

REVIEW

Pollution effects on asthmatic children in Europe, the PEACE study

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Introduction

The Pollution Effects on Asthmatic Children in Europe (PEACE) study was designed to study the relationship between short-term changes in air pollution and lung function, respiratory symptoms and medication use. In recent years several studies showed effects of particles with a 50% cut-off aerodynamic diameter of $10\mu\text{m}$ (PM_{10}) on the respiratory health of children [1–4]. These results raised questions about the possible acute health effects of current air pollution levels in Europe. Further, in Western as well as in Central-Eastern Europe there was only limited data available on PM_{10} levels in urbanized and nonurbanized locations. Thus, the goals of the PEACE study were to obtain comparable data on particle concentrations during winter time in various urban and nonurban locations in Europe, to assess the relationship between short-term fluctuations in air pollution and short-term fluctuations in respiratory health in children with chronic respiratory symptoms and to evaluate if medical characteristics of the subjects were related to differences in response to air pollution. In addition, the elemental composition of the particles was determined to evaluate the hypothesis that certain elements such as transition metals in the particles are more closely associated with health than PM_{10} mass concentrations [5].

Materials and methods

Within the PEACE study 14 European centres collaborated (see appendix 1). The study was conducted in the winter of 1993–94 following a standardized protocol [6]. Two panels of at least 75 children each were followed during at least two months. Children between 6 and 12 years with chronic respiratory symptoms were selected by a parent completed screening questionnaire. The criteria for selection were: reporting in the last 12 months of wheeze (apart from colds), attacks of shortness of breath with wheezing, dry cough (apart from colds), and/or doctor diagnosed asthma

ever in life. One panel was selected from an urban region, the other panel lived in an area in which air pollution concentrations were thought to be considerably lower, the so-called suburban or rural location (hereafter referred to as suburban panels). See also appendix 1 and Fig. 1. Suburban panels were included to evaluate differences in effects of air pollution related to the level and composition of air pollution, in panels experiencing the same meteorological characteristics.

To further characterize the children, skin prick tests to common allergens (*Dermatophagoides pteronyssinus*, cat fur, pollen of timothy grass and birch and two locally important allergens) were applied, baseline lung function was measured and a detailed questionnaire on housing characteristics, environmental tobacco smoke (ETS) exposure and parental education was administered to the parents. Methods are given in detail elsewhere [6].

Exposure to air pollution was monitored on a daily basis at sites not influenced by sources in the immediate vicinity, so called 'background' sites. Daily variations in health status were measured by twice-daily PEF measurements and a symptom diary. The symptoms in the diary were cough, phlegm, runny/stuffed nose, woken up with breathing problems, shortness of breath, wheeze, attack(s) of shortness of breath with wheeze, fever, eye irritation and sore throat. Medication use was also recorded.

Daily prevalence and incidence of symptoms and medication use were calculated from the diaries for each panel and analysed using logistic regression with correction for autocorrelation. Morning and evening PEF were separately recalculated to daily individual deviations from child specific means [1–2,6] and analysed using linear regression with correction for autocorrelation.

Independent variables were 24 h average concentrations of PM_{10} , Black Smoke (BS), SO_2 , NO_2 . From about half of the locations the soluble concentrations of nickel, zinc, vanadium, iron, silicon, sodium and lead in PM_{10} were determined with Inductively Coupled Plasma Mass Spectrometry (ICP-MS). These were included as independent variables as well. Nickel, zinc, vanadium, iron were included because of the capability of these transition metals to generate free radicals shown in toxicological studies [7–11]. Iron was also related to respiratory health in an

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Figure 1. Approximate location of urban sites.

epidemiological study [12]. Silicon, sodium and lead were included as possible tracers for soil dust, sea spray, and leaded gasoline emissions, respectively. Current day concentration (lag0), previous day concentration (lag1), concentration of 2 days before (lag2) and the average of lag 0–6 days (7 day mean) were analysed separately. As potential confounders, temperature, time trend and weekend/holidays were taken into account. The regression slopes of the air pollution components from the linear and logistic regression models for each panel were used to calculate combined effect estimates. A combined fixed effect estimate was calculated as the weighted mean of the panel-specific slopes with the weights being inversely proportional to the panel-specific variance. In case of heterogeneity in the effect estimates, combined effect estimates using random effect estimation were calculated with a noniterative method with unequal weights [13].

