Pollution Effects on Asthmatic Children in Europe

The PEACE study

Willem Roemer

STELLINGEN

1. De stelling dat de luchtverontreinigingsniveaus in steden veel hoger zou zijn dan daarbuiten is wat betreft PM_{10} in noord, west, en midden Europa niet juist.
Dit proefschrift

2. Er bestaat een sterke correlatie tussen de dagelijkse variaties in PM_{10} concentraties van verschillende locaties in midden en West Europa.
Dit proefschrift

3. Voor studies naar de acute effecten van luchtverontreiniging is het noodzakelijk dat er methoden worden ontwikkeld die het mogelijk maken om adequaat te corrigeren voor confounding die wordt veroorzaakt door het optreden van acute respiratoire infecties.
Dit proefschrift

4. De concentratie van oplosbaar ijzer in PM_{10} hangt sterker samen met acute gezondheidseffecten dan de PM_{10} massa concentratie.
Dit proefschrift

5. In panel studies naar de acute effecten van luchtverontreiniging moet meer aandacht worden besteed aan het correct modelleren van tijdstrends in de afhankelijke variabelen, net zoals dat gebeurt in mortaliteits tijdserie studies.
Dit proefschrift

6. Het evalueren van confounding gebeurt grondiger wanneer de gevonden associatie niet verklaarbaar is, dan wanneer deze wel verklaarbaar is.
(J. Schuit. Stellingen bij het proefschrift: Regular physical activity in old age. Wageningen 1997)

7. De stelling '...the lack of fundamental data on the physiologic effects of a mixture of gases and particulate matter over a period of time is a severe handicap in evaluating the effects of atmospheric pollutants on persons of all ages and in various stages of health' is na bijna vijftig jaar onderzoek nog steeds waar.
(Air pollution in Donora, PA. Epidemiology of the unusual smog episode of October 1948. Preliminary report. Public health bulletin No. 306. Federal security Agency Public Health Service. 1949. p. 162)

8. Het beeld dat men krijgt uit de wetenschappelijke literatuur van de acute effecten van luchtverontreiniging wordt beïnvloed door publicatie bias.

9. De tijdwinst die in epidemiologisch data analyse geboekt kan worden door de steeds sneller wordende computers wordt te niet gedaan door 'ook nog even dit te analyseren'.

10. Integratie van allochtonen in het arbeidsproces in Nederland wordt bemoeilijkt door de hoge eisen die werkgevers stellen aan de beheersing van de Nederlandse én Engelse taal.

11. Uit het feit dat iemand niet van hardlopen houdt kan men niet concluderen dat de persoon in kwestie a-sportief is.

Stellingen behorende bij het proefschrift 'Pollution effects on asthmatic children in Europe. The PEACE project'. Willem Roemer, Wageningen, 15 december 1998.

Pollution Effects on Asthmatic Children in Europe

The PEACE study

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Pollution Effects on Asthmatic Children in Europe

The PEACE study

Proefschrift

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Abstract

This thesis is based upon the 'Pollution Effects on Asthmatic Children in Europe (PEACE)' study. The PEACE study is a multi-centre study of the acute effects of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}), Black Smoke (BS), SO_2 and NO_2 on respiratory health of children with chronic respiratory symptoms. The aims of the PEACE study were to obtain comparable data on particle concentrations during winter time in various urban and non urban 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, to evaluate if medical characteristics of the subjects are related to differences in response to air pollution and to evaluate if the composition of the particles is related to the response to air pollution.

The study was conducted in the winter of 1993-1994 by 14 research centres in Europe. 2010 children, divided over 28 panels in urban and suburban locations were followed during at least two months. Exposure to air pollution was monitored on a daily basis. Health status was monitored by daily Peak Expiratory Flow (PEF) measurements and a symptom diary. The association between respiratory health and air pollution levels was calculated with time series analysis, adjusting for time trends, temperature and day of the week.

The difference of particle concentrations across countries appeared to be considerably larger than the difference between the urban and suburban location within countries. PM_{10} and BS concentrations in the urban area were on average 22% and 43% higher than the corresponding suburban area concentrations respectively. PM_{10} concentrations from all Western and Central European locations were significantly correlated in time. No clear associations between PM_{10}, BS, SO_2 or NO_2 and morning PEF, evening PEF, prevalence of respiratory symptoms or bronchodilator use could be detected. There were no consistent differences in effect estimates between subgroups based on urban vs. suburban, geographical location or mean levels of PM_{10}, BS, SO_2 and NO_2. None of the predefined potentially more sensitive subgroups showed a consistent association between air pollution, PEF and respiratory symptoms. Daily concentrations of most elemental concentrations in PM_{10} were not associated with daily variation in PEF or prevalence of respiratory symptoms or bronchodilator use. However, daily iron and silicon concentrations were related to daily phlegm prevalence.

No clear relation could be established between changes in PM_{10}, BS, SO_2 or NO_2 and changes in respiratory health. This lack of response is not in agreement with earlier studies with comparable levels of exposure to particulate matter. Concentrations of iron and silicon in PM_{10} were associated with prevalence of phlegm and were a better predictor of health effects than PM_{10} mass concentrations.

Contents

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General introduction

History

The effects of air pollution can be chronic as well as acute (1). Elevated levels of air pollutants with a duration of several days (so-called episodes) can occur both in summer and in winter. During a summer episode the concentration of ozone (O_3) increases due to photochemical reactions of air pollutants emitted by traffic and industry. In a classical winter episode increased use of fossil fuel combustion in combination with stagnant weather conditions can yield high concentrations of sulphur dioxide (SO_2) and particulate matter. In this thesis the focus will be on the acute effects of winter type air pollution.

In the twentieth century three major winter-time episodes have been documented which had large acute effects on morbidity and mortality. The three episodes were characterised by stagnant weather in the winter whereas emissions were dominated by coal combustion for industrial or domestic purposes.

The first episode occurred between 1 and 5 December 1930 along the Meuse Valley in Belgium. During five days a fog covered a large part of Belgium and caused emitted air pollutants to be trapped in the Meuse Valley. Hundreds of people reported to have respiratory problems and 63 persons died on 4 and 5 December after only a few hours of sickness, compared to an expected number of 6 deaths. When the fog finally disappeared on 6 December the respiratory health improved (2, 3). The second well documented event occurred in 1948 in Donora (Pennsylvania, USA). During the last week of October a heavy smog settled down over the area surrounding Donora (smog comes from the combination of the words 'smoke' and 'fog'). Also here the air was trapped in the valley and air pollution accumulated in Donora. During the next days 20 persons died, of which 17 on the same day, whereas during that week less than 2 were expected. After the smog had disappeared it was estimated that 43% of the population had been affected to some degree. Especially the older age groups showed a higher incidence of respiratory symptoms and more severe respiratory symptoms than the younger age groups. People with pre existing respiratory or heart disease were also more severely affected (4). The third major episode occurred when London was covered with dense fog between 5 and 8 December 1952. Daily average concentrations of Black Smoke and SO_2 exceeded 4000 and 3000 $\mu g/m^3$ respectively, due to the low wind speed and the temperature inversion in the atmosphere. Between 3,500 and 4,000 deaths from respiratory or heart diseases during or directly after the smog period were attributed to the fog. In addition to people in the higher age categories or with pre existing respiratory or cardiac disorders, also the very young (below 1 years of age) were at higher risk (5). The London smog episode of 1952 was in England an important inducement to take measures against emissions of soot , which resulted in the Clean Air Act in 1956.

In later years also in other West European countries measures were taken and in the next decades the levels of air pollutants such as SO_2, BS and Total Suspended Particulates (TSP) gradually decreased. Most important reasons for this decline were the replacement of coal in industrial processes, house heating and power generation by low sulphur oil or natural gas. On the other hand traffic intensity increased, which caused higher levels of NO and NO_2 in areas with higher traffic intensity. Smog episodes during winters still occurred in Western Europe, partly caused by long range transport from Central and Eastern Europe (6). SO_2 and BS concentrations as high as in London in 1952 were not reached in Western Europe, but effects on mortality, respiratory symptoms and lung function still could be shown (6, 7, 8). In Eastern Europe daily mean SO_2 concentrations could still go up to 2500 $\mu g/m^3$ during these episodes (9).

Acid aerosols are mentioned as one of the air pollution components associated with mortality during the 1952 London smog episode (5). In 1952 acidity was not measured routinely, but measurements during the winters of 1963-1971 showed median 24 hour sulphuric acid levels of 5.3, with a maximum of 134 $\mu g/m^3$ (10). Nowadays levels in Europe are much lower. Measurements in Czech Republic and Germany during the winters of 90-91 and 91-92 showed that the average daily acidity concentration expressed as sulphuric acid during winter time was at most 0.8 $\mu g/m^3$, with a maximum daily concentration of 7.7 $\mu g/m^3$ (11). During measurements in the Netherlands from 1987 to 1990 acid aerosols expressed as daily sulphuric acid concentration never came above 5.5 $\mu g/m^3$ (12). Given these lower levels of acid aerosols, their relevance is probably limited when studying health effects of air pollution in Europe.

Developments in particle measurements

The 1952 smog episode was a landmark for the studies on the acute effects of air pollution. Increased levels of BS and SO_2 were found to be associated with increased mortality and morbidity. Subsequent studies in Europe used BS or TSP as measure of particle concentrations. However, both methods have their limitations with regard to the relevance in the health effect assessment. TSP measures the mass of particles with a diameter up to 50 μm which are suspended in air. Most particles larger than 10 μm are removed in the mouth or nose prior to entering the lower respiratory tract (13). Thus, in many cases TSP does not adequately reflect the concentration of particles which reach the trachea and lungs. The size of the particles sampled with the BS sampler is below 5 μm (13) but because it measures the reflectance of a sampled filter (14), it does not account for the portion of particle mass that does not absorb light. In addition, the formulas which are used to transform reflectance to mass concentrations are based on older studies in which the air pollution mixture was different from today (15). For these reasons the mass concentrations calculated from BS do not represent the total mass concentration of the fraction which can reach the trachea and lungs. BS still can be useful to characterise the composition of the air pollution mixture as the main fraction of light absorbing particles in ambient air is formed by elemental carbon (15). To overcome the limitations of the above mentioned methods a measurement method was developed which measures the concentration of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}). PM_{10} is the mass concentration of that fraction which can pass through nose and mouth and is therefore more relevant for evaluation of effects of air pollution on respiratory health.

PM_{10} mass concentrations do not give information about the composition of the particles but by analysis of the sampled PM_{10} particles on their elemental content or other components such as polycyclic aromatic hydrocarbons (PAH) information about the toxicity can be obtained.

Motive of thesis

In recent years several studies were published which used PM_{10} as measure of particle exposure. These studies showed effects of air pollution on respiratory health, sometimes even below the 1987 WHO guidelines (1) and the US EPA standard (16). Pope (17) followed a symptomatic and an asymptomatic panel of children. In both panels, negative associations between PEF and PM_{10} were found with the strongest association in the symptomatic panel. Daily concentrations of PM_{10} went up to 251 $\mu g/m^3$, but the associations were also observed below 150 $\mu g/m^3$. In another study (18) the same authors followed a school-based panel of children with chronic respiratory symptoms, and a panel of asthma patients. PM_{10} ranged from 11 to 195 $\mu g/m^3$. A negative association between PEF and PM_{10} was found in both panels, which remained when days with PM_{10} concentrations above 150 $\mu g/m^3$ were excluded. In the Netherlands several studies were conducted as well. Hoek (19) found reduced FVC, FEV_1 and MMEF after an air pollution episode in a general population sample of 7-12 year old children. Maximum 24 hour concentrations of SO_2 and PM_{10} were 105 $\mu g/m^3$ and 174 $\mu g/m^3$ respectively. During three consecutive winters between 1988-1990 Hoek and Brunekreef (20) repeatedly tested school children with spirometry. During these winters, 24 hour concentrations were never above 126 $\mu g/m^3$ for PM_{10}, never above 94 $\mu g/m^3$ for SO_2 and for NO_2 never above 70 $\mu g/m^3$. PEF and MMEF were negatively associated with PM_{10} and NO_2. Roemer (21) studied a panel of symptomatic children and found associations between PEF and PM_{10} and between PEF and SO_2. PM_{10} 24 hour averages were only one day above 150 $\mu g/m^3$, reaching 174 $\mu g/m^3$. SO_2 24 hour concentrations were always below 105 $\mu g/m^3$ during the measurement period. In some of the above mentioned studies (21, 17, 18) or other panel studies (22, 23) which studied the effects of winter time air pollution, incidence or prevalence of respiratory symptoms or the use of asthma medication were also found to be related to air pollution levels. Reviews on the relation between particulate matter and various health endpoints (24, 25, 26, 27) concluded that there was an association.

These results raised questions about the possible acute health effects of current air pollution levels in Europe. In the last years, several reviews were published which summarised what is known about the association between particulate matter and respiratory health. (24, 25, 27, 28, 29, 30). Recently, WHO (31) and the Health Council of the Netherlands (32) concluded that no judgement could be made of particle concentrations below which no effects would be expected. In the United States the EPA decided to add $PM_{2.5}$ to the standards for particulate air pollution (33).

In Western Europe the levels of coarse particulates and SO_2 were reduced during the last decades, but simultaneously the traffic emissions increased. Thus, the composition of the air pollution mixture had changed and the levels of indicator air pollutants such as PM_{10} or TSP reported in earlier studies may not have the same meaning as nowadays. On the other hand, in Central-East Europe levels of SO_2 and particulates were still high because of the widespread use of coal in industry, energy production and space heating. In addition, in West as well as in Central-East Europe there was limited or no comparable data available on PM_{10} levels in urbanised and non-urbanised locations, and the possible association of PM_{10} concentrations with respiratory health.

While earlier studies have suggested that subjects with chronic respiratory symptoms are more sensitive to air pollution , it is not known which subgroups in this wide group are the most sensitive. In particular, no previous panel study has conducted objective medical characterisation at baseline.

Associations between PM_{10} and respiratory health have been described with particle mass as the exposure variable. This is mainly because only PM mass concentrations are routinely available. However, it is unlikely that mass is directly responsible for the observed health effects. One hypothesis for the mechanism is that chemicals on the surface of particles induce oxidative lung injury (34). Data on the possible association between elemental concentrations in PM_{10} in Europe and respiratory health is scarce.

Goal of thesis:

The goals of the study described in this thesis are:

- To obtain comparable data on particle concentrations during winter time in various urban and non urban 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;
- To evaluate if medical characteristics of the subjects are related to differences in response to air pollution;
- To evaluate if the elemental composition of the particles is related to the response to air pollution.

Study design

A complication in air pollution epidemiology is that the health endpoints under study have other causes which usually are a stronger cause than air pollution. It is important that the confounding effects of these other factors are eliminated when studying the effects of air pollution. This elimination can be achieved among others by the choice of study design.

For the assessment of short-term effects of air pollution time series studies are very useful. Time series studies assess the association between two variables distributed in the same units of time and during the same period. The underlying hypothesis is that the variation in air pollution levels in the consecutive units of time in a specific place is related to the variation of health indicator values on the same units of time or in closely following units (35). The main advantage of this design is that each subject serves as its own control which reduces the noise. Only factors which vary in time can act as confounder. Very often time series studies use data which are collected routinely such as air pollution data from measurement networks and hospital admissions or mortality from public health surveillance systems. Examples of these studies can be found in various review articles (24, 25, 26, 36). Disadvantage of studies using routinely available data is that no individual data are being collected on exposure, confounding and effect modifying variables.

A special type of time series studies are panel studies. Panel studies involve repeated individual measurements of the health outcome in a (small, e.g. less than 100) cohort of people, usually over a relatively short period of time, with commonly aggregated data on exposure (35). Individual characteristics of the subjects which do not vary in time can be used to study possible effect modification.

A common problem in the analysis of time series is that there is autocorrelation present in the observations. This means that the observations of a measured variable are correlated with each other in time. For example, if the units of time in a certain time series are days, first order autocorrelation means that the observation on a given day is correlated with the observation on the next day. An example are respiratory symptoms. It is more likely that a person reports cough on a day which was preceded by a day on which he also reported cough than when the day was preceded by a day without cough report. Also air pollution exhibits autocorrelation. A day with high levels of air pollution is more likely to be followed by another day with high levels than a day with low levels because of persistence of weather conditions. Standard regression methods assume independent observations and when applying these to autocorrelated data, the standard errors are likely to be underestimated.

Already in 1955 panel studies on the effects of air pollution were conducted in London by Lawther (37). In these studies diaries were used in which subjects could note whether they felt better, the same or worse than the day before. The diary studies were repeated with 5 year intervals until 1968. By plotting the values of SO_2, BS and the diary results along each other Lawther derived that the condition of the patients worsened when peaks in SO_2 and BS measurements occurred. Lawther mainly applied a graphical analysis of the data, probably because the statistical tools to analyse time series data were limited. In later years Korn and Whittemore developed a two stage technique in which in the first stage individual regression coefficients were calculated and in the second stage these individual coefficients were combined (38). With these and other newly developed statistical techniques it is possible to relate relatively small changes in respiratory health and air pollution with each other, correcting for the effects of autocorrelation.

To study the acute effects of air pollution on respiratory health the Pollution Effects on Asthmatic Children in Europe (PEACE) study was designed. The PEACE study is a multicenter panel study in children with chronic respiratory symptoms. The participation of many study centres spread over Europe ensured that a large range of climatic regions and air pollution mixtures was included. This made it possible to study the relation between the composition of the air pollution mixture and the response to air pollution. Exposure to air pollution was measured on a daily basis. One of the characteristics of a panel study is the relatively high frequency of health outcome measurements. These should be easy to perform in order to minimise the burden for the subjects. In the PEACE study, mini-Wright PEF meters were used for daily lung function measurements and a diary was used to gather data on respiratory symptoms and medication use.

Structure/contents of thesis:

Chapter 2 describes the general design and protocol of the PEACE study. This includes the selection and characterisation of the subjects, health effect measurements, exposure measurements, quality assurance, data management and analysis. The results of the air pollution measurements during the study period in the study locations are described in chapter 3. Chapter 4 describes the association between short-term changes in air pollution levels and short-term changes in the lung function of the study subjects and evaluates if differences in association among the study centres can be explained by characteristics of the air pollution mixture. Chapter 5 evaluates the association between short term changes in air pollution levels and the prevalence of respiratory symptoms and medication use. It is attempted to explain differences in association between the study centres by characteristics of the air pollution mixture. Differences in reaction to air pollution among individual subjects are explored in chapter 6. By stratification on individual characteristics of subjects we attempted to identify subgroups of the population which react differently to air pollution. Chapter 7 describes the association between elemental concentrations in PM_{10}, lung function and the prevalence of respiratory symptoms and medication use. Chapter 8 summarises and discusses the main results.

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2

The PEACE study: Design and protocol*

Abstract

The PEACE study is a study of the acute health effects of short term changes in ambient air pollution on children with chronic respiratory symptoms. The study was conducted in the winter of 1993-1994 following a standardised protocol by 14 research centres in Europe. Two panels of at least 75 children each were followed during at least two months. Children of primary school age, 6-12 years old, who had experienced chronic respiratory symptoms in the year preceding the study or had ever been told by a doctor that they had asthma, were selected. 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. Exposure to air pollution was monitored on a daily basis. Health status was monitored by daily PEF measurements and a symptom diary. Subject characterisation was done by questionnaire, skin prick test and pulmonary function using forced expiratory manoeuvres. Daily prevalence and incidence of symptoms and medication use were calculated from the diaries and analysed using logistic regression with correction for autocorrelation. PEF was analysed using linear regression with correction for autocorrelation. Independent variables were 24 hour average concentrations of PM_{10}, Black Smoke, SO_2 and NO_2. As confounders temperature, time trend and weekend/holidays were taken into account.

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Introduction

The PEACE study (acronym for Pollution Effects on Asthmatic Children in Europe) is a study of the acute health effects of short term changes in air pollution on children with chronic respiratory symptoms. The study was conducted in the winter of 1993-1994 following a standardised protocol by 14 research centres in Europe. In this paper, the background, design, methodology and results of the PEACE study are described.

Background

Over the last decades, concentrations of air pollution components such as SO_2 and airborne, coarse particulates have decreased in many areas in Europe. This decrease can be ascribed to emission abatement measures and changes in energy production for industrial processes and space heating (1). Levels of other pollutants such as NO_2 and O_3 have increased during the same period, mostly due to higher intensity of motor vehicle traffic[2]. Previous epidemiological studies on health effects of air pollution in Europe used indicator pollutants such as SO_2, Total Suspended Particulate matter (TSP) and Black Smoke at higher levels than we encounter in most European areas today (3, 4, 5). More recent studies using the same and other indicators such as PM_{10} (particles with a 50% cut-off aerodynamic diameter of 10 μm) have shown effects of air pollution on respiratory symptoms and lung function at lower levels, sometimes below current WHO air quality guidelines for Europe (6, 7, 8, 9). These findings suggest that perhaps due to the changing composition of air pollution, effects of air pollution can be seen below levels of indicator pollutants which were thought to be safe. Another reason maybe that the recent studies were conducted at levels which were hard to find in earlier days and thus these levels were difficult to evaluate in the earlier studies. Therefore new, quantitative data are needed to evaluate health effects of current air pollution levels. In order to achieve this, standardisation of methodology as well as the execution of epidemiological studies using such standardised methodology is needed. In the framework of the ENVIRONMENT Research Programme of the Commission of the European Communities, a collaborative study was funded that sought to develop a standardised methodology for panel studies of effects of short-term changes in air pollution on the respiratory system. In the PEACE project, 14 research centres participated which were distributed over 10 European countries. Of these 14 centres, 5 were from four different EC member states (Greece, Italy, Germany, the Netherlands), 5 were from Central or Eastern European countries (Poland, Hungary, Czech Republic) and 4 were from Scandinavian countries (Finland, Sweden (which became EC member states since the start of the study) and Norway). Figure 1 shows the approximate locations of the urban study sites. Table 1 gives the names of the study centres, principal investigators and study locations.

Objectives of the study

The objectives of the PEACE study were to:

1. develop and standardise epidemiological methods to document the relationship between short-term changes in exposure to air pollution and short-term changes in the health status of subjects with chronic respiratory symptoms.
2. test the feasibility of these methods in small studies among children living in a number of urban areas spread over Europe, and among children living at some distance away from these urban areas for comparison.
3. collect information on the relationship between exposure to airborne particulate matter and other air pollution components in selected urban areas and changes in health status among selected groups of susceptible individuals.

Figure 1. Approximate location of urban sites

The *main hypothesis* of the study was that the daily variation of respiratory health of children with chronic respiratory symptoms is associated with the daily variation of ambient air pollution. The reason to perform the study in various countries was to obtain a large range of exposures. As an illustration the mean concentrations of PM_{10} and SO_2 in the urban locations during the study period are shown in figure 2. Because the composition of air pollution and climatic circumstances differ from country to country, comparison of the strength of the associations between countries may give information on the relative importance of different air pollution components.

Study design

The design of the study (10) was that panels of selected children were followed during at least two months in the winter of 1993/94. Exposure to air pollution and health status were monitored on a daily basis during the observation period. Each participating

Table 1. Participating centres

Principal investigator	Institute	Locations (urban, control)
G. Baldini	Pediatric clinic, University of Pisa, Pisa, Italy	Pisa, Torre del Lago Puccini
B. Brunekreef*	Department of Epidemiology and Public health, University of Wageningen, 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. Haluszka	TBC and Lung Diseases- Pediatric 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. Lebret	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.

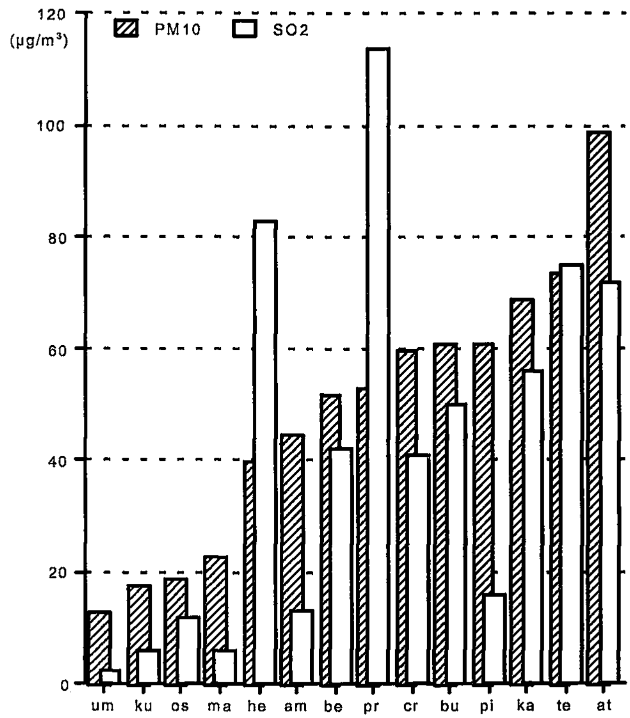

Figure 2. Mean concentrations of PM_{10} and SO_2 in urban locations during the study period (um = Umeå, ku = Kuopio, os = Oslo, ma = Malmö, he = Hettstedt, am = Amsterdam, be = Berlin, pr = Prague, cr = Cracow, bu = Budapest, pi = Pisa, ka = Katowice, te = Teplice, at = Athens)

centre had to select two panels of at least 75 children each. One panel was selected from an urban region, the other panel (the control population) lived in an area in which air pollution concentrations were thought to be considerably lower than in the urban area. Children of primary school age, 6-12 years old, who had experienced chronic respiratory symptoms in the year preceding the study or had ever been told by a doctor that they had asthma, were studied. These children were selected because they are considered to be a sensitive subgroup of the general population. The children were selected from the general population with a screening questionnaire.

For further subject characterisation, questions were asked about doctor-diagnosed bronchitis and pneumonia, about serious respiratory disease in infancy and about respiratory allergy in a detailed questionnaire. Determination of atopy by skin prick test and pulmonary function using forced expiratory manoeuvres was used for additional characterisation, in order to evaluate whether these characteristics are related to a subject's response to air pollution.

Ambient air pollution (SO_2, NO_2, NO, PM_{10} and Black Smoke) was measured at fixed sites on a daily basis. In several studies health effects were related to the concentration of particles, rather than SO_2. In recent studies PM_{10} was used as the particle indicator and was related to health effects (6, 7, 8, 9). SO_2 was chosen because many studies (3, 4, 5) evaluated this pollutant and to make a distinction possible between countries with different PM_{10}-SO_2 ratios. NO_2 and NO were included as indicators of traffic related pollutants. NO is a primary pollutant which predominantly can be measured close to the source. Once emitted NO will react quickly to NO_2. Black Smoke has been measured in this study for several reasons. First, the older European epidemiological studies (2) and more recent studies in Athens (11) and Barcelona (12) have used Black Smoke measurements as the only method of measuring airborne particles. Second, several countries in the EC have formulated their particulate matter air quality guideline in terms of Black Smoke. Third, increasing emissions from diesel engines in urban areas result in increasing soot concentrations in urban air. Determination of Black smoke is one simple method to give some information about the nature of the collected particulate mass.

The exposure estimate was refined by obtaining information on sources of indoor air pollution in the home by questionnaire, by obtaining information on activity patterns of the children by diary and by measurements of NO_2 concentrations in homes of participants with passive samplers .

With a Mini-Wright peak flow meter Peak Expiratory Flow was recorded on two different times of the day, in the morning when getting up and in the evening before going to bed. In addition, parents recorded respiratory symptoms and the use of medication for respiratory conditions of their participating child on each day of the study period.

As far as was feasible within the financial and organisational constraints of the project the methods which were used in the individual centres were standardised. Complete standardisation was achieved with the Screening Questionnaire, Detailed Questionnaire, Diary, Peak Flow meters and Skin Prick Test. PM_{10} and Black Smoke measurement equipment was supplied by the co-ordinating centres to most of the participating centres.

Selection of study locations

For the urban areas, mostly children from the centre of the city were selected, as the highest concentrations of pollutants emitted by motorised traffic and heating of homes were to be expected there. In the urban areas measurement sites had to be present where

SO_2 and NO_2 were measured on a daily basis. The control areas had to fulfil the following criteria: 1) no large emissions from motorised traffic; 2) no large industrial sources; 3) sufficient size; 4) close to a measurement site of an existing air pollution monitoring network; 5) not strongly influenced by major source areas nearby.

By having each participating centre select an urban and a control population, a comparison can be made of the strength of the association in urban versus control areas. This design might also give some indication about which pollutants are related to health effects by comparing areas with different ratios between pollutants.

Selection of subjects

Children between 6-12 years of age were selected because at that age, children usually do not smoke, are unaffected by occupational exposure and can easily be reached in large numbers through the primary school system.

Subjects were approached by handing out screening questionnaires at school or by mail which had to be filled out and returned by their parents. The screening questionnaire is an adapted version of questions from the WHO questionnaire for assessing respiratory symptoms in children (13) and of a questionnaire developed by the University of Groningen, The Netherlands, based on the ATS questionnaire for children. The reproducibility of the questionnaires was established (14). Kappa values indicated a good reproducibility for the asthma-like symptoms. The question on nightly coughing is taken from a study on asthma prevalence symptoms in New Zealand (15). Children were selected randomly from those who were willing to participate and who had a positive answer on one of the following questions:

1) Has your child been bothered *in the past twelve months* by a wheezy chest, *apart* from colds?
2) Has your child been bothered *in the past twelve months* by attacks of shortness of breath with wheezing?
3) Has your child had a dry cough at night *in the past twelve months*, apart from coughing with a cold or chest infection?
4) Has a *doctor ever* said your child had asthma?

As it was expected that some subjects would drop out before the end of the study period, at least 80 subjects were to be included at the start of the measurement period.

Population characterisation

In order to detect possible differences in responses to air pollution between subjects which differ in health characteristics a detailed population characterisation was performed.

Detailed Questionnaire. A detailed questionnaire was administered to the parents of all children participating in the actual panel study. It consisted of questions about respiratory symptoms, allergy, medication use and several risk factors for respiratory symptoms such as smoking in the home. The full questionnaire is available upon request from the authors.

Skin prick testing. As atopy is related to bronchial reactivity, respiratory symptoms and PEF variability (16,17) it might be that children with an atopic constitution react differently to air pollution compared to non-atopic children. Skin prick testing was used for identification of atopic subjects. The tests were carried out with the ALK skin prick system (ALK laboratories, Denmark). The protocol for skin prick testing is based on the protocol used in the European Community Respiratory Health Survey (ECRHS) (18). There are several climatic regions in Europe and each has a different distribution of allergens. A common set of four single allergens was used for all areas which covered the most important allergens in the participating countries. These allergens were house dust mite (*D. pteronyssinus*), cat fur and pollen of timothy grass (*Phleum pratense*) and birch (*Betula verrucosa*). A positive control (histamine) and a negative control (diluent) were applied in each test. Two locally important allergens were added by each individual centre. These were mostly dog fur and *Cladosporium herbarum* in the Scandinavian countries and The Netherlands, grass mix (*Alopecurus pratensis, Dactylis glomerata, Festuca pratensis, Lolium perenne, Phleum pratense*) and mould mix (*Aspergillus fumigatus, Cladosporium herbarum, Penicillium notatum, Botrytis cinerea*) or dog fur in Central and Eastern Europe and *parietaria officinalis* in Southern Europe. The allergens were centrally ordered and distributed by the co-ordinating centre. A child was considered atopic if there was a wheal reaction of more than 2 mm on one of the tested allergens together with a negative control equal or less then 1 mm and a positive control of more than 0 mm.

Pulmonary function testing. Forced expiratory manoeuvres were performed following the protocol of the European Community for Coal and Steel (ECCS)(19, 20). The equipment used in the centres was not identical but had to fulfil the technical requirements of the ECCS. Selection of values was done according to the ECCS (19,20). The measured values were expressed as a percentage of the predicted values calculated from the reference equations of Zapletal (21).

Acute health effect measurements

The diary. At the start of the study period the children received a diary and a mini Wright Peak Flow meter. Every day the children measured in presence of the parents the PEF three times in the morning and three times in the evening before taking medication. The highest values of both the morning and evening attempts were used in the data analysis. At the end of every day the parents, together with the children noted whether the child experienced respiratory symptoms during the day, to what degree they experienced this symptom (slight, moderate/severe) and whether respiratory medication had been taken. Recording of severity was considered important because slight symptoms probably would have been missed when a yes/no recording system was used. The diary form is added in Appendix A. The use of the diary and the mini Wright Peak Flow meter was demonstrated during a home visit in presence of the child and at least one of the parents. In the diary, information about time activity patterns of the child (time spent outside, out of home town) was also recorded by the parents on a daily basis.

Exposure assessment

Air sampling sites and equipment. Ambient air pollution concentrations were measured on a daily basis at fixed sites in the urban and control area. In the urban area at least PM_{10}, Black Smoke, SO_2 and NO_2 was measured on a daily basis. In the control area the minimum requirements were PM_{10}, Black Smoke and NO_2 measurements on a daily basis. The measurement sites were chosen so that they were close to the living area of the participating children, and not strongly influenced by local sources in the direct vicinity (so-called 'background sites'). To obtain data on SO_2 and NO_2 most centres used data from continuous monitors in existing air quality monitoring networks, so the potential for standardisation of these measurements was limited. Non-continuous monitors for collecting PM_{10} and Black Smoke samples were supplied by the co-ordinating centre to most of the participating centres.

The PM_{10} equipment consisted of the Harvard PM_{10} impactor (produced by Air diagnostics and Engineering, Inc., Maine, USA) and a pump unit with a critical orifice for flow control and an elapsed time indicator (produced by University of Wageningen). The Harvard PM_{10} impactor was chosen because it is a economical sampler that has been compared extensively with reference equipment such as the dichotomous sampler (22, 23, 24). The Harvard Impactor has a size selective inlet that collects particles smaller than 10 μm with an efficiency of 50% at 10 μm. Teflon filters with a pore size of 2 μm were supplied by the co-ordinating centre. Before and after sampling the filters were conditioned during 24 hours at about 44% relative humidity with a constant temperature of about 20°C [25] and weighed to determine the PM_{10} mass concentration. The centres that used the Harvard Impactor were provided with a detailed protocol for using the Harvard Impactor. Centres that already had PM_{10} samplers to their disposal, were subjected to a 10-day site-by-site comparison with the Harvard PM_{10} Impactor. Black Smoke measurements were made according to the OECD method[26]. The sampler is an inverted funnel, a filterholder, and a pump unit with flow control by means of a critical orifice and a vacuum gauge. The centres that were provided by the co-ordinating centre with a Black Smoke sampler used a detailed protocol for using the Black Smoke sampler.

Potential confounders and effect modifiers

Because each child served as its own control, only variables which are correlated in time with air pollution can act as confounders. Stable factors such as sex or factors which are unlikely to correlate with daily changes in air pollution such as smoking in the home can not act as confounder. Information on potential confounders such as ambient temperature and relative humidity was obtained from meteorological institutes on a daily basis. To make a correction possible for the potential confounding effect of fever, the occurrence of fever was noted in the diary. Dates of holidays and official smog alerts were also recorded.

