution are demonstrated.

Air pollution measurements

Pollutants (SO_2, NO_2, particle strong acidity (PSA) and total suspended particles (TSP)) and meteorological variables (temperature, relative humidity, pressure, wind speed and wind direction) were routinely measured each day at one central site in Sokolov. Twenty four hour means were calculated for each of these measures. In addition, acid aerosols were measured with a size selective impactor and ammonia denuder, starting in December 1990. Concentrations of sulphates were determined by ion chromatography, and acidity by pH measurement of 24 h integrated samples of particles less than 2.5 µm aerodynamic diameter. Measurements were taken every second day until the end of August 1991. Starting in October 1991, acid aerosols were measured every day. Mass concentration of PM10 was measured at the same location and schedule. A detailed description of the exposure assessment has been given previously [18, 19]. The analyses presented here were restricted to the second winter (1991–1992), because full information on inhalable particles and acidity was available only in this period (fig. 1).

Study population

Children with asthma or related chronic respiratory disease, who regularly attended out-patient clinics in Sokolov or Chodov (15 km north east of Sokolov), were recruited. Participating children lived within a 25 km radius of Sokolov, the majority within 5 km. A questionnaire on the history of disease was distributed at the beginning of the study and completed by a parent or a guardian. A local physician examined each child and assessed the asthma and allergy status. Eighty nine children from the main study [8] participated during the winter 1991–1992 (September 1, 1991 to March 31, 1992). The children were 6–14 yrs of age at the end of 1991. Seventy six of these 89 children had doctor-diagnosed asthma confirmed by the examination, but only 46 of the children were taking medication during the winter period under investigation.

Peak expiratory flow was (PEF) measured twice each day with a mini-Wright peak flow meter (range 60–800 $L \cdot min^{-1}$). Instructions on measurement techniques, including breathing techniques, holding and maintenance of the meter, were given to the child and a parent. The highest PEF value out of three attempts was recorded in the morning and in the evening before use of medication. If medication was used, a second measurement was conducted 10 min afterwards. Each day, information on the presence of cough during the previous night, cough during the day, dyspnoea at rest, dyspnoea during the previous night, dyspnoea on exertion,

runny nose, phlegm, and fever was collected with a diary. Fever was defined as rectal body temperature above 38.5°C. In addition, school absence and time spent outdoors were recorded. Use of asthma medication was noted, including time, amount and prescription name. Prescriptions containing theophylline or cortisone were converted to milligrams active substance used. Beta-agonist use was coded as number of puffs. None of the children used aerosol medication with combinations of a beta-agonist and cortisone.

Questionnaires were mailed back to the study centre each week. Responses and compliance were monitored by a study co-ordinator, who stayed in contact with the participants throughout the study period. Data collection started in January 1991 and ended in the middle of June 1992. In total, 97 children were enrolled. PEF measurements were regarded as invalid if values were the same for more than 14 days. Measurements during the first 2 weeks were discarded to eliminate learning effects. Three children who provided less than 30 days with valid PEF measurements were excluded.

Statistical analysis

Linear regression models were used to analyse the PEF data, while logistic regression models were applied to binary data. PEFs in the evening before use of medication were centred on the child-specific mean over the entire period. The average deviation (ΔPEF = daily mean deviation of PEF) across all participants was calculated for each day. Day-specific prevalences of each symptom were calculated based on the number of children participating on the given day. Cough included reporting of cough during the day or during the previous night. Dyspnoea included shortness of breath at rest, on exertion, or during the previous night. Day-specific indicators of any theophylline or beta-agonist use was similarly calculated. Model selection was based on the time-series analyses of the day-specific means, and has been described in detail previously [8]. The final model included a linear trend, temperature, and indicators of day of the week.