Combined effect estimates were also calculated within predefined subgroups. Effect estimates for urban and

suburban children were compared evaluate the potential additional effect of urban air pollution over air pollution in suburban or rural locations. Effect estimates from different European areas were compared to evaluate climatic influences or regional differences in the toxicity of the air pollution mixture. Effect estimates from areas with different mean mass concentrations and ratios of air pollution components were compared to evaluate possible modification of effects by the mean level and composition of air pollution.

Subgroup analysis

For the evaluation of possible differences in response to air pollution, subgroups of subjects were defined. Subgroups were defined on the basis of medication use, presence of specific chronic respiratory symptoms, gender, atopy and baseline lung function. Three subgroups based on combinations of medication use and specific symptoms were evaluated: (1) children having asthma symptoms (wheeze

Table 1. Average (maximum) 24 h air pollution concentrations in $\mu\text{g}/\text{m}^3$ during the winter of 1993/94

	Urban location				Rural location			
	PM ₁₀	BS	SO ₂	NO ₂	PM ₁₀	BS	SO ₂	NO ₂
Umeå	13.4 [40.5]	4.6 [33.2]	2.7 [11.6]	25.0 [74.6]	11.5 [29.0]	5.3 [91.9]	4.0 [15.2]	15.3 [49.3]
Malmö	22.9 [59.0]	8.2 [36.8]	6.0 [16.6]	20.7 [42.5]	16.2 [38.0]	4.5 [15.6]	4.0 [15.6]	8.9 [21.8]
Oslo	19.3 [63.0]	27.6 [104.0]	12.4 [42.0]	49.3 [123.3]	11.2 [31.0]	13.1 [47.0]	3.4 [38.0]	20.8 [57.3]
Kuopio	17.7 [60.4]	12.6 [56.9]	6.0 [32.4]	–	13.0 [37.3]	7.9 [47.1]	–	13.7 [51.4]
Amsterdam	45.3 [122.9]	16.5 [64.7]	13.2 [33.6]	46.4 [75.9]	44.4 [242.2]	13.6 [58.1]	8.5 [41.5]	26.5 [54.3]
Berlin	52.3 [117.3]	24.5 [65.0]	42.3 [115.2]	38.3 [72.1]	43.0 [105.5]	22.0 [74.0]	26.1 [107.7]	21.2 [53.4]
Hettstedt	40.3 [95.1]	42.0 [170.0]	83.3 [498.5]	26.5 [93.6]	32.9 [95.2]	25.5 [97.3]	64.9 [331.9]	26.1 [69.4]
Budapest	60.9 [161.7]	48.9 [134.6]	49.7 [121.7]	35.3 [67.5]	52.1 [117.0]	30.0 [80.1]	41.0 [88.3]	25.4 [58.6]
Katowice	68.7 [157.0]	55.5 [151.4]	55.7 [152.0]	68.7 [176.0]	73.8 [140.0]	57.9 [113.9]	56.0 [141.0]	69.5 [134.0]
Cracow	60.1 [184.0]	34.9 [112.0]	41.3 [136.0]	–	56.1 [219.0]	42.7 [123.0]	14.0 [37.0]	–
Prague	52.7 [188.0]	29.4 [108.4]	113.9 [419.4]	44.7 [89.1]	49.6 [159.0]	20.8 [56.2]	30.8 [76.1]	12.9 [23.9]
Teplice	74.0 [205.0]	59 [163]	75 [211]	49 [87]	32 [174]	22 [83]	20 [54]	13 [29]
Pisa	61.8 [131.0]	19.7 [42.6]	15.7 [30.4]	68.1 [119.6]	69.5 [149.0]	29.3 [95.6]	8.2 [25.0]	32.7 [74.5]
Athens	98.8 [201.0]	109.2 [238.0]	72.4 [156.2]	74.9 [116.0]	50.0 [115.0]	33.5 [188.0]	–	19.7 [49.8]

or asthma diagnosis) and using respiratory medication; (2) children having asthma symptoms and not using respiratory medication; and (3) children reporting dry cough at night (without wheeze or asthma diagnosis) and not using medication. Medication use was defined as the use of bronchodilators (such as salbutamol, albuterol, fenoterol, terbutaline) or maintenance/preventive medication (such as cromolyn, theophylline, antihistamine or corticosteroid) on any day during the study period. The association between PEF and air pollution was calculated with individual linear regression with correction for autocorrelation in the residuals. The distribution of these individual coefficients in the above-defined subgroups was studied.