To take into account possible effect modifiers, information about the presence of important sources of indoor air pollution was collected in the Detailed Questionnaire. Questions were selected from the "New Standard Environmental Inventory Questionnaire for estimation of indoor concentrations" (27). Some questions have been added to cover topics that were not sufficiently dealt with (humidity of the home and presence of pets).

Quality Control

Standardised methods and materials were used for Screening Questionnaire, Detailed Questionnaire, Diary, Peak Flow meters and skin prick test. In most centres also PM_{10} and Black Smoke measurements were performed with standardised equipment and protocols. Prior to and during the study, an extensive quality control program was implemented. The main elements of the program were:

- Visits by members of the co-ordinating centre to the local centres to discuss the protocol and visit the selected areas and air sampling sites;
- Back-translation of screening questionnaires and diaries to English by non-medically trained professional translators;
- Double punching of 10% of the screening questionnaires, detailed questionnaires and diaries to estimate the error rate in data entry. In case of high error rate all data were double punched;
- Determination of field workers' coefficient of variation in performing skin prick test;
- Comparison of equipment used in determination of Forced Expiratory flows and volumes with a portable spirometer during site visit;
- Checks of PEF meters on malfunctioning before and after study by checking on mechanical errors like damaged springs, cracks or objects in the PEF meter etc.;
- Judgement of the comparability of the measurement methods employed in the existing air quality monitoring networks by two external air pollution experts;
- Determination of differences in PM_{10} filter weighing by letting the centres weigh a set of filters that was circulated among all centres;
- Determination of differences in Black Smoke reflectance reading by letting the centres measure a set of filters that was circulated among all centres;
- Collection of field blanks and duplicate measurements at those centres which did not rely on existing air quality measurement networks for PM_{10} and Black Smoke measurements;
- Field comparison of other PM_{10} equipment that was used with Harvard PM_{10} impactor;
- Checklist for deviations from the protocol.

Data analysis

The analysis started by removing the first two diary days of each subject to eliminate a possible training period. Subjects which had no fluctuations in their PEF measurements for a longer period were removed. On days the subjects reported to have been out of their home town for more than 8 hours the diary variables were set to missing. Subjects who had more than 40% of missing days in their diaries were removed from the dataset to avoid large changes in composition of the reporting group of children on every day. With the data of the remaining subjects, some descriptive analyses were performed first. This included description of age, prevalence of chronic respiratory symptoms (screening questionnaire), prevalence of atopy and the results of forced expiratory manoeuvres in the panel. The goal of these analysis was to describe the separate panels. Because the panels were highly selected, it was not considered useful to test differences between urban and control panels. Next, the symptoms in the diaries were recoded from 0, 1, 2 to 0 (no symptom) and 1 (slight, moderate or severe symptom). Variables on group level were then calculated from the individual data in the diaries: daily PEF population mean deviation and daily incidence and daily prevalence of respiratory symptoms and medication use. The daily PEF population mean deviation was calculated by calculating daily individual deviations first:

$\text{PEF dev}_{a,i} = \text{PEF}_{a,i} - \text{PEF}_a$

where $\text{PEF dev}_{a,i}$ = PEF deviation of child a on day i ;

$\text{PEF}_{a,i}$ = PEF of child a on day i ;

PEF_a = mean PEF of child a over the measurement period.

The daily PEF population mean deviation is the daily mean of the individual deviations. This variable was calculated separately for morning and evening PEF. It takes into account the day-to-day changes in composition of the group of children who are reporting and represents the deviation from the population mean, expressed in l/min. Daily prevalence was defined as the fraction of children for whom the presence of a respiratory symptom/medication use was reported from those children providing valid diary data for that symptom on that day. Daily incidence was defined as the fraction of children reporting a symptom/medication use from the children who reported to have no symptom on the previous day. PEF population mean deviation, prevalence and incidence of acute respiratory symptoms, concentrations of air pollutants and temperature were described with simple statistics and by plots against time. Tabulations of the dependent variables by days of low, intermediate and high air pollution concentration were performed. Dependent variables were the PEF population mean deviation and the prevalence of respiratory symptoms and medication use.

The association between air pollutants and PEF population mean deviation was calculated by means of linear regression with the number of reporting children on every day as weight. This analysis included correction for autocorrelation in the residuals as in previous diary studies it was found that PEF showed autocorrelation (6, 7, 8, 28). Therefore, ordinary regression techniques were not appropriate models. The association between air pollution and daily incidence of symptoms and medication use was evaluated using a logistic regression model with additional modelling of the autocorrelation of the residuals as in previous studies incidence also showed autocorrelation[29]. The association between prevalence and air pollution was also evaluated with logistic regression but under the assumption of normally distributed residuals and modelling of autocorrelation. This was done because when analysing prevalence with binomial distributed residuals the residuals showed underdispersion. In the first phase of the analysis of the respiratory symptoms only upper respiratory symptoms (URS = runny/stuffed nose, sore throat), lower respiratory symptoms (LRS = shortness of breath, wheeze, asthma attacks) and bronchodilator use (such as salbutamol, albuterol, fenoterol, terbutaline) were analysed.

After identification of autocorrelation and description of time trends, air pollutant coefficients were estimated without taking confounders into account. The independent variables were 24 hour average concentrations of PM_{10}, Black Smoke, SO_2, NO_2 and NO. These were entered separately as linear terms. The selection of representations of air pollution was primarily based on findings in previous studies (6, 7, 8). Lags of 0, 1, 2 days and the average of lag 0-6 days were analysed. Wherever possible the 24 hour averages were calculated in such way that the 24 hour mean of the continuous air pollution measurements coincided with the 24 hour period of the non-continuous measurements. The sample change time for the non-continuous air pollutants differed between locations, so a definition was established such that in all centres lag 0 included at least 16 hours of exposure before the health effect measurement.

After the preliminary models without confounders, a fixed set of confounders was included in the models. The use of a fixed set was done in order to ensure comparability between centres. The confounders which were included in both the analysis of PEF population mean deviation and symptom incidence as well as symptom prevalence were minimum temperature (as a linear variable), a dummy variable indicating normal school days versus holidays/weekends and time trend. The decision which lag of minimum temperature was included as confounder in the models was done on the basis of the data, by analysing which lag (0, 1, 2 or 7 day mean) had the smallest p-value in the expected direction on PEF population mean deviation or symptom incidence or symptom prevalence in a dataset consisting of data from both urban and control area. The expected direction was lower PEF population mean deviation with lower temperature and higher symptom incidence or prevalence with lower temperature. Time trend was included in different ways in the analysis of the PEF population mean deviation and symptom incidence and prevalence. In the analysis of the PEF population mean deviation, a linear trend was included to correct for lung growth over time and a square root term to correct for a stronger increase in time during the first weeks that was apparent in several panels. Because the occurrence of symptoms was assumed to be largely due to factors that were not measured, an adjustment was made for trends with a longer period that were unlikely to result from acute effects of air pollution episodes. Thus, time trend was included in the incidence and prevalence analysis as a linear, quadratic and cubic term. To check if all long term time trends really were removed, the mean of the residuals of a given observation and 13 preceding observations was calculated from the model without air pollution variables and divided by its standard error. If this ratio indicated a probability of random occurrence of less than 1%, a dummy variable was included in the model for that period. This was done for PEF as well as symptom prevalence and incidence analysis. To check if the results were influenced by daily fluctuations in the number of reporting children, or by school holidays a period was specified for each separate location in which the number of children was stable and which did not include school holidays. Data sets were restricted to that period and results of the analysis were compared to the original analysis.

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3

Wintertime PM_{10} and Black Smoke concentrations across Europe: results from the PEACE study*

Abstract

In the framework of the PEACE study, measurements of particles less than 10 μm (PM_{10}) and Black Smoke (BS) in ambient air have been made at 28 sites in ten countries in Europe. For about two months in the winter of 1993/94 24-hour average measurements were conducted. Each centre studied both an urban and a more rural site. The difference of particle concentrations across countries appeared to be considerably larger than the difference between the urban and rural location within countries. The median PM_{10} concentration ranged from 11 $\mu g/m^3$ at three rural Scandinavian sites to 92 $\mu g/m^3$ in Athens, Greece. The median BS concentration ranged from 3 $\mu g/m^3$ in Umeå, Sweden to 99 $\mu g/m^3$ in Athens, Greece. The most striking difference across countries was the low particle concentration found at the eight Scandinavian locations. PM_{10} and BS concentrations in the urban area were on average 22% and 43% higher than the corresponding rural area concentrations respectively. The correlation between the particle concentration measured at the urban and the more rural site exceeded 0.70 at almost all sites. PM_{10} concentrations from all Western and Central European locations were significantly correlated. No or a low correlation was found between these locations and the South-European and Scandinavian locations. PM_{10} and BS measured at the same site were highly correlated at most sites. However, the median PM_{10}/BS ratio ranged from 0.67 to 3.67 across sites. PM_{10}/BS ratios were close to unity for Athens, the Central European sites and Oslo. There was a tendency of lower PM_{10}/BS ratios in the urban area, consistent with the contribution of (diesel) motor vehicle emissions.

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Introduction

Recent epidemiologic studies have documented that elevated ambient particle levels are associated with adverse health effects (1). In these studies ambient particulate matter concentrations have been characterised with a variety of measures including total suspended particulate matter (TSP), particulate matter with a 50% cutoff diameter of 10 μm (PM_{10}) and Black Smoke (BS). Studies conducted in the USA have generally used the gravimetric measures TSP and more recently PM_{10}. In many European studies the concentration of Black Smoke (BS) has been used. This difference resulted from the different practices in air quality networks, since many epidemiologic studies have used routinely collected air pollution data. As a result, little is known about PM_{10} concentrations in Europe.

In a recent review of health effects of particles, the authors assumed a PM_{10}/BS ratio of 1 comparing different studies, while acknowledging the probability of variability in the actual ratio (1). Few published data are available about the actual relationship between PM_{10} and BS (2). Differences between gravimetric measures such as PM_{10} and BS may be caused by both analysis and sampling differences. The BS method involves analysis of the reflectance of a filter instead of the filter weight. Reflectance of a filter is mostly determined by the soot (elemental carbon) content of particles rather than by total particle mass (3, 4, 5). Studies in different locations have indeed documented a high correlation of BS with particulate elemental (or total) carbon (6, 7, 8).

The comparison between gravimetric measures and BS is also influenced by the particle sizes that are sampled by the 'gravimetric sampler' and the BS sampler. The cut size of the BS sampler is not well defined. It was estimated in wind tunnel tests that the 50% cutoff diameter for the BS sampler was 4.4 μm, mainly governed by particle losses in tubing (9). The exact cut size is probably not critical since the major fraction of dark smoke or elemental carbon is generally present in fine particles. This is consistent with the main sources of elemental carbon, being incomplete combustion processes in diesel motor vehicles, industrial and domestic burning of coal and wood burning (5, 10, 11, 12). At sites near major roads, a significant coarse elemental carbon fraction may be present due to resuspension of tire wear (13).

In 1993 the PEACE study, a multi-centre study of acute Pollution Effects on Asthmatic Children in Europe was initiated (14). The PEACE study involved 14 research centres in 10 countries spread over Europe. To assess exposure to air pollution, the concentration of both PM_{10} and Black Smoke was measured during a winter period on a daily basis, at an urban and a rural location. To the extent possible a standard protocol for selecting sampling sites, sampling methods and sample analysis has been followed by the 14 centres.

The purpose of this paper is first to describe PM_{10} and BS concentrations across Europe. The second purpose is to describe differences in PM_{10} and BS concentration between the urban and more rural location within countries. The third purpose is to describe the variability of the ratio of PM_{10} and BS across Europe. The fourth purpose is to describe the correlation of daily PM_{10} and BS concentrations across Europe.

Methods

Study design

Each of the 14 research centres measured daily average concentrations of PM_{10} and BS in outdoor air at one urban and one more rural site. SO_2 and NO_2 data were generally collected from existing air quality networks. The 'rural' site had to be selected such that meteorologic conditions were similar to those of the urban area. However, significant local sources of air pollution had to be absent. Most centres selected small towns in the vicinity of the urban area. However, three centres selected suburbs of the urban area (Table 1). We will use the term 'rural area' throughout this paper, regardless of the exact location of the 'non-urban' site. Daily measurements were made for a minimum of two months in the winter of 1993/94.

Study locations

The PEACE study locations covered Europe both from East to West and from South to North (figure 1). The urban and rural locations that were studied by each centre and some information about local sources of air pollution and geography are shown in table 1. In all tables of this paper the centres have been classified according to their geographical position in Europe: Scandinavian, West-European, Central European and South-European locations. In most urban areas motorised traffic was considered to be an important source of air pollution. For the Central European cities and Athens industrial sources were considered to be important. Burning of coal for domestic heating was important in both the urban and rural area in most Central European locations.

Figure 1. Urban PEACE study locations and median PM_{10} concentration ($\mu g/m^3$)

Within each study area urban/rural background sites had to be selected for conducting measurements, that is sites that were not influenced by air pollution sources in the direct vicinity of the measurement site (such as traffic, industries). Only in the urban area of Athens the measurement site was not a background site. In Athens measurements were made about 20 meter away from a moderately busy street (> 3000 vehicles/day). Sampling height had to be more than 1.5 m. Actual sampling heights ranged from 1.5 to 7 m. Given the background nature of the sites, this variation was not considered problematic.

Measurement methods

Study period, sample change times and the PM_{10} and BS samplers that were used are shown in table 2. Study period is defined as the period for which measurements were available for both the urban and rural location. The period between mid January and mid March was included in the study period of most centres. Sample change times could not be standardised.

Table 1. Characterisation of PEACE study locations, winter 1993/94

Urban location	Main urban area sources and other characteristics	inhabitants urban area (x 1000)	Rural area	Distance (U-R)[1] (km)
Umeå, Sweden	traffic	80	Holmsund; wood burning	15
Malmö, Sweden	traffic, gas heating plant	251	Olofstrom; wood burning	120
Oslo, Norway	traffic; centre; basin	450	suburbs, up the hills; wood burning	5
Kuopio, Finland	traffic; peat power plant	80	suburbs, separated by forests	10
Amsterdam, the Netherlands	traffic	700	Meppel	75
Berlin, Germany	traffic; centre of former west	3,400	suburb in former west	10
Hettstedt, Germany[2]	industry, coal heating; valley	40	Zerbst	50
Budapest, Hungary	residential area	2,000	Szentendre	15
Katowice, Poland	industry, coal heating	370[3]	Pszczyna; coal heating	40
Cracow, Poland	industry, traffic, coal; valley	750	Rabka; coal heating, valley	70
Prague, Czech Republic	coal heating, traffic; valley	1,200	Benesov; coal heating; valley	30
Teplice, Czech Republic	industry, coal heating	130	Prachatice; coal heating	250
Pisa, Italy	traffic; valley	100	Torre del Lago Puccini; fireplaces	20
Athens, Greece	Traffic, industry; basin	3000	Peania; separated by mountains	20

1 Distance between and urban - rural location; 2 In former German Democratic Republic; 3 part of agglomeration of 2.5 million inhabitants.

Different PM_{10} samplers were used, but the Harvard impactor (15) was used by 10 centres. The impactor was operated at 10 l/min and manufactured by Air Diagnostics and Engineering Inc. Naples, Maine, USA. Except for Budapest and Cracow, the same type of sampler was used for the measurements at the urban and rural location. With the exception of Budapest and Cracow, PM_{10} measurement involved collection of particles on a filter -after passing a size selective inlet- followed by gravimetric analysis. Before and after exposure filters were weighed after conditioning for 24 hrs at about 20 °C and constant relative humidity. Most centres used desiccators to achieve a constant relative humidity, since a climate controlled weighing room was not available. Across centres the mean realised relative humidity ranged from 35 to 55%. Most centres used analytical balances with a reading precision of 10 mg. After collection from the field, exposed filters were stored in a refrigerator at 4 °C before weighing to limit losses of volatile components (5). The 10 centres that used the Harvard impactor, followed a detailed operation manual prepared by the co-ordinating centre (16). All these centres used the same Andersen 37 mm 2 μm pore size Teflon filters.

Black Smoke measurements were conducted using the method of the Organization for Economic Cooperation and Development (3). The method involves collection of particles on a Whatman 1 paper filter using a low volume sampler. The reflectance of the filter is then measured using a reflectometer. First, the reflectometer reading is set to 100 using one blank Whatman 1 filter. Next, the reflectance of exposed filters is measured. A filter with a darker stain will have a lower reflectance. The measured reflectance was next transformed into $\mu g/cm^2$ using the formula describing the Standard Smoke curve (17). Different types of samplers were used. However, eight centres used a sampler designed by the National Institute of Public Health and the Environment (RIVM) for operation in the Dutch national air quality network. The sampler consists of an inverted funnel inlet, PVC tubing, metal filter holder, vacuum gauge, dry gas meter and a critical orifice. With the exception of Cracow and Athens the same sampler was used for the urban and rural location. The samples of all centres excluding Cracow were measured with EEL43 type reflectometers. All centres except Pisa and Oslo used Whatman 1 paper filters. In Pisa a cellulose nitrate membrane filter was used, in Oslo a Whatman 40 paper filter.

SO_2 and NO_2 concentration data were obtained from existing air quality networks, thus less standardisation was possible. Continuous fluorescence monitors were used at both the urban and rural site for SO_2 measurements by nine centres. Impinger methods were used in the rural areas of Cracow and Oslo and both areas of Katowice, Umeå and Malmö. In Oslo, Umeå and Malmö H_2O_2 solutions were used followed by sulphate analysis by ion chromatography. In Katowice the West Gaeke method was used. In the urban area of Oslo differential optical absorption spectroscopy (DOAS) was used. No SO_2 measurements were available for the rural areas of Athens and Kuopio. Continuous chemiluminescence monitors were used at both the urban and rural site for NO_2 measurements by ten centres. Impinger methods based upon the Saltzman method were used in both areas of Katowice. In Umeå a NaI coated filter was used for sampling NO_2. In the urban area of Oslo DOAS was used.

Table 2. Study period, sample change time and sampling methods for PM_{10} and BS, PEACE study

Location	Study period (day/month/year)	Urban location PM_{10} sampler	Urban location BS sampler	Urban location Sample change time	Rural location PM_{10} sampler	Rural location BS sampler	Rural location Sample change time
Umeå	5/1/94 - 27/3/94	HI[1]	OECD-M[2]	0	HI	OECD-M	0
Malmö	17/1/94 - 18/3/94	HI	OECD-M	9	HI	OECD-M	9
Oslo	3/12/93 - 9/2/94	Dichot[3]	NILU[4]	8	Dichot	NILU	8
Kuopio	8/2/94 - 5/4/94	HI	RIVM-W[5]	12	HI	RIVM-W	14
Amsterdam	27/11/93 - 28/2/94	'Dichot'[6]	RIVM-W	15	'Dichot'	RIVM-W	15
Berlin	27/1/94 - 25/3/94	HI	OECD	12	HI	OECD	12
Hettstedt	6/10/93 - 27/3/94	HI	RIVM-W	8	HI	RIVM-W	8
Budapest	15/1/94 - 17/3/94	HI	RIVM-W	11	ß-gauge	RIVM-W	11
Katowice	1/3/94 - 3/4/94	HI	RIVM-W	7	HI	RIVM-W	6
Cracow	17/1/94 - 3/4/94	ß-gauge	RIVM		HI	OECD	
Prague	25/1/94 - 10/4/94	HI	RIVM-W	10	HI	RIVM-W	8
Teplice	3/1/94 - 6/3/94	Hivol	NILU	8	Hivol	NILU	8
Pisa	20/1/94 - 20/3/94	Hivol	OECD	12	Hivol	OECD	12
Athens	13/1/94 - 10/3/94	HI	RIVM	16	HI	OECD	16

1 Harvard impactor; 2 modified OECD (different dimensions, but retaining required face velocity); 3 Sierra Andersen 245 dichotomous sampler; 4 NILU-FK sequential sampler following OECD; 5 RIVM sampler (following OECD), W = reflectance measured by WAU; 6 inlet similar to the Sierra Andersen 241 dichotomous sampler inlet (18).

A more detailed description of the PM_{10}, BS, SO_2 and NO_2 methods can be found in the PEACE study manual (16) and a report describing the air pollution measurement methods used in the PEACE study (19).

Meteorologic data were obtained from existing meteorologic stations. The collected information included ambient temperature, relative humidity, wind speed and barometric pressure.

Quality assurance and control

An effort was made to limit and assess methodological differences between the participating centres. First, the same PM_{10} and BS samplers were obtained for centres that did not have samplers available. In addition, the same consumables such as filters were centrally obtained by the co-ordinating centre. Second, a common protocol was followed by all centres. In addition, a detailed operation manual was used by the centres using the Harvard impactor and RIVM sampler. Third, site visits were conducted by the co-ordinating centre to increase comparability of selection of sampling sites and measurement procedures. Fourth, each centre was required to collect at least 10 field blanks and 10 field duplicates to assess the performance of the particle measurement methods. Fifth, a comparison program was conducted to evaluate differences between PM_{10} and BS measurements conducted by different centres. The program involved a field comparison of the Harvard impactor with other PM_{10} samplers for 10 days and a round robin test of the analysis of filters (weighing, reflectance measurement). The design and results of the comparison program are reported in a separate paper (20).

Data analysis

Since most concentration distributions deviated from the normal distribution, non-parametric methods were used to test associations between concentrations at different locations. Concentration differences between urban and rural area were tested using Spearman's non-parametric rank test. The Spearman rank correlation coefficient was calculated to describe the relationship between BS and PM_{10}.

Scatterplots of PM_{10} versus BS were prepared to judge the linearity of the associations. A smoothed curve was added to the plot to help interpretation, using the GPLOT procedure of the Statistical Analysis System (SAS). Since only moderate deviations from linearity were present, linear regression was used to assess the relationship between PM_{10} and BS. Observations with a Cook's D influence statistic (21) larger than 1 were excluded from the regression analyses, because it was considered undesirable that one day largely determined the association for the other 60 days. This resulted in one exclusion in the rural area of Amsterdam and one exclusion in the rural area of Athens.

Results

Meteorologic conditions varied widely across the different locations. The average minimum temperature ranged from -15 °C in Umeå to +8 °C in Athens. Differences between the urban and rural location were small, as expected from the generally small distance between these locations.

The limit of detection (DL) for BS was 1 $\mu g/m^3$ or lower for all centres (table 3). The mean coefficient of variation for BS measurements was below 10% for all centres, except Kuopio where low concentrations occurred. The DL for PM_{10} was below 15 $\mu g/m^3$ for all centres, except Prague. For the Scandinavian centres the DL was below 6 $\mu g/m^3$. The mean coefficient of variation for PM_{10} measurements was below 10% for all centres, except Hettstedt.

Concentration patterns

The distribution of PM_{10} and BS concentrations is shown in tables 4 and 5. A map of median PM_{10} concentrations is shown in figure 1. Certain factors limit the interpretation of these data. In Hettstedt the pump used for PM_{10} sampling often failed at low temperatures. Since high wintertime particle concentrations are generally associated with low temperatures, the PM_{10} distribution is an underestimate of the true distribution. In Budapest and Cracow different samplers were used for PM_{10} measurements at the urban and rural location. A field comparison at the same site in Budapest showed that PM_{10} concentrations measured with the urban sampler were 18%

Table 3. Detection limits and precision of PM_{10} and BS measurements, PEACE study.

	PM_{10}				BS			
Location	DL[1] ($\mu g/m^3$)	n[2]	RSD (%)[3]	n	DL ($\mu g/m^3$)	n	RSD (%)	n
Umeå	6	10	6	10	0	10	6	22
Malmö	4	20	NA		NA		NA	
Oslo	1	10	NA		1	10	NA	
Kuopio	1	10	10	9	0	10	22	10
Amsterdam	11	12	8	11	1	15	6	14
Berlin	15	10	8	12	0	10	10	13
Hettstedt	14	48	24	6	0	20	NA	
Budapest	2	10	NA		0	20	3	10
Katowice	2	10	4	10	1	10	6	10
Cracow	NA		NA		NA		NA	
Prague	42[5]	32	NA		NA		NA	
Teplice	0	10	NA		NA[4]		NA	
Pisa	1	10	1	10	1	10	10	10
Athens	13	10	3	10	1	10	4	10

1 detection limit, calculated as three times the standard deviation of field blanks; 2 number of field blanks or field duplicates; 3 relative standard deviation (coefficient of variation) calculated as the mean percentage difference between duplicate samples divided by the square root of two; 4 analyses conducted by NILU, Oslo; 5 without one outlier 25 $\mu g/m^3$; NA: not available.

higher than measured with the rural sampler (19). In Cracow no comparison between samplers was conducted. BS concentrations in Cracow and its rural location below 30 $\mu g/m^3$ were set to 15 $\mu g/m^3$. The value of 15 $\mu g/m^3$ was reported on 37 (45%) and 32 (42%) days for the urban and rural area respectively.

The lowest PM_{10} concentrations were found at the Scandinavian locations. For nine centres PM_{10} concentrations were significantly higher at the urban location. Pooled over all locations, the median ratio of urban/rural PM_{10} was 1.22.

BS concentrations were lowest at the Swedish sites. The BS concentrations in Kuopio and Oslo were in the same range with the concentrations in Amsterdam, Berlin and Pisa. The highest concentration was again found in the urban area of Athens. For ten centres BS concentrations in the urban area were significantly higher than in the corresponding rural area. Pooled over all locations the median ratio of urban/rural BS was 1.43. The lowest SO_2 concentrations were found in Scandinavia and Amsterdam (Figure 2a). The highest levels were found at the Central European sites and Athens. Most urban areas had considerably higher concentrations than the rural area. Pooled over all locations, the median ratio of urban/rural SO_2 was 1.56.

NO_2 concentrations were more uniform across Europe (figure 2b). At the Central European sites concentrations were not higher than at the other sites. The high concentration in Pisa can be explained by site characteristics. This site is a traffic influenced site, in contrast to the site used for particle sampling. For 11 of 13 locations urban concentrations were (substantially) higher than rural concentrations. Pooled over all locations, the median ratio of urban/rural NO_2 was 1.78.

To obtain some indirect information on sources that influence particle concentrations an analysis of the variability of concentrations with day of the week was made. Data from all locations were pooled to obtain these results (table 6). The reported ratios were obtained from a linear regression model with the logarithm of the air pollution concentration as the dependent variable and indicator variables for centre, Saturday and Sunday as independent variables. This model assumes that the percentage difference between weekend days and weekdays is the same across locations. BS and NO_2 concentrations were lower on Sundays compared to weekdays.

Table 4. Distribution of daily average PM_{10} concentrations ($\mu g/m^3$) in the winter of 1993/94.

	Urban location					Rural location					
	P10[1]	P50	P90	Mean	Max	P10	P50	P90	Mean	Max	N[2]
Umeå*	3	12	24	13	40	3	11	20	12	29	74
Malmö*	10	21	40	23	59	7	14	28	16	38	60
Oslo*	7	17	36	19	63	4	11	20	11	31	68
Kuopio*	7	15	33	18	60	5	11	23	14	37	57
Amsterdam	19	34	84	42	113	15	30	100	45	242	86
Berlin*	16	47	95	52	117	12	38	93	43	105	58
Hettstedt*	19	39	68	41	95	10	30	58	31	92	118
Budapest*	21	54	109	61	162	20	51	94	52	117	62
Katowice*	32	63	103	63	157	29	65	124	74	140	33
Cracow	19	52	110	59	184	21	43	122	56	219	77
Prague	18	50	96	53	188	17	46	93	50	159	76
Teplice*	26	56	153	75	205	10	28	66	33	174	56
Pisa*	36	57	96	62	131	40	66	106	70	149	52
Athens*	38	92	177	99	201	24	44	87	50	115	57

[1] P10 = 10-th percentile, P50 = 50-th percentile, P90 = 90-th percentile; [2] number of sampling days (only days with valid measurements on both locations); * PM_{10} at urban site significantly different (two sided p-value < 0.05) from PM_{10} at rural site.

Table 5. Distribution of daily average BS concentrations ($\mu g/m^3$) in the winter of 1993/94.

	Urban location					Rural location					
	P10[1]	P50	P90	Mean	Max	P10	P50	P90	Mean	Max	N[2]
Umeå	1	3	10	5	33	1	4	11	5	20	67
Malmö*	3	6	18	8	37	1	4	9	4	16	61
Oslo*	12	21	50	28	104	3	10	27	13	47	68
Kuopio*	3	11	23	13	57	1	6	15	8	47	57
Amsterdam*	5	12	31	15	48	4	10	31	14	58	92
Berlin*	5	21	53	24	65	2	13	52	22	74	58
Hettstedt*	16	36	72	42	170	9	21	49	26	97	160
Budapest*	14	44	82	49	135	6	27	59	29	80	62
Katowice	23	41	114	56	151	20	54	100	58	114	33
Cracow*	15	33	68	34	112	15	35	92	43	123	77
Prague*	6	25	65	30	108	7	17	37	21	56	76
Teplice*	10	45	126	59	163	5	19	40	22	83	63
Pisa*	11	18	33	20	43	13	26	48	29	96	46
Athens*	54	99	184	109	238	12	26	64	34	188	57

[1] P10 = 10-th percentile, P50 = 50-th percentile, P90 = 90-th percentile; [2] number of sampling days (only days with valid measurements on both locations); * BS at urban site significantly different (two sided p-value < 0.05) from BS at rural site.

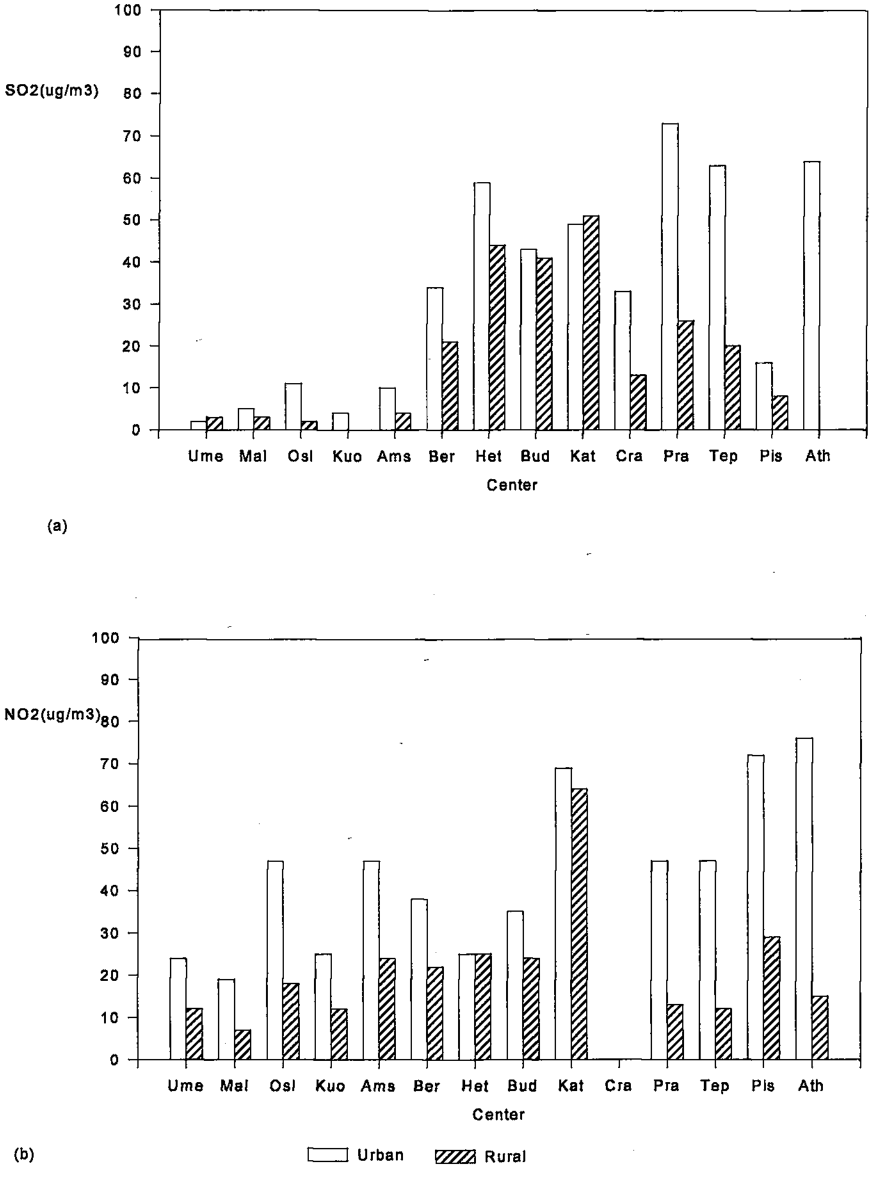


Figure 2. Median of daily average concentration by centre and location type: (a) SO_2, (b) NO_2

Table 6. Variation of air pollution concentrations with day of the week.

	Urban locations		Rural locations	
	Saturday	Sunday	Saturday	Sunday
PM_{10}	0.95 (0.85, 1.05)[1]	0.93 (0.84, 1.04)	0.98 (0.87, 1.11)	0.97 (0.87, 1.09)
BS	0.94 (0.83, 1.07)	0.80 (0.70, 0.91)	0.93 (0.80, 1.08)	0.81 (0.69, 0.93)
SO_2	0.96 (0.85, 1.08)	0.86 (0.77, 0.97)	1.09 (0.95, 1.24)	1.02 (0.89, 1.17)
NO_2	0.90 (0.83, 0.98)	0.75 (0.69, 0.81)	0.94 (0.84, 1.06)	0.77 (0.68, 0.86)

1 Ratio of the concentration on Saturday compared to concentrations on weekdays (Monday through Friday), calculated from a linear regression model with log(PM_{10}) as the dependent variable and indicator variables for centre, Saturday and Sunday as independent variables. In parentheses the 95% confidence interval of this ratio. Data from all 28 locations pooled.

PM_{10} - BS relationships

The median PM_{10}/BS ratio showed a considerable variability across Europe, ranging from 0.67 to 3.67 (Table 7). For nine centres PM_{10}/BS ratios were lower at the urban area. Intercepts and slopes from a linear regression analysis with PM_{10} as the dependent and BS as the independent variable are shown in table 8. Intercepts from all models, except urban Athens, were significantly larger than 0. The majority of regression slopes was between 0.5 and 1.5.

PM_{10} and BS measured at the same location were highly correlated for most sites (table 9). Correlations below 0.70 were found in Malmö, Hettstedt and the urban area of Budapest.

A significant correlation ($p<0.01$) of the PM_{10} concentration between all pairs of West and Central European urban sites was found. The Spearman correlation coefficient ranged from 0.44 to 0.85, with a median of 0.71. For the rural locations, the corresponding median Spearman correlation coefficient was 0.72. For BS, the median Spearman correlation coefficient was 0.65 and 0.63 among West-Central European urban and rural sites respectively. No correlation was found between urban PM_{10} at these sites and Pisa, Athens and the Scandinavian sites Oslo, Kuopio and Umeå. A significant but low correlation ranging from 0.31 to 0.53 was found with the PM_{10} concentration of Malmö. The PM_{10} concentration of Athens was uncorrelated with any of the 13 other sites. Among the Scandinavian sites only the correlation between Kuopio and Malmö was significant ($r=0.49$). Because of the study periods no correlation between pollution of Oslo and Kuopio could be calculated.

