Acute effects of winter air pollution on respiratory health

Saskia van der Zee

STELLINGEN

1. Het stilleggen van het gemotoriseerde verkeer in Nederlandse steden tijdens episoden van wintersmog is geen zinvolle maatregel om gezondheidseffecten te beperken. *(Dit proefschrift)*

2. De in Nederland gedurende de winter optredende dagelijkse variaties in PM_{10} concentraties gaan bij kinderen gepaard met effecten op de piekstroom die door de WHO (1992) als 'matig'worden geclassificeerd. *(Dit proefschrift)*

3. Ondanks het gebruik van (extra) luchtwegmedicijnen zijn juist kinderen die luchtwegmedicijnen gebruiken gevoelig voor de effecten van fijn stof. *(Dit proefschrift; Peters et al., 1997)*

4. De incidentie van griep en griepachtige aandoeningen in de algemene populatie zoals geregistreerd door de Nederlandse peilstations, kan in panel studies naar acute effecten van luchtverontreiniging worden gebruikt om te corrigeren voor het potentieel verstorende effect van het optreden van respiratoire infecties. *(Dit proefschrift)*

5. Kinderen met chronische luchtwegklachten en allergie lijken een risicogroep te vormen voor wat betreft de negatieve effecten van PM_{10}. *(Dit proefschrift)*

6. De stelling van Hill (1965) dat biologische plausibiliteit in epidemiologische studies geen strikte voorwaarde is voor causaliteit omdat "biological plausibility depends upon the knowledge of the day" is bij uitstek van toepassing op PM_{10}.

7. Uit gezondheidskundig oogpunt is het van belang, dat 'bruin worden' zo snel mogelijk weer uit de mode raakt *(Elwood & Jopson, 1997; Serraino et al., 1998).*

8. De milieuproblemen rond Schiphol komen niet uit de lucht vallen.

9. Als mannen kinderen konden krijgen, zouden de problemen in de Nederlandse kraamzorg een stuk kleiner zijn dan nu het geval is.

10. Het toenemend gebruik van e-mail is een verrijking voor het sociale leven van een AIO.

11. "'t Is op de wereld slecht verdeeld: de ene heeft een lieve poes, de ander heeft een hond" *(Hans Dorrestijn; het complete anti-hondenboek, p. 110).*

Stellingen behorend bij het proefschrift: 'Acute effects of winter air pollution on respiratory health'.
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Acute effects of winter air pollution on respiratory health

Promotoren:	dr. ir. B. Brunekreef Hoogleraar in de Gezondheidsleer, in het bijzonder de relatie tussen milieu, arbeid en gezondheid
	dr. D.S. Postma Hoogleraar Longziekten, Rijksuniversiteit Groningen
Co-promotor:	dr. ir. G. Hoek Toegevoegd onderzoeker leerstoelgroep Gezondheidsleer

Saskia van der Zee

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Voor Peter en Bram

Abstract

In this thesis, acute respiratory health effects of exposure to winter air pollution are investigated in panels of children (7-11 yr) and adults (50-70 yr) with and without chronic respiratory symptoms, living in urban and non-urban areas in the Netherlands. The study was performed during three consecutive winters starting in 1992/1993. Each winter, subjects performed twice daily measurements of Peak Expiratory Flow (PEF) and registered the occurrence of respiratory symptoms and medication use in a diary. Air pollution concentrations were measured daily in both areas.

The contrast in the concentrations of particulate air pollutants (PM_{10}, Black Smoke and sulfate) between urban and non-urban areas was small, but there was more contrast in the concentrations of the gaseous pollutants SO_2 and NO_2.

In symptomatic children from both areas, significant associations were observed between PM_{10}, Black Smoke (BS) and sulfate concentrations and the prevalence of lower respiratory symptoms (LRS) and PEF decrements. Particle concentrations were also associated with bronchodilator use in the urban areas, but not in the non-urban areas. However, differences in use of maintenace medication might be responsible for this. In non-symptomatic children, significant associations were observed between PM_{10} and BS concentration and the prevalence of PEF decrements, but of smaller magnitude than for symptomatic children. No associations with respiratory symptoms were observed.

In symptomatic adults living in urban areas, PM_{10}, BS, sulfate and SO_2 concentrations were associated with the prevalence of decrements in morning PEF, but not in evening PEF. Although especially BS was also associated with upper respiratory symptoms, particle concentrations were not associated with LRS or bronchodilator use. In symptomatic subjects living in non-urban areas, and in non-symptomatic adults from both urban and non-urban areas, no consistent associations between air pollution concentrations and indicators of respiratory health were found.

Separate analyses in children, based on the presence/absence of objective medical characteristics showed that PM_{10} was most consistently associated with respiratory health indicators in symptomatic children who had either high total serum IgE level or a positive skin prick test.

In conclusion, low levels of particulate air pollution were associated with adverse effects on respiratory health in 7-11 yr children, while in 50-70 year old symptomatic adults only a weak effect was found. Although there was a tendency of more consistent particle effects in the urban panels, the differences with the non-urban panels were small and might reflect differences in asthma medication use.

Contents

Chapter 1

General introduction

Background

Severe winter air pollution episodes in the Meuse Valley, Belgium in 1930, in Donora-Webster, Pennsylvania, USA in 1948 and in London, UK in 1952 have left little doubt that high air pollution concentrations can cause severe health effects including mortality[1-3]. Air pollution episodes are caused by stagnant weather conditions that generally persist for some days, and can occur both in summer and in winter. In summer, high concentrations of ozone (O_3) occur due to photochemical reactions of air pollutants emitted by traffic and industry. In classical winter episodes, increased fossil fuel use due to usually cold weather caused high concentrations of sulfur dioxide (SO_2) and particulate matter. In this thesis, acute respiratory health effects of winter type air pollution in the Netherlands are investigated.

In the winters of 1985 and 1987, relatively serious episodes of winter type air pollution hit the Netherlands. The episodes were characterized by elevated levels of SO_2 and particulate matter, to a large extent transported over long distances from Germany and source areas in Eastern Europe. In 1985 as well as in 1987, temporary decreases in lung function in children were observed that were associated with these episodes[4,5]. The same episodes were associated with health effects in Germany[6,7].

In recent years, emissions of SO_2 have decreased in Germany and Eastern Europe, and it was considered unlikely that winter smog episodes of the same magnitude as in 1985 and 1987 would occur again in the near future in the Netherlands. However, at the same time the composition of the air pollution mixture was changing; due to the continuing increase in motorized traffic intensity, the contribution of traffic related compounds became more important. Traffic is an important source of carbon monoxide (CO), nitrogen oxides (NO_x), volatile organic compounds (VOC) and particulate matter, both direct and indirect through the formation of secondary aerosols[8]. Studies from the United States in the early nineties suggested that particulate matter concentrations, expressed as the concentration of particles with a 50% cutoff diameter of 10 μm (PM_{10}), were associated with acute health effects independently of SO_2[9,10].

In February 1991, a high pressure system with easterly winds and subfreezing temperatures occurred for the first time since the winter of 1987 in the Netherlands. SO_2 concentrations increased to only about 100 $\mu g/m^3$ (24 hour average), while PM_{10} concentrations increased to about 170 $\mu g/m^3$. In a panel of

children with chronic respiratory symptoms, Peak Expiratory Flow (PEF) decreases and increases in airway symptom prevalence and the use of medication were observed in this episode[11]. These observations raised the question whether the definition of winter air pollution episodes as episodes with increased levels of both SO_2 and particulate matter is still valid. They also raised the question how large the additional effect is of automobile traffic in large cities during winter air pollution episodes on the levels of the air pollution components that are thought to be of health relevance.

Recent epidemiological studies in the Netherlands investigating acute health effects of winter air pollution episodes have been concentrated on populations living outside the big cities[11-13], as the emphasis was on secondary pollutants and on long range transport of air pollutants. It was not clear to what extent inhabitants of big cities were exposed to higher levels of PM_{10} and other compounds of the complex winter air pollution mixture. Model calculations have suggested that during periods of stagnant weather conditions in winter, even without predominantly easterly winds, guidelines and standards for a number of air pollution components could be exceeded within the largest cities in the Netherlands[14]. Model calculations also suggested that traffic bans in big cities during winter air pollution episodes would result in a considerable decrease in the concentration of suspended particulates and other traffic-related pollutants inside the biggest cities[14]. The Dutch Health Council suggested that not much was known about the toxicity of locally produced air pollutants during periods of winter smog, and that an adequate evaluation of the health benefits potentially associated with traffic bans was not possible[15].

Since the start of the study in 1992, a large number of epidemiological studies have been published documenting effects of relatively low levels of PM_{10} on mortality, morbidity, respiratory symptoms and lung function. Those studies have been summarized in recent reviews[16-19]. They point clearly and consistently to adverse PM_{10} effects at low levels of exposure, and so far it has not been possible to establish a 'safe' PM_{10} concentration, below which no health effects occur.

Goals of the study:

The goals of the study were to:

- assess the exposure of city dwellers to winter air pollution as characterized by the concentrations of fine particulate matter and other components in air
- document effects on health in selected population groups associated with this exposure
- assess the contribution of traffic exhaust to exposure and health effects
- identify subgroups of the population that are especially susceptible to the effects of winter air pollution

Study design

The study was designed as a panel study to detect health effects of short-term variations in air pollution concentrations. During three consecutive winters starting in 1992/1993, subjects living in large urban areas in the Netherlands were followed for at least 3 months. Simultaneously, subjects living in non-urban 'control' communities were studied to assess the contribution of traffic exhaust in the urban area. Children (7-11 yr) and older adults (50-70 yr) with and without chronic respiratory symptoms were selected from the general population with a screening questionnaire. All panel members were examined with skin prick test, determinations of total and specific serum IgE, and bronchial reactivity to metacholine. During the study periods which generally lasted three months, daily measurements of Peak Expiratory Flow (PEF) were made, and the occurrence of respiratory symptoms and medication use was registered in a diary. Air pollution was monitored daily on central sites in each community.
The study was performed during three winters, because weather conditions vary from winter to winter, and previous experience has shown that one cannot rely on observations obtained in just one or two winters[20]. During the winter of 1993/1994, children with chronic respiratory symptoms were investigated in the framework of the multicenter Pollution Effects on Asthmatic Children in Europe (PEACE) study[21].
As study areas were chosen: Rotterdam and Bodegraven/Reeuwijk in the winter of 1992/1993, Amsterdam and Meppel in the winter of 1993/1994 and Amsterdam and Nunspeet in the winter of 1994/1995. Rotterdam and

Amsterdam are the two largest cities in the Netherlands with approximately 600,000 and 720,000 inhabitants, respectively.

Because source areas are located to the east of the Netherlands, air pollution episodes in the Netherlands are generally associated with easterly winds. Thus, non-urban areas were selected to the east of the urban areas in order to limit transport of polluted air from the Dutch urban to the non-urban area during air pollution episodes. During the first winter, the non-urban area was selected close (± 30 km) to the urban area. This was done to ensure comparable levels of exposure to air pollution transported over long distances. During the second and third winters, the non-urban areas were selected at a larger distance from the urban area in trying to maximize the contrast in air pollution, which was found to be small in the first winter. Small towns were selected instead of small villages, because a reasonable number of inhabitants (± 25,000) was necessary to find sufficient subjects that fulfilled the selection criteria. The term 'non-urban' area will be used throughout this thesis, despite the fact that the 'non-urban' areas were in fact small towns.

Exposure to air pollution was characterized by the concentration of PM_{10}, Black Smoke, NO_2, SO_2 and the major ions of fine particles (sulfate, nitrate, ammonium, H^+) in ambient air at fixed sites in each community. During the winter of 1994/1995, $PM_{2.5}$ was measured as well, because of the increased interest in health effects of smaller particles in recent years. In the urban areas, background sites were used to estimate exposure instead of sites that were more influenced by traffic, because background concentrations are more representative for exposure of city dwellers than concentrations that are heavily influenced by local sources. A series of separate studies was conducted to evaluate the association between ambient and personal particle concentrations[22]. In these studies, indoor particle concentrations were measured too in order to evaluate to what extent particles penetrate indoors, where people spend most of their time.

Children between 7-11 years of age were selected because at that age, children are able to participate in all parts of the study, usually do not smoke and can easily be reached in large numbers through the primary school system. Moreover, children may be a sensitive subgroup of the population. Children generally spend more time outside and are more physically active than most adults and thus, inhaled pollutant doses will be comparatively larger.

In addition, older adults between 50-70 years of age were studied. Most time-

series studies investigating acute effects of air pollution on lung function and respiratory symptoms have focused on children. However, studies investigating effects of air pollution on mortality have suggested that the elderly are a susceptible subgroup[23]. To our knowledge, it has never been investigated if older adults are also sensitive to acute effects of air pollution on lung function and respiratory symptoms. An age range of 50-70 yr was selected because we had doubts if older subjects would be able to complete a long study.

Children and adults with and without chronic respiratory symptoms were selected. A number of studies have suggested that children with chronic respiratory symptoms are especially susceptible to the effects of PM_{10}[9-11]. However, those children may modify their response through alterations in medication use, so that functional and/or symptomatic responses are repressed. In children without chronic respiratory symptoms this will not occur as these will not generally be under medication. Morover, comparing effects of air pollution in children with and without chronic respiratory symptoms simultaneously would enable use to investigate if children with chronic respiratory symptoms are indeed more susceptible.

The few panel studies that investigated acute effects of air pollution on lung function and respiratory symptoms in adults have mainly investigated asthma patients[24-28]. It is not clear whether adults with mild chronic respiratory symptoms are also susceptible to acute effects of air pollution on these respiratory health indicators. The reason to study adults without chronic respiratory symptoms was the same as for children with chronic respiratory symptoms.

At the beginning of the study period, all subjects were medically characterized with a metacholine challenge test in order to assess bronchial hyperreactivity (BHR). In addition, atopy was investigated with total serum IgE concentrations and skin prick tests for major inhalant allergens (house dust mite, cat, dog, birch, pollen and fungi). The purpose was to identify objective medical characteristics that were associated with the response to air pollution, in addition to the presence/absence of chronic respiratory symptoms. It has been suggested that exposure to ambient air pollution interacts with exposure to allergens[29,30], which in turns suggests that atopic subjects may be more susceptible to the effects of air pollution. Subjects with BHR react to inhalation of exogenous stimuli (in this case, metacholine) with a significant decline in lung function due to acute constriction of the airways. This might indicate that those

subjects also react stronger to air pollutants. Therefore, it was evaluated whether the response to air pollution was different in subjects characterized not only by the presence/absence of chronic respiratory symptoms but also by the presence/absence of atopy and BHR.

Structure of the thesis

Chapter 2 describes the air pollution concentrations that were measured in the urban and non-urban areas. Chapter 3 presents the results of a separate study in 9-11 yr old children, in which self-recorded PEF measurements were compared with supervised PEF measurements. Chapter 4 evaluates if the incidence of influenza and influenza-like-illness in the general population can be used to adjust for the potential confounding effect of respiratory infections in the analysis of panel studies. The chapters 5 and 6 describe the association between short term changes in air pollution and respiratory health indicators in children and adults, respectively. Chapter 7 evaluates if the response to air pollution was different in children characterized by not only the presence of chronic respiratory symptoms, but also by objective measurements of atopy and bronchial hyperresponsiveness. In chapter 8, finally, the main results are discussed.

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Chapter 2

Characterization of particulate air pollution in urban and non-urban areas in the Netherlands

Saskia C. van der Zee, Gerard Hoek, Hendrik Harssema and Bert Brunekreef

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Abstract

During the winters of 1992/1993, 1993/1994 and 1994/1995 a monitoring study was performed in three urban and three non-urban areas in the Netherlands.
PM_{10}, Black Smoke (BS), sulfate, nitrate, ammonium (non-organic secondary aerosols, 'NOSA') and aerosol acidity were measured on a daily basis in both the urban and non-urban areas. During the third winter, $PM_{2.5}$ was measured as well. The elemental composition of PM_{10} was analyzed for one third of the filters collected during the winter of 1993/1994 with Inductively Coupled Plasma (ICP). PM_{10} and BS concentrations were on average 13% and 19% higher in the urban area than in the non-urban area. NOSA concentrations were on average 8% lower in the urban area. $PM_{2.5}$ concentrations were similar in the urban and non-urban area. Higher elemental concentrations in PM_{10} were found in the urban area for all elements except Si. The contrast between elemental concentrations in PM_{10} was for most elements larger than for PM_{10} mass concentration.
The small contrast in particle concentrations between urban and non-urban areas in the Netherlands is probably a result of the small size of the country, the high population density, the lack of small scale geographical and meteorological differences, and the importance of long range transport of air pollutants.
Both the absolute concentrations of PM_{10}, BS and NOSA and the urban–non-urban differences depended strongly on wind direction. Easterly winds resulting in an influx of air masses from Central and Eastern Europe were associated with high concentrations and minimal urban- non-urban differences. Winds from the sea resulted in low concentrations but larger relative differences between urban and non-urban areas.

Introduction

In recent years, concern about particulate air pollution has increased. Particulate matter with a 50% cut off diameter of 10 μm (PM_{10}) has been associated in epidemiological studies with increased mortality, morbidity and decreased lung function[1-3]. Industrial activity and motorized traffic play an important role in the formation of particles, both direct and indirect through the formation of secondary aerosols[4]. Thus, particle concentrations are expected to be higher in urban areas compared to non-urban areas. Recently, Hoek *et al.* [5] reported on wintertime concentrations of PM_{10} and Black Smoke in 14 urban and 14 non-urban locations in Europe. Measurements were conducted in the framework of a multicenter epidemiological study of Pollution Effects on Asthmatic Children in Europe (PEACE) during the winter of 1993/1994. Differences in median PM_{10} and Black Smoke concentrations between urban and non-urban locations were relatively small (on average 22% and 43%). Daily PM_{10} concentrations from all Western and Central European locations were significantly correlated. This suggests that the formation and subsequent transport of secondary aerosols plays an important role in determining particle concentrations. However, no data on secondary aerosols or $PM_{2.5}$ were available in the study described by Hoek *et al.* [5].

This paper describes a monitoring study of particulate air pollution that was performed in three urban and three non-urban areas in the Netherlands during the winters of 1992/1993,1993/1994 and 1994/1995. The main purpose of the measurements was characterization of human exposures in the framework of an epidemiological study. This study was funded by the Dutch government and designed to compare acute health effects of episodes of wintertype smog on city dwellers and inhabitants of small towns. Part of the study (1993/1994) was performed in the framework of the PEACE study, but the characterization of particulate air pollution in the Netherlands was more extensive than was already reported by Hoek *et al.* [5]. In addition to measurements of PM_{10} and Black Smoke, daily measurements of non-organic secondary aerosols (sulfate, nitrate and ammonium) and aerosol acidity were conducted during three consecutive winters in both the urban and the non-urban areas. A subset of the PM_{10} filters measured in the winter of 1993/1994 was analyzed for elemental composition. These additional data allow a more detailed analysis of differences in PM_{10} mass concentration between urban and non-urban areas.

$PM_{2.5}$ was measured in the winter of 1994/1995 because of the increased interest in health effects of smaller particles in recent years. In the United States the new air quality standard for particulate matter includes $PM_{2.5}$ limit values[6]. In the

European community, $PM_{2.5}$ monitoring will become obligatory as well. So far, only a few studies[7,8] have reported on $PM_{2.5}$ concentrations in Europe.
The purpose of this paper is (1) to describe particle concentrations and differences between particle concentrations in urban and non-urban areas in the Netherlands and (2) to relate this to wind direction and episodic weather conditions in order to obtain (indirect) information on sources.

Methods

Study description

Table 1 presents a description of locations and study periods. It also shows which compounds were measured and at what frequency. We will use the term 'non-urban' area throughout this paper, despite the fact that the 'non-urban' areas were in fact small towns.

Table 1. Characteristics of sites of the particulate air pollution study in the Netherlands.

Winter	Location	Type	Site no.	Inhabitants*	Study Period	Measured compounds and frequency
92/93	Rotterdam	urban	1	596,023	4/2/93-28/4/93	PM_{10}, BS**, NOSA† (daily)
	Bodegraven/ Reeuwijk	non-urban	2	31,802	4/2/93-28/4/93	PM_{10}, BS (daily); NOSA (3/week; starting 4/3/93)
93/94	Amsterdam	urban	3	719,856	13/11/93-28/2/94	PM_{10}, BS, NOSA (daily); elements (1/3 days)
	Meppel	non-urban	4	24,217	13/11/93-28/2/94	PM_{10}, BS, NOSA (daily); elements (1/3 days)
94/95	Amsterdam	urban	3	719,856	16/11/94-8/3/95	PM_{10}, $PM_{2.5}$, BS, NOSA (daily)
	Nunspeet	non-urban	5	25,716	16/11/94-8/3/95	PM_{10}, BS, NOSA (daily); $PM_{2.5}$ (3/week)

* *number of inhabitants on 1/1/93*
** *Black Smoke*
† *NOSA = non organic secondary aerosols (sulfate, nitrate and ammonium)*

Figure 1 shows the locations of the sites. During the first winter, we selected a non-urban area close (± 30 km) to the urban area. During the second and third winters, we selected the non-urban areas at a larger distance from the urban area in trying to maximize the contrast in air pollution, which was found to be small in the first winter. Small towns were selected instead of small villages, because for the epidemiological purpose of the study, a reasonable number of inhabitants (≥ 25,000) was necessary. Due to meteorological and emission source distribution

25,000) was necessary. Due to meteorological and emission source distribution reasons, air pollution episodes in the Netherlands are generally associated with wind directions from south to east. Thus, non-urban areas were selected to the east of the urban areas in order to limit transport of polluted air from the urban to the non-urban areas during air pollution episodes.

24 Hour measurements were made starting at 3 PM. The measurement sites in the urban areas were city background sites. In the Netherlands, an urban site is considered a background site if in a circle of 35 m around the site less than 2,750 motor vehicles pass during 24 hours[9]. As it was felt that this distance criterion might not be strict enough, 100 m was considered as the distance criterion for this study. In addition, within 100 m of the site no other important emission sources should be present (construction work, small industry).

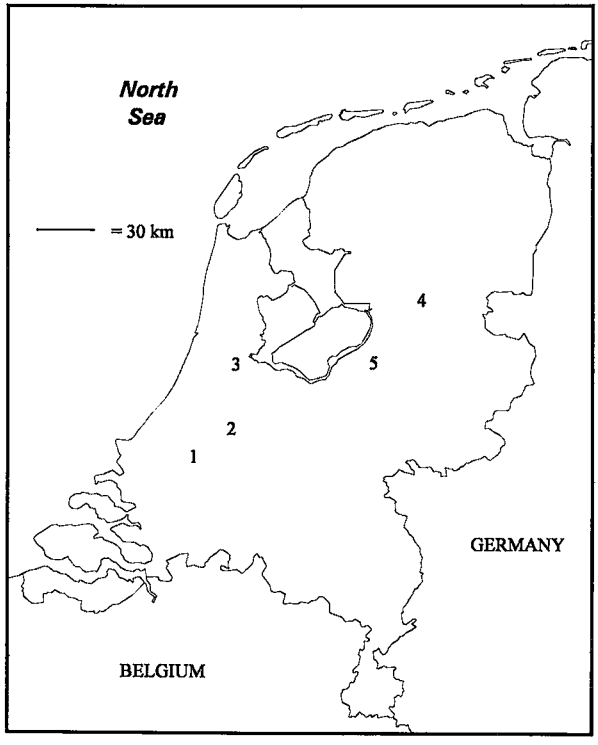

Figure 1. Location of the measurement sites. 1 = Rotterdam (urban area 1992/1993), 2 = Bodegraven/Reeuwijk (non-urban area 1992/1993), 3 = Amsterdam (urban area 1993/1994 and 1994/1995), 4 = Meppel (non-urban area 1993/1994), 5 = Nunspeet (non-urban area 1994/1995).

The measurement sites in the non-urban areas were also selected so that they were not influenced by local air pollution sources.
Sampling height was approximately 1.5 m at all measurement sites, for all compounds, except for Black Smoke that was measured at 3 m.

Sampling methods
Measurements of PM_{10} were made with an instrument described by Liu and Pui[10], equipped with an inlet similar to the Sierra Anderson 241 dichotomous sampler, using Schleicher & Schuell TE37 teflon filters (pore size 1 μm). The inlet was compared to the Sierra Andersen inlet in a series of 33 collocated measurements[11]. The estimated regression equation was 6.0 + 0.90*Sierra-PM_{10} ($r = 0.93$), where Sierra-PM_{10} is the PM_{10} concentration measured with the Sierra Anderson sampler.
$PM_{2.5}$ measurements were made using a Harvard Impactor[12]. The impactor was operated at 10 l/min and manufactured by Air Diagnostics and Engineering Inc. Naple, Maine, USA. Andersen 37 mm teflon filters (pore size 2 μm) were used. Only three $PM_{2.5}$ measurements per week were made in the non-urban area due to limited availability of the equipment.
Both for the PM_{10} and the $PM_{2.5}$ measurements, flows were measured at the beginning and end of each 24-h sampling period with a calibrated rotameter. The exact sampling period was recorded on a timer with a precision of 1 minute.
Before and after exposure filters were weighed on an analytical balance with a reading precision of 10 μg, after conditioning at 20 °C and 44% relative humidity for 24 hours. After collection from the field, exposed filters were stored in a refrigerator at 4 °C before weighing to limit losses of volatile components[5].
Black Smoke sampling was performed using the method of the Organization for Economic Cooperation and Development[13]. The method involves collection of particles on a Whatman 1 paper filter using a low volume sampler. Sampling volumes were determined using calibrated dry gas meters. The reflectance was measured using an EEL 43 reflectometer. During the first and second winters, the reflectance was set to 100 using a stack of five blank Whatman 1 filters. Next, the reflectance was measured on the same stack of five blank filters. During the third winter, the reflectance was measured according to the OECD protocol in which the reflectance of a filter is measured directly on top of a white tile, after setting the reflectometer to 100 with one blank Whatman 1 filter. The reflectance measured during the first two winters was transformed into reflectances measured according to the OECD protocol as described by Hoek *et al.*[14]. The reflectance of exposed filters was transformed into $\mu g/cm^2$ using an equation

describing the Standard Smoke curve[15].

Sampling of nitrate, sulfate, ammonium and aerosol acidity was performed with an annular denuder filter pack system (ADS). The impactor was designed to remove particles with a 50% cut off diameter of 2.1 μm at a flow rate of 10 l/min[16]. At the beginning and end of each 24-h sampling period the inlet flow was measured with a calibrated rotameter. The sampling method and the extraction of the filters for the determination of sulfate, nitrate and ammonium is described in detail by Hoek *et al.*[17]. Ammonium concentration was determined using a modified indophenol method according to NEN 6472[19] and measured spectrophometrically. Sulfate and nitrate were determined by ion chromatography (Dionex DC-100). H^+ was determined by direct pH measurement using the procedures of Koutrakis *et al.*[19].

Information about the ambient concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) were obtained from the nearest measurement sites of the National Air Quality Monitoring Network[9]. Data from city background stations in Rotterdam and Amsterdam were used for the urban areas. Data for the non-urban areas were obtained from Zegveld, Witteveen and Lelystad, located approximately 10, 40 and 30 km away from the non-urban areas in the three consecutive winters. SO_2 and NO_2 were measured by continuous monitors based on fluorescence and chemiluminescence respectively[9].

The elemental composition of PM_{10} was determined for one third of the filters during the winter of 1993/1994. We were not able to analyze all filters for budgetary reasons. The filters were selected so that every third day was analyzed, and that the same days were analyzed for the urban and the non-urban area. Analyses with ICP (Inductively Coupled Plasma) were conducted by the Department of Soil Science and Plant Nutrition of Wageningen University.

The PM_{10} filters were extracted with a strong (4.5 N HF + 1 N HCl) acid solution, providing total element concentrations. However, this "hard extraction" was preceded by a weak extraction (1:100 dilution of the strong acid solution). With the "weak" extraction, only easily soluble ("leachable") elements are extracted. This was thought to be a better indicator of the biologically available fraction than the total element concentration. Therefore we have focussed on the "leachable" concentrations. Detailed information on the extraction method, and the subsequent analysis and calculation of the elemental composition is described by Janssen *et al.*[7]. The following 7 elements were analyzed: V, Na, Si, K, Fe, Mn and Cu. These elements were selected because they can be considered as tracers for specific sources.

Meteorology

Meteorological data for the urban areas were obtained from Rotterdam and Amsterdam Airports, respectively. Data for the non-urban areas were obtained from Zegveld, Eelde and Lelystad, located approximately 10, 50 and 30 km away from the non-urban areas in the three consecutive winters. Data were measured in 1-hour intervals and transformed into 24-h mean values (wind velocity) or 24-h minimum values (temperature), from 3 pm to 3 pm. For wind direction, 24-h mean wind direction was calculated. If necessary, hourly wind directions were transformed (wd = wd + 360° or wd = wd-360°) to avoid problems in calculating the mean of directions ranging from 0° to 360°. Next, we calculated how many hours the wind came from a direction of less than 45° from the mean wind direction. If this was the case during more than 12 hours, the daily mean wind direction was classified as: ENE (30-90°), ESE (90-150°), S (150-210°), WSW (210-270°), WNW (270-330°) and N (330-30°). If not, the wind direction was classified as 'Variable'.

Data analysis

Since most concentrations were not normally distributed, median concentrations are presented instead of mean concentrations. In addition to the maximum concentration the 90-th percentile is presented, as a more stable characterization of typical high values. To allow direct comparison between the urban and the non-urban area studied during one winter, only days with valid observations in both locations have been included. The ratio between urban and non-urban concentration was calculated for each day. Next, the median ratio was calculated. In order to assess the statistical significance of the percentage difference between urban and non-urban concentrations, we tested whether the ratios were significantly different from unity using Wilcoxon's signed rank test (after substracting 1 from the ratios). The sum of the sulfate, nitrate and ammonium concentration was calculated and reported as non-organic secondary aerosol ('NOSA').

The concentrations measured during the three winters were combined in order to calculate overall concentrations and median ratios between urban and non-urban concentrations. Spearman rank correlation coefficients were calculated to describe the relationship between concentrations measured in the urban and in the non-urban area.

In order to obtain information about the sources of particulate air pollution, median concentrations were calculated for different wind directions. Also, the differences in concentrations between urban and non-urban areas were investigated by

calculating the median ratios for the various wind directions. To allow direct comparison only days with the same wind direction in the urban and non-urban area were included. The concentrations measured during the three winters were combined in order to obtain more data. For PM_{10}, BS and the gaseous precursor pollutants SO_2 and NO_2 enough days of observation were available to calculate median concentrations for all 7 wind directions described in the meteorology section. For NOSA, for which fewer days of measurements were available, the wind directions north and west-north-west, and east-north-east and east-south-east were combined in order to obtain enough days of observation.

For the elements, with concentrations available for only 33 days, south and west-south-west were combined as well. Thus we only have information on the combined wind directions 'ENE + ESE' and 'S + WSW'.

Results

Data quality

During each winter, between 5 and 15 field blanks and field duplicates were taken for PM_{10}, Black Smoke, and ADS compounds. For $PM_{2.5}$, which was only measured during the third winter, 19 field blanks and 13 field duplicates were taken.

Table 2. Detection limits and precision of particle and elemental measurements.

	DL* ($\mu g/m^3$)	n**	RSD†	n**
PM_{10}	12.0	34	8.7	32
$PM_{2.5}$	7.7	19	9.7	13
Black Smoke	1.2	41	7.9	34
Sulfate	0.07	34	8.6	25
Nitrate	0.11	34	10.3	24
Ammonium	0.08	34	6.1	25
$H^{+‡}$	0.10	10	-	-
Weak extraction	DL* (ng/m^3)	n**	RSD†	n**
V	1.6	6	10.9	3
Na	15.0	6	5.0	3
Si	21.9	6	30.2	3
K	29.4	6	9.3	3
Mn	1.4	6	25.0	3
Fe	17.8	6	14.3	3
Cu	2.6	6	26.0	3
Strong extraction	DL* (ng/m^3)	n**	RSD†	n**
V	0.5	6	12.9	3
Na	8.5	6	6.7	3
Si	75.7	6	34.1	3
K	20.0	6	12.0	3
Mn	1.3	6	24.9	3
Fe	28.3	6	26.8	2
Cu	0.7	6	25.6	3

* *detection limit, calculated as three times the standard deviation of field blanks.*
** *number of field blanks or field duplicates taken during the three winters*
† *relative standard deviation (coefficient of variation) calculated as the mean percentage difference between duplicate samples divided by the square root of 2*
‡ *expressed as H_2SO_4*

Detection limits and repeatability, expressed as coefficient of variation (CV) are presented in table 2. Detection limits of "leachable" and total elements are shown as well. Detection limits were derived from the study reported by Janssen *et al.*[4] who used exactly the same method and PM_{10} samplers to analyze PM_{10} filters that had been sampled for 8 hours. Thus, the detection limits reported by Janssen *et al.*[4] were divided by three. For more information regarding the quality control of the ICP analyses we refer to Janssen *et al.*[4].

The ion balance between cations and anions on the teflon filters was calculated to determine the reliability of the sulfate, nitrate, ammonium and H^+ measurements. If the ion balance was below 0.5 or above 2.0, sulfate, nitrate, ammonium and H^+ data were excluded. However, this criterion was only applied when NOSA concentrations were sufficiently high. The rationale for this was that at low NOSA concentrations, other ions may be more important. We arbitrarily determined 'sufficiently high' as >3 $\mu g/m^3$ for sulfate and >2 $\mu g/m^3$ for nitrate and ammonium. No lower limit was set for H^+ since this contributes little to the ion balance. The ion balance criterion resulted in the exclusion of a small percentage ($<3\%$) of the data. The median ion balance calculated over the three winters was 0.91.

Particle concentrations

Table 3 gives a summary of the concentrations measured during the three winters in urban and non-urban areas. It shows that the PM_{10} concentration was respectively 17%, 4% and 20% higher in the urban area than in the non-urban area during the three consecutive winters. The percentage difference in Black Smoke concentration was 37%, 12% and 11%. When the three winters were combined, the percentage differences were 13% and 19% for PM_{10} and Black Smoke, respectively.

The median concentrations of sulfate, nitrate and ammonium during the second and third winter were slightly lower in the urban area than in the non-urban area. During the first winter, only 18 days with valid NOSA concentrations for both areas were available. Calculated over the three winters, respectively 7%, 8% and 10% lower sulfate, nitrate and ammonium concentrations were measured in the urban area than in the non-urban area.

Table 3. Air pollution concentrations (24 h average) during the three winters in urban and non-urban areas(concentrations in µg/m³) and median of the daily ratio between concentration in urban and non-urban areas

	Urban, 92/93				Non-urban, 92/93			Ratio $C_{urban}/C_{non\text{-}urban}$
	N	Median	90-p	Max	Median	90-p	Max	Median†
PM_{10}	74	47	90	143	36	79	104	1.17**
Black Smoke	72	15	29	56	10	28	38	1.37**
SO_2	98	23	45	152	9	21	43	2.31**
NO_2	93	52	79	94	33	60	83.2	1.55**
sulfate	18	7.0	13.2	13.3	5.7	10.7	12.5	1.17*
nitrate	18	6.0	13.2	17.0	6.8	13.2	14.5	1.05
ammonium	18	3.8	6.3	7.1	3.8	5.9	6.2	1.11
NOSA	18	16.7	30.8	35.7	16.4	28.4	29.7	1.13
$H^{+‡}$	17	0.14	0.42	0.53	0.05	0.24	0.34	-§
	Urban, 93/94				Non-urban, 93/94			Ratio $C_{urban}/C_{non\text{-}urban}$
PM_{10}	99	36	87	123	33	100	242	1.04*
Black Smoke	105	12	32	65	10	36	58	1.12**
SO_2	118	10	25	34	5	23	42	1.80**
NO_2	117	47	61	76	24.1	46.2	54	1.82**
sulfate	76	2.6	12.1	23.6	2.8	14.2	22.8	0.89**
nitrate	76	2.2	10.8	23.9	2.9	12.0	24.1	0.84**
ammonium	53	1.4	6.4	8.6	1.7	6.8	8.9	0.84**
NOSA	53	5.8	26.1	48.5	7.2	30.2	52.8	0.84**
H^+	76	0.07	0.47	1.72	0.07	0.63	1.68	-
	Urban, 94/95				Non-urban, 94/95			Ratio $C_{urban}/C_{non\text{-}urban}$
PM_{10}	111	29	51	90	24	44	97	1.20**
$PM_{2.5}$	44	14	38	58	15	34	68	1.01
Black Smoke	101	6.9	19.4	36.1	5.8	22	43	1.11**
SO_2	112	6.1	14.8	24.4	3.7	7.3	17.0	1.73**
NO_2	111	45	65	82	21	41	57	2.06**
sulfate	81	1.6	5.5	9.5	1.9	5.6	17.7	0.93*
nitrate	78	1.4	5.0	13.5	1.9	5.6	15.1	0.94
ammonium	78	1.1	3.5	7.4	1.3	3.7	6.6	0.88**
NOSA	78	4.6	13.7	30.4	5.2	14.4	39	0.93*
H^+	81	0	0.23	1.22	0.02	0.20	0.63	-

† *median of the daily ratios $C_{urban}/C_{non\text{-}urban}$ is not always equivalent to the ratio of the median concentrations*

‡ *expressed as H_2SO_4*

§ *no median ratio $C_{urban}/C_{non\text{-}urban}$ was calculated due to the large number of very low concentrations*

* *significantly different from 1, $p<0.05$ (Wilcoxon signed rank test)*

** *significantly different from 1, $p<0.01$ (Wilcoxon signed rank test)*

$PM_{2.5}$ concentrations were only measured during the third winter and were similar in urban and non-urban area. The H^+ concentrations were very low during the three winters. Only a few concentrations were above the detection limit and therefore, H^+ concentrations were not used in further analyses. SO_2 and NO_2, which are important precursor pollutants for particles, were found at concentrations of approximately a factor two higher in the urban areas than in the non-urban areas.

Table 4 gives a summary of the "leachable" and total element concentrations in one third of the PM_{10} samples measured during the winter of 1993/1994. The concentrations of all elements except Si were higher in the urban area than in the non-urban area.

Table 4. "Leachable" and total element concentrations (24 h average) in PM_{10} samples from urban and non-urban areas measured in the winter of 1993/1994 (concentrations in ng m^{-3})

		Urban			Non-urban			Ratio $C_{urban}/C_{non\text{-}urban}$
Leachable	N	Median	90-p	Max	Median	90-p	Max	Median†
V	33	7.9	15.5	26.3	6.3	17.0	38.8	1.26**
Na	33	322	1502	5718	227	946	1553	1.41**
Si	33	196	583	2041	306	620	4480	0.85
K	33	252	499	805	201	537	659	1.11
Mn	33	14	39	94	12	31	74	1.35**
Fe	33	207	627	893	163	451	1911	1.26**
Cu	33	19	51	120	24	57	188	1.23
Total		Urban			Non-urban			Ratio $C_{urban}/C_{non\text{-}urban}$
V	33	7.9	16.8	27.3	5.9	17.8	39.7	1.23**
Na	33	325	1497	5709	269	943	1548	1.41**
Si	33	1560	3039	7504	1735	3868	15773	0.92
K	33	241	572	882	208	592	1254	1.10
Mn	33	15	41	98	11	31	82	1.36**
Fe	9	352	1186	1186	397	815	815	1.07
Cu	33	21	86	193	27	67	209	1.29

† *median of the daily ratios $C_{urban}/C_{non\text{-}urban}$ is not always equivalent to the ratio of the median concentrations*

* *significantly different from 1, $P<0.05$ (Wilcoxon signed rank test)*

** *significantly different from 1, $P<0.01$ (Wilcoxon signed rank test)*

The differences in ("leachable") Si, K and Cu concentrations between urban and non-urban area were not statistically significant. The V, Na, Mn and Fe concentrations were significantly higher in the urban area than in the non-urban area. The percentage differences between urban and non-urban areas in elemental concentrations were consistently larger than for PM_{10} mass. Except for Si and Fe the weak extraction resulted in a near 100% extraction of all elements.