The association between respiratory symptom prevalence and air pollution was calculated within the subgroups in each panel separately, followed by calculation of a subgroup-specific combined effect estimate for all panels (see above).

Results

The lowest air pollution concentrations were found at the Scandinavian locations, whereas the highest concentrations were found in Southern and Eastern Europe (Table 1). The difference of particle concentrations across countries appeared to be considerably larger than the difference between the urban and suburban/rural location within countries. PM₁₀ and BS concentrations in the urban area were on average 22% and 43% higher than the corresponding suburban/rural area concentrations, respectively. This difference was larger for SO₂ and NO₂. The Spearman correlation between the particle concentrations measured at the urban and the suburban/rural site exceeded 0.70 at almost all sites.

PM₁₀ concentrations from all Western and Eastern European locations were also significantly correlated, consistent with similar meteorological conditions and long range transport. On the contrary, no or a low correlation was found between pollution levels in Western and Eastern European locations on the one hand and pollution levels in Southern-Europe and Scandinavian locations on the other. PM₁₀ and BS measured at the same site were highly correlated at most sites. Correlations between SO₂ and NO₂ were lower. See also [14].

Combined estimates of the effect of air pollution on Peak Expiratory Flow (PEF) are shown in Table 2. There was no clear association between PM₁₀, BS, SO₂ or NO₂ and evening PEF. Only PM₁₀ lag1 was negatively associated with evening PEF. Further analysis showed that this was only in locations where BS was high compared to PM₁₀ concentrations. Morning PEF was not associated with air pollution. There were no consistent differences in effect estimates between subgroups based on urban vs suburban/rural location, geographical location or mean levels of PM₁₀, BS, SO₂ and NO₂. Table 2 also shows the combined effect estimates of air pollution on the prevalence of respiratory symptoms and medication use. No clear associations between PM₁₀, BS, SO₂, NO₂ and symptom prevalence or medication use could be detected. Incidence of respiratory symptoms and medication use was also not associated with air pollution. There were no consistent differences in effect estimates between subgroups based on urban vs. suburban/rural location, geographical location or mean levels of PM₁₀, BS, SO₂ and NO₂ or ratio of mean PM₁₀ and BS concentration. More details can be found elsewhere [15].

Table 2. Combined effect estimates and 95% confidence intervals (95% CI) for 100 µg/m³ increase in air pollution on evening PEF and prevalence of respiratory symptoms and medication use

	Mean* (95% CI)	Prevalence		
		Phlegm OR† (95% CI)	LRS OR† (95% CI)	Bronchodilator use OR† (95% CI)
PM ₁₀				
Lag0	0.4 (−0.1, 0.9)	0.99 [0.92, 1.05]	0.93 [0.85, 1.01]	0.99 [0.93, 1.05]
Lag1	−0.6 (−1.1, −0.1)	1.02 [0.94, 1.11]	1.00 [0.91, 1.10]	0.93 [0.86, 1.02]
Lag2	0.2 (−0.5, 0.9)	0.98 [0.92, 1.05]	0.94 [0.86, 1.03]	0.99 [0.91, 1.07]
7 day mean	0.0 (−1.7, 1.7)	0.89 [0.71, 1.10]	0.88 [0.62, 1.23]	0.85 [0.66, 1.10]
Black smoke				
Lag0	0.1 (−0.5, 0.7)	1.02 [0.96, 1.08]	0.93 [0.83, 1.04]	0.99 [0.92, 1.06]
Lag1	−0.3 (−0.9, 0.3)	1.03 [0.93, 1.14]	0.92 [0.81, 1.04]	0.94 [0.87, 1.02]
Lag2	0.4 (−0.2, 1.0)	0.97 [0.88, 1.08]	0.93 [0.82, 1.04]	0.97 [0.90, 1.05]
7 day mean	0.6 (−1.5, 2.7)	0.90 [0.63, 1.28]	0.90 [0.55, 1.47]	0.88 [0.60, 1.29]
SO ₂				
Lag0	0.1 (−0.3, 0.5)	0.97 [0.92, 1.03]	0.96 [0.89, 1.04]	0.99 [0.92, 1.06]
Lag1	0.0 (−0.4, 0.4)	0.98 [0.91, 1.06]	0.99 [0.88, 1.13]	0.94 [0.88, 1.01]
Lag2	0.1 (−0.4, 0.6)	0.96 [0.87, 1.06]	0.90 [0.78, 1.03]	0.97 [0.87, 1.08]
7 day mean	0.2 (−0.5, 0.9)	0.80 [0.60, 1.06]	0.88 [0.58, 1.33]	0.88 [0.68, 1.13]
NO ₂				
Lag0	0.4 (−0.5, 1.3)	0.98 [0.91, 1.06]	1.06 [0.89, 1.27]	0.96 [0.87, 1.06]
Lag1	0.0 (−0.9, 0.9)	0.98 [0.86, 1.12]	0.91 [0.78, 1.05]	0.98 [0.85, 1.12]
Lag2	0.2 (−0.7, 1.1)	0.97 [0.86, 1.08]	0.86 [0.72, 1.01]	0.99 [0.89, 1.10]
7 day mean	0.6 (−3.1, 4.3)	0.79 [0.55, 1.15]	0.89 [0.48, 1.67]	0.82 [0.52, 1.30]