Table 7. Median of daily average PM_{10}/BS concentration ratios in the winter of 1993/94.

	Urban location P50[1]	Rural location P50	N[2]
Umeå	3.19	2.45	62
Malmö	3.67	3.51	60
Oslo	0.67	0.89	66
Kuopio	1.61	2.37	57
Amsterdam	2.92	3.35	86
Berlin	2.03	2.45	58
Hettstedt	1.12	1.36	116
Budapest	1.33	1.79	62
Katowice	1.26	1.37	32
Cracow	1.67	1.26	77
Prague	1.94	2.27	76
Teplice	1.37	1.33	56
Pisa	3.20	2.44	39
Athens	0.88	1.65	57

1 50-th percentile; 2 number of measurement days.

Table 8. Results of linear regression analysis of daily average PM_{10} (dependent variable) and BS concentrations in the winter of 1993/94 (both in $\mu g/m^3$).

	Urban location Intercept + Slope (standard error)	Rural location Intercept + Slope (standard error)
Umeå	9 (1) + 1.04 (0.15)	7 (1) + 1.08 (0.13)
Malmö	15 (2) + 0.95 (0.17)	11 (2) + 1.10 (0.27)
Oslo	3 (2) + 0.58 (0.05)	4 (1) + 0.52 (0.04)
Kuopio	9 (2) + 0.65 (0.10)	8 (1) + 0.66 (0.07)
Amsterdam	14 (3) + 1.91 (0.15)	9 (3) + 2.49 (0.15)
Berlin	22 (4) + 1.23 (0.12)	19 (4) + 1.10 (0.13)
Hettstedt	19 (3) + 0.60 (0.08)	10 (3) + 0.96 (0.10)
Budapest	31 (8) + 0.61 (0.14)	18 (4) + 1.17 (0.10)
Katowice	26 (5) + 0.70 (0.08)	15 (5) + 1.06 (0.08)
Cracow	19 (5) + 1.16 (0.13)	12 (5) + 1.04 (0.10)
Prague	13 (3) + 1.35 (0.07)	15 (5) + 1.69 (0.19)
Teplice	15 (5) + 0.98 (0.07)	9 (5) + 1.07 (0.17)
Pisa	22 (6) + 1.83 (0.27)	28 (4) + 1.35 (0.13)
Athens	6 (8) + 0.85 (0.06)	14 (4) + 1.13 (0.10)

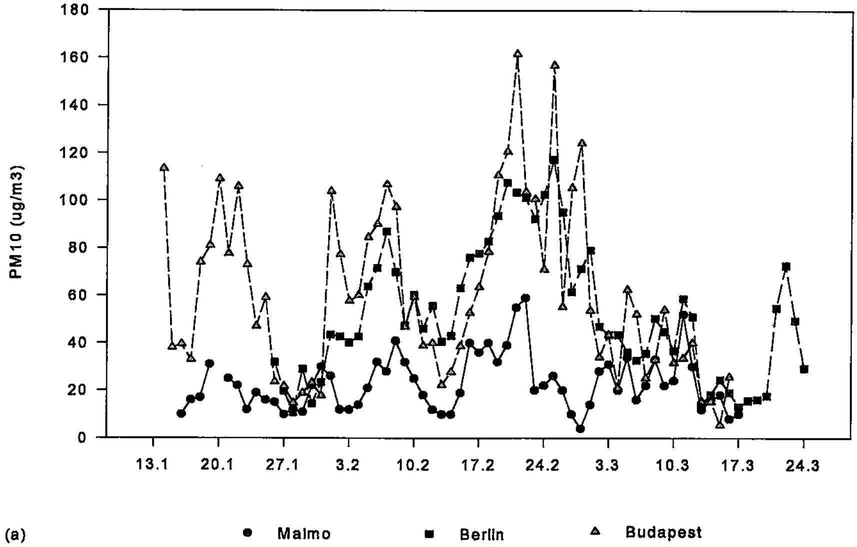
The correlations between PM_{10} concentrations across countries were not only by a common episode in February 1994. The median of the Spearman correlations of urban PM_{10} between all West and Central European sites was 0.66 excluding the episode, compared to 0.71 for all days.

February 1994 episode

From February 17 until March 2, 1994 PM_{10} concentrations were increased at several locations. The time pattern of PM_{10} at some selected urban locations is shown in figures 3a and 3b. Boxplots of the distribution of the ratio of the daily concentrations in this period to the median concentration are shown in figure 4. Figure 4 illustrates that this episode occurred at all West- and Central European sites. On average, daily PM_{10} concentrations during the episode were between 1.5 (Katowice) and 2.4 (Amsterdam) times higher than the median concentration. PM_{10} concentrations in Kuopio, Umeå, Malmö, Athens and Pisa were not increased consistently in this period. In Malmö increased concentrations were observed in the first days of the episode only. In Oslo measurements had stopped already.

The episode period was characterised by minimum temperatures below 0 °C, low windspeed and high relative humidity. Barometric pressure was not higher than average. The lowest temperatures and the highest atmospheric pressure were present before the period with the highest concentrations.

We next investigated whether the percentage difference in PM_{10} concentration at the 8 Central and West European sites between the urban and rural area was larger during the episode than on other non-episode days. Non-episode days were defined as days outside the episode period and without days with either an urban or a rural PM_{10} concentration exceeding 70 $\mu g/m^3$. Except for Teplice, the percentage differences between urban and rural sites were not substantially different during episode and non-episode days. Excluding Teplice, the urban/rural PM_{10} ratio averaged over the Central and West European sites was 1.13. In Teplice the median ratio on 32 non-episode days was 1.63 whereas the median ratio was 2.90 during the February 1994 episode.



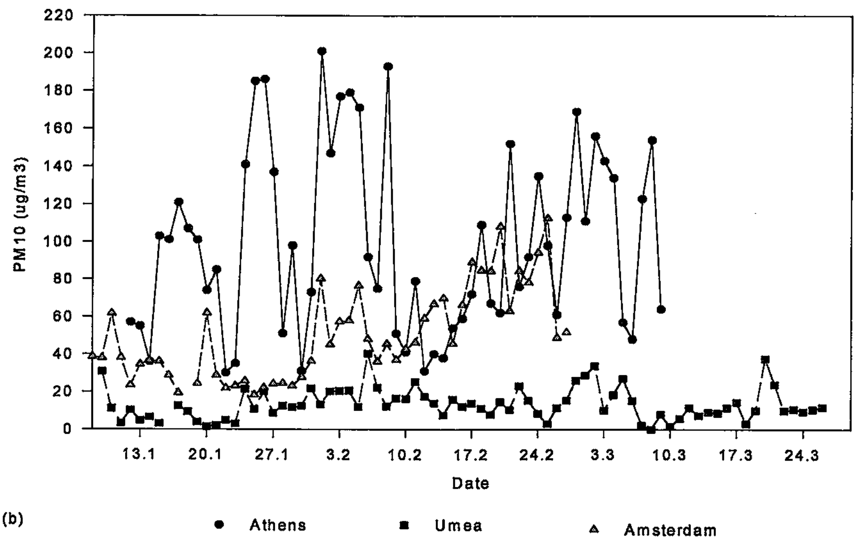


Figure 3. PM_{10} concentration versus day of study (a) Malmö, Berlin, Budapest (b) Athens, Umeå, Amsterdam.

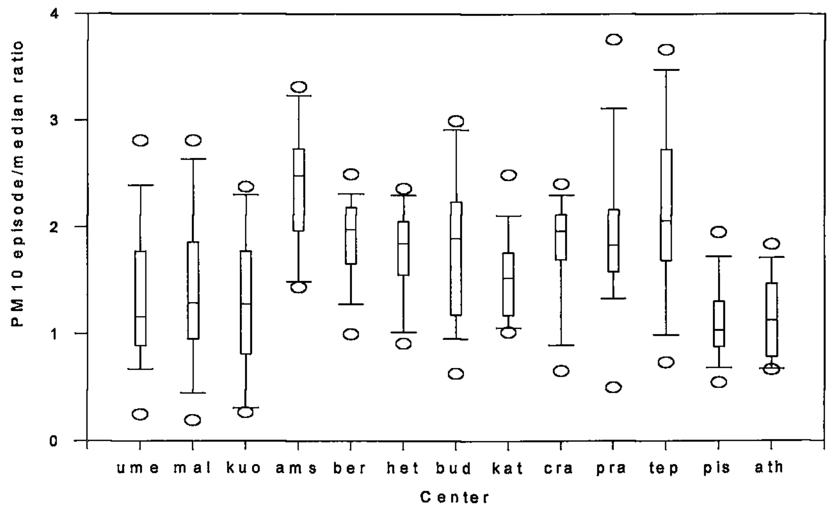


Figure 4. Distribution of ratio of PM_{10} concentration to the median in episode February 1994. Box represents 25-th, 50-th (inside box) and 75-th percentile. Whiskers are 10-th and 90-th percentile.

Discussion

Concentration patterns

Ambient particulate matter concentrations differed substantially across 10 European countries. The median PM_{10} concentration ranged from 11 to 92 $\mu g/m^3$, the median BS concentration from 3 to 99 $\mu g/m^3$. The lowest particle concentrations were observed at the Scandinavian locations. This is consistent with the low emission density of the important precursor pollutants NO_2 and SO_2 in Scandinavia (22, 23). In addition, the emission density of elemental carbon in Scandinavia is low compared to other European countries (12). This is probably caused by absence of large industrial source areas and low population density. The low NO_2 and especially SO_2 concentrations measured in the Scandinavian countries support this. The PM_{10} concentrations in Scandinavia were in the low range of the concentrations measured in the USA (24).

PM_{10} concentrations in Central Europe were among the highest. However, the concentration difference of the PM_{10} concentrations in these locations and Amsterdam/Berlin was considerably smaller than the difference in the primary pollutant

SO_2. This observation is consistent with the pattern of differences found between 1991-1992 wintertime PM_{10} and SO_2 in Erfurt in the former German Democratic Republic and Sokolov (Czech Republic) and 24 locations in the USA (23). The PM_{10} concentrations measured at the Central European PEACE study sites were similar to the mean wintertime PM_{10} concentrations reported for Erfurt and Sokolov, being 64 and 54 $\mu g/m^3$ respectively. A study conducted in Katowice in 1989 found an average TSP concentration of 300 $\mu g/m^3$ measured at a background site 9 meter above the ground (25). Andersen impactor measurements suggested that the major part of particle mass was present in the size fractions below 2.6 μm (24). PM_{10} concentrations measured in the PEACE study were considerably lower. This is probably a result of decreased industrial emissions and decreased use of coal for domestic heating since 1989. Favourable meteorologic conditions in the PEACE study winter may also have played a role. In the winter of 1992/1993 in Teplice an average PM_{10} concentration of 140 $\mu g/m^3$ was measured (26).

The highest PM_{10} and BS concentrations were found in the urban area of Athens. High BS and SO_2 concentrations in Athens have been reported before (27, 28). High summertime PM2.5 concentrations (average 81 $\mu g/m^3$) with high fractions of sulphate (10 $\mu g/m^3$), organic and elemental carbon (sum 21 $\mu g/m^3$) have been measured before (29). Emissions from industrial sources and especially (diesel powered) motorised traffic contribute to these high concentrations (27, 28). The location of Athens in a basin near the sea and the narrow streets in the centre are also factors. Although the measurement site in Athens is located closer to a busy road than the other sites, it is unlikely that this fully explains the high concentrations. Measurements conducted in the Dutch National Air Quality Network comparing PM_{10} concentrations in considerably busier streets with urban background sites, have found only small differences in particle mass concentrations (30). Furthermore, NO_2 concentrations in Athens were less extreme than PM_{10} and BS concentrations when compared to the other PEACE study sites.

PM_{10} concentrations in the urban areas were on average 22% higher than in the corresponding rural areas, less than found for the gaseous pollutants SO_2 (56%) and NO_2 (78%). The smaller difference probably reflects the importance of long range transport in determining particle concentrations. Significant long range transport has been documented for several major components of particulate matter, such as sulphate, nitrate, ammonium and elemental carbon (5). A second explanation could be the presence of particle sources such as domestic coal and wood burning in the rural area. In Central European towns individual heating with low chimneys is more common than in urban areas where district heating is more common. Large differences were found for Athens, Teplice and Oslo (especially BS). At these locations the physical separation was substantial. In Athens a mountain ridge separates the urban from the rural area. In Teplice the distance between the two sites exceeds 250 km. In Oslo the urban area is situated in a basin, while the 'rural' area was selected higher in the hills frequently above the inversion layer. In Switzerland annual average PM_{10} concentrations in 1993 ranged from 10 $\mu g/m^3$ for alpine sites to 33 $\mu g/m^3$ for urban sites (31). Mean PM_{10} concentrations at suburban and rural were between 16 and 24 $\mu g/m^3$ in the Swiss study.

Urban BS concentrations were on average 43% higher than in the corresponding rural area, twice the difference for PM_{10}. This is in agreement with the sources of BS and PM_{10}. The most important sources of BS or elemental carbon are primary emissions of motorised vehicles and domestic coal and wood burning, which are generally higher in urban areas (10, 12). PM_{10} consists of particles from more sources, including resuspended soil dust and secondary aerosol components such as sulphate and nitrate. Larger urban-rural differences have been reported before in reviews of elemental carbon concentrations in older studies (10, 12). This could be explained by either the small distance between the urban and rural area in the PEACE study, by different emission patterns and by measurement differences. The first interpretation is supported by the small differences in diesel soot concentrations found between locations in the centre and suburbs of Vienna (11). Only at a rural hill site much lower soot concentrations were found (11). The third explanation is that the paper filter used in the BS method is not efficient for collection of submicrometer particles (32). Mass median diameters of ambient elemental carbon of 0.3 and 0.5 μm have been reported (12). Thus, the BS method might underestimate differences between urban and rural areas. Finally, since elemental carbon is mainly determined by submicrometer particles, significant transport over large distances may occur. For the Portuguese town Aveiro it has been calculated that about 50% of EC was due to long range transport and about 30% to motor vehicle emissions (33).

BS and PM_{10} also showed a different day of the week pattern. BS but not PM_{10} concentrations on Sundays were on average 20% lower than on weekdays, both in the urban and rural area. The observation that NO_2 concentrations were about 25% lower on Sundays in both areas, whereas SO_2 concentrations were only slightly decreased in the urban area, supports the interpretation that decreased motorised traffic emissions on Sundays explains the lower BS concentrations. Tendencies towards lower BS and NO_2 concentrations on Sundays were found at nearly all locations. The tendency for SO_2 was less consistent. All Central European locations tended to have lower SO_2 concentrations on Sunday. The Hettstedt data had a relatively large impact on the estimated average. Exclusion of the urban Hettstedt data resulted in a non-significant 9% decrease on Sundays.

PM_{10} - BS associations

PM_{10} and BS concentrations measured at the same site were highly correlated. This is an important observation for epidemiological studies evaluating the association in time of daily mortality or morbidity and ambient particulate matter. Both particle measures probably pick up the same signal in the health variable. This allows comparison between (European) studies using BS as the exposure variable and (North American) studies using PM_{10} as the exposure variable.

However, the PM_{10}/BS ratio in this study varied from 0.67 to 3.67. Most previous studies have evaluated the TSP-BS association. Measurements in London from 1955 to 1962 showed that the TSP concentration was on average two times higher than the BS concentration (34). The TSP/BS ratio appeared to increase with year of study, attributed to the reduction of dark particles in ambient air. TSP/BS ratios at six British sites with different source characteristics in 1970 ranged from less than 1 to larger than 3 (35). The ratio less than unity was observed in the heating season in a city with heavy industry and domestic coal burning. A study in the USA at 16 mostly industrial sites found a TSP/BS ratio of about 9 (36). At a location where particle concentrations were largely dominated by wind blown dust, the TSP concentration was about 10 times higher than the BS concentration (37). Two studies compared concentrations obtained by gravimetric analysis of glass fibre filters from a BS-sampler with standard BS concentrations obtained through reflectance measurements (6, 38). In the study conducted in 1977-1978 at four urban British sites the ratio of mean gravimetric particulate matter and mean BS was about 2 in winter and 2.7 in summer. At the fifth site where domestic coal burning was still an important source, the ratio measured in wintertime was almost 1 (6). Measurements conducted in 1980/81 in Berlin showed a ratio of the gravimetric and BS concentration of 1.2 in winter and 1.5 in summer. Finally, a linear regression analysis with PM_{10} as the dependent and BS as the independent variable for 1993 in Bristol found a significant intercept of about 10 $\mu g/m^3$ and slopes of 2.0 in winter and 3.7 in summer (2). The data from the PEACE study and previous studies suggest that the ratio of BS to a gravimetric particle metric varies substantially with time, location and season. This suggests that BS data should only be transformed into PM_{10} data when a recent validation study is available at a comparable site.

PM_{10}/BS ratio at the Central European locations, Oslo and Athens were closest to unity. For the former sites this was expected since domestic coal burning is still an important source of ambient particles as was the case in London when the BS calibration curve was constructed. One explanation for both Oslo locations is the presence of precipitation on many days. Another explanation could be that while motorised traffic resulted in substantial BS concentrations, other (industrial) sources are largely absent resulting in relatively low PM_{10} concentrations. For the urban area of Athens the low PM_{10}/BS ratio is consistent with the large contribution of diesel soot emissions to ambient particles. Diesel soot particles were found to be about three times darker than coal combustion particles (4,12), consistent with the higher percentages of elemental carbon in diesel particles compared to particles emitted from coal combustion (5).

Except for urban Athens, regression models from all locations showed a significant positive intercept. The intercept can be interpreted as either the coarse fraction of PM_{10} or the fine fraction of PM_{10} that does not co-vary with elemental carbon. The positive intercept has been found in other studies comparing TSP with BS (6, 35, 37) and PM_{10} with BS (2), as well.

February 1994 episode

The simultaneous increase of PM_{10} concentrations in a large part of West and Central Europe during an episode in February 1994, is consistent with the description of a major winter episode in January 1985 (39). Measurements and model calculations showed that in January 1985 high SO_2 concentrations were found in large areas of Western Europe. No PM_{10} concentration data were available. In addition, no data from Central Europe were available. Only during the last day of the 1985 episode increased SO_2 concentrations were observed at South Scandinavian sites. A significant contribution of long range transport was suggested using trajectory analysis (38). The present study documented simultaneously increased particle concentrations over an even larger area. From the Scandinavian sites only Malmö showed increased concentrations during the early days of the episode. Trajectory analyses were not available for the present study.

The present study using a reasonably well standardised methodology has documented for the first time PM_{10} concentrations in a large number of European countries with very different meteorologic conditions and air pollution sources. Large differences in PM_{10} and BS concentrations were found between countries. Differences of particle concentrations between urban and rural locations in the same country were generally small. During an episode in February 1994 increased PM_{10} concentrations were observed at all Western and Central European sites, but not at in Northern and Southern Europe.

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4

Daily variations in air pollution and Peak Expiratory Flow in a multicentre study*

Abstract

The PEACE study is a multicenter panel study of the acute effects of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}), Black Smoke (BS), SO_2 and NO_2 on respiratory health of children with chronic respiratory symptoms.

Measurements were conducted in the winter of 1993/94. Combined effect estimates of air pollution on Peak Expiratory Flow (PEF) were calculated from the panel specific effect estimates. Fixed effects models were used and in case of heterogeneity, random effect models. No clear associations between PM_{10}, BS, SO_2 or NO_2 and morning or evening PEF could be detected. Only PM_{10} lag1 was negatively associated with evening PEF, but only in locations where BS was high compared to PM_{10} concentrations. There were no consistent differences in effect estimates between subgroups based on urban vs. control, geographical location or mean levels of PM_{10}, BS, SO_2 and NO_2. The lack of association could not be attributed to lack of statistical power, low levels of exposure or incorrect trend specifications.

In conclusion, the PEACE project did not show clear effects of PM_{10}, BS, SO_2 or NO_2 on morning or evening PEF.

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Introduction

Recent studies have demonstrated acute effects of air pollution on pulmonary function of children (1, 2, 3, 4, 5) using air pollution indicators such as particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}), sulphur dioxide (SO_2) and Black Smoke (BS). In some of these studies (3,4,5) it was not possible to disentangle the effects of the separate air pollution indicators. Effects could be seen below the 1987 World Health Organization (WHO) air quality guidelines (6). These WHO air quality guidelines for Europe were based on older epidemiological studies using indicator pollutants such as Total Suspended Particulates (TSP), BS and SO_2, and at higher concentrations of these pollutants than encountered in most European areas today. Concentration and composition of air pollution have changed over the last decades in many areas in Europe (7). Components such as SO_2 and airborne, coarse particulates have decreased due to emission abatement measures and changes in energy production, industrial processes and space heating. Levels of other pollutants such as NO_2 and O_3 have increased during the same period, mostly due to increased motor vehicle traffic. Thus, information is needed to evaluate how the response to air pollution depends on the composition of the current air pollution mixture. The possible difference in response to air pollution characterised by high SO_2 and particulate levels, and air pollution characterised by high levels of NO_2 and diesel soot is of specific interest. East European countries still experience the classical type of air pollution, whereas West European countries experience more motor vehicle air pollution. A comparison of health effects between urban areas and suburban or rural areas is of interest to detect effects of primary urban emissions.

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. It is a collection of panel studies that were conducted in the winter of 1993/1994 in 14 different centres in Europe. All centres used the same protocol for data collection and data analysis. Design, methods and results of the individual panels have been reported in a special issue of the European Respiratory Review (8, 9, 10,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). In this paper the effect estimates on PEF for the separate panels are used to calculate combined effect estimates for various air pollutants. In addition to combining effect estimates of all locations, we also investigated differences between based on geographic location, urban/suburban location and composition of air pollution mixture.

The combination of panel specific effect estimates of air pollution on the prevalence of respiratory symptom and medication use will be presented in chapter 5. The evaluation of differences in response between subjects within a panel, such asthmatics vs. non asthmatics and atopics vs. non-atopics is the topic of chapter 6.

Methods and Material

PEACE study

The PEACE study was a collaboration of 14 European centres (figure 1, chapter 2): Amsterdam (the Netherlands), Kuopio (Finland), Oslo (Norway), Berlin and Hettstedt (Germany), Pisa (Italy), Athens (Greece), Cracow and Katowice (Poland), Prague and Teplice (Czech Republic), Budapest (Hungary), Umeå and Malmö (Sweden). Each centre selected two panels, one panel in an urban area and one panel in a suburban or rural area (hereafter to be referred to as suburban panel). The suburban panel was selected from a community which had no major traffic emissions, had no large industrial sources, had sufficient size to select enough subjects and was close to a site of an existing air pollution measurement network. Suburban panels were included to evaluate differences in effects of air pollution caused by level and composition of air pollution, in panels paired by meteorological characteristics.

Children between 6-12 years with chronic respiratory symptoms were selected by a parent completed screening questionnaire. The criteria for selection were: reporting of recent wheeze (apart from colds), recent attacks of shortness of breath with wheezing, recent dry cough (apart from colds) and/or doctor diagnosed asthma, ever in life. To further characterise the children, skin prick tests to common allergens were applied, 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 (chapter 2).

Peak Expiratory Flow (PEF) was measured each day in the morning and in the evening for at least two months in the winter of 1993/94. Three PEF measurements were performed in standing position, prior to medication use. All three readings were noted in the diary. For analysis the highest of the three readings was used. All subjects used the mini Wright Peak Flow meter. A parent completed a daily diary for the child recording the presence of respiratory symptoms and use of medication for respiratory symptoms. To avoid large changes in composition of the reporting group of children on separate days children were included in the analysis if they had valid PEF measurements and respiratory symptom data on more than 60% of the days.

Concurrent air pollution measurements were performed in both the urban and suburban locations. Daily 24 hour measurements of PM_{10}, BS, SO_2 and NO_2 were made at sites not influenced by nearby sources, so called background sites. More information about the measurement methods is given elsewhere (24, chapter 2 and 3).

All panels were analysed separately. Individual daily PEF readings were transformed into a daily population variable representing the population mean for each day of the individual deviations from the child specific mean PEF (1,2). This was done separately for morning and evening PEF resulting in ΔPEF_{am} and ΔPEF_{pm}. The association between daily levels of air pollutants and daily levels in ΔPEF_{am} and ΔPEF_{pm} was calculated by means of linear regression weighted by the number of reporting children on each day. Correction for autocorrelation of residuals was made assuming a first order autoregressive structure. The explanatory variables were 24 hour average concentrations of PM_{10}, BS, SO_2 and NO_2, analysed separately because of the high correlation ($r>0.6$) between the pollutants. 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. Minimum temperature, a dummy variable indicating normal school days versus holidays/weekends and time trend were included as potential confounders. The regression slopes are expressed as l/min change in PEF per 100 $\mu g/m^3$ increase in air pollution.

Statistical methods and analysis

We have chosen for a combined analysis of panel specific effect estimates using meta analysis techniques and not for a pooled analysis because of the computational complexity of the latter. A pooled analysis, involving the creation of one large dataset of all individual data, would require interaction terms for each term included in the regression equation to allow for, for example, panel specific time trends. Combined effect estimates were calculated for the regression slopes of lag0, lag1 , lag2 and the 7 day mean on ΔPEF_{am} or ΔPEF_{pm}. A combined fixed effect estimate was calculated as the weighted mean of the panel-specific slopes with the weights inverse proportional to the panel specific variance. The Standard Error (SE) of the combined slope was calculated as the inverse of the square root of the sum of the weights (25). This fixed effect mean assumes that the variability of panel specific slopes is caused by sampling errors only and that there is no variance present caused by other factors. Panel specific regression slopes and the combined regression slope were plotted with 95% Confidence Intervals (95% CI). Heterogeneity of panel specific slopes was evaluated by a visual inspection followed by a chi-square test for homogeneity (25). In this visual inspection heterogeneity was suspected in case the combined slope was not contained in the 95% CI of all panel specific slopes (26). In case of homogeneity the combined slope calculated as a fixed effect was considered an appropriate estimate. A conservative cut-point of a p-value smaller than 0.25 was chosen to determine heterogeneity. In case of heterogeneity ($p<0.25$) combined effect estimates using random effect estimation were calculated with the non-iterative method with unequal weights (25). Random effect estimation takes into account the within study variance and the between study variance. Next, combined effect estimates were calculated within pre-defined strata. Location (urban vs. suburban) was used to evaluate the potential additional effect of urban air pollution sources over suburban areas. Geographical location was used to evaluate climatic influences or regional differences in air pollution. Four groups were defined: North (Umeå, Oslo, Malmö, Kuopio), West (Amsterdam, Berlin), East (Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest) and South (Pisa, Athens). Strata based on concentrations of air pollution components were defined to evaluate possible interactions between the composition of air pollution and the effects of air pollution. BS served as indicator of fine black particles emitted by traffic or coal combustion, SO_2 as indicator of air pollution caused by fossil fuel combustion with high amounts of sulphur and NO_2 as indicator of traffic related air pollution. Strata based on the ratio between the mean concentrations of PM_{10} and BS served to indicate the proportion of carbonaceous particles.

To correct for other factors, a weighted multiple linear regression was performed with the panel specific regression slopes, with the inverse of the panel specific variance of the slope used as weights. The calculated SE of the regression slope was corrected according to Berlin and Longnecker (27). Independent variables were mean concentrations of PM_{10}, BS, SO_2 and NO_2, the ratio PM_{10}/BS and geographical position. To evaluate unmeasured differences between urban and suburban locations a dummy indicator for location was included in the regression models. Children may react differently to air pollution (28), thus the reaction of a panel to air pollution might be influenced by panel composition. This may affect the relationship between the regression slopes and indicators of air pollution composition. The percentage of atopic children, the percentage of children in a panel who were selected only on basis of a positive answer to cough and the mean prevalence of bronchodilator use of a panel served as indicators of panel composition and were therefore included in the regression models as possible effect modifiers. Children who were selected only on the basis of a positive answer to the nightly dry cough question had a lower prevalence of lower respiratory symptoms, upper respiratory symptoms and phlegm than children selected on asthma symptoms (29) and reacted differently in the Finnish panels (28). A formal analysis of subgroups within the PEACE panels is presented in chapter 6.

Results

A total of 66,879 questionnaires were handed out, 51,786 (77%) were received back and 8,308 children (16%) fulfilled the selection criteria. The design called for 75 children in each panel, i.e. a total of 2,100 children in 28 locations. From the 2,371 children who were enrolled, 2,010 were included in analysis. The children included in

Table 1. Characteristics of PEACE panels.

		PM_{10}*	BS*	SO_2*	NO_2*	subjects	atopic†	cough‡	bron§
Umeå	urban	13.4	4.6	2.7	25.0	75	54	15	10
(Sweden)	suburban	11.5	5.3	4.0	15.3	72	61	17	22
Malmö	urban	22.9	8.2	6.0	20.7	78	50	28	18
(Sweden)	suburban	16.2	4.5	4.0	8.9	82	55	34	8
Kuopio	urban	17.7	12.6	6.0	28.4	85	64	54	3
(Finland)	suburban	13.0	7.9	-	13.7	84	64	58	7
Oslo	urban	19.3	27.6	12.4	49.3	56	41	36	3
(Norway)	suburban	11.2	13.1	3.4	15.3	68	49	55	10
Amsterdam	urban	45.3	16.5	13.2	46.4	55	51	38	4
(The Netherlands)	suburban	44.4	13.6	8.5	26.5	71	41	44	3
Berlin	urban	52.3	24.5	42.3	38.3	50	60	4	17
(Germany)	suburban	43.0	22.0	26.1	21.2	66	59	3	8
Hettstedt	urban	40.3	42.0	83.3	26.5	75	33	21	2
(Germany)	suburban	32.9	25.5	64.9	26.1	63	19	10	5
Katowice	urban	68.7	55.5	55.7	68.7	72	49	35	1
(Poland)	suburban	73.8	57.9	56.0	69.5	73	30	15	3
Cracow	urban	60.1	34.9	41.3	-	73	7	51	1
(Poland)	suburban	56.1	42.7	14.0	-	76	53	31	1
Teplice	urban	74.3	58.9	74.8	48.8	91	16	56	3
(Czech Republic)	suburban	32.4	22.0	19.9	12.5	77	26	36	1
Prague	urban	52.7	29.4	113.9	44.7	66	48	2	5
(Czech Republic)	suburban	49.6	20.8	30.8	12.9	68	81	14	20
Budapest	urban	60.9	48.9	49.7	35.3	76	40	45	2
(Hungary)	suburban	52.1	30.6	41.0	25.4	63	58	33	5
Pisa	urban	61.6	19.7	15.7	68.1	68	81	0	4
(Italy)	suburban	69.5	29.3	8.2	32.7	60	59	19	6
Athens	urban	98.8	109.2	72.4	74.9	87	16	53	4
(Greece)	suburban	50.0	33.5	-	19.7	80	22	31	7

* mean concentration during study period in $\mu g/m^3$; † percentage of children in panel with one or more positive skin prick test reactions; ‡ percentage of children in panel selected only on basis of question on nightly coughing; § mean prevalence (%) of bronchodilator use in panel during study period

the analysis did not differ from the excluded children with respect to responses on screening questions, skin prick testing and lung function levels. In table 1 the most important characteristics of the panels and results of air pollution measurements are summarised. A wide range of air pollution concentrations was included, with low concentrations of both gaseous and particle components in Northern Europe, higher concentrations in Western Europe and the highest concentrations in Central and Southern

Europe. The ratio between the mean concentration of PM_{10} and BS varied widely between sites, but did not show a geographical pattern. More details on air pollution can be found in chapter 3.

The weighted means of the panel specific estimates are presented in table 2. In all 28 locations PM_{10} and Black Smoke measurements were performed. No SO_2 measurements were done in Kuopio suburban location and Athens suburban location, no NO_2 measurements were done in Cracow urban and suburban location. For these components 26 panel specific regression slopes were available of each representation. Heterogeneity was predominantly present in the effect estimates of the 7 day means of the air pollution components. Most combined effect estimates were positive, but mostly non significant. A positive association means that an increase in air pollution is associated with an increase in PEF, which is opposite to the expected association. A significant positive association was found between SO_2 lag2 and ΔPEF_{am}. The only significant negative association was found for PM_{10} lag1 with ΔPEF_{pm}.

Table 2. Combined effect estimates with 95% Confidence intervals (95% CI) of air pollution on PEF, expressed in l/min per 100 µg/m³.

		ΔPEF_{am}			ΔPEF_{pm}		
	N†	mean	(95% CI)	p_{hom}‡	mean	(95% CI)	p_{hom}‡
PM_{10}							
lag0	28	0.5	(-0.1, 1.1) §	0.78	0.4	(-0.1, 0.9) §	0.93
lag1	28	0.1	(-0.5, 0.7) ¶	0.21	-0.6	(-1.1, -0.1) §	0.78
lag2	28	0.5	(-0.1, 1.1) §	0.38	0.2	(-0.5, 0.9) ¶	0.07
7 day mean	28	0.2	(-1.6, 2.0) ¶	< 0.01	0.0	(-1.7, 1.7) ¶	< 0.01
Black Smoke							
lag0	28	0.5	(-0.1, 1.1) §	0.74	0.1	(-0.5, 0.7) §	0.52
lag1	28	-0.1	(-0.9, 0.7) ¶	0.17	-0.3	(-0.9, 0.3) §	0.64
lag2	28	0.3	(-0.6, 1.2) ¶	0.09	0.4	(-0.2, 1.0) §	0.29
7 day mean	28	0.9	(-1.6, 3.4) ¶	<0.001	0.6	(-1.5, 2.7) ¶	0.03
SO_2							
lag0	26	0.2	(-0.2, 0.6) §	0.73	0.1	(-0.3, 0.5) §	0.88
lag1	26	0.2	(-0.2, 0.6) §	0.85	0.0	(-0.4, 0.4) §	0.75
lag2	26	0.6	(0.2, 1.0) §	0.76	0.1	(-0.4, 0.6) §	0.76
7 day mean	26	0.6	(-1.3, 2.5) ¶	<0.0001	0.2	(-0.5, 0.9) §	0.28
NO_2							
lag0	26	0.7	(-0.2, 1.6) §	0.61	0.4	(-0.5, 1.3) §	0.56
lag1	26	1.1	(-0.1, 2.3) ¶	0.07	0.0	(-0.9, 0.9) §	0.51
lag2	26	0.6	(-0.5, 1.7) ¶	0.15	0.2	(-0.7, 1.1) §	0.64
7 day mean	26	0.2	(-3.0, 3.4) ¶	<0.01	0.6	(-3.1, 4.3) ¶	< 0.0001

† Number of panel specific estimates; ‡ p value χ^2 test on homogeneity; § Fixed effects model; ¶ Random effects model

Stratification according to urban or suburban location of the effect estimates for ΔPEF_{pm} did not show clear differences between the strata and none of the combined effect estimates reached statistical significance (table 3). The heterogeneity detected in table 2 was still present. Stratification according to geographical location in Europe (North, West, East, South) also did not show consistent differences among locations. None of the combined effect estimates reached statistical significance in any of the strata (table 4). Lag1 effect estimates are presented because these have been reported most frequently in literature, 7 day mean effect estimates because these showed most heterogeneity. Figures 1a-c show the effect estimates of PM_{10} lag1 on ΔPEF_{pm} plotted against the mean concentrations of PM_{10}, BS and the ratio PM_{10}/BS. With increasing mean PM_{10} concentration the variability of the effect estimates of PM_{10} decreased (fig. 1a). This is because with increasing mean concentration the variation in concentration increases, which improves the precision of the effect estimate. PM_{10} slopes tended to be negative for

Table 3. Combined effect estimates with 95% confidence intervals (95% CI) of air pollution on ΔPEF_{pm}, expressed in l/min per 100 $\mu g/m^3$. Stratified on location.