Table 5 presents the Spearman correlation coefficients for the particle, gaseous and elemental concentrations measured in the urban and the non-urban areas. The correlation between PM_{10}, $PM_{2.5}$, BS and NOSA concentrations measured in the urban and the non-urban areas was higher than 0.7 for all winters. For the gaseous pollutants SO_2 and NO_2, the correlations were higher than 0.6, except for SO_2 in the third winter ($R=0.31$). SO_2 levels were extremely low during this winter. The correlation between all elements was higher than 0.5 except for Cu ($R=0.19$).

Table 5. Spearman correlations between air pollution concentrations measured in urban and non-urban area

	92/93	93/94	94/95
PM_{10}	0.80	0.92	0.75
$PM_{2.5}$	-	-	0.88
Black Smoke	0.90	0.94	0.85
SO_2	0.76	0.73	0.31
NO_2	0.83	0.65	0.65
Sulfate	0.82	0.94	0.91
Nitrate	0.90	0.93	0.86
Ammonium	0.82	0.95	0.92
NOSA	0.83	0.94	0.91
V	-	0.71	-
Na	-	0.90	-
Si	-	0.55	-
K	-	0.68	-
Mn	-	0.61	-
Fe	-	0.85	-
Cu	-	0.19	-

Wind direction and particle concentrations

Table 6 shows that three to fivefold higher PM_{10} and BS concentrations were measured with ENE and ESE winds, compared to winds from the N and WNW. This was the case for both the urban and the non-urban area. The percentage differences between urban and non-urban area were greatest with N and WNW winds and least (and non-significant) with ENE winds. The NO_2 concentration in the urban area was relatively constant for the various wind directions. In the non-urban area the highest NO_2 concentrations were associated with ESE and S winds. The difference in SO_2 concentration between urban and non-urban area was greatest with WNW winds and least with ENE winds.

Table 6. Median concentrations of PM_{10}, Black Smoke, SO_2 and NO_2 (in $\mu g/m^3$) in urban and non-urban area, by wind direction

		Urban				Non-urban				Median ratio $C_{urban}/C_{non\text{-}urban}$†			
	N	PM_{10}	BS	SO_2	NO_2	PM_{10}	BS	SO_2	NO_2	PM_{10}	BS	SO_2	NO_2
WNW	19	28	6.7	10.9	44	22	4.5	3.6	13	1.26**	1.55**	2.43**	3.25**
N	9	23	7.9	4.3	44	19	4.0	2.0	14	1.42	1.70**	1.33**	2.30**
ENE	14	62	18.5	9.9	47	66	18.4	11.3	23	1.04	1.00	1.24	1.93**
ESE	27	55	23.1	13.6	52	51	21.9	9.3	33	1.12*	1.20**	1.71**	1.45**
S	42	39	12.0	12.1	52	30	10.1	5.7	34	1.10**	1.18**	2.12**	1.48**
WSW	74	29	6.4	7.4	41	25	5.4	5.0	20	1.13**	1.15**	1.61**	2.04**
VAR	21	37	14.9	11.9	56	34	11.5	5.6	33	1.09	1.10*	2.29**	1.71**

† *median of the daily ratios $C_{urban}/C_{non\text{-}urban}$ is not always equivalent to the ratio of the median concentrations*

* *significantly different from 1, $P<0.05$ (Wilcoxon signed rank test)*

** *significantly different from 1, $P<0.01$ (Wilcoxon signed rank test)*

Table 7 shows that the NOSA concentrations were very low when the wind came from the sea (N and WNW, WSW). By far the highest concentrations were found with easterly winds. This was the case for both the urban and the non-urban area. When the wind was from WSW, NOSA concentrations in the urban area were significantly lower than in the non-urban area. For the other wind directions, no significant differences in NOSA concentrations were found.

Table 8 shows that for all elements except sodium higher concentrations were measured on days with easterly winds compared to days with S and WSW winds, both in the urban and the non-urban area. The difference is twofold or more for all

Table 7. Median concentrations of non-organic secondary aerosols (in µg/m³)in urban and non-urban area, by wind direction

		Urban				Non-urban				Median ratio $C_{urban}/C_{non\text{-}urban}$†			
	N	Sulfate	Nitrate	Ammonium	NOSA	Sulfate	Nitrate	Ammonium	NOSA	Sulfate	Nitrate	Ammonium	NOSA
N+WNW	17	1.01	0.74	0.37	1.97	1.07	0.83	0.45	2.51	1.17*	1.08	1.14	1.18
ENE+ESE	29	6.57	7.17	3.66	16.23	6.97	6.70	3.99	16.86	0.92	0.93	0.97	0.92
S	25	2.76	3.07	1.94	8.01	3.10	3.36	2.31	9.20	1.01	0.90	1.06	0.97
WSW	57	1.33	1.16	0.69	3.12	1.67	1.70	1.05	4.27	0.88**	0.79**	0.81**	0.82**
VAR	13	3.46	1.43	2.18	8.21	2.75	3.38	2.81	11.27	1.05	1.02	0.93	0.87

† *median of the daily ratios $C_{urban}/C_{non\text{-}urban}$ is not always equivalent to the ratio of the median concentrations*
* *significantly different from 1, $p<0.05$ (Wilcoxon signed rank test)*
** *significantly different from 1, $p<0.01$ (Wilcoxon signed rank test)*

Table 8. Median concentrations of elements (in ng/m³) in urban and non-urban area, by wind direction

		Urban							Non-urban							Median ratio $C_{urban}/C_{non\text{-}urban}$†						
	N	V	Na	Si	K	Mn	Fe	Cu	V	Na	Si	K	Mn	Fe	Cu	V	Na	Si	K	Mn	Fe	Cu
ENE+ESE	9	9.8	133	564	429	20	404	32	9.0	131	594	479	17	366	29	0.88	1.02	0.88	0.94	1.29	1.06	0.98
S+WSW	15	8.6	742	123	222	9	157	17	6.2	329	234	171	6	79	13	1.47**	1.60**	0.64	1.16*	1.70**	1.51**	1.38*

† *median of the daily ratios $C_{urban}/C_{non\text{-}urban}$ is not always equivalent to the ratio of the median concentrations*
* *significantly different from 1, $p<0.05$ (Wilcoxon signed rank test)*
** *significantly different from 1, $p<0.01$ (Wilcoxon signed rank test)*

elements, except Vanadium. No statistically significant differences in elemental concentrations between urban and non-urban area were found when the wind was from the east. When the wind was from S and WSW, significantly higher concentrations were found in the urban area for all elements except Si.

Air pollution episodes

During the three winters, four episodes occurred with elevated particle concentrations. An episode was arbitrarily defined as a period of at least three days with a PM_{10} concentration higher than 70 $\mu g/m^3$ in either the urban or the non-urban area. The end of an episode was defined if the concentration was below 70 $\mu g/m^3$ on two consecutive days.

Figure 2 shows a plot of the PM_{10} and sulfate concentration in the urban and non-urban area during the four episodes, and during the period before and after the episodes. The last episode occurred at the very end of the study period, so that concentrations for only two days could be plotted after the episode.

The first episode (11/2/93-16/2/93) was characterized by winds from east to south-east, a low wind speed (2-3 m/s), minimum temperatures around 0 °C, and high barometric pressure (1037 mbar). Mean PM_{10} concentration was 122 $\mu g/m^3$ in the urban area and 86 $\mu g/m^3$ in the non-urban area (figure 2). We started the NOSA measurements on March 4, 1993 so we do not have information on sulfate concentrations during the first episode.

During the second episode (10/3/93-16/3/93) meteorological conditions were different; wind was from the south, barometric pressure was not higher than average (1020 mbar), temperatures were relatively high (around 6 °C), wind speed was on average 3 m/s. The episode was preceded by two days with easterly winds. Mean PM_{10} concentration during the episode was 82 $\mu g/m^3$ in the urban area and 62 $\mu g/m^3$ in the non-urban area. Mean sulfate concentration was 10 $\mu g/m^3$ in the urban area and 7 $\mu g/m^3$ in the non-urban area.

During the third episode (22/11/93-2/12/93) barometric pressure varied between 1009 and 1033 mbar, temperature was low (around -5 °C), and winds were from south to east in the urban area but predominantly from the east in the non-urban area. Wind speed was, on average, lower in the non-urban area (3.2 m/s) than in the urban area (4.7 m/s). Thus, slightly different meteorological conditions were observed in the urban and non-urban area. Not only PM_{10} but also sulfate concentrations were substantially elevated. Both PM_{10} and sulfate concentrations were slightly lower in the urban area than in the non-urban area (mean concentration 84 resp. 13 $\mu g/m^3$ in the urban area vs 87 resp. 15 $\mu g/m^3$ in the non-urban area).

The fourth episode was from 18/2/94 untill 26/2/94. A week before the start of this episode, temperature dropped (-5 °C), wind was from the east and wind speed was high in both the urban and the non-urban area. This resulted in a dust storm on 14/2 and 15/2 in the non-urban area. This dust storm was reported in the local newspapers and caused by strong winds blowing dust from the dry, bare agricultural soils.

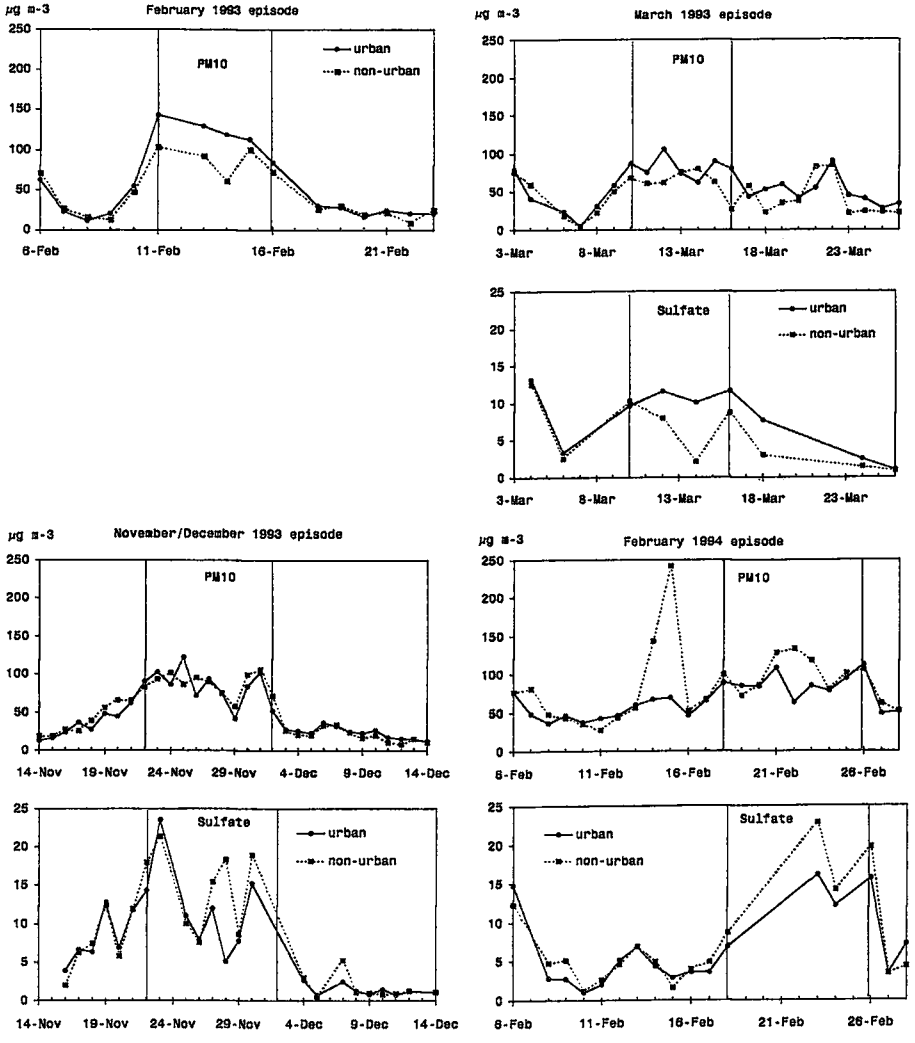

Figure 2. Daily PM_{10} and sulfate concentration before, during and after the four air pollution episodes

On 15/2/94, this resulted in a PM_{10} concentration of 242 $\mu g/m^3$, the highest measured during the study period. Sulfate concentration, however, was very low (1.7 $\mu g/m^3$) on this day. PM_{10} concentrations in the urban area were not elevated on 14/2 and 15/2 despite the even higher wind velocity. After 15/2, wind speed decreased and reached mean velocities of around 2 m/s in the non-urban area and around 4 m/s in the urban area. The direction was still from the east in both areas and temperatures remained low (-8 °C in the urban area, -5 °C in the non-urban area). Barometric pressure was not elevated. PM_{10} and sulfate concentration during this episode were higher in the non-urban area (103 $\mu g/m^3$ resp. 18 $\mu g/m^3$) than in the urban area (89 $\mu g/m^3$ resp. 15 $\mu g/m^3$). During the winter of 1994/1995, no air pollution episodes occurred as a result of mild meteorological conditions. There were few days with easterly winds, compared to the other two winters.

Discussion

Particle concentrations

The PM_{10} and Black Smoke concentrations measured during the winter of 1993/1994 have already been discussed and compared to concentrations in other European countries by Hoek *et al.*[5]. Since the concentrations measured during the three winters were not very different from the concentrations measured during the winter of 1993/1994, we refer to this paper[5]. $PM_{2.5}$ concentration was on average 55% of the PM_{10} concentration. This is very similar to the value of 0.60 suggested by Dockery and Pope[1] as a typical North-American $PM_{2.5}/PM_{10}$ ratio.

Concentrations of aerosol acidity were very low during the three winters. Median concentration was below 0.1 $\mu g/m^3$ and the maximum concentration was only 1.7 $\mu g/m^3$. In previous studies in the Netherlands[17] and other European countries[20,21] low levels of aerosol acidity were reported as well. This contrasts with the much higher levels that are found in the North-Eastern part of the United States and Canada[22].

Median sulfate, nitrate and ammonium concentrations measured in the urban areas during the three winters were 2.4, 1.9 and 1.4 $\mu g/m^3$, respectively. For the non-urban areas, this was about 10% higher. During the first winter two- to threefold higher NOSA concentrations were found than during the second and the third winter. In a previous monitoring study in the Netherlands, performed during the period 1987-1990 at 8 sites, Hoek *et al.*[17] reported median sulfate, nitrate and ammonium concentrations in the range of 4-8 $\mu g/m^3$, 4-6 $\mu g/m^3$ and 3-4 $\mu g/m^3$, respectively. No substantial differences were observed between winter and

summertime concentrations in this study[17]. Brauer *et al.*[21] reported on NOSA concentrations measured between December 1990- June 1992 in two cities in Germany (former GDR) and the Czech Republic. During winter mean sulfate concentration was 8 $\mu g/m^3$ in both cities; mean nitrate concentration was 4 $\mu g/m^3$ in both cities and mean ammonium concentration was in the range of 4-5 $\mu g/m^3$. No separate winter and summertime concentrations were reported for nitrate and ammonium[21].

The balance between the determined cations and anions was close to unity during the three winters, which suggests that the low median NOSA concentrations in the second and third winter were not a result of analytical errors. Although the ion balance was only calculated for days with sufficiently high NOSA concentrations (> 3 $\mu g/m^3$ for sulfate, > 2 $\mu g/m^3$ for ammonium and nitrate), those days occurred at the beginning and at the end of the study period and thus it is not likely that analytical errors occurred during the other days. The low NOSA concentrations during the second and third winter are probably also not a result of lower emissions of precursor pollutants in Central and Eastern Europe. The large concentration difference between the first and the second/third winter and the high sulfate and nitrate concentrations observed during episodes in the second winter argue against this interpretation. In addition, Central European NO_2 emissions have probably increased in the past decade due to increased motorized vehicle use. This is inconsistent with the lower nitrate concentrations compared to the study reported by Hoek *et al.*[17]. The percentage of days with westerly winds, associated with low particle concentrations was 50%, 45% and 60% during the three consecutive winters. Thus, the higher NOSA concentrations during the first winter can also not be explained by a lower percentage of days with westerly winds. We have no other explanations for the fact that during the first winter, two to threefold higher NOSA concentrations were measured than during the second and third winter.

We reported both "leachable" and total elemental concentration of one third of the PM_{10} filters collected during the winter of 1993/1994. For all elements except Si and Fe the major part (>80%) was leachable (15% for Si, 50% for Fe). Similar percentages were reported by Janssen *et al.*[7]. The low percentage of Si that was leached with the "weak extraction" is consistent with the notion that Si is part of the matrix of resuspended soil particles and thus not easily soluble. The high percentages for V and Na were expected on the basis of the surface concentration of V and the high solubility of sea salt respectively. Mn, K, Cu and Fe concentrations are affected by multiple sources, including soil dust. The high leachibility compared to Si suggests that either other sources than soil dust are

more important or that these elements are less fixed in the matrix of soil particles. The first explanation is supported by the fact that higher Mn, K, Cu and Fe were found in the urban area than in the non-urban area.
Leachable and total elemental concentrations in PM_{10} were in the same range as reported by Janssen *et al.*[7]. For most elements, total concentrations were lower than measured in PM_{10} at several rural/(sub)urban sites in North America[23,24].

Differences in particle concentrations between urban and non-urban area
PM_{10} concentrations were on average 13% higher in the urban areas than in the corresponding non-urban areas. Hoek *et al.*[5] found on average 22% higher concentrations in the urban areas than in the non-urban areas in 14 European study locations. Since 1993 the Dutch Air Quality Monitoring Network has been routinely measuring PM_{10} at 19 urban and rural sites, spread over the country. Small differences (<20%) in annual mean PM_{10} concentration were observed in 1993 and 1994 between the North-Eastern part of the Netherlands (lowest concentrations) and the more urbanized and industrial southern and western part[25]. This small contrast is in line with the results of our study. The small size of the country (200x300 km), and the absence of mountains are factors that might explain the lack of contrast. Consequently, there are no physical barriers or small scale meteorological differences that result in different particle concentrations. In Switzerland (about the same size as the Netherlands) annual mean PM_{10} concentration, measured at a dozen urban, rural and alpine sites ranged between 33 $\mu g/m^3$ (urban) and 10 $\mu g/m^3$ (alpine)[26]. In the European study reported by Hoek *et al.*[5], twofold urban- non-urban differences were found for locations with mountain ranges between urban and non-urban area, such as Athens (Greece) and Teplice (Czech Republic).
Black Smoke levels were on average 19% higher in the urban area than in the non-urban area. In the European study a mean difference of 43% was found[5]. Black Smoke concentrations can be used as an estimate for the concentrations of elemental carbon (EC)[27,28]. Chow *et al.*[29] reported a fourfold difference in EC concentration between three urban and three rural areas in San Joaquin Valley, California.
We had expected to find a larger contrast between urban and non-urban areas, because EC is a primary pollutant from motorized traffic (diesel soot)[4], and traffic intensity is higher in the urban areas than in the non-urban areas. The Dutch Air Quality Monitoring Network reported twofold higher annual mean Black Smoke concentrations in the urbanized Western part of the Netherlands compared to the rural North-Eastern part, over the years 1993 and 1994 [30]. Due to the

epidemiological purpose of our study, we selected the non-urban areas south of this 'cleanest' part, where population density is higher. In addition, our non-urban areas were in fact small small towns, with around 25,000 inhabitants and thus a higher traffic intensity than in rural areas. This possibly resulted in a smaller contrast in Black Smoke concentration between the urban and non-urban areas.

The concentration of sulfate, nitrate and ammonium was on average respectively 7%, 8% and 10% lower in the urban areas than in the non-urban areas. The fact that higher NOSA concentrations were observed in the non-urban area contrasts with the the fact that the precursor pollutants SO_2 and NO_2 were found in twofold higher concentrations in the urban area. This is consistent with the slow formation process of secondary aerosols. During winter conditions in Europe, the transformation of gaseous precursor pollutants to secondary aerosols is mainly through aqeous phase oxidation. This process is slower than the photochemical gas phase oxidation, which is the predominant formation mechanism during summer[21,31,32]. For example, aqueous phase SO_2 oxidation rate is 0.2%-1% hr^{-1} depending on the amount of catalyzation by transition metals on the surface of aerosols[31]. Given this slow oxidation rate and the relative short distance between urban and non-urban areas it is not likely that large concentration gradients occur.

In the study reported by Hoek *et al.*[17], around 10% higher sulfate levels were found in an urban location than in a non-urban location. Nitrate and ammonium concentrations were similar in the urban and non-urban location. In general, NOSA-levels showed small and non-significant differences between sites[17]. Suh *et al.*[33] studied the spatial variation of sulfate measured at 7 sites within the metropolitan area of Philadelphia and one 'background' site 30 km upwind from the city, during the summers of 1992 and 1993. Concentrations were uniform across all sites including the background location.

The concentrations of all elements except Si were higher in the urban area compared to the non-urban area. Significantly higher concentrations of Na, Mn, V and Fe were found in the urban area than in the non-urban area. For Na, a tracer for marine aerosol[34] this is due to the closer proximity of the urban area to the sea. Fe is a tracer for both soil dust and heavy industry[34]. The 26% higher Fe concentration in the urban area is probably a result of its location in the more industrialized western part of the country, given the fact that the Si concentration is higher in the non-urban area. The same is probably true for V, a tracer for oil combustion[34] and Mn, which is a tracer for several sources including soil dust, industry and traffic[35]. In general the differences in element concentration between urban and non-urban location were modest, but larger than the differences in PM_{10} mass concentration.

Wind direction and particle concentrations

A limitation of this part of the study was that we used local wind direction data only. Back trajectories were not available. This may have resulted in some misclassification of days, as local wind direction will not always represent the origin of the air mass.

On days with easterly winds, PM_{10} and Black Smoke concentrations were 2-4 fold higher than on days with wind from the sea, both in the urban and the non-urban area. The relative difference in PM_{10} and BS concentration between urban and non-urban area was greatest when the wind was north and west-north-west. This is caused by the low supply of long range air pollution, and therefore local air pollution sources were more important on a relative scale. When circulation was from the east, which was usually the case during air pollution episodes, there was (almost) no difference between PM_{10} and Black Smoke concentrations in urban and non-urban area. This is consistent with long range transport being the most important source of air pollution in these conditions.

The lowest levels of sulfate, nitrate and ammonium were found when relatively clean air was coming in from the sea (WSW, N and WNW winds). Six to ten-fold higher concentrations were found with easterly winds, caused by the relatively high emissions of gaseous precursor pollutants in Central and Eastern Europe and the fact that the air was transported over a large continental area providing enough time for oxidation.

The slightly higher NOSA concentrations in the non-urban area were limited to days with west-south-westerly winds, especially for nitrate and ammonium (21% and 19% higher concentrations in the non-urban area, respectively). With west-south-westerly winds air is transported from the urban to the non-urban area. Thus, the difference might be a result of the formation of ammonium nitrate from NO_2 and NH_3, emitted in the urban and surrounding agricultural areas, during its transport to the non-urban areas.

The dataset with elemental concentrations was small which limits the conclusions that can be drawn when relating those concentrations to wind direction. However, we found that the highest concentrations of all elements except Na were found with easterly winds. This was true for both the urban and the non-urban area, suggesting that long distance transport is an important factor in determining element concentrations. For the marine aerosol related element Na, concentrations were threefold lower with easterly winds compared to days with wind from the sea.

Air pollution episodes

On non-episode days, median PM_{10} concentration in the urban area was 15% higher than in the non-urban area. Median sulfate concentration was 7% lower in the urban area compared to the non-urban area. The situation during episode-days depended on the type of episode.

The first episode (11-16 Feb 1993) with stagnant weather conditions resulted in a 42% higher PM_{10} concentration in the urban area, compared to the non-urban area. This is probably due to the fact that more local sources of particulate air pollution were present in the urban area. We did not have information on sulfate concentrations during this episode. The second episode, with southerly winds and a relatively high temperature, resulted in a 32% higher PM_{10} concentration in the urban area compared to the non-urban area. Sulfate concentration was 43% higher in the urban area. The third and fourth episodes were characterized as transport episodes. They both resulted in higher PM_{10} concentrations in the non-urban area than in the urban area. Also, the increase in sulfate concentration was larger in the non-urban area. This indicates that long distance transport plays an important role in determining particle concentrations and that due to its location, the non-urban area was affected more by German and Central/Eastern European sources.

In conclusion, urban wintertime PM_{10} and BS concentrations were only slightly higher than simultaneously measured concentrations in non-urban areas. Concentrations of sulfate, nitrate and ammonium were slightly lower in the urban area. Concentrations of leachable V, Na, Mn and Fe in PM_{10} samples were increased in the urban area. The increase was larger than observed for particle mass. Both the absolute concentrations and the urban-non-urban difference depended strongly on wind direction. Easterly winds resulting in an influx of air masses from Central and Eastern Europe were associated with high concentrations and minimal urban-non-urban differences. Winds from the sea resulted in low concentrations but larger relative differences between urban and non-urban areas.

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Chapter 3

A comparison of supervised Mini Wright and spirometer Peak Flow measurements with unsupervised Mini Wright Peak Flow measurements

Saskia C. van der Zee and Bert Brunekreef

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Abstract

In the framework of a panel study on acute effects of air pollution, Peak Expiratory Flow (PEF) was measured with different methods during a four months study period in a panel of 65 Dutch school children, age 9-11 yr. Every week, PEF was measured at school with spirometry and with a Mini Wright meter under supervision. In addition, children monitored their own PEF at home with a Mini Wright meter in the morning and in the evening.

The aim of this study was to compare within- and between-measurement variability between supervised (spirometry, Mini Wright) and unsupervised (Mini Wright) PEF measurements. For this purpose, all three measurements that each maneuver consisted of were used.

We found that, as anticipated, the amount of measurement error was larger in unsupervised than in supervised PEF readings, but the differences were not great. We concluded that the larger amount of measurement error is far outweighed by the advantages of self-recorded measurements in terms of ease, cost and amount of data obtainable.

Introduction

Panel studies investigating acute effects of ambient air pollution on respiratory health follow subjects over time, so that individuals serve as their own controls. This reduces variability in the outcome variables (e.g. lung function) since between-individual variability does not play a role. However, data from longitudinal studies are still affected by intra-individual variability in the outcome variable. Sources of intra-individual variability in pulmonary function can be classified as either biologic variation or measurement error[1].

The contribution of ambient air pollution levels to the biologic variation in pulmonary function is usually small. Group mean decrements associated with elevated concentration levels are generally in the order of 1 or 2 percent[2,3]. Other, possibly more important, sources of biologic variation include time of day or year, host characteristics (such as increased airway responsiveness) and other environmental exposures such as allergen exposure or respiratory infections[4].

Given the fact that generally, air pollution contributes only to a small part of total variability in pulmonary function, it is often hard to detect statistically significant effects of air pollution. The power to detect statistically significant effects increases with decreasing measurement error in the measurement of the outcome variable, and with an increasing number of observations.

Different instruments, including spirometers and Mini Wright Peak Flow meters have been used in longitudinal air pollution studies to measure Peak Expiratory Flow (PEF). Mini Wright meters can be used for self-monitoring at home, or for measurement of PEF under supervision. Self-monitoring of PEF has great advantages in terms of cost, ease and amount of data obtainable. However, a number of recent studies have raised concern about the reliability of self-recorded PEF measurements[5-8]. In this study, the amount of measurement error in supervised (spirometry, Mini Wright) and unsupervised (Mini Wright) PEF measurements was compared.

In the framework of a study on acute effects of air pollution, we measured PEF with spirometry and a Mini Wright meter weekly at school, in a panel of 9-11 yr old school schildren, during a study period of four months. In addition, the children monitored their own PEF at home twice a day with a Mini Wright meter. Each PEF measurement consisted of three maneuvers that were used to assess the contribution of measurement error. This study design enabled us to compare unsupervised and supervised PEF measurements within subjects, performed on the

same days but with differences in measurement device and measurement time.

Methods

Study population

The measurements were performed in the framework of a study on acute effects of air pollution on childrens respiratory health that we conducted in the South West of the Netherlands. 95 children of grades 6 and 7 of two selected primary schools participated in the study. In these grades, the children are generally between 9 and 11 years old. The children were not selected on the basis of whether or not they had chronic respiratory symptoms. The study was conducted from January 15 to May 14, 1996.

Self recorded Peak Flow measurements

During the study period, Peak Flow was measured with a Mini Wright Peak Flow meter (Clement Clarke) in the homes of the children. The childrens parents had been instructed on the use of the Mini Wright meter during an information evening at school. Parents who could not attend this instruction evening were instructed at home. The children were instructed on the first test day at school. PEF was measured twice a day, in the morning before breakfast and in the evening before going to bed. Children were instructed to perform the PEF measurements before any medication was taken. Every test consisted of three maneuvers and participants were asked to note all three readings in a diary.

Spirometry

Pulmonary function tests (spirometry) were performed each week at school. All tests were performed between 8:30 am and 3:00 pm, but most tests were performed before noon. Each child was tested about the same time of the day on each occasion. Measurements were performed on Mondays in one school and on Tuesdays in the other school. Because of school holidays, no measurements could be performed during one week in February and during one week in May. The maximum number of spirometric tests performed during the study period was 16. Spirometry was performed according to the protocol of the ECCS[9]. A more detailed description of the protocol has been published before[10]. A rolling-seal dry spirometer (Vicatest 5) coupled with automatic data acquisition software has been used. Two spirometric devices were used. In total, four technicians have

performed lung function tests, but the majority (75%) of the measurements was performed by two technicians. In order to avoid possible differences between devices or technicians, children were measured on the same device each week and, if possible, by the same technician.
Peak Flow values obtained from spirometry were transformed to BTPS, using the air temperature of the test room. More details can be found elsewhere[10].

Supervised Mini Wright measurements
Directly (5-10 minutes) preceding spirometry, an additional Peak Flow measurement was made using a Mini Wright Peak Flow meter (Clement Clarke). This measurement was performed under supervision of a technician, who recorded the readings of three different maneuvers. The purpose of these additional PEF measurements was to compare them to the PEF values measured with spirometry, and to the self-recorded Mini Wright PEF-measurements. The same Mini Wright meter was used for all children, during the full study period. The same technician supervised and recorded the Mini Wright PEF measurements each week. They were performed in a class room next to the room where spirometric testing was conducted.

Quality control
Every two weeks, the children were asked to take their diaries with them to school. They were inspected by the technician who supervised the PEF-measurements at school, and irregularities (i.e. a great number of missing values, strange PEF-values) were discussed with the children. In addition, the supervised PEF-measurements enabled us each week to inspect if the children were able to perform technically acceptable PEF-measurements.
At the end of the study period, all Mini Wright meters were disassembled and cleaned in the laboratory. When Mini Wright meters were found to be dirty, for example containing food particles that might obstruct the spring mechanism, the data collected with that meter were not used in the analysis. Data from children who had received a new Mini Wright meter during the study period (because the old meter was lost or broken) were excluded as well.

Data analysis

For the four PEF variables, the maximum of the three measurements that each maneuver consisted of was used in further analyses, unless stated otherwise.

Diary information about self-recorded PEF was only used for those days when spirometry at school was performed. For each child separate plots of self-recorded morning and evening PEF were made to check for implausible values. Those were arbitrarily defined as: the highest PEF-value is more than 80 l/min higher than the second highest PEF-value. These values were made missing. The first two spirometric tests were excluded from the analysis. The rationale for this was to allow the children to get used to the procedure. The majority (91%) of spirometric tests and supervised Mini Wright PEF-measurements were performed before noon. Tests performed after noon were excluded from the analysis, to reduce the time span during which the measurements at school were performed.

To allow optimal comparison between the four PEF representations, only days with four non-missing PEF values were used in the analysis. For each child the number of days with four valid PEF values during the study period was calculated. Children with less than eight days with four valid PEF values were exluded from the analysis.

To evaluate the time trend in PEF during the study period, the population mean deviation in PEF was calculated. This was done by first calculating individual mean deviations by substracting the childs mean PEF from each individual PEF value. Next, the mean of the individual mean deviations was calculated for each day of study. The mean PEF measured in the panel during the whole study period was added to these deviations. This gives a mean population PEF for each week of measurement, taking into account that the composition of the panel may vary from week to week.

The variation in Peak Flow within subjects was investigated for the four Peak Flow variables separately. For this purpose, the variation in Peak Flow within subjects was divided into 'within-measurement' and 'between-measurement' variation. The variation within-measurements can be used to obtain an estimate of measurement error, using the three repeated measurements that each maneuver consisted of.

One way to describe the within-measurement variation was by calculating the Coefficient of Variation within measurements (CV_{within}). For each subject and each day of measurement, a CV was calculated as the standard deviation of the three repeated measurements divided by the mean of the three repeated measurements. Next, for each subject the median of those CV's during the study period was

calculated and reported as CV_{within}.

One way to describe the between-measurement-variation is by calculating the Coefficient of Variation between measurements ($CV_{between}$). $CV_{between}$ was calculated for each subject as the standard deviation divided by the mean value of all measurements, using the maximum of the three repeated PEF measurements. The maximum was used because this is general practice when analyzing PEF data[11] and thus enabled us to compare the variation coefficients to values reported in the literature.

$CV_{between}$ was calculated both for the original PEF-values and for PEF-values that were adjusted on an individual basis for a linear time trend ($CV_{between, detrended}$). This was done because part of the 'between-measurement' variation is due to the increase of PEF with time, and we wanted to exclude this source of variation from some of our analyses.

Another way to describe the between- and within measurement variation is by calculating the within- and between measurements variance on an individual basis with analysis of variance (ANOVA). The unit of these variance components is $(l/min)^2$. ANOVA uses the mean of the three repeated PEF-measurements in calculating the between measurements variance so in this respect, it differs from $CV_{between}$ which is based on the maximum of the three values. The contribution of 'measurement error' to the total variation can be estimated by calculating the between/within variance ratio F. The variance ratio F was calculated for the original and the detrended PEF-values ($F_{detrended}$).

Wilcoxon's signed rank test was used to test the differences in CV's, variances, and variance ratios, since the data were not normally distributed. For CV the mean was reported in addition to the median because the mean is usually reported in the literature.

Results

Analyses were based on data from 65 of the 95 subjects. Data were excluded from 6 subjects that had received a new Mini Wright meter during the study period; 7 from subjects whose Mini Wright meter was classified as 'dirty' at the end of the study period, and 17 who had valid information for all PEF variables on less than eight days of observation.

Plots of mean population PEF versus week of study (after exclusion of the first 2 weeks) are shown in figure 1. There was an increase of around 10% in the PEF-

variables that were measured under supervision (PEF_{spiro} and PEF_{MWsup}) during the study period. The increase in the self-recorded PEF-variables (PEF_{MWmo} and PEF_{MWev}) was smaller (about 5%). The trend in the four PEF-variables could be described sufficiently with a linear trend term.

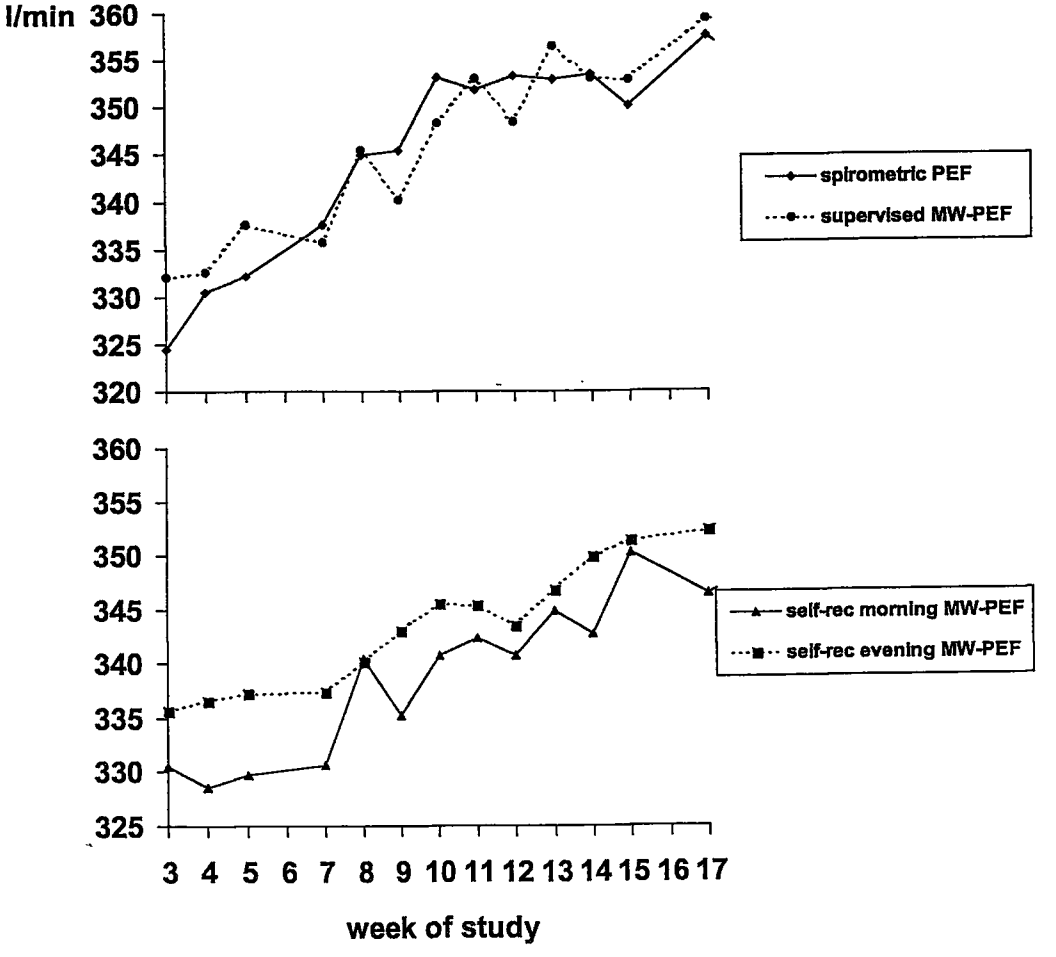

Figure 1. Group mean Peak Flow versus week of study, for the four Peak Flow variables

Characteristics of the study population and the Peak Flow measurements are presented in table 1. There was little difference in the mean value of PEF measured in various ways. Self-recorded Mini Wright PEF was slightly higher in the evening than in the morning, as one would expect from circadian variation alone (table 1).

Table 1. Characteristics of the study population and Peak Flow measurements

# Children	65
# Girls	41 (63%)
Age*	10.1 (9-12)
# Days/child	10.8 (8-14)
Recent wheeze**	8 (12.5%)
Recent asthma attacks**	5 (7.8%)
Medication use†	7 (10.9%)
PEF_{spiro}‡	345 (220-509)
PEF_{MWsup}	346 (235-514)
PEF_{MWmo}	339 (222-512)
PEF_{MWev}	344 (226-512)
Time PEF_{spiro}§	10:10 (8:59-11:19)
Time PEF_{MWsup}	10:03 (8:55-11:12)
Time PEF_{MWmo}	7:38 (6:36-8:09)
Time PEF_{MWev}	20:07 (17:29-21:18)

* *at the beginning of the study period*

** *in last 12 months (data available for 64 children)*

† *current use of airway medication (data available for 64 children)*

‡ *Peak Flow in l/min; mean, minimum and maximum of individual children during the study period (using the maximum of the three repeated measurements)*

§ *Mean time at which the measurements were performed; mean, minimum and maximum of individual children during the study period*

$CV_{between}$ was lower for supervised Mini Wright PEF than for spirometric PEF and self-recorded Mini Wright PEF in the morning. The differences were small, but significant for both the original and the detrended values. $CV_{between}$ for supervised Mini Wright PEF did not differ from $CV_{between}$ for self-recorded Mini Wright PEF in the evening. CV_{within} was slightly, but significantly lower for supervised than for self-recorded Mini Wright PEF and spirometric PEF (table 2)

Table 2. Coefficient of variation (%) within- and between measurements; mean and range of the individual children

	$CV_{between}$*			$CV_{between, detrended}$**			CV_{within}†		
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
PEF_{spiro}	6.5	5.8‡	3.2-19.7	5.2	4.8‡	2.3-17.8	3.1	3.0‡	1.6-8.1
PEF_{MWsup}	5.3	4.8§	1.8-12.7	4.2	4.1§	1.5-8.5	2.7	2.5¶	0.8-8.0
PEF_{MWmo}	6.4	5.7‡	1.3-17.3	5.3	4.8‡	1.2-15.1	3.5	3.2‡	0.9-9.6
PEF_{MWev}	5.7	5.2	1.5-16.1	4.7	4.2	1.2-14.8	3.4	2.9‡	0.6-8.7

* *Coefficient of Variation between measurement days, calculated as the standard deviation divided by the mean of PEF during the study period, using the maximum of the 3 repeated measurements. Significance levels are not reported*

** *as *, using Peak Flow values that were individually detrended*

† *Coefficient of Variation within measurements, calculated for each subject as the median of the CV-within's for each day of measurement (calculated as the standard deviation divided by the mean for the three repeated measurements)*

‡ *sign. different ($p<0.01$) from PEF_{MWsup} (Wilcoxon Signed Rank test)*

§ *sign. different ($p<0.01$) from PEF_{spiro} and PEF_{MWmo}*

¶ *sign. different ($p<0.01$) from PEF_{spiro}, PEF_{MWmo} and PEF_{MWev}*

Table 3 shows that there were no significant differences in the between-measurements variance for the four PEF variables, as calculated with ANOVA. However, the within-measurement variance was larger for self-recorded PEF (PEF_{MWmo} and PEF_{MWev}) than for supervised PEF (PEF_{spiro} and PEF_{MWsup}). Also, the contribution of within-measurement variation to the total variation was larger for self-recorded PEF than for supervised PEF, as indicated by the significantly smaller value of F for self-recorded PEF (table 3).