*Mean effect estimates expressed as L/min per 100 µg/m³; †mean odds ratio per 100 µg/m³. LRS = lower respiratory symptoms.

Potentially more sensitive subgroups were defined based on presence of specific chronic respiratory symptoms, respiratory medication use, atopy, sex and baseline lung function. The association between PEF and air pollution was positive in asthmatic children using respiratory medication whereas the associations tended to be negative in children selected on 'dry cough at night' who were not using respiratory medication. The prevalence of bronchodilator use was not associated with air pollution in the group of asthmatics using medication. Among asthmatics not using medication, no consistent associations were seen. The association between daily symptom prevalence and air pollution levels was not different between these subgroups. See also [16].

Finally, the relationship between soluble elemental concentrations in PM₁₀ and acute respiratory health effects was explored in some of the locations of the PEACE study. Median concentrations of iron ranged from 105 (Oslo) to 1110 (Athens) ng/m³ in the urban and from 32 (Kuopio) to 517 (Pszczyna) ng/m³ in the suburban locations. Daily concentrations of most elements were not associated with daily variation in PEF or prevalence of respiratory symptoms or bronchodilator use. Silicon and iron concentrations

tended to be negatively associated with PEF, and were positively associated with the prevalence of phlegm (Table 3). In two pollutant models PM₁₀ effect estimates on phlegm prevalence were reduced and lost significance whereas the effect estimates of iron or silicon essentially did not change. The effects of silicon and iron could not be separated. See also [17].

Discussion

No clear association between changes in PM₁₀ mass concentration, BS, SO₂ and NO₂ and changes in PEF or incidence or prevalence of respiratory symptoms could be detected in the PEACE study. These results are at variance with those of several previous panel studies conducted in the USA and Europe [18], using similar methodologies, at levels of PM₁₀ which were comparable to those in at least some of the areas studied in the PEACE study. Several possible explanations for this discrepancy are discussed below. We will start by discussing several forms of potential bias that may have occurred in the PEACE study but are not unique to it. Then we will focus on some aspects that could be more specific to the PEACE study.

Table 3. Combined effect estimates and 95% confidence intervals (95% CI) of air pollution on evening PEF and prevalence of respiratory symptoms and medication use in centres which provided data on soluble elemental concentrations in PM₁₀