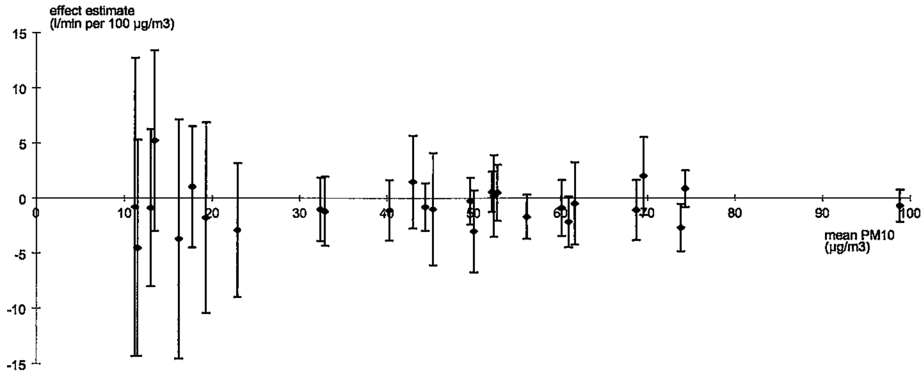
	Urban			suburban		
	N†	mean (95% CI)	p_{hom}‡	N†	mean (95% CI)	p_{hom}‡
PM_{10}						
lag0	14	0.4 (-0.3, 1.1)§	0.97	14	0.4 (-0.4, 1.2)§	0.54
lag1	14	-0.4 (-1.1, 0.3)§	0.80	14	-0.8 (-1.6, 0.0)§	0.53
lag2	14	-0.2 (-1.2, 0.8)¶	0.07	14	0.7 (-0.1, 1.5)§	0.32
7 day mean	14	-0.8 (-3.5, 1.9)¶	<0.01	14	1.2 (-0.4, 2.8)§	0.37
Black Smoke						
lag0	14	0.2 (-0.6, 1.0)§	0.51	14	0.0 (-1.1, 1.1)§	0.40
lag1	14	-0.1 (-0.9, 0.7)§	0.81	14	-0.6 (-1.7, 0.5)§	0.32
lag2	14	0.2 (-0.6, 1.0)§	0.34	14	0.7 (-0.4, 1.8)§	0.27
7 day mean	14	-0.8 (-3.6, 2.0)¶	0.08	14	2.3 (-0.7, 5.3)¶	0.20
SO_2						
lag0	14	0.1 (-0.4, 0.6)§	0.91	12	0.4 (-0.4, 1.2)§	0.54
lag1	14	0.1 (-0.4, 0.6)§	0.83	12	-0.1 (-0.9, 0.7)§	0.40
lag2	14	0.1 (-0.4, 0.6)§	0.87	12	0.2 (-0.6, 1.0)§	0.35
7 day mean	14	0.1 (-0.8, 1.0)§	0.28	12	0.5 (-0.8, 1.8)§	0.29
NO_2						
lag0	13	0.4 (-0.8, 1.6)§	0.63	13	0.4 (-0.8, 1.6)§	0.34
lag1	13	-0.3 (-1.5, 0.9)§	0.30	13	0.3 (-0.9, 1.5)§	0.65
lag2	13	-0.1 (-1.3, 1.1)§	0.43	13	0.5 (-0.8, 1.8)§	0.67
7 day mean	13	0.3 (-5.3, 5.9)¶	< 0.0001	13	1.6 (-2.9, 6.1)¶	0.11

† Number of panel specific estimates; ‡ p value χ^2 test on homogeneity; § Fixed effects model; ¶ Random effects model.

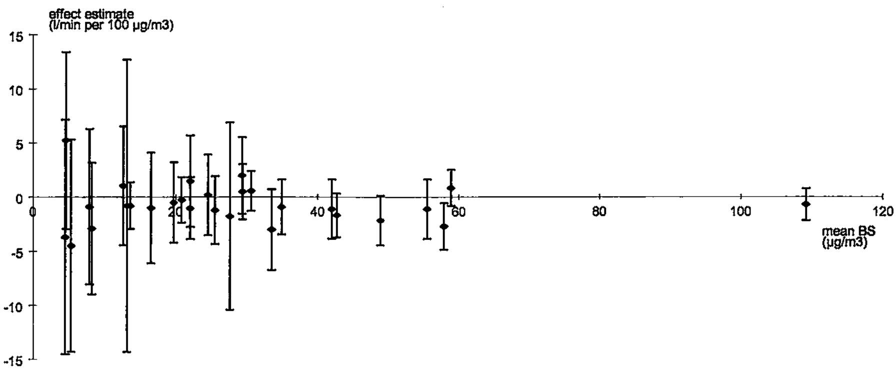
Table 4. Combined effect estimates with 95% confidence intervals (95% CI) of air pollution on ΔPEF_{pm}, expressed in l/min per 100 $\mu g/m^3$. Stratified on geographical location.*

	North				West				East				South			
	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡
PM_{10}																
lag1	8	-0.7	(-3.4, 2.0) §	0.80	4	-0.3	(-1.9, 1.3) §	0.79	12	-0.7	(-1.4, 0.0) §	0.34	4	-0.6	(-1.8, 0.6) §	0.30
7 day mean	8	1.9	(-4.8, 8.6) §	0.36	4	0.0	(-5.0, 5.0) ¶	0.08	12	-0.3	(-2.7, 2.1) ¶	<0.001	4	0.6	(-3.9, 5.1) ¶	0.12
Black Smoke																
lag1	8	-0.1	(-2.9, 2.7) §	0.89	4	1.1	(-2.5, 4.7) §	0.76	12	-0.3	(-1.2, 0.6) ¶	0.23	4	-0.5	(-3.0, 2.0) ¶	0.17
7 day mean	8	1.1	(-5.6, 7.8) §	0.32	4	2.9	(-7.7, 13.5) ¶	0.02	12	0.2	(-2.3, 2.7) ¶	0.06	4	-1.4	(-4.6, 1.8) §	0.71
SO_2																
lag1	7	2.6	(-4.2, 9.4) §	0.96	4	1.6	(-1.8, 5.0) ¶	0.21	12	0.0	(-0.5, 0.5) §	0.37	3	1.1	(-1.7, 3.9) §	0.95
7 day mean	7	6.8	(-7.2, 20.8) §	0.89	4	2.0	(-2.1, 6.1) §	0.38	12	0.3	(-0.8, 1.4) ¶	0.16	3	17.2	(-19.4, 53.8) ¶	0.07
NO_2																
lag1	8	0.0	(-2.0, 2.0) §	0.97	4	1.7	(-2.4, 5.8) ¶	0.21	10	-0.3	(-1.4, 0.8) §	0.30	4	1.5	(-2.8, 5.8) ¶	0.13
7 day mean	8	1.3	(-5.4, 8.0) ¶	0.13	4	-1.5	(-9.3, 6.3) §	0.55	10	0.6	(-3.7, 4.9) ¶	0.01	4	2.3	(-15.5, 20.1) ¶	<0.001

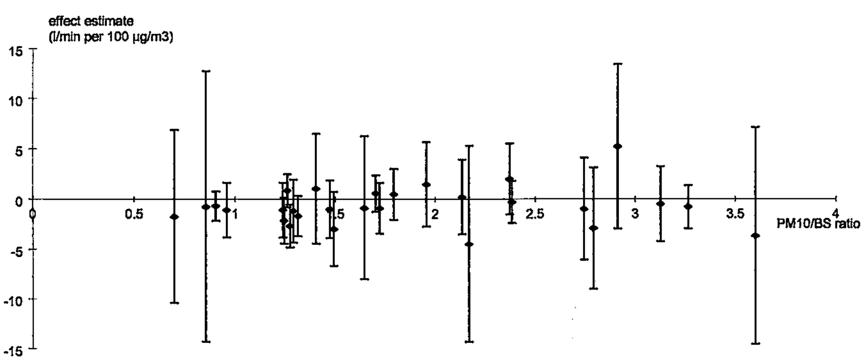
* North: Umeå, Malmö, Kuopio, Oslo; West: Amsterdam, Berlin; East: Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest; South: Pisa, Athens. † Number of panel specific estimates; ‡ p value χ^2 test on homogeneity; § Fixed effects model; ¶ Random effects model.



a)



b)



c)

Figure 1. Panel specific estimates (95% Confidence intervals) of PM_{10} lag1 on ΔPEF_{pm} against a) mean PM_{10} concentration b) mean BS concentration c) ratio mean PM_{10} concentration/mean BS concentration

locations with the highest BS concentrations (fig. 1b) and locations with a low PM_{10}/BS ratio (fig. 1c).

Table 5 shows stratification on basis of mean BS concentration. Significant positive associations of lag2 and 7 day mean concentrations of PM_{10} and BS were found in the Medium stratum, a significant negative association in the High stratum with PM_{10} lag1. In the adjusted regression analysis none of the effect estimates decreased or increased significantly with mean BS concentrations. Stratification in tertiles of the ratio between

Table 5. Combined effect estimates with 95% confidence intervals (95% CI) of air pollution on ΔPEF_{pm}, expressed in l/min per 100 $\mu g/m^3$. Stratified on tertiles of mean BS concentration and tertiles of ratio PM_{10} and BS.

	Mean BS concentration*											
	Low				Medium				High			
	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡
PM_{10}												
lag0	9	-0.1	(-1.7, 1.5)§	0.80	10	0.8	(-0.1, 1.7)§	0.92	9	0.3	(-0.4, 1.0)§	0.48
lag1	9	-0.7	(-2.3, 0.9)§	0.88	10	0.1	(-0.8, 1.0)§	0.94	9	-1.1	(-1.8, -0.4)§	0.28
lag2	9	0.2	(-1.5, 1.9)§	0.36	10	1.2	(0.3, 2.1)§	0.43	9	-0.4	(-1.4, 0.6)¶	0.10
7 day mean	9	-1.0	(-6.6, 4.6)¶	0.20	10	1.8	(0.3, 3.3)§	0.46	9	-1.6	(-4.5, 1.3)¶	0.01
Black Smoke												
lag0	9	0.0	(-2.9, 2.9)§	0.46	10	0.8	(-0.9, 2.5)¶	0.21	9	-0.1	(-0.8, 0.6)§	0.82
lag1	9	-0.3	(-3.1, 2.5)§	0.93	10	0.3	(-1.1, 1.7)§	0.58	9	-0.5	(-1.5, 0.5)¶	0.14
lag2	9	0.8	(-2.0, 3.6)§	0.67	10	2.1	(0.7, 3.5)§	0.33	9	-0.2	(-1.0, 0.6)§	0.60
7 day mean	9	-2.1	(-10.1, 5.9)¶	0.22	10	3.3	(1.1, 5.5)§	0.44	9	-1.4	(-4.1, 1.3)¶	0.14

	PM_{10}/BS ratio**											
	Low				Medium				High			
	N†	mean	(95% CI)	p_{hom}‡	N†	mean	(95% I)	p_{hom}‡	N†	mean	(95% CI)	p_{hom}‡
PM_{10}												
lag0	9	0.2	(-0.6, 1.0)§	0.78	10	0.8	(-0.1, 1.7)§	0.68	9	0.4	(-0.8, 1.6)§	0.80
lag1	9	-0.9	(-1.7, -0.1)§	0.41	10	-0.4	(-1.3, 0.5)§	0.69	9	-0.3	(-1.5, 0.9)§	0.71
lag2	9	-0.7	(-1.5, 0.1)§	0.38	10	1.4	(0.5, 2.3)§	0.42	9	0.3	(-0.9, 1.5)§	0.37
7 day mean	9	-2.3	(-5.0, 0.4)¶	0.03	10	2.5	(0.8, 4.2)§	0.97	9	0.1	(-4.3, 4.5)¶	0.04
Black Smoke												
lag0	9	-0.1	(-0.9, 0.7)§	0.87	10	1.0	(-0.5, 2.5)¶	0.22	9	-1.7	(-4.5, 1.1)§	0.58
lag1	9	-0.6	(-1.4, 0.2)§	0.29	10	0.4	(-0.9, 1.7)§	0.60	9	0.7	(-2.3, 3.7)§	0.81
lag2	9	-0.3	(-1.1, 0.5)§	0.72	10	1.8	(0.2, 3.4)¶	0.14	9	1.3	(-1.6, 4.2)§	0.84
7 day mean	9	-1.9	(-4.3, 0.5)¶	0.22	10	4.3	(1.9, 6.7)§	0.51	9	-1.3	(-7.0, 4.4)§	0.47

* Low: mean BS concentration <=19.7 $\mu g/m^3$, medium: 19.7 $\mu g/m^3$ < mean BS concentration <=30.6 $\mu g/m^3$, high: mean BS concentration >30.6 $\mu g/m^3$; ** Low: ratio PM_{10}/BS <=1.3, medium: 1.3 < ratio PM_{10}/BS <=2.1, high: ratio PM_{10}/BS >2.1; † Number of panel specific estimates; ‡ p value χ^2 test on homogeneity; § Fixed effects model; ¶ Random effects model.

mean concentration of PM_{10} and Black Smoke shows that the most of the combined effect estimates of PM_{10} and BS in the Low stratum were negative and in the Medium and High strata predominantly positive (table 5). Effect estimates for lag1 of PM_{10} and BS became more positive with increasing ratio. Adjusted regression analysis showed that this trend was borderline significant ($p<0.10$) for the effect estimates of BS lag1 and of the 7 day means of PM_{10} and BS. Significant positive combined effect estimates were present in the Medium stratum for lag2 and the 7 day means of PM_{10} and BS, significant negative effect estimates for PM_{10} lag1 in the Low stratum. SO_2 and NO_2 effect estimates were not significantly related to mean BS concentrations or to PM_{10}/BS ratios (not presented).

Stratification on basis of mean concentration of PM_{10}, NO_2 or SO_2 did not show obvious patterns. Stratification of the effect estimates of air pollution on ΔPEF_{am} did not show clear patterns and if there were significant associations in the strata these were in the unexpected direction (data not shown).

Discussion

The combination of the panel specific estimates to an aggregate estimate did not show a clear effect of air pollution on PEF. The only significant negative association was PM_{10} lag1 with evening PEF. An explanation for the lack of effect might be that air pollution levels were too low to have a demonstrable effect on respiratory health. However, in most locations air pollution levels were reached at which earlier studies documented clear associations (1,2,3,4). The absence of effect can not be attributed to a lack of statistical power. The combined effect estimates had narrow confidence intervals. Before taking into account heterogeneity an increase of 10 $\mu g/m^3$ PM_{10} only would have to be related to a reduction in PEF of 0.06 l/min to become significant at 5% probability level. In relative terms, this is a reduction of 0.02%, assuming a mean PEF of 300 l/min. This is one fourth of the reduction which was calculated in a review using data from earlier panel studies (30). The lack of effect can probably not be attributed to incorrect specification of long term time trends in the panel analysis. We used a more detailed model than earlier panel studies (1, 2, 4, 5) to allow for training effects. Residuals were checked and if a period longer than 14 days was found with positive or negative residuals this was corrected with dummy variables (see chapter 2). This procedure did not materially affect effect estimates. In addition, two panels were selected which had a large contribution in the combined effect estimate and which had an effect estimate opposite to expected. These panels were reanalysed using a non-parametric function of time to allow a more flexible relationship (31). Specifically, loess was used with the span selected by

Akaike's Information Criterion. When negative autocorrelation was present in the residuals the span was increased. The effect estimates obtained with these models were similar to the effect estimates used here. Acute respiratory infections are known to have influence on children's lung function (32) and episodes of respiratory infections may have biased the effect estimates, depending on the association in time between respiratory infections and air pollution. However, fever was recorded in the diaries of the subjects and in none of the panels sudden increases of the prevalence of fever were noted. However, fever may not be sensitive enough to detect upper respiratory infections but unfortunately we do not have other data available to evaluate the influence of respiratory infections. It is possible that subgroups within the panels, such asthmatics, non medication users or atopics did react. This will be explored in a separate paper.

Tests on heterogeneity indicated that differences existed between some panel specific estimates. These differences are unlikely to be caused by differences in study design, methods or data analysis because all centres used the same protocol for fieldwork and data analysis (see chapter 2). Factors which serve as an indicator of the composition of air pollution such as mean concentrations of PM_{10}, SO_2 and NO_2 were not able to explain the variation. Urban/suburban locations did not show differences between effect estimates. An explanation might be that the contrast between urban and suburban was not large with regard to levels of PM_{10} and BS (chapter 3). Also geographical location was not able to explain much variation. This is in contrast with another European multicenter study (APHEA) in which the distinction between Western and Eastern European cities explained heterogeneity in the effect estimates of BS and SO_2 on mortality (33). In the PEACE study, the only significant negative association between air pollution and PEF was between PM_{10} lag1 and ΔPEF_{pm} in centres with high BS concentrations or in centres with a low ratio between PM_{10} and BS. Removal of the centre with extreme BS concentrations (Athens urban) did not change these results. BS measures the reflectance of a sampled filter (34) and does not account for the portion of aerosol mass that does not absorb light (35). The main fraction of light absorbing particles in ambient air is formed by elemental carbon (36) and the size of the particles sampled with the BS sampler is below 5 μm. (35). The formulas which are used to transform reflectance to mass concentrations are based on older studies in which the air pollution mixture was different from today (36). For this reason, the BS figures should be interpreted as an indication of elemental carbon and not as mass concentrations. Thus, these results suggest that particulate matter mixtures with a relatively high amount of elemental carbon - to which diesel and coal combustion contribute (6) - were more likely to affect PEF than mixtures with low elemental carbon content. However, this is contradicted by the fact that in this study daily variations in BS were not related to variations in PEF.

Stratification of the associations between air pollution and ΔPEF_{am} did not show clear patterns. This might be explained by the timing of the morning PEF measurement. This was done just after getting up, which means that a long period of indoor exposures preceded the measurement. This may have obscured a possible association of ΔPEF_{am} with outdoor air pollution.

In conclusion, the PEACE project did not show clear effects of PM_{10}, BS, SO_2 or NO_2 on ΔPEF_{am} or ΔPEF_{pm}. Only PM_{10} lag1 was associated with ΔPEF_{pm}, especially in locations where BS was high compared to PM_{10} concentrations.

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5

Acute respiratory symptoms, medication use and short-term changes in air pollution in a multicentre study*

Abstract

The PEACE study is a multicenter panel study of the acute effects of thoracic particles (PM_{10}), Black Smoke (BS), sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) on respiratory health of children with chronic respiratory symptoms during the winter of 1993-1994.

Combined effect estimates of air pollution on respiratory symptom prevalence and medication use were calculated from the panel specific effect estimates. Fixed effects models were used and in case of heterogeneity, random effect models.

No clear associations between PM_{10}, BS, SO_2, NO_2 and symptom prevalence or medication use could be detected. Heterogeneity in panel specific associations was not explained by location, geographical position, mean levels of PM_{10}, BS, SO_2 , NO_2 and ratio of PM_{10} and BS. The lack of association could not be attributed to lack of statistical power, low levels of exposure or incorrect trend specifications.

In conclusion, the PEACE project did not show clear effects of PM_{10}, BS, SO_2 or NO_2 on the prevalence of respiratory symptoms or medication use.

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Introduction

Recent studies have demonstrated acute effects of winter air pollution on pulmonary function (1, 2, 3, 4, 5), respiratory symptoms (1, 2, 3, 5) and medication use (1, 3) in groups of children using air pollution indicators such as particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}), sulphur dioxide (SO_2) and Black Smoke (BS). In some of these studies it was not possible to disentangle the effects of the separate air pollution indicators. Effects could be seen below the 1987 World Health Organisation (WHO) air quality guidelines (6). The WHO air quality guidelines for Europe were based on older epidemiological studies using indicator pollutants such as Total Suspended Particulates (TSP), BS and SO_2, and at higher concentrations of these pollutants than encountered in most European areas today. Concentration and composition of air pollution have changed over the last decades in many areas in Europe (7). Components such as SO_2 and airborne, coarse particulates have decreased due to emission abatement measures and changes in energy production, industrial processes and space heating. Levels of other pollutants such as nitrogen dioxide (NO_2) and ozone (O_3) have increased during the same period, mostly due to increased motor vehicle traffic. Thus, information is needed to evaluate how the response to air pollution depends on the composition of the current air pollution mixture. The possible difference in response to air pollution characterised by high SO_2 and particulate levels, and to air pollution characterised by high levels of NO_2 and diesel soot is of specific interest. East European countries still experience air pollution with lower levels of traffic related pollutants but higher levels of coal-burning related pollutants such as SO_2 and particles, whereas West European countries experience more motor vehicle air pollution. A comparison of health effects between urban areas and suburban or rural areas is of interest to detect effects of primary urban emissions.

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. It is a collection of panel studies that were conducted in the winter of 1993/1994 in 14 different centres in Europe. All centres used the same protocol for data collection and data analysis. Design, methods and results of the individual panels have been reported in a special issue of the European Respiratory Review (8, 9, 10,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23).

In this paper the effect estimates for the separate panels are used to calculate combined effect estimates for various air pollutants on respiratory symptom prevalence using meta-analysis techniques. In addition to combining effect estimates of all locations, we also investigated differences between based on geographic location, urban/suburban location and composition of air pollution mixture.

The combination of panel specific effect estimates of air pollution on Peak Expiratory Flow (PEF) are presented in chapter 4. The evaluation of differences in response between subjects within a panel, such asthmatics vs. non asthmatics and atopics vs. non-atopics will be presented in chapter 6.

Methods and Material

PEACE study

The PEACE study was a collaboration of 14 European centres: Amsterdam (the Netherlands), Kuopio (Finland), Oslo (Norway), Berlin and Hettstedt (Germany), Pisa (Italy), Athens (Greece), Cracow and Katowice (Poland), Prague and Teplice (Czech Republic), Budapest (Hungary), Umeå and Malmö (Sweden). Each centre selected two panels, one panel in an urban area and one panel in a suburban or rural area (hereafter to be referred to as suburban panel). The suburban panel was selected from a community which had no major traffic emissions, had no large industrial sources, had sufficient size to select enough subjects and was close to a site of an existing air pollution measurement network. Suburban panels were included to evaluate differences in effects of air pollution caused by level and composition of air pollution, in panels paired by climate and meteorological characteristics.

Children between 6-12 years with chronic respiratory symptoms were selected by a parent completed screening questionnaire. The criteria for selection were: reporting of recent wheeze (apart from colds), recent attacks of shortness of breath with wheezing, recent dry cough (apart from colds) and/or doctor diagnosed asthma, ever in life. To further characterise the children, skin prick tests to common allergens were applied, 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 in chapter 2.

Peak Expiratory Flow (PEF) was measured each day in the morning and in the evening for at least two months. All centres used the mini Wright Peak Flow meter. A parent completed a daily diary for the child recording the presence and severity of respiratory symptoms and use of medication for respiratory symptoms. To avoid large changes in composition of the reporting group of children on separate days children were included in the analysis if they had valid PEF measurements and respiratory symptom data on more than 60% of the days.

Concurrent air pollution measurements were performed in both the urban and suburban locations. Daily 24 hour measurements of PM_{10}, BS, SO_2 and NO_2 were made at sites not influenced by nearby sources, so called background sites. More information about the measurement methods is given elsewhere (24, chapter 2 and 3).

All panels were analysed separately. The symptoms in the diaries were re-coded to 0 (no symptom) and 1 (slight, moderate or severe symptom) and daily prevalence was calculated. Daily prevalence was defined as the fraction of children for whom the presence of a respiratory symptom/medication use was reported from those children providing valid diary data for that symptom on that day. The association between symptom prevalence and air pollution was evaluated with logistic regression but under the assumption of normally distributed residuals. This was done because when analysing prevalence with binomial distributed residuals the residuals showed underdispersion. The observations were weighted by the number of reporting children on each day and correction for autocorrelation of residuals was made assuming a first order autoregressive structure. The respiratory symptoms cough, phlegm and the symptom combinations upper respiratory symptoms (runny/stuffed nose, sore throat), lower respiratory symptoms (shortness of breath, wheeze, asthma attacks) were analysed. Prevalence of bronchodilator use (such as salbutamol, albuterol, fenoterol, terbutaline) was also analysed.

The explanatory variables were 24 hour average concentrations of PM_{10}, BS, SO_2 and NO_2, analysed separately because of the high correlation ($r>0.6$) between these pollutants. 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. Minimum temperature, a dummy variable indicating normal school days versus holidays/weekends and time trend were included as possible confounders. Time trend was included as a linear, quadratic and cubic term to correct for long term time trends which can obscure the relationship between short-term changes in air pollution and acute respiratory symptoms. The regression slopes of the air pollution components from the logistic regression models for each panel were used to calculate a combined effect estimate.

Statistical methods and analysis

We have chosen for a combined analysis of panel specific effect estimates using meta analysis techniques and not for a pooled analysis because of the computational complexity of the latter. A pooled analysis, involving the creation of one large data-set of all individual data, would require interaction terms for each term included in the regression equation to allow for, for example, panel specific time trends. Combined effect estimates were calculated for the regression slopes of lag0, lag1 , lag2 and the 7 day mean and expressed as an Odds Ratio (OR) for a 100 $\mu g/m^3$ increase in the concentration of an air pollution component. A combined fixed effect estimate was calculated as the weighted mean of the panel-specific slopes with the weights being the inverse of the variance of the slope. The Standard Error (SE) of the combined slope was calculated as the inverse of the square root of the sum of the weights (25). This fixed effect mean assumes that the variability of panel specific slopes is caused by sampling errors only and that there is no variance present caused by other factors. Panel specific regression slopes and the combined regression slope were plotted with 95% Confidence Intervals (95% CI). Heterogeneity of panel specific slopes was evaluated by a visual inspection followed by a chi-square test for homogeneity (25). In this visual inspection heterogeneity was suspected in case the combined slope was not contained in the 95% CI of all panel specific slopes (26). In case of homogeneity the combined slope calculated as a fixed effect was considered an appropriate estimate. A conservative cut-point of a p-value smaller than 0.25 was chosen to determine heterogeneity. In case of heterogeneity ($p<0.25$) combined effect estimates using random effect estimation were calculated with the non-iterative method with unequal weights (25). Random effect estimation takes into account the within study variance and the between study variance. Next, combined effect estimates were calculated within pre-defined strata. Location (urban vs. suburban) was used to evaluate the potential different effect of urban air pollution sources over suburban areas. Geographical location was used to evaluate climatic influences or regional differences in air pollution. Four groups were defined: North (Umeå, Oslo, Malmö, Kuopio), West (Amsterdam, Berlin), East (Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest) and South (Pisa, Athens). Strata based on concentrations of air pollution components were defined to evaluate possible modification of effects by the composition of air pollution. BS served as indicator of fine black particles emitted by traffic or coal combustion, SO_2 as indicator of air pollution caused by fossil fuel combustion with high amounts of sulphur and NO_2 as indicator of traffic related air pollution. Strata based on the ratio between the mean concentrations of PM_{10} and BS served to indicate the proportion of carbonaceous particles.

To correct for other factors, a weighted multiple linear regression was performed with the panel specific regression slopes, with the inverse of the panel specific variance of the slope used as weights. The calculated SE of the regression slope was corrected according to Berlin and Longnecker (27). Independent variables were mean concentrations of PM_{10}, BS, SO_2 and NO_2, the ratio PM_{10}/BS and geographical position. To evaluate unmeasured differences between urban and suburban locations a dummy indicator for location was included in the regression models. Children may react differently to air pollution (28), thus the reaction of a panel to air pollution might be influenced by panel composition. This may affect the relationship between the regression slopes and indicators of air pollution composition. The percentage of atopic children, the percentage of children in a panel who were selected only on basis of a positive answer to cough and the mean prevalence of bronchodilator use of a panel served as indicators of panel composition and were therefore included in the regression models as possible effect modifiers. Children who were selected only on the basis of a positive answer to the nightly dry cough question had a lower prevalence of lower respiratory symptoms, upper respiratory symptoms and phlegm than children selected on asthma symptoms (29) and reacted differently in the Finnish panels (28). A formal analysis of subgroups within the PEACE panels is presented in chapter 6.

Results

From the 66,879 questionnaires handed out in all centres, 51,786 (77%) were received back. From these, 8,308 children (16%) fulfilled the selection criteria. The design called for 75 children in each panel, or a total of 2,100 children in 28 locations. From the 2,371 children who were enrolled, 2,010 were included in analysis. The children included in the analysis did not differ from the excluded children with respect to responses on screening questions, skin prick testing and lung function levels. In table 1 the most important characteristics of the panels and results of air pollution measurements are summarised. A wide range of air pollution concentrations was observed, with low concentrations of both gaseous and particle components in the Northern Europe, higher concentrations in Western Europe and the highest concentrations in Central and Southern Europe. The ratio between the mean concentration of PM_{10} and BS varied widely between sites, but did not show a geographical pattern. More details are presented in chapter 3. The mean daily prevalence of respiratory symptoms within the panels ranged from 15 to 35% (cough), 3-22% (phlegm), 18-44% (upper respiratory symptoms), 2-16% (lower respiratory symptoms) and from 1-22% for bronchodilator use.

Table 1. Characteristics of PEACE panels.

		PM_{10}*	BS*	SO_2*	NO_2*	subjects	atopic†	cough‡	bron§
Umeå	urban	13.4	4.6	2.7	25.0	75	54	15	10
(Sweden)	suburban	11.5	5.3	4.0	15.3	72	61	17	22
Malmö	urban	22.9	8.2	6.0	20.7	78	50	28	18
(Sweden)	suburban	16.2	4.5	4.0	8.9	82	55	34	8
Kuopio	urban	17.7	12.6	6.0	28.4	85	64	54	3
(Finland)	suburban	13.0	7.9	-	13.7	84	64	58	7
Oslo	urban	19.3	27.6	12.4	49.3	56	41	36	3
(Norway)	suburban	11.2	13.1	3.4	15.3	68	49	55	10
Amsterdam	urban	45.3	16.5	13.2	46.4	55	51	38	4
(The Netherlands)	suburban	44.4	13.6	8.5	26.5	71	41	44	3
Berlin	urban	52.3	24.5	42.3	38.3	50	60	4	17
(Germany)	suburban	43.0	22.0	26.1	21.2	66	59	3	8
Hettstedt	urban	40.3	42.0	83.3	26.5	75	33	21	2
(Germany)	suburban	32.9	25.5	64.9	26.1	63	19	10	5
Katowice	urban	68.7	55.5	55.7	68.7	72	49	35	1
(Poland)	suburban	73.8	57.9	56.0	69.5	73	30	15	3
Cracow	urban	60.1	34.9	41.3	-	73	7	51	1
(Poland)	suburban	56.1	42.7	14.0	-	76	53	31	1
Teplice	urban	74.3	58.9	74.8	48.8	91	16	56	3
(Czech Republic)	suburban	32.4	22.0	19.9	12.5	77	26	36	1
Prague	urban	52.7	29.4	113.9	44.7	66	48	2	5
(Czech Republic)	suburban	49.6	20.8	30.8	12.9	68	81	14	20
Budapest	urban	60.9	48.9	49.7	35.3	76	40	45	2
(Hungary)	suburban	52.1	30.6	41.0	25.4	63	58	33	5
Pisa	urban	61.6	19.7	15.7	68.1	68	81	0	4
(Italy)	suburban	69.5	29.3	8.2	32.7	60	59	19	6
Athens	urban	98.8	109.2	72.4	74.9	87	16	53	4
(Greece)	suburban	50.0	33.5	-	19.7	80	22	31	7

* mean concentration during study period in $\mu g/m^3$; † percentage of children in panel with one or more positive skin prick test reactions; ‡ percentage of children in panel selected only on basis of question on nightly coughing; § mean prevalence (%) of bronchodilator use in panel during study period.

The OR's calculated from the combined estimates are presented in table 2. In all 28 locations PM_{10} and BS measurements were performed. No SO_2 measurements were done in Kuopio suburban location and Athens suburban location, no NO_2 measurements were done in Cracow urban and suburban location. Further, the prevalence of bronchodilator use was very low and showed little variation in Katowice urban location and Cracow suburban location which resulted into non converging models. Most

Table 2. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for $100\ \mu g/m^3$ increase in air pollution on symptom prevalence and medication use.