Table 3. Between- and within-measurement variance, and between/within variance ratio F calculated with ANOVA.

	$MSM_{between}$[†]		$MSM_{between,\ detrended}$[‡]		MSE_{within}[§]		F[¶]		$F_{detrended}$[¶¶]	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
PEF_{spiro}	962	241-8555	662	75-7494	119*	51-1206	9.0	0.9-27	5.7*	0.9-20
PEF_{MWsup}	837	175-5673	597	85-4904	113*	20-639	8.6	1.1-52	4.7*	1.0-47
PEF_{MWmo}	721	71-8823	584	22-4179	188**	28-2883	5.1	0.3-108	3.3**	0.3-108
PEF_{MWev}	759	71-4307	545	69-3316	170**	16-4113	3.6	0.6-258	2.4**	0.2-203

† *Between-measurements variance component (l/min)², calculated with ANOVA using the original PEF-values.*

‡ *as †, using PEF-values that were individually detrended*

§ *Within-measurements variance component (l/min)², calculated with ANOVA.*

¶ *Between-within measurements variance ratio F for the individual children. Significance levels are not reported*

¶¶ *as ¶, using PEF-values that were individually detrended.*

* *sign. different ($p<0.01$) from PEF_{MWmo} and PEF_{MWev} (Wilcoxon Signed Rank test)*

** *sign. different ($p<0.01$) from PEF_{spiro} and PEF_{MWsup} (Wilcoxon Signed Rank test)*

Discussion

In this study, we investigated the within- and between-measurement variation of supervised and unsupervised PEF measurements. It was shown that within-measurement variation in PEF was larger for self-recorded Mini Wright measurements than for supervised Mini Wright measurements. The differences were small, but statistically significant. No consistent differences were observed in between-measurement variation. There was a tendency of more within- and between measurement variation in spirometric PEF than in supervised Mini Wright PEF. However, the difference was only significant when the variation was expressed as CV, and not when expressed as variance components derived from ANOVA.

Within- and between measurement variation were expressed as variance components derived from ANOVA, ans as CV_{within} and $CV_{between}$. The latter was done in order to be able to compare the variation to values reported in the literature.

Compared to supervised PEF measurements, self-recorded PEF measurements have great advantages in terms of cost, ease and amount fo data obtainable. Recently, however, a number of studies comparing self-recorded and electronically stored PEF measurements have raised concern about the reliability of self-recorded PEF measurements. They reported that errors were made in reading and transcribing the PEF values and that a substantial number of the values were invented[5-8]. Two studies[5,6] investigated adult subjects for occupational asthma and found that written values corresponded precisely to electronically stored values in only approximately 50% of the cases. Verschelden *et al.*[7] compared self-recorded to electronically stored PEF values in 20 asthmatic adults who were asked to asses PEF twice daily during a three month period, and reported that 22% of the values were invented. Redline *et al.*[8] reported that in a panel of asthmatic children in the US, the number of invented PEF values increased over time during a three weeks study period and was 37% in the third week of study. This population differed from our study population with respect to socio-economic status, since the children resided in areas with 40% or more of the population living at or below poverty level.

We did not store PEF values electronically and thus, we can not directly test the reliability of unsupervised PEF measurements. However, the design of the study enabled us to compare unsupervised with supervised PEF measurements,

performed on the same day. The within-measurement variation, and the ratio of the within- and between measurement variation were used as indirect estimates of the quality of unsupervised PEF measurements.

Within-measurement variation in PEF may result from measurement error and from true, biological variation. Biological variation within a test session can occur in subjects with Maneuver Induced Bronchospasm (MIB), which is defined as a monotonic decline in recorded PEF within a test session[12,13]. Enright *et al.*[4] found evidence for MIB in only 4.4% of tests performed by asthmatics and 3.3% of tests performed by healthy subjects. Thus, it is not likely that MIB contributed much to the within-test variation. Therefore, we assumed that the role of biological variation was limited and that the within-measurement variation was indicative for the amount of measurement error.

Measurement error can arise from a number of factors[4] including instrumental characteristics; sub-optimal technical performance of the subject caused by lack of cooperation or comprehension; errors in the algorithm formulas used to obtain PEF-values from volume-time curves (spirometry); errors in reading precision or transcribing of the data (Mini Wright meters).

In the analysis of variance, the between/within variability ratio F was significantly larger for unsupervised than for supervised PEF measurements. The (detrended) median values of 3.2 and 2.4 for morning and evening PEF indicate that measurement error contributes respectively 24% and 29% to the total intra-individual variability in PEF. For spirometric PEF and supervised Mini Wright PEF these percentages were 15% and 17%, respectively. Although the contribution of measurement error to the total variability was significantly larger in unsupervised than in supervised PEF measurements, the differences were not great. This was especially true when measurement error was expressed as CV_{within}. Median CV_{within} was 3.2% and 2.9% for unsupervised morning and evening PEF respectively, 2.5% for supervised Mini Wright PEF and 3.0% for spirometric PEF.

A limitation of our study is that the amount of 'measurement-error' was calculated using the three repeated measurements that each maneuver consisted of. However, when analyzing PEF data in relation to air pollution, generally the highest of three repeated measurements is used[11]. Since it was not possible to calculate the measurement error for the highest value, the measurement error for the mean was used as a proxy for the amount of error in the highest value. The crucial underlying assumption was that measurement error for the mean and maximum of three PEF values are correlated. Although, unfortunately, we were not able to

test this assumption, it seems likely that factors that can lead to errors in the measurement of the mean value (such as reading precision and transcription) can also lead to errors in the measurement of the highest value. Probably, measurement error affects the maximum value even more than the mean value, because in the mean value the error can be averaged out.

The supervised and self-recorded Mini Wright measurements differed not only with respect to supervision, but also with respect to measurement time and the Mini Wright meter used. However, it does not seem likely that these factors were responsible for the observed differences in within-measurement variability. No significant differences in within-measurement variability were found between self-recorded morning and evening PEF, and this does not indicate that measurement time was an important factor.

In our population of children, the absolute value of spirometric PEF agreed closely with the absolute value of Mini Wright PEF, in contrast to reports in the literature that Mini Wright PEF is usually overestimating volume based spirometric PEF[15,16].

Strong increases of PEF with time were observed for all four PEF variables. The increase was approximately 10% for supervised PEF readings and 5% for unsupervised PEF readings, significantly more than is expected on the basis of lung growth alone[17]. This may be the result of substantial physiological training of (the control over) respiratory muscles, since the children performed unsupervised PEF measurements at home twice daily during four months. In a previous study performed at our department[18] in 7-11 yr old children using spirometry, it was also found that PEF increased substantially more than expected from normal lung growth only during a three months study period.

The absolute values of $CV_{between}$ for the various PEF-variables were comparable to values reported in the literature. $CV_{between}$ for spirometric PEF (mean 6.5%) was in the same range as reported for other Dutch school children[10,19]. $CV_{between}$ for supervised Mini Wright measurements (5.3%) was well comparable to the value of 5.2% reported in another Dutch study where Mini Wright PEF was measured under supervision in exercising healthy children[20]. $CV_{between}$ for self-recorded morning-PEF in our study was on average 6.4%. This was in the lower range of values documented for children with chronic respiratory symptoms in 13 panels from 10 European countries[21]. Our study population consisted of healthy school children, which is probably the reason for the lower $CV_{between}$ observed in our study. $CV_{between}$ for self-recorded evening PEF was also lower in our panel (5.7%) than in a panel of Dutch children with chronic respiratory symptoms (8.5%)[22].

There is less literature concerning within-test session reproducibility of PEF. Timonen *et al.*[23] calculated a mean CV_{within} of 6.7% for spirometric PEF, measured in 7-12 yr old children who performed spirometry on four days. This value is substantially higher than the 3.1% found in our study but this might partly reflect the smaller number of tests (n=4), and the fact that the mean of the CV_{within}'s for the four test days was calculated while in our study the median of the, on average, 11 test days was calculated.

In two other studies[14,24] the within-session reproducibility was expressed as the value below which the difference between two measurements will lie with probability 95%. This value was 40 l/min in a panel of healthy subjects and patients with lung disease[14] and 30 l/min in a study with trained children and adults, 17% of which had asthma[24]. In both studies PEF was measured with Mini Wright meters, recorded by the subjects without supervision. Provided the Peak Flow values are from a normal distribution, this is estimated by $1.96*\sqrt{2}*sd$[25] which would, in our study, result in values of 28 l/min (morning PEF) and 27 l/min (evening PEF) so that our values compare favorably with those quoted from the literature. To our knowledge, no literature is available reporting the within-test session reproducibility of supervised Mini Wright measurements.

Errors in the measurement of the outcome variable increase the standard error of the air pollution coefficients, but, when random, do not lead to biased effect estimates. We have shown that the amount of error in the measurement of self-recorded PEF was larger than for supervised PEF, but that the differences were not great. We conclude that in this population of Dutch school children, the slightly larger amount of measurement error in the self-recorded Peak Flows is far outweighed by the advantages of self-recorded measurements in terms of ease, cost and amount of data obtainable.

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Chapter 4

Incidence of influenza-like illness, measured by a GP sentinel system, is associated with day-to-day variations in respiratory health in panel studies

Saskia C. van der Zee, Gerard Hoek and Bert Brunekreef

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Abstract

The association between the incidence of influenza and influenza-like-illness (ILI) in the general population, and respiratory health in selected panels was investigated during three consecutive winters starting in 1992/1993. Eight panels of subjects were investigated each winter using a daily diary: children (7-11 yr) and adults (50-70 yr) with and without chronic respiratory symptoms, living in urban and non-urban areas in the Netherlands. The incidence of ILI in the general population was registered by the Dutch network of General Practitioner (GP) sentinel stations. The ILI incidence was low (median 0.1%/week, maximum 1.2%/week). Nevertheless, a higher ILI incidence was associated with a lower level of Peak Expiratory Flow (PEF), and increased reporting of respiratory symptoms and bronchodilator use in all groups of panels. The combined effect estimates calculated for the three winters indicated that for an influenza epidemic reaching peak ILI incidences of 122 cases/10,000 subjects, a decrement in PEF of up to 6% was found, and an increase in symptom reporting and bronchodilator use by factors of up to 2.9 and 4.5, respectively. This implies that in panel studies on acute effects of air pollution, the ILI incidence might be used to adjust for the potential confounding effect of acute respiratory infections.

Introduction

Panel studies follow groups of selected subjects for a certain period of time with regular observations of respiratory health status, and have been used frequently in air pollution epidemiology[1-3]. Changes that occur in respiratory health can also be of interest with respect to asthma management or occupational exposure.
Viral airway infections are an important determinant of respiratory health status. Virus induced upper respiratory tract infections are the most common triggers of acute asthma symptoms in children and induce bronchial hyperresponsiveness during and following the infections[4,5]. Also in adults there is a correlation between asthma severity and concomitant upper respiratory tract infections[6,7].
In most panel studies, respiratory infections are not the primary variable of interest, but given their effect on respiratory health, the need exists to adequately control for respiratory infections in the populations studied. Objective data on respiratory infections are not easily obtained in panel studies. For this reason, we investigated whether a surrogate variable, the incidence of influenza and influenza-like-illness (ILI), registered by the Dutch network of General Practitioner (GP) sentinel stations, was associated with indicators of respiratory health status (Peak Expiratory Flow (PEF), respiratory symptoms, bronchodilator use) in panels of children and adults with and without chronic respiratory symptoms.
The incidence of ILI is being monitored by the sentinel stations to obtain information on influenza virus activity. However, in practice it is not always possible to distinguish between influenza and other respiratory viruses such as rhino-, respiratory syncitial (RS)-, adeno-, corona-, entero- and parainfluenza viruses, as was evident from virological surveillance of respiratory specimens of patients diagnosed with ILI by the sentinel stations[8-10]. Thus, we hypothesize that the incidence of ILI might be a surrogate variable not only for influenza virus activity but for other respiratory virus activity as well.
Data were collected in the framework of a large study investigating the association between winter air pollution and respiratory health in panels, selected from different urban and non-urban areas in the Netherlands.

Materials and methods

Study design

The study was carried out during three consecutive winters starting in 1992/1993. During each winter, panels of children (7-11 yr) and adults (50-70 yr) with and without chronic respiratory symptoms were selected from an urban and a non-urban area, based on a screening questionnaire. Different subjects were studied each winter. During the three months study periods daily measurements of PEF were made, and the occurrence of acute respiratory symptoms and bronchodilator use was registered in a daily diary. As study areas were chosen: Rotterdam and Bodegraven/Reeuwijk (1992/1993), Amsterdam and Meppel (1993/1994) and Amsterdam and Nunspeet (1994/1995). Figure 1 in chapter 2 of this thesis shows the locations of the areas. Air pollution was monitored daily on central sites in each community. A total of 22 panels were studied during the three winters. A detailed description of the study design and the population selection will be described in a separate paper[11].

Health measurements

During the study period, participants performed PEF measurements twice daily using Mini Wright peak flow meters, once in the morning before breakfast and once in the evening before going to bed. Subjects were instructed to perform the PEF measurements before any medication was taken. Every test consisted of three maneuvers and participants were asked to note all three readings in a diary. The highest of the three PEF readings was used for analysis.

The diary was also used to register the occurrence of acute respiratory symptoms and medication use. Symptoms included 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 and fever.

Influenza surveillance

Data on influenza morbidity were obtained from the Dutch Institute of Primary Health Care (NIVEL). This institute operates a registration network of 46 sentinel general practices (GP), covering about 1% of the Dutch population. The sentinel stations are spread over the country in proportion to population density. The number of new patients with influenza or influenza-like illness (ILI), and the distribution of the patients over 19 different age-groups, is registered by the

GP's every week from Monday to Friday. Diagnoses made or advice given by telephone are entered in the weekly return form as well.

ILI must satisfy the three following criteria:

1. an acute beginning, i.e. a prodromal stage of no more than three to four days
2. the infection must be accompanied by a rise in rectal temperature to at least 38 °C
3. at least one of the following symptoms must be present: cough, coryza, sore throat, frontal headache, retrosternal pain and myalgia

Incidences were calculated according to age group per 10,000 of the practice population per week. They were reported separately for the northern, eastern, southern and western part of the country and for three different degrees of urbanization[12]:

1. rural municipalities 2. urbanized rural municipalities combined with municipalities with urban characteristics and 3. urban municipalities with a population of 100,000 or more. Due to the relatively small number of sentinel General Practices in the country, no combinations of regions and degree of urbanization could be made.

Data analysis

Influenza data

For the urban areas, incidences for the highest degree of urbanization were used. For the non-urban areas, incidences were used for the appropiate regions. Age-specific incidences were used for the age-groups 5-9 yr and 10-14 yr (children), and the age-groups 50-54, 55-59, 60-64 and 64-69 (adults). For the children, a weighted average was calculated to obtain an estimate for children in the age of 7-11 yr by attributing weights to the incidences for age 5-9 and 10-14 of three and two, respectively. For the adults, the mean incidence for the four age groups was calculated.

These week-specific incidences were assigned to the 7 days of each week, assuming that the incidence on each day of the week was the same. The association between the incidence of ILI (ILI_0) and acute respiratory health was examined. In addition, the association between the mean ILI incidence in the preceding week and respiratory health was evaluated. For this purpose, a 7-day moving average was calculated for each day of study using the ILI incidence of the same day and the 6 preceding days (ILI_{0-6}). For example, if the ILI incidence (ILI_0) is 10 in the week from 1-7 January and 30 in the week from 8-14 January,

ILI_{0-6} was calculated as ((1*30)+(6*10))/7 = 90/7 = 12.9 for 8 January, as ((2*30)+(5*10))/7 = 110/7 = 15.7 for 9 January etc.

To evaluate the persistence in time of the association between ILI incidence and acute respiratory health, the association between the mean ILI incidence of 7-13 days earlier (ILI_{7-13}) and the mean of 14-20 days earlier (ILI_{14-20}) and acute respiratory health was evaluated as well.

Symptom diary and PEF measurements

For each subject, the first two days of measurement were removed to eliminate a possible training effect. Subjects with missing diary information (PEF or symptoms) on more than 40% of the days were removed from the dataset. All statistical analyses were conducted using SAS[13].

The individual PEF values in each panel were transformed into population mean deviations to remove the effect of different groups of children contributing to the mean on different days. First, each individual PEF reading for subject i was transformed into a mean deviation by subtracting the mean PEF for subject i. Next, the mean of the individual mean deviations was calculated for each day of study.

After recoding the symptoms in the diary to 0 (no symptom) and 1 (slight or moderate/severe symptom), daily prevalence was calculated for each panel as the fraction of children for whom presence of a respiratory symptom was reported, using data only from those children with non-missing diary information for each separate day. The symptoms shortness of breath, wheeze and attacks of shortness of breath with wheeze were combined as lower respiratory symptoms (LRS). Runny/stuffed nose and sore throat were combined as upper respiratory symptoms (URS). Medication use was analyzed only with respect to bronchodilators (such as salbutamol, fenoterol, terbutalin) and was recoded as 0 (no bronchodilator use) or 1 (any bronchodilator use). For the study reported here, only LRS, URS, cough, phlegm and bronchodilator use were analyzed.

The association between the incidence of ILI and PEF population mean deviation was analyzed with linear regression, weighted for the number of reporting subjects on each day. Minimum daily temperature, time trend and an indicator variable for day of week (school/working day versus weekend/holiday) were included in the model as potential confounders. In most panels the increase of PEF with time was non-linear with a stronger slope in the beginning of the study period, which was interpreted as a learning effect. Therefore, both a linear and a

square root term were included to adjust for time trend. A first order autocorrelation model of the residuals resulted in uncorrelated residuals in all panels. The time series analysis was performed with PROC MODEL, using the Yule-Walker estimation method, for morning and evening PEF separately.

The association between the incidence of ILI and the daily prevalence of symptoms and medication use was evaluated with logistic regression but under the assumption of normally distributed residuals and modelling of autocorrelation using PROC MODEL. This was done because when a binomial distribution was assumed the residuals showed substantial underdispersion. The number of subjects reporting on each day was used as weight. The same potential confounders were included as in the analysis of PEF data. Time trends in symptom prevalence were non-linear as well and were modeled with a linear, quadratic and cubic term. An exception was made for the adults in 1992/1993 where the study period was so short (around 5 weeks) that modeling with three trend terms led to the removal of short-term trends. In these panels only a linear trend term was included.

Four groups were defined: symptomatic children, non-symptomatic children, symptomatic adults and non-symptomatic adults. Urban and non-urban panels were combined because we did not expect the association between ILI incidence and respiratory health to differ between urban and non-urban locations.

A chi-square test was applied to test for heterogeneity in the effect estimates of the five or six panels within each of the four groups (symptomatic and non-symptomatic children and adults). In case of heterogeneity (defined as $p<0.25$), combined effect estimates were calculated using random effects estimation[14].

Odds Ratios for the association between ILI incidence indices and the prevalence of symptoms and bronchodilator use were expressed for an increase in ILI incidence of 20 cases/10,000, both for children and adults. The regression coefficients for the association with PEF were expressed as l/min for an increase in ILI incidence of 20 cases/10,000. This range was selected because during influenza epidemics the ILI incidence was generally higher than 20 cases/10,000 subjects; an incidence of 20 cases/10,000 subjects was therefore considered a relevant range during winters with and without noticable influenza epidemics during the observation periods.

Table 1. Characteristics of the panels of symptomatic and non-symptomatic children (7-11 yr) and adults (50-70 yr) from urban and non-urban areas studied in the Netherlands during the winters of 1992/93, 1993/94 and 1994/95

							Symptom prevalence (%):		
				Panel size	Study period (dd/mm/yy)	No of days	Wheeze and shortness of breath*	Chronic cough†	Use of airway medication‡
1992/93	Urban	children	symptomatic	31	22/01/93-19/04/93	88	37	72	19
	Urban	children	non-symptomatic	43	as above		0	0	0
	Non-urban	children	symptomatic	48	21/01/93-19/04/93	89	49	54	26
	Non-urban	children	non-symptomatic	60	as above		0	0	0
	Urban	adults	symptomatic	21	10/03/93-19/04/93	41	43	30	26
	Urban	adults	non-symptomatic	15	as above		0	0	0
	Non-urban	adults	symptomatic	-§	-		-	-	-
	Non-urban	adults	non-symptomatic	-§	-		-	-	-
1993/94	Urban	children	symptomatic	55	03/11/93-06/03/94	124	33	73	11
	Urban	children	non-symptomatic	56	as above		0	0	0
	Non-urban	children	symptomatic	71	17/11/93-06/03/94	110	32	71	21
	Non-urban	children	non-symptomatic	77	as above		0	0	0
	Urban	adults	symptomatic	63	03/11/93-06/03/94	124	48	38	18
	Urban	adults	non-symptomatic	56	as above		0	0	0
	Non-urban	adults	symptomatic	70	20/11/93-06/03/94	107	43	32	26
	Non-urban	adults	non-symptomatic	73	as above		0	0	0
1994/95	Urban	children	symptomatic	56	25/11/94-05/03/95	101	22	98	19
	Urban	children	non-symptomatic	38	as above		0	0	0
	Non-urban	children	symptomatic	59	23/11/94-05/03/95	103	32	85	27
	Non-urban	children	non-symptomatic	39	as above		0	0	0
	Urban	adults	symptomatic	54	24/11/94-05/03/95	102	39	41	12
	Urban	adults	non-symptomatic	40	as above		0	0	0
	Non-urban	adults	symptomatic	58	23/11/94-05/03/95	103	44	29	23
	Non-urban	adults	non-symptomatic	39	as above		0	0	0

* *In past 12 months*
† *Dry cough apart from cold in past 12 months (children); daily cough during day/night in winter for 3 months a year (adults)*
‡ *Daily use of airway medications (children); current use of asthma medication (adults)*
§ *Not studied in this winter*

Results

In table 1 some characteristics of the panels are shown, for subjects that were used in the data analysis. Chronic cough was the screening symptom with the highest prevalence for children. For adults, recent wheeze and shortness of breath had a slightly higher prevalence than chronic cough. Use of airway medication was reported in the screening questionnaire for a minority of the subjects. During the winter of 1993/1994 the average panel size was larger than during the other winters, and the study period was longer.

Table 2 presents some characteristics of the age specific incidences of influenza and influenza-like-illness ($ILI_{0\text{-}6}$) that were reported by the Dutch Institute of Primary Health Care during the study periods. In figure 1 the incidence of $ILI_{0\text{-}6}$/10,000 subjects versus day of study is plotted for children from urban and non-urban areas in the winters of 1992/1993 and 1993/1994.

During the winter of 1992/1993, an influenza epidemic occurred that started in the beginning of February and peaked during the third week of February, reaching maximum incidences of 67 and 65 cases/10,000 children in urban and non-urban area, respectively. During the winter of 1993/1994, an early influenza epidemic occurred in November. ILI incidence showed a sharp increase starting in the third week of November, peaking during the second week of December and decreasing sharply afterwards, reaching background values around New Year. The epidemic was more severe in the urban than in the non-urban area, reaching maximum incidences of 122 and 56 cases/10,000 children, respectively. For adults, a similar time-course of ILI incidence was observed. Maximum incidences were 70 and 39 in the urban and the non-urban area, respectively. During the third winter no major influenza epidemics occurred. The maximum incidence rates were at or below 20 cases/10,000 subjects.

As figure 1 shows, there was a strong correlation between the ILI incidence for urban and non-urban areas. Pearson correlation coefficients were between 0.87 and 0.96 during the winters of 1992/1993 and 1993/1994, but were lower (0.70 for children and 0.14 for adults) during the winter of 1994/1995 when no influenza epidemics occurred.

Table 3 presents the mean and range of the prevalence of acute respiratory symptoms and bronchodilator use and PEF for the combined panels. Symptomatic panels had a higher prevalence of acute respiratory symptoms and a lower PEF than non-symptomatic panels. For both children and adults, the

prevalence of LRS and bronchodilator use in the non-symptomatic panels was so low that they could not be analyzed.

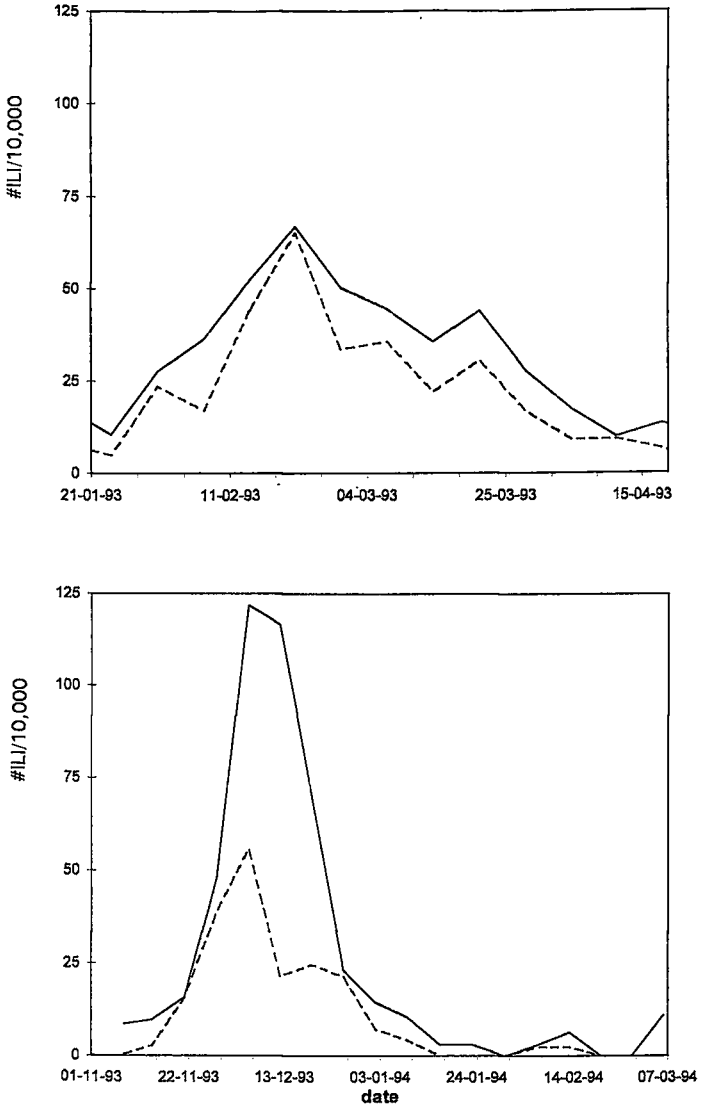

Figure 1. Mean incidence of influenza and influenza-like illness (ILI) versus day of study in children in the general population, registered by the Dutch network of sentinel stations during the winter of 1992/1993 (upper plot) and 1993/1994 (lower plot). ILI incidence was expressed per 10,000 children of the practice population per week, using data from sentinel stations representative for urban areas (solid line) and non-urban areas (dotted line).

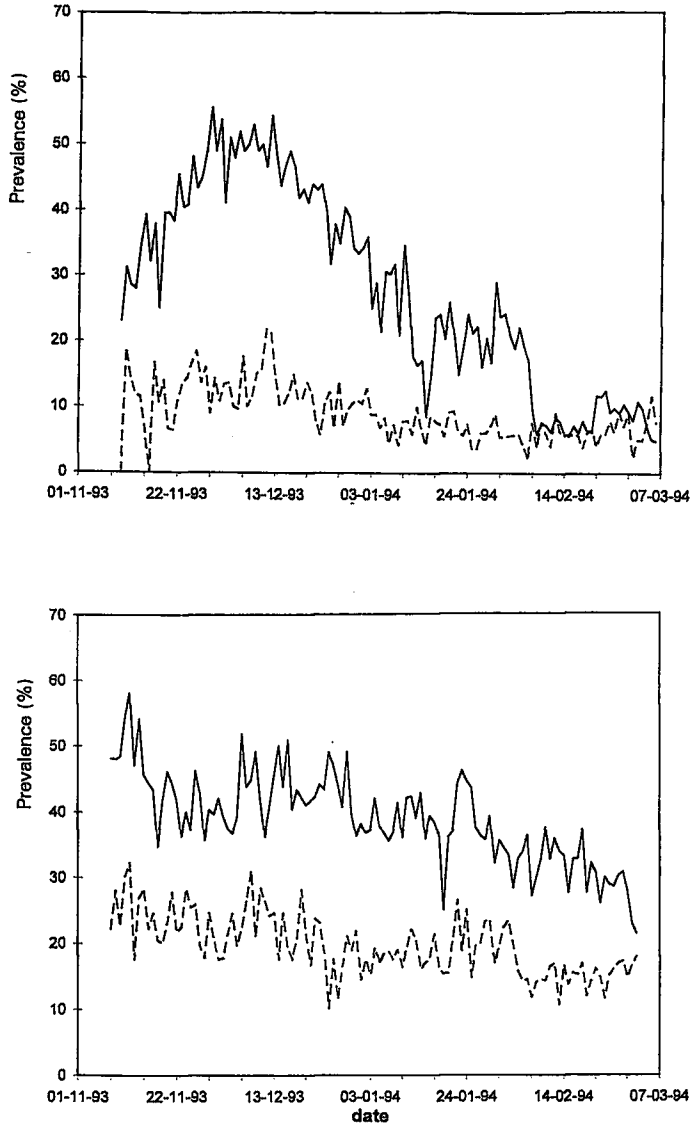

Figure 2. Prevalence of cough (solid line) and Lower Respiratory Symptoms (dotted line) versus day of study, for symptomatic children (upper plot) and symptomatic adults (lower plot) from the urban area studied during the winter of 1993/1994. The prevalence during the first days is not plotted because not all subjects participated during these days.

Table 2. Mean, median and range of the incidence of influenza and influenza-like illness (ILI) in the general population, registered by the Dutch network of sentinel stations during the study periods that the panel study was performed. ILI incidence was calculated as the mean of the same day and the 6 preceding days (ILI_{0-6}) according to age group (7-11 yr and 50-70 yr), per 10,000 of the practice population per week, using data from sentinel stations representative of the urban and non-urban areas studied in each winter.

			Study period (dd/mm/yy)	Mean	Median	Range
1992/93	Urban	children	22/01/93-19/04/93	34	37	10-67
	Non-urban	children	21/01/93-19/04/93	25	23	5-65
	Urban	adults	10/03/93-19/04/93	17	12	6-34
	Non-urban	adults	-*	-	-	-
1993/94	Urban	children	03/11/93-06/03/93	26	9	0-122
	Non-urban	children	17/11/93-06/03/93	12	3	0-56
	Urban	adults	03/11/93-06/03/94	16	6	0-70
	Non-urban	adults	20/11/93-06/03/94	11	6	0-39
1994/95	Urban	children	25/11/94-05/03/95	3	2	0-10
	Non-urban	children	23/11/94-05/03/95	4	2	0-20
	Urban	adults	24/11/94-05/03/95	4	4	0-10
	Non-urban	adults	23/11/94-05/03/95	8	8	2-13

* *Not relevant, because no panels of adults from a non-urban area were studied during this winter*

For most symptoms there was a large difference between the minimum and maximum of prevalence, which is partly a result of strong time trends. A number of examples of time trends in the prevalence are presented in figure 2, where the prevalence of LRS and cough is plotted against day of study during the winter of 1993/1994 for symptomatic children and adults in the urban area. It shows that non-linear time trends occurred, especially for the children panels. In general, the more commonly reported symptoms like cough, URS and phlegm showed stronger time trends than LRS and bronchodilator use.

Table 3. Mean and range of pooled Peak Expiratory Flow (PEF) and prevalence (%) of acute respiratory symptoms and bronchodilator use in the combined panels of symptomatic and non-symptomatic children and adults† studied during the winters of 1992/1993, 1993/1994 and 1994/1995.*

	Morning PEF‡	Evening PEF	Cough	Phlegm	URS	LRS	Bronchodilator use
Symptomatic children	323 (205-444)	329 (207-453)	35 (17-55)	17 (7-32)	36 (20-54)	9 (2-20)	4 (0-11)
Non-symptomatic children	348 (245-463)	352 (252-471)	17 (5-35)	7 (0-17)	22 (7-41)	1 (0-5)	-
Symptomatic adults	428 (183-662)	435 (183-662)	33 (24-45)	35 (26-47)	29 (19-43)	25 (17-35)	12 (8-17)
Non-symptomatic adults	491 (325-695)	497 (334-704)	7 (1-19)	6 (2-16)	10 (2-21)	2 (0-9)	-

* *Pooled PEF and prevalences were calculated as the mean of the panel-specific prevalences and Peak Flow, weighted for the number of person-days that each panel contributed. Similarly, the minimum and maximum of panel-specific prevalences were used to calculate a weighted minimum and maximum for the combined panels. Only the period when the composition of the panel was more or less constant was used.*

† *Urban and non-urban panels were combined*

‡ *In l/min*

The Pearson correlation coefficients between ILI_{0-6} and the potential confounding variables that were included in the model, are presented in table 4. A strong negative correlation was observed between ILI_{0-6} and day of study for the adults in the urban area in 1992/1993, and for both children and adults in the non-urban area in 1993/1994. In the urban area in 1993/1994, a moderately strong negative correlation between ILI_{0-6} and day of study was observed for children and adults. The correlation between ILI_{0-6} and daily minimum temperature was weak in all panels, except for children in the winter of 1992/1993 when moderate associations were observed.

Table 4. Spearman correlation coefficients between the mean incidence of influenza-like-illness of 0-6 days earlier (ILI_{0-6}) and day of study, and between ILI_{0-6} incidence and ambient temperature, in panels children and adults from urban and non-urban areas during the winters of 1992/1993, 1993/1994 and 1994/1995

		Children		Adults	
		Day of study	T†	Day of study	T
1992/93	Urban	-0.36**	-0.49**	-0.86**	-0.14
	Non-urban	-0.30**	-0.45**	-	-
1993/94	Urban	-0.68**	0.12	-0.52**	0.03
	Non-urban	-0.85**	-0.01	-0.84**	0.16
1994/95	Urban	-0.30**	0.23*	0.07	-0.06
	Non-urban	-0.08	0.09	-0.32**	-0.25*

† *Minimum hourly temperature (in °C) of 24-hr values*
* *$P<0.05$*
** *$P<0.01$*

The association between ILI incidence and indicators of respiratory health was analyzed for both same day (ILI_0) and previous week (ILI_{0-6}) incidence. Although the results were fairly similar, ILI_{0-6} tended to be more strongly associated with respiratory health indicators. Therefore, only the results of the analyses with ILI_{0-6} are presented here.

Table 5 presents the combined effect estimates for the association between ILI_{0-6} and PEF, and the prevalence of symptoms and bronchodilator use. The results of the chi-square test for homogeneity are shown as well. Table 5 shows that in all four groups of panels, a higher ILI_{0-6} incidence was associated with a lower level of PEF and a higher prevalence of respiratory symptoms and bronchodilator

Table 5. Combined[†] effect estimates and Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between an increase in ILI$_{0-6}$ incidence[‡] of 20 cases/10,000 subjects and Peak Expiratory Flow (PEF), symptom prevalence and bronchodilator use

		Change in l/min (95% CI)	OR (95% CI)	p$_{hom}$[§]
Symptomatic children	Morning PEF	-2.72 (-5.13 to -0.31)*	-	<0.01
	Evening PEF	-3.18 (-5.69 to -0.67)*	-	<0.01
	LRS	-	1.02 (0.82-1.27)	0.06
	URS	-	1.11 (0.93-1.33)	<0.01
	Cough	-	1.17 (0.96-1.42)	<0.01
	Phlegm	-	1.14 (0.91-1.41)	<0.01
	Bronchodilator	-	1.07 (0.98-1.18)	0.41
Non-symptomatic children	Morning PEF	-1.56 (-3.48 to 0.36)	-	<0.01
	Evening PEF	-2.16 (-4.00 to -0.32)*	-	<0.01
	URS	-	1.14 (1.00-1.30)*	0.18
	Cough	-	1.19 (1.05-1.34)*	0.06
	Phlegm	-	1.09 (0.85-1.40)	0.02
Symptomatic adults	Morning PEF	-2.28 (-5.73 to 1.17)	-	<0.01
	Evening PEF	-1.40 (-3.26 to 0.46)	-	0.05
	LRS	-	1.12 (0.93-1.35)	0.01
	URS	-	1.10 (0.85-1.43)	<0.01
	Cough	-	1.21 (0.90-1.63)	<0.01
	Phlegm	-	1.13 (0.87-1.46)	<0.01
	Bronchodilator	-	1.28 (1.09-1.52)*	0.06
Non-symptomatic adults	Morning PEF	-1.10 (-2.02 to -0.18)*	-	0.37
	Evening PEF	-0.64 (-3.19 to 1.91)	-	0.06
	URS	-	1.09 (0.88-1.35)	0.31
	Cough	-	1.26 (0.82-1.94)	0.02
	Phlegm	-	1.16 (0.81-1.66)	0.16

† *In case of heterogeneity ($p<0.25$, chi-square test on homogeneity), results of random effects models are presented, otherwise fixed effect models. Combined effect estimates were calculated for panels studied during the winters of 1992/93, 1993/94 and 1994/95 in urban and non-urban areas in the Netherlands, for panels of symptomatic and non-symptomatic children and adults separately*

‡ *Mean ILI incidence of 0-6 days earlier*

§ *P-value chi-square test on homogeneity*

* $P<0.05$

use. In some cases the associations reached statistical significance. Considerable heterogeneity was present in the panel-specific effect estimates within each group of panels, indicating that there was more than random variation (due to sampling error) between panels. The panel-specific effect estimates are presented in table 6 for evening PEF, URS, LRS and bronchodilator use. Table 6 shows that there was indeed considerable variation in the panel-specific effect estimates and corresponding confidence intervals. However, the vast majority of the panel-specific effect estimates were in the expected direction of lower PEF and more symptoms and bronchodilator use, a number of them reaching statistical signifance. During the third winter, the smaller range in ILI incidence generally resulted in larger confidence intervals but despite this, significant associations with URS and LRS were observed. For morning PEF, cough and phlegm a similar pattern was observed (not shown).

In table 7 the association of the mean ILI incidence of 7-13 days earlier (ILI_{7-13}) and of 14-20 days earlier (ILI_{14-20}) and a number of respiratory health indicators is shown. It shows that ILI_{7-13} was also associated with a lower evening PEF and a higher prevalence of URS and bronchodilator use, but compared to ILI_{0-6} the effect estimates were generally smaller. ILI_{14-20} was not associated with indicators of respiratory health. The same pattern was observed for morning PEF and the other respiratory symptoms (not shown).