	Mean* (95% CI)	Prevalence		
		Phlegm OR† (95% CI)	LRS OR† (95% CI)	Bronchodilator use OR† (95% CI)
Iron‡				
Lag0	-0.1 (-0.8, 1.0)	1.05 [0.93, 1.19]	1.09 [0.95, 1.24]	1.08 [0.99, 1.17]
Lag1	-0.3 (-1.0, 0.4)	1.15 [1.02, 1.30]	1.04 [0.88, 1.23]	0.98 [0.90, 1.07]
Lag2	-0.4 (-1.1, 0.3)	1.13 [1.00, 1.28]	0.96 [0.80, 1.15]	1.05 [0.96, 1.14]
7 day mean	-0.2 (-3.0, 2.6)	1.25 [0.98, 1.59]	0.96 [0.66, 1.40]	0.90 [0.66, 1.23]
Silicon‡				
Lag0	-0.2 (-0.8, 0.4)	1.05 [1.00, 1.10]	1.00 [0.94, 1.06]	1.00 [0.95, 1.05]
Lag1	-0.4 (-0.9, 0.1)	1.09 [1.03, 1.15]	1.04 [0.98, 1.11]	0.98 [0.95, 1.02]
Lag2	-0.4 (-0.8, 0.0)	1.05 [0.99, 1.11]	1.01 [0.93, 1.10]	1.01 [0.97, 1.04]
7 day mean	-0.7 (-2.0, 0.6)	1.18 [1.02, 1.37]	0.87 [0.71, 1.05]	0.87 [0.79, 0.96]
PM ₁₀ ‡				
Lag0	-0.1 (-0.6, 0.8)	1.00 [0.94, 1.07]	1.00 [0.87, 1.15]	0.99 [0.92, 1.08]
Lag1	-1.1 (-1.8, -0.4)	1.12 [1.01, 1.23]	0.99 [0.87, 1.12]	0.98 [0.90, 1.06]
Lag2	-0.8 (-1.6, 0.0)	1.00 [0.94, 1.07]	0.89 [0.79, 1.01]	0.92 [0.85, 1.00]
7 day mean	-1.6 (-4.0, 0.8)	1.03 [0.79, 1.36]	0.89 [0.56, 1.44]	0.82 [0.59, 1.14]

*Mean effect estimates expressed as L/min per increase in concentration; †mean odds ratio per increase in concentration; ‡increase of 1000 ng/m³ (iron, silicon), 100 µg/m³ (PM₁₀). LRS = lower respiratory symptoms.

Exposure assessment and air pollution

Would we have found different associations with air pollution if we had measured other components in the air pollution mixture?

This is unlikely for PM_{2.5} as PM₁₀ and PM_{2.5} are highly correlated [19]. Aerosol acidity measurements in Czech Republic [20], Germany [21] and in the Netherlands [22] showed very low levels during wintertime which reduces the possibility that acidity would be associated with acute effects on respiratory health. We did not have information about the number of ultrafine particles and can not evaluate if this measure may have been a better indicator for health effects as was suggested by Peters *et al.* [23].

The PEACE study was the first epidemiological study to evaluate the association between soluble transition metals in PM₁₀ and respiratory health, but did not provide strong evidence of a relation. First, we only found some associations with respiratory health for iron and silicon and not for other transition metals. Second, iron was not more consistently associated with respiratory health than PM₁₀ mass (PEF) and silicon (PEF and phlegm). Third, associations were found only for phlegm and less consistently PEF. Other studies have documented the strongest associations with PM for lower respiratory symptoms and bronchodilator

use [1–3,18]. With these endpoints we did not observe any association.

To estimate the exposure of the panels to air pollution fixed air pollution measurement sites were used and one might wonder if this represents well enough the personal exposure of the subjects who spent most of the time indoors. However, recent studies support the use of outdoor measurements of PM as a measure of exposure in panel studies [24–26] as outdoor measurements were found to be highly correlated with personal measurements over time in these studies.

Sensitive subgroups

Did we study the most sensitive subjects in the population?

As explained in the methods section, the PEACE study investigated children with chronic respiratory symptoms only, and we can not compare our findings to nonsymptomatic children within the study itself. The subgroups we defined within the study were not different from each other with respect to associations between air pollution and respiratory health. This is in contrast with a recent study [27] in which children with elevated serum IgE levels and bronchial hyperresponsiveness were more susceptible to air pollution than children without these characteristics.

Explanations for the discrepancy with that study may be the differences in medical characterization and the longer study period (see below). In the PEACE study medication use and chronic respiratory symptoms were related to response to air pollution such that children with asthmatic symptoms using bronchodilators showed an increase in PEF with an increase in air pollution levels. This seems to indicate that these children counteract the effects of air pollution with bronchodilators. Pope [2] and Silverman [28] have reported a similar finding. However, the prevalence of bronchodilator use did not increase with increasing air pollution levels in the group of asthmatic children who used bronchodilators. However, this might also indicate that the children increased the daily dose of the bronchodilators which is not reflected in changes in the proportion of children using bronchodilators on any given day.