First order autocorrelation of the error terms was detected and considered in all analyses. The numbers of children participating each day were used as weights to adjust for fluctuation in the size of the panel. Polynomial distributed lag structures [20] were estimated for day-specific time-series to evaluate the impact of prior exposure. On the basis of polynomial distributed lag analyses, current values and 5 day means were used to compare immediate and delayed impacts of air pollutants [8]. A 5 day mean was defined as the average of the pollution concentration on the current and four prior days. In case of missing data, the mean of the available measurements was taken. All effect estimates were expressed as changes associated with a difference of approximately one interquartile range of the exposure. A p-value of less than 0.05 considered significant.

Results

Exposure to air pollution

Episodes of elevated air pollution for more than 7 days occurred repeatedly during the winter 1991–1992. A mean SO_2 concentration of 71 $\mu g \cdot m^{-3}$ (maximum 383 $\mu g \cdot m^{-3}$) was measured during the period of analysis (fig. 1 and table 1). Total suspended particulates (TSPs) had a mean of 88 $\mu g \cdot m^{-3}$ (maximum 325 $\mu g \cdot m^{-3}$), and PM10 a mean of 55 $\mu g \cdot m^{-3}$ (maximum 171 $\mu g \cdot m^{-3}$). Sulphate concentrations of fine particles (SO_4) averaged 8.0 $\mu g \cdot m^{-3}$ (maximum 23.8 $\mu g \cdot m^{-3}$). Particle strong acidity (PSA) was below the detection limit [21] on 79% of the days, despite high SO_2 concentrations. High exposure to air pollution occurred between the middle of November and the middle of December 1991. Much lower air pollution concentrations were recorded during the 5 week period between mid-December and mid-January.

Table 2. – Pearson's correlation coefficients (r) between 24 h mean temperature and air pollution from September 1, 1991 until March 31, 1992

		TSP	PM10	SO_4	PSA	Temp
SO_2	r	0.57	0.65	0.70	0.51	-0.49
	p-value	0.0001	0.0001	0.0001	0.0001	0.0001
	n	202	149	166	183	201
TSP	r		0.87	0.70	0.43	-0.03
	p-value		0.0001	0.0001	0.0001	0.64
	n		159	175	192	211
PM10	r			0.77	0.47	-0.31
	p-value			0.0001	0.0001	0.0001
	n			148	157	159
SO_4	r				0.63	-0.24
	p-value				0.0001	0.0015
	n				175	174
PSA	r					-0.14
	p-value					0.059
	n					191

Temp: temperature. For abbreviations see legend to table 1.

Table 1. – Distributions of 24 h mean temperature and air pollution between September 1, 1991 and March 31, 1992

	n	Missing	Minimum	25%	Median	75%	Maximum
Temperature °C	211	2	-8.1	1.2	3.4	8.5	18.4
SO_2 $\mu g \cdot m^{-3}$	202	11	3	22	46	88	383
TSP $\mu g \cdot m^{-3}$	212	1	14	46	75	116	325
PM10 $\mu g \cdot m^{-3}$	159	54	3	29	47	73	171
SO_4 $\mu g \cdot m^{-3}$	175	38	0.5	3.6	6.7	11.8	23.8
PSA $\mu g \cdot m^{-3}$	192	21	0.00	0.01	0.12	0.31	4.80

TSP: total suspended particulates; PM10: inhalable particulate matter with aerodynamic diameter ≤10 μm; PSA: particle strong acidity; SO_4: fine particle sulphate concentration; n: number of observations.

A second distinct air pollution episode occurred at the end of January 1992, when SO_2 concentrations stayed above 200 µg·m^{-3} for 12 days. On the first day of this air pollution episode, January 25, 1992, sulphate concentrations were 23.2 µg·m^{-3} and the maximum PSA concentration (4.8 µg·m^{-3}) was detected. These measurements were confirmed by a second, independent sample [18]. The concentrations of the air pollutants were highly correlated (table 2). Sulphate concentrations were most strongly correlated with SO_2, TSP and PM10. PM10 itself was strongly correlated with TSP, and less so with SO_2. The acidity of particles showed the least correlation with the pollutants compared to the correlation between all other pollutants. All pollutants other than TSP were elevated at low temperatures.