	Cough		Phlegm		URS		LRS		Bronchodilator use	
	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)
PM_{10}										
lag0	28	0.96 (0.92, 0.99)§	28	0.99 (0.92, 1.05)¶	28	0.97 (0.94, 1.01)§	28	0.93 (0.85, 1.01)¶	25	0.99 (0.93, 1.05)§
lag1	28	0.97 (0.92, 1.02)¶	28	1.02 (0.94, 1.11)¶	28	0.96 (0.92, 0.99)§	28	1.00 (0.91, 1.10)¶	25	0.93 (0.86, 1.02)¶
lag2	28	0.99 (0.96, 1.03)§	28	0.98 (0.92, 1.05)¶	28	0.96 (0.93, 1.00)§	28	0.94 (0.86, 1.03)¶	25	0.99 (0.91, 1.07)¶
7 day mean	28	0.90 (0.73, 1.09)¶	28	0.89 (0.71, 1.10)¶	28	0.81 (0.69, 0.94)¶	28	0.88 (0.62, 1.23)¶	25	0.85 (0.66, 1.10)¶
Black Smoke										
lag0	28	0.96 (0.92, 1.01)§	28	1.02 (0.96, 1.08)§	28	0.98 (0.92, 1.04)¶	28	0.93 (0.83, 1.04)¶	25	0.99 (0.92, 1.06)§
lag1	28	1.02 (0.95, 1.09)¶	28	1.03 (0.93, 1.14)¶	28	0.94 (0.89, 1.00)¶	28	0.92 (0.81, 1.04)¶	25	0.94 (0.87, 1.02)§
lag2	28	0.99 (0.95, 1.04)§	28	0.97 (0.88, 1.08)¶	28	0.93 (0.87, 1.01)¶	28	0.93 (0.82, 1.04)¶	25	0.97 (0.90, 1.05)§
7 day mean	28	0.95 (0.75, 1.21)¶	28	0.90 (0.63, 1.28)¶	28	0.81 (0.70, 0.94)§	28	0.90 (0.55, 1.47)¶	25	0.88 (0.60, 1.29)¶
SO_2										
lag0	26	0.93 (0.89, 0.98)§	26	0.97 (0.92, 1.03)§	26	0.94 (0.89, 1.00)¶	26	0.96 (0.89, 1.04)§	23	0.99 (0.92, 1.06)§
lag1	26	0.98 (0.93, 1.04)¶	26	0.98 (0.91, 1.06)¶	26	0.96 (0.93, 1.00)§	26	0.99 (0.88, 1.13)¶	23	0.94 (0.88, 1.01)¶
lag2	26	0.94 (0.88, 1.00)¶	26	0.96 (0.87, 1.06)¶	26	0.95 (0.91, 0.98)§	26	0.90 (0.78, 1.03)¶	23	0.97 (0.87, 1.08)¶
7 day mean	26	0.84 (0.69, 1.03)¶	26	0.80 (0.60, 1.06)¶	26	0.83 (0.69, 1.00)¶	26	0.88 (0.58, 1.33)¶	23	0.88 (0.68, 1.13)¶
NO_2										
lag0	26	0.96 (0.90, 1.02)§	26	0.98 (0.91, 1.06)§	26	0.95 (0.89, 1.00)§	26	1.06 (0.89, 1.27)¶	24	0.96 (0.87, 1.06)§
lag1	26	1.00 (0.91, 1.08)¶	26	0.98 (0.86, 1.12)¶	26	0.98 (0.93, 1.04)§	26	0.91 (0.78, 1.05)¶	24	0.98 (0.85, 1.12)¶
lag2	26	0.94 (0.88, 1.00)§	26	0.97 (0.86, 1.08)¶	26	0.95 (0.89, 1.00)§	26	0.86 (0.72, 1.01)¶	24	0.99 (0.89, 1.10)§
7 day mean	26	0.98 (0.72, 1.34)¶	26	0.79 (0.55, 1.15)¶	26	0.82 (0.59, 1.14)¶	26	0.89 (0.48, 1.67)¶	24	0.82 (0.52, 1.30)¶

†Number of panel specific estimates; ‡ p value χ^2 test on homogeneity; § Fixed effects model; ¶ Random effects model; URS = upper respiratory symptoms; LRS = lower respiratory symptoms.

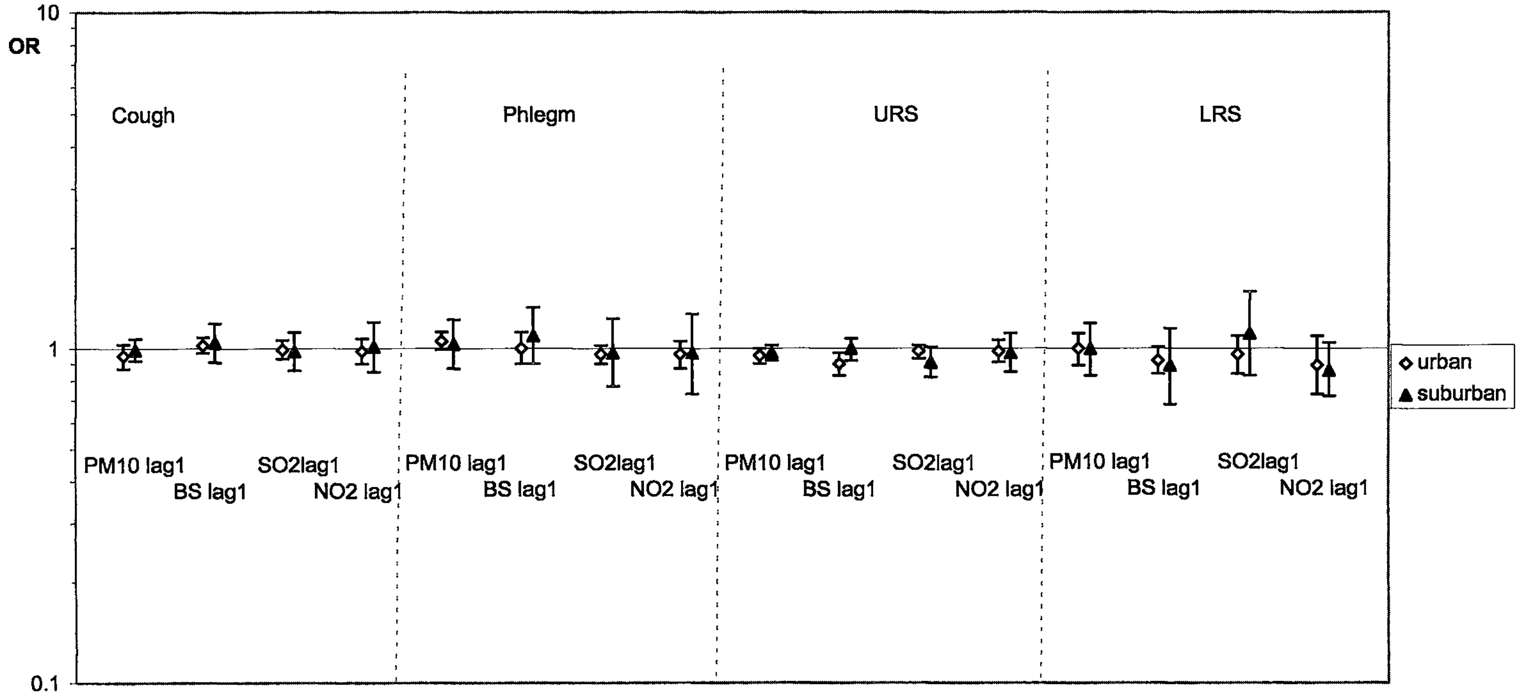


Figure 1a. Odds ratio's (OR) with 95% Confidence Intervals stratified on location (urban, suburban). OR's of a 100 μg/m^3 increase in lag1 of PM_{10}, BS, SO_2 and NO_2 on prevalence of cough, phlegm, upper respiratory symptoms (URS) and lower respiratory symptoms (LRS).

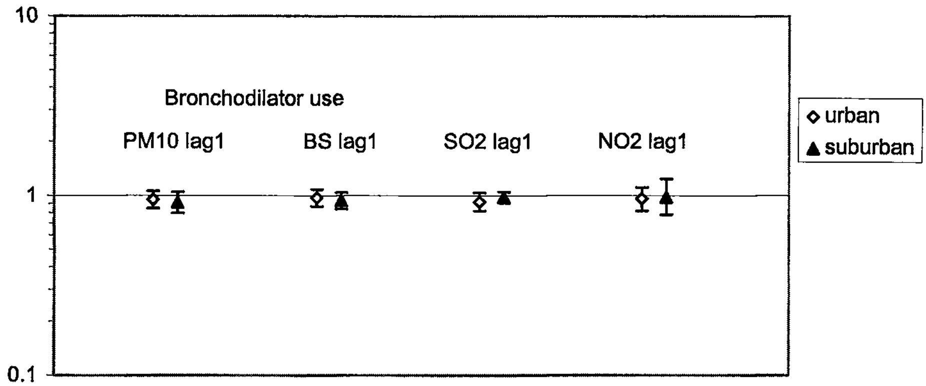
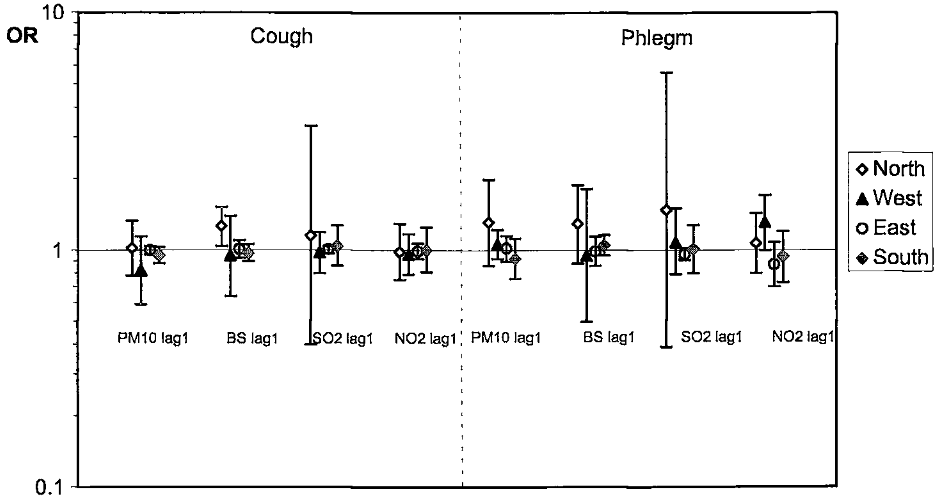


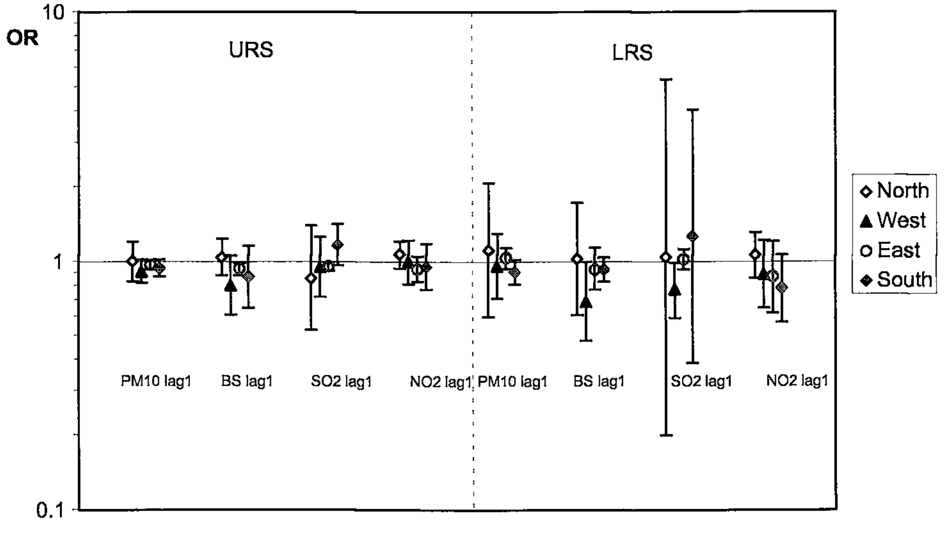
Figure 1b. Odds ratio's (OR) with 95% Confidence Intervals stratified on location (urban, suburban). OR's of a 100 µg/m³ increase in lag1 of PM_{10}, BS, SO_2 and NO_2 on prevalence of bronchodilator use.

combined OR's were below 1.00, with significant OR's for PM_{10} and SO_2 lag0 on cough prevalence and PM_{10} lag1 and 7 day mean, BS 7 day mean and SO_2 lag2 on upper respiratory symptoms prevalence. An OR below one means that an increase in air pollution was associated with a decrease in prevalence, which is opposite to the expected association. Heterogeneity was present for all effect estimates of all components on all symptoms and medication use, but most consistently for 7 day mean effect estimates. The stratification on urban and suburban location did not show clear differences between the strata. As an illustration stratum specific OR's of PM_{10} lag1 , BS lag1, SO_2 lag1 and NO_2 lag1 on the symptom and medication use prevalence are shown in figure 1a-b. OR's (borderline) significantly below 1.00 occurred in both urban and suburban location and test on heterogeneity still heterogeneity. Regression analysis also did not show a clear difference between urban and suburban locations. This was also the case for the other representations of the air pollutants.

As an example of the geographical stratification the stratum specific OR's of lag1 of PM_{10}, BS, SO_2 and NO_2 are shown in fig 2a-c. Generally, the East stratum had the smallest confidence intervals, probably caused by the large range in air pollution concentrations and the relatively large number of included locations. The North stratum had for PM_{10} and BS the highest OR's for the respiratory symptoms cough, phlegm, upper respiratory symptoms and lower respiratory symptoms. Most of these were insignificant except for BS lag1 on cough prevalence, namely 1.26 (95%CI 1.04-1.52). Further some significant OR's in the unexpected direction could be seen in the East and West stratum. On the other



a)



b)

Figure 2a-b. Odds ratio's (OR) with 95% Confidence Intervals stratified on geographical location: North (Umeå, Oslo, Malmö, Kuopio), West (Amsterdam, Berlin), East(Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest), South (Pisa, Athens). OR's of a 100 µg/m³ increase in lag1 of PM_{10}, BS, SO_2 and NO_2 on prevalence of a) cough and phlegm b) Upper respiratory symptoms (URS) and Lower Respiratory Symptoms (LRS).

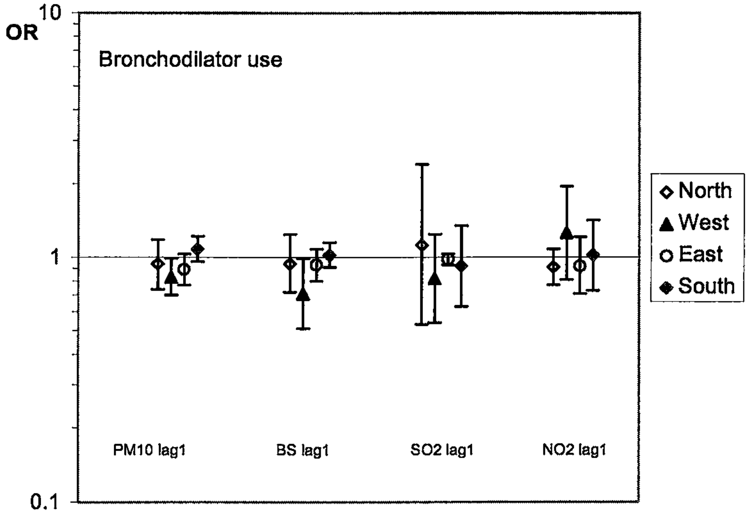
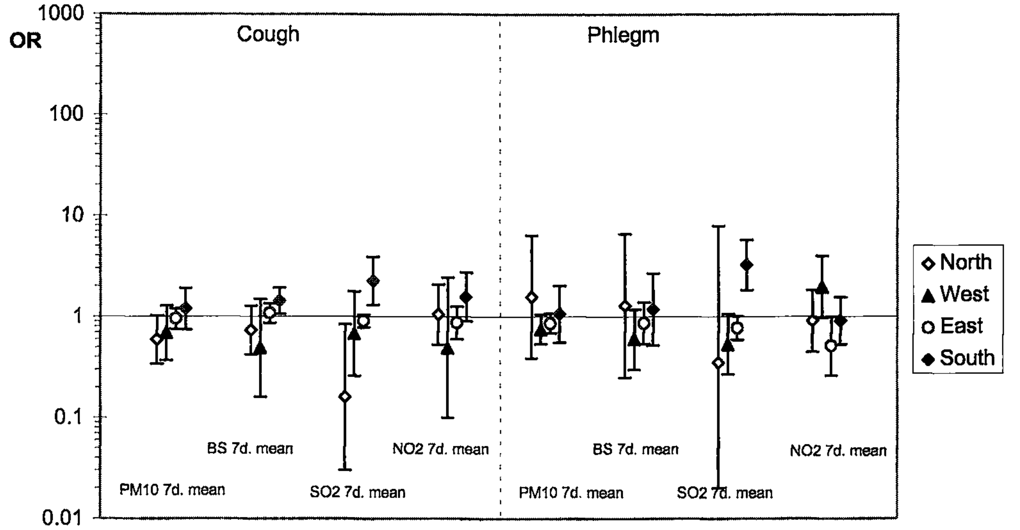


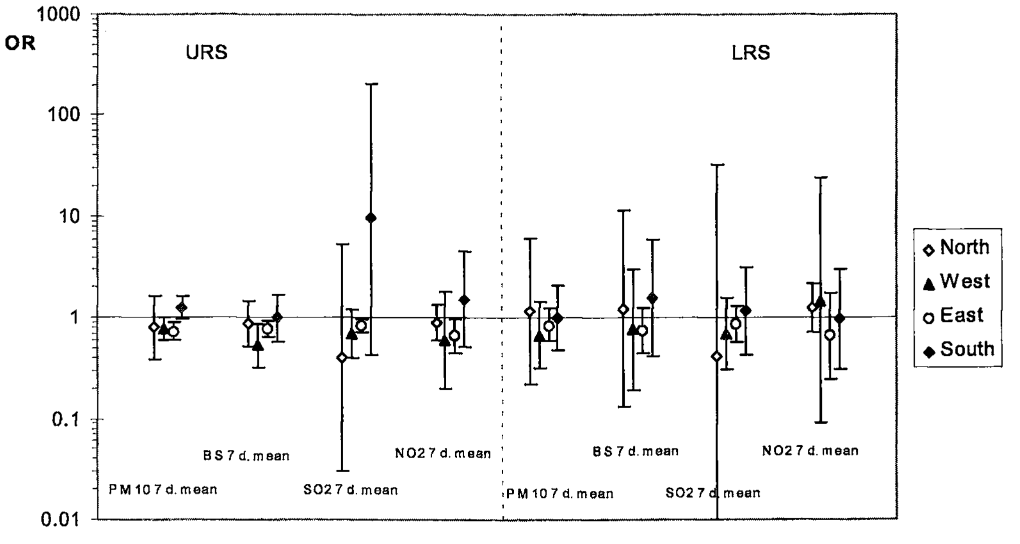
Figure 2c. *Odds ratio's (OR) with 95% Confidence Intervals stratified on geographical location: North (Umeå, Oslo, Malmö, Kuopio), West (Amsterdam, Berlin), East(Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest), South (Pisa, Athens). OR's of a 100 $\mu g/m^3$ increase in lag1 of PM_{10}, BS, SO_2 and NO_2 on prevalence of bronchodilator use.*

hand, the stratum specific OR's for the 7 day mean concentrations (fig 3a-c) were significant in the South stratum for cough with BS 7 day mean and SO_2 7 day mean and for phlegm with SO_2 7 day mean. Heterogeneity was still present within the strata. The regression analysis with the geographical location included as dummies resulted in mostly insignificant differences between the locations. In addition there was no consistent pattern.

Stratification on tertiles of the mean concentration of PM_{10}, BS, SO_2, NO_2 did not show consistent increasing or decreasing OR's with increasing mean concentration. Heterogeneity was still present in the subgroups. Stratification on PM_{10}/BS ratio showed for some representations and symptoms an increase in OR with a decrease in PM_{10}/BS ratio (table 3). More specifically, in the low stratum, the OR's for PM_{10} and BS on cough and phlegm prevalence were above 1.00 for lag1 and 7 day mean, with the OR for BS 7 day mean on cough prevalence becoming significant. In the other strata the OR's were mostly below 1.00. These trends were not significant in the regression analysis with the



a)



b)

Figure 3. Odds ratio's (OR) with 95% Confidence Intervals stratified on geographical location: North (Umeå, Oslo, Malmö, Kuopio), West (Amsterdam, Berlin), East (Hettstedt, Cracow, Katowice, Teplice, Prague, Budapest), South (Pisa, Athens). OR's of a 100 $\mu g/m^3$ increase in 7 day mean of PM_{10}, BS, SO_2 and NO_2 on prevalence of (a) cough, phlegm, (b) upper respiratory symptoms (URS) and lower respiratory symptoms (LRS).

Table 3. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for 100 $\mu g/m^3$ increase in PM_{10} and Black Smoke (BS) on symptom prevalence and medication use, stratified on ratio of mean concentration of PM_{10} and BS concentration (tertiles)[*].

	PM_{10}/BS ratio					
	Low		Medium		High	
	N[†]	OR (95% CI)	N[†]	OR (95% CI)	N[†]	OR (95% CI)
Cough						
PM_{10} lag1	9	1.02(0.97,1.08)[§]	10	0.95(0.88,1.03)[¶]	9	0.89 (0.76, 1.03)[¶]
PM_{10} 7 day mean	9	1.22(0.87,1.73)[¶]	10	0.79(0.59,1.05)[¶]	9	0.74 (0.53, 1.03)[¶]
BS lag1	9	1.06(0.98,1.13)[¶]	10	0.96(0.87,1.07)[¶]	9	0.99 (0.75, 1.32)[¶]
BS 7 day mean	9	1.29(1.02,1.64)[¶]	10	0.76(0.49,1.17)[¶]	9	0.74 (0.44, 1.21)[§]
Phlegm						
PM_{10} lag1	9	1.11(1.00,1.24)[¶]	10	0.98(0.79,1.21)[¶]	9	0.97 (0.88, 1.07)[§]
PM_{10} 7 day mean	9	1.24(0.89,1.72)[¶]	10	0.64(0.46,0.88)[¶]	9	0.88 (0.59, 1.32)[¶]
BS lag1	9	1.08(0.95,1.23)[¶]	10	0.98(0.80,1.21)[¶]	9	0.94 (0.68, 1.30)[¶]
BS 7 day mean	9	1.42(0.89,2.28)[¶]	10	0.52(0.28,0.94)[¶]	9	0.86 (0.41, 1.81)[¶]
Upper respiratory symptoms						
PM_{10} lag1	9	0.96(0.91,1.02)[§]	10	0.96(0.90,1.01)[§]	9	0.96 (0.89, 1.03)[§]
PM_{10} 7 day mean	9	0.90(0.65,1.23)[¶]	10	0.75(0.63,0.90)[§]	9	0.79 (0.59, 1.05)[¶]
BS lag1	9	0.93(0.88,0.98)[§]	10	0.93(0.83,1.03)[¶]	9	0.93 (0.70, 1.24)[¶]
BS 7 day mean	9	0.88(0.72,1.07)[§]	10	0.75(0.58,0.96)[§]	9	0.63 (0.39, 1.05)[§]
Lower respiratory symptoms						
PM_{10} lag1	9	0.99(0.89,1.09)[§]	10	0.92(0.81,1.04)[§]	9	1.12 (0.87, 1.44)[¶]
PM_{10} 7 day mean	9	1.34(0.84,2.14)[¶]	10	0.62(0.38,1.00)[¶]	9	0.88 (0.47, 1.68)[¶]
BS lag1	9	0.94(0.82,1.09)[¶]	10	0.87(0.69,1.10)[¶]	9	0.86 (0.53, 1.39)[¶]
BS 7 day mean	9	1.24(0.78,1.97)[¶]	10	0.51(0.26,0.99)[¶]	9	1.84 (0.38, 8.82)[¶]
Bronchodilator use						
PM_{10} lag1	8	1.01(0.91,1.12)[§]	9	0.85(0.68,1.05)[¶]	9	0.99 (0.91, 1.08)[§]
PM_{10} 7 day mean	8	0.81(0.49,1.36)[¶]	9	0.82(0.49,1.37)[¶]	9	1.14 (0.88, 1.47)[§]
BS lag1	8	0.97(0.87,1.07)[§]	9	0.89(0.73,1.10)[¶]	9	0.94 (0.76, 1.16)[§]
BS 7 day mean	8	0.76(0.45,1.30)[¶]	9	0.90(0.43,1.90)[¶]	9	1.54 (0.58, 4.06)[¶]

[*] Low: ratio PM_{10}/BS $<=1.3$, medium: $1.3<$ratio PM_{10}/BS $<=2.1$, high: ratio PM_{10}/BS >2.1;
[†] Number of panel specific estimates; [§] Fixed effects model; [¶] Random effects model;

PM_{10}/BS ratio as a continuous variable . For bronchodilator use prevalence this pattern was reverse, higher OR's in the high stratum, but the OR's remained insignificant. The other symptoms and the OR's for other air pollution representations did not show this pattern.

Discussion

The OR's calculated from the panel specific effect estimates did not indicate that the daily prevalence of respiratory symptoms or bronchodilator use in this study was positively associated with daily concentrations of PM_{10}, BS, SO_2 and NO_2. Earlier studies in children sampled from the general population did not show an effect of wintertime air pollution on respiratory symptoms (4, 30, 31). Other studies on winter air pollution showed a relation between air pollution and respiratory symptom prevalence (1, 2, 3) and medication use (1, 3). These studies were mostly conducted in children with chronic respiratory symptoms. The lack of effect in this study can not be explained by low levels of exposure. In all but the Northern European locations the air pollution concentrations were similar or even higher than the levels in the studies mentioned above which showed effects. The statistical power was also sufficient. In case of the daily prevalence of bronchodilator use or lower respiratory symptoms and a 10 $\mu g/m^3$ increase of PM_{10} lag1, an OR of 1.01 would have reached statistical significance at 5% probability level. This is a much smaller increase than the OR of 1.029 (bronchodilator use) and 1.03 (lower respiratory symptoms) per 10 $\mu g/m^3$ increase in PM_{10} concentration which were calculated from earlier studies (32). Misspecification of long term time trends in respiratory symptom prevalence can bias the relation between acute effects and short term changes in air pollution. In the original analysis third order polynomials were used to correct for long term time trends caused by unmeasured factors. This is a more detailed adjustment than previous studies (1, 2, 3, 5) in which linear trends or no trends were specified. Trends in the PEACE panels were highly non-linear, however. Residuals were checked and if a period longer than 14 days was found with positive or negative residuals this was corrected with dummy variables (chapter 2). This procedure did not materially affect effect estimates In addition, 9 symptom prevalences from panels which had a large contribution in the combined effect estimate and which had an OR opposite to expected were selected and reanalysed using a non-parametric function of time to allow a more flexible relationship (33). Specifically, loess was used with the span selected by Akaike's Information Criterion. In case negative autocorrelation was present in the residuals the span was increased. The effect estimates obtained with these models were similar to the effect estimates used here. Thus, it seems unlikely that long term trends were not correctly specified. Episodes of respiratory infections may have obscured the relationship between air pollution and symptom prevalence, depending on the association in time between respiratory infections and air pollution levels. The prevalence of fever was calculated from the children's diaries, but in none of the panels a sudden increase in fever prevalence was detected. Fever may not be sensitive enough to detect episodes of respiratory infections but unfortunately no other data were available.

Tests on heterogeneity indicated that differences existed between the panel specific estimates. These differences were larger than in the analysis of the PEF data. It is unlikely that this was caused by differences in study design, methods or data analysis because all centres used the same protocol for fieldwork and data analysis (chapter 2). A probable cause for the larger heterogeneity might be linguistic and cultural differences in respiratory symptom reporting and medication use, although we tried to eliminate this by back translations of the diary forms. Factors which serve as an indicator of the composition of air pollution such as urban/suburban location and mean concentrations of PM_{10}, BS, SO_2 and NO_2 were not able to explain the variation. The contrast between urban and suburban was not large with regard to levels of PM_{10} and BS, however (chapter 3). In another European multicenter study (APHEA) the distinction between Western and Eastern European cities explained heterogeneity in the effect estimates of BS and SO_2 on mortality (34). In the analysis of the symptom prevalences in the PEACE study geographical location showed inconsistent patterns and was not able to explain heterogeneity. Only when stratifying on the PM_{10}/BS ratio there appeared to be an effect in the Low stratum. This was not very strong as only one significant positive association was found, between BS 7 day mean and prevalence of cough. Furthermore, BS itself was not related to symptom prevalence in the unstratified analysis. Still, the pattern is in agreement with the analysis of the PEF data in the PEACE project, in which evening PEF was related to air pollution only in the locations with a low PM_{10}/BS ratio (chapter 4).

In conclusion, the PEACE project did not show clear effects of PM_{10}, BS, SO_2 or NO_2 on respiratory symptom prevalence or medication use. Stratification on location, geographical position, mean air pollution concentrations and PM_{10}/BS ratio did not show clear patterns.

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6

Inhomogeneity in response to air pollution in European children (PEACE project)*

Abstract

The PEACE study is a multi-centre panel study of the acute effects of particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}), Black Smoke (BS), sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) on respiratory health of children with chronic respiratory symptoms. In the complete panels no consistent association between air pollution and respiratory health was found. We evaluated whether potentially more sensitive subgroups in the panels did show air pollution effects.

To evaluate heterogeneity in response to air pollution, effect estimates of air pollution on Peak Expiratory Flow (PEF) and respiratory symptoms were calculated in subgroups based on presence of 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 there the associations tended to be negative in children selected only on cough and not using respiratory medication. Among asthmatics not using medication, no consistent association was seen. The association between daily symptom prevalence and air pollution levels was not different between these subgroups.

None of the predefined potentially more sensitive subgroups showed a consistent association between air pollution, PEF and respiratory symptoms

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Introduction

There are indications that some groups of children are more sensitive to air pollution than others and that medication use modifies the relation between respiratory health and air pollution. Pope (1) reported associations between respiratory health indicators (except medication use) and particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}) to be stronger in school children selected on respiratory symptoms by a screening questionnaire than in subjects selected on the basis of diagnosed asthma. It was hypothesised that this difference was caused by management of respiratory health by medication use as in the patient based sample the subjects usually used asthma medication whereas in the school based sample the subjects rarely did. In another panel study by Pope (2) a sample selected on basis of asthmatic symptoms but without medication use reacted stronger than an asymptomatic sample. Peters showed that medication use attenuated the associations between sulphate levels and respiratory health (3). Besides medication use other factors are related to the response of a child to air pollution. In a study by Roemer (4) children selected on asthmatic attacks in the previous year had a stronger association between increases in PM_{10} or sulphur dioxide (SO_2) and decreased PEF levels than children selected on chronic cough. Timonen reported differences in association between PEF, respiratory symptoms and PM_{10}, Black Smoke (BS), SO_2 and nitrogen dioxide (NO_2) in subgroups of children selected on cough or on asthmatic symptoms in the Finnish PEACE panel (5). Pershagen showed a relationship between wheezing bronchitis and chronic exposure to outdoor NO_2 levels in girls but not in boys (6). Brunekreef (7) reported that the association between lung function and chronic exposure to air pollution assessed as truck traffic density was stronger in girls than in boys. Atopy and lung function were related to PEF variability (8) and the prevalence of acute respiratory symptoms (9), so it might be that children with an atopic constitution or a lower lung function react differently to air pollution compared to non-atopic children or children with a better lung function. To our knowledge, in epidemiological panel studies objective data to characterize subjects (such as skin prick tests) have not been evaluated with respect to the response to air pollution.

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. It is a collection of panel studies that were conducted in the winter of 1993/1994 in 14 different centres in Europe. In this paper the PEACE data were stratified to investigate if subgroups within the panels, based on predefined characteristics reacted differently on short term changes in air pollution. In the complete panels no consistent association between air pollution and respiratory health was found (10). In this paper we evaluate whether potentially more sensitive subgroups (using predefined characteristics) in the panels did show air pollution effects. Specifically we hypothesized that children selected on asthma symptoms but not using medication; children with atopy; children with low baseline lung function and girls reacted stronger to air pollution than the complete panel.

Methods and Material

PEACE study

The PEACE study is a collaboration of 14 European centres: Amsterdam (the Netherlands), Kuopio (Finland), Oslo (Norway), Berlin and Hettstedt (Germany), Pisa (Italy), Athens (Greece), Cracow and Katowice (Poland), Prague and Teplice (Czech Republic), Budapest (Hungary), Umeå and Malmö (Sweden). All centres used the same protocol for data collection and data analysis. Design, methods and results of the individual panels (11) as well as combined effect estimates for the complete panels have been reported elsewhere (10). Each centre selected two panels, one panel in an urban area and one panel in a suburban or rural area (hereafter to be referred to as suburban panel). The suburban panel was selected from a community which had no major traffic emissions, had no large industrial sources, had sufficient size to select enough subjects and was close to a site of an existing air pollution measurement network. Suburban panels were included to evaluate differences in effects of air pollution caused by level and composition of air pollution, in panels paired by meteorological characteristics. The subject selection and characterisation was somewhat different in Hettstedt. Therefore, in this paper the data from Hettstedt are excluded.

Children between 6-12 years with chronic respiratory symptoms were selected by a parent completed screening questionnaire. The criteria for selection were: reporting of recent wheeze (apart from colds), recent attacks of shortness of breath with wheezing, recent dry cough (apart from colds) and/or doctor diagnosed asthma, ever in life. To further characterise the children, determination of atopy by skin prick test and pulmonary function using forced expiratory manoeuvres was used. Skin prick tests were carried out with the ALK system (ALK laboratories, Horsholm, Denmark). A common set of four single allergens was used for all areas which covered the most important allergens in the participating countries. These allergens were house dust mite (*D. pteronyssinus*), cat fur and pollen of timothy grass (*Phleum pratense*) and birch (*Betula verrucosa*). A positive control (histamine) and a negative control (diluent) were applied in each test. Two locally important allergens were added by each individual centre (11). A child was considered atopic if there was a wheal reaction of more than 2 mm on one of the tested allergens together with a negative control equal or less then 1 mm and a positive control of more than 0 mm. Forced expiratory manoeuvres were performed following the protocol of the European Community for Coal and Steel (ECCS) (12, 13). The equipment used in the centres was not identical but had to fulfil the technical requirements of the ECCS. Selection of values was done according to the ECCS(12, 13). The measured values were expressed as a percentage of the predicted values calculated from the reference equations of Zapletal (14).

Peak Expiratory Flow (PEF) was measured each day in the morning and in the evening for at least two months. All centres used the mini Wright Peak Flow meter. A parent completed a daily diary for the child recording the presence and severity of respiratory symptoms and use of medication for respiratory symptoms.

Concurrent air pollution measurements were performed in both the urban and suburban locations. Daily 24 hour measurements of PM_{10}, BS, SO_2 and NO_2 were made at sites not influenced by nearby sources, so called background sites. More information about the measurement methods is given elsewhere (11, 15).

Statistical methods

Our analytical approach consisted of the calculation of the association between air pollution and respiratory health in the above defined subgroups within the individual panels. Next, the regression slopes calculated for the individual panels were combined to obtain an average slope in the subgroups, such as atopics and non-atopics. To avoid large changes in day-to-day composition of the reporting group, children were included in the analysis if they had valid PEF measurements and respiratory symptoms on more than 60% of the days. In addition, only children with non missing information on sex, skin prick testing, lung function testing and with a positive response to one of the screening questions were included to avoid differences in the total number of children in the different subgroup analyses. Subgroups were defined on the basis of medication use, selection question, sex, atopy and lung function. Atopy subgroups were based on the skin prick test results. Lung function subgroups were made by dividing the values expressed as percent of predicted maximal mid expiratory flow (MMEF) or forced expiratory volume in 1 second (FEV_1) into quartiles. To avoid that subjects with different lung function levels were categorised in the same group, quartiles were calculated over the whole group, independently of centre. To increase the contrast, the children with the worst lung function were compared to the children with a 'normal' lung function. More specifically, a comparison was made between the subjects in the lowest quartile vs. the subjects above the median. Three subgroups based on medication use and selection questionnaire were made: selected on asthmatic symptoms (wheeze or asthma diagnosis) and using respiratory medication (AST^+), selected on asthmatic symptoms and not using respiratory medication (AST^-) and as third group selected only on the question on nightly coughing and not using medication ($COUGH^-$). 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. There were a only few subjects selected only on the question on nightly coughing and using medication (n=23), so these were left out in this subgroup analysis.