Statistical power

Was the statistical power of the study sufficiently large to detect associations between air pollution and respiratory health?

The statistical power of this study was certainly high enough to detect an association. Given the standard errors in Table 2 and assuming a mean PEF of 300 L/min, an increase of $10 \mu\text{g}/\text{m}^3$ PM_{10} would have to be related to a reduction in PEF of only 0.02% to become significant at the 5% probability level. Compared to an overview by Dockery *et al.* [18] in which PEF reductions between 0.04% and 0.25% for a $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM_{10} were reported, it is clear that the PEACE study with its large volume of data had no lack of statistical power.

Information bias

Was the accuracy and precision of our measurements sufficiently high?

The actual use of the PEF meters might have been overestimated in the PEACE study [29]. Checks were performed in order to identify subjects who 'invented' PEF values. These checks consisted of identifying extremely high values and long periods with no variation in the PEF measurements. The checks can not detect invented values that vary around the mean PEF value. If the proportion of these invented values is not correlated to the exposure levels, the SE of the effect estimate will be increased and the effect estimate will be biased towards the null. Invented values in symptom diary data are more difficult to detect and it is possible that the prevalence of reported respiratory symptoms declines over time due to decreasing motivation. By inclusion of a third order polynomial during the analysis we attempted to correct for such long-term time trends which

makes it unlikely that decreasing motivation has biased the effect estimates.

Publicity about smog episodes might increase the awareness of parents and cause an increase in symptom prevalence reporting. This will generally lead to a bias away the null and thus can not be an explanation for the lack of effect in the PEACE study. In addition, only in one location (Prague) a smog alert was issued during the winter of 1993–94.

The validity of parental reporting of symptoms in children might be another explanation for the lack of effect in the PEACE study [30]. On the other hand, previous panel studies which showed an effect of air pollution on respiratory health [1–3] also used parental symptom reporting which indicates that this method is able to measure effects of air pollution on respiratory health.

We will now turn to two related aspects which were more specific to the PEACE study and which may explain some of the differences with other panel studies.

Time trend

Were we able to sufficiently take time trends in the data into account?

In all peak flow analyses, linear and square root time trend terms were introduced to correct for lung growth and training effects. Also, the first two days in the diary were discarded to remove a potential learning effect. In the analysis of daily incidence and prevalence of symptoms, a third order polynomial was included to correct for time trends. Residuals were inspected and if necessary, large deviations were additionally modelled with dummy variables. This adjustment usually resulted in only small changes of the effect estimates of air pollution, however. In recent years, modelling of time series with nonparametric smoothing techniques has become common [31]. These techniques are more flexible than the parametric techniques we used for modelling irregular time trends. We selected some panels which had a large contribution in the combined effect estimate or which had an effect estimate opposite to expected. These panels were reanalysed using a nonparametric smoothing function of time. This procedure did not materially change effect estimates, however. Compared to previous panels studies time trends were more carefully modelled as these studies modelled linear time trends or no time trends at all.

Length of the study period

Was the study period sufficiently long to adequately establish associations between air pollution and respiratory health?

The period of analysis was in most PEACE panels not more than two months. Earlier panel studies generally lasted three

months [1–3] or more so the PEACE study had a relatively short period of observation. This might mean that it is more difficult to separate the effects of air pollution from the effects of unexpected events that also influence respiratory health. Because of the importance of subject co-operation, panel studies are much more limited in time than for instance studies on daily mortality and hospital admissions which use routinely collected data. Panel studies are therefore more vulnerable to unmeasured factors or events which occur during the study and are associated with air pollution as well as health. It is reasonable to expect that 2-month time series studies on mortality or hospital admissions will also show more variability in their results.

Respiratory infections and interdependence of panel results

Have we been able to adequately adjust for respiratory infections?