Table 3. – Average characteristics of the 89 children from Sokolov, Czech Republic

	Mean	Min	25%	Med	75%	Max
Lung function						
$PEF_{morning}$ L·min^{-1}	294	175	238	292	350	449
$PEF_{evening}$ L·min^{-1}	302	145	241	304	359	508
Symptoms*						
Cough	20	0	5	13	24	100
Dyspnoea	10	0	0	1	9	100
Phlegm	10	0	0	1	12	83
Runny nose	22	0	5	12	30	100
Fever and absenteeism*						
Fever	1	0	0	1	2	9
School absence	9	0	2	7	12	60
Medication use*						
Beta-agonist	2	0	0	0	0	100
Theophylline	9	0	0	0	10	99

*: percentage of days. $PEF_{morning}$ and $PEF_{evening}$: peak expiratory flow measured in the morning and evening, respectively. Min: minimum; Med: median; Max: maximum.

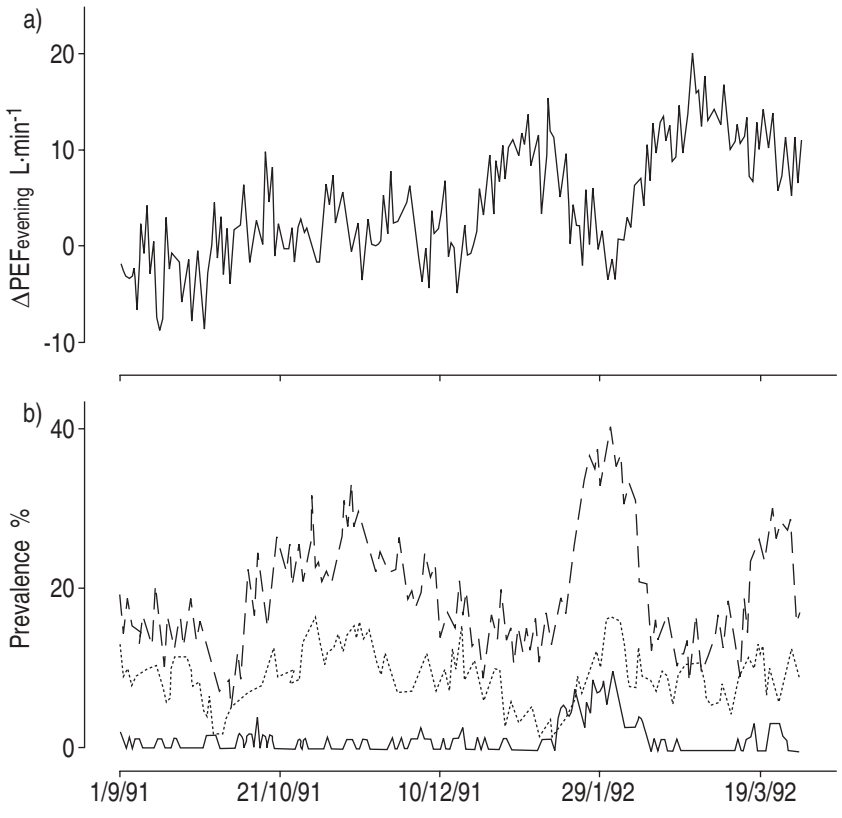

Fig. 2. – a) Changes in evening peak expiratory flow ($\Delta PEF_{evening}$); and b) symptom prevalence, during the winter of 1991–1992 in Sokolov, Czech Republic, in asthmatic children. — — —: cough; ———: fever; - - - - - - -: phlegm.