The association between PEF levels and air pollution levels was calculated by means of linear regression for each child separately. This analysis included correction for first order autocorrelation in the residuals. The distribution of these individual coefficients in the above defined subgroups was next studied. To correct for subject characteristics, weighted multiple linear regression was performed with the individual coefficients as dependent variable and subgroup indicators as independent variables, with the weights being the inverse of the variance of the individual coefficients. Cook's distance was calculated to evaluate the influence of each observation (16). Observations with extreme value's (>1.0) for Cook's distance were deleted to test the stability of the calculated slopes. The symptoms in the diaries were re-coded to 0 (no symptom) and 1 (slight, moderate or severe symptom) and daily prevalence was calculated within subgroups. All panels were analysed separately. Daily prevalence within a subgroup was defined as the fraction of children for whom the presence of a respiratory symptom/medication use was reported from those children providing valid diary data for that symptom on that day within that subgroup. The association between subgroup specific symptom prevalence and air pollution was evaluated with logistic regression but under the assumption of normally distributed residuals. This was done because when analysing prevalence with binomial distributed residuals the residuals showed substantial underdispersion. The observations were weighted by the number of reporting children within a subgroup on each day. Correction for autocorrelation of residuals was made assuming a first order autoregressive structure. The respiratory symptoms cough, phlegm and the symptom combinations upper respiratory symptoms (runny/stuffed nose, sore throat), lower respiratory symptoms (shortness of breath, wheeze, asthma attacks) were analysed. Bronchodilator use prevalence was analysed as well.

The regression slopes of the air pollution components from the logistic regression models of the separate panels were used to calculate a combined effect estimate for each subgroup. To avoid that calculations were based on few subjects or few symptom reports which may lead to extreme effect estimates, data from a subgroup of a specific panel were only included if they consisted of more than 5 subjects and had a mean prevalence of more than 3%. A combined fixed effect estimate was calculated as the weighted mean of the subgroup-specific slopes with the weights being the inverse of the variance of the slope. The Standard Error (SE) of the combined slope was calculated as the inverse of the square root of the sum of the weights. Heterogeneity of subgroup-specific slopes was

Table 1. Characteristics of included subjects by panel

		subjects* n	atopic† n (%)	MMEF‡ quartile n(%)	COUGH-§ n (%)	AST+§ n (%)	AST-§ n (%)
Umeå	urban	72	40 (56)	27 (38)	11 (15)	25 (35)	36 (50)
(Sweden)	suburban	69	43 (62)	21 (30)	10 (15)	36 (52)	23 (33)
Malmö	urban	64	31 (48)	22 (34)	15 (23)	22 (34)	25 (39)
(Sweden)	suburban	69	38 (55)	21 (30)	21 (30)	19 (28)	28 (41)
Kuopio	urban	85	53 (62)	24 (28)	45 (53)	11 (13)	28 (33)
(Finland)	suburban	82	49 (60)	14 (17)	44 (54)	14 (17)	21 (26)
Oslo	urban	40	19 (48)	11 (28)	6 (15)	8 (20)	26 (65)
(Norway)	suburban	49	27 (55)	13 (27)	7 (14)	18 (37)	24 (49)
Amsterdam	urban	52	27 (52)	14 (27)	18 (35)	11 (21)	23 (44)
(The Netherlands)	suburban	61	23 (38)	18(30)	27 (44)	13 (21)	21 (34)
Berlin	urban	46	28 (61)	23 (50)	2 (4)	14 (30)	30 (65)
(Germany)	suburban	57	34 (60)	23 (40)	2 (4)	11 (19)	44 (77)
Katowice	urban	68	33 (49)	22 (32)	24 (35)	3 (4)	40 (59)
(Poland)	suburban	71	21 (30)	26 (37)	10 (14)	6 (9)	54 (76)
Cracow	urban	42	3 (7)	9 (21)	21 (50)	2 (5)	19 (45)
(Poland)	suburban	60	32 (53)	4 (7)	20 (33)	10 (17)	29 (48)
Teplice	urban	75	12 (16)	9 (12)	44 (59)	3 (4)	27 (36)
(Czech Republic)	suburban	75	20 (27)	5 (7)	25 (33)	15 (20)	34 (45)
Prague	urban	66	32 (49)	25 (38)	1 (2)	19 (29)	46 (70)
(Czech Republic)	suburban	68	55 (81)	24 (35)	4 (6)	29 (43)	30 (44)
Budapest	urban	67	27 (40)	9 (13)	29 (43)	10 (15)	28 (42)
(Hungary)	suburban	58	34 (59)	8 (14)	18 (31)	5 (9)	34 (59)
Pisa	urban	44	35 (80)	11 (25)	0 (0)	16 (36)	28 (64)
(Italy)	suburban	48	27 (56)	5 (10)	8 (17)	14 (29)	25 (52)
Athens	urban	68	12 (18)	7 (10)	31 (46)	8 (12)	26 (38)
(Greece)	suburban	65	15 (23)	8 (12)	14 (22)	17 (26)	29 (45)
Total		1621	770 (48)	405 (25)	457 (28)	359 (22)	778 (48)

* number of subjects; † children in panel with one or more positive skin prick test reactions; ‡ children in panel in lowest MMEF quartile; § children in panel selected on nightly coughing only, no medication use during study period (COUGH-); selected on asthma question, no medication use during study period (AST-); selected on asthma question, medication use during study period (AST+)

evaluated by a chi-square test for homogeneity (17). In case of homogeneity the combined slope calculated as a fixed effect was considered an appropriate estimate. A conservative cut-point of a p-value smaller than 0.25 was chosen to determine heterogeneity. In case of heterogeneity ($p<0.25$) combined effect estimates using random effect estimation were calculated (17). The combined effect estimate was expressed as an Odds Ratio (OR) for a 100 $\mu g/m^3$ increase in air pollution.

The explanatory variables for PEF as well as symptom prevalence were 24 hour average concentrations of PM_{10}, BS, SO_2 and NO_2, analysed separately because of the high correlation ($r>0.6$) between pollutants. 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. Minimum temperature, a dummy variable indicating normal school days versus holidays/weekends and time trend were included as possible confounders in PEF as well as prevalence analysis. Time trend was included in the prevalence analysis as a linear, quadratic and cubic term to correct for long term time trends. In the PEF analysis time trend was included as a square root and a linear term to correct for a possible training effect and lung growth, respectively.

Results

The characteristics of the included subjects by panel are presented in table 1. The percentage atopics within the panels ranges from 7% in the urban location of Cracow up to 81% in the suburban location of Prague. Also the prevalence of positive responses on the selection questions show a wide range. These differences probably reflect the slight modifications in selection procedure which some centres made during the fieldwork. The subgroup consisted of children who were selected on asthmatic symptoms but who did not use any medication during the diary period.

A wide range of air pollution concentrations was included, ranging from low concentrations of both gaseous and particle components in Scandinavia, higher concentrations in Western Europe and the highest concentrations in Central and Southern Europe. Mean concentrations during the study period ranged for PM_{10} from 11.2 $\mu g/m^3$ (Oslo, suburban) to 98.8 $\mu g/m^3$ (Athens, urban), for BS from 4.5 $\mu g/m^3$ (Malmö, suburban) to 109.2 $\mu g/m^3$ (Athens , urban), for SO_2 from 2.7 $\mu g/m^3$ (Umeå, urban) to 113.9 $\mu g/m^3$(Prague, urban) and for NO_2 from 8.9 $\mu g/m^3$ (Malmö, suburban) to 74.9 $\mu g/m^3$ (Athens, urban). More information about the air pollution concentrations is presented in chapter 3.

Association between air pollution and PEF

Table 2 shows the median of regression coefficients of air pollution representations on evening PEF in the subgroups. There was no consistent pattern of differences in reaction to air pollution between the subgroups based on sex, atopy or lung function. Regression analysis including all subgroup indicators simultaneously, confirmed this pattern.

Table 2 also shows that the median coefficients in the AST^+ group were positive for all components with significant median coefficients for BS 7 day mean, SO_2 lag0, lag1, 7day mean and NO_2 lag1. On the other hand, most of the median coefficients in the $COUGH^-$ group were negative, with PM_{10} lag1 reaching significance. The median coefficients of AST^- were generally positive but none of the coefficients differed significantly from zero. Restriction of the data to the centres with the highest mean prevalence of bronchodilator use in AST^+ (Berlin (Germany), Prague (Czech Republic), Malmö and Umeå (Sweden), Pisa (Italy), Athens (Greece), Amsterdam (the Netherlands)) showed that the median coefficients of AST^+ became more positive and increased in significance. Median coefficients of AST^+ in the other centres did not differ consistently from zero anymore. Table 4 shows the results of the stratification on selection questions and medication use. For phlegm prevalence, the OR's in the $COUGH^-$ group are mostly above 1.00 for PM_{10}, BS and NO_2, but almost all non-significant. The OR's in the other two groups are predominantly below 1.00. For lower respiratory symptom prevalence the OR's are generally below 1.00. Stratification of effect estimates on cough and upper respiratory symptoms neither showed consistent differences (not presented).

The prevalence of bronchodilator use was not related to any air pollution component in AST^+. For example, the OR's of PM_{10} were for lag0 0.98 (95% CI 0.89-1.07), lag1 0.97 (0.85-1.09), lag2 0.98 (0.87-1.10) and 7 day mean 1.21 (0.71-2.07). Restriction of the data to the centres with the highest mean prevalence of bronchodilator use also did not show significant associations.

Table 2. Median individual coefficients in subgroups of total PEACE study population. Coefficients expressed as L/min change in evening PEF per 100 μg/m³ increase in air pollutant.

	Sex		Atopy		selection-medication*			lung function MMEF		lung function FEV_1	
	boy	girl	-	+	COUGH$^-$	AST$^-$	AST$^+$	lowest quartile	above median	lowest quartile	above median
PM_{10}											
lag0	1.1	-0.5	-0.1	0.8†	-0.9	0.7	1.6	-0.1	-0.1	0.6	0.3
lag1	-0.5	-0.9	-0.8	-0.4	-1.3‡	-0.3	0.0	-1.4†	-0.5	-0.7	-0.9‡
lag2	-0.5	1.2‡§	0.4†	0.2	0.0	0.2	2.1	-0.4	0.4	0.6	-0.1
7 day mean	0.1	1.0	0.5	0.6	-0.9	1.7	1.2	0.1	-0.4	2.6†	-0.9§
BS											
lag0	0.7†	0.2	-0.2	1.5†	-0.3	0.2	2.6†§	0.3	0.6	0.0	1.2†
lag1	0.9	-0.3	0.2	0.6	-1.3	0.4	2.4	-0.9	1.8	0.3	0.3
lag2	0.2	0.1	-0.2	0.6	-0.9	0.2	2.3†	-2.0	0.1	-0.2	0.1
7 day mean	2.5	2.0	1.8	2.7	-1.2	2.5	10.3‡§	2.7	1.5	4.3	2.5
SO_2											
lag0	1.9‡	1.4	0.7	2.2†	1.1	1.1	5.3‡	0.4	2.1‡	-0.2	2.1‡§
lag1	0.8	0.2	0.3	1.1	-1.1	0.3	4.5‡§	0.8	0.2	1.9	0.1
lag2	0.3	1.5	0.3	1.3	-0.6	1.0	1.3	0.4	1.6†	0.7	1.6
7 day mean	2.7	0.7	1.4	3.2	-1.3	2.0	12.1‡	3.2†	1.4	4.4†	3.0†
NO_2											
lag0	0.9	0.7	0.3	1.0	0.0	0.9	1.9	0.1	0.8	2.7†	0.6
lag1	-0.3	-0.5	-1.1	0.5	-2.0	-0.7	3.3‡§	-1.8	-1.1	-0.3	-0.1
lag2	-0.8	1.2	1.2	-0.8	-1.6†	0.9	0.9	1.0	-0.8†	1.7	-0.7†§
7 day mean	0.3	1.5	1.0	0.2	-1.7	0.5	5.9	2.6†	-1.4†§	1.9	-0.3§

* COUGH$^-$: selected on nightly coughing only, no medication use during study period; AST$^-$: selected on asthma question, no medication use during study period; AST$^+$: selected on asthma question, medication use during study period.
† $p<0.10$, ‡ $p<0.05$ sign rank test; § $p<0.05$ Wilcoxon rank-sum or Kruskal-Wallis test to test in difference in distribution

Table 3. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for 100 $\mu g/m^3$ increase in air pollution on symptom prevalence, in atopic and non-atopic subjects.

	upper respiratory symptoms				lower respiratory symptoms				Bronchodilator use			
		non-atopic		atopic		non-atopic		atopic		non-atopic		atopic
	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)
PM_{10}												
lag0	25	0.94 (0.86, 1.02)¶	25	0.98 (0.92,1.04)§	19	0.91 (0.78, 1.06)¶	23	1.05(0.87, 1.26)¶	9	0.95 (0.75, 1.22)¶	22	0.96 (0.89, 1.04)§
lag1	25	0.92 (0.87, 0.97)§	25	0.99 (0.93,1.05)§	19	0.96 (0.83, 1.12)¶	23	0.99(0.84, 1.17)¶	9	1.09 (0.81, 1.47)¶	22	0.92 (0.81, 1.05)¶
lag2	25	0.95 (0.88, 1.01)¶	25	0.95 (0.90,1.01)§	19	0.90 (0.80, 1.01)§	23	0.97(0.85, 1.11)¶	9	1.19 (0.89, 1.59)¶	22	1.00 (0.84, 1.20)¶
7 day mean	25	0.63 (0.45, 0.86)¶	25	0.88 (0.68,1.15)¶	19	0.68 (0.33, 1.41)¶	23	0.89(0.50, 1.59)¶	9	0.83 (0.48, 1.43)§	22	1.02 (0.59, 1.76)¶
Black Smoke												
lag0	25	1.02 (0.96, 1.08)§	25	1.00 (0.90,1.12)¶	19	0.86 (0.76, 0.97)§	23	1.09(0.88, 1.36)¶	9	1.03 (0.86, 1.22)§	22	0.99 (0.86, 1.14)§
lag1	25	0.93 (0.85, 1.02)¶	25	0.92 (0.82,1.02)¶	19	0.90 (0.79, 1.01)§	23	0.87(0.69, 1.10)¶	9	1.00 (0.64, 1.58)¶	22	0.88 (0.74, 1.06)¶
lag2	25	0.92 (0.84, 1.01)¶	25	0.91 (0.81,1.01)¶	19	0.93 (0.76, 1.13)¶	23	0.93(0.75, 1.16)¶	9	1.03 (0.87, 1.22)§	22	1.03 (0.86, 1.22)¶
7 day mean	25	0.57 (0.39, 0.82)¶	25	0.89 (0.59,1.32)¶	19	0.52 (0.20, 1.34)¶	23	0.90 (0.36, 2.23)¶	9	0.94 (0.35, 2.52)¶	22	0.99 (0.44, 2.20)¶
SO_2												
lag0	23	0.86 (0.76, 0.98)¶	23	0.89 (0.76,1.04)¶	17	0.91 (0.65, 1.28)¶	21	0.98 (0.74, 1.29)¶	7	0.95 (0.83, 1.09)§	20	0.94 (0.83, 1.07)§
lag1	23	0.94 (0.88, 1.01)§	23	0.97 (0.89,1.06)§	17	1.08 (0.77, 1.51)¶	21	0.98 (0.72, 1.32)¶	7	1.00 (0.88, 1.15)§	20	0.87 (0.69, 1.08)¶
lag2	23	0.96 (0.89, 1.02)§	23	0.81 (0.70,0.94)¶	17	1.06 (0.80, 1.41)¶	21	0.83 (0.62, 1.10)¶	7	1.04 (0.91, 1.18)§	20	1.06 (0.79, 1.42)¶
7 day mean	23	0.52 (0.35, 0.78)¶	23	0.72 (0.45,1.18)¶	17	0.69 (0.34, 1.40)¶	21	1.09 (0.50, 2.38)¶	7	0.45 (0.09, 2.11)¶	20	0.71 (0.36, 1.40)¶
NO_2												
lag0	24	0.96 (0.88, 1.05)§	24	0.85 (0.77,0.94)§	18	1.14 (0.96, 1.35)§	22	1.13 (0.87, 1.47)¶	9	0.94 (0.71, 1.23)§	22	0.95 (0.82, 1.09)§
lag1	24	0.86 (0.75, 0.99)¶	24	1.06 (0.93,1.22)¶	18	0.77 (0.60, 1.00)¶	22	0.98 (0.76, 1.27)¶	9	1.41 (0.90, 2.21)¶	22	0.98 (0.85, 1.14)§
lag2	24	0.98 (0.90, 1.07)§	24	0.90 (0.79,1.03)¶	18	0.79 (0.60, 1.02)¶	22	0.89 (0.66, 1.21)¶	9	0.98 (0.58, 1.63)¶	22	1.11 (0.88, 1.42)¶
7 day mean	24	0.49 (0.28, 0.85)¶	24	1.00 (0.60,1.69)¶	18	0.51 (0.18, 1.48)¶	22	0.82 (0.28, 2.39)¶	9	0.76 (0.34, 1.69)§	22	1.18 (0.52, 2.68)¶

† Number of panel specific estimates; § Fixed effects model; ¶ Random effects model

Table 4. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for 100 $\mu g/m^3$ increase in air pollution on cough and phlegm prevalence, in subjects selected only on cough and subjects selected on asthmatic symptoms.

	Phlegm						Lower respiratory symptoms					
	COUGH$^-$		AST$^+$		AST$^-$		COUGH$^-$		AST$^+$		AST$^-$	
	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)
PM_{10}												
lag0	22	1.02 (0.87,1.21) ¶	23	0.98 (0.83,1.17) ¶	25	0.95 (0.85,1.06) ¶	7	0.96 (0.54,1.70) ¶	24	0.87 (0.75,1.00) §	22	1.00 (0.84,1.18) ¶
lag1	23	1.09 (0.92,1.29) ¶	24	1.04 (0.92,1.18) §	25	1.03 (0.94,1.13) ¶	7	0.86 (0.59,1.26) §	24	0.98 (0.82,1.18) ¶	22	1.06 (0.90,1.24) ¶
lag2	23	0.97 (0.79,1.19) ¶	23	0.99 (0.84,1.16) ¶	25	0.97 (0.87,1.08) ¶	7	0.80 (0.54,1.18) §	24	0.91 (0.76,1.09) ¶	22	1.02 (0.83,1.24) ¶
7 day mean	23	1.38 (0.68,2.81) ¶	23	1.14 (0.66,1.99) ¶	25	0.73 (0.46,1.15) ¶	7	0.96 (0.13,6.89) ¶	24	0.94 (0.52,1.70) ¶	22	0.80 (0.51,1.24) ¶
Black Smoke												
lag0	23	1.09 (0.93,1.29) ¶	23	0.92 (0.71,1.18) ¶	25	0.99 (0.90,1.10) §	7	0.79 (0.43,1.44) ¶	24	0.96 (0.79,1.16) §	22	0.97 (0.77,1.23) ¶
lag1	23	1.07 (0.85,1.34) ¶	24	0.99 (0.78,1.24) ¶	25	1.12 (0.98,1.27) ¶	7	0.80 (0.52,1.24) §	24	0.81 (0.63,1.04) ¶	22	0.94 (0.74,1.21) ¶
lag2	23	1.02 (0.83,1.25) ¶	23	0.94 (0.79,1.12) §	25	1.01 (0.91,1.11) §	7	0.91 (0.59,1.41) §	24	0.97 (0.73,1.28) ¶	22	1.00 (0.82,1.22) ¶
7 day mean	22	2.02 (0.84,4.86) ¶	24	0.76 (0.31,1.84) ¶	25	0.52 (0.27,1.00) ¶	7	0.95 (0.09,9.53) ¶	24	0.94 (0.39,2.25) ¶	22	0.61 (0.34,1.11) ¶
SO_2												
lag0	21	1.05 (0.69,1.61) ¶	21	0.92 (0.68,1.23) ¶	23	0.87 (0.79,0.96) §	7	0.46 (0.23,0.93) §	22	0.94 (0.80,1.10) §	20	1.12 (0.97,1.30) §
lag1	21	0.92 (0.74,1.14) ¶	21	0.73 (0.44,1.22) ¶	23	0.99 (0.85,1.15) ¶	7	0.65 (0.19,2.22) ¶	22	1.04 (0.75,1.44) ¶	20	0.99 (0.87,1.14) §
lag2	21	0.88 (0.70,1.11) ¶	21	0.97 (0.81,1.17) §	23	0.94 (0.79,1.11) ¶	7	0.96 (0.52,1.77) §	22	0.80 (0.58,1.10) ¶	20	1.04 (0.92,1.19) §
7 day mean	21	0.89 (0.45,1.74) ¶	22	0.58 (0.28,1.21) ¶	23	0.60 (0.34,1.06) ¶	7	0.31 (0.09,1.07) §	22	1.42 (0.57,3.57) ¶	20	0.84 (0.46,1.55) ¶
NO_2												
lag0	21	1.11 (0.77,1.60) ¶	23	1.07 (0.76,1.49) ¶	23	0.97 (0.87,1.08) §	6	0.98 (0.46,2.07) ¶	23	1.03 (0.78,1.36) ¶	20	1.35 (1.15,1.58) §
lag1	21	1.00 (0.74,1.37) ¶	23	0.92 (0.63,1.35) ¶	23	0.96 (0.82,1.12) ¶	6	1.09 (0.60,2.00) ¶	23	1.01 (0.80,1.28) §	20	0.83 (0.58,1.17) ¶
lag2	20	0.85 (0.64,1.14) ¶	23	0.99 (0.77,1.26) §	23	1.08 (0.92,1.26) ¶	6	0.81 (0.51,1.28) §	23	0.78 (0.57,1.06) ¶	20	0.87 (0.63,1.20) ¶
7 day mean	21	4.37 (1.08,17.66) ¶	23	0.80 (0.29,2.22) ¶	23	0.56 (0.26,1.20) ¶	6	1.33 (0.29,6.09) §	23	1.47 (0.42,5.14) ¶	20	0.28 (0.08,1.01) ¶

† Number of panel specific estimates; § Fixed effects model; ¶ Random effects model.

Figure 1 shows the OR's of lag1 of air pollution components on symptom prevalence after stratification on percentage of predicted MMEF. The OR's of the children with a percentage of predicted MMEF above the median value are all below 1.00, with PM_{10}, BS and SO_2 lag1 being significant for upper respiratory symptom prevalence and PM_{10}, BS and NO_2 lag1 for lower respiratory symptom prevalence. The children in the first quartile (low lung function) had OR's which were predominantly above 1.00, BS lag1 on cough significantly. The OR's of lag0 of PM_{10}, BS, SO_2 and NO_2 on symptom prevalence showed the same pattern, whereas lag2 and 7 day did not (not presented).

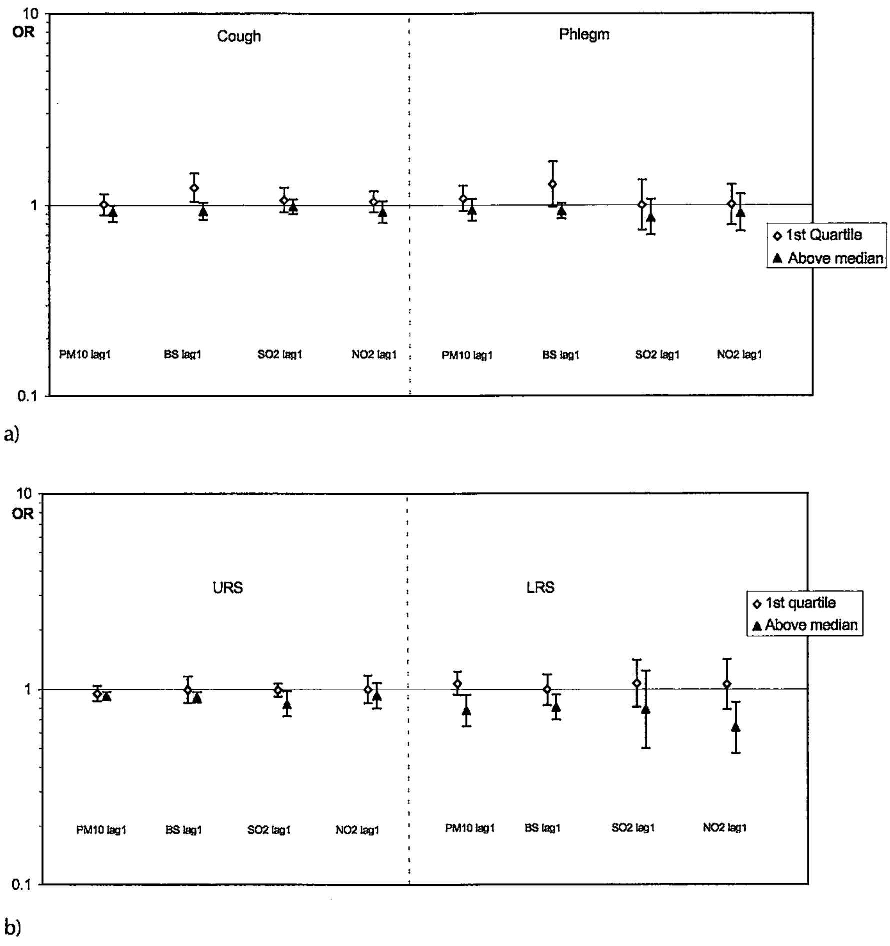

Figure 1. Odds ratio's (OR) with 95% Confidence Intervals stratified on percent predicted MMEF. OR's of a 100 µg/m³ increase in lag1 of PM_{10}, BS, SO_2 and NO_2 on prevalence of (a) cough, phlegm, (b) URS (=upper respiratory symptoms), LRS (=lower respiratory symptoms).

Finally, stratification on sex of the outcomes of symptom prevalence analysis did not reveal clear differences in response to air pollution between boys and girls.

Discussion

Associations between air pollution and evening PEF tended to be negative in children selected on cough only. In asthmatic children using respiratory medication, significant positive associations between air pollution and PEF were found. Asthmatic children not using medication did not show any association with air pollution. This pattern was not confirmed by the respiratory symptom results. In none of the subgroups a consistent association with respiratory symptoms was found. In atopic children and children with a low lung function no air pollution effects on PEF and respiratory symptoms were found.

The results of the stratification based on selection question and medication use of effect estimates of air pollution on evening PEF presented in this paper showed that the AST^+ group had positive coefficients. An explanation might be that the children counteract the effects of air pollution on evening PEF by medication use during the day. This is supported by the fact that in the groups not using respiratory medication the coefficients were less positive (AST^-) or even negative ($COUGH^-$) and that the median coefficients are most positive in the centres with the highest mean daily prevalence of bronchodilator use. The fact that the prevalence of bronchodilator use in the AST^+ group was not related to air pollution weakens this argument. However, it might be that children increased the daily dose of bronchodilator use, which is not reflected in the daily prevalence.

From these results it appears that negative associations between air pollution and evening PEF mainly occur in the $COUGH^-$ group. The regression slope for PM10 lag 1 in the $COUGH^-$ group translates into a –0.4% change of evening PEF associated with a 100 $\mu g/m^3$ concentration change, only slightly lower than the combined effect estimate of –0.7% reported by Dockery and Pope (18). Cough only children differ on certain characteristics from the asthmatic children. The mean daily prevalence of lower respiratory symptoms was lower in the $COUGH^-$ group than in the other groups. An earlier analysis of the PEACE data showed that children selected only on cough had a lower PEF variability than children selected on asthmatic symptoms (8). In the Finnish panels children selected on cough only had a lower prevalence of atopy and higher percentage of predicted MMEF (19) compared to children selected on asthmatic symptoms. In contrast to the outcome in this study, the asthmatic children in the Finnish panels tended to react stronger on air pollution than the cough only children (5). This was also observed in an earlier panel study in the Netherlands (4).

In this study the difference in reaction between $COUGH^-$ and AST^+ was less pronounced with regard to the effect estimates of air pollution on morning PEF than on evening PEF. The morning PEF measurements were done after getting up and before taking medication and was preceded by a long period of exposure to indoor environmental factors. These exposures may have obscured the relatively weak signal of air pollution while at the same time the medication use did not exert its counteracting effect in the AST^+ group. The difference in response is not reflected in the effect estimate of air pollution on symptom prevalence as the OR's differed not clearly between AST^+, AST^- and $COUGH^-$. These results differ from the results from the study by Peters (3) in which the children using medication showed larger PEF decrements and smaller OR's on symptom prevalence than children not using medication.

Stratification on sex, atopy or lung function did not show consistent differences in the whole population between effect estimates of air pollution on PEF or symptom prevalence. Studies which showed a difference in response between boys and girls focused on chronic effects in general population samples (7, 20) whereas the PEACE study was designed to study acute effects in symptomatic children.

One of the possible explanations of the lack of acute effects of fluctuations in daily air pollution concentrations on PEF or symptom prevalence and medication use in the individual panels of the PEACE was that subgroups of children within a panel biased the panel effect estimate towards the null or even in the opposite direction (21). On the basis of the above presented results this explanation is unlikely for the symptom prevalence analysis. The relation between PEF and air pollution differs indeed between certain subgroups but still no clear effects of air pollution on PEF can be detected. Other possible explanations for this lack of effect are discussed elsewhere (21).

This study failed to show an effect of particulate air pollution on children's respiratory health. This might mean that there really was no association between particulate air pollution and children's respiratory health during the winter of 1993-19194 and that in other studies which did show associations in children panels (1, 2, 4) the composition or level of air pollution was different or that they suffered from residual confounding. It might be that the exposure parameters used in this study were not relevant for respiratory health. One hypothesis is that not the mass of particles but the number of ultrafine particles is of importance (22) and that the correlation in time between ultrafine particle numbers and PM_{10} mass concentration is low. A panel study in Germany showed somewhat stronger health effects for particle numbers than for PM_{10} (23), but in the Finnish PEACE panel this was not confirmed (24).

In conclusion, none of the predefined potentially more sensitive subgroups showed a consistent association between air pollution, PEF and respiratory symptoms. In asthmatic children using respiratory medication, significant positive associations between air pollution and PEF were found. Asthmatic children not using medication did not show any association with air pollution.

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7

PM_{10} elemental composition and acute respiratory health effects in European children*

Abstract

The ability of particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}) to cause respiratory health effects possibly depends on their composition. We evaluated whether soluble elemental concentrations in PM_{10} were related to acute respiratory health effects. The Pollution Effects on Asthmatic Children in Europe (PEACE) study is a multicenter study of the acute effects of PM_{10} and other components on respiratory health of children with chronic respiratory symptoms in urban and suburban panels.

1208 children, divided over 17 panels were followed during at least two months. Exposure to air pollution was monitored on a daily basis. Health status was monitored by twice daily Peak Expiratory Flow (PEF) measurements and a symptom diary.

Median concentrations of iron ranged from 105 to 1110 ng/m^3 in the urban and from 32 to 517 ng/m^3 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. In two pollutant models PM_{10} 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 separated.

In conclusion, daily iron and silicon concentrations were related to daily phlegm prevalence.

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Introduction

Several studies have shown acute effects of particles with a 50% cut off aerodynamic diameter of 10 μm (PM_{10}) on morbidity and mortality (1). The mechanism through which PM_{10} is related to respiratory health is unclear. One hypothesis for the explanation of acute respiratory effects associated with PM_{10} is that certain elements such as transition metals in the particles cause damage by the generation of free radicals and that PM_{10} mass concentrations serve as a proxy for these elements (2). Especially iron is mentioned as from earlier studies it is known that iron is able to generate hydroxyl radicals through the Fenton reaction (3,4). PM_{10} particles sampled in Edinburgh, United Kingdom were able to generate hydroxyl radicals *in vitro*, possibly through involvement of iron (5). Other transition metals (titanium, vanadium, chromium, manganese, cobalt, nickel, copper, zinc) from a variety of urban or combustion source samples were also related with lung injury and radical activation in animal experiments(5, 6, 7, 8, 9). Epidemiological studies on the acute effects of elemental concentrations in PM_{10} on respiratory health are scarce. One study in the Netherlands showed that airborne iron was associated with exacerbation of respiratory symptoms and with increased maintenance medication use, independently of PM_{10} (10). A study on daily mortality in Rotterdam, the Netherlands showed that total iron content in total suspended particulates (TSP) was less consistently associated with mortality than TSP mass (11). A limitation of these studies is that total iron content was used as the exposure measure. The conditions in the human airways and macrophages are such that probably only soluble elements will be released from the inhaled particles.

In this paper we evaluate if soluble elemental concentrations in PM_{10} are related to acute effects on respiratory health, using data of the (Pollution Effects on Asthmatic Children in Europe) PEACE study.

Material and methods

PEACE study

The PEACE study is a collaboration of 14 European centres: Amsterdam (the Netherlands), Kuopio (Finland), Oslo (Norway), Berlin and Hettstedt (Germany), Pisa (Italy), Athens (Greece), Cracow and Katowice (Poland), Prague and Teplice (Czech Republic), Budapest (Hungary), Umeå and Malmö (Sweden). All centres used the same protocol for data collection and data analysis. Design, methods and results of the individual panels (12) as well as combined effect estimates for PM_{10} and other components are reported elsewhere (14). Each centre selected two panels, one panel in an urban area and one panel in a suburban or rural area (hereafter to be referred to as suburban panel). The suburban panel was selected from a community which had no major traffic emissions, had no large industrial sources, had sufficient size to select enough subjects and was close to a site of an existing air pollution measurement network.

Children between 6-12 years with chronic respiratory symptoms were selected by a parent completed screening questionnaire. The criteria for selection were: reporting of recent wheeze (apart from colds), recent attacks of shortness of breath with wheezing, recent dry cough (apart from colds) and/or doctor diagnosed asthma, ever in life.

Peak Expiratory Flow (PEF) was measured each day in the morning and in the evening for at least two months in the winter of 1993/94. For analysis the highest of three readings was used. All centres used the mini Wright Peak Flow meter. A parent completed a daily diary for the child recording the presence and severity of respiratory symptoms and use of medication for respiratory symptoms. 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. To avoid large changes in composition of the reporting group of children on separate days children were included in the analysis if they had valid PEF measurements and respiratory symptom data on more than 60% of the days.

Concurrent air pollution measurements were performed in both the urban and suburban locations. Daily 24 hour measurements of PM_{10}, BS, SO_2 and NO_2 were made at sites not influenced by nearby sources, so called background sites. More information about the measurement methods and combined effect estimates of PM_{10}, BS, SO_2 and NO_2 on respiratory health for all panels are given elsewhere (12, 13, 14).

Filter analysis

The filters were transferred, by use of plastic tweezers, into 15 mL polypropylene tubes with screw caps. In an attempt to differentiate between easy and difficult bioavailable fractions of elements, a two-step extraction was conducted, based on the procedure described by Janssen et *al.* (15). In the first step, the PM_{10} filters were extracted with 10 mL of a weak acid solution (0.05 M HF and 0.01 M HNO_3). The tubes were agitated end-over-end for 4 hrs, centrifuged, and 8 mL of the extract was transferred to another polypropylene tube and analysed. In the second extraction step, 100 times higher concentrations of the acids were used. Only the results of the weak extraction have been used to study associations with respiratory health. The extracts were analysed by use of low resolution inductively coupled plasma mass spectrometry (ICP-MS; VG PQ2+, Fisons Elemental, Winsford, Cheshire, UK). The instrument was run in dual mode (analogue and plus counting), and the samples were introduced in a segmented flow mode by use of an auto-sampler (Gilson 222, Gilson, Villiers, France). Concentrations of elements Al, As, B, Ba, Bi, Ca, Cd, Ce, Co, Cr, Cs, Cu, Fr, La, Li, Mg, Mn, Mo, Na, Ni, Pb, Rb, Si, Sn, Sr, Ti, V, W, Zn, Zr were determined.