To evaluate whether ILI_{0-6} and ILI_{7-13} were associated with respiratory health indicators independently, the two variables were both included in the same model. The effect estimates and standard errors were comparable to the models where the ILI indices were analyzed separately. For example, in non-symptomatic children the effect estimates for an increase in ILI_{0-6} and ILI_{7-13} incidence of 20 cases/10,000 subjects in association with evening PEF were -2.16 (95% CI: -4.00 to -0.32) and -3.00 (95% CI: -5.46 to -0.54) when analyzed separately, and -2.22 (95% CI: -3.78 to -0.66) and -2.42 (95% CI: -4.90 to 0.06) when both variables were included in the same model. Although the correlation between ILI_{0-6} and ILI_{7-13} was high, especially during the winters of 1992/1993 and 1993/1994 when influenza epidemics occurred, these results indicate that collinearity was apparently not a major problem, and that the ILI incidence 0-6 days earlier and 7-13 days earlier were associated with respiratory health independently.

Table 6. Panel specific and combined[†] effect estimates and Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between an increase in ILI$_{0\text{-}6}$-incidence[‡] of 20 cases/10,000 subjects and evening Peak Flow, and the prevalence of Upper Respiratory Symptoms (URS), Lower Respiratory Symptoms (LRS) and bronchodilator use

			Change in l/min (95% CI)	OR (95% CI)		
			Evening PEF	URS	LRS	Bronchodilator
Symptomatic children	Urban	1992/93	0.54 (-3.81 to 4.89)	0.72 (0.50-1.03)	1.59 (0.80-3.16)	0.90 (0.42-1.90)
	Non-urban	1992/93	-3.32 (-5.77 to -0.87)*	1.12 (0.93-1.34)	0.97 (0.61-1.54)	1.21 (0.82-1.80)
	Urban	1993/94	-1.83 (-2.63 to -1.03)*	1.10 (1.05-1.16)*	1.05 (0.98-1.12)	1.03 (0.94-1.14)
	Non-urban	1993/94	-7.91 (-10.48 to -5.34)*	1.41 (1.19-1.66)*	1.02 (0.77-1.35)	1.50 (1.02-2.21)*
	Urban	1994/95	-4.49 (-11.49 to 2.51)	3.16 (1.28-7.84)*	6.16 (1.15-32.9)*	0.80 (0.14-4.49)
	Non-urban	1994/95	-1.06 (-7.06 to 4.94)	0.77 (0.47-1.25)	0.63 (0.39-1.00)	2.01 (0.54-7.49)
	Combined		*-3.18 (-5.69 to -0.67)**	*1.11 (0.93-1.33)*	*1.02 (0.82-1.27)*	*1.06 (0.97-1.16)*
Non-symptomatic children	Urban	1992/93	-2.01 (-5.62 to 1.60)	1.20 (0.67-2.15)	-	-
	Non-urban	1992/93	-3.00 (-5.06 to -0.94)*	0.88 (0.64-1.21)	-	-
	Urban	1993/94	-0.34 (-3.51 to 0.05)	1.15 (1.07-1.24)*	-	-
	Non-urban	1993/94	-3.12 (-4.65 to -1.59)*	1.30 (1.10-1.54)*	-	-
	Urban	1994/95	-14.2 (-28.0 to -0.36)*	3.03 (0.45-20.7)	-	-
	Non-urban	1994/95	-1.36 (-6.24 to 3.52)	0.77 (0.44-1.37)	-	-
	Combined		*-2.16 (-4.00 to -0.32)**	*1.14 (1.00-1.30)**	-	-
Symptomatic adults	Urban	1992/93	-14.3 (-25.0 to -3.58)*	3.05 (1.40-6.63)*	1.30 (0.82-2.08)	1.95 (1.32-2.87)*
	Non-urban	1992/93	-	-	-	-
	Urban	1993/94	-1.16 (-1.42 to -0.40)*	1.12 (1.00-1.24)*	1.08 (1.00-1.18)*	1.18 (1.03-1.35)*
	Non-urban	1993/94	-0.18 (-1.63 to 1.27)	1.03 (0.89-1.21)	1.05 (0.94-1.17)	1.15 (1.04-1.27)*
	Urban	1994/95	0.30 (-10.3 to 10.9)	0.53 (0.29-0.98)	1.63 (0.83-3.20)	1.75 (0.97-3.17)
	Non-urban	1994/95	-7.13 (-12.9 to -1.33)*	1.36 (0.78-2.38)	1.54 (1.06-2.22)*	1.68 (0.97-2.91)
	Combined		*-1.40 (-3.26 to 0.46)*	*1.10 (0.85-1.43)*	*1.12 (0.93-1.35)*	*1.28 (1.09-1.52)**
Non-symptomatic adults	Urban	1992/93	4.56 (-2.18 to 11.3)	0.50 (0.20-1.26)	-	-
	Non-urban	1992/93	-	-	-	-
	Urban	1993/94	-1.17 (-2.09 to -0.25)*	1.13 (0.95-1.33)	-	-
	Non-urban	1993/94	1.43 (-2.14 to 5.00)	1.22 (0.77-1.94)	-	-
	Urban	1994/95	-0.38 (-5.65 to 4.89)	0.62 (0.23-1.71)	-	-
	Non-urban	1994/95	-5.99 (-12.9 to 0.97)	3.72 (0.53-26.2)	-	-
	Combined		*-0.64 (-3.19 to 1.91)*	*1.09 (0.88-1.35)*	-	-

[†] *In case of heterogeneity ($P<0.25$, chi-square test on homogeneity), results of random effects models are presented, otherwise fixed effect models.*

[‡] *Mean ILI incidence of 0-6 days earlier*

* *$P<0.05$*

Table 7. Combined[†] effect estimates and Odds Ratios with 95% confidence intervals (95% CI) for the association between an increase in ILI incidence (mean of 7-13 days earlier: ILI_{7-13} and mean of 14-20 days earlier: ILI_{14-20}) of 20 cases/10,000 subjects and evening PEF, the prevalence of Upper Respiratory Symptoms (URS) and bronchodilator use.

		ILI_{7-13}[‡]	ILI_{14-20}[§]
Symptomatic children	Evening PEF[¶]	-1.30 (-3.42 to 0.82)	0.26 (-1.34 to 1.86)
	URS	1.08 (0.94 to 1.24)	0.96 (0.90 to 1.02)
	Bronchodilator use	1.22 (0.88 to 1.70)	0.98 (0.81 to 1.20)
Non-symptomatic children	Evening PEF	-3.00 (-5.46 to -0.54)*	-0.52 (-2.14 to 1.10)
	URS	1.15 (0.96 to 1.37)	1.01 (0.88 to 1.16)
Symptomatic adults	Evening PEF	-0.84 (-2.42 to 0.74)	0.00 (-0.66 to 0.66)
	URS	1.05 (0.96 to 1.14)	0.94 (0.76 to 1.16)
	Bronchodilator use	1.07 (1.00 to 1.15)*	0.77 (0.57 to 1.03)
Non-symptomatic adults	Evening PEF	0.28 (-0.64 to 1.20)	0.62 (-0.30 to 1.54)
	URS	1.14 (0.99 to 1.31)	1.21 (0.85 to 1.73)

† *In case of heterogeneity ($P<0.25$, chi-square test on homogeneity), results of random effects models are presented, otherwise fixed effect models*

‡ *Mean ILI incidence of 7-13 days earlier*

§ *Mean ILI incidence of 14-20 days earlier*

¶ *Change in l/min*

* $P<0.05$

Discussion

In this study, we have shown that the incidence of influenza and influenza-like-illness (ILI), registered by the Dutch network of GP sentinel stations, was associated with respiratory health in panels of symptomatic and non-symptomatic children and adults selected from defined geographical areas.
The combined effect estimates calculated for the three winters indicated that an increase in ILI incidence of 20 cases/10,000 subjects was associated with a 0.1 - 1% lower level of PEF, and with an increase in the prevalence of respiratory symptoms and bronchodilator use in the range of 2% - 28%. For a major influenza epidemic reaching peak ILI incidences of 122 cases/10,000 subjects, this corresponds to PEF decrements of up to 6%, and to an increase in symptom reporting and bronchodilator use by factors of up to 2.9 and 4.5, respectively.
The most consistent associations with respiratory health were found if the incidence of ILI was expressed as the mean of the preceding week (ILI_{0-6}). ILI_{7-13} was also independently associated with indicators of respiratory health, but no association between ILI_{14-20} and respiratory health was found.
A positive association was found between the incidence of ILI and the prevalence of the respiratory symptoms URS (runny/stuffed nose, sore throat), LRS (wheeze, shortness of breath, attacks of shortness of breath with wheeze), cough and phlegm. This is consistent with the knowledge of the mechanisms of respiratory viruses, including influenza viruses[15]. In first instance respiratory viruses cause upper respiratory tract infections. This frequently triggers a response in the lower airways leading to prolonged morbidity, especially in subjects with pre-existing airway disease. The induction or amplification of bronchial hyperresponsiveness may be an important mechanism by which lower respiratory symptoms are produced[4,5]. Epidemiological studies have also shown that several types of viral infection can exacerbate asthma symptoms in children[16-18]. The importance of respiratory infections in adult asthamtic attacks is less clear, although associations have been reported as well[6,7].
In our study an increase in ILI incidence of 20 cases/10,000 subjects was associated with a significant increase in bronchodilator use of 28% and a non-significant increase in asthma symptoms (LRS) of 6% in adults. This suggests that respiratory viruses play a role in the exacerbations of asthma in adults, too.
In children an increase in ILI incidence of 20 cases/10,000 subjects was associated with a smaller, and non-significant increase in bronchodilator use and

LRS of 6% and 2%, respectively.

Can some sort of bias have produced the association between ILI incidence and respiratory health? Potential confounders that might bias the observed associations are meteorologic variables (mainly ambient temperature), air pollution and long term time trend. Air pollution is a potential confounder since it might be associated independently with both respiratory infections and respiratory health. However, exposure to low level air pollution is probably not a major determinant of respiratory infections; in addition, the correlation between PM_{10} (as an indicator for air pollution) and ILI incidence was low. We have adjusted for ambient temperature, and for long term time trend (generally in the order of weeks) in PEF and the prevalence of symptoms. However, those factors might be associated with respiratory infections in the panels and thus, the potential of overadjustment exists, resulting in an underestimation of the coefficients for ILI incidence.

In the Netherlands, the occurrence of major influenza epidemics is generally reported by the mass media. Reporting bias might have occurred due to subject's increased awareness of respiratory symptoms during influenza epidemics. However, it is not likely that this type of bias was an important factor because our study was focusing on effects of air pollution. Moreover, associations between ILI incidence and respiratory health were also observed during the third winter when no influenza epidemics occurred.

The panel-specific effect estimates within the four groups (symptomatic and non-symptomatic children and adults) showed considerable heterogeneity. When the third winter, with a small range in ILI incidence was excluded, heterogeneity was still present.

This heterogeneity may have different reasons. First, the influenza viruses involved in influenza epidemics may differ from season; virological surveillance has confirmed that this was indeed the case[8,9]. Second, the amount of misclassification that occurs when using the incidence of ILI, registered by the sentinel stations, as an indicator for the respiratory infection load in selected panels might differ between panels. Third, with the statistical models used the potential of overadjustment for time trend exists, as mentioned before; and the extent to which this occurred might differ between panels.

The ILI incidence was below 0.1%/week on most days during the study period with a maximum of 1.2%/week. This is probably an underestimation of the true ILI incidence in th Dutch population, as not all patients will seek medical

assistance. No information was available about the incidence of less serious respiratory infections (e.g. common cold); ILI is the only respiratory illness that is monitored by the sentinel stations.

During the third winter, when the ILI incidence was lowest, relatively large effect estimates were found. This indicates that the associations are not only observed during influenza epidemics. Rather, it raises the question whether the association between ILI incidence and respiratory health is the result of influenza virus activity or whether ILI incidence might reflect the activity of other respiratory viruses too. Virological surveillance of respiratory specimens of patients diagnosed with ILI by the sentinel stations has shown that during the winters of 1992/1993 and 1993/1994, in those patients where respiratory viruses could be isolated, the influenza virus was detected in 69% and 73% of the cases, respectively[8,9]. In the winter of 1994/1995, when no influenza epidemics occurred, this was only 36%[10]. Rhinoviruses were detected in respectively 14%, 12% and 26% of the patients during the three consecutive winters. Rhinoviruses are the most common causative agent of common cold in the community. They peak in early autumn and spring, but are perennial in their occurrence[4]. Comparing rhinoviruses and influenza, there is no doubt that influenza viruses produce the most severe symptoms[19]. Thus, the majority of the people suffering from rhinovirus infection will not seek medical assistance.

Other respiratory viruses (including adeno-, corona-, entero-, RS-, and parainfluenza viruses) were detected in 13%, 15% and 38% of the patients with ILI during the three winters[8-10]. When interpreting these data, it should be noted that the virological surveillance has only been carried out in 15-25% of the total number of patients with ILI, and the number of respiratory specimens taken was not completely proportional to the ILI incidence. Of those patients with ILI for which respiratory specimens were taken, a respiratory virus could be isolated in only 33%, 31%, and 34% of the cases during the three winters, respectively. Also, the respiratory surveillance refers to the period October-April, which is longer than our study period, and respiratory specimens were taken from all sentinel stations and all age groups, while we have used data from selected regions and age groups. Nevertheless, these results suggest that during winters without influenza epidemics, the incidence of ILI is mainly an indicator for other respiratory viruses than the influenza virus. However, when influenza epidemics occur, the pattern of ILI incidence seems to reflect mainly influenza activity and to a lesser extent, the activity of other respiratory viruses.

The observed association between ILI incidence and respiratory health in selected panels implies that in panel studies, the incidence of ILI might be used to adjust for the potential confounding effect of respiratory infections. For example, when investigating the effect of ambient air pollution on respiratory health, respiratory infections can confound the association if they coincide with periods with high or low air pollution. Since the effect of air pollution on respiratory health is in the same order of magnitude, or less[20,21] than the effect of elevated ILI incidence, this might lead to substantial over- or underadjustment of the effect of air pollution. Our study has also shown that the ILI incidence of the previous week (0-6 days earlier) and of two weeks earlier (7-13 days earlier) were independently associated with indicators of respiratory health thus, should both be taken into account when adjusting for the potential confounding effect of respiratory infections.

In conclusion, the incidence of ILI, registered by the Dutch sentinel station registration network was associated with reduced PEF and increased reporting of symptoms and bronchodilator use in panels of symptomatic and non-symptomatic children and adults, selected from defined geographical regions in the Netherlands.

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Chapter 5

Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms

Saskia C. van der Zee, Gerard Hoek, H. Marike Boezen, Jan P. Schouten, Joop H. van Wijnen and Bert Brunekreef

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Abstract

The goal of this study was to investigate to what extent different air pollution components are associated with acute respiratory health effects in children with and without chronic respiratory symptoms ('symptomatic' and 'non-symptomatic' children).

During three consecutive winters starting in 1992/1993, Peak Expiratory Flow (PEF) and respiratory symptoms were registered daily in panels of symptomatic and non-symptomatic children (7-11 yr), living in urban areas with high traffic intensity in the Netherlands. Simultaneously, panels of children living in non-urban areas were studied. Daily measurements of PM_{10}, Black Smoke (BS), sulfate, SO_2, and NO_2 were performed in both areas.

The contrast in particle concentrations (PM_{10}, BS and sulfate) between urban and non-urban areas was small, but there was more contrast in the concentrations of SO_2 and NO_2. In symptomatic children from both areas, significant associations were observed between PM_{10}, BS and sulfate concentrations and the prevalence of lower respiratory symptoms (LRS) and PEF decrements. Particle concentrations were also associated with bronchodilator use in the urban areas, but not in the non-urban areas. After stratification by medication use, stronger associations were found in medicated children than in non-medicated children. The magnitude of the estimated effects was in the order of a twofold increase in bronchodilator use, a 50% increase in LRS and an 80% increase in PEF decrements for a 100 $\mu g/m^3$ increase of the 5-day mean PM_{10} concentration. In non-symptomatic children, significant associations were observed between PM_{10} and BS concentration and PEF decrements in both areas, but of smaller magnitude than for symptomatic children. No associations with respiratory symptoms were observed.

The results suggest that symptomatic children are more susceptible to the effects of particulate air pollution than non-symptomatic children, and that use of asthma medication does not prevent the adverse effects of particulate air pollution in symptomatic children.

Introduction

Severe winter air pollution episodes in the past have been associated with serious health effects, such as increased hospital admissions and mortality[1]. Over the last decades, concentrations of 'traditional' winter air pollution components such as SO_2 and airborne coarse particulates have decreased in the Netherlands and other European countries. This decrease can be ascribed to emission abatement measures and changes in energy production for 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 higher intensity of motorized traffic. Motorized traffic also plays an important role in the formation of particulate air pollution, both direct and indirect through the formation of secondary aerosols[2]. Recent studies have demonstrated that current levels of particulate air pollution are associated with adverse health outcomes, even at concentrations well below the 1987 WHO Air Quality Guidelines for Europe[3,4].

Also in the Netherlands associations were reported between low levels of winter air pollution and respiratory health among children[5-7]. However, those studies have mainly been conducted in non-urban areas. It was not clear to what extent such associations would be different in urban areas where the contribution of local sources to the air pollution mixture is greater than in non-urban areas.

The uncertainties surrounding acute effects of wintersmog episodes in large urban areas, led us to perform a large epidemiological 'winter smog' study that was conducted during three consecutive winters starting in 1992/1993. The study was designed to compare acute health effects of winter air pollution in selected panels of children and adults, with and without chronic respiratory symptoms, living in urban and non-urban areas. This paper describes the results for the panels of children. The results for the panels of adults will be described in a separate paper.

Methods

Study design

The study was carried out during three consecutive winters starting in 1992/1993. During each winter, panels of children (7-11 yr) with and without chronic respiratory symptoms were selected from an urban and a non-urban area. The children were selected from the general population of children with a

screening questionnaire. During the three months study periods daily measurements of Peak Expiratory Flow (PEF) were made, and the occurrence of acute respiratory symptoms and bronchodilator use was registered in a daily diary. Air pollution was monitored daily on central sites in each community.

Study population

As study areas were chosen: Rotterdam and Bodegraven/Reeuwijk (1992/1993), Amsterdam and Meppel (1993/1994), and Amsterdam and Nunspeet (1994/1995). Figure 1 in chapter 2 of this thesis shows the locations of the areas. The Netherlands is a country with a very high population density. The southern, and especially the western parts, are most urbanized. The north-eastern part has a relatively low population density. All major cities are located in the western part. Rotterdam is an industrialized city with approximately 600,000 inhabitants. It is located in the center of the Rijnmond area (an agglomeration of industrial cities). Amsterdam (720,000 inhabitants) has a relatively small industrial area; local air pollution is caused primarily by emissions from motorized traffic. In addition to local air pollution, transport of air pollution from other parts of the Netherlands and from other European countries contributes to air pollution levels in Dutch cities.

For the urban panels the objective was to select children with high exposure to traffic related air pollution. Therefore, both in Rotterdam and Amsterdam areas in the inner city were selected with a high traffic intensity and a high population density, and with no industrial sources.

The non-urban panels were selected from communities which had no major traffic emissions, no large industrial sources and had sufficient size to select enough children.

During the first winter (1992/1993), we selected a non-urban area close (± 30 km) to the urban area. During the second and third winters, we selected the non-urban areas at a larger distance from the urban area in trying to maximize the contrast in air pollution, that was found to be small in the first winter.

Screening questionnaires were used to obtain information on chronic respiratory symptoms. The questionnaires were distributed through the schools or by mail to all children aged 7-11 yr, and had to be filled out and returned by their parents. The screening questionnaire was an adapted version of questions from the WHO questionnaire for children[8]. During the first winter (1992/1993), a slightly different questionnaire was used compared to the second and third winters. The reason for this was that during the winter of 1993/1994, the study was performed in the

framework of the Pollution Effects of Asthmatic Children in Europe (PEACE) study and thus the PEACE protocol was followed[9]. Children were considered 'symptomatic' if they had a positive answer to one or more of the screening questions listed in table 1.

Table 1. Selection questions of screening questionnaire during the three winters

	1992/93	1993/94 and 1994/95
recent asthma:	Has your child been bothered in the past year by attacks of shortness of breath with wheezing?	Has your child been bothered in the past 12 months by attacks of shortness of breath with wheezing?
chronic cough:	Does your child cough like this almost daily for three months a year? (this question follows two other questions on cough during the day or night, on most days during the autumn/winter season)	Has your child had a dry cough at night in the past 12 months, apart from coughing with a cold or chest infection?
doctor diagnosed asthma:	Has a doctor ever said your child has asthma?	Has a doctor ever said your child has asthma?
recently treated by a specialist for asthma:	Has your child been treated for asthma by a specialist during the past year?	-
recent wheeze:	-	Has your child been bothered in the past 12 months by a wheezy chest, apart from cold?

Children without any reported symptoms on the screening questionnaire were considered 'non-symptomatic'. Symptomatic and non-symptomatic children were selected randomly from those who met the selection criteria. Target panel size for both symptomatic and non-symptomatic panels was 75 subjects per panel during the winters of 1992/1993 and 1993/1994. During the winter of 1994/1995 target panel size was 60 subjects for symptomatic panels and 40 subjects for non-symptomatic panels. A detailed questionnaire on chronic respiratory symptoms, sources of indoor air pollution (smoking, housing characteristics) and parental education was administered to the parents. To further characterize the

children they were examined with skin prick test, determination of IgE, number of peripheral blood eosinophils, lung function and bronchial reactivity to metacholine. Methods and results of these analyses will be published elsewhere. The study was approved by the Medical Ethical Committee of the Groningen University Hospital and the Medical Ethical Committee of the Municipal Health Service in Amsterdam. Informed consent was signed by the parents of all children.

Exposure assessment

24-Hour measurements of PM_{10} and Black Smoke were made at fixed sites in both the urban and non-urban areas. In addition, 24-hour measurements of non-organic secondary aerosols (sulfate, nitrate and ammonium) and aerosol acidity were made. Measurements were from 3 PM to 3 PM. The particle measurement sites were chosen such that they were close to the residence of the participating children, and not strongly influenced by local sources such as traffic and industry in the direct vicinity ('background sites'). Information about the ambient concentrations of SO_2 and NO_2 in Rotterdam was obtained from a city-background station of the National Air Quality Monitoring Network, operated by the National Institute of Public Health and Environmental Protection. In Amsterdam, information was obtained from a city-background station of the Air Quality Monitoring Network operated by the Environmental Research Institute of the City of Amsterdam. Data for the non-urban areas were obtained from the nearest measurements sites of the National Air Quality Monitoring Network, located in Zegveld, Witteveen and Lelystad during the three consecutive winters. Those measurement sites were located approximately 10, 40 and 30 km away from the non-urban areas, respectively. SO_2 and NO_2 concentrations were provided as 1-hour means and transformed into 24-hour average concentrations from 3 PM to 3 PM. More information about the measurement methods is reported elsewhere[10].

Temperature was measured in 1-hour intervals and the minimum between 3 PM and 3 PM was recorded. Data for the urban areas were obtained from Rotterdam and Amsterdam Airports, respectively. Data for the non-urban areas were obtained from Zegveld, Eelde and Lelystad, located approximately 10, 40 and 30 km away from the non-urban areas in the three consecutive winters.

Data on the weekly incidence of influenza and influenza-like illness (ILI) were obtained from the Dutch Institute of Primary Health Care (NIVEL). A detailed analysis of the ILI incidence data in relation to the health data collected in our panels will be reported elsewhere[11].

Health measurements

During the study period, participants performed PEF measurements twice daily using Mini Wright peak flow meters, once in the morning before breakfast and once in the evening before going to bed. Subjects were instructed to perform the PEF measurements before any airway medication was taken. Every test consisted of three maneuvers and participants were asked to note all three readings in a diary. The highest of the three PEF readings was used for analysis.

The diary was also used to register the occurrence of acute respiratory symptoms and medication use. Symptoms included 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 and fever. During the winters of 1993/1994 and 1994/1995, the symptoms eye irritation and sore throat were included as well. Subjects were instructed to indicate whether the symptoms were absent, slight, or moderate/severe on each day. In order to assess medication use, subjects had to write down the name of the medication and the number of units taken. The use of the diary and Mini Wright meter was demonstrated during a home visit in presence of the child and at least one of the parents.

Data analysis

All panels were analysed separately. Next, combined effect estimates were calculated for symptomatic and non-symptomatic panels, and for urban and non-urban areas separately.

For each subject, the first two days of measurement were removed to eliminate a possible training effect. Subjects with missing diary information (PEF or symptoms) on more than 40% of the days were removed from the dataset. All statistical analyses were conducted using SAS[12].

For the analysis of PEF data, a different approach was used compared to other panel studies, including the PEACE study[5,9,13,14]. Those studies were focusing on population average responses, whereas our approach is focusing on the fraction of children that is experiencing substantial PEF-decrements. A comparison between the two approaches is described by Hoek *et al.*[15]. In short, it shows that small decrements in population mean PEF are accompanied by large increases in the fraction of children that have a substantial decrease in PEF.

For each individual subject the median morning and evening PEF was calculated. Percentage morning decrements were calculated for each measurement day for each subject by subtracting the individual median of morning PEF from the

morning PEF measured on that day and dividing the difference by the individual median of morning PEF. The prevalence of morning decrements larger than 10% and 20% respectively was calculated as the number of children experiencing such a decrement divided by the total number of children reporting valid PEF measurements on each day of study. The percentage evening decrements were calculated the same way.

After recoding the symptoms in the diary to 0 (no symptom) and 1 (slight or moderate/severe symptom), daily prevalence was calculated for each panel as the fraction of children for whom presence of a respiratory symptom was reported, using data only from those children with non-missing diary information for each separate day. The symptoms shortness of breath, wheeze and attacks of shortness of breath with wheeze were combined as lower respiratory symptoms (LRS). Cough was analysed separately. Runny/stuffed nose and sore throat were combined as upper respiratory symptoms (URS). Medication use was divided into bronchodilators (such as salbutamol, fenoterol, terbutalin), maintenance medication (such as cromoglycate, theophyllin, anti-histaminica and inhaled corticosteroids) and an "other" category, and was recoded as 0 (no medication use) or 1 (any medication use), for bronchodilator and maintenance medication use separately. For the study reported here, only LRS, URS, cough, phlegm and bronchodilator use were analysed.

The explanatory variables were 24 hour average concentration of PM_{10}, Black Smoke, SO_2, NO_2, sulfate and nitrate, analysed separately. Current day concentration (lag 0), previous day concentration (lag 1), concentration of two days before (lag 2) and the average concentration of 0-4 days before (5 day mean) were analyzed separately.

The association between air pollution and the prevalence of PEF decrements, symptoms and bronchodilator use was evaluated with logistic regression but under the assumption of normally distibuted residuals using PROC MODEL. This was done because when a binomial distribution was assumed the residuals showed considerable underdispersion. The number of subjects reporting on each day was used as weight, and correction for autocorrelation of residuals was made assuming a first order autoregressive structure. Minimum daily temperature, an indicator variable for day of week (school day versus weekend/holiday), time trend, and the incidence of influenza and influenza-like-illness (ILI) in the general population were included in the model as potential confounders. Time trend was included as a linear, quadratic and cubic term because in most panels strong non-

linear time trends were observed in the prevalence of symptoms, medication use and PEF-decrements.

The incidence of ILI, registered by the Dutch network of sentinel stations, was included in the model with two variables representing respectively the mean incidence of 0-6 days earlier and 7-13 days earlier. A motivation of the selection of these variables, as well as an association between ILI incidence and respiratory health in the panels will be reported elsewhere[11].

Combined effect estimates were calculated for symptomatic and non-symptomatic panels, and for urban and non-urban areas separately, using the regression slopes from the panel-specific logistic regression models for the three winters. Combined effect estimates were calculated as the weighted mean of the panel-specific slopes, with the weights being the inverse of the panel-specific variances of the slopes. The standard error of the combined slope was calculated as the inverse of the square root of the sum of weights. Odds Ratios were calculated for an increase of 100 $\mu g/m^3$ in PM_{10} concentration, an increase of 40 $\mu g/m^3$ in Black Smoke, SO_2 and NO_2 concentration and an increase of 15 $\mu g/m^3$ in sulfate concentration.

To test whether the association between air pollution and respiratory health differed significantly between urban and non-urban areas, a weighted linear regression was performed with the panel-specific regression slopes as the dependent variable and an indicator for area (urban vs non-urban area) as the independent variable. The inverse of the panel-specific variances of the slopes were used as weights. The weighted regression analysis was performed for symptomatic and non-symptomatic children separately.

A number of multiple regression models including two pollutants simultaneously have been specified for the symptomatic panels, in an attempt to separate effects from specific components of the air pollution mixture. This was done for the following combinations of pollutants: PM_{10} and SO_2, PM_{10} and BS, PM_{10} and sulfate, and BS and sulfate. The same lags were evaluated simultaneously for both pollutants.

Results

From the 12,331 screening questionnaires handed out during the three winters, 5,770 (47%) were returned. The response was slightly lower in the urban areas (42%) than in the non-urban areas (52%). Of the 5,770 children who returned questionnaires, 931 (16%) were eligible and willing to participate in the symptomatic panels, whereas 1,198 (21%) were eligible and willing to participate in the non-symptomatic panels. From the 396 symptomatic and 399 non-symptomatic children that were enrolled, respectively 320 and 313 were included in the final analysis.

In the tables 2a, 2b and 2c some characteristics of the panels are shown.

Table 2a. Characteristics of the panels, three winters combined

	Symptomatic		*Non-symptomatic*	
	Urban area	*Non-urban area*	*Urban area*	*Non-urban area*
Original sample size	193	203	196	203
Final sample size*	142	178	137	176
winter 1992/1993	31	48	43	60
winter 1993/1994	55	71	56	77
winter 1994/1995	56	59	38	39

** smaller than original sample size because subjects with >40% missing diary information were excluded*

Table 2b. Screening prevalence of symptoms and medication use (% in final sample)

	Symptomatic		*Non-symptomatic*	
	Urban area	*Non-urban area*	*Urban area*	*Non-urban area*
% Recent wheeze	44	46	0	0
% Recent asthma	29	37	0	0
% Chronic cough	83	71	0	0
% Doctor diagnosed asthma	26	38	0	0
% Daily medication use	16	24	0	0

*Table 2c. Mean daily prevalence (%) of symptoms, medication use and PEF-decrements, and mean PEF**

	Symptomatic		*Non-symptomatic*	
	Urban area	*Non-urban area*	*Urban area*	*Non-urban area*
Lower Respiratory Symptoms	8.4	9.1	0.8	1.1
Upper Respiratory Symptoms	37	35	21	23
Cough	35	35	16	18
Phlegm	15	19	7.4	6.3
Bronchodilator use	4.8	3.4	-	-
Maintenance medication use	8.5	15.5	-	-
>10% decrements in evening PEF	10.5	10.8	9.4	7.3
Mean evening PEF (l/min)	329	329	346	358

** pooled prevalences and PEF were calculated as the mean of the panel-specific prevalences and PEF, weighted for the number of person-days that each panel contributed*

Table 2c shows that the prevalence of >10% decrements in evening PEF was on average 10.6% in the symptomatic panels and 8.3% in the non-symptomatic panels. Symptomatic panels had a higher prevalence of acute respiratory symptoms than non-symptomatic panels. In symptomatic urban panels the prevalence of maintenance medication was almost twofold lower than in symptomatic non-urban panels (8.5% and 15.5%, respectively). Bronchodilator use was not reported in the non-symptomatic panels during the three winters. Lower Respiratory Symptoms (LRS) were rarely reported in the non-symptomatic panels; during the winters of 1992/1993 and 1994/1995, the panel-specific prevalences of LRS were too low to be analyzed. Only during the winter of 1993/1994 the mean panel-specific prevalence of LRS was relatively high (1.2% in the urban area and 2.0% in the non-urban area). In table 3 the results of the air pollution measurements are presented. The median concentrations of PM_{10} and BS were only slightly higher in the urban areas than in the non-urban areas. There was more contrast in the concentration of the gaseous pollutants SO_2 and NO_2. The median concentration of sulfate was slightly lower in the urban than in the non-urban areas. Concentrations of aerosol acidity were very low during the three winters (not shown). Only a few concentrations were above the detection limit (0.10 $\mu g/m^3$) and therefore, concentrations of aerosol acidity were not used

in further analyses.

During the winters of 1992/1993 and 1993/1994, air pollution episodes occurred resulting in elevated particle concentrations in both the urban and non-urban areas. During the winter of 1994/1995 no air pollution episodes occurred as a result of mild meteorological conditions. For a more detailed description of the air pollution concentrations and episodes we refer to another paper[10].

Spearman correlations between the various air pollutants and potential confounding variables were calculated separately for the urban and non-urban areas during the three winters (not shown). During the first two winters, when air pollution episodes occurred, a high correlation ($R>0.7$) was observed between PM_{10} and the other indicators of particulate air pollution Black Smoke and sulfate. The correlation between SO_2 and indicators of particulate air pollution varied between 0.5 and 0.8 and was slightly higher than the correlation between NO_2 and indicators of particulate air pollution (except for Black Smoke). The correlation between SO_2 and NO_2 was approximately 0.5. During the winter of 1994/1995, lower than the above correlations were found between all air pollutants. There were no clear differences in correlations between urban and non-urban areas. Air pollutants and temperature were moderately high correlated, while low correlations were observed between air pollutants and the potential confounders day of study and incidence of influenza-like-illness.

Table 4 presents the associations between air pollution indices and the prevalence of >10% decrements in evening PEF, respiratory symptoms and bronchodilator use in symptomatic children. In the urban areas, the prevalence of >10% decrements in evening PEF, LRS and bronchodilator use was positively associated with PM_{10}, Black Smoke and sulfate. Many associations reached statistical significance. SO_2 was also positively associated with those respiratory health indicators but less consistent than the particulate pollutants. NO_2 was positively associated with bronchodilator use but not with LRS or >10% decrements in evening PEF. No associations were observed between air pollution indices and the prevalence of URS and cough. With phlegm and the prevalence of >10% decrements in morning PEF, no associations were observed either (not shown). In the non-urban areas, associations between particle concentrations and >10% decrements in evening PEF and LRS were in the same direction as in the urban area, but statistically significant associations were reached less frequently. As opposed to what was found in the urban areas, particle concentrations were not consistently associated with bronchodilator use. However, the differences in

Table 3. Median and maximum of 24-hr average air pollution concentrations , and median and range of temperature and incidence of influenza-like illness observed during the study periods in urban and non-urban areas

		Study period dd/mm/yy	*no of days*	*PM_{10}*	*Black Smoke*	*Sulfate*	*SO_2*	*NO_2*	*T*[†]	*ILI_{0-6}*[‡]
1992/1993	Urban	22/1/93-19/4/93	88	48 (146)	15 (56)	5.3 (17)	23 (152)	51 (94)	4.2 (-2.9; 9.8)	37 (10-67)
	Non-urban	21/1/93-19/4/93	89	35 (104)	10 (38)	5.9 (15)	8.9 (43)	33 (83)	2.8 (-4.4; 9.8)	23 (5-65)
1993/1994	Urban	3/11/93-6/3/94	124	37 (123)	12 (65)	2.7 (24)	11 (34)	48 (76)	2.7 (-8.1; 10.0)	9 (0-122)
	Non-urban	17/11/93-6/3/94	110	35 (242)	10 (58)	2.8 (23)	5.0 (42)	25 (54)	1.0 (-10.9; 9.3)	3 (0-56)
1994/1995	Urban	25/11/94-5/3/95	101	29 (90)	6.9 (28)	1.7 (10)	6.0 (24)	47 (82)	3.8 (-5.0; 11.5)	2 (0-10)
	Non-urban	23/11/94-5/3/95	103	24 (97)	5.8 (43)	1.9 (18)	3.6 (17)	22 (57)	3.1 (-11.1; 11.3)	2 (0-20)

* *air pollution concentrations in $\mu g/m^3$*

† *minimum hourly temperature (in °C) of 24-hr values*

‡ *mean of incidence of influenza-like illness in the previous week*

Table 4. Odds Ratios (OR) with 95% confidence int ervals (95% CI) for the association between air pollution and the prevalence of> 10% decrements, acute respiratory symptoms and bronchodilator use in symptomatic children, calculated from combined effect estimates. OR's for an increase of 100 μg/m³ in PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2 and 15 μg/m³ for sulfate.

	Urban areas					*Non-urban areas*				
	Evening PEF	*LRS*	*URS*	*Cough*	*Broncho*	*Evening PEF*	*LRS*	*URS*	*Cough*	*Broncho*
PM_{10}										
lag 0	1.42 (1.05-1.92)*	1.34 (1.02-1.75)*	1.00 (0.85-1.18)	1.05 (0.90-1.23)	1.29 (0.99-1.67)	1.32 (1.02-1.70)*	1.01 (0.84-1.22)	1.08 (0.97-1.21)	1.07 (0.97-1.19)	0.82 (0.61-1.10)
lag 1	1.28 (0.97-1.68)	1.48 (1.15-1.89)*	1.04 (0.89-1.21)	0.94 (0.81-1.10)	1.17 (0.90-1.52)	1.10 (0.86-1.41)	1.04 (0.87-1.24)	0.95 (0.85-1.06)	1.09 (0.98-1.20)	1.09 (0.82-1.45)
lag 2	1.54 (1.19-1.98)*	1.30 (1.03-1.65)*	1.11 (0.95-1.30)	1.05 (0.91-1.22)	1.30 (1.01-1.66)*	1.10 (0.87-1.38)	1.04 (0.87-1.23)	1.00 (0.90-1.11)	1.01 (0.91-1.13)	1.03 (0.78-1.36)
5 day mean	1.83 (1.24-2.70)*	1.52 (1.07-2.18)*	0.95 (0.71-1.25)	1.02 (0.79-1.33)	2.10 (1.35-3.28)*	1.89 (1.17-3.03)*	1.61 (1.09-2.36)*	0.88 (0.69-1.13)	1.09 (0.85-1.39)	0.72 (0.40-1.29)
Black Smoke										
lag 0	1.29 (0.94-1.76)	1.17 (0.89-1.54)	1.04 (0.88-1.23)	1.11 (0.95-1.30)	1.41 (1.12-1.78)*	0.96 (0.75-1.23)	0.96 (0.76-1.20)	1.02 (0.89-1.16)	1.04 (0.92-1.18)	0.99 (0.71-1.39)
lag 1	1.14 (0.87-1.48)	1.16 (0.91-1.49)	1.03 (0.89-1.21)	0.93 (0.80-1.08)	1.16 (0.92-1.45)	1.18 (0.98-1.42)	1.02 (0.84-1.24)	1.01 (0.90-1.13)	1.11 (1.00-1.23)*	1.05 (0.76-1.46)
lag 2	1.21 (0.95-1.53)	1.29 (1.04-1.61)*	1.01 (0.87-1.17)	1.05 (0.91-1.21)	1.36 (1.09-1.69)*	1.05 (0.86-1.27)	0.89 (0.73-1.10)	1.00 (0.89-1.12)	1.02 (0.91-1.13)	0.82 (0.60-1.12)
5-day mean	1.51 (1.01-2.26)*	1.64 (1.14-2.36)*	1.03 (0.78-1.37)	1.04 (0.79-1.36)	1.82 (1.19-2.80)*	1.33 (0.87-2.03)	1.55 (1.09-2.21)*	0.99 (0.76-1.29)	1.10 (0.86-1.42)	0.82 (0.46-1.47)
Sulfate										
lag 0	1.27 (0.93-1.73)	1.15 (0.86-1.54)	1.08 (0.92-1.27)	0.95 (0.81-1.11)	1.03 (0.78-1.36)	0.89 (0.66-1.21)	0.93 (0.70-1.22)	1.03 (0.89-1.20)	1.14 (1.00-1.31)*	1.18 (0.70-2.00)
lag 1	1.04 (0.78-1.38)	1.28 (1.00-1.63)*	1.13 (0.97-1.33)	0.98 (0.84-1.14)	1.12 (0.86-1.46)	0.85 (0.65-1.10)	1.30 (1.01-1.67)*	1.02 (0.88-1.19)	1.09 (0.95-1.25)	1.53 (0.97-2.40)
lag 2	1.30 (1.01-1.68)*	1.22 (0.96-1.54)	1.01 (0.87-1.19)	1.02 (0.88-1.19)	1.12 (0.88-1.43)	1.11 (0.86-1.42)	1.26 (0.99-1.61)	1.00 (0.86-1.15)	0.96 (0.84-1.10)	0.87 (0.58-1.30)
5-day mean	1.99 (1.18-3.34)*	1.83 (1.16-2.87)*	0.90 (0.64-1.27)	0.75 (0.54-1.03)	1.77 (1.10-2.84)*	1.18 (0.68-2.06)	1.58 (0.96-2.60)	1.26 (0.98-1.62)	1.14 (0.88-1.49)	2.76 (1.34-5.70)*
SO_2										
lag 0	1.32 (0.96-1.80)	1.35 (1.01-1.79)*	0.97 (0.82-1.14)	0.90 (0.77-1.05)	0.92 (0.72-1.18)	1.20 (0.91-1.58)	0.91 (0.69-1.19)	0.94 (0.81-1.09)	1.08 (0.94-1.23)	0.86 (0.59-1.25)
lag 1	0.83 (0.60-1.14)	1.23 (0.93-1.64)	1.10 (0.94-1.28)	1.12 (0.96-1.30)	1.45 (1.13-1.86)*	0.89 (0.68-1.17)	0.91 (0.69-1.22)	0.97 (0.83-1.13)	0.98 (0.85-1.12)	1.18 (0.80-1.74)
lag 2	1.67 (1.28-2.19)*	1.18 (0.90-1.53)	1.03 (0.88-1.19)	0.98 (0.85-1.13)	1.02 (0.81-1.30)	0.84 (0.65-1.08)	1.06 (0.83-1.37)	0.98 (0.85-1.13)	0.94 (0.82-1.08)	0.99 (0.70-1.39)
5-day mean	1.50 (0.90-2.51)	1.56 (0.97-2.52)	1.08 (0.78-1.49)	1.12 (0.83-1.50)	1.17 (0.69-1.97)	0.64 (0.34-1.23)	1.16 (0.64-2.12)	0.67 (0.47-0.94)*	1.06 (0.75-1.49)	0.57 (0.25-1.30)
NO_2										
lag 0	0.96 (0.78-1.19)	1.12 (0.92-1.36)	0.96 (0.87-1.07)	1.02 (0.93-1.13)	1.16 (0.98-1.38)	1.10 (0.93-1.29)	1.07 (0.93-1.23)	0.99 (0.92-1.07)	1.03 (0.96-1.11)	0.88 (0.72-1.09)
lag 1	0.88 (0.73-1.06)	0.91 (0.76-1.09)	0.92 (0.84-1.01)	0.93 (0.85-1.02)	1.24 (1.06-1.44)*	0.99 (0.86-1.15)	1.04 (0.91-1.20)	0.97 (0.90-1.04)	1.01 (0.94-1.09)	1.07 (0.87-1.32)
lag 2	1.01 (0.84-1.22)	1.11 (0.93-1.32)	0.98 (0.89-1.08)	1.03 (0.94-1.13)	1.14 (0.98-1.33)	0.93 (0.81-1.08)	1.01 (0.89-1.16)	1.02 (0.95-1.10)	1.01 (0.95-1.08)	0.97 (0.80-1.18)
5-day mean	0.76 (0.52-1.10)	1.05 (0.70-1.58)	0.96 (0.75-1.22)	1.02 (0.81-1.27	1.37 (0.95-1.98)	0.99 (0.71-1.39)	1.45 (1.12-1.89)*	0.89 (0.75-1.06)	1.02 (0.86-1.20)	1.12 (0.74-1.70)

OR significantly different from 1 (P<0.05)

effect estimates between urban and non-urban panels were generally small and the confidence intervals showed considerable overlap. There was essentially no association with SO_2 and NO_2 in the non-urban areas. The prevalence of >10% decrements in morning PEF showed a consistent positive association with PM_{10} and BS (not shown in table 4). Statistically significant associations were found with lag 2 and 5-day mean concentrations, and for BS also with previous day concentration. For example, Odds Ratios for lag 2 of PM_{10} and BS were 1.23 (95% CI: 1.01-1.50) and 1.26 (95% CI: 1.06-1.49), respectively.