Characteristics of the participants

The children had participated in the panel study for 7 months before September 1991. On average the children completed their diaries on 86% of the days. Table 3 presents a distribution of the average PEF of the panellists, and prevalence of respiratory symptoms, fever and school absenteeisms, as well as use of medication. The panel consisted of children with low lung function as well as a child with average PEF above 500 L·min^{-1}. The graphical presentation of the mean deviation in PEF (fig. 2) suggests a steady increase in the lung function of the children over time. A weekly increase of 0.50 L·min^{-1} (95% confidence interval (95% CI) 0.37–0.62) in PEF in the evening was estimated in linear regression models.

The most prevalent respiratory symptoms were cough and runny nose. Dyspnoea and phlegm were reported less frequently. Reports of fever were rare, but some of the children were absent from school repeatedly. Use of medication was generally low, despite reports of symptoms. The prevalences for cough and phlegm (fig. 2) were elevated for an elongated time from mid-October 1991 to the end of November 1991. A second period with elevated prevalence of cough (above 35%) for 11 days was observed after January 24, 1992. The trend of the prevalences as estimated in the logistic regression analyses was negative for the respiratory symptoms and use of medication. Only school absence and fever increased over time, reflecting the increases at the end of January.

Associations between health outcomes and air pollution

The children showed a stronger association between decreases in mean deviation of peak expiratory flow in the evening ($\Delta PEF_{evening}$) and air pollution than between decreases in mean deviation of peak expiratory flow in the morning ($\Delta PEF_{morning}$) and air pollution (table 4). Linear regression analysis for ΔPEF adjusted for mean temperature, a linear trend, and day of the week. Generally, concentrations of air pollutants on the concurrent day were only weakly related to lung function measurements. The 5 day mean of SO_4 was the strongest predictor for $\Delta PEF_{morning}$ and $\Delta PEF_{evening}$. The effect estimates for the air pollutants did not depend on inclusion or exclusion of 24 h mean temperature in the models. However, temperature was positively associated with PEF, and the $PEF_{evening}$ increased by 1.01 L·min^{-1} for a temperature rise of 5°C (95% CI 0.19–1.83).

Table 4. – Changes in peak expiratory flow (ΔPEF) for an increase in air pollutants adjusted for trend, temperature and weekend (*versus* weekdays) with 95% confidence intervals in parentheses

	IQR	Lung function			
		$\Delta PEF_{morning}$		$\Delta PEF_{evening}$	
	$\mu g \cdot m^{-3}$	$L \cdot min^{-1}$		$L \cdot min^{-1}$	
Current day					
SO_2	67	-0.15	(-0.62 to 0.32)	-0.41	(-0.96 to 0.14)
TSP	70	-0.30	(-0.95 to 0.35)	0.23	(-0.52 to 0.98)
PM_{10}	45	-0.76	(-1.55 to 0.02)	-0.83	(-1.76 to 0.10)
SO_4	8	-0.19	(-1.01 to 0.63)	-0.63	(-1.52 to 0.27)
PSA	0.3	0.01	(-0.28 to 0.30)	-0.30	(-0.65 to 0.05)
Five day mean					
SO_2	65	-1.03	(-2.16 to 0.10)	-1.67*	(-2.76 to -0.58)
TSP	60	-0.74	(-2.02 to 0.54)	-0.57	(-1.83 to 0.69)
PM_{10}	35	-0.64	(-1.93 to 0.64)	-1.21	(-2.55 to 0.13)
SO_4	6.5	-1.49*	(-2.78 to -0.20)	-1.88*	(-3.08 to -0.67)
PSA	0.3	-0.66	(-1.54 to 0.21)	-1.22*	(-2.06 to -0.38)

IQR: interquartile range. *: $p<0.05$. For further definitions see legend to table 1.