The instrument was calibrated by use of multi-element standard solutions made up by mixing certified single standard solutions with the acid solution, respectively, in proportions expected to reflect the elemental composition of the samples.

The filter extraction and analysis were done in one laboratory (Lund, Sweden). The instrument performance was checked by including a separate commercial certified reference multi element standard solution, diluted with the extraction solutions, once every 20 samples in all sample series. The coefficients of variation calculated from all these available reference samples were for iron 15.8%, nickel 8.6%, zinc 8.3%, vanadium 9.4%, sodium 8.4% and lead 8.8%. For silicon, which was not included in the certified reference solution, the coefficient of variation was calculated from the method calibration solution and was 12.6%

Results of field blanks were subtracted from the results of exposed filters. Because not all centres used the same filter and because the mean field blank values differed between centres with the same type of filters, filter and centre specific mean field blanks were calculated. If no field blanks were provided by a centre, the mean field blank values of the other centres with the same type of filter were used.

In Finland about 50% of the filters from the urban site were not available anymore for analysis by ICP-MS. Results of an additional urban site which had highly correlated PM_{10} concentrations (16) were used to estimate the missing values. A regression model was calculated with the non missing data of the urban site as dependent variable and the data from the additional site as independent variable. The resulting model was used to predict missing observations. The method was not used for nickel, lead and silicon as for those elements the correlation between the non-missing observations in urban and additional site was considered too low (R^2 <0.50) to give reliable estimates.

Statistical methods

All panels were analysed separately, using the same methods that were used before for PM_{10} and other components (12, 14). Individual daily PEF readings were transformed into a daily population variable representing the population mean for each day of the individual deviations from the child specific mean PEF (12,17, 18). This was done separately for morning and evening PEF resulting in ΔPEF_{am} and ΔPEF_{pm}. The association between daily elemental concentrations and daily levels in ΔPEF_{am} and ΔPEF_{pm} was calculated by means of linear regression weighted by the number of reporting children on each day. Correction for autocorrelation in the residuals was made using a first order autoregressive model.

The symptoms in the diaries were re-coded to 0 (no symptom) and 1 (slight, moderate or severe symptom) and daily prevalence was calculated. Daily prevalence was defined as the fraction of children for whom the presence of a respiratory symptom/medication use was reported from those children providing valid diary data for that symptom on that day. The association between symptom prevalence and air pollution was evaluated with logistic regression, weighted by the number of reporting children on each day and correcting for first order autocorrelation in the residuals. The respiratory symptoms cough, phlegm and the symptom combinations upper respiratory symptoms (runny/stuffed nose, sore throat), lower respiratory symptoms (shortness of breath, wheeze, asthma attacks) were analysed. Prevalence of bronchodilator use (such as salbutamol, albuterol, fenoterol, terbutaline) was also analysed.

The explanatory variables were 24 hour average concentrations of elemental concentrations, entered separately into the regression models. From the available elements we chose *a priori* a limited number to be included in the time series analysis. Other elements were not analysed. Nickel, zinc, vanadium, iron were included because of the capability of these transition metals to generate radicals in toxicological studies. Additional reasons for the inclusion of vanadium and iron were that vanadium can serve as a tracer for oil combustion, and iron has been shown to be related to acute effects on respiratory health (10). Silicon, sodium and lead were included as possible tracers for soil dust, sea spray, and leaded car fuel, 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. Minimum temperature, a dummy variable indicating normal school days versus holidays/weekends and time trend were included as potential confounders. Time trend was included as a linear and square root term for the PEF analysis and as a third order polynomial in the prevalence analysis. Influential observations were identified by calculating Cook's distance (19). Observations with a Cook's D larger than 0.8 were excluded from analysis to avoid that one or a few observations would determine the association for the whole set of observations. 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 inverse proportional to the panel specific variance. The Standard Error (SE) of the combined slope was calculated as the inverse of the square root of the sum of the weights (20). Heterogeneity of panel specific slopes was evaluated by a chi-square test for homogeneity (20). In case of homogeneity the combined slope calculated as a fixed effect was considered an appropriate estimate. A conservative cut-point of a p-value smaller than 0.25 was chosen to determine heterogeneity. In case of heterogeneity ($p<0.25$) combined effect estimates using random effect estimation were calculated with the non-iterative method with unequal weights (20).

Table 1. Characteristics of panels.

		PM_{10}*	SO_2*	NO_2*	subjects	cough†	bron‡
Umeå	urban	13.4	2.7	25.0	75	15	10
(Sweden)	suburban	11.5	4.0	15.3	72	17	22
Kuopio	urban	17.7	6.0	28.4	85	54	3
(Finland)	suburban	13.0	-	13.7	84	58	7
Oslo	urban	19.3	12.4	49.3	56	36	3
(Norway)	suburban	11.2	3.4	15.3	68	55	10
Amsterdam	urban	45.3	13.2	46.4	55	38	4
(The Netherlands)	suburban	44.4	8.5	26.5	71	44	3
Berlin	urban	52.3	42.3	38.3	50	4	17
(Germany)	suburban	43.0	26.1	21.2	66	3	8
Hettstedt	urban	40.3	83.3	26.5	75	21	2
(Germany)	suburban	32.9	64.9	26.1	63	10	5
Katowice	urban	68.7	55.7	68.7	72	35	1
(Poland)	suburban	73.8	56.0	69.5	73	15	3
Budapest (Hungary)	urban	60.9	49.7	35.3	76	45	2
Athens	urban	98.8	72.4	74.9	87	53	4
(Greece)	suburban	50.0	-	19.7	80	31	7

* mean concentration during study period in $\mu g/m^3$

† percentage of children in panel selected only on basis of question on nightly coughing

‡ mean prevalence (%) of bronchodilator use in panel during study period

Results

From the 28 panels of the PEACE study, for 17 panels enough filters for ICP-MS analysis were available to perform time series analysis with the elemental concentrations as independent variable. Table 1 shows the characteristics of the included locations and panels. PM_{10} levels are lowest in Northern Europe and higher in Eastern and Southern Europe. More details on PM_{10} levels during the study period can be found elsewhere (13). In table 2 some descriptive statistics of the elemental concentrations are presented. A large range in elemental concentrations can be seen, with again generally lower concentrations in Northern Europe and higher concentrations in East and South Europe. The median and maximum concentrations tend to be higher in the urban locations compared to the suburban locations. Especially iron, zinc, silicon and lead show a large contrast between urban and suburban locations in most centres, but for the other elements in some centres also large differences can be found.

Spearman correlation between elemental concentrations and PM_{10} mass concentrations were positive in all locations for most elements. The median correlations of the locations were 0.70 (iron), 0.49 (nickel), 0.71 (zinc), 0.60 (vanadium), 0.76 (lead) and 0.39 (silicon). Only the correlation between sodium and PM_{10} was negative in most locations, with a median correlation of -0.08. A more detailed discussion of the elemental concentrations is not within the scope of this paper and will be published elsewhere.

The effect estimates of the elemental concentrations on ΔPEF_{am} and ΔPEF_{pm} do not show a significant effect (table 3). The coefficients of iron and silicon are predominantly negative but do not reach significance. The effect estimates of PM_{10} on ΔPEF_{am} and ΔPEF_{pm} for the included 17 panels are also presented in table 3 and show only for PM_{10} lag1 on ΔPEF_{pm} a significant negative association. After specification of a two pollutant model with the concentrations of PM_{10} and iron or PM_{10} and silicon simultaneously included, the effect estimates of neither PM_{10} nor iron or silicon showed clear associations with PEF (not shown). Most elements do not show a consistent positive association with prevalence of phlegm, lower respiratory symptoms and bronchodilator use (table 4). Only iron and silicon have consistently positive Odds Ratios with phlegm, most of them (borderline) significant. To illustrate the variability of the Odds Ratios across centres the individual panel and the combined effect estimates for silicon lag1 are plotted in figure 1. Most of panel specific OR's are above 1, several of them significantly. There is no effect estimate of Kuopio urban available as the regression model did not converge, probably due to the low number of observations.

Table 2. Median (maximum) 24 hour mean soluble elemental concentrations (ng/m³)

		n*	iron		nickel		zinc		vanadium		sodium		lead		silicon	
Umeå (Sweden)	urban	65	124	(1010)	0.8	(5.1)	15.4	(60.3)	1.5	(13.9)	311	(1301)	7.0	(34.9)	142	(3967)
	suburban	64	65	(230)	1.0	(6.2)	14.6	(87.6)	2.0	(16.8)	253	(1117)	5.0	(54.5)	70	(1668)
Kuopio (Finland)	urban	57	124	(1880)	1.0	(5.3)†	18.9	(56.0)	3.8	(17.7)	278	(787)	5.1	(18.1)†	104	(4873)†
	suburban	57	32	(732)	1.3	(4.7)	13.3	(75.7)	2.2	(16.3)	253	(768)	4.5	(14.0)	0	(2538)
Oslo (Norway)	urban	67	105	(905)	0.2	(1.7)	6.9	(55.8)	2.0	(9.2)	236	(1282)	22.9	(202.5)	89	(4015)
	suburban	68	49	(389)	0.0	(0.6)	3.1	(23.0)	1.3	(8.4)	157	(1034)	10.5	(53.3)	30	(1396)
Amsterdam (The Netherlands)	urban	66	187	(1200)	2.8	(22.8)	54.1	(666.2)	6.6	(37.4)	926	(7461)	20.8	(177.2)	126	(3324)
	suburban	58	70	(3776)	0.0	(1678.8)	15.9	(117.8)	3.3	(20.8)	283	(4576)	14.6	(93.0)	71	(8539)
Berlin (Germany)	urban	44	536	(1180)	2.9	(8.5)	91.5	(473.5)	5.7	(31.4)	482	(1925)	64.8	(228.0)	380	(1877)
	suburban	47	283	(1290)	2.4	(24.9)	86.6	(695.3)	4.9	(31.6)	441	(1847)	37.7	(209.1)	88	(2934)
Hettstedt (Germany)	urban	31	146	(933)	1.0	(6.6)	309.1	(2049.1)	2.2	(13.7)	445	(1429)	116.4	(562.3)	162	(1515)
	suburban	30	133	(501)	1.1	(6.2)	60.9	(171.8)	1.9	(13.9)	401	(1573)	28.3	(258.7)	11	(980)
Katowice (Poland)	urban	28	881	(2510)	4.0	(8.8)	121.3	(730.8)	4.2	(8.9)	573	(1854)	115.8	(346.7)	2048	(5105)
	suburban	29	517	(1210)	2.2	(38.2)	69.0	(417.1)	2.8	(9.4)	536	(1398)	82.1	(181.2)	1320	(2814)
Budapest (Hungary)	urban	39	363	(1060)	4.2	(16.5)	71.9	(314.0)	7.4	(48.6)	229	(693)	49.7	(215.6)	900	(2406)
Athens (Greece)	urban	56	1110	(2830)	5.3	(46.1)	92.8	(477.2)	8.6	(24.0)	695	(3974)	377.1	(769.8)	936	(3474)
	suburban	55	147	(568)	2.4	(19.0)	22.7	(104.2)	5.3	(18.8)	742	(3441)	45.5	(157.8)	303	(1956)

*number of observations: †no estimates of missing values possible (n = 28)

Table 3. Combined effect estimates with 95% Confidence intervals (95% CI) of air pollution on PEF.

	N[†]	ΔPEF_{am} mean	ΔPEF_{am} (95% CI)	ΔPEF_{pm} mean	ΔPEF_{pm} (95% CI)
iron[*]					
lag0	17	-0.2	(-1.1, 0.7)[¶]	0.1	(-0.8, 1.0)[¶]
lag1	17	-0.1	(-0.8, 0.6)[§]	-0.3	(-1.0, 0.4)[§]
lag2	17	-0.6	(-1.3, 0.1)[§]	-0.4	(-1.1, 0.3)[§]
7 day mean[‡]	15	1.1	(-1.5, 3.7)[¶]	-0.2	(-3.0, 2.6)[¶]
nickel[*]					
lag0	17	-0.3	(-1.1, 0.5)[§]	0.2	(-0.5, 0.9)[§]
lag1	17	-0.6	(-1.5, 0.3)[§]	-0.2	(-0.9, 0.5)[§]
lag2	17	-0.2	(-1.5, 1.2)[¶]	-0.8	(-2.0, 0.3)[¶]
7 day mean[‡]	15	0.8	(-1.8, 3.4)[¶]	0.8	(-2.3, 4.0)[¶]
zinc[*]					
lag0	17	-0.1	(-0.8, 0.6)[§]	-0.2	(-0.8, 0.4)[§]
lag1	17	-0.2	(-0.8, 0.4)[§]	0.0	(-1.1, 1.2)[¶]
lag2	17	-0.2	(-1.6, 1.1)[¶]	-0.5	(-1.6, 0.7)[¶]
7 day mean[‡]	15	1.3	(-4.1, 6.7)[¶]	0.7	(-3.9, 5.3)[¶]
vanadium[*]					
lag0	17	0.0	(-1.3, 1.3)[¶]	0.2	(-0.7, 1.2)[§]
lag1	17	0.3	(-1.1, 1.6)[¶]	-0.1	(-1.3, 1.1)[¶]
lag2	17	0.2	(-1.1, 1.5)[¶]	-0.1	(-1.7, 1.5)[¶]
7 day mean[‡]	15	1.3	(-2.3, 4.8)[¶]	0.5	(-3.6, 4.7)[¶]
sodium[*]					
lag0	17	-0.1	(-0.7, 0.5)[¶]	-0.1	(-0.5, 0.3)[§]
lag1	17	0.0	(-0.4, 0.4)[§]	-0.2	(-0.8, 0.4)[¶]
lag2	17	0.1	(-0.3, 0.5)[§]	0.0	(-0.4, 0.4)[§]
7 day mean[‡]	15	-1.4	(-3.5, 0.7)[¶]	-0.6	(-2.4, 1.2)[¶]
lead[*]					
lag0	17	0.1	(-0.2, 0.5)[§]	0.1	(-0.4, 0.7)[¶]
lag1	17	0.0	(-0.6, 0.6)[¶]	-0.4	(-0.7, 0.0)[§]
lag2	17	0.3	(-0.4, 1.0)[¶]	-0.1	(-0.7, 0.4)[¶]
7 day mean[‡]	15	1.4	(-0.7, 3.5)[¶]	0.2	(-2.0, 2.4)[¶]
silicon[*]					
lag0	17	-0.6	(-1.2, 0.0)[¶]	-0.2	(-0.8, 0.4)[¶]
lag1	17	0.0	(-0.4, 0.4)[§]	-0.4	(-0.9, 0.1)[¶]
lag2	17	-0.3	(-0.8, 0.2)[¶]	-0.4	(-0.8, 0.0)[§]
7 day mean[‡]	15	-0.1	(-0.9, 0.7)[§]	-0.7	(-2.0, 0.6)[¶]
PM_{10}[*]					
lag0	17	0.5	(-0.2, 1.2)[§]	0.1	(-0.6, 0.8)[§]
lag1	17	-0.1	(-1.0, 0.8)[§]	-1.1	(-1.8, -0.4)[§]
lag2	17	0.3	(-0.5, 1.1)[§]	-0.8	(-1.6, 0.0)[§]
7 day mean[‡]	17	-0.8	(-3.0, 1.4)[¶]	-1.6	(-4.0, 0.8)[¶]

[*] Expressed as l/min per 1000 ng/m^3 (iron, sodium, silicon), 300 ng/m^3 (zinc), 100 ng/m^3 (lead), 20 ng/m^3 (vanadium), 10 ng/m^3 (nickel), 100 μg/m^3 (PM_{10}); [†] Number of panel specific estimates; [‡] From Hettstedt urban and suburban location filters were only available once every three days, reliable 7 day means could not be calculated; [§] Fixed effects model; [¶] Random effects model.

Table 4. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for increase in air pollution on prevalence of phlegm, lower respiratory symptoms and bronchodilator use.

	Phlegm		lower respiratory symptoms		bronchodilator use	
	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)
iron*						
lag0	17	1.05 (0.93, 1.19)¶	17	1.09 (0.95, 1.24)¶	16	1.08 (0.99, 1.17)§
lag1	17	1.15 (1.02, 1.30)¶	17	1.04 (0.88, 1.23)¶	16	0.98 (0.90, 1.07)§
lag2	17	1.13 (1.00, 1.28)¶	17	0.96 (0.80, 1.15)¶	16	1.05 (0.96, 1.14)§
7 day mean	15	1.25 (0.98, 1.59)¶	15	0.96 (0.66, 1.40)¶	14	0.90 (0.66, 1.23)¶
nickel*						
lag0	17	1.00 (0.89, 1.12)§	17	0.93 (0.84, 1.03)§	16	0.99 (0.89, 1.11)§
lag1	17	0.96 (0.83, 1.12)¶	17	0.93 (0.84, 1.03)§	16	0.98 (0.84, 1.14)¶
lag2	17	0.88 (0.73, 1.06)¶	17	0.88 (0.68, 1.15)¶	16	1.06 (0.95, 1.17)§
7 day mean	15	1.04 (0.84, 1.30)¶	15	0.57 (0.35, 0.92)¶	14	1.01 (0.78, 1.32)¶
zinc*						
lag0	17	0.97 (0.91, 1.04)§	17	0.95 (0.85, 1.07)§	16	0.95 (0.88, 1.03)§
lag1	17	0.97 (0.87, 1.08)¶	17	0.95 (0.80, 1.12)¶	16	1.04 (0.92, 1.17)¶
lag2	17	0.99 (0.88, 1.12)¶	17	0.87 (0.74, 1.01)¶	16	1.03 (0.91, 1.17)¶
7 day mean	15	1.02 (0.70, 1.50)¶	15	0.74 (0.43, 1.25)¶	14	1.02 (0.58, 1.79)¶
vanadium*						
lag0	17	0.93 (0.80, 1.09)¶	17	0.91 (0.81, 1.01)§	16	1.01 (0.88, 1.17)¶
lag1	17	0.93 (0.83, 1.05)¶	17	0.97 (0.87, 1.08)§	16	1.00 (0.90, 1.12)¶
lag2	17	0.95 (0.87, 1.03)§	17	0.92 (0.74, 1.13)¶	16	1.04 (0.95, 1.13)§
7 day mean	15	0.85 (0.61, 1.18)¶	15	0.45 (0.22, 0.91)¶	14	1.20 (0.73, 1.96)¶
sodium*						
lag0	17	1.00 (0.94, 1.06)¶	17	1.07 (0.99, 1.14)¶	16	0.99 (0.96, 1.03)§
lag1	17	1.01 (0.98, 1.04)§	17	0.99 (0.92, 1.06)¶	16	0.97 (0.94, 1.00)§
lag2	17	1.00 (0.96, 1.03)§	17	0.99 (0.92, 1.08)¶	16	0.98 (0.95, 1.03)§
7 day mean	15	1.19 (0.99, 1.43)¶	15	1.11 (0.92, 1.33)¶	14	0.87 (0.70, 1.07)¶
lead*						
lag0	17	1.01 (0.94, 1.08)¶	17	0.99 (0.95, 1.03)§	16	1.01 (0.97, 1.05)§
lag1	17	1.03 (0.95, 1.12)¶	17	1.01 (0.97, 1.06)§	16	1.00 (0.96, 1.03)§
lag2	17	1.01 (0.98, 1.04)§	17	0.97 (0.88, 1.06)¶	16	0.99 (0.92, 1.06)¶
7 day mean	15	1.04 (0.89, 1.22)¶	15	0.95 (0.67, 1.36)¶	14	0.89 (0.70, 1.12)¶
silicon*						
lag0	17	1.05 (1.00, 1.10)¶	17	1.00 (0.94, 1.06)§	16	1.00 (0.95, 1.05)¶
lag1	16	1.09 (1.03, 1.15)¶	17	1.04 (0.98, 1.11)¶	16	0.98 (0.95, 1.02)§
lag2	17	1.05 (0.99, 1.11)¶	17	1.01 (0.93, 1.10)¶	16	1.01 (0.97, 1.04)§
7 day mean	15	1.18 (1.02, 1.37)¶	15	0.87 (0.71, 1.05)¶	14	0.87 (0.79, 0.96)§
PM_{10}						
lag0	17	1.00 (0.94, 1.07)§	17	1.00 (0.87, 1.15)¶	16	0.99 (0.92, 1.08)§
lag1	17	1.12 (1.01, 1.23)¶	17	0.99 (0.87, 1.12)¶	16	0.98 (0.90, 1.06)§
lag2	17	1.00 (0.94, 1.07)§	17	0.89 (0.79, 1.01)¶	16	0.92 (0.85, 1.00)§
7 day mean	15	1.03 (0.79, 1.36)¶	15	0.89 (0.56, 1.44)¶	16	0.82 (0.59, 1.14)¶

*Increase of 1000 ng/m³ (iron, sodium, silicon), 300 ng/m³ (zinc), 100 ng/m³ (lead), 20 ng/m³ (vanadium), 10 ng/m³ (nickel), 100 μg/m³ (PM_{10}); † Number of panel specific estimates; § Fixed effects model; ¶ Random effects model.

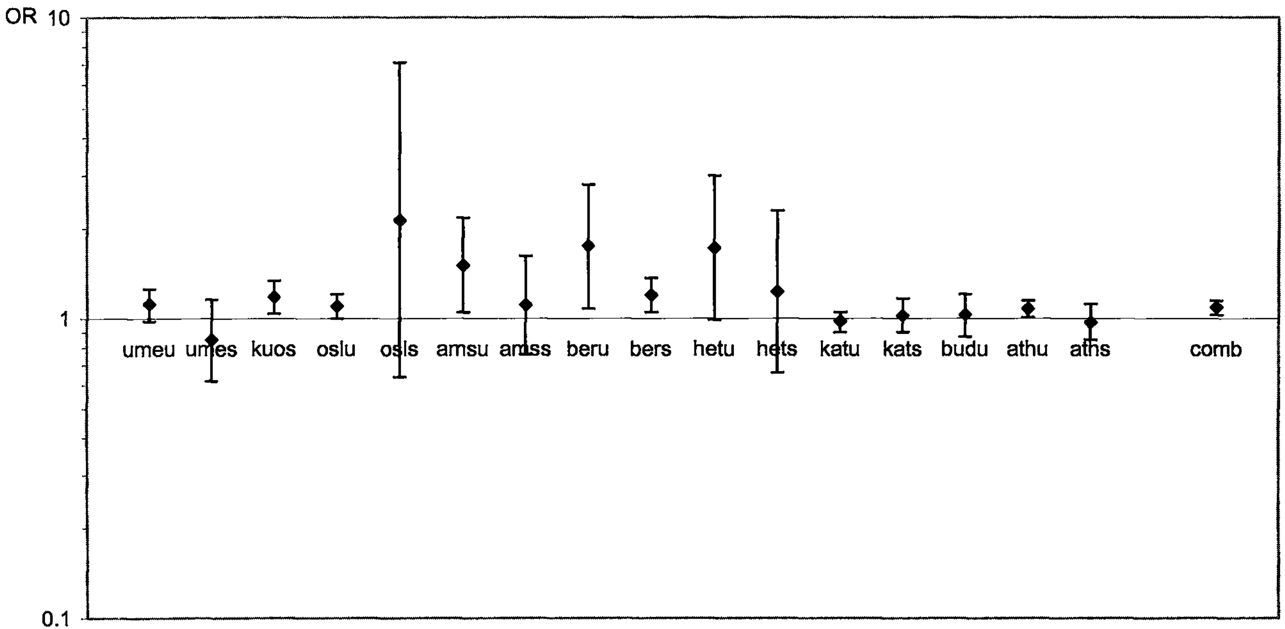

Figure 1. Individual panel and combined effect estimates of silicon lag1 concentrations on phlegm prevalence. Expressed as Odds Ratio (OR) per 1000 ng/m³ increase of silicon concentration. Umeu = Umeå urban, Umes = Umeå suburban, Kuos = Kuopio suburban, Oslu = Oslo urban, Osls = Oslo suburban, Amsu = Amsterdam urban, Amss = Amsterdam suburban, Beru = Berlin urban, Bers = Berlin suburban, hetu = Hettstedt urban, hets = Hettstedt suburban, Katu = Katowice urban, Kats = Katowice suburban, budu = Budapest urban, athu = Athens urban, Aths = Athens suburban, comb = combined effect estimate.

The combined effect estimate of PM_{10} lag 1 on phlegm shows a positive significant association with phlegm as well, but the other representations are close to 1 (table 4). When specifying a two pollutant model with the concentrations of PM_{10} and iron or PM_{10} and silicon simultaneously included, the PM_{10} effect estimates on phlegm prevalence were reduced and lost significance (table 5). The effect estimates of iron and silicon essentially did not change and in spite of increased confidence intervals silicon effect estimates remained significant.

The effect estimates of elemental concentrations on prevalence of upper respiratory symptoms or cough did not show a clear association (not shown). Restriction of the data to the 8 panels with the highest inter quartile ranges in elemental concentration did not change the pattern for any combination of exposure and health outcome variable. Stratification on urban/suburban locations showed that in the suburban locations the associations tended to be more in the expected direction than in the urban locations. Stratification on geographical location defined as North (Umeå, Oslo, Kuopio), West (Amsterdam, Berlin), East (Hettstedt, Katowice, Budapest) and South (Athens) showed that the associations between silicon and phlegm tended to be stronger in West and North than in East or South. For example OR (95 % confidence intervals) for silicon lag1 were: North 1.11 (1.04-1.18), West 1.25 (1.11-1.40), East 1.01 (0.94-1.09) and south 1.04 (0.95-1.15).

Table 5. Combined Odds ratios (OR) and 95% confidence intervals (95% CI) for PM_{10} and iron or silicon together on prevalence of phlegm.

	$N^{\dagger}$	OR (95% CI)	$N^{\dagger}$	OR (95% CI)
		PM_{10} and iron analysed together		
		PM_{10}^{*}		iron*
lag0	17	0.97 (0.89, 1.06)§	17	1.06 (0.89, 1.25)¶
lag1	17	1.07 (0.94, 1.22)¶	17	1.08 (0.94, 1.25)¶
lag2	17	0.93 (0.78, 1.10)¶	17	1.12 (0.97, 1.30)¶
7 day mean	15	0.64 (0.36, 1.15)¶	15	1.20 (0.78, 1.86)¶
		PM_{10} and silicon analysed together		
		PM_{10}^{*}		silicon*
lag0	17	0.88 (0.75, 1.04)¶	17	1.10 (1.02, 1.18)§
lag1	17	1.02 (0.86, 1.20)¶	17	1.10 (1.02, 1.18)§
lag2	17	0.95 (0.80, 1.13)¶	17	1.04 (0.97, 1.11)¶
7 day mean	15	0.68 (0.41, 1.14)¶	15	1.19 (0.98, 1.46)¶

*Increase of 1000 ng/m^3 (iron, silicon), 100 $\mu g/m^3$ (PM_{10}); † Number of panel specific estimates; § Fixed effects model; ¶ Random effects model.

Discussion

The elemental concentrations measured showed a wide range across 17 European locations, with generally higher concentrations in the urban locations. Also within the locations the concentrations showed a large range. Concentrations of most elements were not associated with daily variation in morning or evening PEF nor with daily prevalence of respiratory symptoms and bronchodilator use. Iron and especially silicon were positively associated with the prevalence of phlegm and tended to have negative associations with PEF.

The elemental concentrations showed a larger difference between urban and suburban locations than PM_{10} mass concentrations. Also the difference between geographical locations was larger for elemental concentrations than for PM_{10} mass. PM_{10} mass concentrations between urban and suburban locations differed on average 22% (13). The difference between elemental concentrations for elements such as silicon, iron, zinc and lead was in several locations more than twofold. An explanation for this difference can be that not all elements have been determined which contribute to PM_{10} mass concentration, such as sulphur (from sulphates), nitrogen (from nitrates) and carbon. The fact that silicon and iron are higher in urban locations might be caused by a higher traffic intensity which causes re-suspension of road dust (15). Industrial sources may also contribute to the iron level. The higher lead concentrations can be caused by a higher traffic intensity, but also by industrial emissions. The differences in zinc concentrations can be caused by resuspended road dust, smelting operations, coal and wood combustion and wearing down of vehicle tyres (21).

Iron, silicon and PM_{10} mass tended to be negatively related to daily variations in PEF. Two pollutant models could not separate the independent effects of PM_{10}, silicon or iron on PEF. Prevalence of phlegm was related to iron and silicon concentrations but also to PM_{10}. In two pollutant models, PM_{10} lost its importance. PM_{10} lag1 was not associated with phlegm prevalence when the results of all PEACE panels were combined (OR 1.02 with 95% confidence interval 0.94-1.11) (14). Earlier studies showed mixed results about associations between phlegm prevalence and PM_{10} levels. In a panel of symptomatic children in the Netherlands phlegm prevalence was not related to PM_{10} (22) whereas in a panel of asthmatic children in the Czech Republic there was a positive association between phlegm prevalence and PM_{10} levels (23).

A panel of adult asthma patients in the Netherlands showed an association between elemental concentrations and respiratory health (10). In that study iron concentrations were related to PEF, to the prevalence of medication use and to the prevalence of moderate or severe respiratory symptoms (shortness of breath and attacks of shortness of breath with wheeze but not phlegm). The maximum daily iron concentrations were generally higher compared to the concentrations found in the PEACE panels, but this might be because total iron was determined and not the soluble fraction as in the PEACE study. Further this study was performed in the vicinity of a steel factory. These factors might explain the larger effect estimates of iron on phlegm prevalence in the PEACE study compared to those of the Dutch study for the same increase in concentration, besides the differences in population and health endpoints.

Phlegm prevalence was related to silicon and iron which are elements with a predominantly crustal origin and which mainly form the coarse fraction of PM_{10}. Elements which have industrial, combustion or traffic exhaust sources such as nickel, zinc, vanadium and lead and which mainly form the smaller fraction of PM_{10} were not related to PEF nor to prevalence of respiratory symptoms and bronchodilator use. A study in the Netherlands (15) showed that 58% of the total silicon content in PM_{10} measured at a background site was extracted with a weak extraction step. For iron this was 81%. In addition, the median soluble concentrations of silicon and iron were higher in PM_{10} than in $PM_{2.5}$ namely 165 and 9 ng/m^3 respectively (silicon) and 351 and 86 ng/m^3 respectively (iron). These figures show that in that study soluble silicon and iron concentrations predominantly originated from the coarse fraction. We can not verify this in the PEACE study as we did not measure $PM_{2.5}$.

Iron and other transition metals are mentioned as elements which might be responsible for the association between PM_{10} and respiratory health (2), which is not the case for silicon. Silicates often have iron complexed onto their surface (24) which can be an explanation for the association between silicon and phlegm prevalence in this study. Neither iron or silicon showed clear associations with phlegm prevalence in a two pollutant model with both iron and silicon concentrations as exposure variable.

In conclusion, the composition of particulate matter differs between urban and suburban locations even when PM_{10} mass differs only to a limited extent. Daily iron and silicon concentrations were related to daily phlegm prevalence. Daily levels of other elements were not related to PEF or to daily prevalence of respiratory symptoms and bronchodilator use.

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8

General discussion

Introduction

Overall, no clear association between changes in PM_{10} mass concentration, BS, SO_2 and NO_2 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 previous panel studies conducted in the USA and Europe, using similar methodologies, at levels of PM_{10} that were comparable to those in at least some of the areas studied in the PEACE study. Some possible explanations for this discrepancy will be discussed below.

In chapter 2 the three objectives of the PEACE study as a whole were introduced, namely development and standardisation of epidemiological methods, the testing of the feasibility of these epidemiological methods and as third objective the collection of information on the relationship between exposure to airborne particulate matter and other air pollution components in selected urban areas and changes in health status among selected groups of susceptible individuals. In the following discussion only the third objective will be discussed, an extensive evaluation of the first two objectives can be found elsewhere (1,2).

Exposure to air pollution

The PEACE study has documented, for the first time in Europe, PM_{10} concentrations measured in many different areas with standardised measurements. It has shown that in the winter of 1993/1994, there were large gradients from North to South in Europe, with low levels in most Scandinavian sites, higher levels in western European areas, still higher levels in central and eastern European areas, and highest levels in Athens, Greece. PM_{10} and BS concentrations in the urban area were on average 22% and 43% higher than in the corresponding suburban area concentrations, respectively. The correlation of daily concentrations PM_{10} between urban and suburban location was high, more than 0.70 in most locations. The meteorological conditions were similar in most urban and suburban locations due to the relatively small distance between them. In addition, PM_{10} concentrations of all Western and Central European locations were significantly correlated with median correlation coefficients of 0.71 and 0.72 for the urban and suburban sites respectively. Only in Athens (Greece), Teplice (Czech Republic) and Oslo (Norway) a considerable difference in mean concentrations PM_{10} and/or BS could be seen between the urban and suburban location. The distance between urban and suburban location in Teplice was relatively large (250 km), whereas the suburban location for Athens was located behind a mountain range. The urban location of Oslo was located in a basin, while the suburban location was higher in the hills, frequently above the inversion layer. Despite the small contrast of PM_{10} between urban and suburban locations within study areas, the range in mean air pollution concentrations over all locations was considerable. The maximum 24 hour concentrations during the study period ranged from 31 $\mu g/m^3$ (Oslo suburban location) to 242 $\mu g/m^3$ (Amsterdam suburban location) for PM_{10} and from 16 $\mu g/m^3$ (Malmö suburban location) to 499 $\mu g/m^3$ (Hettstedt suburban location) for SO_2. These levels are comparable or higher than earlier studies in which associations were found between respiratory health and particulate air pollution (3, 4, 5, 6).

The elemental composition of PM_{10} showed a larger contrast between urban and suburban locations. Median concentrations for elements like iron, zinc, silicon and lead were in the urban locations sometimes two times higher than in the suburban locations. Generally only the urban and suburban site were significantly ($p<0.01$) correlated with each other for the concentrations of iron, zinc, vanadium, lead, nickel, silicon and sodium. For iron, lead, silicon and zinc also the concentrations measured at the sites in the Netherlands and Germany were significantly correlated with each other. Median Spearman correlations were 0.65 for iron, 0.68 for lead, 0.59 for silicon and 0.64 for zinc. For vanadium significant correlations were found between the sites in Germany and between the sites in Kuopio and Umeå. The lack of correlation between the sites in the various countries seems to indicate that local sources are important for elemental concentrations in PM_{10}. This is in contrast with the PM_{10} mass concentrations where all Central and western European sites were correlated with each other. As with PM_{10} mass concentration, generally lower elemental concentrations were found in Northern Europe and higher concentrations in East and South Europe. Thus, a large range in concentrations and mixes of air pollutants was found in this study.