Both in the urban and the non-urban areas, 5-day mean concentrations appeared to be more related to respiratory health indicators than present day or lagged exposure variables.

Separate analyses for medicated and non-medicated symptomatic children were conducted to evaluate differences in response to air pollution. For this purpose, children were divided in those who did or did not report use of bronchodilators or maintenance medication during the study period.

Table 5 presents the associations between PM_{10} concentrations and evening PEF, LRS and bronchodilator use after stratification for medication use. It shows that In the urban panels, PM_{10} was strongly associated with LRS in the medicated children, but not in the non-medicated children. The association between PM_{10} and decrements in evening PEF was not more pronounced in medicated children, however. Medicated children reported significantly more LRS and bronchodilator use with increasing PM_{10} concentration in the urban areas, but not in the non-urban areas. Although results are only presented for PM_{10}, similar results were found for BS and to a lesser extent for SO_2.

The associations between air pollution indices and respiratory health indicators in non-symptomatic children are presented in table 6. In both the urban and non-urban areas, air pollution indices were positively associated with the prevalence of >10% decrements in evening PEF. The most consistent associations were observed for PM_{10} and Black Smoke. Positive associations were also found between air pollution indices and the prevalence of >10% decrements in morning PEF in the urban areas, but not in the non-urban areas (not shown). No associations were observed between the prevalence of cough, phlegm and URS, and air pollution indices in the urban areas. In the non-urban areas, there was a tendency towards associations in the unexpected direction of a lower prevalence with higher air pollution concentrations for all pollutants except sulfate.

Table 5. Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between air pollution and the prevalence of > 10% decrements in evening PEF and acute respiratory symptoms in medicated and non-medicated symptomatic children, calculated from combined effect estimates. OR's for an increase of 100 μg/m³ in PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2 and 15 μg/m³ for sulfate.

	Urban areas, medicated children (n=34)			*Non-urban areas, medicated children (n=47)*		
	Evening PEF	*LRS*	*Bronchodilator use*	*Evening PEF*	*LRS*	*Bronchodilator use*
PM_{10}						
lag 0	1.37 (0.81-2.31)	1.80 (1.17-2.75)*	1.44 (1.07-1.93)*	1.45 (0.93-2.25)	0.96 (0.76-1.22)	0.83 (0.59-1.17)
lag 1	1.41 (0.86-2.32)	2.09 (1.43-3.07)*	1.30 (0.97-1.74)	1.37 (0.94-1.99)	1.09 (0.87-1.37)	1.04 (0.75-1.45)
lag 2	1.40 (0.87-2.26)	1.72 (1.19-2.50)*	1.37 (1.02-1.83)*	1.33 (0.92-1.91)	1.04 (0.83-1.31)	1.07 (0.78-1.46)
5 day mean	1.41 (0.68-2.94)	2.67 (1.52-4.70)*	2.25 (1.34-3.79)*	2.25 (1.06-4.81)*	1.24 (0.76-2.02)	0.75 (0.38-1.50)
	Urban areas, non-medicated children (n=107)			*Non-urban areas, non-medicated children (n=129)*		
	Evening PEF	*LRS*	*Bronchodilator use*	*Evening PEF*	*LRS*	*Bronchodilator use*
PM_{10}						
lag 0	1.36 (0.92-2.00)	1.09 (0.76-1.56)	-	1.20 (0.88-1.64)	0.94 (0.68-1.30)	-
lag 1	1.23 (0.86-1.75)	1.15 (0.80-1.63)	-	1.00 (0.76-1.32)	0.78 (0.57-1.08)	-
lag 2	1.55 (1.12-2.13)*	1.31 (0.94-1.83)	-	1.04 (0.80-1.36)	0.93 (0.69-1.24)	-
5-day mean	2.00 (1.15-3.47)*	1.24 (0.76-2.04)	-	1.90 (1.10-3.30)*	3.70 (1.84-7.44)*	-

OR significantly different from 1 (P<0.05)

There were no statistically significant differences between the Odds Ratios in urban and non-urban areas (table 6). In contrast to the findings among the symptomatic children, statistically significant associations among the non-symptomatic children were mainly found at 0- and 1-day lags, and not when using the 5-day means as exposure variables. In the non-symptomatic panels, the prevalence of LRS was so low that analyses resulted in extreme effect estimates and standard errors in all winters except 1993/1994, when the mean prevalence was relatively high. The combined effect estimates for the three winters were (nearly) identical to the panel-specific effect estimates for the winter of 1993/1994, since the other winters hardly contributed to the weight. Therefore, the associations with LRS are not presented in the tables. However, in the winter of 1993/1994, a generally positive correlation between particle indices and respiratory health was observed, especially in the non-urban panel where the effect estimates were more stable due to the higher prevalence. For example, the effect estimates for LRS in association with PM_{10}-lag1 were 1.44 (95% CI: 0.54-3.83) in the urban area and 1.58 in

Table 6. Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between air pollution and the prevalence of >10% decrements in evening PEF and acute respiratory symptoms in non-symptomatic children, calculated from combined effect estimates. OR's for an increase of 100 μg/m³ in PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2 and 15 μg/m³ for sulfate.

	Urban areas			*Non-urban areas*		
	Evening PEF	*URS*	*Cough*	*Evening PEF*	*URS*	*Cough*
PM_{10}						
lag 0	1.32 (1.04-1.67)*	1.07 (0.87-1.31)	1.09 (0.90-1.31)	1.40 (1.09-1.80)*	1.13 (1.00-1.28)	1.00 (0.91-1.11)
lag 1	1.06 (0.84-1.34)	1.08 (0.88-1.32)	0.92 (0.76-1.11)	1.30 (1.03-1.64)*	0.95 (0.83-1.08)	0.88 (0.80-0.97)*
lag 2	1.15 (0.93-1.42)	0.97 (0.80-1.19)	0.94 (0.79-1.13)	1.14 (0.90-1.44)	0.87 (0.77-0.99)*	0.96 (0.86-1.04)
5 day mean	1.27 (0.93-1.74)	1.06 (0.71-1.59)	0.90 (0.64-1.27)	1.41 (0.93-2.14)	0.86 (0.63-1.17)	0.96 (0.81-1.14)
Black Smoke						
lag 0	1.45 (1.12-1.87)*	1.09 (0.88-1.36)	0.92 (0.75-1.12)	1.60 (1.29-2.00)*	1.04 (0.90-1.20)	0.94 (0.84-1.05)
lag 1	1.13 (0.90-1.43)	1.17 (0.96-1.43)	1.06 (0.88-1.27)	0.92 (0.76-1.12)	0.98 (0.86-1.12)	0.90 (0.82-0.99)*
lag 2	1.26 (1.03-1.54)*	0.91 (0.74-1.11)	1.05 (0.88-1.25)	1.14 (0.94-1.38)	0.90 (0.79-1.03)	0.92 (0.83-1.01)
5-day mean	1.42 (1.01-1.99)*	1.18 (0.78-1.80)	0.99 (0.71-1.38)	1.14 (0.80-1.76)	0.92 (0.67-1.24)	0.87 (0.74-1.03)
Sulfate						
lag 0	1.15 (0.87-1.51)	1.21 (0.97-1.51)	1.09 (0.89-1.34)	1.33 (0.95-1.86)	1.09 (0.90-1.32)	1.17 (1.01-1.35)*
lag 1	1.11 (0.86-1.44)	0.97 (0.79-1.19)	0.87 (0.71-1.07)	0.93 (0.69-1.24)	0.96 (0.79-1.15)	1.05 (0.90-1.23)
lag 2	1.10 (0.86-1.40)	1.06 (0.85-1.30)	1.10 (0.90-1.33)	1.19 (0.92-1.55)	0.96 (0.80-1.14)	0.95 (0.83-1.10)
5-day mean	1.29 (0.87-2.15)	1.23 (0.75-2.01)	0.81 (0.52-1.26)	1.35 (0.63-2.88)	1.34 (0.98-1.84)	1.15 (0.86-1.53)
SO_2						
lag 0	1.13 (0.88-1.47)	0.92 (0.76-1.11)	0.93 (0.78-1.11)	1.10 (0.87-1.39)	1.07 (0.92-1.25)	0.86 (0.76-0.97)*
lag 1	1.16 (0.90-1.50)	1.10 (0.91-1.34)	1.02 (0.84-1.23)	1.07 (0.85-1.35)	0.85 (0.72-1.00)	0.95 (0.83-1.08)
lag 2	1.10 (0.87-1.39)	0.83 (0.70-0.99)*	0.97 (0.83-1.15)	1.10 (0.88-1.38)	0.94 (0.80-1.10)	0.94 (0.82-1.06)
5-day mean	1.33 (0.89-2.00)	0.66 (0.42-1.03)	1.04 (0.69-1.57)	1.14 (0.66-1.96)	0.78 (0.52-1.18)	0.87 (0.68-1.12)
NO_2						
lag 0	1.13 (0.94-1.35)	1.05 (0.92-1.20)	1.02 (0.89-1.17)	1.14 (0.98-1.33)	1.03 (0.94-1.13)	0.93 (0.87-1.00)
lag 1	1.14 (0.97-1.34)	0.97 (0.86-1.11)	0.91 (0.81-1.04)	1.08 (0.94-1.25)	0.97 (0.89-1.07)	0.90 (0.84-0.97)*
lag 2	1.05 (0.89-1.23)	0.95 (0.84-1.08)	1.01 (0.89-1.14)	0.99 (0.85-1.15)	1.01 (0.92-1.09)	0.96 (0.90-1.03)
5-day mean	1.17 (0.84-1.63)	1.08 (0.75-1.56)	1.05 (0.74-1.48)	1.21 (0.89-1.63)	0.98 (0.80-1.21)	0.93 (0.82-1.05)

* *OR significantly different from 1 ($P<0.05$)*

Table 7. Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between air pollution and the prevalence of > 10% decrements in evening PEF and acute respiratory symptoms in symptomatic children from the urban area, calculated from combined effect estimates obtained in two-pollutant models. OR's for an increase of 100 µg/m³ in PM_{10}, 40 µg/m³ for Black Smoke and SO_2 and 15 µg/m³ for sulfate.

	first pollutant			*second pollutant*			
	Evening PEF	*LRS*	*Bronchodilator use*		*Evening PEF*	*LRS*	*Bronchodilator use*
PM_{10}				**SO_2**			
lag 0	1.33 (0.95-1.87)	1.24 (0.91-1.68)	1.29 (0.97-1.71)	lag 0	1.14 (0.80-1.61)	1.29 (0.94-1.76)	0.95 (0.72-1.25)
lag 1	1.45 (1.05-2.01)*	1.48 (1.10-1.99)*	0.84 (0.62-1.15)	lag 1	0.75 (0.51-1.09)	1.04 (0.75-1.46)	1.71 (1.26-2.32)*
lag 2	1.22 (0.89-1.67)	1.27 (0.95-1.71)	1.29 (0.96-1.74)	lag 2	1.56 (1.13-2.13)*	1.05 (0.77-1.43)	0.94 (0.70-1.28)
5 day mean	1.81 (1.04-3.16)*	1.46 (0.89-2.42)	1.84 (1.06-3.19)*	5 day mean	1.03 (0.50-2.10)	1.13 (0.60-2.13)	0.76 (0.45-1.30)
PM_{10}				**Black Smoke**			
lag 0	1.28 (0.85-1.93)	1.51 (1.04-2.18)*	1.16 (0.86-1.57)	lag 0	1.04 (0.71-1.55)	0.94 (0.65-1.36)	1.31 (0.98-1.75)
lag 1	1.03 (0.69-1.56)	1.86 (1.30-2.67)*	1.33 (1.00-1.76)*	lag 1	1.04 (0.72-1.50)	0.76 (0.54-1.07)	1.05 (0.79-1.38)
lag 2	1.59 (1.07-2.35)*	1.22 (0.84-1.78)	1.00 (0.74-1.34)	lag 2	0.85 (0.60-1.20)	1.14 (0.82-1.57)	1.34 (1.03-1.76)*
5-day mean	0.74 (0.27-2.05)	1.80 (0.68-4.77)	2.49 (0.80-7.81)	5-day mean	0.86 (0.37-1.86)	1.07 (0.47-2.42)	1.45 (0.58-3.64)
PM_{10}				**Sulfate**			
lag 0	1.39 (0.92-2.09)	1.61 (1.08-2.40)*	1.59 (1.13-2.24)*	lag 0	1.06 (0.73-1.55)	0.87 (0.61-1.25)	0.77 (0.55-1.06)
lag 1	1.22 (0.78-1.88)	1.42 (0.98-2.07)	1.05 (0.74-1.49)	lag 1	0.97 (0.66-1.42)	1.02 (0.78-1.42)	1.11 (0.79-1.56)
lag 2	1.32 (0.88-1.97)	1.24 (0.87-1.76)	1.27 (0.91-1.78)	lag 2	1.18 (0.84-1.67)	1.07 (0.78-1.47)	1.05 (0.76-1.44)
5-day mean	1.11 (0.53-2.32)	1.76 (0.95-3.28)	2.21 (1.21-4.05)*	5-day mean	1.58 (0.73-3.40)	1.21 (0.62-2.37)	0.95 (0.50-1.79)
Black Smoke				**Sulfate**			
lag 0	1.23 (0.83-1.83)	1.21 (0.85-1.72)	1.58 (1.20-2.09)*	lag 0	1.19 (0.82-1.73)	1.06 (0.76-1.49)	0.90 (0.67-1.20)
lag 1	1.10 (0.77-1.58)	0.91 (0.65-1.27)	1.17 (0.88-1.56)	lag 1	1.03 (0.71-1.49)	1.32 (0.95-1.84)	1.04 (0.78-1.40)
lag 2	0.94 (0.67-1.31)	1.17 (0.86-1.58)	1.32 (1.00-1.73)*	lag 2	1.37 (0.95-1.96)	1.09 (0.79-1.50)	0.93 (0.71-1.23)
5-day mean	1.02 (0.49-2.10)	1.47 (0.82-2.62)	1.82 (0.90-3.68)	5-day mean	1.96 (0.82-4.70)	1.23 (0.62-2.45)	1.10 (0.50-2.41)

* *OR significantly different from 1 ($P<0.05$).*

The association between nitrate concentration and respiratory health was analysed as well. However, due to the high correlation with sulfate (R between 0.75 and 0.87) the effect estimates for nitrate were nearly identical to those for sulfate, and therefore, the results are not presented. Sulfate was chosen to serve as an indicator for secondary aerosols, representing particles that mainly result from long distance transport.

Table 7 presents the associations between air pollution indices and selected respiratory health indicators in symptomatic children in urban areas, calculated from two-pollutant models. In two-pollutant models where PM_{10} and SO_2 were included simultaneously, an independent effect of PM_{10} remained whereas no consistent pattern was observed for SO_2. In models of PM_{10} with BS, and of PM_{10} with sulfate, the PM_{10} effects generally remained, whereas the estimates for BS and sulfate often became non-significant. In models of BS with sulfate no consistent pattern emerged. Two-pollutant models in the symptomatic panels from the non-urban areas also indicated that the associations wihth PM_{10} were most consistent (not shown), but the pattern was less clear than for the urban panels, as less consistently positive assocations were also observed in the one-pollutant models.

The associations with 5-day mean concentrations generally became less consistent in the two-pollutant models, probably because of the high correlation among these variables.

Discussion

In this study, we have found that in symptomatic children living in urban areas, the daily prevalence of lower respiratory symptoms (LRS), bronchodilator use and decrements in evening PEF had a consistent positive association with the concentration of PM_{10}, Black Smoke and sulfate. There was also a positive association with SO_2, but not with NO_2. After stratification for medication use, the prevalence of LRS was strongly associated with particle concentrations in medicated children, but not in non-medicated children. In two-pollutant models evaluating indicators of particulate air pollution (PM_{10}, BS and sulfate) and SO_2 simultaneously, independent effects were found more consistently for particles than for SO_2. In symptomatic children living in non-urban areas weaker and less consistent positive associations were observed with indicators of particulate air pollution. No associations with the gaseous pollutants SO_2 and NO_2 were found. In

non-symptomatic children, the daily prevalence of PEF decrements was positively correlated with PM_{10} and BS in both the urban and non-urban areas. The prevalence of upper respiratory symptoms (URS), cough and phlegm was not associated with air pollution in any of the subgroups.

In a review article, Dockery and Pope[3] combined the results of the then available panel studies from the US and Europe, and calculated that an increase in PM_{10} concentration of 100 $\mu g/m^3$ was associated with an increase in the prevalence of LRS and bronchodilator use of respectively 30% and 29%. Although the definition of LRS was not exactly the same as in our study, these effect estimates correspond well to the ones from our study; we found that for symptomatic children in the urban area an increase in same-day PM_{10} concentration was associated with an increase of 34% and 29% in the prevalence of LRS and bronchodilator use, respectively. For URS and cough, smaller increases of 7% and 12% were reported by Dockery and Pope[3]. Thus, the fact that in our study, larger relative increases were found for LRS and bronchodilator use than for URS and cough is in agreement with earlier panel studies.

Both in the urban and non-urban symptomatic panels, 5-day mean concentrations appeared to be more related to respiratory health indicators than present day or lagged exposure variables. This is in line with other studies[14,16] and suggests that changes in respiratory status might reflect cumulative exposure of several days prior to the measurement.

Although the medicated children in the urban areas increased their bronchodilator use in association with elevated particle concentrations, the strongest increase in LRS was observed in this subgroup. Apparently, increased bronchodilator use did not prevent the adverse effects of particles on respiratory health. This is in agreement with the results of stratified analyses based on medication use in a panel study of mild asthmatic children in Sokolov, Czech Republic[17]. Medicated children increased their beta-agonist use in association with increased particle concentrations, but this did not prevent adverse effects on other health outcomes (in that case decreases in PEF and increases in the prevalence of cough[17]. The authors speculated that this was a result of inadequate supplies of asthma medication in the Czech Republic. In the Netherlands, however, this is not a plausible explanation. Apparently, medication use does not suppress the adverse effects of particulate air pollution in asthmatics, as was suggested in other studies[13,28].

Compared to other panel studies, a different approach was used to analyse PEF

data, focusing not on decrements in population average PEF but on the fraction of children that is experiencing substantial PEF decrements. In a re-analysis of data from seven panels including school children, symptomatic and non-symptomatic children, Hoek *et al.*[15] have compared the two approaches. It was demonstrated that an increase of 10 $\mu g/m^3$ of the same day PM_{10} concentration was associated with a decrement in the population mean PEF of 0.07%. A significant increase of the prevalence of >10% PEF decrements of 2.7% was associated with the same exposure. For an increase of 100 $\mu g/m^3$ this corresponds to an Odds Ratio of 1.31, a value very similar to the Odds Ratios found in our study. An advantage of the approach proposed by Hoek *et al.*[15] is that, as in symptom analysis, it provides effect estimates that focus on the fraction of the population experiencing a specific (adverse) response.

Can some sort of bias have caused the associations between particle concentration and respiratory health observed in our study? It is unlikely that selection processes could have caused bias in this time series study because each child served as its own control. Bias due to the low response may have occurred in the unlikely case that within the subgroup of children with/without chronic respiratory symptoms, response was associated with susceptibility to winter air pollution.

Observer bias in symptom reporting might have occurred when parents of the children were informed by the mass media about air pollution episodes. However, during the study period all air pollutant concentrations were below the limits used in the Dutch smog alert system, and no warnings were issued. Potential confounders that might bias the association between air pollution and respiratory health in time series studies are meteorologic variables (mainly ambient temperature), respiratory infections and long term time trends. All associations were adjusted for ambient temperature and for non-linear long term time trends (generally in the order of weeks) in the prevalence of symptoms, bronchodilator use and PEF decrements. The adjustment for time trends was more detailed than in previous panel studies which either specified no time trend or a linear trend. The incidence of influenza-like illness (ILI) in the general population, registered by a GP sentinel system, was used to adjust for the potential confounding effect of respiratory infections. In previous panel studies, no adjustments for the potential confounding effect of respiratory infections were made. We will report in a separate paper[11] that the ILI incidence in the general population was associated with respiratory health in selected panels.

In our study, effects on PEF were somewhat larger for symptomatic than for non-symptomatic children. In a previous Dutch study in school children, the association between particulate air pollution and lung function was reported to be similar in children with and without chronic respiratory symptoms[7]. In contrast, Neas *et al.*[18] found that children without chronic respiratory symptoms appeared to be less susceptible to the effects of air pollution on PEF than were symptomatic children. Pope and Dockery[14] observed effects on PEF in both symptomatic and asymptomatic children, but in symptomatic children stronger associations were found.

In our study, air pollution indices were not associated with respiratory symptoms in the non-symptomatic panels, whereas in symptomatic panels an association with LRS and bronchodilator use was found. However, both LRS and bronchodilator use were never or rarely reported in the non-symptomatic panels. The finding that air pollution indices were not associated with respiratory symptoms in the non-symptomatic panels is in agreement with other studies. In two Dutch studies[6,7] no association between particulate air pollution and respiratory symptoms was observed in mainly healthy school children. Pope and Dockery[14] reported positive associations between PM_{10} and the prevalence of URS, LRS and cough in both symptomatic and non-symptomatic panels, but the associations were weaker, and generally non-significant, in the non-symptomatic panels. LRS could be analyzed in the asymptomatic panel[14] because the definition was different from ours (i.e. trouble breathing, wheeze, dry cough instead of shortness of breath, wheeze, asthma attacks).

Thus, non-symptomatic children appear less susceptible to the acute effects of air pollution than symptomatic children because these do not develop the asthmatic symptoms that are most affected by increasing levels of air pollution.

It can not easily be concluded from the one-pollutant models which indicator for air pollution (PM_{10}, Black Smoke, sulfate or SO_2) was most consistently associated with respiratory health in the panels, although the associations with sulfate were less consistent in the non-symptomatic panels. Therefore, two-pollutant models evaluating two air pollution indicators simultaneously were specified for the symptomatic panels in an attempt to separate effects from specific components. The concentrations of PM_{10}, BS sulfate and SO_2 were intercorrelated, as meteorology is a dominating factor in determining day-to-day variations in air pollution concentrations. However, as indicated by the standard errors associated with the regression coefficients, this did not lead to collinearity problems. The two-

pollutant models indicated that SO_2 was less consistently associated with respiratory health than indicators for particulate air pollution, which was expected given the low SO_2 concentrations that were observed in our study. They also indicated that in symptomatic panels in the urban areas, PM_{10} was more consistently associated with health outcomes than BS and sulfate. BS can be considered as an indicator of fine black particles (elemental carbon) emitted by diesel engines which is generally found in the fine particle fraction. Sulfate is also present in the fine fraction and serves as an indicator for secondary aerosols, representing particles that mainly result from long-range transport. The finding that the most consistent assocations were found with PM_{10} contrasts with two previous time series studies performed in Amsterdam which found that BS was more strongly associated with health outcomes than PM_{10}[16,19].

In symptomatic children, PM_{10} and BS concentrations were more strongly and consistently associated with bronchodilator use, and to a lesser extent LRS, in the urban areas than in the non-urban areas. After stratification by medication use it was shown that the differences in response between urban ans non-urban panels were restricted to the medicated children. We can not rule out that differences in use of maintenance medication are responsible for this. Calculated over the three winters, the mean prevalence of maintenance medication was almost twofold lower in the urban areas (8.5%) than in the non-urban areas (15.5%). As a result, children in the urban areas might have to rely more on bronchodilators during periods with high air pollution than children in the non-urban areas. Separate analyses for children who used only bronchodilators during the study period, and for children who used both bronchodilators and maintenance medication could demonstrate if use of maintenance medication diminishes the response to air pollution, but the number of children that used bronchodilators only was too small for a meaningful analysis. Moreover, in such an analysis the amount of maintenance medication used by each child during the study period should be taken in account. The percentage of the medicated children that ever reported use of maintenance medication did not differ between urban and non-urban panels (76.5% and 78.7%, respectively), but children in the non-urban areas obviously took their maintenance medication more often, given the higher prevalence. Thus, we can not conclude that the tendency of stronger particle effects on LRS and especially bronchodilator use in the urban areas reflects a more toxic air pollution mixture in the urban area, since we can not exclude that differences in medication use are responsible for this. Moreover, in the non-symptomatic panels no tendency

of stronger associations in the urban areas was observed. The results of our study are to some extent at variance with the results of the PEACE study; in 14 urban and 14 non-urban symptomatic panels, including the 1993/1994 panels of our study, generally no clear effects of air pollutants on PEF, respiratory symptoms or bronchodilator use were found in both urban and non-urban panels[20]. The main difference between the two studies is that in the Dutch studies, we were able to combine findings from three different winter periods whereas in the PEACE study, the observation period was about two months in one winter only. The Dutch studies may therefore have been less vulnerable to the effect of unmeasured events during that particular period. Another difference is that we were able to control at least to some extent for the role of respiratory infections through the data from the GP sentinel system on ILI.

In this study, exposure assessment was based on fixed site ambient air concentrations measured at one location in both areas. In the urban areas, a background location was selected instead of a site more directly influenced by traffic emissions, because the measurement site needed to be representative for other locations in the study area. It might be questioned whether exposure to air pollution was adequately characterized by fixed site ambient air concentrations only. However, the resulting misclassification would probably result in a downward bias of the observed association between air pollution and health endpoints. Recent studies in the Netherlands[29,30] have shown that the time series correlation between ambient and personal PM_{10} was reasonably high. No consistent differences were found in the strength of the correlation between ambient and personal PM_{10} between children living in Amsterdam and children living in the non-industrial small town Wageningen[29].

Transient decrements of FVC and FEV_1 of 10% have been considered as the border between mild and moderate response[31,32]. The effect estimates observed in our study indicate that in symptomatic children, an increase of 83% in the number of subjects with a PEF response of that magnitude was associated with an increase in 5-day mean PM_{10} concentration of 100 $\mu g/m^3$. An increase of 52% is observed for the prevalence of LRS in symptomatic children, whereas a twofold increase in bronchodilator use is associated with a 100 $\mu g/m^3$ increase in 5-day mean PM_{10} concentration. In non-symptomatic children in both urban and non-urban areas, particle effects on PEF were of smaller magnitude than for symptomatic children, and no associations with respiratory symptoms were observed.

In conclusion, this study suggests that symptomatic children are more susceptible to particulate air pollution than non-symptomatic children, and that use of asthma medication does not suppress the adverse effects of particulate air pollution.

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Chapter 6

Acute effects of air pollution on respiratory health of 50-70 year old adults

Saskia C. van der Zee, Gerard Hoek, H. Marike Boezen, Jan P. Schouten, Joop H. van Wijnen and Bert Brunekreef

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Abstract

Elderly subjects, and subjects with pre-existing disease are often considered to be at higher risk of experiencing adverse effects of air pollution than young, healthy adults. The air pollution mixture in cities may be different from the mixture in non-urban areas, due to the concentration of sources in urban areas. We therefore investigated the association between daily changes in respiratory health and air pollution in 50-70 year old adults with and without chronic respiratory symptoms, living in urban and non-urban areas.

Subjects were selected from the general Dutch population with a screening questionnaire. During three consecutive winters starting in 1992/1993, Peak Expiratory Flow (PEF) and respiratory symptoms were registered daily in a diary. Daily measurements of PM_{10}, Black Smoke, sulfate, SO_2 and NO_2 were conducted.

The contrast in particle concentrations (PM_{10}, Black Smoke and sulfate) between urban and non-urban areas was small, but there was more contrast in the concentrations of the gaseous pollutants SO_2 and NO_2. In symptomatic subjects living in urban areas, PM_{10}, Black Smoke, sulfate and SO_2 concentrations were associated with the prevalence of large decrements in morning PEF (more than 20% below the median). Especially Black Smoke was also associated with upper respiratory symptoms. In symptomatic subjects living in non-urban areas, no significant and consistent associations between air pollution indicators and the health endpoints were observed. The differences in effect estimates between urban and non-urban symptomatic panels were small and non-significant, however. In non-symptomatic adults from both urban and non-urban areas, no consistent associations between air pollution and respiratory health were found.

In conclusion, weak air pollution effects were found only in symptomatic adults in the urban area, but the differences in effect estimates with the non-urban area were small.

Introduction

Severe winter air pollution episodes in the past have been associated with serious health effects, such as increased hospital admissions and mortality[1]. Over the last decades, concentrations of 'traditional' winter air pollution components such as sulfur dioxide (SO_2) and airborne coarse particulates have decreased in the Netherlands and other European countries. This decrease can be ascribed to emission abatement measures and changes in energy production for 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 higher intensity of motorized traffic. Motorized traffic also plays an important role in the formation of particulate air pollution, both direct and indirect through the formation of secondary aerosols[2]. Recent studies have demonstrated that current levels of particulate air pollution are associated with respiratory morbidity and lung function, even at concentrations well below the 1987 World Health Organization (WHO) Air Quality Guidelines for Europe[3,4]. Previous studies conducted in the Netherlands have also demonstrated associations between low levels of winter air pollution and respiratory health of children[5-7]. These studies have mainly been conducted in non-urban areas. It was not clear to what extent such associations would be different in urban areas where the contribution of local sources to the air pollution mixture is greater than in non-urban areas.

Most time-series studies investigating acute effects of air pollution on lung function and respiratory symptoms have focused on children. The few studies that have been performed in adults have mainly investigated asthma patients[8-11]; one study focused on a random sample of the general population[12]. Previous panel studies in children have demonstrated acute effects of air pollution in, among others, children with mild chronic respiratory symptoms[5,13,14]. It is not clear whether adults with mild chronic respiratory symptoms are also susceptible to acute effects of air pollution such as transient changes in lung function and respiratory symptoms. One study reported that pulmonary function of smoking adults with mild to moderate chronic obstructive pulmonary disease was affected by exposure to particles with a 50% cutoff aerodynamic diameter of 10 μm (PM_{10}), but this study was based on only two measurements of pulmonary function per subject[15].

Studies investigating effects of air pollution on mortality have suggested that the

elderly are a susceptible subgroup[16]. To our knowledge, it has never been investigated if older adults are also sensitive to acute effects of air pollution on lung function and respiratory symptoms. These considerations led us to perform a large study during three consecutive winters starting in 1992/1993. The study was designed to compare acute health effects of winter air pollution of subjects living in urban and non-urban areas. Selected panels of school children (7-11 yr) and older adults (50-70 yr) with and without chronic respiratory symptoms were studied. This paper describes the results for the adult panels. The results for the children are reported elsewhere[17].

Methods

Study design

The study was carried out during three consecutive winters starting in 1992/1993. During each winter, panels of adults (50-70 yr) with and without chronic respiratory symptoms were selected from an urban and a non-urban area. During the first winter the study had a pilot character, and no panels were studied in the non-urban area.

The adults were selected from the general population with a screening questionnaire. During study periods which generally lasted three months, daily PEF measurements were made, and the occurrence of respiratory symptoms and bronchodilator use was registered in a diary. Air pollution was monitored daily on central sites in each community.

Study population

As study areas we chose: Rotterdam (1992/1993), Amsterdam and Meppel (1993/1994), and Amsterdam and Nunspeet (1994/1995). Figure 1 in chapter 2 of this thesis shows the locations of the areas. Rotterdam is a port and industrial city with approximately 600,000 inhabitants. Amsterdam, the nation's capital (720,000 inhabitants), has a relatively small industrial area; local air pollution is caused primarily by emissions from motorized traffic. In addition to local air pollution, transport of air pollution from other parts of the Netherlands and from other European countries contributes to air pollution levels in Dutch cities. Meppel (32,000 inhabitants) and Nunspeet (24,000 inhabitants) are small non-industrial towns. As we wanted to maximize exposure contrasts between urban and non-urban sites, both in Rotterdam and Amsterdam parts of the inner city

were selected with a high traffic intensity and a high population density, and no local industrial sources.

A random sample of names and addresses from subjects with the Dutch nationality and an age between 50 and 70 yr was obtained from the respective municipal authorities. Subjects were approached by mail. Screening questionnaires were used to obtain information on chronic respiratory symptoms. The screening questionnaire consisted of selected questions from the questionnaire used in the European Community Respiratory Health Survey[18]. Subjects were considered eligible for the panel with chronic respiratory symptoms if they reported a positive answer to one or more of six questions about wheeze/asthma (wheeze with shortness of breath; wheeze without a cold; shortness of breath at normal walking pace; need to recover breath while walking at own pace; asthma attacks in last 12 months; current use of asthma medication), or to one or more of five questions about cough/phlegm (last 12 months: daily cough upon rising, or during day/night for 3 months a year; last 12 months: daily production of phlegm upon rising, or during day/night for 3 months a year; 3 weeks of productive cough during last 3 years). During the winter of 1994/1995, the selection question of productive cough was omitted as it was felt that it selected subjects with 'smokers cough' primarily. Subjects without any reported symptoms on the screening questionnaire were considered eligible for the 'non-symptomatic' panels. Only subjects who signed informed consent letters were included in the study. Symptomatic and non-symptomatic subjects were selected randomly from those who fulfilled the selection criteria. The panel size we aimed for was 30 subjects in the pilot-study in 1992/1993, and 75 subjects in each panel in 1993/1994, 60 symptomatic and 40 non-symptomatic subjects in 1994/1995. In addition, a detailed questionnaire on chronic respiratory symptoms, sources of indoor air pollution (smoking, housing characteristics) and socio-economic status was administered to the subjects. The study was approved by the Medical Ethical Committee of the University Hospital Groningen and the Medical Ethical Committee of the Municipal Health Service in Amsterdam.

Exposure assessment

Detailed information about the measurement sites and methods is given elsewhere[19]. Briefly, 24-hour measurements of PM_{10} , Black Smoke and fine aerosol sulfate, nitrate, ammonium and strong acidity were made at fixed sites in

the urban and non-urban areas. Measurements ran from 3 PM to 3 PM. The particle measurement sites were chosen such that they were close to the living area of the participating subjects, and not strongly influenced by local sources such as traffic and industry. Information about the ambient concentrations of SO_2 and NO_2 was obtained from the nearest routine monitoring network station. SO_2 and NO_2 concentrations were transformed into 24-hour average concentrations from 3 PM to 3 PM. Minimum temperature between 3 PM and 3 PM was used in the analysis. Temperature data from the nearest site of the Dutch Royal Meteorological Society were used.

Data on the weekly incidence of influenza-type illnesses were obtained from a sentinel system operated by the Dutch Institute of Primary Health Care (NIVEL). We recently documented that these data were associated with the outcome variables measured in our panels[20], for which reason we include them as potential confounders of the association between air pollution and respiratory health in this study.

Health measurements

During the study period, participants performed PEF measurements twice daily using Mini Wright peak flow meters, once in the morning before breakfast and in the evening before going to bed. Subjects were instructed to perform the PEF measurements before any medication was taken. Every test consisted of three maneuvers and participants were asked to note all three readings in a diary. The highest of the three PEF readings was used for analysis. The diary was also used to register the occurrence of acute respiratory symptoms and medication use (cough, phlegm, runny/stuffed nose, woken up with breathing problems, shortness of breath, wheeze, attack(s) of shortness of breath with wheeze and fever). During the winters of 1993/1994 and 1994/1995, the symptoms eye irritation and sore throat were included as well. Subjects were instructed to indicate whether the symptoms were absent, slight, or moderate/severe on each day. Medication use was assessed by having the subjects indicate the name of the medication and the number of units taken. The appropriate use of the diary and Mini Wright meter was demonstrated during a home visit.

Data analysis

The methods of the PEACE study were used to analyse the association between air pollution and respiratory health[21,22]. Here only a brief overview and the

deviations are discussed. All panels were analysed separately. Next, combined effect estimates were calculated for symptomatic and non-symptomatic panels, and for urban and non-urban areas separately.

The symptoms shortness of breath, wheeze and attacks of shortness of breath with wheeze were combined as lower respiratory symptoms (LRS). Runny/stuffed nose and sore throat were combined as upper respiratory symptoms (URS). Only LRS, URS, cough, phlegm and bronchodilator use were analysed. For the analysis of Peak Expiratory Flow data, we analysed the daily prevalence of 10% and 20% decrements below the individual median of morning and evening PEF[23]. We preferred this method to the analysis of population mean PEF[21,22] because it better demonstrates the clinical significance of PEF associations. The explanatory variables were 24 hour average concentration of PM_{10}, Black Smoke, SO_2, NO_2 sulfate and nitrate, analysed separately. Current day concentration (lag 0), previous day concentration (lag 1), concentration of two days before (lag 2) and the average concentration of 0-4 days before (5 day mean) were analysed separately.