While the prevalence of cough and dyspnoea did not increase in association with increased levels of air pollution on the same day, some indications were found that the children experienced phlegm and runny nose more frequently (table 5). Logistic regression analyses of the binary outcome variables adjusted for 24 h mean temperature, a linear trend, and weekend. A stronger delayed effect was observed for all respiratory symptoms, which was most closely associated with 5 day means of SO_2, SO_4 and PSA (table 5). The prevalence of fever increased with elevated levels of SO_2 and SO_4 on the same day, and was even more pronounced with 5 day means of SO_2, SO_4 and PSA (table 6). School absence showed no association with exposure to air pollution on the same day, but was predicted by prolonged exposure to SO_2 and SO_4. The use of β-agonists was associated with concurrent exposure to TSP and prolonged exposure to all winter-type pollutants (table 6). The children increased their maintenance asthma medication (theophylline) in association with 5 day means of all air pollutants. Prevalence of symptoms was reduced at higher temperatures for cough, phlegm and dyspnoea, whilst the symptoms runny nose, fever, school absence and use of asthma medication did not show an effect of temperature.

Are coinciding respiratory infections an alternative explanation for the observed associations?

The strong association between fever and SO_2, SO_4 and PSA could raise the suspicion that an influenza epidemic might have coincided with the air pollution episode at the end of January. During this period, fever prevalence rose to approximately 10% from earlier

Table 5. – Odds ratios for respiratory symptoms associated with an increase in air pollutants by one interquartile range (see table 4) adjusted for trend, temperature and weekend (*versus* weekdays) with 95% confidence intervals in parentheses

	Cough		Dyspnoea		Phlegm		Runny Nose	
Current day								
SO_2	0.99	(0.96 to 1.02)	0.99	(0.95 to 1.03)	1.02	(0.99 to 1.06)	1.00	(0.98 to 1.03)
TSP	0.99	(0.96 to 1.03)	1.01	(0.96 to 1.07)	1.06*	(1.01 to 1.11)	0.99	(0.96 to 1.02)
PM_{10}	1.01	(0.97 to 1.06)	0.99	(0.92 to 1.07)	1.09*	(1.03 to 1.16)	1.03	(0.99 to 1.07)
SO_4	1.06*	(1.01 to 1.11)	1.00	(0.92 to 1.08)	1.10*	(1.04 to 1.17)	1.08*	(1.04 to 1.12)
PSA	1.02	(1.00 to 1.04)	1.00	(0.96 to 1.03)	1.03*	(1.01 to 1.05)	1.02*	(1.01 to 1.04)
Five day mean								
SO_2	1.04	(1.00 to 1.08)	1.01	(0.96 to 1.07)	1.16*	(1.11 to 1.21)	1.07*	(1.04 to 1.10)
TSP	1.00	(0.96 to 1.04)	1.03	(0.97 to 1.09)	1.10*	(1.05 to 1.16)	1.02	(0.99 to 1.05)
PM_{10}	1.07*	(1.03 to 1.12)	1.06	(0.99 to 1.13)	1.12*	(1.06 to 1.18)	1.06*	(1.02 to 1.10)
SO_4	1.09*	(1.04 to 1.14)	1.09*	(1.02 to 1.16)	1.16*	(1.10 to 1.22)	1.16*	(1.12 to 1.20)
PSA	1.11*	(1.08 to 1.14)	1.02	(0.98 to 1.07)	1.15*	(1.11 to 1.19)	1.16*	(1.14 to 1.19)

*: $p<0.05$. For definitions see legend to table 1.

Table 6. – Odds ratios for prevalences of fever, school absence and medication use associated with an increase in air pollutants by one interquartile range (see table 4) adjusted for trend, temperature and weekend (*versus* weekdays) with 95% confidence intervals in parentheses