Exposure to ambient air pollution is also determined by the time spent outdoors. The daily mean number of hours spent outdoors was remarkably similar in all locations. The mean was approximately 2 hours in most locations. The highest was in Hettstedt suburban location, 2.8 hours, the lowest in Cracow urban location, 1.3 hours. These figures do not indicate large differences between countries in time spent outdoors by schoolchildren. The question if personal exposure to ambient air pollution is adequately estimated by a fixed site monitor will be discussed below.

Association between respiratory health and air pollution

In the PEACE study, no clear relationship could be detected between air pollution and lung function, respiratory symptoms and medication use (chapter 4 and 5) when combining the results of all panels.

Some clear differences can be seen in chapter 4, 5 and 6 between the composition of the panels in the PEACE study. Taking into account that not all centres used exactly the same inclusion criteria, differences can still be seen in, for example, prevalence of chronic and acute respiratory symptoms or percentage of atopic children in the panels. These differences were found not only between panels in different countries, but also between panels within countries. Because each child served as its own control, only variables which are correlated in time with air pollution can act as confounders. Stable factors such as sex, or factors which are unlikely to correlate with daily changes in air pollution such as smoking in the home can not act as confounder. Thus, differences in panel composition do not confound the results presented in chapter 4 and 5. Panel composition can act as an effect modifier when the proportion of sensitive subjects would be markedly different between panels. In chapter 6 we tried to identify sensitive subjects in the panels on the basis of medical characteristics. The subgroups which were hypothesised to be more sensitive did not differ from the other groups. Atopy and lung function level were not related to the response to air pollution. Medication use and chronic respiratory symptoms were related to response on 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 the children counteract the effects of air pollution with bronchodilators. A similar reaction was also suggested by Pope (6) and Silverman (7). However, the prevalence of bronchodilator use did not increase with increasing air pollution levels in the group with asthmatic children and bronchodilator use, but this might also indicate that the children increase the daily dose of the bronchodilators.

When using soluble concentrations of iron, nickel, zinc, vanadium sodium, lead and silicon in PM_{10} as exposure variables, silicon and iron were related to PEF and phlegm prevalence (chapter 7). The other elements were not related to any of the health effect measurements. Specification of two pollutant models indicated that iron and silicon concentrations in PM_{10} were a better predictor of health effects than PM_{10} mass. This might mean that the elemental composition of the particulate matter is of importance in the association with health effects.

Interpretation of lack of association

Several factors could have influenced the results of this study, which suggests that there is no strong and consistent relationship between PEF or respiratory symptoms and PM_{10} in the full population. In previous panel studies in which effects were shown (3, 5, 6) a clear dose response relationship could already be seen by simply tabulating respiratory symptom prevalence or peak flow levels by ordered categories of air pollution exposure. This was not the case in most panels of the PEACE study. We suspect that in these previous panel studies, variations in respiratory health endpoints caused by other factors than air pollution were of insufficient magnitude to obscure relationships between air pollution and respiratory health.

Air pollution

It could be that PM_{10} levels were too low to have a demonstrable effect on respiratory health. For a few locations this might have been true, but in most locations PM_{10} levels were reached at which earlier studies showed an association between respiratory health and PM_{10} (3, 4, 5, 6). Another possibility is that the composition of the air pollutant mix was different in comparison to these earlier studies. The results of stratification on indicators of air pollution composition in chapter 4 and 5 showed no clear differences between the effects estimates of air pollutants on respiratory health in the various strata. Given the fact that the PEACE study locations included a large range in concentrations, climatic regions, locations and mixtures of air pollutants it seems unlikely that in all locations a non toxic composition was present.

It can be that other components which we did not measure are a better predictor of health effects than PM_{10} and that if these were measured these would have been related to respiratory health. Recent evaluations of epidemiological evidence on the health effects of particulate air pollution suggested this for particulates with an 50% cut off aerodynamic diameter of 2.5 μm ($PM_{2.5}$) (8, 9). A study by Janssen *et al.* (10) in the Netherlands showed a high correlation between PM_{10} and $PM_{2.5}$ (Pearson R 0.94) which makes it unlikely that $PM_{2.5}$ as exposure variable would have given other associations. Another potentially important component is aerosol acidity. A study in the Czech Republic showed associations with respiratory health in asthmatic children and particle acidity, but the authors concluded that given the low levels this probably was caused by other highly correlated pollutants such PM_{10} or by bias of respiratory infections (11). Measurements in Germany (12) and in the Netherlands (13) also showed very low levels which reduces the possibility that acidity would be associated with acute effects on respiratory health. An alternative hypothesis is that not the mass of particles but the number of ultra-fine particles is of importance (14) and that the correlation in time between ultra-fine particle numbers and PM_{10} mass concentration is low. A panel study in Germany showed somewhat stronger health effects for particle numbers than for PM_{10} (15), but in the Finnish PEACE panel this was not confirmed (16).Thus, the question if the number of ultrafine particles is a more relevant exposure estimate still remains open as the results are mixed and we do not have data available from other panels to evaluate this. Only a more refined characterisation of particulate air pollution composition by means of elemental composition of PM_{10} showed some effects on respiratory health (chapter 7).

Statistical power

The statistical power of this study was high enough to detect an association. As was demonstrated in chapter 4 an increase of 10 $\mu g/m^3$ PM_{10} would have to be related to a reduction in PEF of only 0.02% to become significant at 5% probability level. Compared to an overview by Dockery *et al.* (17) in which PEF reductions between 0.04% and 0.25% for a 10 $\mu g/m^3$ increase in PM_{10} are reported, this study does appear to have enough power. A similar calculation for the prevalence of respiratory symptoms leads to the same conclusion. So, lack of statistical power does not explain the lack of significant relationships between air pollution and respiratory health in this study.

Time trends

Another possible explanation for the lack of effect is that long term time trends in Peak Flow or in respiratory symptom incidence or prevalence were not sufficiently removed by our data analysis strategy. 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 removed to correct for a learning effect. In the analysis of daily incidence and prevalence, a third order polynomial was included to correct for time trends. Residuals were inspected and in case significant deviations from the modelled long-term time trends were still detected, these were modelled with dummy variables. This usually resulted in small changes of the effect estimates of air pollution. In addition, panels were selected which had a large contribution in the combined effect estimate and which had an effect estimate opposite to expected. These panels were reanalysed using a non-parametric function of time to allow a more flexible relationship (18). This procedure did not materially affect effect estimates which makes it unlikely that long term time trends were still present in the data. Compared to previous panels studies time trends were more carefully modelled as these studies used linear or no time trends at all. On the other hand, the period of analysis was in most of the PEACE panels not more than two months. This is a relatively short period and it might mean that it is more difficult to separate the effects of air pollution from the effects of unexpected events which also influence the respiratory health.

Respiratory infections

Respiratory infections are known to be related with acute respiratory symptoms (19, 20) and have been suggested as possible confounder in the relation between respiratory health and air pollution (11). 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. In the diary, the parents could write down if the child had fever. The prevalence of fever over 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 influenza prevalence as measured by the participating family doctors in the sentinel system was a predictor of outcome variables in the Dutch panels (21). 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. One could also argue that previous panel studies (3, 5, 6) were influenced respiratory infections, but then these respiratory infections should have correlated over the whole range of concentrations of air pollution as in these studies a clear dose response relationship could already be seen by simply tabulating respiratory symptom prevalence or peak flow levels by ordered categories of air pollution exposure.

Information bias

Comparing manually recorded PEF readings to electronically recorded PEF readings in a panel of asthmatic children in the US has shown that manual records may overestimate the actual use. The difference between actual use and manually recorded use increased over time (22). Although large differences may exist between socio-economic status and other characteristics of the USA panel and the PEACE panels, the actual use might also be overestimated in the PEACE study. By checking the individual PEF measurements on long periods with no variation and on extremely high values we tried to identify subjects which 'invented' PEF values. These checks did not detect invented values which 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 if the proportion of invented values is very high. Invented values in symptom diary data are more difficult to detect and it is also not unlikely that these were present in the analysed data. In these type of data 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 these 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 from 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 and 1994.

The validity of parental reporting of symptoms in children might be another explanation for the lack of effect in the PEACE study. A study evaluating this issue by comparing parental reports with reported symptoms by children showed that the latter were more prevalent but did not agree well with parental reports. The similar association with pulmonary function did not suggest that any of the two was superior to the other (23). In addition, previous panel studies which showed an effect of air pollution on respiratory health (3, 5, 6) also used parental symptom reporting which indicates that this method is able to measure effects of air pollution on respiratory health.

Exposure assessment

To estimate the exposure of the panels to air pollution fixed air pollution measurement sites were used. One might wonder if this represents well enough the personal exposure of the subjects who spent most of the time indoors. If the misclassification is nondifferential, theoretically this misclassification of exposure would lead to a bias which would drive the association between health endpoints and air pollution towards the null. Older personal exposures studies showed that the correlation between personal and ambient levels of respirable particles was low (24). Most of the older personal exposure studies used cross-sectional data: personal exposure of different subsets of subjects were measured on different days. Thus, only one or very few measurement per person were available. A correlation coefficient was then calculated using all measurements from all subjects on all days. This correlation is influenced by the cross sectional variation in personal exposure to tobacco smoke and other indoor sources. As panel studies relate day to day variations in outdoor concentrations to day to day variations in respiratory health, the correlation between personal and ambient concentrations within a person over time is more relevant than the variation between people (25). In recent years several studies were published which estimated the relationship over time between personal exposure

Table 1. Odds Ratios (OR) wit 95% confidence intervals for the association between air pollution and prevalence of lower respiratory symptoms and bronchodilator use in Dutch urban locations. OR's for an increase of 100 μg/m³ PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2.

	Lower respiratory symptoms		Bronchodilator use	
	PEACE winter	three winters combined*	PEACE winter	three winters combined*
PM_{10}				
lag0	1.22 (0.83, 1.79)	1.34 (1.02, 1.75)	1.33 (0.85, 2.08)	1.28 (0.99, 1.67)
lag1	1.29 (0.89, 1.91)	1.53 (1.18, 1.98)	0.75 (0.47, 1.20)	1.16 (0.89, 1.51)
lag2	1.24 (0.88, 1.76)	1.36 (1.06, 1.74)	1.07 (0.71, 1.61)	1.28 (0.99, 1.65)
7 day mean	1.18 (0.74, 1.91)	1.67 (1.14, 2.44)	1.38 (0.89, 2.14)	2.18 (1.38, 3.43)
Black Smoke				
lag0	1.22 (0.88, 1.69)	1.17 (0.89, 1.54)	1.01 (0.71, 1.45)	1.41 (1.12, 1.78)
lag1	0.81 (0.57, 1.15)	1.17 (0.91, 1.49)	0.81 (0.55, 1.19)	1.15 (0.92, 1.45)
lag2	1.35 (0.98, 1.84)	1.29 (1.04, 1.61)	1.40 (0.99, 1.97)	1.36 (1.09, 1.69)
7 day mean	1.24 (0.81, 1.89)	1.64 (1.14, 2.36)	1.35 (0.91, 2.06)	1.82 (1.19, 2.80)
SO_2				
lag0	1.13 (0.73, 1.76)	1.35 (1.01, 1.80)	1.37 (0.81, 2.32)	0.92 (0.72, 1.18)
lag1	0.95 (0.62, 1.47)	1.23 (0.93, 1.64)	1.09 (0.65, 1.84)	1.45 (1.13, 1.86)
lag2	1.11 (0.74, 1.67)	1.18 (0.91, 1.53)	0.99 (0.61, 1.62)	1.02 (0.80, 1.29)
7 day mean	1.20 (0.67, 2.13)	1.56 (0.97, 2.51)	1.36 (0.78, 2.34)	1.16 (0.69, 1.95)
NO_2				
lag0	1.06 (0.83, 1.36)	1.12 (0.92, 1.36)	0.86 (0.65, 1.13)	1.16 (0.98, 1.38)
lag1	0.90 (0.71, 1.14)	0.91 (0.76, 1.09)	1.22 (0.92, 1.62)	1.24 (1.06, 1.44)
lag2	0.96 (0.75, 1.32)	1.11 (0.93, 1.32)	1.44 (1.09, 1.90)	1.14 (0.98, 1.33)
7 day mean	1.15 (0.59, 2.54)	1.05 (0.70, 1.57)	2.13 (0.91, 4.97)	1.37 (0.95, 1.98)

* winters of 92/93, 93/94 (PEACE study) and 94/95.

and outdoor concentrations of particles. A recent study performed by Janssen (25) in a group of Dutch schoolchildren concluded that the correlation in time between data obtained from fixed site monitors and from personal exposure measurements was reasonably high for PM_{10}. This was also the case in a group of non-smoking adults (26). These results were confirmed by a review by Wallace (27) which included new analyses of personal exposure data from earlier studies. Thus, these results support the use of outdoor measurements as a measure of exposure in panel studies.

Observation period and dependency

Combination of the results of three panel studies conducted in urban areas in the Netherlands in three consecutive winters resulted in associations between air pollution and respiratory health that were generally in the expected direction of more air pollution leading to worse respiratory health (28). As an illustration associations between symptom prevalence and air pollution in Amsterdam urban location (29) and results from the three winters are presented in table 1. Generally, the effect estimate of the three winters combined are stronger. This difference might be caused several factors. First, the effect estimates of the PEACE winter in Amsterdam were sensitive to the timing of smog episodes during the measurement period. In the PEACE winter an air pollution episode occurred in Amsterdam during the first weeks of the measurement period of the PEACE study. When the preceding weeks were included in the analysis allowing for a better separation of time trend and air pollution effects, the effect estimates of air pollution on respiratory health became stronger. These results have been included in the combined estimate for the three winters. Secondly, the results from the three winters were adjusted for influenza prevalence from the family doctor sentinel system, which gave stronger effect estimates than without adjustment. Finally, three independent winters were available making confounding by unmeasured factors less likely.

The results from the separate PEACE panels were not completely independent. In chapter 3 we showed that the particle measurements in the western and central European locations were correlated with each other. In the winter of 1993-1994 an influenza epidemic occurred in Europe (30) which possibly influenced the occurrence of respiratory symptoms in the panels. Thus, this epidemic may have reduced the independence of the panels is even more, together with a possible bias in all panel specific effect estimates. Concluding, the selection of the period to be analysed is important and instead of performing in one winter several panel studies in various locations it might be better to perform several panel studies in various winters, to reduce dependency between panels. In addition, as respiratory infections are much more common in the winter than in the summer, we suggest that panel studies in summer may be less susceptible to distortion of the air pollution effect estimates through lack of control for respiratory infections in the data analysis. In winter studies, longer observation periods might be needed to reduce and to able to better adjust for the effect of unmeasured confounders such as influenza epidemics. Further, development and application of more sensitive methods to account for respiratory infections in panel studies is called for.

Conclusions

No clear relation could be established between changes in PM_{10}, Black Smoke, SO_2, NO_2 and changes in respiratory health. This lack of response is not in agreement with earlier studies with comparable levels of exposure to particulate matter. Concentrations of iron and silicon in PM_{10} were associated with prevalence of phlegm and were a better predictor of health effects than PM_{10} mass concentrations.

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Summary

This thesis describes the 'Pollution Effects on Asthmatic children in Europe' (PEACE) study. **Chapter 1** describes the background and objectives of the PEACE study. In recent years several studies showed effects of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) on the respiratory health of children, sometimes even below the 1987 WHO guidelines. These results raised questions about the possible acute health effects of current air pollution levels in Europe. The composition of the air pollution mixture had changed over the last decades. Further, in West as well as in Central-East Europe there was limited or no comparable data available on PM_{10} levels in urbanised and non-urbanised locations, and the possible association of PM_{10} concentrations with respiratory health. Thus, the goals of this thesis are to obtain comparable data on particle concentrations during winter time in various urban and non-urban 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, to evaluate if medical characteristics of the subjects are related to differences in response to air pollution and to evaluate if the elemental composition of the particles is related to the response to air pollution.

In **chapter 2** the design and protocol of the PEACE study are described. The PEACE study is a study of the acute health effects of short term changes in ambient air pollution on children with chronic respiratory symptoms. The study was conducted in the winter of 1993-1994 following a standardised protocol by 14 research centres in Europe. Two panels of at least 75 children each were followed during at least two months. Children of primary school age, 6-12 years old, who had experienced chronic respiratory symptoms in the year preceding the study or had ever been told by a doctor that they had asthma, were selected. 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. Exposure to air pollution was monitored on a daily basis. Health status was monitored by daily PEF measurements and a symptom diary. Subjects were characterised by questionnaire, skin prick testing and pulmonary function testing using forced expiratory manoeuvres. Daily prevalence and incidence of symptoms and medication use were calculated from the diaries and analysed using logistic regression with correction for autocorrelation. PEF was analysed using linear regression with correction for autocorrelation. Independent variables were 24 hour average concentrations of PM_{10}, Black Smoke, SO_2 and NO_2. As confounders temperature, time trend and weekend/holidays were taken into account.

Chapter 3 describes the PM_{10} and Black Smoke concentrations measured during the PEACE study. The difference of particle concentrations across countries appeared to be considerably larger than the difference between the urban and rural location within countries. The median PM_{10} concentration ranged from 11 $\mu g/m^3$ at three rural Scandinavian sites to 92 $\mu g/m^3$ in Athens, Greece. The median BS concentration ranged from 3 $\mu g/m^3$ in Umeå, Sweden to 99 $\mu g/m^3$ in Athens, Greece. The lowest particle concentrations were found at the eight Scandinavian locations. PM_{10} and BS concentrations in the urban area were on average 22% and 43% higher than the corresponding rural area concentrations respectively. The correlation between the particle concentration measured at the urban and the more rural site exceeded 0.70 at almost all sites. PM_{10} concentrations from all Western and Central European locations were significantly correlated. No or a low correlation was found between these locations and the South-European and Scandinavian locations. PM_{10} and BS measured at the same site were highly correlated at most sites. However, the median PM_{10}/BS ratio ranged from 0.67 to 3.67 across sites. There was a tendency of lower PM_{10}/BS ratios in the urban area, consistent with the contribution of (diesel) motor vehicle emissions.

Combined effect estimates of air pollution on Peak Expiratory Flow (PEF) were calculated from the panel specific effect estimates in **chapter 4**. Fixed effects models were used and in case of heterogeneity, random effect models. No clear associations between PM_{10}, BS, SO_2 or NO_2 and morning or evening PEF could be detected. Only PM_{10} lag1 was negatively associated with evening PEF, but only in locations where BS was high compared to PM_{10} concentrations. There were no consistent differences in effect estimates between subgroups based on urban vs. suburban, geographical location or mean levels of PM_{10}, BS, SO_2 and NO_2.

In **chapter 5** combined effect estimates of air pollution on respiratory symptom prevalence and medication use were calculated. Fixed effects models were used and in case of heterogeneity, random effect models. No clear associations between PM_{10}, BS, SO_2, NO_2 and symptom prevalence or medication use could be detected. There were no consistent differences in effect estimates between subgroups based on urban vs. suburban, geographical location or mean levels of PM_{10}, BS, SO_2 and NO_2 or ratio of mean PM_{10} and BS concentration.

In **chapter 6** is evaluated whether potentially more sensitive subgroups in the panels did show air pollution effects. Effect estimates of air pollution on Peak Expiratory Flow (PEF) and respiratory symptoms were calculated in subgroups based on presence of 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 only on cough and not using respiratory medication. Among asthmatics not using medication, no consistent association was seen. The association between daily symptom prevalence and air pollution levels was not different between these subgroups. We concluded that none of the predefined potentially more sensitive subgroups showed a consistent association between air pollution, PEF and respiratory symptoms

The relationship between soluble elemental concentrations in PM_{10} and acute respiratory health effects is explored in **chapter 7**. Median concentrations of iron ranged from 105 to 1110 ng/m^3 in the urban and from 32 to 517 ng/m^3 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. In two pollutant models PM_{10} 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 separated.

In **chapter 8** the main findings of the PEACE study are summarised and discussed. No clear association between changes in PM_{10} mass concentration, BS, SO_2 and NO_2 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 previous panel studies conducted in the USA and Europe, using similar methodologies, at levels of PM_{10} that were comparable to those in at least some of the areas studied in the PEACE study. Several possible explanations are discussed. It can be that other components which were not measured are a better predictor of health effects than PM_{10} and that if these were measured these would have been related to respiratory health. This is unlikely for $PM_{2.5}$ and aerosol acidity and we were unable to evaluate this for the number of ultrafine particles. Lack of statistical power, information bias, inadequate exposure assessment or incorrect time trend correction are also ruled out as possible explanation. Respiratory infections may have biased the effect estimates and the relative short study period may have complicated the separation of air pollution effects from the effects of unexpected events which also influence the respiratory health.

Concluding, no clear relation could be established between changes in PM_{10}, Black Smoke, SO_2, NO_2 and changes in respiratory health. Concentrations of iron and silicon in PM_{10} were associated with prevalence of phlegm and were a better predictor of health effects than PM_{10} mass concentrations.

Samenvatting

Dit proefschrift beschrijft de 'Pollution Effects on Asthmatic Children in Europe' (PEACE) studie. In **Hoofdstuk 1** worden de aanleiding en doelstellingen van de PEACE studie beschreven. In de laatste jaren zijn er een aantal studies gepubliceerd die een samenhang aantoonden tussen stofdeeltjes in de buitenlucht met een aërodynamische diameter kleiner dan 10 μm (PM_{10}) en de respiratoire gezondheid van kinderen. Deze relaties konden soms zelfs worden aangetoond bij PM_{10} concentraties beneden de richtlijnen van de Wereld Gezondheid Organisatie uit 1987. Deze resultaten riepen vragen op over mogelijke acute effecten op de gezondheid van de huidige luchtverontreiniging niveaus in Europa. In de afgelopen tientallen jaren is de samenstelling van de luchtverontreiniging veranderd. Daarbij kwam dat er zowel in West als in Centraal-Oost Europa weinig tot geen vergelijkbare gegevens over de PM_{10} niveaus in stedelijke en niet-stedelijke gebieden aanwezig waren. Hierdoor waren er ook geen gegevens over de mogelijke relatie van PM_{10} niveaus met acute effecten op de gezondheid. De doelstellingen van dit proefschrift zijn dan ook het verkrijgen van vergelijkbare gegevens over de concentratie van stofdeeltjes tijdens de winter in verscheidene stedelijke en niet stedelijke locaties in Europa, het beschrijven van de relatie tussen korte termijn veranderingen in luchtverontreiniging en korte termijn veranderingen in de respiratoire gezondheid van kinderen met chronische respiratoire symptomen, het evalueren van mogelijke verschillen in reacties op luchtverontreiniging tussen groepen deelnemers met verschillende medische karakteristieken en het beschrijven van de relatie tussen de elementaire samenstelling van de stofdeeltjes en de respiratoire gezondheid van de deelnemers.

In **hoofdstuk 2** worden het design en het protocol van de PEACE studie beschreven. De PEACE studie is een studie naar de acute gezondheidseffecten van korte termijn veranderingen in luchtverontreiniging bij kinderen met chronische respiratoire symptomen. De studie is uitgevoerd in de winter van 1993-1994 volgens een gestandaardiseerd protocol in 14 onderzoekscentra in Europa. Twee panels van minimaal 75 kinderen zijn gedurende minimaal 2 maanden gevolgd. Kinderen van 6 tot 12 jaar die chronische respiratoire symptomen hadden gerapporteerd in het jaar voorafgaand aan de studie of ooit door een arts als astmatisch waren gediagnostiseerd werden geselecteerd. Eén panel werd geselecteerd uit een stedelijk gebied, het andere panel woonde in een gebied waar gedacht werd dat de luchtverontreiniging concentraties lager zouden zijn. Expositie aan luchtverontreiniging werd dagelijks gemeten. De gezondheidstoestand werd gemeten door dagelijkse PEF metingen (de maximale snelheid waarmee lucht in de longen wordt uitgeblazen) en een symptoom dagboekje. De deelnemers werden gekarakteriseerd door een vragenlijst, huidprik test en longfunctie metingen. Dagelijkse prevalentie en incidentie van luchtweg symptomen en medicijngebruik werden berekend uit de data van de dagboekjes en geanalyseerd met behulp van logistische regressie, met correctie voor autocorrelatie. PEF werd geanalyseerd met behulp van lineaire regressie, gecorrigeerd voor autocorrelatie. De onafhankelijke variabelen waren de 24-uurs gemiddelden van PM_{10}, Zwarte Rook (een maat voor de aanwezigheid van zwarte stofdeeltjes in de lucht), SO_2 (zwavel dioxide) and NO_2 (stikstof dioxide). In deze analyses is gecorrigeerd voor temperatuur, tijdstrend en weekend of vakantie dagen.

Hoofdstuk 3 beschrijft de PM_{10} en Zwarte Rook concentraties zoals die gemeten zijn tijdens de PEACE studie. Het verschil in deeltjes concentraties tussen de landen was groter dan het verschil tussen de stedelijke en niet-stedelijke locaties in de landen. De mediane PM_{10} liep van 11 $\mu g/m^3$ in drie niet-stedelijke Scandinavische locaties tot 92 $\mu g/m^3$ in Athene, Griekenland. De mediane Zwarte Rook concentratie bedroeg 3 $\mu g/m^3$ in Umeå, Zweden tot 99 $\mu g/m^3$ in Athene, Griekenland. De laagste deeltjes concentraties werden in de acht Scandinavische locaties gevonden. PM_{10} en Zwarte Rook concentraties in de stedelijke gebieden waren gemiddeld 22% en 43% hoger dan in het bijbehorende niet-stedelijke gebied. De correlatie tussen de deeltjesconcentraties in de stedelijke en niet-stedelijke gebieden was meer dan 0.70 in bijna alle lokaties. PM_{10} concentraties waren in alle West en Centraal Europese locaties significant met elkaar gecorreleerd. Geen of een lage correlaties was er tussen deze lokaties en de Zuid Europese en Scandinavische lokaties. PM_{10} en Zwarte Rook concentraties die op dezelfde lokatie waren gemeten waren meestal hoog gecorreleerd. Toch varieerde de mediane PM_{10}/Zwarte Rook ratio van 0.67 tot 3.67 over de lokaties. De stedelijke gebieden hadden meestal een lagere PM_{10}/Zwarte Rook ratio dan de niet-stedelijke, wat overeenkomt met de bijdrage van de emissie van (diesel) motorvoertuigen.

Gecombineerde effect schattingen van luchtverontreiniging op PEF werden berekend met de panel specifieke effect schattingen in **hoofdstuk 4.** Hiervoor werden fixed effecten modellen gebruikt en in geval van heterogeniteit, random effect modellen. Er werden geen duidelijke associaties gevonden tussen PM_{10}, Zwarte Rook, SO_2 of NO_2 en ochtend of avond PEF. Alleen PM_{10} lag1 was negatief geassocieerd met avond PEF, maar alleen in die locaties waar Zwarte Rook hoog was in vergelijking met PM_{10} concentraties. Er waren geen consistente verschillen tussen de effect schattingen van de subgroepen gebaseerd op de indeling in stedelijk *versus* niet-stedelijk, geografische locatie of gemiddeld niveau van PM_{10}, Zwarte Rook, SO_2 en NO_2. In **hoofdstuk 5** zijn gecombineerde effekt schattingen berekend van luchtverontreiniging op de prevalentie van respiratoire symptomen en medicijngebruik volgens dezelfde methodiek als in hoofdstuk 4. Er werd geen duidelijke relatie gevonden tussen PM_{10}, Zwarte Rook, SO_2, NO_2 en de prevalentie van symptomen of medicijngebruik. Er was geen consistent verschil tussen de effect schattingen van de subgroepen gebaseerd op stedelijk versus niet-stedelijk, geografische locatie of gemiddeld niveau van PM_{10}, Zwarte Rook, SO_2 en NO_2 of de ratio van gemiddeld PM_{10} en Zwarte Rook.

In **hoofdstuk 6** is geëvalueerd of mogelijk gevoeligere subgroepen in de panels effecten van luchtverontreiniging ondervonden. Hiertoe zijn subgroepen geformeerd op basis van atopie, geslacht, basis longfunctie, de aanwezigheid van chronische luchtweg symptomen of het gebruik van luchtweg medicijnen en in de subgroepen zijn effect schattingen van luchtverontreiniging op PEF en luchtweg symptomen berekend. De associatie tussen PEF en luchtverontreiniging was positief bij astmatische kinderen die luchtweg medicijnen gebruikte terwijl deze associatie meestal negatief was bij kinderen die alleen waren geselecteerd op hoesten en geen luchtwegmedicijnen gebruikte. Bij de astmatici die geen luchtwegmedicijnen gebruikte was er geen consistente associatie. De associatie tussen symptoom prevalentie en luchtverontreiniging niveaus verschilde niet tussen de subgroepen. De conclusie hieruit is dat geen van de vooraf gedefinieerde mogelijk gevoeligere subgroepen een consistente samenhang vertoonde tussen luchtverontreiniging, PEF en luchtweg symptomen.

In **hoofdstuk 7** is de relatie tussen de concentraties van oplosbare elementen in PM_{10} en acute effecten op de respiratoire gezondheid beschreven. Mediane concentraties van ijzer varieerde van 105 tot 1110 ng/m^3 in de stedelijke en van 32 tot 517 ng/m^3 in de niet-stedelijke locaties. Dagelijkse concentraties van de meeste elementen hingen niet samen met de dagelijkse variatie in PEF of de prevalentie van luchtweg symptomen of bronchodilator gebruik. Silicium en ijzer concentraties neigden negatief samen te hangen met PEF en hingen positief samen met de prevalentie van slijm opgeven. In statistische modellen met daarin tegelijkertijd twee luchtverontreinigingscomponenten werden de effect schattingen van PM_{10} op slijm gereduceerd en verloren hun significantie terwijl de effect schattingen van ijzer of silicium in essentie niet veranderden.

In **hoofdstuk 8** worden de belangrijkste bevindingen van de PEACE studie samengevat en bediscussieerd. Er was geen duidelijke samenhang tussen veranderingen in PM_{10} massa concentratie, Zwarte Rook, SO_2 of NO_2 en veranderingen in PEF, incidentie of prevalentie van luchtweg symptomen in de PEACE studie. Deze resultaten komen niet overeen met resultaten van eerdere panel studies uit de Verenigde Staten en Europa, die gelijksoortige methoden gebruikten bij PM_{10} niveaus die vergelijkbaar waren met de niveaus van een aantal locaties in de PEACE study. Een paar mogelijke verklaringen voor deze discrepantie worden besproken. Het zou kunnen zijn dat andere componenten die niet gemeten zijn een betere samenhang vertonen met effecten op de gezondheid dan PM_{10} en dat als die componenten waren gemeten deze zouden zijn gerelateerd aan de respiratoire gezondheid. Voor $PM_{2.5}$ en zure aerosolen is dit onwaarschijnlijk en voor ultrafijne stofdeeltjes kon dit niet worden nagegaan. Andere mogelijke oorzaken zijn een gebrek aan statische power, informatie bias, inadequate expositie schattingen of onvoldoende correctie voor trends in de tijd, maar ook deze worden onwaarschijnlijk geacht. Respiratoire infecties zouden de effect schattingen kunnen hebben vertekend. De relatief korte meetperiode kan het moeilijk hebben gemaakt om de effecten van luchtverontreiniging te scheiden van de effecten van onverwachte gebeurtenissen die ook de respiratoire gezondheid beïnvloedden.

De conclusie is dat er geen duidelijke samenhang kon worden aangetoond tussen veranderingen in PM_{10}, Zwarte Rook, SO_2, NO_2 en veranderingen in de respiratoire gezondheid van kinderen met chronisch respiratoire symptomen. De concentraties van ijzer en silicium hingen samen met de prevalentie van slijm opgeven en deden dit sterker dan de PM_{10} massa concentratie.

APPENDIX A: DIARY FORM PEACE STUDY

PEAKFLOW AND RESPIRATORY SYMPTOMS

		Monday 1 Feb.	Tuesday 2 Feb.	Wednesday 3 Feb.	Thursday 4 Feb.	Friday 5 Feb.	Saturday 6 Feb.	Sunday 7 Feb.
Fill out in the morning after getting up:	Time:							
PEAKFLOW Measure three times (before taking medication) and write down the outcomes								
Fill out in the evening before going to sleep:	Time:							
PEAKFLOW Measure three times (before taking medication) and write down the outcomes								
RESPIRATORY SYMPTOMS								
Write down in every square if your child has had these symptoms and in which degree	Cough							
0 = absent	Phlegm							
1 = slight	Runny/stuffed nose							
2 = moderate/severe	Woken up with breathing problems							
	Shortness of breath							
	Wheeze							
	Attack(s) of shortness of breath with wheeze							
	Fever							
	Eye irritation							
	Sore throat							
Medication for respiratory symptoms								
Write down the number of inhalations or capsules of the medicines your child has taken	Brand:							
	Brand:							
	Brand:							
Did your child stay home because she/he was feeling ill? (yes or no)								
Was A Doctor Seen Because Of Respiratory Symptoms (yes or no)								
Did anyone smoke inside the home? (yes or no)								
How long has your child been outside? (write down to the nearest hour)								
Has your child been out of town? (yes or no, if yes indicate where else)								

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Curriculum Vitae

Willem Roemer werd op 17 september 1967 geboren in Rosmalen. De middelbare school werd doorlopen aan het Sint Janslyceum in 's-Hertogenbosch waar in 1986 het VWO diploma werd gehaald. In september 1986 begon hij aan de studie Gezondheidswetenschappen aan de Rijksuniversiteit Limburg in Maastricht, waarbinnen de afstudeerrichting Biologische Gezondheidkunde werd gekozen. Tijdens deze studie volgde hij in 1990 een vak milieukunde aan de Universiteit van Utrecht. In 1990-1991 verbleef hij voor een milieu-epidemiologisch afstudeervak naar de acute effecten van luchtverontreiniging bij de vakgroep Humane Epidemiologie en Gezondheidsleer aan de Landbouwuniversiteit Wageningen. In 1991-1992 verrichte hij een milieu epidemiologische stage bij CETESB in Sao Paulo, Brazilië. In september 1992 studeerde hij af aan de Rijksuniversiteit Limburg. Van november 1992 t/m januari 1993 was hij gedetacheerd bij het Rijks Instituut voor Volksgezondheid en Milieu met als taak het analyseren van epidemiologische data. Vanaf februari 1993 tot juni 1998 heeft hij als toegevoegd onderzoeker gewerkt bij de vakgroep Humane Epidemiologie en Gezondheidsleer, later de leerstoelgroep Gezondsheidsleer aan de Landbouwuniversiteit Wageningen. De projecten waaraan hij werkte waren voornamelijk (internationale) projecten over de effecten van buitenlucht verontreiniging zoals PEACE (Pollution effects on Asthmatic Children in Europe), Wintersmog project en CESAR (Central European study on air pollution and respiratory health). Verder heeft hij van juni tot september 1997 een aanstelling gehad bij het European Centre for Environmental Health van de World Health Organization in Bilthoven. Van augustus tot en met november 1998 was hij werkzaam als stafmedewerker bij GG en GD Amsterdam, afdeling Medische Milieukunde.