The association between air pollution and the prevalence of PEF-decrements, symptoms and bronchodilator use was evaluated with logistic regression, adjusting for first order autocorrelation. The number of subjects reporting on each day was used as weight. Minimum daily temperature, an indicator variable for day of week (Monday-Friday vs Saturday/Sunday), time trend, and the incidence of influenza and influenza-like-illness (ILI) in the general population were included in the model as potential confounders. Time trend was included as a linear, quadratic and cubic term. This was done because in some panels non-linear time trends were observed in the prevalence of symptoms, medication use and PEF-decrements. An exception was made for the 1992/1993 pilot study, in which the study period was so short (around 6 weeks) that modeling with three time trends resulted in removal of short term time variations. For this winter only a linear trend was specified. The incidence of ILI, registered by the Dutch network of sentinel practices, was included in the model with two variables representing respectively the mean incidences of 0-6 days earlier, and 7-13 days earlier[20]. ILI was an addition to the confounders used in the PEACE study[21,22].

Combined effect estimates were calculated for symptomatic and non-symptomatic panels, and for urban and non-urban areas separately, using the regression slopes from the panel-specific logistic regression models for the three winters. Combined effect estimates were calculated as the weighted mean of

the panel-specific slopes, with the weights being the inverse of the panel-specific variances of the slopes. The standard error of the combined slope was calculated as the inverse of the square root of the sum of weights. All statistical analyses were conducted using SAS[24].

Results

From the 11,519 screening questionnaires handed out during the three winters, 4,464 (39%) were returned. The response was similar in the urban and non-urban areas (38% and 40%, respectively). Of the 4,464 returned questionnaires, 751 subjects (17%) were eligible and willing to participate in the symptomatic panels, whereas 601 subjects (13%) were eligible and willing to participate in the non-symptomatic panels. From the 326 symptomatic and 274 non-symptomatic subjects that were enrolled, respectively 266 and 223 were included in the final analysis, the remainder generally having too few observations.

In table 1 some characteristics of the panels are shown. Mean age was about 60 years in all panels. Recent shortness of breath and wheeze, chronic cough and chronic phlegm were the symptoms with the highest prevalences in the symptomatic panels. Symptomatic panels had a higher prevalence of acute respiratory symptoms than non-symptomatic panels. The prevalence of >10% decrements in morning PEF was on average 6.3% in the symptomatic panels and 4.1% in the non-symptomatic panels, but was substantially higher for non-symptomatic panels from the urban area (6.0%) than for non-symptomatic panels in the non-urban area (2.2%). In the non-symptomatic panels, bronchodilator use was not reported, whereas Lower Respiratory Symptoms were rarely reported. In the symptomatic panels, bronchodilator use was higher in the non-urban area (17%) than in the urban area (8%).

For both symptomatic and non-symptomatic panels, time trends occurred in the prevalence of acute respiratory symptoms and decrements in PEF that were not always linear. Therefore, time trend was adjusted for by specifying a third order polynomial of day of study.

In table 2 the results of the air pollution measurements are presented. The median concentrations of PM_{10} and Black Smoke were only slightly higher in the urban areas than in the non-urban areas. There was more contrast in the concentration of the gaseous pollutants SO_2 and NO_2. The median

Table 1. Characteristics of the panels, three winters combined

	symptomatic, urban area	symptomatic, non-urban area	non-symptomatic, urban area	non-symptomatic, non-urban area
Original sample size	173	153	140	134
Final sample size*	138	128	111	112
Winter 1992/1993	21	-	15	-
Winter 1993/1994	63	70	56	73
Winter 1994/1995	54	58	40	39
Gender (% men)	50	48	40	46
Mean age (s.d.)	59.1 (6.1)	61.0 (6.2)	58.9 (5.6)	60.1 (6.3)
Screening prevalence of symptoms and medication use				
(% in final sample)				
% Recent wheeze and shortness of breath	43	44	0	0
% Chronic cough	38	31	0	0
% Chronic phlegm	40	33	0	0
% Recent asthma attacks	8	12	0	0
% Current use of asthma medication	17	25	0	0
*Mean daily prevalence (%) of symptoms, medication use and PEF-decrements, and mean PEF***				
Lower Respiratory Symptoms	20	27	1.8	1.8
Upper Respiratory Symptoms	35	26	13	8.6
Cough	36	31	8.6	7.8
Phlegm	34	35	7.4	3.9
Bronchodilator use	7.7	17	-	-
>10% decrements in morning PEF	6.8	5.7	6.0	2.2
>20% decrements in morning PEF	1.5	0.8	0.2	0.4
Mean morning PEF (l/min)	439	425	487	507

* *smaller than original sample size because subjects with >40% missing diary information were excluded*

** *pooled prevalences and PEF were calculated as the mean of the panel-specific prevalencesand PEF, weighted for the number of person-days that each panel contributed*

Table 2. Median and maximum of 24-hr average air pollution concentrations ($\mu g/m^3$), and median and range of temperature (°C), and incidence of influenza-like-illness (incidence/10,000 subjects per week), observed during the study periods in urban and non-urban areas.

		study period dd/mm/yy	N_{days}	PM_{10}	Black Smoke	sulfate	SO_2	NO_2	T*	ILI$_{0-6}$**
1992/1993	urban	10/3/93-19/4/93	41	53 (106)	14 (44)	6.3 (13.5)	25 (61)	52 (94)	5.6 (-0.3;9.8)	12 (6-34)
	non-urban	-	-	-	-	-	-	-	-	-
1993/1994	urban	3/11/93-6/3/94	124	37 (123)	12 (65)	2.7 (24)	11 (34)	48 (76)	2.7 (-8.1;10.0)	6 (0-70)
	non-urban	20/11/93-6/3/94	107	34 (242)	10 (58)	2.7 (23)	5.0 (42)	25 (54)	1.2 (-10.9;9.3)	6 (0-39)
1994/1995	urban	24/11/94-5/3/95	102	29 (90)	6.9 (28)	1.6 (10)	6.0 (24)	47 (82)	3.8 (-5.0;11.3)	4 (0-10)
	non-urban	23/11/94-5/3/95	103	24 (97)	5.8 (43)	1.9 (18)	3.6 (17)	22 (57)	3.1 (-11.1;11.3)	8 (2-13)

* *minimum daily temperature*
** *mean of incidence of influenza-like-illness in the previous week*

Table 3. Range of Spearman correlation coefficients between 24-hr average concentration of air pollutants and potential confounding variables, calculated separately for the three winters in urban and non-urban areas (n = 5).

	PM_{10}	Black Smoke	sulfate	SO_2	NO_2	T†	day of study	ILI$_{0-6}$*	ILI$_{7-13}$**
PM_{10}	1	0.45 to 0.84	0.54 to 0.78	0.31 to 0.78	0.16 to 0.72	-0.57 to 0.19	-0.31 to 0.30	-0.37 to 0.51	-0.49 to 0.05
Black Smoke	-	1	0.52 to 0.84	0.21 to 0.75	0.54 to 0.88	-0.64 to 0.03	-0.43 to 0.17	-0.31 to 0.43	-0.36 to 0.04
sulfate	-	-	1	0.29 to 0.69	0.25 to 0.65	-0.58 to 0.41	-0.26 to 0.08	-0.25 to 0.24	-0.32 to 0.02
SO_2	-	-	-	1	0.47 to 0.51	-0.53 to 0.23	-0.53 to 0.25	-0.21 to 0.43	-0.37 to 0.50
NO_2	-	-	-	-	1	-0.53 to -0.08	-0.51 to 0.20	-0.23 to 0.40	-0.27 to 0.20
T	-	-	-	-	-	1	-0.14 to 0.25	-0.25 to 0.16	-0.25 to 0.18
day of study	-	-	-	-	-	-	1	-0.86 to 0.07	-0.81 to 0.21
ILI$_{0-6}$	-	-	-	-	-	-	-	1	0.16 to 0.76
ILI$_{7-13}$	-	-	-	-	-	-	-	-	1

* *mean of incidence of influenza-like-illness in the previous week (mean of 0-6 days before)*
** *mean of incidence of influenza-like-illness in week before previous week (mean of 7-13 days before)*
† *daily minimum temperature*

concentration of sulfate was slightly lower in the urban than in the non-urban areas. Concentrations of aerosol acidity were very low during the three winters (not shown). Only a few concentrations were above the detection limit of 0.10 $\mu g/m^3$ and therefore, concentrations of aerosol acidity were not used in further analyses.

Table 3 presents the range of the Spearman correlations between the various air pollutants and potential confounding variables, calculated separately for the urban and non-urban areas during the three winters. A high correlation was observed between PM_{10} and the other indicators for particulate air pollution Black Smoke and sulfate. The correlations between other air pollutants, and between air pollutants and temperature were moderately high. Low correlations were observed between air pollutants and the potential confounders day of study and influenza-like illness incidence. The correlation between the concentrations measured for the same component in the urban and the non-urban areas was for PM_{10}, Black Smoke and sulfate higher than 0.7 for all winters. For SO_2 and NO_2, the correlations were higher than 0.6, except for SO_2 in the third winter ($R=0.31$) when SO_2 levels were extremely low.

Both for symptomatic and non-symptomatic subjects, the association between nitrate concentration and respiratory health was analysed as well. However, due to the high correlation with sulfate (R between 0.75 and 0.87) the effect estimates for nitrate were nearly identical to those for sulfate, and therefore, the results are not presented. Sulfate was chosen to serve as an indicator for secondary aerosols, representing particles that mainly result from long distance transport in the Netherlands.

Table 4 presents the associations between air pollution and the prevalence of >10% and >20% decrements in morning PEF, respiratory symptoms and bronchodilator use in symptomatic subjects. It shows that, in the urban areas, consistently positive associations were found between the prevalence of >20% decrements in morning PEF and the concentration of PM_{10}, Black Smoke, sulfate and SO_2, with many associations reaching statistical significance. However, no associations were observed with the prevalence of >10% decrements in morning PEF, and with the prevalence of both >10% and >20% in evening PEF (not shown). Only for BS the association was more consistent across the different PEF variables. For previous day Black Smoke (borderline) significant associations were found for all PEF variables. For the 10% and 20% evening PEF decrements OR were 1.32 (0.98-1.77) and 4.24 (2.47-7.29) respectively.

Table 4. Odds Ratios (OR) with 95% confidence intervals for the association between air pollution and the prevalence of >10% decrements, acute respiratory symptoms and bronchodilator use in symptomatic adults, calculated from combined effect estimates. OR's for an increase of 100 μg/m³ in PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2 and 15 μg/m³ for sulfate.

	Urban areas					*Non-urban areas*				
	>10% in pefmo	*>20% in pefmo*	*LRS*	*URS*	*Broncho*	*>10% in pefmo*	*>20% in pefmo*	*LRS*	*URS*	*Broncho*
PM_{10}										
lag 0	0.84 (0.55-1.28)	2.08 (1.05-4.12)*	0.97 (0.80-1.17)	1.09 (0.93-1.29)	0.98 (0.82-1.17)	0.99 (0.67-1.45)	1.11 (0.43-2.81)	1.02 (0.91-1.14)	0.99 (0.85-1.14)	0.98 (0.90-1.06)
lag 1	0.93 (0.63-1.37)	1.49 (0.80-2.77)	0.97 (0.81-1.16)	1.12 (0.96-1.32)	0.97 (0.82-1.15)	0.98 (0.70-1.39)	1.36 (0.62-2.97)	1.05 (0.95-1.16)	1.13 (0.99-1.28)	1.05 (0.97-1.13)
lag 2	0.69 (0.47-1.00)	1.31 (0.69-2.51)	1.02 (0.86-1.22)	1.09 (0.93-1.27)	0.93 (0.79-1.10)	1.10 (0.81-1.49)	0.72 (0.28-1.84)	0.95 (0.86-1.06)	1.04 (0.92-1.19)	1.00 (0.93-1.08)
5 day mean	0.62 (0.32-1.21)	1.35 (0.41-4.43)	0.91 (0.67-1.24)	1.37 (1.01-1.87)*	0.73 (0.53-1.01)	1.07 (0.63-1.81)	0.69 (0.16-2.94)	0.99 (0.82-1.18)	1.27 (0.99-1.62)	1.10 (0.94-1.28)
Black Smoke										
lag 0	1.10 (0.79-1.55)	1.82 (1.05-3.16)*	0.96 (0.80-1.15)	1.18 (1.01-1.38)*	0.99 (0.84-1.15)	1.10 (0.73-1.68)	2.77 (0.89-8.60)	1.07 (0.93-1.22)	0.96 (0.82-1.12)	0.96 (0.87-1.07)
lag 1	1.40 (1.05-1.86)*	1.93 (1.22-3.04)*	0.95 (0.81-1.11)	1.29 (1.12-1.48)*	1.02 (0.87-1.18)	0.94 (0.67-1.33)	1.09 (0.47-2.53)	1.09 (0.97-1.22)	1.08 (0.95-1.23)	1.04 (0.95-1.13)
lag 2	0.93 (0.69-1.25)	1.27 (0.78-2.06)	0.99 (0.85-1.16)	0.97 (0.84-1.12)	0.89 (0.77-1.03)	1.07 (0.77-1.47)	0.84 (0.34-2.08)	0.99 (0.89-1.11)	0.99 (0.87-1.13)	1.01 (0.93-1.11)
5-day mean	1.50 (0.94-2.40)	4.24 (2.46-7.29)*	0.96 (0.75-1.24)	1.51 (1.17-1.95)*	0.78 (0.59-1.03)	1.09 (0.60-1.99)	1.31 (0.28-6.26)	1.00 (0.81-1.22)	1.14 (0.86-1.50)	1.05 (0.87-1.26)
Sulfate										
lag 0	0.90 (0.64-1.25)	1.79 (1.00-3.20)*	0.93 (0.79-1.11)	1.08 (0.93-1.26)	0.99 (0.85-1.15)	1.16 (0.80-1.68)	0.79 (0.29-2.16)	0.99 (0.87-1.12)	0.92 (0.79-1.07)	1.04 (0.94-1.15)
lag 1	1.10 (0.82-1.49)	1.63 (1.04-2.55)*	1.00 (0.85-1.18)	1.10 (0.96-1.27)	0.99 (0.86-1.15)	1.04 (0.74-1.45)	1.22 (0.60-2.49)	1.05 (0.93-1.18)	1.03 (0.89-1.19)	1.03 (0.94-1.13)
lag 2	0.83 (0.60-1.15)	1.39 (0.83-2.34)	1.02 (0.87-1.20)	0.99 (0.86-1.14)	0.97 (0.84-1.12)	0.95 (0.68-1.31)	1.51 (0.76-2.99)	0.97 (0.87-1.08)	1.09 (0.94-1.26)	1.02 (0.93-1.13)
5-day mean	1.38 (0.76-2.48)	3.56 (1.02-12.48)*	0.94 (0.67-1.30)	1.46 (1.06-2.01)*	0.93 (0.67-1.30)	1.31 (0.69-2.46)	2.40 (0.75-7.69)	0.94 (0.77-1.14)	1.23 (0.91-1.65)	1.07 (0.89-1.29)
SO_2										
lag 0	0.86 (0.60-1.23)	1.33 (0.66-2.71)	1.01 (0.84-1.20)	1.15 (0.97-1.37)	1.09 (0.93-1.28)	0.79 (0.48-1.29)	0.79 (0.22-2.88)	1.11 (0.94-1.30)	0.97 (0.79-1.20)	1.04 (0.91-1.18)
lag 1	0.97 (0.68-1.39)	1.98 (1.03-3.79)*	0.97 (0.82-1.16)	1.06 (0.90-1.26)	1.05 (0.89-1.24)	1.08 (0.68-1.72)	0.71 (0.13-4.02)	1.04 (0.88-1.22)	1.20 (0.98-1.47)	1.08 (0.95-1.22)
lag 2	0.87 (0.63-1.20)	1.16 (0.61-2.19)	0.94 (0.80-1.10)	0.97 (0.82-1.14)	0.85 (0.72-0.99)*	0.84 (0.38-1.86)	1.23 (0.16-9.45)	0.92 (0.80-1.07)	0.99 (0.81-1.21)	1.02 (0.88-1.18)
5-day mean	1.06 (0.57-1.98)	1.76 (0.45-6.91)	0.71 (0.53-0.95)*	1.27 (0.91-1.76)	0.91 (0.65-1.25)	0.82 (0.37-1.82)	0.64 (0.08-5.40)	1.01 (0.77-1.32)	1.26 (0.86-1.83)	1.14 (0.91-1.41)
NO_2										
lag 0	0.98 (0.78-1.22)	0.96 (0.59-1.57)	0.96 (0.86-1.07)	1.11 (1.01-1.23)*	1.02 (0.93-1.12)	1.21 (0.97-1.53)	2.65 (1.50-4.66)*	1.00 (0.93-1.09)	1.04 (0.95-1.14)	1.01 (0.95-1.07)
lag 1	1.19 (0.96-1.46)	1.18 (0.77-1.82)	0.92 (0.83-1.01)	1.06 (0.97-1.15)	0.98 (0.90-1.07)	0.98 (0.77-1.23)	0.97 (0.58-1.63)	1.00 (0.92-1.07)	1.06 (0.96-1.16)	0.96 (0.90-1.02)
lag 2	0.97 (0.79-1.21)	0.81 (0.53-1.24)	0.96 (0.87-1.06)	0.96 (0.88-1.04)	0.96 (0.88-1.04)	0.97 (0.78-1.20)	0.92 (0.58-1.46)	0.99 (0.92-1.07)	1.00 (0.91-1.10)	1.02 (0.96-1.08)
5-day mean	0.90 (0.58-1.41)	0.24 (0.08-0.74)*	0.74 (0.59-0.95)*	0.97 (0.75-1.25)	0.85 (0.67-1.08)	0.92 (0.61-1.40)	1.18 (0.54-2.56)	0.92 (0.80-1.06)	1.09 (0.89-1.33)	0.95 (0.83-1.08)

* *OR significantly different from 1 ($p<0.05$)*

Table 5. Odds Ratios (OR) with 95% confidence intervals (95% CI) for the association between air pollution and the prevalence of > 10% decrements in evening PEF and acute respiratory symptoms in non-symptomatic adults, calculated from combined effect estimates. OR's for an increase of 100 μg/m³ for PM_{10}, 40 μg/m³ for Black Smoke, SO_2 and NO_2 and 15 μg/m³ for sulfate.

	Urban areas		*Non-urban areas*	
	> 10% in pefmo	*URS*	*> 10% in pefmo*	URS
PM_{10}				
lag 0	1.14 (0.59-2.19)	1.00 (0.73-1.37)	0.30 (0.11-0.86)*	0.98 (0.76-1.26)
lag 1	2.03 (1.16-3.56)	1.22 (0.92-1.61)	1.28 (0.63-2.62)	1.22 (0.97-1.53)
lag 2	0.68 (0.38-1.21)	0.89 (0.66-1.20)	0.37 (0.16-0.85)*	0.91 (0.70-1.19)
5 day mean	1.13 (0.47-2.76)	1.04 (0.58-1.86)	0.09 (0.02-0.37)*	1.34 (0.70-2.54)
Black Smoke				
lag 0	1.27 (0.72-2.24)	1.01 (0.76-1.35)	0.73 (0.42-1.27)	1.00 (0.71-1.40)
lag 1	1.10 (0.68-1.77)	1.03 (0.79-1.33)	1.44 (0.94-2.21)	1.45 (1.11-1.89)*
lag 2	0.94 (0.59-1.48)	0.96 (0.75-1.24)	0.86 (0.55-1.34)	0.67 (0.50-0.89)*
5-day mean	0.89 (0.41-1.91)	0.98 (0.59-1.61)	0.34 (0.10-1.18)	1.31 (0.60-2.86)
Sulfate				
lag 0	1.87 (1.11-3.15)*	0.92 (0.69-1.23)	0.86 (0.38-1.93)	1.12 (0.81-1.53)
lag 1	1.69 (1.08-2.66)*	1.13 (0.88-1.46)	1.08 (0.58-2.00)	1.30 (0.96-1.78)
lag 2	0.97 (0.58-1.62)	0.99 (0.76-1.29)	0.66 (0.35-1.23)	0.87 (0.62-1.21)
5-day mean	2.63 (0.82-8.45)	1.08 (0.61-1.92)	0.13 (0.04-0.50)*	1.47 (0.74-2.92)
SO_2				
lag 0	0.77 (0.39-1.52)	1.10 (0.81-1.48)	2.12 (0.98-4.62)	0.73 (0.49-1.07)
lag 1	0.94 (0.51-1.73)	1.23 (0.92-1.65)	0.87 (0.38-1.99)	1.71 (1.18-2.46)*
lag 2	0.86 (0.48-1.55)	0.85 (0.64-1.13)	0.13 (0.04-0.36)*	0.65 (0.44-0.97)*
5-day mean	1.01 (0.35-2.95)	1.01 (0.56-1.79)	0.03 (0.00-0.24)*	1.06 (0.43-2.61)
NO_2				
lag 0	0.85 (0.57-1.26)	0.95 (0.79-1.15)	0.71 (0.48-1.04)	1.05 (0.87-1.27)
lag 1	1.00 (0.69-1.49)	0.95 (0.80-1.12)	1.12 (0.76-1.65)	1.00 (0.82-1.21)
lag 2	0.81 (0.56-1.17)	1.00 (0.85-1.17)	1.09 (0.76-1.58)	0.88 (0.73-1.06)
5-day mean	0.44 (0.18-1.08)	0.98 (0.63-1.51)	0.54 (0.25-1.20)	0.90 (0.50-1.62)

** OR significantly different from 1 (P<0.05)*

In the urban areas there was also a tendency towards a positive association between the prevalence of URS and indicators for particulate air pollution, especially Black Smoke. No consistent associations were observed between air pollution and the prevalence of LRS and bronchodilator use. With phlegm and cough no associations were observed either (not shown).

In the symptomatic panels in the non-urban areas no consistent associations

were observed between air pollution and respiratory health (table 4). Especially for PM10 and sulfate effect estimates for the >20% decrements in morning PEF were similar to those of the urban area however.

The associations between air pollution and respiratory health in non-symptomatic subjects are presented in table 5. It shows that in the urban areas there was a tendency towards a positive association between sulfate and the prevalence of >10% decrements in morning PEF. This association was not found in the non-urban areas. No consistent associations between other respiratory health indicators and air pollution were observed in non-symptomatic subjects from the urban and the non-urban areas. The prevalence of >20% decrements in PEF was so low in the non-symptomatic panels that it could not be analyzed.

Discussion

In this study, we have found that in symptomatic adults living in urban areas the daily prevalence of >20% decrements in morning PEF had a positive association with SO_2 and indicators of particulate air pollution, especially Black Smoke. The prevalence of URS was also positively associated with BS and, to a lesser extent, with PM10 and sulfate. No associations were observed between air pollution and the prevalence of other respiratory health indicators, including bronchodilator use, LRS, >10% decrements in morning PEF and >10% and >20% decrements in evening PEF. NO_2 was not related to any of the health endpoints. In symptomatic adults living in non-urban areas, no significant and consistent associations between air pollution concentrations and indicators of respiratory health were observed. The differences in effect estimates between urban and non-urban were generally small and non-significant however. In non-symptomatic adults, no consistent associations were observed at all.

No consistent pattern of associations with air pollution was found for most of the health endpoints that we studied. However, for >20% morning PEF decrements consistent associations were found in the symptomatic urban panel. We do not believe that these associations represent chance findings resulting from the large number of evaluated associations. The consistent pattern of associations with the different evaluated lags supports this. In addition, an association with URS is observed as well. The lack of associations with 10% morning PEF decrements and both evening PEF variables casts some doubt on the observed associations however. Only for Black Smoke, some (borderline)

significant associations were observed for the other PEF variables. The fact that no particle effects on evening PEF were observed is not in agreement with other studies that were mostly performed in children[3]. The same is true for the lack of association with LRS and bronchodilator use. The few panel studies that focused on adult symptomatic (mainly asthmatic) subjects also found that increased particle concentrations were most consistently associated with increased reporting of shortness of breath[8,9], lower respiratory symptoms and bronchodilator use[10]. We therefore interpret the observed pattern of associations with caution, indicating at most a weak effect of outdoor air pollution.

Potential confounders that might bias the association between air pollution and respiratory health in time series studies are meteorologic variables (mainly ambient temperature), respiratory infections and long term time trends. All associations were adjusted for ambient temperature and for non-linear long term time trends in the prevalence of symptoms, bronchodilator use and PEF-decrements. The adjustment for time trends was more detailed than in previous panel studies which either specified no time trend or a linear trend. The incidence of influenza-like illness (ILI) in the general population, registered by a GP sentinel system, was used to adjust for the potential confounding effect of respiratory infections. In previous panel studies, no adjustments for the potential confounding effect of respiratory infections were made. We report in a separate paper[20] that the ILI incidence in the general population was associated with respiratory health in selected panels.

It is unlikely that the low response rate to the screening questionnaire resulted in a biased effect estimate. In time series studies each subject serves as his/her own control thus effect estimates are valid for the selected panel. Only in the unlikely case that we preferentially selected subjects that were more (or less) susceptible to air pollution, the effect estimates for the panel could be different from that of the base study population.

In this study, exposure assessment was based on fixed site ambient air concentrations measured at one location in both areas. It might be questioned whether exposure to air pollution was adequately characterized by fixed site ambient air concentrations only; if not, the resulting misclassification would probably result in a downward bias of the observed association between air pollution and health endpoints. Compared to children, adults generally spend less time outdoor and consequently, the amount of misclassification in exposure assessment might be larger. A number of recent studies in the Netherlands[25-27]

have shown that the time series correlation between ambient and personal PM_{10} and especially $PM_{2.5}$ is high. For 10-12 yr old children and 50-70 yr old adults, the median correlation coefficient between ambient and personal PM_{10} was 0.63 and 0.50, respectively, which shows that the amount of misclassification in adults was only slightly higher than for children.

Compared to other panel studies, a different approach was used to analyse Peak Expiratory Flow data, focusing not on decrements in population mean PEF but on the fraction of subjects that is experiencing substantial PEF decrements. In a re-analysis of data from seven panel studies of school children, symptomatic and non-symptomatic children, Hoek and co-workers[23] have compared the two approaches and demonstrated that an increase of 100 $\mu g/m^3$ of the same-day PM_{10} concentration was associated with a decrement in population mean evening PEF of 0.7%. The corresponding Odds Ratios for the prevalence of >10% and >20% decrements were 1.31 and 1.41, respectively. Morning PEF data were not available in all studies and were therefore not included in the re-analysis[23]. In our panels of symptomatic adults from the urban areas, the Odds Ratios for the association between an increase of 100 $\mu g/m^3$ in same-day PM_{10} concentration and the prevalence of >10% and >20% decrements in evening PEF were 1.05 and 0.71, respectively (both non-significant). For morning PEF Odds Ratios of 0.95 (non-significant) and 2.41 (95% CI: 1.22-4.78) were found for >10% and >20% decrements, respectively. A possible explanation for the observed association with morning PEF, rather than with evening PEF might be that morning PEF is less affected by medication used during the day. Since morning PEF is more determined by allergen exposure at night[28] than is evening PEF, pollution-allergen interaction might be another explanation. Controlled human exposure studies have indicated that exposure to gaseous air pollutants may increase the airway responsiveness of asthmatics to inhaled allergen such as house dust mites[29,30]. Recently, it has been reported that in a murine model of allergic asthma, PM was able to enhance mite-induced airway responsiveness[31], suggesting that this might be a reasonable explanation. To our knowledge, no controlled human exposure studies investigating pollution-allergen interactions have been performed with particulate air pollution. Allergic reactions to indoor allergens include irritation of the upper respiratory tract, which might also explain the observed association between particles and URS.

No association between indicators of air pollution and respiratory health was observed in the panels of non-symptomatic adults. To our knowledge, only one

other panel study[12] has been performed on adults not selected for chronic respiratory symptoms. In that study, sulfate concentration was associated with lower respiratory symptoms, while coefficient of haze (a more general measure of particulates) was not. Neither sulfates nor coefficient of haze were associated with upper respiratory symptoms. SO_2 and NO_2 were not associated with any respiratory health outcome. The results of this study agree with the results of our study in non-symptomatic adults, although in our study no association with LRS was observed.

Associations between particulate air pollution and respiratory health indicators were observed in symptomatic adults from the urban areas, but not from the non-urban areas. However, especially for sulfate the 20% morning PEF effect estimates in the non-urban areas were similar. In addition, confidence intervals for the urban and non-urban areas overlapped widely. If the observed difference is interpreted as a true difference between the urban and non-urban areas, it might be explained by the higher asthma medication use in the non-urban symptomatic panels, as it has been suggested that medication use attenuates the association between air pollution and respiratory health[13,32]. Bronchodilator use was not associated with particle concentrations and the health outcomes for which particle effects were observed in the urban panels (morning PEF and URS) are probably least affected by asthma medication use. Despite this, it can not be ruled out that differences in asthma medication use are responsible for the observed differences in response between urban and non-urban panels. The differences in response between urban and non-urban symptomatic panels is not explained by differences in the fraction of atopic subjects (49% in urban and 46% in non-urban area). Exclusion of the data from the first winter from the calculation of a combined estimate for the urban panel, resulted in effect estimates that were similar to those presented. Most estimates were even slightly larger when the first winter was excluded. Thus, the difference is not due to the fact that in the first winter, with relatively high particle and SO_2 concentrations, only subjects in the urban area were studied. Another, more speculative explanation might be that urban particles are more toxic, per $\mu g/m^3$, than the non-urban particles. This might be due to the larger number of ultrafine particles (UFP; <0.1 μm) in urban air, or to a more toxic chemical composition of urban particles.

Transient decrements of FVC and FEV1 of 20% have been considered as the border between moderate and severe response[33,34]. The effect estimates

observed in our study indicate that in symptomatic adults from urban areas, an increase in 5-day mean BS concentration of 40 $\mu g/m^3$ is associated with a fourfold increase in the number of subjects with a response that could be characterized as severe. Although the prevalence of >20% decrements in morning PEF was low (1.5%), this refers to a substantial 60 events per 1000 person-days that are attributable to elevated BS concentrations.

The association between SO_2 and morning PEF we observed in symptomatic, urban panels was found at very low SO_2 concentrations, with medians of 25, 11 and 6 $\mu g/m^3$ during the three winters, respectively, and maximum concentrations never higher than 61 $\mu g/m^3$. Although within 24 hour time periods, higher short-term concentrations are observed, direct SO_2 effects seem unlikely at these levels[1]. We think that SO_2 in these circumstances serves as an indicator for a more complex mixture which contains the actual responsible component(s). Black Smoke was more consistently associated with the prevalence of >20% decrements in morning PEF and URS than PM_{10} and sulfate. BS can be considered as an indicator of fine black particles (elemental carbon) emitted by diesel engines which is generally found in the fine to ultrafine particle fraction.

In conclusion, weak particle effects were observed in symptomatic adults from urban areas, but not from non-urban areas. The differences in effect-estimates between urban and non-urban symptomatic panels were small and non-significant, however. In non-symptomatic adults from both urban and non-urban areas no particle effects were observed.

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Chapter 7

Children with chronic respiratory symptoms and atopy respond more strongly to air pollution than non-symptomatic, non-atopic children

Gerard Hoek, Saskia C. van der Zee, H. Marike Boezen, Jan P. Schouten, Dirkje S. Postma, Jorrit Gerritsen, Joop H. van Wijnen and Bert Brunekreef

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Abstract

Studies in various locations have found effects of daily variations of ambient air pollution on acute respiratory symptoms and Peak Expiratory Flow (PEF). Some panel studies have suggested that subjects with chronic respiratory symptoms reported in a questionnaire experience stronger effects than non-symptomatic subjects. Panel members have not usually been characterized with objective tests, however. The purpose of this study was to evaluate whether the response to air pollution differed across subgroups defined by questionnaire and objective medical characteristics.

With a screening questionnaire, 7-11 year old children with and without chronic respiratory symptoms were selected. Medical characterization included skin prick testing for common allergens and determination of total serum IgE as measures of atopy, and measurement of bronchial hyperresponsiveness (BHR) to methacholine. Participants reported PEF measured twice-daily at home, bronchodilator use and acute respiratory symptoms in a daily diary. Daily measurements of PM_{10} were performed at fixed sites. Logistic regression analyses adjusting for confounders were conducted in four subgroups for each medical characteristic: symptomatic with/without BHR, elevated total IgE or positive skin prick test, and non-symptomatic with/without these characteristics.

The most consistent association between PM_{10} and respiratory health was found in symptomatic children who had either high total serum IgE or a positive skin prick test. In these children associations both with PEF and acute respiratory symptoms was found. Associations between PM_{10} and PEF were found both in symptomatic and non-symptomatic children and in atopic and non-atopic children. Presence of high serum IgE or a positive skin prick test was not related to a stronger response to PM_{10} in non-symptomatic children.

Introduction

Studies in a variety of locations have observed associations between daily changes of ambient air pollution concentrations and respiratory health[1,2]. Effects of especially particulate matter on daily mortality, hospital admissions, medication use, respiratory symptoms and lung function have been found[1,2]. An important issue in characterizing health effects of ambient air pollution is whether specific subgroups of the population experience more serious effects than others. Sensitive subgroups of the population may differ in their response to air pollution both qualitatively (i.e., having responses that others do not experience) and quantitatively (larger magnitude of the same response). Effects on respiratory symptoms and lung function have mostly been studied using the panel study design: a group of selected subjects report on a daily basis respiratory symptoms, medication use and Peak Expiratory Flow in a diary for several months. Characterization of panel study participants has in most studies been limited to information available from questionnaires, such as presence of specific chronic respiratory symptoms, medication use, age and gender. Several panel studies have suggested that children with chronic respiratory symptoms[3,4] or asthma[5,6] are a sensitive subgroup. Controlled exposure studies have confirmed that asthmatics are more sensitive to exposure to SO_2 and sulfuric acid[7]. Asthmatics are not a homogenous group, however, and it is possible that specific subgroups respond more strongly than others.

The present study was performed in the framework of a series of panel studies of children selected to have either specific chronic respiratory symptoms or no chronic respiratory symptoms[8]. In non-symptomatic children associations between especially PM_{10} and evening PEF were found. In symptomatic children associations between PM_{10} and evening PEF, lower respiratory symptoms and bronchodilator use were found[8]. The purpose of the present analysis was to evaluate whether the response to ambient air pollution was qualitatively and/or quantitatively different in children characterized by not only the presence / absence of chronic respiratory symptoms, but also by objective measurements of atopy and bronchial responsiveness.

Methods

Study design and methods

The design of the study and methods of exposure and health effect characterization have been reported before[8,9]. Briefly, during three consecutive winters starting in 1992/1993 selected panels of children reported the presence of acute respiratory symptoms, medication use and PEF in a daily diary. With a screening questionnaire panels of approximately equal size of children with and without chronic respiratory symptoms were selected. Children were selected into the 'symptomatic' panel if they had one or more positive answers to the questions about attacks of shortness of breath with wheeze in the past 12 months, cough at night in the past 12 months, wheeze in the past 12 months, doctor diagnosed asthma ever. Children were selected into a 'non-symptomatic' panel if they had no positive answer at all. In each winter children were selected from one urban and one non-urban area. Thus the study included six panels of symptomatic and six panels of non-symptomatic children (three winters, one urban and non-urban area per winter).

During the approximately three months study periods, participants performed PEF measurements twice daily using Mini Wright peak flow meters, in the morning before breakfast and in the evening before going to bed. Subjects were instructed to perform the PEF measurements before any medication was taken. The highest of the three PEF readings at each test was used for analysis. Only evening PEF was analyzed in this paper, since evening PEF was most strongly related to air pollution in the main study[8]. For the PEF analysis we first calculated the individual median PEF over the study period for each subject. Next PEF decrements of >10% were calculated below the individual median. The diary was also used to record the occurrence of lower respiratory symptoms (LRS = shortness of breath, wheeze and attacks of shortness of breath with wheeze), upper respiratory symptoms (URS = runny/stuffed nose and sore throat), cough and phlegm and bronchodilator use. Daily prevalence of >10% evening PEF decrements, respiratory symptoms and bronchodilator use were next calculated.

Exposure to ambient air pollution was characterized by daily 24-hour average measurements of PM_{10}, Black Smoke and fine aerosol sulfate and nitrate at fixed sites in the selected urban and non-urban areas during the full study period[9]. Measurements were conducted from 3 pm to 3 pm. Information about the ambient concentrations of SO_2 and NO_2 was obtained from the nearest routine

monitoring network station. Temperature data from the nearest site of the Dutch Royal Meteorological Institute were obtained. Data on the weekly incidence of influenza-type illnesses were obtained from a sentinel system operated by the Dutch Institute of Primary Health Care (NIVEL).

Subject characterization

Children were characterized at baseline by measurement of bronchial responsiveness to methacholine, determination of total serum IgE and skin prick testing with common allergens. Methods of determination of bronchial responsiveness and total IgE were reported before[10,11]. Subjects with a fall of 20% or greater in FEV_1 at a cumulative dose of 2.0 mg methacholine or less were considered to have bronchial hyperresponsiveness (BHR). Serum total IgE was measured with a sandwich enzyme immunoassay[12]. The median (60 kU/l) was used as the cutoff to define subjects with 'high' and 'low' IgE levels[11]. Skin prick testing was performed using the methods of the PEACE study[13], which were based upon the European Community Respiratory Health Survey[14]. Briefly, children were tested with allergens from house dust mite, cat fur, dog fur, birch, pollen of timothy grass and Cladosporium herbarum. Each test included a positive control (histamine) and a negative control (diluent). All allergens were obtained from ALK laboratories, Denmark. A child was considered atopic if there was a wheal reaction of more than 2 mm to one of the tested allergens and the positive control was more than 0 mm and the negative control was equal to or less than 1 mm.

Data analysis

For each evaluated medical characteristic separately, children were divided into four subgroups based upon symptom status and presence/absence of a medical characteristic. For BHR we thus defined symptomatic children with BHR; symptomatic children without BHR; non-symptomatic children with BHR and non-symptomatic children without BHR. The association between air pollution and respiratory health was analyzed for the different winters and towns separately. Logistic regression with additional modeling of first order autocorrelation of the residuals was performed. All associations were adjusted for non-linear time trends (linear, quadratic and cubic terms), influenza epidemics, minimum temperature and day of the week (weekdays versus weekend/holidays). These methods were the same as used in the main study[8]. For each subgroup six

logistic regression slopes were available for each combination of health outcome and exposure variable. These estimates were combined into a weighted average slope per subgroup, using the inverse of the square of the standard error as the weight. The standard error of the combined mean slope was calculated as the inverse of the square root of the sum of the weights.

Because the focus of this paper is on comparing responses across subgroups of the children, we will only report on associations between PM_{10} and respiratory health. Associations between air pollution and respiratory health were most consistent for PM_{10} in the main study[8]. We evaluated the concentration of the same day (lag 0), previous day (lag 1), two days ago (lag 2) and the mean of the previous five days in separate models. In evaluating the responses in the subgroups we considered the statistical significance of the association between the evaluated lag and a specific health endpoint and the consistency of the association for the four lags. For example, a significant Odds Ratio above unity for one lag accompanied by three non-significant Odds Ratios below unity was not considered as evidence for a consistent association between the specific health endpoint and PM_{10}.

All calculations were performed using the Statistical Analysis System (SAS) version 6.12 on an Alpha mainframe computer.

Results

Population of children

In total 633 children were included in the study of which 320 were symptomatic and 313 were non-symptomatic according to the baseline questionnaire. Valid data on total serum IgE, bronchial responsiveness and skin prick test were obtained from 79, 87 and 96% of the children respectively. The percentage of children with valid data did not differ between symptomatic and non-symptomatic children for bronchial responsiveness and skin prick test. There was a tendency (p-value of a Chi square test 0.07) towards a lower percentage of valid data for non-symptomatic children (76%) compared to symptomatic children (82%) for total serum IgE.

Symptomatic children more frequently had high serum total IgE, a positive skin prick test and bronchial hyperresponsiveness than non-symptomatic children. Among symptomatic and non-symptomatic children, the prevalence of elevated serum total IgE was 59% versus 41%, a positive skin prick test 49% versus

27% and of BHR 55% versus 30% respectively. All these differences were statistically significant ($p < 0.01$). Thus there was a reasonable number of children in all subgroups defined on the basis of both symptom status and objective clinical measurements.