	Fever		School absence		Medication use			
					β-agonist		Theophylline	
Current day								
SO_2	1.16*	(1.02 to 1.32)	1.00	(0.96 to 1.04)	1.05	(0.95 to 1.17)	1.02	(0.98 to 1.05)
TSP	0.98	(0.81 to 1.17)	0.98	(0.94 to 1.02)	1.14*	(1.02 to 1.28)	1.01	(0.97 to 1.05)
PM_{10}	1.05	(0.88 to 1.25)	1.03	(0.98 to 1.09)	1.05	(0.89 to 1.24)	1.01	(0.96 to 1.07)
SO_4	1.35*	(1.09 to 1.67)	1.05	(0.99 to 1.12)	1.07	(0.90 to 1.28)	1.04	(0.99 to 1.09)
PSA	1.07	(1.00 to 1.14)	1.01	(0.98 to 1.03)	0.96	(0.87 to 1.06)	1.00	(0.98 to 1.03)
Five day mean								
SO_2	1.52*	(1.29 to 1.80)	1.10*	(1.05 to 1.15)	1.32*	(1.16 to 1.50)	1.05	(1.00 to 1.09)
TSP	1.08	(0.89 to 1.31)	0.99	(0.94 to 1.04)	1.23*	(1.07 to 1.41)	1.03	(0.99 to 1.08)
PM_{10}	1.13	(0.95 to 1.34)	1.03	(0.99 to 1.09)	1.21*	(1.05 to 1.40)	1.05	(1.00 to 1.10)
SO_4	1.99*	(1.63 to 2.43)	1.09*	(1.03 to 1.15)	1.27*	(1.10 to 1.47)	1.07*	(1.02 to 1.12)
PSA	1.47*	(1.34 to 1.61)	1.14*	(1.11 to 1.18)	1.12*	(1.02 to 1.23)	1.05*	(1.02 to 1.08)

*: $p<0.05$. For definitions see legend to table 1.

Table 7. – Analyses of respiratory morbidity* adjusted for trend, temperature and weekend (*versus* weekdays) and fever prevalence of the sample with 95% confidence intervals in parentheses, from two models, with (Model 2) or without (Model 1) an interaction term

	Model 1		Model 2		
	5 day mean of SO_4 (6.5 µg·m^{-3})	Fever prevalence (0.1)	5 day mean of SO_4 (6.5 µg·m^{-3})	Interaction (0.1×6.5 µg·m^{-3})	Fever prevalence (0.1)
Lung function					
$PEF_{morning}$ L·min^{-1}	-1.34* (-2.53 to -0.16)	-4.16* (-7.56 to -0.76)	-0.73 (-2.09 to 0.62)	-3.51 (-7.12 to 0.11)	1.91 (-4.95 to 8.77)
$PEF_{evening}$ L·min^{-1}	-1.44* (-2.48 to -0.40)	-5.77* (-9.07 to -2.47)	-0.98 (-2.20 to 0.24)	-2.75 (-6.34 to 0.85)	-0.84 (-7.94 to 6.26)
Respiratory symptoms					
Cough	1.01 (0.96 to 1.06)	2.08* (1.76 to 2.45)	0.98 (0.92 to 1.04)	1.11 (0.93 to 1.33)	1.74* (1.20 to 2.52)
Dyspnoea	1.07* (1.00 to 1.15)	1.18 (0.93 to 1.49)	1.09* (1.01 to 1.19)	0.89 (0.68 to 1.16)	1.45 (0.84 to 2.51)
Phlegm	1.09* (1.03 to 1.15)	1.72* (1.43 to 2.06)	1.00 (0.94 to 1.07)	1.47* (1.21 to 1.79)	0.87 (0.56 to 1.33)
Runny nose	1.07* (1.02 to 1.11)	2.11* (1.86 to 2.41)	1.06* (1.01 to 1.11)	1.03 (0.89 to 1.19)	2.02* (1.50 to 2.73)
School absenteeism					
School absence	0.91* (0.84 to 0.97)	3.81* (3.10 to 4.68)	0.96 (0.87 to 1.05)	0.82 (0.65 to 1.03)	5.33* (3.38 to 8.41)
Medication use					
Beta-agonist	1.31* (1.12 to 1.54)	0.70* (0.40 to 1.23)	1.19* (1.00 to 1.43)	1.94* (1.00 to 3.79)	0.20* (0.04 to 0.88)
Theophylline	1.05 (1.00 to 1.10)	1.17 (1.00 to 1.37)	1.08* (1.01 to 1.14)	0.88 (0.73 to 1.05)	1.45* (1.00 to 2.08)