Respiratory infections have been suggested as possible confounder in the relation between respiratory health and air pollution [20]. We were unable to collect detailed data on respiratory infections in the panels, and depending on the association in time between respiratory infections and air pollution, associations between air pollution and respiratory health indicators may have become completely obscured or even reversed in our data. The prevalence of fever in the measurement period was very low, with no large fluctuations, and asking about fever may not be a sensitive tool for assessing respiratory infections, which may often lead to symptoms and reduced lung function without causing fever. Data from a sentinel system available in the Netherlands suggested that the prevalence of influenza-like illness as measured by the participating family doctors in the sentinel system was a predictor of outcome variables in the Dutch panels [32]. Depending on the correlation in time between air pollution and the influenza prevalence, influenza or other respiratory infections may have biased the effect estimates of air pollution on respiratory health in either direction. In addition, the results from the separate PEACE panels were not completely independent from each other. The particle measurements in the western and central European locations were correlated with each other and in the winter of 1993–94 an influenza epidemic occurred in Europe [33] which possibly influenced the occurrence of respiratory symptoms in the panels. So, this epidemic may have reduced the independence of the panels even more. It is interesting to note that the Dutch part of the PEACE study was part of a larger series of panel studies which spanned three winters instead of one, and which included nonsymptomatic children as well. Also all subjects were characterized by measuring bronchial hyperreactivity and serum IgE in

addition to the skin prick tests used in the PEACE study, and we were able to adjust our associations for influenza. The results of these studies show clear effects of air pollution on symptomatic children compared to nonsymptomatic children [34]. They also show that subjects with bronchial hyperreactivity and increased serum IgE were more sensitive [27].

Concluding remarks

No clear relation could be established between changes in PM₁₀, black smoke, SO₂, NO₂ and changes in respiratory health in the PEACE study. There were no clear differences in reaction between subgroups based on medical characteristics. Concentrations of iron and silicon in PM₁₀ were associated with prevalence of phlegm, which suggested that more focus on particle composition is needed in future studies.

In retrospect the major limitation of the PEACE study seems to have been the short observation period. This made the study vulnerable to any event or factor that was affecting respiratory health in the study weeks in ways that could have obscured relationships between air pollution and respiratory health. Especially the comparison with the Dutch companion studies suggests that increasing the length of the observation period, preferably including several seasons or years, provides better opportunities to tease out the relatively small effects of air pollution from the background 'noise' in respiratory health indicators.

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Appendix 1. Participating centres

Principal investigator	Institute	Locations (urban, suburban/rural)
G. Baldini	Paediatric clinic, University of Pisa, Pisa, Italy	Pisa, Torre del Lago Puccini
B. Brunekreef*	Department of Epidemiology and Public health, University of Wageningen, The Netherlands	Amsterdam, Meppel
J. Clench-Aas	Norwegian Institute for Air Research, Kjeller, Norway	Oslo, Oslo outskirts
N. Englert	Federal Environmental Agency, Berlin, Germany	Berlin, Berlin outskirts
B. Forsberg	Department of Environmental Health, Umeå University, Umeå, Sweden	Umeå, Holmsund
J. Haluszk	TBC and Lung Diseases-Paediatric division, Rabka, Poland	Cracow, Rabka
A. Kalandidi	Department of Hygiene and Epidemiology, University of Athens, Athens, Greece	Athens, Koropi/Peania/Spata/Palini
F. Kotesovec	District Institute of Hygiene, Teplice, Czech Republic	Teplice, Prachatice
E. Lebre	National Institute of Public Health and the Environment†, Bilthoven, The Netherlands	Statistical assistance
G. Niepsuj	Silesian Medical Academy, Zabrze, Poland	Katowice/Chorzow, Pszczyna
J. Pekkanen	National Public Health Institute, Kuopio, Finland	Kuopio, Kuopio outskirts
P. Rudnai	National Institute of Hygiene, Budapest, Hungary	Budapest, Szentendre
V. Vondra	Institute of pulmonary diseases, Prague, Czech Republic	Prague, Vlasim/Benesov/Votice
H. Welinder	Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden	Malmö, Älmhult/Olofström
H.E. Wichmann	GSF-Institute of epidemiology, Neuherberg, Germany	Hettstedt, Zerbst

*Co-ordinator; †this Institute provided statistical assistance. TBC: tuberculosis, GSF: Forschungszentrum für Umwelt und Gesundheit GmbH.