There was considerable overlap between the presence/absence of high total serum IgE, a positive skin prick test and bronchial hyperresponsiveness. Percentage agreement and Kappa values for the agreement between total IgE and skin prick test were 71% and 0.43; 65% and 0.26 for the agreement between bronchial hyperresponsiveness and skin prick test; 61% and 0.21 for the agreement between total IgE and bronchial hyperresponsiveness.

A description of the subgroups for which the association with air pollution was analyzed is presented in table 1. Children with bronchial hyperresponsiveness were younger than children without BHR, both in symptomatic and in non-symptomatic children. Among symptomatic children with high IgE there were fewer girls than in the other subgroups.

Table 1. Population characteristics of different subgroups of children

		Age, yr	Girls, %	N
non-symptomatic	Low IgE	9.7 (1.1)	47*	142
non-symptomatic	High IgE	9.6 (1.2)	55	97
symptomatic	Low IgE	9.7 (1.1)	62	108
symptomatic	High IgE	9.5 (1.1)	40	155
non-symptomatic	SPT-	9.6 (1.1)	52	217
non-symptomatic	SPT+	9.7 (1.2)	50	82
symptomatic	SPT-	9.4 (1.1)	57	158
symptomatic	SPT+	9.6 (1.1)	44	149
non-symptomatic	BHR-	9.8 (1.2)*	52	190
non-symptomatic	BHR+	9.3 (1.0)	55	82
symptomatic	BHR-	9.8 (1.2)	59	126
symptomatic	BHR+	9.3 (1.0)	45	155

Note: Presented are mean and SD in parentheses; SPT = skin prick test; BHR = bronchial hyperresponsiveness, low IgE is total serum IgE < 60 kU/l.

** differences between four subgroups statistically significant ($p < 0.05$)*

The prevalence of large PEF decrements was highest in the subgroup of symptomatic children who also had high total IgE or a positive skin prick test or BHR. Prevalences were similar in the other subgroups (Table 2). Cough prevalence was highest among the symptomatic children, with a small increase in children with especially high IgE. Prevalence of LRS and especially bronchodilator use was very low among non-symptomatic children. The highest prevalence of LRS and bronchodilator use occurred among symptomatic children who also had high total IgE or a positive skin prick test or BHR.

Table 2. Mean prevalence (%) of 10% evening PEF decrements and acute respiratory symptoms in subgroups of children defined by presence/absence of chronic respiratory symptoms according to a baseline questionnaire and objective medical characteristics

Subgroup	10% PEF decrements	Cough	LRS	Bronchodilator use	N
Non-symptomatic, low IgE	7.6	14.2	0.5	0.0	142
Non-symptomatic, high IgE	8.3	19.3	1.8	0.3	97
Symptomatic, low IgE	7.7	29.9	4.0	1.3	108
Symptomatic, high IgE	11.6	38.5	12.4	6.6	155
Non-symptomatic, SPT-	7.8	16.2	0.9	0.0	217
Non-symptomatic, SPT+	9.2	19.2	1.3	0.4	82
Symptomatic, SPT-	8.9	32.3	4.4	1.4	158
Symptomatic, SPT+	11.1	38.6	13.1	6.7	149
Non-symptomatic, no BHR	8.0	17.3	0.8	0.0	190
Non-symptomatic, BHR	8.3	16.6	1.6	0.4	82
Symptomatic, no BHR	7.7	33.5	6.0	2.9	126
Symptomatic, BHR	11.7	36.2	10.9	5.2	155

Note: LRS = shortness of breath, wheeze and attacks of shortness of breath with wheeze

Air pollution data

The average PM_{10} concentration ranged from 27 $\mu g/m^3$ in the non-urban area in winter three to 55 $\mu g/m^3$ in the urban area in winter one[8,11]. Twenty-four hour average PM_{10} concentrations of 90 $\mu g/m^3$ and higher were observed in all three

winters. On only one day the daily average PM_{10} concentration exceeded 150 $\mu g/m^3$, the 24-hr Air Quality Standard in the USA.

Associations in subgroups based on serum total IgE

In non-symptomatic children with low IgE, a significant positive association (Odds Ratio above unity) between PM_{10} and PEF was found for all four evaluated lags (Table 3). No association between PM_{10} and cough was found. In non-symptomatic children with high IgE, borderline significant associations with PEF and cough were found with PM_{10} lag0, but not with the other lags. Prevalences of LRS and bronchodilator use were too low to be analyzed for both subgroups of non-symptomatic children.

Table 3. Association between PM_{10} and prevalence of >10% evening PEF decrements, cough, bronchodilator use and lower respiratory symptoms (LRS) in subgroups of children defined by presence (+) or absence (-) of chronic respiratorysymptoms from a baseline questionnaire (Sy) and high total serum IgE (IgE), adjusted for confounders. Odds Ratios (OR) with 95% confidence intervals (95% CI) for an increase of 100 $\mu g/m^3$ in PM_{10} concentration.

		Sy-IgE- (n=142)	Sy-IgE+ (n=97)	Sy+IgE- (n=108)	Sy+IgE+ (n=155)
Pollutant	Effect variable				
PM_{10} lag0	10% PEF	1.36 (1.05-1.75)*	1.38 (0.97-1.97)	1.37 (0.93-2.02)	1.30 (1.00-1.68)*
PM_{10} lag1	10% PEF	1.36 (1.08-1.73)*	0.88 (0.63-1.22)	1.05 (0.72-1.52)	1.40 (1.11-1.76)*
PM_{10} lag2	10% PEF	1.54 (1.21-1.95)*	0.77 (0.56-1.07)	1.24 (0.90-1.72)	1.40 (1.12-1.75)*
PM_{10} mean	10% PEF	2.02 (1.40-2.92)*	0.68 (0.41-1.13)	1.18 (0.65-2.16)	2.32 (1.58-3.39)*
PM_{10} lag0	Cough	0.94 (0.81-1.10)	1.17 (0.99-1.38)	1.16 (1.00-1.35)*	1.11 (0.98-1.26)
PM_{10} lag1	Cough	0.80 (0.68-0.94)*	0.91 (0.77-1.07)	0.97 (0.83-1.13)	1.06 (0.94-1.20)
PM_{10} lag2	Cough	1.03 (0.89-1.20)	0.94 (0.80-1.10)	0.98 (0.84-1.14)	1.04 (0.92-1.17)
PM_{10} mean	Cough	0.92 (0.66-1.28)	0.99 (0.75-1.31)	0.98 (0.72-1.34)	1.24 (0.98-1.56)
PM_{10} lag0	Bronchodilator			1.01 (0.80-1.27)	1.06 (0.87-1.29)
PM_{10} lag1	Bronchodilator			0.83 (0.63-1.10)	1.09 (0.90-1.32)
PM_{10} lag2	Bronchodilator			1.01 (0.80-1.27)	1.13 (0.95-1.35)
PM_{10} mean	Bronchodilator			0.64 (0.35-1.18)	1.40 (0.95-2.06)
PM_{10} lag0	LRS			0.85 (0.64-1.14)	1.22 (1.02-1.45)*
PM_{10} lag1	LRS			1.09 (0.82-1.46)	1.20 (1.02-1.42)*
PM_{10} lag2	LRS			1.31 (1.01-1.69)*	1.17 (0.99-1.37)
PM_{10} mean	LRS			1.86 (1.20-2.89)*	1.71 (1.29-2.25)*

** OR significantly different from 1 (P<0.05)*

In symptomatic children with low IgE, no consistent association of PM_{10} with PEF and bronchodilator use was found. There was one significant association between PM_{10} and cough at lag0, but Odds Ratios for the other lags were below 1. There was a consistent association with LRS, being significant for two of the evaluated lags. In symptomatic children with high total IgE consistently positive associations between PM_{10} and PEF and LRS were found. Odds Ratios for bronchodilator use and cough were above unity as well, with some of them borderline significant.

Associations in subgroups based on skin prick test

In non-symptomatic children without a positive skin prick test, only a weak association of PM_{10} with PEF was found. No association between PM_{10} and cough was found. In the non-symptomatic children with a positive skin prick test consistently positive associations were found between PM_{10} and PEF and cough. Bronchodilator use and LRS prevalences were too low to be analyzed in both subgroups of non-symptomatic children.

In symptomatic children without a positive skin prick test, most Odds Ratios were above unity for PEF, cough and LRS but only one of them was statistically significant (cough with PM_{10} lag0). In symptomatic children with a positive skin prick test consistent associations were found between PM_{10} and PEF, LRS and bronchodilator use (Table 4). The magnitude of the effect estimates was similar to those observed for symptomatic children with high IgE (table 3), with the exception of the lack of association with cough.

Associations in subgroups based on bronchial hyperresponsiveness

In non-symptomatic children without hyperresponsiveness a tendency towards a positive association with PEF was found but none of the associations was statistically significant (table 5). Non-symptomatic children with hyperresponsiveness had a consistently positive association with PEF, but not with cough. Bronchodilator use and LRS prevalences were too low to be analyzed in both subgroups of non-symptomatic children.

In symptomatic children without hyperresponsiveness consistently positive associations with PEF and LRS were found. In symptomatic children who were hyperresponsive consistent associations were found with LRS. The associations in this subgroup were less consistent than observed in the subgroups of symptomatic children with high IgE or a positive skin prick test (tables 3 and 4).

Table 4. Association between PM_{10} and prevalence of >10% evening PEF decrements, cough, bronchodilator use and lower respiratory symptoms (LRS) in subgroups of children defined by presence (+) or absence (-) of chronic respiratory symptoms from a baseline questionnaire (Sy) and a positive skin prick test (SPT), adjusted for confounders. Odds Ratios (OR) with 95% confidence intervals for an increase of 100 $\mu g/m^3$ in PM_{10} concentration.

		Sy-SPT- (n=217)	Sy-SPT+ (n=82)	Sy+SPT- (n=158)	Sy+SPT+ (n=149)
Pollutant	Effect variable				
PM_{10} lag0	10% PEF	1.33 (1.08-1.64)*	1.50 (1.04-2.18)*	1.28 (0.98-1.67)	1.25 (0.94-1.67)*
PM_{10} lag1	10% PEF	1.12 (0.93-1.36)	1.33 (0.95-1.88)	1.05 (0.82-1.34)	1.27 (0.98-1.64)
PM_{10} lag2	10% PEF	1.02 (0.85-1.23)	1.13 (0.80-1.59)	1.01 (0.80-1.26)	1.35 (1.05-1.73)*
PM_{10} mean	10% PEF	1.17 (0.87-1.58)	1.73 (0.96-3.13)	1.45 (0.95-2.21)	2.21 (1.43-3.42)*
PM_{10} lag0	Cough	1.09 (0.97-1.22)	1.10 (0.91-1.35)	1.14 (1.01-1.29)*	1.01 (0.88-1.16)
PM_{10} lag1	Cough	0.85 (0.76-0.96)*	1.06 (0.87-1.30)	1.03 (0.91-1.16)	1.02 (0.90-1.17)
PM_{10} lag2	Cough	0.95 (0.85-1.07)	1.07 (0.88-1.29)	0.96 (0.85-1.09)	1.05 (0.92-1.19)
PM_{10} mean	Cough	0.93 (0.73-1.19)	1.46 (1.06-2.01)*	1.03 (0.80-1.33)	1.05 (0.81-1.36)
PM_{10} lag0	Bronchodilator			1.08 (0.85-1.37)	1.03 (0.83-1.28)
PM_{10} lag1	Bronchodilator			0.95 (0.72-1.25)	1.15 (0.93-1.42)
PM_{10} lag2	Bronchodilator			1.08 (0.83-1.39)	1.11 (0.92-1.34)
PM_{10} mean	Bronchodilator			0.99 (0.58-1.69)	1.56 (1.03-2.37)*
PM_{10} lag0	LRS			0.99 (0.74-1.34)	1.22 (1.02-1.47)*
PM_{10} lag1	LRS			1.26 (0.95-1.66)	1.28 (1.08-1.52)*
PM_{10} lag2	LRS			1.09 (0.85-1.39)	1.26 (1.08-1.48)
PM_{10} mean	LRS			1.60 (0.87-2.95)	1.76 (1.32-2.33)*

Table 5. Association between PM_{10} and prevalence of >10% evening PEF decrements, cough, bronchodilator use and lower respiratory symptoms (LRS) in subgroups of children defined by presence (+) or absence (-) of chronic respiratory symptoms from a baseline questionnaire (Sy) and bronchial hyperresponsiveness (BHR), adjusted for confounders. Odds Ratios (OR) with 95% confidence intervals for an increase of 100 $\mu g/m^3$ in PM_{10} concentration.

		Sy-BHR- (n=217)	Sy-BHR+ (n=82)	Sy+BHR- (n=126)	Sy+BHR+ (n=155)
Pollutant	Effect variable				
PM_{10} lag0	10% PEF	1.21 (0.98-1.51)	2.03 (1.25-3.31)*	1.51 (1.09-2.09)*	1.23 (0.93-1.62)
PM_{10} lag1	10% PEF	1.16 (0.95-1.41)	1.24 (0.80-1.91)	1.24 (0.92-1.66)	1.16 (0.89-1.51)
PM_{10} lag2	10% PEF	1.09 (0.90-1.33)	1.48 (1.00-2.18)*	1.70 (1.30-2.22)*	1.16 (0.90-1.48)
PM_{10} mean	10% PEF	1.27 (0.93-1.72)	1.66 (0.81-3.42)	3.06 (1.91-4.91)*	1.45 (0.91-2.30)
PM_{10} lag0	Cough	1.09 (0.97-1.21)	0.91 (0.71-1.16)	1.10 (0.96-1.26)	1.02 (0.89-1.17)
PM_{10} lag1	Cough	0.89 (0.80-0.99)*	0.86 (0.67-1.10)	0.91 (0.80-1.04)	1.09 (0.96-1.24)
PM_{10} lag2	Cough	0.96 (0.86-1.07)	0.98 (0.79-1.23)	0.93 (0.81-1.06)	0.98 (0.86-1.12)
PM_{10} mean	Cough	0.95 (0.79-1.14)	0.90 (0.56-1.42)	0.88 (0.68-1.16)	0.88 (0.68-1.15)
PM_{10} lag0	Bronchodilator			1.06 (0.91-1.23)	0.90 (0.69-1.16)
PM_{10} lag1	Bronchodilator			0.98 (0.83-1.14)	1.19 (0.94-1.52)
PM_{10} lag2	Bronchodilator			0.99 (0.87-1.12)	0.97 (0.76-1.24)
PM_{10} mean	Bronchodilator			0.86 (0.63-1.18)	1.24 (0.81-1.90)
PM_{10} lag0	LRS			1.21 (0.93-1.58)	0.99 (0.81-1.22)
PM_{10} lag1	LRS			1.23 (0.92-1.64)	0.98 (0.98-1.42)
PM_{10} lag2	LRS			1.06 (0.80-1.41)	1.28 (1.07-1.52)*
PM_{10} mean	LRS			1.63 (1.07-2.49)*	1.92 (1.37-2.69)*

OR significantly different from 1 ($P<0.05$)

Discussion

The prevalence of acute respiratory symptoms, medication use and 10% evening PEF decrements recorded in a daily diary differed both with symptom status and objective clinical characteristics. Associations between PM_{10} and respiratory health were found for most of the evaluated subgroups. In non-symptomatic children with and without high IgE (or a positive skin prick test or BHR), associations were found with PEF and generally not with acute respiratory symptoms. In symptomatic children with high IgE (a positive skin prick test), associations were found with PEF, lower respiratory symptoms and bronchodilator use. Associations in this subgroup were more statistically significant and consistent than in symptomatic children without high IgE (positive skin prick test). Symptomatic children with bronchial hyperresponsiveness did not have a more consistent association with PM_{10} than the other subgroups.

Subgroups of children were defined based upon both reporting of (chronic) respiratory symptoms in a baseline questionnaire and objective clinical characteristics.

Several studies have documented significant associations between the presence of respiratory symptoms, low lung function, atopy, increased serum IgE and bronchial responsiveness in children[15-17]. In a longitudinal study Clough *et al.*[15] showed that in 7-8 yr old children, both atopy derived from a skin prick test and the type of symptom (cough vs wheeze) were independently associated with bronchial responsiveness, FEV_1, diurnal variability of PEF and symptoms reported in a diary[15]. In a study of 11-yr old children, Burrows *et al.*[16] found that BHR was associated with an asthma diagnosis, high IgE and baseline lung function. In a study of 11-yr old New Zealand children a significant correlation between bronchial responsiveness and serum IgE was found, both for children with and without asthma / wheeze[17]. While the clinical characteristics and symptom reporting evaluated in the present study are mutually correlated, there is considerable discrepancy as well.

Reporting of acute respiratory symptoms in a daily diary was most strongly determined by the symptom status of the child. Presence of a clinical characteristic further increased the prevalence of acute respiratory symptoms and medication use, especially in symptomatic children. In contrast, the prevalence of 10% evening PEF decrements was only increased in symptomatic children with high IgE or a positive skin prick test or BHR. Symptomatic children

without these clinical characteristics had similar PEF decrements as the non-symptomatic children. One explanation for this contrast is that parents of the child completed both the baseline questionnaire and the daily diary whereas PEF is the result of a more objective measurement. The subgroup of symptomatic children without presence of a clinical characteristics may either reflect misclassification or symptoms without associated lung function decrements. Fifty-seven of the symptomatic children did not have any of the three evaluated clinical characteristics.

One implication of the present study is that especially the PEF associations with PM_{10} are not restricted to one sensitive subgroup. In fact, the magnitude of the Odds Ratios in the non-symptomatic children with low IgE were similar to those for the symptomatic children with high IgE. Neither symptom status nor presence of a clinical characteristic was strongly related to the PEF response. Small population mean lung function decrements associated with ambient air pollution have been observed before in children without chronic respiratory symptoms[4,18,19]. The present study shows that PM_{10} is also related to the prevalence of decrements of PEF of $>=10\%$ below the individual median in non-symptomatic children. We have suggested before that this is a clinically more relevant measure than the small changes ($<1\%$) in population mean PEF[20]. The Odds Ratios found in non-symptomatic are comparable and sometimes even higher than the overall Odds Ratio of 1.31 reported for a number of panel studies of children with chronic respiratory symptoms[20].

It has been documented before that symptomatic children experience stronger effects of exposure to ambient air pollution than non-symptomatic children[4]. We earlier reported similar findings for the present study population when we only classified the children with respect to symptoms from the baseline questionnaire[8]. The main difference with the non-symptomatic children was that in symptomatic children associations with both PEF and acute respiratory symptoms and bronchodilator use were found[8]. The present study documents that symptomatic children with high serum total IgE had a more consistent association with PM_{10} than symptomatic children with low serum total IgE. In the symptomatic children with high IgE more associations were statistically significant ; all Odds Ratios were above unity and the Odds Ratio were generally larger for the corresponding lag – health endpoint combination. The latter differences were most striking for PEF and bronchodilator use. Results for skin prick testing were very similar to those for total serum IgE.

Why do symptomatic children with high IgE or a positive skin prick test experience stronger effects from PM_{10}? In general, subjects in a population may be more sensitive to air pollution because of increased exposure, increased inhaled dose at the target organ, decreased reserve capacity and/or increased sensitivity of receptors. With the exception of increased exposure to air pollution, any of these mechanisms may explain the findings of the present study. Two controlled human exposure studies have suggested that exposure to gaseous air pollutants may increase airway responsiveness to inhaled allergens such as house dust mite[21,22]. To our knowledge no similar data exist for particulate air pollution. If this interaction is also valid for PM_{10}, it is plausible that children with high serum IgE or atopy have a stronger response to PM_{10}. Polyaromatic hydrocarbons (PAH) extracted from diesel exhaust particles (DEP) were shown to directly enhance IgE production from human B-cells[23]. PAH-DEP did not induce IgE production but enhanced ongoing IgE production. This fits with our observation of increased responses in subjects with high total serum IgE.

In a controlled exposure study of normal, atopic non-asthmatic, mild asthmatic and moderate/severe asthmatic adults to high concentrations of SO_2, decrements in FEV_1, increases in airway resistance were mostly found in the two asthmatic subgroups[24]. Much smaller responses occurred in the atopic subgroup and no response was found in the normals. Respiratory symptoms in association with SO_2 were found in asthmatics but not in non-asthmatic atopics and normal subjects, which is in agreement with our study[24]. In agreement with our study, atopic subjects did not experience a stronger overall effect than non-atopic normal subjects.

The subgroup of symptomatic children with BHR had less consistent associations with PM_{10} than the symptomatic children with high serum IgE or a positive skin prick test. In addition, hyperresponsive symptomatic children did not have more consistent associations with air pollution than the other subgroups defined by symptoms and BHR. This does not imply that bronchial responsiveness is irrelevant for the response of children to air pollution. In an analysis of the same children as included in the present study, we showed that the response to outdoor air pollution in the subgroup of children with high IgE and BHR was more consistent than in the subgroup of children with high IgE without BHR[11]. A study among adults showed that presence of BHR was associated with an increased response to air pollution[10].

In conclusion, the most consistent association between PM_{10} and respiratory health was found in symptomatic children who had either high total serum IgE or a positive skin prick test. In these children associations both with PEF and acute respiratory symptoms were found. Associations between PM_{10} and PEF were found both in symptomatic and non-symptomatic children and in atopic and non-atopic children. Presence of high serum IgE or a positive skin prick test was not related to a stronger response to PM_{10} in non-symptomatic children.

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Chapter 8

General discussion

Main findings

Air pollution measurements, performed in urban and non-urban areas during three consecutive winters have shown that the contrast in particle concentrations between both areas was small. PM_{10} and Black Smoke (BS) concentrations were on average 13% and 19% higher in the urban areas than in the non-urban areas, whereas sulfate concentrations were 7% lower in the urban than in the non-urban areas. There was more contrast in the concentrations of the gaseous pollutants SO_2 and NO_2; about twofold higher concentrations were found in the urban areas than in the non-urban areas.

Self-recorded Mini Wright Peak Expiratory Flow (PEF) measurements were an important outcome variable in our panel study. In a separate study in 9-11 yr old children, self-recorded morning and evening Mini Wright PEF measurements were compared with spirometric and supervised Mini Wright PEF measurements, performed at school. An estimate of measurement error was made using the three maneuvers that each of the measurements consisted of. The amount of measurement error was only slightly larger for self-recorded than for supervised PEF measurements.

The incidence of influenza and influenza-like-illness (ILI) in the general population, registered by the Dutch network of General Practitioners sentinel stations, was associated with respiratory health in all four groups of panels (symptomatic and non-symptomatic children and adults) that were investigated in this study. Therefore, the incidence of ILI in the general population was used to adjust for the potential confounding effect of acute respiratory infections in the analysis of the association between air pollution and indicators of respiratory health.

In symptomatic children (7-11 yr) positive associations were observed between particle (PM_{10}, BS and sulfate) and SO_2 concentrations and the prevalence of defined (below 10% of median) decrements in evening PEF and lower respiratory symptoms (LRS). In symptomatic children from urban areas, but not from non-urban areas, particle concentrations were also positively associated with bronchodilator use. Stratified analyses for medicated and non-medicated symptomatic children showed that in the urban areas, the prevalence of LRS was strongly associated with particle concentrations in medicated children, but not in non-medicated children. In non-symptomatic children, PM_{10} and BS concentrations were significantly associated with $>10\%$ decrements in evening

PEF in both urban and non-urban areas. No associations with respiratory symptoms were observed.

In the panels of adults (50-70 yr) the associations between air pollutants and respiratory health were generally less clear than in the panels of children. As opposed to what was found for symptomatic children, air pollution concentrations were not associated with LRS, bronchodilator use or decrements in evening PEF in symptomatic adults. However, an association between increased particle and SO_2 concentrations and large (below 20% of median) decrements in morning PEF, and between BS and upper respiratory symptoms (URS) was found in symptomatic, urban adults. Those associations were not found in the non-urban areas. In non-symptomatic adults from both urban and non-urban areas, no consistent associations between air pollution and respiratory health were found.

Thus, consistent with the small differences in air pollution concentrations between urban and non-urban areas, the associations between air pollution and health endpoints did not differ significantly between urban and non-urban panels. For symptomatic children and adults, however, significant associations were found more often in the urban panels, although the differences with non-urban panels were generally small and non-significant.

In the panels of children, we also investigated if the response to air pollution differed across subgroups based on the presence/absence of certain medical characteristics. It was demonstrated that the strongest associations between PM_{10} and respiratory health occurred in symptomatic children with increased serum total IgE level or a positive skin prick test. For symptomatic children with bronchial hyperresponsiveness (BHR), less consistent associations with PM_{10} were found. This documents that there was heterogeneity of response within the subgroup of symptomatic children that could be explained by objectively determined allergy status.

Interpretation and comparison of air pollution effects with other studies

Air pollution concentrations

Median PM_{10} concentration measured during the three winters was 36 $\mu g/m^3$ in the urban areas and 30 $\mu g/m^3$ in the non-urban areas. PM_{10} concentrations were in the high range of the concentrations measured in North-America[1], where mean winter PM_{10} concentration measured in 23 communities varied between 14

and 33 $\mu g/m^3$. During the winter of 1993/1994, the measurements were performed in the framework of a multicenter epidemiological study of Pollution Effects on Asthmatic Children in Europe (PEACE). Air pollution measurements were performed simultaneously in 14 urban and 14 non-urban locations across 10 European countries[2]. PM_{10} concentrations measured in the Netherlands were higher than those measured in Scandinavia, but lower than those measured in Central European and Southern European countries, where median PM_{10} concentrations were on average 14, 48 and 65 $\mu g/m^3$, respectively[2].

In our study, median BS concentration measured during the three winters was 11 $\mu g/m^3$ in the urban areas and 8.5 $\mu g/m^3$ in the non-urban areas. This is substantially lower than the concentrations measured in the PEACE study in Central and Southern European locations, where median concentrations were on average 33 and 42 $\mu g/m^3$, respectively[2]. The median BS concentration was on average 8 $\mu g/m^3$ in the Scandinavian locations[2].

Concentrations of aerosol acidity were very low during the three winters. Median concentration was below 0.1 $\mu g/m^3$ and the maximum concentration was only 1.7 $\mu g/m^3$. In previous studies in the Netherlands[3] and other European countries[1,4] low levels of aerosol acidity were reported as well. This contrasts with the much higher levels that are found in the North-Eastern part of the United States and Canada. In these regions, annual mean concentrations of 2.5 $\mu g/m^3$ and 24-hour mean concentrations of 39 $\mu g/m^3$ have been measured[5].

The contrast in particle concentrations between urban areas (Rotterdam and Amsterdam) and non-urban areas was relatively small. The concentrations of the secondary aerosols sulfate and nitrate were on average 8% and 7% lower in the urban areas than in the non-urban areas, which contrasts with the fact that twofold higher concentrations were found in the urban areas of the precursor pollutants SO_2 and NO_2 . This probably reflects the importance of long range transport in determining their concentrations; the formation of secondary aerosols from gaseous precursor pollutants is a slow process which therefore can occur at large distance from the source area.

PM_{10} concentration was on average 13% higher in the urban areas than in the non-urban areas. This small contrast is consistent with the results of the PEACE study, where on average 22% higher concentrations were found in the urban areas than in the corresponding non-urban areas. Twofold urban–non-urban differences were found for locations with mountain ranges between urban and

non-urban area, such as Athens in Greece and Teplice in the Czech Republic, however[2].

BS levels were on average 19% higher in the urban areas than in the non-urban areas. In the PEACE study a mean difference of 43% was found[2]. BS concentrations can be used as an estimate for the concentrations of elemental carbon[6,7] (EC). We had expected to find a larger contrast between urban and non-urban areas, because EC is a primary pollutant from motorized traffic[8] (diesel soot) and traffic intensity is higher in the urban areas than in the non-urban areas. Apparently, EC concentrations were also largely determined by long range transport. Another explanation might be that so-called background sites were used to estimate exposure in the urban areas instead of sites that were more influence by traffic. Previous work has shown clearly higher concentrations of BS in roadside measurements than at some distance from the road[9,10].

The small contrast in particle concentrations between urban and non-urban areas in the Netherlands is, in addition to the small size of our country and the importance of long-range transport of air pollutants, probably a result of the high population density and the lack of small scale geographical and meteorological differences. As a result, the whole country can be considered to be part of one single airshed.

During the winter of 1994/1995, $PM_{2.5}$ was measured as well because of the increased interest in health effects of smaller particles in recent years. Median $PM_{2.5}$ concentration was 14 $\mu g/m^3$ in the urban area and 15 $\mu g/m^3$ in the non-urban area. $PM_{2.5}$ concentration was on average 55% of the PM_{10} concentrations, which is very similar to the value of 0.60 suggested by Dockery and Pope[11] as a typical North-American $PM_{2.5}/PM_{10}$ ratio.

Comparison of $PM_{2.5}$ concentrations to levels measured in other countries is hampered by the fact that $PM_{2.5}$ was measured only in the winter of 1994/1995, when air pollution levels were relatively low. Data collected in six US cities over an eight year period indicated a range of annual mean $PM_{2.5}$ concentrations of 11 to 30 $\mu g/m^3$ [12]. European data on $PM_{2.5}$ concentrations are scarce. Measurements in Kuopio, Finland indicated a median $PM_{2.5}$ concentration of 15 $\mu g/m^3$ during a six weeks period in the spring of 1995[13]. During the winter of 1991/1992, $PM_{2.5}$ concentration measured in Erfurt, Eastern Germany, was on average 46 $\mu g/m^3$ [14].

Air pollution and respiratory health; comparison with other studies

In a review article, Dockery and Pope[11] combined the results of the then available panel studies from the US and Europe, and calculated that an increase in PM_{10} concentration of 100 $\mu g/m^3$ was associated with an increase in the prevalence of LRS and bronchodilator use of respectively 30% and 29%. For URS and cough, smaller increases of 7% and 12% were reported. Thus, the fact that in our panels of children, associations were found mainly for LRS and bronchodilator use is in agreement with earlier panel studies. In symptomatic children in the urban areas an increase of 100 $\mu g/m^3$ in same-day PM_{10} concentration was associated with an increase of 34% and 29% in the prevalence of LRS and bronchodilator use, respectively, which corresponds well to the numbers reported by Dockery and Pope[11]. In a re-analysis of data from seven panel studies, Hoek *et al.* [15] found that an increase in PM_{10} concentration of 100 $\mu g/m^3$ was associated with an increase of 31% in the prevalence of >10% decrements in evening PEF. This corresponds well to the Odds Ratios of 1.42 and 1.32 that were found in the panels of symptomatic and non-symptomatic children, respectively. The results of our study do not correspond with the results of the PEACE study, however. In 28 panels of 6-12 yr old symptomatic children, including the 1993/1994 panels of our study, no clear association could be established between changes in air pollution indices including PM_{10} and changes in PEF, respiratory symptoms and bronchodilator use[16]. The main difference between the two studies is that in our study, the findings from three different winters with relatively long study periods were combined whereas in the PEACE study, the observation period was about two months during one winter only. Our study may therefore have been less vulnerable to the effects of unmeasured events during the study period. Another difference is that we were able to control at least to some extent for the role of respiratory infections through the data from the GP sentinel system on ILI.

The few panel studies that have focused on adult subjects have found that increased particle concentrations were most consistently associated with lower respiratory symptoms[17-21]. This is not in agreement with the results of symptomatic adults in our study, where the clearest associations were found with upper respiratory symptoms. The fact that no consistent associations between particles and evening PEF were found is also not in agreement with other studies[15]. We do not have a good explanation for the fact that in our panels of symptomatic adults effects were found on URS rather than on LRS, and on

morning PEF rather than on evening PEF. The lack of particle effects on LRS and bronchodilator use, which contrasts with the results of other panel studies in adults, might be explained by differences in composition of the panels. The other studies[17-21] have focused on asthmatic patients whereas our study focused on relatively healthy, symptomatic adults most of whom did not have asthma. Other factors that may explain discrepancies between the results of panel studies such as: differences in air pollution levels, statistical power, length of the study period, adjustment for time trends or respiratory infections are described in detail by Roemer *et al.*[22]. However, it does not seem likely that these factors apply here.

No associations between indicators of air pollution and respiratory health was observed in the panels of non-symptomatic adults. To our knowledge, only one other panel study[23] has been performed in adults not selected for chronic respiratory symptoms. In that study, indicators of particulate air pollution were not consistently associated with respiratory health outcomes[23], which is in agreement with the results of our study.

Air pollution and respiratory health; urban–non-urban differences

In symptomatic children, a similar pattern of particle effects on evening PEF and LRS was observed in urban and non-urban panels, but statistically significant associations were observed more frequently in the urban panels. However, the differences in effect estimates between urban and non-urban panels were generally small and the confidence intervals showed considerable overlap. For bronchodilator use, more consistent differences were found: particle concentrations were associated with increased bronchodilator use in the urban panels but not in the non-urban panels. After stratification for medication use, it was shown that these differences were restricted to the medicated children. We can not rule out that differences in use of maintenance medication are responsible for this. Calculated over the three winters, the mean prevalence of maintenance medication was almost twofold lower in the urban areas (8.5%) than in the non-urban areas (15.5%). As a result, children in the urban areas might have to rely more on bronchodilators during periods with high air pollution than children in the non-urban areas.

Separate analyses for children who used bronchodilators only during the study period, and for children who used both bronchodilators and maintenance medication could demonstrate if use of maintenance medication diminishes the

association between air pollution and bronchodilator use, but the number of children that used bronchodilators only was too small for a meaningful analysis. Moreover, in such an analysis the amount of maintenance medication used by each child during the study period should be taken in account. The percentage of children that ever reported use of maintenance medication did not differ between urban and non-urban panels (18% and 21%, respectively), but children in the non-urban areas obviously took their maintenance medication more often, given the higher mean daily prevalence.

Anti-inflammatory medication (inhaled corticosteroids and cromoglycates), anti-histaminica and theophyllin were classified as maintenance medication. Theofyllin is in fact a bronchodilator, but was considered as maintenance medication because of its longlasting effect. Anti-inflammatory medication was not considered separately because, like anti-histaminica and theophyllin, it is generally prescribed on a daily basis. Use of medication that is prescribed 'as needed' is more likely to vary with air pollution concentrations.

We did not perform separate analyses for subjects using anti-inflammatory medication, because the subgroups per panel would become too small for a meaningful analysis.

To our knowledge, our study and the PEACE study are the only studies that systematically evaluated if acute effects of ambient air pollution differ between urban and non-urban panels. The results of our study are at variance with the results of the PEACE study, where neither for bronchodilator use nor for any of the other respiratory health indicators a tendency of larger effect estimates in the urban areas was observed[16]. However, the comparison with the PEACE study is hampered by the fact that no clear air pollution effects were found in both urban and non-urban panels[16].

Associations between particle concentrations and some respiratory health indicators (morning PEF and URS) were observed in symptomatic adults from the urban areas, but not from the non-urban areas. The differences in effects estimates between urban and non-urban panels were generally small and the confidence intervals showed considerable overlap If, nevertheless, the observed difference is interpreted as a true difference between the urban and non-urban panels, it might be explained by the higher prevalence of bronchodilator use in the non-urban panels (17%, compared to 8% in the urban panels), although bronchodilator use was not associated with particle concentrations.

For both non-symptomatic children and adults, there were no indications that the observed associations between air pollution and respiratory health differed between urban and non-urban panels.
The lack of clear differences in response to air pollution between urban and non-urban panels does not indicate that the urban air pollution mixture is more toxic than the non-urban air pollution mixture.

Air pollution and respiratory health in children and adults
In the panels of 50-70 yr old adults, the associations between air pollutants and indicators of respiratory health were less clear than in the panels of 7-11 yr old children. Several factors might be responsible for this. Compared to children, adults generally spend less time outdoor and consequently, the amount of misclassification in exposure might be larger. The mean time spent outside, recorded in the diaries, was approximately 2 hours per day for children, and 1 hour per day for adults. Recent studies in the Netherlands have documented that the median time series correlation coefficient between ambient and personal PM_{10} was 0.63 for 10-12 yr old children and 0.50 for 50-70 yr old adults[24,25]. This shows that the amount of misclassification was only slightly higher for adults than for children. However, the above mentioned study in adults included only non-smoking subjects with no smokers in the household[25]. Our panels of adults also included smokers, so the amount of misclassification of exposure might be larger than reported above[25].
Compared to adults, children have a relatively high physical activity, which results in high inhaled pollution doses. This is especially true when the pollution dose is expressed per kg bodyweight or per cm^2 lung surface area. In addition, children's lungs are growing and not yet completely developed, which might also explain why they appear more sensitive to the adverse effects of air pollution.
Another explanation for the observed less clear effects of air pollution in symptomatic adults than in symptomatic children might be that the selection criteria used to define adults as 'symptomatic' were not strict enough. Different screening questionnaires and criteria were used for children and adults, although in both groups the purpose was to select subjects with asthmatic symptoms or chronic cough (and phlegm, for adults). Comparison of objective medical characteristics between symptomatic and non-symptomatic panels however, does not suggest that the screening criteria used to identify symptomatic adults were less stringent than for children (table 1).

Table 1. Medical characteristics of symptomatic and non-symptomatic children and adults that took part in the Dutch study on the effects of winter air pollution on respiratory health

	Children		Adults	
	symptomatic (n=311)	non-symptomatic (n=300)	symptomatic (n=261)	non-symptomatic (n=217)
FEV_1 *	2.17	2.26	2.86	3.24
FEV_1, % pred**	105	106	100	115
FEV_1/FVC†	0.88	0.91	0.75	0.80
BHR,≥10%‡	73%	55%	71%	49%
BHR,≥20%§	55%	30%	41%	14%
SPT+¶	49%	27%	33%	26%
IgE+¶¶	59%	41%	55%	44%

* *Forced Expiratory Volume in 1 second, in liters*

** *FEV_1 as percentage of predicted*

† *ratio between FEV_1 and Forced Vital Capacity*

‡ *bronchial hyperreactivity defined by a decrement of more than 10% in FEV_1 after inhalation of a cumulative methacholine dose of 2 mg*

§ *bronchial hyperreactivity defined by a decrement of more than 20% in FEV_1 after inhalation of a cumulative methacholine dose of 2 mg.*

¶ *skin prick test positive: a positive skin prick test to at least one of the six tested common allergens*

¶¶ *above median total serum IgE level (established separately for children and adults)*

Subgroup analyses based on symptom-status and an objective medical characteristic in the children panels indicated that allergic, symptomatic subjects were most susceptible to the effects of air pollution. The fraction of allergic subjects (defined as a positive skin prick test) in the symptomatic panels was lower for adults (33%) than for children (49%), which might partly explain the observed weaker effects of air pollution effects in symptomatic adults.

Another explanation might be that the symptomatic adults in our study were well medicated, possibly better than the children. Although the mean daily prevalence of maintenance medication use was only slightly larger for symptomatic adults (15%) than for symptomatic children (12%), the mean prevalence of bronchodilator use was three times larger (12.4% and 4.1%, respectively). The percentage of symptomatic subjects that reported asthma attacks in the previous

12 months in the screening questionnaire, was substantially lower for adults (9%) than for children (33%). Although the wording of the question was different for children and adults, this might reflect that the adults were better medicated than the children.

To our knowledge, only one other study reported by Peters *et al.*[21] has directly compared acute health effects of air pollution in panels of children and adults. In that study, asthmatic children (7-15 yr) and non-smoking asthmatic adults (32-80 yr), recruited from children's hospitals and outpatient clinics, were followed during two consecutive winters in three Eastern European cities. Five-day mean concentrations of SO_2 were associated with an increased respiratory symptom score in both children and adults, but consistent particle effects were not observed in both groups. Associations with medication use were not reported. Five-day mean concentrations of PM_{10}, sulfate and SO_2 concentrations were significantly associated with decreased evening PEF in children, but not in adults[21], which is in agreement with the results of our study. However, the association between 5-day mean PM_{10}, sulfate and SO_2 concentrations and respiratory symptoms appeared to be stronger in adults than in children. For example, an increase in 5-day mean PM_{10} concentration of 48 $\mu g/m^3$ (interquartile range) was associated with a 0.43% decrease in evening PEF in both children and adults, but only in children this decrement was statistically significant. The same increase in 5-day mean PM_{10} concentration was associated with a significant increase of 14.5% in respiratory symptom score in adults, and with a non-significant increase of 6.1% in children. Thus, the differences in response between children and adults were more pronounced in our study than in the study reported by Peters *et al.*[21].