*: regression coefficients or odds ratios are presented for an increase of 6.5 µg·m^{-3} SO_4 and an increase in fever prevalence of 10% as it occurred during the January episode. For definitions see legends to tables 1 and 3.

low prevalences (fig. 2). This period of increased fever began 5 days before the second major SO_4 episode. Twenty five children reported fever between January 20, 1992 and February 4, 1992, while 50 children experienced no fever during the same period. Data were missing for 14 children. A restricted regression analysis for SO_4 as an indicator pollutant considering only the time between September 1, 1991 and December 31, 1991 was conducted in order to evaluate the stability of the results. The results for ΔPEF remained almost unchanged ($\Delta PEF_{evening}$ -1.60 L·min^{-1} per 6.5 µg·m^{-3} 5 day mean of SO_4 (95% CI -2.69 to -0.51 L·min^{-1}). However, the odds ratios (ORs) estimated for the associations between respiratory symptoms and SO_4 concentrations were close to 1.00, and no longer statistically significant. The associations between fever and SO_4 persisted (OR 1.66 for an increase of 6.5 µg·m^{-3} 5 day mean of SO_4 (95% CI 1.10 to 2.49)).

In order to evaluate the role of fever as an independent risk factor or as an effect modifier, further analyses were conducted: 1) the prevalence of fever in the sample of children under observation was incorporated as an independent risk factor into the model; 2) an interaction between the prevalence of fever in the sample and the exposure to a 5 day mean of SO_4. The results for a 5 day mean of SO_4 are presented in table 7. A decrease in lung function and an increase in reports of cough, phlegm, and runny nose were noted in association with the prevalence of fever. As expected, school absence was strongly correlated with fever. The associations between a 5 day mean of SO_4 and PEF, dyspnoea, phlegm, runny nose and use of β-agonist remained, although most effect estimates were smaller. Including an interaction term between the fever prevalence and a 5 day mean of SO_4 into the model suggested that the associations between SO_4 and lung function were non-significant in the absence of fever. A strong but not significant negative association was observed in the presence of fever. Increased levels of SO_4 were associated with dyspnoea, runny nose and theophylline, independent of the presence of fever. The association between phlegm and SO_4 was only observed whilst the children reported fever. The use of β-agonists increased in association with SO_4 and appeared to further increase at times when the sample recorded fever.

Discussion

Asthmatic children from Sokolov, Czech Republic, showed a small, statistically significant association between lung function and winter air pollution. Respirable particles characterized by measurements of SO_4 were associated with decreases in PEF. Other pollutants, such as SO_2 and PSA, showed smaller but statistically significant effect estimates. Generally, weaker associations were observed for the $PEF_{morning}$ than $PEF_{evening}$.

A recent review [10] presented a meta-analysis of panel studies published so far. Combined effect estimates were calculated for a 10 µg·m^{-3} increase of PM_{10} (daily mean) and resulted in a 0.08% decrease for PEF in the evening. For the children from Sokolov, a decrease of 0.06% was observed for an increase of 10 µg·m^{-3} PM_{10} on the same day (300 L·min^{-1} = 100%). However, an

increased 5 day mean of 5 $\mu g \cdot m^{-3}$ SO_4, an exposure which occurred repeatedly in Sokolov, was associated with a 0.48% decrease in lung function. Formation of sulphuric acid from SO_2 can occur either *via* oxidation on aerosol surfaces catalysed by transition metals or oxidation in cloud water or fog [22]. Relatively high SO_4 concentrations were accompanied by low particle acidity [19]. Some evidence concerning the role of acid aerosols in the exacerbation of respiratory disease was collected [9, 13, 21, 23], but, given the low concentrations, it did not appear to play an important role in Sokolov.

Prevalence of the respiratory symptoms increased in association with concurrent and prolonged exposure to SO_4, showing stronger associations for the 5 day means than the same day. Other pollutants, such as SO_2 and PSA, showed similar or weaker effects. Respiratory symptoms assess different aspects of the respiratory health in children. Phlegm and runny nose are symptoms of the upper respiratory tract, whilst cough and dyspnoea are symptoms of the lower airways. The data presented here suggested that both the upper and lower airways were affected by air pollution. Other indicators for increased morbidity, such as the prevalence of school absence, fever and the use of asthma medication, showed associations with elevated levels of SO_2 and SO_4. Both beta-agonist and theophylline use appeared to be related to increased exposure to air pollution.

Weather conditions or viral epidemics are potential confounders, which might cause over- or underestimation of true associations. All regression analyses controlled for temperature, which was clearly associated with the lung function measurements, but did not alter the effect estimates for the air pollutants. Respiratory infections would be characterized by symptoms like cough or runny nose and reduced lung function, and in more severe cases phlegm and dyspnoea. In addition, fever could be an indicator for an influenza epidemic. Graphical presentation of the data (figs. 1 and 2) suggested the strongest associations between air pollution and symptoms or PEF at the end of January. A coincidence of an influenza epidemic and elevated air pollution levels during this period might lead to spurious associations. No explicit data on the presence of an influenza epidemic are available for Sokolov. Mortality data are available for Thüringen, a German state situated approximately 30 km northwest of Sokolov. There were no abnormal increases of mortality observed during January or February 1992 in comparison to a standardized mortality curve (Mey, personal communication). However, serum levels for influenza virus b were elevated between January 17, 1992 and March 15, 1992 in Thüringen (Robert-Koch Institut, Berlin, personal communication). In order to evaluate the role of viral infection, additional analyses were conducted including the fever prevalence observed in the sample as an independent variable into the regression analyses. These analyses suggested that the effect estimates which were obtained without adjustment for the prevalence of fever might be overestimated.

Interdependencies between viral infections and air pollution still remain an open question. In areas with higher air pollution, respiratory infections or respiratory illnesses were more prevalent [1, 3]. PÖNKÄ [24] addressed this issue in a longitudinal study, showing that increased levels of SO_2 on a weekly basis might be associated with absenteeism and respiratory infections. Absenteeism from schools and kindergartens alone was found to be associated with PM10 concentrations [25, 26]. In the data presented here, the coincidence between an air pollution episode and indicators for morbidity was striking, given the prolonged presence of elevated virus titre in serum from the middle of January to the middle of March.

Only weak associations were found between concurrent air pollution concentrations and health outcomes in the panel of children from Sokolov. POPE and co-workers [6] compared a school-based sample of children with respiratory symptoms with a panel of asthma patients. Asthma patients showed polynomial distributed lag structures for PM10 and PEF, suggesting that a 5 day mean would show bigger effect estimates than concurrent exposure to PM10. The school-based sample showed an immediate effect of particulate air pollution on PEF and symptoms, but the asthma panel did not. There are two possible explanations for these findings. Firstly, bronchodilator use, which increased in the asthma panel in association with PM10, might have suppressed decreases in PEF. The results of experimental studies [27–29] suggested that effect estimates for air pollution on symptoms might be underestimated when medication is used concurrently by asthmatic patients. Secondly, the observed associations might be present only after a prolonged exposure to air pollution. This could indicate that the observed health outcomes might be related to inflammatory processes, as proposed recently [30], which need some time to manifest themselves.

The results presented here for the panel from Sokolov, Czech Republic, are consistent with reported associations between air pollution and small decreases in lung function [4, 5, 7, 9, 31–35]. Short-term effects could be responsible for an overall increased prevalence of respiratory diseases as observed in association with air pollution [1–3, 24, 36]. Exacerbation of respiratory infections might even contribute to the observed associations between air pollution and hospital admissions [37], or mortality [38–43].

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