Susceptible subgroups

The results of our study suggested that symptomatic children were more susceptible to the adverse effects of ambient air pollution than non-symptomatic children. In symptomatic children, particle concentrations were most consistently associated with LRS and bronchodilator use. In non-symptomatic children, however, both LRS and bronchodilator use were never or rarely reported. Thus, non-symptomatic children appear less susceptible to the effects of air pollution than symptomatic children because they do not develop the asthmatic symptoms that are most affected by increasing levels of air pollution.

Children were considered symptomatic if they had reported either chronic cough or asthmatic symptoms (wheeze or doctor diagnosed asthma) in the previous year. Thus, symptomatic children are not a homogenous group, and it is possible that specific subgroups respond more strongly than others. A number of previous studies have suggested that asthmatic children are more susceptible to the effects of air pollution than children with chronic cough[27,28]. We did not perform separate analyses for children selected for chronic cough and for asthmatic symptoms, as in the above mentioned studies. However, separate analyses were performed for symptomatic children who did and did not report use of asthma medication during the study period. The strongest associations between particle concentrations and respiratory health indicators were observed in children using medication. This suggests that children with asthmatic symptoms, serious enough to receive medication, are especially susceptible to the effects of particulate air pollution, and that medication use does not prevent the effects on respiratory health. This is in agreement with the results of stratified analyses based on medication use in a panel study of mild asthmatic children in Sokolov, Czech Republic[28]. Medicated children increased their beta-agonist use in association with increased particle concentrations, but this did not prevent adverse effects on other health outcomes[28].

Our study was the first in which panel members were extensively medically characterized with respect to both bronchial hyperreactivity (BHR) and atopy. Stratified analyses were performed in subgroups based on the presence/absence of objective medical characteristics, for symptomatic and non-symptomatic children separately. It was demonstrated that the strongest effects of PM_{10} on respiratory health occurred in symptomatic children with elevated total serum IgE level or a positive skin prick test. For symptomatic children with BHR less consistent associations with PM_{10} were found. This documents that there was heterogeneity of response within the subgroup of symptomatic children that could be explained by objectively determined allergy status.

In a separate publication we have reported the results of stratified analyses based on the presence/absence of two objective medical characteristics (elevated IgE and BHR) in this group of children, regardless of the presence of chronic respiratory symptoms[29]. It was documented that the strongest associations occurred in the subgroup with both BHR and elevated total serum IgE level. The strength of the observed associations between PM_{10} and respiratory health

indicators was of the same magnitude as was found in the subgroup of symptomatic children with elevated total serum IgE level.
BHR is related to (the severity of) asthma. Asthmatic children have been reported to have a higher prevalence of BHR than children with dry cough as their only respiratory symptom[30,31]. Thus, it appears that allergic asthmatic children (with BHR) are most susceptible to the adverse effects of ambient air pollution. This is consistent with several controlled exposure studies that suggested an interaction between exposure to ambient air pollutants and major allergens. Prior exposure to gaseous air pollutants appeared to increase the airway responsiveness of asthmatics to inhaled allergen such as house dust mite[32,33]. However, since we do not have data on indoor allergen exposure, we can not verify this hypothesis in this epidemiological study.

Mechanisms of particle effects

The results of our study add to the large data base of studies that have reported on health effects associated with acute exposure to particulate air pollution[11]. The exact mechanisms for the observed particle effects are still unknown, however. One explanation is that the acidity of particles determines their health effects[34]. In our study, this is not a likely explanation, since the acidity concentrations were very low. An alternative explanation is that the number of ultrafine particles ($< 0.1\ \mu m$) is the major factor contributing to the health effects of particulate air pollution. The relatively large surface area and surface reactivity would play a major role in causing effects in pulmonary tissue[35]. Data from animal experiments have suggested that ultrafine particles have higher deposition chance and lower clearance rates in lower airways and have a larger pulmonary toxicity per unit mass than fine- and coarse mode particles[36,37]. A time series study from Germany in asthmatic adults suggested that exposure to ultrafine particles was more closely associated with some respiratory health indicators than exposure to PM_{10}[38]. A panel study from Finland conducted among children could not replicate this finding, however[39]. Since ultrafine particles were not measured in our study, we can not investigate if they were more closely associated with respiratory health outcomes than other indicators of particulate air pollution. However, if ultrafine particles would be primarily responsible for the observed particle effects in our study, one might expect stronger associations with BS than with the other indicators for particulate air pollution. BS is a measure of diesel exhaust, which is known to contain large numbers of ultrafine,

black particles[40]. Measurements performed in an urban area in Finland showed that the number of ultrafine particles in ambient air was indeed more closely correlated to the BS concentration than to the PM_{10} concentration[39].

In our study, BS appeared to be more consistently associated with decrements in morning PEF and URS than PM_{10} and sulfate in symptomatic adults from the urban areas. However, in symptomatic children from the urban areas, PM_{10} was more consistently associated with health outcomes than BS (and sulfate), as was indicated by the results of the two-pollutant models including two indicators for particulate air pollution simultaneously. This does not strongly support the hypothesis that the number of ultrafine particles was the major factor contributing to the health effects, although we have no data to test this.

Another hypothesis is that the chemical composition of the particles, especially soluble transition metals attached to the surface of the particles, determines their health effects. Toxicological studies in rats have suggested that iron attached to the surface of fly ash particles can cause inflammatory reactions in the lung, possibly through the formation of free radicals[41]. Another study confirmed that the free radical activity of PM_{10} causes inflammatory reactions in rats, and that iron may play a role in this reaction[42]. A panel study from the Netherlands among adult asthma patients found that ambient iron concentrations were related to respiratory health indicators independently of PM_{10}[18]. In the PEACE study, it was evaluated whether soluble elemental concentrations in PM_{10}, including iron, were related to acute respiratory health effects[43]. Iron and silicium concentrations tended to be negatively associated with PEF and positively with the prevalence of phlegm, but not with the prevalence of other respiratory symptoms and bronchodilator use. No associations were found with the other elements including the transition metals zinc, vanadium and nickel[43]. Thus, the results of the PEACE study do not provide strong evidence for the hypothesis that soluble transition metals would be responsible for PM_{10} effects. However, interpretation is hampered by the fact that no PM_{10} effects were observed in the PEACE study[16].

Alternatively, the observed particle effects may not be attributable to one compound (or factor) but to the combined action of the diverse components in the pollutant mix. The fact that PM_{10} effects have been observed consistently across so many communities in different countries, with different sources of particulate air pollution and different chemical and physical characteristics of the particles might support this last hypothesis.

The most consistent particle effects were oberved in allergic, symptomatic children, which might be explained by particle-allergen interactions. Several studies have suggested that diesel exhaust particles can alter the allergic respiratory response[44]. One explanation for this might be that the particles adsorb allergens and then function as adjuvants by prolonging the retention of the allergen so as to provide for an enhanced immune response. In addition, diesel exhaust particles may divert the immune response toward IgE production[44]. Both in vitro and in vivo experiments[44], also in humans[45], have shown that exposure to diesel exhaust particles preferentially enhances the IgE response.

Potential biases and limitations

Selection bias

It is unlikely that the low response could have caused bias in our study, because each subject served as its own control. Bias due to the low response may only have occurred in the unlikely case that within the subgroup of subjects with/without chronic respiratory symptoms, response was associated with susceptibility to air pollution.

Subjects who are experiencing relatively few respiratory symptoms during the study period may have lost their motivation and may have stopped to fill out their diary. If this happened, at the end of the study period only subjects with relatively high symptom prevalence would be reporting. This was limited by removing subjects with missing diary information (PEF or symptoms) on more than 40% of the days from the dataset. In addition, non-linear time trends were specified.

If removal of subjects from the dataset is associated with susceptibility to air pollution it might also lead to bias. Subjects who lost motivation because they never experienced symptoms might be the subjects that are less susceptible to air pollution. However, symptom reporting did not appear to be related to 'drop-out' during the study, because the fraction of subjects that were removed from the dataset was similar in the symptomatic and non-symptomatic panels.

Information bias

Observer bias in symptom reporting might have occurred when subjects were informed by the mass media about air pollution episodes. However, during the

study period all air pollutant concentrations were below the limits used in the Dutch smog alert system, and no warnings were issued.

It is possible that a subject was suffering from respiratory symptoms in such a degree that he or she was not able to perform the PEF measurements. This could have led to underestimation of the association between air pollution and PEF. The results of our study do not indicate that more consistent associations were found between air pollution and respiratory symptoms than between air pollution and PEF, however.

In this type of data it is possible that the prevalence of reported symptoms declines over time due to decreasing motivation. Trend adjustment with a linear, quadratic and cubic trend term in the analysis makes it unlikely that decreasing motivation has biased effect estimates.

Mini Wright meters with a range from 60 to 800 l/min were used in our study to measure daily variations in PEF. It is known that Mini Wright meters may give inaccurate readings, and that the inaccuracy varies across the range of the meters: they may overread by about 70 l/min in the middle range and underread by about 50 l/min in the high range[46]. Because each subject serves as its own control, this can only lead to biased effect estimates when there is a large variation in PEF within a subject between days. The degree of overestimation is relatively constant between 300-450 l/min and for most children, PEF varies within this range. However, we can not exclude that for children with a low mean PEF decrements in PEF can be slightly overestimated. Similarly, we can not exclude that for adults with a high mean PEF decrements in PEF can be slightly underestimated. However, we do not expect that this form of bias is very important since the degree in which the *difference* in PEF is incorrectly estimated is limited.

Compliance

Recently, a number of studies comparing self-recorded and electronically stored PEF measurements have raised concern about the reliabiity of self-recorded PEF measurements. They reported that errors were made in reading and transcribing the PEF values and that a substantial number of the values were invented[47-50]. Two studies[47,48] investigated adult subjects for occupational asthma and found that written values corresponded precisely to electronically stored values in only approximately 50% of the cases. Verschelden *et al.*[49] compardd self-recorded to electronically stored PEF values in 20 asthmatic adults who were asked to asses PEF twice daily during a three month period, and reported that 22% of the values were invented. Redline *et al.*[50] reported that in a panel of asthmatic children in

the US, the number of invented PEF values increased over time during a three weeks study period and was 37% in the third week of study. This population differed from our study population with respect to socio-economic status, since the children resided in areas with 40% or more of the population living at or below poverty level.

We did not store Mini Wright PEF values electronically and thus, we do not know the amount of error in the measurement of this outcome variable in our study. However, in a separate study in 9-11 yr old children, we attempted to obtain an indirect estimate of the quality of self-recorded PEF measurements. The contribution of measurement error to the total intra-individual variability was compared between self-recorded and supervised PEF measurements. Self-recorded Mini Wright measurements were performed in the morning and the evening at home during a 4 months study period. In addition, weekly PEF measurements were made at school during morning hours with spirometry and a Mini Wright meter under supervision. To obtain an estimate of measurement error all three maneuvers that each measurement consisted of were used.

It was calculated that the contribution of measurement error to the total variability in self-recorded Mini Wright PEF measurements was 24% in the morning and 29% in the evening. For Mini Wright measurements that were performed at school under supervision this percentage was 17%, and for spiromteric PEF 15%. Thus, although the contribution of measurement error to total variability was larger in self-recorded than in supervised PEF measurements, the difference was not great. We concluded that the advantage of self-recorded measurements in terms of ease, cost and amount of data obtainable far outweighs this disadvantage.

A limitation of the separate study was, that measurement error was calculated for the mean of the three repeated measurements, whereas the maximum of three repeated PEF measurements was used to investigate the association with air pollution in our main study. Since it is, by definition, not possible to calculate measurement error for a maximum value, the measurement error for the mean was used as a proxy for the amount of error in the maximum. An important underlying assumption was that measurement error for the mean and the maximum of three PEF's are correlated.

Another limitation is that errors in reading precision and transciption of the data are reflected in our definition of measurement error, but that this is not necessarily true for invented values. Invented values may even lead to an

underestimation of 'measurement error' if the same invented value is recorded for the three maneuvers.

In our main study, a number of attempts were made to optimize data quality. The diaries were inspected in the presence of the participating subject every 4 weeks and irregularities (i.e. a great number of missing values, strange PEF-values) were discussed. At the end of the study period, all individual plots of PEF versus day of study were inspected. We tried to identify subjects that 'invented' PEF values by checking for long periods with no variation and on extremely high values. These checks did not detect invented values which vary around the mean PEF value. Invented values in symptom diary data are more difficult to detect and it is possible that these were present in the analyzed data.

In conclusion, information bias may have played a role, particularly through errors in the measurement of the outcome variable. However, when random, those errors increase the standard errors of the air pollution coefficients but do not lead to biased effect estimates.

Confounding

Because in this study only associations between time varying variables were studied, time invariant variables such as age, sex and socio-economic status can not confound associations between exposure and effect. Potential confounders that might bias the association between air pollution and respiratory health are meteorologic variables (mainly ambient temperature), respiratory infections, long term time trends, medication use and day of week. Adjustment for low ambient temperature was made by including minimum daily temperature as an independent variable in the regression models. Respiratory infections are an important determinant of respiratory health status, both in children[51,52] and in adults[53,54]. If respiratory infections coincide with periods with high or low air pollution this can confound the association between air pollution and health. Objective data on respiratory infections are not easily obtained in panel studies. For this reason, we investigated whether a surrogate variable, the incidence of influenza and influenza-like-illness (ILI), registered by the Dutch network of General Practitioner (GP) sentinel stations, was associated with respiratory health in panels selected from defined geographical areas. We showed that a higher ILI incidence was associated with a decrease in PEF and an increase in the reporting of respiratory symptoms in panels of symptomatic and non-symptomatic children and adults. To our knowledge, an attempt to adjust for the potential confounding

effect of respiratory infections was made in only two previous panel studies[21,55]. In these studies, the presence of fever[55] and the presence of respiratory infections with fever[21], recorded in the diaries were used. However, 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. Only the prevalence of the same day were used in the analysis; previous lags were not evaluated[21,55]. We found that the most consistent associations with respiratory health were found if the incidence of ILI was expressed as the mean of the preceding week.

The incidence of ILI is being monitored by the sentinel stations to obtain information on influenza virus activity, but virological surveillance has shown that in practice, it is not always possible to distinguish between influenza- and other respiratory viruses. Analysis of the three winters suggested that during the winter of 1994/1995, when no influenza epidemics occurred, the incidence of ILI was mainly an indicator for other respiratory viruses than the influenza virus[56]. However, during the winters of 1992/1993 and 1993/1994, when influenza epidemics occured, the pattern of ILI incidence seemed to reflect mainly influenza activity and to a lesser extent the activity of other viruses[57,58].

Trends were observed in PEF measurements and the prevalence of respiratory symptoms and bronchodilator use. Especially in the children panels, strong and non-linear trends were observed for a number of outcome variables. Trends in symptom or medication reporting can occur due to decreased motivation, seasonal effects or respiratory infections. Trends in PEF measurements can occur due to training effects and (in children) due to growth. For each subject, PEF values were expressed as percentage of that subjects median PEF value during the whole study period. Next the prevalence of PEF values that were more than 10% and more than 20% below the median PEF was calculated. It is possible that due to the increase of PEF with time (especially in children) the days with defined PEF decrements occurred mainly in the beginning of the study period. However, all associations were adjusted for non-linear long term time trends with a third order polynomial in the prevalence of PEF decrements, symptoms and bronchodilator use. The adjustment for time trends was more detailed than in previous panel studies which either specified no time trend or a linear trend.

An indicator variable for day of week (school/working day versus weekend/holiday) was included in all models. This was done because

weekends/holidays might be independently associated with both air pollution concentrations and the reporting of symptoms/timing of the PEF measurements. Use of airway medication can diminish the association between air pollution and respiratory health, because subjects can increase their medication use in response to air pollution. Rather than adjusting for medication use in the models we chose to analyze medication use as an endpoint. In addition, stratified analyses were performed for medicated and non-medicated children. Although this evaluation suggests the absence of serious confounding bias, it can not be excluded that due to error in the measurement of confounders, some bias may have occurred[60].

Exposure assessment

Exposure was estimated by measuring the concentrations of ambient air pollutants at fixed urban and non-urban background sites. This may not adequately reflect exposures of individual subjects, because people spend most of their time indoors. Moreover, exposure is affected by activity patterns. Measurements of personal exposure are therefore considered a more accurate estimate of the subjects true exposure. In panel studies, day-to-day variations in exposure to air pollution are related to day-to-day variations in respiratory health. Therefore, the correlation in time between fixed site and personal concentration within persons determines if fixed sites can be used as a measure of exposure.

Recent studies in the Netherlands have shown that the time series correlation between ambient and personal PM_{10} was reasonably high[24,25], while a high correlation was found between ambient and personal $PM_{2.5}$[59]. Personal $PM_{2.5}$ concentrations were also highly correlated with ambient PM_{10} concentrations[59]. No consistent differences were found in the strength of the correlation between ambient and personal PM_{10} between children living in Amsterdam and children living in the non-industrial small town Wageningen[24]. Nevertheless, it is obvious that fixed site concentrations on some days underestimate and on other days overestimate the true personal exposure. However, random errors in the measurements of the exposure variable have been shown to result in a bias towards the null value of the association between exposure and effect[60].

In the urban areas, background sites were used to estimate exposure instead of sites that were more influence by traffic. For subjects who live along busy roads this may lead to an underestimation of exposure. Nevertheless, background sites were preferred because background concentrations are more representative for

exposure of city dwellers than concentrations at sites that are heavily influenced by local sources.

Twenty-four hour mean concentrations were used as exposure estimates. One might argue if this is the best averaging time of the biologically relevant exposure. The highest peak value during the day might, for example, provide a better estimate of exposure. However, previous studies[61,62] have shown that, especially for particles, cumulative exposures over several days were most consistently associated with health outcomes. Moreover, since air pollution was mainly dominated by long range transport, it is likely that the maximum and the mean of the concentration are highly correlated. For SO_2 and NO_2 it has been documented that the concentration between 1-hour maximum and 24-hour average concentration was above 0.95[63].

Implications

Previous panel studies have found that an increase in PM_{10} concentration of 100 $\mu g/m^3$ was associated with a decrease in population mean PEF of 0.8%[11]. The medical importance of such small effects, that are not necessarily adverse, have been discussed before[64,65]. In our study, a different approach was used to analyze PEF data, focusing not on decrements in population mean PEF but on the fraction of subjects that is experiencing substantial PEF decrements. Hoek *et al.*[15] have compared the two approaches and demonstrated that, in a re-analysis of seven panel studies, an increase of 100 $\mu g/m^3$ of the same day PM_{10} concentration was associated with a decrement in population mean of 0.7%, while the relative increase in the prevalence of PEF decrements greater than 10% associated with the same exposure was 31%. This demonstrates that susceptible individuals in the population show a much larger response than the population mean response. Transient decrements of FVC and FEV_1 of 10% and 20% have been considered as the border between mild and moderate response, respectively[64,65]. The effect estimates observed in our study indicate that in symptomatic children, an increase in same day PM_{10} concentration of 100 $\mu g/m^3$ is associated with an increase of 42% in the number of subjects with an evening PEF response that could be characterized as moderate. This PEF response is accompanied by a similar increase of 34% in the prevalence of LRS and 29% in bronchodilator use.

The results of our study suggest that 50-70 yr old adults are less susceptible to the effects of ambient air pollution than 7-11 yr old children. They also suggest that symptomatic children are more susceptible to the adverse effects of ambient air pollution than non-symptomatic children. Moreover, combination of the results of several subgroup analyses in children raises the suggestion that allergic asthmatic children are most susceptible to the effects of PM_{10}. Future studies investigating particle-allergen interactions, including controlled exposure studies, are needed to further elucidate the mechanisms that might be responsible for this.

The results of our study also demonstrate that use of asthma medication does not always prevent the adverse effects of particulate air pollution. Moreover, they suggest that there are differences in asthma treatment regimes between urban and non-urban areas, which might explain why the adverse effects of particulate air pollution were mainly found in the urban areas. Further research investigating acute effects of air pollution in children using maintenance medication, and simultaneously in children using bronchodilators only is needed to answer this question.

In our study, adverse effects of PM_{10} were found at average concentrations that ranged from 27 $\mu g/m^3$ in the non-urban area in the winter of 1994/1995 to 55 $\mu g/m^3$ in the urban area in the winter of 1992/1993. The in 1987 established Dutch 24-hour PM_{10} standard of 140 $\mu g/m^3$ was exceeded on only two days, and all air pollution concentrations were well below the limits used in the Dutch winter smog alert system. The present study and several other recent studies support the need of revised air quality guidelines, that have already been developed for the European Union.

Conclusions

This study has shown that low levels of particulate air pollution were associated with adverse effects on respiratory health in 7-11 yr old symptomatic children. In 50-70 yr old symptomatic adults a weak effect of particulate air pollution on respiratory health was found. Symptomatic children appeared to be more susceptible to the effects of ambient air pollution than non-symptomatic children. No association between air pollution and respiratory health was found in non-symptomatic adults. Subgroup-analyses based on medical characteristics in the panels of children indicated that symptomatic children with atopy were most

susceptible to the effects of PM_{10}. The contrast in particle concentrations between urban and non-urban areas was small. Although there was a tendency of more consistent particle effects in the urban panels, the differences with the non-urban panels were small and might reflect differences in asthma medication use.

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Summary

Chapter 1 describes the background and design of the study presented in this thesis. In classical winter air pollution episodes, increased fossil fuel use due to usually cold weather caused high concentrations of SO_2 and particulate matter. Over the last decades, however, the composition of the winter air pollution mixture has changed due to a continuing decrease in SO_2 emissions and a continuing increase in motorized traffic intensity. As a result, the contribution of traffic related compounds to the air pollution mixture became more important. Especially in the past decade, awareness about the health effects of particulate matter with a diameter smaller than 10 μm (PM_{10}) has increased. Studies in the early nineties reported acute health effects of relatively low levels PM_{10}, independently of SO_2. This raised the question whether the definition of winter air pollution episodes as periods with high concentrations of both SO_2 and particulate matter (not defined as PM_{10}) was still valid. They also raised the question to what extent inhabitants of urban areas with high traffic intensity were exposed to PM_{10} and other components of the air pollution mixture. The study described in this thesis was designed to provide answers to these questions. It was performed simultaneously in urban areas and in smaller 'control' communities during three consecutive winters. As study areas were chosen: Rotterdam and Bodegraven/Reeuwijk (1992/1993), Amsterdam and Meppel (1993/1994), and Amsterdam and Nunspeet (1994/1995). Each winter, panels of children (7-11 yr) and adults (50-70 yr) with and without chronic respiratory symptoms were followed in both areas. Subjects performed twice daily measurements of Peak Expiratory Flow (PEF) and registered the occurrence of respiratory symptoms and medication use in a diary. Air pollution concentrations were measured daily in both areas.

Chapter 2 describes the results of the air pollution measurements. The contrast in the levels of particulate air pollutants between urban and non-urban areas was relatively small. Median PM_{10} concentration, measured during the three winters was 36 $\mu g/m^3$ in the urban areas and 30 $\mu g/m^3$ in the non-urban areas. Median Black Smoke (BS) concentration was 11 $\mu g/m^3$ and 8.5 $\mu g/m^3$, respectively. The concentrations of the secondary aerosols sulfate and nitrate were on average 8% and 7% lower in the urban areas than in the non-urban areas, which contrasts with the fact that twofold higher concentrations were found in the urban areas of the precursor pollutants SO_2 and NO_2.

The small contrast in particle concentrations between urban and non-urban areas in the Netherlands can be explained by the high population density and the importance of long-range transport of air pollutants. Due to the small size of the country and the absence of mountain ranges, there are no physical barriers or small-scale meteorological differences that result in different particle concentrations.

In our main study, the participating children and adults performed twice daily PEF measurements at home with a Mini Wright meter. However, a number of recent studies had raised concern about the reliability of such unsupervised PEF measurements. **Chapter 3** describes the results of a separate study in 9-11 yr old children comparing supervised and unsupervised PEF measurements. In the study described in chapter 3, PEF was measured every week at school with spirometry and with a Mini Wright meter under supervision. In addition, children monitored their own PEF at home with a Mini Wright meter in the morning and in the evening. The aim was to compare within- and between-measurement variability between supervised (spirometry, Mini Wright) and unsupervised (Mini Wright) PEF measurements. For this purpose, all three measurements that each maneuver consisted of were used. The within-measurement variability was considered as a proxy for the amount of measurement error. We found that, as anticipated, the amount of measurement error was larger in unsupervised than in supervised PEF readings, but the differences were not great. We concluded that the advantages of self-recorded measurements in terms of ease, cost and amount of data obtainable far outweighs this disadvantage.

In **chapter 4**, we investigated whether the incidence of influenza and influenza-like-illness (ILI) in the general population, registered by the Dutch network of General Practitioners, could be used to adjust for the potential confounding effect of respiratory infections in panel studies. A higher ILI incidence was associated with a lower level of PEF, and increased reporting of respiratory symptoms and bronchodilator use in all groups of panels. The combined effect estimates calculated for the three winters indicated that for an influenza epidemic reaching peak ILI incidences of 122 cases/10,000 subjects, a group mean decrement in PEF of up to 6% was found, and an increase in symptom reporting and bronchodilator use by factors of up to 2.9 and 4.5, respectively. This implies that in panel studies

on acute effects of air pollution, the ILI incidence might be used to adjust for the potential confounding effect of acute respiratory infections.

Chapter 5 describes to what extent differents components of the winter air pollution mixture were associated with acute respiratory health effects in children with and without chronic respiratory symptoms ('symptomatic' and 'non-symptomatic' children). In symptomatic children from both urban and non-urban areas, significant associations were observed between particle concentrations (PM_{10}, BS and sulfate) and the prevalence of lower respiratory symptoms (LRS) and PEF decrements. Particle concentrations were also associated with bronchodilator use in the urban areas, but not in the non-urban areas. We can not rule out that differences in use of maintenance medication were responsible for this, since the mean daily prevalence of maintenance medication use was almost twofold lower in the urban areas than in the non-urban areas.
In non-symptomatic children, significant effects of PM_{10} and BS concentrations on PEF were observed in both areas, but of smaller magnitude than for symptomatic children. No associations with respiratory symptoms were observed.

Chapter 6 describes the association between air pollution and respiratory health in adults. In symptomatic adults living in urban areas, PM_{10}, BS, sulfate and SO_2 concentrations were associated with the prevalence of large decrements in morning PEF (more than 20% below the median) but not in evening PEF. Although especially Black Smoke was also associated with upper respiratory symptoms, particle concentrations were not associated with lower respiratory symptoms or bronchodilator use. In symptomatic subjects living in non-urban areas, and in non-symptomatic adults from both urban and non-urban areas, no consistent associations between air pollution concentrations and respiratory health indicators were found.

In the panels of children, we also investigated if the response to air pollution differed across subgroups based on the presence/absence of the following medical characteristics: a positive skin prick test against one of a number of common allergens, elevated serum total IgE level, and bronchial hyperresponsiveness (BHR) against metacholine. The results are described in **chapter 7**. Separate analyses were performed in four subgroups for each of the medical characteristics separately: symptomatic with/without the characteristic, and non-symptomatic

with/without the characteristic. The most consistent associations between PM_{10} and indicators of respiratory health were found in symptomatic children who had either high total serum IgE or a positive skin prick test. Presence of high serum IgE or a positive skin prick test was not related to a stronger response to PM_{10} in non-symptomatic children.

In **chapter 8** the results of the study are summarized, compared with findings from other studies and interpreted. In addition, potential biases and limitations of the study design are discussed, and the implications and conclusions are presented. This study has demonstrated that there was a small contrast in particle concentrations between urban and non-urban areas in the Netherlands. In 7-11 year old children, particle concentrations were associated with adverse effects on respiratory health. Symptomatic children appeared to be more susceptible to the effects of particulate air pollution than non-symptomatic children. In 50-70 year old symptomatic adults only a weak effect of particulate air pollution on respiratory health was found, while no effect was found in non-symptomatic adults. Although there was a tendency of more consistent particle effects in the urban panels, the differences with the non-urban panels were small and might reflect differences in asthma medication use.

Subgroup analyses based on medical characteristics in the panels of children indicated that symptomatic children with atopy were most susceptible to the effects of PM_{10}.

Samenvatting

Hoofdstuk 1 geeft de achtergrond en opzet weer van het onderzoek dat in dit proefschrift beschreven wordt. In het verleden werden episoden van wintersmog gekenmerkt door hoge concentrates zwaveldioxide (SO_2) en zwevend stof, als gevolg van het toegenomen gebruik van fossiele brandstoffen tijdens perioden met doorgaans koud weer. In de afgelopen decennia echter is de SO_2 uitstoot fors afgenomen, terwijl de intensiteit van het gemotoriseerde verkeer sterk is toegenomen. Als gevolg daarvan werd de bijdrage van verkeersgerelateerde componenten aan het wintersmogmengsel steeds belangrijker. Vooral in het afgelopen decennium is de bezorgdheid over gezondheidseffecten van fijn stof met een diameter kleiner dan 10 μm (PM_{10}) toegenomen. Studies uit het begin van de jaren negentig hebben laten zien dat al bij relatief lage PM_{10} concentraties acute effecten op de gezondheid optraden, onafhankelijk van de concentratie SO_2. Dit riep de vraag op of de definitie van wintersmog episoden als perioden met hoge concentraties van zowel SO_2 als zwevend stof (niet gedefinieerd als PM_{10}) nog wel juist was. Ook riep het de vraag op in welke mate bewoners van grote steden met veel verkeer blootgesteld worden aan PM_{10} en andere componenten uit het wintersmogmengsel. Het onderzoek dat in dit proefschrift wordt beschreven is opgezet om deze vragen te beantwoorden. Het werd gelijktijdig in grote steden en in kleinere 'controle'plaatsen uitgevoerd gedurende drie opeenvolgende winters. Als onderzoeksgebieden werden gekozen: Rotterdam en Bodegraven/Reeuwijk (1992/1993), Amsterdam en Meppel (1993/1994) en Amsterdam en Nunspeet (1994/1995). De deelnemers aan het onderzoek voerden een winter lang dagelijkse piekstroommetingen uit en noteerden het optreden van luchtwegklachten en medicijngebruik in een dagboekje. In beide gebieden werden 'panels' kinderen (7-11 jaar) en volwassenen (50-70 jaar) met en zonder chronische luchtwegklachten gevolgd. De gehaltes luchtverontreinigende stoffen werden dagelijks gemeten in beide gebieden.

Hoofdstuk 2 beschrijft de resultaten van de luchtmetingen. Het verschil in fijn stof concentraties tussen stedelijke en niet-stedelijke gebieden was relatief klein. De mediane ($\approx$ gemiddelde) PM_{10} concentratie, gemeten tijdens de drie winters was 36 $\mu g/m^3$ in de stedelijke en 30 $\mu g/m^3$ in de niet-stedelijke gebieden. De mediane zwarte rook (ZWR) concentratie was respectievelijk 11 en 8.5 $\mu g/m^3$. De

concentraties van de secundaire aerosolen sulfaat en nitraat waren in de stedelijke gebieden zelfs respectievelijk 8% en 7% lager dan in de niet-stedelijke gebieden. Dit staat in contrast met het feit dat de concentratie SO_2 en NO_2, waaruit sulfaat en nitraat gevormd wordt, tweemaal zo hoog was in de stedelijke gebieden. Het geringe verschil in stofconcentraties tussen stedelijke en niet-stedelijke gebieden kan worden verklaard doordat Nederland een klein land is zonder fysieke barrières (bergen) en met nauwelijks meteorologische verschillen die zouden kunnen leiden tot verschillen in stofconcentraties. Over grote afstanden (vanuit het buitenland) getransporteerde luchtverontreiniging is daarom bepalend voor de fijn stofgehaltes die in Nederland worden gemeten. Doordat Nederland bovendien dichtbevolkt is en bijna als één groot stedelijk gebied beschouwd kan worden zijn de verschillen tussen in grote steden en in kleinere plaatsen gemeten concentraties gering.

In het onderzoek werd door alle deelnemende kinderen en volwassenen tweemaal per dag, thuis, de piekstroom (PEF) gemeten met behulp van een Mini Wright meter. In een aantal recente publikaties werd echter getwijfeld aan de betrouwbaarheid van dergelijke, niet onder toezicht uitgevoerde PEF metingen. **Hoofdstuk 3** beschrijft de resultaten van een aparte studie in 9-11 jaar oude kinderen, waarbij gedurende één winter PEF metingen die onder toezicht van de onderzoekers op school werden uitgevoerd, zijn vergeleken met PEF metingen die door de kinderen op dezelfde dag thuis werden uitgevoerd. Op school werd de PEF elke week gemeten met spirometrie en met een Mini Wright meter onder toezicht. Thuis werd door de kinderen 's ochtends en 's avonds een PEF meting uitgevoerd met een Mini Wright meter. Het doel was het vergelijken van de variabiliteit binnen en tussen de beide onder toezicht uitgevoerde metingen (spirometrie, Mini Wright) en de beide niet onder toezicht uitgevoerde metingen thuis. Hiertoe werden alle drie de pogingen waaruit een meting bestaat geanalyseerd. De variabiliteit binnen een meting werd beschouwd als benadering voor de grootte van de meetfout. Zoals verwacht vonden we dat de 'meetfout' groter was in zelf-gerapporteerde dan in onder toezicht uitgevoerde metingen, maar de verschillen waren niet heel groot. We concludeerden dat de voordelen van zelf-gerapporteerde metingen in termen van eenvoud, kosten en hoeveelheid data die verzameld kunnen worden hier ruimschoots tegen opwegen.

In **hoofdstuk 4** is onderzocht of de incidentie van griep- en griepachtige

aandoeningen ('ILI') in de algemene populatie, gebruikt kan worden om te corrigeren voor het potentieel verstorende effect van luchtweginfecties in panel studies. De ILI incidentie wordt in Nederland geregistreerd door een netwerk van huisartsenpraktijken (peilstations). Een hogere ILI incidentie in de algemene populatie bleek gepaard met een lager niveau van de PEF, en toegenomen luchtwegklachten en medicijngebruik in alle panels. De gecombineerde effectschattingen geven aan dat tijdens een griepepidemie met een maximale ILI incidentie van 122 gevallen/10.000 inwoners, een groepsgemiddelde PEF daling tot 6% optrad, en dat de rapportage van klachten en medicijngebruik toenam met factoren tot respectievelijk 2,9 en 4,5. Dit geeft aan dat de ILI incidentie in panel studies gebruikt kan worden om te corrigeren voor het potentieel verstorende effect van acute luchtweginfecties.

Hoofdstuk 5 beschrijft in welke mate de verschillende componenten uit het wintersmogmengsel geassocieerd waren met acute luchtwegeffecten bij kinderen met en zonder chronische luchtwegklachten ('symptomatische' en 'niet-symptomatische' kinderen). Bij symptomatische kinderen uit zowel stedelijke als niet-stedelijke gebieden werden statistisch significante verbanden gevonden tussen stofconcentraties (uitgedrukt als PM_{10}, ZWR en sulfaat) en de prevalentie van symptomen van de onderste luchtwegen en PEF dalingen. Alleen in de stedelijke gebieden waren stofconcentraties ook geassocieerd met een toegenomen gebruik van luchtwegverwijdende medicijnen (bronchodilatoren). Het kan echter niet worden uitgesloten dat verschillen in het gebruik van onderhoudsmedicijnen tussen beide gebieden hiervoor verantwoordelijk zijn. Deze werden in de niet-stedelijk gebieden namelijk bijna twee keer zoveel gebruikt als in de stedelijke gebieden. Bij niet-symptomatische kinderen uit beide gebieden hing de PM_{10} en zwarte rook concentratie samen met een significant verlaagde PEF, maar het effect was minder sterk dan bij symptomatische kinderen. Er werden geen associaties met luchtwegklachten gevonden.

In **hoofdstuk 6** wordt de relatie tussen luchtverontreiniging en gezondheidseffecten bij volwassenen beschreven. Bij symptomatische volwassenen uit stedelijke gebieden hingen PM_{10}, ZWR, sulfaat en SO_2 concentraties samen met het optreden van grote dalingen van de ochtend PEF (meer dan 20% beneden de mediaan), maar niet van de avond PEF. Hoewel vooral zwarte rook ook geassocieerd was met symptomen van de bovenste luchtwegen, waren de stofconcentraties niet

geassocieerd met een toename in symptomen van de onderste luchtwegen en medicijngebruik. Bij symptomatische volwassenen uit de niet-stedelijke gebieden, en bij niet-symptomatische volwassenen uit zowel stedelijke als niet-stedelijke gebieden, werden geen consistente en significante associaties gevonden.

In de kinderpanels is ook onderzocht of de respons op luchtverontreiniging verschilde tussen subgroepen, gebaseerd op de aan/afwezigheid van de volgende medische kenmerken: een positieve huidpriktest tegen tenminste één van een aantal veel voorkomende allergenen, een verhoogd totaal serum IgE gehalte, en bronchiale hyperreactiviteit (BHR) tegen metacholine. De resultaten worden beschreven in **hoofdstuk 7**. Er werden aparte analyses uitgevoerd in vier groepen voor elk van de medische kenmerken afzonderlijk: symptomatisch/niet-symptomatisch, met/zonder het betreffende kenmerk. Het meest consistente verband tussen PM_{10} en indicatoren van de respiratoire gezondheid werd gevonden bij symptomatische kinderen met ofwel een verhoogd IgE gehalte, ofwel een positieve huidpriktest. Bij niet-symptomatische kinderen hing de aanwezigheid van een verhoogd IgE gehalte of positieve huidpriktest niet samen met een sterkere respons op luchtverontreiniging.

In **hoofdstuk 8** worden de resultaten van het onderzoek samengevat, vergeleken met bevindingen uit de literatuur en geïnterpreteerd. Ook worden potentiële bronnen van vertekening en beperkingen van het onderzoek bediscussieerd, en worden de implicaties en conclusies gegeven. Dit onderzoek heeft laten zien dat er een gering verschil was in fijn stofconcentraties tussen stedelijke en niet-stedelijke gebieden in Nederland. Bij 7-11 jarige kinderen waren hogere stofconcentraties geassocieerd met negatieve effecten op de respiratoire gezondheid. Symptomatische kinderen leken gevoeliger te zijn voor de effecten van fijn stof dan niet-symptomatische kinderen. Bij 50-70 jaar oude volwassenen werd slechts een zwak effect op de respiratoire gezondheid gevonden, terwijl bij niet-symptomatische volwassenen geen effect werd aangetoond. Hoewel er een tendens bestond van meer consistente associaties met fijn stof in de stedelijke gebieden, waren de verschillen met de niet-stedelijke gebieden klein en zouden ze veroorzaakt kunnen worden door verschillen in medicijngebruik. Subgroep analyses gebaseerd op medische kenmerken bij de kinderen suggereerden dat symptomatische kinderen met atopie het meest gevoelig waren voor de effecten van PM_{10}.

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Curriculum Vitae

Saskia Catharina van der Zee werd op 6 oktober 1967 geboren in Houten. In 1985 behaalde zij haar VWO diploma aan het Maaslandcollege in Oss. In datzelfde jaar begon ze met haar studie Milieuhygiëne aan de Landbouwuniversiteit in Wageningen (LUW). In augustus 1991 studeerde zij af met als hoofdvakken Gezondheidsleer, Luchthygiëne en -verontreiniging en Toxicologie. Daarna was ze vier maanden aangesteld als toegevoegd onderzoeker bij het Centrum voor Epidemiologie van het RIVM. Van januari t/m augustus 1992 was ze werkzaam als projectleider Binnenlucht bij de Onderzoeksdienst voor Milieu en Grondmechanica in Amsterdam (OMEGAM). In september 1992 werd zij als assistent in opleiding (AIO) aangesteld bij de vakgroep Humane Epidemiologie en Gezondheidsleer van de LUW. In het kader van deze aanstelling werd het in dit proefschrift beschreven onderzoek uitgevoerd. Behalve als AIO was ze tijdelijk aangesteld als toegevoegd onderzoeker op een onderzoeksproject naar acute effecten van luchtverontreiniging in Europa, de PEACE studie (Pollution Effects on Asthmatic Children in Europe). Sinds 1 juni 1997 werkt ze als stafmedewerker Medische Milieukunde bij de GG&GD in Amsterdam.